United Kingdom Molecular Epidemiology Group

MEG UK

Environmental Cancer, Nutrition and Individual Susceptibility
EU Network of Excellence

London, United Kingdom
30th November 2012

UKMEG / ECNIS²-sponsored Workshop on Design of Future Molecular Epidemiology Studies and New Biomarkers

More information:

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Workshop Organisation:

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Invited Speakers:

Keynote Lectures

Paolo Vineis, London, UK
Stephen Rappaport, Berkeley, USA
Regina Santella, New York, USA
David Phillips, London, UK

Paul Elliott, London, UK
Manolis Kogevinas, Barcelona, Spain
Eiliv Lund, Tromsø, Norway
Franco Merlo, Genoa, Italy
Greet Schoeters, Mol, Belgium
Raj Singh, Leicester, UK
Panagiotis Georgiadis, Athens, Greece
Volker Manfred Arlt, London UK

Registration now open

Workshop Registration:

* Members	£ 60.-
(*Current membership of UKEMS or ECNIS)	
Non-Members	£ 80.-
** Full-time students	£ 20.-

(**Full-time students must send a letter of confirmation of their status from their supervisor with the registration form)

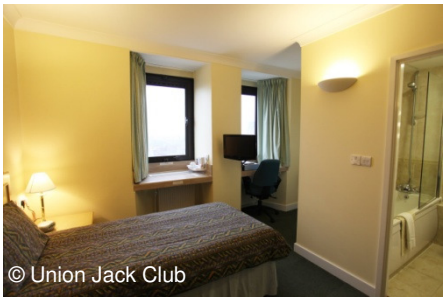
Registration is now open

Registration deadline 16th November 2012

The number of participants is limited to a maximum of 100 persons. Registration will be made on a first come-first served basis.

Hotel Accommodation:

Special arrangements have been made for all workshop participants to stay at the conference venue in the "Union Jack Club" (www.ujclub.co.uk) at the "Temporary Honorary Members Tariff" starting at £ 52.- per night for a single room (see leaflet attached).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Note: All participants are responsible for their own booking arrangements.

Conference Venue Map:

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Waterloo Conference Centre & Union Jack Club

Sandell Street/Waterloo

London SE1 8UJ

Scientific Programme

Time	Session
08.15 – 08.45 am	***Registration***
	Chairs: Volker Arlt (London) & Soterios Kyrtopoulos (Athens)
08.45 – 09.30 am	***- Keynote Lecture -*** **Paolo Vineis** (Imperial College, London, UK): **Towards the exposome**
09.30 – 10.00 am	**Paul Elliott** (Imperial College, London, UK): **Metabolic phenotyping in epidemiology and the metabolome-wide association study (MWAS)**
10.00 – 10.30 am	**Manolis Kogevinas** (CREAL, Barcelona, Spain): **Environmental molecular epidemiology studies in mother-child cohorts in Europe**
10.30 – 11.00 am	***Coffee Break***
	Chairs: Montse GarciaClosas (London) & Andrew Collins (Oslo)
11.00 – 11.45 am	***- Keynote Lecture -*** **Stephen Rappaport** (University of California, Berkley, CA, USA): **Omics open doors to useful biomarkers**
11.45 – 12.00 pm	**Raj Singh** (University of Leicester, Leicester, UK): **Development of mass spectrometric methods for DNA adductomics**
12.00 – 12.15 am	**Panagiotis Georgiadis** (National Hellenic Research Foundation, Athens, Greece): **Epigenomics in molecular epidemiology - experience from the EnviroGenomarkers project**
12.15 – 12.30 am	**Volker Arlt** (King's College London, London, UK): ***TP53* mutational signature for aristolochic acid: AT → TA transversions in urothelial cancer**
12.30 – 01.30 pm	***Lunch Break***
	Chairs: Susan Duthie (Aberdeen) & Jill McKay (Newcastle)
01:30 – 02:15 pm	***- Keynote Lecture -*** **Regina Santella** (Columbia University, New York, NY, USA): **Epigenetic biomarkers in molecular epidemiology studies of cancer**
02.15 – 02.40 pm	**Eiliv Lund** (University of Tromsø, Tromsø, Norway): **Exploring trajectories of gene expression in blood in a prospective design – the Norwegian Women and Cancer postgenome biobank study**
02.40 – 03.05 pm	**Greet Schoeters** (Flemish Institute for Technological Research, Mol, Belgium): **Transcriptomics in environmental health surveillance, a promising new tool**
03.05 – 03.30 pm	***Coffee Break***
	Chairs: Andrew Povey (Manchester) & Volker Arlt (London)
03.30 – 03.55 pm	**Franco Merlo** (National Cancer Research Institute, Genoa, Italy): **Biomarkers of prenatal exposure to dietary compounds and micronuclei frequency in newborns: findings of the NewGeneris European prospective mother–child study**
03.55 – 04.40 pm	***- UKMEG Award 2012 Lecture -*** **David Phillips** (King's College London, UK): **DNA adducts and other smoking guns**
04.40 pm	***End of Workshop*** ***(Note: Participants are welcome to stay in The Union Jack Bar for a drink)***

Towards the exposome

Paolo Vineis
MRC-HPA Centre for Environment and Health, Imperial College London, London, UK.

One of the major challenges of environmental epidemiology is to develop novel approaches to the assessment of exposure to environmental pollutants by characterizing the external and the internal components of the exposome, during critical periods of life. I describe a project ("Exposomics") that will centre on 1) exposure assessment at the personal and population levels within existing European short- and long-term population studies, exploiting tools and methods which we will develop for personal exposure monitoring (PEM) (*e.g.* portable sensors, smartphone-based technologies, high-resolution chemical analysis); and 2) multiple "omic" technologies for the analysis of biological samples (internal markers of external exposures). The search for the relationships between external exposures (as measured by PEM, which has not previously been used in large scale studies) and global profiles of molecular features (as measured by omics) in the same individuals constitutes a novel advance towards the development of "next generation exposure assessment" for environmental chemicals and their mixtures. The linkage with disease risks opens the way to what are defined here as 'exposome-wide association studies' (EWAS). This multidisciplinary project will: I) 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*. II) 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. We will mainly investigate particles (especially ultrafine particulates), black carbon, reactive oxygen species, and disinfection by-products. III) Use the above exposome measurements to model exposure to air pollution and water contamination in large population cohorts, through novel statistical modeling. Together, this will lead to formulating 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.

Metabolic phenotyping in epidemiology and the metabolome-wide association study (MWAS)

Paul Elliott
MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK.

Metabolic phenotyping (metabonomics) has emerged as a powerful approach for the capture of biomarker information on a range of diseases and diseases traits. We have developed the concept of the Metabolome-Wide Association Study (MWAS) as a means of identifying novel molecular biomarkers and associated metabolic pathways underlying disease risk [1]. MWAS involves spectroscopic screening - via proton Nuclear Magnetic Resonance (1H NMR) spectroscopy and mass spectrometry (MS) - to capture environmental and lifestyle information from dietary, gut microbial and xenobiotic sources as well as metabolic information linked to genetic variation. The aim is to identify potential biomarkers associated with disease risk and other factors such as gender, ethnicity, drug exposure, dietary and other lifestyle information. We have demonstrated proof-of-concept of the MWAS approach in epidemiology using data from the INTERMAP Study, an international co-operative investigation on macro- and micronutrients, foods, urinary metabolites and other factors influencing blood pressure (BP). In INTERMAP, we used 1H NMR spectroscopy of two 24-hour urinary collections per person to provide metabolic profiles for each of 4,630 men and women from UK, USA, China and Japan. Unlike genetic variants which are categorical, urinary metabolite concentrations are continuous with dynamic range that can vary over orders of magnitude between individuals, presenting analytical challenges in dealing with the vast array of multivariate information generated. Our investigations to date on east Asian and Western population samples in INTERMAP show major differences in metabolic phenotypes across populations – including between north and south China, China and Japan, Japanese and Japanese Americans living in Hawaii, as well as regional variations within countries and inter-individual differences within populations. Selected metabolites varying across countries at differing risks of cardiovascular disease were quantified and found to relate to BP of individuals generating new hypotheses concerning BP variation.

References

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Environmental molecular epidemiology studies in mother-child cohorts in Europe

Manolis Kogevinas[1,2]
[1]*Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain;* [2]*National School of Public Health, Athens, Greece.*

I will refer to the possibilities of research and on the challenges in environmental molecular epidemiology studies in mother-child cohorts in Europe. The potential health effects of environmental exposures are examined in pregnancy and birth cohort studies that include more than 350,000 mother–child pairs in 19 European countries [1]. All cohorts collected some biological specimens of children or parents. The most commonly examined exposures are passive smoking, maternal occupation, outdoor air pollution, allergens, water contamination, ionizing or nonionizing radiation, noise, metals and persistent organic pollutants. All cohorts have information on birth outcomes, nearly all on asthma, allergies, childhood growth and obesity and fewer collected information on child neurodevelopment. The use of exposure biomarkers has been limited on the evaluation of POPs, cotinine and some metals. The use of biomarkers of effect is scarce, while genetic research involves huge numbers. The collection of repeated samples is a challenge for several of the emerging exposures evaluated. The evaluation of phthalates, for example, done once during pregnancy may not be informative given the short half-life. Exposures vary rapidly in early years and an evaluation of children in different ages including biological samples would be advisable. The issue of mixtures is being discussed but few studies are big enough and measured many concomitant exposures using biomarkers. The NewGeneris study is an exception as are newly funded FP7 projects on the Exposome (Exposomics and Helix). Even like that, the issue of mixtures will require the development of additional methods. The use of –omics in large epidemiological studies (example EnviroGenoMarkers project) is still limited and experience on their use is now being developed. The development of techniques, e.g. for the measurement of adducts, using minimal amounts of blood may enhance the capacity for large analyses of stored samples. The impressive resource of existing birth cohort data and the availability of molecular techniques coupled with new techniques on exposure assessment will undoubtedly provide huge possibilities for research on environment and child health.

References

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Omics open doors to useful biomarkers

Stephen M. Rappaport
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The exposome, representing the totality of human exposures beginning at conception, has been proposed as an analog of the genome in studies of disease etiology. Functionally, the exposome can be defined by comprehensive sets of bioactive molecules in the blood, and omic tools can be used to discover biomarkers of causal exposure and biomarkers of disease progression. Models of disease pathways provide insight into omic connections and also permit differentiation between biomarkers of exposure and biomarkers of disease. A two-stage scheme is presented for 1) profiling omic features in serum to discover molecular biomarkers of exposure and biomarkers of disease and 2) for applying these biomarkers in follow-up studies. The data-driven component, referred to as an exposome-wide-association study (EWAS), employs metabolomics, proteomics and adductomics to interrogate components of the serum exposome and, ultimately, to identify, validate and differentiate biomarkers of exposure and biomarkers of disease. Proof-of-concept studies for EWAS have already identified promising new biomarkers of major chronic diseases, including cardiovascular disease, diabetes and cancer. Follow-up studies follow knowledge-driven designs to explore disease causality, prevention, diagnosis, prognosis and treatment.

Development of mass spectrometric methods for DNA adductomics

Rajinder Singh
Cancer Biomarkers and Prevention Group, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK.

Human exposure to genotoxic carcinogens is not confined to a single compound but instead to mixtures of different chemicals, which can react with the nucleophilic sites in DNA to form multiple adducts. The interaction of different chemicals may lead to additive, synergistic or antagonistic effects in terms of DNA adduct formation and carcinogenic activity resulting from changes in metabolic activation to reactive intermediates and DNA repair. Therefore, there is a requirement for adductomic approaches for the screening of DNA adducts, mass spectrometry offers the potential for the detection of multiple DNA adducts simultaneously. The majority of adducted 2'-deoxynucleosides show a common fragmentation following positive electrospray ionisation-tandem mass spectrometry with the neutral loss of 116u following collision induced dissociation, which corresponds to the loss of the 2'-deoxyribose resulting in the adducted base [B+H2]+ being the major product ion formed. Screening of adducted 2'-deoxynucleosides using a triple quadrupole mass spectrometer may be achieved by either using a series of selected reaction monitoring (SRM) transitions or constant neutral loss (CNL) scanning for the [M+H]+ to [M+H-116]+ transition. For sensitive detection of the DNA adducts enzymatically hydrolysed DNA samples require enrichment prior to mass spectrometric analysis by the removal of the abundant unmodified 2'-deoxynucleosides, which may lead to overloading of the column and concomitant matrix effects if not removed. This can be achieved by employing online column-switching or pre-concentration with micro-scale solid phase extraction tips. A further challenge is to adequately chromatographically separate structurally diverse DNA adducts ranging from small hydrophilic to more hydrophobic modifications in a single chromatography run. The sensitivity of CNL is lower when compared to SRM, however it offers the possibility for the discovery of previously uncharacterised DNA adducts. Mass spectrometry provides adduct structural information allowing the investigation of adductomic profile differences in DNA following exposure to mixtures of genotoxic carcinogens.

Epigenomics in molecular epidemiology - experience from the EnviroGenomarkers project

Panagiotis Georgiadis[1], Ingvar A. Bergdahl[2], Domenico Palli[3], Bo G Jönsson[4], Soterios A. Kyrtopoulos[1]

[1]National Hellenic Research Foundation, Institute of Biological Research and Biotechnology, Athens, Greece; [2]Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [3]Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute, Florence, Italy; [4] Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden.

Epigenetic modifications may be induced by environmental chemicals and the subsequent altered gene expression may persist throughout life. Aberrant DNA methylation is common in many types of cancer and changes in the methylation pattern early or before the clinical onset of cancer development may be relevant for cancer detection, diagnosis and prognosis. We have therefore, investigated the association between epigenome-wide methylation in leukocytes and blood levels of persistent organic pollutants (POPs) and heavy metals as well as the possible implications of the altered epigenome to the development of breast cancer or lymphoma. CpG genome-wide methylation and levels of pollutants were determined in 200 individuals from the EPIC-Italy and 200 from the NorthSweden cohort. When blood was collected, the donors were asymptomatic. Half of them (the other half being the controls) developed either breast cancer or Non-Hodgkin lymphoma (50 for each disease and cohort) two to fifteen years after blood donation. Genome-wide DNA methylation was assessed using the Illumina BeadChip, which interrogates >484,000 CpG sites. The statistical analysis was completed for the breast cancer sub-cohort. We found an association between DNA methylation and cadmium exposure (*false discovery rate<0.05*) for 14 CpGs mapped to 6 genes and 5 "open sea" regions with significant overlap between the two countries. Among the genes with altered methylation pattern are the AHRR (aryl hydrocarbon receptor repressor; *4 sites)*, F2RL3 and GPR15 (G-protein-coupled receptor 15). There was a significant correlation between dioxin-like polychlorinated biphenyls (PCBs) and methylation at a site of INHBA (inhibin β A subunit) which is a key player in hormonal regulation. In addition hexachlorobenzene seems to influence a battery of CpG sites which correspond to 25 genes including RPA3 (replication protein A3) and TREX2 (three prime repair exonuclease2), important members of the DNA repair machinery and DEK (DAK oncogene) oncogene. Although no obvious statistical association was observed between methylation and breast cancer several genes known to be implicated to breast cancer were among those with the highest differences between cases and controls (1‰). In conclusion, DNA methylation arrays are likely to accelerate the pace of methylation biomarker discovery for a wide variety of exposures and diseases. *Research support by the European Union (Grant number 226756).*

_TP53_ mutational signature for aristolochic acid: AT to TA transversions in urothelial cancer

Volker M. Arlt
Analytical and Environmental Sciences Division, MRC-HPA Centre for Environment and Health, King's College London, London, UK.

Molecular epidemiology studies have established a link between ingestion of Chinese herbs containing aristolochic acid (AA) and chronic nephropathy, now termed aristolochic acid nephropathy (AAN), as well as urothelial cancer. It is now nearly 20 years since the first description of AAN but recent data have also demonstrated that AA is the primary etiological agent in Balkan endemic nephropathy (BEN) and associated urothelial cancer where diet seems to be the likely route of AA exposure [1]. AA has been classified as a Group I human carcinogen by the International Agency for Research on Cancer (IARC) and *Aristolochia* spp. and herbs that can be confused or substituted for *Aristolochia* have been banned in many countries. Unfortunately, these regulatory measures have been shown to be wholly inadequate in preventing exposure to AA, and there is growing evidence that AA exposure is causing a large unrecognized burden of disease in Asia with potentially devastating public health implications. This is in line with a more recent study showing that AA exposure contributes to the high incidence of upper urinary tract urothelial carcinoma in Taiwan where medicinal use of *Aristolochia* plants is widespread [2]. AA-DNA adducts are established biomarkers of AA exposure that have been detected in urothelial tissue from AAN and BEN patients. Further, mechanistic evidence demonstrating that the urothelial tumour DNA has a distinct *TP53* mutational signature consisting of AT to TA transversion mutations which is otherwise infrequent in *TP53* in other cancer genomes provides a strong molecular link that AA directly contributes to the development of these urothelial tumours [3]. This characteristic *TP53* mutation pattern can also be recapitulated experimentally in mammalian cells that immortalised after AA treatment [4]. More public health measure needs to be implemented to reduce the global disease burden of AAN and to help to eradicate this preventable disease.

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DNA methylation biomarkers in molecular epidemiology studies of cancer

Regina M. Santella
Department of Environmental Health Sciences, Columbia University, New York, NY, USA.

Alterations in DNA methylation, both gene-specific and global, are now recognized as frequent events in carcinogenesis. We have been investigating whether changes in white blood cell (WBC) DNA methylation can be used to understand the impact of environmental exposures including early life factors, and identify individuals at high risk for cancer development as well as whether the analysis of methylated tumor DNA in plasma can be used for early detection of cancer. In a nested case control study of hepatocellular cancer, Sat2 but not LINE-1 repetitive elements were hypomethylated in baseline WBC of cases compared to controls [1]. Initial studies used a candidate gene approach to investigate gene-specific methylation in plasma DNA finding subject's positive years prior to clinical diagnosis [2]. More recently Illumina methylation arrays have been used to analyze tumor/nontumor tissues to identify additional genes and improve overall prediction [3]. Ongoing studies are determining whether methylation in these genes can be found in WBC as well as plasma DNA. Studies in breast cancer have also shown that Sat2 but not LINE-1 is hypomethylated in WBC of cases compared to controls but these bloods were collected after diagnosis so may have been impacted by disease or treatment [4]. Studies of breast tumor tissue methylation found that both global hypomethylation in Sat2 and LINE-1 and gene-specific hypermethylation were associated with prognosis [5]. While information is still limited to date, these studies suggest that analysis of DNA methylation markers may provide useful information on risk, disease status and prognosis.

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Exploring trajectories of gene expression in blood in a prospective design – the Norwegian Women and Cancer postgenome biobank study

Eiliv Lund
Institute of Community Medicine, University of Tromsø, Tromsø, Norway.

Ten years after the description of the human genome cancer epidemiology has already passed the gene-environment enthusiastic period of whole genome association studies, GWAS, and moves now into the post-GWAS analyses or functional studies. So far post-GWAS analyses have mostly been looking at epigenetics i.e. methylation and microRNA. Whole genome transcriptomics or mRNA analyses are less frequent, mainly due to the effect of RNase in stored biological samples that is neither buffered nor stored in liquid nitrogen. The NOWAC (Norwegian Women and Cancer study) postgenome biobank with its 50 000 blood samples and 800 biopsies with buffer collected 2003-10 is one of a few larger prospective studies with blood and tissue samples suitable for whole genome transcriptomics. The implementation of functional genomics in a prospective study including biological material from time of diagnosis and also post diagnostic has been named globolomic. This design opens up for both traditional risk assessments, but also for dynamic studies of the carcinogenic process. The latter aspect is challenging the current statistical methods. We will present preliminary data on the time dependent gene expression or trajectories in peripheral blood from six years before diagnosis till time of diagnosis for 100 random genes based on 700 pairs of breast cancer (in situ and invasive) in a nested control design in the postgenome cohort. The trajectories of gene expression over time for in situ, invasive stage 1 and metastatic cancer will be compared based on pattern recognisition methods. The results indicates that the main hypothesis of the study, that gene expressions in peripheral blood could serve as functional markers of the carcinogenic process, might be realistic.

Transcriptomics as part of environmental health surveillance, a promising new tool

Greet Schoeters[1,2]
[1]*Unit Environmental Risk and Health, Flemish Institute for Technological Research (VITO), Mol, Belgium;* [2]*Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.*

Biomonitoring gives the unique opportunity to look inside the body to exposure, effects and susceptibility to environmental chemicals. The traditional "one by one chemical" approach is excellent to follow temporal and spatial exposure trends. But the remaining challenge in environmental health studies is to evaluate combined exposures and how they affect the pathways towards disease. We tested the hypotheses that changes in gene transcripts in peripheral blood cells sensor chemicals that enter the circulation as well as the altered functioning of organs and tissues. Toxicogenomics in large scale population studies is still in an exploratory phase. In the Flemish Environment and Health Surveillance program (FLEHS) we study changes in gene expression in peripheral blood cells as an indicator of systemic changes. A longitudinal study with healthy adults allowed to evaluate the intra- and interindividual short and long term variability in gene expression and showed that expression patterns in genes of peripheral blood cells were relatively stable with time. Transcriptomics of peripheral blood cells are applied to evaluate spatial trends in gene expression in residents from different regions. Analysis of the large data sets and the interpretation in terms of biological significance for health and exposure is still a challenge. Currently we explore its use for establishing exposure profiles and for linking gene expression data with exposure biomarkers and with effect biomarkers in a well characterized birth cohort of 200 mothers child pairs. Gene expression analysis suggests several changes in genes and pathways as intermediate between chemical exposure and birth outcome parameters. The interpretation and further validation of these outcomes is needed. *The studies are partially supported by the Ministry of the Flemish Community (Department of Economics, Science and Innovation; Flemish Agency for Care and Health; and Department of Environment, Nature and Energy) and by the European framework projects OBELIX (FOOD- ref.227391).*

Biomarkers of prenatal exposure to dietary compounds and micronuclei frequency in newborns: findings of the NewGeneris European prospective mother–child study

Domenico Franco Merlo (on behalf of the NewGeneris Consortium)
Epidemiology, Biostatistics and Clinical Trial, National Cancer Research Institute, Genoa, Italy.

The EU project "Newborns and Genotoxic exposure risks" (NewGeneris) aimed to test the hypothesis that maternal exposure to dietary compounds with carcinogenic and immunotoxic properties results in *in utero* exposure and molecular events in the unborn child leading to increased risk of cancer and immune disorders in later childhood. Results concerning the relations between *in utero* exposure to dietary and/or environmental carcinogens and well established and new biomarkers of exposure/early biological effect, including 36 gene expression profile, GWAS and the *in vitro* cytokinesis blocked MN assay (CBMN assay) in T lymphocytic are reported. Exposure biomarkers were measured in cord blood: acrylamide (AA-) and its metabolite glycidamide (GA-), and ethylene oxide (EtO-) hemoglobin adducts, BPDE-, ^{32}P-bulky-, M_1dG-, and O^6-MG-DNA adducts, and the AR, DR and ERα CALUX levels in plasma. Some 1500 pregnant women were enrolled between 2006 and 2010 in Heraklion, Greece (Rhea cohort); Barcelona and Sabadell, Spain (IMNA cohort); Bradford, England (Born in Bradford cohort); Copenhagen, Denmark (Danish biobank), and Oslo, Norway (BraMat cohort) and blood samples were collected from 1151 mother-infant dyads. following a standardized protocol. Statistical analysis was conducted according to a priory defined statistical analysis plan. Statistical modeling (multiple binomial regression) accounted for the potential confounding effect of socio-demographic, reproductive, and life-style factors. Exposure biomarkers showed a large variation in the European populations. No evidence of linear relationships was detected between Hb-adducts and micronucleated binucleated (MNBN) or mononucleated cells (MNMONO). A significant association was found between M_1dG-DNA adduct levels and the frequency of MNBN cells although no linear exposure-effect relation was observed. ERα-CALUX plasma levels were significantly associated with the frequency of MNBN and MNMONO cells and AR-CALUX with the frequency of MNMONO cells. Statistically significant lower MNBN were associated with over expression of 7 genes while no association between gene expression with significant changes of the frequency of MNMONO was observed. Statistically significant relations were observed between exposure biomarkers levels and gene expression. Unsupervised GWAS analyses on the interactions between exposure biomarkers and MNBN revealed a cluster of significant SNPs only for AR-CALUX. SNPs from a priory selected list of biotransformation phase I and II genes were also investigated for association with MNBN. Three SNPs had a significant effect on the occurrence of MNBN frequency.

UKMEG Award 2012

DNA adducts and other smoking guns

David H. Phillips
Analytical and Environmental Sciences, MRC-HPA Centre for Environment and Health, King's College London, London, UK.

The formation of DNA adducts by environmental carcinogens, and their biological consequences, have been central to studies shedding light on the aetiology of cancer and to investigations elucidating the pathways of activation of many such agents. A range of detection methods have emerged that have made it possible to monitor human exposure to carcinogens and to investigate hypotheses of the causative agents of several cancers. These include revealing the potential causative role of tobacco smoking in many different cancers. More recently, the cause of Balkan endemic nephropathy has been discovered by such methods. It is anticipated that investigating populations from areas of high cancer incidence, for example oesophageal cancer, will similarly reveal evidence of causative agents. In experimental studies, identifying the structures of DNA adducts, the reactive intermediates that have formed them and the mutations that they lead to can together provide compelling evidence for cancer risk, and assist interspecies comparisons. Concerns over the risk to humans of tamoxifen, widely prescribed for breast cancer although it is a potent rat liver carcinogen, have been somewhat allayed by such studies. In future, high throughput approaches to DNA (and protein) adduct detection will facilitate identifying the causes of many more cancers, as well as identifying the origins of the multiple mutations detected in human tumours.

2012 Temporary Honorary Member Tariffs

	Room	Room & Breakfast	Room, Dinner & Breakfast
SINGLE	£52.00	£60.00	£75.00
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SINGLE ENSUITE	£66.50	£74.50	£89.50
TWIN TV	£90.50	£106.50	£136.50
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SUPERIOR	£140.00	£156.00	£186.00
SUITE	£160.00	£176.00	£206.00

Book ahead of arrival and we offer you breakfast at a discounted price and our dinner menu which changes regularly offering two courses along with a pint of beer, glass of wine or a soft drink.

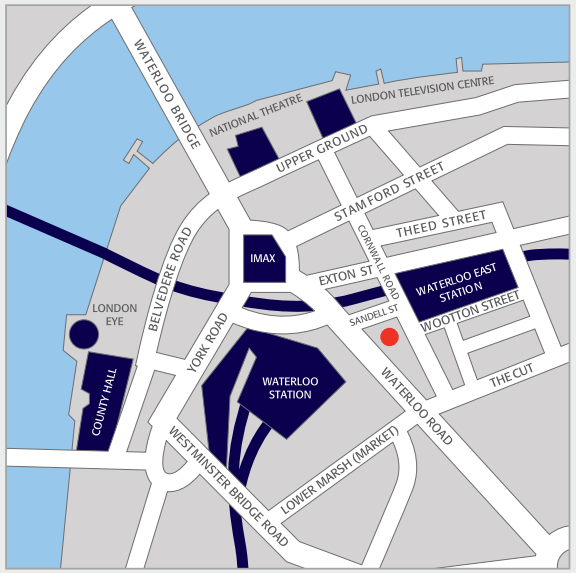
Family rooms are suitable for 2 adults and 2 children (bunk bed) up to the age of 18. Prices quoted are for adults and children over 12. Children under the age of 3 are free in all cases when sharing parent's room.

A baby's cot can be provided.

A discount of 10% is given on continuous accommodation bookings of 7 days or more.

All prices subject to change.
All charges are inclusive of VAT at the current rate

Find or Contact Us



Union Jack Club, Sandell Street
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For all enquiries please call

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(24hr Switchboard)

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