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# Recent Researches in Medicine & Medical Chemistry

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## Plenary Lecture 1

### Creatinaemia in Neonates: From Biochemical Quantification to Clinical Interpretation



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**Abstract:** Recognition of acute renal failure (ARF) in neonates is of relevance to adapt medical treatment and as prognostic indicator during neonatal stay. The incidence of ARF in neonates however is extremely variable due to the absence of a robust definition of renal impairment in neonates and due to the use of fixed cut off values for serum creatinine (Scr) despite maturational differences within the preterm age. We therefore aimed to describe postnatal Scr trends and its covariates in a cohort of extreme low birth weight (ELBW, i.e. < 1000 g) infants.

Serum creatinine (Scr) reflects to a certain extent glomerular filtration rate in neonates, but also depends on the technique used to quantify Scr [Jaffe colorimetry or enzymatic quantification]. We compared observations of maternal-neonatal ELBW samples in whom Jaffe or compensated Jaffe (maternal) and enzymatic quantification (neonate) were applied. Finally, in an attempt to quantify differences between these techniques, we compared postnatal Scr trends in two consecutive cohorts of extremely low birth weight (ELBW) neonates before and following a switch from Jaffe to enzymatic Scr quantification. Postnatal Scr (day 1,2,3,4,5,6,7,14,21,28,42) in a cohort of 151 ELBW neonates (Jaffe) was compared to 116 more recently admitted ELBW neonates (enzymatic).

Firstly, ELBW neonates display trends similar to heavier neonates, but peak Scr is higher, the subsequent decrease slower. Raised creatinemia in ELBW neonates reflects both immaturity (the lower GA, the higher the peak Screea and the slower the subsequent decrease) and morbidity (ventilation, Apgar, ibuprofen). Secondly, the quantification method affect the paradigm that creatinaemia at birth is similar to maternal creatinaemia. Creatinaemia values in mothers and neonates depend on the method used. Method-specific reference values are needed. Finally, while clinical characteristics were similar, median postnatal Jaffe Scr (66,88,96,95,86,82,77,68,60,54 and 49 mmol.l-1) remained significantly higher compared to enzymatic quantification (51,64,80,77,72,70,65,49,39,36 and 31 mmol.l-1, all at least  $p < 0.001$ ) throughout postnatal life (day 1,2,3,4,5,6,7,14,21,28,42). The difference in within-day median values fluctuated between 11-24 mmol.l-1. It was therefore concluded that there is no fixed absolute difference between both techniques. A similar comparison between Jaffe and enzymatic quantification (pre)term neonates with a birth weight above 1 000 g confirms these findings.

Consequently, clinicians and researchers should use the appropriated age-dependent references values, dependent on the quantification technique used and Scr centiles (dependent on gestational and postnatal age) should be used to evaluate individual observations.

**Brief Biography of the Speaker:** Karel Allegaert, MD, PhD graduated from the Katholieke Universiteit Leuven as medical doctor (1994), with a subsequent training in Pediatrics/Neonatology (2001) and Clinical Pharmacology (2005). Following the presentation of his PhD defence (neonatal analgesia: towards an integrated approach), he further combined clinical care as a consultant of the neonatal intensive care unit, University Hospitals Leuven with clinical research with specific emphasis on perinatal clinical pharmacology (special populations, including preterm neonates and pregnancy). He was appointed as associated professor of the Katholieke Universiteit Leuven in 2005, and subsequently further developed these research activities, currently reflected in about 200 publications in national and international journals, conference proceedings and chapters in book. His clinical research has (FWO clinical doctoral grant) and still is supported by a Fundamental Clinical Investigatorship (2009-2013) of the FWO Vlaanderen. This research also resulted in several awards of the Belgian Academy of Medicine and Sciences (Govaerts award for Clinical Toxicology 2006-2008, and Heymans Award Clinical Pharmacology 2002-2004), the Belgian Pain Society (2005), and the Galenus price, clinical research pharmacology, Belgium (2009).

## Plenary Lecture 2

### Contribution of Knee Joint Mechanics to the Structure and Properties of Articular Cartilage



**Dr. Daniel M. Espino**

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**Abstract:** The aim of this session is to discuss how loading conditions that the knee joint is exposed to influence the structure and mechanical properties of the underlying articular cartilage. This is important as cartilage degeneration, as occurs during osteoarthritis, involves changes to structure and properties. Different joints across the body are exposed to different movements and, thus, loading. For example, the loads and stresses experienced by the hip are different to those experienced by the knee during walking or running. Different joints also experience different rates of cartilage degeneration. The ankle, while exposed to higher stress experiences little cartilage degeneration unlike the hip or knee. Variation in structure and mechanical properties occur across different joints, within a joint and within a joint component. The knee is a good example of this.

The medial and lateral components of the knee are exposed to different types of loading. During walking, the lateral femoral condyle of the knee rotates unlike the more static medial condyle. However, most compressive loads pass through the medial knee. The patella, menisci and ligaments all affect loading distribution across the knee. Variation in the structure and properties of articular cartilage across the knee joint are thus examined based on these differences in the conditions that articular cartilage across the knee is exposed to.

The session includes:

- background to the knee, its anatomy and physiological loading;
- description of the differences in the structure of articular cartilage;
- detail of the mechanical properties typically measured (including different testing regimes) and their variation across the knee;
- discussion of trends between structure and properties of cartilage and physiological loading across the knee joint.

**Brief Biography of the Speaker:** Daniel is currently a Research Fellow at the University of Birmingham, funded by an Intra-European Personal Fellowship. Over the last 10 years he has developed his research experience in Bio-medical Engineering through modelling and mechanical testing of connective tissues of the body. Recently, this has included investigating articular cartilage and its involvement in knee joint mechanics. He obtained his PhD in Bio-Engineering at the University of Aberdeen. Following his PhD, he was awarded a Junior Fellowship by the British Heart Foundation which he held at the University of Birmingham. He has since developed his expertise outside the UK, as a Research Fellow at both the University of Auckland (New Zealand) and the Istituto Ortopedico Rizzoli in Bologna (Italy).

He has been invited to present his research in the Czech Republic, Switzerland and the UK. He has served on the conference committee for the International Conference of Systems Biology and Bioengineering and the 2nd Workshop on 3D Physiological Human. He has also been invited to the editorial boards for the Open Journal of Orthopedics, International Journal of Biological Engineering, International Journal of Engineering & Technology and the Journal of Clinical Rehabilitative Tissue Engineering Research.

## Plenary Lecture 3

### Current Understanding of Cellular Mechanism on Sarcopenia



**Associate Professor Kunihiro Sakuma**  
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**Abstract:** The expected increase in the aging population will have a significant impact on society and the health system in the coming years and decades. Enhancing healthspan, “healthy aging”, and thus extending the time that the elderly are able to function independently is a significant task and is imperative. Sarcopenia, the age-related loss of skeletal muscle, is characterized by a deterioration of muscle quantity and quality leading to a gradual slowing of movement, a decline in strength and power, and an increased risk of fall-related injuries. Sarcopenia is largely attributed to various molecular mediators affecting fiber size, mitochondrial homeostasis, and apoptosis. Researchers indicate defects of Akt-mTOR and RhoA-SRF signaling in sarcopenic muscle. In contrast, many studies failed to show significant activation in ubiquitin-proteasome system (UPS), most potent regulator for muscle mass. In the quadriceps muscle of aged mice, our recent data clearly showed the p62/SQSTM1 and Beclin-1 protein, which represent lysosome-autophagy system. In contrast to rapid atrophy (cachexia, starvation, hindlimb suspension, etc), more slower muscle atrophy with age does not seem to be regulated by UPS.

**Brief Biography of the Speaker:** I graduated from the doctoral program in University of Tsukuba, Japan 1996. From 1996 to 2000, I worked as researcher in Department of Physiology, Institute for Developmental Research of Aichi Human Service Center. At this time, I studied mainly the molecular mechanism of merosin-deficient congenital muscular dystrophy. From 2000 to 2005, I worked as assistant professor, Department of Legal Medicine, Kyoto Prefectural University of Medicine. In this place, my major concern was the functional role of calcineurin on muscle regeneration and hypertrophy. My research interests, now in the Research Center for Physical Fitness, Sports and Health, Toyohashi University of Technology, focus on molecular mechanism of sarcopenia and this attenuating strategy (nutrient, pharmaceutical, exercise, etc), and particularly on autophagy process in sarcopenia. I am author of about 50 papers published in international journals and invited book chapters. I participated in the member of Editorial Board of several journal (International Journal of Biomedical Science, World Journal of Neurology, etc).

## Plenary Lecture 4

### Neonatal Mass Urine Screening for Inborn Errors of Metabolism in the Province of Quebec: An Update



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**Abstract:** The Provincial Mass Urinary Screening Program for inherited metabolic disorders was instigated nearly four decades ago in the Province of Quebec and the Nunavut region as part of a preventive genetic medicine program. It is supported financially by the Quebec Ministry of Health and Social Services. More than 2 800 000 babies have been screened for inborn errors of amino acids and organic acids. Newborn urine samples are collected on filter paper (Whatman-GE 903) by parents at 21 days of age. Means have been put in place to inform parents about the urine screening program. Voluntary compliance is good at 90%. Samples are analyzed using a multiplex thin layer chromatography technique with a sequential-four reagent staining methodology. Two unidimensional ascending solvent migrations are performed for higher resolution in 1-butanol-acetic acid-water, 13-3-5. We analyze 500 samples per day totalizing 77 000 samples/year in 2011. We screen for 25 disorders: 1) those causing severe clinical problems which necessitate immediate therapeutic intervention, such as urea cycle disorders and organic acidurias; 2) those necessitating surveillance and follow-up in metabolic disorders and transport disorders. We detected and confirmed many organic acidurias: 69 cases of methylmalonicaciduria, 5 methylcrotonylglycinurias, 2 oxoprolinurias, and 1 glutaric aciduria type I. Regarding urea cycle disorders, we confirmed 18 cases of argininosuccinic aciduria, 5 citrullinurias type I (classic), 3 citrullinurias type II, 4 hyperargininurias, and 1 case of Triple H syndrome. Concerning amino acid transport disorders, we found 150 cases of homozygous cystinuria and 1028 heterozygous cystinurias, 16 cases of Fanconi syndrome, 57 cases of Hartnup disease and 72 cases of dicarboxylicaminoacidurias. Certain inborn errors of metabolism, notably disorders of amino acid transport, such as cystinurias, Fanconi syndrome, Hartnup syndrome, dicarboxylicaminoaciduria, can be detected only by analyzing urine samples. In summary, the technical approach used is rapid, simple, reproducible and at low-cost. The use of filter paper facilitates the urine collection by parents, shipping by mail and storage of samples. Our screening program is a dynamic model that has evolved throughout the years to screen as many treatable disorders as possible before the onset of symptoms and prevented clinical problems in hundreds of children.

**Brief Biography of the Speaker:** Dr Auray-Blais is the Director of the Quebec Provincial Mass Urinary Screening Program for hereditary metabolic disorders since its inception more than 35 years ago. She is a pioneer in mass urine screening having developed the infrastructure, techniques and methodology permitting the urinary screening of 2 800 000 newborn babies in the province of Quebec for 25 disorders of amino acids and organic acids. She holds a Ph.D. in radiobiology from the Faculty of Medicine and Health Sciences at the Université de Sherbrooke and postdoctoral studies from Duke University Medical Center in North Carolina, US. She has a masters degree in Health Law from the Faculty of Law at the University de Sherbrooke and a bachelors degree in biochemistry. She is the author of 150 publications, abstracts and articles. She is a professor in the Service of genetics in the Department of Pediatrics at the Faculty of Medicine and Health Sciences at the Université de Sherbrooke and a researcher at the Clinical Research Centre Étienne-Le Bel in the Mother-Child Axis. She is the Scientific Director for the Waters-CHUS Expertise Centre in Clinical Mass Spectrometry. She is the principal investigator and co-investigator in numerous research grants. She has received awards for her involvement and expertise in screening inborn errors of metabolism in newborns in the Province of Quebec.

## Plenary Lecture 5

### Quantitative Structure-Activity Relationship Study on Polyphenols as Inhibitors of $\alpha$ -Glucosidase



**Assistant Professor Vesna Rastija**  
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**Abstract:** Polyphenols are products of the secondary metabolism of plants. They are common constituents of plant food and beverages as tea and wine. The two main of polyphenols are phenolic acids and flavonoids. Phenolic acids are divided into hydroxybenzoic acids and hydroxycinnamic acids. Common subfamilies of flavonoids are flavonols, flavanones, flavones, flavan-3-ols (catechins), anthocyanins, chalcones, and isoflavones. During the last decades numerous studies have evidenced about health effects of polyphenols that arise mostly from the antioxidative activity. Diabetes mellitus is a chronic disease caused by an inherited or acquired deficiency in insulin secretion and by decreased responsiveness of the organs to secreted insulin, which results in increased blood glucose levels.  $\alpha$ -Glucosidase [EC. 3. 2. 1. 20] is a membrane-bound enzyme located at the epithelium of the small intestine, which catalyses the cleavage of glucose from disaccharides. Inhibitors of this enzyme may be effective in retarding carbohydrate digestion and glucose absorption to suppress hyperglycaemia.

Polyphenols contained in medicinal plants, which are used in the treatment of diabetes, may explain their therapeutic activity. They may affect glycemia through different mechanism, but mainly due to an inhibition of  $\alpha$ -glucosidase and/or  $\alpha$ -amylase.

The aim of our study was to derive a quantitative structure-activity relationship (QSAR) analysis for the  $\alpha$ -glucosidase inhibition potential of polyphenols by the application of a series of molecular descriptors that encode physicochemical and quantum-chemical properties, as well as two-dimensional (2D) and three-dimensional (3D) structural features of the molecules in question. The QSAR models, thus obtained, could provide some insights into the mechanism of action of polyphenols as inhibitors of  $\alpha$ -glucosidase.

**Brief Biography of the Speaker:** Vesna Rastija graduated from the Faculty of Education in Osijek (biology and chemistry) in 1994. After the graduation she taught the chemistry and biology in elementary school for a three years. Since 1997 she has been employed as a teaching assistant of Chemistry on Faculty of Agriculture in Osijek. Vesna has made my master thesis on the Institute "Rudjer Boskovic" in Zagreb in area of inorganic and structural chemistry, and 2001 earned a Master of Science degree at the Faculty of Science (University of Zagreb). She defended a doctoral thesis on Faculty of Pharmacy and Biochemistry in Zagreb and obtained a doctoral degree (science, chemistry) on 14 March 2007 at the Faculty of Science (University of Zagreb). Title of the doctoral thesis was: "Chromatographic analysis of polyphenols in wines from Croatia".

She is currently employed as assistant professor at Department of Chemistry, Faculty of Agriculture Osijek, University of J. J. Strossmayer Osijek, Croatia. Until now she has published a 14 journal articles. She is a member of Croatian Chemical Society.



## Plenary Lecture 6

### Targeting Fabry Disease Biomarkers Using Mass Spectrometry-Based Metabolomics



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**Abstract:** Fabry disease is an X-linked, multisystemic lysosomal storage disorder characterized by the accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3) in biological fluids, vascular endothelium, heart, and kidneys. Treatment by enzyme replacement therapy is provided to both males and females depending on the severity of symptoms. We devised rapid and efficient tandem mass spectrometry methodologies using a Waters Quattro micro-HPLC Alliance system to quantify two urinary Fabry disease biomarkers: Gb3 (4 min-assay) and globotriaosylsphingosine (lyso-Gb3) (6 min-assay) analyses normalized to creatinine (creat). We characterized urinary lyso-Gb3 by time-of-flight mass spectrometry on a Waters Synapt UPLC-QTOF MS (Ultra-Performance Liquid Chromatography-Time-of-flight mass spectrometry) system, since it was previously only detected in blood. Validation of both methodologies for clinical use gave good coefficients of variation for intra-day and inter-day assays (<13%). Normal values were established for adult Gb3 (<25 ug/mmol creat) and lyso-Gb3 (none found in the control cohort). Other objectives of this study were to identify and characterize novel disease-specific biomarkers in patients affected with Fabry disease that reliably reflect disease progression and severity, and thereby facilitate the evaluation of new therapies by improved monitoring of the response to treatment. We employed a time-of-flight mass spectrometry metabolomic approach. Urine and plasma samples from untreated and treated Fabry patients were evaluated and compared to age-matched controls. All samples were analyzed on a UPLC-QTOF MS Synapt system. Results processed with MarkerLynx (Waters) were downloaded in EZInfo (Umetrics) for multivariate data analysis such as principal component analysis (PCA) and orthogonal partial least square-discriminant analysis (OPLS-DA). We detected specific analogs in both biological fluids under study: in plasma, we found three novel lyso-Gb3 analogs at m/z 802; m/z 804; and m/z 820 and four other urinary analogs of lyso-Gb3 at m/z 758; m/z 774; m/z 800; and m/z 836. A m/z 784 analog was found in both biological fluids. Area counts for Fabry analogs were compared to controls. We found that some urinary analogs presented higher area counts than lyso-Gb3. We confirmed that all analogs are lyso-Gb3 sphingosine moiety modifications. Correlations between the presence and amounts of various disease-specific analogs and specific indices of clinical severity are in progress. To our knowledge, this metabolomic study using time-of-flight mass spectrometry is the first to demonstrate the presence of analogs of lyso-Gb3 potentially quantifiable by tandem mass spectrometry. The next step will be to synthesize efficient standards to accurately measure the amounts of these biomarkers in biological fluids. This will lead to the evaluation of correlations to determine disease-severity and progression in Fabry disease patients.

**Brief Biography of the Speaker:** Dr. Auray-Blais is the Director of the Quebec Provincial Mass Urinary Screening Program for hereditary metabolic disorders since its inception more than 35 years ago. She is a pioneer in mass urine screening having developed the infrastructure, techniques and methodology permitting the urinary screening of 2 800 000 newborn babies in the province of Quebec for 25 disorders of amino acids and organic acids. She holds a Ph.D. in radiobiology from the Faculty of Medicine and Health Sciences at the Universite de Sherbrooke and postdoctoral studies from Duke University Medical Center in North Carolina, US. She has a masters degree in Health Law from the Faculty of Law at the University de Sherbrooke and a bachelors degree in biochemistry. She is the author of 150 publications, abstracts and articles. She is a professor in the Service of genetics in the Department of Pediatrics at the Faculty of Medicine and Health Sciences at the Universite de Sherbrooke and a researcher at the Clinical Research Centre Etienne-Le Bel in the Mother-Child Axis. She is the Scientific Director for the Waters-CHUS Expertise Centre in Clinical Mass Spectrometry. She is the principal investigator and co-investigator in numerous research grants. She has received awards for her involvement and expertise in screening inborn errors of metabolism in newborns in the Province of Quebec.

## Plenary Lecture 7

### Gender Differences in the Phosphorus Content of the Sino-atrial Nodes and Other Cardiac Regions of Monkeys



**Professor Yoshiyuki Tohno**

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**Abstract:** To examine whether there were gender differences in the sino-atrial node (SAN), the author investigated the gender differences in the SAN using monkey hearts by direct chemical analysis from a viewpoint of element contents. The used rhesus and Japanese monkeys consisted of 30 males (average age=6.5±7.5 years) and 30 females (average age=12.2±10.3 years), ranging in age from newborn to 30 years. The SAN tissues were removed from the anatomical position of monkey hearts and were confirmed by means of histological observation. After incinerating with nitric acid and perchloric acid, element contents of the SANs, such as Ca, P, S, Mg, Zn, Fe, and Na, were determined by inductively coupled plasma-atomic emission spectrometry. In addition, gender differences in the right atrial walls, left ventricular walls, mitral valves, and left coronary arteries of monkeys were also investigated as controls. It was found that the P content was significantly higher in females than in males in the SANs of the monkeys, but the other six element contents, Ca, S, Mg, Zn, Fe, and Na, were not significantly different between males and females in the SANs of monkeys. Regarding the P content, a similar finding was also obtained in both the right atrial walls and the left ventricular walls of monkeys, but it was not obtained in the mitral valves and the left coronary arteries of monkeys. The P content of tissue is mostly determined by the nucleic acid (DNA and RNA) content and the phospholipid content of tissue. Nucleic acids in the cell nucleus and the cytosol, and phospholipids in the cell membrane are all indicators of metabolically active cells. It is reasonable to presume that the P content in the SAN indicates the active cell density, namely, the number of active cells per volume. Therefore, there is a possibility that the active cell density of the SAN is significantly higher in females than in males.

**Brief Biography of the Speaker:** Yoshiyuki Tohno was born in Osaka, Japan, in 1944. He graduated from Nara Medical University, Japan, in 1969. He received the Medical Doctor degree from Nara Medical University, Japan, in 1984. From 1984 to 1996, he was an Associate Professor at the Department of Anatomy, Nara Medical University. From 1996 to 2009, he was a Professor at the Department of Anatomy, Nara Medical University. In 2009, the title of Professor emeritus was bestowed upon him from Nara Medical University. Since 2004, he has been a Visiting Professor at Fujian Medical University, P. R. China. From 2009 to present, he has been a Visiting Professor at the Department of Anatomy, Faculty of Medicine, Chiang Mai University, Thailand. He is mainly interested in compositional changes of human tissues, such as the arteries, cardiac valves, sino-atrial node, myocardium, brain, cartilages, bones, ligaments, and tendons with development and aging. He is an active member of New York Academy of Sciences, a member of International Association of Bioinorganic Scientists, a member of Fuzhou Giant Panda Research Center, P. R. China, a member of Primate Research Institute of Kyoto University, Japan, and on the Editorial Boards of Nephrology: Advances and Applications and ISRN Vascular Medicine.

## Plenary Lecture 8

### Regulation of Morphogenesis and Gene Expression by Mechanical Forces



**Professor Lev V. Belousov**  
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**Abstract:** In recent decades an extensive amount of data was accumulated, pointing to important role of endogenous mechanical forces in regulating several aspects of cell activities: movements, acquiring of polarity, vesicular transport and gene expression. We review these data with a special emphasis to the regulative role of self-produced mechanical stresses in morphogenesis and cell differentiation. We show that the interaction of the passive (coming outside a given embryo part) and the active (generated inside this very part) mechanical stresses is an important link in self-organizing circuits which are driving forth embryonic development. The applications of this concept to medicine and biotechnology are discussed.

**Brief Biography of the Speaker:** Born 1935 July 18th in Sankt-Petersburg (former Soviet Union). In 1952-1957 I was a graduate student and in 1957-1960 a postgraduate student, Lomonosow Moscow State University (MSU), Faculty of Biology. In 1961 I got a Candidate Degree (equivalent of the European and USA Doctors degree) for the dissertation entitled "Cellular Processes in Development of Hydroid Polyps". Since 1984 I am Professor of Embryology, MSU. In 2002 got a title of Honorary Professor, MSU (which does not mean a retirement from the former position). My main field of interest is embryonic morphogenesis, including its biophysical, cellular and model aspects. Author of more than 200 papers, including 4 monographs (among them "The Dynamic Architecture of a Developing Organism", Kluwer Acad Publ., 1998). Member of the Russian Academy of Natural Sciences. American Association of Anatomists, Editorial Boards of the Russian Journal of Developmental Biology and Rivista di Biologia (Theoretical Biology Forum). Awarded by Carlo Bondy Prize (University of Perugia, Italy) and Alexander Kowalevsky Prize (Russian Academy of Sciences).

## Plenary Lecture 9

### Clinical Pharmacology of Non-Opoids in Young Women: The Impact of Pregnancy, Postpartum and Co-Medication



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**Abstract:** To assess potential pregnancy related changes, iv loading dose (2 g) paracetamol pharmacokinetics shortly following caesarean section were collected and compared to a similar dataset of 14 female healthy volunteers. Individual pharmacokinetics were calculated assuming a linear one compartment model with instantaneous input, first order output. Median clearance (15.5 vs 20.3 l/h,  $p < 0.01$ ) and distribution volume (43.7 vs 58.3 L,  $p < 0.001$ ) were significantly higher post caesarean section. Even after correction for body surface area, this increase in clearance (9.6 vs 10.9 l/h.m<sup>2</sup>) remained significant ( $p < 0.05$ ). Immediately following caesarean, paracetamol clearance (+35%) and distribution volume (+30%) are increased compared to healthy adult volunteers. When further focusing on within pregnancy differences, covariates of between subject variability (preterm vs term, maternal disease vs healthy, twin vs singleton) within this cohort were explored (Mann Whitney U). Median clearance was 20.3 (11.8-62.8) l/h or - when corrected for body surface area – 10.9 (range 7-28.3) l/h.m<sup>2</sup>. No significant effect of twin (n=8) pregnancy or maternal co-morbidity (n=3) was observed, but median clearance after preterm delivery (n=12, <37 weeks gestational age) was significantly higher (23.2 vs 19.8 l/h and 12.6 vs 10.2 l/h.m<sup>2</sup>, both  $p < 0.05$ ) compared to term (n=22) delivery. Similarly, there was a difference in median distribution volume (0.75 vs 0.69 l/kg,  $p < 0.05$ ), resulting in the absence of differences in median elimination half life (108 vs 119 min). Women who underwent a preterm caesarean had a higher paracetamol clearance compared to term cases. Consequently, we suggest to reconsider iv paracetamol dosing, with potential additional value to either use higher doses or shorter time intervals in preterm cases. We encourage caregivers to perform similar within-pregnancy studies for other drugs administered in this population because of absence of pharmacokinetic data.

**Brief Biography of the Speaker:** Karel Allegaert, MD, PhD graduated from the Katholieke Universiteit Leuven as medical doctor (1994), with a subsequent training in Pediatrics/Neonatology (2001) and Clinical Pharmacology (2005). Following the presentation of his PhD defence (neonatal analgesia: towards an integrated approach), he further combined clinical care as a consultant of the neonatal intensive care unit, University Hospitals Leuven with clinical research with specific emphasis on perinatal clinical pharmacology (special populations, including preterm neonates and pregnancy). He was appointed as associated professor of the Katholieke Universiteit Leuven in 2005, and subsequently further developed these research activities, currently reflected in about 200 publications in national and international journals, conference proceedings and chapters in book. His clinical research has (FWO clinical doctoral grant) and still is supported by a Fundamental Clinical Investigatorship (2009-2013) of the FWO Vlaanderen. This research also resulted in several awards of the Belgian Academy of Medicine and Sciences (Govaerts award for Clinical Toxicology 2006-2008, and Heymans Award Clinical Pharmacology 2002-2004), the Belgian Pain Society (2005), and the Galenus price, clinical research pharmacology, Belgium (2009).

## Plenary Lecture 10

### Implementation of Clinical Pharmacology Course in the Curriculum for Pregraduate Medical Students and Its Vital Importance



**Dr. Hundie Tesfaye**

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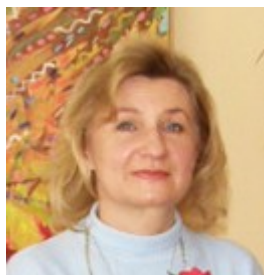
**Abstract:** General pharmacology is usually taught as a preclinical subject during the early years of studying medicine. In most countries, the practice of medicine begins in the years before graduation and in most medication errors are blamed on newly qualified young Physicians, who have not had a thorough grounding in Clinical Pharmacology, therapeutic drug monitoring (TDM), and Clinical Toxicology, when treating special populations and clinical conditions in particular. Evidence of poor prescribing is widespread including overuse of medicines, underuse of effective medicines, events of avoidable adverse drug reactions. Junior doctors who have recently graduated may be responsible for much of the prescribing that takes place in hospitals and are implicated in many of the adverse medication events. Analysis of such events suggests that lack of knowledge and training underlies many of them and dedicated training can make improving. It is a matter of increasing concern that recent changes to undergraduate medical education may have reduced exposure to clinical pharmacology, a discipline dedicated to optimal practice in relation to medicines. In modern medical practice and this era of evidence based medicine, students may learn from many sources including high quality scientific literatures, books, both in hard copy and electronic forms. With the large amount of theoretical information that medical students need to absorb there is little time to learn about rational pharmacotherapy and its application to patient management. Therefore the teaching of clinical pharmacology including therapeutic drug monitoring before graduation may be a valuable method of training future young physicians in order to lead to better drug utilization and rational prescription.

The aim of this paper is to demonstrate innovative and visible way of better educating medical students for better medicine utilization and optimal patient care by case oriented interactive teaching and learning methodology.

**Brief Biography of the Speaker:** The author is MD, and PhD graduate of the Charles University, in Prague. Trained as Paediatrician and later as Clinical Pharmacologist, holds Board Certificate from the Institute for Postgraduate Education in Medicine. His present position is consultant in clinical pharmacology at the faculty hospital. The main interest and consultancy area of the author is in particular therapeutic drug monitoring in needy patients including, paediatric and geriatric populations given their pharmacokinetic/pharmacodynamic differences and vulnerability. The author participated in bioequivalence studies and clinical trials including as principal investigator and co-investigator. He is also dedicated to aid dosage adjustment for transplantation patients, oncology patients and others in intensive care including those with renal failure. The author participates in pregraduate and post graduate education both as a faculty member and as invited speaker in the field of clinical pharmacology. With dedication for safe and better use of medicines for human wellbeing, the author is recently recipient of a grant FRVS 2011 to include clinical pharmacology education in the curriculum targeting 5th year medical students.

## Plenary Lecture 11

### Current Situation and New Possibilities in Pharmacology of Parasitic Infections



**Dr. Gabriela Hrcakova**  
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**Abstract:** Parasitic worms are exceptionally successful infectious agents and as many as two billion individuals harbour these parasites, mostly in developing countries. Millions of humans are simultaneously infected with filariae, hookworms, whipworms, large round worms and /or schistosomes. The most dangerous parasitic infection of the Northern hemisphere is alveolar echinococcosis and a closely related cystic echinococcosis. Only a few classes of anthelmintic drugs were discovered by an empirical approach in the last century. Of these benzimidazole carbamates and praziquantel are still used to treat various human infections. However, their limited efficacy against the larval stages of helminths and increasing drug resistance indicate the need of an alternative treatment approaches and searching of the novel drugs among the natural-product extracts. In our study we focussed on medically important larval stages of several nematode and cestode species, and cestode laboratory model *Mesocestoides vogae*. Our findings demonstrated that the efficacy of benzimidazole carbamates and praziquantel can be markedly improved after their incorporation into suitable drug carriers, which changed pharmacokinetic properties of drugs such as short plasma circulation time and the bioavailability. Application of the immunomodulatory substances such as polysaccharide glucan and flavonoid silymarin offered a very effective tool to activate the host immune defence, which is down-regulated by parasite-derived molecules. Finally, our approach to combine drug with natural substance entrapped in carriers proved to have multiple advantages over the classical therapy, regarding the drug efficacy and host pathologyphysiology.

**Brief Biography of the Speaker:** Gabriela Hrcakova graduated the University of P.J.Safarik , Faculty of Sciences in Kosice, Slovakia where she completed Master's degree in biology. She achieved PhD degree in 1993 from the Institute of Parasitology, Slovak Academy of Sciences of the Slovakia and got position as research scientist. Currently she is principal investigator and Head of laboratory of Molecular and Experimental Pharmacology at this Institute and the externallecturer at School of Biology of Faculty of Sciences. Since 2009 she works for private Pharmaceutical Company in Slovakia as Consultant in Pharmacology. Her background in the pharmacology of infectious diseases extends over more than 20 years of research. She studies the effects of anthelmintic drugs and natural immunomodulators on host pathophysiology, cell biology and signalling, modulation of molecular and immunological pathways and biomarker expression using multidisciplinary approach. She is author or co-author of over 55 scientific papers and chapter in international book on *Toxocara* nematode published by CABI Publisher, UK. She regularly presents results at international conferences.

## Plenary Lecture 12

### Reverse Rate-Dependent Nature of Drug-Induced Changes in Action Potential Duration Is an Intrinsic Property of Mammalian and Human Myocardium



**Professor Peter P. Nanasi**  
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**Abstract:** All currently used class 3 antiarrhythmics carry serious proarrhythmic risk, which is associated with lengthening of action potential duration (APD) in a reverse rate-dependent manner, i.e. lengthening of APD is greater at longer than at shorter cycle lengths. Although several theories have been developed so far to explain this reverse rate-dependency, its mechanism has not been fully clarified. Here we propose a simple mechanism to explain the reverse rate-dependency of drug effects in the mammalian heart. Rate-dependent drug-effects of various origin were studied using agents known to lengthen or shorten action potentials allowing thus to determine the drug-induced changes in APD as a function of the cycle length. Both drug-induced lengthening and shortening of APD displayed reverse rate-dependency in human, canine, and guinea pig preparations, but not in rabbit and rat myocardium. Similar results were obtained when repolarization was modified by injection of inward or outward current pulses in isolated canine cardiomyocytes. In contrast to reverse rate-dependence, drug-induced changes in APD well correlated with baseline (pre-drug) APD values in all preparations studied. Since the net membrane current, determined from the action potential waveform was inversely proportional to APD, and consequently to cycle length, it is concluded that that reverse rate-dependency may simply reflect the inverse relationship linking net membrane current to APD. In summary, reverse rate-dependency is an intrinsic property of drug action in the hearts of species showing positive APD - cycle length relationship, including humans. This implies that development of a pure K<sup>+</sup> channel blocking agent without reverse rate-dependent effects has little chance to succeed. A more promising approach might be to combine prolongation of action potential duration with interventions suitable to minimize arrhythmogenesis at slow heart rates. This can likely be achieved by combining K<sup>+</sup> channel blocking drugs with blockers of plateau inward currents, such as L-type Ca<sup>2+</sup> current and window Na<sup>+</sup> current. This view is supported by the results obtained by either combining two distinct molecules, or by applying single drugs having intrinsically combined modes of action.

**Brief Biography of the Speaker:** Peter P. Nanasi was born in 1956, at Debrecen, Hungary. He graduated from the University Medical School of Debrecen with an M.D. degree in 1980. He obtained his Ph.D. degree in 1992, and he received the D.Sc. degree from the Medical Branch of the Hungarian Academy of Sciences in 1999. From 1980, he has been working at the Department of Physiology, University of Debrecen - as a full professor since 2002. At the same time, he is the chairman of the "Department of Oral Physiology and Pharmacology" at the Faculty of Dentistry since 2001. During his career, he has spent 2 years in the United States, at the Children's Hospital Medical Center and at the Department of Pharmacology and Cell Biophysics, University of Cincinnati, Ohio with professors David A. Lathrop and Shirley H. Bryant. His research interest covers the physiology and pharmacology of cardiac ion channels, including the frequency-dependent interactions, regulation of action potential duration, and cellular mechanisms of antiarrhythmic and proarrhythmic actions. He is member of the Physiological Society, British Pharmacological Society, European Working Group on Cardiac Cellular Electrophysiology, MyoNaK, and the International Academy of Cardiovascular Sciences. He has published 119 full length papers (IF=310) and 6 book chapters in English language. He was also involved in more than 160 lectures and posters in the field of cellular cardiac electrophysiology.

## Plenary Lecture 13

### Pharmacogenomics of Romany People



**Professor Bela Melegh**

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**Abstract:** The Roma (Romani, Gypsy) people represent a unique population of the world as they do not belong to a single nation state; they use numerous different languages, and they belong to various social, cultural, and religious groups. They are dispersed throughout Europe and often migrate from region to region. Having no written history or genealogy, their origin and migration during the nomadic periods of their history remains unknown. Their population size is estimated to be in the range of 10-15 million in Europe, with the largest populations in Eastern-Europe. Their population growth rate is higher than that of the surrounding populations. The geographically dispersed Roma populations, often referred to as the “invisible minority”, have been socially marginalized and historically often persecuted. Previous genetic and linguistic studies suggest an Indian origin. We analyzed data from six Roma groups by genotyping hundreds of thousands of SNPs, and confirmed that the Roma have shared ancestry with Europeans and South Asians. We estimate that the Roma harbor 83% West Eurasian ancestry with an average estimate of about 27 generations or 800 years for an admixture date of the ancestral groups, consistent with the historically attested arrival of the Roma to Europe from India. They differ genetically from the major EU populations in several medical aspects, as well. They have unique diseases with specific founder mutations, including specific neuromuscular phenotypes. When compared with other populations, we have been able to verify unique signatures in pharmacogenetically relevant SNPs and haplotypes in MDR1, and various CYP metabolizing systems based on analyzing biobanks of Roma population samples. Besides these multiple-metabolizing systems, we have identified differences in specific metabolizing enzymes or systems, like VKORC1, MTHFR, PON1, and P2RY12, as well as other systems that also contribute directly or indirectly to personalized therapy, like APOA5, GCKR, MLXIPL, GALNT2, and TRIB1.

**Brief Biography of the Speaker:** Bela Melegh, MD, PhD, DSc, graduated at the University of Pecs; now he is professor of medical genetics and pediatrics, head of the Department of Medical Genetics, University of Pecs, Hungary. His long-term scientific interest includes the investigation of the investigation of carnitine in humans, carnitine deficiency conditions. As a natural extension, this led to the inclusion of some neuromuscular diseases, including mtDNA and triplet extension associated conditions to the research fields. He is a leader of the national biobank consortium (member of Biobanking and Biomolecular Research Infrastructure; BBMRI); using biobank collections his group performs population genetic research also on many rare and common disease entities; the group has numerous international collaborations. The Roma collection provides an exceptional position for pharmacogenomic research in his department. He is currently president of Hungarian Society of Human Genetics, he is board member of European Society of Human Genetics, member of the European Board of Human Genetics. Dr. Melegh is authored over 200 peer-reviewed research articles.



## Plenary Lecture 14

### Therapy-Related Leukemia/Myelodysplastic Syndrome in Multiple Myeloma



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**Abstract:** Although recent advances in combination chemotherapy, high-dose radiotherapy, and combination of chemotherapy and radiotherapy have prolonged the survival time of cancer patients, developments of therapy-related malignancy have increased. We experienced 9 cases of therapy-related leukemia/myelodysplastic syndrome (TRL/TMDS) during the treatment of multiple myeloma (MM). Of 177 MM cases treated with combination chemotherapy for induction or maintenance therapy in our department between 1988 and 2008, 9 cases were diagnosed of TRL/TMDS. There were 6 males and 3 females and the median age at the diagnosis of TRL/TMDS was 69 years (54-78yrs). All 4 cases of TRL were myelogenous leukemia. In 5 cases of TMDS, there were 2 refractory anemia, 1 refractory anemia with excess blasts (RAEB) and 2 chronic myelomonocytic leukemia (CMML). In 6 cases, the cumulative dose of melphalan exceeded 800 mg. The remission induction chemotherapy was performed in 3 cases and complete remission was achieved in 1 case and 2 were partial remission. In cases of TMDS, transfusion alone was performed in 2 cases, and controlling the white blood cell count alone in 3 cases. Regarding the outcome, the median survival time was 6 months (follow-up period: 1-40 months). One patient has survived for more than 40 months, while 8 cases died caused of TRL or TMDS. The prevention of TRL/TMDS has become an important problem and careful long-term follow-up with periodic blood test is necessary after chemotherapy.

**Brief Biography of the Speaker:** Associate Professor Kazuhiko Natori entered Tokyo college of Pharmacy division of biochemical pharmacy at April 1983 and graduated at March 1987. In 1989, he entered Toho university school of medicine and graduated March 1995. Now, he is head of Hematology & Oncology since 2009, and central director of chemotherapy center and chairman of chemotherapy committee since 2010. He is member of council as for Japan Society of Clinical Oncology and Japanese Society of Chemotherapy. Also he is member of council as for small study parties. He is mainly related to the chemotherapy whole now. The theme of the research is double cancer, cancer family history and carcinogenesis. He wants to amplify knowledge to the chemotherapy whole and to live in the future.

## Plenary Lecture 15

### Significant Number of Elderly Patients Live with Potentially Toxic Levels of Digoxin Most Probably Overlooked for Long Enough



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**Abstract:** Digoxin continues to be an important drug in long-term heart failure patient management. Digoxin serum levels monitoring is aimed to optimise therapy, whereas the concentration required for optimal efficacy without risking toxicity remains not clearly defined even post Digitalis Investigation Group (DIG) recommendation.

**Objectives:** This study was aimed to assess how frequently occur the so-called toxic digoxin levels in elderly patients being treated in faculty hospitals.

**Methods:** Retrospective search for serum digoxin trough levels record as determined throughout the period of two years was conducted in two independent hospital facilities. Only digoxin levels > 2ng/mL in patients older than 65 years were included. Potassium and serum creatinine levels were also evaluated if available with consecutive digoxin levels. Data from 301 hospitalised patients (91 males, 210 females) were valid for the purpose of this study.

**Results:** Total of 427 trough levels (sampled shortly before the next doses) from patients within age 66-100 years were found to be above the upper therapeutic limits of the older dates or post DIG study recommendations. Serum digoxin levels recorded showed values, Max. 6.19, Mean  $3.129 \pm 0.70$ , Mode 2.8, and Median 3 ng/mL, respectively. Women were found to have high digoxin levels more than twice frequently as men on similar oral doses of 0.125 - 0.250 mg per day in this study. Although elevated in some individuals, plasma potassium and serum creatinine did not show clear relation with serum digoxin concentrations.

In conclusion, this retrospective study demonstrated that significant number of elderly patients live with potentially toxic levels of digoxin most probably for long time, before being discovered. The levels are far from the range recommended post DIG study and warrant special attention to this patient population.

**Brief Biography of the Speaker:** The author is MD, and PhD graduate of the Charles University, in Prague. Trained as Paediatrician and later as Clinical Pharmacologist, holds Board Certificate from the Institute for Postgraduate Education in Medicine. His present position is consultant in clinical pharmacology at the faculty hospital. The main interest and consultancy area of the author is in particular therapeutic drug monitoring in needy patients including, paediatric and geriatric populations given their pharmacokinetic/pharmacodynamic differences and vulnerability. The author participated in bioequivalence studies and clinical trials including as principal investigator and co-investigator. He is also dedicated to aid dosage adjustment for transplantation patients, oncology patients and others in intensive care including those with renal failure. The author participates in pregraduate and post graduate education both as a faculty member and as invited speaker in the field of clinical pharmacology. With dedication for safe and better use of medicines for human wellbeing, the author is recently recipient of a grant FRVS 2011 to include clinical pharmacology education in the curriculum targeting 5th year medical students.

## Plenary Lecture 16

### The Neurotrophic Roles of Extracellular Guanosine



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**Abstract:** In addition to adenine-based purinergic intercellular signaling systems involving adenine, adenosine and adenosine phosphates, over the last 20 years analogous guanine-based systems have been identified. Most of these systems are involved in "trophic" effects which affect the growth, differentiation and survival of various cells. Guanine-based purinergic signaling specifically has been investigated in cells of the nervous system and muscle. Guanine-based purines are released from cells, and when cells are damaged the release increases substantially. Under conditions simulating ischemia, the extracellular concentration of guanine-based purines such as guanosine is as high or higher than that of their adenine-based counterpart, adenosine. To date, most of the effects of extracellular guanosine are long term 'trophic' influences—relating to growth, proliferation and survival of cells. Recently, we discovered that guanosine may have potentially important implications for the biology of the nervous system. First, extracellular guanosine, unlike adenosine, does not cause apoptosis and actually protects against apoptosis caused by a number of stimuli through activation of the cell survival pathways such as MAPKinase and PI3Kinase/AKT. In addition to its neuroprotective activity, guanosine also improved motor behaviour and stimulated adult intrinsic progenitor/stem cells that assist in the restoration of function in both chronic spinal cord injury and a proteasome-induced chronic Parkinson's model. There is evidence that, in some cases, guanosine produces its effects by entering cells and interacting with neurotrophic factors. However, there is further evidence that guanosine may interact with unique receptors on the surface of cells as well. Moreover, guanosine is metabolized to guanine by the enzyme purine nucleoside phosphorylase (PNP). Experimental studies have indicated that exogenous extracellular guanosine is relatively persistent compared with adenosine, but a large proportion of guanosine is metabolized to guanine. Emerging evidence indicates that guanine may also have its own extracellular signaling system that is distinct from guanosine. This would be of particular interest since guanine deaminase, the enzyme that metabolizes guanine, shows 50-fold regional variations in the brain. This degree of regional variation is characteristically associated with enzymes that degrade neurotransmitters. It appears that the concept of intercellular signaling by guanine-based purines is now well substantiated. Since GTP, GMP, guanosine and guanine have different biological effects, different receptive mechanisms and likely different signal transduction mechanisms, we are presented with an intriguing theory that the extracellular interconversion of these guanine derivatives provides an extra layer of intercellular signal regulation.

**Brief Biography of the Speaker:** Dr. Jiang graduated with a medical degree and undertook postgraduate clinical training and specialized as a Pathologist in China. Then she obtained M.Sc. in Biophysics in Shanghai and a Ph.D in Neurobiology from the Federal Institute for Neurobiology in Germany. She undertook her postdoctoral training at McMaster University and won a national award for research excellence. Her research program addresses the mechanisms responsible for the neuroprotection and neurorestoration following central nervous disorders, particularly, stroke and spinal cord injury. Currently, Dr. Jiang is an associate professor in Neurosurgery and Neurobiology, and the head of Hamilton NeuroRestorative Group (NRG). She is author of over 90 papers published in international journals and invited book chapters. She has been frequently invited to present her work nationally and internationally. She is on the Editorial Board of the European J Inflammation, and a reviewer for a large number of scientific journals and a member of committee and external reviewers for national and international peer-review grant agencies.

## Plenary Lecture 17

### **Applicability Didactical Instruments PUD-BJ In Improving Individual's Handwriting Style In Medical Purposes During The Rehabilitation Of Individuals After The Stroke**



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**Abstract:** Successfulness of the contemporary method of initial literacy was the research's matter. Our aim was to manufacture innovative instruments for reading and writing that can be used for preschool children – electronic didactic tablets, anatomically designed pen and sound picture books, and to test them in practice in kindergartens, first grades of nine-year primary school, programmes for children with special needs and with illiterate adults. Moreover, we questioned the current method of the initial literacy. We do not believe in the reasonableness of writing over-dimensional letters on the blackboard and in the notebook as this takes children too much energy and is completely inadequate since we do not write with the shoulder and the elbow, but we with the twist of the wrist and usually with three fingers.

That is why we started to think how we could make initial reading and writing easier and of a shorter way to literacy. The idea's concept was an electronic didactic tablet. To make reading more pleasant, there is a picture book, available in classic and electronic sound form.

Furthermore, to make the writing table even more useful and attractive we added additional electronic devices which enable:

- the display of the number of the repetitions of writing on electronic tablet (LCD display),
- rewarding the user after certain number of repetitions with automatic sound play of melodies from the sound picture book,
- the possibility of connecting with the PC which would increase didactic tablet's applicability (vocal dictating letters, keeping statistics...).

The results of the research showed extraordinary successfulness of our innovative method after only a fourteen day usage of the instruments. In conclusion we came to cognition of didactical instruments applicability in improving individual's handwriting style and in medical purposes during the rehabilitation of individuals after the stroke.

**Brief Biography of the Speaker:** Jozica Bezjak is a professor of education at the University of Primorska. In the field of education she graduated, made her master and her PhD she made out of contemporary materials and technologies at the University of Ljubljana, Faculty of natural sciences and engineering. She takes the science research of new materials and technologies out of medicine and technique – shape memory alloys, contact materials in microelectronics and technik. Her second degree she achieved in a special field of engineering pedagogic: »ING – PEAD IGIP«. Afterwards he made her second PhD out of engineering pedagogic at the Alpen Adria University of Klagenfurt in Austria. Science 1986 she take her research, science and pedagogic work on the different science and pedagogic institutions: University of Ljubljana, Faculty of natural sciences and engineering, University of Ljubljana, Faculty of pedagogic, University of Primorska, Alpen Adria University Klagenfurt, University Usti nad Labin (Czech Republic). At the University Usti nad Labin she taught courses at the graduated and post-graduated program mathematic-technic, physic-technic and pedagogic.

More than 692 works of her is to find in COBISS, of which more than 20 monographs. She received numerous of honors and awards – Sokrates excellence SOVA for the highest achievements in the field academic didactic ("special engaged and excellent teaching in higher education"), she was awarded with the highest national award of Slovenia for the highest achievements in scientific research and teaching (2005). She is the president of the Association of Teachers of technical creativity of Slovenia. Over the last ten years (2003 - 2011) was also president of the Organizing and Scientific Committee and editor of the International Scientific Symposium "Technical creativity in school's curricula with the form of projectlearning "From idea to the product" - from the kindergarten to the technical faculty", Portoroz, Slovenia.

## Plenary Lecture 18

### Reversible Canalicular Mrp2 Localization Induced by Intracellular Redox Status



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**Abstract:** Multidrug resistance-associated protein 2 (MRP2/ABCC2) and bile-salt export pump (BSEP/ABCB11) are involved in the formation of bile-salt-independent and -dependent bile flow, respectively. MRP2 is expressed statically on the canalicular surface, but MRP2 dynamic insertion and internalization processes are also important, because the steady-state expression level of MRP2 is directly dependent on its turnover rate. The disruption of these turnover rates is suggested to lead to cholestatic jaundice. Disrupted canalicular localization of MRP2 has been observed in patients with chronic cholestatic disorder and hepatic failure, i.e., primary biliary cirrhosis (PBC) and hepatitis C virus (HCV) infection. Oxidative stress markers were also closely correlated in these chronic liver failure patients. These observations suggest that both mRNA expression of canalicular transporters and their localization are equally important in human liver failure. We have shown that Mrp2 internalization is observed when acute oxidative stress is induced in rat livers. Mrp2 localization returns to the canalicular membrane after replenishment of intracellular glutathione (GSH). Microtubule polymerization and protein kinase A (PKA) are essential factors in the Mrp2 sorting process, which suggests that the balance between PKC activation and PKA activation is a key regulation targets of reversible Mrp2 trafficking. On the other hand, radixin is required for the canalicular localization of Mrp2. A change in the phosphorylation status of radixin reversibly regulates the protein interaction between the phosphorylated radixin (p-radixin) and Mrp2, and the redox-sensitive canalicular localization of Mrp2.

**Brief Biography of the Speaker:** Toshiharu Horie graduated from the University of Tokyo, Faculty of Pharmaceutical Sciences in 1972. After he graduated from its Graduate School of Pharmaceutical Sciences, he got a position of an assistant professor in Tokyo University of Pharmacy and Life Sciences, and then, became an associate professor in 1992. He moved to Chiba University, Faculty of Pharmaceutical Sciences as a professor in 1994 and became a professor of Chiba University, Graduate School of Pharmaceutical Sciences in 2001. His research area is biopharmaceutics and drug toxicity.

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