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7th Euro-Global Summit on

Toxicology & Applied Pharmacology

October 24-26, 2016 Rome, Italy

Scientific Tracks & Abstracts

(Day 1)

Euro Toxicology 2016

Occupational Toxicology | Nano Toxicology

Session Chair
Ashley Roberts
Intertek Scientific & Regulatory Consultancy, Canada

Session Co-Chair
Vesna Matovic
University of Belgrade, Serbia

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Title: Change of rodent carcinogenicity testing
Gerd Bode, University of Gottingen, Germany

Title: Attenuation of adverse health effects of metallic nanoparticles with innocuous bioprotectors: Mechanistic hypotheses and experimental results
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Title: The insect repellent N,N-diethyl-m-toluamide (DEET) induces angiogenesis via allosteric modulation of the M3 muscarinic receptor in endothelial cells
Samuel Legeay, University of Angers, France

Title: Targeted screening of succinic semialdehyde dehydrogenase deficiency (SSADHD) employing an enzymatic assay for γ-hydroxybutyric acid (GHB) in biofluids
Cédric Wernli, University of Applied Science and Arts, Switzerland

Susanne Bremer Hoffmann, J Clin Toxicol 2016, 6:6(Suppl)
http://dx.doi.org/10.4172/2161-0495.C1.021

Nanomedicines in the European translational process

Susanne Bremer Hoffmann
Joint Research Centre-European Commission, Italy

In 2013, the World Health Organization (WHO) released an update of the report on "Priority Medicines for Europe and the World" with the aim to bridge the gap between public health needs and the current research and development priorities. The European Commission has recognized the opportunities offered by nanotechnology in the health care sector for the development of new diagnostic/therapeutic concepts and funds a wide range of projects in order to fully exploit the potential of nanotechnology. These research activities generate ideas, knowledge and prototypes addressing unmet medical needs that need now to be further progressed into clinical applications. In order to support the translation of such nanomedicines towards clinical use, the European Nanomedicine Characterization Laboratory (EU-NCL) has been established. The EU-NCL provides a comprehensive set of characterization tests (physical, chemical, *in vitro* and *in vivo* biological properties) allowing researchers and SMEs to better define critical quality and safety attributes of their products before entering into clinical investigations. The knowledge base generated by the EU-NCL will additionally support competent authorities to further understand regulatory needs of this emerging product category and will boost the regulatory science in the field.

Biography

Susanne Bremer Hoffmann holds a PhD degree in Biology obtained for her work on the development of immunotherapies against leukemia. After Post-doctoral Research at the Federal Institute for Risk Assessment in Germany, she joined the Joint Research Centre of the European Commission and became a Team Member of the European Centre for the Validation of Alternative Methods (EURL-ECVAM) where she was involved in validation studies of toxicological *in vitro* tests. She collaborated in several framework projects including public-private partnerships and is now a Team Member of the EU-NCL assessing the toxic potential of nanomaterials by using *in vitro* test.

Bremer-Hoffmann@ec.europa.eu

Notes:

Bulent Ozpolat, J Clin Toxicol 2016, 6:6(Suppl)
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Development of novel targeted therapies for triple negative breast cancer: Targeting EF2-kinase

Bulent Ozpolat
University of Texas, *USA*

Triple-negative breast cancer refers to any breast cancer which is clinically characterized as more aggressive and less responsive to standard treatments, and is associated with poor overall patient prognosis. Therefore, there is an urgent need to develop effective and safe therapies against triple negative breast cancer due to poor prognosis and lack of targeted therapies. Recently, we found that EF2-Kinase (EF2K) is significantly overexpressed in breast cancer cell lines compared with normal breast epithelium and its expression is associated with poor patient overall survival. However, its regulation and the role in breast cancer progression and tumorigenesis are not known. We demonstrated, for the first time, that inhibition of EF2K blocked proliferation, colony formation and invasion and tumorigenesis of TNBC tumors. We also discovered that FOXM1 and a microRNA directly binds and regulates EF2K gene expression and targeting of these molecules recapitulates the effects of EF2K targeting inhibit proliferation, invasion migration and tumor growth in TNBC models. We demonstrated blocked tumor growth tumor xenografts and significantly enhanced the *in vivo* efficacy of chemotherapy. Inhibition of FOXM1-miRNA/eEF2K axis significantly reduced Src/Fak/Paxillin, IGF-1R, PI3K/Akt/mTOR, cyclinD1, c-myc, HIF1 alpha and VEGF and induced significant apoptosis in tumors. Overall, our studies suggest that EF2-Kinase plays an important role in TNBC tumorigenesis and progression and EF2K targeted therapies provide the proof of concept for translation into Phase-I clinical trials in patients.

Biography

Bulent Ozpolat is an Associate Professor at the Department of Experimental Therapeutics at MD Anderson Cancer Center, Houston, TX, USA. He earned his PhD degree in Immunology from The University of Texas, M.D. Anderson Cancer Center, Houston Graduate School of Biomedical Sciences after getting his MD degree from The University of Dokuz Eylul University, Izmir, Turkey. He completed his graduate and Post-doc Training at the departments of Cancer Biology and Immunotherapy at MD Anderson Cancer Center. His research focuses on identification of novel survival pathways including EF2-Kinase (eEF2K) and autophagy pathways as well as regulation of cell death mechanism such as autophagic and apoptotic cell death; and development of molecularly targeted therapies using tumor-targeting nanotherapeutics (i.e. liposomes, immunoliposomes and metal-magnetic nanoparticles) in aggressive type of solid tumors (i.e. breast, pancreatic and ovarian cancers) and hematological cancers such as leukemia and lymphoma for the delivery of therapeutic cargo including siRNA, microRNA small molecule inhibitors, peptides, proteins, cytokines and anticancer agent. He is a Member of Center for Targeted Therapy and Non-Coding RNA Center and received many research awards in recognition of research excellence. He has published more than 50 papers, 9 book chapters and 12 review articles in peer-reviewed high impact journals and contributed to textbooks.

Bozpolat@mdanderson.org

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7th Euro-Global Summit on
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Change of rodent carcinogenicity testing

Gerd Bode[1] and **Jan Willem van der Laan**[2]
[1]University of Gottingen, Germany
[2]Medicines Evaluation Board, Netherlands

Rodent carcinogenicity studies are not meant to produce a toxicology result/tumor count, but to extrapolate (translate) these data and develop a prediction of potential cancer risk for patients. If there is a real risk, then either no approval can be granted or a rigid risk/benefit analysis will justify any treatment of humans. Altogether, there are too many positive results from such long-term rat or mouse studies. The need for the 2 year rodent assay to assess a carcinogenic potential is questioned already for years. From retrospective analyses of various datasets (PhRMA, FDA, JPMA and common EU+FDA) it was concluded that based on genotoxicity and non-genotoxic mechanisms, detectable in pharmacology and chronic toxicity data (usually present at the end of phase 2 in the development of a new pharmaceutical) the outcome of the 2-yr rat carcinogenicity study can be predicted with reasonable assurance at the two extremes of the spectrum: Negative predictions can be made when predictive carcinogenic signals are absent and positive predictions are possible when such signals are present. In between a category of compounds still remain for which the outcome cannot be predicted with sufficient certainty and where experimental studies may have added value to identify real hazards. These hypotheses are being tested in an ongoing common exercise by agencies and industries. Such prospective evaluations are necessary to justify any revision of the present recommendations of the ICH guideline S1. Until 2017, sponsors will be strongly encouraged to submit carcinogenicity assessment documents (CADs) to drug regulatory agencies (DRAs) for all investigational pharmaceuticals with ongoing or planned 2-yr rat carcinogenicity studies. The CAD would address the overall carcinogenic risk of the investigational drug as predicted by the available knowledge and a rationale for why the conduct of long-term studies would or would not add value to that assessment, in the latter case by a request of a "virtual" waiver. Drug regulatory agencies will independently review the submitted documents and evaluate the degree of concordance with sponsors. During this prospective evaluation period waiver requests will not be granted but the data are intended solely for collecting experience. Submitted CADs will finely be compared to the real outcome of the 2-yr carcinogenicity studies and/or any other factors of a weight of evidence evaluation. Main objective will be the assessment of accuracy of the predictions, with emphasis on the "Virtual" waivers. This paper will inform about the details of the retrospective analyses leading to the new hypothesis and will report about preliminary results of this prospective exercise. Hopefully, further contributing participation can be stimulated.

gerd-bode@t-online.de

Notes:

I A Minigalieva et al., J Clin Toxicol 2016, 6:6(Suppl)
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Attenuation of adverse health effects of metallic nanoparticles with innocuous bioprotectors: Mechanistic hypotheses and experimental results

I A Minigalieva[1], B A Katsnelson[1], L I Privalova[1], M P Sutunkova[1], V B Gurvich[1], O H Makeyev[2], I E Valamina[2], V Y Shur[3] and **E V Shishkina[3]**
[1]The Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, Ekaterinburg, Russia
[2]Ural Medical University, Russia
[3]Ural Federal University, Russia

Especially high health risks associated with impacts of metallic and metal oxides nanoparticles (Me-NPs) contaminating working environments of not only the emerging nano-industry but also of some long-existing traditional technologies makes it necessary, along with keeping respective dangerous exposures as low as possible, to look for ways of increasing the organism's resistance to them (the "biological prophylaxis"). Theoretical premises of beneficial interventions in toxicokinetics and toxicodynamics of Me-NPs are inferred from understanding general and specific key mechanisms of their adverse action and on our previous experience in the field of such bio-protection against other toxics. Based on these premises, we proposed several "bio-prophylactic complexes" (BPCs) comprising mainly pectin, some vitamins, glutamate, glycine, N-acetylcysteine, omega-3 PUFA and different essential trace elements. Results of several *in vivo* experiments with NPs of metallic silver and of copper oxide as well as with binary and trinary combinations of Me-NPs characteristic of workroom air pollution in different industries have proved that, against the background of such BPCs' oral administration, the pulmonary and systemic toxicity of Me-NPs and even their genotoxicity can be markedly attenuated. Therefore, we recommend to further develop this vector of nano-toxicological research. Our previous positive experience in organizing first a selective and then a large-scale biological prophylaxis of adverse health effects of many other toxicants makes us expect that it would be no less practicable and effective in the field of nano-toxicology as well.

ilzira-minigalieva@yandex.ru

Notes:

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Blood cancers from environmental exposure near an oil refinery

James Dahlgren and **Patrick Talbott**
USA

The oil refinery located in Hooven, Ohio operated from 1931 to 1986 producing gasoline, jet fuels, diesel, home-heating oils and sulfur. The refinery has a history of leaks, spills, fires, explosions and air pollution while operating. Dozens of nearby residents sustained exposures to odors and emissions from numerous accidental releases and fires while the plant was operating. After the plant closed, continuing exposure included contaminated soil and ground water that led to massive vapor intrusion and air pollution. Many homes had monitoring wells in the basements that documented the presence of shallow pools of liquid petroleum. Environmental investigations revealed a large (236 acre) plume of non-aqueous liquid phase hydrocarbons (80% gasoline) floating on the groundwater beneath the village of Hooven in 2003. Ground water testing beneath homes in the 1990's revealed benzene at maximum levels of 3.6 PPM. Soil vapor levels were not available. We present 4 cases of lymphohematopoietic cancers in residents who lived in the air plume and had documented exposure to low levels of benzene. All 4 individuals resided for years within a few hundred yards of the refinery. There were 2 cases of multiple myeloma, 1 case of acute myeloid leukemia (AML), and Hodgkin's lymphoma. Modeled levels of benzene ranged from 0.125 to 3.12 PPM years. These levels of exposure are consistent with the current research on environmental exposure and blood cancers. A study by the state revealed a significant excess of other cancers in the area.

Biography

James Dahlgren, MD, is a Board Certified Internist Retired Assistant Professor from UCLA School of Medicine. He has been in Private Practice of internal medicine with a sub specialty in toxicology for over forty years. He has studied and treated thousands of patients with toxic chemical injuries including numerous victims of toxic chemical poisoning including the subjects dramatized in the Erin Brockovich movie. He has been treating and evaluating people with exposures of oil field chemicals since the 1970's.

Notes:

Pieranna Chiarella et al., J Clin Toxicol 2016, 6:6(Suppl)
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Urine sediment as DNA source in the study of susceptibility biomarkers

Pieranna Chiarella, Damiano Carbonari, Pasquale Capone, Delia Cavallo, Sergio Iavicoli, Antonella Mansi, Renata Sisto and **Giovanna Tranfo**
Istituto nazionale Assicurazione Infortuni sul Lavoro, Monte Porzio, Italy

Several genes encoding for enzymes involved in xenobiotic biotransformation and oxidative stress response have been shown to be polymorphic within the human population. These genes are particularly noteworthy in the occupational toxicology field being useful to identify individuals with higher susceptibility to specific toxic agents, allowing implementation of measures to reduce the exposure risk. Although blood is the first choice biological matrix to extract genomic DNA, there are some critical issues hindering its use in occupational studies: 1) blood draw invasiveness 2) difficulty to achieve consent from donors 3) need of the authorized medical doctor for blood sample collection 4) safety issues during blood processing 4) time-length of cell isolation procedure. Since urine is the routine sample used in the bio-monitoring of occupational exposure to chemical agents, the use of the same sample would be advantageous for both purposes, i.e. biomarker determination and genotyping. Here we report an effective method to isolate genomic DNA from urinary sediment. The protocol is not based on use of commercial kit, is cheap, rapid and allows determining the genotypic status of individuals using PCR and RFLP analysis. Before applying this procedure to exposed workers, we tested the efficacy on urine harvested from our institute donors and carried out genotyping analysis of GSTT1 and GSTM1 enzymes. In conclusion, at least for the genotyping analysis, urine sediment represents a suitable alternative to whole blood. This approach might be extended further to identify specific gene and protein biomarkers of dose/exposure in the occupational and environmental setting.

Biography

Pieranna Chiarella has completed her PhD at the Department of Histology and Medical Embryology from Sapienza University of Rome and worked as Post-doc at the University of Rome Campus Bio-Medico and as Staff Member at the European Molecular Biology Laboratory. She is currently Researcher at INAIL, Department of Occupational and Environmental Medicine, Epidemiology and Hygiene in Monte Porzio Catone (Rome-Italy).

p.chiarella@inail.it

Notes:

Yazan Akkam et al., J Clin Toxicol 2016, 6:6(Suppl)
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Oxidized graphene exhibits toxicity toward single-celled eukaryotes

Yazan Akkam[1], Rob Sleezer[2], Ravi Barabote[2], Gregory Salamo[2] , Ralph Henry[2] and **David McNabb[2]**
[1]Yarmouk university, Jordan
[2]University of Arkansas, USA

Graphene possesses physical characteristics ideal for next-generation electronic and photonic devices and is being explored for medical applications in drug delivery, photo-thermal therapy, and bionic devices. Oxidation and functionalization of graphene changes its dispersion in aqueous medium and provide methods to tailor its functional properties. The aim of our study is to evaluate the safety of commercial graphene (CG) and functionalized graphene (FG) by taking advantage of 2 genetically tractable eukaryotic models: *Saccharomyces cerevisiae* and *Candida albicans*. The CG and FG samples were characterized by X-ray photoelectron spectroscopy, scanning electron microscopy and atomic force microscopy. Further, the toxicity of CG and FG were tested using various assays, including cell growth and cell viability. Cell growth was measured via microdilution assay, spot plating and measurement of optical density. Cell viability was investigated using various metabolic assays, propidium iodide staining and growth curves. X-ray photoelectron spectroscopy confirmed the oxidation of CG to FG, and determined the percentage of oxidation. Atomic force microscopy was used to determine the average size of the graphene particles, while scanning electron microscopy provided a view of particle morphology. All cell growth assays demonstrated that FG, but not CG, interfered with the growth of both yeast species in a dose-dependent manner. Furthermore, our data suggests that exposure of cells to FG, but not CG, is toxic and leads to loss of cell viability. Our next goal is to understand how cell exposure to FG may influences genome-wide gene expression, thereby revealing cellular activities sensitive to FG exposure.

Biography

Yazan Akkam has completed his PhD from University of Arkansas and Post-doctoral studies on Nanotoxicity from Institute for Nanosciences and Engineering, Arkansas. He is the Head of Department of Pharmaceutical Sciences, Faculty of Pharmacy, Yarmouk University, Jordan. Also, he is a Member of the National Committee for the Management of Nanomaterials- Ministry of Environment, Jordan.

yazan.a@yu.edu.jo

Notes:

José Fernando Santos Almeida et al., J Clin Toxicol 2016, 6:6(Suppl)
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Crime, re-offense and substance abuse of patients with severe mental disorder

José Fernando Santos Almeida and **Diana Moreira**
Instituto Universitário da Maia, Portugal

There are clinical variables related to severe violence by mentally ill as hostility, behavior influenced by the hallucinatory activity, grandiosity- with unrealistic belief of superiority, the delirious activity of suspicion/persecution and accelerated motor behavior hyperactivity, highly responsive to stimuli and hyperarousal or excessive instability. Other important factors to match, when we address violence committed by these patients are substance abuse, premorbid personality and ecological problems, namely, the quality of life in the family. Falk et al. concluded that persistent violence was associated with male gender, personality disorder, convicted of a violent crime before the age of 19, offenses related to drugs, non-violent crime, substance use and mental disorder. The decrease in consumption of substances is very important when we want to prevent criminal recidivism of these patients even when patients are set free after serving a safety measure for a crime they have committed. In order to prevent criminal recidivism when they were released, we implemented a psychiatric care intervention with these patients.

Biography

José Fernando Santos Almeida is a Psychiatrist and completed his PhD from Instituto de Ciências Biomédicas Abel Salazar (Universidade do Porto). He is a Professor and President of Scientific Council of Instituto Universitário da Maia and Editor-Chief of *Psiquiatria, Psicologia & Justiça*.

afernandalmeida@sapo.pt

Notes:

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The insect repellent N,N-diethyl-m-toluamide (DEET) induces angiogenesis via allosteric modulation of the M3 muscarinic receptor in endothelial cells

Samuel Legeay
University of Angers, France

The insect repellent N,N-diethyl-m-toluamide (DEET) has been reported to inhibit AChE (acetylcholinesterase) and to be associated with increased risk of cancer. In the present paper, we demonstrate that DEET specifically stimulates endothelial cells that promote angiogenesis which increases tumor growth *in vivo*. DEET activates cellular processes that lead to angiogenesis including proliferation, migration and adhesion. This is associated with an enhancement of NO production and VEGF expression in endothelial cells. M3 silencing or the use of a pharmacological M3 inhibitor abrogates all of these effects which reveals that DEET-induced angiogenesis is M3 sensitive. The experiments involving calcium signals in both endothelial and HEK cells overexpressing M3 receptors, as well as binding and docking studies demonstrate that DEET acts as an allosteric modulator of the M3 receptor. In addition, DEET inhibited AChE which increased acetylcholine bioavailability and binding to M3 receptors and also strengthened pro-angiogenic effects by an allosteric modulation.

Biography

Samuel Legeay is a PharmD PhD student at the University of Angers in France (west part of France). He worked mainly on two different subjects: In USA at Augusta University (Georgia) on the regulation of hypertension in diabetic conditions and at the University of Angers (France) on the impact of mosquito repellents in angiogenesis. He has 2 published articles in PubMed and 1 book chapter and is a member of the French Society of Pharmacology and Therapeutics.

salegeay@gmail.com

Notes:

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Targeted screening of succinic semialdehyde dehydrogenase deficiency (SSADHD) employing an enzymatic assay for γ-hydroxybutyric acid (GHB) in biofluids

Cédric Wernli
University of Applied Science and Arts, Switzerland

Introduction: An enzymatic assay for quantification of γ-hydroxybutyric acid (GHB) in biofluids can be employed for targeted screening of succinic semialdehyde dehydrogenase deficiency (SSADHD) in selected populations. We used a two-tiered study approach, in which the first study (proof of concept) examined seven urine samples derived from patients with SSADHD and five controls, and the second study (feasibility study) examined a broader sample population of patients and controls, including plasma.

Objective: Aim of this study was to evaluate split samples of urine and plasma (anonymized) by enzymatic assay, gas chromatography alone (proof of concept) and gas chromatography-mass spectrometry, and the results compared.

Method: Multiple detection methods have been developed to detect GHB. We evaluated an enzymatic assay which employs recombinant GHB dehydrogenase coupled to NADH production, the latter quantified on a Cobas Integra 400 Plus.

Results: In our proof of concept study, we analyzed 12 urine samples (five controls, seven SSADHD) and in the feasibility study, we evaluated 33 urine samples (23 controls, 10 SSADHD) and 31 plasma samples (14 controls, 17 SSADHD). The enzymatic assay carried out on a routine clinical chemistry analyzer was robust, revealing excellent agreement with instrumental methods in urine (GC-FID: $r=0.997$, $p \leq 0.001$; GC-MS: $r=0.99$, $p \leq 0.001$); however, the assay slightly over-estimated GHB levels in plasma, especially those in which GHB levels were low. Conversely, correlations for the enzymatic assay with comparator methods for higher plasma GHB levels were excellent (GC-MS; $r=0.993$, $p \leq 0.001$).

Conclusion: We have evaluated the capacity of this enzymatic assay to identify patients with SSADHD via quantitation of GHB. The data suggests that the enzymatic assay may be a suitable screening method to detect SSADHD in selected populations using urine. In addition, the assay can be used in basic research to elucidate the mechanism of the underlying disease or monitor GHB-levels for the evaluation of drug candidates.

Biography

Cédric Wernli worked for about 10 years as a Lab Technician in the Clinical Chemistry laboratory in Toxicology department at the University Hospital in Basel. After his studies in Pharmacy at University of Basel (MSc in Pharmacy, 2013), he passed the board exam as a Pharmacist in October 2013. Since then, he works as a PhD-student at the University of Basel in coorperation with the University of Applied Science and Arts Northwestern Switzerland in developing quantitative lateral flow immunoassays for therapeutic drug monitoring in whole blood.

cedric.wernli@fhnw.ch

Notes:

Day 1 October 24, 2016

Drug Toxicology | Human & Health Toxicology | Toxicologic Pathology

Session Chair
Yiqun Deng
South China Agricultural University, China

Session Co-Chair
Mahmoud M El Mas
Alexandria Univeristy, Egypt

Session Introduction

Title: **Characterization and regulation of the expression of drug transporters in human skin**
Hanan Osman Ponchet, DMPK Research, France

Title: **Vancomycin-induced skin eruptions with susceptibility alleles to SJS/TEN**
Liping Yang, Beijing Hospital, Dongcheng, P R China

Title: **Kidney cell assays for *in vitro* safety profiling of single stranded oligonucleotides**
Marcel Gubler, F. Hoffmann-La Roche Ltd, Switzerland

Title: **East Indian sandalwood oil (EISO) alleviates inflammatory and proliferative pathologies of psoriasis**
Manju Sharma, Vancouver Prostate Centre, Canada

Title: **Fall in leukocyte count for monitoring of immunosuppressive and anti-cancer drug therapy**
Frieder Keller, University Hospital Ulm-University of Ulm, Germany

Title: **Evaluation of the effects of experimental PCB toxication on oxidative and antioxidative status in central nervous systems tissues and the protective effect of curcumin**
Halef Okan Doğan, Cumhuriyet University, Turkey

Hanan Osman Ponchet, J Clin Toxicol 2016, 6:6(Suppl)
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Characterization and regulation of the expression of drug transporters in human skin

Hanan Osman Ponchet
DMPK Research, France

Most identified drug transporters belong to ATP-binding cassette (ABC) and solute carrier (SLC) families. It has been recently recognized that like drug metabolizing enzymes, some of drug transporters play an important role in pharmacokinetics and drug exposure and may be involved in clinically relevant drug-drug interactions for systemic drugs. However very little is known about the role of drug transporters in human skin in the disposition of topically applied drugs. Expression profile of SLC and ABC transporters included in the regulatory guidelines as the most likely clinical sources of drug interactions was characterized in *ex vivo* human skin using TaqMan real-time RT-PCR. Moreover, the effect of rifampicin treatment and solar simulator irradiation on the expression of drug transporters in human skin was investigated as well as the localization of the drug transporters within the different layers of human skin. SLC and ABC transporters have a very specific expression profile in human skin compared to liver and kidney. In addition, expression of ABCC1 (MRP1) and SLC47A1/2 (MATE1 and MATE2) is shown for the first time in human skin. The role of drug transporters in drug absorption in human skin will be presented and discussed.

Biography

Hanan Osman Ponchet has completed her PhD from University of Burgundy (France) and Post-doctoral studies from University Hospital of Geneva (Switzerland) and National Institute of Agronomy Research (France). She is currently Metabolism Manager in the Department of Drug Metabolism and Pharmacokinetics at Galderma, a global dermatology company. She has more than 15 years of experience in DMPK and has published more than 30 research publications and patents, and has given invited oral presentations at several different scientific conferences.

hanan.osman-ponchet@galderma.com

Notes:

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Vancomycin-induced skin eruptions with susceptibility alleles to SJS/TEN

Liping Yang
Beijing Hospital, Dongcheng, P R China

Background & Objective: The glycopeptide antibiotics, vancomycin and teicoplanin, are the mainstay of therapy for severe gram-positive organisms such as methicillin-resistant *Staphylococcus aureus*. We report a case of Stevens–Johnson syndrome (SJS) induced by sequential therapy with teicoplanin and vancomycin, in a patient with chronic obstructive pulmonary disease (COPD).

Case Summary: A 74-year-old Han Chinese with 1-year history of COPD was admitted for treatment of infective endocarditis. After teicoplanin therapy for 12 days, he developed pruritus and maculopapular over his trunk and limbs. His rash spread rapidly to most parts of the body surface area, 7 days after his anti-infection therapy was switched to vancomycin. This was stopped, but he developed SJS when teicoplanin was reintroduced. This patient recovered from his drug eruptions when both teicoplanin and vancomycin were stopped. Pharmacogenetic analyses revealed he was heterozygous with respect to 2 variants (rs2844682 of MUC21 and rs750332 of BAG6).

What is new & Conclusion: Cross-reactivity between vancomycin and teicoplanin is rare. SJS attributable to sequential treatment with these 2 antibiotics has not been reported previously. Care should be taken when prescribing vancomycin in patients with a previous documented skin eruption to teicoplanin, especially in those who carry any susceptibility alleles to SJS/TEN.

Biography

Liping Yang has completed her PhD from RMIT University in Australia. She is the Vice-Director of Pharmacy Department, Beijing Hospital, a large-scale general hospital. She has published more than 90 papers in reputed journals and has been serving as an Editorial Board Member of repute. Since 2003, she has served as a Clinical Pharmacist, Senior Clinical Pharmacist, Associate Professor and Professor for the Pharmacy Department, Beijing Hospital, China. Her major interests are pharmacogenomics, drug-drug interaction, evidence-based medicine, Chinese medicine and rational drug use in clinical setting.

yanglp_2000@hotmail.com

Notes:

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Kidney cell assays for *in vitro* safety profiling of single stranded oligonucleotides

Marcel Gubler
F Hoffmann-La Roche Ltd, Switzerland

Chronic treatment of patients with classical low molecular weight drugs like aminoglycoside antibiotics, antivirals and immune-suppressants are known to induce kidney toxicities. Particularly molecules with high renal clearance can accumulate in proximal tubule epithelial cells (PTECs) of the kidney cortex where high tissue concentrations induce damage to tubular structures and may lead to loss of organ function. Similar toxicities have also been observed with other drug modalities such as for example some single stranded oligonucleotides (SSOs). SSOs represent a class of novel drugs to modulate gene expression in many different diseases for which there is no adequate treatment currently available. In order to secure development of renal safe drugs, we have established assays with animal and human primary as well as immortalized PTECs for profiling of nephrotoxic reference compounds side-by-side with SSOs that had previously been tested in rats for signs of organ damage. Using assays of cell function, viability, and death, we have been able to clearly discriminate safe from toxic molecules. Overall, the observed effects were similar across PTECs derived from animals and humans and correlated with the *in vivo* findings for the molecules tested in rats. Thus, we believe that our cellular assays will be useful for rapid *in vitro* profiling of SSOs for selection of safe compounds on human cells prior to clinical testing.

Biography

Marcel Gubler received his PhD in Life Sciences at the Federal Institute of Technology (Zürich, Switzerland) in 1988, followed by 2-years Post-doctoral Fellowship at the Massachusetts Institute of Technology (Cambridge, MA). Subsequently, he joined Preclinical Research at F. Hoffmann-La Roche Ltd (Basel, Switzerland), where he worked on novel targets for antibacterial therapies. In 2000, he changed to the Department of Metabolic Diseases to focus on drug treatments for obesity, diabetes and renal diseases. Since 2014, he has been investigating mechanisms of renal toxicity of different drug modalities in the Department of Drug Disposition and Safety, F. Hoffmann-La Roche Ltd.

marcel.gubler@roche.com

Notes:

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East Indian sandalwood oil (EISO) alleviates inflammatory and proliferative pathologies of psoriasis

Manju Sharma[1], **Corey Levenson**[2], **Ian Clements**[2], **Paul Castella**[2] and **Michael E Cox**[1]
[1]Vancouver Prostate Centre, Canada
[2]Santalis Pharmaceuticals, USA

Psoriasis, a chronic inflammatory skin disease marked by hyper-proliferation and aberrant differentiation of keratinocytes, affects 2-3% of the population in the United States. Research into the pathogenesis of psoriasis has been hampered by the lack of animal models that accurately reflect the biology of psoriatic phenotype. We have previously reported that EISO has significant anti-inflammatory properties in skin models. We hypothesized that EISO might provide therapeutic benefit to psoriasis patients due to its anti-inflammatory and anti-proliferative properties. The clinical relevance of this hypothesis is supported by interim results from an on-going proof-of-concept Phase 2 clinical trial in which topically applied EISO is demonstrating to be well tolerated and helpful in alleviating mild to moderate psoriasis symptoms. We have evaluated the ability of EISO to affect the psoriatic phenotype using organotypic psoriasis tissue and normal (non-psoriatic) human skin models from MatTek Corporation. Treatment of the psoriasis tissue model with EISO reverted psoriatic pathology, as demonstrated by histologic characterization and expression of keratinocyte proliferation markers, Ki67 and psoriasin. These phenotypic affects correlated with greatly suppressed production of ENA-78, IL-6, IL-8, MCP-1, GM-CSF and IL-1β. Demonstration of the ability of EISO to abrogate these psoriasis symptoms in well-characterized *in vitro* psoriatic tissue models supports the hypothesis that the clinically observed symptom alleviation is due to suppression of intrinsic tissue inflammation reactions in afflicted lesions. This study presents systems to further study the underlying mechanisms that cause psoriasis, and to help direct and accelerate the development of more effective therapies.

Biography

Manju Sharma is an MD and Doctor of Naturopathy working currently as a Scientist at Vancouver Prostate Centre, Vancouver General Hospital, Canada for the last 10 years. Prior to this, she worked in the Department of Pathology and Lab Medicine, VGH for 10 years on various projects including molecular diagnosis of tuberculosis, multi-drug resistant tuberculosis, human solid tumors, kidney disorders, medicinal herbal plants like *Echinacea* which is widely used all over Europe and North America for the treatment of cough and cold: Active principles and their mode of action on various human viral and bacterial diseases. She has published over 75 papers in medical journals and has made several presentations in the field of Medicine.

msharma@prostatecentre.com

Notes:

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7th Euro-Global Summit on
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Fall in leukocyte count for monitoring of immunosuppressive and anti-cancer drug therapy

Frieder Keller
University Hospital Ulm-University of Ulm, Germany

Background: The therapeutic window between efficacy on the one side and toxicity on the other side is very narrow for many immunosuppressive, anti-viral and anti-cancer drugs. The present contribution is to review the literature data and our own experience with regard to the value of a leukocyte monitoring for efficient drug therapy.

Methods: If there is leukocytopenia at least an effect can be assumed. Since the beneficial effect and the adverse effect are frequently better correlated than the drug concentration and the target effect, monitoring of leukocytes might be more cost-effective than monitoring of drug concentrations. A selective PubMed research was undertaken, therefore, to look for publications where the monitoring of leukocytes is used for targeting the drug dose.

Results: The use of cyclophosphamide has been successfully introduced for treatment of systemic vaxculitis by adjusting the dose to the leukocyte count. A leukocyte nadir was found to indicate a better prognosis in lung cancer and testicular cancer patients. A better outcome has been associated with cancer chemotherapy targeting neutropenia than with lower dose. This is in agreement with our own experience on the intravenous cyclophosphamide pulse therapy in IgA nephritis. This regimen applies also to the monitoring of azathioprine or mycophenolate and to ganciclovir and valganciclovir or cidofovir. However, a threshold nadir for leukocyte count must be defined to avoid persistent agranulocytosis.

Conclusion: Leukocytopenia is an effect of immunosuppression, of anti-viral or anti-cancer drug therapy. This easy to measure lab parameter can be used for pharmacodynamic monitoring of the efficacy of the critical dose drug therapy.

Biography

Frieder Keller has completed his MD and Post-doctoral studies from Free University, Berlin. He was Head of Nephrology Division at Ulm University and is a Teacher in Clinical Medicine. He has published more than 250 papers in PubMed cited journals and is serving as an Editorial Board Member of *Clinical Nephrology*.

frieder.keller@uni-ulm.de

Notes:

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Evaluation of the effects of experimental PCB toxication on oxidative and antioxidative status in central nervous systems tissues and the protective effect of curcumin

Halef Okan Doğan[1], **Eray Alçiğir**[2], **Begüm Yurdakök**[2], **Kübra Doğan**[3], **Sevil Atasoy**[2] and **Fatma Meriç Yilmaz**[4]
[1]Cumhuriyet University, Turkey
[2]Ankara University, Turkey
[3]Sivas Numune Hospital, Turkey
[4]Yildirim Beyazit University, Turkey

In this study, we evaluated the effect of prenatal PCB toxication on oxidant and antioxidant status in the central nervous system (CNS) tissues and the protective effect of curcumin. Animals were divided into a control group and 2 experimental groups. Group 1 (n=10) was considered as a control group. In group 2 (n=10), we exposed the pregnant rats to PCB mixture. In group 3, (n=10) we exposed pregnant rat to PCB mixture and curcumin. We measured plasma neuron specific enolase (NSE) concentrations in all pups. We also measured total antioxidant status (TAS) level and total oxidant status (TOS) level in the tissue (brain, cerebellum, pons and medulla oblongata) homogenisats of CNS. In this study, the TOS level was found higher in brain and cerebellum in group 2 and 3 than control group. However, we did not find any change in TOS and TAS level in medulla oblongata and pons in group 2 and 3. The concentration of NSE was higher in group 2 than control group. We also found that the use of curcumin had not any effect on the TOS and TAS concentrations. In conclusion; the main effected part of the central nervous systems are brain and cerebellum in terms of TOS concentrations. We did not find any effect of curcumin to increase TAS concentrations and decrease the concentration of TOS in brain and cerebellum. Additionally, NSE can be used as a useful biomarker to determine the damages found in the CNS in case of prenatal PCB toxication.

Biography

Halef Okan Doğan graduated from Ankara Numune Education and Research Hospital as a Clinical Biochemist in 2013. He is a Biochemistry Laboratory Director in the Cumhuriyet University, School of Medicine. He has published 9 papers in different scientific journals.

halefokan@gmail.com

Notes:

Pharmacology & Toxicology | Food Toxicology

Session Chair
Giovanni Pagano
Federico II Naples University, Italy

Session Co-Chair
Qing Xia
National Center of Biomedical Analysis, China

Session Introduction

Title: **Natural and synthetic cannabinoids: The good, the bad, and the tragic**
Anna Radominska Pandya, University of Arkansas for Medical Sciences, USA

Title: **Endothelin modulation of the cyclosporine/NSAIDs cardiovascular and renal interactions**
Mahmoud M El Mas, Alexandria Univeristy, Egypt

Title: **Effect of exposure area on nerve agent absorption through skin *in vitro***
Christopher Dalton, Defence Science and Technology Laboratory, UK

Title: **Folic acid and vitamin B12 as possible panacea against nicotine induced pancreatic β-cell apoptosis and dysfunction**
Sandip Mukherjee, Serampore College, India

Title: **Guidance on the selection of cohorts for extended one-generation reproduction toxicity study (OECD 443)**
Alan Poole, European Centre for Ecotoxicology & Toxicology of Chemicals, Belgium

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Natural and synthetic cannabinoids: The good, the bad, and the tragic

Anna Radominska Pandya
University of Arkansas for Medical Sciences, USA

K2, also called "Spice" or "Synthetic Marijuana," is a rapidly emerging drug of abuse that possesses psychoactive properties similar to those of Δ9-tetrahydrocannabinol (Δ9-THC). K2 use has exploded in many sections of the population including teenagers and first time drug users. Use of K2 can result in extreme agitation, hallucinations, supraventricular tachycardia, syncope and seizures. The presence of more than 20 different K2-aminoalkyl indoles (AAIs) have been reported in various K2s, but the two most commonly observed are JWH-018 and JWH-073; however, new generations of structurally related compounds are constantly being produced. Our studies demonstrate for the first time that the native K2s undergoes extensive metabolism by cytochrome P450s and UDP glucuronosyltransferases. Due to the activity of these enzymes, a variety of hydroxylated metabolites, have been biosythesized and excreted in human urine primarily as glucuronidated conjugates. These metabolites were identified and characterized using LC-MS/MS and HPLC-UV/Vis, and steady state kinetic analyses were also investigated. We have also shown that these K2 products cause psychoactive effects similar to those of Δ9-THC by activating CB1 cannabinoid receptors (CB1Rs) in the central nervous system. Moreover, CBRs were able to bind several hydroxylated and glucuronidated K2-AAI metabolites with an affinity similar to that of the parent compound. Finally, our *in vivo* data demonstrates that K2 metabolites retain biological activity in mice. The fact that some hydroxylated derivatives and their glucuronides can retain their biological activity makes the study of these compounds essential for understanding their severe toxicity and pharmacokinetics/dynamics. We hypothesize that the severe effects observed for some K2 users could be related to a defect in their metabolism.

Biography

Anna Radominska Pandya serves as a Professor in the Department of Biochemistry and Molecular Biology at UAMS; and she is the Editor in Chief for *Drug Metabolism Review*. She received her PhD from the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw, Poland. She has published 175 papers in various peer-reviewed journals, and she has received twelve R01 grants from the NIH and DoD. Her research interests include: The regulation and suppression of human UGTs and their role as anti-proliferative agents in cancer models, the interactions between UGTs and cannabinoid receptors, the delivery of UGT genes and drugs into cancer cells using nanomaterial, and the roles of UGTs in the biotransformation of drugs including resveratrols and drugs of abuse such as marijuana and synthetic cannabinoids.

RadominskaAnna@uams.edu

Notes:

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Endothelin modulation of the cyclosporine/NSAIDs cardiovascular and renal interactions

Mahmoud M El Mas
Alexandria University, Egypt

The combined use of cyclosporine (CSA) and nonsteroidal anti-inflammatory drugs (NSAIDs) in arthritic conditions is common in clinical practice. Because CSA or NSAIDs negatively impacts cardiovascular/renal functions when used individually, we asked if these two drug modalities would provoke more detrimental consequences when used together. The roles of endothelin receptor, inflammatory and fibrotic pathways in these interactions have also been investigated. The treatment of rats with celecoxib, but not indomethacin, blunted the CSA-evoked increases in blood pressure (BP), renal perivascular fibrosis and arteriolar endothelin receptor expression (increases in ETA and decreases in ETB receptors). Alternatively, exaggerated nephrotoxicity was seen upon simultaneous treatment with CSA plus indomethacin as evidenced by greater elevations in serum creatinine and renal oxidative stress; renal infiltration of inflammatory cells and worsening of fibrotic and necrotic profiles; and increased renal ET-1 and COX-2 expression. Unlike indomethacin, renal structural, oxidative, and molecular abnormalities caused by CSA were largely eliminated in rats treated concurrently with celecoxib. ETA receptor blockade by atrasentan ameliorated the hypertension and concomitant renal abnormalities caused by CSA/indomethacin regimen. On the other hand, ETB receptor blockade (BQ788) caused celecoxib-sensitive hypertension and renal dysfunction and potentiated the hypertensive effect of CSA. These findings suggest that COX-1/COX-2 selectivity of NSAIDs is pivotal for identifying their cardiovascular and renal impacts on CSA toxicity. Celecoxib, but not indomethacin, is more advantageous as an add-on therapy to CSA for arthritis management. The reliability of the current experimental findings needs to be corroborated with appropriate clinical investigations.

Biography

Mahmoud M El Mas completed his PhD in 1990 from Joint Scheme between Leeds University, UK and Alexandria University, Egypt. He pursued Post-doctoral Training at East Carolina University, USA. He is Chair of Pharmacology and Toxicology, Pharmacy, Alexandria University, Egypt and Chair of National Scientific Committee on Pharmacology Faculty Promotion. His publications include: 107 papers in top international journals and 90 abstracts in international conferences. His research expertise is: Cardiovascular/renal neurobiology of drugs of abuse (ethanol, nicotine) and immune-suppressants. He holds Editorial Board positions in 9 international journals. His Awards are: Khalifa Award for Education in the Field of Scientific Research (United Arab Emirates), State Prize for Scientific Encouragement (twice), State Prize for Scientific Excellence, ACDIMA award (Jordon), Alexandria University Honorary Award.

mahelm@hotmail.com

Notes:

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Effect of exposure area on nerve agent absorption through skin *in vitro*

Christopher Dalton
Defence Science and Technology Laboratory, UK

Diffusion cells are used to determine the penetration of chemicals through skin *in vitro*. The cells have a limited surface area defined by the edge of the donor chamber. Should the penetrant spread rapidly to this containment limit the penetration rate can be accurately quantified. For the hazard assessment of small droplets of toxic chemicals, such as cholinesterase inhibitors, limiting skin surface spread *in vitro* could lead to underestimation of percutaneous penetration and hence underestimation of systemic toxicity *in vivo*. The current study investigated the dependency of the percutaneous penetration of undiluted radiolabelled nerve agents [VX and soman (GD), 10µl] on skin surface spread (pig and guinea pig) using Franz-type glass diffusion cells with an area available for diffusion of either 2.54 cm^2 or 14.87 cm^2. Both VX and GD spread to the edge of 2.54 cm^2 cells, but not to the 14.87 cm^2 cells over the study duration. Amounts of VX and GD penetrating pig and guinea pig skin in the 2.54 cm^2 cell were less than in the 14.87 cm^2 cell (except for GD under unoccluded conditions), however, penetration rates expressed per unit area were similar. Artificial limitation of skin surface spread *in vitro* does not impact percutaneous penetration *in vitro* as long as penetration is expressed in terms of mass per unit area.

Biography

Christopher Dalton is a Principal Scientist at Defence Science Technology Laboratory (Dstl) in UK. He completed his BSc (Chemistry), MSc (Toxicology) and PhD (Toxicology) at University of Birmingham, England, UK. His research interest includes "The percutaneous penetration of chemicals". He is a Chartered Biologist and European Registered Toxicologist.

CHDALTON@dstl.gov.uk

Notes:

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Folic acid and vitamin B_{12} as possible panacea against nicotine induced pancreatic β-cell apoptosis and dysfunction

Sandip Mukherjee and **Ankita Bhattacharjee**
Serampore College, India

Cigarette smoking in regular habits affects our bodies in various ways and nicotine is the more abundant and most significant components of cigarette smoke. Epidemiological evidence strongly suggests an association between cigarette smoking and pancreatic injury. However, effects of cigarette smoking on pancreatic islets are still controversial. Impact and underlying mechanism of actions of folic acid and vitamin B_{12} on nicotine induced damage in pancreatic islets of rats are examined in the present study. Male Wister rats were exposed to nicotine with or without supplementation of folic acid and vitamin B_{12}. Folic acid and vitamin B_{12}, in combination, blunted the nicotine induced impairment in glucose tolerance, and levels of HbA1c and insulin in rats. Pro-inflammatory cytokines like TNF-α and IL-6, generation of reactive oxygen species, nitric oxide production and other oxidative stress parameters were also attenuated by folic acid and vitamin B_{12} in nicotine treated rats. Both, folic acid and vitamin B_{12} in combination also limits the nicotine induced changes in cell cycle and excessive apoptosis of the pancreatic β-cell along with altered Bcl-2, Bax, caspase-3 and caspase-9 expression and up regulation of iNOS and TNF-α. Nicotine-induced alteration in loss of mitochondrial membrane potential ($\Delta\psi m$) and release of cytochrome c also reversed by folic acid and vitamin B_{12} supplementation. In conclusion, folic acid and vitamin B_{12} protects against islet cellular oxidative stress, which is a critical step in nicotine-mediated islet injury, and improves islet cell functional status by scavenging free radicals, inhibiting the generation of pro-inflammatory mediators and apoptosis.

Biography

Sandip Mukherjee received his PhD degree in the year 2007 from Jadavpur University, Kolkata, India and has published over 24 research articles and book chapter. He is an Assistant Professor (Senior Grade) at Department of Physiology, Serampore College since 2008. He has been serving as Reviewer in different international journals with repute.

sm_kdc@yahoo.co.in

Notes:

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Guidance on the selection of cohorts for extended one-generation reproduction toxicity study (OECD 443)

Alan Poole
European Centre for Ecotoxicology & Toxicology of Chemicals, Belgium

The extended one-generation reproduction toxicity study (EOGRTS; OECD test guideline 433) is a new and technically complex design to evaluate the putative effects of chemicals on fertility and development, including effects upon the developing nervous and immune systems. In addition to offering a more comprehensive assessment of developmental toxicity, the EOGRTS provides important improvements in animal welfare through reduction and refinement of use of experimental rodents in a modular study design. The challenge to the practitioner however is to know how the modular aspects of the study should be triggered on the basis of prior knowledge of a particular chemical, or on earlier findings in the EOGRTS itself, requirements of specific regulatory frameworks not withstanding. The purpose of this document is to offer guidance on science-based triggers for these extended evaluations.

Biography

Alan Poole earned his PhD from the University of Surrey and is a Fellow of the Royal College of Pathologists. He worked for the UK Medical Research Council before moving to Smith Kline and French to lead a team involved in preclinical development of pharmaceuticals. He was later employed by Dow Chemical in Switzerland where he worked addressing safety of industrial chemicals. He has published widely and is currently the Secretary General of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC).

alan.poole@ecetoc.org

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Workshop

(Day 2)

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Vesna Matovic
University of Belgrade, Serbia

Co-treatment with PCBs potenciates Cd nephrotoxicity

The nephrotoxic effect of cadmium (Cd) and polychlorinated biphenyls (PCBs), as widely spread toxic environmental pollutants that enter food chain and pose risk to human health, was investigated and compared with Cd—agent of well-known nephrotoxicity. Six groups of rats were receiving 0.3, 0.6, 1.25, 2.5, 5 or 10 mg Cd/kg b.w./day as aqueous solutions of $CdCl_2$, while nine groups were treated with different dose combinations of Cd and PCBs, as Aroclor 1254 dissolved in corn oil, (1.25, 2.5 or 5 mg Cd/kg b.w./day with 2,4 or 8 mg PCBs/kg b.w./day). Two groups receiving only water or corn oil served as controls. Treatment of all animals was performed by oral gavage and lasted for 28 days. Cadmium levels were determined in blood and kidneys. Urea and creatinine in serum and relative kidney weight were determined. Blood and kidney Cd levels in groups treated with Cd only as well as in co-treated groups were significantly higher if compared with controls, although PCBs did not exert significant effect on Cd content. Urea levels were significantly higher in rats treated with all combinations of Cd and PCBs if compared with groups treated with Cd only, while only highest dose of Cd combined with different doses of PCBs resulted in higher creatinine levels and relative kidney weight. Synergistic interactions between Cd and PCBs have been proven for urea levels indicating more profound nephrotoxic potency of this mixture when compared to Cd induced effect on kidneys.

Biography

Vesna Matovic has completed her PhD at Faculty of Pharmacy, University of Belgrade, Serbia. She is Head of Department of Toxicology "Akademik Danilo Soldatovic" and President of Serbian Society of Toxicology. She has published more than 250 papers in reputed journals and has been serving as an Editorial Board Member and reviewer.

vevodi@pharmacy.bg.ac.rs

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Scientific Tracks & Abstracts

(Day 2)

Euro Toxicology 2016

Environmental Toxicology | Risk Assessment | Metal Toxicity

Session Chair
Marcelo L Larramendy
National University of La Plata, Argentina

Session Co-Chair
May Azzawi
Manchester Metropolitan University, UK

Session Introduction

Title: **Potentialities of synchrotron radiation (SR) fourier transform infrared microscopy (FTIRM) for environmental toxicology and pharmacology**
Lisa Vaccari, Elettra Sincrotrone Trieste, Italy

Title: **Effects of linuron on a rooted aquatic macrophyte in sediment-dosed test systems**
Gertie H P Arts, Alterra Wageningen University and Research Centre, The Netherlands

Title: **Nickel related Staphylococcus aureus infections in atopic dermatitis**
Anna Magdalena Bogdali, Jagiellonian University Medical College in Krakow, Poland

Title: **Coal-burning type of endemic fluorosis in China – From basic research to clinic prevention**
Zhi-Zhong Guan, Guizhou Medical University, P. R. China

Title: **Assessment of levels of heavy metals in fluted pumpkin (Telfairia occidentalis) leaves planted at varying distances away from mega refueling service stations in Nigeria**
Uduak Luke, University of Uyo Teaching Hospital, Nigeria

Title: **^{137}Cs in soil and milk in the region of Zagreb, Croatia**
Branko Petrinec, Institute for Medical Research and Occupational Health, Croatia

Title: **Converging effects of a PCB mixture, bisphenol A and chlorpyrifos on the expression of genes regulating neural progenitor identity, interneuron development and gliogenesis in developing rat hippocampus**
Walter Lichtensteiger, GREEN Tox, Switzerland

Lisa Vaccari, J Clin Toxicol 2016, 6:6(Suppl)
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Potentialities of synchrotron radiation (SR) fourier transform infrared microscopy (FTIRM) for environmental toxicology and pharmacology

Lisa Vaccari
Elettra Sincrotrone Trieste, Italy

The setting up of new methodologies for the assessment of material toxicology is a field of research continuously evolving in order to answer the new and urgent questions of the modern era. In this framework, SR-FTIRM is emerging as a valuable tool for *in vitro* and *ex vivo* toxicological studies. The technique is able to provide biochemical information on the sample under investigation in a label-free, safe and spatially-resolved manner, through the investigation of the vibrational motions of the molecular constituents. In this presentation, a short introduction of Elettra Sincrotrone Trieste, III generation Synchrotron Facility in Italy will be given, focusing on the activities in the toxicology field at SISSI beamline, the infrared laboratory at Elettra. Several topics will be covered, such as: The chemical characterization of asbestos bodies versus environmental particulates (anthracosis) in human lung tissues from asbestos exposed and control patients; the biochemical modifications on crustacean (*Porcellio scaber*) digestive glands upon exposure to diverse nanoparticles, (tungsten, zinc and silver oxides), the concentration of which in environmental systems is increasing as a consequence of anthropogenic activities. The correlation between chemical state, concentration and shape of the nanoparticles on animal toxicity will be highlighted and; an overview on the *in vitro* capabilities of SR-FTIRM will be given, focusing on the possibility to monitor in real-time on live single cells the effects of therapeutics and stressor agents in general. A comparison with more conventional analytical approaches such as flow cytometry will be presented.

Biography

Lisa Vaccari has been the Leader of the SISSI infrared beamline at the Elettra Sincrotrone Trieste since 2006. She is an expert in Bio-spectroscopy and pioneered the exploitations of microfabrication capabilities for the design and fabrication of IR-suitable microfluidic devices for performing *in vitro* bio-experiments under physiological conditions. She has experience in several other analytical techniques and she is actively involved in several projects in the fields of "Environmental toxicology, toxicology of nanomaterials, cellular toxicology of drugs and chemicals".

lisa.vaccari@elettra.eu

Notes:

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Effects of linuron on a rooted aquatic macrophyte in sediment-dosed test systems

Gertie H P Arts[1] and **Helena Burešová**[2]
[1]Alterra Wageningen University and Research Centre, The Netherlands
[2]Gis-geoindustry, Czech Republic

Effects of linuron on the sediment-rooted aquatic macrophyte *Myriophyllum spicatum L*. Were studied in sediment-dosed test systems following an OECD test guideline with extended test duration. Sediment, pore water, overlying water and macrophyte shoots were sampled weekly for chemical analyses. Linuron was stable in the sediments. Sediment and pore water concentrations were in equilibrium after 48 h. Overlying water concentrations increased over time, but did not reach equilibrium with pore water concentrations and were 1000 times lower. Mass balances showed a rapid uptake of linuron by macrophyte roots. Known pathways and the compound's properties support the conclusion that Myriophyllum takes up linuron from pore water directly through the roots. Modeling supported the conclusions that high concentrations in the shoots could be explained by translocation of linuron by the roots to the shoots. The fluxes calculated for linuron support this interpretation. At the experimental start, several pathways played a role, i.e. linuron fluxes from pore water to overlying water and from pore water to roots. The flux from pore water to overlying water decreased later, while the translocation fluxes from roots to shoots increased. Hence, effects on macrophytes in this type of sediment toxicity test should be expressed in terms of pore water concentrations. Sensitivity of water- and sediment-dosed test systems will be discussed in the light of compound properties.

Biography

Gertie H P Arts studied Biology at the Radboud University in Nijmegen, The Netherlands. She has completed her PhD in the Natural Sciences from the same university. She works at Alterra as a Senior Scientist in the Environmental Risk Assessment team. She has a focus on aquatic macrophyte ecotoxicology and risk assessment. She has published more than 100 papers in reputed journals and reports, and is serving as an Editor for the Journal of Environmental Toxicology and Chemistry.

Gertie.Arts@wur.nl

Notes:

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Nickel related *Staphylococcus aureus* infections in atopic dermatitis

Anna Magdalena Bogdali
Jagiellonian University Medical College in Krakow, Poland

Pollution of the air, water and food by metals results in changes of microbiota because metals are common enzymatic cofactors of bacterial cells. Concentration of nickel in the air in Krakow is approximately 20 ng/m^3 in PM10. Nickel allergy is often found in patients with atopic dermatitis. Number of colonies of *Staphylococcus aureus* increases in acute phase and is reduced in remission of atopic dermatitis. Thus, it is believed that staphylococcal-derived infections exacerbate allergic inflammation. Nickel participates in virulence of *Staphylococcus aureus* and is required as a cofactor for bacterial enzymes including urease that can regulate pH. It is still unknown whether nickel-sensitive urease can regulate pH of the skin changed in patients with atopic dermatitis. In our current studies, 85% of patients with atopic dermatitis is infected by difficult to treat infections by methicillin-resistant *Staphylococcus aureus*. Bacterial infections are initiated by specific adhesion of a bacterium to the target environment. *Staphylococcus aureus* can attach to nickel nanostructures with dimensions comparable to the size of a single bacterium. Changes of cytokine milieu due to nickel action on T cells can increase number of immature Th0 and it can also promote staphylococcal infections because it reduces bacterial clearance. Thus, more immature T cells less cellular immune mechanisms protecting against staphylococcal infections. Therefore we believe that nickel allergy can promote *Staphylococcus aureus* infections in atopic dermatitis. All these studies are required to fully understand patho-mechanism of atopic dermatitis that is useful for more individual and consequently better treatment of patients.

Biography

Anna Magdalena Bogdali graduated with her Master's degree at the Department of Biochemistry, Biophysics and Biotechnology of Jagiellonian University in Krakow. She completed her PhD on Atopic Dermatitis from Jagiellonian University Medical College in Medical Biology. She participated in the Socrates/Erasmus and 6th and 7th Framework European Programs. She stayed in the Angioedema Hungarian Center at the Semmelweis University in Budapest and she is involved in projects on hereditary angioedema concerning genetic background and immune mechanisms at the Jagiellonian University Medical College in Krakow. Her interests are immune and genetics mechanisms mostly related to T cells in the skin and circulatory system.

anna.bogdali@gmail.com

Notes:

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Coal-burning type of endemic fluorosis in China – From basic research to clinic prevention

Zhi-Zhong Guan
Guizhou Medical University, P R China

Endemic fluorosis widely occurs in the world and is characterized by skeletal and dental fluorosis and a vast array of pathological changes in whole bodies, which has been proved by our large number of basic investigations. Coal-burning type of endemic fluorosis is the severest one, which was confirmed in China in 1970's. This type of endemic fluorosis is primarily induced by fluoride-contaminated food and air indoor caused by smoke emitted during burning coal, which contains a high concentration of fluoride. In China, about 36 millions of people live in such areas of coal-burning type of endemic flruosis. Among the population, 18 millions are suffered from dental fluorosis and 1.5 millions skeletal fluorosis. Since 1980, an efficient strategy relating integrated control has been carried out for eliminating the disease in in China. After taking the measurement for many years, the adapted coal-burning stoves have been set up and the improve health education obtained in most of families in the endemic fluorosis areas, which brings the significant decline of fluoride contamination on food and air indoor. The strategy has successfully resulted in a significant decrease in the numbers of the patients with dental and skeletal fluorosis, and in a great improvement in health conditions of the people lived in the areas. At present, the coal-burning type of endemic fluorosis in China has been efficiently controlled at present. Importantly, it is necessary to take a long-period of integrated control for efficiently eliminating the hazard of coal-burning type of endemic fluorosis.

Biography

Zhi-Zhong Guan completed his PhD from Karolinska Institutet, Sweden in 1997. He is the Director of the Key Lab of the Endemic and Ethnic Diseases in Education Ministry of China. He has published more than 400 papers (including more than 100 SCI collected papers) in peer-reviewed journals and has been serving as an Editorial Board Member or reviewer of several journals.

1457658298@qq.com

Notes:

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Assessment of levels of heavy metals in fluted pumpkin (*Telfairia occidentalis*) leaves planted at varying distances away from mega refueling service stations in Nigeria

Uduak Luke[1], **F E Uboh**[2] and **Hope Cletus**[2]
[1]University of Uyo Teaching Hospital, Nigeria
[2]University of Calabar, Nigeria

Bioaccumulation of heavy metals has been reported to be common in leafy vegetables planted in gardens located at 20 meters away from traffic-congested highways, automobile mechanic workshops and refueling service stations. This study assessed the level of some heavy metals in the leaves of fluted pumpkin (*Telfairia occidentalis*) planted at varying distances (10, 20, 30, 40 and 50 m) away from mega refueling service stations (MRSS) in three Southern Nigerian States. The leaves harvested after three months of planting were processed using standard procedures for heavy metals determination. The heavy metals (Pb, Ni, Mn, Cd, and Zn) were determined following standard atomic absorption spectrophotometric methods. The results showed that the levels of Pb, Cd and Ni accumulated in the leaves were significant ($p<0.05$) between, but not within, the different distances. Also, the levels of the heavy metals recorded in these leaves followed the order: 10 m>20 m>30 m>40 m>50 m. However, the levels of these heavy metals in the leaves planted at 10 and 20 m away from MRSS were significantly ($p<0.05$) higher, compared to the levels recorded for 30, 40 and 50 m, respectively. These observations indicated that planting of *Telfairia occidentalis* leaves within 20 m distance from MRSS is likely to expose the leaves to the risk of heavy metals contamination and bioaccumulation and; the vegetables planted within this range from MRSS may be hazardous for human consumption. Therefore, it may be concluded that it is safer to cite farmlands for *Telfairia occidentalis* beyond 30 m from MRSS to reduce the rate of exposure to MRSS-related heavy metals contamination, and bioaccumulation of the heavy metals in the leaves.

uduakluke@gmail.com

Notes:

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^{137}Cs in soil and milk in the region of Zagreb, Croatia

Branko Petrinec, Iva Franulovic, Marko Šoštaric, Dinko Babic, Zdenko Franic and **Gordana Marovic**
Institute for Medical Research and Occupational Health, Croatia

At the Institute for Medical Research and Occupational Health in Zagreb, Croatia, research on environmental radioactivity has been carried out over a number of years. After the Fukushima accident in March of 2011, we have paid a special attention to its possible impact on the radioactivity of soil and precipitation in Northwest Croatia (Zagreb region). Before and after the accident, we determined the activity concentrations of ^{137}Cs (A) in soil samples taken from 3 adjacent surface layers (depths of 0-5 cm, 5-10 cm and 10-15 cm) as well as in samples of milk. Before the accident, A in the soil was nearly uniform, only slightly increasing with increasing depth. Shortly after the accident, we observed an increase of A in the topmost layer, which was in agreement with the values of A measured in fallout. In subsequent years, we have detected both the penetration of ^{137}Cs deeper into the soil and the overall decrease in A. In 2010, the values of A in milk were quite uniform over the months, amounting to about 35 Bqm^{-3}. In 2011, this increased to 199 Bqm^{-3} in average, mainly due to the large values measured in the summer months; we attribute this effect to the influx of the radioactive matter from Fukushima. In consequence of the increased presence of ^{137}Cs, the estimated yearly effective dose due to the intake of ^{137}Cs via milk in 2011 was 200 nSv, which can be compared with 73 nSv in the period of 2010-2015.

Biography

Branko Petrinec obtained his PhD degree from the Physics Department of the University of Zagreb. He is a Research Associate at the Institute for Medical Research and Occupational Health in Zagreb, and an Assistant Professor at the Department of Physics of the Josip Juraj Strossmayer University in Osijek. He has published more than 20 papers in reputed journals. He was the President of the Scientific Committee of the Tenth Symposium of the Croatian Radiation Protection Association. In 2011, he was the Laureate of the CRPA Young Scientists Award.

petrinec@imi.hr

Notes:

conferenceseries.com

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7th Euro-Global Summit on
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Converging effects of a PCB mixture, bisphenol A and chlorpyrifos on the expression of genes regulating neural progenitor identity, interneuron development and gliogenesis in developing rat hippocampus

Walter Lichtensteiger[1], Catherine Bassetti-Gaille[1], Hubert Rehrauer[2,3,4], Jelena Kühn Georgijevic[2,3,4], Margret Schlumpf[1] and **Jesus A F Tresguerres[5]**
[1]GREEN Tox, Switzerland
[2]Institute of Veterinary Pharmacology and Toxicology, Switzerland
[3]University of Zurich, Switzerland
[4]Swiss Federal Institute of Technology, Switzerland
[5]Universidad Complutense, Madrid

Developmental exposure to polychlorinated biphenyls (PCBs), bisphenol A (BPA) or the pesticide chlorpyrifos (CPF) impairs hippocampus-dependent behaviors (learning) in adult offspring. In a search for shared effects on gene networks, we treated pregnant rats with PCB mixture Aroclor1254 (5, 0.5 mg/kg), BPA (5, 0.5 mg/kg), or CPF (3, 1 mg/kg) in the feed (PCB, BPA) or subcutaneously (CPF). Transcriptome analysis was done in hippocampus from offspring at postnatal day six (PND6) by NGS. In male hippocampus, analyses revealed common effects on genes regulating hippocampal development. At behaviorally active doses, all chemicals showed upregulation of Gli3, neuregulin1, Erbb4, Sox6, Sox11, Pou2f2/Oct2, Pou3f2/Brn2 and Wnt receptors Fzd3 and Fzd6. microRNA-24 was down-regulated, indicating possible interactions with post-transcriptional regulation of Sox6. Pou2f1/Oct1, Pou3f3/Brn1, Sox2 and Sox17 was affected by only two treatments. Effects on Sox6, Nrg1, Erbb4, Oct1 were confirmed by real time RT PCR. Analyses of proteins and female hippocampus are in progress. Involvement of Nrg1, its receptor Erbb4 and Sox6 suggests effects on interneuron development. In postmitotic interneurons of PND6, Sox6 controlled interneuron subtype diversity. Expression changes were observed in interneuron-related genes. The increase of Sox6 mRNA levels relative to mRNA levels of Sox5, its counterpart in postmitotic corticofugal projection neurons also suggests a specific effect in interneurons. Sox6 further controls gliogenesis in hippocampus; Sox6 overexpression represses specification and terminal differentiation of oligodendrocyte precursors. In conclusion, our investigation revealed convergent actions of different types of behaviorally active chemicals on genes involved in the control of major developmental processes in hippocampus.

Biography

Walter Lichtensteiger has served as a Professor of Pharmacology and Toxicology at the University of Zurich, Switzerland, with teaching obligations at the Swiss Federal Institute of Technology (ETH), Zurich and after retirement, he founded the spin-off company GREEN Tox (Group for Reproductive, Endocrine and Environmental Toxicology) in 2005, together with Margret Schlumpf. GREEN Tox focuses on "Research and continuous education on environmental chemicals". He is a member of several committees of the OECD programme for testing of chemicals.

walter.lichtensteiger@access.uzh.ch

Notes:

Gentic Toxicology | Toxicology Testing | Forensic Toxicology

Session Chair
Stefano Bonassi
IRCCS San Raffaele Pisana, Rome, Italy

Session Co-Chair
Wei Zheng
Purdue University, USA

Session Introduction

Title: **Mechanistic study of TEMPO-associated oxidative stress and genotoxicity**
Nan Mei, National Center for Toxicological Research, USA

Title: **Pharmacokinetic studies of protein drugs and assessment of their metabolism**
Eric Ezan, Health Technology Program-CEA, France

Title: **A 52-week safety study in *Cynomolgus macaque* for genetically modified rice expressing Cry1Ab/1Ac protein**
Qing Xia, National Center of Biomedical Analysis, China

Title: **Fifteen years' experience treating cells with inorganic arsenic, a molecule able to induce genetic/genomic instability and epigenetic changes even after its removal**
Fabio Caradonna, University of Palermo, Italy

Title: **mRNA and miRNA expression patterns associated to pathways linked to metal mixture health effects**
Rojas E, Universidad Nacional Autonoma de Mexico, Mexico

Title: **Computational prediction of interaction of lumefantrine with human topoisomerase II beta complexed to DNA**
Carmen Lucia Bassi Branco, Federal University of Mato Grosso, Brazil

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Mechanistic study of TEMPO-associated oxidative stress and genotoxicity

Nan Mei, Xiaoqing Guo, Zuhong Zhang, Stacey L Dial, Vasily N Dobrovolsky, Si Chen and **Lei Guo**
National Center for Toxicological Research, USA

The biological consequences of exposure to piperidine nitroxides is a concern, given their widespread use in manufacturing processes and their potential use in clinical applications. Previously, we have demonstrated that TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), a low molecular weight free radical, can induce cytotoxicity and genotoxicity in mammalian cells. Extending this earlier work, the present study investigates the underlying mechanisms of TEMPO-associated oxidative stress and genotoxicity, particularly the roles of reactive oxygen species (ROS) and mitogen-activated protein kinase (MAPK) signaling. Our results demonstrate that TEMPO induced time- and concentration-dependent intracellular ROS production and glutathione depletion in mouse lymphoma L5178Y cells. TEMPO also induced apoptosis as demonstrated by increased caspase-3/7 activity, an increased proportion of annexin V stained cells, and decreased expression of anti-apoptotic proteins including Bcl-2, Bcl-xL and Mcl-1. N-acetylcysteine, a ROS scavenger, attenuated the ROS production and apoptosis induced by TEMPO. Moreover, Western blot analyses revealed that TEMPO activated γ-H2A.X, a hallmark of DNA damage, and c-Jun N-terminal kinases (JNK); a key member in the mitogen-activated protein kinase (MAPK) signaling pathway. Addition of SP600125, a JNK-specific inhibitor, blocked TEMPO-mediated JNK phosphorylation and also attenuated TEMPO-induced apoptosis. These findings indicate that TEMPO-induced apoptosis and toxicity are, at least in part, mediated by oxidative stress and activation of JNK in the MAPK pathway.

Biography

Nan Mei after graduating from Hebei Medical University, China in 1984, started his scientific career in clinical cancer research and diagnosis as a Physician in a university hospital. In 1997, he received his PhD degree from the University of Occupational and Environmental Health, Japan. He then extended his training on assessing DNA damage as a Post-doctoral Fellow at the Cross Cancer Institute, Canada. In 2002, he joined the US FDA/NCTR. Currently his research focuses on genetic toxicology and toxicogenomics. He has published more than 80 peer-reviewed research articles in prestigious journals and 11 book chapters.

Nan.Mei@fda.hhs.gov

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Pharmacokinetic studies of protein drugs and assessment of their metabolism

Eric Ezan
Health Technology Program - CEA, France

Among the growing number of therapeutic proteins on the market, there is an emergence of bio-therapeutics designed from our comprehension of the physiological mechanisms responsible for their peripheral and tissue pharmacokinetics. Most of them have been optimized to increase their half-life through glycosylation engineering, polyethylene glycol conjugation or Fc fusion. However, our understanding of biological drug behaviors is still in its infancy compared to the huge amount of data regarding small molecular weight drugs accumulated over half a century. Unfortunately, therapeutic proteins share few resemblances with these drugs. For instance drug-targeted-mediated disposition, binding to glycoreceptors, lysosomal recycling, large hydrodynamic volume and electrostatic charge are typical critical characteristics that cannot be derived from our anterior knowledge of classical drugs. However, the numerous discoveries made in the last two decades have driven and will continue to drive new options in biochemical engineering and support the design of complex delivery systems. Most of these new developments will be supported by novel analytical methods for assessing *in vitro* or *in vivo* metabolism parameters.

Biography

Eric Ezan studied Biological Engineering at the University of Compiegne, France. After a first experience at the University of Waterloo (Ontario), he obtained a PhD degree at the University Paris V in Pharmacological Sciences (1989). He then joined the Institute Pasteur of Paris for two-year Post-doctoral experience. He was recruited by the CEA (Alternative Energies and Atomic Energy Commission) in 1991, where he became the Head of the Laboratory for Drug Metabolism at the CEA in 2000. This laboratory located at Saclay, south of Paris, is involved in the development of immunological methods and mass spectrometry for the discovery of biomarkers and quantification of small molecular weight drugs and biologicals for preclinical and clinical applications. The laboratory also became a leader in the use of mass spectrometry approaches for the detection biological weapons. In 2014, he joined the CEA Program for the development of health technology.

Eric.EZAN@cea.fr

Notes:

Qing Xia, J Clin Toxicol 2016, 6:6(Suppl)
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A 52-week safety study in *Cynomolgus macaque* for genetically modified rice expressing Cry1Ab/1Ac protein

Qing Xia
National Center of Biomedical Analysis, China

A 52-week feeding study in *Cynomolgus macaques* was carried out to evaluate the safety of Bt-rice Huahui 1 (HH1), a transgenic rice line expressing Cry1Ab/1Ac protein. Monkeys were fed a diet with 20% or 60% HH1 rice, 20% or 60% parental rice (Minghui 63, MH63), normal diet, normal diet spiked with purified recombinant Cry1Ab/1Ac fusion protein or bovine serum albumin (BSA) respectively. During the feeding trail, clinical observations were conducted daily, and multiple parameters, including body weight, body temperature, electrocardiogram, hematology, blood biochemistry, serum metabolome and gut microbiome were examined at regular intervals. Upon sacrifice, the organs were weighted, and the macroscopic, microscopic and electron microscopic examinations were performed. The results show no adverse or toxic effects of Bt-rice HH1 or Cry1Ab/1Ac fusion protein on monkeys. Therefore, the present 52-week primate feeding study suggests that the transgenic rice containing Cry1Ab/1Ac is equivalent to its parental rice line MH63.

Biography

Qing Xia has completed her PhD from the Second Military Medical University and Post-doctoral studies from Duke University School of Medicine. She is the Vice Director of National Center of Biomedical Analysis, Beijing, China. She has published more than 20 papers in reputed journals and has been serving as a Member of the Chinese Committee of Bio-Safety on Transgenic Products.

qxia@ncba.ac.cn

Notes:

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Fifteen years' experience treating cells with inorganic arsenic, a molecule able to induce genetic/genomic instability and epigenetic changes even after its removal

Fabio Caradonna
University of Palermo, Italy

Treating V79-Cl3 cells with 10 μM sodium arsenite (SA) for 24 h, we observed severe alterations in spindle morphology and aneuploidy; treating rat astrocytes with SA, we detected HSP70 induction and DNA damage. We assumed that SA induced in dividing cells early genetic instability. Subsequently, we stabilized those V79-Cl3 cells *in vitro* dividing at the end of SA-treatment and maintained for long without SA (ASO cells). In ASO cells, we observed chromosomal rearrangements, increased spontaneous mutations, genome-wide DNA hypomethylation (GWDH), similarly to exposed cells. We inferred that a short-term SA exposure has long-term effects and that GWDH enhances the genetic instability. Consequently, we evaluated GWDH in HaCaT keratinocytes at several time points during expanded growth following SA removal. We found a persistent GWDH and some specific gene promoters (*DNMT3A*, *DNMT3B*, *HMLH1*) methylation changes. We suggest that the SA-treated cells undergo epigenetic reprogramming at gene/genome level that is durable over many cell generations in the absence of SA, contributing to long-lasting genomic instability SA-induced. Obtaining several individual clones isolated at different time points from the growing ASO cells, we observed in someone, chromosomal and morphological instability, higher ROS and berrant DNA methylation. We also noted that all the ASO clones with low SOD1 and high ROS acquired a transformed phenotype and moreover, increase of ROS was accompanied by defective telomerase activity. We propose that cells escaping the SA-induced death, perpetuate the memory of past exposure via ROS because of antioxidant and telomerase activity impairment and ultimately they acquire a transformed phenotype.

Biography

Fabio Caradonna has completed his PhD and Postdoc on Cellular Biology at University of Palermo. He is Specialist in Clinic Pathology and in Bioethics. He is a group leader of "Genetics and Cell Biology" lab of STEBICEF Department (University of Palermo). He is an official Reviewer of country and national projects and Editor in Chief of *Journal of Carcinogenesis & Mutagenesis*. He has an excellent experience in "Cytogenetics, Genotoxicity, DNA/chromosome methylation assessment". He is an Assistant Professor of Human Genetics and Cytogenetics, Supervisor for PhD thesis and has published 31 ISI papers, 13 book chapters and 58 meeting abstracts.

fabio.caradonna@unipa.it

Notes:

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mRNA and miRNA expression patterns associated to pathways linked to metal mixture health effects

Rojas E, Martinez Pacheco M, Rodriguez Sastre A and **Valverde M**
Universidad Nacional Autonoma de Mexico, Mexico

Metals are a major category of globally distributed pollutants that tend to accumulate in select tissues. Metal mixtures are a potential threat to human health by increasing disease risk. Recently, experimental data have linked altered miRNA expression with exposure to several metals, including As, Cd and Pb. Although, several human populations are exposed to low concentrations of As-Cd-Pb mixture, there are few data at respect to miRNA expression patterns. Thus, this study aims to evaluate global miRNA and mRNA expression changes induced by a metal mixture ($NaAsO_2$, $CdCl_2$ and $Pb(C_2H_3O_2)_2 \cdot 3H_2O$) to explore the role of miRNA-222 as a post-transcriptional regulator of *RAD51C*, a gene involved in homologous recombination of double-strand break DNA repair. Our results show that miRNA expression profile responsible for the mRNA expression changes induced by metal mixture exposure are involved in cellular processes, including DNA repair, cell death, growth and proliferation related to the metal-associated pathologies (cardiovascular diseases and cancer). On the other hand, we found that miR-222 directly negatively regulates *RAD51C* expression and impairs homologous recombination of double-strand break DNA repair, generating genetic instability that could be related with cell transformation.

Biography

Rojas E has completed his PhD from UNAM, Mexico. He is a Full Professor in Biomedical Research Institute. He has published more than 75 papers in reputed journals that has been cited more than 4500 times, and had been serving as an Editorial Board Member of *Mutation Research Reviews* and *Mutation Research Genetic Toxicology and Environmental Mutagenesis.*

emilior@biomedicas.unam.mx

Notes:

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Computational prediction of interaction of lumefantrine with human topoisomerase II beta complexed to DNA

Carmen Lucia Bassi Branco
Federal University of Mato Grosso, Brazil

Lumefantrine (LF) is used in artemisinin-based combination therapies against malaria worldwide. It is genotoxic and mutagenic to human lymphocytes *in vitro* and may interact non-covalently with DNA minor groove surface. Considering that DNA binders are often topoisomerase inhibitors; in this study, we investigated the potential non-covalent interaction of LF with human topoisomerase II beta (hTOP2β) complexed to DNA by molecular docking study. Computer-assisted molecular analyses have been performed for predicting the possible interactions between hTOP2β-DNA complex and LF. The hTOP2β-DNA complex bound to LF was then assessed for interactions, energetic contributions, and for identification of the best correlation between the LF conformations and their associated scores. The fused-tricyclic 9*H*-fluorene rings in the LF chemical structure promote the intercalative binding into cleaved DNA sites present in hTOP2β-DNA complex. Since this is a polycyclic aromatic moiety, it gives the LF molecule the necessary planarity and aromaticity for intercalative binding to DNA base pairs in the cleavage sites, which showed aromatic interactions of -8.6 kcal/mol in the binding computational analysis for predicted binding affinity energy. The N-dibutyl moiety and hydroxyl group from LF accommodate into the major groove and hydrogen bond to nitrogen and oxygen atoms on the base-pair in the DNA segment. The N-dibutyl moiety also interacts with residues on the major groove side. The (4-chlorophenyl) methylidene moiety protrudes into the DNA minor groove side facing nearby residues from this protein–DNA interface. The hypothesis on the interaction of LF with topoisomerase II needs to be investigated using other approaches.

Biography

Carmen Lucia Bassi Branco has completed her PhD at São Paulo University in 2004 and Post-doctoral studies at the same university in 2007. She is Professor at the Federal University of Mato Grosso since 2009, where she develops research in the mutagenesis area.

cbassi@cpd.ufmt.br

Notes:

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Plenary Session

(Day 2 - Breakout)

Fawzy Elbarbry, J Clin Toxicol 2016, 6:6(Suppl)
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Modulation of drug metabolizing enzymes by dietary doses of sulforaphane; role in its anti-hypertensive and anti-oxidant effect in spontaneously hypertensive rats

Fawzy Elbarbry
Pacific University, USA

Aim: We have previously demonstrated that exposure of spontaneously hypertensive rats (SHR) to sulforaphane (SF) results in resisting the normal progressive rise in blood. This study aims to investigate the potential effect of these dietary doses of SF on hepatic drug metabolizing enzymes in SHR.

Methods: Rats were treated for eight weeks with SF (20 or 40 mg/kg) added to drinking water. At the end of treatment rats were euthanized, followed by preparation of liver microsomes and cytosols. The activity and/or protein expression of selected cytochrome P450 (CYP) enzymes and microsomal epoxide hydrolase (mEH) were measured in hepatic microsomes. Cytosolic fraction was utilized to measure total glutathione (GSH) level and activity of selected antioxidant enzymes.

Results: At the high dose, SF treatment resulted in a significant reduction of CYP1A2 and CYP2C9 activities that were accompanied by a parallel decline in their apoproteins. Similarly, activities of CYP2B1/2 and mEH were inhibited only by high dose SF treatment. No effect of SF was observed on the rest of the studied phase I enzymes. On the other hand, both low and high doses of SF resulted in a significant induction of both hepatic glutathione level and activities of superoxide dismutase (SOD) and catalase. Only the high dose SF induced the activities of hepatic glutathione-S-transferases (GST), glutathione reductase (GR) and glutathione peroxidase (GPx) to a significant effect.

Conclusion: This study demonstrates that dietary doses SF has the potential to offer chemoprevention through stimulation of the endogenous antioxidants and inhibiting CYP enzymes involved in bioactivation of procarcinogens.

Biography

Fawzy Elbarbry has completed his PhD and Post-doctoral studies from University of Saskatchewan College of Pharmacy (Canada). He joined Pacific University School of Pharmacy in 2008 as an Assistant Professor and in 2012, he was promoted to Associate Professor. He is also a Clinical Pharmacist at a major health-system in Oregon. He has published more than 30 papers and book chapters in reputed journals and more than 50 meeting proceedings and abstracts. He has been serving as an Editorial Board Member and frequent Reviewer for several publishers and granting agencies.

fawzy.elbarbry@pacificu.edu

Notes:

Govindasamy Mugesh, J Clin Toxicol 2016, 6:6(Suppl)
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Reactive oxygen species (ROS), oxidative stress and antioxidants: Enzyme mimetic selenium compounds as redox regulators

Govindasamy Mugesh
Indian Institute of Science, India

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the biological system's ability to detoxify these reactive intermediates. It is well known that oxidative stress is responsible for several disease states. Both Type I and II diabetics display increased levels of ROS such as free radicals and the onset of diabetes is closely associated with oxidative stress. It has also been associated with diverse diseases, including cancer, renal disease and neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Although plants and animals maintain the level of antioxidants, such as glutathione (GSH), vitamins C, A and E as well as enzymes such as catalase, superoxide dismutase and various peroxidases, insufficient levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress. Our group focuses on the development of enzyme mimetic redox modulators that can be used as drugs for diseases associated with enhanced level of ROS and that can combat oxidative stress without affecting the cellular antioxidant systems. In this lecture, various selenium compounds and their effect on ROS in mammalian cells will be discussed.

Biography

Govindasamy Mugesh received his PhD in 1998 from the Indian Institute of Technology, Bombay. He is an author of more than 120 publications in international peer reviewed journals. He received several awards and recognitions. His research interests include the chemistry of thyroid hormone metabolism and development of novel therapeutics for endothelial dysfunction and neurodegenerative diseases. He serves in the editorial boards of *Organic & Biomolecular Chemistry*, *ACS Omega*, *Bioorganic Chemistry and Scientific Reports*.

mugesh@ipc.iisc.ernet.in

Notes:

Mohanan P V, J Clin Toxicol 2016, 6:6(Suppl)
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Toxicology of polymeric biomaterials: A regulatory approach

Mohanan P V
Sree Chitra Tirunal Institute for Medical Sciences and Technology, India

Polymeric biomaterials are widely used in clinical applications such as for drug delivery, tissue engineering, bio-medical sensing, skin grafting, medical adhesives etc. Polymeric biomaterials are chosen for different applications depending on their properties. They act as substitutes for soft and hard tissues in the body. The objective of the toxicological studies of polymeric materials, intended for the fabrication of medical devices, is to investigate the potential biological hazards by careful observations for unexpected adverse reactions or events in humans during clinical use of the medical devices. The toxicity/biocompatibility evaluation of polymeric materials assesses the risk of adverse health effects due to normal use and likely misuse of a device. Adverse health effects could result from exposure to the materials from which a device is made; preclinical assessment of the toxic potential of such materials or components is needed to minimize the potential hazard to the patient. It was well aware that the medical device comprises several components made from different materials; the ideal procedure from a toxicological point of view would be, to evaluate extracts of the components separately. However, in some situations this is not practical, and extracts of the whole device may be used instead. The amount of leachable substances released to the extraction media is related to the surface area and thickness of the product to be extracted. The range of potential biological hazards is wide and may include; short term effects (like acute toxicity, irritation, sensitization, haemolysis and thromobogenicity) and long term effects (such as sub chronic and chronic toxicity, sensitization, genotoxicity, carcinogenicity and effects on reproduction including teratogenicity). Due to the diversity of medical devices, it is recognized that not all the tests identified in a category will be necessary or practical for any given device. It is indispensable for testing that each device shall be considered on its own merits. The details of the toxicity assays will be discussed during the presentation.

Biography

Mohanan P V is working as a Scientist & Head, Toxicology Division, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST). He has Postdoctoral experience from the University of Tsukuba, Japan and Doctoral degree from the University of Kerala. As a toxicologist at SCTIMST with more than 28 years of experience, he has been intimately associated with all the medical devices/technologies developed at SCTIMST. As a Scientist, he has established his own area of research and pursued them with several externally funded projects as Principal Investigator. He has made significant contributions for the development of medical device industry and medical device regulations in India, and India getting GLP membership in OECD countries. He is the senior most GLP Inspector (DST, New Delhi) of the country and a Certified Biological Safety Specialist. He received several national and international awards and honors like, certificate of appreciation from the Hon. Minister of Science and Technology, Govt. of India for the contribution to India getting full adherent status on GLP from OECD, JSPS Fellowship, JSPS Bridge Fellowship, Country Correspondent for the World Library of Toxicology, Senior Toxicologist Fellowship from IUTOX, USA. He was the Secretary General of Society of Toxicology, India and presently he is the General Secretary of Indian JSPS Alumni Association. He is a Fellow of Society of Toxicology, Fellow of Society of Applied Biotechnology and Fellow of Academy of Sciences for animal welfare. He has authored 137 peer reviewed full papers, 4 book chapters, edited 3 books and 4 conference proceedings.

mohanpv10@gmail.com

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Scientific Tracks & Abstracts

(Day 2 Break Out)

Pharmacological and Toxicological Methods | Systems Pharmacology | Toxicovigilance

Session Chair
Swamy KB
Mahsa University-Jalan Elmu Off Jalan University, Malaysia

Session Co-Chair
Fawzy Elbarbry
Pacific University, USA

Session Introduction

Title: **Dark purple glutinous rice *Var. Luem Pua* tea prevents DSS-induced colitis in mice**
J Sattayasai, Khon Kaen University, Thailand

Title: **A new pegylated recombinant *E.coli* L-asparaginase preparation (MC0609): Comparative pharmacokinetic/pharmacodynamic characterisation in Beagle dog and influence of anti-PEG IgM antibodies on the pharmacokinetics in B6D2F1 mice**
Poppenborg Sabine M, Medac GmbH, Germany

Title: **CCR-2 neutralization augments murine fresh bone marrow cells activation by *S. aureus* via ROS production and cytokine response**
Ajeya Nandi, University of Calcutta, India

Title: **Changes in rat urinary heme metabolites predict the magnitude of the neurotoxic effects induced by a mixture of lead, arsenic and manganese**
Vanda Maria Falcão Espada Lopes de Andrade, Universidade de Lisboa, Portugal

Title: **X-ray fluorescence imaging in toxicology**
Yulia Pushkar, Purdue University, USA

Title: **Effect of soy bean on histomorphometric parameters of stomach and biochemical factors of blood serum in animal model**
Simin Fazelipour, Islamic Azad University, Iran

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Dark purple glutinous rice *Var. Luem Pua* tea prevents DSS-induced colitis in mice

J Sattayasai[1], K Thipart[1], N Techataweewan[1], W Mawthong[1], A N L Noenplab[2] and **N Sattayasai[3]**
[1]Khon Kaen University, Thailand
[2]Phitsanulok Rice Research Center, Thailand
[3]University of Phayao, Thailand

Inflammatory Bowel Disease (IBD) is characterized by chronic and relapsing inflammation of the gastrointestinal tract which is associated with increased risk of developing colitis-associated cancer. Although many chemical-induced colitis models were developed, dextran sulfate sodium (DSS)-induced colitis model was widely used to assess the therapeutic potential of treatments for IBD. In this study, the effects of aqueous extract of dark purple glutinous rice var. Luem Pua (LP) tea on DSS-induced colitis were evaluated. Aqueous extract of LP tea was prepared and dose used was expressed as dried weight of LP tea. Female ICR mice were forced fed with distilled water or LP extract 2 or 5 g/kg/day for seven consecutive days. On each day, 2 hours after feeding, water containing 2% DSS was supplied to all groups except the control group. DSS-induced colitis was scored with disease activity index (DAI) and the colon length, represented the severity of inflammatory lesions in colon, and spleen weight, represented inflammation stage, were evaluated. The results showed that LP extract antagonized the reduction of the colon length, the increase in DAI and the increase in spleen weight caused by DSS indicated the reduction of the inflammation by LP extract treatment. Recently, we have shown that LP contains quite high level of cyanidin-3-glucoside (C3G) with a high antioxidant activity. C3G is one of the active anthocyanin suggested to have benefit in IBD. Our data suggest that drinking LP tea might have the beneficial effects in preventing and treating colitis and IBD.

Biography

J Sattayasai has completed her PhD from Monash University. She is now an Associate Professor of Pharmacology.

sjinta@kku.ac.th

Notes:

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A new pegylated recombinant *E.coli* L-asparaginase preparation (MC0609): Comparative pharmacokinetic/pharmacodynamic characterisation in Beagle dog and influence of anti-PEG IgM antibodies on the pharmacokinetics in B6D2F1 mice

Poppenborg Sabine M
Medac GmbH, Germany

A new pegylated recombinant *E. coli* L-asparaginase (PEG-rASNase MC0609) was designed by medac GmbH (Germany) to improve pharmacokinetic (PK) characteristics of pegylated L-asparaginase in comparison to pegaspargase (Oncaspar®) used as first-line treatment in patients with acute lymphoblastic leukaemia (ALL). Comparative PK, pharmacodynamic (PD) and immunogenicity studies were performed in Beagle dogs after single-dose intravenous (i.v.) administration of MC0609 or pegaspargase. Striking differences in PK and PD properties between both pegylated preparations were observed. The different PK characteristics were confirmed by a population pharmacokinetic (PopPK) analysis. PK parameters of pegaspargase in Beagle dog were in the same range than the parameters determined in paediatric ALL patients. Therefore, the Beagle dog was considered a clinically relevant model for PK evaluation of pegaspargase. In addition, the potential impact of pre-existing anti-PEG antibodies on the ASNase activity of PEG-rASNase MC0609 and pegaspargase was investigated in immune competent B6D2F1-hybrid mice. Anti-PEG IgM antibodies were successfully induced in mice after repeated i.v. administration of 40 kDa PEG-Diol without being conjugated to a carrier. All animals detected "positive" for anti-PEG IgM antibodies and control animals (without prior PEG-Diol pre-sensitisation) were treated once i.v. with PEG-rASNase MC0609 or pegaspargase. ASNase activity profiles were obviously not influenced by the IgM positivity of animals. No accelerated decrease of ASNase activity was observed irrespective of successful PEG-Diol pre-sensitisation and presence of acquired anti-drug-IgG and/or anti-PEG IgM antibodies.

Biography

Poppenborg Sabine M has completed her PhD from University of Bielefeld, Germany, University of Montpellier, France and Post-doctoral studies from MRC Medical Research Council, Cambridge, UK. Since 2007, she is a Scientist in the Pharmacology/Toxicology unit of medac Gesellschaft für klinische Spezialpräparate mbH, Germany, a pharmaceutical company specialised on products for oncology, autoimmune diseases and urology.

s.poppenborg@medac.de

Notes:

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Ajeya Nandi et al., J Clin Toxicol 2016, 6:6(Suppl)
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CCR-2 neutralization augments murine fresh bone marrow cells activation by *S. aureus* via ROS production and cytokine response

Ajeya Nandi and **Biswadev Bishayi**
University of Calcutta, India

Recruitment of monocytes from the bone marrow into the bloodstream and then to the sites of infection is regulated by CCL-2/CCR-2 signaling. But, involvement of CCL-2/CCR-2 signaling in the killing of *S. aureus* by murine fresh bone marrow cells is a pertinent question. The intermittent link of ROS and NF-κB/p38-MAPK mediated MCP-1 production in CCR-2 signaling has prompted to determine whether neutralization of CCR-2 augments the response of murine fresh bone marrow cells (FBMC) after *S. aureus* infection utilizing ROS production and cytokines in the killing of *S. aureus*. It was observed that FBMCs treated with anti-CCR-2 antibody released less ROS and NO on encountering *S. aureus* infection compared to CCR-2 non-neutralized FBMCs also correlating with reduced killing of *S. aureus* in CCR-2 neutralized FBMCs. Staphylococcal catalase and SOD also found to play a role in protecting *S. aureus* from the ROS mediated killing of FBMC. CCR-2 neutralized FBMCs infected with *S. aureus* exhibit less production of TNF-α, IFN-γ and IL-6 with increased IL-10 as compared to CCR-2 intact FBMCs. *S. aureus* infection to CCR-2 intact FBMCs pretreated with either NF-κB or p-38-MAPK blocker caused less MCP-1 suggesting that NF-κB or p-38-MAPK is required for MCP-1 production by FBMCs. Moreover, blocking of CCR-2 along with NF-κB or p-38-MAPK showed elevated MCP-1 production and reduced CCR-2 expression. Therefore, inhibition of CCR-2 exacerbates the murine fresh bone marrow cells response to *S. aureus* infection by utilizing the ROS production and by regulating the cytokine response.

Biography

Ajeya Nandi has gained her Post-graduate degree in Human Physiology from University of Calcutta, India in 2013. She is working as DST-INSPIRE Fellow in the Immunology Laboratory of University of Calcutta since 2013 and submitted her PhD thesis. She has published quite a good number of research articles. Her research has focused on the role of TLR-2 and CCR-2 in the host pathogen interaction during acute Staphylococcal infection.

ajeyan294@gmail.com

Notes:

Vanda Maria Falcão Espada Lopes de Andrade, J Clin Toxicol 2016, 6:6(Suppl)
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Changes in rat urinary heme metabolites predict the magnitude of the neurotoxic effects induced by a mixture of lead, arsenic and manganese

Vanda Maria Falcão Espada Lopes de Andrade
Universidade de Lisboa, Portugal

Arsenic (As), manganese (Mn) and lead (Pb) are neurotoxic metals/metalloids that occur as mixtures in specific settings, like mines. Efforts have been made to identify biochemical biomarkers (BMs) of neurotoxicity which can aid an early detection, progression or outcome of treatments. The complexity of the nervous system, individual variability and ubiquity of neurotoxic mixtures, is leading to the belief that multiparameter analysis through the integration of various markers may establish robust correlations between BMs and individual's health status. Metals, including As, Mn and Pb, induce specific and different changes in heme metabolites excretion patterns, and its accumulation can cause neurotoxicity. The aim of this work was to generate 2 predictive models: (A) simpler and designed to detect neurotoxicity and (B) to predict the magnitude of these effects, individually. A group of Wistar rats were co-exposed for 8 days to Pb, As and Mn; a control group was used. Motor activity was evaluated and 24 h urine was collected. Urinary delta-aminolevulinic acid (ALA U) and total porphyrins (Porf U) were determined by spectrophotometry and combined by multiple regressions to detect motor activity decrement (model A). The urinary porphyrin profile was determined by HPLC and used to predict the number of ambulation's and rearing using the same statistical method (model B). All subjects were correctly classified regarding to motor activity decrease (model A) and average errors of 2 ambulation or rearing counts were obtained with model B. This work suggests that BMs integration methodologies are promising to assess "Real-Life" scenarios of exposure to chemical mixtures.

Biography

Vanda Maria Falcão Espada Lopes de Andrade graduated in Biology in 1992 and obtained a Master's degree in Animal Biodiversity Conservation in 1998, both from Faculdade de Ciências da Universidade de Lisboa. She has completed her PhD in Pharmacy/Toxicology from Faculdade de Farmácia da Universidade de Lisboa, Portugal in 2014. She is Assistant Professor in Escola Superior Agrária de Santarém, Instituto Politécnico de Santarém since 2013, where she coordinates the curricular units of Toxicology since 2014; and since 2015, Pollution and Ecotoxicology. She has published 9 papers in international journals, performed 15 communications (4 oral presentations and 11 poster presentations) and 8 seminars.

vandaandrade70@gmail.com

Notes:

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X-ray fluorescence imaging in toxicology

Yulia Pushkar
Purdue University, USA

Atomic transitions in elements, including Mn, Fe, Cu, Zn, Pb relevant in toxicology can be excited upon interaction with X-rays in 10-13 keV energy range. Recording resulting X-ray fluorescence (XRF) with high spatial resolution results in quantitative images of metal ion distributions in tissue sections. Different X-ray focusing optics allows for tissue level imaging (5-20 micron) resolution or subcellular level imaging (30-200 nm) of distributions of biologically relevant (Fe, Cu, Zn) and toxic (Mn, Pb). Development of beamlines with high X-ray photon flux at 3rd generation synchrotron sources allows to obtain high resolution XRF maps of ppm amounts of elements in thin tissue sections. Using XRF, we studied Mn distribution in rat model of occupational Mn exposure. We found that globus pallidus and substantia nigra compacta are areas in the brain that accumulate most Mn. Imaging the Mn distribution in dopaminergic neurons, we determined that intracellular Mn range between 40–200 micromolar; concentrations as low as 100 micromolar have been observed to cause cell death in cell cultures. This is a first direct link between Mn exposure and Parkinson's disease. We have previously reported localized Cu-rich aggregates in astrocytes of the subventricular zone in rodent brains with Cu concentrations in the hundreds of millimolar. Based on a [S]/[Cu] ratio and X-ray absorption spectroscopy, metallothionein is proposed as a binding protein. An analysis of metallothionein (1,2) knockout mice by XRF will be presented.

Biography

Yulia Pushkar has completed her PhD in Biophysics at Freie Universität Berlin, Germany and Post-doctoral studies at University of California, Berkeley & Lawrence Berkeley National Lab. She is an Associate Professor of Physics and has published over 60 research articles including these in Science, Nature, Journal of American Chemical Society and PNAS.

ypushkar@purdue.edu

Notes:

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Effect of soy bean on histomorphometric parameters of stomach and biochemical factors of blood serum in animal model

Simin Fazelipour[1], **Zahra Tootian**[2] and **Reyhaneh Hooshmand Abasi**[2]
[1]Islamic Azad University, Iran
[2]University of Tehran, Iran

Introduction & Objective: In the modern world, soy bean as a valuable meal is used for providing protein and some essential body needs. The stomach also as a part of alimentary canal has its own role in mechanical and chemical digestion. The objective of this study is evaluation of the effects of soy meal on histological and histometrical features of the stomach and also on biochemical factors of blood serum.

Methods: In this experimental study, a total of thirty immature female mice of Balb/C were selected at three weeks of age. Then on the basis of three types of diets, the mice were divided into three groups as; the group A or control, fed on a diet of full protein, the group B fed on a diet of 40% soy meal and the group C fed on a diet of 20% soy meal. After three months, the mice were anesthetized, and blood samples were obtained from the heart for determining the serum level of some hematologic factors such as urea, total protein, cholesterol and LDL. Then the stomach was removed, some tissue sections were prepared and stained with H&E. After histological study, the stomach was subjected to histometric evaluation. The histometric data were surveyed by a light microscope equipped with Axiovision software and the thickness of mucosa, submucosa, musculature, also depth of the pits and the number of parietal cells were measured. For data analysis, one way ANOVA was used to compare the control group with experimental groups and Tukey test was used to compare the groups with each other. The significance level was considered as $P<0.05$

Findings: Soya bean consumption didn't cause histological changes.In the more precisely histometric study, the results showed that in non glandular portion of the stomach, between the control group compared with the groups fed on soy meal, there was significant increase in thickness of mucosa in the experimental group B (676±99.45) compared with the control group (427±77.53) and also in thickness the muscular layers in the experimental group C)233.30±84.69) compared with the control group (104.05±11.71), ($P<0.05$). In the glandular portion also significant increase in thickness of mucosa in the experimental group B (1041.36±167.02) and C (1331.73±143.32) compared with the control group (615.29±83.14), in depth of pits in the experimental group B 134.53±14.60) and C (154.29±20.25) compared with the control group (94.79±12.93), in parietal cells in the experimental group B (15.66±4.45) and C (30.50±13.61) compared with the control group (9.83±1.47) and muscular layers in the experimental group B 211.59±53.68) and C (195.72±67.89) compared with the control group (155.73±28.23) was observed ($P<0.05$). However a significant decrease in serum level of cholesterol in the experimental group B (87.76±20.53) and C (83.03±16.06) compared with the control (117.70±20.71), serum level of urea in the experimental group B (36.23±10.43) and C (40.58±12.14) compared with the control group (65.33±7.28) and also LDL value in the experimental group B (5581.6±470.90) and C (5689.1±479.79) compared with the control group (6907.1±37.64) was observed ($P<0.05$).

Conclusion: It seems that long term consumption of soy bean could affect on the stomach mucosa and proliferation of parietal cells and also could decrease the serum levels of cholesterol, urea and LDL.

simin_fazelipour@yahoo.com

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Pharmacology | Current Advances

Session Chair
Lisa Vaccari
Elettra Sincrotrone Trieste, Italy

Session Co-Chair
Alan Poole
European Centre for Ecotoxicology & Toxicology of Chemicals, Belgium

Session Introduction

Title: From the lungs to the brain: The fantastic voyage of nanoparticles targeting beta-amyloid (Aβ)
Giulio Sancini, University of Milano, Italy

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Title: Pre-activation of acetylcholine M3 receptor leads to cannabinoid type 1 receptors regulation: A new cross talk mechanism involving intracellular calcium mobilization in SH-SY5Y human neuroblastoma cells
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Title: Determination of some blood hydrocarbons contents, oxidative stress markers and haematological indices of rats orally exposed to bonny light crude oil
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Title: Nutraceuticals for hypertension care: A network based approach
Matteo Micucci, University of Bologna, Italy

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Ayşegül Küçük, Kütahya Dumlupınar University, Turkey

Title: The effect of proton pump inhibitors on bone mineral density in rats
Layla Ezzat Borham, Umm Al-Qura University, Saudi Arabia

Title: Beneficial effects of phloretin on oxidative and inflammatory reaction in rat model of cecal ligation and puncture induced sepsis
Omid Sabzevari, Tehran University of Medical Sciences, Iran

Title: Carbon monoxide modulates infection-induced proinflammatory cytokine milieu in human placenta
Nazeeh Hanna, Winthrop University Hospital, USA

Title: Flavonoid effects on antihypertensive pharmacological therapy: Modulation on lipid profile, inflammation and association of ACE (I/D) polymorphism in treatment response
Marina M de Jesus Romero-Prado, Centro Universitario de Ciencias de la Salud, Mexico

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From the lungs to the brain: The fantastic voyage of nanoparticles targeting beta-amyloid (Aβ)

Giulio Sancini
University of Milano, Italy

The brain is always confronted with the dilemma of the protection from noxious substances from the blood and the delivery of vital metabolites. Endothelial cells, forming together with other cells the blood-brain barrier (BBB), are known as the "Gatekeepers" of this trafficking. On the one hand, the protection from toxic molecules is achieved by the obstruction of the paracellular pathway with tight junctions that fuse brain capillary endothelia into a continuous tubular cell layer. On the other hand, vital molecules are transported from the blood by means of active trans-cellular mechanisms. Recent applications in nanomedicine focuses on nanoparticles (NP) as they are promising tools for site-specific delivery of drugs and diagnostic agents, through the possibility to functionalize their surface with target-specific ligands.Treatment options for Alzheimer's disease (AD) are limited because of the inability of drugs to cross the BBB. Previously, we showed that intraperitoneal administration of liposomes functionalized with phosphatidic acid and an ApoE-derived peptide (mApoE-PA-LIP) reduces brain beta-amyloid (Aβ) burden and ameliorates impaired memory in AD mice. Among the different administration routes, pulmonary delivery is a field of increasing interest not only for the local treatment of airway diseases but also for the systemic administration. We investigated lung administration as an alternative, non-invasive NP delivery route for reaching the brain. Our results show that mApoE-PA-LIP were able to cross the pulmonary epithelium *in vitro* and reach the brain following *in vivo* intratracheal instillations. Lung administration of mApoE-PA-LIP to AD mice significantly decreased total brain Aβ (–60%; $p<0.05$) compared to untreated mice. These results suggest that pulmonary administration could be exploited for brain delivery of NP designed for AD therapy.

Biography

Giulio Sancini is Assistant Professor of Physiology; Specialist in Applied Pharmacology, he has focused his research activity mainly on neurosciences, nanomedicine and nanotoxicology. His research has been funded by European FP7 (NAD Project, nanoparticles for diagnosis and therapy of Alzheimer's disease, winner of The Best Project award in the field of Industrial Technologies) and FP6 (BONSAI project). He has published more than 45 papers in reputed journals and has been serving as an Editorial Board Member of repute. He is Head of the Physiology Unit at the Dept. of Medicine and Surgery of the University of Milano-Bicocca.

giulio.sancini@unimib.it

Notes:

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BTEX is implicated in gasoline-induced oxidative stress in male albino Wistar rats

Friday E Uboh, Saviour U Ufot and **Uduak O Luke**
University of Calabar, Nigeria

The plasma and liver tissue hydrocarbon contents, superoxide dismutase (SOD) and catalase (CAT) activities, malondialdehyde (MDA) and glutathione (GSH) levels of rats orally exposed to gasoline were assessed in this study. Eighteen adult male albino *Wistar* rats (210.0±20.0 g), distributed into three groups, of six rats each were used in the study. Rats in groups one and two, which served as controls, were given distilled water and sunflower oil respectively, while rats in group three (test group) were given 2 ml/kg b.wt. of gasoline in sunflower oil vehicle, for thirty, sixty and ninety days. At the end of the respective exposure periods, the animals were sacrificed, and relevant tissues collected and processed for analyses. The types and concentrations of hydrocarbons in the plasma and liver tissues were analysed by gas chromatography with flame ionized detector (GC-FID), while SOD and CAT activities, MDA and GSH levels were analysed by standard spectrophotometric methods. The results obtained from this study showed the presence of benzene, toluene, ethylene and xylene (BTEX) in the plasma and liver tissues of rats exposed to gasoline at concentrations significantly ($p<0.05$) higher than the respective concentration recorded for the controls; and that the plasma and liver tissue MDA level was significantly ($p<0.05$) higher, while SOD, CAT and GSH activities were significantly ($p<0.05$) lower in test rats, compared respectively to the control groups. However, the plasma and liver tissue BTEX, MDA, SOD, CAT and GSH activities recorded in rats exposed for sixty and ninety days were significantly ($p<0.05$) different from the activities recorded in rats exposed for thirty days, while no significant ($p>0.05$) difference was recorded between sixty and ninety days of exposure. This suggests that BTEX are largely absorbed from the GIT, and distributed within the body tissues, including the blood and liver tissues, following sub-chronic oral exposure to gasoline. Hence, that the raised plasma and liver tissue MDA, and reduced SOD, CAT and GSH activities in test animals may be attributed to the raised tissue BTEX levels. The results of this study therefore give a strong indication that BTEX is likely implicated in gasoline induced oxidative stress in rats.

Biography

Friday E Uboh completed his PhD from University of Calabar, Calabar, Nigeria, and is presently an Associate Professor of Biochemistry, with Toxicology as his area of research interest. He served as the acting Head of Biochemistry Department in the Department of Biochemistry University of Calabar, Calabar, Nigeria, from 2011 to 2013. He is a member of Nigerian Society of Biochemistry and Molecular Biology, and Institute of Public Analysts of Nigeria. He has more than 60 papers published in reputable journals, and is a reviewer and Editorial Board Member of many journals of repute. He has also presented many conference papers locally and internationally.

fridayuboh@yahoo.com

Notes:

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Pre-activation of acetylcholine M3 receptor leads to cannabinoid type 1 receptors regulation: A new cross talk mechanism involving intracellular calcium mobilization in SH-SY5Y human neuroblastoma cells

Pietro Marini
University of Aberdeen, UK

Cannabinoids are well known analgesic agents and common drugs of abuse. Both acute and chronic use of these drugs is associated with the development of tolerance and dependence. So far, the mechanism(s) underlying the acute dependence induced by drugs of abuse remain poorly understood and their elucidation is crucial for the understanding of the mechanisms underlying the chronic dependence. Preliminary results, clearly demonstrate that pre-stimulation of the cholinergic system increases levels of intracellular calcium in response to acute stimulation of cannabinoid receptors, thus suggesting a crucial role of the cholinergic system in the regulation of CB1 receptors activity, through the mobilization of intracellular calcium. Moreover, there is ample evidence that increases of intracellular calcium activate a series of transcription factors involved in gene regulation. However, the role played by acetylcholine and by intracellular calcium in the regulation of these transcription factors in the context of the CB1 receptor stimulation is largely unexplored. The novel findings presented here demonstrate a new cross talk mechanism between M3 and CB1 receptors that potentially could lead to a new pharmacological approach (development of combination therapies) while maintaining the desired effect (analgesia) could limit the development of dependence induced by the cannabinoid receptor stimulation.

Biography

Pietro Marini has completed his PhD in Pharmacology, Toxicology and Pharmacognosy from La Sapienza University of Rome and Post-doctoral studies from Italian National Reasearch Council. He has published papers and book chapters in reputed journals moslty related to the cannabinoid recepotors pharmacology.

p.marini@abdn.ac.uk

Notes:

conferenceseries.com

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Determination of some blood hydrocarbons contents, oxidative stress markers and haematological indices of rats orally exposed to bonny light crude oil

Saviour U Ufot[1], **Friday E Uboh**[1], **Uduak O Luke**[2] and **Patrick E Ebong**[1]
[1]University of Calabar, Nigeria
[2]University of Uyo Teaching Hospital, Nigeria

This study assessed the concentrations of blood benzene, toluene, ethylmethylene, xylene, and total polycyclic aromatic hydrocarbons (PAH), some oxidative stress markers (MDA, SOD and CAT) and haematological indices in male albino Wistar rats orally exposed to bonny light crude oil (BLCO). Eighteen rats, weighing 150–l80 g, and distributed into three groups of six rats each, were used in this study. Rats in groups one and two, which served as the control groups, were respectively administered distilled water and vegetable oil only; while rats in group three (test group) were orally administered 60 mg/kg bwt of BLCO daily for 30 days. At the end of the exposure period, the animals were sacrificed and the blood samples collected for the analysis of some haematological indices, blood oxidative stress markers and hydrocarbon concentrations. All the analyses were carried out using standard laboratory methods. The results showed that blood benzene, toluene, ethylmethylene, xylene, and total polycyclic aromatic hydrocarbons (PAH) recorded for rats exposed to BLCO (0.066±0.004, 0.641±0.032, 0.470±0.030, 0.112±0.009, and 12.540±0.720 ug/dl, respectively) were significantly ($p<0.05$) higher compared with the concentrations recorded for rats in group one (0.020±0.001, 0.015±0.001, 0.010±0.000, 0.031±0.001, and 2.270±0.120 µg/dl, respectively) and two (0.021±0.001, 0.016±0.001, 0.010±0.001, 0.031±0.001, and 2.271±0.011 µg/dl, respectively). It was also observed from the results of this study that exposure to BLCO produced a significant ($p<0.05$) oxidative stress condition (decreased blood CAT and SOD activities and increased MDA concentration), and haematotoxicity (decreased RBC, Hb, PCV, and increased WBC and some differential cells) in male rats, compared with the control rats. It may therefore be concluded that benzene, toluene, ethylmethylene, xylene, and polycyclic aromatic hydrocarbons (PAH) are likely implicated in crude oil induced oxidative stress and haematotoxicity recorded in this study for male rats.

Biography

Saviour U Ufot completed his BSc in Biochemistry and MSc in Pharmacology from University of Calabar and Ibadan respectively. He completed his PhD in Biochemistry (Biochemical and Environmental Toxicology) from University of Calabar in 2014. He was a Lecturer in the Department of Pharmacology, University of Ilorin, Nigeria from 1993 to 1998. He is presently working with Total Exploration and Production Nigeria Limited as a Health, Safety and Environment specialist. He has published over 14 papers in reputable journals and has attended many scientific seminars and conferences.

sufot2001@yahoo.com

Notes:

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Nutraceuticals for hypertension care: A network based approach

Matteo Micucci, Chiarini A and **Budriesi R**
University of Bologna, Italy

Several diseases with a high incidence including those pertaining cardiovascular system, are due to modifications of many molecular networks influencing each other's. The network based approach is based on the strategy named "network target multi components" and "network target single chemical" strategies. In different traditional systems, including Traditional Chinese Medicine (TCM) and ayurveda, poly-herbal formulations are considered efficient approaches to the treatment of multifactorial diseases. Nutraceutical science is mainly aimed at identifying the chemical composition and the mechanisms of action of complex mixtures, including the vegetal extracts. In this study, we focused on primary hypertension, representing a multifactorial pathology strongly predisposing to cardiovascular events. Many vegetal extracts with antihypertensive activities modulate several targets determining multiple cardiovascular beneficial effects. Among others, extracts from *Olea europaea L.* leaves and *Hibiscus sabdariffa L.* flowers interfere with different pathways, producing a hypotensive activity. In this work, we evaluated the cardiovascular effects and the toxicological profile of a Nutraceutical Formulation (NF) based on a mixture of a *Olea europaea L.* leaves extract (OEE) and a *Hibiscus sabdariffa L.* flowers extract (HSE) in the ratio of 13:2 using *in vitro* biological assays. The NF exerted a vasorelaxant effect (IC50=2.38 mg/mL) and a negative chronotropic effect (IC50=1.04 mg/mL) at concentrations lower than those producing smooth muscle spontaneous contractility alterations in the other organs. These experimental data suggest a potential application of this food supplement for contributing and managing preclinical hypertension.

Biography

Matteo Micucci completed his graduation in Pharmacy at Bologna University. In 2010, he worked in the laboratory of Dr. RRJ Arroo, Leicester School of Pharmacy, De Montfort University, UK. He was a Guest Scientist in the Department of Chemistry of Natural Substances, University of Naples "Federico II", Italy. He awarded European PhD in Pharmaceutical Sciences at Bologna University in 2012. He is a Scientific Consultant, in the field of Nutraceutical, Alternative and Complementary Medicines, at Segreteria Particolare of a Senator of the Italian Republic. He is a Research Fellow Scientist at Department of Pharmacy and Biotechnology, University of Bologna.

matteo.micucci2@unibo.it

Notes:

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Effects of lornoxicam and intravenous ibuprofen on erythrocyte deformability liver and renal blood flow in rats

Ayşegül Küçük[1], Hande Arpacı[3], Faruk Metin Çomu[2], Bahadır Kösem[4], Seyfi Kartal[4], Volkan Şıvgın[3], Hüseyin Cihad Turgut[5], Muhammed Enes Aydın[3], Derya Sebile Koç[3] and **Mustafa Arslan[3]**
[1]Kütahya Dumlupınar University, Turkey
[2]Kırıkkale University, Turkey
[3]Ankara University, Turkey
[4]Turgut Özal University Hospital, Turkey
[5]Gazi University, Turkey

Change in blood supply is responsible for anesthesia related abnormal tissue and organ perfusion. Decreased erythrocyte deformability and increased aggregation may be detected after surgery performed under general anesthesia. It was shown that non-steroidal anti-inflammatory drugs decrease erythrocyte deformability. Lornoxicam and/or ibuprofen intravenous administration for postoperative pain management is becoming more common. In this study, we aimed to investigate effects of lornoxicam (2 mg/kg) and ibuprofen (30 mg/kg) on erythrocyte deformabil-ity, liver and renal blood flow in male rats. 18 male Wistar albino rats were randomly divided into three groups as lornoxicam group (group L), ibuprofen group (group İ) and control group (group C). İntravenous administrations were done in all groups except group C. Liver and renal blood flows were conducted by laser Doppler and the euthanasia via intra-abdominal blood uptake was performed. Erythrocyte deformability was measured using a constant flow filtrometry system. Lornoxicam and ibuprofen increased the relative resistance which shows the erythrocyte deformability of rats (p=0.016). Comparison of group L and group I revealed no statistically dif-ferent results (p=0.694) where group L and group I revealed statistically higher results than group C (p=0.018, p=0.008). Liver and renal blood flows were significantly lower than that measured in group C. We believe that lornoxicam and ibuprofen may lead to functional disorders related to tissue perfusion as a result of both decreased blood flow and erythrocyte deformability. Further studies regarding these issues are thought to be essential.

Biography

Ayşegül Küçük has completed her PhD from Erciyes University and Post-doctoral studies from Erciyes University School of Medicine. She is a member in Department of Physiology at the Medical Faculty of Dumlupinar University. She has published more than 25 papers in reputed journals.

kucukaysegul@hotmail.com

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The effect of proton pump inhibitors on bone mineral density in rats

Layla Ezzat Borham[1,2], **Magda M Hagras**[3], **Altaf Abdulkhaliq**[1] and **Mohammed Badawood**[4]
[1]Umm Al-Qura University, Saudi Arabia
[2]Cairo University, Egypt
[3]Suez Canal University, Egypt
[4]King Abdul Aziz University, Saudi Arabia

Background: Increased con¬cerns rose towards the side effects of chronic use of proton pump inhibitors (PPIs). The relationship between prolonged use of PPIs and bone metabolism is still not totally established.

Aim: Aim of this study is to examine the association between the use of (PPIs) and the risk of development osteoporosis.

Method: 180 adult male rats were assigned to three groups (60 rats each). Group I served as control; whereas, group II (a, b), (i.p) omeprazole 20 mg/kg/day was administered for four and eight weeks respectively; group III (a, b), (i.p) omeprazole 40 mg/kg/day was given for the same period. At the end of drug treatment, 20 rats from each subgroup were examined for bone mineral density (BMD), bone mineral content (BMC), serum calcium, phosphorus, parathormone, tartrate resistant acid phosphatase type 5b (TRACP5b), insulin-like growth factor 1(1GF-1) and osteoprotegerin (OPG). The remaining 10 rats from each subgroup were left without treatment for the next four weeks to detect the reversal effects of the drug.

Results: BMD and BMC decreased in a dose and time dependent manners with recovery. Serum calcium and phosphate decreased at the dose 40 mg/kg for eight weeks with recovery of calcium after discontinuation of therapy but not phosphate. Parathormone increased compared to control with no recovery. TRACP5b increased at 20, 40 mg at eight weeks with no recovery. IGF1 decreased in dose and time dependent manner, recovery only for 20 mg for four weeks. OPG showed no change.

Conclusion: The chronic use of high doses of omeprazole could adversely affect bone homeostasis.

Biography

Layla Ezzat Borham is a Professor of Clinical Pharmacology at Cairo and Umm Al-Qura Universities since 2004. She completed his MSc and MD at Cairo University Medical School. She has been working in Faculty of Medicine, Umm Al-Qura University, KSA for 15 years. During this period, she carried out a lot of scientific and social serving activities through her publications, scientific committee memberships, lectures and administrative work. In addition, she works in the Ministry of Health hospitals and primary health care centres giving awareness lectures to health care providers and patients. She has been awarded a Golden Prize from Umm Al-Qura University for her overall services at the University.

borhaml@hotmail.com

Notes:

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Beneficial effects of phloretin on oxidative and inflammatory reaction in rat model of cecal ligation and puncture induced sepsis

Omid Sabzevari, M Aliomrani, M R Sepand, S Sabzevari, H Mirzaei and **S Nekonam**
Tehran University of Medical Sciences, Iran

Introduction: Sepsis is a debilitating systemic disease and described as a severe and irregular systemic inflammatory reaction syndrome (SIRS) against infection. We employed CLP (Cecal Ligation and Puncture) model in rats to investigate anti-inflammatory and antioxidant effects of phloretin, as a natural antioxidant agent, and its protective effect on liver tissue damage caused by sepsis.

Methods: Male Wistar albino rats were randomly divided into 3 groups: Sham group, CLP induced sepsis group and phloretin treated CLP group. Sepsis was induced by CLP method. 50 mmol/kg phloretin was administered intraperitoneally in 2 equal doses immediately after surgery.

Results: It was observed that blood urea nitrogen (BUN) and tumor necrosis factor alpha (TNF-α) levels were dramatically increased in the CLP induced sepsis group (43.88±1.905 mg/dl, 37.63±1.92, respectively) when compared to the sham group. Moreover, tissue glutathione (GSH) and liver nuclear factor κB (NF-κB p65) transcription factor values were higher in CLP induced sepsis group. This elevation was considerably reduced in the phloretin treated CLP group. No significant differences were observed in serum creatinine and creatinine phosphokinase levels.

Conclusions: The present study suggested that phloretin, as a natural protective agent, acts against tissue damages introduced following the experimental sepsis induced model, likely caused by free oxygen radicals.

Biography

Omid Sabzevari has completed his PhD from Surrey University, and Fellowship at Toronto University Faculty of Pharmacy. He is President of Iranian Society of Toxicology (IranTox) and President of Iranian Association of Pharmaceutical Scientists (IranAPS). He is Head of Basic and Clinical Toxicology Research Centre, TUMS. He is a Scientist in the fields of Mechanistic Toxicology & Pharmacology and Food Safety and has published more than 50 papers in reputed journals, and has been serving as an Editorial Board Member of repute. He was listed among Top 1% Scientists of the World according to ESI/ISI in May 2012.

omid@tums.ac.ir

Notes:

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Carbon monoxide modulates infection-induced proinflammatory cytokine milieu in human placenta

Nazeeh Hanna
Winthrop University Hospital, USA

There is growing recognition that cytokines and inflammatory mediators present at the maternal-fetal interface play a fundamental role in regulating labor. IL-10 is an essential pro-pregnancy cytokine and therapies leading to its placental induction might be useful in preventing preterm deliveries. Although toxic in high concentrations, inhaled carbon monoxide (CO) in low concentrations can confer potent anti-inflammatory effects. Several pre-clinical and clinical studies have used CO as a therapeutic agent for a variety of vascular complications and sepsis; no published studies have evaluated the utility for this novel anti-inflammatory gas for preventing preterm delivery. The objective of this work is to investigate the role of CO in modulating infection-induced proinflammatory cytokine milieu in human placenta. Using placental explants culture system, samples from normal second trimester placentas were treated with LPS (250 ng/ml), 108 heat killed *E. coli* or 108 heat killed *Urealyticum parvum* with or without exposure to CO (250ppm) for 18 hours. Conditioned media were collected and analyzed for cytokines production using Bio-PlexTM array. Cultured tissues were analyzed by western blots for COX-2 and heme oxygenase-1 expression. To determine if CO exposure will induce cytotrophoblasts cell death, early pregnancy cytotrophoblasts cell lines (HTR8) were exposed to RA or CO (for 18 hours). Apoptosis was analyzed by FACS array. Our data indicate that CO effectively inhibits infection-induced proinflammatory mediators in second trimester placentas. Moreover, CO induced the pro-pregnancy cytokine IL-10 pointing to a potential role of CO in treatment of preterm labor.

Biography

Nazeeh Hanna is the Chief of Neonatology at Winthrop University Hospital. He is also the President-elect of the American Society for Reproductive Immunology. He is currently a Professor of Pediatrics, State University of New York at Stony Brook. He is an established Investigator who has international recognition for his work in reproductive immunology. His research track is focused in the area of "Developmental immunology and the impact of maternal exposure to environmental toxicants on preterm births".

NHanna@winthrop.org

Notes:

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Flavonoid effects on antihypertensive pharmacological therapy: Modulation on lipid profile, inflammation and association of ACE (I/D) polymorphism in treatment response

Marina M de Jesus Romero-Prado, Jiménez A, Miramontes M V and **Curiel J**
Centro Universitario de Ciencias de la Salud, Mexico

Introduction: In previous works, we demonstrated that dietary flavonoids have additional benefits on blood pressure, lipid profile, inflammation and electrocardiography parameters when they are added to antihypertensive pharmacological therapy.

Aim: Aim of this study is to analyze the possible role of Angiotensin Converting Enzyme (ACE) polymorphism (I/D) in response to the addition of dietary flavonoids (DF) to pharmacological antihypertensive therapy (AHT) in hypertensive young people.

Method: 37 male and 42 female patients with hypertension grade I (n=27) or II (n=52) received 425.8±13.9 mg gallic acid equivalents (GAE) from dietary flavonoids were added to AHT based on captopril (50 mg/day) or telmisartan (40 mg/day) during six months. Clinical registrations (SBP/DBP, BMI) were made during 15-days periods; lipid profile, hs-CRP and Leptin were measured in plasma at zero, one, three and six months; the ACE (I/D) polymorphism was determined by standard methods.

Results: Patients with AHT+DF compared to AHT showed differences in SBP ($p<0.004$), DBP ($p<0.017$), weight ($p<0.022$), BMI ($p<0.028$) and triglycerides ($p<0.004$); hs-PCR levels showed differences by ACE (I/D) polymorphism I/D vs. D/D ($p<0.009$). The genotypes D/D and I/I were associated to highest frequency of hypercholesterolemia and low HDL-C levels, respectively.

Conclusion: The response of FRD added to AHT has beneficial effects on BMI, BP, lipids and inflammation parameters and may be associated to ACE (I/D) polymorphisms.

Biography

Marina M de Jesus Romero-Prado completed her PhD from Autonomous University of Madrid (UAM), Spain. She is a Molecular Biologist, Geneticist and works at Experimental and Clinical Therapeutics Institute at University of Guadalajara. She has published her discoveries in "Expression regulation of growth hormone gene and molecular and cellular research about biological potential of mesenchymal stem cells". Her incursion as Leader in clinical protocols has served to bind the basic and applied research in complementary and translational medicine.

rpm78091@cucs.udg.mx

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Scientific Tracks & Abstracts

(Day 3)

Day 3 October 26, 2016

Clinical Toxicology | Reproductive Toxicology

Session Chair
Eva Cecilie Bonefeld-Jørgensen
Aarhus University, Denmark

Session Co-Chair
Jikai Wen
South China Agricultural University, China

Session Introduction

Title: **COX_2 inhibition decreases ischemic damage to rat retina–function or structure**
Yoram Oron, Tel Aviv University, Israel

Title: **Activation of the estrogen receptor by human serum extracts containing mixtures of perfluorinated alkyl acids from pregnant women's serum**
Christian Bjerregaard-Olesen, Aarhus University, Denmark

Title: **Tamoxifen and its derivatives bind to and act at cannabinoid receptors CB1 and CB2 with high affinity**
Anna Radominska Pandya, University of Arkansas for Medical Sciences, USA

Title: **Beta-blockers and sperm function**
Banihani S A, Jordan University of Science and Technology, Jordan

Title: **Individualised clinical toxicology: Physiological intermolecular modulation spectroscopy (PIMS), a technology to forsee drugs efficacy prior to administration**
Pierre Eftekhari, Inoviem Scientific, France

Title: **The utility of the minipig as an animal model in regulatory toxicology**
Gerd Bode, University of Gottingen, Germany

Title: **Dioxin-like POPs: Induced aryl hydrocarbon receptor transactivity in the Danish pregnant women**
Manhai Long, Aarhus University, Denmark

Title: **Genotypic and phenotypic patterns of antimicrobial susceptibility of *Helicobacter pylori* strains among Egyptian patients**
Marwa Saad Fathi, Ain Shams University, Egypt

Title: **Neuropharmacological and cochleotoxic effects of styrene can worsen the noise impact**
Pierre Campo, Institut National de Recherche et de Sécurité, France

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COX2 inhibition decreases ischemic damage to rat retina–function or structure

Yoram Oron
Tel Aviv University, Israel

Extensive ischemia results in massive (≥80%) death of ganglion cells (GC) and a virtually complete loss of function as judged by b-wave disappearance in ERG. Hence this type of protocol is suited only to study the prevention of ischemic damage, but not post-insult treatment and effects on the extent and kinetics of recovery. We, therefore, studied the effects of COX species inhibition on mild ischemic damage (30% decrease in GC). Selective COX1 inhibition had no effect, while selective COX2 inhibitor, Vioxx, markedly improved retinal function (ERG b-wave amplitude) recovery after initial damage. Although GC number was also affected by Vioxx, the effect was not statistically significant at this low level of damage. Vioxx also potentiated ischemic induction of HSP70. Our results strongly suggest the involvement of COX2 (possibly via inhibition of HSP70 induction) in the mechanism of retinal ischemic damage. Moreover, we propose that studies of neuro-protection at low level damage should use functional assays, such as ERG or behavioral measurements, to follow the efficacy of the treatment.

Biography

Yoram Oron has completed his PhD from the Hebrew University, Jerusalem and Post-doctoral studies from University of Virginia, School of Medicine. He is currently Professor Emeritus of Pharmacology at the Sackler Faculty of Medicine, Tel Aviv University and the Chief Scientific Officer of two drug startup companies. He has published more than 110 papers in reputed journals and has been serving as a Reviewer in a number of reputed journals.

medfair@post.tau.ac.il

Notes:

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Activation of the estrogen receptor by human serum extracts containing mixtures of perfluorinated alkyl acids from pregnant women's serum

Christian Bjerregaard-Olesen, Mandana Ghisari and **Eva C Bonefeld-Jørgensen**
Aarhus University, Denmark

Humans are exposed to a variety of perfluorinated alkyl acids (PFAAs). Several studies have found xenoestrogenic activity of single PFAAs. Studies on mixture effects of the PFAAs are however sparse. In the present study, we aimed to determine the xenoestrogenic activity in human serum extracts containing mixtures of PFAAs. Recently, we developed a method to extract the PFAAs from serum with simultaneous removal of endogenous hormones and interfering steroid metabolites. We used this method to extract the PFAAs from serum of 397 Danish pregnant women followed by analysis of estrogen receptor (ER) transactivation using MVLN cells carrying an estrogen response element luciferase reporter vector. Using 17β-estradiol (E2) concentration-transactivation curves, we calculated the E2-equivalents (EEQ) for the extracts containing the PFAAs. 52% of the PFAA serum extracts agonized the ER transactivation and 46% enhanced the E2-induced ER transactivation. We found positive associations between the ER transactivation and the PFAA serum levels. For the relatively few PFAA extracts that antagonized the ER in the presence of 24 pM E2 (n=38, 10%), we found inverse associations between the ER transactivation and the PFAA serum levels. The results indicated that the PFAA extracts induced the ER in a non-monotonic concentration dependent manner. The median EEQ of the extracts containing the PFAAs corresponds to the effect of 0.5 pg E2 per mL serum. In conclusion, we observed that most of the extracts containing the PFAA mixtures from pregnant women's serum agonized the ER and enhanced the E2-induced effects in non-monotonic concentration-dependent manners.

Biography

Christian Bjerregaard-Olesen is defending his PhD thesis entitled, "Perfluoroalkyl acids in serum of Danish pregnant women: Levels, time trends, extraction and *ex vivo* xenoestrogenicity" on October 21st 2016 in Deparment of Public Health, Aarhus University in Denmark. Additionally, he has completed his Master's degree in Chemistry. He has published six papers in peer-reviewed journals and further four are in preparation.

cbjr@ph.au.dk

Notes:

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Tamoxifen and its derivatives bind to and act at cannabinoid receptors CB1 and CB2 with high affinity

Anna Radominska Pandya
University of Arkansas for Medical Sciences, USA

Tamoxifen (Tam) is classified as a selective estrogen receptor modulator and is chemotherapeutic agent for treatment of estrogen receptor (ER)-positive breast cancer, due to its ability to act as an ER antagonist. We have shown that Tam and its cytochrome P450-generated metabolite 4-hydroxy-Tam (4OH-Tam) also exhibit cytotoxic effects in ER-negative breast and pancreatic cancer cells. These observations suggest that Tam and 4OH-Tam can produce cytotoxicity via ER-independent mechanism(s) of action. Cannabinoids compounds have also been shown to exhibit anti-proliferative and apoptotic effects in ER-negative breast cancer cells, and estrogen can regulate expression levels of CBRs. This study investigated whether CBRs might serve as novel molecular targets for Tam and 4OH-Tam and we have shown that they bind to CB1 and CB2 with significant affinity. Furthermore, Tam and 4OH-Tam exhibit inverse activity at CB1 and CB2 in membrane preparations, reducing basal G-protein activity and also act as CB1/CB2R-inverse agonists regulating the downstream intracellular effector adenylyl cyclase in intact cells. These results suggest that CBRs are molecular targets for Tam and 4OH-Tam and may contribute to the ER-independent cytotoxic effects reported for these drugs. Therefore, we hypothesize that the cytotoxicity observed in these cells may be attributed in part to the binding of these drugs to CB1 and/or CB2 causing activation or suppression of downstream genes regulating cell proliferation. If our hypothesis is correct, CBRs could constitute a novel molecular target and structural scaffolds for which effective, non-toxic, natural and synthetic cannabinoids might be developed for treatment of various types of cancer.

Biography

Anna Radominska Pandya serves as a Professor in the Department of Biochemistry and Molecular Biology at UAMS. She is the Editor in Chief for Drug Metabolism Review. She received her PhD from the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw, Poland. She has published 175 papers in various peer-reviewed journals, and has received twelve R01 grants from the NIH and DoD. Her research interests include: The regulation and suppression of human UGTs and their role as anti-proliferative agents in cancer models, the interactions between UGTs and cannabinoid receptors, the delivery of *UGT* genes and drugs into cancer cells using nanomaterial, and the roles of UGTs in the biotransformation of drugs including resveratrols and drugs of abuse such as marijuana and synthetic cannabinoids.

radominskaanna@uams.edu

Notes:

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Beta-blockers and sperm function

Banihani S A
Jordan University of Science and Technology, Jordan

Beta-blockers (or histamine-2 receptor antagonists) are a subtype of acid reducers commonly used to treat the acid-related gastrointestinal diseases (i.e., ulcer, dyspepsia and gastro-esophageal reflux disease). Even though, these drugs, especially ranitidine and famotidine, are commonly used worldwide, their effects on sperm function are still indistinct. This work integratively discusses and summarizes the effect of B-blockers on sperm function. The effects of nizatidine and ranitidine on sperm function are still controversial. Cimetidine has adverse effects on sperm function. In contrast, to date, famotidine does not appear to alter sperm function. Further studies are considered very significant to explain the role of B-blockers on sperm function.

Biography

Banihani S A has completed his PhD from Cleveland Clinic/Cleveland State University, USA in the fields Clinical-Bioanalytical Chemistry and Molecular Medicine with full GPA. Currently, he is the Vice Dean of Faculty of Applied Medical Sciences at Jordan University of Science and Technology. He has published more than 25 papers in reputed journals. He has two major research interests: Male Infertility and Clinical Nutrition.

sabanihani@just.edu.jo

Notes:

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Individualised clinical toxicology: Physiological intermolecular modulation spectroscopy (PIMS), a technology to forsee drugs efficacy prior to administration

Pierre Eftekhari
Inoviem Scientific, France

Toxicology today is in need of new insight. In air of individualised medicine the relation between desired clinical effect and toxic or side-effects should be considered simultaneously. Genomics, proteomics, metabolomics and omics in general, although extremely valuable, are globally lacking clinical relevance. Therefore, there is a need for new methodologies and new tools enabling us to make a bridge between predicted omics-based drug toxicity and clinics. Here, I shall present Physiological Intermolecular Modulation Spectroscopy (PIMS) a cutting edge techology meant to stratify the patients as responders or non-responders in regard to a pharmacological active agent. PIMS provides individual fingerprints based on drug-induced macromolecular modulation directly on human tissue extracts. I will explain the scientific background of PIMS and present the results from two different clinical studies (transversal and longitudinal), using peripheral blood mononuclear cells (PBMC) isolated from patients with ulcerative colitis and Crohn's disease for the prediction of infliximab effect.

Biography

Pierre Eftekhari has completed his PhD from Strasbourg University. He has more than 19 years of experience in Drug Development and is the President of Inoviem Scientific, a company dedicated to cutting edge solutions in drug development. He has published more than 30 papers in reputed journals and filed several patents.

p.eftekhari@inoviem.com

Notes:

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The utility of the minipig as an animal model in regulatory toxicology

Gerd Bode
University of Gottingen, Germany

Gratitude is within the ethical tradition of Japanese towards experimental animals, because these provide valuable data for efficacy and safety of pharmaceutical compounds before first administration to humans. Researchers must therefore develop strict responsibilities to use these models under strict adherence to the 3Rs (Refine, Reduce, Replace). Models should be relevant; and a relevant model is an animal which expresses receptors/epitopes like humans, reveals comparable pharmacodynamic effects and resembles humans in regard to kinetic parameters like metabolism, exposure levels, protein binding and bioavailability. For primary or secondary pharmacodynamics, next to traditional species, also transgenic or disease models are being used, but for non-clinical safety studies predominantly traditional rodents or non-rodents are tested. The undesirable adverse reactions are often so subtle, that for optimal assessments excellent knowledge of specific or spontaneous reactions is needed. The model must easily be available, costs acceptable and no paucity of historical data representing an obstacle. There will be a continuation of using rats and mice for toxicity evaluations, but for non-rodents a growing refusal is felt in using dogs and monkeys. This paper deals with the utility of the minipigs as an animal model in regulatory toxicology. The advantages or disadvantages will be illustrated. The Gottingen minipig is a genetically managed model unlike the dog and monkey toxicology models. The basis of the small size of the Gottingen minipig does not involve defective genes. Commercial interests in the pig as an agricultural production species have driven the area of pig genomics. There is no equivalent economic driver for progress in the dog or the non-human primate. The Gottingen minipig is well positioned for the performance of toxicogenomics studies. The close sequence homology between pigs and humans suggest that minipigs could be useful for the testing small molecules but also for biotechnology products. The minipig is the only non-rodent model where transgenic animals can be readily generated, and reproductive technologies are well developed in the pig. The biology of the minipig is comparable; practically all study types can be performed in the minipig. For reproductive toxicology studies the minipig offers numerous advantages although the lack of placental transfer of macromolecules may limit the role of the minipig in reproductive testing of biotechnology products. For safety pharmacology studies the minipig is an advantageous model, particularly as regards the cardiovascular system. The immune system of the pig is better characterized than that of the dog and as an omnivore the GI-tract reveals similar characteristics. Overall, the mini-pig should be carefully considered as an alternative to dogs and monkeys; but of course, more comparative data is needed for a rigorous assessment of the usefulness and the predictivity of this species for human drug-induced desired and adverse reactions.

gerd-bode@t-online.de

Notes:

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Dioxin-like POPs: Induced aryl hydrocarbon receptor transactivity in the Danish pregnant women

Manhai Long and **Eva C Bonefeld Jørgensen**
Aarhus University, Denmark

Human exposure to lipophilic persistent organic pollutants (POPs) including polychlorinated dibenzo-*p*-dioxins/furans (PCDDs/PCDFs), polychlorinated biphenyls (PCBs) and organochlorine pesticide is ubiquitous. The individual is exposed to a complex mixture of POPs being life-long beginning during critical developmental windows. Exposure to POPs elicits a number of species- and tissue-specific toxic responses, many of which involve the aryl hydrocarbon receptor (AhR). We aimed to assess the actual level of dioxin-like activity in serum of 806 Danish pregnant women collected during 2011-2013. The bioaccumulated lipophilic serum POPs were extracted by solid phase extraction and clean-up on Supelco multi-layer silica column and florisil column. The integrated AhR transcriptional activity in the serum fraction was determined using the Hepa 1.12cR mouse hepatoma cell line carrying an AhR-luciferase reporter gene and expressed as pg TCDD equivalent (TEQ) per gram lipid after adjusted for the serum lipid. The AhR transactivity data was evaluated for possible association to the serum levels of 14 PCB congeners, 10 organochlorine pesticides and/or lifestyle factors. The preliminary results showed that 91.3% samples elicited agonistic AhR transactivity. The median level of AhR transactivity was 195 pg TEQ/g lipid. Pearson correlation analysis showed a weak positive correlation between dioxin-like activity and PCB 105. No significant correlation between serum dioxin-like activity and pregnant women age, gestational day at blood draw, BMI, smoking status and social economic status were observed.

Biography

Manhai Long obtained her PhD degree in Medicine in 2007 from Aarhus University and works as Associate Professor of Human Toxicology at the Faculty of Health, Aarhus University, Denmark. She has participated in several international and national projects. She has published more than 30 papers in the international journals and has been serving as peer reviewer of several international journals.

ml@ph.au.dk

Notes:

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Genotypic and phenotypic patterns of antimicrobial susceptibility of *Helicobacter pylori* strains among Egyptian patients

Marwa Saad Fathi
Ain Shams University, Egypt

Backgrounds & Study Aim: *Helicobacter pylori* is currently recognized as one of the most common chronic bacterial infections worldwide. Eradication of bacteria is effective in healing peptic ulcers, preventing ulcer relapses and potentially decreasing the risk of progression to gastric carcinoma. For successful eradication of bacteria, it is imperative that the clinician be aware of the current antimicrobial susceptibility profiles of isolates within the region. Therefore, the aim of this study is to compare the phenotypic & genotypic patterns of antibiotics susceptibility to *Helicobacter pylori* strains among Egyptian patients in order to attain a clinical utility from such patterns.

Patients & Methods: 30 symptomatic cases were enrolled. *H. pylori* infection was diagnosed by upper endoscopy as well as biopsy was taken. Antimicrobial susceptibility to *Helicobacter pylori* strains was assessed in all subjects by disc diffusion & e-testing methods. Further molecular characterization for genes encoding antimicrobial resistance of isolated strains was done.

Results: For metronidazole, amoxicillin and ciprofloxacin, we compared the phenotypic and genotypic patterns of resistance as detected by PCR amplification of the resistance genes. E test results were 100%, 50% & 87.5% for metronidazole, ciprofloxacin & amoxicillin respectively from 16 isolated *H. pylori* strains.

Conclusion: Improving the knowledge of resistance mechanisms, the elaboration of rational and efficacious associations for the treatment *H. pylori* infection are of high importance especially in determining the therapeutic outcome. Further progress should ultimately focus on the establishment of a cheap, feasible and reliable laboratory test to predict the outcome of a therapeutic scheme

Biography

Marwa Saad Fathi currently works as an Assistant Professor of Medical Microbiology & Immunology at Faculty of Medicine, Ain Shams University. She had her MD degree from Ain Shams University in 2009. She is currently studying a Specialized Diploma in Medical Microbiology at University College, London. She is working as a Director of Medical Mycology Lab at Misr University for Science & Technology (MUST). Her publications exceed 20 papers in important focused journals since 2009.

dr.marwasaad@gmail.com

Notes:

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Neuropharmacological and cochleotoxic effects of styrene can worsen the noise impact

Pierre Campo and **Ludivine Wathier**
Institut National de Recherche et de Sécurité, France

It is well-known that occupational noise exposure can damage workers' hearing. It is also well accepted that a combined exposure to noise with cochleotoxic substances such as antibiotics, cisplatin, or chemicals (styrene, toluene and ethylbenzene) can exacerbate the noise effects. Although solvent-induced cochlear impairments can be only assessed after a long incubation period, the pharmacological impact of styrene on the central nervous system (CNS) can be rapidly objectified by measuring the threshold of the middle-ear acoustic reflex (MER) trigger. MER can be precious for preserving the hearing performances of workers. The aim of the study was to evaluate the effects of a noise (both continuous and impulse) and a low concentration of styrene [300 ppm<(threshold limit value x 10) safety factor] on the peripheral auditory receptor, and on the CNS in rats. The impact of the different conditions on hearing loss was assessed using distortion product oto-acoustic emissions, and histology studies of cochleae. Although the LEX, 8 h (8-hour time-weighted average exposure) of the impulse noise was lower (80 dB SPL sound pressure level) than that of the continuous noise (85 dB SPL), it appeared more detrimental to the peripheral auditory receptors. If the co-exposure to styrene and continuous noise was less damaging than the exposure to continuous noise alone, the traumatic effects of impulse noise on the organ of corti were enhanced by the co-exposure to styrene. The neuropharmacological effects of the solvent explain these surprising results. Actually the CNS effects of styrene may account for this apparent paradox. Based on the present results, the temporal structure of the noise should be reintroduced as a key parameter in hearing conservation regulations.

Biography

Pierre Campo has completed his PhD in Nancy (France) and Postdoctoral studies at Hearing Research laboratory. Currently, he is the Head of Ototoxic and Neurotoxic laboratory at INRS (France). He has published more than 30 publications. He is an Associated Editor at International Journal of Audiology and a Specialist in noise and solvent interactions on hearing. He concieved the EchoScan audio, a new equipment to evaluate the auditory fatigue in factories after a workday.

pierre.campo@inrs.fr

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Session Introduction

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Title: Concomitant exposure of bacoside A and bromelain relieves dichlorvos toxicity in mice serum
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Title: Determination of chromium by ETAAS in hair and urine of tannery workers: The interest of alternative biological matrices
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Title: Flexibility for automated cell based assays
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Title: Biological effects of nanoparticles on fish
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Title: Anti-inflammatory effect and toxicology analysis of oral delivery quercetin nanosized emulsion in rats
Gabriela Hädrich, Universidade Federal do Rio Grande, Brazil

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Proposed criteria for the evaluation of the scientific quality of mandatory rat and mouse feeding trials with whole food/feed derived from genetically modified plants

Kerstin Schmidt[1], Janine Döhring[2], Christian Kohl[3], Maria Pla[4], Esther J. Kok[5], Debora C.M. Glandorf[6], René Custers[7], Hilko van der Voet[8], Jutta Sharbati[9], Ralf Einspanier[9], Dagmar Zeljenková[10], Jana Tulinská[10], Armin Spök[11], Clare Alison[12], Dieter Schrenk[13], Annette Pöting[14], Ralf Wilhelm[3], Joachim Schiemann[3], Pablo Steinberg[2]

[1]BioMath GmbH, Germany
[2]University of Veterinary Medicine Hannover, Germany
[3]Julius Kühn Institute (JKI), Germany
[4]Universitat de Girona (UDG), Spain
[5]Wageningen University and Research Centre, The Netherlands
[6]National Institute for Public Health and the Environment/ Centre for Safety of Substances and Products, The Netherlands
[7]VIB (Flanders Institute for Biotechnology), Belgium
[8]Wageningen University and Research Centre, The Netherlands
[9]Freie Universität Berlin, Germany
[10]Slovak Medical University, Slovakia
[11]Alpen-Adria Universität Klagenfurt, Austria
[12]Roger Alison Ltd., United Kingdom
[13]University of Kaiserslautern, Germany
[14]Federal Institute for Risk Assessment, Germany

In recent years, animal feeding trials conducted with whole food/feed have been a focal issue in the controversy on the safety assessment of genetically modified (GM) plants and derived food/feed. Within the scientific community and among stakeholders, quite different views have been expressed on how these studies should be conducted, analysed and interpreted, what they might add in terms of information relevant to safety and whether 90-day rodent feeding trials should be mandatory. In the context of the ongoing debate on GMO risk assessment in Europe, it is crucial to investigate: Criteria for evaluating the scientific quality of subchronic, chronic toxicity and carcinogenicity studies with whole food/feed in rats and mice. This will help risk assessors in evaluating this type of studies when provided in the course of a pre-market risk assessment and will create a basis for further general debate. This talk specifically addresses the question on how to evaluate whole GM food/feed feeding trials. It does so by proposing a list of key quality criteria for the evaluation of 90-day and extended feeding trials with whole food/feed derived from GM plants. The proposed quality criteria should be taken into account when evaluating a feeding trial in the frame of an application to regulatory bodies and are not intended to be applied in other cases in which a feeding trial is performed to answer a specific open question in basic research.

Biography

Kerstin Schmidt completed her University degree in Mathematics with specialisation in Statistics and Probability Theory. In 1990, she established her own company BioMath, an internationally operating consultancy for research institutions and industrial partners in statistics and informatics, especially in the life sciences. She has been accompanying more than 100 projects in Toxicology, several of them joint/ international projects. She works as a Lecturer for Statistics and Experimental Design at the University of Rostock. In April 2016, she submitted her Doctoral thesis entitled "Statistical aspects and methods of the risk assessment and post-market environmental monitoring of genetically modified plants".

kerstin.schmidt@biomath.de

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The effect of the first- and second-generation of antipsychotic drugs on SH-SY5Y brain cells and their toxicity

Israa J Hakeem
University of Birmingham, Edgbaston, UK

Antipsychotic drugs are primarily used to manage several psychiatric disorders, including schizophrenia, bipolar mania and related mental illnesses. The present study examined the effect of the first and second generation of antipsychotic drugs on neuronal and non-neuronal cells. The toxicity of both-generation of antipsychotics was tested in both the SH-SY5Y brain cell line and the COS7 kidney cell line. According to the LC50 values for chlorpromazine (1st generation), Trifluoperazine (1st generation) and Olanzapine (2nd generation), the neurotoxicity of the two classes in SH-SY5Y exceeded their common cytotoxicity in COS7 cells, indicating that neuronal cells are at greater risk of cell death with low concentrations of antipsychotics at micro-molar comparing to non-neuronal cells. Detailed studies looking at the mechanisms of cell death induced by these antipsychotic drugs indicate that both apoptosis and necrosis play a role, while autophagy does not.

Biography

Israa J Hakeem is a PhD student at the University of Birmingham. She has completed her Master's degree in Forensic Science from Anglia Ruskin University and received Bachelor's degree in Biochemistry.

ixh308@bham.ac.uk

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Concomitant exposure of bacoside A and bromelain relieves dichlorvos toxicity in mice serum

Sonam Agarwal and **Renu Bist**
Banasthali University, India

Current study emphasizes the toxic effects of dichlorvos on serum in terms of oxidative stress. Meanwhile, a protective action of bacoside A and bromelain was investigated against the biochemical alterations in serum. Experimental design included six groups of mice: Saline was given as a vehicle to the control mice (group I). Mice belonging to groups II, III and IV were administered with dichlorvos (40 mg/kg b.w.), bromelain and bacoside A, respectively. Fifth group received a combination of bromelain and bacoside A. In group VI, bacoside A and bromelain were administered 20 minutes prior to exposure of dichlorvos. Thiobarbituric acid reactive substances (TBARS), protein carbonyl content (PCC), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and reduced glutathione (GSH) level were used as biochemical test of toxic action for dichlorvos intoxication. Significantly increased TBARS and PCC level in second group suggests that dichlorvos enhances the production of free radicals in serum of mice ($p<0.05$). Antioxidants treatment significantly decreased the levels of TBARS and PCC ($p<0.05$). Dichlorvos administration causes a significant reduction in the level of CAT, SOD, GPx and GSH ($p<0.05$) which was restored significantly by co-administration of bromelain and bacoside A in dichlorvos exposed mice ($p<0.05$). Treatment of bromelain and bacoside A in combination served as better scavengers of toxicity induced by dichlorvos.

Biography

Sonam Agarwal is pursuing PhD in Biotechnology from Department of Bioscience and Biotechnology, Banasthali University, Rajasthan, India. She has completed her MSc in Biotechnology from MITS University, Rajasthan, India. Her research work highlights "The role of bacoside A and bromelain against dichlorvos incited toxicity in serum and kidneys of mice".

sonam.2mits@gmail.com

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Determination of chromium by ETAAS in hair and urine of tannery workers: The interest of alternative biological matrices

Mohammed Riffi[1], **Okacha Abdelmalek**[1], **Rania Abtroun**[1], **Mohammed Azzouz**[2], **Mohammed Reggabi**[2] and **Barkahoum Alamir**[1,3]
[1]CHU Bab el Oued, Algeria
[2]Biologie Toxicology Laboratory, Algeria
[3]National Center of toxicology, NIP, Algeria

Introduction: The human hair occupies a prominent place as markers of exposure to xenobiotics in the domain of forensic toxicology. However, interest of using this matrix is a considerable improvement for the assay of metals; also, chromium has attracted the attention of toxicologists because the accidents observed in industrial settings using this metallic element (cement industry, paint, leather, automotive, etc.).

Objective: This study is related to the assessment of worker exposure in a tannery, located in Algiers, more accurately on the Rouiba-Reghaia industrial estate, by measuring the capillary and urinary chromium of the population groups investigated, and then study the correlation between total content of chromium in hair and urine.

Patients & Methods: The study was carried out in September 2012, and focused on 50 subjects exposed (49 men and 1 woman) and 16 controls. It was preceded by the establishment analytical development and validation of an analytical method for the determination of chromium in hair and urine by graphite furnace atomic absorption spectrometry (GFAAS). Statistical calculations were performed using the software LXSTAT MS Excel 2012.

Results & Discussion: The hair chromium average of the tanning workers were significantly higher (urinary Cr=2.48 µg/L, Cr capillary=4.93 ng/mg) than other groups. Washing the hair appears to be effective for decontaminating the exogenous chromium, this latter may reflect a recent exposure to chromium.

Conclusion: Human hair may offer the advantage for biological monitoring, first, to get information on the use of means of protection, and give some idea about the route of exposure (inhalation or ingestion).

Biography

Mohammed Riffi has completed his PhD from Tlemcen University and Post-doctoral studies from Algiers University School of Medicine. He has a membership of SoHT. He has published one paper in Toxicologie analytique et Clinique.

mohamedtox@hotmail.fr

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Flexibility for automated cell based assays

Lena Schober, Moriz Walter and **Andrea Traube**
Fraunhofer Institute for Manufacturing Engineering and Automation IPA, Germany

The use of automated systems for biological tasks is in great demand. Nevertheless, there are a lot of barriers at the moment limiting the successful application of automated systems. By the lack of flexibility and the demand for skilled computer scientists & engineers just the two main aspects stated by experts shall be mentioned. The Fraunhofer IPA has a strong background on automated cell culture technologies. The expertise, gained in the successful "tissue-factory" light-house project, let us rethink the overall process chain and overcome established principles. A concept that has a strong link to current industry 4.0 concepts and applies a seamless integration throughout the value-added chain will be presented. The main idea is to provide maximal transparency through digitalization and the design of smart automates. The interface to the customer-pharmaceutical company, regulatory board or consumer is the disruptive change with regard to state of the art attempts. Starting with the vision of full transparency down to the bench, the overall infrastructure and test processes need to be reconsidered.

Biography

Lena Schober completed her Engineering degree in Biotechnology from University of Applied Sciences Esslingen in 2009. Since 2009, she is working as a Research Fellow for the Fraunhofer Society. She owns particular knowledge and practical experience in Cell and Tissue Engineering and focuses on the "Development of automated cell application systems for research and clinical use". She thereby contributed to the Fraunhofer Project "Mass customized organ replicates-tissue engineering on demand" and advanced the transfer of the biological process to the automated system, also referred to as "tissue factory", and performed the validation of produced *in vitro* systems.

lena.schober@ipa.fraunhofer.de

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Acute toxicity test of dichromate potassium ($K_2Cr_2O_7$) in grey mullet (*Mugil cephalus*)

Abdolreza Jahanbakhshi[1] and **Elnaz Erfanifar**[2]
[1]Gorgan University of Agricultural Sciences and Natural Resource, Iran
[2]Offshore Fisheries Research Center Chabahar, Iran

The main aim of the present study was to examine the sensibility of marine fish *Mugil cephalus* to dichromate potassium ($K_2Cr_2O_7$) in the toxicity test programs. All fishes were exposed to ($K_2Cr_2O_7$) at various chosen concentrations 0, 5, 10, 20, 30, 40, 50, 55 ppm (range finding test). Then, fish were exposed to 6 concentrations of ($K_2Cr_2O_7$) (control, 60, 70, 80, 90, 100 ppm). Number of mortality was registered after 24, 48, 72 and 96 h. LC_{50} values were determined with probite analysis. The 96 hour LC_{50} value of ($K_2Cr_2O_7$) to the fish was found to be 83.07 ppm. By comparing the sensitivity of this metal to common reference toxicants, we conclude that grey mullet can be used as a suitable model for toxicity determinations in eco-toxicological studies. Further studies should examine other contaminants of this species to assess their suitability for detecting toxicity, as well as complex mixtures of pollutants, in order to develop aquatic ecosystem monitoring programs.

jahanbakhhsi@gau.ac.ir

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Biological effects of nanoparticles on fish

Zeinab H Arabeyyat
University of Hull, UK

It is important to develop early warning tools of nanoparticle-induced biological effects for aquatic species to be able to monitor any possible impacts. In this study, early zebrafish (*Danio rerio*) embryos have been experimentally exposed *in vitro* to 1.925 mg/L of 4 nm, 10 nm AgNPs and to silver ions (0.018 mg/L) alone, up to 96 hpf. Five targeted genes have been employed for analysis: Peroxisomal membrane protein 2 (Pxmp 2), hypoxia inducible factor (HIF), superoxide dismutase (SOD), mucosal secretion protein (Muc) and catalase (CAT) genes. A global approach employing suppression subtractive hybridization (SSH) has also been used in parallel to identify novel genes that may be involved in the fish embryo response as a result of exposure to nanoparticles. The results show that 4 nm AgNPs are taken up by zebrafish embryos at a concentration of 1.925 mg/L. AgNP uptake resulted in significantly up-regulated Pxmp 2 and HIF mRNA transcript levels in exposed embryos. An increased trend in up-regulation of *SOD* was also observed, while, Muc and CAT remained unchanged. No corresponding significant differences were observed in any of the transcript levels analyzed following exposure to larger sized 10 nm AgNPs or silver ion exposure alone. An up-regulation of solute carrier family 25, membrane 5 and Cytochrome c oxidase subunit I; and down-regulation of spermatogenesis associated protein 2 and Actin alpha, cardiac muscle lb mRNA expressions identified by SSH approach have also been observed. These results suggest that 4 nm AgNPs are available for uptake and, as a result cause changes in mRNA expression in developing embryos.

Biography

Zeinab H Arabeyyat has completed her MSc in Biotechnology from Jordan and is currently a final year PhD student in Aquatic Toxicology Research Group at the University of Hull in UK. She has attended many international conferences in Norway and local conferences in Jordan and UK. She is a Lecturer in the Faculty of Marine Sciences at the University of Jordan.

Z.H.Arabeyyat@2013.hull.ac.uk

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Anti-inflammatory effect and toxicology analysis of oral delivery quercetin nanosized emulsion in rats

Gabriela Hädrich
Universidade Federal do Rio Grande, Brazil

This study evaluates the advantage of the quercetin encapsulation in nanosized emulsion (QU-NE) administered orally in rats in order to demonstrate its anti-oedematous and antioxidant effects as well as its toxicity. The nanocarriers were prepared using the hot solvent diffusion with the phase inversion temperature methods. The nanocarriers physicochemical properties were then investigated. The anti-edematous activity was tested using paw edema in rats. In addition, NF-kB expression in subcutaneous tissue of the paws was accessed by immunohistochemistry while the lipid peroxidation was analyzed in the liver by malondialdehyde reaction with thiobarbituric acid. Hematological, renal and hepatic toxicity as well as the genetic damage were also evaluated. The results demonstrated that QU-NE exhibited pronounced anti-oedematous property comparable to drug diclofenac. This effect was associated with NF-κB pathway inhibition. The lipid peroxidation was also only reduced in rats treated with QU-NE. Besides this, no genetic damage, hematological, renal or hepatic toxicities were observed after administration of QU-NE. These results suggest that quercetin nanosized emulsion exhibits anti-oedematous and antioxidant properties and does not demonstrate toxic effects. This indicates that it has a potential application in the treatment of inflammatory diseases.

Biography

Gabriela Hädrich is pursuing her PhD from Federal University of Rio Grande, Brazil. She is a visiting PhD student at Martin-Luther Universität Halle-Wittenberg, Germany. She has completed her Master degree in Health Sciences in 2014 and has expertise in Nanotechnology applied to health and microbiology.

gabihadrich@yahoo.com.br

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Molecular nanoprobes and nanosensors: A new generation of biosensing nanoplatforms for toxicological and biomedical monitoring

Tuan Vo Dinh
Duke University, USA

This lecture provides an overview of recent developments in our laboratory for several plasmonic nanoplatforms and biosensing technologies that allow sensing of nucleic acid biomarkers (e.g., mRNAs and miRNAs) for toxicology research and biomedical diagnostics. MicroRNAs (miRNAs) have been implicated in post-transcriptional regulation of many gene expressions and control of different processes such as apoptosis, DNA repair, oxidative stress response, cancer and cellular development. In recent years, miRNAs have attracted great interest in the field of toxicology. When organisms are exposed to toxic species, miRNA expressions are altered, thus affecting mRNA transcription and protein translation and leading to adverse biological effects. Discoveries in miRNAs research have opened new insights in toxicology. We will discuss the development of a new generation of nanotechnology-based biosensing systems designed to detect miRNA biomarkers. The technologies involve interactions of laser radiation with metallic nanoparticles, inducing very strong enhancement of the electromagnetic field on the surface of the nanoparticles. These processes, often called 'plasmonic enhancements', produce the surface-enhanced Raman scattering (SERS) effect that could enhance the Raman signal of molecules on these nanoparticles more than a million fold. The SERS-based nanoprobe technologies, referred to as 'Molecular Sentinel' nanoprobes, use a label-free sensing modality for detecting miRNAs. In the field of biosensing of individual cells, a unique advance has been the development of optical nanosensors, which have dimensions in the nanometer (nm) size scale. Using lasers as excitation sources for these nanosensors, it has become possible to probe physiological parameters (e.g., pH), toxicants (e.g., carcinogens), exposure biomarkers (e.g., DNA adducts) and monitor molecular pathways (e.g., apoptosis) in a single living cell for toxicological research and assessment. These nanosensors lead to a new generation of nanophotonic tools that can detect the earliest signs of chemical exposure and health effect at the single-cell level and have the potential to drastically change our fundamental understanding of the life process itself. Examples of using these sensing tools for disease detection and toxicology research will be discussed. Spectrochemical detection using plasmonic nanomaterials and nanobiosensing technologies are definitely bringing a bright future to toxicological and medical research and could ultimately lead to the development of new modalities of environmental exposure sensing, early diagnostics, drug discovery and toxicological monitoring.

Biography

Tuan Vo Dinh is R Eugene and Susie E Goodson Distinguished Professor of Biomedical Engineering, Professor of Chemistry, and Director of the Fitzpatrick Institute for Photonics at Duke University. After completing High School in Vietnam, he pursued his education in Europe where he received a BS in Physics in 1970 from EPFL (Swiss Federal Institute of Technology) in Lausanne, Switzerland, and a PhD in Physical Chemistry in 1975 from ETH (Swiss Federal Institute of Technology) in Zurich, Switzerland. Before joining Duke University in 2006, he was Director of the Center for Advanced Biomedical Photonics, Group Leader of Advanced Biomedical Science and Technology Group, and a Corporate Fellow at Oak Ridge National Laboratory (ORNL). His research has focused on the development of advanced technologies for the protection of the environment and the improvement of human health. His research activities involve nanophotonics, biophotonics, nano-biosensors, biochips, molecular spectroscopy, bioimaging for medical diagnostics and therapy (nano-theranostics), toxicology research, personalized medicine and global health. He has received seven R&D 100 Awards for Most Technologically Significant Advance in Research and Development for his pioneering research and inventions of innovative technologies. He has received the Gold Medal Award, Society for Applied Spectroscopy (1988), and so on. He has authored over 400 publications in peer-reviewed scientific journals. He holds over 37 US and international patents, five of which have been licensed to private companies for commercial development.

tuan.vodinh@duke.edu

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