WESTERN PHARMACOLOGY SOCIETY

51ST Annual Meeting
January 27th – January 31st, 2008
Waikoloa Marriott Resort
Kona, Hawaii

Meeting Organizer: Lubo Zhang

Meeting Coordinator: Linda Hedley

2007-2008 WPS Officers

President	Lubo Zhang
President Elect	Carlos Villalón
Immediate Past President	Sandy Clanachan
Secretary	Linda Hedley
Treasurer/Editor	Iain Buxton
Councilor for Electronic Communications	Nigel Shankley
Councilor for Student Affairs	Magda Morton
Councilor	Larry Brunton

51st ANNUAL WESTERN PHARMACOLOGY SOCIETY MEETING, Kona, Hawaii Jan 27- 31, 2008

	SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY
7:00 – 8:00 am		Continental Breakfast Welcome: 7:50 – 8:00		(*Naupaka I-III*)	
8:00 – 12:00 noon **(10:15 – 10:30 Break)**		**Symposium I:** *(Naupaka IV)* Fetal Origins of Cardiovascular Disease *Chair:* Kent Thornburg, OHSU	**Symposium II:** *(Naupaka IV)* Estrogen and Woman's Health *Chair:* Guantam Chaudhuri, UCLA	**Symposium III:** *(Naupaka IV)* DNA Methylation and Cancer Therapy *Chair:* Lawrence Sowers, LLU	**Symposium IV:** *(Naupaka IV)* Chronic Fatigue Syndrome *Chair:* Judy Milkovits, UNSOM & WPI
12:00 noon – 1:00 pm			**WPS Council Meeting** *(Lehua Ballroom I)*	**Keith and Eva Killam Award Lecture** *(Naupaka IV)* *Recipient:* William P. Scheimann	
1:00 – 3:00 pm **3:00 – 6:00 pm**	**Meeting Registration** *(Naupaka Lanai)*	**Free Time: Have Fun!**		**WPS Business Meeting** *(Lehua Ballroom I-II)* *1 p.m. -2 p m.*	**Symposium V:** *(Naupaka IV)* Pharmacogenomics from ASCEPT
6:00 – 7:00 pm	**Tom Burks Memorial Lecture** *(Naupaka IV)* Louis J. Ignarro, Nobel laureate, 1998	See Marriott concierge for booking activities: Snorkeling, Diving, Whale watching, Volcano excursions and Golf			**Cocktail Hour** *(Naupaka Lanai)*
7:00 – 9:00 pm	**Opening Ceremony & Reception** *(Naupaka Lanai)*	**Poster Session I:** *(Naupaka V-VII)* Wine and Cheese	**Poster Session II:** *(Naupaka V-VII)* Wine and Cheese	**Poster Session III:** *(Naupaka V-VII)* Wine and Cheese	**Annual Banquet** *(Naupaka IV)*

President's Welcome Message

On behalf of the Western Pharmacology Society, I welcome you to the 51st Annual WPS Meeting at the Waikoloa Marriott Resort on Hawaii's beautiful Kona Coast.

The WPS is one of the oldest Pharmacology societies, holding its first meeting in San Francisco in 1958. WPS is an international Society with major membership from the western regions of the United States, Canada, and Mexico with many other countries represented. Over the years, the Society has extended a welcome to those who have attended the annual meetings from Europe, Australia, and New Zealand. This year, we are delighted to have a joint symposium with Australasian Society of Clinical and Experimental Pharmacology and Toxicology (ASCEPT), which brings scientists from Australia, New Zealand, and the United Kingdom to the meeting.

The goal of the meeting is to share current science and promote the success of future pharmacologists. This is reflected by this year's scientific program, which includes five focused symposia: Estrogen and Woman's Health, Fetal Origins of Cardiovascular Disease, DNA Methylation and Cancer Therapy, Pharmacogenomics, and Emerging Understanding in Chronic Fatigue Syndrome. In the tradition of the society, symposia will be held in the morning with afternoons free for golf, swimming, sightseeing and all around fun and relaxation. The poster sessions will be conducted in the evenings; refreshments will be served. These sessions are invariably well received as give our students an opportunity to present their work and receive constructive criticism and suggestions from many expert scientists in attendance. I would like to encourage all participants, especially graduate students and postdoctoral fellows, to take advantage of this and other opportunities during the meeting for informal collegial interaction and exchange of ideas.

WPS honors two of its past members who were instrumental in the growth and success of the Society. The meeting will begin with the Tom Burks Memorial Award Lecture on Sunday evening at 6:00 pm followed immediately by a hosted reception. I am delighted that Nobel Laureate, Professor Louis Ignarro from the University of California Los Angeles will deliver the Tom Burks keynote lecture describing the history and discovery of nitric oxide as a signaling molecule. The Keith and Eva Killam Award Lecture will be given on Wednesday at 2:00 pm by Dr. William Schiemann, Associate Professor in the Department of Pharmacology at the University of Colorado Health Sciences Center. He will speak on the significance of TGF-β signaling and angiogenesis in progressing human malignancies through the development of novel chemo-preventive agents. Bill is no stranger to the WPS having presented a poster at the 1990 meeting in Banff.

Best wishes for a great week,

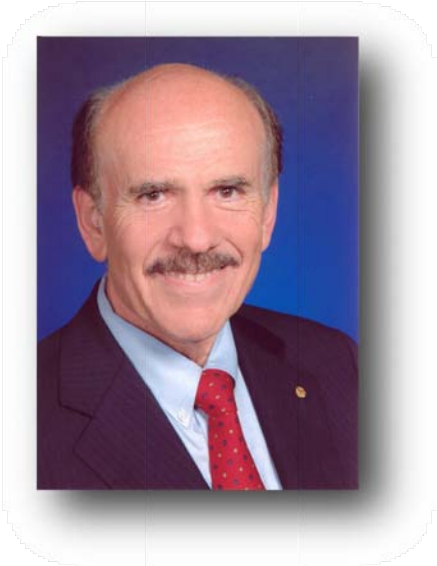
Lubo Zhang, Ph.D.
Professor of Physiology and Pharmacology

Sunday 6. p.m., Naupaka IV

Thomas F. Burks Memorial Lecture:

Thomas F. Burks ll, Ph.D., executive vice president for research and academic affairs at The University of Texas Health Science Center at Houston and professor of pharmacology at the University's Medical School, died on March 2, 2001 in Denton while traveling on university business. Tom, 62, was a distinguished research scientist and long-time member and promoter of WPS. He received his Ph.D. at the University of Iowa's College of Medicine. Burks was assistant professor of pharmacology in 1967 at the University of New Mexico School of Medicine and was appointed associate professor in 1971. He conducted postdoctoral work at the Laboratory of Neuropharmacology at the National Institute for Medical Research in London, England. In 2003 the first annual Memorial Lecture in honor of Thomas Burks was delivered at the 2003 WPS meeting in Reno, Nevada organized by his friend and colleague Iain Buxton.

This year Nobel Laureate, Professor Louis Ignarro from the University of California Los Angeles will deliver the Tom Burks Plenary lecture describing the history and discovery of nitric oxide as a signaling molecule.



Louis J. Ignarro was born on May 31, 1941 in Brooklyn, New York. He attended Columbia University as an undergraduate and received his PhD degree in pharmacology from the University of Minnesota in Minneapolis with a minor in Cardiovascular physiology. His work was published in 4 back to back articles in the Journal of Pharmacology and Experimental Therapeutics.

Dr. Ignarro accepted a postdoctoral position at the National Institutes of Health in the Laboratory of Chemical Pharmacology in the National Heart, Lung and Blood Institute and there studied the chemistry of beta adrenergic receptors.

Geigy Pharmaceuticals recruited Dr. Ignarro in 1968 with an attractive package including the responsibility of heading the biochemical and anti-inflammatory program. Geigy allowed Dr. Ignarro the freedom to pursue basic research in biochemical pharmacology, which led to his interest in studying the relatively new cyclic nucleotide, cyclic GMP. When Geigy Pharmaceuticals merged with Ciba Pharmaceuticals, he decided to try his hand at academic research and teaching. In January of 1973, he accepted the position of Assistant Professor of Pharmacology at Tulane University School of Medicine in New Orleans to continue his research on cyclic GMP. There, the discovery that EDRF was nitric oxide led to an avalanche of studies that created an exciting new field in biological research.

He is currently a distinguished professor of pharmacology at the UCLA School of Medicine's department of molecular and medical pharmacology in Los Angeles, which he joined in 1985, where he loves teaching medical and graduate students.

He was co-recipient of the 1998 Nobel Prize in Physiology or Medicine for demonstrating the signaling properties of nitric oxide. In addition, he received the Basic Research Prize of the American Heart Association in 1998, in recognition of his outstanding contributions to the advancement of cardiovascular science. That same year, he was inducted into the National Academy of Sciences and the following year, into the American Academy of Arts and Sciences. He is the founder of the Nitric Oxide Society, and founder and editor-in-chief of "Nitric Oxide Biology and Chemistry."

The Tom Burks Memorial Lecture

"The History and Discovery of Nitric Oxide as a Signaling Molecule in Physiology"

Louis J. Ignarro, Ph.D.
Department of Molecular and Medical Pharmacology,
UCLA School of Medicine, Center for the Health Sciences
Los Angeles, CA

The field of nitric oxide (NO) research has developed in explosive proportions since the discovery of endogenous NO in 1986. The biological importance of NO was first suggested by the observations that nitroglycerin and related nitrovasodilators elicit vascular smooth muscle relaxation by liberating NO in the smooth muscle. NO was shown to be a potent smooth muscle relaxant that worked by activating cytosolic guanylate cyclase and elevating smooth muscle levels of cyclic GMP. These observations were quickly followed by those demonstrating that NO inhibits platelet aggregation by mechanisms also involving cGMP. Guanylate cyclase was found to contain heme as a prosthetic group, which functioned to bind NO and alter the configuration of the active site to increase access to the substrate, MgGTP. Activation of guanylate cyclase by NO results in a 200- to 400-fold increase in Vmax and a 3-fold decrease in Km for MgGTP. The cyclic GMP system represents the principal signal transduction mechanism by which NO elicits many of its physiological effects in the mammalian species. More recently, however, cyclic GMP-independent pathways have been discovered which can account for certain biological actions of NO. The most important is S-nitrosylation of proteins and consequent modification of protein function. This mechanism is important in both physiological and pathophysiological actions of NO. For example, NO appears to inhibit vascular and tumor cell proliferation by inhibiting ornithine decarboxylase via S-nitrosylation of active site cysteine residues. There are many similar examples. NO plays important regulatory roles not only in blood vessels per se but also in the peripheral nervous system, where NO is the principal neurotransmitter of the nonadrenergic-noncholinergic neurons that innervate various tissues including the erectile tissue. The neurotransmitter NO directly relaxes vascular and nonvascular smooth muscle to cause the erectile response. NO may function in a similar way also in the gastrointestinal tract, in the genitourinary tract, and in the airways.

Based on these properties of NO, new drugs can be developed as vasodilators, antiplatelet and antiproliferative agents for the treatment of hypertension, atherosclerosis, stroke, angina pectoris, heart failure, vascular complications of diabetes, gastrointestinal ulcers, impotency and other vascular disorders. An excellent example of this is the development of sildenafil, which has revolutionized the treatment of erectile dysfunction. Another good example is nebivolol, a unique beta-1 receptor blocker with vasodilator properties attributed to NO. Nutritional supplements containing L-arginine and antioxidants have emerged, which promote the production and action of NO, and are used for promoting heart health and athletic performance.

NO elicits many other actions in mammalian systems including inhibition of cell proliferation, airway bronchodilation, antimicrobial effects, other host defense effects, and also modulates learning and memory as well as other central functions. There are undoubtedly many as yet unknown functions of NO. This allows for an extensive opportunity to develop novel drugs for the diagnosis, prevention and treatment of a multitude of cardiovascular disorders.

The Killam Memorial Award:

The Keith F. Killam Jr. Memorial Award was created by the Society to recognize important contribution by young investigator in pharmacology. Originally offered as the Syntex Prize in Pharmacology by the society, the award was renamed following the death of Professor Killam in 1998. This year following the death of Keith's wife Eva K. Killam in July of 2006, the award name has been changed in memory of both Keith and Eva Killam.

Eva Killam was a founding member and past President of the Western Pharmacology Society. Along with her late husband Keith F. Killam, Jr., Eva Killam was among the original faculty members of the UC Davis School of Medicine when it opened the doors to its first students in 1968. She began her career at UC Davis as a professor of physiology, but later transferred to the Department of Pharmacology, where she joined her husband, who founded the department and served as its chair.

Killam was born in New York and completed her undergraduate degree in biology from Sarah Lawrence College. She earned her doctorate in pharmacology from the University of Illinois and came to California as a junior research pharmacologist at UCLA School of Medicine.

In addition to her research and teaching duties at UC Davis, Eva was very active in other professional organizations, serving as the first female president of the American College of Neuropsychopharmacology and as president of the American Society of Pharmacology and Experimental Therapeutics. She also served as editor-in-chief of the *Journal of Pharmacology and Experimental Therapeutics* for many years. Eva Killam served as a professor of pharmacology at US Davis School of Medicine until her retirement in 1991.

The 2008 Killam Award

This year's recipient of the Keith and Eva Killam Memorial Award is William Schiemann. Dr. Schiemann received his B.S. in Premedicine from the University of Nevada, Reno in 1990. During his undergraduate studies in the Laboratory of Iain Buxton, at the University of Nevada School of Medicine, Bill investigated the signal transduction systems stimulated by Adenosine receptors in pregnant and nonpregnant myometrium. In 1991, he joined the Department of Pharmacology at the University of Washington where, under the guidance of Dr. Neil Nathanson, he characterized the signal transduction systems stimulated by the receptors for Leukemia Inhibitory Factor. In 1996, Dr. Schiemann joined the laboratory of Dr. Harvey Lodish at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. As a postdoctoral fellow in Dr. Lodish's laboratory, Bill developed an intense interest in the signaling systems stimulated by TGF-β and, more importantly, in determining how aberrations in this signaling system contribute to the formation of human diseases, particularly breast cancer. Dr. Schiemann joined the faculty in the Department of Pediatrics at National Jewish as an Assistant Professor in 2001, and now is an Associate Professor in the Department of Pharmacology at the University of Colorado Health Sciences Center, where he continues to investigate the role of TGF-β in both suppressing and promoting mammary tumorigenesis.

Wednesday 2 p.m., Naupaka IV

The Keith and Eva Killam Memorial Award Lecture

New Inroads in Understanding the TGF-β Paradox in Mammary Epithelial Cells

William Schiemann, PhD
Department of Pharmacology
University of Colorado Health Sciences Center

TGF-β regulates all stages of mammary gland development and suppresses breast cancer formation by preventing cell cycle progression in mammary epithelial cells (MECs). Unfortunately, genetic and epigenetic events often negate the cytostatic function of TGF-β in MECs, an event that ultimately enables malignant MECs proliferate, invade, and metastasize when stimulated by TGF-β. The conversion of TGF-β from tumor suppressor to tumor promoter is referred to as the "TGF-β Paradox" and molecular mechanisms that underlie this phenomena remain poorly defined. We recently discovered that the expression and activity of αvβ3 integrin and Src are essential for TGF-β stimulation of MEC proliferation, invasion, and epithelial-mesenchymal transition (EMT). Mechanistically, β3 integrin interacts with the TGF-β type II receptor (TbR-II), leading to its Tyr phosphorylation by Src, and to its activation of p38 MAPK. We further show that oncogenic messages transduced *via* this signaling axis requires Src to phosphorylate TbR-II on Tyr284, which coordinates the docking of the SH2 domains of Grb2 and Shc to TbR-II, and in mediating EMT and invasion stimulated by αvβ3 integrin and TGF-β. More importantly, the ability of TGF-β to stimulate breast cancer growth and pulmonary metastasis in mice absolutely required TbR-II Tyr284 phosphorylation, which activated p38 MAPK in developing and progressing mammary tumors. Moreover, malignant MECs that become "addicted" to this oncogenic signaling axis readily acquire resistance to small molecule chemotherapeutics designed to antagonize TGF-β receptors, thereby necessitating the development of alternative approaches to prevent oncogenic signaling by TGF-β.

More recently, we defined a novel TAB1:xIAP:TAK1:IKKb:NF-kB signaling axis that forms aberrantly in breast cancer cells, and in normal MECs following their induction of EMT by TGF-β. Once formed, this signaling axis enables oncogenic signaling by TGF-b in part *via* activation of NF-kB and its consequential production of proinflammatory cytokines, and of Cox-2, which inhibits TGF-β signaling *via* a PGE2- and GSK3β-dependent mechanism. In addition, TAK1-deficiency abrogated the ability of TGF-β to induce the invasion of breast cancer cells, as well as restored their ability to undergo cytostasis in response to TGF-β. Finally, expression of a dominant-negative TAB1 mutant dramatically reduced the growth of mammary tumors in normal mice, as well as in their immunocompromised counterparts, suggesting a potentially important role of NF-κB in regulating innate immunity by TGF-β.

Collectively, we have discovered two distinct signaling axes that mediate oncogenic signaling by TGF-β in normal and malignant MECs. Importantly, interdicting the ability of TGF-β to activate either oncogenic pathway abrogated the tumor promoting activities of TGF-β and partially restored its cytostatic function in breast cancer cells. Our findings indicate that oncogenic signaling by TGF-β is evolutionarily and functionally redundant to that mediated by growth factor receptors; they also suggest that selective targeting of oncogenic TGF-β signaling axes may serve to "normalize" malignant tissues in such a way that cancer itself is converted from an acute, symptomatic, and life-threatening disease to one that is chronic, asymptomatic, and manageable through the normal lifespan of affected individuals.

Kona 2008

Meeting Program

Sunday, January 27th

3:00 - 6:00 pm

Registration and Check In:
WPS Registration Desk, Naupaka Lanai

Pick up your meeting backpack, program book, and badge. The desk will be open Sunday the 27th till 6 pm and each day through Wednesday from 8:00 am till noon and again in the afternoon from 1:00 pm till 4 pm.
Late registrants are welcome.

6:00 – 7:00 pm

TOM BURKS MEMORIAL LECTURE: *(Naupaka IV)*

Louis J. Ignarro, Ph.D.
Department of Molecular and Medical Pharmacology,
UCLA School of Medicine, Center for the Health Sciences

"The History and Discovery of Nitric Oxide as a Signaling Molecule in Physiology"

7:00 – 9:00 pm

Opening Reception
Naupaka Lanai

Refreshments and Hors D'Oeuvres will be served. A cash bar will be available for those wishing drinks other that wine, beer and soft-drinks.

Kona 2008

Monday, January 28th

7:00 – 8:00 am	**Continental Breakfast** *(Naupaka I-III)*
8:00 – 12:00 N	**Symposium I: FETAL ORGANS OF CARDIOVASCULAR DISEASE** *(Naupaka IV)*
8:00 – 8:05 am	Introduction, *Chair*: Kent Thornburg, OHSU
8:05 – 8:50 am	**Programming Towards Obesity and Diabetes** *Sherin U. Devaskar; David Geffen School of Medicine at UCLA*
8:50 – 9:35 am	**Developmental Origins of Hypertension: Does Programmed Oxidative Stress Underlie Renal and Vascular Mechanisms?** *Susan Bagby, M.D., Oregon Health & Science University, Portland, OR*
9:35 – 10:20 am	**Developmental Programming of Coronary Artery Dysfunction by Early Gestation Dexamethasone Exposure**. Jeffrey L Segar, *M.D., University of Iowa Carver College of Medicine, Iowa City, IA*
10:20 – 10:30 am	**Coffee Break**
10:30 – 11:15 am	**Pro- and Anti- Proliferation in Immature Cardiac Myocytes: Who Wins?** *Kent Thornburg, Ph.D., Heart Research Center, Oregon Health & Science University, Portland, OR*
12:00 – 6:00 pm	**Lunch on Your Own** ***Time to enjoy the beach, pool, and activities!***
6:00 – 10:00 pm	**Poster Session I and Reception** *(Naupaka V-VII)* **(Posters M1 – M 24)** Refreshments and Hors D'Oeuvres will be served. A cash bar will be available for those wishing drinks other that wine, beer and soft-drinks.

Kona 2008

Tuesday, January 29th

7:00 – 8:00 am	**Continental Breakfast** *(Naupaka I-III)*
8:00 – 12:00 N	**Symposium II: ESTROGEN AND WOMAN'S HEALTH** *(Naupaka IV)*
8:00 – 8:05 am	Introduction, *Chair*: Gautam Chaudhuri, UCLA
8:05 – 8:50 am	**Hormone Therapy and Cardiovascular Disease: The Estrogen Paradox** *Gautam Chaudhuri, M.D., David Geffen School of Medicine at University of California, Los Angeles, CA*
8:50 – 9:35 am	**Alternatives to Estrogen Therapy in Menopausal Women**. *Lauren Nathan, M.D., David Geffen School of Medicine at University of California, Los Angeles, CA*
9:35 – 10:20 am	**Estrogen for the Prevention of Coronary Heart Disease in Perspective.** *Howard N. Hodis, M.D., Keck School of Medicine, University of Southern California*
10:20 – 10:30 am	**Coffee Break**
10:30 – 11:15 am	**Postmenopausal Hormones are a Reasonable Option for Short-Term Relief of Vasomotor Symptoms, But Not For Long Term Cardioprotection.** *Jacques Rossouw, M.D., National Heart, Lung and Blood Institute, Bethesda, MD*
12:00 – 6:00 pm	**Lunch on Your Own** ***Enjoy…. Humpback Whale watching!***
12:00 – 1:00 pm	WPS Councilors Meeting (*Lehua Ballroom 1)*
6:00 – 10:00 pm	**Poster Session II and Reception** *(Naupaka V-VII)* **(Posters T25 – T48)** Refreshments and Hors D'Oeuvres will be served. A cash bar will be available for those wishing drinks other that wine, beer and soft-drinks.

Kona 2008

Wednesday, January 30th

7:00 – 8:00 am	**Continental Breakfast** *(Naupaka I-III)*
8:00 – 12:00 N	**Symposium III: DNA METHYLATION AND CANCER THERAPY** *(Naupaka IV)*
8:00 – 8:05 am	Introduction, *Chair*: Lawrence Sowers, LLU
8:05 – 8:50 am	**DNA Methylation, Epigenetic Control and Gene Reactivation** *Lawrence Sowers, Ph.D., Loma Linda University School of Medicine, Loma Linda, CA*
8:50 – 9:35 am	**Epigenetic Silencing In Cancer: Cause and Consequence** *Paula M. Vertina, Ph.D., Emory University School of Medicine, Atlanta, GA.*
9:35 – 10:20 am	**Use of Expression Microarrays To Identify Epigenetically Silenced Cancer Genes** *Martina L. Veigl, Ph.D., Case Western Reserve University, Cleveland, OH.*
10:20 – 10:30 am	**Coffee Break**
10:30 – 11:15 am	**Aberrantly Silenced Genes - A Potential Reservoir Of Diverse Phenotypes In Developing Cancers** *W. David Sedwick, Ph.D., Case Western Reserve University, Cleveland, OH.*
12:00 N – 1:00 pm	**THE KEITH AND EVA KILLAM MEMORIAL LECTURE:**
	New Inroads in Understanding the TGF-b Paradox in Mammary Epithelial Cells *William Schiemann, PhD, Department of Pharmacology University of Colorado Health Sciences Center*
1:00 – 6:00 pm	**Lunch on Your Own**
	Enjoy…Snorkeling!

Kona 2008

More Wednesday

1:00 – 2:00 pm **WPS Business Meeting,** *(Lehua Ballroom I – II)*
An agenda will be available on site. Matters such as the WPS joining IUPHAR will be presented.

6:00 – 10:00 pm **Poster Session III and Reception** *(Naupaka V-VII)*
(Posters W49 – W72)

Refreshments and Hors D'Oeuvres will be served. A cash bar will be available for those wishing drinks other that wine, beer and soft-drinks.

Kona 2008

Thursday, January 31th

7:00 – 8:00 am	**Continental Breakfast** (*Naupaka I-III)*
8:00 – 12:00 N	**Symposium IV: CHRONIC FATIGUE SYNDROME** *(Naupaka IV)*
8:00 – 8:05 am	**Introduction**, *Chair:* Judy Mikovits, UNSOM & WPI
8:05 – 8:50 am	**Diagnosis and Treatment of CFS** *Daniel L. Peterson, MD, Whittemore Peterson Institute for Neuroimmune Disease Reno, NV*
8:50 – 9:35 am	**Immune Abnormalities in Chronic Fatigue Syndrome** *Nancy Klimas, MD, University of Miami Miller School of Medicine Miami, FL*
9:35 – 10:20 am	**Role of Viral Infections in Chronic Fatigue Syndrome** *Konstance Knox, PhD, Wisconsin Viral Research Group, Milwaukee, WI*
10:20 – 10:30 am	**Coffee Break**
10:30 – 11:15 am	**Virus interactions, the Innate Immune Response and Inflammation** *Francis W Ruscetti, PhD, Cancer and Inflammation Program, Center for Cancer Research National Cancer Institute Frederick, MD*
12:00 – 1:00 pm	**Lunch on Your Own**

Enjoy…the afternoon symposium!

More Thursday

1:00 – 3:00 pm	**Symposium IV: PHARMACOGENOMICS, ACSEPT** *(Naupaka IV)*
1:00 – 1:45 p.m.	**Evolution of Pharmacogenetics** *Andrew Somogyi, Ph.D., University of Adelaide, Adelaide, Australia.*
1:45 – 2:30 p.m.	**Pheno- or Genotype For The Cyp2c19 Drug Metabolism Polymorphism: The Influence of Disease.** *Nuala Helsby, Ph.D., University of Auckland, Auckland, New Zealand.*
2:30 – 3:15 p.m.	**VARIABILITY IN OPIOID EFFICACY: HOW MUCH IS DUE TO PHARMACOGENOMICS?** *Janet Coller, Ph.D., University of Adelaide, Adelaide, Australia*
3:15 – 3:25 p.m.	**Refreshment Break**
3:25 – 4:05 p.m.	**Thiopurine Pharmacogenetics – Drug Efficacy and Safety** *John Duley, Ph.D., University of Queensland, Brisbane, Australia*
4:05 – 4:50 p.m.	**Warfarin Pharmacogenetics: Ready for Clinical Translation?** *Munir Pirmohamed, Department of Pharmacology, The University of Liverpool, UK*
6:00 – 7:00 pm	**Reception,** (*Naupaka Lanai)*
7:00 – 10:00 pm	**Banquet Dinner and Awards Ceremony** *(Naupaka IV)* A cash bar will be available for those wishing drinks other than wine, beer and soft-drinks.

SPEAKER ABSTRACTS

SYMPOSIUM I

Fetal Organs of Cardiovascular Disease

***Chair*: Kent Thornburg, OHSU**

Speakers:

Sherin Devaskar, MD
Susan P. Bagby, MD
Jeffrey Segar, MD
Kent Thornburg, PhD

Monday January 27, 2008
8:00 am

Naupaka IV

PROGRAMMING TOWARDS OBESITY AND DIABETES

Sherin U. Devaskar; David Geffen School of Medicine at UCLA (sdevaskar@mednet.ucla.edu)

Epidemiological studies have linked postnatal nutritional modifications superimposed on aberrant fetal nutrient/metabolic status to various adult onset chronic diseases including obesity and diabetes mellitus. Mimicking this paradigm, employing rat and mouse models, tissue-specific and timing dependent mechanisms have been deciphered. Transcriptional and post-translational signaling processes were observed to be dysregulated, some of which present soon after birth and persist in the adult in a sex-specific manner. Studies in males demonstrate the development of diabetes mellitus, while investigations in females reveal transgenerational persistence of this phenotype. The basis for this transgenerational transmission relate to permanent modifications in the histone code that epigenetically alter gene expression. Compensation for aberrant gene expression is accomplished by post-translational mechanisms targeted at maximizing function which subsequently deteriorates resulting in disease. This presentation will focus on investigations surrounding the hypothalamus and nutrient transporters with particular emphasis on the insulin responsive glucose transporter. Particularly its expression, insulin responsive post-translational processing and translocation, and certain insulin signaling processes that link the insulin receptor to the glucose transporter have been discerned.

DEVELOPMENTAL ORIGINS OF HYPERTENSION: DOES PROGRAMMED OXIDATIVE STRESS UNDERLIE RENAL AND VASCULAR MECHANISMS?

Bagby, S.P., Roullet, J.B., Xue,H. Department of Medicine, Oregon Health & Science University, Portland, OR 97239 (bagbys@ohsu.edu)

Increased risk of hypertension in adult life is a consistent feature in humans born small for gestational age. Early animal models of maternal nutrient restriction (MNR) emphasized roles of reduced nephron number and accelerated growth ("catch-up") in creating mismatch between body size and excretory capacity, driving renal adaptations. However, that uninephrectomy in mature adults yields little risk of hypertension suggests additional factors. Recent studies have dissociated nephron number and hypertension. In children born small, vascular dysfunction precedes hypertension and includes vascular hyperreactivity to stress and impaired endothelial vasodilatory function. MNR in rodents produces, in adult hypertensive offspring, vascular hyperreactivity to Angiotensin II (AngII). In addition to classic signaling modes, AngII - via the AT1 receptor - normally activates an NADPH oxidase-dependent/EGF receptor-transactivating pathway in mediating vasoconstriction. In MNR models, AngII hyperreactivity is associated with increased NADPH oxidase activity but could reflect structural effects of hypertension. In a microswine model of late gestation/early lactation maternal protein restriction, we find endothelium-independent mesenteric hyperreactivity to AngII in normotensive juvenile offspring, largely mediated by enhanced signaling via the NADPH-oxidase-dependent pathway. AngII hyperreactivity also involves renal vasculature, a site with unique relevance to hypertension. Finally, in rodent MNR models, early short-term antioxidant interventions can prevent vascular dysfunction and hypertension. It thus seems probable that developmental hypertension reflects interactions of several programmed pathways: early pro-oxidant pathways activated in utero by MNR may persist to drive vascular dysfunction and adversely impact renovascular adaptations to nephropenia. Loss of antioxidant capacity with aging might explain the slow evolution of overt hypertension. Most exciting, short-term antioxidant interventions in early postnatal life may ameliorate development of disease.

DEVELOPMENTAL PROGRAMMING OF CORONARY ARTERY DYSFUNCTION BY EARLY GESTATION DEXAMETHASONE EXPOSURE.

Jeffrey L Segar. Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA. (*jeffrey-segar@uiowa.edu*)

Epidemiological studies suggest that exposure to an adverse intrauterine environment predisposes to the development of cardiovascular disease, including hypertension and coronary artery disease. The mechanism(s) linking this relationship is not known but may be related to increased exposure of the developing fetus to circulating glucocorticoids. In an ovine model of developmental programming involving maternal dexamethasone (dex) administration early in gestation (27-28 day gestation, term being 145 days), we have demonstrated altered coronary artery reactivity and endothelial dysfunction in 4 mo old offspring but not the near-term fetus. Coronary artery superoxide production, measured by lucigenin-enhanced chemiluminescence and dihydroethidium fluorescence was increases in dex-exposed sheep relative to controls. Coronary arteries reactivity to angiotensin II was also enhanced, an effect abolished by either endothelial removal or incubation with membrane permeable superoxide dismutase and catalase. Angiotensin II also significantly increased endothelial superoxide production and NADPH oxidase activity in coronaries from dex-exposed offspring, but not controls. Coronary artery smooth muscle cell proliferation is increased in dex-exposed animals, as is expression of Proliferating Cell Nuclear Antigen (PCNA). These findings demonstrate that early gestation glucocorticoid exposure elicits alterations in coronary vascular smooth muscle structure and function similar to those seen with the development of atherosclerosis. Glucocorticoid-induced alterations in coronary physiology may provide a mechanistic link between an adverse intrauterine environment and later cardiovascular disease.

PRO- AND ANTI- PROLIFERATION IN IMMATURE CARDIAC MYOCYTES: WHO WINS?

*Thornburg, K, Louey, S., Chattergoon, N., Sundgren, N., Jonker, S., O'Tierney, P., Giraud, G
Heart Research Center, Oregon Health & Science University, Portland, OR 97239-3098
(*thornbur@ohsu.edu*)

Fetuses that grow slowly face elevated risks for coronary heart disease and heart failure as adults. Their hearts are vulnerable, in part because they have fewer myocytes. In late gestation, ovine cardiomyocytes gradually lose their ability to proliferate as they become binucleated. Proliferation before this terminal differentiation event determines the number of heart cells at birth and may set the number for life. The mechanisms that turn off the proliferation switch are unknown but mechanical, hypoxic and nutrient stressors are known to alter the rate of proliferation and maturation of cardiomyocytes. IGF-1 stimulates proliferation of fetal cardiac myocytes via the mitogen activated protein kinase and phosphoinositol-3-kinase (PI_3K) pathways. Thyroid hormone in the form of 3'-5'-3 tri-iodo-L-thyronine (T_3) suppresses cardiomyocyte proliferation and signals via classical and PI_3K pathways. Competition for the actions of pro and anti proliferative growth factors appears to be important in regulating the numbers of, and the maturation of, heart cells at birth. The story is complicated by the role of cortisol, which normally rises in the last few weeks of gestation. Cortisol is a pro proliferative growth factor by itself, but it also stimulates deiodinases that convert the inactive thyroxine (T4) to active T3, the anti proliferation agent. How does this work in the stressed fetus? The behavior of cardiomyocytes in compromised fetuses that have grown under conditions of placental insufficiency is surprising. Growth is stunted and proliferative activity among cardiomyocytes is powerfully suppressed; also, the number of cells exiting the cell cycle is small—while cortisol levels are high and IGF-1 levels are low. *Funded by NICHD.*

SPEAKER ABSTRACTS

SYMPOSIUM II

Estrogen and Woman's Health

***Chair*: Gauntam Chaudhuri, UCLA**

Speakers:

Gautam Chaudhuri, MD
Lauren Nathan, M.D.
Howard N. Hodis, M.D.
Jacques Rossouw, M.D.

Tuesday, January 29, 2008
8:00 am

Naupaka IV

HORMONE THERAPY AND CARDIOVASCULAR DISEASE: THE ESTROGEN PARADOX

*Chaudhuri, G., Department of Obstetrics and Gynecology, David Geffen School of Medicine at University of California, Los Angeles, CA 90095 (gchaudhuri@mednet.ucla.edu)

Estrogen-progesterone therapy has been used for the control of hot flashes in post-menopausal women. However, the Women's Health Initiative (WHI) study has raised concerns about the adverse effects of estrogen-progesterone therapy on the cardiovascular system. The mean age at which hormone therapy was administered in the WHI study was around 63, whereas the average age when menopause occurs is around 51 years. An early step in the development of atherosclerosis is the adhesion of monocytes to the endothelial cells following expression of the vascular cell adhesion molecular 1 (VCAM-1). In ovariectomized (OVX) animals, fed a cholesterol enriched diet, administration of estrogen continuously from the time of OVX attenuates atherogenesis. Estrogen does this by decreasing both VCAM-1 and monocyte chemoattractant protein-1 (MCP-1). However, if estrogen is administered after the development of atherosclerosis, the beneficial effects are not observed. It is proposed that estrogen increases the production of both nitric oxide (NO) and prostacyclin (PGI_2) from the healthy endothelial cells, which account for the attenuation of atherosclerosis. Both NO and PGI_2 prevent platelet aggregation as well as adhesion of circulating white blood cells to the endothelium. On the other hand, in the presence of abnormal endothelium as observed in atherosclerosis, production of NO and PGI_2 are decreased and hence the beneficial effects of estrogen are not observed. In the absence of NO and PGI_2 production by endothelial cells of atherosclerotic vessels by estrogen, the coagulation factors, which are increased following estrogen administration predominates and hence the cardiovascular complications are increased in atherosclerotic vessels.

ALTERNATIVES TO ESTROGEN THERAPY IN MENOPAUSAL WOMEN.

*Nathan, L. Department of Obstetrics and Gynecology, David Geffen School of Medicine at University of California, Los Angeles, CA 90095 (lnathan@mednet.ucla.edu)

The treatment of menopausal symptoms remains an important health concern. Vasomotor instability and atrophic vaginitis are two of the most common conditions adversely affecting quality of life amongst menopausal women. Until recently, estrogen therapy was the mainstay of treatment for these conditions. However, the Women's Health Initiative hormone trial has raised concerns regarding the safety of estrogen therapy. Therefore, alternatives to estrogen therapy for treatment of menopausal symptoms have assumed increasing importance. Approximately 75% of menopausal women experience vasomotor symptoms. Vasomotor symptoms resemble a heat dissipation response and likely occur as a result of narrowing of the hypothalamic thermoregulatory set point, mediated by a change in the activity of noradrenergic and serotonergic systems. Estrogen withdrawal is necessary but not sufficient for vasomotor symptoms to occur. Estrogen is the most effective agent for alleviation of vasomotor symptoms. Other groups of pharmacologic agents, such as selective serotonin and norepinephrine reuptake inhibitors, have also been shown to alleviate vasomotor symptoms, but not to the same degree as estrogens. The efficacy of these alternatives depends on the specific agent being utilized and the patient population studied. Side effects limit their utility in some women. Herbal therapies have not shown significant benefit in the management of vasomotor symptoms. Atrophic vaginitis is another common condition resulting from estrogen withdrawal and can adversely affect quality of life through direct and indirect effects on sexual function. Local vaginal administration of estrogen is effective in the management of atrophic vaginitis and is associated with fewer risks than systemic estrogen therapy owing to less systemic absorption. It remains a treatment option for women who otherwise are not candidates for systemic estrogen therapy.

POSTMENOPAUSAL HORMONES ARE A REASONABLE OPTION FOR SHORT TERM RELIEF OF VASOMOTOR SYMPTOMS, BUT NOT FOR LONG TERM CARDIOPROTECTION.

Rossouw, JE., Division of Prevention and Population Sciences, National Heart, Lung and Blood Institute, Bethesda, MD 20892 (*rossouwj@nih.gov*)

The Women's Health Initiative trial data suggest that HT given for 4-5 years starting within 10 years of the menopause is relatively neutral, with no effect (or possibly even a reduction) in CHD and mortality, but remaining risk for stroke and breast cancer. However, women initiating HT when they are more distant from the menopause are at increased risk of CHD, particularly if they have persistent vasomotor symptoms. Though the relatively more beneficial outcome in women close to the menopause is somewhat reassuring for limited use during that period of life, for prevention of disease the more important question is whether HT initiated at that earlier period will continue to have benefit with long term use over several decades. The answer to this question is unknown (and unknowable with any certainty). Ongoing surrogate outcome trials in younger women cannot address it, observational data on long-term users are particularly confounded by powerful successful user and compliance biases, and the very long-term trials with clinical outcomes that would be needed for definitive results are not feasible. What we do know is that as women grow older their arteries grow older, and that HT has adverse effects in older women with older arteries. Thus, any potential early benefit may reverse to harm over time. The narrow therapeutic window of HT in terms of timing (in addition to its off-target effects) compares poorly to the more accepted strategies for long-term prevention of CHD such as lipid-lowering and control of high blood pressure. These strategies can be employed with benefit at any age and any stage of disease.

ESTROGEN FOR THE PREVENTION OF CORONARY HEART DISEASE IN PERSPECTIVE

Howard N. Hodis, M.D., Harry J. Bauer and Dorothy Bauer Rawlins Professor of Cardiology, Professor of Medicine and Preventive Medicine, Professor of Molecular Pharmacology and Toxicology, Director, Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California (*athero@usc.edu*)

Contrary to the many consistent observational and case control studies that support the reduction of coronary heart disease (CHD) with hormone therapy (HT), randomized controlled trials have shown no apparent benefit. However, it is now understood that the characteristics of women who participated in observational studies are markedly different from those of women enrolled in randomized controlled trials. Data indicate that the discordance in findings between observational studies and randomized controlled trials is likely related to age and timing of initiation of HT relative to the proximity of menopause. When data from randomized controlled trials are analyzed across the entire age range of participants, the effects of HT on CHD are null. However, when analyzed by age and time since menopause, randomized controlled trials are in agreement with observational studies indicating that HT reduces both total mortality and CHD when initiated in younger postmenopausal women in close proximity to menopause. On the other hand, randomized controlled trials indicate that when initiated in older postmenopausal women distant from menopause, HT has no beneficial effect on total mortality or CHD. The distinct difference in outcomes between these two subgroups of women accounts for the apparent discordance between observational studies and randomized controlled trials. Randomized controlled trials have shown that the adverse effects associated with HT are low, especially rare in young postmenopausal women (<1 event/1,000 treated women) and comparable to adverse effects of other pharmacological agents used for the primary prevention of CHD. Additionally, the cumulative data indicate that HT is at least as effective as other pharmacological agents in the reduction of total mortality and CHD when used for the primary prevention of CHD in women.

SPEAKER ABSTRACTS

SYMPOSIUM III

DNA Methylation and Cancer Therapy

***Chair*: Lawrence Sowers**

Speakers:

Lawrence Sowers, PhD
Paula M. Vertino, PhD
Martina L. Veigl, PhD
W. David Sedwick, PhD

Wednesday, January 30, 2008
8:00 am

Naupaka IV

DNA METHYLATION, EPIGENETIC CONTROL AND GENE REACTIVATION

*Sowers, L.C., Herring, J., Rogstad, D., and Lao, V.V., Department of Biochemistry and Molecular Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lsowers@llu.edu)

The control of gene activity in complex organisms requires a complex interaction between DNA and histone protein modifications. At a molecular level, methylation of specific cytosine residues is associated with gene silencing, while several modifications of histones including acetylation and methylation are involved in chromatin condensation, decondensation and gene activity. The mechanism by which cytosine methylation initiates a sequence of events leading to chromatin condensation and gene silencing will be discussed. Recently developed stable-isotope labeling methods will be described that allow examination of DNA replication and DNA methylation in replicating human cells. The mechanism of action of nucleoside analogs that can interfere with cytosine methylation and result in gene reactivation will be discussed. Funding was provided by the National Institute of General Medical Sciences and the National Cancer Institute.

EPIGENETIC SILENCING IN CANCER: CAUSE AND CONSEQUENCE

Paula M. Vertino, Emory University School of Medicine, Atlanta, GA. (pvertino@emory.edu)

The research interests of my laboratory focus on the epigenetic basis of human carcinogenesis. Aberrant gene silencing resulting from alterations in DNA methylation and chromatin structure play an important role in the inactivation of tumor suppressor genes in human cancers. We use a number of approaches ranging from the detailed molecular analyses of individual genes, to tumor biology and functional genomics, to investigate the molecular mechanisms underlying these gene silencing events, and how the epigenetic silencing of certain genes contributes to human carcinogenesis. Our studies of TMS1/ASC, a gene identified in our lab that is methylated and silenced in human breast and other cancers indicate that local chromatin architecture and the presence of specific histone modifications plays a critical role in normal, and abnormal DNA methylation patterning. Functional studies have revealed a role for TMS1 in apoptotic signaling, and in particular, the ability of normal breast epithelial cells to undergo programmed cell death in response to loss of extracellular matrix contacts. It is our hypothesis that epigenetic silencing of TMS1 provides a mechanism for such cells to resist apoptosis, a critical step in early breast cancer development. A recent focus of our lab is to combine genome-wide methylation studies with bioinformatics to ask why certain genes are targets of epigenetic gene silencing in cancer. We have found that one aspect driving the aberrant methylation of certain gene loci is an underlying susceptibility dictated by local sequence context. We are developing computational models based on DNA sequence features that are capable of predicting genes that are prone to aberrant methylation in cancer cells. The further refinement of such models will ultimately allow the identification of local sequence/structural features that contribute to the risk of aberrant methylation. Moreover, the ability to identify those genes at risk of epigenetic silencing will provide novel molecular targets for further study as potential biomarkers for improved cancer diagnosis and treatment planning.

USE OF EXPRESSION MICROARRAYS TO IDENTIFY EPIGENETICALLY SILENCED CANCER GENES

Martina L. Veigl and W. David Sedwick, Case Western Reserve University, Cleveland, OH. (*mlv2l@case.edu*)

There is general agreement that progress from pre-malignant to malignant phenotypes can be modulated through a series of progressive mutations in critical genes and that these required changes may vary between tumors. It is also becoming clear that these mutations are accompanied by other events that alter function of genes critical to cancer development and that epigenetic silencing of genes can play a vital role at many interfaces in this process. This presentation discusses the use of gene expression profiling to define unique tumor phenotypes and to identify important proteins involved in development of malignancy. Reversal of gene silencing by drugs that interfere with DNA methyltransferase I reveals that most tumors have unique gene expression phenotypes in which a significant number of genes have been silenced by aberrant methylation of CpG islands in their promoters. Studies illustrate the application of high-throughput approaches to defining important cancer genes among these genes that are altered for expression. Special emphasis will be placed on approaches using reversal of gene silencing to reveal a large set of genes that are known or suspected to be involved in tumor development. In studies to be discussed, comparative microarray analyses of colon cancer cells are used to demonstrate this process. Genes discovered by this approach are compared to genes delineated by similar approaches in lung and other cancers and during development through analysis of promoter methylation phenotypes and additionally by comparison to CAN gene targets (Candidate Cancer Genes) in colon cancers [Science (2007) 314:268]. Interpretive complications caused by heterozygous interaction between epigenetically silenced and mutated alleles and by apparent regulatory relationships between epigenetically regulated genes and downstream targets will also be discussed. [Supported by RO1 CA101983 & P30 CA43703 (Gene Expression & Genotyping Facility – Case Comprehensive Cancer Center)].

ABERRANTLY SILENCED GENES - A POTENTIAL RESERVOIR OF DIVERSE PHENOTYPES IN DEVELOPING CANCERS

W. David Sedwick and Martina L. Veigl, Case Western Reserve University, Cleveland, OH. (*w.sedwick@case.edu*)

Epigenetic modification of promoters provides a mechanism underlying diversity in organisms that is expressed at the cellular level. These modifications are manifested as gene expression changes that can effect differentiative processes that lead to large phenotypic effects on organisms. These mechanisms can be manifested as normal events during development or as aberrant events affecting cancer or leading to developmental diseases. Tumors from different individuals display large differences in expression phenotype resulting from aberrant methylation of gene expression control regions in different genes. These phenotypic differences result from gene silencing caused by chromatin alterations that typically occur at CpG islands in promoter regions in which the CpG dinucleotides are methylated and chromatin is associated with a unique set of modified histones, DNA binding proteins and other regulatory molecules. Significantly, these silenced genes can be activated by disrupting the mechanisms maintaining methylation of these promoter regions. Drug-induced release of silenced genes in cancer cells is largely reversible. However, each tumor cell that survives such drug treatment exhibits a unique constitutive gene expression phenotype and even silenced genes in which expression is not altered are modified in the methylation patterns of putative controlling regions found in their promoters. These effects may have important implications for the ultimate fate of cells surviving therapies designed to restore gene expression in tumors exhibiting gene silenced phenotypes. [Supported by RO1 CA101983 & P30 CA43703 (Gene Expression & Genotyping Facility – Case Comprehensive Cancer Center)].

SPEAKER ABSTRACTS

SYMPOSIUM IV

Chronic Fatigue Syndrome

***Chair*: Judy Mikovits**

Speakers:

Daniel L. Peterson, MD
Nancy Klimas, MD
Konstance Knox, PhD
Francis W Ruscetti, PhD

Thursday, January 31, 2008
8:00

Naupaka IV

DIAGNOSIS AND TREATMENT OF CFS

Peterson, D.L., Whittemore Peterson Institute, Incline Village, Nevada 89450 (dan@ishere.com)

Chronic Fatigue Syndrome (Myalgic Encephalomyelitis as it is known in other parts of the world), is a very disabling disorder. It presents in sporadic as well as epidemic forms and has been recognized for many years, but has only been intensively studied and researched since the early 1980s. A cohesive research definition was established in 1988 and revised in 1994 by the CDC. More recently, the Canadian Consensus Document established a working definition for practicing physicians that includes indicators of prognosis and suggests diagnostic and therapeutic strategies. In addition to severe disabling fatigue, patients frequently have nonrestorative sleep, cognitive dysfunction, myalgias, arthralgias, and GI complaints. The incidence in the United States is estimated to be approximately 300 per 100,000 population. The market potential for a single diagnostic test would be approximately $125,000,000 per year and the market for a therapeutic agent is estimated to be approximately $250,000,000 per year. Many studies have been performed throughout the world in order to determine the pathogenesis and etiology. The most consistent findings include immune abnormalities, particularly low Natural Killer cell function and evidence of subsets of patients demonstrating unique patterns of mRNA gene expression. A subset of patients has evidence of viral reactivation, particularly with the herpes viruses including HHV-6 variant A. Due to a presumed immunologically-mediated disorder, a number of therapies have been instituted including immune modulatory agents such as intravenous gammaglobulin and Ampligen (Poly I: Poly C12 U). To date, therapeutic results have been mixed. There is currently no FDA-approved pharmacological agent specifically for Chronic Fatigue Syndrome/ME. The patients classically are markedly disabled and respond only partially to symptomatic therapy. New diagnostics and therapeutic strategies are clearly indicated for this very disabling illness. Current developments in the area of demographics, subseting of the heterogeneous patient group, and potential strategies for more efficient diagnosis and treatment will be presented.

IMMUNE ABNORMALITIES IN CHRONIC FATIGUE SYNDROME

Nancy Klimas, MD, University of Miami Miller School of Medicine And Miami VA Medical Center
Miami, FL, USA (nancy.klimas@med.va.gov)

After 20 years of research, a number of underlying pathophysiologic abnormalities have been well defined in Chronic Fatigue Syndrome. Immune dysfunction seen has been well characterized, and will be reviewed in this session. Chronic immune activation with cytotoxic lymphocyte cellular dysfunction predominates. Cytokine shift to Th2 patterns with pro-inflammatory cytokine expression occurs in the subset of patients with the most profound symptoms. Genomic studies confirm these earlier findings, and note some linked abnormalities of cortisol regulatory peptides and mitochondrial regulatory pathways. Our own work also demonstrates reductions of granzymes and perforins, in both NK and CD8 cells with the lowest values seen in the patients with more severe illness. This sort of abnormality supports the possibility of reactivated viruses, given the key roles the cytotoxic lineage cells play in viral control. Immune modulatory interventions have been attempted, and will be reviewed in this session. Translational studies of autologous ex vivo expanded cytotoxic T cells had some success, but further studies have not been funded. A phase 1 study of a TNF monoclonal antibody was also promising, and phase 2 studies are being considered. A phase 1 study with thalidomide also showed some early promise, though the dose was limited by low dose toxicity. Isoprinosine, an immunomodulator widely available in Eurroep and Canada, has shown promise in a phase 2 study, and phase 3 studies are being considered. An immunomodulator antiviral product, Ampligen has completed phase 3 trials and is under FDA review at this time. Antiviral studies focused on reactivated herpes family viruses are also underway, though one must raise the question whether concomitant or serial studies to attempt to correct the underlying immune defect may also be necessary. It is also possible that reducing the antigen lode would lead to a correction of the underlying immune activation and function. It is important to include measures of immune function in intervention trials that focus on other areas of dysfunction, as the interaction of immune system with endocrine and autonomic function seems to play a significant role in the maintenance of this illness.

ROLE OF VIRAL INFECTIONS IN CHRONIC FATIGUE SYNDROME

*Knox, KK and Carrigan, DR. Wisconsin Viral Research Group; 10437 Innovation Drive; Milwaukee, Wisconsin; 53226. (*kknox@wisconsinlab.com*)

Viruses have been long suspected to play a role in the etiology of chronic fatigue syndrome (CFS) due to the frequent occurrence of an abrupt onset combined with such parainfectious signs and symptoms as persistent lymphadenopathy and fever. A likely candidate for such a virus is the neurotropic and leukotropic human herpesvirus six (HHV-6), particularly the A variant of the virus, HHV-6A. HHV-6 is ubiquitous with over 90% of children becoming infected by two years of age and an incidence of latent infection by HHV-6 in over 70% of normal adults lung tissues. Interestingly, HHV-6, and especially HHV-6A, has been indicted as the cause of multiple sclerosis (MS), a severe demyelinating disease of the central nervous system. In this context, we compared the incidence of active HHV-6 infections in CFS patients and patients with relapsing-remitting MS at the time of disease relapse using three established diagnostic methodologies, nested plasma PCR, antigenemia in peripheral blood leukocytes and rapid HHV-6 culture. Using cross section samples of blood from patients with CFS and healthy control subjects, a statistically significant ($p<0.001$) higher frequency of HHV-6 infections were observed in the CFS patients with incidences of 22% (11/49), 22% (16/73) and 37% (28/75) for PCR, rapid culture and antigenemia, respectively. Similarly, a significantly ($p< 0.0002$) increased frequency of HHV-6 infection was seen in the MS patients compared to controls with PCR, rapid culture and antigenemia being positive in 24% (6/25), 50% (14/28) and 46% (13/28), respectively. Therefore, we conclude that both CFS patients and patients with relapsing-remitting MS have active HHV-6 infections in their blood leukocytes significantly more frequently than healthy controls.

DENDRITIC CELLS HIJACKED BY HUMAN VIRUSES: PATHOGENIC RELEVANCE AND THERAPEUTIC OPPORTUNITIES.

*Ruscetti, F.W.[1], Jones, K.S.[2], Peterson, D.L[3] and Mikovits, J.A.[3], [1]LEI, CCR and [2] SAIC, National Cancer Institute, Frederick, MD and [3] Wittemore-Peterson Institute, Reno, NV

(*ruscettif@ncifcrf.gov*)

Dendritic cells (DCs) act not only as gate keepers for detection of, but also as target cells for many viruses which has important implications for viral dissemination and persistence. All subsets of DCs are equipped with several sets of receptors recognizing virus-associated molecular signatures, and are at the interface between the innate and adaptive immune response to control viral infections. These viral-DC interactions are of particular pathogenic relevance because they can alter the orchestration of the immune response. For example, DC can efficiently capture and be infected by cell free human T cell leukemia virus type 1 (HTLV-I), the etiologic agent of T cell leukemia and inflammatory neurologic diseases. HTLV-1 is poorly infectious in vitro for other cell types. Both exposed and infected DC can efficiently transfer HTLV-1 to autologous primary CD4+ T cells resulting in long term productive infection and interleukin-2 independent transformation. A candidate to play a role in the viral etiology of chronic fatigue syndrome (CFS) is the A variant of human herpesvirus six (HHV-6A). Both HHV6A exposed and infected DC can efficiently transfer HHV-6A to primary T cells resulting in productive infection. Transmission of the virus to T cells resulting in infection can occur with or without viral replication in DC. Unique among herpes viruses, HHV6A encodes an integrase gene which allows the virus to integrate in the host genome where the virus can remain latent. Reactivation of the virus from latently infected T cells results in productive infection of DC. In conclusion, many viruses associated with human diseases are able to modulate DC development and function resulting in evasion of immune recognition, a generalized immunosuppression and/or chronic inflammation.

SPEAKER ABSTRACTS

SYMPOSIUM V

Pharmacogenetics

Australasian Society of Clinical and Experimental Pharmacology and Toxicology (ASCEPT),

Chaired by Andrew Somogyi

Speakers:

Andrew Somogyi, PhD
Nuala Helsby, PhD
Janet Coller, PhD
John Duley, PhD
Munir Pirmohammed, PhD

Thursday, January 31, 2008
2:00 pm

Naupaka IV

EVOLUTION OF PHARMACOGENETICS

*Somogyi, A.A, Discipline of Pharmacology, University of Adelaide, Adelaide, 5005, Australia. (andrew.somogyi@adelaide.edu.au)

Pharmacogenetics dates back more than 2,000 years to observations by Pythagoras, however it was not until the 1950s when some enzyme polymorphisms (eg. N-acetyltransferase, G6PD) were discovered that the term was coined by Vogel. Pharmacogenetics then went into decline as being too esoteric a subject. In the 1970s the discovery of the CYP2D6 polymorphism and its resultant effect on drug toxicity and response led to many observations of pharmacogenetic-based variations in pharmacokinetics. These and other discoveries and the subsequent ability to genotype led to the term pharmacogenomics. Today, there are an increasing number of genes for which polymorphisms have been identified that are associated with variable drug response whether it be at the drug metabolizing enzyme, transporter or receptor level and, mainly through a candidate genes(s) approach. Increasing use of genome-wide analysis is identifying hitherto unpredictable new genes associated with disease and drug response. Although some old and most new drugs coming onto the market have a "pharmacogenomic footprint", the clinical and practical usefulness of pharmacogenomics has been generally lacking. To date, clinical translation of pharmacogenetics has focused on narrow therapeutic index drugs for toxicity (eg. azathioprine) and more recently for efficacy and toxicity (eg. warfarin) purposes. Pharmacogenetics and genomics will be advanced through lower cost, rapid whole genome sequencing methods combined with sophisticated algorithms allowing individualised dosage recommendations but not necessarily their adoption. However, complicating this is the influence of changes in gene expression by environmental and genetic factors. Therefore translation of pharmacogenetics into "personalised medicine" will depend on many factors including clinical relevance, environmental-genetic interactions, cost and education.

PHENO- OR GENOTYPE FOR THE CYP2C19 DRUG METABOLISM POLYMORPHISM: THE INFLUENCE OF DISEASE.

Helsby, N. A.* Molecular Medicine and Pathology, Faculty of Medical and Health Sciences, Private Bag 92019, University of Auckland, Auckland, New Zealand. (n.helsby@auckland.ac.nz)

A genotyping approach for pharmacogenes such as *CYP2C19* is advocated to personalise therapy, since individuals with the homozygous null allele genotype are poor metabolisers (PM) of many drugs. The bioactivation and clinical disposition of cyclophosphamide may involve CYP2C19 and a clinical review of NZ patients treated with this drug revealed a higher incidence of treatment failure in Polynesian patients. Up to 5% of Caucasians and 20% of Asians are CYP2C19 poor metabolisers (PM). However, the incidence of *CYP2C19* genetic variants in Pacific populations is less well studied. Inhabitation of the South Pacific probably involved migration of people via Papua New Guinea (PNG). Recently we undertook a genotypic analysis of three geographically isolated regions of PNG. The incidence of PM in these populations is extremely high (>48%) and one region (Iruna) may have the highest *CYP2C19*3* variant frequency reported for any population. Thus *CYP2C19* variants may be over-represented in Polynesia and a clinical study to determine the role of *CYP2C19* variants in the clinical response to cyclophosphamide in NZ Polynesian lupus nephritis patients is ongoing. However the relationship between genotype and phenotype may only be valid for young healthy populations. We have demonstrated that advanced cancer decreases CYP2C19 activity independent of genotype: 40% of patients who were *genotypic extensive metabolisers* were phenotypic poor metabolisers. Understanding the mechanism(s) responsible for decreased CYP2C19 activity in disease will be important. Moreover, to achieve successful "personalised medicine" based on genotype alone may not be adequate and additional *phenotypic testing* of pharmacogenes may be required. *Funded by AMRF and Cancer Society NZ*.

VARIABILITY IN OPIOID EFFICACY: HOW MUCH IS DUE TO PHARMACOGENOMICS?

*Coller, J.K., Discipline of Pharmacology, University of Adelaide, Adelaide, SA 5005, Australia (*janet.coller@adelaide.edu.au*)

The use of opioids for the treatment of acute and chronic pain and dependence is often complicated by their narrow therapeutic index and large inter-patient variability in response (efficacy and safety). Aside from factors which influence a patient's pain sensitivity (physiological pain mechanisms, psychological, cultural and environmental factors), pharmacogenomics has also been demonstrated to influence opioid efficacy. This is evident at the pharmacokinetic level where genetic variability in drug metabolising enzymes (eg CYP2D6) and transporters (eg ABCB1) influence the plasma, and perhaps more importantly, the brain concentrations of opioids and their metabolites. In addition, more recent evidence has also supported a role of genetic variability in receptors (eg OPRM1) and signal transduction pathways in altering opioid pharmacodynamics. This presentation will discuss our current knowledge regarding the contribution of pharmacogenomics to inter-patient variability in opioid efficacy via pharmacokinetic and pharmacodynamic mechanisms and the current limitations of translating this knowledge into routine clinical practice.

THIOPURINE PHARMACOGENETICS – DRUG EFFICACY AND SAFETY

*Duley, J., Florin, T., Marinaki, A., Sanderson, J., and Ansari, A. Mater Health Services and University of Queensland, Brisbane, Australia; Purine Research Laboratory, St. Thomas' Hospital, London, U.K. *(john.duley@mater.org.au)*

The thiopurine drugs - azathioprine, mercaptopurine and thioguanine - have established roles as immunosuppressive agents in management of chronic inflammatory conditions and organ transplant rejection, and to treat haematological neoplasia. However, side effects lead to drug withdrawal in up to 25% of patients and non-responsiveness affects another 25%. An understanding of the pharmacogenetics of these drugs has facilitated prediction of toxicity and helped improve efficacy. Thiopurines are primarily inactivated by thiopurine methyltransferase (TPMT), which reduces the amount of drug available to form the cytotoxic thioguanine nucleotides. TPMT is genetically polymorphic, 1/300 of the population being completely deficient of activity and 11% are carriers with half-normal activity. Prior knowledge of TPMT status can avoid exposing a deficient patient to potentially fatal thiopurine therapy and provides one of the best examples of predictive pharmacogenetics. Carriers have better than average response on lower doses. As for many drugs, thiopurine metabolism is determined by more than one pathway, and other genetic variables have recently been described. Another polymorphic enzyme, ITPase, has been correlated with some side effects, and genetic differences in folate metabolism may also affect thiopurine response. New research throws light on the seemingly contradictory effects of xanthine oxidase. The roles of gene promoters and drug transporters have been queried, and somatic mutations in leukemia have been shown to affect TPMT levels. Thiopurine pharmacogenetics illustrate: a model for improving both drug efficacy and safety; a rapidly increasing market (over 10,000 TPMT tests per year in the UK); increasing government/FDA regulation; and evolving research that is providing directions for other pharmacogenetic models. *Funded by St Thomas' Charitable Trust.*

WARFARIN PHARMACOGENETICS: READY FOR CLINICAL TRANSLATION?

Munir Pirmohamed, Department of Pharmacology, The University of Liverpool, Ashton Street, Liverpool, L69 3GE, UK (*munirp@liv.ac.uk*)

Warfarin is one of the most widely used drugs in the world, for treatment of venous thromboembolism and prevention of strokes in patients with atrial fibrillation. It is however a difficult drug to use because of its narrow therapeutic index, unpredictability in dose requirements, and propensity to cause bleeding. The use of pharmacogenetics may provide some insights into the reasons for inter-patient variability in warfarin response, and thereby improve the benefit-harm ratio with warfarin. Investigation of the determinants of warfarin response is however complicated by the fact that multiple genetic and environmental factors determine outcome, and if these are not all captured, we run the risk of developing dosing algorithms that will be inadequate, and provide a false sense of security. To date, studies have consistently shown an association between warfarin maintenance dose requirements and two genes, CYP2C9 and VKORC1. Together with dose and body weight, some studies have suggested that almost 60% of the variance in dose requirements can be accounted for, although this figure seems lower in prospective studies. In order to advance warfarin pharmacogenetics into the clinic, there have been several developments including the formation of the International Warfarin Pharmacogenetics Consortium, randomised controlled trials and the possibility of identifying new genetic determinants through whole genome association studies. These developments, together with the use of different methodologies to develop warfarin dosing algorithms, will be discussed in the presentation. *Funded by the Department of Health, United Kingdom.*

ABSTRACT TITLES
& Assignments

POSTER SESSION I

Monday Evening 6 pm

"M" Poster Exhibits
&
Reception

Naupaka V-VII

M1 DISSOCIATION OF mRNA AND PROTEIN LEVELS FOR HUMAN MYOMETRIAL TREK-1 SUGGESTS NON-GENOMIC CONTROL OF TREK-1 EXPRESSION DURING LABOR

Tichenor, J.N., Mcglothlin, K. Gala, R. and Buxton, I.L.O. Departments of Pharmacology and Obstetrics and Gynecology, University of Nevada School of Medicine, Reno, NV 89557 (*jtichenor@medicine.nevada.edu*)

M2 ROLE OF SEX STEROID HORMONES IN THE REGULATION OF UTERINE ARTERY MYOGENIC TONE DURING PREGNANCY IN HIGH-ALTITUDE EWES

Xiao, D., Chang, K., *Zhang, L., Center for Perinatal Biology, Department of Physiology and Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA (*lzhang@llu.edu*)

M3 ROLE OF SEX STEROID HORMONES IN THE REGULATION OF PKC-MEDIATED UTERINE ARTERY CONTRACTIONS DURING PREGNANCY IN HIGH-ALTITUDE EWES

Chang, K., Xiao, D., *Zhang, L., Center for Perinatal Biology, Department of Physiology and Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA (*lzhang@llu.edu*)

M4 ENDOTHELIAL P2Y RECEPTORS TRANSACTIVATE ENDOTHELIAL VEGF RECEPTORS CONSISTENT WITH A ROLE IN ANGIOGENESIS STIMULATION

Yokdang, N., Rumjahn, S.M. and Buxton, I.L.O., Department of Pharmacology, University of Nevada School of Medicine, Reno, NV 89509 (*ibuxton@medicine.nevada.edu*)

M5 PURINERGIC REGULATION OF ANGIOGENESIS *VIA* VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2 SIGNALING

Rumjahn, S.M., Baldwin, K. and Buxton, I.L.O. Department of Pharmacology, University of Nevada School of Medicine, Reno, NV (*rumjahn@unr.edu*)

M6 A RARE CASE OF GASTRIC SARCOIDOSIS

Patel, K., Patel, J.K., Ren, S.,Odumosu, O.O., Gintautas, J., Patel, A.A. Jamaica Hospital Medical Center, New York, NY, 11418 *(jgintautas@jhmc.org)*

M7 PRESENTATION OF CELIAC SPRUE WITHOUT IRON DEFICIENCY ANEMIA

Patel, J.K., Patel, J., Patel, K., Doshi, K., Gintautas, J.*, Patel, A.A. Jamaica Hospital Medical Center, New York, NY, 11418 *(jgintautas@jhmc.org)*

M8 TO tPA OR NOT TO tPA? THAT IS THE QUESTION.

Joshi, S.G., Ventura, J.G., Cervellione, K.L., Gintautas, J.*, Thakore, H. Jamaica Hospital Medical Center, New York, NY, 11418 *(jgintautas@jhmc.org)*

M9 IS THERE A USE FOR MRI'S FOR THE DIAGNOSIS OF STROKE?

Vo, H.Q., Joshi, S.G., Cervellione, K.L., Saraiya, B, Gintautas, J*, Thakore, H. Jamaica Hospital Medical Center, Jamaica, NY, 11418 *(jgintautas@jhmc.org)*

M10 5-AZA-2'-DEOXYCYTIDINE, AN INNOVATIVE MULTI-EPIGENETIC INHIBITOR OF REPRESSIVE DNA AND HISTONE MODIFICATIONS

Oshiro, M.M.[1], Wozniak, R.J.[3], *Futscher, B.W[1,2]., [1]Arizona Cancer Center, [2]Department of Pharmacology & Toxicology, College of Pharmacy, The University of Arizona, Tucson, AZ 85724, USA. [3]Department of Pharmacology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53706, USA. (bfutscher@azcc.arizona.edu)

M11 MITOCHONDRIAL GSH LEVELS ARE DECREASED IN HEARTS FROM CFTR KNOCKOUT MICE

Jeanblanc, C., Xiang, S.Y., Duan, D., and Buxton, I.L.O. Department of Pharmacology, University of Nevada School of Medicine, , Reno, NV 89557

M12 CHRONIC HYPOXIA DIFFERENTIALLY REGULATES PKCε AND PKCδ PROTEIN EXPRESSION IN H9c2 CELLS.

Patterson, A, *Zhang, L. Center for Perinatal Biology, Department of Pharmacology & Physiology, Loma Linda University School of Medicine, Loma Linda, CA 92350. (lzhang@llu.edu)

M13 MATERNAL TRANSIENT FOOD RESTRICTION RESULTS IN IMPROVED CARDIAC RECOVERY FROM ISCHEMIA/REPERFUSION INJURY IN MALE ADULT OFFSPRING.

Lawrence, J.,[1] Xiao, D.,[1] Yang, S.[2] and *Zhang, L.,[1] [1]Centre for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92354; [2]Department of Chemistry, California State University, San Bernardino, CA 92407 (lzhang@llu.edu)

M14 SEROTONINERGIC SYSTEM PARTICIPATE IN THE DEVELOPMENT OF MYOCARDITIS IN RABBITS

Lychkova, A.E., Central R&D Gastroenterology Institute, Moscow, Russian Federation. (lychkova@mail.ru)

M15 SMAD3 OVEREXPRESSION ALONE INCREASES CONTRACTILITY AND OVERRIDES SMAD7 INHIBITION OF COLLAGEN SECRETION IN PRIMARY CARDIAC MYOFIBROBLASTS

Bedosky, K.M., Cunnington, R.H., Rattan, S.G. and *Dixon, I.M.C. University of Manitoba, Canada (idixon@sbrc.ca)

M16 EFFECT OF FETAL HYPOXIA ON HEART SUSCEPTIBILITY TO ISCHEMIA AND REPERFUSION INJURY IN THE FEMALE ADULT RAT

Xue, Q. and *Zhang, L. Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

M17 REAL-TIME Q-T INTERVAL CHANGES IN CONSCIOUS AND ANESTHESIZED GUINEA PIGS.

Clay E.R, Dong, Y., Walker, M.J. Dept. Anesthesiology, Pharmacology & Therapeutics, UBC, Canada. (rsdaa@interchange.ubc.ca)

M18 ALTERED CHARACTERISTICS OF AGONIST-INDUCED CA^{2+} RESPONSES IN DISEASED HUMAN VALVULAR MYOFIBROBLASTS.

*Liang, W.[1], McDonald, P.[2], McManus, B.[2], van Breemen, C.[2] and Wang, X.[2] [1]School of Biological Sciences, Nanyang Technological University, Singapore 637551; [2]The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, University of British Columbia, Vancouver, BC V6Z 1Y6, Canada. (*willmann@ntu.edu.sg*)

M19 METABOLIC PROFILE OF RATS WITH STREPTOZOTOCIN-INDUCED TYPE 1 DIABETES.

Kwok, E.W.Y., †Liu, G.Y., Leung, J.Y.T., Lim, S.L. and *Pang, C.C.Y., †School of Agriculture and Biology, Shanghai Jiao Tong University, Shanghai, P. R. China, 200240; Department of Anaesthesiology, Pharmacology & Therapeutics, University of British Columbia, Vancouver, Canada, V6T 1Z3 (*ccypang@interchange.ubc.ca*)

M20 CO-IMMUNOPRECIPITATION OF cGMP-PROTEIN KINASE TYPE I & II AND MYOSIN PHOSPHATASE SUGGEST A ROLE FOR THEIR FUNCTIONAL INTERACTION IN HUMAN UTERINE QUIESCENCE AT TERM.

Milton, D., Dennemeyer, S. Gala, R. and Buxton, I.L.O. Departments of Pharmacology and Obstetrics and Gynecology, University of Nevada School of Medicine, Reno, NV (ibuxton@medicine.nevada.edu)

ABSTRACT TITLES
& Assignments

POSTER SESSION II

Tuesday Evening 6 pm

"T" Poster Exhibits
&
Reception

Naupaka V-VII

T1 PRENATAL NICOTINE EXPOSURE CAUSED A GENDER-RELATED INCREASE IN VASCULAR CONTRACTIONS TO ANGIOTENSIN II IN ADULT MALE OFFSPRING.

*Xiao, D.,[1] Huang, X.,[1] Xu, Z.,[1,2] Yang, S.[3] and Zhang, L.,[1,2] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China; [3]Department of Chemistry and Biochemistry, California State University, San Bernardino, CA 92407 (dxiao@llu.edu)

T2 PRENATAL COCAINE EXPOSURE DIFFERENTIALLY REGULATES VASCULAR CONTRACTILITY IN ADULT MALE AND FEMALE OFFSPRING.

Xiao, D.,[1] Huang, X., Yang, S.[2] and *Zhang, L.,[1] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Department of Chemistry and Biochemistry, California State University, San Bernardino, CA 92407 (Lzhang@llu.edu)

T3 PRENATAL NICOTINE EXPOSURE CAUSED A GENDER-RELATED INCREASE IN ANGIOTENSIN II-INDUCED BLOOD PRESSURE ELEVATION IN ADULT OFFSPRING.

*Xiao, D.,[1] Xu, Z.,[1,2] Mao, C.P.,[2] Longo, L.D.[1] and Zhang, L.,[1,2] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China (dxiao@llu.edu)

T4 ALTERATION IN MUSCARINIC RECEPTOR- AND ADRENOCEPTOR-MEDIATED VASORELAXTION IN ACUTE HYPERTHYROID RATS.

Honda, H.[1,2], Iwata, T.[2], Matsuda, H.[2], Kondo, M.[2], Moroe, H.[2], Kumasaka, K.[2] and Ozaki, M.[3], [1]Center for Experimental Pharmacy, School of Pharmacy, Tokyo University of Pharmacy and Life Science, Tokyo 193-0392 Japan. [2]Second Department of Physiology, School of Medicine, Showa University, Tokyo, 142-8555, Japan. Department of Pharmacy, Tokai University Hachioji Hospital, Tokyo, 192-0032, Japan (hhonda@ps.toyaku.ac.jp)

T5 PRENATAL NICOTINE EXPOSURE RESULTS IN REDUCED CARDIAC RECOVERY FROM ISCHEMIA/REPERFUSION INJURY IN ADULT OFFSPRING.

Lawrence, J.,[1] Xiao, D.,[1] Xue, Q.,[1] Rejali, M.,[2] Yang, S.[2] and *Zhang, L.,[1] [1]Centre for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92354; [2]Department of Chemistry, California State University, San Bernardino, CA 92407 (lzhang@llu.edu)

T6 **ROLE OF ALPHA$_1$-ADRENOCEPTORS ON VASCULAR REACTIVITY IN FRUCTOSE-FED RATS**

*McNeill, J.H., Tran, L.T. and Vasudevan, H., Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC Canada (*jmcneill@interchange.ubc.ca*)

T7 **EFFECT OF COCAINE AND NOREPINEPHRINE ON PROTEIN KINASE C-ε EXPRESSION IN FETAL CARDIOMYOCYTES.**

Meyer, K.D., *Zhang, L. Center for Perinatal Biology, Department of Pharmacology & Physiology, Loma Linda University School of Medicine, Loma Linda, CA 92350. (*lzhang@llu.edu*)

T8 **FETAL COCAINE EXPOSURE ABOLISHES CARDIAC ISCHEMIC PRECONDITIONING-INDUCED PROTECTION IN ADULT MALE RATS**

Meyer, K.D., *Zhang, L. Center for Perinatal Biology, Department of Pharmacology & Physiology, Loma Linda University School of Medicine, Loma Linda, CA 92350. (*lzhang@llu.edu*)

T9 **EFFECT OF LONG-TERM HIGH ALTITUDE HYPOXIA ON FETAL PULMONARY VASCULAR CONTRACTILITY**

Xue, Q., Ducsay, C.A., Longo, L.D. and *Zhang, L. Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (*lzhang@llu.edu*)

T10 **PRENATAL NICOTINE ALTERS AT1/AT2 RECEPTOR EXPRESSION IN HEART AND KIDNEY OF NEONATE OFFSPRING.**

*Xu, Z., Xiao, D., Mao, C., Huang, X., Zhang, H., and Zhang, L., Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350; and Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China (*zxu@llu.edu*)

T11 **EFFECT OF FETAL NICOTINE EXPOSURE ON CENTRAL AT1/AT2 RECEPTOR mRNA AND PROTEIN LEVELS IN NEONATE OFFSPRING**

Mao, C., *Xu, Z., Xiao, D., and Zhang, L., Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350; Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China. (zxu@llu.edu)

T12 **COMPARISON OF THE ORAL PHARMACOKINETICS OF FLUCONAZOLE AND ITRACONAZOLE IN MEXICANS.**

Flores-Murrieta, F.J., Carrasco-Portugal, M.C. and Landa, C., Unidad de Farmacología Clínica y Experimental, Instituto Nacional de Enfermedades Respiratorias, Escuela Superior de Medicina del IPN and Instituto Nacional de Rehabilitación. Mexico City, Mexico. (*fjfloresmurrieta@yahoo.com.mx*)

T13 COMPARISON OF NIMESULIDE ORAL PHARMACOKINETICS IN RATS AFTER ADMINISTRATION OF TWO SUSPENSIONS.

Carrasco-Portugal, M.C. and Flores-Murrieta, F.J., Unidad de Farmacología Clínica y Experimental, Instituto Nacional de Enfermedades Respiratorias and Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del IPN. Mexico City, Mexico.
(miris22@hotmail.com).

T14 EVALUATION OF THE INFLUENCE OF MALNUTRITION ON THE ORAL PHARMACOKINETICS OF NIMESULIDE IN RATS.

Carrasco-Portugal, M.C., Camacho-Vieyra, A.G. and Flores-Murrieta, F.J., Unidad de Farmacología Clínica y Experimental, Instituto Nacional de Enfermedades Respiratorias, Laboratorio de Farmacología, Instituto Nacional de Pediatría & Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del IPN. Mexico City, Mexico.(*miris22@hotmail.com*)

T15 *IN SILICO* MODELS INFORM *IN VITRO* MODELS IN ELUCIDATING PHARMACODYNAMIC MECHANISMS: A CASE WITH β_2-ADRENERGIC RECEPTOR AGONISTS.

Soriano-Ursúa Marvin A.[a,b], Correa-Basurto José[a,b,c] Valencia-Hernández Ignacio[c], Arellano-Mendoza Mónica G[c] and Trujillo-Ferrara José G. [a,c]. [a]Departamento de Farmacología, [b]Departamento de bioquímica y [c]Sección de Estudios de Posgrado e Investigación. Escuela Superior de Medicina, Instituto Politécnico Nacional. Plan de San Luis y Díaz Mirón, 11340, México. *(jcorreab@ipn.mx)*

T16 ANTIFIBROTIC EFFECT OF CURCUMIN ON PROLONGED BILE DUCT OBSTRUCTION- INDUCED CIRRHOSIS IN RATS.

Reyes-Gordillo K., Segovia j., Shibayama M., Tsutsumi V., Vergara P., Moreno G.M., and Muriel P*. Cinvestav-IPN., México city, (*pamuriel@cinvestav.mx*).

T17 DANDY-WALKER SYNDROME IN AN OTHERWISE HEALTHY 64-YEAR-OLD FEMALE

Kaur, N.P., Sinnadurai, A., Santucci, T., Gintautas, J.*, Nandakumar, T. Jamaica Hospital Medical Center, New York, NY, 11418 *(jgintautas@jhmc.org)*

T18 A CASE OF TREATMENT-RESISTENT CHRONIC LYME DISEASE WITH SUCCESSFUL SYMPTOM REDUCTION WITH EXTENDED USE OF CEFTRIAXONE.

February, M., Cervellione, K.L., Gintautas, J.*, Bagheri, F. Jamaica Hospital Medical Center, New York, NY, 11418 *(jgintautas@jhmc.org)*

T19 ADENOCARCINOMA OF THE HEPATIC FLEXURE AND THE DESCENDING COLON WITH MANY COLONIC POLYPS REQUIRING OPEN SUBTOTAL ILEOSIGMOID ANASTOMOSIS

Odumosu, O.O., Cervellione, K.L., Satani, D., Patel, K., Gintautas, J., Patel, A.A.
Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

T20 A RARE CASE OF MERKEL CELL CARCINOMA METASTASIS TO THE HEAD AND BODY OF THE PANCREAS

Patel, K., Siegel, J[†]., Podani, J., Cervellione, K.L., Santucci, T.; Gintautas, J.*, Jamaica Hospital Medical Center, New York, NY, 11418; [†]Lenox Hill Hospital, New York, NY, (*jgintautas@jhmc.org*)

ABSTRACT TITLES
& Assignments

POSTER SESSION III

Wednesday Evening 6 pm

"W" Poster Exhibits
&
Reception

Naupaka V-VII

W1 THE DAMAGE OF SYSTEMIC LUPUS ERYTHEMATOSUS ON ARTERIAL WALL ENDOTHELIAL FUNCTION IN RELATIVELY YOUNG PATIENTS

Cypiene,A.[1], Laucevicius, A.[1], Venalis, A.[1], Dadoniene, J.[1], Rugiene, R.[1], Ryliskyte, L.[1], Petrulioniene, Z.[1], Kovaite, M.[1], Skorniakov, V.[1], Griciene P[2] and Gintautas, J.[3]* [1]Vilnius University, Vilnius, Lithuania, [2]Department of Pediatrics State University of New York, Upstate Medical University, Syracuse, NY [3]Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

W2 EFFECT OF THE GABAPENTIN IN THE SLEEP-WAKE CYCLE IN RATS WITH TEMPORAL LOBE EPILEPSY.

Quijada A*, Santillan A, Mexicano G, Ayala Guerrero F. Laboratory of Neurosciences, Faculty of Psychology, National Autonomus University of Mexico. (ariloui@hotmail.com)

W3 PLATELET AGGREGATION IN PATIENTS RECEIVING STATINS, FULLY OR PARTIALLY METABOLIZED BY CYP3A4

Polena, S.[a], Gupta, M.P.[a], Shaikh, H.[a], Zazzali, K.[a], Coplan, N.[a], Gintautas, J.[b]*, Labana, S.S.[b], Soffer, D.[a]. [a]Lenox Hill Hospital, New York, NY, 10021; [b] Jamaica Hospital Medical Center, Jamaica, NY, 11418 (*jgintautas@jhmc.org*)

W4 STRESS IN MALE RAT BRAIN TREATED WITH SINGLE AND REPEATED DOSE OF ABUSE DRUGS

*Calderon, G.D.[1], Labra, R.N.[1], Barragán, M.G.[1], Hernández, G.E.[2], Trujillo, J.F.[2], Juarez, O.H.[2], Osnaya, N[3], Garcia, A.R.[3] 1.Lab. Neuroquímica. 2.Lab Farmacología. 3.Lab. Patología Exptl. Subdirección de Medicina Experimental. Secretaría de Salud. México. (*Solodavid2001@yahoo.com.mx*).

W5 CORONARY DISEASE RISK FACTORS IN YOUNG PATIENTS WITH DIASTOLIC DYSFUNCTION

Polena, S.[a], Morreta, A.[a], Novella, J.[a], Coplan, N.[a], Gintautas, J.[b]*, Saraiya, B.[a] and Gupta, M[a]. [a]Lenox Hill Hospital, New York, NY, 10021; [b] Jamaica Hospital Medical Center, Jamaica, NY, 11418 (*jgintautas@jhmc.org*)

W6 CADMIUM EFFECTS ON A RAT MEMORY MODEL

Tepox-Padrón A.,[a] Ríos-Dávila V.M., [a] Miliar-García A,[b,c] Zepeda H.,[b] Picazo O.,[b] Espinosa J.,[b] Soriano M.,[a] Padilla-Garcia M.,[e] Trujillo-Ferrara J,[a,c] Correa-Basurto J. [a,d,f,*] [a]Departamento de Bioquímica, [b]SEPI-ESM-IPN, Laboratorio de Biología Molecular, [c]SEPI-ESM-IPN, [d]Departamento de Física, ESFM-IPN. [e]Laboratorio de Biología Molecular, Universidad Anahuac. [f]Departamento de Farmacología, ESM-IPN. Plan de San Luis y Díaz Mirón,11340 Mexico City, México. (*atepoxp0300@ipn.mx*).

W7 AN UNUSUAL RADIOLOGIC PRESENTATION OF ADENOCARCINOMA OF THE LUNG

Shamalov, V., Canseco, A.P., Rocher, M., Hechevarria, J.M., Thurm, C., Gintautas, J.*, Bagheri, F. Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

W8 FREE RADICALS INDUCED BY CADMIUM DUE TO A DECREASE OF SOD 1 AND SOD 2 EXPRESSIONS IN RAT BRAIN.

Ríos-Dávila V.M., [a] Tepox-Padrón A., [a] Miliar-García A,[b,c] Rosales-Hernández M.C.,[a,c] Ramirez-Rosales D.,[d] Padilla-Garcia M.,[e] Zamorano-Ulloa R.,[d] Trujillo-Ferrara J,[a,c] Correa-Basurto J. [a,d,f,*] [a]Departamento de Bioquímica, [b]SEPI-ESM-IPN, Laboratorio de Biología Molecular, [c]SEPI-ESM-IPN, [d]Departamento de Física, ESFM-IPN. [e]Laboratorio de Biología Molecular, Universidad Anahuac. [f]Departamento de Farmacología, ESM-IPN. Plan de San Luis y Díaz Mirón,11340 Mexico City, México. (*vriosd0300@ipn.mx*)

W9 EFFECTS OF INHIBITORY AMINO ACIDS ON ADENOSINE RELEASE IN THE MOUSE HIPPOCAMPUS

*Saransaari, P. and Oja, S.S. Brain Research Center, Medical School, FI-33014 University of Tampere, Tampere Finland *(pirjo.saransaari@uta.fi)*

W10 GENDER DIFFERENCES IN BRAIN PERIPHERAL BENZODIAZEPINE RECEPTOR (PBR) EXPRESSION AND SEIZURES PRODUCED BY HEPTACHLOR DURING DEVELOPMENT.

Garcia, E.F. and Woolley, D.E., Neurobiology, Physiology and Behavior, College of Biological Sciences, University of California, Davis, CA 95616-8519 *(dewoolley@ucdavis.edu)*

W11 EFFECT OF TOPICAL DINITROFLUOROBENCE (DNFB) ON MURINE LANGERHANS CELLS.

Trejo-Mondragón, M.[1], Galván-Nava, N.[1], Ponce-Sánchez, A., [3], Sánchez-Ruiz, J.[4], Aguirre-Zárate, P.[4], Tellez-Hernández, B.[5], Alvarez-Pérez, J.[5], Herrera-Enriquez, M.[5], Castel-Rodríguez, A.E.[5], Elinos-Báez, M.[5], Villanueva-Rodríguez, L.G.[2], *Ramírez-González, M.D. Departments of *Pharmacology and [5]Tissue and Cell Biology, School of Medicine, National Autonomous University of Mexico (UNAM). Mexico City 04510 *(mdrg@servidor.unam.mx)*

W12 CONTRIBUTION OF LANGERHANS CELLS TO DRUG-INDUCED ADVERSE REACTIONS

Villanueva-Rodriguez, L.G.[1], Trejo-Mondragón, M.[2], Castell-Rodríguez, A. E.[3], *Ramírez-González, M.D. Departments of Pharmacology and [3]Tissue and Cell Biology, School of Medicine, National Autonomous University of Mexico (UNAM). Mexico city 04510 *(mdrg@servidor.unam.mx)*

W13 APPLICATION OF PEDAGOGY THEORIES INTO MEDICAL PHARMACOLOGY EDUCATION.

*Ramírez-González, M.D. Department of Pharmacology, School of Medicine, National Autonomous University of Mexico, Mexico City 04510 *(mdrg@servidor.unam.mx)*

W14 EFFECT OF CHRONIC ADMINISTRATION OF SUGAR CANE (AZ) ON TAIL FLICK AND FORCED SWIMMING TESTS.

Aranda-Flores, W.[1], Valdez-Reyes, J.[1], Soriano-Flores, S.[1], Cruz-Salas, L.[1], Milán-Chávez, R., Flores-Robles, E., *Ramírez-González, M.D. Departments of *Pharmacology and Biochemistry, School of Medicine, and [1]School of Chemistry, National Autonomous University of Mexico. Mexico City *(mdrg@servidor.unam.mx)*

W15 PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY OF DRUGS IN A PEDIATRIC HOSPITAL OF MEXICO

Juárez-Olguín H, Calderón-Guzmán D, Flores-Pérez J, Guillé-Pérez A, Flores-Pérez C, Pérez-Guillé G. Laboratory of Pharmacology, INP, Universidad Nacional Autónoma de México. Mexico City, 04530, Mexico (*juarezol@yahoo.com)*

W16 PATTERNS OF DRUGS PRESCRIPTION IN PEDIATRIC PATIENTS DURING TWO PERIODS IN MEXICAN PRIVATE HOSPITAL

*Hernández, G.E.[1], Trujillo, J.F.[1], Hernández, S.D.[1], Morales, R.A.[2], Rodríguez, P.R.A.[2], Calderón, G.D.[2], 1. Lab. Farmacología, 2. Lab. Neuroquímica, Instituto Nacional de Pediatría, México. (ernestinahg@aol.com)

W17 PRESCRIPTION DRUG USE PATTERNS IN A MEXICAN NATIONAL PEDIATRIC INSTITUTE

*Hernández, G.E.[1], Trujillo, J.F.[1], Hernández, S.D.[1], Araujo, V.L.F.[3], Rodríguez, P.R.A.[2], Calderón, G.D.[2], 1. Lab. Farmacología, 2. Lab. Neuroquímica, 3. Farmacia, Instituto Nacional de Pediatría, México. (ernestinahg@aol.com)

W18 GENDER-DEPENDENT EFFECT OF PRENATAL COCAINE EXPOSURE ON CORONARY ARTERY MYOGENTIC TONE OF ADULT OFFSPRING.

Xiao, D.,[1] Yang, S.[2] and *Zhang, L.,[1] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Department of Chemistry and Biochemistry, California State University, San Bernardino, CA 92407 (Lzhang@llu.edu)

W19 PRENATAL COCAINE TREATMENT CAUSES DNA METHYLATION AND DOWNREGULATION OF PKCε GENE EXPRESSION IN THE HEART OF ADULT MALE OFFSPRING.

Zhang, H. and *Zhang, L. Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

W20 FETAL COCAINE EXPOSURE CAUSES A GENDER-RELATED DOWNREGULATION OF CARDIAC PKCε EXPRESSION IN OFFSPRING.

Zhang, H. and *Zhang, L. Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

COMPLETE ABSTRACTS
for
POSTER SESSION I

Monday Evening 6 pm

M1 DISSOCIATION OF mRNA AND PROTEIN LEVELS FOR HUMAN MYOMETRIAL TREK-1 SUGGESTS NON-GENOMIC CONTROL OF TREK-1 EXPRESSION DURING LABOR

Tichenor, J.N., Mcglothlin, K. Gala, R. and Buxton, I.L.O. Departments of Pharmacology and Obstetrics and Gynecology, University of Nevada School of Medicine, Reno, NV 89557 (*jtichenor@medicine.nevada.edu*)

Stretch-activated potassium channels (SAKs) have been shown to regulate nitrergic stimulation in gastro-intestinal smooth muscle and may contribute to the quiescence of other smooth muscles in organs that undergo distention, such as the uterus. We therefore, previously, investigated the mRNA expression of one such SAK channel, TREK-1 from human pregnant laboring and non-laboring myometrium via real-time quantitative RT-PCR and found that it is significantly down regulated during labor when comparing 16 non-laboring patients to 9 laboring patients. Based on these data, we hypothesized a down regulation of protein levels during labor. We have since quantified protein levels from plasma membrane fractions from 27 non-laboring patients, and 13 laboring patients and found that levels of TREK-1 protein expression are higher in laboring patients, meaning there is an apparent dissociation between levels of mRNA and protein during labor. We hypothesize that nearing the onset or during the early stages of labor, TREK-1 mRNA is down-regulated while TREK-1 protein expression, having been up-regulated to maintain pre-labor quiescence, has not yet fully left the membrane surface explaining the apparent dissociation of mRNA and protein. Therefore, we further hypothesize that TREK-1 expression in non-plasma membrane fractions (Golgi and ER) will reveal a sequestered fraction of TREK-1 channel protein. Functional tissue studies have shown that there is an increase in the number and/or duration of contractions upon specific blockade of SAK channels. These findings help to confirm that SAK channels play an important role in maintaining the relative quiescence of uterine smooth muscle during pregnancy and may help to initiate the onset of labor by becoming down-regulated and/or leaving the membrane surface at that time. This mechanism may be improperly regulated during preterm labor. (*This work was supported by a March of Dimes National Prematurity Initiative grant and by NIH RO1 HD053028*).

M2 ROLE OF SEX STEROID HORMONES IN THE REGULATION OF UTERINE ARTERY MYOGENIC TONE DURING PREGNANCY IN HIGH-ALTITUDE EWES

Xiao, D., Chang, K., *Zhang, L., Center for Perinatal Biology, Department of Physiology and Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA (*lzhang@llu.edu*)

Pregnancy is associated with a significant decreased in vascular resistance of the uterine artery and an increase in uterine blood flow. We have demonstrated a significant decrease in pressure-dependent myogenic tone in pregnant uterine arteries, which is regulated by the sex steroid hormones estrogen and progesterone. Given that chronic hypoxia has profound effects on uterine artery contractility during pregnancy, we tested the hypothesis that chronic hypoxia alters hormonal effects on myogenic response of the uterine artery. Pregnant (d 30) and nonpregnant ewes were divided between normoxic control and chronically hypoxic (maintained at high altitude, 3,801m, Pao_2: ~60 Torr for 110 days) groups. Uterine arteries were isolated from nonpregnant and d 140 pregnant ewes, and were treated with 17β-estradiol ($E_2\beta$, 0.3 nM), progesterone (P_4, 30 nM), $E_2\beta$ inhibitor ICI 182780 (10 μM), and P_4 inhibitor RU 486 (1 μM) for 48 h in tissue culture medium. In pressurized resistance-sized uterine arteries, we measured vascular diameter (μm) and $[Ca^{2+}]_i$ simultaneously as a function of intravascular pressure. The myogenic tone in uterine arteries from pregnant compared with nonpregnant sheep was significantly decreased in low-pressure range (≤60 mmHg) but not in the range of 70 mmHg to 100 mmHg. Vascular wall $[Ca^{2+}]_I$ was not significantly different between nonpregnant and pregnant uterine arteries. Treatment of nonpregnant uterine arteries with $E_2\beta$ and P_4 resulted in a significant decrease in myogenic tone in the low-pressure range. In pregnant vessels, ICI 182780 and RU 486 significantly increased

myogenic tone. The results demonstrate significant alterations of myogenic response of the uterine artery during pregnancy at high altitude. (supported in part by NIH grant HD31226).

M3 ROLE OF SEX STEROID HORMONES IN THE REGULATION OF PKC-MEDIATED UTERINE ARTERY CONTRACTIONS DURING PREGNANCY IN HIGH-ALTITUDE EWES

Chang, K., Xiao, D., *Zhang, L., Center for Perinatal Biology, Department of Physiology and Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA (lzhang@llu.edu)

Previous studies have demonstrated that PKC-induced contractions of the uterine artery decrease significantly during pregnancy. The sex steroid hormones estrogen and progesterone played an important role in the down-regulation of PKC-induced contractions through their direct genomic effects on the uterine artery. Given that chronic hypoxia has profound effects on uterine artery contractility during pregnancy, the present study tested the hypothesis that chronic hypoxia alters hormonal effects on the uterine artery. Pregnant (d 30) and nonpregnant ewes were divided between normoxic control and chronically hypoxic (maintained at high altitude, 3,801m, Pao_2: ~60 Torr for 110 days) groups. Uterine arteries were isolated from nonpregnant and d 140 pregnant ewes. Arteries were treated with 17β-estradiol ($E_2\beta$, 0.3 nM), progesterone (P_4, 30 nM), the $E_2\beta$ inhibitor ICI 182780 (10 μM), and the P_4 inhibitor RU 486 (1 μM) for 48 h in tissue culture medium, and the PKC activator PDBu-induced contractions were determined. In nonpregnant uterine arteries, $E_2\beta$, P_4, or combination of $E_2\beta$ and P_4, had no significant effects on KCl-induced contractions, but significantly increased PDBu-mediated contractions. The ERK inhibitor PD098059 blocked the effect of the steroid hormones. In pregnant uterine arteries, ICI 182780 but not RU 486 significantly decreased KCl-induced contractions. Neither ICI 182780 nor RU 486 had significant effects on PDBu-induced contractions in pregnant vessels. The results suggest significant changes in tissue response pattern of the uterine arteries to sex steroid hormones during pregnancy at high altitude, which may lead to impairment in normal adaptation of uterine blood flow during pregnancy. (supported in part by NIH grant HD31226).

M4 ENDOTHELIAL P2Y RECEPTORS TRANSACTIVATE ENDOTHELIAL VEGF RECEPTORS CONSISTENT WITH A ROLE IN ANGIOGENESIS STIMULATION

Yokdang, N., Rumjahn, S.M. and Buxton, I.L.O., Department of Pharmacology, University of Nevada School of Medicine, Reno, NV 89509 (ibuxton@medicine.nevada.edu)

We have shown that human breast cancer cells secrete nucleoside diphosphate kinase (NDPK-B) that generates ATP in the presence of ADP and a phosphoryl donor. This finding is consistent with the hypothesis that breast tumor cell-secreted NDPK increases extracellular ATP levels in the immediate environment of metastatic tumors. We and others have shown that extracellular ATP levels activate endothelial cell (EC) receptors for ATP ($P2Y_{1/2}$) which mediate increased capillary permeability, cell migration, release of vasoactive factors, and together with factors such as vascular endothelial cell growth factor (VEGF), promote formation of new blood vessels. We have now linked breast cancer cell-secreted NDPK extract to angiogenesis by showing that NDPK-B promotes EC migration and angiogenesis in culture *via* P2Y receptor activation consistent with a role for P2Y receptor activation in metastatic tumor mediated angiogenesis. While VEGFR activation is thought to provide the single greatest stimulus to new blood vessel formation, P2Y receptors also appear to play a role. Here, we demonstrate that P2Y receptors activate VEGF receptor type 2 in the absence of the growth factor. $P2Y_{1/2}$ receptors activated by ATP and the P2Y1 specific agonist 2-methylthio-ATP, induce phosphorylation of EC VEGFR-2. VEGFR-2 transphosphorylation was measured in Western blots using the anti-phospho-KDR/Flk-1/VEGFR2 antibody. These data confirm that nucleotide receptor signaling causes activation and potentiation of VEGFR2-RTKs. The hypothesis that P2Y signaling activates VEGFR2 suggests the possibility that ATP and VEGF, both produced by metastatic tumor cells, may result in a synergistic effect to produce maximal angiogenic stimulation lowering the requirement for VEGF. (*This work was supported by NIH ND053028 and NIH CA09563.*)

M5 PURINERGIC REGULATION OF ANGIOGENESIS *VIA* VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2 SIGNALING

Rumjahn, S.M., Baldwin, K. and Buxton, I.L.O. Department of Pharmacology, University of Nevada School of Medicine, Reno, NV (*rumjahn@unr.edu*)

MDA-MB-435S human breast cancer cells (435S) secrete a nucleoside diphosphate kinase (NDPK-B) that we have proposed supports metastases by providing local stimulation of ATP-P2Y receptors, and is inhibited by epigallocatechin gallate (EGCG) and ellagic acid (EA). We hypothesize that 435S cell-secreted NDPK-B supports tumor formation by modulating ATP levels locally to activate endothelial cell (EC) P2Y receptor-mediated tubulogenesis (*in vitro* angiogenesis). We have previously shown that $P2Y_1$ receptor activation by NDPK-generated nucleotide (100 µM ATP) or by 10 µM 2-methyl-thio-ATP (2MS-ATP) promoted tubulogenesis on collagen and was blocked by the $P2Y_1$ antagonist MRS2179 (10 µM). Physiological amounts of purified as well as 435S cell-secreted NDPK also promoted angiogenesis that was attenuated by NDPK depletion or 10 µM MRS2179, confirming a $P2Y_1$ receptor-mediated pathway. We observed that blocking Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) signaling using the tyrosine kinase inhibitor SU1498 blocks the observed P2Y receptor-mediated angiogenesis. These results support the notion that secreted NDPK mediates angiogenesis via P2Y receptor signaling involving the VEGF receptor 2 and suggests that novel inhibitors of NDPK may be useful as cancer therapeutics. We propose that the P2YR-VEGFR2 signaling interaction may be important in describing VEGF signaling required for vascular homeostasis in both tumor as well as normal vasculature. (*This work was supported by NIH RO1 HD053028 and NIH CA09563.)*

M6 A RARE CASE OF GASTRIC SARCOIDOSIS

Patel, K., Patel, J.K., Ren, S.,Odumosu, O.O., Gintautas, J., Patel, A.A. Jamaica Hospital Medical Center, New York, NY, 11418 *(jgintautas@jhmc.org)*

Sarcoidosis is a systemic, noncaseating, granulomatous disease of unknown etiology that can involve nearly any organ in the body. Involvement of the gastrointestinal (GI) tract is uncommon and occurs in less than 1% of sarcoidosis cases. The GI tract can be involved as an isolated site of disease or a part of systemic sarcoidosis. A 24-year-old female diagnosed with sarcoidosis of the liver 8 years prior to current admission, which was under remission, presented with burning epigastric pain and nausea for the previous 6 weeks. Abdominal examination revealed massive splenomegaly without hepatomegaly. There were post-inflammatory hyperpigmented skin lesions on the legs and right wrist. Laboratory tests revealed leucopenia, microcytic anemia, thrombocytopenia and mild elevation of liver enzymes. Chest x-ray and CT scan revealed bilateral mediastinal lymphadenopathy. EGD showed grade II non-bleeding esophageal varices and nodular antral mucosa with ulceration. Multiple biopsies taken from antral area revealed noncaseating epitheloid granulomas suggestive of sarcoidosis. *H.pylori* was detected by rapid urease test in biopsy specimen. The patient was given omeprazole along with nutritional therapy which included iron supplements and multivitamins. On follow-up visit 2 weeks later, the patient was symptom free. Asymptomatic gastric sarcoidosis is much more common than symptomatic gastric sarcoidosis. Endoscopically, GI sarcoidosis presents as ulcerations, atrophic gastritis, nodular irregularities, polypoid lesions, segmental mucosal thickening and nondistensibility mimicking linitis plastica and elevated friable mucosa from the surface or musocal hyperemia. It is sometimes misdiagnosed as peptic ulcer disease, Crohn's disease, malignancy, Menetrier's disease or gastritis. Treatment depends on disease activity and involvement of other organs. Most cases require tapering corticosteroids for 6 months. Alternate agents in GI sarcoidosis may include antacids, metoclopramide and proton pump inhibitor.

M7 PRESENTATION OF CELIAC SPRUE WITHOUT IRON DEFICIENCY ANEMIA

Patel, J.K., Patel, J., Patel, K., Doshi, K., Gintautas, J.*, Patel, A.A. Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

Celiac disease (CD) is a complex autoimmune disease that affects the small bowel in genetically predisposed individuals after ingestion of gluten. Once thought to be a disease presenting in childhood, it is now becoming apparent that it can present in adulthood, even if no previous intolerance to glutens was present. CD has great variation in its clinical presentation and is often left undiagnosed. The most common presenting symptoms are chronic diarrhea and iron deficiency anemia (IDA) with malabsorption. A 41-year-old female presented with complaints of watery diarrhea and 10 lb. weight loss during the previous 4 months. The patient denied any other symptoms. She had no significant past medical history, allergies, travel history or medication usage. On physical examination, dry oral mucosa was present; abdominal exam was normal. Labs showed normal hemoglobin and iron panel, mild elevation of liver enzymes and positive anti-endomysial, anti-gliadin and anti-tissue transglutaminase antibodies. Urine and stool analyses were normal. Biopsies from endoscopy showed acute & chronic inflammation with acute cryptitis, duodenal mucosa with erosion, villous flattening and prominent intra-epithelial lymphoid aggregates with intra-epithelial lymphocytes without granulomas. Diagnosis of celiac sprue was made; strict gluten free diet (GFD) was perscribed. Patient had improved symptoms at 4-month follow-up. In adults, anemia, either microcytic or macrocytic, is one of the most frequent signs of CD secondary to deficiency of iron, folic acid and/or B12 and may be its only manifestation. Gluten free diet is the best treatment for this disease. There are many foods high in gluten content that need to be avoided, including cereals, pasta, processed cheeses and meats, ice cream, and jellies.

M8 TO tPA OR NOT TO tPA? THAT IS THE QUESTION.

Joshi, S.G., Ventura, J.G., Cervellione, K.L., Gintautas, J.*, Thakore, H. Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

Tissue plasminogen activator (tPA) is a clot dissolving drug that, when used in patients during a stroke, helps to restore blood flow to the brain. Since blood clots account for approximately 80% of stroke occurrences, tPA can be very useful for it's treatment. tPA should be administered within three hours of onset of stroke symptoms, and should not be used in cases of hemorrhagic stroke given that it can cause bleeding. Therefore, both timely and accurate diagnosis is important. All patients with a discharge diagnosis of stroke in 2006 were identified. Of the first 159 reviewed, 16 (10%) were given tPA (ave. age 67). Clinical information was collected from charts. Patients not receiving tPA (i.e. 143) were due to unknown onset of symptoms or symptom onset more than three hours prior to examination. Before tPA was given, CT scans for 10 individuals revealed ischemic stroke; 4 were negative. Fifteen patients had repeat CT scans after administration of tPA, which showed the following: 11 (73%) no change, 3 (20%) hemorrhagic changes, and 1 (7%) worsening infarct. Data regarding clinical outcome revealed the following within 24 hours of tPA: 8 (50%) exhibited significant clinical improvement; 6 (38%) had no change or minimal improvement; no deaths occurred (2 unavailable). Our results support the hypothesis that tPA in ischemic stroke can be beneficial for improvement of clinical symptoms and prevent worsening impact on the brain. Since short-term outcome has been shown to be predictive of outcome at 3 months, the use of tPA is likely to have lasting functional and clinical benefits. Our results suggest that more widespread use of tPA may be beneficial for improving stroke outcome and should therefore be further explored.

M9 IS THERE A USE FOR MRI'S FOR THE DIAGNOSIS OF STROKE?

Vo, H.Q., Joshi, S.G., Cervellione, K.L., Saraiya, B, Gintautas, J*, Thakore, H. Jamaica Hospital Medical Center, Jamaica, NY, 11418 *(jgintautas@jhmc.org)*

Stroke is the sudden death of brain cells in a localized area due to inadequate blood flow. It is the third leading cause of death in the United States and the leading cause of disability. When a patient presents with symptoms of stroke, CT scans are the initial diagnostic tests. Even if results are negative, MRI's are not often completed due to cost and availability of a scanner. All patients with a discharge diagnosis of stroke during 2006 who had a CT performed upon admission were identified. Those with positive CT results were excluded. Seventy-two patients had negative CT findings. Of these, 40 (56%) had subsequent MRI's. Thus, a total of 40 subjects were included in this study. CT findings and MRI findings were compared in order to determine the rate of false negative CT scans. Of 40 negative CT scans, MRI's replicated the negative finding in 18 cases (45%). Of the 22 cases (55%) with positive findings, evidence of lacunar stroke was present in 4 cases and evidence of ischemic stroke was present in 18 cases.
Our results provide evidence of the usefulness of MRI scan to diagnose stroke, particularly ischemic, even when initial CT results are not indicative of the diagnosis. Of the original 72 with negative CT results, 44% did not have a follow-up MRI, possibly impacting the diagnosis and treatment of the patient. Since 55% of the negative CT scan findings were proven false by MRI's, we believe there is a clinical need for the use of MRI for stroke screening. Future studies need to examine the extent to which these results impact patient care.

M10 5-AZA-2'-DEOXYCYTIDINE, AN INNOVATIVE MULTI-EPIGENETIC INHIBITOR OF REPRESSIVE DNA AND HISTONE MODIFICATIONS

Oshiro, M.M.[1], Wozniak, R.J.[3], *Futscher, B.W[1,2]., [1]Arizona Cancer Center, [2]Department of Pharmacology & Toxicology, College of Pharmacy, The University of Arizona, Tucson, AZ 85724, USA. [3]Department of Pharmacology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53706, USA. *(bfutscher@azcc.arizona.edu)*

The epigenetic silencing of tumor suppressor genes is a common event during carcinogenesis, and often involves aberrant DNA methylation and repressive histone modification of gene regulatory regions, resulting in the formation of a transcriptionally repressive chromatin state. The identification of inhibitors that target these aberrant epigenetic modifications is the primary focus of our research interest. To that end, our work has identified 5-aza-2' deoxycytidine (5-aza-CdR) as a multi-epigenetic inhibitor that acts as a DNA and Histone methyltransferase inhibitor. Treatment of the breast tumor cell lines MDA-MB-231, BT549, and UACC 1179 with 5-aza-CdR induced transcriptional reactivation of the tumor suppressor genes Maspin and Desmocollin3. Importantly, we identified that the reactivation was closely and consistently linked with significant decreases in promoter H3 lysine-9 di-methylation. Moreover, 5-aza-CdR treatment resulted in global decreases in H3 lysine-9 di-methylation, an effect that was linked to its ability to mediate dose-dependant; post-transcriptional decreases of the histone methyltransferase, G9A. To extend these studies we conducted qPCR analysis of 16 primary breast tumor and 11 normal breast specimens, and show that G9A is significantly over expressed in tumor versus normal specimens. Our data clearly show 5-aza-CdR to be a multifaceted epigenetic inhibitor that targets both DNA and histone methylation. Although, 5-aza-CdR is an effective epigenetic inhibitor, we have developed an ELISA based methyltranserase assay to screen for novel multi-epigenetic inhibitors. Utilizing this tool, we have begun the initial screening of Telik's, TRAP Technology compound library to identify innovative epigenetic inhibitors. *Funded grant number CA65662 to BWF.*

M11 MITOCHONDRIAL GSH LEVELS ARE DECREASED IN HEARTS FROM CFTR KNOCKOUT MICE

Jeanblanc, C., Xiang, S.Y., Duan, D., and Buxton, I.L.O. Department of Pharmacology, University of Nevada School of Medicine, , Reno, NV 89557

Our previous work suggests that the PKC/PKA-activated Cl^- channel ($Cl_{-PKC/PKA}$), which are encoded by the CFTR gene, play a critical role in ischemic preconditioning-imparted cardioprotection against ischemia/reperfusion injury. In this study we tested our hypothesis that $Cl_{-PKC/PKA}$ may be a glutathione (GSH) transporter in the regulation of cellular GSH homeostasis and the maintenance of high mitochondrial GSH concentrations. We employed differential centrifugation and Percoll®-density gradient centrifugation to obtain highly purified sarcolemmal membrane (SM) and mitochondrial membrane (MT) proteins from the ventricles of both wild-type (WT) and CFTR knockout (KO) mice (10 hearts pooled as one sample). Marker enzyme activity assays were used to determine enrichment and separation from other organelles (lysosome, microsome, endoplasmic reticulum, *etc*.) Using this approach, the mitochondrial fraction was highly purified and judged to be relatively free of cytosolic and SM contamination. Concentrations of GSH in the fractionated cardiac mitochondria from the KO mice were measured by HPLC separation over a Platinum EPS column with isocratic acetate buffer (pH 3.0) as the mobile phase, and compared with those from WT mice. GSH was quantified using a Hewlett-Packard electrochemical detector under oxidizing conditions. KO mice had a profound (77±14.3%, mean ± SD) decrease in cardiac mitochondrial GSH concentrations (2470.4±711.8 nmol/mg protein) compared to controls 391.0±32.3 nmol/mg protein, n=3, P=0.03). These results suggest that $Cl._{PKC/PKA}$ may be a key component of GSH transport for the maintenance of high [GSH] in the mitochondrial matrix and thus, plays a crucial role in the regulation of cellular GSH homeostasis and redox control of cardiac myocytes in the face of oxidative stress during ischemia/reperfusion. (*Supported by NIH HL63914, HD053028 & NCRR P20RR15581*).

M12 CHRONIC HYPOXIA DIFFERENTIALLY REGULATES PKCε AND PKCδ PROTEIN EXPRESSION IN H9c2 CELLS.

Patterson, A, *Zhang, L. Center for Perinatal Biology, Department of Pharmacology & Physiology, Loma Linda University School of Medicine, Loma Linda, CA 92350.
(*lzhang@llu.edu*)

Ischemic injury and myocardial infarction stemming from coronary artery disease is among the leading causes of death in the United States. Our recent studies have demonstrated that chronic hypoxia during fetal development significantly decreased PKCε protein expression in the heart of adult offspring resulting in an increased heart susceptibility to ischemia and reperfusion injury. The present study tested the hypothesis that chronic hypoxia directly affects the expression of PKCε and PKCδ in fetal rat cardiomyocytes. Studies were performed in an embryonic rat cardiac cell line H9c2 cells. Cells were grown and divided into four groups, exposing to normoxia (21% O_2), 10.5% O_2 (73 mmHg), 3% O_2 (21 mmHg), and 1% O_2 (7 mmHg), respectively, for 24 hours. Protein was isolated and Western immunoblotting was performed to determine the levels of HIF-1α, PKCε, and PKCδ. Hypoxia treatments of cells with 3% O_2 and 1% O_2 for 2 hours significantly stabilized and increased HIF-1α levels. Treatments of cells with 1% O_2, but not 10.5% O_2 and 3% O_2, for 24 hours significantly decreased PKCε protein levels. In contrast, hypoxia had no significant effect on PKCδ protein levels in H9c2 cells. The results suggest that chronic hypoxia differentially regulates PKCε and PKCδ protein levels, and directly inhibits PKCε protein expression in fetal rat cardiomyocytes. (Supported in part by NIH grants HL82779 & HL83966)

M13 MATERNAL TRANSIENT FOOD RESTRICTION RESULTS IN IMPROVED CARDIAC RECOVERY FROM ISCHEMIA/REPERFUSION INJURY IN MALE ADULT OFFSPRING.

Lawrence, J.,[1] Xiao, D.,[1] Yang, S.[2] and *Zhang, L.,[1] [1]Centre for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92354; [2]Department of Chemistry, California State University, San Bernardino, CA 92407 (lzhang@llu.edu)

In a previous study, nicotine treatment has been shown to result in a transient reduction in food intake and decreased body weight gain in pregnant rats. The offspring had significantly reduced birth weight and reduced body weight during the first 20 days of life. Both male and female adult offspring experienced a significant increase in ischemia/reperfusion injury, with greater injury being seen in female offspring. Although the increased injury seen in the nicotine-treated offspring is likely due to nicotine exposure, the possible effect of transient reduction in maternal food intake cannot be excluded. In the present study, pregnant Sprague-Dawley rats were fed with the same mass of food intake by the control and nicotine-treated rats in the previous study. The maternal body weight was measured throughout gestation as well as the body weight of the offspring after birth. The hearts of adult offspring were excised and mounted on the Langendorff apparatus. The reduced food intake resulted in reduced body weight gain in maternal rats. Offspring body weight showed no difference between the control-fed and food-restricted groups. The Langendorff study showed a significant difference in male and female offspring. Female offspring showed no difference in recovery from ischemia/reperfusion injury between control-fed and food-restricted groups. However male offspring from food-restricted mothers showed a significant improvement in recovery of left ventricle function from ischemia/reperfusion injury. The results demonstrate that increased ischemia/reperfusion injury seen in offspring of prenatal nicotine exposure is not caused by the transient reduction in maternal food intake. Furthermore, they suggest a cardioprotective effect of offspring of transient prenatal undernutrition. (*Supported in part by NIH grants HL82779 & S06GM073842)*

M14 SEROTONINERGIC SYSTEM PARTICIPATE IN THE DEVELOPMENT OF MYOCARDITIS IN RABBITS

Lychkova, A.E., Central R&D Gastroenterology Institute, Moscow, Russian Federation. (lychkova@mail.ru)

Serotoninergic system role in the development of myocarditis in rabbits was studied. Acute and chronic experiments were carried out on 42 Chinchilla rabbits (3,5-4 kg) under Nembutal anesthesia (40 mg/kg). Model of myocarditis was made by combined stimulation of the vagus and sympathetic trunk at the V-VI cervical vertebrae level and by inhibition of a beta-adrenoreceptors by inderal (1 mg/kg). Myocard electrocardiogram was registered. Morphological study of a heart was made. Combined stimulation of the vagus and sympathetic trunk and inhibition of a beta-adrenoreceptors led to slowing of the heart frequency contractions of 14-22%. After 15 minutes after slowing effect appearance visual myocard surface of the 16% of rabbits lost structure and became “polish-like’. Systolic blood pressure decreased from 135±5.2 to 78.4±3.0 mm Hg and diastolic pressure from 74.0±4.7 mm Hg. The amplitude of R wave in ECG decreased on 12.0±0,1%, wave T flattened on 5.0±0.22%, and QT interval increased by 9.0±0.1%. The very first minutes of a myocarditis were accompanied by a substantial drop in acetylcholine and noradrenaline levels and by an increase in serotonin concentration. Preliminary introduction of inhibitors of 5-HT1,2 and 5-HT3,4 receptors inhibited miocarditis development. Serotoninergic nervous system participates in the development of myocarditis through increased vessel permeability, reduced myocardial muscle excitability.

M15 SMAD3 OVEREXPRESSION ALONE INCREASES CONTRACTILITY AND OVERRIDES SMAD7 INHIBITION OF COLLAGEN SECRETION IN PRIMARY CARDIAC MYOFIBROBLASTS

Bedosky, K.M., Cunnington, R.H., Rattan, S.G. and *Dixon, I.M.C. University of Manitoba, Canada (idixon@sbrc.ca)

Transforming Growth Factor beta 1 (TGF-β_1) exerts many of its effects through canonical post receptor R-Smad proteins including Smad3. The activation of TGF-β_1 is commonly associated with cardiac extracellular matrix remodelling, including elevated collagen synthesis and deposition by cardiac fibroblasts and closely related contractile myofibroblasts. We have previously demonstrated elevated expression of Smad3 in the post-myocardial infarction (post-MI) heart. While Smad3 and Smad7 have been implicated in the regulation of fibroblast function, the independent effects of Smad3 overexpression in the absence of TGF-β_1 has not been carried out in cardiac myofibroblasts. We investigated the effects of overexpressed Smad3 and Smad7 in serum-free cultures with and without TGF-β_1 stimulation (10 ng/mL for 24 hours) on contractility (using *in vitro* collagen gel deformation assays and IDL-based digital image analysis) and on secretion of mature collagen I N-terminal peptides (P1NP estimation). Gel deformation analysis revealed that Smad3 overexpression alone was associated with significantly increased myofibroblast contractility. Simultaneous overexpression of Smad3 and Smad7 with TGF-β_1 resulted in maximal myofibroblast contractility similar to that observed in the presence of both Smad3 overexpression and exogenous TGF-β_1 stimulation. Further, P1NP analysis revealed that Smad3 overexpression alone was associated with significantly increased type I collagen secretion when compared to overexpressed Smad7. This difference was elevated further in the presence of TGF-β_1. Smad3 overexpression superceded Smad7 mediated inhibition of collagen secretion when stimulated with TGF-β_1 in cultured myofibroblasts. Together, our results show that Smad3 overexpression is sufficient to exert a strong effect on cardiac myofibroblast contractility and overrides inhibitory Smad7 when examining collagen secretion, and does so independently of TGF-β_1 stimulation. (Supported by the Canadian Institutes of Health Research).

M16 EFFECT OF FETAL HYPOXIA ON HEART SUSCEPTIBILITY TO ISCHEMIA AND REPERFUSION INJURY IN THE FEMALE ADULT RAT

Xue, Q. and *Zhang, L. Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

Epidemiologic studies suggest that prenatal exposure to adverse *in utero* environment is associated with an increased risk of ischemic heart disease in postnatal life. Our previous studies have demonstrated that prenatal chronic hypoxia increases the heart susceptibility to ischemia and reperfusion injury in male adult offspring. The present study is to determine whether and to what extent prenatal hypoxia increases the susceptibility of female adult heart to ischemia and reperfusion injury. Time-dated pregnant rats were divided between normoxic and hypoxic (10.5% oxygen from day 15 to day 21) groups. Hearts were isolated from 3-month old female progeny and were studied using a Langendorff preparation. After a baseline recording, hearts were subjected to 25 minutes of ischemia and 1 hour of reperfusion. Preischemic values of left ventricular function were the same between the control and hypoxic rats. However, prenatal hypoxia significantly attenuated the postischemic recovery of left ventricular function. These results suggest that prenatal chronic hypoxia increases the susceptibility of female adult heart to ischemia and reperfusion injury. (*supported in part by NIH grant HL83966*)

M17 REAL-TIME Q-T INTERVAL CHANGES IN CONSCIOUS AND ANESTHESIZED GUINEA PIGS.

Clay E.R, Dong, Y., Walker, M.J. Dept. Anesthesiology, Pharmacology & Therapeutics, UBC, Canada. (rsdaa@interchange.ubc.ca)

Potential new drugs are investigated early in development for their potential to cause arrhythmias. In vitro this involves determination of HERG channel blockade. However, HERG blockade in vitro does not always correlate with QT prolongation of the ECG or with ventricular arrhythmias. The QT effects of drugs are easily studied in guinea pigs and a method for assessing the ECG effects of drugs given intravenously or by inhalation are described. The latter route is particularly useful for aerosols. Advances in computer software make it possible to perform real-time analysis of ECGs. Power Lab 26T (ADC), running Chart 5 Pro v5.5.5. software was used to monitor blood pressure and ECGs on a continuous basis before, during, and after, drug infusions and inhalations. Drugs, with or without HERG channel blocking actions, were tested in the system for dose and time effects. The technique allows for contemporaneous appreciation of the effects of drugs in terms of real time graphical printouts. Sodium nitroprusside, isoproterenol and dofetilide produced expected effects on heart rate and blood pressure when infused. Only dofetilide widened the QT interval of the ECG (both corrected and uncorrected). A novel PDE inhibitor was also tested by intravenous infusion in anesthetized guinea pigs, as well as by aerosol administration in conscious animals. Whether conscious or anesthetized, digital analysis produced analyzable date and allowed for real time effects of drugs on QT to be readily detected. Thus both time and dose effects on QT as well as blood pressure and heart rate were easily detected and analyzed. While the software requires “training” the method provides an easy to use screen for ECG effects.

M18 ALTERED CHARACTERISTICS OF AGONIST-INDUCED CA^{2+} RESPONSES IN DISEASED HUMAN VALVULAR MYOFIBROBLASTS.

*Liang, W.[1], McDonald, P.[2], McManus, B.[2], van Breemen, C.[2] and Wang, X.[2] [1]School of Biological Sciences, Nanyang Technological University, Singapore 637551; [2]The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, University of British Columbia, Vancouver, BC V6Z 1Y6, Canada. (willmann@ntu.edu.sg)

Valvular myofibroblasts (VMFs) are present in large numbers in the cardiac valve. Although the functional roles of VMFs *in vivo* remain to be determined, evidence suggests the cells’ ability to contract *in vitro*. Since Ca^{2+} is important in the contractility of many cell types, we hereby examined Ca^{2+} responses induced by different agonists in normal and rheumatic VMFs. The agonists used were histamine (Hist), adenosine 5’-triphosphate (ATP) and 5-hydroxytryptamine (5-HT), all of which are important mediators in cardiac functions. Cytosolic Ca^{2+} concentrations ($[Ca^{2+}]_i$) in fura-2-loaded VMFs were measured with ratiometric fluorescence microscopy. VMFs were challenged with a single concentration of each agonist in either Ca^{2+}-containing (+Ca) or Ca^{2+}-free (-Ca) physiological salt solution (PSS). From the resulting Ca^{2+} response, area under curve (AUC) was calculated from the point of drug addition (i.e. baseline) until the response has reached the first peak (i.e. maximum). Our data showed that more Ca^{2+} was mobilized in normal than in rheumatic VMFs, suggesting possible Ca^{2+}-mobilizing dysfunction in the initial phase of a response in disease conditions. The most prominent difference was observed with 5-HT stimulation in +Ca PSS, where normal VMFs showed significantly greater AUC than rheumatic VMFs. The investigation of agonist-induced Ca^{2+} signaling characteristics in VMFs may thus provide information pertaining to Ca^{2+}-associated changes and their consequences in cardiac valvular diseases. *Funded by Singapore Ministry of Education Academic Research Fund (RG63/06)*.

M19 METABOLIC PROFILE OF RATS WITH STREPTOZOTOCIN-INDUCED TYPE 1 DIABETES.

Kwok, E.W.Y., †Liu, G.Y., Leung, J.Y.T., Lim, S.L. and *Pang, C.C.Y., †School of Agriculture and Biology, Shanghai Jiao Tong University, Shanghai, P. R. China, 200240; Department of Anaesthesiology, Pharmacology & Therapeutics, University of British Columbia, Vancouver, Canada, V6T 1Z3 (ccypang@interchange.ubc.ca)

Diabetes mellitus is a disorder in which plasma glucose is consistently elevated above the normal range. The initiating factor of high blood glucose is a defect in the release of insulin (type 1 diabetes) or development of resistance to the action of insulin coupled with inadequate secretion of insulin (type 2 diabetes). Streptozotocin (STZ) is a toxin most commonly used to induce type 1 diabetes by selective destruction of pancreatic β cells. We examined if STZ causes hyperlipidemia and insulin resistance, which are characteristics of type 2 diabetes. Wistar rats were injected with STZ (60 mg/kg, i.v.) or the vehicle. At 4 weeks after STZ-induction of diabetes, plasma triglyceride, glucose and insulin were determined, and insulin sensitivity was assessed by euglycemic insulin clamp. The STZ-treated rats had reduced plasma insulin and hyperglycemia, but did not require insulin supplementation for survival, unlike typical type 1 diabetic animals. Furthermore, these rats had markedly reduced sensitivity to insulin, but normal plasma triglyceride. Blood pressure and heart rate were similar in the STZ and control rats. These results suggest that hyperglycemia or STZ interferes with glucose utilization but not metabolic disposition of triglycerides. *Funded by the Heart & Stroke Foundation of B.C. & Yukon.*

M20 CO-IMMUNOPRECIPITATION OF cGMP-PROTEIN KINASE TYPE I & II AND MYOSIN PHOSPHATASE SUGGEST A ROLE FOR THEIR FUNCTIONAL INTERACTION IN HUMAN UTERINE QUIESCENCE AT TERM.

Milton, D., Dennemeyer, S. Gala, R. and Buxton, I.L.O. Departments of Pharmacology and Obstetrics and Gynecology, University of Nevada School of Medicine, Reno, NV (ibuxton@medicine.nevada.edu)

Nitric oxide (NO) mediated increases in cGMP are completely dissociated from relaxation in human uterus (Buxton, I.L.O., *et al., Br. J. Pharmacol.* 134: 206-214.). We examined the regulation of myosin phosphatase (MYPT) and suggested that PKG does not interact with MYPT-1 in uterine smooth muscle. While such a possibility might help to explain why activation of PKG in myometrium does not relax the muscle, it would require a disparate system of MYPT regulation in uterine *versus* other smooth muscles and is thus highly speculative. We have discovered that both cGMP-dependent protein kinase type I and II (PKGI, II) are co-expressed in human uterine smooth muscle cells, consistent with our hypothesis that PKGII and not PKGI regulates MYPT-1 and that PKGII is activated by particulate and not following activation of the soluble guanylyl cyclase by NO. In Western blot experiments in non-pregnant human myometrium, immunoprecipitation of PKGI reveals that PKGI and MYPT-1 are binding partners while PKGII and MYPT-1 are not, suggesting that in this state of the tissue, the classical interaction of PKGI with MYPT that is thought to activate the phosphatase holds true. However, in pregnant non-laboring myometrium, MYPT-1 is also found associated with PKGII. The appearance of a PKGII:MYPT-1 binding interaction in the pregnant non-laboring state of the tissue suggests a functional role for PKGII consistent with quiescence of the tissue that is required to maintain gestation. In the laboring myometrium however, the interaction of PKGI and MYPT-1 appears to be enhanced while the interaction of MYPT-1 with PKGII is lost. The disappearance of a PKGII:MYPT-1 interaction is consistent with removing a relaxation influence in the contracting tissue. Loss of the PKGII:MYPT-1 interaction is not explained on the basis of binding of PKGII selectively to the leucine zipper positive form of MYPT-1. Moreover, the demonstration that a PKGI:MYPT-1 interaction is unaltered in labor calls into question the role of PKGI in regulating the phosphatase. The possibility that a particular PKG isozyme (I *vs.* II) interacts with a particular MYPT isoform (LZ^+ *vs.* LZ^-) in the caveolar preparation is not supported. (*This work was supported by NIH RO1 HD053128*.)

COMPLETE ABSTRACTS
for

POSTER SESSION II

Tuesday Evening 6 pm

T1 PRENATAL NICOTINE EXPOSURE CAUSED A GENDER-RELATED INCREASE IN VASCULAR CONTRACTIONS TO ANGIOTENSIN II IN ADULT MALE OFFSPRING.

*Xiao, D.,[1] Huang, X.,[1] Xu, Z.,[1,2] Yang, S.[3] and Zhang, L.,[1,2] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China; [3]Department of Chemistry and Biochemistry, California State University, San Bernardino, CA 92407 (dxiao@llu.edu)

Epidemiologic studies suggest that prenatal exposure to maternal cigarette smoking is associated with an increased risk of hypertension in postnatal life. The present study tested the hypothesis that prenatal nicotine exposure enhances vascular contractile responses to angiotensin II (Ang II) in adult male offspring. Nicotine was administered to pregnant rats *via* subcutaneous osmotic minipumps throughout gestation and up to 10 days after delivery. Aortas and mesenteric arteries were isolated from adult male offspring at the age of 5 months old. Ang II-induced contractions of aortas and mesenteric arteries were significantly enhanced in male offspring of prenatal nicotine exposure. The enhanced contractions of aortas were not affected by inhibition of eNOS activity. Ang II type I receptor (AT_1R) blocker, losartan completely blocked Ang II-induced contractions in both control and nicotine-treated offspring. However, AT_2R blocker, PD123319 enhanced Ang II-induced contraction in control but suppressed it in nicotine-treated animals. Nicotine significantly increased AT_1R but decreased AT_2R protein levels, and increased the ratio of AT_1R/AT_2R in the aorta of male offspring. Furthermore, the enhanced contractions were associated with an increased $[Ca^{2+}]_i$ at the low dose but not at higher doses of Ang II in mesenteric arteries after prenatal nicotine exposure. The results suggest that prenatal nicotine exposure alters vascular functions *via* changes in Ang II receptors and signaling pathways in adult male offspring, which may lead to an increased risk of hypertension in later life. (*supported in part by NIH grants HL82779 & S06GM073842*)

T2 PRENATAL COCAINE EXPOSURE DIFFERENTIALLY REGULATES VASCULAR CONTRACTILITY IN ADULT MALE AND FEMALE OFFSPRING.

Xiao, D.,[1] Huang, X., Yang, S.[2] and *Zhang, L.,[1] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Department of Chemistry and Biochemistry, California State University, San Bernardino, CA 92407 (*Lzhang@llu.edu*)

Cocaine abuse is a significantly problem among pregnant women. The present study tested the hypothesis that prenatal cocaine exposure differentially regulates vascular contractility in adult male and female adult offspring. Pregnant rats received cocaine (30 mg/kg/day) or saline from days 15 to 21 of gestational age. Aortas were isolated from aduld male and female offspring at the age of 3 months old. Cocaine had no effect on KCl-induced contractions of aorta in either male or female offspring. Cocaine did not alter norepinephrine (NE)-induced contractions of aorta in male, but significantly enhanced it in female offspring. Pretreatment with endothelial nitric oxide synthase (eNOS) inhibitor, N^G-nitro-L-arginine (L-NNA) significantly increased NE-induced dose-dependent contractions in saline control but not in prenatally cocaine-treated male offspring. However, L-NNA significantly increased NE-induced dose-dependent contractions in both saline control and prenatally cocaine-exposed female offspring. In addition, cocaine had no effect on either acetylcholine-induced endothelium-dependent or sodium nitroprusside-induced endothelium-independent relaxations of aortas from either male or female offspring. The results suggest that prenatal cocaine exposure alters vascular functions in adult offspring in a gender-specific manner, which may lead to an increased risk of cardiovascular dysfunction in later life. (*supported in part by NIH grants HL82779 & S06GM073842*)

T3 PRENATAL NICOTINE EXPOSURE CAUSED A GENDER-RELATED INCREASE IN ANGIOTENSIN II-INDUCED BLOOD PRESSURE ELEVATION IN ADULT OFFSPRING.

*Xiao, D.,[1] Xu, Z.,[1,2] Mao, C.P.,[2] Longo, L.D.[1] and Zhang, L.,[1,2] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China (dxiao@llu.edu)

Epidemiologic studies suggest that prenatal exposure to maternal cigarette smoking is associated with an increased risk of elevated blood pressure (BP) in postnatal life. The present study tested the hypothesis that prenatal nicotine exposure causes an increase in BP response to angiotensin II (Ang II) in adult offspring. Nicotine was administered to pregnant rats *via* subcutaneous osmotic minipumps throughout gestation and up to 10 days after delivery. At 5-months of age, we measured BP and heart rate (HR) in male and female offspring. The body weight of adult offspring was not significantly different between saline control and nicotine-treated animals. Similarly, the baseline BP and HR in both male and female adult offspring were not significantly changed by prenatal nicotine exposure. Acute subcutaneous injection of Ang II caused a significantly increase in BP associated with a decrease in HR in adult offspring. Ang II-induced systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (ΔMAP) elevations were significantly enhanced in male but not in female offspring. In addition, Ang II-induced decreased HR was not significant difference between saline control and nicotine-treated offspring. However, nicotine significantly delayed the time course of HR in response to Ang II stimulation in male but not in female adult offspring. The results suggest that prenatal nicotine exposure alters cardiovascular system response in adult offspring in a gender-specific manner, which may lead to an increased risk of hypertension in male offspring later in life. (*supported in part by NIH grants HL 82779 & HL83966*)

T4 ALTERATION IN MUSCARINIC RECEPTOR- AND ADRENOCEPTOR-MEDIATED VASORELAXTION IN ACUTE HYPERTHYROID RATS.

Honda, H.[1,2], Iwata, T.[2], Matsuda, H.[2], Kondo, M.[2], Moroe, H.[2], Kumasaka, K.[2] and Ozaki, M.[3], [1]Center for Experimental Pharmacy, School of Pharmacy, Tokyo University of Pharmacy and Life Science, Tokyo 193-0392 Japan. [2]Second Department of Physiology, School of Medicine, Showa University, Tokyo, 142-8555, Japan. Department of Pharmacy, Tokai University Hachioji Hospital, Tokyo, 192-0032, Japan (hhonda@ps.toyaku.ac.jp)

This study was undertaken to investigate the effects of acute hyperthyroidism on the vasorelaxing responses to acetylcholine and isoprenaline in isolated rat aortae. Hyperthyroidism was induced by subcutaneous injections of L-thyroxine (0.5 mg/kg/day) for 3 days. In the aortae, acetylcholine-induced relaxation was significantly greater in hyperthyroid rats than in control rats, while there was no significant difference in isoprenaline-induced relaxation between hyperthyroid and control rats, N^G-nitro-L-arginine (L-NOARG), an inhibitor of nitric oxide (NO) synthase, reduced acetylcholine- and isoprenaline-induced relaxations in both hyperthyroid and control rats and in the presence of L-NOARG no significant difference in the acetylcholine-induced relaxation was seen between the two groups of rats. Indomethacin, a cyclo-oxygenase inhibitor, showed no significant effect on both acetylcholine- and isoprenaline- induced relaxations in both control and hyperthyroid rats. 17-Octadecynoic acid, a cytochrome P-450 mono-oxygenase inhibitor, reduced the both acetylcholine- and isoprenaline-induced relaxation in both hyperthyroid and control rats, and acetylcholine-induced relaxation was still greater in hyperthyroid rats than in control rats. These results indicate that an acute hyperthyroidism significantly enhances muscarinic receptor- but not adrenoceptor-mediated relaxations of the aortae and L-NOARG abolished an enhancement by acute hyperthyroidism of muscarinic receptor-mediated relaxation, suggesting that these results may be due to an alteration in muscarinic receptor-mediated NO systems of the aortae at an early

stage of the disease.

T5 PRENATAL NICOTINE EXPOSURE RESULTS IN REDUCED CARDIAC RECOVERY FROM ISCHEMIA/REPERFUSION INJURY IN ADULT OFFSPRING.

Lawrence, J.,[1] Xiao, D.,[1] Xue, Q.,[1] Rejali, M.,[2] Yang, S.[2] and *Zhang, L.,[1] [1]Centre for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92354; [2]Department of Chemistry, California State University, San Bernardino, CA 92407 (*lzhang@llu.edu*)

Prenatal nicotine exposure due to maternal cigarette smoking is a major insult that leads to an increased risk of cardiovascular disease in adulthood. The present study tested the hypothesis that prenatal nicotine exposure increases heart susceptibility to ischemia/reperfusion (I/R) injury in adult offspring. Nicotine was administered to pregnant rats *via* subcutaneous osmotic minipumps throughout gestation. Nicotine treatment resulted in a rapid and transient decrease in food-intake and a moderate decrease in maternal body weight gain. Hearts were isolated from adult male and female offspring and subjected to I/R in a Langendorff preparation. Nicotine significantly attenuated left ventricle (LV) developed pressure, heart rate, and coronary flow rate in female but not male hearts at baseline. Additionally, nicotine significantly increased LV infarct size and attenuated postischemic recovery of LV function in both male and female offspring with more pronounced effects in females. In female but not male hearts, nicotine significantly decreased postischemic coronary flow rate. However, coronary nitric oxide release was decreased in male but not female hearts. Caspase-3, -8, and -9 levels were not significantly changed in either female or male hearts. However, nicotine caused a significant decrease in protein levels of PKCε in both male and female hearts and a decrease in PKCδ levels in female hearts only. The results suggest that prenatal nicotine exposure causes *in utero* programming of PKC isozyme gene expression pattern in the developing heart and increases heart susceptibility to I/R injury in adult offspring. (*Supported in part by NIH grants HL82779 & S06GM073842*)

T6 ROLE OF ALPHA$_1$-ADRENOCEPTORS ON VASCULAR REACTIVITY IN FRUCTOSE-FED RATS

*McNeill, J.H., Tran, L.T. and Vasudevan, H., Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC Canada (*jmcneill@interchange.ubc.ca*)

Complications associated with the metabolic syndrome are altered vascular reactivity and elevated blood pressure. These alterations are governed by a host of diverse factors. Two mechanisms implicated in this process are increased sympathetic drive and altered cyclooxygenase (COX)-dependent regulation of vascular tone. We have previously demonstrated the roles of the sympathetic nervous system and COX-2 in the development of hypertension in fructose-fed rats. However, little is known regarding the crosstalk between these pathways. In these studies, we used the fructose-fed rat to investigate the contribution of α_1-adrenoceptors and COX in modulating blood pressure and vascular reactivity, respectively. High fructose feeding and prazosin, an α_1-adrenoceptor antagonist, treatment were initiated simultaneously and carried out for nine weeks. Prazosin was given at a dose of 1 mg/kg/day via oral gavage. Changes in phenylephrine (PE)-induced vasoconstriction were studied in isolated aortic and superior mesenteric arteries in the presence and absence of a COX-2 selective inhibitor, NS-398, a COX-1 selective inhibitor, SC-560, and a non-selective inhibitor, indomethacin. In vivo blockade of α_1-adrenoceptors decreased blood pressure while the in vitro effects of stimulating α_1-adrenoceptors were decreased upon COX-2 blockade. In conclusion, we hypothesize that the COX-2 pathway is interrelated with the α_1-adrenergic pathway, which elevates blood pressure subsequent to high fructose feeding. *Funded by a program grant from the Heart and Stroke Foundation of BC & Yukon.*

T7 EFFECT OF COCAINE AND NOREPINEPHRINE ON PROTEIN KINASE C-ε EXPRESSION IN FETAL CARDIOMYOCYTES.

Meyer, K.D., *Zhang, L. Center for Perinatal Biology, Department of Pharmacology & Physiology, Loma Linda University School of Medicine, Loma Linda, CA 92350. *(lzhang@llu.edu)*

Studies in our lab have demonstrated that administering cocaine to pregnant rats causes a long-term decrease in expression of protein kinase C-ε (PKC-ε) in the male offspring. We have shown that this decrease is due to increased DNA methylation at specific sites within the PKC-ε promoter. While this effect has been clearly demonstrated, the responsible mechanism has not been determined. Maternal cocaine administration not only causes the fetal heart to be exposed to cocaine but also causes fetal hypoxia and increases the heart's exposure to catecholamines. The goal of our current study is to determine whether and to what extent direct effect of cocaine is responsible for the down-regulation of PKC-ε gene expression in fetal cardiomyocytes. To establish an *in vitro* model a fetal cardiac cell line, H9c2, and freshly isolated fetal rat cardiac myocytes were grown and treated with cocaine or norepinephrine. After treatment protein was collected from cells and PKC-ε protein levels were determined using Western blot. RNA was also collected from cells after treatment. PKC-ε mRNA levels were determined using real-time RT-PCR. Cocaine exposure was found to directly decrease PKC-ε protein expression in a time- and dose-dependent manner in both H9c2 cells and primary fetal cardiomyocytes. However, cocaine exposure did not decrease the PKC-ε mRNA levels in the cell line. Norepinephrine exposure also causes a decrease in the expression of PKC-ε protein. The effect of norephinephrine on PKC-ε mRNA expression is currently under investigation. *Funded by NIH 5R01HL082779 to LZ.*

T8 FETAL COCAINE EXPOSURE ABOLISHES CARDIAC ISCHEMIC PRECONDITIONING-INDUCED PROTECTION IN ADULT MALE RATS

Meyer, K.D., *Zhang, L. Center for Perinatal Biology, Department of Pharmacology & Physiology, Loma Linda University School of Medicine, Loma Linda, CA 92350. *(lzhang@llu.edu)*

We have previously shown that prenatal cocaine exposure increases cardiac sensitivity to ischemia reperfusion injury and decreases expression of protein kinase C-ε (PKC-ε) in the heart of adult male rats. Multiple studies have suggested that PKC-ε plays an important role in the ischemic preconditioning pathway. The present study tested the hypothesis that prenatal cocaine exposure down-regulates ischemic preconditioning-mediated protection in the adult heart. Pregnant rats were administered intraperitoneally either saline or cocaine (15 mg/kg) twice daily from day 15 to day 21 of gestational age. Hearts were isolated from 3-month old male offspring and were subjected to ischemia and reperfusion (20 min/40 min) injury in a Langendorff preparation. Pre-ischemic values of left ventricular function were the same between the saline control and cocaine-treated animals. Ischemic preconditioning of two short periods of 5-min ischemia significantly enhanced post-ischemic functional recovery of the left ventricle in the saline control animals. This was associated with a significant decrease in myocardial infarct size. The protection effect of ischemic preconditioning was blocked with a selective PKC-ε inhibitor. In the cocaine-treated animals, there were no significant differences in the post-ischemic recovery of left ventricular function and infarct size with or without the ischemic preconditioning treatment. In all groups, pre- and post-ischemic coronary flow rate was not significantly affected. The results demonstrate that prenatal cocaine exposure inhibits the cardio-protection of ischemic preconditioning and sensitizes the heart to ischemic and reperfusion injury, which is likely mediated by the ablation of PKC-ε signaling in the myocardium. *Funded by the NIH 5R01HL082779 to LZ.*

T9 EFFECT OF LONG-TERM HIGH ALTITUDE HYPOXIA ON FETAL PULMONARY VASCULAR CONTRACTILITY

Xue, Q., Ducsay, C.A., Longo, L.D. and *Zhang, L. Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

Perinatal hypoxia is associated with an increased risk of pulmonary hypertension. The present study tested the hypothesis that long-term high altitude hypoxia differentially regulates contractility of fetal pulmonary arteries (PA) and veins (PV). Fourth generation PA and PV were isolated from near-term fetuses of normoxic control and chronically hypoxic (maintained at high altitude 3,801 m for 110 days, PaO_2: 60 mmHg) pregnant ewes. KCl-induced contractions were significantly higher in PV than PA, which were not changed by hypoxia. Additionally, hypoxia did not alter the media thickness of pulmonary vessels. In PA, hypoxia significantly enhanced norepinephrine (NE)-induced contractions. Inhibition of eNOS with L-NNA had no effect on NE-induced contractions in either control or hypoxic PA. In PV, hypoxia had no effect on NE-induced contractions in the absence of L-NNA. L-NNA significantly increased NE-induced contractions in both control and hypoxic PV. In the presence of L-NNA, NE-induced contractions of PV were significantly decreased in hypoxic animals. Acetylcholine caused relaxations of PV but not PA, and hypoxia significantly decreased acetylcholine-induced relaxation in PV. Additionally, hypoxia significantly decreased sodium nitroprusside-induced relaxations of both PA and PV. eNOS were identified in the endothelium of both PA and PV, and eNOS levels were significantly higher in PV than PA. Hypoxia had no significant effect on eNOS levels in either PA or PV. The results suggest that chronic hypoxia selectively increases NE-induced contractions in fetal PA but decrease them in fetal PV. Although eNOS-mediated relaxation is minimum in near-term fetal PA it functions in PV, which is significantly decreased by hypoxia. Furthermore, hypoxia decreases smooth muscle sensitivity to nitric oxide-induced relaxation in both PA and PV. (*supported by NIH grant HD31226*)

T10 PRENATAL NICOTINE ALTERS AT1/AT2 RECEPTOR EXPRESSION IN HEART AND KIDNEY OF NEONATE OFFSPRING.

*Xu, Z., Xiao, D., Mao, C., Huang, X., Zhang, H., and Zhang, L., Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350; and Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China (zxu@llu.edu)

Prenatal nicotine exposure affects cardiovascular function in the offspring. Given that the renin-angiotensin-system (RAS) plays an important role in cardiac and renal functions, the present study tested the hypothesis that prenatal nicotine treatment alters angiotensin receptors AT1 and AT2 expression in offspring kidneys and hearts. Pregnant rats were administrated subcutaneously with nicotine (2.1 mg/day) or 0.9% NaCl solution as control *via* osmotic minipumps from gestational day 4 up to 10 days after delivery. Hearts and kidneys were isolated from two weeks old and one month old neonate rats, and AT1 and AT2 receptor protein and mRNA levels were determined by Western blot analysis and real-time RT-PCR. Prenatal nicotine treatment significantly decreased kidney weight and the kidney/body weight ratio in 2-week-old neonate rats. Both renal AT1 and AT2 receptor protein and mRNA levels were significantly increased by prenatal nicotine in male offspring rats of 30 day-old, whereas AT1 receptor mRNA and protein levels were decreased in the female kidney. AT2 receptor mRNA and protein increased in the kidney of male offspring with history of exposure to prenatal nicotine, and female AT2 protein in the kidney decreased by prenatal nicotine. In the heart of offspring, prenatal nicotine increased AT1 mRNA expression on postnatal day 14. On postnatal day 30, male heart AT1 and AT2 gene increased in prenatal nicotine group. Heart AT2 protein in male offspring decreased by prenatal exposure to nicotine, while female cardiac AT2 mRNA was reduced too. Together, the data demonstrate that prenatal nicotine can affect neonate kidney development and renal and cardiac AT1 and AT2 expression at

gene or protein level, or at both levels. The influence of nicotine during pregnancy on the development of angiotensin receptors can differ between male and female.

T11 EFFECT OF FETAL NICOTINE EXPOSURE ON CENTRAL AT1/AT2 RECEPTOR mRNA AND PROTEIN LEVELS IN NEONATE OFFSPRING

Mao, C., *Xu, Z., Xiao, D., and Zhang, L., Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350; Perinatal Biology Center, Soochow University School of Medicine, Suzhou, China. (zxu@llu.edu)

Nicotine is one of major risk factors in cigarette smoking. A number of studies have demonstrated that prenatal exposure to nicotine during pregnancy can affect the development of the central nervous system in both fetuses and offspring. Because local renin-angiotensin-system (RAS) in the brain is important in the control of physiological, behavioral, and neuroendocrine functions, the present study determined the long-term effects of chronic infusion of nicotine by subcutaneous osmotic minipumps implanted in pregnant rats on angiotensin receptor subtypes-AT1 and AT2 in the brain of the neonate offspring. Subcutaneously release of nicotine (2.1 mg/day) or vehicle (saline solution) by osmotic minipumps started from gestational day 4 up to 10 days after delivery. After birth, offspring pups from both control and prenatal nicotine exposure groups were raised under the same condition. One month after birth, brains of the neonates were collected to determine AT1 and AT2 receptor mRNA and protein levels using real-time RT-PCR and Western blotting in both male and female offspring. Prenatal nicotine treatment caused a significant increase in AT1 receptor mRNA and protein levels in the brain of male, but not female offspring. In contrast, prenatal nicotine exposure significantly decreased AT2 to AT2 receptor mRNA and protein levels in the brain of female offspring, without affecting AT2 receptor levels in male offspring. The results provide new evidence that chronic exposure to nicotine during pregnancy can influence the development of angiotensin receptors of the local RAS in the brain of neonate offspring, and prenatal nicotine-induced changes of the brain angiotensin receptors in the neonate offspring are receptor subtype (e.g., AT1 or AT2) and gender specific.

T12 COMPARISON OF THE ORAL PHARMACOKINETICS OF FLUCONAZOLE AND ITRACONAZOLE IN MEXICANS.

Flores-Murrieta, F.J., Carrasco-Portugal, M.C. and Landa, C., Unidad de Farmacología Clínica y Experimental, Instituto Nacional de Enfermedades Respiratorias, Escuela Superior de Medicina del IPN and Instituto Nacional de Rehabilitación. Mexico City, Mexico. (*fifloresmurrieta@yahoo.com.mx*)

Fluconazole and itraconazole are antimycotics widely used in therapeutics in Mexico, however, so far limited information about their pharmacokinetics is available. It has been reported that physicochemical characteristics of these compounds are a quite different, leading to different pharmacokinetic profile. On the other hand, it has been described that pharmacokinetics of some drugs may vary in Mexicans when compared with Caucasians, may be due to a reduced metabolism of drugs metabolized by CYP3A4. Based on these results, it is important to carry out local studies in order to establish dosage regimens according the characteristics of each population. Therefore, the purpose of this study was to compare the oral pharmacokinetics of fluconazole and itraconazole in Mexicans and to compare our results with those reported in other populations. Two groups of 16 subjects were volunteered for this study that was approved by the Institutional Research and Ethics Committees. All subjects gave written informed consent for participation. After an overnight fast, volunteers received an oral dose of 100 mg fluconazole or itraconazole and blood samples were obtained at selected times for 96 h. Plasma was obtained and analyzed by HPLC and pharmacokinetic parameters were obtained. As expected, plasma fluconazole levels were higher than itraconazole due to a lower volume of distribution. Additionally, less variability was observed for fluconazole. On the other hand, when data obtained in Mexicans

were compared with those obtained in other populations, no difference was observed, suggesting that there is not interethnic differences in the pharmacokinetics of itraconzole and fluconazole.

T13 COMPARISON OF NIMESULIDE ORAL PHARMACOKINETICS IN RATS AFTER ADMINISTRATION OF TWO SUSPENSIONS.

Carrasco-Portugal, M.C. and Flores-Murrieta, F.J., Unidad de Farmacología Clínica y Experimental, Instituto Nacional de Enfermedades Respiratorias and Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del IPN. Mexico City, Mexico. (miris22@hotmail.com).

Nimesulide is a non-steroidal anti-inflammatory agent that is widely used in the treatment of inflammatory pain. The drug belongs to the class II of Biopharmaceutical Classification System (low solubility, high permeability) and therefore, absorption of this drug is limited by its dissolution. It has been established that complex formation of insoluble sustances with cyclodextrins may increase their oral bioavailability since solubility is improved. In order to provide further evidence in this topic, a comparison on the oral pharmacokinetics of two suspensions of nimesulide in rats was carried out. Two groups of 7 rats were employed. One group received an oral dose of 10 mg/kg of a suspension prepared with 0.5% carboxymethylcellulose solution in water, whereas the other group received a commercially available formulation containing the complex of nimesulde-ß cyclodextrins (Eskaflam®). Blood samples were obtained at selected times for a period of 12 hours and analyzed by an HPLC method. Pharmacokinetic parameters were obtained and values were as follows: Cmax 1.18 ± 0.16 and 1.93 ± 0.12 µg/ml, Tmax 5.25 ± 1.03 and 3.21 ± 0.91 h and AUC 8.65 ± 1.19 and 13.74 ± 0.70 µg.h/ml for carboxymethylcellulose and Eskaflam®, respectively. Values of Cmax and AUC were increased and a reduction of Tmax was observed, indicating an improved absorption of nimesulide in the formulation containing ß-cyclodextrins.

T14 EVALUATION OF THE INFLUENCE OF MALNUTRITION ON THE ORAL PHARMACOKINETICS OF NIMESULIDE IN RATS.

Carrasco-Portugal, M.C., Camacho-Vieyra, A.G. and Flores-Murrieta, F.J., Unidad de Farmacología Clínica y Experimental, Instituto Nacional de Enfermedades Respiratorias, Laboratorio de Farmacología, Instituto Nacional de Pediatría & Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del IPN. Mexico City, Mexico.(*miris22@hotmail.com*)

Malnutrition is a health problem in Mexico. It has been established that malnutrition may produce important changes in the pharmacological response to drugs, since changes in the pharmadynamics and pharmacokinetics may occur. It has been described that a reduction of plasma proteins, and in hepatic enzymes may occur. Due to these changes, absorption, distribution and elimination of drugs may be modified. On the other hand, nimesulide is a non-steroidal anti-inflammatory agent that is widely used in the therapeutics. This drug is importantly bound to plasma proteins and is metabolized through cytochrome P-450, two systems that are altered in malnutrition. In order to establish if malnutrition may modify the pharmacokinetics of nimesulide, a comparison of pharmacokinetic parameters obtained in control and undernourishment rats was carried out. Two groups of 8 rats were employed in this study. After 45 days of birth, group 1 received a standard balanced diet for 30 days, whereas, group 2 received a hypoproteic diet for the same period. Then, rats received an oral dose of 10 mg/kg nimesulide and blood samples were drawn at selected times for 12 hours. Whole blood levels were determined by HPLC and pharmacokinetic parameters were obtained. Parameters obtained were: Cmax 1.18 ± 0.13 and 1.03 ± 0.10 µg/ml, Tmax 5.25 ± 1.03 and 7.48 ± 1.09 h and AUC_{12h} 8.64 ± 1.19 and 8.27 ± 0.85 µg.h/ml. It is concluded that malnutrition seems not to importantly modify the oral pharmacokinetics of nimesulide.

T15 *IN SILICO* MODELS INFORM *IN VITRO* MODELS IN ELUCIDATING PHARMACO-DYNAMIC MECHANISMS: A CASE WITH β_2-ADRENERGIC RECEPTOR AGONISTS.

Soriano-Ursúa Marvin A.[a,b], Correa-Basurto José[a,b,c] Valencia-Hernández Ignacio[c], Arellano-Mendoza Mónica G[c] and Trujillo-Ferrara José G. [a,c]. [a]Departamento de Farmacología, [b]Departamento de bioquímica y [c]Sección de Estudios de Posgrado e Investigación. Escuela Superior de Medicina, Instituto Politécnico Nacional. Plan de San Luis y Díaz Mirón, 11340, México. (*jcorreab@ipn.mx*)

In this work, the results about the interaction of a new agonist (BR-AEA) and other ligands (agonist or antagonist) on β_2 adrenoceptor (β_2AR) are presented. It was developed using computational tools (*docking*) on β_2AR which was characterized by X-ray crystallography technique (pdb codes: 2r4r and 2r4s; Rasmussen *et al*., 2007) and comparing the *docking* results to those obtained on β_2AR which was modelled by homology studies using the rhodopsin as target (Gouldson *et al.* 2004). Thus computational affinities were compared to the experimental results (relaxing effects on tracheal smooth muscle of guinea pig by BR-AEA) which were carry out with and without antagonists. The results showed that the *docking* results correspond with those results obtained from *in vitro* model (K_d values of 0.11 and 0.17 μM, respectively). This data allow us the design of drugs with potential action on the β_2AR. Taking this case, we described the importance of this theoretical methodology for screening test in the drug design as well as in the prediction of interactions with receptors and the elucidation of pharmacodynamic mechanisms. In conclusion, it is evident that *in silico* models can play an important roll as a tool for pharmacologists. *We are grateful to CONACyT, COFAA, and SIP-IPN for scholarships and financial support to the authors.*

T16 ANTIFIBROTIC EFFECT OF CURCUMIN ON PROLONGED BILE DUCT OBSTRUCTION- INDUCED CIRRHOSIS IN RATS.

Reyes-Gordillo K., Segovia j., Shibayama M., Tsutsumi V., Vergara P., Moreno G.M., and Muriel P*. Cinvestav-IPN., México city, (*pamuriel@cinvestav.mx*).

The aim of this work was to evaluate the pharmacological effects of curcumin (anti-inflammatory and antioxidant compound) on liver damage by prolonged bile duct ligation (BDL) in rats. We used the 4-week BDL-rat model to produce hepatic damage and to test the beneficial properties of curcumin. Four groups of rats (n=8) were performed. The first group underwent a sham operation. In the second group the animals were BDL. The rats in the third group were BDL and received curcumin (100mg/kg/day-p.o.). The fourth group received curcumin. Serum was obtained for determination of γ-glutamyl transpeptidase (γ-GTP), alanine aminotransferase (ALT) activities, and bilirubin concentration. Glycogen, reduced and oxidized glutathione and the extent of lipid peroxidation were esteemed in liver homogenates. TGF-β, mRNA and protein were determined by RT- PCR and Western blot, respectively. Curcumin prevented significantly the elevation of serum enzyme activities caused by BDL. GSH was oxidized, GSSG was statistically augmented and GSH/GSSG ratio decreased significantly by BDL; curcumin preserved within normal values all these parameters. Glycogen was decreased markedly by BDL but curcumin prevented almost completely this effect. Fibrosis was quantified by measuring hydroxyproline; BDL increased collagen content nearly 5-fold; this effect was prevented partially but significantly by curcumin. BDL increased TGF-β (mRNA and protein) while curcumin suppressed partially this mediator of fibrosis. Our results indicate that curcumin was highly effective in preventing hepatic cirrhosis. It blocks oxidative stress, elevation of serum markers of hepatic injury and possesses strong antifibrogenic effects. Moreover, the mechanism of action is probably associated with its antioxidant properties to reduce TGF-β that contributes to the accumulation of matrix proteins in chronic hepatic disease.

T17 DANDY-WALKER SYNDROME IN AN OTHERWISE HEALTHY 64-YEAR-OLD FEMALE

Kaur, N.P., Sinnadurai, A., Santucci, T., Gintautas, J.*, Nandakumar, T. Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

Dandy-Walker syndrome is a congenital brain malformation involving the cerebellum and the surrounding fluid filled spaces. Symptoms of the disease usually present in infancy. Its' features include an enlargement of the fourth ventricle, a partial or complete absence of the cerebellar vermis, a cyst formation in the posterior fossa and sometimes accompanying hydrocephalus. Symptoms usually include slow motor development and enlargement of the skull but can also present as irritability, convulsions, unsteadiness and jerky eye movements. It is often associated with other CNS structural anomalies. A 64-year-old female presented with severe, generalized, sporadic headaches for 6 months with associated blurred vision and loss of balance. She denied any other symptoms and had no significant personal or family medical history. On examination she had ataxic gait and blurring of vision. Initial labs were normal. Lumbar puncture was done which was not indicative of any infective pathology. After lumbar puncture, the patient reported subsided symptoms, likely due to relieved pressure from cerebral spinal fluid. CT and MRI scans showed mild communicating hydrocephalus and a posterior fossa cyst communicating with an enlarged fourth ventricle; this is indicative of Dandy-Walker syndrome. During right ventriculoperitoneal shunt placement, Dandy-Walker syndrome was confirmed. The patient had significant improvement of symptoms. This case illustrates the presence of previously undiagnosed Dandy-Walker, which is usually seen in infancy, in an otherwise healthy adult patient who presented with headaches, gait abnormality and problems with vision. This case is unusual in that the patient displayed no significant symptoms until the age of 64, as well as the absence of a family history of the congenital abnormality. Patient's symptoms improved after placement of a ventriculoparietal shunt to relieve the hydrocephalus.

T18 A CASE OF TREATMENT-RESISTENT CHRONIC LYME DISEASE WITH SUCCESSFUL SYMPTOM REDUCTION WITH EXTENDED USE OF CEFTRIAXONE.

February, M., Cervellione, K.L., Gintautas, J.*, Bagheri, F. Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

Lyme disease (Lyme borreliosis) is the most common tick-borne disease in the U.S.A.. If left untreated, arthritis, severe headaches, encephalitis and cognitive disorders can persist indefinitely. For late stage Lyme disease (LD) with persistent symptoms, recommended treatment is a minimum of four weeks of IV ceftriaxone. Prolonged use of ceftriaxone to treat persistent symptoms is controversial. A 47-year-old female presented to a Lyme specialist after two years of misdiagnosis. She was currently experiencing weakness, joint pain, fever, headaches and swollen glands that had gradually worsened for the past two years. Upon presentation, diagnosis was confirmed and the patient began an extensive antibiotic regimen (Table). Since 12 months, numerous attempts to stop IV treatment have spawned reoccurrence of symptoms. To this point, the patient has experienced no infections or morbidities due to the IV treatment. This case suggests efficacy and safety of the extended use of ceftriaxone to maintain stabilization when downward titration is problematic. Though we do not support the extended use of IV antibiotics in most cases, this treatment course does prove beneficial in cases such as the one presented here.

Time After Dx	Daily Antibiotic Treatment	Outcome
0-3 months	Amoxil 3g; probenecid 1g	Mild Improvement
3-4.5 months	Amoxil 3.5g; probenecid 1g; fluconazole 100mg	Mild Improvement
4.5-6 months	Diflucan 100mg; amoxil 3.5g; probenecid 1g; 1g clarithromycin	Mild Improvement
6-9 months	Diflucan 100mg; probenecid 1g; clarithromycin 1g; cefuroxime axeti 500mg; levofloxacin 500mg	Mild Improvement
9-15 months	IV ceftriaxone 4mg; diflucan 200mg; probenecid 1g; clarithromycin 1g; levofloxacin 500mg	Greatly improved

T19 ADENOCARCINOMA OF THE HEPATIC FLEXURE AND THE DESCENDING COLON WITH MANY COLONIC POLYPS REQUIRING OPEN SUBTOTAL ILEOSIGMOID ANASTOMOSIS

Odumosu, O.O., Cervellione, K.L., Satani, D., Patel, K., Gintautas, J., Patel, A.A. Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

An adenocarcinoma is a malignant tumor in the epithelial tissue. Polyps are projecting masses of overgrown tissue; around 35% of polyps develop into adenocarcinoma. Colon cancer often does not produce noticeable symptoms until the advanced stages, at which point changes in bowel habits, bloody stool, or stool with mucous can be present. Though multiple adenocarcinomas may be present in the colon, they often occur in close proximity to one another because they metastasize out from the preliminary affected area. A 54-year-old male presented with 1-month history of abdominal pain, diarrhea, one episode of painless rectal bleeding, and 10lbs weight loss. Physical examination revealed mild tenderness in the hypogastric region. Rectal exam was unremarkable; stool was negative for blood. Abnormal lab results included: hemoglobin=10.3 gm/dl; hematocrit=32.3%; red blood cell size=66.2 femtoliters; platelets 452,000/mm^3. Colonoscopy showed multiple masses throughout the colon. Results of biopsies were: invasive, moderately differentiated adenocarcinoma in the hepatic flexure and the descending colon; pre-malignant polyps in the ascending colon; and non pre-malignant polyps in the transverse colon and the sigmoid colon. An open, subtotal colectomy with ileosigmoid anastomosis was performed, which required removal of approximately 90% of the colon. The average colon is approximately 5' in length. The approximate distance between the adenocarcinomas in our patient was 2'. This area did not have pre-malignant polyps or adenocarcinoma present. This is rare in cases of colon cancer with multiple adenocarcinomas present. Though the polyps in these areas and in the sigmoid colon were not malignant, the high likelihood of cancer developing led to the decision to perform such a drastic surgery. Patient prognosis is very poor.

T20 A RARE CASE OF MERKEL CELL CARCINOMA METASTASIS TO THE HEAD AND BODY OF THE PANCREAS

Patel, K., Siegel, J[†]., Podani, J., Cervellione, K.L., Santucci, T.; Gintautas, J.*, Jamaica Hospital Medical Center, New York, NY, 11418; [†]Lenox Hill Hospital, New York, NY, (*jgintautas@jhmc.org*)

Merkel cell carcinoma (MCC) is a rare, cutaneous, malignant tumor of neuroendocrine cells. It has a high propensity for local recurrence and regional lymph node metastasis. MCC usually manifests as a rapidly growing, painless, intracutaneous nodule that is flesh-colored or has a bluish-red hue. The most commonly affected sites are the head and neck (50%) and extremities (30%). A 65-year-old male presented with complaints of abdominal pain of increasing severity for the past two weeks as well nausea, yellowish discoloration of urine and non-bloody vomiting for 48 hours. There was a past medical history of MCC (10 months prior), which was treated by excision of buttock mass and dissection of lymph nodes. He had since been receiving chemotherapy and radiation. On physical exam, the patient had yellowish sclera; liver was palpable and there was mild tenderness at the right quadrants. There were papular raised Merkel's lesions over the lower abdomen and extremities. CT scan revealed two masses, one in the pancreas just anterior to the portal vein (2.8cm diameter) and one in the pancreas head (2.2 x 3.5 cm). Dual sphinctetomies of the bile duct and pancreatic duct were performed. The patient tolerated the procedure well, and there was resolution of presenting symptoms. To our knowledge, this is only the third case of MCC metastatic to the pancreas, and the first with multiple growths on the pancreas. Time from initial diagnosis of MCC to occurrence of metastasis to the pancreas was less than one year, even with preventative chemotherapy and radiation therapy after initial excision, illustrating the diseases aggressive nature.

COMPLETE ABSTRACTS
for
POSTER SESSION III

Wednesday Evening 6 pm

W1 THE DAMAGE OF SYSTEMIC LUPUS ERYTHEMATOSUS ON ARTERIAL WALL ENDOTHELIAL FUNCTION IN RELATIVELY YOUNG PATIENTS

Cypiene,A.[1], Laucevicius, A.[1], Venalis, A.[1], Dadoniene, J.[1], Rugiene, R.[1], Ryliskyte, L.[1], Petrulioniene, Z.[1], Kovaite, M.[1], Skorniakov, V.[1], Griciene P[2] and Gintautas, J.[3]* [1]Vilnius University, Vilnius, Lithuania, [2]Department of Pediatrics State University of New York, Upstate Medical University, Syracuse, NY [3]Jamaica Hospital Medical Center, New York, NY, 11418 (*jgintautas@jhmc.org*)

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune disease in which inflammatory activity may lead to arterial wall endothelial dysfunction and premature aging of the arteries. The aim of this study was to assess whether endothelium-dependent flow-mediated dilatation (FMD) was modified in young age SLE patients and which risk factors may influence on this parameter. We examined 34 SLE patients (age 36.5±9,11 years) with high disease activity (SLEDAI 20.35±9,75) and 104 controls persons (age 38,51± 9,28 years). The FMD test in a brachial artery was performed by the ultrasound system (Logiq 7, General Electric). Anthropometric data, mean blood pressure (MBP), serum lipid profile, C-reactive protein (CRP) in both groups were measured using standard procedures. There were no differences in patients' age, body mass index (BMI), creatinine, but triglycerides ($p<0.001$), CRP ($p<0.001$), MBP ($p=0,009$) were significantjy higher in SLE patients compared to controls. FMD was not significant decreased in SLE patients compared to the controls (8,66±5,21 vs 8,78± 3,41%; $p=0.90$). Linear regression (only for SLE patients) indicated (adjusted $r^2=0,692$, $p<0,001$) direct relationships between FMD and vessel diameter ($p<0,001$), disease duration ($p=0,020$), BMI ($p=0,017$), creatinine ($p=0,033$) but not presence of SLE. Our results showed that FMD in SLE patients is best explained by vessel diameter, disease duration, BMI, and creatinine. Relationship between SLE and FMD still remains unclear. Although there are evidences at least of indirect impact of SLE on arterial wall endothelial function.

W2 EFFECT OF THE GABAPENTIN IN THE SLEEP-WAKE CYCLE IN RATS WITH TEMPORAL LOBE EPILEPSY.

Quijada A*, Santillan A, Mexicano G, Ayala Guerrero F. Laboratory of Neurosciences, Faculty of Psychology, National Autonomus University of Mexico. (ariloui@hotmail.com)

The present study has as objective to analyze the effects of the gabapentin (40mg/kg i.p.) on the sleep in rats with temporal lobe epilepsy originated by the seizures induced with kainic acid (10mg/kg i.p.)The rats Wistar were chronically implanted to register its sleep-wake cycle. A registration control was obtained during 10 continuous hours, continued by four similar periods after the administration of the drugs. The obtained data indicates that the gabapentin controlled the epileptic seizures partially but not during the first day of experimental registration, seizures and total inhibition of sleep were observed. It was observed starting from the second experimental registration the complete disappearance of the seizures, as well as progressive recovery of the sleep, reaching in that day of registration the levels control, in contrast with previously obtained data that they show that the seizures are prolonged more time. In conclusion, the gabapentin protects partially against the seizures induced with kainic acid and it favors the recovery of the sleep.

W3 PLATELET AGGREGATION IN PATIENTS RECEIVING STATINS, FULLY OR PARTIALLY METABOLIZED BY CYP3A4

Polena, S.[a], Gupta, M.P.[a], Shaikh, H.[a], Zazzali, K.[a], Coplan, N.[a], Gintautas, J.[b]*, Labana, S.S.[b], Soffer, D.[a]. [a]Lenox Hill Hospital, New York, NY, 10021; [b] Jamaica Hospital Medical Center, Jamaica, NY, 11418 (*jgintautas@jhmc.org*)

Clopidogrel therapy is the standard for prevention of cardiovascular events. Clopidogrel is converted into an active thiol by the cytochrome P450 CYP 3A4 enzyme. Recent studies suggest that statins metabolized by CYP3A4 attenuate the anti-aggregatory effect of clopidogrel. We evaluated the effect of CYP3A4-metabolized statins (atorvastatin, group 1) and partially-CYP3A4-metabolized statins (simvastatin, group 2) on platelet aggregation inhibition (PAI) when given concomitantly with clopidogrel as compared to patients who were statin naïve (group 3). PAI was measured by PlateletWorks (Helena Laboratories ICHOR) using ADP 20µmol as an agonist. All patients were on clopidogrel therapy (75mg/day). Non-responsiveness was defined as a PAI of < 35%. There was no statistical difference in mean PAI between groups; a higher prevalence of clopidogrel non-responders was noted in group 1 compared to group 3 (p=0.002). Multivariate analysis, adjusting for unequal presence of metabolic syndrome and hypertension, we found no statistical difference between groups.

Characteristics	Group 1 (68)	Group 2 (48)	Group 3 (55)	p-value
Age (mean)	64.5	65.8	61.6	
Sex (Male)	48 (70%)	32 (66%)	39 (71%)	n.s.
Smokers	28 (41%)	17 (35%)	24 (43%)	n.s.
Met. Syndrome	47 (67%)	29 (60%)	24 (43%)	p=0.02
HTN	58 (85%)	28 (57%)	37 (67%)	p<.001
DM	28 (41%)	16 (33%)	14 (25%)	n.s.
Clopidogrel non-responders	33 (48%)	19 (39%)	15 (27%)	p=0.002
PAI (mean)	41.50%	41.70%	43.80%	n.s.

Our data suggests that statins, either fully or partially metabolized by CYP3A4, do not influence PAI, even after adjusting for the risk factors. We concluded that concomitant statins with clopidogrel therapy does not influence the effect of clopidogrel in PAI.

W4 STRESS IN MALE RAT BRAIN TREATED WITH SINGLE AND REPEATED DOSE OF ABUSE DRUGS

*Calderon, G.D.[1], Labra, R.N.[1], Barragán, M.G.[1], Hernández, G.E.[2], Trujillo, J.F.[2], Juarez, O.H.[2], Osnaya, N[3], Garcia, A.R.[3] 1.Lab. Neuroquímica. 2.Lab Farmacología. 3.Lab. Patología Exptl. Subdirección de Medicina Experimental. Secretaría de Salud. México. (*Solodavid2001@yahoo.com.mx*).

Marijuana (Mar) is the main illegal drug consumed in Mexico according to recent national survey and the mechanism involved in oxidative stress is not well known. The aim of this study was to determine if Mar and nalbuphine (Nal) are a contributing factor to increase the risk of oxidative damage. Male wistar rats were used and a single and repeated intraperitoneal dose of Mar (250mg/kg) and Nal (10mg/Kg) administered. All animals were sacrificed to measure glutathione (GSH), lipid peroxidation (TBARS) and 5-Hydroxyindole-3-acetic Acid (5-HIAA) levels in brain homogenates as well as Na^+, K^+ ATPase and total ATPase activity. GSH and 5-HIAA showed significant ($p<0.05$) change in experimental group. TBARS levels increased significantly ($p<0.05$) in all the experimental respect control groups. Na^+, K^+ ATPase and total ATPase activity showed significant ($p<0.05$) changes in experimental vs control groups. These results indicate that Mar and Nal induced changes in cellular regulation and biochemical responses as consequence of oxidative stress in brain.

W5 CORONARY DISEASE RISK FACTORS IN YOUNG PATIENTS WITH DIASTOLIC DYSFUNCTION

Polena, S.[a], Morreta, A.[a], Novella, J.[a], Coplan, N.[a], Gintautas, J.[b]*, Saraiya, B.[a] and Gupta, M[a]. [a]Lenox Hill Hospital, New York, NY, 10021; [b] Jamaica Hospital Medical Center, Jamaica, NY, 11418 (*jgintautas@jhmc.org*)

Diastolic dysfunction (DD) is a common entity associated with advanced age and hypertension, often present in patients with ischemic heart disease. The correlation of DD and coronary artery disease (CAD) in asymptomatic young patients is not known. We sought to determine the prevalence of CAD risk factors in asymptomatic young patients with DD. Here we present data from a retrospective chart review of CAD risk factors in asymptomatic patients diagnosed with DD during an echocardiograph examination. We screened all patients that had an echocardiographic examination at our institution (Lenox Hill Hospital) from January 2004 until July 2007. DD was diagnosed if an impaired filling pattern with an E/A ratio less than one was noted on the mitral inflow pulse wave doppler. Patients with DD or were older than 65 years were excluded from the study. One-hundred and one patients met study criteria. Data regarding the presence of risk factors was collected, as displayed in the below Table. The mean age of patients was 48±6; 51 (50%) were male. Data regarding presence of risk factors are presented in the below Table.

Risk Factors	Present
Hypertension	53% (54/101)
Hyperlipidemia	31% (31/101)
Smoking	19% (19/101)
Diabetes Mellitus	22% (23/101)
Peripheral Vascular Disease	8% (8/101)
Family History	17% (17/101)

Our study suggests that hypertension is the most prevalent CAD risk factor found in patients with DD, followed by hyperlipedemia and diabetes. We cannot predict in our study if the presence of CAD risk factors is higher in young patients with DD compared with patients without. Larger trials with control arms are necessary to draw further conclusions.

W6 CADMIUM EFFECTS ON A RAT MEMORY MODEL

Tepox-Padrón A.,[a] Ríos-Dávila V.M., [a] Miliar-García A,[b,c] Zepeda H.,[b] Picazo O.,[b] Espinosa J.,[b] Soriano M.,[a] Padilla-Garcia M.,[e] Trujillo-Ferrara J,[a,c] Correa-Basurto J. [a,d,f,*] [a]Departamento de Bioquímica, [b]SEPI-ESM-IPN, Laboratorio de Biología Molecular, [c]SEPI-ESM-IPN, [d]Departamento de Física, ESFM-IPN. [e]Laboratorio de Biología Molecular, Universidad Anahuac. [f]Departamento de Farmacología, ESM-IPN. Plan de San Luis y Díaz Mirón,11340 Mexico City, México. (atepoxp0300@ipn.mx).

Alzheimer's disease, which is the most frequent cause of dementia in the elderly, has been related to oxidative stress. In this study, we investigated the relationship between Alzheimer's disease and the intraperitoneal administration of cadmium, an environmental contaminant that affects some organs of the body like the brain, lungs, kidney, testis and liver. Several studies suggest that these toxic effects are generated by oxidative stress damage. We applied a Pavlovian model after 30 days of treatment with cadmium, and assessed the changes in memory and motor activity in rats. The results suggest that there is not any significative difference between the groups without treatment and those with low-doses of cadmium. However, in the groups with higher doses we found a statistically significant increase in the percentage of learning compared to the control group. Currently, we are searching (molecular biology) for some proteins related to the process of memory such as muscarinic receptors, cholin-acetyltransferase, acetylcholinesterase secretases among others. *Funded by grants from CONACyT (62488) and SIP-IPN (20070140).*

W7 AN UNUSUAL RADIOLOGIC PRESENTATION OF ADENOCARCINOMA OF THE LUNG

Shamalov, V., Canseco, A.P., Rocher, M., Hechevarria, J.M., Thurm, C., Gintautas, J.*, Bagheri, F.
Jamaica Hospital Medical Center, New York, NY, 11418 (jgintautas@jhmc.org)

Adenocarcinoma is a malignant tumor originating in glandular tissue. It usually presents radiologically as a solitary pulmonary nodule or mass, most often with ill-defined and spiculated contours and lobulations. A 52-year-old male was brought in after being found unconscious for an unknown duration of time. Upon awakening, he was confused and lethargic with unsteady gait. He denied any history of similar episodes or related symptoms. Medical history included hypertension, asthma and hypercholesterolemia; he had a history of alcohol abuse, marijuana use, 25-years of cigarette smoking, and asbestos exposure. He was currently taking albuterol. One year prior he had a positive CT scan with left lung mass. He was advised to follow-up, but was noncompliant. Upon admission, patient had bilateral wheezing and left middle crackles. Blood pressure was high. Chest x-ray suggested cavitating lesion in the left lung. Chest CT with contrast revealed a 4.7 cm mass in the left upper lobe with significant necrosis and cavitation. There was patchy infiltrate in the surrounding posterior segment of the left upper lobe and nodular densities in the left and right lower lobes. Brain MRI showed hemorrhagic nodules in the right occipital-parietal region with moderate edema. Lung cancer with brain metastasis was suspected. Linezolid and metronidazole were started for possible actinomyces, nocardia and/or anaerobic infection. Left upper lobe lung mass wedge resection was performed. Poorly differentiated adenocarcinoma with extensive necrosis was identified. The patient was referred to chemotherapy. Here, adenocarcinoma presented radiologically as a large cavitation, which is unusual for this type of tumor. Patients presenting with symptoms consistent with a diagnosis of adenocarcinoma may have radiological exams similar to the one presented here.

W8 FREE RADICALS INDUCED BY CADMIUM DUE TO A DECREASE OF SOD 1 AND SOD 2 EXPRESSIONS IN RAT BRAIN.

Ríos-Dávila V.M., [a] Tepox-Padrón A., [a] Miliar-García A,[b,c] Rosales-Hernández M.C.,[a,c] Ramirez-Rosales D.,[d] Padilla-Garcia M.,[e] Zamorano-Ulloa R.,[d] Trujillo-Ferrara J,[a,c] Correa-Basurto J. [a,d,f,*]
[a]Departamento de Bioquímica, [b]SEPI-ESM-IPN, Laboratorio de Biología Molecular, [c]SEPI-ESM-IPN, [d]Departamento de Física, ESFM-IPN. [e]Laboratorio de Biología Molecular, Universidad Anahuac. [f]Departamento de Farmacología, ESM-IPN. Plan de San Luis y Díaz Mirón,11340 Mexico City, México. (vriosd0300@ipn.mx)

Cadmium is an environmental contaminant, which can induce several toxic effects in different tissues. Although the mechanisms of these toxic effects are unclear, some reports suggest that Reactive Oxygen Species (ROS) are responsible for tissue damage. In brain, oxidative stress is related to several degenerative diseases, such as Alzheimer's disease. We investigated the effect on the rat brain induced by Cadmium intraperitoneal administration during 45 days by means of ROS biochemical techniques and Electronic Paramagnetic Resonance (EPR). Furthermore, we evaluated the expression of some antioxidant enzymes such as superoxide dismutase 1 and 2 (SOD1 and SOD2), catalase (CAT) and glutathione peroxidase (GPX1). Whereas the EPR results showed a dose-dependent presence of ROS, biochemical measurements showed no significant difference of these molecules between doses. By measuring the proteins generated by CAT and GPX1, it was found that the expression of these antioxidants showed no significant difference between doses. On the other hand, mRNA expression for SOD1 and SOD2 was decreased as the doses increased. In conclusion, results suggest a mechanism of cellular damage by increased levels of ROS secondary to a decreased mRNA, SOD1 and SOD2 expression, probably due to DNA damage induced by Cadmium in regions that express SOD proteins. *Funded by grants from CONACyT (62488) and SIP-IPN (20070140).*

W9 EFFECTS OF INHIBITORY AMINO ACIDS ON ADENOSINE RELEASE IN THE MOUSE HIPPOCAMPUS

*Saransaari, P. and Oja, S.S. Brain Research Center, Medical School, FI-33014 University of Tampere, Tampere Finland (pirjo.saransaari@uta.fi)

Adenosine is a neuromodulator which inhibits the synaptic release of neurotransmitters and hyperpolarizes postsynaptic neurons. However, only little data are available of the effects of inhibitory neurotransmitters and modulators on the release of adenosine. We studies here these effects on the release of peloaded [^{3}H]adenosine from hippocamal slices from developing (7-day-old) and young adult (3-month-old) mice under normoxic and ishemic conditions. In normoxia adenosine release was about 3-fold greater in adults than in developing mice. GABA and glycine (both 0.1 mM) did not markedly affect the release, whereas 0.1 mM β-alanine and L-serine (both 0.1 mM) were significantly inhibitory at both ages. Taurine depressed concentration dependently the release in developing mice but had no effect in adults. In ischemia, adenosine release increased 8-fold in developing mice and 5-fold in adults. GABA was not either effective in ischemia. β-Alanine and L-serine were again markedly inhibitory in developing mice, whereas no significant effects were seen in adults. In developing mice glycine was also inhibitory in ischemia but taurine enhanced the release at both ages. We hae earlier demonstrated that taurine release is markedly increased in many cell-damaging conditions. The simultaneous release of these two inhibitory neuromodulators, taurine and adenosiine, may constitute an important protective mechanism under ischemic conditions. *Funded by the competitive reserach funding of Pirkanmaa Hospital district, Finland.*

W10 GENDER DIFFERENCES IN BRAIN PERIPHERAL BENZODIAZEPINE RECEPTOR (PBR) EXPRESSION AND SEIZURES PRODUCED BY HEPTACHLOR DURING DEVELOPMENT.

Garcia, E.F. and Woolley, D.E., Neurobiology, Physiology and Behavior, College of Biological Sciences, University of California, Davis, CA 95616-8519 (dewoolley@ucdavis.edu)

Heptachlor is an insecticide that contaminated the milk supply in Oahu during the 1980s and early '90s. Heptachlor is a GABA-A antagonist and causes seizures. It also increases PBRs in rat brains. PBRs are found on outer mitochondrial membranes in glia, rather than neurons, and is necessary for steroidogenesis in brain. We compared the effects of acute oral administration of heptachlor (60 mg/ml oil/kg body wt) from postnatal days 0 to 60 on brain PBR expression and on seizure severity in male and female rats. At birth heptachlor did not change levels of PBRs and did not produce seizures in either gender. From 5 through 60 days of age brain PBR expression was increased 25-200% compared to age and gender matched controls one and 2 hours after administration in female rats. However in males, PBR expression was only increased from 30 through 60 days of age and only at one hour. By contrast, seizure incidence and intensity were greater in males than in females from 10 to 20 days of age at both one and 2 hours. Thus, the gender difference in PBR expression was the opposite of the gender difference in seizure intensity, suggesting that the increased PBRs in females were responsible for the decreased seizure intensity. Next, we compared the gender difference in seizure intensity produced by heptachlor with seizures produced by a non-chemical means, i.e., maximal electroshock (MES), and found that there was no gender difference in MES seizures. Thus the gender differences were due to the action of heptachlor. *Funded by a grant from the Heptachlor Research and Education Foundation.*

W11 EFFECT OF TOPICAL DINITROFLUOROBENCE (DNFB) ON MURINE LANGERHANS CELLS.

Trejo-Mondragón, M.[1], Galván-Nava, N.[1], Ponce-Sánchez, A., [3], Sánchez-Ruiz, J.[4], Aguirre-Zárate, P.[4], Tellez-Hernández, B.[5], Alvarez-Pérez, J.[5], Herrera-Enriquez, M.[5], Castel-Rodríguez, A.E.[5], Elinos-Báez, M.[5], Villanueva-Rodríguez, L.G.[2], *Ramírez-González, M.D. Departments of *Pharmacology and [5]Tissue and Cell Biology, School of Medicine, National Autonomous University of Mexico (UNAM). Mexico City 04510 *(mdrg@servidor.unam.mx)*

Contact hypersensitivity is a severe skin condition that can be replicated in the laboratory using topic DNFB. In this work we used 300 male 8-weeks old CD-1 (40±3 g) and Balb-c (20±2 g) mice treated with 40 µl of DNFB dissolved in acetone: mineral oil (1:1) as vehicle. During the experiment, groups of five mice were kept in Plexiglas cages with 12:12 dark: light cycle, 21-23 °C room temperature, food and water *ad libitum.* Mice's ear inflammation (EI) was measured with a vernier at 24 h intervals. Langerhans cells (LC) were quantified by immunehystochemical staining of MHC II molecules. LC number were measured either 24 after a sensitization test (SEN), using 0.6% DNFB, and eight days after the challenge test with 0.3% DNFB (CHA). Statistical analysis was done using ANOVA followed by t test. EI reaches maximum at 24 h after and it is longer lasting with larger doses of DNFB. Following SEN, DNFB caused larger EI and decrease in the number of LC than vehicle ($P<0.05$) and these responses are larger in CD-1 than in Balb-c mice ($P<0.05$). Following CHA, EI and the decrease in the number of LC are larger than during SEN ($P<0.05$). These data indicate that CD-1 rather than Balb-c mice can be more useful for hypersensitivity testing *in vivo*. *Medical students from (1) UNAM and (2) LaSalle University; and students from (3) Chemistry and (4) Preparatory School, UNAM.*

W12 CONTRIBUTION OF LANGERHANS CELLS TO DRUG-INDUCED ADVERSE REACTIONS

Villanueva-Rodriguez, L.G.[1], Trejo-Mondragón, M.[2], Castell-Rodríguez, A. E.[3], *Ramírez-González, M.D. Departments of Pharmacology and [3]Tissue and Cell Biology, School of Medicine, National Autonomous University of Mexico (UNAM). Mexico city 04510 *(mdrg@servidor.unam.mx)*

Drug-induced adverse reactions (DIAR) occur in 2-3 % or 10-15% in ambulatory or hospitalized patients. Contact or delayed hypersensitivity (HS, DHS) are DIAR that can be observed following a single exposure to drugs and/or during acute or chronic treatments. Many drug types can trigger HS and/or DHS and its severity strongly depends on the underlying physiological and physiopathological condition of the patient, particularly when related to virus infections or parasite infestations. Skin is the largest organ of the human body frequently involved in DIAR. HS and DHS reactions can vary from minor skin rash to severe necrotic tissue damage. Langerhans cells (LC) are the first sentinels for the immune surveillance function of the skin immune system, and are known to be altered during either topic or systemic drug application. In this review we analyzed the value of experimental models to study HS and DHS reactions and the possible mechanisms through which LC may contribute to DIAR.*Medical students from [1]LaSalle University and [2]National Autonomous University of Mexico.*

W13 APPLICATION OF PEDAGOGY THEORIES INTO MEDICAL PHARMACOLOGY EDUCATION.

*Ramírez-González, M.D. Department of Pharmacology, School of Medicine, National Autonomous University of Mexico, Mexico City 04510 *(mdrg@servidor.unam.mx)*

Adult and cognitive theories of education highlight the importance of previous knowledge and experience as the foundation for the elaboration of new knowledge. For young adult's education, one of the main reasons for long term learning failure appears to be related to the low scoring attributed to basic sciences during the first years of medical education. One possible explanation for this pedagogic distortion may be related to the educator's assumption that integration between reference knowledge and learning outcome is fully a student's task. The underlying question relates to how students, or professors, are prepared to integrate information within coherent bodies of unforgettable knowledge? In this work, a distinction is made between integrated and integrative knowledge in as much as the second one implies application of medical pharmacology knowledge for drug prescription. The application of pedagogy theoretical principles is illustrated with a set of examples of reference knowledge from basic and clinical sciences upon which pharmacology learning outcomes, and so learning objectives, could be constructed disregarding the modular or departmental organization of medical schools.

W14 EFFECT OF CHRONIC ADMINISTRATION OF SUGAR CANE (AZ) ON TAIL FLICK AND FORCED SWIMMING TESTS.

Aranda-Flores, W.[1], Valdez-Reyes, J.[1], Soriano-Flores, S.[1], Cruz-Salas, L.[1], Milán-Chávez, R., Flores-Robles, E., *Ramírez-González, M.D. Departments of *Pharmacology and Biochemistry, School of Medicine, and [1]School of Chemistry, National Autonomous University of Mexico. Mexico City *(mdrg@servidor.unam.mx)*

Oral chronic administration of carbohydrates can reproduce in rats a human-like syndrome X characterized by obesity, dislipidemias, hypertension and diabetes. In this work we explored pain sensitivity (tail flick test, TFT) and psicomotor integration (forced swimming test, FST) in male Wistar rats (80±3 g) treated with 30% aqueous solution of standard sugar *ad libitum* for 100 weeks (AZ). Control rats received tap water *ad libitum* (AG). Animals were kept with 12:12 dark:light cycle, 21-23 °C of room temperature and free access to rat chow. Methods used were TFT at 56 °C; FST at 22 °C; glucose tolerance test (GTT) at 10h at 22 °C; and *in vitro* glucose uptake using reverted intestine sacs (IGU). Statistical analysis was done with ANOVA followed by t test. When compared with AG rats, AZ increased TFT latency and induced larger immobility in FST ($P<0.05$); AZ-induced increase in body weight is attenuated by swimming ($P<0.05$) and occurs with minor but significant increases in glycemia ($P<0.05$); AZ induced a hyperinsulinemic state as indicated by smaller AUC in GTT and enhanced intestinal disacharadase activity as suggested by larger AUC in IGU ($P<0.05$). These data indicate that AZ model appears to reproduce alterations in pain sensitivity and psicomotor disruption as observed in patients with chronic untreated diabetes and hypertension likely due to metabolic adaptation.

W15 PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY OF DRUGS IN A PEDIATRIC HOSPITAL OF MEXICO

Juárez-Olguín H, Calderón-Guzmán D, Flores-Pérez J, Guillé-Pérez A, Flores-Pérez C, Pérez-Guillé G. Laboratory of Pharmacology, INP, Universidad Nacional Autónoma de México. Mexico City, 04530, Mexico (*juarezol@yahoo.com)*

Detection and register of adverse drug reaction related with the patterns of drug consumption contribute to have secure drugs and planning programs in the hospital. The aim of this work is to describe the activities of pharmacovigilance (PV) and pharmacoepidemiology (PE) of drugs used in a Pediatric Hospital of Mexico. For PV and PE studies we have established a program for detection and registration of adverse drug effects and also we are able to describe the patterns of drug prescription, acting as reference center that support major objectives ordered by Minister of Health. In general, adverse effects detected have been similar to those reported in literature, PV activities show that there is a relation between in increases in incidence of adverse drug reaction and the prescription of a large number of drugs however and there is not special adverse effect appears until now. PE activities reveal that antibiotics are the most frequently prescribed drugs and next are drugs used for gastrointestinal diseases. As conclusions based of this experience is that If PE of the hospital is known drug consumption can be optimally planned, and PV demonstrate that if polytherapy is not necessary, it must be avoided. PV and PE activities have enriched both the clinical practice and our staff work, since it has consistently forced us to seek better options for the adequate use of drugs.

W16 PATTERNS OF DRUGS PRESCRIPTION IN PEDIATRIC PATIENTS DURING TWO PERIODS IN MEXICAN PRIVATE HOSPITAL

*Hernández, G.E.[1], Trujillo, J.F.[1], Hernández, S.D.[1], Morales, R.A.[2], Rodríguez, P.R.A.[2], Calderón, G.D.[2], 1. Lab. Farmacología, 2. Lab. Neuroquímica, Instituto Nacional de Pediatría, México. **(*ernestinahg@aol.com*)**

The aim of this work was to determine the prescription patterns in the intensive care unit of pediatric patients, making a retrospective analysis of the records of individual dose that were prepared in pharmacy service during two periods: For period I (September 2002 to November 2003) 81 patients were treated: 27 boys, 29 girls and 25 without register of gender. 4058 dose were prepared from 44 different drugs. The seven drugs more frequently prescribed were Furosemide with 1185 dose (29.20%), Spironolactone 663 (16.31%), Phenobarbital 473 (11.65%), Ursodesoxycolic Acid 377 (9.29%), Omeprazole 265 (6.53%), Theophiline 147 (3.62%) and Captopril 118 (2.9%). During period II (February 2006 to July 2007) were 4424 dose from 45 different drugs were prescribed, and 106 patients: 25 boys, 40 girls and 41 without register of gender were treated. The seven drugs more frequently administered were Teophiline 1241 dose (28.05%), Furosemide 588 (13.29%), Spironolactone 529 (11.96%), Omeprazole 476 (10.76%), Sildenafil 398 (9.00%), Captopril 297 (6.71%) and Hydralazine 193 (4.36%). The results show that the pediatric patients consumed one to eight different drugs simultaneously. There is also a risk in the incidence of adverse reactions and drug interactions. From the first therapeutic group, the diuretics were the most used. For the second one were the bronchodilatators. The prescription pattern of drugs for pediatric patients from the intensive care unit needs to be followed to assess the effectiveness and safety in this population. In Mexico, the manpower pharmacy, made the pediatric dose from adult presentations, using the weight and age of children because there is not a special pediatric form.

W17 PRESCRIPTION DRUG USE PATTERNS IN A MEXICAN NATIONAL PEDIATRIC INSTITUTE

*Hernández, G.E.[1], Trujillo, J.F.[1], Hernández, S.D.[1], Araujo, V.L.F.[3], Rodríguez, P.R.A.[2], Calderón, G.D.[2], 1. Lab. Farmacología, 2. Lab. Neuroquímica, 3. Farmacia, Instituto Nacional de Pediatría, México. (ernestinahg@aol.com)

The aim of this work was to determine the prescription patterns for pediatric patients, in a public hospital of the third level in Mexico. A retrospective analysis of the dispensing records from the pharmacy service during twenty three months (January 2006 to November 2007) was made. In this period 15,270 patients were treated in the hospital. 327,563 units (dosage forms: tablets, capsules and coated tablets) of 124 different drugs were administered. The ten drugs most frequently used were Prednisone with 77,720 units (23.73%), Methotrexate 28,500 (8.70%), Captopril 25,500 (7.80%), Topiramate 16,520 (5.04%), Potassium Chloride 16,300 (4.98%), Spironolactone 15,310 (4.67%), Ranitidine 10,120 (3.09%), Paracetamol 8,522 (2.60%), Furosemide 8,160 (2.49%) and Mefenamic Acid 7,780 (2.38%). In Mexico the physicians, adjust the pediatric dose from adult presentations, using the weight and age of children because there is not a special pediatric form of the medicines available. This information is a support to develop new pharmaceutical forms for pediatric patients. However, the use of drugs in this population in the hospital needs to be followed to assess the effectiveness and safety in this population.

W18 GENDER-DEPENDENT EFFECT OF PRENATAL COCAINE EXPOSURE ON CORONARY ARTERY MYOGENTIC TONE OF ADULT OFFSPRING.

Xiao, D.,[1] Yang, S.[2] and *Zhang, L.,[1] [1]Center for Perinatal Biology, Department of Physiology & Pharmacology, Loma Linda University School of Medicine, Loma Linda, CA 92350; [2]Department of Chemistry and Biochemistry, California State University, San Bernardino, CA 92407 (Lzhang@llu.edu)

Cocaine abuse is a significant problem among pregnant women. The present study tested the hypothesis that prenatal cocaine exposure alters myogenic reactivity of rat coronary arteries in adult offspring. Pregnant rats received cocaine (30 mg/kg/day) or saline from days 15 to 21 of gestational age. In pressurized coronary septal arteries from 3-month old offspring, we measured, simultaneously in the same tissue, vascular diameter and vessel wall intracellular Ca2+ concentrations ([Ca2+]i) as function of intraluminal pressure. In both saline and cocaine exposured groups, membrane depolarization with KCl caused a rapit increase in [Ca2+]i and a decrease in diameter, which were not altered by cocaine exposure. Pressure-dependent myogenic responses were significantly decreased in male but increased in female offspring in response to prenatal cocaine exposure. However, presure-induced increases in [Ca2+]i were not significantly different between cocaine and saline groups in either male or female offspring. The ratio of changes in diameter to changes in [Ca2+]i in presurized arteries was significantly less in male but greater in female offspring of cocaine-treated animals. In addition, pretreatment with NOS inhibitor, N^G-nitro-L-arginine did not alter coronary artery myogenic responses in either saline control or cocaine-exposed animals. The results suggest that prenatal cocaine exposure down-regulates pressure-dependent myogenic tone of the coronary artery in male offspring, which is, at least, partly due to a decrease in Ca2+ sensitivity of myogenic mechanism. The opposite effects in female offspring suggest a potential role of sex hormones in the cocaine-mediated programming of adult vascular reactivity. (*supported in part by NIH grants HL82779 & S06GM073842*).

W19 PRENATAL COCAINE TREATMENT CAUSES DNA METHYLATION AND DOWNREGULATION OF PKCε GENE EXPRESSION IN THE HEART OF ADULT MALE OFFSPRING.

Zhang, H. and *Zhang, L. Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

We have demonstrated that prenatal cocaine exposure leads to a gender-dependent decrease in PKCε protein as well as mRNA levels and increase in heart susceptibility to ischemic and reperfusion injury in adult male offspring. The present study tested the hypothesis that DNA methylation plays a key role in epigenetic modification of PKCε gene expression pattern in the heart. Pregnant rats were administered intraperitoneally either saline or cocaine (15 mg/kg) twice daily from day 15 to day 21 of gestational age. Hearts were isolated from 3-week-old and 3-month-old male and female offspring. Methylation specific PCR analysis of putative regulatory regions of the PKCε gene in the hearts revealed a significant increase in methylation of CpG islands in 4 putative transcription binding sites namely MTF-1 (2) and SP-1 (2) in cocaine-treated animals. In vitro as well as in vivo interaction of the transcription factor SP-1 with the target SP-1 binding sites was demonstrated by Electromobility Shift Assay (EMSA) and Chromatin Immunoprecipitation (ChIP) assay. Reporter gene assays showed that the SP-1 binding sites played a strong stimulatory role of PKCε gene transcription. Methylation of the SP-1 binding sites significantly decreased SP-1 binding to the PKCε promoter. Cocaine did not affect nuclear SP-1 levels or the binding of SP-1 to the unmethylated SP-1 binding sites. In the case of MTF-1, although in vitro EMSA binding was present but both supershift and ChIP assay did not find positive binding. These findings suggest that the lasting and life-long pathophysiological effect on cardiac function caused by chronic cocaine exposure during fetal development is mediated in part by increased DNA methylation of the PKCε gene. (supported in part by NIH grants HL82779 & HL83966)

W20 FETAL COCAINE EXPOSURE CAUSES A GENDER-RELATED DOWNREGULATION OF CARDIAC PKCε EXPRESSION IN OFFSPRING.

Zhang, H. and *Zhang, L. Center for Perinatal Biology, Loma Linda University School of Medicine, Loma Linda, CA 92350 (lzhang@llu.edu)

It has been demonstrated that prenatal cocaine exposure leads to an increased heart susceptibility to ischemic and reperfusion injury in adult rats. However the underlying mechanism has yet to be discovered. Previous experiments in our laboratory demonstrated that cocaine increased DNA methylation of PKCε gene promoter and decreased PKCε expression in the fetal heart. The present study is to determine PKCε expression pattern in the heart of offspring after prenatal cocaine treatment. Pregnant rats were administered intraperitoneally either with saline or cocaine (15 mg/kg) twice daily from day 15 to day 21 of gestational age. Hearts were isolated from 3-week-old and 3-month-old male and female offspring. PKCε and PKCδ protein and mRNA levels were measured by Western immunoblot and real-time RT-PCR, respectively. Cocaine had no effect on PKCδ protein expression in the hearts of offspring. PKCε protein levels were significantly decreased in the cocaine groups compared with saline treatments in both 3-week-old and 3-month-old rats only in male, but not female hearts. Accordingly, mRNA levels of PKCε in both 3-week-old and 3-month-old males, but not females, were significantly decreased in cocaine-treated animals. The results suggest that fetal exposure to cocaine causes downregulation of PKCε gene expression in the heart that persists into adulthood in a gender-specific manner. The finding of the gender-dependent decrease of PKCε expression in male hearts in 3-week-old offspring indicates a minimum role of sex steroid hormones in the regulation of fetal programming of PKCε expression pattern caused by cocaine treatment. (supported in part by NIH grants HL82779 & HL83966)

NOTES