Spectrum Conferences & Expos

Abstract Book

ISTAP2023

International Summit on Toxicology and Applied Pharmacology

April 27-28, 2023 | Valencia, Spain

FOREWORD

Spectrum Conferences delightedly welcomes you to its International Summit on Toxicology and Applied Pharmacology (ISTAP2023) which is going to be held during April 27-28, 2023 in Valencia, Spain.

The meeting brings together World Class participants and young researchers looking for opportunities for exchanges that cross the traditional discipline boundaries and allows them to resolve multidisciplinary challenging problems that only a venue of this nature can offer. Through this event, you will be able to share the state-of-the-art developments and cutting-edge technologies in the broad areas of Toxicology and Applied Pharmacology.

We sincerely hope that ISTAP2023 serves as an international platform for meeting researchers from around the world, widen professional contact, and creating new opportunities, including establishing new collaborations.

We're looking forward to an excellent meeting with scientists from different countries around the world and sharing new and exciting results in Toxicology and Applied Pharmacology.

COMMITTEES

Organising Committee

Dr. Weiping Shao,	Sr. Director and Head of US GxP Testing Laboratories at AstraZeneca, USA
Prof. Sanjay K. Srivastava	Texas Tech University Health Sciences Center, USA
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Improve the Quantitation of Biologics in Biodistribution Studies and PK Analysis

Weiping Shao
Sr. Director & Head of US GxP Testing Laboratories at AstraZeneca, USA

Abstract
An understanding of therapeutic drug concentrations and pharmacokinetic (PK) profile in circulation and its target tissues and fluids is critical in determining its in vivo efficacy and safety. Measurement of drug concentrations in tissues and fluids, on the other hand, presents many challenges. One of the challenges is the variability from assays, sample collection and sample processing such as tissue homogenization, which results in inaccurate quantitation of drug concentrations. Normalization of drug concentrations can be a viable solution to address the issue. Here we present normalizing approaches to improve drug quantification in biodistribution studies as well as the determination of partition and PK profile of therapeutic drug at the pharmacologic site of action.

Biography:
Dr. Weiping Shao is currently Sr. Director and Head of US GxP Testing Laboratories at AstraZeneca, where he leads regulated bioanalysis and scientific innovation to support the development of biologics modalities from pre-clinical to clinical across all therapeutic areas. Weiping brings more than 20 years of experience and leadership in pharmaceutical /biotech industry, including his previous role as Vice President and Head of Biologics Services at a global CRO, Director and Head of Bioanalytical Operations at Regeneron Pharmaceuticals, Inc and Research Fellow at Merck. He has built and led cross-functional organizations that support biologics development, bioanalytical services and biomarker discovery. Weiping has published over 40 peer reviewed manuscripts/commentaries, filed US patents and co-authored industry Best Practices. He holds leadership roles at ISBER organization, chairs conferences and has given numerous presentations. He earned his Ph.D. from Nanjing University and completed his post-doctoral Fellowship in Biochemistry at University of California, San Diego.

Multi Residue Screening and Quantitation Method for 40 Toxicologically Significant PFAS plus 30 Internal Stable Isotopes in Fish and Baby Formula Using High Resolution-TOF-MSMS-MRM-HR Technique

Dan Safarpour,
CEO, Symbiotic Research, USA

Abstract
In recent years high resolution mass (HRMS) spectrometric multi-residue analytical methods have grown in interest and value within the industry. As regulations expand to target more chemical contaminants in plastics, food, feed, water, animal tissues, drug products, etc. at increasingly lower concentrations, the methodology used to screen and detect these compounds in regulated products and commodities must also advance. In this presentation, feasibility of utilization of high-resolution Time of Flight mass spectrometry equipped with liquid-chromatography/tandem mass spectrometry (LC-HR-TOF-MS/MS) as a positive identification and quantification of PFAS contaminants in food matrices. An AB SCIEX X500B Quadrupole Time-of-Flight (QTOF) Mass Spectrometer equipped with electro spray ionization (ESI) has been used in this work for the identification and quantification of targeted PFAS compounds that are known to be potentially harmful. The method development, which is still "Work in Progress", has been investigated to screen for these residues in foods. Additionally, while QTOF provides the benefit of accurate mass determination for compound identification, such method could possibly be adapted to any other HRMS platform with MS/MS capabilities. This method can be a valuable addition to the existing multi-residue analytical methods currently available in the literature.

Biography
Dr. Dan Safarpour received a B.S. in Chemistry in 1991 from the University of Arkansas, Fayetteville and a Ph.D. in Environmental Analytical Chemistry in 2001 from Rutgers University, Cook College, New Brunswick, New Jersey. Dr. Dan Safarpour started his professional career as residue chemist atAltheimer Laboratory of the University of Arkansas in Fayetteville, Arkansas. In 1993, he began employment with American Cyanamid Company, Princeton, New Jersey as an Analytical Chemist in the Toxicology Analysis laboratory.

Later, within Cyanamid Global Research Center, he moved to other research group called Metabolism, Residue, Environmental Fate and Eco-Toxicology (MREE) Group as a Residue Chemist/Study Director. In 2000, American Cyanamid Company was acquired by BASF Corporation, at which time he joined the Formulations Analysis Group. In September 2001, he joined Taxolog, Inc, a pharmaceutical/biotechnology startup company. As a group leader at Taxolog, he was brought on-board to build an analytical group capable of conducting formulations analysis support as well as metabolism and bioanalytical to determine metabolite structures to protect company IP on pharmaceutically active metabolites and co-drugs. Dr. Safarpour led his team in compiling analytical R&D and dossier preparation for filing several IND, CTX and aNDA in partnership with Pfizer corporation. Dr. Safarpour has been published in journals such as Journal of Pharmaceutical and Biomedical Analysis (JPBA), Journal of Chromatography, Electrophoresis, Journal of Associations of Officials in Analytical Chemistry (JAOAC) and Journal of Pesticide Science. Per invitation from US-EPA regulatory bodies, Dr. Safarpour has contributed a chapter on Application of Capillary Electrophoresis to Pesticide Analysis to the Encyclopedia of Agrochemicals. Dr. Safarpour has given numerous oral presentations in national and international conferences in the areas of separation sciences, process and formulations analysis, human and plant metabolism, bioanalytical, and residue chemistry. His presentations have focused on the use of cutting-edge technologies such as UPLC, HPLC, CE, and GC, as well as UPLC-MS-QTOF, HPLC-MS-Triple Quad platforms and CE-MS. Dr. Safarpour has chaired symposium in peptide-protein friendly instrumentations arena, judged poster presentations at ACS functions such as the Triangle Chromatography Discussion Group (TCDG). Since 2003 until 2015, Dr. Safarpour has served on the peer review committee for prestigious journals such as JPBA, JAOAC and Electrophoresis. In early 2009, Dr. Safarpour, with former colleagues, employees founded a new life sciences contract research organization called Symbiotic Research, LLC. In 2017, he sold Symbiotic Research to a German conglomerate-Tentamus GmbH. In 2018, together with Tentamus GmbH, Dr. Safarpour acquired animal research facility Genesis Midwest, LLC out of Wisconsin USA to enable Symbiotic Research to provide in-life and analytical package study services to its global Animal Health and Agrochemical clients. In 2014, Dr. Safarpour was hired by International Atomic Energy Agency (IAEA) Food Safety division as an “Expert Lecturer” to consult the agency by traveling to developing countries and guiding the subject nations on matters related to building laboratories and laboratory infrastructures capable of analyzing agricultural food products by LCMS and ultimately helping those nations to be able to export their raw agricultural products globally in an attempt to expand their GDP growth and aid in global food sustainability.

Toxicological Studies in the Development of Novel Therapeutics

Bram Ramjiawan
St. Boniface Hospital and Research Centre, Canada

Abstract

Every jurisdiction has requirements for the conduct of toxicology studies. These studies are a must prior to initiation of human testing (Phase 1 Trials), as well as during ongoing latter phase human studies. As these tests are vital for the development of novel therapeutic agents, their relevance, applicability, conduct, and results monitoring and reporting must be carefully looked into. The presentation will focus on the crucial elements that are required prior to clinical trial initiation and shall identify specific tests typically recommended for late phase clinical trials. Details on the type, design, conduct and considerations of bench and pre-clinical in vivo toxicological studies such as dose toxicity, teratogenicity, carcinogenicity will be discussed with a highlight on both scientific and regulatory requirements that need to be satisfied pre-trial. Ethical principles will also be presented with emphasis on how key toxicology results are to be handled in the case of inclusion in Institutional Review Board submissions and consent documents for participants, among others

Biography:

Dr. Bram Ramjiawan is the Director of Research, Innovation and Regulatory Affairs and Director of Research, Asper Clinical Research Institute at the St. Boniface Hospital and Research Centre in Winnipeg, Canada. Dr. Ramjiawan is responsible for the Office of Clinical Research which oversees and ensures that all clinical, regulatory and business issues are handled as required by National (Health Canada) and international agencies (EU, FDA). Prior to joining the hospital, Dr. Ramjiawan spent 15 years with the Government of Canada (National Research Council) as an Industrial Technology advisor who specialized in Life Sciences and Biomedical Technologies. Dr. Ramjiawan is a seasoned biomedical researcher that has contributed to the development of numerous biomedical technologies that have either been licensed to Multinational and National Companies or spun-off into stand alone successful Canadian business. Dr. Ramjiawan is an adjunct professor of Pharmacology and Therapeutics in the Max Rady College of Medicine, Faculty of Health Sciences at the University of Manitoba. He is also the co-chair of the St. Boniface Hospital Research Ethics Committee. Dr. Ramjiawan is an active member of many National and International organizations. At the international level, he is a reviewer for numerous bodies including the United States National Institute of Health and for the European Union Commission on Health Science and Ethics. Dr. Ramjiawan is on the editorial board of Numerous Scientific Journals.

Melanoma Therapy: Challenges and Opportunities

Sanjay K. Srivastava
Texas Tech University Health Sciences Center, USA

Abstract

Melanoma harboring BRAF mutations frequently develop resistance to BRAF inhibitors, limiting the impact of treatment. Here, we establish a mechanism of resistance and subsequently identified a suitable drug combination to overcome the resistance. Single treatment of BRAF mutant melanoma cell lines with vemurafenib or dabrafenib (BRAF inhibitors) alone or in combination with trametinib (MEK1/2 inhibitor) resulted in overexpression of Mcl-1. Overexpression of Mcl-1 in A375 and SK-MEL-28 by transfection completely blocked BRAF and MEK1/2 inhibitor-mediated inhibition of cell survival and apoptosis. Melanoma cells resistant to BRAF inhibitors showed massive expression of Mcl-1 as compared to respective sensitive cell lines. Silencing of Mcl-1 using siRNA completely sensitized resistant melanoma cells to growth suppression and induction of apoptosis by BRAF inhibitors. In vivo, vemurafenib resistant A375 xenografts implanted in athymic nude mice showed substantial tumor growth inhibition when treated with a combination of vemurafenib and Mcl-1 inhibitor or siRNA. Immunohistochemistry and western blot analyses demonstrated enhanced expression of Mcl-1 and activation of ERK1/2 in vemurafenib-resistant tumors whereas level of Mcl-1 or p-ERK1/2 was diminished in the tumors of mice treated with either of the combination. Biopsied tumors from the patients treated with or resistant to BRAF inhibitors revealed overexpression of Mcl-1. Interestingly, piperlongumine significantly suppressed the growth of BRAF-inhibitor resistant cell lines as well as tumor growth in vivo by inhibiting Mcl-1 and its upstream regulator STAT-3

Biography:

Dr. Sanjay K. Srivastava is a University Distinguished Professor and Chairman of the Department of Immunotherapeutics and Biotechnology, and Associate Dean for Graduate Programs at the Texas Tech University Health Sciences Center. He is also James 'Buddy' Davidson Endowed Professor of Pediatric Pharmacology and Oncology. He has extensive research experience in the field of cancer chemoprevention and therapeutics. Dr. Srivastava is a serial innovator with several patents to his credit. His inventive contributions are supported by an excellence in research. Named in Stanford University's list for the World's Top 2% Scientists for 2020 & 2021, Dr. Srivastava has a track record of being a productive scientist, authoring more than 160 research articles in high impact journals and holding an H-index of 57, demonstrating just how impactful his research contributions have been over the years. His research has been funded by National Cancer Institute or other agencies, and he has received numerous prestigious awards. The major focus of his laboratory is on delineating the signaling mechanisms responsible for

tumor growth, angiogenesis and metastasis in different cancer models including pancreatic, ovarian, breast, melanoma and glioblastoma. His recent research focuses on understanding the mechanism of chemotherapeutic drug resistance in melanoma, breast and glioblastoma. Forthelast10+ years, hehas also beenrepurposingexisting non-cancer drugsforcancertherapy. For example, his group has shown the anticancer effects of few anti-psychotic drugs for breast cancer, brain cancer, and pancreatic cancer therapy. He also showed the anti-tumor effects of anti-malarial and anti-helminthic drugs for drug resistant breast cancer. Dr. Srivastava has me ntorednumeroustrainees(undergraduatestudents,post- doctoralfellows andgraduatestudents), whoare nowestablishedresearchers/facultyat different places. His research has been highlighted by media and news agencies.

Identifying 'Missing' Drug Metabolites of Toxicological Importance

Donglu Zhang
Genentech, USA

Abstract

Toxicological and Pharmacological activities can depend on drug metabolites that are covalently bound to enzymes, receptors, and DNA targets. Practically, it is challenging to characterize and quantify these ‘missing’ metabolites because of their covalent natures. The talk will focus on biotransformation pathways and strategies to characterize these metabolites that were covalently bound to DNAs and proteins.

Biography

Donglu Zhang is a Senior Fellow in DMPK at Genentech. He is interested in applying drug metabolism studies in drug design and development of both small molecules and antibody-drug conjugates (ADCs). He received the Sir James Black Award for discovery of and original research on Eliquis from British Pharmacological Society (2018) and the Ondetti and Cushman Award for invention of mass defect filtering method (MDF) from Bristol-Myers Squibb (2007). He is on Editorial Board of Drug Metabolism and Disposition and Xenobiotica. He received his Ph.D. in Organic Chemistry from University of Utah under the direction of C. Dale Poulter.

Image Processing in Toxicology: A Review

Gayatri Shashikant Mirajkar
Arvind Gavali College of Engineering, India

Abstract

A basic component of clinical diagnostic judgement is the interpretation of cellular morphological changes in relation to fundamental knowledge of anatomy and physiology [13]. The establishment of test systems (assays) for assessing the effects of chemical substances on target cellular, molecular, or biochemical processes is one of the initial phases in drug development and toxicity assessment.Imaging makes it easier to characterise complicated cellular biology dynamics and enables researchers to evaluate a comprehensive view of the biological response to chemical exposures in the environment [1].

But high throughput imaging technologies for documenting cell morphology over time from each well of multi-well test plates have only lately become readily accessible (e.g., 96 – and 384 – well plates) [13].Even while these computers can now create thousands of images quickly, the results still require laborious and arbitrary human interpretation.Therefore, automating the interpretation and classification of numerous rapidly generated images is necessary for the successful integration of these technologies into a high-throughput process for toxicity screening.Deep Learning performed using Deep Convolutional Neural Networks can automate the phases of interpretation and categorization (DNNs).

In recent years, Deep Convolutional Neural Networks (DNNs) have revolutionised computer vision by performing a number of tasks at human-level levels, including the classification of objects in images [2–4], [16].Numerous computer applications, such as facial recognition [5–6], autonomous vehicles [7–9], astronomy [8–9], and agriculture [9], use DNNs.DNNs have numerous uses in biology and biomedicine because of their adaptability in application [10].

In [11] a method is proposed which processes pictures of light microscopy slides and successfully identifies differentiating stem cells. Convolutional neural networks are utilised. It was observed that the image-based results' accuracy was on par with that of results from conventional transcription-based approaches to detection. The method also had the benefit of being quick and affordable.

Deep learning was utilised by Jimenez-Carretero et al. [12] to automatically detect chemical toxicity using picture tests.From microscope images of fluorescently marked cell nuclei, the

technique was able to properly identify toxicity across a broad spectrum of toxicity mechanisms, even from medications with different modes of action than those the model was first trained on.

In [13], the automation of the image analysis of a significant number of images produced by photomicrographs from multi-well cell culture plates is proposed.Microscopy is frequently used in high-throughput chemical screening techniques to take these pictures.Manually analysing the numerous photos is a laborious and arbitrary task.A technique was created that automatically classifies digital assay photos using deep learning to automate this subjective and time-consuming manual process [13].To conduct binary and multi-class classification, a convolutional neural network (CNN) was trained [17].The binary classifier classified assay images with higher than 95% accuracy into healthy (comparison to untreated controls) and altered ("Healthy," "Intermediate," and "Altered") categories [13].

In order to identify the precise causal agent of a variety of fatal diseases, bacterial categorization is essential in medical science.Microbiologists have a difficult duty to complete: classifying bacteria that are spherical, rod-shaped, spiral-shaped, comma-shaped, or corkscrew-shaped, with diameters between 0.2 and 20 microns.The manual identification of bacteria requires accuracy and precision and is a deliberate, time-consuming, and hard operation.Phenotype and genotype typing schemes are two techniques for categorising microorganisms.These are utilised to ascertain the morphological and staining characteristics of the bacterium.Another method, phylogenetic analysis, is used to evaluate highly conserved genes among various species. This method created a phylogenetic tree and also shows how closely related various creatures are to one another [14].

Historically, algorithmic approaches have been used for image analysis to extract quantitative information from video microscopy data, but these methods are frequently labour-intensive, time-consuming, and computationally expensive [14].Quantitative digital microscopy has been significantly enhanced by data-driven methods using deep learning.Automatic, accurate, and quick image analysis is one of the benefits.DeepTrack 2.0, proposed in [14] can be used to design, train, and validate deep-learning solutions for digital microscopy [14].

An automated technique to identify and categorise bacteria from microscopic images using deep convolutional neural networks (CNN) used with a "Xception architecture" based on transfer learning is shown in [15].The authors suggest a smart microscope that uses five deep learning phases to classify epidemic pathogens using an effective convolutional neural network methodology.(1) A training dataset of the given images, (2) CNN training, (3) the production of testing data, (4) the CNN-generated model using testing data, and (5) the evaluation of the categorised photos.CNN can increase the accuracy of pathogen diagnosis, which now relies on manually adjusted feature extraction that is prone to human error.

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Biography:

Gayatri Mirajkar (Senior Member, IEEE) received the Bachelor of Engineering degree in Electronics Engineering from Karmaveer Bhaurao Patil College of Engineering, Satara, India, the Master of Technology in Electronics and Telecommunication Engineering from Dr Babasaheb Ambedkar Technological University, Lonere, India, in 2005, and the PhD degree in Electronics Engineering from Shivaji University, Kolhapur, India in 2014. She has published several papers in journals and conferences. She has presented her research contributions at IEEE International Conferences in Greece, Hong Kong. She is currently working as Professor in the Electronics and Telecommunication Engineering department of Arvind Gavali College of Engineering, Satara, India. Her research interests include biomedical image analysis, signal denoising, biometrics, cognition, restoration techniques.

Toxicological Effects of Textile Wastewater on Environment and Human Health

Ahmet Baba
Bogazici University, Turkey

Abstract

As the world water resources are getting in shortages as well Climate changes. Water must be under scope of all of us as world water resources are getting even more smaller and drinkable part is only 1% of all worlds including ocean and seas. Farming is getting so harsh and so hard tiresome work for human but while all need farming for food sources which requires more water. Brans and retailers in fast fashion in Textile world on earth are most water consuming and even highest carbon footprint with not so less emissions. At most stages water consumption has been lowered to best efficient points and unfortunately this led to highest concentration of hazardous chemicals in less water. As a result of all these water consumptions must be recycled and re-used in most sectors especially in textile as at farming stage for 1 kg of cotton 10's of thousands of tons of water is required and mostly 97% dumped in ground after use if not recycled. The water to be recycled and reused must be clear and clean in toxicological aspects as well for world resources and ground water health for drinking or farming like human consumption. So partially I have been working on toxicological results of textile wastewater after last 3 years of my further life and wanted to share one with you all. Chlorobenzene formation to be stopped in my target in today's presentation.

Biography:

I am a Chemical Engineer and Mechanical Engineering double degree and made masters on Environmental Eng. Waste water Recycle topics. Have been in market for 26 years , 14 years in Chemical &Mechanical Sectors lately last 12 years in audits ,training, projects in waste water RECYCLE and ZDHC trainings for Zero Discharge of Hazardous Chemicals to environment to keep away from toxicological trouble for flora and fauna, First Environmental and Chemical Toxicology auditor for INDITEX(ZaraGroup) on world and also approved auditor for 105 brands among HIGG FEM verifier section from america

Light as A Novel Environmental Pollutant – Relation With Behavioral And Ophthalmological Changes In Diabetes

Dusan Mladenovic
University of Belgrade, Serbia

Abstract

Light pollution is a global burden of the modern world because of a wide usage of artificial light sources, including cell phones and computers during the night. Light/dark cycle is a major synchronizer of the circadian rhythm of cell functions and physiological parameters, including body temperature, blood pressure, metabolism, hormonal secretion. The master circadian clock located in the suprachiasmatic nucleus of the hypothalamus receives the information on light exposure via retinohypothalamic tract and synchronizes peripheral clocks in virtually all cells via neural (sympathetic nervous system) and humoral signals (melatonin, cortisol). Melatonin is synthesized in the pineal gland in the darkness and apart from synchonizing action, melatonin also exerts antioxidative and antiinflammatory effect. Inhibiton of melatonin synthesis in conditions of light pollution increases the risk of various diseases, including obesity, diabetes, hypertension, anxiety, depression. We aimed to study the effects of shortened daily photoperiod (6/18h light/dark cycle) on diabetic retinopathy and anxiety-like behavior in streptozotocin-treated rats. Shortened daily photoperiod reduced neovascularization and gliosis in the retina of diabetic rats and increased perivascular aquaporin-4 expression. These effects were associated with reduced expression of proinflammatory cytokine genes (IL-1, TNF-α) in both neural retina and retinal pigment epithelium (RPE). Additionally, reduced exposure of diabetic animals to light increased the expression of cholesterol metabolism genes in RPE, including the key gene for cholesterol synthesis (HMGCR), intraretinal cholesterol exchange (APOE), and cholesterol degradation (CYP27). In the retina only the expression of APOE was increased after reduced exposure to the light. Visual cycle, the turnover of retinoids in the retina, was also accelerated by shortened daily photoperiod in diabetic rats, evident as an increase in lecithin-retinol acyltransferase (LRAT), RPE65, SOX9, and OTX2 expression in the RPE. Reduced exposure to light reduced anxiety-like behavior in diabetic rats estimated with open field test and elevated plus maze. Shortened daily photoperiod alleviates diabetic retinopathy in streptozotocin-treated rats by its anti-inflammatory effect, increased intraretinal cholesterol turnover, and acceleration of visual cycle. Additionally, reduced light exposure reduces anxiety-like behavior in streptozotocin-induced model of diabetes. Reduction of cell phone and computer usage during the night and prolonged sleeping synchronized with the

enviromental darkness could be additional lifestyle measures for the delay of the development of diabetic retinopathy and diabetes-associated anxiety.

Keywords:
Light Pollution; Diabetes; Retinopathy; Anxiety-Like Behavior.
This research has been supported by Bilateral Cooperation Call applied between TUBITAK (Turkey) and The Ministry of Education, Science and Technological Development of Serbia MoESTD.

Biography:
Dusan Mladenovic was born in 1980 in Belgrade, Serbia. He is employed as an Associate Professor at the Institute of Pathophysiology, Faculty of Medicine, University of Belgrade. He has completed his PhD thesis in 2014. in the area of Molecular Medicine. His areas of research include neurophysiology and epileptology and he was involved in translational studies in rat models of chemically-induced seizures and hepatic encephalopathy in the Laboratory for Neurophysiology, Institute of Medical Physiology, Faculty of Medicine in Belgrade. Additionally, he is involved in the research of the effect of circadian misalignment on diabetic complications. Dusan Mladenovic has an experience in international collaboration through the bilateral project related to brain disorders induced by an environmental pollutant lindane financed by The Ministry of Science and Technological Development of the Republic of Serbia and The Scientific and Technological Research Council of Turkey. In 2016 and 2017 he spent 10 months at Philipps University of Marburg, Germany, supported by the DAAD (Deutscher Akademischer Austauschdienst) Research Grant for Doctoral Candidates and Young Academics and Scientists. He is an author of 50 articles indexed in JCR list with 651 citations and Hirsch index 14. For his scientific work he was awarded the best young scientist at the Faculty of Medicine, University of Belgrade in 2018. He was also a supervisor of the first international joint PhD thesis at the Faculty of Medicine, realized in a collaboration between University of Antwerp and University of Belgrade.

Antibiotic Residues in Milk – A Global Health Hazard?

Ana Vlăsceanu
Carol Davila University of Medicine and Pharmacy, Romania

Abstract
Usage of antibiotics in food intended for human consumption must not be approved if it could lead to the deposition of residues in meat, milk, and eggs. When using antibiotics for the treatment and prevention of animal diseases, a withholding period must be observed until the residues are minimal or undetectable. Concern over antibiotic residues in animal-derived foods arises in two ways: first, because they pose a risk to human direct toxicity, and second, because they raise the possibility that even low doses of antibiotic exposure could change the microflora, result in disease, or lead to the emergence of resistant strains that would render antibiotic therapy ineffective in clinical situations. We investigated the prevalence of antibiotic residues in pasteurized and unpasteurized milk as well as the presence of bacteria resistant to antibiotics in unpasteurized milk distributed in South Romania. The milk samples were collected from retailers, street vendors, or vending machines and examined using Antic Fast Lateral Flow Rapid Test Kits for the presence of tetracycline and -lactam residues. Presumptive E. coli were counted using inoculated agar without and with antibiotics (ampicillin and tetracycline) based on bacterial cultures (colony forming units per ml, CFU/ml). When food safety rules are not strictly followed to, the use of antibiotics in veterinary medicine and not following the necessary withdrawal times may represent a threat to public health. A significant future hazard to human health is predicted to be the growth of antibiotic resistance among pathogens, in addition to the other negative health effects that exposure to veterinary medications may have.

Biography:
In 2016, Mrs. Asst. Univ. Ana Maria Vlăsceanu. Pharm., PhD started working as an assistant professor at the University of Medicine and Pharmacy of Bucharest's Department of Toxicology. Between 2014 and 2015, she was a PhD student with a scholarship within the Excelis Project (Excellence in scientific, interdisciplinary, doctoral, and postdoctoral research, in the economic, social and medical fields - Excelis, POSDRU/159/1.5/S/138907) (scholarship obtained through competition, project completion in first place). In 2015, she graduated with a master's degree in pharmacology and toxicology from the University of Medicine and Pharmacy in Craiova, Faculty of Pharmacy (grade 10), dissertation: "The influence of the constituents of cigarette smoke on the metabolism of some xenobiotics". She became a specialist pharmacist in the Pharmaceutical Laboratory specialty following training courses through residency in

the period 2016-2019 and passing the exam in the September 2019 session. She obtained the scientific title of PhD in the field of Pharmacy, specialty Toxicology, defending, in 2019, the doctoral thesis, appreciated with the Suma cum laude distinction. The didactic activity consists of the guidance of practical works and the assessment of students from the IV and V study years, the guidance of bachelor's works. The scientific and research activity of Mrs. Asst. Univ. Ana Maria Vlăsceanu. Pharm., PhD includes 3 book chapters published as a co-author in international publishing houses, a book/study aid for students, published as a co-author in a national publishing house recognized CNCSIS, 11 published works (of which 8 in ISI rated/ indexed journals), 5 papers presented at international scientific events, published as abstract in ISI indexed journals, 3 papers presented at other scientific events. Mrs. Asst. Univ. Ana Maria Vlăsceanu. Pharm., PhD attended a series of specialization courses in Toxicology and Pharmacy (European Society of Toxicology in Vitro, ESTIV, Applied In Vitro Toxicology Course, April 14-19, 2019, Bucharest; "Currents in medico-legal toxicology", Murighiol, May 25, 2017, course held by the board members of The International Association of Forensic Toxicologists, TIAFT, within CNML 2017; "Multidisciplinary pharmacotherapeutic approach"). The preoccupation for the scientific activity is also supported by the two editions of the National Congress of Toxicology, with international participation (Bucharest, Romania 2015 and 2017), that Mrs. Asst. Univ. Ana Maria Vlăsceanu Pharm., PhD contributed as President of the Organizing committee. The research carried out in the scientific activity focused on areas such as pharmacotoxicological testing methods (experimental models for testing the action and toxicity of some medicinal or toxic substances), Food Safety, spectrofluorimetric studies on cell suspensions, following changes in some cellular parameters, addiction (analytical diagnosis, optimization), Ecotoxicology.

Direct Aqueous Analysis of Poly- and Perfluoroalkyl Substances (PFAS) in Drinking and Bottled Water

Daniel McMillan
Sr Market Development Manager, EMEAI at SCIEX, UK

Abstract

PFAS compounds are ubiquitous in our environment due to overuse and their lack of breakdown, ensuring that this will be a challenge for decades to come. Therefore, it is imperative to provide rigorous and sensitive analytical testing to regulate these compounds and try to limit their possible effects on human health.

In December 2020, the European Parliament and Council of the European Union released a new directive that sets the limit of PFAS in drinking water to 0.5 µg/L for all PFAS compounds identified, and 0.1 µg/L for a subset of PFAS compounds that are particularly concerning for humans. The difference between the limits is dependent on a list of compounds stated within the directive. The 0.1 µg/L limit applies to the compounds included in this list, which contain a perfluoroalkyl moiety with 3 or more carbons (i.e., –CnF2n–, n ≥ 3) or a perfluoroalkylether moiety with 2 or more carbons (i.e., –CnF2nOCmF2m–, n and m ≥ 1). The 0.5 µg/L limit applies to all PFAS compounds in total. This method is suitable for drinking water, surface water and groundwater. Testing of surface and ground water is important to ensure that these water sources are not contaminated and that drinking water sources are not affected.

In this method sub-parts per trillion (ppt) levels of detection for 26 PFAS compounds was achieved with LOD values of 0.2 ng/L in diluent and calculated method detection limits in drinking, ground, and surface water ranging between 0.06 ng/L and 1.12ng/L.

Biography:

Dan has been working in the MS industry for over 20 years as an instrument and applications specialist and is now responsible for developing the food, environmental and forensic markets throughout the EMEAI region. He has worked with major research and regulatory organisations to develop new applications in line with legislation, traditionally in the area of contaminant analysis. Recent changes in the requirements imposed on and the challenges facing laboratories are constantly evolving, and Dan's role is now primarily to ensure Sciex produce relevant solutions and to promote them in the industry.

PFAS - Food Safety, New Regulations and Toxicological Aspects

Ariane Cofré Espinoza,
Bilacon, Germany

Abstract

PFAS (per- and polyfluoroalkyl substances) are a group of man-made chemicals that have been used in a wide range of industrial and consumer products, including food packaging, cookware, and firefighting foam. These chemicals are of concern due to their persistence, bioaccumulation, and potential health effects.
Their ubiquitous occurrence and ability to enter the foodchain have made the non-polymeric PFAS an important focus for food safety laboratories.
In this presentation, we will focus on the perspective of food safety regarding PFAS, including the new legislation within the EU. As a food safety laboratory, one of our tasks is to implement these regulations by developing and validating analytical methods, and by monitoring food samples for PFAS contamination.
We will discuss the development of new analytical approaches for PFAS detection in foodstuff and the necessity for lower limits of quantification (LOQs) in food samples. PFAS are challenging to detect and quantify in food matrices, and many conventional methods have limited sensitivity and accuracy. As a result, there is a growing demand for more sensitive and selective analytical methods, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), that can detect and quantify PFAS at low levels in complex food matrices.
Our findings in different food categories illustrate the exposure by food intake.
Additionally, we will highlight the toxicological aspects of PFAS, by concluding the findings of the European food safety agency (EFSA) including their immunotoxicity and further potential toxicological endpoints. By understanding the current challenges and advancements in PFAS research, we can better protect public health and improve food safety regulations.

Biography:

Ariane Cofré Espinoza is a young scientist who has devoted her academic and professional career to the field of toxicology. She earned her undergraduate degree in Chemistry at Freie Universität Berlin and decided to change for her master's degree to Toxicology at Potsdam. Throughout her studies, the focus was on the area of food toxicology, contaminants, and analytics. Since June 2021, Mrs. Cofré has been working at Bilacon, where she specializes

in the toxicological and regulatory assessment of contaminants in foodstuffs. Her work is focused on ensuring that food products are safe for consumption by assessing the analyzed levels of various contaminants, including heavy metals, pesticides, and other natural and man-made contaminants.

The Role of Analytical Chemistry in PFAS Environmental and Toxicological Issues; Past, Present and Future

Charles R. Powley,
Chief Scientist at STRIDE Center for PFAS Solutions, USA

Abstract

Per- and polyfluorinated alkyl substances (PFAS) are commonly referred to as "forever chemicals that are everywhere" due to their long persistence and poor adsorption to most surfaces due to their surfactant nature and non-stick properties. The documentary "The Devil We Know" and the movie "Dark Waters" have highlighted the specific instance of perfluorooctanoic acid (PFOA) contamination in the Parkersburg, WV, USA area. However, there are over four thousand known PFAS, most of which we know little or nothing about in terms of health effects. The commercialization of liquid chromatography – tandem mass spectrometry (LC-MS/MS) with electrospray ionization around the year 2000 finally provided analysts with a quantitative tool that could detect levels of PFAS in water at part per trillion (ppt) levels, and at ppb levels in soils, sludges, sediments, and biota. Application of LC-MS/MS by academic, commercial, and industrial laboratories soon revealed how ubiquitous these compounds were in surface and ground waters, and even in human blood.

Targeted analysis of 40 or more PFAS using LC-MS/MS has become common, with use of stable isotope internal standards and some novel sample preparation procedures for concentration and purification. Significant challenges involve contamination from a wide variety of fluorinated surfactants and fluoropolymers that can be introduced at all stages of the analysis, from sampling to instrumental determination. Non-target analysis of PFAS is a current growth area with high resolution mass spectrometry yielding particularly useful information, in addition to other approaches both established and under development. The goal is often source identification, which in many cases is not possible due to the wide variety of potential origins over the 70-year history of use. The current state of the art with applications from our laboratory and future directions will be presented.

Keywords:

PFAS; Mass Spectrometry; Targeted Analysis; Non-targeted Analysis

Biography:

Charles Powley is the Chief Scientist at the Center for PFAS Solutions, which is a research lab focused on analysis and remediation of PFAS in drinking water and the environment. He is an analytical chemist with over 35 years of experience in the development and application of analytical methods for trace determination of environmental pollutants and pesticides in water, soil, plants and animal materials. He has published numerous methods in peer-reviewed journals that have become the basis for regulatory and commercial environmental monitoring. He obtained a Ph.D. in analytical chemistry from the University of Illinois followed by postdoctoral research at the University of Georgia.

Development of Long-Acting Delivery Formulation for Artemisinin Using Site-Specific Isopropylation of Parent Molecule

Ilya Tsyrlov
Founder/President, XENOTOX, Inc., Scarsdale, USA

Abstract

A sesquiterpene endoperoxide lactone, artemisinin (AM), has become first-line natural antimalarial drug highly efficient in areas of multidrug resistance. The AM family compounds are characterized by a short half-life. To prevent development of the resistance, they are being used with one or two long acting blood schizontocidal drugs with different biochemical targets in the parasite. However, a widely utilized combination therapy was, in addition to reported adverse drug interactions, attributed to much lower efficacy of AM. A unique 1,2,4-trioxane ring is essential for activity of the parent substrate, as all known AM metabolites were inactive due to the endoperoxide bridge has been reduced to an epoxide. It was reaffirmed, both in vivo and in human liver microsomes that AM to be principally metabolized by CYP2B6 isozyme. Previously, under similar circumstances of highly potent parent drugs, and the CYP2B6 demethylation them into non-active products, we had developed site-directed modification of a substrate molecule by substituting its methyl groups with isopropyl groups. The latter create steric hindrance at CYP2B6 active site thus affecting ligand binding and lowering catalysis. Such strategy was applied in this study. While AM is biosynthesized in Artemisia annual plant extracts from mevalonic acid via dimethylallyl and isopentenyl pyrophosphates, here C-2 dimethylallyl groups at pyrophosphate were substituted with isopropylallyl groups. Isopropylartemisidin (IPAM) molecule appears to retain an intact 1,2,4-trioxane ring incorporating an endoperoxide bridge determined by a specific LC-MS/MS assay. The IPAM was incubated with human liver microsomes from eight different healthy donors, and concentration-time data were assessed by a first-order depletion model. With correlation to the metabolic rate constants for CYP2B6 probe substrates, efavirenz and bupropion, our data revealed that IPAM was metabolized by CYP2B6 at least 12-13 times slower than AM. Using procedure described by Robert et al. (2005), the hydroxylated and glucuronyl-conjugated derivatives of covalent heme adducts were determined in urine of Plasmodium infected mice by means of LC-MS. Namely, the amounts of covalent heme-drug adducts were identically high in infected mice treated with 40 nM AM or 40 nM IPAM, compared to mice treated with 40 nM AM metabolites lacking trioxane ring endoperoxide bridge.

Keywords:
Antimalarial toxicity; Artemisinin; Isopropylartemisidin; CYP2B6

Biography:
Ilya B. Tsyrlov, MD, has completed his PhD in Biochemistry at the age of 27, and thereafter – a higher degree Doctor of Science in Molecular Pharmacology. He has been working as Group leader, Head of the laboratory, Department chair at Russian Academy of Science. In the United States, Tsyrlov served a Senior Scientist at NCI/NIH, and a Research Professor at Mount Sinai School of Medicine. Since 2005, a President/CSO of the XENOTOX, Inc, USA. Incepted and developed the Xenobiotical Virology, an interdisciplinary biomedical field, and also studied site-specific modifications of analgesics, synthetic opioids and antimalarials thus developing long-acting drug delivery formulations. He is the author of 6 monographs and 300+ peer reviewed publications, and has been serving as an editorial board member of reputed journals.

Effects of Third Hand Smoke in Health

Manuela Martins-Green,
University of California, USA

Abstract

Cigarette smoking remains a highly significant health threat for smokers and nonsmokers alike and Second-Hand Smoke (SHS) is much more toxic than directly inhaled smoke. Recently, a new and potentially even greater threat has been discovered. Third Hand Smoke (THS), the accumulation of SHS on environmental surfaces, becomes progressively more toxic with time. We have shown the effects of THS on multiple organ systems. THS exposure of just-weaned mice under conditions that mimic exposure of infants/children living in the houses of smokers leads to propensity for fatty liver disease, lung fibrosis, impaired healing, and results in hyperactive behavior. We have also shown that THS-exposed children display levels of NNAL, a known carcinogen, similar to those of our mouse system. These data, combined with emerging correlations of health problems in children exposed to THS, strongly suggest that those in the homes of smokers are at significant risk for developing liver, lung and healing problems and neurological disorders that impact behavior.

Biography:

Dr. Martins-Green is Professor of Cell Biology in the Department of Molecular, Cell and Systems Biology at the University of California, Riverside. She came to the US from Portugal on a Fulbright Fellowship and received a PhD in Zoology with emphasis in Developmental Biology from the UCD Dec 1987. She then held a postdoctoral fellowship at the LBNL and then received a 3-year NRSA from NCI, and was Adjunct Assistant Professor at Rockefeller University before joining the UC Riverside faculty in 1993-present. Research: Professor Martins-Green is an internationally known researcher in the field of response to injury (including injury caused by tobacco toxins), wound healing and tissue engineering and pioneered the role of chemokines in wound healing and angiogenesis. She has also developed a murine model of chronic wounds to study of the basic cell and molecular mechanisms of chronic wound initiation and development. Her research has been funded by NCI, NIGMS, NAIAD, AHA and TRDRP and she has served on review panels for several agencies, including NIH, DOD and AHA. More on the research in the Biosketch. Honors/Awards Highlights: In addition to her Fulbright Fellowship for PhD studies in the US, her honors include Postdoctoral NRSA 1989-1991, other significant honors and awards include Member of the Standing Committee on Women in Cell Biology of the American Society for Cell Biology (2001-2006) and of the

Advisory Board for the California Tissue Engineering Meeting and of TERMIS. Associate Editor of several journals through the years. She was Chair of the UCR Academic Senate (President of the Faculty) 2004-2006, a member of the committee to hire the new Chancellor at UCR (2008), a member of the All Campus Committee to develop a UC School of Global Health (2006-2010) and on the Board of Director of the Institute of Global Health (2010-2016). She also served as the Chair of the UCR Academic Senate Committee on Diversity and Equal Opportunity and served on the equivalent UC-wide committee. She was appointed to the UCR Chancellor's Council on Climate, Culture and Inclusion (2010-present). In 2008-2009, she won both the Distinguished Service Award and the Innovative Teaching Award for UCR and in 2010 was elected fellow of AAAS. Member of the Wound Healing Society Board of Directors 2011-2014. Was recently elected to the Board of Director of the Wound Healing Foundation as Vice-President for Research 2017-. Was Chair of the Department of Molecular, Cell and Systems Biology 2017-2021. More recently, she received the UC Oliver Johnson Awards for her leadership accomplishments at the UC wide system (2020), received the Wound Healing Society distinguished service award (2021) for leadership in the Wound Healing Society, was included in "Mulheres na Ciencia" in Portugal (2021) and just received the Chancellor's Award for Excellence in Undergraduate Research and Creative Achievement (2022).

Efficacy and Purpose of Drug Repositioning in Cancer

Sanjay Gupta,
Case Western Reserve University, USA

Abstract
Drug discovery and its development for use in the clinic is an expensive and time consuming process. Drug repositioning is the identification of new therapeutic purpose for clinically approved drugs and is more affordable and easily achievable than the drug discovery process. Numerous strategies have been developed for drug repositioning including computational methods to delineate disease mechanisms, decipher signalling pathways, off-target effects and targeted pathways to understand mechanisms of action of drugs. Mechanism-based drug repositioning approaches consider the heterogeneity and complexity of disease whereas reducing the inefficacy and toxicity caused by inter-individual variability. For the last several years our laboratory has worked on drug repositioning combining clinically approved drugs for their synergistic response in cancer therapy. Firstly, we explored the pathways which are altered during cancer progression or due to therapeutic resistance along with agents which are clinically approved for targeting these specific pathways. Our results have identified Akt, NF-κB/p65/RelA, Wnt/β-catenin and EZH2, a subunit of the Polycomb-Repressive Complex 2 as potential therapeutic targets for treatment or in overcoming drug resistance to antiandrogen therapy in prostate cancer1-4. In addition, we have also repurposed clinically approved drugs targeting metabolic pathways in prostate and breast cancers5. Combination of simvastatin, a class of cholesterol lowering drug and metformin, a drug commonly used for treatment of type 2 diabetes significantly and synergistically reduced cell viability and metastatic properties of cancer cells, with minimal adverse effects on normal cells. Apparently, the combination showed minimal toxicity and is similar in efficacy as the chemotherapeutic drug, docetaxel. Our presentation will highlight these findings and will provide recommendations that could accelerate the realization of the full potential of drug repurposing and its future clinical applications.

Keywords:
drug repurposing; combination therapy; therapeutic targets; signalling pathways

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Biography:

Dr. Sanjay Gupta is a Professor and holds Carter Kissell Endowed Chair in Urologic Oncology in the Department of Urology at Case Western Reserve University and the position of Research Director at the Urology Institute, University Hospitals Cleveland Medical Center. He also holds secondary appointments in the Departments of Pharmacology, Pathology, Nutrition and Division of General Medical Sciences at Case Comprehensive Cancer Center. Dr. Gupta had a joint appointment as Research Scientist from 2015 to 2020 at the Louis Stokes VA Medical Center, Cleveland, Ohio. Dr. Gupta obtained faculty position in 2002 at Case Western Reserve University, School of Medicine.

Toxicity of Nanowires and Nanoparticles: Impact of Shape vs. Chemistry on Cell Biomechanics and Internalization

Laurent Charlet
University of Grenoble-Alpes, France

Abstract

Nanomaterials, wethernano particle (NP) ornanowires (NW) interact with cells and organisms in complex ways that can lead to cellular dysfunction, inflammation, or cell death. Here we discuss metallic selenium NP (SeNP), as potential anti-cancer agentin the treatment against resistant cancers such as ovarian cancers, and silver NW (AgNW) for their cytotoxicity towards human skin, as AgNW based flexible conductive transparent networks are considered for future touchscreen displays, paper printed electronics and medical devices and textiles. Methods include standard toxicity tests, atomic force microscopy (AFM) cell membrane stiffness and membrane roughness tests, and synchrotron-based X-ray tomography.

To enhance their biocompatibility and bioavailability, serum albumin- or chitosan-coated SeNPs have been used. They were proven to be well tolerated in vivo at doses that are toxic as soluble Se, while clinical trials have failed to showany chemotherapeutic value of selenium at safe and tolerated doses (<90 µg/day). SeNP cytotoxicity on two ovarian cancer cell types (SKOV-3 and OVCAR-3)was shownto be effective in inhibiting cell growth, with contrasting nanomechanical responses, with regard to surface roughness and membrane stiffness, two properties which increase isassociated with decreased metastatic potential. We further demonstrate a novel role for selenium:while inducing thioredoxin reductase expression, ROS activity and cancer cell cytotoxicity, SeNPscause significant increases in histone 3 methylation, a methylation involved in the activation and repression of gene expression. Therefore a fundamental role for selenium in these epigenetic processes, is demonstrated for the first time for an epigenetic process (Toubhans et al., 2023).

While round AgNPare (like SeNP) quite soluble and been used for more than 70 years as bactericide in aid bands, hospital paint and door handles, few studies address the cytotoxicity of AgNWalthough AgNWsare attractive materials that are anticipated to be incorporatedinto numerous consumer products such as textiles, touchscreen display, paper printed electronics and medical devices thatcould be in direct contact with skin. Our study shows that AgNW are

rapidly and massively internalized inside cells leading to dose-dependent cytotoxicity that was not due to Ag+ release. A material property, nanowire-bending stiffness - function of NW diameter- controls the cytotoxicity of AgNWs to skinhumancells. Both 30- and 90-nm-diameter AgNWs are readily internalized by cells, but thinner NWs are mechanically crumpled by the forces imposed during or after endocytosis, while thicker nanowires puncture the enclosing membrane and release silver ions and lysosomal contents to the cytoplasm, thereby initiating oxidative stress (Lehmann et al, 2019). This finding extends the fiber pathology paradigm and will enable the manufacture of saferproducts incorporating thinner AgNWwith similar critical touchscreen CTN performance parameters, namelyelectrical conductivity and optical transparency.

These observations provide important new insights into the opposite effect of selenium nanoparticles and silver nanowires. Beyondthe classic antioxidant effect of selenium, SeNP novel histone methylation effects offer an exciting opportunity for futureovarian cancer therapy. On the contrary, AgNW toxicity is not due to ionic release (inhibited by sulfide coating formation within the cell) but rather to a a fiber punctuating, which can be avoided in massive use of touchscreens, by the use of thinner - less toxic-nanowires.

Lehmann, S.G., et al. (2019) Crumpling versus Puncturing: A Biomechanical Threshold for the Acute Cellular Toxicity of Silver Nanowires Proc. Nat. Academy of Sciences 116 (30): 14893–14898
Toubhans, B.,et al.(2023) Selenium nanoparticles modulate histone methylation via lysine methyltransferase activity and S-adenosylhomocysteine depletion. Redox Biology (https://doi.org/10.1016/j.redox.2023.102641)

Biography:

Laurent Charlet. Distinguished Professor in Bio-nano-geochemistry atISTerre, University Grenoble Alpes (UGA), France, he earned an Engineering degree in France, and a Ph.D.in Soil and Environmental Sciences at the University of California, USA, followed by two postdocs in Switzerland (EAWAG and Uni Bern). He created the Environmental Geochemistry laboratory at ISTerre and brought it into the global spotlight by performing research at drastically different scales: (i) large-scale multidisciplinary field investigations (on the fate of toxins such as mercury in Amazonian forest and arsenic in SE Asian deltas) and (ii) molecular level investigations at synchrotron facilities(µXAFS, ESR, Mössbauer), particularly ESRF, France, with a special focus on toxicology, chemical issues of importance to human health particularly related to redox-active trace elements, as a basis of risk assessment Public Health Policy. He is the holder of the CNRS Silver Medal for Excellence in Research, an Honorary chair at the University of Swansea (UK), an Honorary member of the Institut Universitaire de France, and 10 years long International Research advisor to the UGA Chancellor. He is presently an Affiliate to LBNL,

Berkeley (USA) and Adjunct Professor at the University of Waterloo (Canada) and Central Michigan University (USA), and has been visiting professor at UC-Berkeley (US), EPFL-Lausanne (Switzerland), and Uni. Utrecht (The Netherlands).His research was published in 283 primary research publications, cumulating above 11,000 citations and corresponding to an h-index of 77.

State-of-the-Art for Assessing Occupational Exposure during Pharmaceutical Manufacturing Process

Mar Crespo
CEO, TOXICONSULTANT S.L., Spain

Abstract
Highly potent Active Pharmaceuticals Ingredients (HPAPIs) are compounds that elicit a biological response at a very low dose.Manufacture, quality controland R&D laboratories must take into account the particularly dangerous nature of these active compounds.Occupational exposure limits (OELs) and Occupational Exposure Bands (OEB) serve to protect workers exposed to hazardous chemicals and Active Pharmaceuticals Ingredients (APIs).In order to define the OEL and OEB, documented review process of the literature, followed by sorting of data into either controlled laboratory in vivo, in silico/read-across, mechanistic/in vitro, or epidemiological/field data categories to estimate points of departure and uncertainty factors (UFs) should be considered.Nevertheless, to assess the exposure, the occupational toxicologist must define exposure scenarios for each manufacturing step. Considering that the air concentration of the API may vary depending upon operational conditions (e.g., compression, weighting, mixture), specific risk should be assessed on case by case. The TIER 2 tool ART 1.5 validated by the European Chemical Agency (ECHA) is useful to predict in different scenarios of manufacturing the airborne concentration of the API. The TIER 2 approach takes pharmaceutical production site specific input as physical state of the API, dustiness, quantities of API, etc. On the other hand, for a substance that is not respirable, the results from oral toxicity studies can be applied directly in an extrapolation to the inhalation route without the need to take account of bioavailability. The dosimetry model MPPD predicting the fractional deposition in the respiratory tract could permit both bioavailability adjustments and the most correct election of a point of departure (PoD) as the toxicological point to an estimated low effect level or no effect level. Definitely, the State-of-the Art of combining Hazard (theorical) and Exposure (practice) for risk management could support decision on prevent, control, or reduce exposure of workers from a more realistic approach.

Keywords:
Occupational exposure; Highly potent Active Pharmaceuticals Ingredients; ART 1.5; MPPD.

Biography:
Mar Crespo is a pharmacist, MSD in Toxicology, ERT by EUROTOX, with more than fifteen years of successful experience in developing clinical and preclinical reports for the pharmaceutical industry. She is CEO at TOXICONSULTANT S.L. Mar specializes in Occupational Exposure and her background both in clinical and preclinical fields contribute to provide a High-Quality criteria for Risk Assessment . In addition, her knowledge in production

areas inside the pharmaceutical industry help her to have a more realistic view of how to incorporate an API in multiproduct facilities under the point of view of safety and hygiene. Currently, she is a student in the Doctoral Program in Life Science at the Universidad de Alcalá de Henares (UAH) writing her thesis in occupational toxicology. She is also a Professor in the International Master in Toxicology (Mastertox) by Ilustre Colégio Oficial de Químicos de Sevilla (Spain) and a Master Tutor in "Toxicologie Humaine Evaluation risques et Vigilance" for the Université Paris-Saclay and Université de Paris.

The DPP-4 beyond the Glycemic Control: Focus on Renal Cells and Macrophages

Elisa Benetti
University of Turin, Italy

Abstract

Dipeptidyl-peptidase (DPP)-4 is the pharmacological target of gliptins (DPP-4i), drugs commonly prescribed for the treatment of type 2 diabetes (T2DM). However, DPP-4 is involved in many cellular processes, thus suggesting the existence of pleiotropic properties for gliptins. In particular, it has been suggested that DPP-4i could exert beneficial effects in the kidney (the tissue with the highest DPP-4 activity/mg protein) and could have anti-inflammatory properties. Indeed, it is known that DPP-4 could modulate inflammation, in particular through its soluble form (sDPP4) that directly engages immune cells. However, to date, whether these pleiotropic effects contribute to the therapeutic potential of gliptins deserves further investigation.

This study aimed: (i) to investigate the potential modulation of DPP-4 activity/release in tubular renal cells (the renal cells with the higher level of DPP-4) in the presence of physio-pathological stimuli; (ii) to study the effects of gliptins on the shedding of DPP-4 and the growth of human proximal tubular renal cells; (iii) to evaluate the presence of DPP-4 and the effects of two inhibitors, linagliptin(L) e sitagliptin(S), on human macrophages, cells that play a crucial role in the inflammatory response, in which the effects of DPP-4i remain to be clarified.

The release of soluble sDPP-4 (sDPP-4) was evaluated by ELISA in cell-conditioned media of Primary Renal Proximal Tubule Epithelial Cells (RPTEC) in the absence/presence of physio-pathological stimuli (i. e. angiotensin II [Ang II], histamine, TGF-β). THP-1 monocytes were differentiated into macrophages and polarized in M1 (LPS+IFN-γ) or M2 (IL-4+IL-13). Cell migration was evaluated by Boyden chamber assay, DPP-4 expression by western-blot, and its activity by measuring the cleavage of a specific substrate. Macrophages phenotype marker expression was evaluated by Real Time-PCR; pyroptosis by LDH assay in macrophages triggered by LPS/ATP.

The physio-pathological stimuli tested showed not significant modulation of DPP-4 activity in RPTEC. However, Ang II was able to induce a significant increase in sDPP-4 in the conditioned

media (Ang II: +53±56.5 and +60.8±54.5 $p<0.05$, n=7, respectively for ELISA and activity assay). The activity of DPP-4 was detected in all the macrophages phenotypes. Notably, the pro-inflammatory M1 phenotype showed the higher presence of sDPP-4 in the conditioned media. Like in RPTEC, Ang II positively modulated its activity ($p<0.05$). Notably, DPP-4i were able to modulate macrophages polarization and migration. In particular, gliptins induced the gene expression of M2 phenotype markers (CD206: 764.7±107 for L and 729.8±129.1 for S, $p<0.001$ vs basal 100±15%; CCL22: 261.6±7.0 for L and 223.1±24.6 for S, vs basal 100±71%, respectively $p<0.01$ and $p<0.05$) and a parallel promotion of M2 migration with a maximum effect at 100nM for L (185.8±44.03 vs basal 100±27% $p<0.05$, n=5) and at 10□M for S (198.4±46.1 vs basal 100±27%, $p<0.01$, n=5). On the contrary, the ability to migrate of M1 cells was decreased (54.2±9.4 for L100nM vs basal 100±9%, $p<0.001$ and 76.5±11 for S10□M vs basal 100±9%, $p<0.05$, n=4). In addition, L and S, respectively at 100nM and 10□M, were able to reduce pyroptosis induced by NLRP-3 activation.
In conclusion, our data indicate that DPP-4 inhibitors could exert beneficial effects against the low-grade inflammation linked to T2DM, with a mechanism independent of glycaemic control.

Biography:

Elisa Benetti is an Associate Professor in Pharmacology at the Dept. of Drug Science and Technology of the University of Turin. She is a co-author of more than 40 research papers. Her main research field is the study of new pharmacological strategies for the treatment of type 2 diabetes, focusing in particular on insulin resistance and its link with inflammation. She is a member of the European Association for the Study of Diabetes (EASD) and of the Italian Society of Pharmacology (SIF).

Keeping our Seafood Healthy: The Implications of Pesticide Run-off in Agricultural Catchments

Kirsten Benkendorff
Southern Cross University, Australia

Abstract

Diffuse source pollution in agricultural run-off is a major threat to the health of aquatic ecosystems. The impact of many pesticides on non-target insects and freshwater invertebrates has been well established. However, the potential for seafood species to be exposure to water soluble pesticides in estuarine environments has rarely been considered. Poor water quality in intensive agricultural catchments can increase disease and mortality, leading to fisheries and aquaculture harvest closures. Furthermore, there is potential risk to seafood consumers, if toxic contaminants are bioaccumulated in the flesh. Shellfish (bivalves and crustaceans) are of particular concern, due to their filter feeding activities and close evolutionary relationship to insect pests (respectively). The implications for seafood safety will be demonstrated using two case studies in intensive agricultural catchments on the east coast of Australia. Run-off from hothouses and blueberry farms was found to contain at least 9 pesticides, including high levels of the neonicotinoid insecticide imidacloprid. Ecotoxicology studies confirmed that imidacloprid is toxic to prawns and has sublethal impacts on oysters at environmental concentrations. Furthermore, neonicotinoids can be accumulated in the flesh of oysters and prawns at concentrations that exceed safe residue limits in food. A separate field study in a mixed agricultural catchment, dominated by sugar-cane, detected 13 pesticides in oysters, with mixtures of 7-11 pesticides in individual samples. Several of these pesticides have been banned for use in Europe, Canada or the USA. Most pesticides do not currently have maximum allowable residue limits set for seafood, although the concentrations we detected in oysters were below allowable limits for other food. However, none of the food safety regulations consider the cumulative concentration of multiple different types of pesticides. We detected pesticides from 10 distinct chemical classes, with 8 different modes of action, in oysters. The synergistic interactions from multiple pesticides on seafood health and safety must be considered in future studies, along with improved management to reduce the chance of agriculture pesticides entering the marine food chain.

Keywords:

Pesticides; Seafood; Ecotoxicology; Bioaccumulation

Biography:

Prof. Kirsten Benkendorff is the Director of the National Marine Science Centre, Southern Cross University, Australia. She obtained her PhD from the University of Wollongong in 1999, followed by an Australian Research Council Postdoctoral Fellowship, then a lectureship at Flinders University, before moving to Southern Cross University in 2010. Kirsten is an interdisciplinary marine researcher who applies the tools of chemistry to answer biological questions concerning valuable marine resources. She has made significant contributions towards assessing the impacts of ocean climate change and environmental contaminantson the health, nutritional quality and functional food properties of seafood species. She is also investigating the use of marine molluscs for human medicine and has identified a promising anticancer and anti-inflammatory agent currently in preclinical trials. Kirsten has published over 120 peer-reviewed papers in international scientific journals (H-index = 39). She supports a large team of postgraduate research students and has supervised an international team of 28 PhD, 7 Masters and 33 Honours students to completion. Prior to moving to the National Marine Science Centre, Kirsten was the Director of Higher Degree Research and Training for the School of Science and Engineering. In recognition of her contributions to marine science, Kirsten was awarded the 2000 Young Australian of the Year Award in Science and Technology, a 2008 SA Young Tall Poppy Award and the 2011 Dorothy Hill Award from the Australian Academy of Science.

Endocrine Disruptors: The Hidden Killers

Lucia Grumetto
University of Naples Federico II, Italy

Abstract

Experimental evidence supports that some synthetic chemicals can interfere with the hormonal system of living organisms, and, therefore they are known as Endocrine Disrupting Chemicals (EDCs). They are a heterogeneous class encompassing persistent contaminants such as polychlorinated biphenyls, pesticides, synthetic drugs among which diethylstilbestrol, but, above all, chemicals employed by the industrial world as plasticizer and/or preservatives, such as phthalates, bisphenols, and parabens. Human exposure to EDCs covers the entire life and a routinely exposure to them, even if at low doses, can cause damage effects on human health. The main route of EDCs assumption is the diet, but also through the skin due to the huge variety of personal care products (PCPs) containing them. Although the occurrence of these pollutants does not pose an acute health risk for the population, their levels should be constantly monitored and "hard-wired" into everyday practice because, the impact on health of continuous and simultaneous intake of a huge variety of EDCs from various sources by humans, is complex and still not fully understood.

The investigation of their affinity for phospholipids membranes and for serum proteins, can supply a useful tool to assess their possible passage through biomembranes, their bioavailability, and, of consequence, their toxicity. The achievement of affinity indexes can be performed fruitfully by Liquid Chromatography, employing phosphatidylcholine-like stationary phase, the main biological component of cellular membranes and stationary phases supporting human serum albumin (HSA) or α1- acid glycoprotein (AGP), the main plasma proteins binding xenobiotics. The affinity of compounds for these stationary phases can offer insights into the biodistribution and bioaccumulation processes underlying their toxicity, with an excellent inter-laboratory reproducibility.

Biography:

Prof. Lucia Grumetto is a Member of "Consorzio inter Universitario I.N.B.B, Istituto Nazionale Biostrutture e Biosistemi (http://www.inbb.it)- National Laboratory of Endocrine Disruptors". Member of the Editorial Board of "International Journal of Pharma Research and Health Sciences" and of Frontiers in pharmacology Journal, section Translational Pharmacology. Author of more than 70 research papers and speaker at various symposia. Scientific research in the fields of pharmaceutical sciences, mainly on two research topics: development and

validation of analytical-pharmaceutical methods for the determination of xenobiotics in complex matrices (food, environmental and biological matrices); Biochromatography: determination of in vitro parameters representative of xenobiotics/biostructures interactions and their correlation with biological activity data. Pharmacokinetic evaluations: transdermal passage assessment of actives set up in topical formulations

Advances in Toxicology and New Challenges in Different Industrial Sectors

Gianni Dal Negro
European Registered Toxicologist, Italy

Abstract

The rapidly changing global landscape makes it increasingly urgent to address gaps in traditional Research, Development and Manufacturing processes in the different industrial sectors, especially where the translation of laboratory animal tests to patients/consumers has a low success rate. In Europe, sector-specific legislations call for different restriction levels in the use of laboratory animals for hazard identification and risk assessment, Regulation 1223/2009 on Cosmetic Products being the most restrictive of all with a ban for testing and marketing of cosmetic products tested on animals. In addition, stakeholders (patients, consumers, policy makers, funding bodies) increasingly demand evidence of the value, safety and increased cost-benefit ratio of new products. On the other hand, we are witnessing an increasing pressure by the Society and Policy Makers towards phasing out laboratory animal use in the different disciplines including toxicology. Nowadays, there is an increasing interest and commitment of European and extra-European Regulatory Agencies to take new technologies and approaches into account, in the perspective of their possible embracement and inclusion in guidelines, provided criteria in their qualification process are addressed. New approaches in animal and non-animal testing are expected to at least match present quality, safety, ethical and economic standards. However, although science and technology evolve at an incredibly fast pace, this pace is not regular, which makes extrapolations and predictions of possible timelines for a completely animal-free Research and Development extremely hard to make. This talk will provide an overview of the current landscape in Toxicology in different industrial sectors, including the challenges being tackled by the scientific community and the paradigm shift that Toxicology is undergoing.

Biography:

Dr. Gianni Dal Negro is a European Registered Toxicologist with over 30 years of experience in Research and Development applied to both the regulatory and non-regulatory areas in the pharmaceutical sector. In his career, he has been a member of international committees and he has contributed to international initiatives relevant to the 3Rs (science, legislation, regulatory requirements); amongst them, he has represented the European Federation of Pharmaceutical Industries and Associations (EFPIA) in the ECVAM Scientific Advisory Committee (ESAC) and he has served as Industry Chair of the European Partnership for Alternative Approaches

to Animal Testing (EPAA). Before retiring, Dr. Dal Negro has covered roles of increasing responsibility at GlaxoSmithKline Ltd in UK, such as Head of Cellular and Biochemical Pathology, Head of Investigative Toxicology, World-wide Director of 3Rs, and Director of Complex In Vitro Platforms. Dr. Dal Negro has authored and co-authored several papers in peer-reviewed journals. He is currently a member of the Editorial Board of the Journal Toxicology In Vitro (Elsevier) and member of the EUROTOX Registration Committee.

Practical Applications of Pharmacogenetics

Ana Sabater
Associate Director at EUGENOMIC, Spain

Abstract
Why in treatments with anticoagulants and/or antiplatelet, is it necessary to take into account the patient's genetics and checking drug interactions?
Because, the consequences of not considering this may be very serious and can result in a very different effect on the treatment: haemorrhage, and in the opposite case, thrombosis.
The "protocols" of anticoagulation therapy are often too rigid. Unfortunately, there are no established algorithms for deciding on the most appropriate dose or drug(s), depending on the patient's genetics.
The logic to follow should be to know the patient's genetics, see which the most appropriate drugs are, and never the other way around, this is, checking genetics after the event has already happened.
As a result, it is known that haemorrhages happen, also thrombosis, although in a smaller proportion.
Avoiding it via pharmacogenetics may be a powerful option.

Biography:
Linked to the world of health and the IT business for more than 14 years, Ana Sabater leads the EUGENOMIC project, a reference in genetics and pharmacogenetics in Europe. Her training in IT and marketing, as well as her commitment to personalized and quality healthcare, have led her to the development and commercialization of the innovative pharmacogenetic interpretation software g-Nomic®, a cutting-edge tool for medical prescription.
In the field of training, Ana Sabater lectures on practical applications of pharmacogenetics at the University of Barcelona and has given more than 40 international presentations on pharmacogenetics.

Effects of Derivatives from Adipose-Derived Stem Cells on Ischemia/Reperfusion-Induced Cardiac Damage: Role of Microrna221/222

Yuh-Lien Chen
National Taiwan University, Taiwan

Abstract

Cardiovascular disease is a major health problem and a leading cause of death and disability in both industrialized and developing countries. For patients with myocardial infarction (MI), percutaneous coronary intervention (PCI) is a timely and effective myocardial reperfusion therapy, which can reduce the damage caused by acute myocardial ischemia and limit the progression of MI. While this technique can improve outcomes from myocardial infarction, the reperfusion process itself can lead to heart cell death, known as cardiac ischemia/reperfusion (I/R) injury. I/R injury involves a complex series of events including increased oxidative stress, induction of inflammation, triggering cardiomyocyte apoptosis, and can exacerbate cardiac injury and account for up to 50% of infarct size. Recent studies have shown that adipose-derived stem cells (ADSCs) play a crucial role in wound repair. The aim of this study was to investigate the effects of adipose-derived stem cell derivatives, conditioned medium, and exosomes (ADSC-CM and ADSC-Exo) on the heart of I/R mice and to explore the underlying mechanisms. Ejection fraction (EF) and fraction shortening (FS) levels were significantly reduced in I/R animals compared to control animals. In contrast, mice treated with ADSC-CM or ADSC-Exo had significantly increased EF and FS compared to I/R-treated mice, and exhibited better cardiac function under ADSC-CM and ADSC-Exo treatment. ADSC-CM or ADSC-Exo treatment significantly reduced I/R-induced cardiac apoptosis, as detected by TdT-mediated dUTP nick-end labeling (TUNEL) assay. Furthermore, the expression of apoptosis-related proteins, p53 upregulated modulator of apoptosis (PUMA) and p-p53, was significantly reduced in cardiac tissues from ADSC-CM or ADSC-Exo-treated I/R mice compared with control mice. Dysregulation of miRNA expression has been reported in numerous studies involving various pathophysiological processes, including cardiovascular diseases. MiR-221/222 plays the important role in inflammation, cardiovascular function, and tissue metabolism. Our laboratory previously showed that PUMA is a target gene of miR-221/222. I/R manipulation significantly decreased miR221/222 expression, whereas ADSC-CM or ADSC-Exo treatment increased miR-221/222 expression, as detected by RT-qPCR. We also observed that cardiac I/R surgery significantly increased apoptosis in miR-221/222 knockout (KO) mice, whereas miR221/222 mimics or ADSC-CM or ADSC-Exo treatment reduced the effect of I/R surgery. Therefore, I/R causes

cardiac injury, and ADSC-CM and ADSC-Exo can reduce cardiac injury by the miR-221/222 pathway.

Keywords:
Ischemia/Reperfusion, Adipose-Derived Stem Cell. Apoptosis, MicroRNA221/222

Biography:
Dr. Yuh-Lien Chen is a University Professor and Chairman of the Institute of Anatomy and Cell Biology in College of Medicine, National Taiwan University. She completed her Ph.D. from Institute of Anatomy, College of Medicine, National Taiwan University.She is the author of more than 100 peer-reviewed publications. The main focus of her laboratory is to investigate the development, related mechanisms and prevention of cardiovascular diseases. The major results are: (1) Isolation, culture and application of stem cells from umbilical cord interstitium or adipose tissue: Our laboratory has successfully isolated stem cells from umbilical cord interstitium or adipose tissue, which can repair damaged skin flaps, reduce cardiac ischemia/reperfusion injury and further explore its related mechanisms. The experimental results show that stem cells isolated and cultured from human adipose tissue and umbilical cord mesenchyme can be used for academic research, and can also be used in future clinical medicine to overcome the problems of tissue deficiency, organ damage, aging, and clinical reconstruction and plastic surgery. (2) To explore the cause of inflammation in cardiovascular disease or respiratory disease: the experimental results clarified that ischemia/reperfusion caused severe damage to cardiomyocytes and programmed cell death. In addition, it is also clarified that suspended particulate matters (PMs) can significantly increase lung epithelial cell inflammation or epithelial-mesenchymal transition both in vivo and in vitro, and explore its mechanism in depth.(3) The role of miR-221/-222 in the inflammatory process and its antioxidant properties: miR-221-222 is closely associated with cell adhesion molecule (ICAM-1), programmed cell death-associated protein (PUMA), and fibrosis-related protein (ETS-1) levels. Wild bitter melon fruit extract has anti-inflammatory and anti-oxidative activities in vitro and in vivo, through the signal transduction pathway of miR-221/-222/PI3K/AKT/NF-κB.

Role of Chemokine Receptors as Targets of Protective Drugs in Neurological Diseases: From Apoptosis to Repair Mechanisms in the Injured Brain

José Joaquín Merino Martín
Complutense University of Madrid, Spain

Abstract

The CXCR4 receptor upon binding its ligands triggers multiple signaling pathways that orchestrate cell migration, hematopoiesis, cell homing, and retention in the bone marrow. The RANTES chemokine ligand binds to CCR5 in the brain and the canonical ligand of CXCR4 is CXCL12, also known as stromal cell-derived factor 1 (SDF-1). These alfa and beta chemokines (chemotactic cytokines) are expressed in the brain (neurons, astrocytes, microglia and blood vessels). Neuroinflammation can be modulated by neuron-glial signaling through soluble factors, including CX3CL1 chemokine. This delta chemokine is expressed by neurons as a transmembrane protein but can be by proteolytic cleavage as a soluble form. Among delta chemokines, the CX3CR1 (receptor)/CX3CL1 (ligand) axis play a role in neurogenesis, neuroprotection, HIV-1 cognitive impairment, cancer, etc; collectively, chemokine receptors are targets of neuroprotectants and antitumoral drugs.

Chemokines are pleiotropic molecules involved in neurodegeneration/neurorepair, stem cell recruitment; this talk highlight its dual role as neuroprotective/apoptotic factors because this inflammatory mediators contribute to the progression of neuroinflammatory and neurological diseases (epilepsy, Alzheimer, Parkinson, etc). This talk highlights my published findings on the dual role of chemokines as apoptotic or protective/neuroplastic cytokines in CNS pathology. Firstable, I discuss the neuroplastic role of CCR5/RANTES in the hippocampus of stressed rats as well as the impairment of memory by blocking CCR5 in maraviroc (a CCR5 blocker)-stressed animals; additionally, I describe the apoptotic role of caspase-3 activation in AMD-3100 (a CXCR4 antagonist)-treated cortical neurons in conjunction with cytochrome c release and Bax/Blc-2 cytosol/mitochondrial ratio by western blot in cortical neurons at 7 DIV. Finally, CX3CL1 could be an inflammatory predictor of dementia that reflect the long-term heavy metal accumulation in patients (Hg or Al). Thus, chemokines can predict the progression of dementia and are targets of neuroprotective and neuroplastic drugs in neurological diseases independently of its classical role as HIV-1 coreceptors.

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Keywords:

Chemokines; Neuroprotective Drugs; Maraviroc; AMD-3100; Neuroinflammation.

Biography:

Dr. José Joaquín Merino Martín. PhD in Biochemistry and Molecular Biology by Complutense University of Madrid (UCM) Researcher and Profesor of Pharmacology (UCM) 55 international papers (43 pubmed indexed), 130 impact factor (total score) and 1400 citations Review Editor for Frontiers in Molecular Neuroscience (Q1, impact factor 6.2) Ramon and Cajal Researcher (5 years) in Biomedical centers and University Certificado de excelencia investigadora I3 positivo Coeditor of a Spetial Issue for Neuroglia in Alzheimer (Current Alzheimer Research) Postdocts in USA and Spain Research areas: neurological diseases, stem cells (HSC and MSC), chemokines, cell adhesion molecules, hormons and neural plasticity, toxicology of heavy metals.

Design of a Preclinical In Vitro Human Innervated Skin Model for Drug Development

Verónica Rivero Hernández
Miguel Hernandez University, Spain

Abstract

The present proof of concept centres in the design of a human based preclinical organoid-skin model for pain research and drug discovery that increases the clinical translation of preclinically validated drug candidates. A major hurdle of animal-based preclinical results is their poor clinical translation which represents an attrition in drug development. Thus, the generation of preclinical models that increase the clinical translatability of preclinical results is an urgent necessity in biomedicine. This is now achievable by combining recent advances in sensory neuron transdifferentiation from skin cells, compartmentation of neural cultures in microfluidic chambers, high microelectrode density arrays for electrophysiological measurements and 3D bioprinting. Although creating a prototype of innervate human skin is a notable challenge, we have significantly progressed in all parts needed and are currently working on assembling them into a functional platform. Validation of this preclinical advanced human organoid will be very useful to investigate the pathophysiology of peripheral neuropathies along with the preclinical validation of drug candidates. Furthermore, it will be also useful to evaluate the safety of drug candidates and cosmetic ingredients.

Biography:

Verónica has a Degree in Biochemistry, Master in Bioengineering (Applied Toxicology and Pharmacology) and PhD in Cellular and Molecular Biology (2017). She started with toxicology research on endocrine disruptors in the Department of Applied Biology at Miguel Hernandez University (UMH) and the Institute of Environmental Medicine at Karolinska Institutet in Stockholm. She began her specialization in ion channels pharmacology as researcher in R&D projects at the Institute of Molecular and Cell Biology (IBMC) of the UMH, now known as IDiBE, in collaboration with the company Lipotec-Diverdrugs, gaining extensive experience in high-throughput toxicological and pharmacogenomic screening for the development of new active compounds in the cosmetic and dermopharmaceutical field. She developed her PhD thesis based on the implementation of a new automated electrophysiology technique for high-throughput screening and drug discovery funded by the Dravet Syndrome Foundation (Spanish Delegation) in the thesis project "Pharmacogenomic screening for Dravet Syndrome". After, she has played for 4 years the role of project leader at Antalgenics S.L focusing on the

identification of new targets and techniques for in vitro drug discovery and preclinical studies of candidates for use in sensorial neurobiology and skin pathologies. She is currently working in the Sensorial Neurobiology group of IDiBE, involved in a project to generate a preclinical in vitro human skin model innervated by sensory neurons using tissue engineering and 3D bioprinting.

Betaine Supplementation - Pathophysiology Of Hepatoprotective Effects

Milena Veskovic
University of Belgrade, Serbia

Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver diseases in the general population. NAFLD consists of three major entities including steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis. According to "multiple-hit" hypothesis, steatosis makes liver vulnerable to various second-hits that lead to inflammation and further hepatocytes damage. The principal causes of steatosis are insulin resistance and hyperinsulinemia, which lead to increased lipolysis in adipose tissue with subsequent inflow of free fatty acids (FFA) to the liver and stimulation of hepatic de novo lipogenesis. Lipotoxic effects of FFAs cause mitochondrial dysfunction and oxidative stress that lead to the activation of inflammatory response and progression of steatosis to NASH. Altered function of mitochondria results in reactive oxygen species (ROS) overproduction leading to increased lipid and protein peroxidation that consequently alters lipid metabolism in the liver, playing thus significant role in steatohepatitis development. Autophagy is impaired in NAFLD and contributes to the accumulation of damaged organelles and proteins in hepatocytes, ultimately leading to apoptosis.

Betaine, 3-methyl glycine is a nontoxic amino acid, a methyl-group donor and exerts antioxidative effects by increasing the amount of sulfur-containing amino acids. It represents an important nutrient that can be found in grains, spinach, shrimps and beet, and dietary intake is an important source of betaine, even there is endogenous synthesis from choline, especially in the liver and kidney. Betaine balances high extracellular osmolarity and regulates cell volume. In the liver, betaine primarily functions as a methyl group donor. Additionally, betaine may induce epigenetic silencing of genes involved in lipogenesis contributing to alleviation of steatosis.

We aimed to study the effects of betaine on liver morphological and ultrastructural changes, as well as on oxidative stress, apoptosis, autophagy and inflammation in the liver. To investigate the effects of betaine on NAFLD, mice C57BL/6 were treated with betaine solution in drinking water (1.5% solution ad libitum) for 6 weeks.

Betaine supplementation reduced steatosis and inflammation evident on histology, and improved serum lipid profile by decreasing total cholesterol, LDL and increasing HDL. Betaine exerts hepatoprotective effects by reducing lipid peroxidation and nitrosative stress in NAFLD through an increase in liver antioxidant enzyme activities such as paroxonase, arylesterase, superoxide dismutase, catalase and glutathione peroxidase and by restoring glutathione content. Betaine was shown to alleviate the course of NAFLD by increasing autophagy processes in Beclin 1- and Akt/mTOR-dependent manner, but independently on AMPK activation. Potential additional mechanisms of betaine in MCD-diet induced NAFLD in mice are antiapoptotic and anti-inflammatory effects by reducing the expression of TNF, IL-6 and by increasing anti-inflammatory IL-10. Betaine treatment prevents initial fibrogenesis by decreasing TGF-β expression in the MCD diet-induced NAFLD.

This research has been supported by Bilateral Cooperation Call applied between TUBITAK (Turkey) and the Ministry of Education, Science and Technological Development of Serbia MoESTD

Keywords:
Nafld, Betaine, Oxidative Stress, Autophagy

Biography:
Milena Veskovic was born in 1987. In Leskovac, Serbia. She is employed as an Assistant Professor at the Institute of Pathophysiology, Faculty of Medicine University of Belgrade in Serbia. She has 10 years of experience in academic career. Milena Veskovic has finished her PhD thesis in 2019 in the area of Physiological and Pharmaceutical Sciences through international supervision of doctoral thesis „Cotutelle“, by collaboration with Antwerp University, Belgium, which was the first International doctorate at Faculty of Medicine. She has an expertise in hepatology research that include non-alcoholic and alcoholic fatty liver disease, liver fibrosis and metabolic syndrome. Additionally, she is recently widening the research area towards neurophysiology, including circadian misalignment, mood and behavioral disorders. Milena Veskovic has an experience in international collaboration through the bilateral project related to neurological disorders financed by The Ministry of Science and Technological Development of the Republic of Serbia and The Scientific and Technological Research Council of Turkey. Dr Veskovic is an author in 21 publications indexed in JCR list with 350 citation and Hirsch index 11.

Toxicology and Pharmacodynamics of Withaferim A: Implications for Dosing WithaniaSomnifera Extract for the Prevention of GVHD in Allogeneic Stem Cell Transplantation

Vikram Gota
ACTREC, Tata Memorial Centre, India

Abstract

Withaferin-A (WA) is the principle component of Withaniasomnifera (Ashwagandha). It has several biological activities including anti-cancer, anti-diabetic, neuroprotective, hepatoprotective and immune-modulatory properties. The acute and sub-acute toxicity of oral WA was investigated in mice. In the acute toxicity study, up to 2000 mg/kg of WA was well tolerated without any signs of toxicity or death. In the sub-acute toxicity study, mice were orally administered 10, 70 and 500 mg/kg of WA respectively, daily for 28 days. Upon physiological, serum chemistry, hematology and histopathogical examination, no features suggestive of drug-induced toxicity were observed at any dose levels, thereby confirming the No-Observed Adverse Effect Level (NOAEL) to be at least 500 mg/kg. Further, a mouse model of graft-versus-host-disease (GVHD) model was developed using MHC-mismatched allogeneic bone marrow transplantation. Prophylactic use of WA in this model mitigated GVHD associated target organ damage to the gut, liver, lungs and skin. Consequently, GVHD associated morbidity (severity of clinical score) and mortality were significantly reduced by WA at a dose of 1 mg/kg. This ensures at least a 500-fold difference in the NOAEL dose and the therapeutic dose which augurs well for the clinical development of WA. Further, treatment with WA resulted in significant decrease in inflammatory cytokines such as IL-2, IFN-γ, TNF-α and IL-6, establishing its role as a potent immunomodulator. Currently we are planning a phase 2 clinical trial of Withaniasomnifera extract (WSE) containing 4.5% WA for the prevention of GVHD. The large therapeutic window coupled with potent immunomodulatory property of its active principle, WA, is likely to establish WSE as a safe and effective pharmacological intervention for the prophylaxis of GVHD alongside drugs such as methotrexate, cyclosporine-A, and mycophenolate mofetil.

Biography:

Dr. Vikram Gota completed his MD in pharmacology from Christian Medical College, Vellore, following which he briefly worked as a Clinical Investigator in BA/BE studies. Thereafter, he joined the INDO-Oxford (INDOX) Cancer Trials Network at Tata Memorial Centre, Mumbai, where he received training in the design and conduct of phase I clinical trials. During this time he also obtained the post graduate diploma in clinical trials from the London School of Hygiene and Tropical Medicine, University of London. He is presently the officer-in-charge of the department of clinical pharmacology at the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre. His research interests include early clinical development and pharmacokinetics driven optimization of drugs used in cancer. He is involved with the geriatric clinic at TMH since 2019 focusing on rational therapeutics, potentially inappropriate medications and drug-drug interactions, among other things. Hehas worked as an investigator in several phase I clinical trials including first-in-human studies of investigational new drugs.

Targeting EZH2 in Triple Negative Breast Cancers Using Combinatorial Treatment

Eswar Shankar
The Ohio State University, USA

Abstract

There has been a steady rise in the global incidence of breast cancer, with 1.7 million new cases added each year and 0.5 million deaths. However, most of the deaths are due to metastases that are resistant to adjuvant therapies. Patients with triple negative breast cancers (TNBC, estrogen receptor (ER)−, progesterone receptor (PR)−, Her2−) have the worst outcomes because of high metastasis rates compared with non-TNBC. Chemotherapy remains the most effective treatment option; however, there is still a largely unmet need to identify novel therapeutic targets in TNBC to increase treatment options and improve patient outcomes. EZH2 is a potential driver of TNBC metastasis, and its high expression strongly associates with the TNBC phenotype as compared with other molecular subtypes of breast cancer. Currently, several EZH2 inhibitors are being developed and undergoing clinical trials; these compounds have proven to be effective in the treatment of hematological malignancies, sarcomas, and malignant rhabdoid tumors. However they do not affect the intrinsic protein stability of EZH2, but typically compete with the cofactor S-adenosylmethionine (SAM) and bind to the SET domain of EZH2. Hence, EZH2 inhibitors are only effective for some malignant blood tumors, and have poor efficacy for solid tumors, such as TNBC. Several studies have shown the involvement of the neurotransmitter dopamine in the proliferation, apoptosis, tumor angiogenesis, and drug resistance of different cancers, including breast cancer. Dopamine D1 receptor (D1R) activation in the TNBC cell line induces apoptosis, autophagy, and phosphorylation of eIF2a. In addition, D1R agonists inhibit the invasion of breast cancer cell lines MDA-MB-231 and BT-20 and regress mammary tumors. Conventional in vitro models utilize monolayers to investigate the effect of drugs on cancer cells, but do not accurately recapitulate the in vivo microenvironment as the cells are subjected to homogeneous growth conditions. Microgels are miniature compartmentalized hydrogels that yield isotropic cell culture conditions. As such, they are suitable microenvironments conducive to tumor spheroid growth. We investigate the efficacy of EZH2 inhibitors and D1R agonists on TNBC tumor spheroids. Single doses of combination therapies, including GSK126 and tazmetostat, EZH2 inhibitors, and A77636 and SKF38393, dopamine agonists, demonstrated a dose-dependent decrease in tumor spheroid area. Furthermore, the combination therapy demonstrated a regression in growth, synergistic decrease in area (CDI < 0.6 for GSK126/A77636), and the induction of necrosis. Furthermore, knockout of EZH2 in TNBC cells resulted in the inability of tumor spheroids to form. Our

findings imply that EZH2 is critical for spheroid formation and growth in TNBC and suggest that targeting EZH2 alongside D1R presents a novel strategy for enhancing EZH2 inhibition.

Biography:

Dr. Shankar received is MSc from Department of Biochemistry, Annamalai University, Tamil Nadu India and completed his Ph.D. from Cochin University of Science and Technology, Kerala, India in Neuroscience, from the Department of Biotechnology. He was a post-doctoral research associate in the Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth, Texas, USA. He was invited by Dr. Sanjay Gupta, Director of Research, Department of Urology, School of Medicine, Case Western Reserve University, Cleveland Ohio to work in drug repurposing and Chemoprevention. Since 2021 Dr. Shankar is an Assistant Research Professor at the The Ohio State University Comprehensive Cancer Center, Columbus, OH. Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH.The research focus of Dr. Shankar is on breast and prostate cancer studying the molecular mechanism attributing to initiation and metastasis identifying targets associated with cancer progression and drug resistance. Over the last 14 years Dr.Shankar's research has evolved in elucidating the mechanisms of oncogenes that orchestrate tumor promotion. In the recent years Dr. Shankar has been involved research to repurpose drugs and come out with combinatorial treatments that synergistically inhibit the growth of metastatic breast cancer. In the current position Dr. Shankar in collaboration with Dr. Bhuvaneswari Ramasamy, MD, Breast Oncologist, Ohio State University's Wexner Medical Center and Dr. Vish Subramaniam, Ph.D. Academy Professor, Department of Mechanical & Aerospace Engineering, and OSU Emeritus Academy is developing combinational treatments to inhibit metastasis withminimal or no toxicity to normal cells. He is also involved in applying induced electricfield (iEF) technology as a non-pharmacological means of treating metastatic cancer. Asevident from his research publications Dr. Shankar has made significant contribution in understanding the molecular signatures altered during this devastating disease. He is funded by the department of defense (DoD) to evaluate the combinatorial effect of dopamine D1 agonist and EZH2 inhibitor GSK126 in arresting triple negative breast cancer progression.

Thank You!

Next Event

ISTAP2024

2nd International Summit on Toxicology and Applied Pharmacology

May 27-29, 2024 | Prague, Czech Republic