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# **RECENT ADVANCES IN CLINICAL MEDICINE**

- **Proceedings of the International Conference on Medical Pharmacology (PHARMACOLOGY '10)**
- **Proceedings of the International Conference on Medical Histology and Embryology (HISTEM '10)**
- **Proceedings of the International Conference on Oncology (ONCOLOGY '10)**
- **Proceedings of the International Conference on Psychiatry and Psychotherapy (PSYCHO '10)**

**University of Cambridge, UK, February 23-25, 2010**

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**Preface**

This year the International Conference on MEDICAL PHARMACOLOGY (PHARMACOLOGY '10), the International Conference on MEDICAL HISTOLOGY AND EMBRYOLOGY (HISTEM '10), the Proceedings of the International Conference on ONCOLOGY (ONCOLOGY '10) and the Proceedings of the International Conference on PSYCHIATRY AND PSYCHOTHERAPY (PSYCHO '10) were held at the University of Cambridge, UK, February 23-25, 2010. The conferences remain faithful to their original idea of providing a platform to discuss pharmacogenetics, physiology of drugs, drug legislation and safety, medicinal chemistry, nanoscience in pharmacology, surgery and histology, immunohistochemistry, embryogenesis, general oncologic issues, chemotherapeutic agents, radiation oncology, mathematical models in cancer, hormone manipulation, immunohistochemistry, alzheimer's disease, autism, neurology, psychotherapy, psychoanalysis etc. with participants from all over the world, both from academia and from industry.

Their success is reflected in the papers received, with participants coming from several countries, allowing a real multinational multicultural exchange of experiences and ideas.

The accepted papers of these conferences are published in this Book that will be indexed by ISI. Please, check it: [www.worldses.org/indexes](http://www.worldses.org/indexes) as well as in the CD-ROM Proceedings. They will be also available in the E-Library of the WSEAS. The best papers will be also promoted in many Journals for further evaluation.

Conferences such as these can only succeed as a team effort, so the Editors want to thank the International Scientific Committee and the Reviewers for their excellent work in reviewing the papers as well as their invaluable input and advice.

The Editors



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## Plenary Lecture 1

### Clinical Pharmacology in Neonates: Extensive Interindividual Variability despite their Young Age



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**Abstract:** Neonatal drug dosing needs to be based on the physiological characteristics of the newborn and the pharmacokinetic parameters of the drug. Size-related changes can in part be modelled based on allometry and relates to the observation that metabolic rate relates to weight by a kg 0.75 trend. Until adult metabolic activity has been reached, ontogeny, i.e. iso-enzyme specific maturation and maturation of renal clearance also contributes to drug metabolism, making iso-enzyme specific documentation of maturation necessary.

Changes in body composition and ontogeny are most prominent in neonates. The body fat content (/kg) is markedly lower and the body water content (/kg) is markedly higher in neonates. These findings have an impact on the distribution volume of both lipophilic and hydrophilic drugs. Drugs are cleared either by metabolism (metabolic clearance) or elimination (elimination clearance). While the first is mainly hepatic, the second route is mainly renal. Both hepatic metabolism and renal clearance display maturation in early life although other co-variables (e.g. polymorphisms, co-administration of drugs, first pass metabolism, disease characteristics) further contribute to the interindividual variability in drug disposition.

Documentation of these maturational processes based on in vivo 'case' studies is of value since these drug-specific observations can subsequently be extrapolated to other drugs which are either already being prescribed or even considered for use in neonates by the introduction of these observations in 'generic physiologically based pharmacokinetic' models.

## Plenary Lecture 2

### Engineering Pharmacology: Pharmacokinetic Models Using Recursive Finite Difference Equations



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University of Medicine and Dentistry of New Jersey  
USA  
and  
Adjunct Associate Professor  
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**Abstract:** Pharmacokinetic models, using recursive finite difference equations (RFDEs), can be derived directly from traditional exponential models. This method has been successfully applied to propofol infusion data. Furthermore, this technique yields identical accuracy, on a subject-specific basis, as the exponential model from which each RFDE model was derived. Specifically, these infusion models are based upon an inhomogenous RFDGE:  $P(k+3) = A?P(k+2) + B?P(k+1) + C?P(k) + R$ . Where A, B, C and R are non-zero constants and P represents plasma propofol levels each kth unit of time. When applied to propofol infusions, RFDE modeling has advantages, over traditional exponential models, in that fewer coefficients are needed and patient-to-patient variation of these coefficients is reduced. However, initial conditions for RFDEs have to be specified. These characteristics, of RFDE modeling of propofol infusions, are similar to those for RFDE modeling of propofol boluses. Based on these findings, as well as those of our prior study, RFDE pharmacokinetic modeling can be applied to both infusion and bolus data of propofol. Further research, on the applications of RFDEs in pharmacokinetics, appears warranted.

#### **Brief Biography of the Speaker:**

Dr. Atlas received his medical degree from Hahnemann University School of Medicine, in Philadelphia, in 1989. In addition, he has a bachelor of engineering degree from Stevens Institute of Technology. Dr Atlas also holds a master of science degree, in biomedical engineering, given jointly from Rutgers University and the University of Medicine and Dentistry of New Jersey.

Dr. Atlas completed his internship, residency and fellowship, in anesthesiology, at the State University of New York Upstate Medical Center. Dr. Atlas is currently an associate professor at New Jersey Medical School, department of anesthesiology, and is a member of the medical staff at University Hospital Newark.

Dr. Atlas has written over 60 scientific publications. He is also adjunct faculty, in the department of biomedical engineering, at both Stevens Institute of Technology and Rutgers University.

## Plenary Lecture 3

### The Role of Local Drug Delivery in the Treatment of Periodontal Diseases



#### Professor Shaila V. Kothiwale

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#### Abstract: Purpose

Diseases of the periodontium continue to be one of the man's most wide spread afflictions. Chronic Periodontitis is one such inflammatory response to microbiological infection resulting in progressive destruction of attachment apparatus with formation of periodontal pocket. The use of controlled release local delivery device to suppress or eradicate the pathogenic microbiota or modulate the inflammatory response has attracted significant interest to limit periodontal tissue destruction. The purpose of this study is to evaluate the clinical and microbiological efficacy of Tetracycline, Metronidazole in sustained release device using non degradable Ethyl cellulose as polymers as a local drug delivery in the periodontal pocket to arrest periodontal disease.

#### Material and methods

3 sites per patient which bled on probing, measuring >6mm associated with molars were randomly allocated to three possible regimes.

The control site C: scaling & root planning

Site A: scaling and root planing with control release tetracycline

Site B: scaling and root planing with control release of Metronidazole.

Base line and follow up measurement (14th day) included clinical parameters with plaque index, gingival index, and probing pocket depth. The microbiological evaluation included Gram stain for cocci and bacilli, and Giemsa stain for spirochetes.

#### Results

In clinical parameters, gingival index revealed a reduction of 69.09% with control site, 77.27% with site A and 83.21% with site B.

Plaque index showed 64.14% reduction in control site, 65.29% in site A, 71.30% in site B and assessment of pocket depth measurement showed 2.27% reduction in control site, 3.27% in site A and 4.58% in site B.

Microbiological evaluation included the reduction of microorganisms by 56.10% in control group, 81.25% in site A and 96.09% in site B.

#### Conclusion

On comparison between and within sites at different intervals, statistically significant improvements were revealed in many clinical and microbiological parameters in all the 3 sites. On comparison between tetracycline plus scaling and root planning and Metronidazole plus scaling and root planning, Metronidazole plus scaling and root planning produced significantly greater effects.

The presentation also includes, presently ongoing projects on newly formulated polymers, namely Hydroxy propyl cellulose (HPC), Hydroxy propyl methyl cellulose (HPMC) and Chitosan with Ornidazole.

#### Brief Biography of the Speaker:

Dr. Shaila V. Kothiwale, is presently a Professor of Periodontics at KLE University, India, where she is engaged in teaching, clinical and research work. Her main area of research interests are LASERS, various bone grafts and Local Drug Delivery systems and Alternative Medicine in Periodontics.

She is presently engaged extensively in working with a new system of various polymers with incorporation of antibiotics in periodontal diseases and prevention of periodontal diseases using medicinal plants. She has authored and co-authored several scientific papers in National and International Indexed Journals. She has delivered key note lectures at different National and International platforms in various speciality conferences like Lasers, Tissue bank and Global aesthetics.

She is a member and an executive member of various organizations. At present she is working on a few chapters of Periodontology to be published under JAYPEE publication.

## Plenary Lecture 4

### In Silico Approaches in Drug Design



**Associate Professor Asad U. Khan**  
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**Abstract:** The aim of this study was to give a hypothesis for designing a drug against most infectious diseases of human being. There are seven steps in the drug discovery process: disease selection, target hypothesis, lead compound identification (screening), lead optimization, pre-clinical trial, and clinical trial and pharmacogenomic optimization. Traditionally, these steps are carried out sequentially, and if one of the steps is slow, it slows down the entire process. These slow steps are bottlenecks and could drastically affect the final outcome of any effort aimed at the drug development. Drug designing is a very time taken and costly process. It is a multistep process where a single mistake in any step could result in loss of huge amount of money and time. According to estimate, the average time and cost for a drug is 12 years and \$270 million from initial discovery to public usage in USA. In silico drug design make the way more easy and time and money saving.

**Brief Biography of the Speaker:**

Asad U Khan, male, molecular biologist, graduated from Biochemistry Department, A M University, Aligarh, India in 1998. He joined Interdisciplinary Biotechnology Unit, A.M University as Asst Professor in 1997 and continued till 2000. He later joined Department of Biochemistry, UMDNJ, New Jersey USA in 2000 for three years as post doctoral Research Associate, working on Transcription biology of Yeast and gene expression. He than resumed his services as Asst Professor in the same department till 2006 and became Associate professor in the Interdisciplinary Biotechnology Unit, AMU, India. He was awarded a prestigious fellowship , BOYSCAST Fellowship from Government of India to work as visiting Scientist in University of Napoli, Italy in 2005. He was also awarded Young Scientist Award of Association of Microbiologist of India in 2006. His work was well recognized and he has been invited several invited talks as well as reviews articles and chapters. He has been in Editorial board of several number of International journals. He has a total of 55 research articles in his credit. He is member of several international associations.

## Plenary Lecture 5

### Long-Term Evaluation of Anti-Interleukin 2 Monoclonal Antibodies as Induction Therapy in Live Donor Kidney Transplantation: A Critical Review



**Assistant Professor Hussein Attia Sheashaa**  
Department of internal medicine & Nephrology  
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**Abstract:** The potential benefits of induction therapy using anti-T-cell antibodies were established. However, the utilization of these agents could be associated with several side effects. Long-term retrospective studies have not shown significant benefit of routine induction by the use of depletion antibody therapy regarding patient and graft survival and it was suggested that patient survival may be impaired as a result of increased early cardiovascular and infection related mortality. Monoclonal antibodies against IL-2 receptors were introduced and tested in the clinical setting. Several reports had documented their therapeutic advantage in cadaveric and live-donors renal transplantation on short-term basis. It was claimed that these agents allow selective immunosuppression without augmented morbidity and/or over-immunosuppression. In my plenary Speech, I'll summarize the advantages and disadvantage of the use of anti- IL-2 antibodies as well as I'll report my center experience.

**Brief Biography of the Speaker:**

Hussein Sheashaa is an assistant professor of Internal medicine and nephrology at Urology and Nephrology Center, Mansoura University, Egypt. His area of expertise is the clinical aspects of live donor kidney transplantation. He authored or co-authored over 60 scientific papers published in reviewed journals or presented at international conferences. He wrote a chapter entitled Schistosomiasis and renal transplantation, a critical review. In: Kidney Transplantation: new research edited by Judith Fox, Nova Science Publisher, inc, pp. 105-123, 2006. He had the opportunity to be a research fellow at Brigham and women's hospital, Harvard University and he is a member of American society of transplantation. Moreover, he is the director of annual Mansoura international hemodialysis course that is held at Urology and Nephrology Center, Mansoura University, Egypt.

## Plenary Lecture 6

### Intensive Care Management of Acute Organophosphate Insecticide Poisoning



**Professor Slavica Vucinic**  
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**Abstract:** Epidemiology: Acute organophosphate insecticide (OPI) poisoning is still an important cause of morbidity and mortality, especially in developing countries. It is estimated that 300000 people die each year, most of them due to deliberate OPI poisoning. Since January 1998 till December 2007, in Serbian National Poison Control Centre 29723 patients were treated, among them 11174 were hospitalized. Pesticide poisonings were registered in 526 patients. Within this group of patients with pesticide poisoning, OP compounds were detected in 296, carbamates in 21, and pesticides having other chemical structures in 209.

Pathophysiology: Better understanding of OPI mechanism of action – irreversible inhibition of acetylcholinesterase, butyrylcholinesterase and all esterase type enzymes, followed by metabolic dysbalance, enforced the development of complex therapeutic regimens.

Therapeutic principles: Patients with acute exposures to organophosphorus compounds should undergo immediate assessment and management of disturbances in airway, breathing, and circulation. Further steps are based on risk assessment and observations during continuous monitoring, including dose ingested, time since ingestion, clinical features, patient factors, and available medical facilities. Patients with moderate or severe organophosphorus poisoning should be admitted to an intensive care unit after resuscitation in order to provide careful titration of antidotes, intubation, ventilation, and inotropes or vasopressors if required. Careful observation is also required because rapid clinical deterioration and death are reported in patients who seemed to be recovering from the acute cholinergic crisis. High quality intensive medical care is a priority as hospital stay may be prolonged, with secondary complications which are an important cause of morbidity and mortality.

Current therapeutic scheme for management of acute poisoning with anticholinesterase pesticides includes general supportive measures (decontamination, respiratory support) and specific pharmacological treatment (atropine, oxime, diazepam). Gastric lavage is the most commonly used form of decontamination in OP poisoning. Since the rate of absorption of OP containing P=O bond from the human bowel is rapid, as indicated by the appearance of symptoms of OP poisoning within a few minutes, gastric lavage should be performed as soon as possible, preferably within 2 hours post ingestion. Administration of oral activated charcoal, in conventional doses, may be considered for reducing further absorption of OP pesticides. However, recent clinical trials designed to evaluate the effectiveness of single and multiple doses of activated charcoal failed to find a significant benefit of either regimen over placebo. Atropine is the mainstay of treatment of effects mediated by muscarinic sensitive receptors, but it is ineffective at the nicotine sensitive synapses, it has limited antimuscarinic effects in CNS and counteracting of convulsions is possible only immediately after exposure. Some toxicologists prefer glycopyrrolate and hyoscine (scopolamine) methylbromide: These agents do not enter the CNS and they are not effective against coma and reduced respiratory drive in patients with anticholinesterase poisoning. Diazepam is used in counteracting convulsions, and it also improves atropine tolerance, reduces central nervous system damage and central respiratory weakness. Oximes reactivate phosphorylated AChE by displacing the phosphoryl moiety from the enzyme by virtue of their high affinity for the enzyme and their powerful nucleophilicity. The rate of reactivation depends on the structure of the phosphoryl moiety bound to the enzyme, the source of the enzyme, the structure and concentration of oxime which is present at the active site, and the rate of aging. Several oximes have been developed, but two (Pralidoxime chloride and Obidoxime) are more commonly used for acute organophosphorus poisoning. They are administered as an infusion which continues until recovery.

Serbian NPCC experience: During the different phases of development of the NPCC in Belgrade, many pyridinium oximes were used in experimental and clinical studies, as well as in routine clinical practice, such as pralidoxime chloride, pralidoxime methylsulphate, trimedoxime, obidoxime, and HI-6. Oxime HI-6 was introduced in clinical practice in Serbia in early 1980s. It was administered to more than 200 patients (with OP poisoning and volunteers). A clinical study with HI-6, administered intramuscularly at doses up to 500 mg, performed in 22 healthy volunteers, revealed no adverse effects, whereas in patients poisoned by several OP insecticides, HI-6 ensured fast reactivation

of AChE in almost all cases except in dimethoate and phosphamidon poisoning. Contrary to these findings, the reports from Asia indicated that pralidoxime treatment was not sufficiently effective in their patients. Despite this controversy we could still recommend oxime use in moderate and severe OPI poisoning. Acute poisoning with organophosphorus pesticides is not frequent in Serbia, however, it represent important clinical feature due to severity, possible complications and their impact on duration and costs of hospitalization. Initial treatment involves prevention of further absorption and provision of supportive care, followed by administration of specific antidotes (carefully titrated atropine, oxime and diazepam).

New therapeutic regimens: Many other treatments have been trialled for use in patients with acute organophosphorus poisoning (a-2 adrenergic receptor agonists-clonidine, butyrylcholinesterase replacement therapy, extracorporeal blood purification, including haemodialysis, haemofiltration, and haemoperfusion, magnesium sulphate, organophosphorus hydrolases and sodium bicarbonate), but at present high quality data are insufficient to make evidence based recommendations and further investigations are necessary.

**Brief Biography of the Speaker:**

Slavica Vucinic MD PhD is an associated professor of internal medicine and clinical toxicology at the Clinic of Emergency and Clinical Toxicology of the National Poison Control Centre, Military Medical Academy in Belgrade, Serbia. Her area of expertise is acute organophosphate poisoning. Besides being an author and co-author of 155 papers, she wrote 6 chapters in different books of emergency medicine and one book in the field of clinical toxicology. She is a Head of two scientific projects in Military Medical Academy concerning the therapy of acute organophosphate poisoning. She is the Head of the Clinic of Emergency and Clinical Toxicology. For the last 7 years she has been a General Secretary of Serbian association of toxicologists. Moreover she is a member of the European Association of Poison Control Centres and Clinical Toxicologists.

## Plenary Lecture 7

### Activation of Genes in Atheroprotection, Regression of Atherosclerosis and Longevity



#### Professor Pauli V. Luoma

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**Abstract:** Coronary heart disease (CHD) has been recognised as the leading cause of death in the world and cerebrovascular disease as the second leading cause. The liver is the principal site for the synthesis of lipids and proteins, and alterations in hepatic function influence plasma lipoprotein levels. This lecture focuses on the effects of gene activation on the atherosclerotic vascular process and the occurrence of atherosclerotic disease.

Our studies originating in the 1970s linked drug-caused gene activation and high protein, phospholipid and cytochrome P450 concentrations in the liver with high apolipoprotein AI and HDL cholesterol and reduced LDL cholesterol levels in plasma and presented the view that gene-activators have exploitable effects against atherosclerosis. Investigations performed in following years have shown that P450-enzymes respond to excess cholesterol and act in maintaining cholesterol homeostasis and that gene-activators act against the atherosclerotic process. The compounds include drugs indicated for lipid disorders such as statins, fibrates, niacin and cholestyramine, as well as compounds for other purposes. Gene-activators generate signalling mediators such as oxysterols and eicosanoids and, via nuclear receptors, upregulate apolipoprotein AI, ABCA1 and other transporters that efflux cell cholesterol, transport it to the liver and eliminate it into bile, and prevent cholesterol absorption in the intestine. P450-derived eicosanoids and their metabolites have vasodilating effects and inhibit inflammatory response. A number of gene-activating agents including statins, niacin, cholestyramine, calcium channel blockers, angiotensin receptor blockers and pioglitazone regress atherosclerosis in coronary and / or carotid arteries. Several of them reduce the occurrence of fatal and /or non-fatal CHD and cerebrovascular disease, and also all-cause mortality, and enhance longevity. Investigational gene-activators include LXR, PPAR and PXR agonists and other compounds with potential as antiatherogenic agents.

#### Brief Biography of the Speaker:

Pauli Luoma graduated from the University of Oulu Medical School, Finland in 1967. In the 1960s he worked as a general practitioner in Municipal Health Service in Northern Finland and as a research associate in the Department of Pharmacology, University of Oulu. He specialized in internal medicine and clinical pharmacology, and worked as postdoctoral fellow in Virginia Commonwealth University (1975-1976) and research fellow of the Academy of Finland (1976-1979). In the 1980s he practised as senior specialist in the Department of Internal Medicine, University Hospital in Oulu, and in the 1990s in Municipal Health Service and as internist in Central Hospitals in Northern Finland. He is docent in clinical pharmacology at the University of Tampere Medical School, Finland (1981), and docent in internal medicine, University of Oulu (1982), and professor (2000). His research interests, now in the Bioinstitute of Medicine, Department of Pharmacology, University of Helsinki, focus on liver function and gene activation, and particularly on cytochrome P450, lipids, proteins and transporters acting in processes that regress atherosclerosis and reduce the occurrence of atherosclerotic disease. He is author of about 70 papers published in international journals and conference proceedings, and invited book chapters.

## Plenary Lecture 8

### Functional Changes in Human Mast Cells by Infectious Diseases; Impact on the Control of Allergic Diseases



**Professor Nobuyuki Fukuishi**  
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**Abstract:** Mast cells have long been acknowledged as the major effector cells of allergic reactions because they possess the high-affinity IgE receptor (Fc $\gamma$ RI), which mediates the release of many inflammatory mediators such as histamine, leukotriene and prostaglandin when crosslinked by antigens. Whereas, mast cells are located at the host-environment interface, including the skin, respiratory system, and gastrointestinal tract. Recently, it has been revealed that mast cells share many features with primary effector cells that belong to the innate immune system. As well, some investigators have demonstrated that mast cell-deficient W/W<sup>v</sup> mice display increased mortality compared with wild-type mice using a model of acute septic peritonitis induced by cecal ligation and perforation (CLP) and that the lethal effects of CLP are prevented by the adoptive transfer of bone marrow-derived mast cells into the peritoneal cavity. Indicating that mast cells are involved in one of the principal members of the innate immune system. However, the changes in the behavior of mast cells following infectious diseases remain unclear. We investigated the effects of infection on the expression of surface receptors and uptake of microbes by mast cells, using bacterial components, and studied the change in cytokine production in mast cells after bacterial uptake.

The change of mRNA expression for Fc $\gamma$ RI was studied using RT-PCR and real-time PCR. The changes of surface expression of Fc $\gamma$ RI were examined using flow cytometry, and degranulation mediated by Fc $\gamma$ RI aggregation was determined by  $\beta$ -Hexosaminidase release assay.

Treatment of lipoteichoic acid (LTA) decreased the expression of Fc $\gamma$ RI mRNA on human mast cells. Peptidoglycan (PGN) up-regulated Fc $\gamma$ RI mRNA, but down-regulated that of Fc $\gamma$ RI $\beta$ , an amplifier of the surface expression of Fc $\gamma$ RI. Both LTA and PGN diminished surface expression of Fc $\gamma$ RI on mast cells detectable by flow cytometry. As well, they also reduced mast cells degranulation mediated by the treatment of antigen-specific IgE. Complement receptor 3, which is closely related to phagocytose bacteria by mast cells, expression was augmented by LTA but not by PGN or CpG-oligodeoxynucleotide. LTA also enhanced the uptake of opsonized bacteria. After bacterial internalization, mast cells augmented the production of pre-inflammatory cytokines, while Th1 and Th2 cytokine production showed no change.

These results indicate that bacterial infections direct human mast cells function towards innate immunity and away from allergic reaction. Applying current knowledge, bacterial components especially TLR2 ligands give new impetus to anti-allergic drug development.

## Plenary Lecture 9

### Novel Approaches for Mineralised Tissue Engineering and Repair



#### Dr Alastair J. Sloan

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**Abstract:** Our studies have shown that mineralised matrices contain reservoirs of bioactive molecules capable of directing tissue repair. Elucidating the release mechanisms of such endogenous growth factors will enhance our understanding of bone healing and regeneration and support the development of novel treatment modalities to enhance bone repair following trauma, disease or surgery. To this end, there is a need for better effective methods of assessing therapeutic approaches to improving bone repair at the cellular and gross tissue level. Experimental modelling of bone regeneration, inflammatory bone destruction and the factors influencing matrix secretion is hampered by the lack of suitable models. Whilst *in vivo* experimentation has yielded considerable information on the processes taking place, they are limited, due to the cost of running such experiments, the difficulty in obtaining clear data and ethical implications. *In vitro* cell culture systems are also limiting as such studies can be far removed from the *in vivo* situation as cell/cell interaction between differing cell types may influence behaviour. *Ex vivo* organotypic cultures, whereby cells and tissues are cultured *in situ* may provide a more suitable model system. This plenary will discuss the strengths and limitations of our novel model systems for mineralised tissue engineering and regeneration and how they may be used in the development of novel treatment modalities.

#### Brief Biography of the Speaker:

Alastair J Sloan is a Senior Lecturer in Bone Biology and Tissue Engineering at the School of Dentistry, Cardiff University. He obtained his BSc in Biomedical Sciences from the University of Wales in 1993 and his PhD in Oral Cell Biology from the University of Birmingham in 1997. Following postdoctoral research, he took a lectureship in Oral Biology at the University of Birmingham, School of Dentistry in 2000 prior to his appointment in Cardiff in 2005. He has a long standing interest in mineralised tissue regeneration, focussing on bone and dentine and the translation of the understanding of these processes to novel clinical treatments. He established the Mineralised Tissue Research Group at the School of Dentistry, Cardiff, whose current interests include osseointegration and bone regeneration, inflammatory mediated mineralised tissue destruction, development of novel organotypic models to investigate tissue injury and repair and the role of stem/progenitor cells in tissue regeneration. He has published over 35 research papers and presented at international conferences on dental research, tissue engineering and regenerative medicine, winning the Mineralised Tissue Group Research Prize of the British Society for Dental Research (BSDR) in 1998. He is currently President Elect of the Pulp Biology and Regeneration Research Group of the International Association for Dental Research and a member of the management committee of the BSDR and holds memberships of, amongst others, TERMIS, The Anatomical Society for GB&I, Institute of Biology and UK Stem Cell Network.

## Plenary Lecture 10

### The Ideal Protoscolicidal: Herbal or Synthetic?



#### Professor Seyed Mahmoud Sadjjadi

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**Abstract:** Hydatidosis is one of the most important parasitic zoonoses in the world and the Middle East. The parasite produces cysts in the liver, lungs, CNS and many other organs in human. Treatment of hydatid disease is mainly surgical, with medical treatment being reserved as coadjuvant treatment. One of the major problems in hydatid cyst surgery is the rupture of the cyst leading to the formation of other secondary hydatid cysts in the abdominal cavity leading to recurrence of the disease. So, in treatment attempts, surgeons utilize several protoscolicidal agents such as cetrimide, silver nitrate, hypertonic saline, povidone iodine and dextrose solutions. In spite of the use of protoscolicidal agents during surgery, a notable rate of the recurrence of the disease in post-operation patients is still observed. Dissemination of protoscoleces during surgery from ruptured cysts cause secondary infection in the host and using protoscolecidal agents before surgery might induce sclerosing cholangitis.

Regarding the above statements different attempts has been made for finding reliable and safe protoscolicidal agents. In this regards, we have used several chemical and herbal extracts both in vitro and in vivo studies on protoscoleces of hydatid cysts. Special attention was focused on garlic (*Allium sativum*), which has been used in herbal medicine for thousands of years for different medical purposes. In our experiments, we compared the in vitro efficacy of different extracts of garlic on protoscoleces according to the exposure time and concentration of the extracts. Different types of garlic extracts including: aqueous extract, chloroformic extract and hydro-alcoholic extract along with cetrimide and silver nitrate solutions as positive control, and normal saline as negative control, were used in our studies. The results showed that chloroformic extract of garlic had the highest protoscolecidal activity. In my plenary Speech, I'll summarize the advantages and disadvantage of the use of herbal and synthetic protoscolicidal as well as I'll report my laboratory experiences.

#### Brief Biography of the Speaker:

Seyed Mahmoud Sadjjadi is a Professor of Parasitology at the Department of Parasitology and Mycology, School of Medicine, Shiraz University of Medical Sciences, Iran. His area of expertise is parasitic helminthes especially zoonotic parasites. The diagnosis and treatment of the parasitic helminthes is his main area of research. He authored or co-authored over 70 scientific papers published in reviewed journals and presented more than 120 research works at international and national conferences. He has co-authored 3 books and wrote a chapter entitled: Epidemiology of echinococcosis in the Middle East and Arabic North Africa In: *Advances in Hydatid Disease Diagnosis and Treatment*, which is under publication in Greece. He had the opportunity to be a research fellow at Liverpool School of Tropical Medicine, Liverpool University and he is member of editorial board of different journals including Iranian Journal of Parasitology. He has supervised more than 15 Ph.D. and MSc. theses.

## Plenary Lecture 11

### Antiviral Drugs and Therapy Perspectives



**Assistant Professor Petia Genova-Kalou**

National Centre of Infectious and Parasitic Diseases

Department of Virology

Head-Leader of Laboratory of Cell Cultures

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**Abstract:** Viruses are microorganisms that are as varied in type as the plants and animals. A particular virulent virus can infect and kill a human host, which is million times larger. The human immune system is the first line of defense against any infectious organisms. However, sometimes this protection proves inadequate to the viral challenge. In this situation humans attempt to provide additional aid in retarding viral reproduction through the use of antiviral drugs. Any of the stages of viral replication can be a target for antiviral intervention. Unfortunately the antiviral chemotherapy must confront three obstacles: (i) a possible interference with the normal cellular metabolism, leading to residual cytotoxic side effects; (ii) the genetic variability of the viruses, producing drug-resistant mutants and (iii) the inability of any antiviral chemotherapeutic agent known to date to eradicate latent viral infection. Viruses have been shown to be particularly adept to developing resistance to drugs, and the effective management of viral diseases may well rely on combination therapy. This may take the form of either targeting a single virus function with multiple agents or using several agents to attack different targets in the viral life cycle. Many viral diseases still require new treatments. These facts ensure that there will be many new challenges for antiviral drug therapy in the future. The evidence from the past suggests that the challenges will be met.

**Brief Biography of the Speaker:**

Petia Genova-Kalou is a Head-Leader of Laboratory of Cell cultures at Department of Virology, National Centre of Infectious and Parasitic Diseases, Bulgaria. Her research focused on the mechanisms of viral replication, pathogenesis, possibly providing novel antiviral strategies, development of novel treatment strategies with newly synthesized metal-based and with natural origin compounds. She authored or co-authored over 30 scientific papers published in reviewed and not peer-review system journals and over 80 abstracts presented at national and international conferences. She wrote four chapters In: Clinical Virology edited by Prof. Stefan Dundarov MD, First Edition, Medicine and Sport Publisher, inc. pp. 27 – 35, pp. 80 – 89, pp. 102 – 108, pp. 192 – 197, 2006. She is the Coordinator of three National Projects to the Bulgarian Ministry of Education and Science and a member of the team of three International Projects. In 2002 her work and efforts were rewarded with a prize a received for "Young Scientist of Bulgaria 2002". She is the Coordinator of three National Projects to the Bulgarian Ministry of Education and Science and a member of the team of three International Projects. She had the opportunity to be a research fellow at National Hellenic Research Foundation (NHRF), Institute of Biological Research and Biotechnology, Greece and Institute Pasteur Hellenic, National Influenza Reference Laboratory of Southern Greece. She had honor as Invited Speaker of William M. Barto Memorial Speaker Series of the Foundation Fulton-Montgomery Community College, a College of the State University of New York, USA.

## Plenary Lecture 12

### Drug-Induced Nephrotoxicity in the Newborn: The State of the Art



**Professor Vassilios Fanos**

Pediatrics University of Cagliari -Italy

Chief Neonatal Intensive Care Unit, Puericultura Institute and  
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**Abstract:** Drug-induced kidney disease is frequent in all age groups (1). In adult patients nephrotoxicity has been related to 8-60% of in-hospital acute kidney injury. Little is known about the epidemiology of drug-induced disorders in the paediatric kidney. Drugs have also been found to be involved in 50% of cases of acute kidney injury in premature newborn. The effects of maternally administered drugs on the fetal and neonatal kidney have been well documented. Recent data suggest in preterm neonates a significant role for maternal consumption and postnatal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) in preterm infants.

In the past it was suggested that drug-induced kidney damage (especially that caused by aminoglycosides or glycopeptides) is less frequent and severe in newborns than in children and adults. However, this subject is controversial and indeed neonatal status may itself be a risk factor for drug-induced nephrotoxicity. In fact, it has been confirmed that low birthweight contributes to development of renal disease also later in life

The actual importance of drugs as causes of nephrotoxicity is not easy to define: the drugs are administered to newborns who are sick and often seriously ill, who present haemodynamic abnormalities and/or electrolyte derangements. All these situations may be important co-factors in bringing about the renal damage

Discussion of drug-induced nephrotoxicity must consider the following points: a drug may give rise to renal damage in different parts of the nephron and different drugs can have the same intracellular target. The proximal tubule is generally to be regarded as the target structure.

By a practical point of view it is very important the correct assessment and early diagnosis of nephrotoxicity.

Aim of this review is to present a comprehensive update on drug-induced nephrotoxicity in the newborn, with special reference to antibiotics and NSAIDs.

**Brief Biography of the Speaker:**

Chief Neonatal Intensive Care Unit, Neonatal Pathology, Puericultura Institute and Neonatal Section University of Cagliari – and Azienda Mista Cagliari, Italy

Treasurer Italian Society of Neonatology (Secretary for 6 years)

Italian Delegate Parliament of UENPS (Union European Neonatal Perinatal Societies)

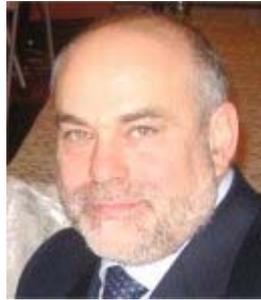
Executive Board Member UMENS (Union MEditerranean Neonatal Societies)

Consultant Referee of 15 International Journals and Board member of 3.

Publications: Author of more than 500 publications (of which 122 papers in Pub Med, including Lancet), 10 books on Neonatology (2 in English: the first published book on Neonatal Nephrology and another on the History of Birth ) and 7 Proceedings of Congresses (4 in English)

Speaker in more than 200 Congresses (50 International). Chairman in several International Congresses; organizer of more than 50 Congresses and Workshops, International.

Area of scientific interest: neonatology, pharmacology, infections, nephrology.

**Plenary Lecture 13****Laboratory Medicine for the Evaluation of Kidney Disease: From the Fetus to the Adult****Dr. Michele Mussap**

Department of Laboratory Medicine  
University-Hospital of Genova, Italy  
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**Abstract:** Spectrum of kidney disease could be roughly divided in chronic kidney disease (CKD) and acute kidney injury (AKI), previously named acute renal failure. CKD mainly consists of steady or progressive loss of renal function with a slow but continuous decrease in glomerular filtration rate (GFR); AKI, on the other hand, is characterized by tubular necrosis, oliguria and tissue damage. CKD has been identified as a worldwide public health problem involving a rising incidence and prevalence of the disease: they are approximately twice what they were 10 years ago. The recognition of CKD as a public health problem has evolved, in part, from the acceptance of the conceptual model, definition, and classification of CKD proposed by the NKF/KDOQI initiative in 2002. CKD has an insidious onset and is generally detected at a time when it is clinically quite advanced; adverse outcomes of CKD can be prevented through early detection and treatment. The public health mandate is clear for governments: detection and prevention are the most cost-effective methods to address CKD and its impact on diabetes and cardiovascular (CV) disease. Early stages of CKD can be detected through routine laboratory measurements. Over the past 100 years, diagnosis, prognosis, and follow-up of renal failure have been based upon serum creatinine measurement and creatinine clearance calculation. Only 60% of patients with decreased GFR had increased serum creatinine and creatinine clearance systematically overestimates GFR 10-40% in healthy subjects, but is greater and more unpredictable in patients with CKD. Therefore, in 2002 the K/DOQI guidelines recommended to use equations estimating GFR based on serum creatinine, being more accurate and precise than estimates of GFR from measurements of serum creatinine alone. However, an accurate, non-invasive, and convenient estimation of GFR has been not identify. Thus, there is a growing demand for a clinically convenient and reliable marker of renal function. The clinical significance of such biochemical markers, e.g.: cystatin C, albuminuria, NGAL, KIM-1, caspases, meprin 1?, TGF-?, etc., will be discussed for the early diagnosis and monitoring of CKD and AKI.

## Plenary Lecture 14

### Chemokines and their Receptors: Potential Therapeutic Targets in Rheumatoid Arthritis



**Dr. Jim Middleton**

Reader, Head of Arthritis Research  
Leopold Muller Arthritis Research Centre  
School of Medicine, Keele University  
RJAH Orthopaedic Hospital  
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**Abstract:** Chemokines are involved in driving the migration of leukocytes into tissues in inflammatory diseases, such as rheumatoid arthritis (RA). Chemokine binding sites on endothelial cells that may transport and present chemokines to blood leukocytes have been identified, including heparan sulphate proteoglycans and DARC. This then results in transendothelial migration of leukocytes into the joint tissues where these cells are fundamental to disease pathophysiology. Furthermore selective chemokine receptors on leukocytes that are responsible for their recruitment have been characterised. In addition, mesenchymal stem cells (MSCs) may be useful in inflammatory diseases and chemokine receptors present on these cells could be involved in homing of MSCs to inflamed tissue leading to anti-inflammatory and immunosuppressive effects. Overall chemokine receptors on endothelial cells, leukocytes and stem cells may provide therapeutic targets for pharmacological intervention in rheumatoid arthritis.

**Brief Biography of the Speaker:**

I did my degree in Biological Sciences at Bath University followed by a PhD at Lancaster University (UK). After postdoctoral positions in Cambridge and Bath, I was a Senior Scientist at Novartis Research Institute, Vienna. Then I joined the Medical School, Keele University at the RJAH Orthopaedic Hospital, Oswestry, where I am currently Reader and Head of Arthritis Research.

## Plenary Lecture 15

### Role of Professional Antigen Presenting Cells in the Genesis of Immune Response to Protein Therapeutics



#### Dr. Suryasarathi Dasgupta

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**Abstract:** Development of neutralizing antibodies, is a crippling concern in the management of patients undergoing administration of protein therapeutics as evidenced in replacement therapy and other treatment procedures. Several issues in the genesis and modulation of such deleterious immune responses have been studied. While authors have focused on the downstream events of the specific immune response and suggested modification of protein therapeutics to eliminate epitopes that interact with B cell receptors, T cell receptors, or MHCII molecules, the mechanisms underlying Ag interaction with APCs, a step upstream of immune effectors, have been grossly neglected. We wish to emphasize that the recent knowledge in understanding the capacities of an APC to handle an Ag and the importance of the surrounding microenvironment in this process are crucial for designing novel protein therapeutics with reduced immunogenicity.

This talk would highlight the increasing interest in understanding the role of critical cells in immune response – viz. the Dendritic Cells and Macrophages.

The scope of this knowledge is not limited to issues concerning immunogenicity.

Antigen presenting cells are essentially "cellular sinks" for an administered therapeutic. They have profound role(s) in catabolism of the therapeutic protein.

This talk will thus try to delineate the delicate balance between half-life of a therapeutic protein and its inherent immunogenicity from the standpoint of these cells.

This type of knowledge might be essential in designing novel protein therapeutic in the future.

#### **Brief Biography of the Speaker:**

I am a researcher in Biomedicine. My broad interest is in how cellular immunology and biochemistry can be integrated to understand therapeutic approaches in a better way. I graduated from the Indian Institute of Technology-Bombay, Mumbai, India with a PhD in Biosciences and Bioengineering. I did postdoctoral research in UMRS 872 Equipe 16, INSERM, PARIS, France, wherein I focussed to understand the genesis of immune response against therapeutic factor VIII in hemophilia A patients with various model systems. I co-authored several peer-reviewed research articles and review articles in reputed international journals. I presented my work in several international conferences on Immunology, Hematology and Glycobiology. My work formed the basis of various projects in our laboratory and resulted in two patents.

I was a member of the European Macrophage and Dendritic cell Society (EMDS) and have been invited to review research and review articles from several journals viz. Arteriosclerosis, Thrombosis and Vascular Biology & Therapeutics and Clinical Risk Management. I have won Young investigator travel award from several international societies and companies which include EMDS, International Congress of Immunology and Tebu-Bio and Novo-Nordisk. Currently I have shifted to Boston where I am working as an instructor at Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA. I am working on understanding how components of commensal microflora can induce immunomodulation.

**Plenary Lecture 16****Strategies for Nerve Regeneration after CNS Injury****Professor Xiaodan Jiang**

Co-authors: Shanshan Song, Zhicheng Xiao, Ruxiang Xu  
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**Abstract:** It was traditionally thought that the central nerve system (CNS) defected the regenerated ability, following the injury. However, the peripheral nerve system (PNS) possesses an ability of regeneration after injury. Also it was found that the axon in CNS might extend into the graft, as soon as the peripheral nerve tissue was transplanted into the injured part of CNS. Therefore, it implied that the axon in CNS also possesses the regeneration ability, and the regeneration of axon in CNS just depended on the microenvironment around them. The microenvironment of CNS doesn't adapt to the nerve regeneration after damage. The different microenvironment between CNS and PNS mainly results from the different types of glial cells--the oligodendrocytes in CNS play an inhibitory role, while the Schwann cells in PNS play an active role in the repairing process following the nerve injury. When CNS is damaged, the injured myelin sheath that composed of oligodendrocytes released a lot of inhibitors for axon-regeneration. On the other hand, glial scar inhibited the axon regeneration by space obstruction and proteoglycan inhibition (e.g. chondroitin sulfate proteoglycans, CSPGs). Therefore, the repair strategies for nerve regeneration of CNS were just as Seed Substitution and Soil Amendment following injury. For example, Soil Improvement was performed by weakening the inhibitors of obstructing the CNS regeneration, removing the glial scar, supplying the advantageous factors, transplanting the endothelial progenitor cells (EPCs) in order to re-establish the microvasculature, and repairing the injured myelin. Seed Substitution was done by transplanting the nerve stem cells (NSCs), and applying the biomacromolecules as the cellular bridges during the CNS regeneration. Finally, the injured CNS can be repaired.

**Brief Biography of the Speaker:**

Xiaodan JIANG is a Professor of Neurosurgery Institute of Guangdong Province, at Zhujiang Hospital of Southern Medical University, China. She graduated in Harbin Medical University of China in 1983 for Bachelor of Medical Science, and in 1989 for Master of Medicine. During 5 years from 1992 to 1997, she got the Scholarship from Culture and Education Minister of Japan Government, graduated and got Medicine PhD degree at Kochi Medical University, Japan in 1997. Returning to China, she has been working at Neurosurgery Institute of Guangdong Province, Southern Medical University, as a Professor, where she has also the scientific responsibility for Nerve Regeneration Group. Her main research interests are focus on the Mechanisms of Injury and Repair of the Central Nervous System (CNS), Molecular Mechanisms of Regulation and Control of Neural Stem Cells (NSCs) Differentiation, and Clinical Therapy Application by NSCs Transplant. In these fields, she authored or co-authored over 20 scientific papers published in international journals recent 2 years, in which the highest impact factor (IF) is 18.7 (Nature Cell Biology, 2008). She edited or participated to edit 8 of Academic Monographs mainly including Neural Stem Cells (ISBN 7-80121-857-4/r.850, Beijing 2006), Empirical Method of Modern Medicine (ISBN 7-117-02631-6/R.2632, Beijing 2009), etc. Also she got 2 of National Invention Patents of China, including Preparative Method of NSCs Medium (ZL02134314.4) and Culture Method of Human NSCs (ZL02134313.6). She has gotten 13600 thousands RMB of Science Funds from China Government since 2000. She also has the Scientific memberships such as IEEE, Electron Microscopy Organization (Japan, China), Anatomy Organization (Japan, China), Neuroscience Association of China, Cytochemistry and Histochemistry Organization (Japan), and Human Biological Tissue Engineering Academic Organization of Guangdong Province. She also is a Review Specialist for Nature Science Fund and Nature Science Technique Award of China. Her PhD students are working in different universities or research institutions in China, USA, and Singapore now.

## Plenary Lecture 17

### The Evolutionary Changes of Erythrocyte from Sea to Land: Cytological Features and Sites of Development



**Professor Alessandra Pica**  
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 Sezione di Biologia Evolutiva e Comparata  
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**Abstract:** The evolutionary changes in size, number, structural and ultrastructural features and sites of origin of erythrocyte are reviewed by comparing the early appearance of coelomocytic hemoglobin-bearing cell of Invertebrates with the typical erythrocyte of submammalian Vertebrates and its phylogenetic variations from the poikilotherm Agnathans, Elasmobranch and Teleost Fishes, Amphibians and Reptiles up to the homeothermic Birds. The earliest hemoglobin-bearing cell becomes apparent in a limited number of marine Invertebrates, such as the Phylum Annelida (segmented marine worms), like a coelomocyte in which hemoglobin pigment is carried together with other constituents. The occurrence of erythrocytes during evolution allows an increasing concentration of hemoglobin that is carried into cells rather than free in hemolymph/coelomic solution. Moreover, cellular sequestration of hemoglobin simplifies its structure that otherwise should be polymeric to avoid its free diffusion out of hemolymph. The definitive structure of the submammalian vertebrate erythrocyte occurs in Fishes, whose erythrocyte feature, mainly ellipsoidal, biconvex and nucleated, is conserved through all submammalian Vertebrates. Among Fishes, the erythrocytes of Chondrichthyes are the largest cells: they are ellipsoidal, flattened and slightly biconvex, due to nuclear bulge. Their number is very low as compared to the Teleosts' counterpart, whose erythrocytes are smaller in size: this is explained by the inverse proportion between size and number of erythrocytes observed in all Vertebrates, including Mammals. The evolutionary advantage of small and numerous erythrocytes, as in Mammals, lies in being the best condition for gas exchange in active metabolic organisms. The endothermic Fishes display the highest values of erythroid parameters that are similar to those of Mammals. Conversely, Antarctic icefish erythrocytes contain the lowest level of hemoglobin, due to their low metabolic rate. The erythrocyte structure, phylogenetically established in Fishes, has been conserved in Amphibians except for its volume - the largest one among all vertebrate and invertebrate erythrocytes - due to the occurrence of a large amount of nuclear DNA, because of repeated DNA sequences typical of Amphibians. As observed in triploid fishes, both cellular and nuclear sizes increase in proportion with the increase in ploidy, while the nucleo-cytoplasmic ratio remains unchanged. Among Reptiles, with the exception of the archaic tuataras, sea turtles show the largest erythrocytes. Avian erythrocytes show a reduced size compared to Reptiles. Among Birds, the largest erythrocytes and the widest variations in the erythrocytic hemogram values between-species are generally described in the smallest birds (as well as in Reptiles). As compared to lower Vertebrates, the increase of avian erythroid parameters towards those of Mammals is a phylogenetic progression related to homeothermy.

The sites of origin of erythrocytes in embryonic Fishes are located in yolk sac and/or in intermediate cell mass, while in adulthood their localization varies from the presplenic tissue of Cyclostomes, to the splenic tissue, scattered in the submucosa of gut of Hagfish, to the neural body of adult lamprey - in which blast cells proliferate between adipocytes, as well as it occurs in bone marrow of Mammals - to the spleen in Elasmobranchs and to the kidneys in Teleosts. Nevertheless, erythropoiesis is generally located in separate sites from those of granulocytopoiesis in most Fishes, in all Urodela, which are both Vertebrates lacking bone marrow. The early bone marrow, during evolution, occurs in Plethodontidae, the Family of lungless salamanders, with the sole lympho-granulopoietic function. The phylogenetic onset of medullary erythropoiesis in the Anurans is a hematologic landmark due, very likely, to protective shielding from ionizing radiation for the radiosensitive hemopoietic stem cells, offered by the bone along with the evolutionary transition from life in water to life on land. In Reptiles, the bone marrow becomes the dominant erythropoietic site in most species, even though the spleen of some lizards can be the major erythropoietic (and thrombopoietic) organ. In Avians and Mammals, erythropoiesis is exclusively housed in bone marrow, with rare exceptions. In all submammals, erythropoiesis completes into the circulating blood through similar maturative stages. Mammalian erythrocyte

denucleation is the final event in the phylogenetic progression of vertebrate red blood cells. In conclusion, the erythrocyte count, hemoglobin concentration, hematocrit and erythrocellular indices of all submammalian Vertebrates are explored through the analysis of their variations as expression of evolutionary progression. The significance of erythrocyte denucleation and loss of organelles, occurring in erythrocytes of all Mammals, in rare species of marine Fishes and Amphibians is discussed too.

**Brief Biography of the Speaker:**

Dr. Alessandra Pica is Confirmed Associate Professor in General and Comparative Hematology and Human Development, Growth and Anatomy, at Faculty of Mathematical, Physical and Natural Sciences of University of Naples, Federico II, Italy. She is teacher of Biology in Doctorate School in Bioethics of University Federico II and member of the Animal Experimentation Ethics Committee (CESA) of National Hospital "A. Cardarelli", Naples, Italy. She is consulting hematologist in the Sea Turtle Rescue and Rehabilitation Program at Zoological Station A. Dohrn and teacher of Hematology of Sea Turtles in Training Course on Sea Turtle Rescue and Rehabilitation RAC/SPA (Regional Activity Centre for Specially Protected Areas - United Nations Environment Program Mediterranean Action Plan (UNEP)) of Zoological Station, A. Dohrn (Naples, Italy) addressed to foreign researchers of Mediterranean Area. Moreover, she is Revisor as Hematology expert for Committee for Research Evaluation (CIVR-MIUR). She is member of the Italian Society of Anatomy, the Italian Society of Histochemistry, the Italian Zoological Society, the Italian Group of Neuromorphology, the Scientific Committee of Interdepartmental Center for Ultrastructural Biological Research (C.I.R.U.B. ), University of Naples Federico II.

She worked at Institute of General Pathology in Naples, Experimental Center of Endocrinology and Oncology, in years 1982-83. Since 1983 she has worked as Researcher at University Federico II, Department of Biological Sciences, Division of Evolutionary and Comparative Biology, and she has been Associate Professor since 2002. In the past years, she was teacher of Human Anatomy, Embryology and Experimental Morphology, Histochemistry and Cytochemistry in the degree course in Biological Sciences at University Federico II and teacher of Hemopathology of Sea water Vertebrates in 1st Level Master in Biotechnology applied to reproduction and repopulation of marine species in the School of Mathematical, Physical and Natural Sciences of University Federico II.

In 2006, she published a monograph entitled "Erythrocytes of the Poikilotherms: a Phylogenetic Odyssey", in collaboration with prof. Chester A. Glomski, State University of New York at Buffalo, USA (Foxwell & Davies, UK 1-432; ISBN 88-8448-010-8).

Her main fields of interest are Comparative Hematology and Oncology. Most of her scientific work is about the characterization of the circulating blood cells and their progenitors in one species at least for each Class of non mammalian Vertebrates, focusing on the function of blood cells of non mammalian Vertebrates compared to their counterparts of Mammals. In the field of Oncology, her research work is mainly about the effects of a treatment with a new anticancer agent on human breast cancer cells.

At present, her main research subjects are the hematological characterization of the Mediterranean loggerhead *Caretta caretta*, the detection of biomarkers of cell damage following X-ray pollution in sea water and the effects of treatment with a new anticancer agent on leukemia cells of children.

## Plenary Lecture 18

### Compositional Changes of Human Tissues and Organs with Aging



#### Professor Yoshiyuki Tohno

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**Abstract:** To elucidate compositional changes of the human tissues and organs with aging, the authors investigated age-related changes of elements in the blood vessels of the arteries, veins, and thoracic duct, cardiac valves, bones of calcaneus, talus, vertebrae, auditory ossicles, and rib, cartilages of the intervertebral disk, xiphoid process, costal cartilage, pubic symphysis, and medial meniscus, ligaments of the posterior longitudinal ligament, anterior cruciate ligament, and ligamentum capitis femoris, tendons of the Achilles tendon, biceps brachii muscle, diaphragm, iliopsoas muscle, and peroneus longus muscle, nerves of the trigeminal, optic, vagus, median, radial, ulnar, femoral, sciatic, and common peroneal nerves, brains of the corpus callosum, anterior commissure, pineal body, and olfactory bulb, and organs of the prostate, uterine tube, and ureter, and reported the results.

With regard to the arteries, we found that the accumulation of Ca, P, and Mg did not occur uniformly in any arteries and that there were two types of the arteries. The first type is one that a significant accumulation of Ca and P occurs with aging, whereas the second type is one that an accumulation of Ca and P hardly occurs with aging. The thoracic and abdominal aortas, coronary, common carotid, splenic, common iliac, internal iliac, external iliac, uterine, internal pudendal, femoral, popliteal, posterior tibial, and dorsalis pedis arteries belonged to the first type, whereas the internal thoracic, cerebral, pulmonary, axillary, brachial, radial, ulnar, and obturator arteries belonged to the second type.

In addition, we found that the accumulation of Ca and P was accompanied by increase of Mg and decrease of S in most, but not all of human arteries.

In the present conference, we present mainly the compositional changes of the arteries of the coronary and uterine arteries and brains of the corpus callosum, and olfactory bulb and tract with aging.

**Plenary Lecture 19****Promoter Methylation and Protein Expression of the (APC, E-cadherin, MGMT, p15, and p16) Genes in the Clinical Estimation of Oral Cavity Cancer****Professor Dor Mohammad Kordi Tamandani**

Co-authors: K. Moazeni, A. Torkamanzahi, MA. Rigi Ladize,  
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**Abstract:** Nowadays, almost all of the genes in the human genome have been sequenced. The challenge now is to understand the molecular mechanisms that allow these genes to be selectively expressed. Although all genes are transcribed in an organism at some stage of its life cycle, a more restricted number are required for the differentiation of a specialized cell type. Remarkably, it is essential to select not only the correct genes to turn on, but also those that need to be inactivated. Failure to repress genes appropriately has been connected to many human diseases, including neurodevelopmental disorders and cancer. Notable among the mechanisms that stably inactivate genes in a heritable manner is DNA methylation and the associated assembly of repressive heterochromatin. DNA methylation in mammalian cells occurs at the 5-position of cytosine within the CpG dinucleotide. Although CpG islands account for only about 1% of the genome and for 15% of the total genomic CpG sites, these regions contain over 50% of the unmethylated CpG dinucleotides. There are about 45,000 CpG islands, most of which reside within or near the promoters or first exons of genes and are unmethylated in normal cells, with the exception of CpG islands on the inactive X chromosome in general. Oral cancer continues to be a significant health problem that more people die from oral cancer than melanoma, cervical, and ovarian cancer combined. Early diagnosis significantly improves tumor control and survival. The five-year survival for patients with stage I or II oral cancer is 70 percent to 80 percent. In contrast, patients with stage III or IV oral cancer have a survival rate of only 40 percent to 50 percent. Dental health care professionals are commonly required to evaluate patients with potentially malignant oral lesions. Methylation is one of the earliest events in oral carcinogenesis, preceding changes in protein expression level. These advantages make promoter hypermethylation a very attractive diagnostic marker for the early detection of oral cancer. The hypothesis of this project is that the presence of oral cancer leads to changes in promoter hypermethylation. Therefore, is to quantitatively analyze promoter hypermethylation of five genes (APC, E-cadherin, MGMT, p15(INK4B), and p16(INK4A)) in patients and healthy groups. Current studies with tissue DNA reveal these genes are most often inactivated by promoter hypermethylation, allowing for the progression of oral cancer.

**Brief Biography of the Speaker:**

Upon completion of my doctorate in Biotechnology at the University of Panjab, Chandigarh, India in 2008, I joined as faculty at Department of Biology, University of Sistan and Baluchistan, Zahedan -Iran. So, My study will provide help in finding any diagnostic biomarkers in deferent population which can use as targets that finally lead to the development of molecular technique for early diagnosis of cancer patients and susceptible individual. Currently, I have focused on effect of Methylation on oral cavity cancer. Till now I had published many international papers in this regard.

## Plenary Lecture 20

### Pathogenic and Therapeutic Roles of Bid in Hepatocellular Carcinoma

**Professor George G. Chen**  
Department of Surgery  
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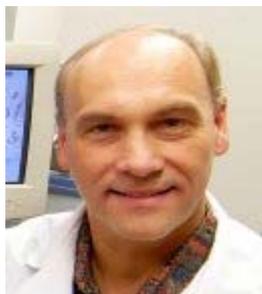
**Abstract:** Bid, a Bcl-2 family protein, is a BH3 domain-only agonist. Specific proximal death signals, such as Fas and TNF- $\alpha$ , are connected with the BH3-only pro-apoptotic members to interact with the multidomain molecules of Bak and Bax, which in turn serve as a pathway towards the amplification loop of the intrinsic mitochondrial-mediated apoptotic pathway. Hepatocellular carcinoma (HCC) expresses a low level of Bid and Bid can be regulated by hepatitis X protein, a carcinogen for HCC. Overexpression of Bid or its truncated form tBid can facilitate apoptotic death of HCC cells and significantly enhance the efficacy of chemotherapy towards HCC in vitro and in vivo. It appears that Bid /tBid plays a role in the development of HCC. Application of Bid/tBid to HCC can significantly promote apoptosis of tumor cells, which is therapeutically significant.

**Brief Biography of the Speaker:**

George G CHEN is a professor at Faculty of Medicine, the Chinese University of Hong Kong (CUHK), Hong Kong, China, where he is also the director of the surgical laboratories and an investigator at the Cancer Centre of CUHK. His main research interest is in the area of apoptosis in cancers including hepatocellular carcinoma and lung cancer. He authored or co-authored more than 100 scientific papers published in peer-reviewed journals and gave numerous talks at conferences related to his research field. He has been an editor or author for several books and book chapters and been invited to serve editorial boards or a guest editor for a number of journals.

## Plenary Lecture 21

### Genetic Programs of Metastasis



**Professor Georg F. Weber**

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**Abstract:** Malignant tumors are characterized by excessive growth, immortalization, and metastatic spread, whereas benign tumors are subject to growth deregulation and immortalization without expressing gene products that mediate invasion. Gain-of-function mutations of oncogenes or loss-of-function mutations of tumor suppressor genes underlie excessive cell division. Activation of senescence suppressor genes or inactivation of senescence genes underlies immortalization. Based on the phenotypes of knockout mice for various confirmed metastasis genes, we have identified the genetic basis of metastasis formation as aberrant expression or splicing of a unique set of developmentally non-essential genes (stress response genes) that physiologically mediate the homing of immune system cells. Metastasis genes encode homing receptors, their ligands, and extracellular matrix-degrading proteinases, which jointly cause invasion and anchorage-independence. The specific interaction of homing receptors on the tumor cell surface and their cognate cytokine ligands mediates migration and invasion. The organ preference of metastasis formation is determined by the particular identity of the homing receptors expressed on the tumor cell surface and their ligands. Oncogenes act upstream of metastasis genes. Their signaling in cancer cells activates distinct genetic programs leading to cell cycle progression and invasiveness respectively. The identification of genes that direct cancer metastasis implicates their products candidate drug targets.

**Brief Biography of the Speaker:**

Georg F. Weber has made substantial contributions to the exploration of cancer dissemination by defining the genetic basis of metastasis formation as aberrant expression or splicing of stress response genes and by discovering the interaction between the molecules osteopontin and CD44. Georg F. Weber attended medical school in Wuerzburg, Germany. In 1988, he graduated and also completed his doctoral thesis. He worked at the Dana-Farber Cancer Institute, Harvard Medical School from 1990 through 1999. After a stint at Tufts University, 2000-2003, he moved to the University of Cincinnati, where he is currently on the faculty. Georg F. Weber has published over 60 scientific reports, including many in the most respected professional journals, and holds several patents. He is the author of various monographs, most recently a textbook on molecular oncology. While he continues to address fundamental questions, he is researching new venues of diagnosis and therapy of cancer dissemination. As a component of this mission, Georg F. Weber is the founder and Chief Executive Officer of MetaMol Theranostics, a company specialized in diagnosis and treatment of cancer metastasis.

## Plenary Lecture 22

### Novel Family of Human Hormone-Peptides with Strong Anti-Cancer Activity



#### Professor Uziel Sandler

Chair of Computational Biochemistry Department  
Jerusalem College of Technology  
Jerusalem, Israel  
E-mail: sandler@jct.ac.il

**Abstract:** In this talk we present the novel human proteins: Thymus Expressed Apoptosis Factor (TEAF) and Natural Killer Colony Activation Factor (NKCAF). TEAF and NKCAF have similar size and second structure. Structure analysis and blood test showed that TEAF and NKCAF are the hormone-peptides.

TEAF was cloned from human thymus cDNA library. RT-PCR and immuno histochemical studies showed that this protein is expressed solely in the medulla and Hassal's corpuscles of human thymus gland.

We have found that TEAF poses triple anti-cancer activity:

- It kills the cancer cells by inducing both Caspase 8 and Bcl-2 mediated pathways of apoptosis;
- It suppress angiogenesis by inhibiting the expression of the VEGFA and VEGFR1 receptor and by enhancing the expression of IL-10;
- It modulates activity of innate immune response.

It should be noted that TEAF induces apoptosis in proliferating cancer cells like: acute myeloid leukemia cells (U937 pre-meyloid cells), human carcinoma cells, human lung cancer and HeLa cells, while, in contrast, TEAF was unable to induce apoptosis in the healthy cells. The selectivity of TEAF-induced apoptosis is related to the level of T1/ST2 receptor expression. The in vitro results were corroborated by in vivo tumor suppression by TEAF of tumors raised in mice injected with human AML's cells and human and murine carcinoma cells. It is important that TEAF was able to completely eliminate AML cells from bone marrow.

NKCAF was cloned from human cDNA library and is expressed, mainly, in pancreas, kidney and testis. The activated monocytes and CD8 cells express NKCAF as well. It has been found that NKCAF activates Natural Killer cells and promotes release of the perforin and granzyme B. Application of NKCAF to mice injected with human pancreatic cancer cells drastically decreases the tumor size.

#### Brief Biography of the Speaker:

Prof. Uziel Sandler, Chair of Department of Computational Biochemistry of Jerusalem College of Technology and Founder, CEO of ISK LTD.

Professor Uziel Sandler is expert in Nonlinear Properties and Critical Behavior of Condensed Matter, DNA Sequence Analysis and Evolutionary Computations. He is one of the founders of the advanced mathematical discipline called "Fuzzy Dynamics", which describes evolution of complex systems with uncertainty in their dynamics laws. Fuzzy Dynamics has been successfully applied to modeling of the immune system cells' maturation and to modeling of behavior of a neural cell. Prof. Sandler has published more than 70 academic articles in prestigious scientific journals and 3 books. He is also serving as chair in international conferences and as a member in several worldwide committees in the above-mentioned fields.

At 2005 together with Dr. Yoram Devary he has found Immune System Key Ltd. (ISK LTD), the biotechnology company, which has cloned a novel human hormone-peptide with strong anti-cancer activity. He is also serving as chair of Department of Computational Biochemistry and as Professor at the Department of Applied Mathematics of Jerusalem College of Technology.

Prof. Sandler holds a Ph.D. in Theoretical Physics from L.V. Kirensky Institute of Physics, Academy of Science of former USSR.

## Plenary Lecture 23

### Pyothorax-Associated Lymphoma: Our Experiences of Five Cases



#### Associate Professor Kazuhiko Natori

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**Abstract:** Among malignant tumors associated with chronic tuberculous pyothorax, malignant lymphoma is called pyothorax-associated lymphoma (PAL). Since the first report by Shiohara, et al. in 1970, there have been many reports of PAL, with a particularly high incidence in Japan. Involvement of Epstein Barr virus (EBV) in the disease is also suspected. Here we investigated five patients we experienced during the past 17 years from 1986 to 2002 who were diagnosed as having malignant lymphoma of thoracic origin secondary to pyothorax. Patients were four males and one female, all of whom had history of tuberculosis and artificial pneumothorax, and developed PAL after a median period of 49 years. The disease type was non-Hodgkin's B cell lymphoma in all patients. Immunostaining of histopathological specimens from all patients showed that 4 patients were positive for EB virus nuclear antigen 2 (EBNA2) and 2 for latent membrane protein 1 (LMP1). In Japan, artificial pneumothorax was performed more actively than in the United States and Europe as a therapeutic procedure for tuberculosis which was regarded as a national affliction. Onset of PAL appears to be under a strong influence of such treatment, and therefore should be predictable. Thus, those with a history of tuberculosis or pyothorax should be monitored over a long period of time.

## Plenary Lecture 24

### A Short Term Assay for Specific Detection of Carcinogens



**Associate Professor Margarita Pesheva**  
 Sofia University  
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 Bulgaria  
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**Abstract:** Environmental pollution with carcinogenic substances seems to be one of the main factors promoting neoplastic cell degeneration in humans and animals. Although it is obvious as history, the presence of carcinogens in some regions of many countries have to be evidenced. Biomonitoring in such cases requires accurate, sensitive, fast and specific biological methods to assess pollution with carcinogens. Recent validations of the most widely used test of Ames showed that about 50% of the known carcinogens remain undetectable by the test. This provoked the development of other short-term tests, such as alkaline elution, nick-translation, single-cell gel electrophoresis, restriction mutation assay, micronucleous expression, DEL assay. Although some of them were evaluated as promising methods, these assays can not specifically detect carcinogens and are not applicable for large-scale environmental studies.

We have constructed a principally new short-term assay for detection of carcinogens, based on the induction by carcinogens of the transposition of an engineered oncogene like element in *Saccaromyces cerevisiae*, the Ty1 retrotransposon. The natural inertness of yeast cells to genotoxins was eliminated by introduction into the tester cells of a mutation which enhances cellular permeability and increases, in this way, the sensitivity of the test. Each transposition of the engineered oncogene gives rise to a colony of selective medium making the Ty1 assay a quantitative test. The principle novelty of the Ty1 test consists in using a genetic element with structure, cell-cycle and expression control which resemble oncoviruses except that there is no extracellular phase in replication. The test is easy to perform, requires no special equipment, it is fast and cheap.

The characterization of the Ty1 test was done with pairs of laboratory genotoxins that are very similar in chemical structure - one being a carcinogen (for instance benzo (a) pyrene, the second having mutagenic activity without being carcinogen (benzo (e) pyrene). We studied three groups of genotoxins - carcinogen and mutagens, carcinogenic and not carcinogenic heavy metals, free (=carcinogenic) and conjugated (=not carcinogenic) bile acids. Results obtained in concentration-dependent and time-dependent experiments evidenced a positive answer of Ty1 test with all studied carcinogens and negative results with noncarcinogenic mutagens. The Ty1 test has a wider detection spectrum and is positive to carcinogens undetectable with other short-term tests. The specific positive response of Ty1 test to carcinogens was proved in environmental studies. Samples of soil, water and air for which the presence of carcinogens has been evidenced by chemical analyzes were positive in Ty1 test, while negative results were obtained with samples polluted with not carcinogenic mutagens. The results obtained with laboratory and environmental genotoxins evidenced that the Ty1 assay is a short-term test that specifically detects carcinogens.

Several explanations can be proposed for the specific response of Ty1 test to carcinogens. First, the similarity in structure, cell-cycle and function between Ty1 retrotransposons and retroviral oncoviruses may be considered as a precondition for similar responses to carcinogens. Second, the transposition of Ty1 to new locations of the genomic DNA creates genome instability and appearance of different DNA damages as it was found in tumors, induced by carcinogens. While the other short-term tests were developed to detect one genetic damage, the Ty1 test responds positively to all DNA lesions, induced by carcinogens, which increases the detection spectrum. Third, a survey of the literature shows that carcinogens, that are positive in Ty1 test, are also strong generators of reactive oxygen species (ROS). We favor this possibility and studied in details the role of elevated ROS levels for the positive answer of Ty1 test to carcinogens. Data will be presented for proving that the specificity of Ty1 test to carcinogens is due to the induction by Ty1-positives of a burst of ROS, while the Ty1-negative mutagens without carcinogenic potential have little effect of ROS production in yeast cells.

## Plenary Lecture 25

### The Prognosis Value of the hTERT Gene in the Evaluation of Pulmonary Metastasized Testicular Carcinomas



**Dr. Milena Adina Man**

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**Abstract:** Pulmonary metastases are frequently met in testicular cancers. Determining the pulmonary relapse model, studying prognosis factors for defining risk groups and applying different therapeutic strategies with the evaluation of survival represent the study's main objectives.

We've taken into our study patients diagnosed with testicular cancer all presenting pulmonary, pleural or mediastinal metastases. We evaluated the risk factors correlated with survival: the average age is 29.63 ( $p=0.613$ ), place of origin ( $p=0.895$ ), histology ( $p=0.078 > 0, 05$ ); tumor markers for our batch: Beta HCG, AFP (alpha-fetoprotein); LDH does not influence survival ( $p=0.786$ ), ( $p= 0.345$ ) respectively ( $p= 0.153$ ); types of pulmonary metastases: ( $p=0.08 > 0, 05$ ); the presence of other metastases: does not influence survival ( $p= 0.439$ ); the number of metastatic locations ( $p= 0.465 > > 0, 05$ ). Knowing the prognosis factors and how they are used to identify patients into different risk groups is of vital importance of the management of testicular cancer therapy. Identification into good risk and poor risk groups has a statistical significance as a prognosis factor ( $p=0.0254$ ). The data and results of the studies on clinical-imagistic bases are limited

due to the small number of patients included into the study (low incidence). The evaluation of other prognosis factors at an immune-histological, genetic or molecular level allows the redefinition of the prognosis and improvement of the germinal tumors' management. Because the risk factors usually available are not sufficient to identify the subgroups of patients with an unfavorable prognosis, we tried to evaluate new genetic markers which could prove their prognosis value. We emphasized the presence of the hTERT more expressed from a quantitative point of view at the level of testicular tumors with pulmonary metastases compared with tumors without pulmonary metastases. Until the identification of new prognosis factors (for example hTERT), validated by future studies, treatment and conduct will be based on the predictive value of other classical prognosis factors. Long term survival (over 5 years) and the curability rate of patients with testicular

cancer, although in literature is above 90%, our study revealed only a 35.29% survival rate. This justifies the increase of investigations regarding patients with unfavorable risk factors. The diagnosis of metastasis using molecular biological techniques has been attempted with various tissues including blood, pancreatic juice, ascites, lymph nodes, but the methods is still controversial. Micrometastasis, which is not detectable by routine histological examinations, can now be identified by genetic methods. Understanding the biology and tumor cell genetic can become research therapeutic targets.

## Plenary Lecture 26

### Late Untargeted Cytogenetic Effects of Human Radiation Exposure as Possible Markers of Oncopathology



#### Professor Maria Pilinskaya

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**Abstract:** In delayed terms following Chernobyl accident the important role for realization of late medical consequences of human radiation exposure (including oncopathology) take place untargeted cytogenetic effects - hidden, delayed and transmissible chromosome instability and "bystander effect".

For investigation of these cytogenetic effects such models had been modified and applied by us: two-termed (during 48 and 144 hours) cultivation of peripheral blood lymphocytes; G2-bleomycin sensitivity assay; mixed human lymphocytes culture consisted of cells differed by cytogenetic sex markers. The groups of high priority with different intensity of radiation exposure due to Chernobyl accident had been voluntary observed.

In children born to exposed parents increased frequency of chromatid breaks in long-term cultures confirmed expression of delayed chromosome instability in consequent mitosis; appearance of stable aberrations confirmed transmissible chromosome instability.

In exposed groups investigated by means of G2-bleomycin sensitivity assay the individual levels of chromosome aberrations induced by testing concentrations of bleomycin varied in wide range and didn't depend on their initial values. Among control donors, liquidators and Shelter's personnel ~33% persons hypersensitive to bleomycin exposure had been identified that can be considered as genetically caused phenomenon. Among patients recovered from acute radiation sickness ~58% persons expressed hidden chromosome instability that assumed modification of inherited susceptibility to mutagens by high doses of ionizing radiation.

Under joint incubation of targeted lymphocytes received from Chernobyl liquidators with intact female lymphocytes the frequency of chromosome aberrations in bystander cells was significantly higher than their background level that proved induction of chromosome instability in untargeted cells as the result of bystander effect.

The data received confirmed the reality of untargeted cytogenetic effects in delayed terms following Chernobyl accident that can be one of risk factor for human health, especially for induction and promotion of oncopathology.

#### Brief Biography of the Speaker:

Maria A. Pilinskaya is Head of Cytogenetic's laboratory of Department of medical genetics at Research Centre for radiation medicine, Ukraine. Her scientific interests are:

Assessment of mutagenic effects and genetic hazard of environmental factors for human health; biological indication and dosimetry of human radiation exposure; evaluation of nearest and delayed post Chernobyl cytogenetic effects in human; elaboration of cytogenetic criteria (especially cytogenetic oncomarkers) for the selection of risk groups. She is author or co-author over 350 scientific papers published in native and foreign reviewed journals or presented at domestic and international conferences. She is co-author of Russian-English Dictionary-Reference Book "Radiation Cytogenetics" (2009). She had the opportunity to work on probation in the field of FISH-WCP technique at Livermore National Laboratory, USA. She is a member of European Cytogenetists Association.

## Plenary Lecture 27

### Are Core Needle Biopsy Techniques Reliable in Diagnosis of Musculoskeletal Tumors?



**Associate Professor Ahmet Kaya**  
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**Abstract:** Correct histologic diagnosis of musculoskeletal tumors, as soon possible, is quite critic in point of improvement in patients' prognosis, and possibility and success of the limb sparing interventions. To make an accurate histologic diagnosis, adequate tissue sample is required. Open incisional biopsy has traditionally been used for that reason. However, open biopsies have complication rate of 16 % and these complications affect the treatment plan in 8 % of all patients undergoing biopsy . In recent years, core needle biopsies were started to be used instead of incisional biopsies . Compared to open biopsy, core needle biopsies are less invasive, cause fewer potential complications, and incur less expense. The major concern regarding core needle biopsy is that it provides a limited sample and small tissue cores, in which the histologic morphology may not be appreciable.

Both, it has reported that, to a large extent, the use of needle biopsies has replaced open biopsy in musculoskeletal oncology practice and it has also reported that it remains controversial whether accurate histological diagnosis can be made only with the material obtained by needle biopsy of musculoskeletal lesions.

The aim of this study is to evaluate the accuracy of the core needle biopsy techniques in musculoskeletal tumors.

#### **Brief Biography of the Speaker:**

I was born in Isparta, Turkey in 1968. I was graduated from Aegean University Medical faculty on 1991. I realised my compulsory service between 1991 and 1992. After that I attended to orthopaedic residency program in Tepecik Educational and Research Hospital – Izmir – Turkey. I was named as Orthopaedic Surgeon in 1997 and start to work as consultant oerthopaedic surgeon. I was attended to post graduated education in Orthopaedic Oncology. I was named as associate professor of orthopaedics and traumatology in 2009. I am married and have a son. I can speak Turkish and English.

**Plenary Lecture 28****Evaluation of Heat Shock Protein Targeting in Cutting Edge Antitumor Therapeutics**

**Professor Amere Subbarao Sreedhar**  
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**Abstract:** Heat shock proteins (Hsps) forms the most ancient defense system of living cells. Having chaperoning functions, Hsps are highly conserved, abundant and ubiquitously expressed in all cells and tissues. Despite technological advancements and enormous input on target based drug designing to combat cancer, anticancer treatment is still being challenged, which is due to, tumor being a polygenic disease. Comparing with conventional biomarker targeting, tumor specific functions of Hsps identify them as possible markers to target cancer. Therefore in the recent years chemotherapeutic intervention of Hsps has emerged as novel anticancer treatment. Induction of cytostasis or apoptosis are the two major mechanism of action from anticancer drugs, however, understanding the nature and interplay of cellular factors that help in regulating the intra-cellular functions in an orchestrated manner can guide through target based therapies. Increasing cancer incidences with civilization and age, furthermore suggest a need for better understanding of cellular environment during any chemotherapeutic intervention. Cell killing through single drug or combinatorial treatments though proposed to be the current concept of anticancer treatment, cancer immunity and bystander-cell safety opposes the hypothesis. The careful understanding of oncogenesis and tumor suppression suggests activation of alternative cellular mechanisms to combat cancer instead of killing, one such mechanism is forced cellular senescence of tumor cells. I would like to bring forth the current knowledge on Hsps and their central cellular roles and discuss advantages and disadvantages of Hsp targeting in anticancer treatments. Also demonstrate the progressive outlook of Hsp targeting from our ongoing studies and propose Hsp targeting as tumor suppressor mechanism.

**Brief Biography of the Speaker:**

Amere Subbarao Sreedhar is a senior scientist of Centre for Cellular and Molecular Biology, Hyderabad, India. His research interests are molecular basis of stress response, heat shock proteins in biology and medicine, and evaluation of natural products for potential anticancer effects. He has eighteen years of versatile research experience in the areas of developmental biology, biochemical pharmacology, cell and molecular biology, molecular medicine, and plant biochemistry. He is a life member of quite a few scientific societies and editorial member of a few National and International Journals. He published 30 research papers in reviewed journals, wrote book chapters and edited books, and presented 53 research papers at various National and International meetings. He received prestigious National and International research awards such as Japanese Society for Promotion of Science (twice), Fast Track Young Scientist Research award (twice), Physiological Society award from Hungarian Academy of Sciences, National Overseas Research Award etc., to work in various countries and different research laboratories.

**Plenary Lecture 29****Development of Novel Anticancer Agents and Identification of Mode of Action in Eradicating Malignant Cells****Associate Professor Ilana Nathan**

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**Abstract:** Cancer in most cases is still considered an incurable disease and thus there is a critical need to discover new anticancer drugs. In our efforts to search for novel anticancer agents or approaches, we have concentrated on three major groups of compounds, all of which act at least in part by inducing cancer cell death. Structure-function relationships of the newly synthesized compounds, selectivity, mode of action in killing cancer cells and cellular targets were explored.

The first group consists of compounds whose chemical structures comprises aryethylene moiety, the second group consists of iron chelators and the third group consists of naphthoquinones. Both known and newly synthesized compounds were studied for their antitumor efficacy in vitro on cell lines derived from hematological malignancies and some of the compounds were tested on cell lines derived from solid tumors. Based on structure-function relationship studies we found two active subgroups of compounds among the aryethylene derivatives namely, substituted 9-arylideneanthrones (BAs) and members of the triarylvinyl systems and two active groups among the naphthoquinones, namely, chloro- and pyrrolidino-amino-phenyl-naphthoquinones. The iron chelators used are known compounds. The aryethylene derivatives exhibited a high degree of selectivity for cancer cells. Normal cells were relatively resistant to the naphthoquinones studied and iron chelators were active against different cell lines in a range of concentrations that are safe for human use.

The aryethylene derivatives and iron chelators killed the cells by apoptosis while the naphthoquinones induced apoptotic or necrotic cell death depending on time and concentration conditions. Apoptosis induced by members of the different groups was accompanied by the disruption of mitochondrial transmembrane potential and was followed by cytochrome c release and caspases activation.

Apoptosis induced by compounds from the three groups involves oxidative stress, which plays a critical role in mediating cell death. Nevertheless, the source of reactive oxygen species (ROS) varies. The different compounds were found to act through different signaling pathways. Using members of the triarylvinyl systems, the results suggest involvement of FLAP/5-LOX. However, the main sources for ROS production using BAs were NAD(P)H oxidase and mitochondria. The iron chelator mimosine caused formation of hydrogen peroxide and a decrease in reduced glutathione levels probably through its iron-chelating activity via catalase inhibition, while the results obtained with naphthoquinone derivatives suggest NAD(P)H-oxidase involvement in induction of oxidative stress and cell death.

The direct effect of the compounds on mitochondria was studied. The active naphthoquinones and mimosine induce mitochondrial swelling in isolated rat liver mitochondria, via opening of permeability transition pore. While the aryethylene derivatives tested from both subgroups, alone, do not cause mitochondria swelling. However, they protected mitochondria from Ca<sup>2+</sup>-induced swelling. It is possible that these compounds have a direct effect on the mitochondria causing stabilization of their membrane.

Some specific signaling steps were observed for the different compounds. PKC- $\zeta$  is specifically activated at early stage by the aryethylene derivatives. Our finding suggests a role for this enzyme in apoptosis mediated by members of the triarylvinyl family but not to those of the BA family. Treatment with the naphthoquinone derivatives induced a rapid phosphorylation of p38 mitogen-activated protein kinase (p38MAPK). Phosphorylation of extracellular signal-regulated protein kinases (ERK1/2) was observed as well. The results obtained imply that induction of p38 is involved in apoptosis mediated by naphthoquinones, whereas ERK1/2 plays role in cell survival and possibly in necrosis. ICL670 (Exjade®, Deferasirox) a relatively new oral iron chelator was tested against mantle cell lymphoma cells. Our results indicate that the mechanism of ICL670 action includes shortening of cyclin D1 half-life via enhancement of protein degradation. The results point to the role of proteasome in this action.

The various groups of compounds affected the ratio of pro- and anti-apoptotic proteins of the Bcl-2 family. Differences in behaviour were obtained even within the same group of compounds. For example, an increase in the expression of

Bax at both transcriptional and translational levels was seen with two active naphthoquinone derivatives. Moreover, most intriguing was the down regulation of Mcl-1 expression, which is one of the main anti-apoptotic proteins in leukemia, by one of the compounds while down regulation of Bcl-2, was seen with other compounds.

The effect of the different compounds was examined *ex vivo* on CLL and AML cells and on mononuclear cells obtained from healthy donors. The results indicated that the compounds killed the leukemic cells selectively and exhibited different specificities towards CLL and AML cells.

By virtue of the results obtained with members of the triarylvinylic systems, the Hematology Institute in Soroka University Medical Center began a phase I-II clinical trial to evaluate the potential therapeutic effect of clomiphene in advanced and refractory chronic lymphoblastic leukemia and acute myeloid leukemia patients. Our preliminary results revealed that the treatment caused stabilization of leukocyte levels during drug administration and slowed down disease progression in a few treated AML patients.

In summary, our results present novel and known compounds that act by the killing of cancer cells through various mechanisms and thus may provide effective anti-cancer strategies.

**Plenary Lecture 30****A Non-Receptor Protein Tyrosine Kinase, c-Fes, may be a Potential Molecular Target for Advanced Cancer Patients****Professor Shigeru Kanda**

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**Abstract:** Malignant tumour growth is affected by a variety of normal surrounding cellular compartments. Angiogenesis supplies oxygen and nutrients to tumour cells and interstitial tissues (fibroblasts, macrophage/monocytes and osteoclasts) influence invasion and metastatic spread of tumour cells. These biological reactions of normal cells as well as tumour cell behaviors are regulated by protein phosphorylation and subsequent intermolecular interactions. Protein tyrosine kinase is one of the best players in this scenario. Thus, targeting protein tyrosine kinases is an attractive strategy for the treatment of advanced cancer patients.

Fes was originally identified as a cellular counterpart of an oncogene product, v-Fps, and represents a unique structural property with large N-terminal region containing two coiled-coil domains, followed by an SH2 domain and a catalytic domain. Coiled-coil domains are involved in intermolecular oligomerization, and association between the SH2 domain and the catalytic domain is involved in kinase activation. Until recently, most studies on Fes have been performed with myeloid hematopoietic cells, one of the major sites of its expression in normal tissues. Targeting disruption of c-fes gene showed minimal effect. When activated mutant Fes was expressed in the skin, increase in vascularity and hemangioma formation were observed, indicative of its role in angiogenesis. Fes forms oligomers in cells, which is responsible for the regulation of kinase activity, and expression of kinase-dead Fes exerts dominant negative effect on endogenous Fes. Endothelial cells express Fes and no specific synthetic inhibitor for Fes is currently available. We expressed kinase-dead Fes in endothelial cells and examined its role in proangiogenic factor-treated cells. WE found that its expression inhibited FGF-2- and angiopoietin 2 (Ang 2)-directed chemotaxis, and sonic hedgehog- and stromal-derived factor (SDF)-1 $\alpha$ -promoted morphological differentiation. In VEGF-A-treated cells, Fes was activated and was involved in PI3-kinase activation. However, Fes inactivation was compensated by other signaling molecules (VEGF receptor-2, Src and IRS-1) for the PI3-kinase activation in VEGF-A-treated endothelial cells and no dominant negative effect was observed. It is now widely accepted that VEGF-A blockade rapidly cause the resistance to this therapy. One of the mechanisms of this resistance is the alteration of the dependence of tumour angiogenesis from VEGF-A to other proangiogenic factors, such as FGF-2, Ang 2 and SDF-1 $\alpha$ . Thus, it seems likely that the inhibition of Fes activity may be a second line antiangiogenic therapy for VEGF-A-independent tumours.

The role of Fes in solid tumour cell growth was not well examined because of its limited expression in normal epithelial cells. Recently, inactivating mutation of Fes was found in colorectal cancer cells and two groups have shown that kinase-dead Fes was favorable for breast tumourigenesis in mutant mice and colon cancer cell growth in vitro. This tumour-suppressive function of Fes may be cell-type dependent, because downregulation of Fes by siRNA inhibited the proliferation of human renal carcinoma cells and expression of kinase-dead Fes showed no effect on tumor growth in nude mice. Further studies on other tumour cell types are warranted whether inhibition of Fes activity as an antiangiogenic therapy may accelerate tumour growth in vivo.

It is also urgent to find synthetic small molecular weight kinase inhibitors for Fes to examine the role of Fes in normal and pathological conditions. During the screening of previously published synthetic kinase inhibitors, we found that gefitinib, an EGF receptor tyrosine kinase inhibitor inhibits FGF-2- and VEGF-A-induced Fes activity in endothelial cells, and chemotaxis toward FGF-2-, but not VEGF-A. The effect was indirect because gefitinib failed to inhibit purified Fes activity in in vitro kinase assay. It is elusive what is the direct activator of Fes that is sensitive to gefitinib-treatment. Nevertheless, the results suppose the idea that gefitinib may be used as a second line antiangiogenic agent.

**Brief Biography of the Speaker:**

Shigeru Kanda is a Head of the Department of Experimental and Clinical Laboratory Medicine and the Palliative Care Team, National Hospital Organization Nagasaki Hospital, Nagasaki, Japan. He started his career as an urological

surgeon and obtained his Ph.D. with the studies on the growth regulation of renal tubular cells. He worked as a visiting scientist at Ludwig Institute for Cancer Research, Uppsala, Sweden, where he began to study the signal transduction pathways leading to angiogenesis. He authored or co-authored over 85 scientific papers published in peer-reviewed journals. He wrote a chapter entitled Studies of the endothelial cell-specific signal transduction pathways. New paradigm for the development of potent anti-angiogenic therapies. In: Trends in Angiogenesis Research edited by R. V. Zubar, Nova Science Publisher, Inc, pp. 43-69, 2005. and he is members of American Association for Cancer Research and American Society of Biochemistry and Molecular Biology. He is also an Editorial Board of "Oncology Letters".

## Plenary Lecture 31

### The Role of Tight Junctions in Cancer Metastasis



**Dr. Tracey A. Martin**

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**Abstract:** As the most apical structure between epithelial and endothelial cells, Tight Junctions (TJ) are well known as functioning as a control for the paracellular diffusion of ions and certain molecules. It has however, become increasingly apparent that the TJ has a vital role in maintaining cell to cell integrity and that the loss of cohesion of the structure can lead to invasion and thus metastasis of cancer cells. We will present data showing how modulation of expression of TJ molecules results in key changes in TJ barrier function leading to the successful metastasis in breast and prostate cancer. It is apparent that changes in the function and regulation of TJ in cancer is not just a by-product of cancer progression but is integral to its formation and persistence, eventually enabling metastasis and secondary disease. As such, this area of research is of fundamental importance in the effort to understand and alleviate this terrible disease.

**Brief Biography of the Speaker:**

Following her first degree in Microbiology with Genetics, Dr Tracey Martin began her research career with a PhD in microbial molecular ecology at Cardiff University, Wales. In 1997, she became a research fellow at the Department of Surgery, Wales College of Medicine, where she still works. Initially working jointly with MARG and the Wound Healing Research Unit, in 2000 she moved fully to MARG and was appointed as a non-clinical lecturer in August 2003. She was the recipient of an Astra-Zeneca Scholarship at the San Antonio Breast Cancer Symposium in 2002. Her main interests are how tight junctions function between normal and cancerous cells, and the interaction of cancer cells in cell-adhesion and cell-signalling; she is especially interested in VE-cadherin and how this molecule is involved in angiogenesis. In addition, she has also investigated the role of HGF/SF and other cytokines/growth factors in affecting angiogenesis and tight junction function of both endothelial and in breast & prostate cancers, together with the HGF/SF antagonist, NK4 and other anti-angiogenic molecules.

## Plenary Lecture 32

### From Psycho-Analysis to Culture-Analysis: A Culturally Sensitive Revision of Psychology



#### Professor Marwan Dwairy

Clinical, Medical, Educational, and Developmental Psychologist

Medical, Educational, and Developmental Supervisor

Researcher in Cross-Cultural Psychology

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**Abstract:** This lecture re-examines the application of psychodynamic approach to collective cultures such as the Arab/Muslim one. Unlike the rooted idea of separation-individuation process that ends in possessing an autonomous identity or self, individuals from collective cultures maintain their collective identity and self. Adaptation to the interdependent collective system, rather than to independence, is the ultimate goal of healthy development in these societies. The main drama of collective people's life takes place within the intra-familial domain rather than the intra-psychic one. The self is not differentiated from the family's identity, and the internal constructs of control such as ego, self, or super-ego are therefore not autonomous. External pressures are the main source of control, and familial approval is the main source of esteem and joy. Social norms and values explain the consistency in peoples' behavior; individuation and social status explain the individual differences. To deal with threat and shame Arab/Muslims, for example, need social mechanisms to manipulate the external oppressor, such as Mosayara, Istighaba and identification with the oppressor, rather than unconscious defense mechanisms.

To deal with psychological disorders, psychotherapy is applied to restore the intra-psychic order. During therapy, revealing unconscious drives or promoting self actualization may lead to confrontations with the family and the social environment. In these confrontations typically the client is the weakest and therefore the loser. Therapy should not be a tool to change the client's culture. Culture should rather be exploited to bring about therapeutic change. Metaphor therapy and culture-analysis are suggested to help clients who adopt a collective identity or self. In metaphor therapy the inner world is addressed and dealt indirectly and symbolically without bringing unconscious content to the consciousness, thus avoiding guilt or confrontation with the family. In culture-analysis therapist identifies subtle contradictions within the belief system of the client and employ cultural aspects that may facilitate change. Similarly to how a psychoanalyst analyses the psychological domain and brings conflicting aspects to the consciousness (e.g. aggression and guilt) in order to mobilize change, a culturanalyst analyses the client's belief system and brings contradicting aspects to the consciousness in order to mobilize revision in attitudes and behavior. The assumption that underlies culturanalysis is that culture influences people's lives unconsciously. When therapists inquire into and learn about the client's culture, they may find some unconscious aspects that are in conflict with the conscious attitudes of the client. Once the therapist brings these aspects to the awareness of the client, a significant change may be effected. Unlike the unconscious drives which are revealed through psychoanalysis, these intra-culture conflicts are not supposed to be threatening because all aspects revealed are culturally and morally legitimized. This process can be described in humanistic terms too. In much the same way that a Rogerian therapist establishes an unconditional positive regard and empathy to facilitate the coming forward of the real authentic self, a culturanalyst establishes positive regard and empathy to the culture and facilitates the coming forward of more and more aspects of the culture that were denied and that may be employed to effect change. Alternatively, one can understand this process in terms of generating cognitive dissonance within the client's belief system that necessitates change. Regardless of the theoretical explanation, in order to conduct a "within-culture therapy," therapists need to be open and incorporate several aspects of the culture in the therapy in order to create a new dynamic within the client's culture. Beside empathy, a thorough inquiry into the client's culture in order to identify the cultural aspects that may be employed in therapy is needed. Some examples of within-culture therapy will be presented.

#### Brief Biography of the Speaker:

Marwan Dwairy, D.Sc., is associated professor of psychology in Oranim academic college, Israel. He is a licensed expert and supervisor in three areas: educational, medical, and developmental psychology. In addition, he is a licensed clinical psychologist. In 1978, he established the first psychological services center for Arabs in Nazareth, Israel. He continues to serve in his capacity as a supervisor in different psychological centers. He received his

doctorate from the Faculty of Medicine at the Technion in 1991. Professor Dwairy have developed and standardized several psychological tests for Arabs. He served as a professor in several universities: Graduate program at Nova Southeastern University in Florida, Haifa University, Israel, and Technion, Israel. He has done many cross-cultural researches on identity, individuation, parenting, and mental health. He is a reviewer for several journals and served on the editorial board of *Clinical Psychology Review*, and edited a special issue (December, 1999) for that journal devoted to "cross-cultural psychotherapy in the Middle-East." He has published several books, book chapters, and articles in cross-cultural psychology and mental health among Arabs in which he presented his models and theories concerning culturally sensitive psychology. His recent book was:

Dwairy, M. (2006). *Counseling and Psychotherapy with Arabs and Muslims: A Culturally Sensitive Approach*. New York: Teachers College Press, Columbia University.

**Plenary Lecture 33****Influence of Repeated Exposure to Caffeine on Dopamine Transmission: Preclinical Evidence and Possible Implications****Dr. Nicola Simola**

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**Abstract:** Caffeine is one of the most popular psychostimulants in the world and is extensively consumed by both young and adult population. A large body of evidence demonstrates the existence of striking differences between caffeine and other psychostimulants abused by humans, like amphetamines or cocaine. For example, as compared to such substances, caffeine displays weaker rewarding and reinforcing effects. On these bases, and in light of the fact that caffeine exerts very negligible adverse effects, caffeine consumption is usually envisioned as a “safe habit”. In spite of this, however, a wealth of preclinical research has disclosed the capability of caffeine to modulate dopamine transmission in the brain, which plays a pivotal role in addiction phenomena. Together, these pieces of evidence have raised the possibility that caffeine consumption, although harmless by itself, could represent a factor capable of promoting the instatement of an addiction towards other psychoactive substances as well as of precipitating an existing addictive behaviour. In our laboratory the interactions between caffeine and the dopaminergic system have been investigated in a preclinical model of long-term caffeine administration. The results obtained indicate that, in the rat, repeated exposure to caffeine engenders a persistent hyperfunctionality of dopamine transmission in the striatum. In particular, it was observed that subchronic-intermittent caffeine elicited sensitization to its motor stimulant effects, indicative of the occurrence of neuroplastic changes in dopaminergic transmission. Such a sensitization was found to be paired with a decrease in the levels of both the mRNA for adenosine A2A receptors, which deeply interact with dopamine receptors, and the mRNA for the early gene zif-268, the latter being indicative of persistent modifications in the dopamine receptors signalling pathway. Furthermore, rats sensitized to caffeine displayed cross motor sensitization to amphetamine, increase in the expression of zif-268 mRNA, and an elevation in high-affinity dopamine D2 receptors (D2High). Taken together, these findings demonstrate that prolonged exposure to caffeine leads to neuroadaptations involving striatal dopaminergic transmission and corroborate the hypothesis that caffeine consumption may be a risk factor for addictive behaviours.

**Brief Biography of the Speaker:**

Dr. Simola received his M. S. Degree in Pharmaceutical Chemistry and Technology and his Ph. D. Degree in Pharmacology of Drug Abuse from the University of Cagliari, Italy. Currently, Dr. Simola performs his research activity at the Department of Toxicology of the University of Cagliari, having also spent a period as a visiting research fellow at the Institute for Neuroscience of the University of Texas at Austin, U.S.A. (2007-2009). Dr. Simola's research involves the study and development of new therapeutic agents to be used in the treatment of Parkinson's disease, focusing on adenosine receptor antagonists and metabolic enhancers, the development of new preclinical models of early-stage Parkinson's disease, and the study of the interactions between caffeine and other recreational psychostimulants bearing addiction potential. This research activity is carried out in collaboration with Universities and Research Centers in Italy and abroad. Dr. Simola is author of several articles on caffeine, Parkinson's disease, neurodegeneration and related topics which are published in International Scientific Journals, books and proceedings of scientific meetings.

## Plenary Lecture 34

### Emotional Disease Acceptance in Patients with Depressive Disorders and Addictions - Results of a Longitudinal Study with the ERDA Questionnaire



#### Professor Arndt Bussing

Chair of Medical Theory and Complementary Medicine

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**Abstract:** Background: In the treatment of patients with depressive disorders and associated addictions, the cognitive disease acceptance is in most cases the primary focus of therapeutic interventions. According to the concept of the Oberberg Clinics, private specialist emergency clinics which offer comprehensive medical and psychotherapeutic treatment for individuals suffering from emotional, psychosomatic and psychiatric problems, an emotional acceptance is of outstanding relevance for the long-term course of disease. Thus, we have developed an instrument to identify the levels and factors of acceptance, the "Emotional / Rational Disease Acceptance" (ERDA) questionnaire (Bussing et al., Health and Quality of Life Outcomes, 2008). In a multicenter prospective cohort study, we investigated how the weighting of the respective disease acceptance styles may change during the therapeutic intervention.

Methods: We consecutively enrolled 225 patients treated in the Oberberg Clinics Schwarzwald, Weserbergland and Berlin/Brandenburg: 39% were women; 60% men; mean age 50 +/- 9 years; 45% depressive, 44% addictive, 9% anxiety, and 3% other psychiatric disorders. At the start and at the end of their hospital treatment, we anonymously applied the ERDA questionnaire, Beck's Depression Inventory (BDI), SCL-90-R symptom checklist, Escape from Illness (AKU), and the Brief Multidimensional Life Satisfaction Scale (BMLSS).

Results: Reliability analysis of the 21-item ERDA questionnaire (Version 2) revealed a good internal consistency (Cronbach's alpha = 0.88). Exploratory factor analysis revealed 5 factors which explain 63% of variance: Positive Life Construction, Contentedness, Well-being (emotional, ePLC); Rejection Irrational Dealing with Illness (emotional, eRIDI); Rejection of Guilt / Failure (emotional, eRGF), Understanding Causes of Illness (rational, rUCI); Rational Disease Acceptance (RDA). eRIDI and RDA were strongly inter-correlated ( $r=0.55$ ). ePLC correlated strongly with depression (BDI,  $r=-0.60$ ; SCL-90-R/s Global Severity Index,  $r=-0.57$ ), and life satisfaction (BMLSS,  $r=0.57$ ). Escape correlated strongly with eRIDI ( $r=-0.62$ ), and moderately with ePLC, eRGF and RDA ( $r > -0.50$ ). BDI and SCL-90-R correlated moderately with eRIDI and eRGF ( $r > -0.39$ ), and weakly with rUCD and RDA ( $r > -0.29$ ). Life satisfaction correlated moderately with eRIDI and eRGF ( $r < 0.35$ ), and weakly with RDA ( $r=0.22$ ), but not with rUCI ( $r=0.08$ ).

During the hospital stay, both the ERDA and life satisfaction scores of the patients significantly increased, while BDI scores, Global Severity Index of the SCL-90-R and Escape significantly decreased. In patients with addictive, depressive and anxiety disorders, the treatment resulted in strong effects particularly with respect to ePLC (Cohen's  $d = 0.95-1.18$ ), strong effect sizes with respect to RDA in patients with depression and anxiety (0.85-1.55), moderate effect sizes in eRIDI and rUCI (0.53-0.80), and small effect sizes for eRGF particularly in patients with addictions (Cohen's  $d = 0.34$ ). The intervention resulted in strong effect sizes with respect to psychiatric symptoms (BDI, SCL-90-R: 0.83-1.82).

Conclusion: We were able to confirm the ERDA as a reliable and valid instrument which was sensitive to psychotherapeutic treatment effects. Because rational disease acceptance was highly expressed even at the start of treatment, particularly in patients with addictive and depressive disorders, this variable should not be regarded as a relevant marker of patients at risk.

#### Brief Biography of the Speaker:

Studied medicine at the Technical University Aachen from 1984-1991, worked at the Institute of Immunology of Technical University Aachen from 1992-1995, and became head of the Department of Applied Immunology, Krebsforschung Herdecke from 1995-2005. In 2002, he received his *venia legendi* at the University of Witten/Herdecke. Since 2005 he is senior researcher at the Chair of Medical Theory and Complementary Medicine of University Witten Herdecke, and became a full research professor in 2007. Arndt Bussing is editor of the German Journal of Oncology since 2004, and advisory board of the journal Research in Complementary Medicine since 2006.

## Plenary Lecture 35

### The Impact of Discrimination and Acceptance on Psychological Functioning of Refugees and Immigrants in the Netherlands



**Assistant Professor Annet Te Lindert**  
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**Abstract:** This study focuses on the impact of discrimination and acceptance on psychological functioning of 974 immigrants and refugees living in the Netherlands (i.e. Moroccan, Turkish, Antillian and Surinamese immigrants and Iranian refugees). These immigrants live in peaceful coexistence in the Netherlands, nevertheless, they perceive discrimination (e.g. job and general) and lack of acceptance from Dutch mainstreamers. Comparing these immigrant groups is especially interesting because the psychological part of the acculturation process, such as the consequences of discrimination, non-acceptance by Dutch mainstreamers, loneliness, and homesickness, is expected to be different these immigrant groups. Whereas political refugees are forced from their home countries and “pushed” into a new environment, immigrants are generally “pulled” toward their new country. This study aims at getting more insight in the antecedents and moderators/mediators of the psychological part of the acculturation process. Especially, the study looks at the effects of push and pull mechanisms, gender, education and labor market achievement, perceived discrimination, acculturation orientations and psychological and sociocultural outcomes of immigrants and refugees in the Netherlands. Results and implications will be discussed.

## Plenary Lecture 36

### Experience-Dependent Brain Plasticity: A Key Concept for Mental Health and Disease



**Professor Martha Koukkou**  
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**Abstract:** The presentation reviews conceptual issues about the relationships between experience-dependent brain plasticity and the development of cognitive-emotional behavior styles recognizable as normal or deviant. Integrative brain sciences produced findings which show that

(a) Human subjectivity is the product of the neocortical learning and memory functions that create biography (autobiographical memory).

(b) These learning and memory functions extract personal meaning using the brain's intrinsic capacity to generate experience-induced neuronal connectivity that represents the myriad of idiosyncratic associations of experiences, events, objects, names, emotions, actions, decisions. The content of the autobiographical memory characterize the individual's cognitive-emotional and behavior style.

(c) Contents of the autobiographical memory that represent the effects of uncooperative (stress-inducing) interactions of the social environment with the developing individual are maladaptive. Maladaptive memory content underlies the manifestation of neurotic, psychosomatic and psychotic symptoms.

**Brief Biography of the Speaker:**

Martha Koukkou, M.D. is Professor em. of the University of Zurich, Switzerland. She is a psychophysicologist, psychiatrist, and psychotherapist. She received her M.D. from the University of Athens, Greece. Postgraduate work in research and clinic in Germany and U.S.A. Since 1971 in Switzerland where she organized and headed the laboratories of Psychiatric Neurophysiology at the University Hospitals of Psychiatry in Zurich and Bern. After retirement, continuing teaching and research on brain and behaviour as Associate Scientist at The KEY Institute for Brain-Mind Research of the University of Zurich. Publications in the field of electrophysiology of brain information processing during development, sleep, and neurotic and psychotic symptomatology, as well as on modeling of the personal meaning-extracting brain functions which create subjectivity.

## Plenary Lecture 37

### Recent Advances in mGluR5 Receptor Ligands as Potential Treatments for Drug Addiction



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**Abstract:** The type 5 metabotropic glutamate receptor (mGluR5) plays a pivotal role in mediating drug self-administration and drug-seeking behavior. Mice lacking mGluR5 receptors do not self-administer cocaine and are indifferent to its locomotor stimulant effects, and studies conducted by our laboratory and others have shown that mGluR5 receptor antagonists reduce self-administration of alcohol, nicotine, cocaine, heroin, and methamphetamine in rats and/or mice. mGluR5 receptor antagonists also prevent reinstatement of drug-seeking behavior elicited by drug priming or exposure to drug-associated cues, suggesting that these compounds may aid in the prevention of relapse. In contrast, recent studies from our laboratory have shown that positive allosteric modulators (PAMs) of mGluR5 receptors, which increase the activity of the receptor in the presence of glutamate, facilitate the extinction of drug-seeking behavior. We propose that this effect is due to the well-known biochemical cross-talk between mGluR5 and NMDA receptors, and that mGluR5 PAMs facilitate extinction learning as well as other forms of behavioral and synaptic plasticity. Current studies in our laboratory are being conducted to assess the role of adult hippocampal neurogenesis in the facilitation of extinction learning by mGluR5 PAMs. In summary, mGluR5 receptor antagonists may help reduce on-going drug self-administration or aid in the prevention of relapse, while mGluR5 PAMs may aid in the facilitation of extinction learning, perhaps by reducing the salience of drug-associated cues and contextual memories. Several mGluR5 antagonists are currently in clinical trials for the treatment of other medical conditions such as Fragile X Syndrome, migraine, depression, anxiety, and gastroesophageal reflux disease, and mGluR5 PAMs are in development for the treatment of schizophrenia. Eventual approval of these compounds by regulatory agencies will allow for clinical assessment of the potential anti-addictive effects of mGluR5 antagonists as well as the potential pro-cognitive effects of mGluR5 PAMs in facilitating extinction learning.

**Brief Biography of the Speaker:**

Dr. Olive received his B. A. Degree in Psychology from the University of California at San Diego, and his Ph.D. Degree in Neuroscience from the University of California at Los Angeles. Currently, Dr. Olive performs his research activity in the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. Dr. Olive's research involves the study of the role of glutamate neurotransmission in addiction using rodents models, as well as preclinical development of new glutamate-based therapeutics for treatment of drug addiction and alcoholism. This research activity is carried out in collaboration with universities in the United States and abroad. Dr. Olive is author of over 60 publications related to the field of drug addiction which are published in International Scientific Journals, books and proceedings of scientific meetings.

## Plenary Lecture 38

### Creativity and Intelligence as Predisposing Factors of Mental, Social, and Physical Health



**Professor Olga M. Razumnikova**  
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**Abstract:** Research of human intelligence has progressed at different levels of analysis including neurobiology, behavior, and health. First, psychophysiological evidences will concentrate on creative task-induced brain activity, interactive effects of creativity with personality and intelligence on cortical activation patterns using EEG mapping and fMRI. Successful divergent thinking is characterized by functional plasticity in neuronal oscillations and by variability in hemispheric asymmetry that could be explained by various IQ and personality indicators. The results are compatible with a model in which processing speed and emotion jointly influence on performance of creative task via additive effects of the limbico-cortical and thalamo-cortical arousal systems. Second, the clusters of cognitive abilities and personality traits required for creative behavior and their relationships to psychopathology and an impact of genetic and environmental factors in the exposure to this cluster will review. Finally, neurobiological base of the association between an intelligence and adaptation is the interactions of cortical-subcortical regions and plasticity of brain structure in response to training that related to emotional states and cognitive abilities. Perhaps higher intelligence can be a buffer against various forms of mental and psychosomatic diseases. Hierarchical structure of intelligence, including analytical, practical, emotional, and creative aspects of intelligence may be a premium to prevent informational stress-induced health degeneration.

**Brief Biography of the Speaker:**

Olga M. Razumnikova, Dr.Sci. is Professor of the State Technical University in Novosibirsk, Russia. She received her Dr.Sci. from the State Research Institute of Physiology of Russian Academy of Medical Sciences, Siberian Branch. She worked as a chief researcher at the Laboratory of Cognitive Physiology of this Institute. Her research activities are concentrated on integration of neuroscience and social psychology. The specific research areas have been on EEG mapping and assessment of cognitive abilities and personality traits in volunteers. Her current research interest is EEG correlates of creativity, intelligence, and personality. Publications in the fields of electrophysiology of high cognitive functions (memory, attention, and creative thinking) and psychology of individual differences including sex differences in creative thinking.

## Plenary Lecture 39

### Routing Self-Hypnosis an Alternate Hassle Free Method Involving One's Own Mind Creating Innovative Avenues in Psychotherapy



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**Abstract:** Self-hypnosis is a conscious attempt to condition one's own mind to a subconscious state of facilitating a task to occur in reality giving a feeling of self fulfillment. A regular practice of self-hypnosis in a right sense is advisable as it frees the mind from negative emotions viz: fear, anxiety, unwanted hallucinations. The paper focuses on effectiveness of self-hypnosis providing an innovative mental treatment one could practice in a hassle free environment to keep it fit to fight everyday emotional battle as long as one is alive in the physical world , similar to the intake healthy food, multivitamin table, and practicing good physical exercise being the essential factors of physical well-being.

**Brief Biography of the Speaker:**

I started my career as Assistant professor of Chemistry in government Arts and Science college, Tamil Nadu , in INDIA .Later moved to New Delhi quitting govt job and worked as School teacher , completed Mphil, B.Ed, M.Ed degrees shifted back to Chennai ,South INDIA and started working in a school as Chemistry where my children studied .During my School teacher career I taught "A" level and "O" level Chemistry for 15 years. In 2006 resigned school job to join as Assistant professor of Chemistry in an Engineering College. During this period registered for Ph.D degree in Cognitive Psychology .From 2006 to 2009 presented more than 10 papers in the National and International Conferences. Published three papers and few more papers are yet to be published.

I Completed my Ph.D thesis titled " Learning techniques on Information processing ability and Serotonin level in teaching -learning Chemistry" and looking for opportunity to carry out post -doctoral research in Cognitive Psychology, focus area of my research. At present working as Consultant in Cyber School Technologies Solutions Pvt ltd a MNC located at five different countries, and looking out for University Job.

## Plenary Lecture 40

### To Attribute, or not to Attribute, that is the Post-Traumatic Question



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**Abstract:** A significant number of persons worldwide will experience a traumatic event during their lifetime, be it natural (e.g., tornado, hurricane, earthquake) or man-made (e.g., terrorist attacks, sexual assault). The most common difficulty experienced after a traumatic event is some type of anxiety, with the group of symptoms typically labeled post-traumatic stress symptoms (PTSS) being the most common among type. Related or secondary problems can include impairments in social, academic, or employment functioning, depression, and substance use. Although there are numerous evidence-based programs and therapies designed to alleviate PTSS, they are primarily delivered months, sometimes years, after the traumatic event, as only a small percentage of those persons exposed to a trauma will go on to develop clinically significant difficulties. Early identification of those mostly likely to develop significant difficulties has uncovered several variables that are predictive of distress, including preexisting startle sensitivity, coping skills, depression, and personality factors. The present paper will discuss the results of several quasi-experimental studies designed to examine the role of disaster-specific attributions in predicting current and future post-traumatic stress symptoms in both school-age children and young adults. Primary findings include very strong predictive power for attributions (between 36-74% of variance in PTSS symptoms depending on amount of time post-disaster), particularly those involving searching for the meaning behind the disaster, and this predictive ability was far above and beyond the types of coping skills employed, subjective exposure, or objective exposure to the disaster. The significance of these findings to potential identification of and intervention with persons after exposure to trauma will also be addressed.

**Brief Biography of the Speaker:**

Caleb W. Lack, Ph.D. is a licensed clinical psychologist and an Assistant Professor of Psychology at the University of Central Oklahoma. A specialist in cognitive-behavioral therapy, he completed a predoctoral internship in Clinical Child/Pediatric Psychology at the University of Florida and earned his doctorate in clinical psychology from Oklahoma State University in 2006. He is the author of over two dozen scientific articles, books, or book chapters and has presented across the United States and internationally on a variety of topics, including the assessment and treatment of Obsessive-Compulsive Disorder and Tourette's Disorder, stress reactions to natural disasters, and evidence-based psychological practice. To learn more about Dr. Lack or download copies of his publications and presentations, please visit <http://www.caleblack.com>.

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