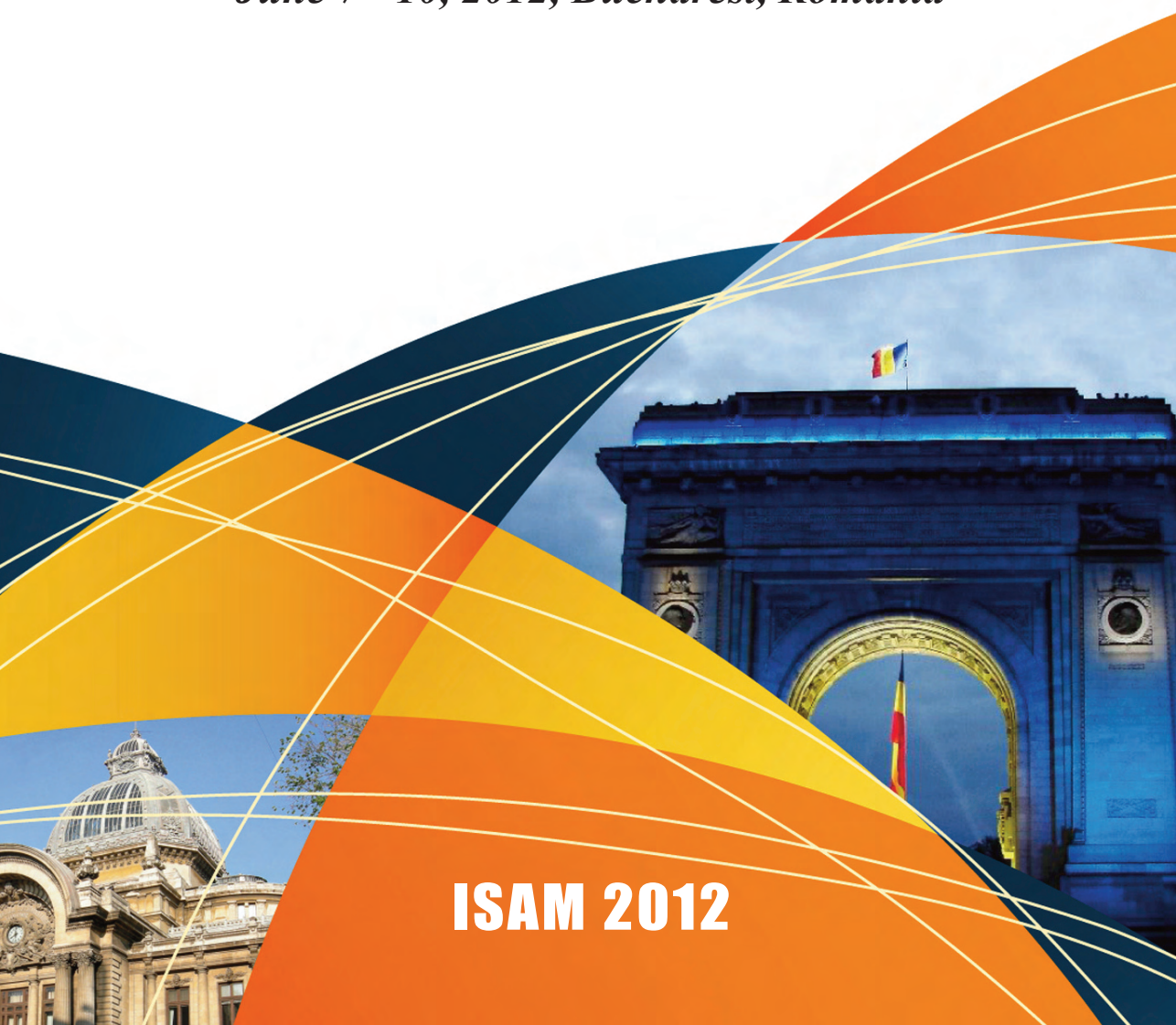
The 10th WORLD CONGRESS of the International Society for ADAPTIVE MEDICINE

INTERCONTINENTAL HOTEL
June 7 - 10, 2012, Bucharest, Romania



ISAM 2012

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The 10th WORLD CONGRESS of the International Society for ADAPTIVE MEDICINE

INTERCONTINENTAL HOTEL
June 7 - 10, 2012, Bucharest, Romania

Congress Venue

4 NICOLAE BĂLCESCU BLVD.
BUCHAREST, 010051
Romania

Front Desk: +40-21-3102020

Fax: +40-21-3120486

Message of the Congress President

Dear Colleagues,

On behalf of the Organising Committee, I have the pleasure of welcoming you to the 10th World Congress of the International Society for Adaptive Medicine (ISAM), which will be held in Bucharest, between 7 and 10 of June, 2012.

This meeting is gathering World experts, from more than 35 countries, who will present the cutting edge advances in medical science, covering the meaning of the transitive verb 'to adapt': „Alter or modify to fit for a new use, new conditions".

Promoting a cultural attitude by putting the change or adaptation in the middle of our debate, we expect that a new thinking will emerge. We anticipate that trans-disciplinar and translational approaches which are to be presented these days are going to contribute to the improvement of medical knowledge in the years to come.

The perspectives that invited speakers (about 120) will offer are as varied as their fields of interest. From imaginative reinvention of medical approaches to the concept of trendsetter in science, I believe the Congress agenda truly includes something for everyone. It was our intention to provide an inspiring atmosphere for fruitful scientific discussion and for initiating new collaborations in this „adaptive medicine" community.

I hope you will enjoy our scientific and social programmes during your stay in Bucharest.

Yours truly,

Professor L.M. Popescu, MD, PhD, h.c. mult.
President of the Organizing Commitee
Bucharest, June 2012

Welcome Message

Dear Delegates:

As Honorary Life President and a Founding Member of the International Society for Adaptive Medicine, it gives me a great pleasure to extend a warm welcome to all the delegates to the 10th World Congress of the ISAM, being held in the Hotel Intercontinental, Bucharest, Romania, under the Chairmanship of Prof. Lawrence Popescu. The 10th World Congress appears to be one of the strongest in its scientific content. The conference indeed provides a very good forum to bring together scientists from different parts of the world and from different disciplines around the focus of adaptation for a cross-fertilization of ideas.

I am most pleased to share with you that our volunteer organization is in great shape. We would be publishing the proceedings from this conference as Volume 7 of the series "Adaptation Biology and Medicine". We already have a venue for the 11th World Congress, which will be held in 2014 in Japan.

I am myself looking forward to a wonderful time in Bucharest, Romania. On behalf of the Society, I do express my gratitude to the Organizers for their dedicated efforts. May you enjoy the conference as well as your stay, and may you also build further lifetime friendships.

Yours Sincerely,

Dr. Pawan K. Singal, PhD, DSc
Honorary Life President
International Society for Adaptive Medicine
Winnipeg, Canada

Organizers

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Content

Program

Time	Thursday, 7th	Friday, 8th	Saturday, 9th	Sunday, 10th
8:30		Symposia *Main Hall* S01 *Hall A* S02 *Hall B* S14 *Hall C* S19	Symposia *Main Hall* S08 *Hall A* S03 *Hall B* S12	Symposia *Main Hall* S10 *Hall A* S16 *Hall B* S20
10:45		*Coffee break*	*Coffee break*	*Coffee break*
11:00		Plenary Lecture *Main Hall* P03	Plenary Lecture *Main Hall* P05	Plenary Lecture *Main Hall* P06
12:00		Symposia *Main Hall* S11A *Hall A* S09A *Hall B* S21 *Hall C* S06	Symposia *Main Hall* S18 *Hall A* S05 *Hall B* S17	
13:30		*Poster viewing*	*Poster viewing*	
14:30		Symposia *Main Hall* S11B *Hall A* S09B *Hall B* S13	Symposia *Hall A* S04 *Hall B* S22	
15:45		*Coffee break*	*Coffee break*	
16:00		Plenary Lecture *Main Hall* P02	Plenary Lecture *Main Hall* P04	
17:00		Symposia *Main Hall* S15 *Hall A* S09C *Hall B* S07		
17:30	Plenary Lecture *Main Hall* P01			
18:30	Plenary Lecture *Main Hall* P07			
19:30				
20:00	*Get together cocktail* *Fortuna Hall*	*Gala Dinner* *Fortuna Hall*		

ISAM Executive Council Meeting will take place on June 7th starting 19:45, in Hall D.

Registration Desk – Ground floor (Open 8:00-18:00, June 7th - 9th)
Technical office – Bolero, 2nd floor (Open 8:00-18:00, June 7th - 9th)

Main Hall – Ronda, 1st floor
Hall A – Rapsodia, 1st floor
Hall B – Salonul Oglinzilor, 1st floor
Hall C – Concerto, 1st floor
Hall D – Simfonia, 2nd floor

Plenary lectures

(in alphabetical order)

P-1 P. Anversa
Harvard University, Boston, USA
Mechanism of Cardiac Repair
Thursday, June 7th, 17:30, *Main Hall (Ronda)*

P-2 S.N. Constantinescu
Ludwig Institute for Cancer Research, Brussels, Belgium
Actors of Blood Regeneration: Erythropoietin, Thrombopoietin and their Receptors
Friday, June 8th, 16:00, *Main Hall (Ronda)*

P-3 Maria-Simonetta Faussone-Pellegrini
Florence University, Florence, Italy
The Interstitial-Stromal Cells: State of the Art
Friday, June 8th, 11:00, *Main Hall (Ronda)*

P-4 R.E. Horch
Friedrich-Alexander Universitat, Erlangen, Germany
Tissue Engineering – Where Do We Stand?
Saturday, June 9th, 16:00, *Main Hall (Ronda)*

P-5 M. Ivan
Indiana University, Indianapolis, USA
The Ever Expanding Universe of Hypoxia
Saturday, June 9th, 11:00, *Main Hall (Ronda)*

P-6 S. Kostin
Max-Planck-Institute, Bad Nauheim, Germany
Dhalla Lecture: Cardiomyocytes in Cardiac Repair
Sunday, June 10th, 11:00, *Main Hall (Ronda)*

P-7 B. Winblad
Karolinksa Institutet, Stockholm, Sweden
Re-Thinking Alzheimer Disease Therapy; Lessons Learned From Ongoing Clinical Trials
Thursday, June 7th, 18:30, *Main Hall (Ronda)*

P-1

MECHANISM OF CARDIAC REPAIR

Piero Anversa
Harvard University, Boston, USA
panversa@partners.org

The identification of cardiac progenitor cells in small and large mammals raises the possibility that the human heart contains a population of stem cells capable of generating cardiomyocytes and coronary vessels. We established the conditions for the isolation and expansion of c-kit-positive hCSCs from small fragments of myocardium discarded at surgery. Additionally, we tested whether these cells have the ability to form functionally competent human myocardium after infarction in immunodeficient and immunosuppressed animals independently of cell fusion. We have documented that c-kit-positive human cardiac cells possess the fundamental properties of stem cells: they are self-renewing, clonogenic and multipotent. hCSCs differentiate predominantly into cardiomyocytes and to a lesser extent into smooth muscle cells and endothelial cells. When locally injected in the infarcted myocardium of immunodeficient mice and immunosuppressed rats, hCSCs generate a chimeric heart, which contains human myocardium composed of myocytes, coronary resistance arterioles and capillary profiles. Importantly, the differentiated human cardiac cells possess only one set of human sex chromosomes excluding cell fusion. Although the human myocardium shows an immature phenotype, it contracts regionally and contributes to the improvement in the hemodynamic performance of the infarcted left ventricle. These experimental findings constituted the basis for pre-clinical studies in large animal models and for the recent phase 1 trial SCIPIO (Stem Cell Infusion in Patients with Ischemic cardiOmyopathy). One million autologous hCSCs were administered by intracoronary infusion ~4 months after multi-by-pass surgery in patients with chronic ischemic cardiomyopathy. No hCSC-related adverse effects were reported. The initial results of the SCIPIO trial are very encouraging; intracoronary infusion of autologous CSCs improved left ventricular systolic function and reduced infarct size in patients with severe heart failure after myocardial infarction.

P-2

ACTORS OF BLOOD REGENERATION: ERYTHROPOIETIN, THROMBOPOIETIN AND THEIR RECEPTORS

Stefan N. Constantinescu
Signal Transduction & Molecular Hematology Unit,
Ludwig Institute for Cancer Research Ltd.,
de Duve Institute, Université catholique de Louvain,
Brussels, Belgium
stefan.constantinescu@bru.licr.org

Erythropoietin (Epo), thrombopoietin (Tpo) and Granulocyte-Colony Stimulating Factor (G-CSF) regulate production of red blood cells, platelets and granulocytes. These cytokines bind to specific receptors displayed at the surface of erythroid, megakaryocytic and granulocytic progenitors, respectively, and induce anti-apoptotic, proliferative and differentiation signals, by activation of JAK2 tyrosine phosphoryation and activation of STAT5/3, MAP-kinase and phosphatydylinositol-3'-kinase pathways. Epo, Tpo and G-CSF maintain steady state myeloid hematopoiesis, and also mediate emergency myeloid production. An increased level of phosphorylation of cytosolic receptor tyrosines mediates the latter effects. Tpo also regulates hematopoietic stem cell (HSC) quiescence, and G-CSF induces liberation of HSCs from the marrow to periphery. The number of myeloid progenitors appears to regulate the percentage of HSCs that are quiescent, and those that enter blood formation. Genetic deletions of distal intracellular receptor regions induce hypersensitivity to cytokines. Such deletions in G-CSFR predispose to acute myeloid leukemia. Activating mutations in TpoR are associated with myeloproliferative neoplasm. In contrast, EpoR is not involved in hematologic malignancies, but Epo treatment might to favor evolution of certain solid cancers, possibly by effects on angiogenesis, or directly on tumors. We will discuss the emerging epigenetic cues that regulate signaling by Epo, Tpo and G-CSF, and whether HSCs are the source of chronic and committed progenitors of acute blood cancers.

P-3

INTERSTITIAL-STROMAL CELLS: STATE OF THE ART

Maria-Simonetta Faussone-Pellegrini
Department of Anatomy, Histology and Forensic Medicine, University of Florence, Florence, Italy
s_faussone@unifi.it

The resident connective tissue cells are usually named "interstitial" or 'stromal cells'. According to authors and depending on where they reside, these cells have received a variety of names. However, so many cell types cannot exist and some of them are likely a unique cell type known with different names. Their morphological characteristics are reviewed with the aim to find criteria for a sure identification and an appropriate name. We conclude stromal and interstitial cells are too vague terms. Fibroblasts are the cells engaged in ground substance and fiber synthesis. Myofibroblasts and myoid cells are not true stromal cells. Interstitial cells of Cajal are located in the gut muscle coat only, have specific morphology and contacts with smooth muscle cells and nerve endings and play spontaneous electrical activity. Interstitial Cajal-like, fibroblast-like and PDGRFα-positive cells are names to be avoided since indicating a similarity with a cell type or a chemical property but not true cell nature or morphology. Telocytes appear as a new interstitial cell type having specific morphology and roles. Possibly, there are many telocyte subtypes and their identification with some of the afore-mentioned cell types, or with pericytes, periendothelial, adventitial, reticular, covering/perigangliar, perineural cells or, in particular, with fibrocytes deserves discussion.

P-4

TISSUE ENGINEERING AND REGENERATIVE MEDICINE – WHERE DO WE STAND?

Raymund E. Horch
Kneser U., Beier J.P., Polykandriotis E., Schmidt V.J., Boos A.M., Bleiziffer O., Sun J., Arkudas A.
Department of Plastic and Hand Surgery And Laboratory for Tissue Engineering and Regenerative Medicine, Friedrich Alexander University, Erlangen-Nuernberg, Germany
Raymund.Horch@uk-erlangen.de

Tissue Engineering (TE) in the context of Regenerative Medicine (RM) has been hailed for many years as one of the most important topics in medicine in the 21st century. While the first clinically relevant TE efforts were mainly concerned with the generation of bioengineered skin substitutes, subsequently TE applications have been continuously extended to a wide variety of tissues and organs. The advent of either embryonic or mesenchymal adult stem cell technology has fostered many of the efforts to combine this promising tool with TE approaches and has merged the field into the term Regenerative Medicine. As a typical example in translational medicine the discovery of a new type of cells called Telocytes that have been described in many organs and have been detected by electron microscopy opens another gate to RM. Besides cell therapy strategies the application of gene therapy combined with tissue engineering have been investigated to generate tissues and organs. The vascularisation of constructs plays a crucial role besides the matrix and cell substitutes. Therefore novel in vivo models of vascularisation have evolved allowing axial vascularisation with subsequent transplantation of constructs. This article is intended to give an overview over some of the most recent developments and possible applications in RM through the perspective of TE achievements and cellular research. The synthesis of tissue engineering with innovative methods of molecular biology and stem cell technology appears to be very promising.

P-5

THE EVER EXPANDING UNIVERSE OF HYPOXIA

Mircea Ivan
Departments of Medicine, Microbiology and Immunology
Indiana University Melvin and Bren Simon Cancer Center
Walther Hall, Indianapolis, USA
mivan@iupui.edu

Hypoxia is a feature of the tumor microenvironment and a key contributor to the failure of conventional cancer treatment; therefore a detailed understanding of this complex process has significant translational implications. The response to oxygen deprivation involves diverse transduction pathways, arguably the best understood being centered on the Hypoxia Inducible Factor (HIF). HIF is directly regulated by the cellular oxygen sensors (HIF-prolyl and asparaginyl hydroxylases) and coordinate the transcription of hundreds of protein-coding genes. Starting with our earlier studies, HIF was also shown to induce non-coding RNA species, and in particular microRNAs. Of these, miR-210 has emerged as a versatile player in cancer biology, impacting cell metabolism, proliferation, DNA repair and angiogenesis.

In parallel, we are investigating additional cellular oxygen sensing pathways. We have recently identified a HIF-independent, dihydroceramide (DHC) - based response to hypoxia. Enzymatic processing of DHCs by the DEGS1 and 2 desaturases meets the criteria of an oxygen sensor, regulating the balance between biologically-active components of ceramide metabolism *in vitro* and *in vivo*.

P-6

CARDIOMYOCYTES IN CARDIAC REPAIR

Sawa Kostin
Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany
Sawa.Kostin@mpi-bn.mpg.de

Cardiac myocytes in mammalian hearts are thought to be terminally differentiated cells unable to fully re-enter the cell cycle. We show that lower vertebrate cardiomyocytes do go through a process of cell dedifferentiaton, proliferation and redifferentiaton to repair myocardial injury. Recently we have demonstrated the underlying mechanism regulating dedifferentiation of adult mammalian cardiomyocytes using varoius in vitro and in vivo models, including myocardial infarction and dilated cardiomyopathy. Specifically, inflammatory cytokines of the interleukin 6 family is induced at high levels in human patients and initiates dedifferentiation of cardiomyocytes. Most importantly, we demonstrate that cardiomyocyte dedifferentiation and loss of sarcomeric structures in diverse cardiac diseases is associated with the re-expression of different fetal markers, such as ANP and smooth muscle actin, and increased expression of stem cell markers Runx1, c-kit and Dab-2. These novel findings imposes a reconsideration of the mechanisms involved in cardiomyocyte dedifferentiaton in adult mammalian hearts that may lead to methods to promote cardiomyocyte regeneration in the human heart.

P-7

RE-THINKING ALZHEIMER'S DISEASE THERAPY; LESSONS LEARNED FROM ONGOING CLINICAL TRIALS

Bengt Winblad
Karolinska Institutet Alzheimer Disease Research Center, Stockholm, Sweden
b-winblad-kaspac@nvs.ki.se

Research into Alzheimer's disease (AD) has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease-modifying therapies. These successes and failures have led to debate about the potential deficiencies in our understanding of the pathogenesis of AD and potential pitfalls in diagnosis, choice of therapeutic targets, development of drug candidates, and design of clinical trials.

Many clinical and experimental studies are ongoing, mainly based on anti-amyloid-β (Aβ) strategies, but the exact role played by Aβ in AD pathogenesis is not yet clear. We need to acknowledge that a single cure for AD is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered.

Preclinical research is constantly providing us with new information on pieces of the complex AD puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets. The first signs of a shift away from linear "one protein - one drug thinking" have already appeared: research is moving from proteins to focus on organelles (eg mitochondria) and also multi-target-directed ligands.

Despite the recent negative results of RCTs on AD, increased collaboration between pharmaceutical companies, basic and clinical researchers will bring us closer to developing an optimum pharmaceutical approach for the treatment of AD. A better understanding of the disease pathogenesis, but also solving methodological problems in clinical trials on AD - eg standardized diagnostic criteria to identify homogenous group of patients, appropriate treatment duration and measures of disease-modifying effects - will help finding a cure for AD.

Symposia

S-01 Symposium
"*Adaptation to hypoxia: friend or foe*"

Chaired by: M. Ivan, Susanne Schlisio

Date: ***Friday, June 8th***
Starting time: ***08:30***
Location: ***Main Hall (Ronda)***

1. **C. Koumenis**
Unfolded Protein Response

2. **G. Melillo**
Pharmacological Applications of HIF Pathway

3. **Susanne Schlisio**
Prolyl Hydroxylases

4. **M. Ivan**
Non-coding RNA in Hypoxia

S01-1

THE ROLE OF THE INTEGRATED STRESS RESPONSE IN HYPOXIA ADAPTATION AND TUMOR GROWTH

Stacey Lehman[1,2], Carly M. Sayers[1,3], Lori Hart[1], Constantinos Koumenis[1]
[1]Department of Radiation Oncology, [2]CAMB Graduate Program, [3]Pharmacology Graduate Program, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
Costas.Koumenis@uphs.upenn.edu

Hypoxia and nutrient deprivation are dynamic features of the tumor microenvironment that contribute to cancer progression and treatment resistance. We previously showed that hypoxia activates the endoplasmic reticulum (ER) kinase PERK thereby inducing phosphorylation of the translation initiation factor eIF2α on ser51. We also demonstrated that the nutrient-sensing kinase GCN2, similarly activates eIF2α phosphorylation in response to amino acid and glucose deprivation. Phosphorylation of eIF2α reduces energy expensive processes, but also promotes more efficient translation of stress-responsive genes, such as ATF4, a transcription factor which promotes adaptation to ER stress. The phosphorylation of eIF2α and the upregulation of ATF4 represent a common mechanism activated by different stresses, thereby termed the Integrated Stress Response (ISR). Disruption of the ISR in cells dramatically affects their proliferation and survival under hypoxia and nutrient stress and their ability to grow tumors. Here, we will present new data supporting a role of the ISR, and particularly GCN2 and ATF4, in promoting tumor angiogenesis and metastasis. Together, our data suggest that transformed cells activate the ISR as an adaptation to oxygen and nutrient deprivation and that disruption of this pathway compromises tumor growth. Targeting the ISR by pharmacological inhibitors is a promising emerging anti-tumor modality.

S01-2

TARGETING THE HYPOXIC TUMOR MICROENVIRONMENT FOR CANCER THERAPY

Giovanni Melillo
Discovery Medicine – Oncology
Bristol-Myers Squibb, Princeton, NJ, USA
Giovanni.Melillo@bms.com

Low oxygen levels (hypoxia and/or anoxia) are frequently detected in human cancers and are a hallmark of the tumor microenvironment. Hypoxia profoundly affects the behavior of cancer cells by inducing a shift in tumor metabolism, increasing the production of angiogenic factors and activating pathways that mediate invasion and metastasis. Overall, a hypoxia tumor microenvironment has a negative influence on the potential efficacy of chemotherapy and radiation therapy, and is ultimately associated with poor patients' prognosis. Conversely, intra-tumor hypoxia may represent a unique opportunity for the development of therapeutic approaches that selectively target hypoxic cells, sparing normal oxygenated tissues. Hypoxia Inducible Factor 1 (HIF-1) is a master regulator of the transcriptional response to low oxygen levels. Several approaches have been pursued to develop small molecules targeting HIF-1. Although the majority of HIF-1 inhibitors identified lack specificity, evidence of target modulation associated with anti-tumor activity has been provided both in xenograft models and in early clinical trials. Combination therapies with antiangiogenic agents, thought to increase intra-tumor hypoxia, may provide a unique setting in which to exploit HIF-targeted therapies. Given the challenges associated with directly targeting HIF-1, many strategies have been proposed to target downstream mediators of HIF transcriptional activity. Evidence will be discussed that highlights novel pathways triggered by intra-tumor hypoxia, which may represent viable targets for the development of novel cancer therapeutics.

S01-3

OXYGEN SENSING AND CANCER

Susanne Schlissio
Ludwig Institute for Cancer Research Ltd
Karolinska Institutet, Stockholm, Sweden
Susanne.Schlisio@licr.ki.se

O_2-sensing is mediated partly via a family of enzymes called EglN prolyl hydroxylases, a family that requires molecular oxygen for enzymatic activity. Our work specifically focuses on how EglN3 execute apoptosis in neural precursors during development and how disruption of this process can lead to certain forms of nervous system tumors. Accordingly, our research is focused on:
(1) The molecular mechanism of how the prolyl hydroxylase EglN3 executes apoptosis in neural precursors during development; and
(2) How failure of developmental apoptosis mediated by EglN3 predisposes to certain forms of nervous system tumors.
Using a genome-wide RNAi-screen, we identified a novel tumor suppressor called KIF1Bβ, a kinesin motor protein. KIF1Bβ is located on chromosome 1p36.2, a region of the genome that is frequently deleted in neural crest derived tumors including neuroblastoma. We recently demonstrated that KIF1Bβ acts downstream of EglN3 and is both necessary and sufficient for neuronal apoptosis when NGF becomes limiting. The underlying mechanism behind EglN3 regulation of KIF1Bβ remains unknown. We have now continued to investigate how this kinesin induces apoptosis.
Further we completed additional EglN3-RNAi screens and identified genes that are involved in apoptosis, transcriptional regulation, and the endosomal system. Interestingly, several of the genes identified in this screen reside on chromosomal loci that are frequently altered in neuroblastoma.

S01-4

NON-CODING RNA IN HYPOXIA

Mircea Ivan
Departments of Medicine, Microbiology and Immunology
Indiana University Melvin and Bren Simon Cancer Center
Walther Hall, Indianapolis, USA
mivan@iupui.edu

Hypoxia is a hallmark of cancer microenvironment and a significant contributor to the failure of conventional antineoplastic therapy. We have previously shown that the hypoxia-activated transcriptome includes noncoding RNAs that play important roles in cancer and ischemic disorders.
Arguably the best understood to date is miR-210, which regulates a variety of cellular processes, including apoptosis, proliferation and energy metabolism. Clinically, miR-210 is upregulated in most solid cancers and generally correlated with adverse prognosis. The presentation highlights our latest understanding of miR-210's biological roles, based on newly developed molecular strategies and animal models.

S-02 Symposium
"*Inflammation and Sepsis*"

Chaired by: F.Lupu, R.P. McEver

Date: ***Friday, June 8th***
Starting time: ***08:30***
Location: ***Hall A (Rapsodia)***

1. **T.E. Mollnes**
Targeting complement activation and CD14-mediated TLR signaling as potential therapy in sepsis

2. **R.P. McEver**
Leukocyte adhesion and signaling on vascular surfaces during inflammation

3. **G.T. Kinasewitz**
Coagulopathy of sepsis: view from the bedside

4. **F. Lupu**
Pathophysiology, staging and therapy of severe sepsis

5. **Cristina Lupu**
Regulation of tissue factor dependent coagulation

S02-1

TARGETING COMPLEMENT ACTIVATION AND CD14-MEDIATED TLR SIGNALING AS POTENTIAL THERAPY IN SEPSIS

Tom E. Mollnes
Somatic Research Center, Nordland Hospital, Bodø and University of Tromsø, Norway
Department of Immunology, Oslo University Hospital and University of Oslo, Norway
t.e.mollnes@medisin.uio.no

Complement and Toll-like receptors (TLR) are main pattern recognition- and effector systems in innate immunity. Thus, they act up-stream in defense against intruding pathogens and endogenous damage signals. An extensive cross-talk between these systems renders them particularly attractive as targets for combined therapeutic intervention. CD14 is a key molecule in the TLR family since it acts as co-receptor for several of the TLRs, including TLR4 and TLR2. C3 and C5 are essential complement components common for all activation pathways. We have shown that combined inhibition of CD14 and complement (C3 or C5) efficiently and synergistically attenuates the inflammatory reaction induced by both Gram-negative and Gram-positive bacteria. Cytokine production, adhesion molecule upregulation, oxidative burst and procoagulant effects were virtually abolished in vitro in human whole blood incubated with bacteria and in vivo in a pig sepsis model by the combined treatment regimen, in contrast to single inhibition of CD14 or complement. We postulate this combined approach as a general treatment regimen to attenuate inflammatory responses induced by innate immunity.

S02-2

LEUKOCYTE ADHESION AND SIGNALING ON VASCULAR SURFACES DURING INFLAMMATION

Rodger P. McEver
Oklahoma Medical Research Foundation, Oklahoma City, USA
odger-mcever@omrf.org

Circulating leukocytes emigrate into lymphoid organs or inflamed sites through sequential adhesive and signaling events. They tether to and roll on endothelial cells, then decelerate, arrest, and crawl into underlying tissues. Selectin-ligand interactions mediate tethering and rolling, whereas integrin-ligand interactions mediate deceleration, arrest, and crawling. L-selectin, expressed on leukocytes, binds to ligands on other leukocytes and some endothelial cells. P-selectin, expressed on activated platelets and endothelial cells, and E-selectin, expressed on activated endothelial cells, bind to ligands on leukocytes. Cell adhesion faces major kinetic and mechanical constraints in flowing blood. Bonds between adhesion molecules must form rapidly, and their lifetimes are affected by the forces applied by shear stress. Clustering of adhesion receptors in membrane domains modulates their functions. Engaging selectin ligands on rolling neutrophils triggers a lipid raft-dependent signaling cascade that serially activates Src family kinases, Syk, Bruton's tyrosine kinase, and p38. These and other signals convert integrin aLb2 to an extended but low-affinity conformation that slows rolling velocities. Signaling through G protein-coupled chemokine receptors activates integrins to an extended and high-affinity conformation that mediates arrest. These signaling pathways cooperate to maximize neutrophil recruitment to sites of inflammation. Dysregulated leukocyte adhesion contributes to inflammatory tissue damage in common diseases.

S02-3

COAGULOPATHY OF SEPSIS: VIEW FROM THE BEDSIDE

Gary T. Kinasewitz
Pulmonary/Critical Care,
University of Oklahoma School of Medicine, Oklahoma, USA
Gary-Kinasewitz@ouhsc.edu

Virtually all patients with severe sepsis develop a coagulopathy irrespective of the underlying organism and site of infection. To quantitate the coagulopathy we developed a simple evolving DIC score based on the absolute value and change in platelet count and prothrombin time (PT), and applied it to 403 prospectively identified ICU patients with severe sepsis. Patients were clinically classified as having capillary leak syndrome (n=39), persistent multiorgan failure with death (n=97) or survival (n=126) or transient organ failure (n=141) if they showed rapid improvement in their MODS score. . The simple evolving DIC score increased with worsening clinical class and was associated with worsening organ failure. Mortality increased from 7% for a simple evolving score of 0 to 74% for a score of 4 ($P < 0.01$). Overall, 87% of those with a score ≤ 1 survived while a majority of those with a score ≥ 2 developed multiorgan failure and 55% died from sepsis. Thus, the simple evolving DIC score which can be calculated at the bedside from 2 readily available global coagulation markers appears to reflect the severity of the underlying disorder, and provides useful prognostic information for the patient with severe sepsis.

S02-4

PATHOPHYSIOLOGY, STAGING AND THERAPY OF SEVERE SEPSIS

Florea Lupu
Oklahoma Medical Research Foundation, Oklahoma City, USA
florea-lupu@cox.net

Severe sepsis is a multi-stage, multi-factorial and life-threatening condition that arises when the innate response of the body to infection injures its own tissues and organs. Patients with severe sepsis can develop a fulminate form of the disease and die within hours with massive disseminated intravascular coagulation (DIC) and cardiovascular collapse, or may develop a protracted organ failure that may lead to delayed death despite supportive therapy. The disease passes through an initial inflammatory/coagulopathic stage triggered by the pathogen, followed by a second stage, driven by ischemia/reperfusion (IR) and oxidative stress. Since rodent models do not accurately replicate this complex pathophysiology we have developed and characterized primate models that mimic the two clinical variants. The model of refractory hypotension and consumptive coagulopathy was used in the development of activated protein C for the treatment of sepsis. The model of persistent multi-organ failure allowed us to identify the histone/nucleosome release and uncontrolled complement activation as major amplifying loops of the initial injury produced by IR/oxidative stress. Currently, we are developing approaches to block the harmful effects of complement activation products and extracellular histones/DNA during the organ failure stage of severe sepsis as potential therapeutic strategy.

S02-5

REGULATION OF TISSUE FACTOR DEPENDENT COAGULATION

Cristina Lupu
Oklahoma Medical Research Foundatio, Oklahoma City, USA
Cristina-Lupu@omrf.org

The tissue factor (TF) pathway triggers blood coagulation. TF is essential for hemostasis, but aberrant expression and activation of TF by monocytes, neutrophils, endothelial cells (EC), and platelets likely contribute to thrombotic complications in various diseases including, but not limited to, cardiovascular disease, diabetes, cancer and sepsis. The major physiological, Kunitz-type regulator Tissue Factor Pathway Inhibitor (TFPI) inhibits the activity of TF-Factor VIIa complex in a Factor Xa-dependent manner, thus controlling the generation of thrombin and ultimately, fibrin. TFPI is constitutively produced by EC, within which locates in lipid rafts/caveolae via a GPI-linkage, a property that confers major anticoagulant functions to the cell-associated forms of TFPI as opposed to the soluble truncated forms of the inhibitor. The proper regulation of TF activity is critical for maintenance of the hemostatic balance. In septic baboons, increased TF-dependent procoagulant activity is partly due to decreased lung-associated TFPI, as well as focal up-regulation of TF concurrently with reduced TFPI within arterial branching areas. Finding ways to up-regulate the cell-associated TFPI to prevent unwanted clotting and to inhibit TF-dependent pathological effects is a still under-investigated area. A newly discovered protein, ADTRP, which regulates TFPI expression and function in EC androgen-dependently, could be instrumental for the design of vascular protection strategies to counteract thrombosis.

S-03 Symposium
"*Advances in stroke*"

Chaired by: N. Bornstein, W.-D. Heiss

Date: ***Saturday, June 9th***
Starting time: ***08:30***
Location: ***Hall A (Rapsodia)***

1. **N. Bornstein**
Secondary stroke prevention

2. **W.-D. Heiss**
Imaging the penumbra: the pathophysiologic basis for therapy of ischemic stroke

3. **Antonio Federico**
Small vessel inherited diseases: clinical and molecular findings

S03-1

SECONDARY STROKE PREVENTION

Natan Bornstein
Stroke Unit, Dept. of Neurology, Sackler School of Medicine,
Tel-Aviv University, Tel-Aviv, Israel
natanb@tasmc.health.gov.il

Patients with TIA or ischemic stroke carry a risk of recurrent stroke between 5 and 20% per year. In patients with TIA or ischemic stroke of noncardiac origin antiplatelet drugs are able to decrease the risk of stroke by 11-15% and the risk of stroke, MI and vascular death by 15-22%. Aspirin is the most widely used drug. It is affordable and effective. Low doses of 50-325 mg aspirin are as effective as high doses and cause less gastrointestinal side effects. Severe bleeding complications are dose-dependent. The combination of aspirin with slow release dipyridamole is superior to aspirin alone for stroke prevention (ESPS-2 and ESPRIT). Both studies have shown approximately 20%-24% relative risk reduction (RRR) of stroke and death. Clopidgrel is superior to aspirin in patients at high risk of recurrence by about 8.7% RRR (CAPRIE). The combination of aspirin plus clopidogrel is not more effective than clopidogrel alone but carries a higher bleeding risk (MATCH and CHARISMA). None of the antiplatelet agents is able to significantly reduce mortality. The recent results of the PRoFESS trial showed no difference between clopidogrel and aspirin with slow release dipyridamole in secondary stroke prevention.

S03-2

IMAGING THE PENUMBRA: THE PATHOPHYSIOLOGIC BASIS FOR THERAPY OF ISCHEMIC STROKE

Wolf-Dieter Heiss
Max Planck Institute for Neurological Research, Cologne, Germany
wdh@nf.mpg.de

The ischemic penumbra defines the perfusion range between the thresholds for functional impairment and irreversible tissue damage. The translation of this experimental concept as the basis for efficient treatment of stroke requires non-invasive methods by which regional flow and energy metabolism can be repeatedly investigated. Positron emission tomography (PET) allows the quantification of cerebral blood flow, metabolic rate for oxygen and oxygen extraction fraction. By these variables a clear definition of irreversible tissue damage and of critically perfused but potentially salvageable tissue (i.e. the penumbra) can be achieved. Further tracers can be used for early detection of irreversible tissue damage (central benzodiazepine receptor ligand flumazenil) and of microglia activation (translocator protein ligand). As a widely applicable clinical tool perfusion/diffusion weighted magnetic resonance imaging is used, and the "mismatch" between the PW- and the DW-abnormalities might serve as an indicator of the penumbra, but has limitations. Based on the concept of the penumbra improvement of perfusion within the time window of opportunity must be the primary goal in treatment of ischemic stroke, and neuroprotective and other strategies can only play a supportive role. By detecting the pathophysiological state of the tissue PET can help in the development of efficient treatment strategies.

S03-3

SMALL VESSEL INHERITED DISEASES: CLINICAL AND MOLECULAR FINDINGS

Antonio Federico
Dept. Neurological, Neurosurgical and Behavioural Sciences, Medical School, University of Siena, Siena, Italy
federico@unisi.it

Advances in molecular genetics lead to identification of several monogenic conditions involving small vessels and predisposing to ischaemic and haemorrhagic strokes and diffuse white matter disease. Cerebral microangiopathies constitute an appreciable portion of all strokes. In middle aged patients, hereditary cerebral small vessel diseases have to be separated from sporadic degenerative cerebral microangiopathy which is mainly due to a high vascular risk load. Features of the following disorders and details for there are here reviewed, namely Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalophaty (CARASIL), COL4A1-related cerebral small vessel diseases, Autosomal Dominant Retinal Vasculopathy with leucodystrophy (AD-RVLC) and neurometabolic diseases such as MELAS and FABRY. The hereditary SVDs albeit with variable phenotypes demonstrate how effects of different defective genes converge to produce the characteristic arteriopathy and microvascular disintegration leading to vascular cognitive impairment.We describe also our experience in Siena, in the diagnosis, research and treatment of these diseases.

S-04 Symposium
"*Multimodal molecules in neuroprotection and neurorecovery treatment*"

Chaired by: A. Alvarez, D.F. Mureşanu

Date: ***Saturday, June 9th***
Starting time: ***14:30***
Location: ***Hall A (Rapsodia)***

1. **D.F. Mureşanu**
Towards a unified theory in brain damage and recovery

2. **A. Alvarez**
Multimodal molecules with pleiotropic neuroprotective in brain protection and recovery

3. **A. Cedazo-Minguez**
Neurotrophic factors in CNS biology

4. **Mihaela Băciuț**
Regeneration of the peripheral nerve - the maxillo-facial surgeon's view

5. **Chung-Hsin Wu**
Adaptive mechanisms of hypothermic neuroprotection in Taiwan leaf-nosed bat

S04-1

TOWARDS A UNIFIED THEORY IN BRAIN DAMAGE AND RECOVERY

Dafin F. Mureşanu
Department of Clinical Neurosciences
"Iuliu Hatieganu" University of Medicine and Pharmacy
Cluj -Napoca, Romania
dafinm@ssnn.ro

Neurotrophicity, neuroprotection, neuroplasticity and neurogenesis are basic biological processes of paramount importance, overlapping and acting under genetic control to generate the endogenous defense activity (EDA) which continually counteracts pathophysiological processes.

Pathophysiological processes share common mechanisms with endogenous basic biological processes (e.g. excitotoxicity and neurotrophicity together with neuroplasticity have, as a common important driver, the NMDAR activity; inflammation has an important contribution for neuroregeneration, stimulating neuroplasticity, via trophic factors).

Every lesion in the nervous system triggers in the first minutes an endogenous neuroprotective reaction. An endogenous repair process, combining neuroplasticity and neurogenesis follow this as a second answer. All these processes are initiated and regulated by neurotrophic factors. The same molecules, due to a complex genetically regulated process, are able to induce, immediately after achieving the endogenous neuroprotective effect, neuroplasticity and neurogenesis as well. Therefore, they have also not only pleotropic activity but also multimodal way.

Neuroprotection, neuroplasticity and neurogenesis, processes that are apparently independent, with different control, represent in fact sequences of the same process (EDA), regulated by neurotrophic factors.

Considering this, neurotrophic factors are important therapeutic agents in most important neurological disorders, including stroke and there are many positive clinical data proving this.

S04-2

MULTIMODAL MOLECULES WITH PLEIOTROPIC NEUROPROTECTIVE IN BRAIN PROTECTION AND RECOVERY

Antón Alvarez
Research Directorate, Antidementia Al-Andalus Foundation, A Coruña, Spain
xantonal@yahoo.es

Neuronal degeneration is a common feature that can be triggered by different mechanisms in medical conditions such as traumatic brain injury, cerebrovascular disorders and Alzheimer's disease. The pathology of these central nervous system disorders is very complex and involves several common pathogenic processes, including excitotoxicity, inflammation, oxidative damage, apoptosis, neurodegeneration and neurotrophic alterations. Glutamate, calcium-calpain, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), reactive oxygen species, amyloid and tau proteins, neurotrophic factors like BDNF (brain-derived neurotrophic factor), IGF-I (insulin-like growth factor) or VEGF (vascular endothelial growth factor), and signaling proteins including kinases such as Akt (serine/threonine protein kinase), GSK3β (glycogen synthase kinase-3 beta) and CDK5 (cyclin-dependent kinase 5) are key molecules contributing to mechanisms of neuronal degeneration, protection and recovery.

Neuroprotection and recovery of neuronal damage are priority goals in the treatment of the aforementioned pathological conditions. Since there is no disease-modifying treatment so far for these disorders, the development of multimodal drugs able to act on different molecular targets constitutes a promissing therapeutic alternative. The multimodal effects of neurotrophic factors, erythropoietin, statins or Cerebrolysin, a peptidergic compound mimicking the activity of endogenous neurotrophic factors, were investigated in different experimental models of stroke, Alzheimer's disease and traumatic brain injury with positive results. Clinical studies also support the efficay of such an intervention in improving symptoms and/or the clinical recovery of patients affected by these disorders.

S04-3

NEUROTROPHIC FACTORS IN CNS BIOLOGY

Angel Cedazo-Minguez
Karolinska Institutet, NVS Department
KI-Alzheimer's Disease Research Center
Stockholm, Sweden
Angel.Cedazo-Minguez@ki.se

Neurotrophic factors are considered as molecular mediators of synaptic plasticity, neurite outgrowth, neuronal cell differentiation and survival. Reduced levels and activities of neurotrophic factors, such as nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF), have been described in a number of neurodegenerative disorders, including Alzheimer's disease (AD). The concept of increasing the expression/activity or, alternatively, the restorative administration of these endogenous protective systems may offer promising therapeutic alternatives. However, while the therapeutic potential of neurotrophic factors has been well-recognized, the translation to the clinic has been disappointing, mostly due to considerable delivery obstacles.

This presentation will briefly review recent findings linking defects in NGF and BDNF to AD pathogenesis, as well as data from preclinical and clinical studies exploring their potential therapeutic possibilities for AD.

S04-4

REGENERATION OF THE PERIPHERAL NERVE – THE MAXILLO-FACIAL SURGEON'S VIEW

Mihaela Băciuț[1], Dafin Mureşanu[2], Grigore Băciuț[3]
[1] Clinic of Maxillofacial Surgery and Implantology, [2] Department of Neurosciences, [3] Clinic of Cranio-Maxillofacial Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
mbaciut@yahoo.com

Surgical procedures performed in maxillofacial surgery imply dissection in the immediate vicinity of sensitive (trigeminal nerve) and motor (facial nerve) branches. A large range of procedures in this field can affect the nerve function postoperatively, spreading over a period of time which seriously influences the life quality of the patient.

Postoperative deterioration of the nerve function can be noticed frequently and is produced by multiple mechanisms.

Direct intraoperative trauma of various degrees, ranging from blunt contusion to laceration, compression by postoperative edema, seroma, hematoma or bone fragments are the most frequently incriminated causes of nervous dysfunction.

Orthognathic surgery is performed increasingly. It implies osteotomies of the maxillary bones to correct their position and/or dimension in cases of maxillofacial deformities. The osteotomy lines of the mandible split the bone through the mandibular canal.

In the postoperative period, anesthesia of various degrees of the lower hemilip and –chin can be noticed and evaluated. Healing is monitored during the follow-up interval and is supposed to imply multiple mechanisms as well.

In order to support the healing, antiinflammatory drugs of different categories and vitamins are administered routinely according to various protocols. Their action is controversial when considering the various regeneration mechanisms. In this regard, healing should be supported with drugs of different categories.

The present study intended to evaluate and discuss the regenerative neurological capacity in patients having undergone maxillofacial surgery procedures.

S04-5

ADAPTIVE MECHANISMS OF HYPOTHERMIC NEUROPROTECTION IN TAIWAN LEAF-NOSED BAT

Chung-Hsin Wu
Department of Life Science, National Taiwan Normal University, Taipei, Taiwan
megawu@ntnu.edu.tw

Hibernation is one of the most fascinating strategies for some animals to survive when environmental temperature is very low and food resources are scarce or absent, furthermore, this kind of the prolonged bouts of torpor can be interrupted periodically by spontaneously brief arousals. In order to go through the harsh conditions, hibernating animals change to an inactive state by strongly suppressing metabolic rate and lowering body temperature to around 0 °C. Suppression of metabolic rate is mainly reflected by reduced heart beat and respiratory rates. It is attractive that why hibernators can survive in the situation of frequent and dramatic fluctuations of body temperature and blood flow without neurological damage. In this study, we investigated hematocrit (Hct) and blood glucose concentration in capillary blood at room temperature (25°C) and during hibernation (0°C) in Taiwan leaf-nosed bat (*Hipposideros terasensis*). The data suggested that natural up-regulation of Hct and blood glucose concentration during hibernation in Taiwan leaf-nosed bat play role in hypothermic neuroprotective mechanisms. Also, Our data showed that suppression of free radical production and of excitotoxin release may contribute to protection when cooling is started during hypoxia ischemia.

S-05 Symposium
"*The management of early and late Parkinson's disease*"

Chaired by: A. Antonini, O. Băjenaru

Date: ***Saturday, June 9th***
Starting time: ***12:00***
Location: ***Hall A (Rapsodia)***

1. **Regina Katzenschlager**
Non-invasive treatment options for motor complications in Parkinson's disease

2. **A. Antonini**
The role of Apomorphine in the treatment of Parkinson's disease

3. **O. Băjenaru**
Interventional treatment of continuous dopaminergic stimulation in advance Parkinson's disease

4. **Tarek Tawfik**
Future strategies in Parkinson's disease treatment

S05-1

NON-INVASIVE TREATMENT OPTIONS FOR MOTOR COMPLICATIONS IN PARKINSON'S DISEASE

Regina Katzenschlager
Neurologische Abteilung, Donauspital / SMZ-Ost, Vienna, Austria
regina.katzenschlager@chello.at

Dopaminergic replacement therapy is usually very effective in relieving the motor symptoms of Parkinson's disease. However, the majority of patients develop motor complications following longer-term treatment. Risk factors include the rate of neuronal loss, younger age at disease onset, high L-dopa dose and initial treatment with short-acting drugs.

Motor fluctuations (ON/OFF fluctuations) can often be ameliorated by adapting the intervals and doses of individual L-DOPA doses, by blocking dopamine degradation using monoamino (MAO)-B inhibitors and catechol-O-methyl transferase (COMT) inhibitors, or by adding dopamine agonists orally or transdermally. In addition, advising patients on the potential impact of meal times on drug absorption is often useful. Dispersible formulations of L-dopa may provide faster relief from OFFs.

In those patients where dyskinesias have developed, treatment options often become limited as dose increases may worsen dyskinesias and decreases may worsen motor function and OFF duration. Amantadine is the only oral drug that has been demonstrated to improve dyskinesias without worsening parkinsonism but the effect size is limited and tolerability may be a concern. When all adaptations of oral and transdermal drugs have been exhausted, invasive or device-aided options such as pump treatments and deep brain stimulation should be considered for eligible patients.

S05-2

THE ROLE OF APOMORPHINE IN THE TREATMENT OF PARKINSON'S DISEASE

Angelo Antonini
Parkinson Unit, IRCCS San Camillo, Venice – Neurology Clinic, University of Padua, Italy
angelo3000@yahoo.com

Apomorphine is the oldest dopaminergic medication and was initially known for its emetic properties. It was initially used for Parkinson's disease over 60 years ago but later ignored for many years following levodopa introduction. It is also the most potent dopamine agonist and its administration can provide symptom relief comparable to levodopa. Apomorphine exerts its antiparkinsonian effect by direct stimulation of striatal postsynaptic dopamine D1 and D2 receptors. The drug has a rapid absorption after subcutaneous injection (Cmax 20 min), and a short half-life (almost 43 min), and this is consistent with its rapid onset of action, with effects apparent within 5–15 minutes of subcutaneous administration. Clinical studies and evidence-based reviews generally support a role for apomorphine infusion as an effective option for patients with PD and severe fluctuations, poorly controlled by conventional oral drug treatment with an improvement in OFF-time between 50% and 80% as well as dyskinesia. While the benefit on off time is consistent across all studies, dyskinesia improvement generally occurs after a few weeks or months of continuous dopaminergic stimulation as a result of wider therapeutic window. Moreover it can be best achieved with apomorphine monotherapy that may require high infusion doses.

Intermittent subcutaneous apomorphine (penjet) may instead be suitable for the long-term acute treatment of OFF episodes in patients with advanced PD. Apomorphine injections can be a particularly helpful in the management of patients who undergo surgical procedures and cannot take medication by mouth or to treat additional severe non-motor symptoms occurring during OFF periods.

S05-3

INTERVENTIONAL TREATMENT OF CONTINUOUS DOPAMINERGIC STIMULATION IN ADVANCE PARKINSON'S DISEASE

Ovidiu Băjenaru
"Carol Davila" University of Medicine and Pharmacy Bucharest, Romania
ovalbajenaru@yahoo.com

Parkinson's disease (PD) is a progressive multifocal neurodegenerative disease characterised by multiple synaptic dysfunctions which clinical impact impairs motor behaviour, sensory, neurocognitive, autonomic functions, sleep, mood and other components of human behaviour. Among these, motor dysfunction is one of the most important factors which impairs patients' daily life activity and quality and the best studied due to its relation to disturbed dopaminergic modulation in the cortico-striatal circuits (even if in these patients also dysfunctions of other structures of the brain - not always related to dopamine modulation - impair the motor behaviour). In advanced stages of the disease these clinical impairments are enhanced in symptomaticaly treated patients by the dopaminergic agents, in particular oral levodopa leading to motor and non-motor complications. These treatment complications are mostly related to the non-physiologic pulsatile stimulation by oral drug administration which are oposed to the tonic, continuous, physiologic dopaminergic synaptic modulation of the indirect striopallidal pathway and probably also of the non-synaptic modulation of neuronal intracellular signaling pathways related to neuroplasticity. In advanced Parkinson's disease in patients whom symptomatic control of their clinical manifestations cannot be obtained any more with the best oral drugs combinations, particular therapeutic approaches are available today. Among these, continuous levodopa administration by an electronic pump directly in the jejunum using a transcutaneous laparoscopic gastrostoma using a special tubular device or deep brain stimulation with a high frequency from an electronic stimulator using a special electrode system stereotaxically inserted bilateraly in the subthalamic nucleus (or in the internal part of the globus pallidus) are common nowadays. We shall present also our personal clinical experience using these methods in the Department of Neurology of the University Emergency Hospital Bucharest.

S05-4

FUTURE STRATEGIES IN PARKINSON'S DISEASE TREATMENT

Tarek Tawfik
Cairo University, Cairo, Egypt

Considerable advances have been made in defining the aetiology, pathogenesis, and pathology of PD and these advances in turn have resulted in development and rapid expansion of the pharmacopoeia available for treatment. However, treatment remains unsatisfactory, as it mainly addresses only the dopaminergic features of the disease and leaves its progressive course unaffected. The future of PD drug treatment will need to focus on the symptomatic management of the non-dopaminergic and non-motor features of the disease and on the need of disease modification on terms of delay or prevention of progression.

S-06 Symposium

"*Experimental models in adaptive medicine*"

Chaired by: M Taggart, Narcisa Tribulova

Date: ***Friday, June 8th***
Starting time: ***12:00***
Location: ***Hall C (Concerto)***

1. **M. Taggart**
A pause for thought – what are they key advantages and disadvantages of rodent models of human pregnancy and preterm labour?

2. **Satoshi Matsuo**
Effects of lower body positive pressure on cardiovascular functions

3. **Narcisa Tribulova**
Myocardial connexin-43 is implicated in adaptation and maladaptation to hypertension as well as in cardioprotective effects of the treatment

S06-1

A PAUSE FOR THOUGHT – WHAT ARE THEY KEY ADVANTAGES AND DISADVANTAGES OF RODENT MODELS OF HUMAN PREGNANCY AND PRETERM LABOUR?

Michael J. Taggart
Institute of Cellular Medicine, Newcastle University, UK.
michael.taggart@newcastle.ac.uk

Preterm birth (PTB) has profound detrimental effects for a healthy life. It's the largest contributor to deaths in children under 1 year of age, causes 75% of all neonatal intensive care admissions and those children who do survive are at increased risk of lifelong debilitating mental and physical health. To improve our understanding of the biology of parturition and, in concert, develop new drugs and drug delivery strategies to treat PTB, we must consider the use of appropriate non-primate models. Rat and mouse (including knockouts) models of pregnancy have been instrumental in improving our understanding of the cellular and tissue mechanisms of uterine activation accompanying labour at term and preterm. However, a marked difference between these rodents and humans is that parturition in the former, but not humans, is precipitated by a marked fall in maternal serum progesterone. Attention has recently returned to considering the benefits of the guinea pig as an additional rodent model of human parturition as serum progesterone withdrawal does not appear to be a pre-requisite for labour onset in this species. Therefore, we analyse whether rigorous cross-species bioinformatic and functional comparisons offer the best opportunity for advancing our understanding of the complexity of parturition and PTB.

S06-2

AGE-RELATED CHANGES IN CARDIOVASCULAR RESPONSES TO LOWER BODY POSITIVE PRESSURE ON DURING WALKING IN WOMEN

Satoshi Matsuo[1]
Takeshi Sota[2], Yukiko Okada[2], Hiroshi Hagino[2], Yasuaki Kawai[1]
[1]Department of Adaptation Physiology, Faculty of Medicine, Tottori University, [2]Department of Rehabilitation, Tottori University Hospital.
smatsuo@med.tottori-u.ac.jp

We investigated the effects of lower body positive pressure (LBPP) on cardiovascular responses during a 15-min walking in young and elderly women. The application of 20 mmHg LBPP reduced ground reaction forces by 31.2 ± 0.5 kgw in both groups. We hypothesized that cardiovascular responses to LBPP during walking were different between the young and elderly subjects.

Applying 20 mmHg of LBPP increased diastolic pressure in both subjects (young: 2 ± 1 mmHg, elderly: 2 ± 1 mmHg). Applying LBPP also increased mean blood pressure (MBP) in elderly subjects (2 ± 1 mmHg) but not in young subjects. After the application of LBPP, MBP decreased in both subjects (young: 3 ± 1 mmHg, elderly: 3 ± 1 mmHg). LBPP reduced heart rate (HR) during walking in both groups, however the reduction in HR occurred more quickly in the young group compared to the elderly group. Applying LBPP also decreased double product (HR × systolic blood pressure) during walking in both groups, suggesting that LBPP reduces myocardial oxygen consumption during exercise. These results suggest that cardiovascular responses to LBPP during walking could change with aging.

S06-3

MYOCARDIAL CONNEXIN-43 IS IMPLICATED IN ADAPTATION AND MALADAPTATION TO HYPERTENSION AS WELL AS IN CARDIOPROTECTIVE EFFECTS OF THE TREATMENT

Narcisa Tribulova [1]
Radosinska J. [2], Bacova B. [1], Benova T. [1], Vinczenczova C. [3],
Knezl V. [4], Slezak J. [1]
[1]Institute for Heart Research,, SAS, Bratislava, Slovakia,
[2]Inst. Physiology, Med. Fac. Comenius University, [3]Faculty of Natural Sciences of Comenius University, [4]Institute of Experimental Pharmacology & Toxicology, SAS, Bratislava, Slovakia
usrdtri@savba.sk

Intercellular gap junction connexin (Cx) channels are important determinants of myocardial conduction and synchronization crucial for heart function. Hypertension-induced structural remodeling in humans is associated with an increased risk of life-threatening cardiac arrhythmias and heart failure. Using immunohistochemistry, electron microscopy, western blotting and real time PCR we have found that altered distribution (lateralization) and down-regulation of Cx43 in spontaneously hypertensive (SHR) were linked with increased propensity to ventricular fibrillation (VF) comparing to age-matched normotensive rats. In contrast, long-term treatment of SHR with either omega-3 fatty acids or antioxidant rich red palm oil resulted in attenuation of myocardial structural and Cx43 remodeling. In addition, the treatment increased expression of Cx43 mRNA or Cx43 protein as well as its functional phosphorylated forms. Consequently, there was a significant suppression of VF incidence in treated SHR. We conclude that abnormal myocardial Cx43 distribution and expression due to cardiac adaptation to hypertension may contribute to increased propensity to malignant arrhythmias. On the other hand, attenuation of hypertension-related myocardial Cx43 abnormalities by treatment with omega-3 fatty acids or red palm oil confers protection from malignant arrhythmias.
This study was supported by VEGA 0046/12 and APVV SK-CZ-0027-11 grants.

S-07 Symposium
"*Advances in dementia research and clinical practice*"

Chaired by: Illana Gozes, B.O. Popescu

Date: ***Friday, June 8th***
Starting time: ***17:00***
Location: ***Hall B (Salonul Oglinzilor)***

1. **K. Jellinger**
Challenges in the neuropathological diagnoses of dementias

2. **Illana Gozes**
Microtubules and brain protection: Davunetide

3. **S. Baloyannis**
The philosophy of dementia

S07-1

CHALLENGES IN THE NEUROPATHOLOGIC DIAGNOSIS OF DEMENTIAS

Kurt A. Jellinger
Institute of Clincal Neurobiology, Vienna, Austria
kurt.jellinger@univie.ac.at

Dementia, defined as deterioration in several cognitive domains, is a major public health problem. It is not only caused by neuronal cell death but particularly by dysfunction/loss of synapses causing default neuronal networks. Consensus criteria for the clinical and neuropathologic diagnosis of different dementia disorders have recently been updated. Morphologic assessment, using immunohistochemistry, molecular biologic and genetic methods can achieve a diagnosis/classification, based on homogenous definitions, harmonized inter-laboratory methods and assessment standards, in almost 99%, without, however, clarifying the etiology of most of these diseases. The new Aging-Alzheimer Association guidelines combine Aβ plaque phases, Braak NFT and CERAD neuritic plaques scores, also considering cerebrovascular disease, Lewy body and other pathologies. However, due to considerable overlap between many dementing disorders, in particular neurodegenerative proteinopathies, studies in human subjects with autopsy confirmation entail numerous biases that affect both their general applicability and the validity of correlations. Further difficulties arise from recent separation of distinct clinicopathologic subtypes ("tangle-intensive" and "plaque-intensive") from classical Alzheimer disease. Although most neurodegenerative dementing disorders are incurable at present, concerted prospective clinicopathologic studies using validated protocols and data fusion are required to overcome the limitations of the current diagnostic framework as a basis for efficient new therapy options.

S07-2

MICROTUBULES AND BRAIN PROTECTION: DAVUNETIDE

Illana Gozes, Oz S
Department of Human Molecular Genetics and Biochemistry,
School of Neuroscience, Sackler Faculty of Medicine,
The Adams Super Center for Brain Studies, Tel Aviv University, Israel
igozes@post.tau.ac.il

Davunetide (NAPVSIPQ; NAP), a neuroprotective peptide that we derived from activity-dependent neuroprotective protein (ADNP), provides protection against ADNP haploinsufficiency. NAP enhances cognitive function, protecting the microtubule network and reducing tau pathology in models of Alzheimer's disease and related tauopathies. We recently found that NAP treatment significantly affected the microtubule tyrosination cycle which is associated with microtubule dynamics in the living cell. This effect was coupled to increased microtubule network area which is directly related to neurite outgrowth. Expression of the microtubule subunit, tubulin beta III, a marker for neuronal differentiation and neurite outgrowth, increased as a consequence of NAP treatment. Measurements of microtubule remodeling in cultured neurons suggests an effect of NAP that increases dynamic Tyr-tubulin compared to control. Finally, high zinc concentrations induce microtubule breakdown and tubulin subunit toxic aggregation but this cellular toxicity was reversed by NAP treatment. Davunetide (NAP) is currently in Phase II/III clinical trial in progressive supranuclear palsy a disease presenting tauopathy (Allon Therapeutics Inc.). Activity in this trial should pave the path to other tauopathies/disease associated with microtubule dysfunction.

Acknowledgements: Gildor Chair, Adams Super Center, Elton Lab., AMN, CFTAU, Allon Therapeutics Inc.

S07-3

THE PHILOSOPHY OF DEMENTIA

Stavros J. Baloyannis
Aristotelian University, Thessaloniki, Greece
sibh844@otenet.gr

Understanding the fundamental nature of mind, from the philosophical viewpoint, became the main subject of the neurophilosophy. Dementias attract reasonably the attention of philosophers, who search for an explanation of mental decline. Although the morphological and functional alterations may interpret the drama of dementia, however they cannot approach the question of the condition of the self in dementia. The memory loss detach obviously the self from the past and isolate it in the present. However, we do not know the dimensions of the interior aspect of time in dementia, which play an important role in the duration and integration of the self. Neuropsychology reveals that demented persons, can retain their identity and the activity and character of their interior life, which is depended on the existential dimensions of the self. The insight of the mental tragedy in dementia is an evidence of an active interior life. The concept of the good and evil, the dignity and the self respect may be unaffected by the loss of memory. A detailed analysis of the interior life and the existential dimensions of the individual may be required for assessing the continuation of the self and the integrity of the Being in dementias.

S-08 Symposium
"*Obesity, fat tissue and coronary heart disease*"

(Recommended by the European Society of Cardiology)

Chaired by: Maria Dorobanțu, Cor deWit

Date: ***Saturday, June 9th***
Starting time: ***08:30***
Location: ***Main Hall (Ronda)***

1. **Gabriela Roman**
Obesity, a global epidemic

2. **R. Bugiardini**
Obesity, gender and coronary heart disease

3. **M. Vintilă**
Abdominal obesity and inflammation

4. **A. Koller**
Coronary vascular tone and obesity

5. **S. Bălănescu**
Intravascular interventions in obese patients

6. **Lina Badimon**
Adipose derived stem cells: future options

S08-1

OBESITY, A GLOBAL EPIDEMIC

Gabriela Roman
"Iuliu Haţieganu" University of Pharmacy and Medicine,
Clinical Center of Diabetes, Nutrition, Metabolic diseases,
Cluj-Napoca, Romania
groman@umfcluj.ro

Obesity is now recognised as a global epidemic and the most prevalent metabolic disease world-wide. Despite significant recent research investment, obesity prevalence rates continue to rise throughout most countries of the world. Last IASO analysis (2010) estimates that approximately 1 billion adults are currently overweight (BMI 25-29.9 Kg/m²), and a further 475 million are obese. When Asian-specific cut-off points for the definition of obesity (body mass index >28 kg/m²) are taken into account, the number of adults considered obese globally is over 600 million. Children are affected as well, up to 200 million school aged children are either overweight or obese, of those 40-50 million are classified as obese. In Europe, approximately 60% of adults (260 million) and over 20% of school-age children (over 12 million) are overweight or obese. The great challenge of obesity is the high risk for type 2 diabetes, cardiovascular diseases and cancer. The disease therefore incurs an increasingly heavy burden not only on overweight and obese citizens themselves but also on health care systems, the efficiency of the workforce and society at large. Prevention of obesity and weight gain at high risk population level is the main strategy to reduce the burden of obesity.

S08-2

OBESITY, GENDER AND CORONARY HEART DISEASE

Raffaele Bugiardini
University Alma Mater of Bologna, Bologna, Italy
raffaele.bugiardini@unibo.it

We examined the influence of relative weight at early stages of the life (30.6±5.9 years) on endothelial function and vascular structure of healthy subjects without traditional risk factors and family history of coronary artery disease (CAD). We also explored the importance of controlling for Glu298Asp polymorphism in the assessment of the effect of weight, as well as possible interrelations of weight with gender.

Subjects were grouped as Glu homozygotes and Asp carriers. In women, Asp-carriers had a significantly lower endothelial function (as assessed by flow mediated dilation; FMD) and greater intima-media thickening (IMT) than Glu298-homozygotes. In men, there was no difference in both FMD and IMT between Asp-carriers and Glu298-homozygotes. A higher body mass index (BMI) was positively associated with lower FMD and greater IMT in Asp carriers, but not in Glu homozygotes. As expected, control for systolic blood pressure a condition known to be related to weight, attenuated the strength of the association.

These data emphasize the importance of weight as a determinant of CAD in women. Even mild-to-moderate overweight increased the risk of sub- clinical atherosclerosis in young healthy women. The eNOS Glu(298)/Asp polymorphism may contribute to these sex related differences in the effect of weight.

S08-3

ABDOMINAL OBESITY AND INFLAMMATION

Marius Vintilă, M. Băluță
"Carol Davila" University of Medicine and Pharmacy
St. Pantelimon Universitary Emergency Hospital, Cardiology Department, Bucharest, Romania
mmvintila@yahoo.com

Abdominal obesity is associated to chronic low-grade inflammation originating from expanding fat tissue. Cross-sectional studies have shown a relationship between adiposity and circulating markers of inflammation.
Adipose tissue is a source of proinflammatory cytokines. Abdominal fat tissue and resident macrophages within this tissue seem to be the primary source of cytokines such as interleukin-6 (IL-6) or tumor necrosis factor-α. These promote inflammation and shift the activation state of adipose tissue macrophages to a proinflammatory phenotype. IL-6 secretion directly might induce the production of CRP in the liver. Adipose tissue-resident macrophages appear to be also the primary source of IL-1F6. IL-1F6 is a new member of the IL-1 family of cytokines that display proinflammatory effects. Regulatory T cells may play also a critical role as determinants of adipose inflammation. They inversely correlated with CD11b+ and CD11c+ adipose tissue macrophages (ATMs). Human visceral fat in morbid obesity was characterized by an increase in CD11c+ ATMs.
Adipose tissue itself is a source and site of inflammation.
Inflammatory markers such as IL-6, TNF-α and adipokines (resistin, adiponectin) are associated with metabolic alterations. Whether obesity "per se" or rather the associated inflammation determine the cardiometabolic risk need to be determined.

S08-4

CORONARY VASCULAR TONE AND OBESITY

Akos Koller [1, 2]
[1]*Department of Pathophysiology and Gerontology, University of Pécs, Pécs, Hungary*
[2]*Department of Physiology, New York Medical College, Valhalla, NY, USA*
akos.koller@aok.pte.hu

Vasomotor adaptation and/or dysfunction of the coronary microvessels is considered to be one of the early developing alterations in obesity, contributing to the disturbed regulation of coronary perfusion. The existence of vascular adaptive mechanisms in coronary vessels was shown by several recent studies. We have found that dilations to acetylcholine (ACh) were not significantly different in obese and lean rats, yet the inhibition of nitric oxide (NO) synthesis reduced ACh-induced dilations only in vessels of lean controls. The presence of the soluble guanylate cyclase (sGC) inhibitor elicited a similar reduction in ACh-induced dilations in the two groups of vessels. Dilations to the NO donor were enhanced in coronary arterioles of obese compared with lean control rats. Moreover, NO donor-stimulated cGMP immunoreactivity in coronary arterioles and also cGMP levels in carotid arteries were enhanced in obese rats, whereas the protein expression of endothelial NOS and the sGC beta1-subunit were not different in the two groups. In Zucker obese rats others found a reduced ET-1-induced constriction of coronary arteries, due to increased ET(B)-mediated generation of NO and diminished elevation of myoplasmic $[Ca^{2+}]_i$. Thus obesity has a complex effect on the vasomotor regulation of coronary microvessels.
AHA FA 0855910D, Hungarian Sci. Res Fund.-OTKA K71591.

S08-5

INTRAVASCULAR INTERVENTIONS IN OBESE PATIENTS

Şerban Bălănescu
Bucharest Emergency Hospital, Romania
SMBALA99@hotmail.com

Obesity induces accelerated atherosclerosis and increased cardiovascular risk by atherothrombotic events. Despite multiple mechanisms that may be kept responsible for negative prognosis in these patients (pts), long term follow-up data suggested that a so-called "obesity paradox" might exist. This is defined by a paradoxical decrease in mortality with increasing body mass index (BMI) in pts with cardiovascular disease.

Endovascular interventions, either coronary or peripheral, should prevail over classic surgery because of increased anesthetic and surgical complications in this group. Difficult arterial access could be managed by using radial artery or facilitated by ultrasound.

Obese pts undergoing coronary angioplasty have similar 5-year outcomes with normal weight counterparts, but they may have a higher rate of target vessel revascularization and early stent thrombosis. Contrary, after peripheral endovascular interventions underweight and normal BMI patients have lower arterial patency, limb salvage and survival rates than obese patients. The former group of pts has a more extensive form of peripheral artery disease at the time of presentation. Obese pts that need endovascular aortic aneurysm repair (EVAR) have extended operation times, but increasing BMI appears to have minor impact on outcomes after EVAR.

Further studies are needed to explain the obesity paradox in this patient population.

S08-6

ADIPOSE DERIVED STEM CELLS: FUTURE OPTIONS

Lina Badimon
Barcelona Cardiovascular Research Center, ICCC-CSIC, Hospital de la Santa, Creu I Sant Pau, IIB-Sant Pau; Ciber OBENU, Instituto Carlos III and Cátedra de Investigación Cardiovascular-UAB, Barcelona, Spain
lbadimon@csic-iccc.org

Adipose tissue, traditionally regarded as an energy storage organ, is now considered an endocrine tissue and a source of adult stem cells, adipose-derived stem cells (ADSC). ADSC share many properties with the well-described bone marrow-derived mesenchymal stem cells (BM-MSC) including ex vivo expansion, differentiation capacity and mesenchymal characteristic lineage markers. ADSC can be easily isolated from human subcutaneous adipose tissue and in great quantities, what make them an attractive alternative for cell therapy purposes. One of the most interesting characteristic of ADSC is their potential to stimulate angiogenesis, reduce apoptosis and exert anti-inflammatory properties suggesting an active role of ADSC in revascularization of ischemic damaged tissues. Most of these effects are believed to be mediated via paracrine activity.

At present, age, adipose tissue depot site, and gender have shown to modify the number and the proliferation, differentiation and angiogenic capacity of ADSC. However, the effect of cardiovascular risk factors on ADSC potential has not been previously addressed. Indeed, several human studies have demonstrated that hypercholesterolemia, diabetes, and hypertension impair the number and function of bone marrow-derived circulating progenitor cells. Yet, the effect of different degree of adiposity and/or metabolic syndrome on the functional capability of adult stem cells, and particularly in ADSC is presently investigated.

S-09-A Symposium
"Mechanisms in cardiovascular adaptation"
- I -

Chaired by: N.S. Dhalla, D. Vinereanu

Date: ***Friday, June 8th***
Starting time: ***12:00***
Location: ***Hall A (Rapsodia)***

1. **N.S. Dhalla**
Mechanisms of cardiac adaptation in hypertrophy due to volume overload

2. **A.G. Fraser**
Diagnosis of myocardial fibrosis

3. **F. Cecchi**
Subclinical LV dysfunction and pathology

4. **R. Weisel**
Cardiac restoration by tissue engineering

S09A-1

ADAPTATION OF HEART FUNCTION IN CARDIAC HYPERTROPHY DUE TO PRESSURE OVERLOAD

Naranjan S. Dhalla
Institute of Cardiovascular Sciences, St. Boniface Hospital Research, Department of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada
NSDhalla@sbrc.ca

Although cardiac hypertrophy is considered to be an adaptive mechanism for the maintenance of heart function, myocardial subcellular alterations occurring at different stages of its development are poorly understood. By employing a rat model of cardiac hypertrophy due to pressure overload, we have examined functional, subcellular and biochemical changes after banding the abdominal aorta at 4 and 8 weeks. The degree of cardiac hypertrophy, as evident from increases in left ventricle (LV) wt and heart wt/body wt ratio, was associated with activation of sympathetic nervous system, as seen from increases in plasma catecholamine levels, at 4 and 8 weeks. Likewise, the activation of renin-angiotensin system, as seen from increases in plasma angiotensin II and angiotensin II converting enzyme levels, was also evident at 4 weeks and 8 weeks. However, LV function was maintained at 4 weeks but was depressed at 8 weeks of inducing pressure overload. The activities of LV sarcolemmal Na^{+}-Ca^{2+} exchanger as well as sarcoplasmic reticular Ca^{2+}-pump and Ca^{2+}-release channels were increased at 4 weeks but were depressed at 8 weeks of cardiac hypertrophy. The observed alterations in Ca^{2+}-transport systems in hypertrophied LV and cardiac function at 8 weeks of pressure overload were prevented by treatment of animals with β-adrenoceptor blockers or angiotensin II receptor antagonists. These observations suggest that the status of subcellular Ca^{2+}-handling systems play a critical role in maintaining heart function during the development of cardiac hypertrophy. (Supported by the Canadian Institutes of Health Research)

S09A-2

DIAGNOSIS OF MYOCARDIAL FIBROSIS

Alan G. Fraser
Wales Heart Research Institute, Cardiff University, UK
fraserag@cf.ac.uk

Interstitial deposition of collagen in the heart is a key step in the progression from chronically increased loading, to diastolic and systolic heart failure. Direct methods of quantifying myocardial interstitial fibrosis by biopsy with quantitative morphometry, which has shown substantial regional variations within the left ventricle, or by biochemical analyses, are not relevant to routine clinical practice. Serum markers of collagen metabolism that correlate with myocardial fibrosis and which have been demonstrated to have diagnostic or prognostic value include the C-terminal propeptide of type I procollagen (PIP), the amino-terminal peptide of type III procollagen (PIIINP), several matrix metalloproteinases (MMP-1, MMP-2, and MMP-9), and tissue inhibitor of MMP levels. Many functional surrogate markers have been validated against biopsies or serum assays, and they can be used to diagnose subclinical and clinical disease and to monitor changes during treatment. Echocardiographic measurements include the velocities and deformation of longitudinal function of the left ventricle, particularly in the septum and both in systole and diastole. Late gadolinium enhancement of magnetic resonance images is a non-specific marker of expansion of the extracellular matrix with increased water content. It is observed in diseases that cause myocardial oedema or replacement fibrosis (scar) such as non-ST segment elevation myocardial infarction, and focal abnormalities related to inflammatory disease such as cardiac sarcoidosis. Diffuse interstitial fibrosis is more difficult to diagnose but it causes an increase in the myocardial extravascular extracellular volume fraction and correlates with a shorter global contrast-enhanced myocardial T(1) time. The test now for the different non-invasive markers is to identify those which should be integrated in the monitoring and therapeutic management of patients because their use demonstrates an impact on the selection of treatment or on clinical outcomes.

S09A-3

SUBCLINICAL LV DYSFUNCTION AND PATHOLOGY

Franco Cecchi
Università di Firenze, Florence, Italy
francocecchi337@gmail.com

Subclinical right or left ventricular dysfunction goes often undiagnosed, due to mild or absent symptoms. It usually occurs in the early stage of Cardiomyopathy, or as a result if ischemic, hypertensive or valvular disease. Its recognition is crucial as appropriate management may slow disease progression and even induce reverse remodelling.

Cardiomyopathies (CM) comprise a group of myocardial diseases, whose overall prevalence is estimated to be at least 3 ‰ in the general population. Their recognition is increasing due to imaging techniques and greater awareness in medical community. They are often familiar inherited diseases, usually with an autosomic dominant, more rarely recessive or x-linked transmission. A variety of gene abnormalities are considered the cause of CM, as they are responsible for Cardiomyocite dysfunction and death. The need of a close cooperation among clinicians, geneticists and molecular biologists, physiologists, in addition to imaging experts, pathologists, neurologists, nephrologists and paediatricians is clearly established. CM are a good model of integration between basic and clinical sciences. A multidisciplinary approach is necessary in order to ensure their correct diagnosis and management. The recently revised (2008) Classification of Cardiomyopathies by the European Society of Cardiology WG of myocardial and pericardial diseases seems to be particularly useful in daily clinical practice.

S09A-4

CARDIAC RESTORATION BY TISSUE ENGINEERING

Richard Weisel
Cardiac Surgery at the University of Toronto, Regenerative Medicine at the Toronto General Research Institute, Toronto, Canada
weisel9377@rogers.com

Following an extensive myocardial infarction, the ventricular frequently thins and dilates resulting in progressive heart failure despite intensive medical therapy. Tissue engineering provides innovative alternative strategies to stabilize the infarcted myocardium and prevent dilatation. Stem cell therapy prevents matrix remodeling by paracrine effects, but cell survival and engraftment is very limited. Biodegradable, porous scaffolds seeded with cells and cytokines increases cell survival and prevents remodeling.

Surgical Ventricular Restoration (SVR) removes the infarcted region and remodels the infarcted ventricle with a patch. The procedure converts a dilated spherical ventricle to a more normal conical shape; it converts a European soccer ball to an American football. The stiff, synthetic patch usually used for SVR renders the remodeled regions scarred and non-elastic. The Surgical Treatment for Ischemic Heart Failure (STICH) trial demonstrated that SVR significantly reduced ventricular volumes but did not improve symptoms, exercise ability, or global ventricular function. Modification of the patch employed for SVR may improve the results obtained. We developed a new biodegradable scaffold seeded with cells and cytokines which enhanced cardiac healing, prevented recurrent dilatation and rejuvenated dysfunctional cardiac resident stem cells.

New biomaterials offer the promise the Tissue Engineering will restore ventricular function after an extensive myocardial infarction.

S-09-B Symposium
"Mechanisms in cardiovascular adaptation"
- II -

Chaired by: O. Binah, F. Cecchi

Date: ***Friday, June 8th***
Starting time: ***14:30***
Location: ***Hall A (Rapsodia)***

1. **D. Vinereanu**
Adaptation of the heart function in athletes

2. **O. Binah**
Investigating inherited cardiac arrhythmias by means of induced pluripotent stem cell-derived cardiomyocytes

3. **F. Kolar**
Distinct effects of various adaptation regimens on ischemic tolerance of chronically hypoxic hearts

4. **B.S. Tuana**
Transcriptional control of dilated cardiomyopathy in the absence of hypertrophy

S09B-1

ADAPTATION OF THE CARDIAC FUNCTION IN ATHLETES

Dragoş Vinereanu
Department of Cardiology,
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
vinereanu@gmail.com

"Cardiac hypertrophy" refers to the remodeling of the cardiomyocytes and adaptation of the cardiac function. This process may be due to cardiac pathology or to exercise training. Exercise training is associated with physiological cardiac adaptation, in order to response to the specific hemodynamic requirements, which are different according to the age, gender, and type of sport; therefore, two morphological forms of athlete's heart can be distinguished, an endurance-trained heart and a strength-trained heart. Overall, "athlete's heart" is characterized by preserved myocardial structure, with a normal pattern of collagen metabolism and ventricular filling pressure, and it is associated with "supranormal" cardiac function, with better diastolic and systolic performance. Although it has been considered that "athlete's heart" is partly caused by increase in mechanical load, certain mechanisms, that allow the heart to enlarge while maintaining a "supranormal function", are not known. Such mechanisms might be related to better ventriculo-arterial coupling, with an improved endothelial and arterial function, related to lower oxydative stress. This lecture will focus on the description of these mechanisms, echo appearance of the athlete's heart, and also on differentiation from pathological hypertrophy, since this represents a serious condition that may be associated with development of coronary heart disease, heart failure, or sudden cardiac death.

S09B-2

INVESTIGATING INHERITED CARDIAC ARRHYTHMIAS BY MEANS OF INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

Ofer Binah
Department of Physiology, Ruth & Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Tel Aviv, Israel
binah@tx.technion.ac.il

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and Long–QT Syndrome (LQTS) are inherited arrhythmias occurring in the absence of structural heart diseases. Despite the paramount advancement in understanding the diverse aspects of CPVT and LQTS, these fatal diseases still present high mortality rates. While it is agreed that the clinical outcome of inherited arrhythmias may be ameliorated by further basic research, accomplishing this goal was hampered by the inability to obtain direct access to the affected (diseased) myocytes, and thus investigate the actual functional derangements resulting from the mutated gene. However, obtaining CPVT and LQTS-specific cardiomyocytes has now become a viable option due to the breakthrough inventions of Yamanaka and co-workers – the generation of human induced pluripotent stem cells (iPSCs). Hence, to decipher in the actual mutated myocytes, the functional changes and the underlying molecular mechanisms of CPVT and LQTS (and other inherited cardiac pathologies), researches are investigating mutated cardiomyocytes differentiated from iPSCs derived from sick individuals. It is anticipated that this technology will provide us the means to profoundly advance our understanding of CPVT and LQTS, and hopefully to improve their future clinical outcome.

S09B-3

DISTINCT EFFECTS OF VARIOUS ADAPTATION REGIMENS ON ISCHEMIC TOLERANCE OF CHRONICALLY HYPOXIC HEARTS

Frantisek Kolar[1],
Neckar J.[1], Borchert G.H.[1], Hlouskova P.[2], Micova P.[2], Novakova O.[2],
Novak F.[2], Hroch M.[3], Papousek F.[1], Ostadal B.[1]
[1]Institute of Physiology, Academy of Sciences of the Czech Republic,
[2]Faculty of Science, Charles University in Prague, and [3]Faculty of Medicine in Hradec Králové, Charles University in Prague, Czech Republic
kolar@biomed.cas.cz

The aim was to find out whether brief reoxygenations during adaptation to chronic continuous hypoxia (CCH) affect cardioprotection. Adult male rats were kept at CCH (FIO2=0.1) for 5−30 days; a subgroup of animals was exposed to room air daily for a single 60-min period. While 5-day CCH did not affect myocardial infarction induced by regional ischemia/reperfusion, 15 and 30 days reduced infarct size from 62% of area at risk in controls to 52% and 41%, respectively. Susceptibility to ischemic arrhythmias exhibited reciprocal development. CCH up-regulated myocardial antioxidant defense systems without affecting malondialdehyde. Reoxygenation abolished both the infarct size-limiting effect of CCH and upregulation of antioxidants, resulting in oxidative stress. Cardiomyocytes from CCH rats exhibited better resistance to injury than cells from normoxic and reoxygenated groups. The cytoprotective effect of CCH was attenuated by the large-conductance Ca^{2+}-activated K^+ (BKCa) channel blocker paxilline, whereas the opener NS1619 reduced injury in the normoxic group but not in the CCH group. Reoxygenation restored the NS1619-induced protection, whereas paxilline had no effect, resembling the normoxic group pattern. Results suggest that CCH is cardioprotective and brief daily reoxygenation blunts its salutary effects, likely by interfering with the activation of mitochondrial BKCa channels and suppressing antioxidant defense.

S09B-4

TRANSCRIPTIONAL CONTROL OF DILATED CARDIOMYOPATHY IN THE ABSENCE OF HYPERTROPHY

Balwant S. Tuana
Department of Cellular and Molecular Medicine, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
btuana@uottawa.ca

The E2F/Rb pathway is comprised of a dozen distinct proteins which are expressed in a cell/tissue specific context to regulate genes involved in proliferation, differentiation, and death. Perturbation of the E2F/Rb pathway through modulation of its members induces changes in the cell cycle which could potentially be targeted in cell growth and death. However, the constellation of E2Fs and Rb family members and their exact role in cardiac growth and development remains to be fully examined. In order to modulate the E2F pathway in vivo in mouse myocardium, we expressed E2F6 (a transcriptional repressor of E2F responsive genes) under the control of the alpha myosin heavy chain promoter. The transgenic (tg) mice exhibited dilated cardiomyopathy (DCM) and microarray, microRNA array and protein expression profiling was utilized to identify targets which were sensitive to E2F6 levels. E2F responsive transcripts involved in cell cycle regulation including E2F1 and E2F3 were up regulated in Tg hearts, but did not induce changes in cardiomyocyte size or number. Western blot analysis indicated that several proteins were down-regulated post-transcriptionally, and microRNA array detected the induction of non-cardiac microRNAs which were linked to a post-transcriptional loss of the gap junction protein connexin-43. A specific activation of the Extracellular receptor kinases (ERK) which has been linked to transcriptional control and DCM was also apparent in E2F6 Tg mice. Thus precise transcriptional control via the E2F/Rb pathway of cardiac gene expression is critical for normal cardiac growth and function. Funded by CIHR.

S-09-C Symposium
"Mechanisms in cardiovascular adaptation"
- III -

Chaired by: A.G. Fraser, Y. Wei

Date: ***Friday, June 8th***
Starting time: ***17:00***
Location: ***Hall A (Rapsodia)***

1. **Y. Wei**
LTBP-2 is a novel biomarker in heart failure - a preliminary study

2. **D. Maurice**
Subcellular signaling in the vascular endothelium: Cyclic nucleotides take their place

3. **J. Kyselovic**
Cardiac microRNAs in human end-stage heart failure

4. **G. Pierce**
The use of a novel dietary supplement to regulate blood pressure: powerful results from a randomized trial

S09C-1

LTBP-2 IS A NOVEL BIOMARKER IN HEART FAILURE - A PRELIMINARY STUDY

Yingjie Wei
State Key Laboratory of Cardiovascular Disease,
National Center for Cardiovascular Disease & Fuwai Hospital,
Chinese Academy of Medical Sciences
Peking Union Medical College, Beijing, China
weiyingjie@fuwaihospital.org

We have observed increased expression of latent TGF-β binding protein (LTBP)-2 mRNA in human failing hearts. This study was aimed to further confirm that LTBP-2 acts as a novel marker in human acute heart failure.
We demonstrated that median level of LTBP-2 in myocardial samples from heart failure patients was significantly elevated, and TGF-β1 significantly promoted LTBP-2 expression in neonatal rat cardiomyocytes. To investigate the potential of LTBP-2 as a biomarker to diagnose heart failure with reduced ejection fraction (HFREF), another cohort of 133 consecutive patients with dyspnea were enrolled. In receiver operating characteristic (ROC) curve analyses to detect HFREF, LTBP-2 achieved an area under curve (AUC) of 0.67 (95% confidence intervals (CI) 0.58–0.75), comparable to the diagnostic ability of NT-proBNP (AUC =0.68, 95% CI 0.59–0.77).
The serum LTBP-2 levels might act as a promising biomarker in HFREF.

S09C-2

ADAPTIVE AND MAL-ADAPTIVE SIGNALING IN CELLS OF THE CARDIOVASCULAR SYSTEM: IT'S NOT HOW MUCH BUT WHERE

Donald H. Maurice
Department of Biomedical and Molecular Sciences,
Cardiac, Circulatory and Respiratory Program,
Queen's University, Kingston, Ontario, Canada
mauriced@queensu.ca

Non-communicable, chronic diseases, including, a) heart diseases, such as atherosclerosis and hypertension, b) stroke, c) cancer and d) diabetes are responsible for ~60% of all deaths in developing and developed countries. Heart diseases and stroke remain leading causes of death and disability. Cancer continues to claim more lives each year and rivals cardiovascular illness as Canada's leading cause of death. Nearly 7% of Canadians are diabetic and an increasing percentage is insulin resistant, placing them at risk of diabetes. Currently, these diseases account for ~75% of health care spending in Canada. Although a majority of Canadians express the opinion that health care systems should emphasize prevention strategies, and state supporting funding of prevention programs, the reality is that participation rates in prevention programs are low. Indeed, in North America, 1 in 3 adults are obese. Most disturbingly, 1 in 5 girls and boys between the ages of 6 and 19 is obese and has two or more risk factors for heart disease, including high blood pressure, high cholesterol, diabetes, current smoking and physical inactivity. Research has unequivocally linked obesity, the metabolic syndrome, 'a clustering of atherosclerotic cardiovascular disease risk factors characterized by visceral adiposity, insulin-resistance, low HDL cholesterol, and a systemic pro-inflammatory state' and other components of "modern life", such as physical inactivity, as factors that increase the burden of chronic disease. Our studies have elucidated some of the mechanisms through which the endothelium integrates these myriad physio-pathological stimuli and takes advantage of the findings to highlight novel potential therapies to promote adaptive endothelial functions and to reduce the chronic disease-associated mal-adaptive actions of the endothelium.

S09C-3

CARDIAC MICRO-RNAs IN HUMAN END-STAGE HEART FAILURE

Jan Kyselovic
Doka G., Krenek P., Mlynarova J., Gonçalvesova E., Hulman M., Klimas J., Peter Musil
Comenius University, Faculty of Pharmacy, Department of Pharmacology and Toxicology, The National Institute of Cardiovascular Diseases Bratislava, Slovak Republic
kyselovic@fpharm.uniba.sk

Heart failure syndrome is a serious health issue that affects 2-3% of population. Identification of responsible regulatory mechanisms which may contribute to development or progression of the disease is highly challenging with respect to developments of novel therapeutic strategies. Myosin is the molecular motor of contraction. In the heart, three distinct myosin heavy chain isoforms coexist in delicate balance. As has been recently shown, the shift from one myosin isoform to other may be one of key factors causing heart failure. In this study we aimed to analyze gene expression of myosin heavy chain isoforms in failing hearts.

We examined samples from left ventricles of 30 patients with end-stage heart failure indicated for heart transplantation. We used quantitative RT-PCR to measure mRNA levels of cardiac myosin heavy chain isoforms (MYH6, MYH7, MYH7B), related transcription factors (GATA4, SRF, NKX-2.5, YY1) and microRNAs (miR-1, -133a, -208a, -208b, -499, -29b), based on bioinformatic predictions and databases.

In adult human failing hearts, we found the slow-twitch myosin heavy chain MYH7 (~98%) to be the predominantly expressed isoform whereas fast-twitch MYH6 isoform constitutes just about 1% of all myosin isoforms. This excessive expression of MYH7 is regulated by several transcription factors and microRNA, which expression is also altered. Conclusively, dysregulated gene expression of myosin heavy chains resulting in MYH7 upregulation and MYH6 downregulation might be an adaptation in heart failure and interesting target for future pharmacotherapy.

Support: VEGA 1/0109/08, VEGA 1/0357/09, VEGA 1/0786/11

S09C-4

THE USE OF A NOVEL DIETARY SUPPLEMENT TO REGULATE BLOOD PRESSURE: POWERFUL RESULTS FROM A RANDOMIZED TRIAL

Grant N. Pierce[1,3]*, Delfin Rodriguez-Leyva[1,3], Randy Guzman[2,4]*
*Co-Principal Investigators
[1]Institute of Cardiovascular Sciences, St Boniface Hospital Research Centre,
[2]Asper Clinical Research Institute, St Boniface Hospital,
Departments of [3]Physiology, [4]Surgery, University of Manitoba,
Winnipeg, Canada
GPierce@sbrc.ca

Flaxseed is an important source of omega-3 fatty acids, antioxidants and fibre. The primary objective of this study was to determine whether consumption of a diet rich in milled flaxseed over six months has any beneficial effects on blood pressure (BP) regulation in patients with peripheral arterial disease (PAD). This is a single centre, placebo-controlled, double-blinded, randomized trial in 110 patients with PAD. Patients received 30 g of milled flaxseed (or placebo)/day. Resting brachial systolic and diastolic pressures were measured. All trial participants were diagnosed with PAD and on anti-hypertensive medication. Baseline systolic and diastolic BP was 143 and 78 mm Hg, respectively. After 6 months of flaxseed treatment, systolic and diastolic BP was 10 mm and 7 mm Hg lower, respectively, than the placebo group ($P< 0.05$). The dosage of anti-hypertensive medication was unchanged by flax. The anti-hypertensive effects of dietary flaxseed were exhibited most by patients who entered the study with systolic BP of >140 mm Hg. We conclude that dietary flaxseed can decrease BP in PAD patients even on anti-hypertensive medication. These decreases in BP would be expected to reduce strokes and myocardial infarctions by at least 30-46%.
Supported by Flax2015, the Agri-food Research and Development Initiative, Canada Bread, CIHR and St Boniface Hospital Foundation.

S-10 Symposium
"*Myocardial ischemia and reperfusion*"

Chaired by: A. Tosaki, J. Slezak

Date: ***Sunday, June 10th***
Starting time: 08:30
Location: ***Main Hall (Ronda)***

1. **R.C. Kukreja**
Role of microRNA in Cardioprotection

2. **A. Tosaki**
The role of heme oxygenase-1 in myocardial ischemia and reperfusion

3. **F. Boucher**
Evolution of cytokine expression and insulin sensitivity in the myocardium after preperfused infarction in rats

4. **D.J. Hausenloy**
Remote ischemic conditioning: Bench to bedside and back again

5. **Tanya Ravingerova**
Lifestyle-related risk factors of cardiovascular diseases alter myocardial response to ischemia via interference with cellular adaptive mechanisms

6. **J. Slezak**
Chronic myocardial ischemia and mediastinal irradiation injury

S10-1

ROLE OF MICRORNA IN CARDIOPROTECTION

Rakesh C. Kukreja
Pauley Heart Center, Division of Cardiology, Virginia Commonwealth University, Richmond, Virginia, USA
rakesh@vcu.edu

MicroRNAs (miRNAs) have emerged as a novel class of endogenous, small, non-coding RNAs that negatively regulate gene expression via degradation or translational inhibition of their target mRNAs. In the heart, miRNAs have been involved in several clinical scenarios including ischemia/reperfusion and preconditioning suggesting that regulation of their function could be used as a novel cardioprotective strategy. In particular, miRNA-1, miRNA-21, miRNA-24, miRNA-29, miRNA-92a, miRNA-126, miRNA-133, miRNA-320, miRNA-199a, miRNA-208 and miRNA-195 have been shown to be regulated after myocardial infarction. Following ischemic preconditioning (IPC), we observed significant increase in miRNA-1, miRNA-21and miRNA-24 in the heart. Treatment with the miRNAs derived from the hearts subjected to IPC protected the hearts against ischemia/reperfusion injury, as shown by a reduction of infarct size as compared with saline or non-IPC miRNA-treated control. This protective effect was abolished by treatment with the miRNA-21 inhibitor. In addition, one of the powerful pharmacological preconditioning agent, sildenafil (Viagra) resulted in upregulation of miRNA-21 in the heart. Pretreatment of hearts with adenoviral vector encoding miR-21eraser prior to sildenafil preconditioning abolished the infarct limiting effect of sildenafil. These results suggest that miRNA-21 is one of important mediator of cardioprotection induced by IPC and sildenafil.

S10-2

CARBON MONOXIDE SIGNALLING IN BIOLOGICAL PROCESSES MEDIATED BY HEMEOXYGENASE-1

Arpad Tosaki
Department of Pharmacology, School of Medicine, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary
tosaki.arpad@pharm.unideb.hu

Cutting edge of biotechnology holds the potential for characterization of events which follow and contribute to pathologically altered physiological functions. Rapidly expanding understanding of basic disease mechanisms will translate into greatly improved healthcare strategies. Heme oxygenase-1 (HO-1)-related mechanisms are a major homeostatic countermeasure by which vertebrate biological systems manage many disease states including myocardial and renal ischemia/reperfusion, hypertension, cardiomyopathy, organ transplantation, endotoxemia, lung diseases, and immunosuppression. In the past decades, significant progress has been made in understanding of the function and regulation of HO-1. Here a summary is presented of current understanding of the role of the HO-1 related endogenous carbon monoxide (CO) production in various diseases, focusing on myocardial ischemia/reperfusion-induced injury. Various factors are considered which influence the HO-1 system in the context of endogenous CO production. An assessment will also be made as to how this evolving understanding may contribute to pharmacological approaches to therapeutic use of HO-1 manipulation. Upregulation of HO-1 is a widely distributed adaptive response to a wide variety of influences, especially oxidative insults. Thus, strategies for use of HO-1 as definitive prophylaxis or treatment for inflammatory pathologies are expected to increasingly make use of pharmacological agents capable of increasing activity of the enzyme.

S10-3

EVOLUTION OF CYTOKINE EXPRESSION AND INSULIN SENSITIVITY IN THE MYOCARDIUM AFTER PREPERFUSED INFARCTION IN RATS

François Boucher
TIMC-IMAG Laboratory, University Grenoble 1 – UJF, La Tronche, France
Francois.Boucher@ujf-grenoble.fr

Pro-inflammatory mediators and chemokines have been shown to play a role in the pathophysiology of heart failure. We have investigated whether such a phenomenon also occurs after short-term myocardial ischemia in-vivo rats. Temporary ischemia induced a progressive cardiac dysfunction and left ventricular (LV) remodelling, characterized by LV free wall thinning and cavity dilation. Besides, a transient and marked increase in TNF-α, IL1ß, IL6, LIX, CINC2, CINC3, MIP3-α and leptin production was also observed in the myocardium 8 days after surgery. Leptin inhibition, by intra-cardiac antisens therapy prevented the development of adverse remodelling and reduced cytokine production. Finally, cardiac insulin sensitivity, assessed by nuclear imaging using a new tracer of glucose uptake, was shown to be transiently reduced concomitantly with leptin overproduction.
These findings support the hypothesis that early events after myocardial infarction, involving leptin-induced metabolic perturbations and cytokine overproduction, may play a role in the adaptive process and remodelling of the myocardium. We suggest that these events might be some of the triggers of the adverse cardiac phenotype that leads to heart failure.

S10-4

REMOTE ISCHEMIC CONDITIONING: BENCH TO BEDSIDE AND BACK AGAIN

Derek J. Hausenloy
British Heart Foundation, The Hatter Cardiovascular Institute, University College London, UK
d.hausenloy@ucl.ac.uk

Cardiovascular disease is the leading cause of death and disability worldwide. Remote ischemic conditioning (RIC) represents a therapeutic strategy for harnessing the body's endogenous protective capabilities against the injury incurred by episode of acute lethal ischemia and reperfusion. It describes the intriguing phenomenon in which transient non-lethal ischemia and reperfusion of one organ or tissue confers resistance in a remote organ or tissue to a subsequent episode of acute lethal ischemia reperfusion injury. In its original conception in the experimental setting, it described intramyocardial protection which could be relayed between two different coronary artery territories. It soon became apparent from animal studies that myocardial infarct size could be dramatically reduced by applying cycles of brief ischemia and reperfusion to an organ or tissue remote from the heart before the onset of myocardial infarction. The concept of remote organ protection has now been extended beyond that of solely protecting the heart to providing a general form of inter-organ protection against ischemia-reperfusion injury. The concept of RIC has been successfully applied in the clinical setting to protect the heart during coronary artery bypass graft surgery, percutaneous coronary intervention and during an acute myocardial infarction. However, the mechanism underlying RIC remain unclear and have been attributed to a neuro-hormonal pathway linking the organ or tissue in which the RIC stimulus is applied to the target organ. Therefore, further basic science studies are now required to elucidate the pathways involved in RIC protection. In my talk, I will provide an overview of history and evolution of RIC, the potential mechanistic pathways underlying its cardioprotective effect, and its emerging application in the clinical setting.

S10-5

LIFESTYLE-RELATED RISK FACTORS OF CARDIOVASCULAR DISEASES ALTER MYOCARDIAL RESPONSE TO ISCHEMIA VIA INTERFERENCE WITH CELLULAR ADAPTIVE MECHANISMS

Táňa Ravingerová[1]
Slávka Čarnická[1], Martina Nemčeková[1], Veronika Ledvényiová[1], Adriana Adameová[2], Marek Zálešák[1], Antigone Lazou[3], František Kolář[4]
[1] Institute for Heart Research, Slovak Academy of Sciences, Centre of Excellence SAS NOREG, [2] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia; [3] School of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece; [4] Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic
Tatiana.Ravingerova@savba.sk

Lifestyle-related risk factors (RF) of cardiovascular diseases, such as stress, hypertension, and metabolic disorders have a negative impact on the heart exposed to ischemia facilitating its lethal injury. On the other hand, some RF-related stimuli including ischemia(hypoxia), high glucose and/or free radicals, may trigger adaptive processes in the heart resulting in its greater resistance to ischemia/reperfusion injury (IRI) known as preconditioning (PC), which is a characteristic feature of the female and acutely diabetic myocardium (recently termed as metabolic PC). We hypothesized that RF may modify cardiac response to ischemia not only by interference with pathophysiological mechanisms of IRI per se, but via suppression of the innate cardioprotection. While hearts of hypertensive (SHR) rats and male counterparts of age-matched females were more sensitive to IRI manifested by a larger extent of irreversible injury (infarction), acute STZ-induced diabetes or fat-cholesterol diet alone did not alter cardiac susceptibility to ischemia. However, combination of RF markedly exacerbated IRI facilitating pro-oxidative and apoptotic processes. On the other hand, PC still conferred an effective protection, although its extent was lower in SHR and older animals. Research shows that protective effects of adaptation may be attenuated in RF-affected heart, although potential of intrinsic cardioprotection is still retained even in pathologically altered myocardium that requires a higher intensity of the preconditioning stimulus. Cardioprotective pleiotropic (independent of the primary) effects of PPAR agonists, hypolipidemic and antidiabetic drugs, indicate a promising approach to reactivate myocardial ischemic tolerance in healthy and diseased myocardium. Grants VEGA-SR 1/0638/12, 2/0054/11, 2/0101/12, APVV-LPP-0393-09, APVV-0523-10, APVV-SK-CZ-0199-11.

S10-6

CHRONIC MYOCARDIAL ISCHEMIA AND MEDIASTINAL IRRADIATION INJURY

Jan Slezak [1]
N. Tribulova [1], M. Ivanova [1], J. Styk [1], K. Frimmel [1], T. Ravingerova [1], M. Fulop [2], L. Okruhlicova [1]
[1] Institute for Heart Research, Slovak Academy of Sciences, [2] Slovak Medical University, Bratislava, Slovak Republic
Jan.Slezak@savba.sk

Chronic ischemic injury of the myocardium is increasingly recognized as an undesired side effect of radiation of cardiovascular system after mediastinal radiation therapy for malignancies.

The study concentrates on pathology of radiation-induced cardiovascular toxicity and on prevention of injury of healthy tissues in areas at risk. Irradiation of the heart with a single dose of 20 Gy delivered to the heart region was performed on male Wistar rats.

Adverse effect of ionizing radiation is mostly mediated by reactive oxygen and nitrogen species, which deplete antioxidant stores. Radiation damage of cardiovascular system shows that endothelial cells are the most radiation sensitive part of vasculature. Microvascular injury leads to myocardial ischemia.

Chronic myocardial underperfusion results in pathophysiological reaction connected with protective mechanism. Myocytes adjust its contraction function which is characterized by down regulation in energy utilization, attenuated level of contractile function, upregulation of stress proteins, cardiomyocyte dedifferentiation and by myocyte remodeling.

Morphologically, chronic hypoperfusion results in loss of myofilaments, increased amount of glycogen and small dark mitochondria, typical signs of hibernating myocardium.

Protection of normal tissue against radiation-induced damage may increase the therapeutic benefit of radiotherapy. Different more or less effective measures to prevent radiation-induced injury and to increase cardiovascular tolerance to irradiation of healthy tissue have been evaluated. Further investigation is needed to determine the most effective prevention of radiation injury to healthy tissues accidentally targeted by radiation.

Supported by VEGA Grant 2/0207/11.

S-11-A Symposium
"*Signaling mechanisms of adaptation to hypoxia*"
- I -

Chaired by: F. Downey, I.Y. Malyshev

Date: ***Friday, June 8th***
Starting time: ***12:00***
Location: ***Main Hall (Ronda)***

1. **P.S. Wang**
Effects of Intermittent Hypoxia on the Production of Testosterone in Rats

2. **Yulia I. Kirova**
The role of oxidative stress in the induction of transcription factors at different stages of adaptation to hypoxia

3. **I.Y. Malyshev**
Hypoxia-induced reprogramming of macrophages: Role in tumorigenesis

S11A-1

EFFECTS OF INTERMITTENT HYPOXIA ON THE PRODUCTION OF TESTOSTERONE IN RATS

Paulus S. Wang [1*]
Yu-Min Cho[2], Hsiao-Fung Pu[2], Chiung-Feng Fang[2], Shyi-Wu Wang [2*]
[1]Department of Physiology, School of Medicine, National Yang-Ming University, Taipei, and [2]Department of Physiology and Pharmacology, Chang Gung University, Taoyuan, Taiwan
pswang@ym.edu.tw

The hypoxia-stimulated response of endocrine systems depends on the variety and duration of hypoxia. Our previous study reported that hypoxia induced the testosterone release in rats. However, the mechanisms are unclear.

Male rats were divided into 2 groups. Chronic intermittent hypoxia (CIH) rats were housed in a 12 % O_2 hypoxic chamber, 8 h/d for 14 days. Normoxic rats were used as control animals. Rats were catheterized and single injected with hCG (5 IU/ml/kg) via right jugular vein. Blood samples (0.3 ml each) were collected at different time intervals. Rat Leydig cells were purified and challenged with hCG (0.01 IU/ml), forskolin (10^{-5} M), 8-bromo-cAMP (10^{-4} M), A23187 (10^{-5} M), cyclopiazonic acid (CPA, 10^{-4} M), or androstenedione (10^{-8} M), and then the media were collected for investigation of cAMP-, Ca^{2+}-, and 17β-hydroxy steroid dehydrogenase(HSD)-related testosterone production. The concentrations of testosterone were measured by the radioimmunoassay. Furthermore, the Leydig cells were incubated with trilostane (10^{-5} M) and/or 25-OH-hydroxycholesterol (25-OH-C, 10^{-5} M), and then the media were collected for pregnenolone assay. The mRNA expression of LH receptor in rat Leydig cells was analyzed by RT-PCR technique. The protein expression of LH receptor in Leydig cells was detected by the Western blot method. We showed that 14-d CIH enhanced the plasma testosterone levels but decreased the serum LH levels. The plasma testosterone levels of CIH group were higher than normoxic group at several time intervals subsequent to the injection. The evoked-release of testosterone and pregnenolone of Leydig cells in vitro were significantly increased in CIH group. Moreover, CIH significant increased the mRNA and protein expressions of LH receptor and expression of P450scc in Leydig cells but not the expression of steroidogenic acute regulatory protein (StAR). In addtion, CIH increased the concentrations of peripheral and testicular serum vascular endothelial growth factor (VEGF). The vessel distribution on testes in CIH rats was more and also more obvious than in normoxic rats.These results su ggested that 14-d CIH induced the functional capacity to secrete testosterone might be partially through the mechanisms involving the induction of LH receptor expression, P450scc activity, cAMP pathway, 17β-HSD activity, and calcium-related pathway in rat Leydig cells. CIH significant increased the testicular angiogenesis.

S11A-2

THE ROLE OF OXIDATIVE STRESS IN THE INDUCTION OF TRANSCRIPTION FACTORS AT DIFFERENT STAGES OF ADAPTATION TO HYPOXIA

Yulia I. Kirova
Department Molecular and Cellular Pathophysiology
Lab. of Bioenergetics, Institute of General Pathology and Pathophysiology,
Russian Academy of Medical Sciences, Moscow, Russia
bioenerg@mail.ru

Hypoxic preconditioning induces two-phase increase of HIF-1α expression in the neocortex of low-resistance rats. The first, brief phase appears after each hypoxic episode and rapidly disappears in normoxic conditions. The second increase of HIF-1α expression occurs in 24 hours after the hypoxic episode. The phase-nature of HIF-1α expression corresponds to the dynamics of urgent and long-term resistance in low-resistance rats, which suggests the HIF-1α involvement in mechanisms of urgent and long-term adaptation. Hypobaric hypoxia or interval normobaric hypoxia in the preconditioning regimen did not significantly influence free-radical production and lipid peroxidation or even suppressed this process within the first day of exposure. Therefore, formation of urgent adaptation to hypoxia can occur in the absence of oxidative stress. In high-resistance rats, hypoxia preconditioning does not influence the HIF-1α protein expression and the adaptation. Severe hypoxia inhibits the HIF-1α protein expression in the neocortex of both rat phenotypes, depresses the formation of urgent resistance, abolishes the induction of long-term adaptation, initiates oxidative stress with increased free-radical production and lipid peroxidation. Therefore, (1) formation of urgent adaptation to hypoxia can occur in the absence of oxidative stress and (2) free-radical processes are not unique trigger mechanism that initiates transcriptional and adaptogenic HIF-1α functions.

S11A-3

HYPOXIA-INDUCED REPROGRAMMING OF MACROPHAGES: ROLE IN TUMORIGENESIS

Igor Yu Malyshev[1,2]
Kruglov S.V. [1,2], Kalish S.V.[1]
[1]*Moscow State University of Medicine and Dentistry, Moscow, Russia*
[2]*Institute of general Pathology and Pathophysiology, Moscow, Russia*
igor.malyshev@mtu-net.ru

Pathogenetic effects of hypoxia may be related with influences on immune responses. Accumulation of macrophages in hypoxia areas is the key point in understanding the mechanisms of hypoxia effects on immunity. We have investigated the effect of hypoxia on the macrophage phenotype and phenotypic plasticity and to determine the resistance to acute hypoxia in C57/BL mice, which have the pro-inflammatory M1 macrophage phenotype, and in BALB/c mice, which have the anti-inflammatory M2 macrophage phenotype. The following results were obtained. 1) The response of macrophages to acute hypoxia has two successive phases, the immediate, anti-inflammatory phase, and the delayed, pro-inflammatory phase. This response was more distinctly inverted in C57/BL6 M1 macrophages than in BALB/c M2 macrophages; 2) the effect of acute hypoxia on macrophage phenotypic plasticity depends on the genetically predetermined, original macrophage phenotype. In this process, a clear regularity was observed: hypoxia increased the capability of macrophages for changing into the pro-inflammatory M1 phenotype, while their capability for changing into the anti-inflammatory M2 phenotype remained virtually unaffected. 3) BALB/c mice were more resistant to acute hypoxia than C57/BL6 mice. Taken together, these data expand our understanding of mechanisms for pathogenetic and protective effects of hypoxia in inflammation and tumorogenesis.

S-11-B Symposium
"*Signaling mechanisms of adaptation to hypoxia*"
- II -

Chaired by: P.S. Wang, G. Melillo

Date: ***Friday, June 8th***
Starting time: ***14:30***
Location: ***Main Hall (Ronda)***

1. **Tatiana Serebrovskaya**
Migration pathways of hematopoietic stem cells in the mechanisms of adaptation to acute and intermittent hypoxia

2. **Benedetta Bussolati**
The plasticity of human renal CD133+ progenitors is modulated by hypoxia through Oct4/miR-145 balance

3. **F. Downey**
Anti-hypertensive effects of adaptation to hypoxia

S11B-1

MIGRATION PATHWAYS OF HEMATOPOIETIC STEM CELLS (HCS) IN THE MECHANISMS OF ADAPTATION TO ACUTE AND INTERMITTENT HYPOXIA

Tatiana V. Serebrovskaya[1]
Nikolsky I.S.[2], Ishchuk V.A.[3]
[1]*Bogomoletz Institute of Physiology, Kiev, Ukraine*
[2]*Institute of Genetic and Regenerative Medicine, Kiev, Ukraine*
[3]*State Institute of Gerontology, Kiev, Ukraine*
sereb@biph.kiev.ua

HSCs play an important role in the homeostasis and turnover of peripheral tissues. Experiments on animals testify that exposure to intermittent hypoxia (IH) promotes induction of distinct HSC chemoattractant gradients and mobilizes HSC from bone marrow to peripheral circulation. This process is regulated by chemokines and cytokines. Present study was designed to compare the effects of intermittent versus acute hypoxia on human HSCs and some immune parameters. A two-week IH program (5 min exposures to 10% O2 with intervening 5 min room air breathing, 4 times a day) caused a decrease in circulating HSCs 1 wk after IH, lowered TNF-α and IL-4 and sharply increased IFN-γ, augmented phagocytic and bactericidal activities of neutrophils, activated complement and some immunoglobulins. In contrast to 2-wk IH program, single IH session increased HSC during hypoxic cycles; this effect subsided within 30 min after hypoxic session. Results raise the possibility that IH induces HSC emigration from niches into the circulation, followed by homing and sequestration in target tissues during post-hypoxic recovery. The IH-induced decrease in blood TNF-α content with simultaneous increase in IFN-γ could contribute to the moderation of infectious-inflammatory processes. Further studies are required to elucidate the fate of IH-activated HSCs in circulating blood and investigate their role within specific tissue compartments.

S11B-2

THE PLASTICITY OF HUMAN RENAL CD133$^+$ PROGENITORS IS MODULATED BY HYPOXIA THROUGH OCT4/MIR-145 BALANCE

Aldo Moggio, Giovanni Camussi, Benedetta Bussolati
Molecular Biotechnology Centre, University of Torino, Italy
benedetta.bussolati@unito.it

The tubular compartment of the nephron displays a high regenerative ability. We previously isolated CD133$^+$ stem/progenitor cells in the tubular compartment of the human kidney. However, their possible contribution to repair is unknown. We here evaluated the possible modulation of CD133$^+$ cells by the hypoxic environment, the molecular mechanisms involved and their possible involvement in renal regeneration.
CD133$^+$ progenitors cultured under hypoxia (1%O_2) showed increased proliferation and clonogenic ability. When injected in vivo, CD133$^+$ hypoxic progenitors showed ability to differentiate in structures resembling the different segments of the nephron. Moreover, hypoxia up-regulated Oct-4 isoforms in CD133$^+$ cells via regulation of the Oct4 promoter. In parallel, hypoxia downregulated microRNA-145, known to act as an Oct4 transcriptional repressor. Epithelial differentiation increased microRNA-145 and reduced Oct4 level, suggesting a balance between Oct4 and microRNA-145. MicroRNA-145 over-expression in CD133$^+$ cells induced down-relation of Oct4 at the protein level, inhibited cell proliferation and stimulated differentiation. Labelled CD133$^+$ progenitors localized into the injured kidneys in a model of acute renal damage and promoted renal functional regeneration. These results suggest that hypoxia may direct CD133$^+$ progenitors toward a more stem phenotype via Oct4A/miR145 balance. The plasticity of renal CD133$^+$ cells could be exploited in renal regeneration after hypoxic damage.

S11B-3

ANTIHYPERTENSIVE EFFECTS OF ADAPTATION TO HYPOXIA

Fred H. Downey[1], Eugenia B. Manukhina[1,2]
[1]*Univ. N. Tex. Hlth. Sci. Ctr., Fort Worth, TX 76107 USA;*
[2]*Inst. Gen. Pathol. and Pathophysiol., Moscow, Russia*
Fred.Downey@unthsc.edu

Adaptation to hypoxia and its effect on blood pressure (BP) has been investigated under many circumstances, in various models, and with varying protocols. Thus, it is not surprising that there is no consensus regarding this clinically relevant topic. BP of people living at high altitude differs little from that of lowlanders, but hypertension is less evident. However, life style and diet are confounding factors. The rise of BP of spontaneously hypertensive rats is blunted by continuous hypoxia and by some protocols of intermittent hypoxia. Hypertensive patients have been treated successfully by adaptation to hypoxia, yet the intermittent hypoxia of sleep apnea causes hypertension. Whether or not adaptation to hypoxia is antihypertensive depends on the balance of vasoconstrictory and vasodilatory mechanisms activated by different hypoxic regimens. Antihypertensive mechanisms include increased vascularity, NO production and storage, reduced vascular Ca^{++}, and improved salt and water metabolism; as well as, blunting of vasoconstrictory mechanisms, including sympathetic activation and angiotensin. Hypertensive responses to stress may also be blunted, with resulting reduction in BP. Clearly, more research is required to understand the effects of hypoxia on BP, especially if adaptation to hypoxia is to be used clinically as a complementary or alternative therapy for hypertension.

S-12 Symposium
"*Cardiac stem cells*"

Chaired by: P.A. Doevendans, M. Pesce

Date: ***Saturday, June 9th***
Starting time: ***08:30***
Location: ***Hall B (Salonul Oglinzilor)***

1. **V. Lionetti**
Self-Renewing heart in the era of stem cells: who have saved the heart of Prometheus?

2. **Elisa-A. Liehn**
Cell therapy after myocardial infarction: present and future

3. **M. Pesce**
Cardiovascular stem cells: from regeneration to engineering

4. **P.A. Doevendans**
Cardiac stem cells: the solution

5. **Mihaela Gherghiceanu**
Cardiac stem and progenitor cells by electron microscopy/tomography

6. **S.F. Yet**
Cytoprotection of heme oxygenase-1 in embryonic stem cells and cardiovascular system

S12-1

SELF-RENEWING HEART IN THE ERA OF STEM CELLS: WHO HAVE SAVED THE HEART OF PROMETHEUS?

Vincenzo Lionetti
Laboratory of Medical Science, Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy
v.lionetti@sssup.it

A heart attack kills off many cells in the heart. Parts of the heart become thin and fail to contract properly following the replacement of lost cells by scar tissue. However, the notion that the same adult cardiomyocytes beat throughout the lifespan of the organ and organism, without the need for a minimum turnover, gives way to a fascinating investigations. Since the late 1800s, scientists and cardiologists wanted to demonstrate that the cardiomyocytes cannot be generated after the perinatal period in human beings. This curiosity has been passed down in subsequent years and has motivated more and more accurate studies in an attempt to exclude the presence of renewed cardiomyocytes in the tissue bordering the ischaemic area, and then to confirm the dogma of the heart as terminally differentiated organ. Conversely, peri-lesional mitosis of cardiomyocytes were discovered initially by light microscopy and subsequently confirmed by more sophisticated technologies. Controversial evidence of mechanisms underlying myocardial regeneration has shown that adult cardiomyocytes are renewed through a slow turnover, even in the absence of damage. This turnover is ensured by the activation of rare clusters of progenitor cells interspersed among the cardiac cells functionally mature. Cardiac progenitor cells continuously interact with each other, with the cells circulating in the vessels of the coronary microcirculation and myocardial cells in auto-/paracrine manner. Much remains to be understood; however, the limited functional recovery in human beings after myocardial injury clearly demonstrates weak regenerative potential of cardiomyocytes and encourages the development of new approaches to stimulate this process.

S12-2

CELL THERAPY AFTER MYOCARDIAL INFARCTION: PRESENT AND FUTURE

Elisa-A. Liehn
Institute for molecular cardiovascular reserach, RWTH Aachen, Germany
eliehn@ukaachen.de

Despite the extensive research, our current knowledge regarding the control of molecular and cellular events after MI is still limited. Moreover, the most promising stem cell-therapy has not offered satisfying results. Therefore, to be able to create efficient therapies, we desperately need to understand how all these processes are modulated and controlled.

The mature scar is a dynamic tissue, rich in cells, vascularized, metabolically active and contractile. Therefore, we should be able to interfere in its metabolism, and induce morphological and functional changes. Indeed, the experimental intramyocardial injection of cells, one month after myocardial infarction, induces cell-specific changes of the scar, improving ventricular function. Despite the fact that cell therapy is considered a novel and potentially new strategy in regenerative medicine, Recent studies imply that paracrine effects and inflammatory modulations by transplanted cells are a key factor for improvement of myocardial function. In this regard, we were able to show that transplantation of biological inactive glass microspheres induced a significant increase in ventricular contractility, but not the apoptotic bodies. Therefore, we conclude that the underlaying mechanism of augmented heart function after cell therapy might be based on inflammatory processes induced by transplantation.

This could represent a new approach in developing therapeutical strategies to improve heart function in patients with extended scar-tissues, for whom all current clinical treatment alternatives have been exhausted.

S12-3

CARDIOVASCULAR STEM CELLS: FROM REGENERATION TO ENGINEERING

Maurizio Pesce
Laboratorio di Ingegneria Tissutale Cardiovascolare, Centro Cardiologico Monzino, IRCCS, Milan, Italy
maurizio.pesce@ccfm.it

The ability to produce differentiated cells maintaining tissue homeostasis is a unique feature of stem cells. This makes them an ideal resource for cell replacement strategies in tissues with ischemic disease. Transplanted cells, regardless of whether they adhere to "stem" cell definition, are expected to engraft into ischemic tissues, proliferate and differentiate into cells repairing the damaged organs. While significant advancements have been made toward the development of clinically approved stem cell preparation protocols, with the introduction of "good manufacturing practice" (GMP) criteria, or the use of "cell enhancement strategies", to enhance innate stem cell functions, the "bulk" expansion methods appear insufficient to maintain "stemness" characteristics. In fact, culture in the presence of soluble cytokines or adhesion onto plastic-made rigid surfaces with stiffness of several orders or magnitude higher than tissue environment, does not preserve the innate ability of stem cells to asymmetrically divide and self renew.

Merging stem cell biology with most recent advances in material screening, bio-engineering and computer modeling is potentially of great help to overcome this hurdle. In fact, the ability to assess cellular responses after confinement into structures with defined bi- or three-dimensional (2D/3D) shapes, specific chemical composition and controlled mechanical stimulation, allows high throughput dissection of stem cells "functiotype" and, thus, modeling a culture environment mimicking the complex biological architecture.

In the course of the presentation, examples from our past and present experience in cardiovascular stem cells science and emerging approaches of high throughput biomaterial screening, bioengineering, bio-computing and (epi)genetic profiling, will be presented as a next step in the devise of enhanced cardiovascular tissue engineering and regenerative medicine.

S12-4

CARDIAC STEM CELLS: THE SOLUTION

Pieter A. Doevendans
Cardiology, Division Heart and Lungs, UMC Utrecht,
The Netherlands
P.Doevendans@umcutrecht.nl

The stem cell field is moving forward in the direction of the clinical arena. By moving from bone marrow mononuclear cells to mesenchymal stem cells has improved clinical outcome. The most recent trials on cardiac stem cells are preliminary, but appear safe and the 1 year outcome is above all expectations. The presentation will focus on the current knowledge we have on cardiac stem cells from various sources and how they can be applied. Also the necessity to differentiate these cells prior to injection will be discussed. In the years ahead the battle between biology and technology will make the developments even more interesting. Currently cardiac stem cells would appear to provide the best solution.

S12-5

CARDIAC STEM AND PROGENITOR CELLS BY ELECTRON MICROSCOPY/TOMOGRAPHY

Mihaela Gherghiceanu
"Victor Babeş" National Institute of Pathology, Bucharest, Romania
mihaela.gherghiceanu@ivb.ro

A highly heterogeneous population of cardiac stem (CSC) and progenitor (CMP) cells has been described by in the mammalian adult heart, but the ultrastructural identity of CSC in tissue remains unknown. Using electron microscopy (EM), we found cells with stem features in the adult mouse heart. These putative CSC are small, round cells, with large nucleus, few endoplasmic reticulum cisternae and mitochondria, but numerous ribosomes. CSC located in the epicardial stem cell niche (CSCN) undergo mitosis and apoptosis. Beside CSC, CMP residing in the CSCN are easily identifiable by EM. Cells with intermediate features between CSC and CMP could also been seen. Moreover, EM shows that CMP are added to the adult cardiomyocytes in the peripheral of working myocardium. Telocytes form a supportive interstitial network for CSC and CMP in the stem cell niche. Complex intercellular communication occurs between the telocytes and CMP through electron-dense nanostructures or through shed vesicles. The presence of CSC and CMP sustain a continuous cardiac renewal process in the adult mammalian heart.

This work was supported by a grant of the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number PN-II-ID-PCE-2011-3-0134.

S12-6

CYTOPROTECTION OF HEME OXYGENASE-1 IN EMBRYONIC STEM CELLS AND CARDIOVASCULAR SYSTEM

Shaw-Fang Yet
National Health Research Institutes, Zhunan, Miaoli County, Taiwan
syet@nhri.org.tw

Embryonic stem cells (ESCs) are promising donor sources in cell therapies for various diseases. Although low levels of reactive oxygen species (ROS) are necessary for the maintenance of stem cells, increased ROS levels initiate differentiation and cell damage. Heme oxygenase (HO)-1 is a stress response protein with antioxidative and anti-inflammatory properties. We hypothesized that HO-1 plays critical roles in ESCs and cardiovascular system. To test our hypothesis, we used induced pluripotent stem (iPS) cells that lack HO-1 and HO-1 knockout mice in our in vitro and in vivo studies. In response to oxidant stress, HO-1-deficient iPS cells accumulate higher levels of intracellular ROS compared with wild-type ESCs and are more susceptible to oxidant-induced cell death. Following LIF and feeder withdrawal, ESC marker gene levels are significantly lower in HO-1-deficient iPS cells. Our results demonstrate that a lack of HO-1 renders ESCs more prone to oxidative stress-induced cell death and differentiation. In animals, lack of HO-1 worsens myocardial injury whereas overexpression of HO-1 protects against myocardial infarction. In a mouse model with angiotensin II infusion, HO-1-deficiency exacerbates abdominal aortic aneurysm formation. Taken together, HO-1 confers cytoprotection not only in ESCs but also in cardiovascular system.

S-13 Symposium
"*Blood Brain Barrier and angiogenesis – role in neurodegeneration*"

Chaired by: Carola Foerster, K. Jellinger

Date: ***Friday, June 8th***
Starting time: ***14:30***
Location: ***Hall B (Salonul Oglinzilor)***

1. **P. Religa**
Cellular mechanisms of vascular structure formation

2. **Carola Foerster**
Role of the blood brain barrier in secondary brain injury development - folly adaptations for survival?

3. **D. Frenkel**
Immunotherapy of cerebrovascular amyloidosis in a transgenic mouse model

4. **B.O. Popescu**
Alteration of blood-brain barrier in neurodegenerative diseases

S13-1

CELLULAR MECHANISMS OF VASCULAR STRUCTURE FORMATION

Piotr Religa
Karolinska Institutet, Stockholm, Sweden
piotr.religa@ki.se

The changes in the vascular structure occur in the most chronic diseases. In cancer, most vessels do not fit into the conventional hierarchy of arterioles, capillaries and venules. Abnormalities involve all components of the vessel wall: endothelial cells, mural cells and basement membrane. Despite the abnormalities, most tumor vessels do have endothelial cells and pericytes. Alzheimer disease (AD) is associated with accumulation of amyloid-beta peptide (Aβ) and microvascular changes in brain that impair blood flow. Combination of these factors can lead to progression of AD. During vasculogenesis, formation of first blood vessels is achieved by differentiation of hemangiogenic stem cells from pluripotent mesenchymal cells, while during angiogenesis new blood vessels form from already existing vessels. The newly formed vessels are composed of endothelial cells and are not stable. Mural cells such as pericytes and smooth muscle cells guide maturation of vessels and their stabilisation. The vessels become also specialized. Unstable vessels go into regression. Our research explores mechanisms involved in formation of vascular structure in cancer and Alzheimer disease.Our performed study indicates that VEGF affects small vessels and change vascular structure by affecting endothelial cells and smooth muscle cells.

S13-2

ROLE OF THE BLOOD BRAIN BARRIER IN SECONDARY BRAIN INJURY DEVELOPMENT - FOLLY ADAPTATIONS FOR SURVIVAL?

Ellaine Salvador[1], Winfried Neuhaus[1], Herman Koepsell[2], Serge Thal[3], Carola Förster[1]

[1] *Department of Anesthesia and Critical Care, University Wuerzburg, Germany*

[2] *Departement of Anatomy and Cell Biology I, University Wuerzburg, Germany*

[3] *Klinik für Anästhesiologie, University Mainz, Germany*

Foerster_C@klinik.uni-wuerzburg.de

Traumatic brain injury (TBI) is the leading cause of death in children and young adults globally. Malignant cerebral edema plays a major role in the pathophysiology which evolves after severe TBI. Added to this is the significant morbidity and mortality from cerebral edema associated with acute stroke, hypoxic ischemic coma, neurological cancers and brain infection. Therapeutic strategies to prevent cerebral edema are limited and if brain swelling persists beyond 24 h, the risks of permanent brain damage or mortality are greatly exacerbated.

During traumatic brain injury (TBI) and stroke, both, oxygen and glucose deprivation (OGD) may be encountered. Due to a higher demand for glucose in the brain in these cases, enhanced levels of glucose transporters are expressed, facilitated glucose transporter-1 (GLUT1) and sodium-dependent glucose transporter-1 (SGLT1). Besides their function as energy supply, glucose may influence brain water homeostasis by a direct hygroscopic effect; a possible cause for early brain edema formation. The present study investigated the expression of sodium-dependent glucose transporters (SGLT) and the effect of their deficiency on brain edema formation after experimental TBI.

S13-3

IMMUNOTHERAPY OF CEREBROVASCULAR AMYLOIDOSIS IN A TRANSGENIC MOUSE MODEL

V. Lifshitz, R. Weiss, D. Frenkel
Department of Neurobiology, George S. Wise Faculty of Life Sciences, The Department of Neurobiology, Tel Aviv University, Tel Aviv, Israel
dfrenkel@post.tau.ac.il

Cerebrovascular amyloidosis (CA) is due to amyloid accumulation in the vessel walls leading to hemorrhagic stroke, and cognitive impairment. CA increases dramatically with age, affecting more than 40% of people over the age of 80 years, and is found in 80% of Alzheimer's disease (AD) cases. Transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine has profound effects on vasculogenesis, angiogenesis, and vessel wall integrity expression levels. TGF-β1 levels correlate positively with the degree of cerebrovascular amyloid in AD cases. We found that over-expression of TGF-β1 in glia cells affects endothelial cells and peripheral immune cross talk, leading to a reduction in macrophage activity, and to an age-related deposition of amyloid around cerebral blood vessels. Weekly nasal vaccination of the proteosome-based adjuvant, Protollin, which is well tolerated in humans, potently decreases vascular amyloid in 13-month-old TGF-ß1 mice following six weeks of treatment. Using MRI we found that while PBS treated animals showed a significant enlargement of the lateral ventricles area, Protollin prevents further brain damage. Using an object recognition test, we found significant improvement in cognition with the Protollin treated group. Our results suggest a novel approach toward therapy for CA utilization of a compound that has been safely tested in humans.

S13-4

ALTERATION OF BLOOD-BRAIN BARRIER IN NEURODEGENERATIVE DISEASES

Bogdan O. Popescu
Department of Neurology, University Hospital, School of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
"Victor Babeş" National Institute of Pathology, Bucharest, Romania
bogdan.popescu@jcmm.org

Neurodegenerative disorders represent frequent pathologies in the elderly, affecting more than 7% of the population over 65's and their prevalence further increases with age. Current treatments for neurodegenerative conditions are only symptomatic and all recent clinical trials designed to identify disease modifying drugs failed. Even though new pathogenic mechanisms in neurodegeneration might be still unraveled, the strategy of counteracting only one such mechanism will probably continue to fail at a clinical level. Recently, different research groups including our own identified blood-brain barrier (BBB) alteration as an aggravating factor for neurodegeneration. Many patients with Alzheimer's disease (AD) or other neurodegenerative disorders were documented to have BBB permeability alteration. No drug target at the BBB level has been clinically tested yet. In this paper I review the data in the field and I present our studies regarding altered expression of tight junction proteins, such as occludin and claudins, in AD and vascular dementia brains.
This paper is supported by the Sectorial Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64109.

S-14 Symposium
"*Response to oxidative stress*"

Chaired by: Eugenia Manukhina, P. Singal

Date: ***Friday, June 8th***
Starting time: ***08:30***
Location: ***Hall B (Salonul Oglinzilor)***

1. **P. Singal**
Subcellular adaptations in response to oxidative stress

2. **A. Srivastava**
Modulation of Oxidant-induced signaling by calcium and calmodulin system in vascular smooth muscle cells

3. **Eugenia Manukhina**
Prevention of Nitric Oxide Overproduction in Protective Effects of Adaptation to Hypoxia

4. **Madhu B. Anand-Srivastava**
Role of ROS in G Protein Expression and signaling in Hypertension

S14-1

SUBCELLULAR ADAPTATIONS IN RESPONSE TO OXIDATIVE STRESS

Pawan K. Singal
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre
Winnipeg, Canada
PSingal@sbrc.ca

It is known that overproduction of the proinflammatory cytokine, tumor necrosis factor (TNFα), provokes tissue injury and organ failure. TNFα has also been shown to be cardiodepressant and is considered to be responsible for various cardiovascular complications. Another cytokine, interleukin-10 (IL-10), has been shown to have anti-inflammatory properties. We have shown that IL-10 counterbalances many adverse cardiac effects of TNFα. TNFα-induced oxidative stress as well as apoptosis were also shown to be mitigated by IL-10. Moreover, improvement in cardiac function after treatment with various drugs was also shown to be associated with an increase in IL-10 content. Based on these data, it is suggested that an optimal balance between IL-10 and TNFα may be a new therapeutic strategy for maintaining cardiac function in adverse conditions. Supported by the Canadian Institutes of Health Research.

S14-2

MODULATION OF OXIDANT-INDUCED SIGNALING BY CALCIUM AND CALMODULIN SYSTEM IN VASCULAR SMOOTH MUSCLE CELLS

Ashok K. Srivastava
Research Centre, Centre hospitalier de l'Université de Montréal (CHUM), Montreal, Canada
ashok.srivastava@umontreal.ca

Increased oxidative stress has been implicated in the pathophysiology of cardiovascular diseases. However, the precise mechanisms by which oxidants contribute to the development of these diseases are not fully identified. Previous work from our laboratory has demonstrated that exogenous hydrogen peroxide (H_2O_2) activates several protein kinases, such as extracellular signal regulated kinase1 and 2 (ERK1/2) and protein kinase B (PKB), key mediators of growth promoting, proliferative and hypertrophic responses in vascular smooth muscle cells (VSMC). Here, by using pharmacological and molecular inhibitors we have investigated a potential role of Ca^{2+}, calmodulin (CaM), and CaM-dependent protein kinase II (CaMKII) in H_2O_2-induced phosphorylation of ERK1/2 and PKB. BAPTA-AM, Calmidazolium and W-7, KN-93 specific inhibitors/ antagonists of Ca^{2+}, CaM and CaMKII, attenuated H_2O_2 and glucose/glucose oxidase-induced ERK1/2 and PKB phosphorylation in a dose-dependent fashion. Transfection of VSMC with CaMKII auto-inhibitory peptide (AIP) corresponding to auto-inhibitory domain (AA 281-309) of CaMKII or with siRNA of CaMKIIα, attenuated H_2O_2-induced phosphorylation of ERK1/2 and PKB. In addition, calmidazolium and KN-93 blocked H_2O_2-induced Pyk2 and IGF-1R phosphorylation. H_2O_2 treatment also induced Thr286 phosphorylation of CaMKII which was inhibited by both calmidazolium and KN-93. These results demonstrate that Ca^{2+}-dependent pathways play a critical role in triggering oxidant-induced signaling events in VSMC. Supported by CIHR.

S14-3

PREVENTION OF NITRIC OXIDE OVERPRODUCTION IN PROTECTIVE EFFECTS OF ADAPTATION TO HYPOXIA

Eugenia B. Manukhina[1,2]
Ludmila M. Belkina[1], Olga L. Terekhina[1], Denis V. Abramochkin[2],
Anna V. Goryacheva[1], Robert T. Mallet[3], H. Fred Downey[3]
[1]Institute of General Pathology and Pathophysiology, Moscow, Russia;
[2]M.V. Lomonosov Moscow State University;
[3]University of North Texas Health Science Center, Fort Worth, USA
Eugenia.Manukhina@unthsc.edu

Nitric oxide (NO) overproduction is a detrimental factor involved in pathogenesis of many diseases. In addition, to direct toxic effects of excessive NO, it reacts with superoxide to produce peroxynitrite, an extremely strong oxidant that damages lipids, DNA, carbohydrates and proteins. Adaptation to hypoxia (AH) is known to be protective to the cardiovascular system. The present study was focused on the role of preventing NO overproduction and alleviating nitrosative stress in adaptation protection against ischemia and reperfusion (IR) injury of the myocardium and blood vessels in rats. AH considerably restricted IR arrhythmias, myocardial infarct size, and endothelial dysfunction of coronary and non-coronary blood vessels. AH completely prevented the IR-induced NO overproduction and accumulation of 3-nitrotyrosine, a marker of nitrosative stress in the left ventricle. Also, AH increased efficiency of NO storage in the vascular wall. Therefore, AH cardioprotection is associated with prevention of NO toxicity in myocardium during IR. Mechanisms for this cardioprotection may include reduced expression and/or activity of NO synthases, and enhanced NO binding to NO stores in vascular walls. In addition, the slight increase in NO production associated with AH may prevent the subsequent NO overproduction by a negative feedback mechanism. Supported by RFBR grant # 10-04-00980.

S14-4

ROLE OF ROS IN G PROTEIN EXPRESSION AND SIGNALING IN HYPERTENSION

Madhu B. Anand-Srivastava
Department of Physiology, Faculty of Medicine, University of Montreal, Montreal, Canada
ashok.srivastava@umontreal.ca

Reactive oxygen species(ROS) that cause oxidative stress play a major role in the pathophysioloy of cardiovascular diseases including hypertension. We have previously shown an enhanced expression of Giα proteins in VSMC from SHR. The present study was undertaken to examine the role of ROS and ROS-mediated signaling in enhanced expression of Giα proteins in vascular smooth muscle cells (VSMC) from SHR. The enhanced expression of Giα-2 and Giα-3 proteins in VSMC from SHR compared to WKY was attenuated by antioxidants such as N-acetyl-L-cysteine (NAC) or diphenyleneiodonium (DPI), captopril, losartan and AG1478, inhibitors of angiotensin converting enzyme, AT1 receptor and epidermal growth factor receptor (EGFR) respectively as well as by the siRNAs of AT1, cSrc and EGFR. Furthermore, the enhanced phosphorylation of EGFR in VSMC from SHR was also restored to control levels by captopril, losartan, PP2, a c-Src inhibitor and N-acetyl-L-cysteine (NAC), whereas enhanced ERK1/2 phosphorylation was attenuated by captopril, losartan, NAC and DPI. Furthermore, NAC also restored the enhanced phosphorylation of c-Src in SHR to control levels. These results suggest that the enhanced levels of endogenous Ang II in VSMC from SHR, transactivate EGFR, which through MAP kinase signaling, enhances the expression of Giα proteins and associated adenylyl cyclase signaling. Supported by grant from CIHR.

S-15 Symposium
"Telocytes"
- I -

Chaired by: G. Bussolati, X. Wang

Date: ***Friday, June 8th***
Starting time: 17:00
Location: ***Main Hall (Ronda)***

1. **X. Wang**
Variation of lung telocytes among human, mouse and rat, and their gene analysis comparing with mesenchymal stem cells and fibroblasts

2. **M.C. Rusu**
Microanatomy of telocytes

3. **Laura-C. Ceafalan**
Telocytes and/or pericytes

4. **G. Bussolati**
Telocytes as origin of GISTs/PEComas

5. **G. Radenkovic**
Patterns of occurrence of interstitial cells of Cajal in the human digestive tract

S15-1

VARIATION OF LUNG TELOCYTES AMONG HUMAN, MOUSE AND RAT, AND THEIR GENE ANALYSIS COMPARING WITH MESENCHYMAL STEM CELLS AND FIBROBLASTS

Yonghua Zheng[1,2], Miaomiao Zhang [3,4], Mengjia Qian [3,4], Chunxue Bai[1,2], Xiangdong Wang[1-4]

[1]Department of Respiratory Medicine, [2]Biomedical Research Center, [3]Shanghai Respiratory Research Institute, [4]Shanghai Key Laboratory of Organ Transplantation, Zhongshan Hospital, Fudan University, Shanghai, China

xiangdong.wang@clintransmed.org

Telocytes have been recently found as one of interstitial cells, with the characteristic of small cellular body and extremely long telopodes, although the functions and phenotypes remain unclear. The present studies aimed at investigating morphological differences of telocytes among species and locations, and specificities of gene profiles between telocytes, mesenchymal stem cells and fibroblasts. We compared lung telocytes among human, mouse and rat and different organs/tissues within rats or mice. We found similar distributions of telocytes within the lung among human, mouse and rat, while the cellular body of lung telocytes in human was longer and flatter with longer telopodes and had more granular materials both in cellular body and telopodes in human, as compared with mouse or rat. About 4000-5000 genes varied between telocytes and others, of which more than 100, 50 or 30 folds of up-regulated genes were 4, 9, or 17 vs stem cells and 10, 20, or 30 vs fibroblasts, respectively. Thus, our data evidencd morphological variations of telocytes between species and organs and different gene profiles of telocytes from mesenchymal stem cells and fibroblast.

S15-2

MICROANATOMY OF TELOCYTES

Mugurel C. Rusu
Anatomy Department, Dental School,
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
anatomon@gmail.com

Telocytes (TCs) are stromal cells which, differently to canonical fibroblasts, are not involved in collagen synthesis. TCs are defined by their moniliform prolongations, the telopodes (Tps). Transmission electron microscopy (TEM) is the only reliable tool to identify TCs/Tps. We evaluated in TEM various tissues: (a) human tongue, larynx, greater omentum, heart, eye iris, trigeminal and stellate ganglia, major salivary glands, oral mucosa, and skin; (b) rat trachea, esophagus, thymus, and heart. Additional immunohistochemical tests using antibodies for CD117/c-kit, CD34, PDGFR-α, vimentin, and alpha-smooth muscle actin were performed. We got ultrastructural evidences of TCs/Tp in the examined samples. Telocytes: (a) build stromal networks, shed vesicles and exosomes; (b) build cellular tandems with other stromal cells; (c) associate with endothelial cells and pericytes; (d) build concentric perineural layers. Hybrid morphologies and/or lack of telopodes complicate the diagnostic of TCs on grids. TEM results are better evaluated when the same samples are labeled with specific antibodies, especially those for the cytokines receptors CD117/c-kit and PDGFR. Stromal networking and signaling, ensured by TCs, and their close relations with various other stromal cells support a stromal signaling/firing system to be postulated. Funding: POSDRU/89/1.5/S/64153.

S15-3

TELOCYTES AND/OR PERICYTES

Laura-C. Ceafalan
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
"Victor Babeş" National Institute of Pathology, Bucharest, Romania
lauraceafalan@yahoo.com

A new line of evidence suggested that, in skeletal muscle, the perivascular compartment represents a complex microenvironment, with more elaborated functions than pericytes, the archetypal phenotype of pericapillary cells. In such areas, a niche for mesenchymal stem cells was recently described. Even though most perivascular cells share a set of markers, they eventually acquire a function related phenotype. Disputed processes such as tissue remodeling and repair rely on angiogenesis. Therefore, a hypothetical continuum, from mesenchymal cells to extracellular matrix secreting fibroblasts and to blood vessel contractile phenotypes (pericytes or smooth muscle cells), must be taken into consideration.

Recently, we demonstrated that this line of differentiation contains a new type of interstitial cells, the telocytes. Based on their particular morphology, they were detected in the perivascular compartment in many different organs. They share some pericytes markers, like PDGFRβ, involved in vessel mural coat recruitment and maintenance, but they also express growth factors like VEGF, the trigger for angiogenesis. Telocytes might represent a versatile population capable of acquiring different fates depending on tissue distribution, including microvessel recruitment and pericyte differentiation.

In view of such recent findings, the identity of the cells categorized so far as pericytes by their immunophenotype should be reconsidered.

S15-4

TELOCYTES AS ORIGIN OF GISTS/PECOMAS

Gianni Bussolati[1,2], Carmen Ardeleanu[1]
[1] *"Victor Babeş" Institute, Bucharest, Romania*
[2] *Dept. Biomedical Science and Human Oncology - University of Torino, Italy*
gianni.bussolati@unito.it

Immuno-phenotypic and structural data provide evidence for tracing tumors of telocyte origin. We advanced the hypothesis that rare stromal tumors of debated origin might derive from Telocytes. In fact, a fraction of both PEComas (peri-endothelial cell tumors) and GISTs (gastro-intestinal and extra-gastrointestinal stromal tumors) share expression of markers described in Telocytes, .such as Melan A, MiTF. CD63, c-KIT (CD117), CD34, S-100, SMA and VEGF. The hypothesis implies the existence, rather than of a uniform entity, of a spectrum of lesions expressing different markers according to the location and the differentiation status. Significantly, Telocytes show distinctive ultrastructural features with thin, extended, projections loaded with vesicles and micro-vescicles loading tumor cells have been described in a fraction of GISTs and of PEComas. In a series of 40 cases of GISTs we have now searched for the expression of markers described also in Telocytes, but proper of Melanomas while typical of PEComas and of CD63, a tetraspanin protein originally described in melanomas and marking exosomes. The results confirm the variability of expression and the existence of a spectrum of differentiation.
Study conducted with the support of: Project PERSOTHER - SMIS-CSNR: 549/12.024

S15-5

PATTERNS OF OCCURRENCE OF INTERSTITIAL CELLS OF CAJAL IN THE HUMAN DIGESTIVE TRACT

Goran Radenkovic
Dept. Histology & Embryology, University of Nis Faculty of Medicine, Nis, Serbia
radenkog@gmail.com

Although the exact role of Interstitial Cells of Cajal (ICC) is still controversial, it is well known that these specialized network-forming cells are involved in the control of digestive motility. It has been also confirmed that ICC are reduced or otherwise affected in several dysmotilities. That is the reason why ICC have a central place in the research dealing with gastrointestinal contractions.

ICC depend on stem cell factor (SCF) signaling via Kit for development and maintenance. Recent studies have shown that ICC are not derived from the neural crest, but rather are mesodermal in origin. However, some findings suggest that the cells present in the inception myenteric plexus (MP) and submucous plexus (SMP) ganglia are "responsible" for ICC differentiation, representing probably the source of SCF.

At the end of the embryonic period of human development, c-kit immunoreactive (c-kit IR) cells form an uninterrupted wide belt, extending throughout the esophagus, stomach (except for the fundus), to the proximal part of duodenum, around the inception of the MP ganglia. C-kit IR cells appear in the distal duodenum and other parts of the gut originating from the midgut, in the beginning of the fetal period of development, in the form of narrow linear rows of cells, situated at the level of the MP. The pattern of appearance of c-kit IR cells in the distal colon differs from that in the other parts of the digestive tract. In terms of three dimensions, these cells are arranged in two concentric tubes, one at the MP level, the other at the luminal surface of the circular layer of the tunica muscularis, at the SMP level. Simultaneous appearance of ICC at the SMP and MP levels in the terminal portion of the colon can be explained by the fact that there are differences in the migration of vagal neural crest cells in particular portions of the digestive tube.

S-16 Symposium
"*Physical activity in adaptive medicine*"

Chaired by: V. Adams, CH Kuo

Date: ***Sunday, June 10th***
Starting time: ***08:30***
Location: ***Hall A (Rapsodia)***

1. **V. Adams**
Molecular alterations in the skeletal and diaphragmatic muscle in heart failure: Impact of exercise training

2. **Shyi-Wu Wang**
Effect of passive repetitive isokinetic training on plasma interleukin (IL-6 and IL-15)

3. **M. Chia**
Focus on fitness and fatness in youth - foolhardy or foolproof?

4. **CH. Kuo**
Physical activity and insulin resistance

5. **I. Ehrenburg**
Interval exercise training and interval hypoxic training in coronary heart disease patients

S16-1

MOLECULAR ALTERATIONS IN THE SKELETAL AND DIAPHRAGMATIC MUSCLE IN HEART FAILURE: IMPACT OF EXERCISE TRAINING

Volker Adams
Heart Center Leipzig, Germany
adav@med.uni-leipzig.de

During the last century, it became more and more evident, that in patients with chronic heart failure the leading symptom exercise intolerance is mainly determined by alterations in the skeletal and diaphragmatic muscle. In addition several studies documented that exercise training is a powerful secondary prevention tool to improve exercise intolerance. With respect to skeletal and diaphragmatic muscle different molecular analysis techniques identified several cellular systems to be affected in CHF and modulated by exercise training programmes. During the presentation several of them will be discussed including:

- Inflammatory system in the skeletal muscle
- Generation and detoxification of reactive oxygen species
- Anabolic and catabolic imbalance due to modulation of the ubiquitin proteasome system
- Occurrence of apoptosis
- Modification of relevant proteins of the contractile machinery by carbonylation and ubiquitinylation

S16-2

EFFECT OF PASSIVE REPETITIVE ISOKINETIC TRAINING ON PLASMA INTERLEUKIN (IL-6 AND IL-15)

Shyi-Wu Wang[1]*, Shu-Lin Lee[2], Kenny Wen-Chyuan Chen[3], Mei-Chich Hsu[4], Mao-Kuan Su[5]

[1]Dept. of Physiol. & Pharmacol., Chang-Gung Univ., Taoyuan, [2]Dept Nutrit. & Health Sci., Chung Chou Ins. Tech, Changhua, [3]Dept. Phys. Edu., Chang Gung Tech. Univ., Taoyuan, [4]Inst Sports Sci., Natl. Taiwan, Sport Univ, Taoyuan, [5]Phys. Edu. Room, Chang-Gung Univ., Taoyuan, Taiwan

swwang@mail.cgu.edu.tw

The aim of the present study is to investigate the changes of plasma IL-6 and IL-15 during and after passive repetitive isokinetic (PRI) training. For the first experiment, thirty young male subjects were enrolled into the ten-week PRI training program and were divided randomly into traditional, low- and high-intensity PRI training groups. Another twenty-two male soccer athletes were recruited into the second experiment, which acute heavy-resistance exercise tests (AHRETs) were exerted before and after the ten-week PRI training. In this study, these subjects were divided into low and high-intensity PRI training groups. Blood sample were collected before and after training immediately. Plasma cytokines' concentrations were measured by ELISA. Significant increased plasma IL-6 was found after high-intensity PRI training. Gradually increased IL-15 level was observed during exercise and to a highest level at post 0 D after low-intensity PRI-training, then decreased gradually during the recovery period. In the second experiment, significant increase of IL-6 was observed at post 120 h after low-intensity PRI training. Significant increase of plasma IL-15 was found at post 0.5, 72, and 120 h, respectively, after PRI training. Our results showed that significant increased plasma IL-15 was observed after AHRET after low- and high-intensity PRI-training.

S16-3

FOCUS ON FITNESS AND FATNESS IN ASIAN YOUTH- FOOLHARDY OR FOOLPROOF?

Michael Chia
National Institute of Education, Nanyang Technological University, Singapore
michael.chia@nie.edu.sg

The keynote address will critically address the oft-held wisdoms of the appropriate amounts of body fatness in child development through pre-adolescence, adolescence and young adulthood and examine the reasons why Singaporean youths lead entrenched sedentary lifestyles. Cogent evidence in adulthood links a lack of physical activity and excessive body fatness with certain disease states like metabolic syndrome and some cancer forms, yet the issues of bodyweight satisfaction and disordered eating among Singaporean youths also need to be addressed. The case for a holistic physical education will be espoused.

S16-4

ALTITUDE TRAINING AS A POWERFUL INTERVENTION IN THE TREATMENT OF INSULIN RESISTANCE

Shu-Man Chen, Chia-Hua Kuo
Committee for General Education, Shih Hsin University, Taipei, Taiwan
Department of Sports Sciences, Taipei Physical Education College, Taipei, Taiwan
kuochiahua@gmail.com

Oxygen is the final acceptor of the electron transported from fat and carbohydrate oxidation, which is the rate-limiting factor for cellular ATP production. Prolonged moderate altitude hypoxia (ranged from 1700 to 2400 M), but not acute high attitude hypoxia (above 4000 M), can effectively improve insulin sensitivity and glucose tolerance for humans and antagonizes obese phenotype in the animals with the genetic defect. In humans, the magnitude of the improvement is varying widely and correlated with baseline plasma DHEA-S levels. Compared to training at sea-level, training at altitude effectively decreases fat mass in parallel with increased muscle mass. This change may be associated with increased perfusion of insulin and fuel towards skeletal muscle that favors muscle competing postprandial fuel in circulation against adipose tissues.

S16-5

INTERVAL EXERCISE TRAINING AND INTERVAL HYPOXIC TRAINING IN CORONARY ARTERY DISEASE PATIENTS

Igor Ehrenburg
Alexey Gorbatchenkov, Ludmila Kotlyarova
Russian State Medical University, Moscow, Russia
igorehrenburg@mail.ru

The effects of interval exercise training (ET) on cycle ergometer (20-60 sessions, 5 or a week) and interval hypoxic training (HT) (15-30 sessions of passive intermittent hypoxia gas mixture breathing, 5 sessions a week) on exercise tolerance and arterial oxygen content in coronary artery disease patients were investigated. The increase of exercise tolerance was more pronounced in the ET group, and appeared only after 15 training sessions in both groups. Plateau of training effect was observed after 60 sessions in ET and after 25 sessions in HT. The training effect of HT was mainly due to the improved of the external lung function and increase of arterial oxygen content. We suggest that HT can be added to the exercise rehabilitation programs in coronary artery disease patients and also may be a save tool to increase aerobic capacity and exercise tolerance in the cases of objective and subjective contraindications to ET. Other possibility is to start the rehabilitation with HT and then switch it to the combination of ET and HT.

S-17 Symposium
"Telocytes"
- II -

Chaired by: D. Cai, Maria Simonetta Faussone Pellegrini

Date: ***Saturday, June 9th***
Starting time: ***12:00***
Location: ***Hall B (Salonul Oglinzilor)***

1. **D. Cai**
Cardiac telocytes in infarcted myocardium

2. **Mihaela Gherghiceanu**
Telocyte junctions: transcellular communication

3. **S. Kostin**
Telocytes and myocardial pathology

4. **M. Taggart**
A critical appraisal of the role(s) of smooth muscle caveolae

5. **T. Gevaert**
From interstitial cells to telocytes in the urinary tract: probably more than passive bystanders

S17-1

CARDIAC TELOCYTES IN INFARCTED MYOCARDIUM

Cai Dongqing
Key Laboratory for Regenerative Medicine, Ministry of Education, Ji Nan University, Guangzhou, China
International Base of Collaboration for Science and Technology (JNU), The Ministry of Science and Technology & Guangdong Province, China
Department of Developmental & Regenerative Biology, Ji Nan University
tdongbme@jnu.edu.cn

Recently, a novel interstitial cell, named as telocyte, is found in myocardium. In our previous study, we reported that the density of cardiac telocytes in base part and the atrium-atria part was significantly higher than that in medium part. In addition, the density of cardaic telocytes in subepicardium was significantly higher than that in the endocardium. However, whether the distribution of cardaic telocytes is experienced change under the MI is still unclear. Our recent studies showed that the density of cardiac telocytes after MI was decreased significantly comparing with non-LAD ligated control group. In addition, it was found that the density of cardiac telocytes was decreased consecutively. In addition, our preliminary results revealed that intramyocardium injection of cardiac telocytes was able to improve the function of infarcted heart after MI. Our findings suggested that cardiac telocytes play an important role in integrity of myocardium and regeneration of MI.

S17-2

TELOCYTE JUNCTIONS: TRANSCELLULAR COMMUNICATION

Mihaela Gherghiceanu
"Victor Babeş" National Institute of Pathology, Bucharest, Romania
mihaela.gherghiceanu@ivb.ro

Telocytes (TCs) form an interstitial network in adult heart. Using electron microscopy (EM) and electron microscope tomography (ET), we investigated the TC's interstitial network and found that TCs establish 'atypical' junctions with virtually all types of cells into the heart. EM and ET showed different types of homocellular junctions connecting TCs in the network (puncta adhaerentia minima, processus adhaerentes and manubria adhaerentia). TCs and CMs are directly connected by 'dot' junctions with nanocontacts or asymmetric junctions. Junctions between stem cells and TCs are either 'stromal synapses' or adhaerens junctions. TCs have direct cell-cell nanocontacts with Schwann cells, endothelial cells and pericytes. All these heterocellular contacts occur by means of minute junctions (point contacts, nanocontacts and planar contacts; 10-30 nm). Therefore, the TC's cardiac network shape the structural support requisite to integrate the overall 'information' from vascular system (endothelial cells and pericytes), nervous system (Schwann cells), immune system (macrophages, mast cells), interstitium (fibroblasts, extracellular matrix), stem cells/progenitors and working cardiomyocytes. This integrative interstitial system might sustain a coordination of multicellular signals, essential for cardiac renewal, regeneration and repair.

This work is supported by the Sectoral Operational Programme Human Resources Development, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64109.

S17-3

TELOCYTES AND MYOCARDIAL PATHOLOGY

Sawa Kostin
Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany
Sawa.Kostin@mpi-bn.mpg.de

Myocardial remodelling during heart failure involves the extracelluar matrix (ECM). Telocytes (TC) are a novel type of myocardial interstitial cells. This study aims at clarifying the role of TCs in ECM remodelling. Human samples from patients with dilated, ischemic or inflammatory cardiomyopathy were analyzed using electron and confocal microscopy. It has been revealed that the number of TCs and telopodes decreased more than two- to three fold in diseased human hearts as compared to controls. A significant correlation was found to exist between the amount of fibrillar collagens and the decrease of TCs in patients with cardiomyopathy. However, the amount of denaturated collagens and an increase in the MMP/TIMP ratio was associated with increased numbers of TCs. Taken together, this study demonstrates that TCs and telopodes are very flexible cell/structures and respond promptly to any quantitative and qualitative change in the ECM composition. Specifically, the number of TCs in diverse cardiac diseases correlates negatively with the degree of fibrosis and mature fibrillar collagens, and correlates positively with denaturated collagens and the number of immunocompetent cells. Thius may further impact the treatment of heart failure in the future.

S17-4

A CRITICAL APPRAISAL OF THE ROLE(S) OF SMOOTH MUSCLE CAVEOLAE

Michael J. Taggart
Institute of Cellular Medicine, Newcastle University, UK
michael.taggart@newcastle.ac.uk

It is 60 years since the pivotal electron microscopic findings of Palade described omega-shaped invaginations of the plasmalemma now termed caveolae. Today we remain curious about the exact roles of these structures in regulating spatiotemporal signalling. The last decade has witnessed considerable advances but there also remains controversies and inconsistencies that need resolving. In smooth muscle caveolae are often closely spaced, within a few nanometres, to components of peripheral sarcoplasmic reticulum. Ablation of caveola, e.g. by knockdown of one of their integral protein components caveolin, results in changes in Ca^{2+} signalling at a local (Ca^{2+} sparks) and global (Ca^{2+} waves) level. Caveolins also regulate the (re)localisation of contractile or relaxatory signalling molecules. Both these findings support the notion that the subcellular spaces created by the caveolae invaginations offer a biophysically favourable environment for amplification of signal transduction. Current important considerationsin the field are (i) In mechanosensitive cells such as smooth muscle, do caveolae act as mechanotransducers? (ii) Are all the proposed molecular interactions with caveolin/caveolae possible in one vascular cell type? (iii) What roles are there for other integral proteins of caveolae? Finally, how similar are the roles of caveolae in smooth muscle compared to other cell types?

S17-5

FROM INTERSTITIAL CELLS TO TELOCYTES IN THE URINARY TRACT: PROBABLY MORE THAN PASSIVE BYSTANDERS

Thomas Gevaert
Université catholique de Louvain, Brussels, Belgium
Thomas.Gevaert@med.kuleuven.be

For many years interstitial cells have been studied in bladder. Two main populations have been described: directly underneath the urothelium and in between the detrusor smooth muscle bundles. Besides morphological characterisation many functional data have been presented. Some populations are thought to fulfil a sensing role whilst others might have pacemaking properties.

It is remarkable that a heterogeneous terminology has been used for interstitial cells in bladder: myofibroblasts, interstitial cells of Cajal or interstitial Cajal-like cells. Reasons for this diverse nomenclature might be the use of different experimental methods (electron microscopy versus light microscopy and immunohistochemistry) and the use of different tissue hosts (human versus animals).

Recently a novel stromal cell type was discovered and termed telocytes. These cells are unique due to the presence of their telopodes. Telocytes are organized in networks and interconnected with gap junctions. Furthermore these cells have a close relation with nerve endings, capillaries and inflammatory cells. In human bladder telocytes have recently been characterized underneath the urothelium. Furthermore changes in telocyte phenotype have been found in bladder disease. In this presentation the localization and function of interstitial cells in bladder is discussed with specific emphasis on the telocyte-population.

S-18 Symposium
"*Measuring health*"

Chaired by: F.A.C. Wiegant, Y. Kawai

Date: ***Saturday, June 9th***
Starting time: ***12:00***
Location: ***Main Hall (Ronda)***

1. **F.A.C. Wiegant**
The challenge of measuring "health" using the ability to adapt

2. **Mei-Chich Hsu**
Effects of swimming on metformin levels and insulin sensitivity in insulin resistant rats

3. **Y. Kawai**
Effects of lower body positive pressure on cardiovascular functions

4. **Shin-Da Lee**
Anti-apoptotic and pro-survival effects of exercise training on hypertensive hearts

5. **H. Morita**
Cardiovascular adaptation/deconditioning in gravitational change

S18-1

THE CHALLENGE OF MEASURING 'HEALTH' USING THE ABILITY TO ADAPT

Fred A.C. Wiegant
M.H. Bakker, W. Dijk, H.A.B. Prins, M.A.S. Huber
Institute of Education, Department of Biology, Faculty of Science, University College Utrecht, The Netherlands
F.A.C.Wiegant@uu.nl

The pathophysiology of disease has dominated the scientific world ever since Hippocrates. Lately, however, renewed interest has been observed in the physiological background of the phenomenon of 'health'. Even though this phenomenon has been defined in many different ways, an encompassing definition that can be aptly used by the scientific community to measure and quantify health has yet to be found. Processes known to underlie health are homeostasis, allostasis, salutogenesis, resilience and robustness. Together, they become especially important during times of stress and disbalance, making the body adapt to a certain 'threat' and ensuring proper functioning of the body. Focus on this ability to adapt could aid in defining health, and making health, as such, measurable and quantifiable. Bodily adaptations can, for example, be measured via a variety of changes in biomarkers and parameters, which link to various organ systems. Potentially, specific stressors could be applied in research, to which allostatic and homeostatic responses of tested individuals might be measured. The addition of this dynamic (adaptive) component to our current definitions of health would, thereby, mean a step forward in health research and could stimulate the development of new therapeutic strategies, optimizing current and future (preventive) health care.

S18-2

EFFECTS OF SWIMMING ON METFORMIN LEVELS AND INSULIN SENSITIVITY IN INSULIN RESISTANT RATS

Mei-Chich Hsu[1],
Kuei-Yu Chien[1], Chia-Hua Kuo[2], Chi-Chang Huan[1], Ku-Fu Hsu[1]
[1]Graduate Institute of Sports Science, National Taiwan Sport University, Taoyuan, Taiwan, [2]Laboratory of Exercise Biochemistry,Taipei Physical Education College, Taipei, Taiwan
meichich@gmail.com

Exercise or metformin medication is widely considered to increase insulin sensitivity and protect against type 2 diabetes. We evaluated the swimming and swimming training effects on the disposition and pharmacokinetics of metformin. Both glucose and insulin levels were examined as well. For the single bout swimming effect study, rats with fructose-induced insulin resistance were assigned into four groups: control group (C, n=8), metformin group (M, n=8), swimming group (S, n=8) and metformin with swimming group (MS, n=8). After 12 h of fasting, the S and MS group swam for 45 min, while the M and C groups were placed in 4 cm deep water for the same time period. For the 4-wk swimming training effect study, fructose-induced insulin resistant rats were assigned into two groups (n=6/group): swimming training with metformin (SM), and non-swimming training with metformin (CM). Blood samples were collected from 12 h-fasted rats at baseline and at different time points after an oral glucose tolerance test (OGTT) with administration of a single dose of metformin. The results from the single bout swimming effect study showed that the MS group increased the time to the maximum concentration, the time to half-life concentration and enhanced insulin sensitivity. This study suggested that swimming before administration of metformin significantly improved insulin sensitivity and the rate of metformin absorption. Results from the 4-wk swimming training effect study revealed that both glucose and insulin levels in the SM group were significantly lower than those in the CM group at 15 min following OGTT. The maximum concentration and area under the serum concentration-time curve for the SM group were significantly lower than CM group. Apparent volume of the distribution and the time-averaged total body clearance for the SM group were significantly faster than M group. There were no significant differences in the time to maximum concentration or the time to half-life concentration between two groups. Our data demonstrate that swimming training reduce the serum levels of metformin. This study revealed that swimming training decreases the metformin accumulation and has addictive effects on the glucose and insulin response to metformin administration in insulin resistant rats.

S18-3

EFFECTS OF LOWER BODY POSITIVE PRESSURE ON CARDIOVASCULAR FUNCTIONS

Yasuaki Kawai, Satoshi Matsuo
Department of Adaptation Physiology, Faculty of Medicine, Tottori University, Yonago, Japan
kawai@med.tottori-u.ac.jp

Lower body positive pressure (LBPP) can be a useful tool for rehabilitation for patients who suffer from pain, muscle weakness, and/or paralysis in the lower extremities. Recently, we have developed a domestic LBPP apparatus which consists of a treadmill in an airtight chamber and a blower outside the chamber. Applying 20 mmHg of LBPP decreases the grand reaction force (apparent body weight) of the subject by 31.0 ± 0.5 kgw. In the present study, we investigated the effects of LBPP on cardiovascular responses during standing still and walking. Exposure to 15 mmHg of LBPP decreased heart rate during walking, but did not change blood pressure significantly in young subjects. As the result, the double product (heart rate x systolic blood pressure) was reduced significantly by the LBPP application. Applying LBPP also decreased the leg circumference of the subjects, implying that it exerts an edema-preventing effect. The present results suggest that LBPP can reduce the work load of the heart and improve fluid turnover in the lower extremities.

S18-4

ANTI-APOPTOTIC AND PRO-SURVIVAL EFFECTS OF EXERCISE TRAINING ON HYPERTENSIVE HEARTS

Shin-Da Lee, Chih-Yang Huang
1Department of Physical Therapy, Graduate Institute of Rehabilitation Science, ChinaMedical University, Taichung, Taiwan
2 Graduate Institute of Basic Medical Science, China Medical University, Taichung, Taiwan
shinda@mail.cmu.edu.tw

Activated cardiac apoptosis was found in hypertension but less information regarding the effects of exercise training on cardiac apoptosis in hypertension was available. The purpose of this study was to evaluate the anti-apoptotic and pro-survival effects of exercise training on hypertensive hearts. Twenty-eight spontaneously hypertensive rats were divided into sedentary group (SHR) and underwent running exercise on treadmill 1 hour daily, 5 sections per week, for 12 weeks (SHR-EX). Fourteen age-matched Wistar Kyoto rats served as a sedentary normotensive group (WKY). After exercise training or sedentary status, the excised hearts were measured by H&E staining, TUNEL assay and Western Blotting. TUNEL-positive apoptotic cells became less in SHR-EX groups than those in SHR. Protein levels of Fas ligand, Fas death receptor, TNF-α, TNF receptor 1, Fas-associated death domain (FADD), activated caspase-8, and activated caspase-3 (Fas-dependent apoptotic pathways), as well as Bid, t-Bid, Bad, p-Bad, Bak, cytochrome c, activated caspase 9 and activated caspase-3 (mitochondria-dependent apoptotic pathways) were decreased in SHR-EX group compared with SHR group. Protein levels of IGF1, IGF1R, p-PI3K, p-Akt, p-Bad, and Bcl2 (cardiac pro-survival pathway) become more activated in SHR-EX groups than SHR and WKY. Exercise training prevented hypertension-enhanced cardiac Fas-dependent and mitochondria-dependent apoptotic pathways and enhanced cardiac pro-survival pathway in rat models. Our findings demonstrate new therapeutic effects of exercise training on hypertensive hearts for preventing apoptosis and enhancing survival.

S18-5

CARDIOVASCULAR ADAPTATION/DECONDITIONING IN GRAVITATIONAL CHANGE

Hironobu Morita
Department of Physiology, Gifu University Graduate School of Medicine, Gifu, Japan
zunzunmorita@gmail.com

Gravity, not only a change in amount of gravity but also a change in direction of gravity, is one of the most common and important disturbance for the cardiovascular system. Hypergravity or posture change from recumbent to upright increases hydrostatic pressure gradient and induces a footward fluid shift, decreases venous return and cardiac output, and then decreases arterial pressure. This decrease in arterial pressure is reflexively corrected by arterial baroreflex and vestibulo-cardiovascular (V-C) reflex. However, the vestibular system is known to be highly plastic, i.e., if subjects are exposed to different gravitational environment, sensitivity of the vestibulo-cardiovascular reflex is altered. Thus, it is possible that the sensitivity of vestibulo-cardiovascular reflex is reduced after spaceflight or long term recumbency, and then orthostatic hypotension is induced. To test this hypothesis, we examined: 1) role of the V-C reflex in AP regulation during gravitational change in rats; 2) whether plastic alteration of V-C reflex was induced by different gravitational environment in rats; 3) methods for human subjects; 4) role of the V-C reflex in AP regulation upon orthostasis in young and aged subjects.

S-19 Symposium
"*Epigenetics and adaptive medicine*"

Chaired by: Ana-Maria Vlădăreanu, J. Drach

Date: ***Friday, June 8th***
Starting time: ***08:30***
Location: ***Hall C (Concerto)***

1. **R.A. Wang**
The molecular adaptation of cell

2. **C. Müller-Tidow**
Genetic mutations and epigenetic alterations in the pathogenesis of myeloid malignancies

3. **Ana-Maria Vlădăreanu**
The adapted therapeutic strategies in hepatitis-viruses related non-Hodgkin lymphomas - a concept of targeted approach

4. **J. Drach**
Mantle cell lymphoma: Recent advances in biology and therapy with novel agents

5. **R. Chaunchaiyakul**
Habitual physical activity and aging on respiratory function

6. **B Mihălțan**
Speleotherapy and respiratory diseases between myths and realities

S19-1

THE MOLECULAR ADAPTATION OF CELL

Rui-An Wang, Qing-Guo Yan
Department of Pathology and Pathophysiology,
The Fourth Military Medical University, Xi'an, China
wangra@fmmu.edu.cn

Adaptation is an important concept in pathology. Although teleology is not respected in the field of natural science, it is very useful and will be much easier to get when we talk about the adaptation. The adaptation is the adjustment of cells in response to the stress and changes of environment. It serves two purposes, first to better fulfill the functional needs, and second, more importantly, to survive. The adaptation includes hyperplasia, which is, the increase in the number of cells; hypertrophy, the increase in the size of the cells; metaplasia, the transformation of tissue types; and atrophy of cells, which is the shrinkage of cell size. Today, we will mainly discuss the molecular changes which facilitate the survival of the cells, and we will focused on cancer cells. In contrary to the common notion that cancers are "resistant to apoptosis", the fact is, malignant tumors show more apoptosis and cancer cells have short lifespan than their normal counterparts. The reasons account for more apoptosis include poor blood supply, gene duplication errors, and immune attacks from the host defense system. In cope with the increased attrition of cells and to keep their families from distinction, cancer cells have to make adjustments to adapt to the environment by increasing the expression of proteins which promote cell survival, push forward the cell proliferation cycle, and the proteins which help deal with the problem of hypoxia. That is why we see increased levels of Bcl-2, cyclin D1, and HIF1 in many cancers, what is known as the "oncogene addiction" of cancer. In fact, when the cells adapt to the environment better, which is, die less as in the situation of increased Bcl-2 expression, the tumor is less malignant and the patients tend to have better prognosis. So the new concept of "molecular adaptation" is a very useful concept for understanding biology of molecular events in the cancer cells.

S19-2

GENETIC MUTATIONS AND EPIGENETIC ALTERATIONS IN THE PATHOGENESIS OF MYELOID MALIGNANCIES

Carsten Müller-Tidow
Department of Medicine A, University of Münster, Münster, Germany
muellerc@uni-muenster.de

Leukemias similar to other cancers are often composed of different cell types and subclones with a clonal origin. Adaptive mechanisms are in place that lead to selection of different clones in different phases of the disease. For example, chemotherapy selects for drug resistant clones. Different leukemia subpopulations are characterized by genetic and presumably epigenetic features. Recent advances in sequencing technology allow genome wide characterization of DNA mutation patterns and of epigenetic alterations. My lab is interested in the mechanisms how epigenetic changes occur in Acute Myeloid Leukemia and how these changes contribute to the leukemic phenotype and drug resistance. In the presentation I will focus on genome wide DNA methylation analyses in acute leukemia subtypes and the association with specific oncogenes and patient age. In addition, I will highlight the relevance of transgenic mouse models to alter DNA methyltransferase (DNMT) activity during leukemogenesis. Our data show that changes in DNMT activity can alter disease course and therapy responsiveness in AML. Taken together, epigenetic alterations determine disease course and drug response in AML.

S19-3

THE ADAPTED THERAPEUTIC STRATEGIES IN HEPATITIS-VIRUSES RELATED NON-HODGKIN LYMPHOMAS – A CONCEPT OF TARGETED APPROACH

Ana-Maria Vlădăreanu[1]
Cristina Ciufu[1], Ana-Maria Neagu[1], Horia Bumbea[1], Victoria Aramă[2]
[1]*Hematology Department Universitary Emergency Hospital, Bucharest*
[2]*"Matei Balş" Institute of Infectious Diseases, Bucharest*
anamariavladareanu@yahoo.com

Patients with chronic lymphoproliferative disorders (CLD) frequently associate hepatitis viruses infections, and therefore pose problems both at presentation and after chemotherapy is started. Specific antiviral therapy protocols should be designed for these patients. There seems to be a strong association between HCV and aggressive histological type of lymphomas. The mechanisms involved in the clearance of HCV from plasma are unclear, but it has been shown that the use of the anti-CD20 monoclonal antibody rituximab, which reversibly depletes B cells, revealed a role on the control of plasma hepatitis C viremia through humoral immunity. Hepatitis virus infection through virus reactivation is a well-known complication, with high risk of mortality in patients with hematological malignancies receiving chemotherapy. Since HBV-infected patients develop severe liver dysfunction at a higher incidence than either patients not infected with virus or HCV-infected patients before starting chemotherapy, it is recommended that HBV-DNA should be tested to detect HBV carriers. HBV reactivation occurred in some patients who had been anti-HBs negative or had a low anti-HBs level. Also, when HBV reactivation occurred, the rituximab chemotherapy could be continued after entecavir administration reduced the HBV-DNA level. Entecavir prophylaxis is not usually applied when immunochemotherapy was started, as it may be started when HBV-DNA level increases. Lamivudine has been shown to have prophylactic efficacy. Close monitoring during immunochemotherapy and at least 6 months after is required, while maintaining a prophylactic antiviral therapy to prevent this potentially fatal condition. The role and timing of antiviral therapy remains to be defined – for HBV early therapy seems to prevent viral reactivation, for HCV the best strategy has not been established.

S19-4

MANTLE CELL LYMPHOMA: RECENT ADVANCES IN BIOLOGY AND THERAPY WITH NOVEL AGENTS

Johannes Drach
Medical University of Vienna, Department of Medicine I, Clinical Division of Oncology, Vienna, Austria
johannes.drach@meduniwien.ac.at

Mantle cell lymphoma (MCL) is a distinct entity within the non-Hodgkin's lymphomas, which is characterized by a specific genetic abnormality (translocation t(11;14) leading to overexpression of cyclin-D1). Clinically, patients with MCL have frequent extranodular manifestations including the bone marrow and the gastrointestinal tract. Historically, MCL was associated with a very poor prognosis (median survival 3 years), but recent developments with more therapeutic options have changed the outcome of patients with MCL. Treatment decisions are mainly based upon age and comorbidities. For young patients with MCL (usually defined by the age below 65 years), an intensive treatment approach including autologous stem cell transplantation has been shown to be superior to standard-dose chemotherapy. Addition of rituximab to induction chemotherapy improves response rates but its effect on survival remains controversial. Therefore, the search for active drugs for the treatment of MCL continues. Among chemotherapeutic agents, bendamustine has shown promising activity, and preliminary data from a randomized clinical trial suggest that rituximab/bendamustine may be equivalent to R-CHOP with respect to treatment outcome, but with a more favorable toxicity profile. Radioimmunotherapy appears to be of limited value in patients with bulky lymphadenopathy. New agents with documented activity in MCL include bortezomib, lenalidomide, and temsirolimus. Studies exploring combinations of new agents with more traditional drugs are currently ongoing to better define their role in the treatment algorithm of MCL.

S19-5

HABITUAL PHYSICAL ACTIVITY AND AGING ON RESPIRATORY FUNCTION

Rungchai Chaunchaiyakul
College of Sports Science and Technology, Mahidol University, Thailand
gmrungchai@gmail.com

Ageing causes opposite horizontal shifting of the lungs and chest wall pressure-volume relationships, with unchanged compliances. The net results of these curve shiftings imply that total elastic work remained unaltered. Effects of habitual physical activity failed to decelerate age-related changes in elastic works of breathing of total respiratory system, lungs and chest wall. Ageing causes different responses during exercise. Younger subjects showed higher respiratory rate (f_b), while the elderly subjects had higher tidal volume (V_T). In addition, all age groups increased V_T during exercise primarily by utilizing inspiratory reserve volume (IRV). Habitual physical activity results in the higher VT with lower f_b during exercise, in which greater minute ventilation is produced.

In conclusion, ageing causes the remarkable reductions of static and dynamic lung volumes which resulted in simultaneous compliance shifting of lungs and chest wall curves. Since total energy stored within the chest wall diminished with advancing age, thus less energy to assist the consecutive inspiration. Habitual physical activity fails to offset the age-related modification of respiratory system.

S19-6

SPELEOTHERAPY AND RESPIRATORY DISEASES BETWEEN MYTHS AND REALITIES

Florin Mihălțan
National Institute of Pneumology „M.Nasta", Bucharest, Romania
mihaltan@starnets.ro

History of speleotherapy is very charged. The special characteristics of the micro-climate of a salt mine include stable air temperature, humidity and lack of airborne pollutants such as pollens, and is unique to each mine. There are many offers of such a therapy from halogenerators used to simulate the salted atmosphere of salt mines to salt pipe , saltwater aerosol or salt mine micro-climate. In our presentation we are discussing the benefits and the consequences of such a therapy. This brought in the scientific articles arguments pro and con and create a debate between the specialists. In the same time we are trying to find the right place of speleotherapy in the algorithm of chronic respiratory diseases without neglecting other benefits for other chronic respiratory diseases. For Romania this type of therapy has a large offer coming from the big number of salt mine underused now but arranged for assisting this sample of patients.

S-20 Symposium
"*Modern trends in adaptive medicine*"

Chaired by: C. Bai, C. Ionescu-Târgovişte

Date: ***Sunday, June 10th***
Starting time: ***08:30***
Location: ***Hall B (Salonul Oglinzilor)***

1. **X. Wang**
Clinical bioinformatics in development of disease-specific biomarkers

2. **R.K. Goyal**
Changing Trends in the Treatment of Diabetic Cardiomyopathy

3. **C. Bai**
Cell phone based Telemedicine - brief introduction

4. **R.K. Li**
Myocardial Resident Bone Marrow Stem Cells Govern Repair after Myocardial Infarction

S20-1

CLINICAL BIOINFORMATICS IN DEVELOPMENT OF DISEASE-SPECIFIC BIOMARKERS

Miaomiao Zhang, Bijun Zhu, Zhihui Ming, Lingyan Wang, Mengjia Qian, Xiaocong Fang, Xiaojin Xu, Yonghua Zheng, Xiaoan Wu, Jiebai Zhou, Yong Zhang, Ding Zhang, Beibei Wang, Lin Shi, Xiangdong Wang*
Biomedical Research Center, Department of Respiratory Medicine, FudanUniversity Zhongshan Hospital, Shanghai, China.
xiangdong.wang@clintransmed.org

Clinical bioinformatics is a new emerging science combining clinical informatics, bioinformatics, medical informatics, information technology, mathematics, and omics science together. Clinical bioinformatics plays an important role in a number of clinical applications. Clinical bioinformatics is a new way to focus on the combination of clinical measurements and signs with human tissue-generated bioinformatics, understand clinical symptoms and signs, disease development and progress, and therapeutic strategy, and map relationships that integrate discrete elements that collectively direct global function within a particular -omic category, with clinical examinations, pathology, biochemical analysis, imaging and therapies. A number of methodologies and computational programs have been developed to integrate selected proteins into the knowledge-based networks via the combination of genomics, proteomics and bioinformatics. Alterations of network biomarkers can be monitored and evaluated at different stages and time points during the development of diseases, named dynamic network biomarkers. Dynamic network biomarkers should be furthermore correlated with clinical informatics, including patient complaints, history, therapies, clinical symptoms and signs, physician's examinations, biochemical analyses, imaging profiles, pathologies and other measurements. Systems clinical medicine is coined as the integration of systems biology, clinical phenotypes, high-throughout technologies, bioinformatics and computational science to improve diagnosis, therapies and prognosis of diseases.

S20-2

CHANGING TRENDS IN THE TREATMENT OF DIABETIC CARDIOMYOPATHY

Ramesh K. Goyal
SPP School of Pharmacy & Technological Management,
NMIMS Deemed University, Mumbai, India
goyalrk@rediffmail.com

In spite of identification of several humoral, cellular and sub-cellular targets and developments of pharmacological and interventional methods for the treatment of heart failure, there occurs greater cardiac morbidity and mortality in diabetics. Even today one has to rely on the currently available antidiabetic, antihypertensives, anti-atherosclerotic and antithrombotic drugs for diabetic cardiomyopathy. In the early stages animal and clinical studies carried out on proper selection of anti-diabetics and antihypertensives related to cardioprotection, we justified the use of selective ACE inhibitors and calcium channel blockers in NYHA class 1-3 cardiac failure. Similarly, metformin was reported to be relatively cardio protective as compared to sulfonylureas, giving rise to a new era for insulin sensitizers. Recently, there has been sudden growth in the interest of herbal drugs for the treatment of various diseases. Many herbal drugs as well as their semi-synthetic analogue have been reported for the beneficial effect in heart failure. We report certain lead molecules like gallotannin from Embelica officinalis, 6-gingerol from Zingiber officinalis, and swertiamarin from Enicostemma littorale having beneficial effect in diabetic associated cardioprotection. Since, no specific therapeutic strategies has been recommended for diabetic cardiomyopathy, we propose have this as holistic approach with potential herbal phytoconstituents having multiple effects for the beneficial effect in diabetic cardiomyopathy.

S20-3

CELL PHONE BASED TELEMEDICINE - BRIEF INTRODUCTION

Chunxue Bai
Shanghai Respiratory Research Institute (SRRI)
Department of Pulmonary medicine, Zhongshan Hospital,
Fudan University, Shanghai, China
bai.chunxue@zs-hospital.sh.cn

In 2008, cell phone user population hit 641 million while the mobile web user population reached 117 million in China. The development of mobile technology gives rise for greater potential to improve the public's health. Leveraging on the development of intelligent sensors, wireless transmitters, as well as a dynamic medical network, we bring forth a new concept of cell phone-based telemedicine specially catered for those suffering from chronic respiratory diseases. Such a cost effective and convenient health care service is enabled though the utilization of wifi/GPRS (General Packet Radio Service) system and GPS (Global Positioning System) in widely used cell phones. Briefly, our cell phone based medical service is composed with the following components: (1) Terminal devices collecting information from the patient whether audio, video, oxygen saturation, heart rate, lung function or other physiological parameters. The breakthrough of our system is to integrate the spirometer with a cell phone unit (ATS News, 2009, vol.35 no.7/8). (2) Electronic transfer of such information over a distance through the internet wirelessly; (3) Terminal devices by which doctors remotely receive patients' information and send feedback and tailored advice back to the patients. (4) An medical center for coordinating, providing technical services and regulating. (5) Software enabling the interactive communication between doctors and patients.

S20-4

MYOCARDIAL RESIDENT BONE MARROW STEM CELLS GOVERN REPAIR AFTER MYOCARDIAL INFARCTION

Ren-Ke Li

Toronto General Research Institute, University Health Network, Department of Surgery, Division of Cardiovascular Surgery, University of Toronto, Toronto, Ontario, Canada.

renkeli@uhnresearch.ca

Heart failure results from cardiomyocyte necrosis after myocardial infarction. The heart achieves limited repair through tissue resident and circulating stem-cells. Resident cardiac stem-cells are believed to be a legacy of cardiac development, residing in myocardial stasis but retaining a capacity for regeneration in times of injury. Here we unveiled inceptive resident cardiac stem-cells of hematopoietic origin that independently directs endogenous repair. Age negatively influences the cardiac recipient environment and the functional capacity of stem-cell transplantation. Whereas a young environment recuperates aged stem-cells, young stem-cells perform inadequately in aged recipients. We address this paradox, revealing a third compartment: resident cardiac stem-cells of hematopoietic origin that govern cardiac repair. Rejuvenation of aged bone marrow increases the regenerative capacity by restoring this resident cardiac stem-cell niche. Cardiac resident stem-cells play an important role in restoration of cardiac function and repair.

S-21 Symposium
"*Pathophysiology of adaptation*"

Chaired by: M. Bhatia, Y.T. Konttinen

Date: ***Friday, June 8th***
Starting time: ***12:00***
Location: ***Hall B (Salonul Oglinzilor)***

1. **M. Bhatia**
Hydrogen Sulfide and Substance P: Novel Inflammatory Mediators and Therapeutic Targets for Acute Pancreatitis

2. **Y.T. Konttinen**
Osteoarthritis as an auto-inflammatory disease caused by condrocyte-mediated inflammatory responses

3. **Chen-Hsen Lee**
The Management of Well Differentiated Thyroid Cancer

4. **A. Cortot**
IBD: from epidemiology to pathophysiology

5. **J-F. Flejou**
Premalignant Lesions in Inflammatory Bowel Diseases - The Pathologist's View

S21-1

HYDROGEN SULFIDE AND SUBSTANCE P: NOVEL INFLAMMATORY MEDIATORS AND THERAPEUTIC TARGETS FOR ACUTE PANCREATITIS

Madhav Bhatia
Department of Pathology, University of Otago, Christchurch, New Zealand
madhav.bhatia@otago.ac.nz

Acute pancreatitis is a common clinical condition. Development of in vivo experimental models of acute pancreatitis and associated systemic organ damage has enabled us to study the role played by inflammatory mediators in the pathogenesis of this condition. Hydrogen sulfide (H2S) plays an important role in cardiovascular, central nervous and gastrointestinal systems and has been shown to act as a vasodilator. We have also shown that H2S acts as a mediator of inflammation. Substance P is an 11 amino acid neuropeptide that is released from nerve endings in many tissues. Subsequent to its release, substance P binds to neurokinin-1 (NK-1) receptors on the surface of effector cells. Using experimental models, recent studies in our laboratory have established the critical role played by H2S and substance P in acute pancreatitis. Studies with experimental animal models of disease will help define the role of these mediators in the pathogenesis of acute pancreatitis, and can lead to the development of novel therapeutic approaches for this condition.

S21-2

OSTEOARTHRITIS AS AN AUTOINFLAMMATORY DISEASE CAUSED BY CHONDROCYTE-MEDIATED INFLAMMATION

Yrjö T. Konttinen
Institute of Clinical Medicine, Department of Medicine, Biomedicum, Hus, Finland
yrjo.konttinen@helsinki.fi

Osteoarthritis (OA) is considered primarily a disease of the hyaline articular cartilage. First biomechanical stresses and strains, simple ”wear and tear”, were considered as its root cause. Then it was realized that biochemical inflammatory and degenerative processes play a role. We suggest a theoretical framework, which ties the old and new dogma to each other, placing cartilage matrix and chondrocyte at the centre stage and pointing the chondrocyte as the primary inflammatory cell.

Articular cartilage lacks blood and lymphatic vessels. When subjected to “wear and tear”, various cartilage extracellular matrix (ECM) derived macromolecular patterns, now recognized as endogenous danger signals (alarmins), are produced and released. Due to the lack of vasculature, they are assumed to accumulate locally at high concentrations. Therefore, they effectively stimulate chondrocytes and chondrocyte progenitors in situ via various pattern-recognizing receptors (PRR), particularly Toll-like receptors (TLRs). This leads to production of pro-inflammatory (e.g. tumour necrosis factor-α) and analgetic (e.g. substance P) mediators. They can via the interstitial cartilage and synovial fluid reach synovial membrane. This leads to a secondary synovitis. Indeed, clinical symptoms in OA manifest as pain - and pain cannot derive from the hyaline articular cartilage because it totally lacks primary afferent nociceptive (PAN) nerves. It is assumed that after these initial phases, secondary mechanisms, like local synovial synthesis and imbalance of complement factors and inhibitors, takes over the perpetuation and amplification of the secondary synovial inflammation.

New data on TLRs and chondrocyte activation in situ in osteochondral cylinders, primary chondrocyte isolates and chondrogenic mesenchymal stem cells will be presented, suggesting that the chondrocytes assume an inflammatory, embryonal chondrocyte-like phenotype in OA.

S21-3

THE MANAGEMENT OF WELL DIFFENRENTIATED THYROID CANCER

Chen-Hsen Lee
Taipei-Veterans General Hospital, National Yang-Ming University and Show-Chwan Health Care System, Chang-Hwa, Taipei, Taiwan
chlee@vghtpe.gov.tw

Thyroid cancer is the most common endocrine malignancy in clinical practice. Most of the thyroid cancers are symptomless and may not progress in size. Most clinicians are following the guidelines of American Thyroid Association in the management on thyroid cancers. Surgeons rarely do not accept referrals from endocrinologists. However, occasionally, there were difficulties in fulfilling the requests of our medical counterparts as patients' safety and postoperative quality of life are our major concerns.

It is generally agreed that a total or near total thyroidectomy is done for well differentiated thyroid cancers (WDTC). A therapeutic central compartment lymph node dissection is preferred in this Institution . Special cautions during operation is needed in cncers with thyroiditis or after repeated fine needle aspiration cytology tests as identification of anatomical structures may be difficult due to dense adhesion. Re-do operation for recurrent thyroid cancers carries higher risks of postoperative hoarseness and hypoparathyroidism. The importance of pre-operative illustration and informed consent are emphasized. WDTC's with surrounding tissue invasion are managed individually.

S21-4

INFLAMMATORY BOWEL DISEASES (IBD): FROM EPIDEMIOLOGY TO PATHOPHYSIOLOGY

Antoine Cortot
Centre Hospitalier Régional Universitaire de Lille, Lille , France
Antoine.CORTOT@chru-lille.fr

IBD pathohysiology depends on the interaction between genetic susceptibility and environmental factors leading to a deregulated immune intestinal response resulting in bowel lesions. IBD epidemiologic variations with time (incidence, prevalence) and space suggest a role for risk environmental factors, but so far only smoking habits and appendectomy have been identified as influencing the risk of occurrence and the course of IBD. Studies of monozygotic and dizygotic twins and the existence of familial aggregation are strong evidence for an important, but not exclusive, role for genetic susceptibility. Since the discovery of NOD2 , the first Crohn's disease –associated gene described in 2001, > 100 risk loci have been associated with IBD, some of them involved in the regulation of innate and adaptive immunity , cellular clearance of infectious agents (autophagy) and mucosal barrier function. Thus new hypothesis include a key role of aberrant responses to the gut microbiome which could be partly influenced by environmental factors generated by modern life. The improvement of life hygiene, the change of food composition and habits, the industrial pollution in developed countries, may influence, directly or by the way of modifying intestinal human microbiota, IBD risk occurrence.

S21-5

PREMALIGNANT LESIONS IN INFLAMMATORY BOWEL DISEASES - THE PATHOLOGIST'S VIEW

Jean-François Fléjou
Service d'Anatomie Pathologique, Pôle de Biologie Médicale et Pathologie
Equipe "Instabilité des Microsatellites et Cancers" , Hôpital Saint Antoine
Hôpitaux Universitaires Est Parisien, Paris, France
jean-francois.flejou@sat.aphp.fr

Although most colorectal cancers (CRC) develop in patients with no previous history of colorectal disease, some high-risk populations have been recognized. This has been shown especially in patients with inflammatory bowel disease (IBD). Recent studies have demonstrated that this increased risk is similar in ulcerative colitis (UC) and Crohn's disease (CD). It has also been shown that in those patients with IBD, cancer develops through an inflammation – dysplasia (or intra-epithelial neoplasia) – carcinoma sequence. Therefore, surveillance is recommended in patients with IBD, resulting in the detection of preneoplastic lesions, and also of cancers at an earlier stage with a better prognosis. Dysplasia can present as a flat lesion, only detectable by systematic random biopsies, or as raised lesions. There have recent changes in the nomenclature and terminology of these lesions (ALM, DALM, RLD etc…) that need clarification. The histological diagnosis of dysplasia remains a difficult task, and it has to be made with recognized criteria and classification. The recent WHO scheme recommends a two-tier classification (low-grade and high grade), very close to the Riddell's classification. It is also recommended to confirm the diagnosis by a second (expert) observer, because of an imperfect diagnostic reproducibility. Some new histological subtypes of dysplasia in IBD have been recognized recently, including serrated and hypermucinous-villous phenotypes. Among potential biomarkers of interest in complement to standard histology, only p53 immunohistochemistry is really used in routine practice at the present time. Interestingly, a basal pattern of p53 expression was described, that may indicate a basal "cryptic" pattern of dysplasia in IBD, similar to the crypt dysplasia described in Barrett's oesophagus. However, the link still has to be made between these morphological subtypes and the molecular alterations involved in the carcinogenesis of colon mucosa in IBD. The example of microsatellite instability is of interest in this field.

S-22 Symposium
"*Current view on adaptive medicine*"

Chaired by: A. Pries, M. Cinteză

Date: ***Saturday, June 9th***
Starting time: ***14:30***
Location: ***Hall B (Salonul Oglinzilor)***

1. **Patrizia d'Alessio**
Quality of Life and inflammation: gender differences in response to dietary supplementation in elderly people in the RISTOMED study

2. **Chi-Chang Huang**
Potassium oxonate-induced proteinuria and acute renal failure in vivo

3. **A. Pries**
Design principles of vascular networks: Angiogenesis, adaptation, heterogeneity and function

S22-1

QUALITY OF LIFE AND INFLAMMATION: GENDER DIFFERENCES IN RESPONSE TO DIETARY SUPPLEMENTATION IN ELDERLY PEOPLE IN THE RISTOMED STUDY

Patrizia d'Alessio[1]
Rita Ostan[2], Luzia Valentini[3], Isabelle Bourdel-Marchasson[4], Alessandro Pinto[5], Fabio Buccolini[6], Claudio Franceschi[2], Marie C. Bené[7]
[1]University Paris Sud-11 & Biopark Cancer Campus 1, Villejuif, France, [2]Department of Experimental Pathology, University of Bologna, Italy, [3]Charité – Universitätsmedizin Berlin, Section of Nutritional Medicine of the Dept. Of Gastroenterology, Berlin, Germany, [4]CHU de Bordeaux, Univ. Bordeaux, Bordeaux, France, [5]Sapienza University of Rome, Experimental Medicine Department - Medical Physiopathology, Food Science and Endocrinology Section - Food Science and Human Nutrition Research Unit, Rome, Italy, [6]Voxnet, Rome Italy, [7]CHU Nancy & University of Lorraine, France
patrizia.d-alessio@inserm.fr

Twenty-five years of gender issue analysis have contributed to the re-definition of diseases. Among cardio-vascular diseases, myocardial infarction is indeed women killer number one, but its symptoms being different from those seen in men, it has not been recognized as such for a long time. The effectiveness of primary prevention of stroke and other cardiovascular events by aspirin tested in seven trials, did not include women. Moreover, Dale et al. (2007) showed that statins reduced the risk of stroke only in men. As cardiovascular disease, many other health issues have been shown to be questionable when looked at under the perspective of gender differences. Quality of Life parameters in particular seem to be experienced differently by men and women. Depression, one of the hallmarks of the aging population particularly affecting women because of greater longevity, has a causal role in the development and course of cardiovascular diseases. Epidemiological data demonstrate that depression or anxiety are approximately twice as common in women as in men. This gender difference emerges during adolescence and persists later in life and into old age. It is moreover well recognized that inflammation contributes to the development of depression. We report preliminary data on a study performed in elderly healthy men and women, examining biological and behavioral responses after 56 days of a specifically developed dietary program with or without anti-inflammatory dietary supplementation with an Orange Peel Extract (OPE) containing d-Limonene, the European study RISTOMED. We show an impact of both gender and initial inflammation status on the effects of dietary control. OPE was more efficient in subjects with an initially high inflammatory status and improved both IL-6 levels and depression scores in women.

S22-2

POTASSIUM OXONATE-INDUCED PROTEINURIA AND ACUTE RENAL FAILURE IN VIVO

Chi-Chang Huang[1,], Wen-Ching Huang[2], Mei-Chich Hsu[1], Shao-Wen Hung[3], Chia-Chung Hou[2,]

[1]Graduate Institute of Sports Science, National Taiwan Sport University, Taoyuan, Taiwan, [2]Dong Jyu Biotechnology Corporation, Taipei, Taiwan, ROC, [3]Agricultural Biotechnology Research Center, Academia Sinica, Taipei, Taiwan

(C.-C. Huang) john5523@mail.ntsu.edu.tw; (C.-C. Hou) d8501002@tmu.edu.tw

Potassium oxonate (PO) is a pyrimidine phosphoribosyltransferasae (EC 2.4.2.10) competitive inhibitor, using as a modulator in a novel antineoplastic combination agent, S-1. PO is also a selectively competitive uricase inhibitor, which inhibits hepatic urate oxidase and induces hyperuricemia of experimental animals. Herein, we report our finding that PO-insulted acute renal failure (ARF), proteinuria and lethal toxicity in mice. The toxicity of PO-induced ARF and the underlying molecular mechanisms is also investigated. Male ICR mice were intraperitoneally administered with PO at increasing doses of 0, 50, 100, 150, 200 and 250 mg/kg/day, designed as group vehicle, PO-50, PO-100, PO-150, PO-200 and PO-250, respectively. The results revealed that PO increased serum levels of potassium, uric acid, markers of renal function (BUN and creatinine), inflammatory biomarker (NF-kB p65 translocation) and ARF-related pathways (IL-6/IL-6sR/STAT3 phosphorylation). The urine production of PO-treated mice was significantly decreased during 24 hours collection in a dose-dependent manner. Additionally, with the decreased urine output, the mortality rate was increased obviously. Only 25% (4/16) of animals survived after 48 h following PO-250 insult. We systematically investigated the possible signaling pathways leading to PO-induced ARF which shed light on the potential renal toxicity of PO.

S22-3

DESIGN PRINCIPLES OF VASCULAR NETWORKS: ANGIOGENESIS, ADAPTATION, HETEROGENEITY AND FUNCTION

Axel R. Pries[1,2]
Bettina Reglin[1], Timothy W. Secomb[3]
[1]*Dept. of Physiology and CCR, Charité, Berlin, Germany*
[2]*Deutsches Herzzentrum Berlin, Berlin, Germany*
[3]*Dept. of Physiology, University of Arizona, Tucson, AZ, USA*
axel.pries@charite.de

Microvascular networks are highly dynamical and heterogeneous structures which have to provide low diffusion distances from capillaries to all tissue cells as well as efficient convective distribution of blood flow through larger vessels. The question how these different and partially conflicting tasks of microvascular networks can be met by the biological processes for their generation and adaptation (angioadaptation), including sprouting and splitting angiogenesis, vascular pruning and structural diameter adaptation, is still under debate. A central concept is the combination of the stochastic processes of angiogenesis with the refining processes of vascular diameter adaptation and pruning. The adaptive processes exhibit negative feedback regulations of relevant functional parameters, including wall shear stress and oxygen partial pressure within a vessel and oxygenation of the tissue. This combination allows the efficient generation and dynamic adaptation of vascular beds with acceptable heterogeneity in levels of local supply. Compromised capability for refining angioadaptation is probably involved in a number of pathologies characterized by excessive heterogeneity, including tumour vascularization, sepsis and aging.

General data

Romania is located at the crossroads of Central and Southeastern Europe. Romania shares borders with: Hungary and Serbia to the west; Ukraine and Moldova to the northeast and east, and Bulgaria to the south. The east side of Romania is partially bordered by the Black Sea.

Romanian is the official language and is related to Italian, French, Spanish, and Portuguese.

Bucharest is the cultural, industrial, administrative and financial capital of Romania, and is located in the southeast of the country. Bucharest lies on the banks of the Dâmbovița River.

Bucharest Climate
Bucharest has a continental climate, meaning hot and dry summers and freezing cold winters. The temperature during the summer is pleasantly warm, but sometimes there are heat waves. The air humidity is low. Occasionally rainstorms could occur.
In brief, weather in Bucharest in June is like a great summer day in England. It can get quite hot in Bucharest, even in June.
Average temperature during June in Bucharest is 22°C during the day and a low of 11°C at night. The evenings are warm, light clothes may be of use up to around 10:00 PM.

Clothes recommended for June in Romania
Summer suits
Summer clothes
T-shirts
Waterproof clothes (rainy time intervals are possible).

Romanian currency
The leu (Romanian pronunciation: singular - *leu* [lew], plural - *lei* [lej]; code RON) is the currency of Romania. It is subdivided into 100 *bani* (singular: ban).

Currency exchange in Romania
Foreign currencies could be exchanged at banks or authorized exchange

offices (In Romanian: "casa de schimb" or "birou de schimb valutar"). International airports and larger hotels also offer currency exchange services.

Exchange rates (may slightly vary) for foreign currencies:
one US dollar = 3.5 Lei (3 lei and 50 bani)
one British Pound = 5.5 Lei (5 lei and 54 bani)
one Euro = 4.5 Lei (4 lei and 50 bani)

Make sure that, before leaving Romania, you convert your leftover RON into the currency of your choice.

Public Banks opening schedule in Romania is generally in between 09:00 – 17:00.

ATM (Bancomat)
You may find available ATM machines within main banks and shopping centers. Few ATMs are available in remote areas or villages. ATMs that have symbols for international networks such as STAR and PLUS will accept also US/ Canadian banking cards.

Credit cards
Major credit cards including American Express, MasterCard and Visa are accepted in large hotels, car rental companies and stores in the main cities.
Contrary to practice in the United States, a PIN is usually required to make credit card purchases.

International dialing from Romania:
00 + country code + area code + telephone #

Romanian metric system
Romania uses the metric system of weights and measures. Speed and distance are measured in kilometers; goods in kilograms and liters; temperatures in Celsius - Centigrade.

Electricity and Socket
Romania's electrical current is 220V; 50Hz and sockets take the standard continental European dual round-pronged plugs.

Places to see in Bucharest

Romanian Athenaeum symbol of national Romanian culture, built in 1888, neoclassical style, with many elements of decoration of French typical architecture;

Old Royal Court, the most significant historical remains of medieval era and *Old Court Church* is the oldest example of religious architecture in Bucharest existing from the feudal era.

Romanian Patriarchate built in 1656-1658 by the ruler Constantin Serban Basarab.

Kretzulescu Church – the monument sums up, through its architecture, the art in the Brâncoveanu era; it was built in 1720-1722 with great care from the chancellor Iordache Safta Kretzulescu; the interior wall was painted by Gheorghe Tattarescu between 1859 and 1860.

Stavropoleos Church, built in 1724-1730.

Ghica Palace, built in 1822 at the order of Prince Grigore Dimitrie Ghica, is an imposing edifice, country representative for the Romanian neo-classical style.

Ştirbei Palace, built in 1835 in neoclassical style according to the French architect Sanjouand's plans, today houses the Museum of Ceramics and Glass.

Şuţu Palace, Gothic style with Romanesque elements, dating from 1834, is today the History and Art Museum for the city of Bucharest.

Cotroceni Palace, built in 1893 according to French architect Paul Gottereau's plans as the permanent residence of Crown Prince Ferdinand, is now in the heritage of the presidential institution.

Parliament Palace, the greatest administrative construction in Europe, with an area that ranks it second in the world (after the Pentagon) and with a volume that places it on the third place in the world (after Cape Canaveral building - U.S.A. and Quetzalcoatl pyramids - Mexico).

National History Museum of Romania, with over 50,000 pieces of great value, illustrating the development of human society in our country.

National Art Museum of Romania, with over 70,000 pieces of Romanian and universal art, hosting works by the Tatarescu, Aman, Grigorescu, Luchian, Pallady, Tonitza, Brancusi, Paciurea, Rembrandt, Rubens, Delacroix, Renoir, Monet etc.

Village Museum is one of the most interesting open-air ethnographical parks in in the world.

"Grigore Antipa" Natural History Museum is the largest museum of its kind in the Danubian countries, owning one of the richest collections of butterflies in Europe.

Art and History Museum of Bucharest has over 150,000 pieces that illustrate the historical evolution of the city.
Arch of Triumph was completed in 1937 by the architect Petru Antonescu to honor the victory of the Romanian Army in the First World War.

Smoking
Currently smoking is not allowed on public transportation and on most trains. Luxury hotels have designated no-smoking floors and most restaurants have no-smoking sections. Smoking is also prohibited in public places such as hospitals, concert halls, and theatres.

General emergency phone number: 112

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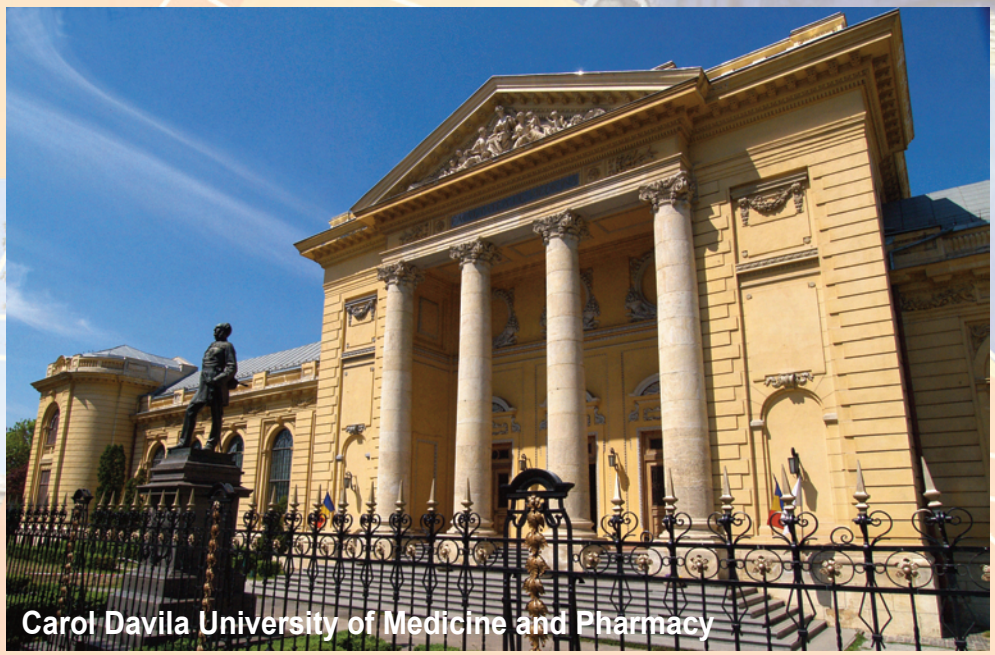
Carol Davila University of Medicine and Pharmacy