

The 13<sup>th</sup> Annual International Dose-Response Conference

**PRECONDITIONING:  
ADAPTIVE RESPONSES IN BIOLOGY  
AND MEDICINE**

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*ABSTRACT BOOK*

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Conference Directors



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## **PRE-CONDITIONING AND THE DOSE-RESPONSE**

### **Intermittent Energetic Challenges, Adaptive Responses and Health: Lessons from the Brain**

*Mark P. Mattson, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD*

### **Adaption by Low Dose Radiation Exposure: A Look at Scope and Limitations for Radioprotection**

*Ron Mitchel, Radiological Protection Research and Instrumentation, Atomic Energy of Canada Ltd. Chalk River Nuclear Laboratories, Chalk River, ON*

### **Optimizing Pre- and Post-conditioning Clinical Outcomes: A Dose Response Perspective**

*Edward J. Calabrese, Ph.D., Environmental Health Sciences, School of Public Health, University of Massachusetts Amherst, Amherst, MA*

**Intermittent Energetic Challenges, Adaptive Responses and Health: Lessons from the Brain**

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Humans evolved in environments where food was not available ad libitum, and so possess robust adaptive physiological and behavioral responses to periods of food scarcity. Emerging research in this Laboratory and elsewhere has shown that intermittent fasting (IF; e.g., fasting for a period of 24 hours twice weekly) and vigorous exercise can increase numbers and strength of synapses and can enhance brain function (cognitive and sensory – motor performance) and mood. We find that the general mechanism by which IF and exercise benefit neurons is by challenging them by increasing their activation state and energy demand, which results in a coordinated engagement of signaling pathways that promote neuroplasticity and cellular stress resistance. The pathways activated by exercise and IF include those involving brain-derived neurotrophic factor (BDNF), mitochondrial biogenesis, DNA repair and removal of oxidatively damaged proteins and organelles. Peripheral changes in energy metabolism that occur during fasting and exercise may also contribute to their beneficial effects on the brain. In this regard, the depletion of glycogen stores in the liver triggers the mobilization of fatty acids from fat cells and the production of ketone bodies. Ketone bodies such as beta-hydroxybutyrate provide an alternative energy source for neurons and may also activate signaling pathways that enhance the ability of the brain to cope with stress. Our studies in animal models of chronic neurodegenerative disorders (Alzheimer's and Parkinson's diseases) and acute brain injury (stroke and severe epileptic seizures) demonstrate robust neuroprotective and neurorestorative effects of IF diets. IF protects the brain by bolstering antioxidant defenses and protein chaperone levels, and by suppressing inflammation. The implications of these findings for strategies for optimizing brain function and reducing the risk of neurodegenerative disorders will be described.

**Adaption by Low Dose Radiation Exposure: A Look at Scope and Limitations for Radioprotection**

**Ron Mitchel**, *Radiological Protection Research and Instrumentation, Atomic Energy of Canada Ltd. Chalk River Nuclear Laboratories, Chalk River, ON, Canada, K0J1J0*

The procedures and dose limitations used for radiation protection in the nuclear industry are based on the assumption that risk is directly proportional to dose, without a threshold. Based on this idea that any dose, no matter how small, will increase risk, radiation protection regulations generally attempt to reduce any exposure to “as low as reasonably achievable” (ALARA). We know however, that these regulatory assumptions are inconsistent with the known biological effects of low doses. Low doses induce protective effects, and these adaptive responses are part of a general response to low stress. Adaptive responses have been tightly conserved during evolution, from single celled organisms up to humans, indicating their importance. This presentation will examine cellular and animal studies that show the influence of radiation induced protective effects on diverse diseases, and examine the radiation dose range that is effective for different tissues in the same animal. The concept of a dose window, with upper and lower effective doses, as well as the effect of multiple stressors and the influence of genetics will also be examined.

**Optimizing Pre- and Post-conditioning Clinical Outcomes: A Dose Response Perspective**

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This study assessed the dosage, temporal and mechanistic relationships between the conditioning dose and the protective effects of preconditioning experiments. Entry criteria for study evaluation required the occurrence of an hormetic-like biphasic dose response for the protective endpoint, and a mechanistic assessment of how the conditioning dose affected the protective endpoint response. The conditioning dose that demonstrated the largest increase in endpoint response during the conditioning period was the same dose that was the optimally protective dose. Cell signaling pathway inhibitors were commonly employed to block the conditioning effect; such inhibitory actions abolished the protective effect at the optimal conditioning dose, identifying a specific hormetic mechanism. Conditioning dose responses often had sufficient doses to assess the nature of the dose response. In each of these cases these mechanism-based endpoints displayed an hormetic dose response. The present analysis reveals that when preconditioning experiments demonstrate a biphasic dose response it can be directly linked to the actions of the conditioning dose based on optimal dosage, temporal relationship and receptor-based and/or cell signaling-based mechanisms. These findings indicate that preconditioning induced biological/biomedical effects represent a specific type of hormetic dose response.

## **CARDIOVASCULAR PRE- AND POST-CONDITIONING**

### **Remote Ischemic Conditioning: From Inspiration to Clinical Translation**

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*Peter Whittaker, Cardiovascular Research Institute and Departments of Physiology & Emergency Medicine, Wayne State University School of Medicine, Detroit MI*

### **Assessing the Promise of Remote Conditioning for Cardioprotection: New Clinical Developments**

*Andrew N Redington, Division of Cardiology, Department of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

### **Cardioprotection: Challenges and Possibilities**

*Derek J Hausenloy, The Hatter Cardiovascular Institute, University College London, London, UK*

### **Cellular Mechanisms Underlying the Cardioprotective Effects of Exercise**

*Rick J. Alleman, Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC*

*David A. Brown, Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC*



**Remote Ischemic Conditioning: From Inspiration to Clinical Translation**

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Remote ischemic conditioning is the phenomenon whereby brief episodes of ischemia-reperfusion applied in a distant organ or tissue render the heart resistant to damage caused by a prolonged ischemic stress. The discovery of remote conditioning, first reported by our laboratory in 1993, was not a serendipitous finding, but, rather, was predicted by mathematical modeling. In the ensuing years, the paradigm has been expanded to encompass a spectrum of remote triggers, including the seminal observation that repeated 5 min periods of limb ischemia, achieved by inflation-deflation of a blood pressure cuff, initiated a profound cardioprotective response. The hallmark of remote ischemic conditioning – i.e., reduction of myocardial infarct size – has been documented and confirmed in multiple models and species. Two major, remaining challenges are to elucidate the cellular and molecular mechanisms responsible for this intriguing form of cardioprotection, and successfully exploit the infarct-sparing effect of remote ischemic conditioning for the treatment of patients with acute myocardial infarction.

## **Assessing the Promise of Remote Conditioning for Cardioprotection: New Clinical Developments**

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Remote ischemic conditioning (RIC) is a powerful, innate, mechanism of protection against ischemia-reperfusion injury. This simple, non-invasive stimulus can be induced in patients by 3-4 cycles of 5-10 minutes inflation (ischemia) and deflation (reperfusion) of a standard blood pressure cuff, placed on a limb. Following our original description of the method in 2002, and our 'first-in-human' RCT showing reduced markers of cardiac damage, and improved myocardial and lung function in children receiving RIC prior to open heart surgery, there have been multiple adult cardiac surgical trials. Most, but not all studies have shown benefit, with recent meta-analyses showing an overall benefit in terms of biomarkers of injury, and in a recently published 5-year follow-up study of one of the largest studies showing early benefit, those randomized to RIC, had a lower rate of adverse events and lower mortality compared to the controls. Other proof-of-principle RCT's show that RIC; reduces myocardial injury and renal failure in abdominal aortic aneurysm surgery; reduces incidence of renal dysfunction due to contrast-induced nephropathy; improves early outcomes in elective percutaneous coronary intervention (PCI); and our own study by Botker et al showing improved myocardial salvage overall, and reduced infarct size, when RIC is administered prior to emergency PCI. The late outcome data from these studies are also emerging. In a follow-up of the CRISP study (RIC in elective PCI) there was a significant reduction in major adverse cardiovascular events (MACE) at 6 years, and both MACE and mortality rates were reduced at 5 year follow up of Botkers original study of RIC in emergency PCI for evolving myocardial infarction (MI). Finally, early experimental data suggests that repeated, daily, RIC may have additional benefits on post-MI remodeling, and a single RCT suggests that daily RIC improves stroke recovery.

### **Cardioprotection: Challenges and Possibilities**

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Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. Therefore novel therapeutic interventions are required to protect the heart against the detrimental effects of acute ischemia-reperfusion injury (IRI). In this regard, 'ischemic conditioning' represents an adaptive response harnesses the heart's own capabilities for protecting against cell death induced by lethal IRI. The conditioning stimulus can be applied to the heart either prior to the index ischemic event (ischemic preconditioning) or at the onset of reperfusion (ischemic postconditioning). It can also be applied remotely to an organ or tissue away from the heart (termed remote ischemic conditioning), thereby facilitating its translation into the clinical setting. The concept of ischemic conditioning has been successfully applied in the clinical setting to protect the heart during coronary artery bypass graft surgery, percutaneous coronary intervention and during an acute myocardial infarction. Despite intensive investigation the mechanisms underlying ischemic conditioning remain unclear, although a number of cardioprotective signaling pathways have been identified. Pharmacological manipulation of this signaling transduction pathway can allow one to mimic the cardioprotective effect of ischemic conditioning (pharmacological conditioning). Crucially, co-morbidities such as age, hypertension, diabetes, hyperlipidemia can impact on the cardioprotective efficacy of 'conditioning'. In this presentation an overview of the history and evolution of ischemic conditioning, the potential mechanistic pathways underlying its cardioprotective effect, and its emerging application in the clinical setting for the benefit of IHD patients, will be provided.

**Cellular Mechanisms Underlying the Cardioprotective Effects of Exercise**

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Numerous pre-clinical and epidemiological studies have documented the cardioprotective efficacy of exercise, yet the mechanisms that underlie exercise-induced preconditioning of the heart are not fully understood. During conditions when reactive oxygen species (ROS) overwhelm endogenous buffering systems, the loss of mitochondrial function is closely linked with the onset of cardiac electromechanical dysfunction. In a series of studies using both short- and long-term treadmill-running protocols, we have established that exercise preconditions the rat heart in the absence of markers of systemic stress. Fluorescence studies in cardiac myocytes from exercised rats indicated that endogenous ROS buffering-capacity was augmented, and correlated with a lower propensity for cell death. During cardiac ischemia-reperfusion, glutathione levels in exercised hearts were better maintained in Langendorff-perfused hearts, which was associated with lower arrhythmia scores and smaller infarct sizes. While resting myocardial glutathione levels were not different between sedentary and exercised animals, the replenishment of glutathione was enhanced in exercised hearts, due to up-regulated glutathione reductase enzyme activity. The beneficial effects of exercise were abolished when NADPH oxidase activity was pharmacologically inhibited during exercise, but remained intact when mitochondrial ROS production was blunted during exercise. These data lead us to believe that ROS produced during exercise ‘trigger’ adaptive responses, and that the source of ROS does not appear to be mitochondrial in origin. Our most recent studies have directly examined mitochondrial energetics in the intact heart using multi-photon microscopy, and preliminary data indicate that the preservation of mitochondrial membrane potential was directly linked to prevention of reperfusion arrhythmia. In conclusion, our studies provide novel insight into adaptive responses following exercise that protects the heart during acute coronary syndromes.

## **NEUROLOGICAL PRE- AND POST-CONDITIONING**

### **Ischemic Tolerance and Neurological Protection**

*John M. Hallenbeck, Chief, Stroke Branch, NINDS, NIH, Bethesda, MD*

### **Post-conditioning and the Transition from Animal Models to Humans for the Treatment of Stroke**

*Roger Simon, MD, Neuroscience Institute, Morehouse School of Medicine, Atlanta, GA*

### **Extending Injury- and Disease-Tolerant Phenotypes by Repetitive Conditioning: Promoting Long-Lasting Protection in the CNS**

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**Ischemic Tolerance and Neurological Protection**

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Ischemic tolerance can be interpreted as a form of hormesis in which a stress that is gauged to be sub-lethal can activate evolutionarily conserved, endogenous protective mechanisms and induce a time-limited tolerance to an otherwise damaging or lethal stress. There are various forms of induced tolerance to ischemic stress that have been modeled preclinically. They include preconditioning in which the sublethal stress is applied shortly before the otherwise damaging ischemia (immediate preconditioning) or that precedes the damaging ischemia by 24-72 hours (delayed preconditioning). Additional forms of induced tolerance include perconditioning (stress superimposed during damaging ischemia) , post-conditioning (stress imposed after damaging ischemia), remote conditioning (another organ or tissue site than brain is exposed to ischemic stress that then induces tolerance to damaging brain ischemia), and cross-conditioning (a non-ischemic stress induces tolerance to ischemia). The stroke field is broadly interested in developing an understanding of the molecular mechanisms that regulate tolerance in order to help guide efforts to develop cytoprotective therapies for strokes. This interest is understandable when one realizes that vascular neurology research has yet to translate a cytoprotective therapy that has been identified by standard reductionist techniques and have it show efficacy in a Phase III clinical stroke trial.

## **Post-conditioning and the Transition from Animal Models to Humans for the Treatment of Stroke**

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Endogenous mechanisms of protection against stroke and acute injury can be demonstrated in brain and other organs. Such therapies might replace or enhance putative pharmacotherapy. The induction of endogenous protection is via a response to sub lethal stress which induces “preconditioning”. The preconditioned organ is then “tolerant” to injury from subsequent severe stress of the same or different etiology (ie brief ischemic stress protects against injury from prolonged epileptic seizures and vice versa). Ischemic preconditioning provides protection against subsequent stroke. Protection is substantial (70% reduction) but delayed and transient (onset at two days, maximum at three days and gone by seven days). Gene expression is unique between brains preconditioned, injured (stroke) or made tolerant. Thus, preconditioning reprograms the brains response to lethal stress (stroke); reprogrammed from an injury induction response to a neuroprotective processes. Transcriptional down regulation is the central feature of the reprogrammed response to injury. This process of neuroprotective gene silencing is driven epigenetically via polycomb group proteins which suppress transcription broadly.

Postconditioning refers to attenuation of injurious processes which occur during reperfusion of ischemic brain (the only approved treatment for acute stroke). Mechanically interrupting reperfusion induces postconditioning which can attenuate reperfusion injury. Postconditioning protects ischemic brain by decreasing reperfusion induced oxygen free radical formation. The free radicals produce injury via mitochondrial damage which can be repaired experimentally with resultant neuroprotection as potent as experimental postconditioning.

The recognition of broad based gene silencing (suppression of thousands of genes) as the phenotype of the ischemic tolerant brain, may explain the failure of all single target drugs for stroke. The risks of reperfusion treatment for stroke may be attenuated by induction of endogenous repair processes. Thus endogenous neuroprotective and repair mechanisms offer translational stroke therapy.

**Extending Injury- and Disease-Tolerant Phenotypes by Repetitive Conditioning:  
Promoting Long-Lasting Protection in the CNS**

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Significant reductions in the extent of acute injury in the CNS can be achieved by exposure to a preconditioning stimulus, but the duration of the protective phenotype is short-lasting. Our work has been directed at extending the period over which such epigenetic changes persist, thereby enhancing translational relevance. Having established in adult mice that a single exposure to systemic hypoxia (2 h of 11% oxygen) provides transient (a few days) protection against cerebral (Miller BA et al., *NeuroReport*, 2000) and retinal (Zhu Y et al., *IOVS*, 2002) ischemia, we then documented that repetitive presentations of this same hypoxic stimulus over a two-week period (six total exposures to 2-h of 11% oxygen, every other day over two wks) extended the duration of ischemic tolerance to one month after the last preconditioning stimulus (Zhu Y et al., *IOVS*, 2007). Protection against stroke for two months could be afforded by a 2-wk intermittent hypoxic preconditioning regimen (Stowe AM et al., *Annals Neurol*, 2011), but only with stochastic increases in stimulus frequency, duration, and intensity, suggestive of tissue- or cell-dependent hormetic dose-response relationships. Given this protracted 'therapeutic window', we then sought to determine whether repetitive hypoxic conditioning (RHC) could also enhance cell survival in chronic neurodegenerative disease. In an inducible mouse model of glaucoma defined by progressive loss of retinal ganglion cell soma and axons over a 10-wk period of elevated intraocular pressure (IOP), significant protection of both soma and axons could be demonstrated – without a reduction in IOP – when animals completed the 2-wk RHC treatment before IOP elevation (Zhu Y et al., *Mol Med*, 2012), or received it during the period of elevated IOP (*manuscript in preparation*). Thus, extending the duration of the adaptive epigenetic phenotype by RHC represents a fundamentally new therapeutic approach for treating glaucoma and other chronic neurodegenerative diseases.

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## **PRE- POST-CONDITIONING AND MEDICAL AND PUBLIC HEALTH IMPLICATIONS**

### **Preconditioning Strategy for Improved Therapeutic Potential of Stem Cell Transplantation Therapy after Ischemic Stroke**

*Shan Ping Yu, Emory University School of Medicine, Atlanta, GA*

### **Implementation of Intermittent Fasting Prescriptions: Breaking Through the Barriers**

*Mark P. Mattson, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD*

### **Pre-conditioning with Low Level Laser (Light) Therapy**

*Tanupriya Agrawal, MD, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA*

*James D Carroll, FRSM, Thor Photomedicine Ltd, Chesham, UK, and Harvard-MIT Division of Health Science and Technology, Boston, MA*

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### **Dose-Response Effects of Low-Level Light Therapy on Brain and Muscle**

*F. Gonzalez-Lima, Departments of Psychology, Pharmacology and Toxicology, University of Texas at Austin, Austin, TX*

### **Neuromodulation with Weak Transcranial Electrical Stimulation: Small Things Making a Big Difference**

*Marom Bikson, Neural Engineering Lab, Department of Biomedical Engineering, The City College of New York of CUNY, New York, NY*

### **Increased Threat Detection, Learning and Attention using Low-Level Transcranial Direct Current Stimulation (tDCS)**

*Vincent P. Clark, Psychology Clinical Neuroscience Center, University of New Mexico and MIND Research Network, Dept. Psychology, University of New Mexico, Albuquerque, NM*

**Preconditioning Strategy for Improved Therapeutic Potential of Stem Cell Transplantation Therapy after Ischemic Stroke**

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Ischemic stroke is a serious threat to human life and health but clinical treatment for stroke is very limited. Stem cell transplantation has emerged as a promising regenerative medicine for stroke and neurodegenerative disorders. It is expected the repair of damaged brain tissues/structures can be achieved using pluripotent/multipotent stem cells derived from embryos, fetuses, or even adult tissues. However, many issues and problems remain to be resolved before successful clinical applications of the cell-based therapy. Among them, poor cell survival, uncertain neuronal differentiation and low efficacy of tissue repair in the harsh microenvironment of the injured brain are some primary issues. We have initiated an effort to develop a combination strategy in stem cell transplantation therapy in order to improve the therapeutic potential of transplanted cells. One of the major focuses has sought to benefit from well-known mechanisms of ischemic/hypoxic preconditioning that activates cellular defense mechanisms and shows marked protective effects against multiple insults found in ischemic stroke and other acute attacks. A sub-lethal hypoxic exposure significantly increases the expression of pro-survival and pro-regenerative factors. So far, a variety of preconditioning triggers have been tested on different stem cells and progenitor cells. Preconditioned cells show much better cell survival, increased neuronal differentiation, and enhanced paracrine effects that lead to increased trophic support and tissue repair. Transplantation of preconditioned cells helps to suppress inflammatory factors and immune responses. The combination therapy also includes strategies for increasing migration and homing of transplanted cells to the lesion site. More importantly, the combination stem cell therapy shows much improved morphological repair as well as functional recovery after ischemic stroke. Although the combination strategy in stem cell transplantation is still an emerging research area, accumulating information from reports over the last few years already indicates it as an attractive, if not essential, prerequisite for transplanted cells.

**Implementation of Intermittent Fasting Prescriptions: Breaking Through the Barriers**

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Compelling evidence from studies of rodents and humans suggest that intermittent fasting (IF), consisting of periodic (1-4 days per week) short (16-36 hours) fasts, can promote optimal health and can prevent and reverse disease processes in many chronic conditions including diabetes, cancers, cardiovascular disease and neurodegenerative brain disorders. In overweight human subjects, IF diets promote long-term weight loss with retention of lean mass, increased insulin sensitivity, and reduced inflammation and oxidative stress. Why, despite the fact that IF is a safe and effective intervention, do health care providers not prescribe IF diets to their patients? Regrettably, the reason for this lack of effort by the medical community is that no one profits from IF prescriptions. The processed food and agriculture industries would lose money if people ate less, and the pharmaceutical industry would 'suffer' if fewer people developed the diseases for which Pharma peddles their drugs. Medical training and practice is focused on technologically advanced treatments and specialists (cardiologists, neurologist, orthopedists, etc.) that it is not their job to tackle the underlying cause (which is often a couch potato lifestyle) of their patients' diseases; instead, they have become drug-dispensing, scalpel-wielding robots. Medical school curricula are devoid of training on the profound health benefits of IF and exercise, and primary physicians often assume that patients will not comply with IF diets. In this presentation I will describe strategies for the implementation of IF diets in which patients are given a specific plan for the diet and for monitoring their progress. The physician and/or an assistant is in close communication with the patient via text messaging, social media, etc. with the purpose of guiding them through the 1 – 2 month period that is often required for a person to adjust to the IF eating pattern.

**Pre-conditioning with Low Level Laser (Light) Therapy**

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Low level laser (light) therapy (LLLT) has been used for nearly 50 years to enhance tissue healing and to relive pain, inflammation and swelling. The photons are absorbed in cytochrome c oxidase (unit four in the mitochondrial respiratory chain) and increase respiratory enzyme activity, oxygen consumption and ATP production. A complex signaling cascade is initiated leading to activation of transcription factors and up- and down-regulation of numerous genes. Many pathways such as anti-apoptosis, antioxidant enzymes, heat shock proteins, anti-inflammatory cytokines are activated by LLLT. Recently it has become apparent that LLLT can be effective if delivered to normal cells or tissue before the actual insult or trauma in a pre-conditioning mode. We have shown that LLLT delivered to normal muscles can dramatically increase the amount of physical work that can be done by the muscle before fatigue becomes limiting. LLLT delivered to normal nerves can increase the pain threshold when measured several hours later. Other workers have shown that LLLT delivered to the heart can protect against a subsequent heart attack. It has been shown that clinically LLLT delivered to a patient before surgery can lead to improved healing of the surgical wound. These examples point the way to wider use of LLLT as a pre-conditioning modality to prevent pain and increase healing after surgical/medical procedures and possible to increase athletic performance.

### **Dose-Response Effects of Low-Level Light Therapy on Brain and Muscle**

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The mechanism of action of LLLT is based on photon energy absorption by cytochrome oxidase, the terminal enzyme in mitochondrial respiration. LLLT may upregulate cytochrome oxidase in brain and muscle *in vivo*. Different LLLT doses were delivered in a single fraction and effects on cytochrome oxidase activity were measured in the temporalis muscle (over the cranium) and in the brain (inside the cranium) in the same animals. Unanesthetized rats were exposed to 660 nm at either 10.9 J/cm<sup>2</sup>, 21.6 J/cm<sup>2</sup>, 32.9 J/cm<sup>2</sup> or no LLLT in home cages. Treatments were delivered via four LED arrays with a power density of 9 mW/cm<sup>2</sup> for total single treatment times of 20 min, 40 min and 60 min for each dose, respectively. Twenty-four hours after the treatment, animals were decapitated and tissues histochemically analyzed for cytochrome oxidase activity. LLLT enhanced brain and muscle cytochrome oxidase following different hormetic dose-responses. A dose of 10.9 J/cm<sup>2</sup> LLLT resulted in increases in cytochrome oxidase activity of 13.6% in brain and 23% in muscle. In turn, a dose of 21.6 J/cm<sup>2</sup> resulted in an increase of only 10.3% in brain, whereas this dose showed the highest effect in muscle (30%). The 32.9 J/cm<sup>2</sup> dose induced no significant increase in cytochrome oxidase activity in brain (3%) or muscle (8%). Therefore the lowest dose given had the most stimulatory effect on brain, while a twice higher dose was more effective in muscle, and the largest dose given was ineffective. Hormetic dose-response effects, such as the one demonstrated on brain and muscle cytochrome oxidase activity were not logarithmic, and showed improvements of up to 30% as compared to control. These hormetic changes in brain cytochrome oxidase activity also supported memory improvements in additional experiments. Together the data support that these hormetic LLLT effects on cytochrome oxidase activity are biologically meaningful.

## **Neuromodulation with Weak Transcranial Electrical Stimulation: Small Things Making a Big Difference**

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Non-invasive neuromodulation technologies using very low intensity currents, including Transcranial Direct Current Stimulation (tDCS), have emerged over the last decade as promising non-invasive therapies for producing lasting functional changes in CNS. Moreover, these interventions are investigated in healthy adults for the purposes of accelerated learning. They are typically low cost, well tolerated, easy to use, and can be combined with either cognitive training or rehabilitative therapy. A fundamental question toward understanding tDCS and related electrical interventions is how can such “weak” electric current produce meaningful changes in in brain function? And more specifically, how can a “generic” waveform produces targeted changes in a broad range of complex brain functions? To address these questions data from computational models and animal brain slices is presenting showing that ongoing endogenous process to the brain provide a substrate for sensitivity to weak applied current and moreover the type of ongoing process provides a mechanistic basis for complex information processing (learning). Specific brain processes are identified that provide a basis for coupling to applied electric current, amplification of effects, and down-stream functional changes. Related issues to dose response are discussed. These insights from computational and animal models provide a basis for rational optimization of tDCS protocols.

**Increased Threat Detection, Learning and Attention using Low-Level Transcranial Direct Current Stimulation (tDCS)**

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The accurate identification of hidden and camouflaged objects in complex environments was an important skill required for survival during human evolution, and is required today in defense, medicine, driving and other aspects of professional and every day life. Our previous studies have used brain imaging combined with transcranial direct current stimulation (tDCS) to increase learning rate in a novel, minimally guided discovery-learning camouflaged threat detection task. Subjects identified threat-related objects concealed in naturalistic virtual surroundings used in real-world training. A variety of brain networks were found using fMRI data collected at different stages of learning, with two of these networks focused in right inferior frontal and right parietal cortex. Anodal 2.0 mA tDCS performed for 30 minutes over these regions in a series of single- and double-blind, randomized studies resulted in a doubling of learning and performance as measured by performance accuracy and  $d'$ , when compared with sham tDCS. This difference was still present after a delay of one day. Additional cognitive and imaging studies suggest that tDCS may increase alerting attentional processes, and may increase glutamatergic neurotransmission. In other studies, no effects of single- vs. double blinding or self-reported skin stimulation were found. Taken together, these brain imaging and stimulation studies suggest that right frontal and parietal cortex are involved in learning to identify camouflaged objects in naturalistic surroundings. Furthermore, they suggest that the application of anodal tDCS over these regions can greatly increase learning, resulting in one of the largest effects on learning of any neuroscience-based manipulation yet reported. Low-dose DC electrical stimulation may eventually be useful to decrease the time required to attain expertise in a variety of work and every-day settings, and may provide a treatment for the symptoms of a variety of brain and mental illnesses including schizophrenia, addiction, stroke and others.

## POSTER SESSION

### ***Drosophila melanogaster* Show a Threshold Effect in Response to Radiation**

*Michael Antosh, Brown University, Institute for Brain and Neural Systems, Providence, RI*

*David Fox, Brown University, Institute for Brain and Neural Systems, Providence, RI*

**Thomas Hasselbacher**, *Brown University, Institute for Brain and Neural Systems, Providence, RI*

*Robert Lanou, Brown University, Department of Physics, Providence, RI*

*Nicola Neretti, Brown University, Department of Molecular Biology, Cell Biology and Biochemistry and Institute for Brain and Neural Systems, Providence, RI*

*Leon N Cooper, Brown University, Department of Physics and Institute for Brain and Neural Systems, Providence, RI*

### **How Radiotherapy Was Historically Used to Treat Pneumonia: Could it be Useful Today?**

*Edward J. Calabrese, School of Public Health and Health Sciences, University of Massachusetts Amherst, MA*

*Rachna Kapoor, School of Public Health and Health Sciences, University of Massachusetts Amherst, North Pleasant Street, Amherst, MA*

**Gaurav Dhawan**, *School of Public Health and Health Sciences, University of Massachusetts Amherst, North Pleasant Street, Amherst, MA*

### **Use of X-rays to Treat Shoulder Tendonitis/Bursitis: A Historical Assessment**

*Edward J. Calabrese, School of Public Health and Health Sciences, University of Massachusetts Amherst, MA*

**Gaurav Dhawan**, *School of Public Health and Health Sciences, University of Massachusetts Amherst, North Pleasant Street, Amherst, MA*

*Rachna Kapoor, School of Public Health and Health Sciences, University of Massachusetts Amherst, North Pleasant Street, Amherst, MA*

### **Model Uncertainty in Cancer Risk Assessment**

*Edward J. Calabrese, University of Massachusetts, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA*

**Dima Yazji Shamoun**, *Mercatus Center at George Mason University, Austin, TX*

### **Risk Assessment Report Card**

*Edward J. Calabrese, University of Massachusetts, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA*

**Dima Yazji Shamoun**, *Mercatus Center at George Mason University, Austin, TX*

### **Low-dose Radiation Prevents Diabetic Complications**

*Jie Cheng, The First Hospital of Jilin University, Changchun 130021, China;*

**Lu Cai**, *Kosair Children's Hospital Research Institute, the Departments of Pediatrics, Radiation Oncology and Pharmacology and Toxicology, University of Louisville, Louisville, KY*



**Protection of Hearts Against Ischemic Insult: Changes in Iron Homeostasis Explain Myocardial Response to Preconditioning**

**Mottie (Mordechai) Chevion**, *The Dr. W. Ganz Chair of Heart Studies, The Hebrew University of Jerusalem Faculty of Medicine, Israel*

*Vladimir Vinokur, Department of Biochemistry and Molecular Biology, The Hebrew University of Jerusalem Faculty of Medicine, Israel*

*Baruch Bulvik, Department of biochemistry and Molecular Biology, The Hebrew University of Jerusalem Faculty of Medicine, Israel*

*Eduard Berenshtein, Department of Biochemistry and Molecular Biology, The Hebrew University of Jerusalem Faculty of Medicine, Israel*

*Ron Eliashar, Head and Neck Surgery, Hadassah University Hospital, Israel*

**Correcting Deficiencies in our Societal Infrastructure for the Application of Science in Medicine**

**Mohan Doss**, *Fox Chase Cancer Center, Philadelphia, PA*

**Investigation of the Cellular and Molecular Mechanisms of Radiation-induced Bystander Effects in a Human Keratinocyte Cell Line**

**Hayley Furlong**, *Dublin Institute of Technology, Centre for Radiation and Environmental Science, Focas Research Institute, Dublin Institute of Technology, Dublin, Ireland*

*Richard Smith, Department of Biology, McMaster University, Hamilton, ON, Canada*

*Jiaxi Wang, Queen's Mass Spectrometry and Proteomics Unit, Department of Chemistry, Queen's University, Kingston, ON, Canada*

*Colin Seymour, Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, ON, Canada*

*Carmel Mothersill, Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, ON, Canada*

*Orla Howe, Dublin Institute of Technology, Centre for Radiation and Environmental Science, Focas Research Institute, Dublin Institute of Technology, Dublin, Ireland*

**Astrocyte Preconditioning by Severe Stress is Glutathione- but not Heat Shock Protein 70-Dependent**

**Amanda M. Gleixner**, *Duquesne University, Graduate School of Pharmaceutical Sciences, Mylan School of Pharmacy, Pittsburgh, PA*

*Elena Serpico, Duquesne University, Graduate School of Pharmaceutical Sciences, Mylan School of Pharmacy, Pittsburgh, PA*

*Deepti B. Pant, Duquesne University, Graduate School of Pharmaceutical Sciences, Mylan School of Pharmacy, Pittsburgh, PA*

*Jessica M. Posimo, Duquesne University, Graduate School of Pharmaceutical Sciences, Mylan School of Pharmacy, Pittsburgh, PA*

*Rehana K. Leak, Duquesne University, Graduate School of Pharmaceutical Sciences, Mylan School of Pharmacy, Pittsburgh, PA*

**Low level radiation and heart disease death rates in four states: An ecological study**

**John Hart**, *Sherman College of Chiropractic, Department of Research, Spartanburg, SC*

**Inter-Relationships between Low Dose Hypersensitivity, Induced Radioresistance and Bystander Effects in Human Cell Lines**

**Cristian Fernandez-Palomo**, Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, ON, Canada

Colin Seymour, Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, ON, Canada

Carmel Mothersill, Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, ON, Canada

**Comparative Acute Toxicity of Silver Nanoparticles Produced by Physical (Top-Down) and Chemical (Bottom-Up) Methods in Zebrafish (*Danio rerio*)**

**Seyed Ali Johari**, Aquaculture Department, Natural Resources Faculty, University of Kurdistan, Sanandaj, Kurdistan, Iran

**Ultraviolet-A photoemission from cells upon  $\beta$ -irradiation and consequent bystander effects**

**Michelle Le**, McMaster University, Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

Fiona McNeill, McMaster University, Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

Colin Seymour, McMaster University, Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

Andrew J. Rainbow, McMaster University, Department of Biology, Hamilton, ON, Canada

Carmel Mothersill, McMaster University, Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

**Physiological Conditioning Hormesis Improves Post-Irradiation Performance in Young and Aging Fruit Flies**

**Giancarlo Lopez-Martinez**, Department of Biology, New Mexico State University, Las Cruces, NM

Daniel A. Hahn, Department of Entomology/Nematology, University of Florida, Gainesville, FL

**Communication of Protective Signals from Fish Sub-Lethally Challenged with *Vibrio anguillarum* VIB1 to Naïve Fish**

**Carmel Mothersill**, McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

Dawn Austin, Institute of Aquaculture, School of Natural Sciences, University of Stirling, Scotland, UK

Colin Seymour, McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

Niall Auchinachie, Institute of Aquaculture, School of Natural Sciences, University of Stirling, Scotland, UK

Cris Fernandez Palomo, McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada

Brian Austin, Institute of Aquaculture, School of Natural Sciences, University of Stirling, Scotland, UK

**Pre-Operative Stress Conditioning: Role for Hyperbaric Oxygen Therapy**

**George A. Perdrizet**, *Kent Hospital Wound and Hyperbaric Medicine Center, Warwick, RI, and the Univ. of Connecticut, Storrs, CT*

**Assessing Predictive Factors and Radiation-Induced Non-Targeted Effects in Blood Serum from Cancer Patients**

**Christine Pinho**, *McMaster University, Hamilton, ON*

*Emilia Timotin, Juravinski Cancer Centre, Medical Physics & Applied Radiation Science, Hamilton, ON*

*Ranjan K. Sur, Juravinski Cancer Centre, Department of Oncology, Hamilton, ON*

*Raimond Wong, Juravinski Cancer Centre, Department of Oncology, Hamilton, ON*

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*Carmel Mothersill, McMaster University, Medical Physics & Applied Radiation Science Hamilton, ON*

**The Effects of Chronic Exposure to Low Levels of Alpha-Emitting Radionuclides on the Health and Reproductive Fitness of Mammals**

**Meloja Satkunam**, *McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada*

*Marilyne Stuart, Atomic Energy of Canada Limited, Chalk River, ON, Canada*

*Ben Su, McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada*

*Colin Seymour, McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada*

*Carmel Mothersill, McMaster University, Department of Medical Physics and Applied Radiation Sciences, Hamilton, ON, Canada*

***Drosophila melanogaster* Show a Threshold Effect in Response to Radiation**

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We investigate the biological effects of radiation using adult *Drosophila melanogaster* as a model organism, focusing on gene expression and lifespan analysis to determine the effect of different radiation doses. Our results support a threshold effect in response to radiation: no effect on lifespan and no permanent effect on gene expression is seen at incident radiation levels below 100 J/kg.

### **How Radiotherapy Was Historically Used to Treat Pneumonia: Could It be Useful Today?**

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X-ray therapy was used to treat pneumonia during the first half of the 20th century. Fifteen studies report that approximately 700 cases of bacterial (lobar and bronchopneumonia), sulfanilamide non-responsive, interstitial, and atypical pneumonia were effectively treated by low doses of X-rays, leading to disease resolution, based on clinical symptoms, objective disease biomarkers, and mortality incidence. The capacity of the X-ray treatment to reduce mortality was similar to serum therapy and sulfonamide treatment during the same time period. Studies with four experimental animal models (i.e., mice, guinea pig, cat, and dog) with bacterial and viral pneumonia supported the clinical findings. The mechanism by which the X-ray treatment acts upon pneumonia involves the induction of an anti-inflammatory phenotype that leads to a rapid reversal of clinical symptoms, facilitating disease resolution. The capacity of low doses of X-rays to suppress inflammatory responses is a significant new concept with widespread biomedical and therapeutic applications.

**Use of X-rays to Treat Shoulder Tendonitis/Bursitis: A Historical Assessment**

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This historical assessment provides a critical review of the human clinical and veterinary literature on the therapeutic efficacy of ionizing radiation for the treatment of shoulder tendonitis and bursitis in the United States over the entire period of its use (human 1936-1961; veterinary 1954-1974). Results from approximately 3,500 human cases were reported in the clinical case studies over 30 articles, indicated that a high treatment efficacy (> 90%) for patients with acute shoulder tendonitis/bursitis. Radiotherapy was often effective with a single treatment. The duration of treatment effectiveness was prolonged, usually lasting the duration of the follow-up period (i.e., typically several years but at times exceeding five years). Therapeutic effectiveness was reduced for conditions characterized as chronic. Similar findings were reported in multiple studies with race horses in the veterinary literature. These historical findings are consistent with the clinical studies over the past several decades in Germany, which have used more rigorous study designs and a broader range of clinical evaluation parameters.

**Model Uncertainty in Cancer Risk Assessment**

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***Dima Yazji Shamoun**, Mercatus Center at George Mason University, 1212 Guadalupe St. #906, Austin, TX 78701, Tel: 703-220-7308, Email: dshamoun@mercatus.gmu.edu*

This paper focuses on the importance of model uncertainty characterization in cancer risk assessment for extrapolation of the dose-response relationship from high- to low-dose. We document federal guidelines on model uncertainty from the early 1980's to the present. Model uncertainty of the low-dose relationship, especially for cancer risk assessment, is an issue that has been gaining increasing attention in the past years. Inadequate model uncertainty characterization can distort cancer risk figures, which mislead decision-makers who use these risk figures to compute the magnitude of the benefits and costs of health regulations. We propose a transparent method of quantifying model uncertainty. Our method incorporates the various federal guidelines and current agency practices of computing potency while taking into account competing findings in the scientific literature.

### **Risk Assessment Report Card**

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Federal guidelines on how regulatory agencies should conduct sound risk assessments date back to the early 1980s. Risk assessment is a widely applied technique by regulatory agencies to evaluate the risk of exposure to potential hazards. In this project we build on the federal guidelines released by the National Academy of Sciences, National Research Council, and the Office of Information and Regulatory Affairs to develop a scoring system as a metric of the quality of risk assessments. More specifically, we identify four broad categories of a sound risk assessment: Analysis, Robustness, Openness, and Review Process. Each category has four sub-categories. We develop a two-tier scoring system. The first tier is a 6-point (0-5) per subcategory scoring system for a maximum score of 80. The second tier is a per-category pass/fail score to better distinguish the strengths and weaknesses of different risk assessments. This methodology can pave the way for a more objective evaluation of the science used by regulatory agencies to regulate risk of exposure to different health, safety, and environmental hazards.



### **Low-dose Radiation Prevents Diabetic Complications**

*Jie Cheng, The First Hospital of Jilin University, Changchun, China*

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There remains lack of an efficient therapeutic, particular a non-invasive, approach to diabetic cardiovascular complications. Induction of hormesis and adaptive response by low-dose radiation (LDR) has been extensively reported. LDR-induced adaptive response are not only resistant to damage caused by subsequently high-dose radiation, but also cross-resistant to other non-radiation challenges such as diseases-related oxidative damage. Oxidative stress is a major cause for diabetic complications. Recently we have demonstrated the preventive or therapeutic effect of LDR on diabetic complications, including diabetic nephropathy, cardiomyopathy and wound healing impairment, in type 1 diabetic mice and rats that were induced with streptozotocin. However, these previous studies have mainly used 50 – 75 mGy whole-body X-irradiation daily for 8 – 16 weeks, whether such exposure conditions are the optimal conditions to protect the kidney without significant toxic effect on normal tissues or animals have not been addressed yet. In the present study, we have examined the preventive effects of different exposure conditions, including different dose levels (12.5, 25 and 50 mGy), exposure frequencies (daily, every other days, and every week), and exposure modes (in whole-body or renal region only) on the renal functional and pathogenic changes of diabetic mice. Diabetic mice were induced with multiple low-dose streptozotocin protocol. Comprehensive evaluation of the multiple sets of experimental evidence, a general conclusion was made that renal regional exposure to 25 mGy X-rays provide a maximal protective effect on diabetes-induced renal damage; These studies demonstrate that LDR as a non-invasive approach has a great potential to be considered a new alternative therapy for the senior diabetic patients with significant renal dysfunction for whom the routine medication can not be given due to renal failure to eliminate their metabolisms.

**Protection of Hearts against Ischemic Insult: Changes in Iron Homeostasis Explain Myocardial Response to Preconditioning**

**Mottie (Mordechai) Chevion**, *The Dr. W. Ganz Chair of Heart Studies, The Hebrew University of Jerusalem Faculty of Medicine, Israel 91120, Tel: +972-544-560-804, Email:*

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Diabetes patients experience increased risk for acute cardiovascular events, including AMI. On the other hand, their rate of post-AMI survival is higher than of non-diabetics. There are conflicting sets of data on diabetic heart response to ischemic preconditioning (IPC). An interesting association between diabetes and iron tissue overload was demonstrated. We review the changes in Fe homeostasis in normoglycemic and diabetic rat hearts.

Two rat models of diabetes were employed: STZ-treated (Type I-like) and Cohen diet-induced diabetes (Type II). Diabetic and normoglycemic control hearts were subjected, *ex-vivo*, to global ischemia/reperfusion (I/R), with or without prior IPC. In some experiments the perfusate contained proteasomal and/or lysosomal proteases inhibitors (PI). Ferritin level (mRNAs and protein), and ferritin saturation with Fe (Fe/ferritin), were monitored.

Unlike controls, no functional improvement was observed in IPC-treated diabetics; post-I/R recovery of diabetic hearts was better than non-diabetics. Basal ferritin protein level in diabetic hearts was double that in non-diabetics. IPC of controls caused 4.2-fold increase in ferritin level, the level was conserved during the subsequent prolonged ischemia. During reperfusion ferritin returned to its basal level. In post-IPC diabetics 2.1-fold increase over its baseline was obtained, reaching the controls' levels. Fe/ferritin content was higher in the diabetic hearts. Ferritin composition in diabetics markedly changed in favor of L-subunits. During prolonged ischemia in diabetics, ferritin levels dropped below their baseline levels. Treatment of diabetic hearts with PI attenuated ferritin degradation, restoring the IPC response. The proteasomal only inhibitor was protective.

The results of rat the diabetic hearts of Cohen and STZ well agreed with each other. In both poor response to IPC was associated with Fe homeostasis impairment. Inhibition of proteasomal degradation of ferritin restored IPC response.

The general significance of the iron based to other mechanisms of IPC and to protection against stress, in general will be discussed.

**Correcting Deficiencies in our Societal Infrastructure for the Application of Science in Medicine**

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Scientific method is inherently self-correcting. When competing hypotheses are proposed, their study would result in the rejection of the invalid ones over time. If the study of a hypothesis is prevented because of the faith in an unverified one, scientific progress is stalled. This has happened in the area of health effects of low dose radiation (LDR). The linear no-threshold (LNT) model hypothesis was recommended by scientific advisory bodies in the 1950s to estimate the LDR cancer risk as a 'conservative' approach. This implied that even the smallest dose of radiation could increase the risk of cancer, resulting in radiation safety policies to keep the radiation doses as low as reasonably achievable. Hence, when the alternative radiation hormesis hypothesis was proposed in 1980, implying LDR could be used to prevent cancers, it could not be studied in humans because of the presumed validity of the unverified LNT model hypothesis. Increasing amount of evidence has accumulated since then for the validity of the radiation hormesis hypothesis. For example, the latest update to the highly influential atomic bomb survivor data shows decreased cancer mortality as radiation dose is increased in the low dose region. This feature cannot be explained with the LNT model but is consistent with radiation hormesis. Assuming radiation hormesis may reduce cancer mortality by ~10%, not studying it in the 1980s has likely resulted in over 14 million estimated preventable cancer deaths during the past two decades worldwide, and also likely stalled progress in reducing other aging-related diseases. Since our society has been guided by advisory committees that ostensibly follow the scientific method, the prolonged period and extent of these casualties are indicative of systemic deficiencies in the societal infrastructure for the application of science in medicine. Identifying and correcting these deficiencies may reduce similar casualties in the future.

### **Investigation of the Cellular and Molecular Mechanisms of Radiation-induced Bystander Effects in a Human Keratinocyte Cell Line**

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The aim of the current study was to further elucidate the cellular and molecular signalling mechanisms associated with radiation-induced bystander effects (RIBE) in Human Keratinocytes, which will hopefully contribute to the development of non-targeted human radiation risk assessments. The first part of this study investigated the unique pathways involved in RIBE to discover significant targets for the intercellular and intracellular signalling events. One of the initial intercellular signalling events discovered involved Calcium on the surface of the cell membrane. Proteomic tools were exploited for the discovery of novel proteins signalled and revealed a role for Annexin II signalling in the early events of RIBE. Further to that, a unique role of intrinsic apoptosis events part of the intracellular signalling was elucidated with an extensive gene expression study. As a result of the data generated two pathways dependent on low-dose radiation are proposed.

The 0.05 Gy dose data revealed the highest influx of calcium in HaCaT cells exposed to radiation-induced bystander media. Gene expression data unveiled an induction of pro-apoptotic genes and an induction of initiator Caspases to drive the cell death process forward. The Annexin II gene was shown to be down-regulated which is suggestive of increased apoptosis, and thus at this dose the HaCaT cells are experiencing intrinsic-apoptosis leading to cell death. The 0.5 Gy dose revealed an influx of calcium in bystander cells, and the MTT cell viability assay suggested a reduction in cell viability at this dose, indicative of increased cell death. However, apoptotic gene expression changes were minor and there was increased anti-apoptotic signalling. The proteomic data demonstrated an increase of Annexin II at this dose. Together with the apoptotic gene data generated, it is clear that either the cell death process is delayed or other

modes of cell death are involved in the bystander process for the 0.5 Gy dose. Overall, the proposed pathways demonstrate clearly that bystander responses in HaCaT cells can be dose-specific, causing unique bystander effects in response to different low-doses of non-targeted irradiation.

### **Astrocyte Preconditioning by Severe Stress is Glutathione- but not Heat Shock Protein 70-Dependent**

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Preconditioning is traditionally recognized as a protective response to subtoxic stress. However, we recently showed that glial astrocytes can be preconditioned by high concentrations of the proteasome inhibitor MG132, or severely proteotoxic stress. The remaining astrocytes that survived severe proteotoxic stress from MG132 were rendered resistant to subsequent MG132 challenges. These results reveal that the preconditioning phenomenon can be generalized to severe stress in some cell types. We also found that two MG132 hits were synergistic in their impact on misfolded, ubiquitinated proteins. Despite this evidence of severe proteotoxicity, stressed astrocytes exhibited higher glutathione and ATP levels after the second hit, revealing compensatory antioxidant and metabolic adaptations. Inhibition of glutathione synthesis with buthionine sulfoximine abolished astrocytic resistance to a second hit, suggesting that severe stress-induced preconditioning was glutathione-dependent. Next, we sought to determine whether heat shock proteins also played an essential role in our preconditioning model. Heat shock proteins such as Hsp70 assist in protein refolding and degradation, thereby attenuating proteotoxic stress. Hsp32 (heme oxygenase-1 or HO1) is also exquisitely stress responsive and is involved in antioxidant defense. We inhibited Hsp70 with the ATPase inhibitor VER155008 and Hsp32 with the competitive inhibitor tin protoporphyrin (SnPP). VER155008 failed to abolish astrocyte resilience in our model. Pilot data show that SnPP also failed to reverse astrocytic resilience. These findings suggest that Hsp70 and Hsp32 probably do not mediate preconditioning with severe proteotoxic stress. As glutathione appears to be more important for astrocyte preconditioning, studies are underway to examine enzymes involved in glutathione synthesis and redox cycling, such as glutathione synthetase and glutathione peroxidase. All of these genes are under control of the stress-inducible transcription factor Nrf2 and may help mediate glutathione-dependent preconditioning in astrocytes.

### **Low Level Radiation and Heart Disease Death Rates in Four States: An Ecological Study**

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Recent papers claimed that low level radiation is a risk factor for cardiovascular disease. The present study tested this claim using an ecological design. Low level radiation in the present study was represented by the surrogate variable land elevation (“elevation”), where higher elevations correlate with higher amounts of low level (natural background) radiation compared to lower elevations. Elevations were measured by the author at the center of counties in four selected states using Google Earth, in feet above sea level. Age-adjusted heart disease mortality rates (HDMR) per 100,000 persons by county were compared according to two corresponding elevation categories: *low* (median elevation or below) versus *high* (above median elevation). Since heart disease may vary by race, two analyses were performed, for whites and blacks. Black persons in low elevation counties had a mean HDMR of 230.9 (SD 74.0) deaths compared to 228.8 (SD 93.1) in the high elevation counties, a difference that was not statistically significant ( $p = 0.9$ ), with a negligible effect size (of 0.03). White persons in low elevation counties had a mean HDMR of 203.5 (SD 36.8) deaths compared to 175.6 (SD 25.4) deaths in the high elevation counties, a difference that was statistically significant ( $p < 0.0001$ ) with a large effect size (of 0.88). These results do not support the claim that low level radiation is a risk factor for cardiovascular disease. Furthermore, these results suggest that in some cases (e.g., in white people), higher amounts of low level (natural background) radiation (related to land elevation) may trigger adaptive responses, which in turn may provide a greater protective effect against HDMR, compared to responses in people in the lower land elevations. Limitations to this study include: a) its (ecological) design, b) non-random selection of the states, and c) other land elevation-related factors could affect HDMR.



### **Inter-Relationships between Low Dose Hypersensitivity, Induced Radioresistance and Bystander Effects in Human Cell Lines**

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**Purpose:** The low-dose hyper-radiosensitivity (HRS) and the increased radio-resistant (IRR) phenomena have been examined in relation to radiation-induced bystander effects (RIBE) in a number of studies. However, discrepancies in the literature make us wonder to what extent HRS/IRR and RIBE are related. The aim of this work was to further investigate whether there is a connection between doses in the HRS region and RIBE. To accomplish this, the highly radiosensitive human glioma cell line (T98G) was compared with the HRS/IRR-negative spontaneously immortalized human keratinocyte cell line (HaCat) for the production of RIBE.

**Methods:** Sets of flasks were exposed to different low-doses of gamma rays from a cobalt-60 source. Survival was assessed using the clonogenic assay as endpoint. Irradiated flasks containing 500 cells were used as controls. To study RIBE, the culture medium from irradiated flasks containing 300,000 T98G was harvested 90 minutes after irradiation, and transferred into reporter flasks containing un-irradiated T98G or HaCat cells in clonogenic densities. Reporters and control flasks were then placed in the incubator during 7 to 9 days to allow for the formation of colonies, which were counted and plotted as survival fraction.

**Results:** The results indicate that the T98G cells produced bystander effects only during their hyper-radiosensitive state. Thus RIBE-signals are produced only at low-doses and disappear when the T98G cells become radioresistant. Moreover, the bystander signals from the irradiated T98G cells reduced the survival of both T98G and HaCat reporter cells.

**Conclusion:** Our results suggest that RIBE is a phenomenon linked to the radiation sensitivity of the cell line. Bystander signals were produced when the cells were radiosensitive, and the induction of radioresistance seemed to interfere with the bystander mechanism.

**Comparative acute toxicity of silver nanoparticles produced by physical (top-down) and chemical (bottom-up) methods in zebrafish (*Danio rerio*)**

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Despite the increasing use of nanomaterials, the possibility of their toxicity in human and other living organisms is one of the challenges of the future. Various chemicals which are used for the production of nanomaterials in chemical methods, itself may cause secondary toxic effects on organisms; conversely, lack of using those chemical in physical production methods, may possibly reduce mentioned secondary effects. To test this hypothesis, in the present study acute toxicity effects of two types of colloid silver nanoparticle (AgNPs) produced by top-down (physical) and bottom-up (chemical) methods were compared on the survival of zebrafish. In support of this hypothesis, the results showed that AgNPs produced by physical method are at least 38 times less toxic than AgNPs produced by chemical methods. 96-h LC50 values of AgNPs produced by chemical and physical methods for zebrafish were estimated to be equal to  $0.014 \pm 0.001$  and  $0.540 \pm 0.032 \text{ mg.l}^{-1}$  respectively; based on these values both studied AgNPs should be classified according to the rules adopted by the Europe Union, as highly toxic chemicals for aquatic organisms. In general it seems that silver nanoparticles, regardless of their production method, have toxic effects on aquatic organisms and so more attention appear to be necessary on the prevention of their accidental or intentional entry to the aquatic ecosystems.

**Keywords:** Aquatic Nanotoxicology, Silver Nanoparticles, Bottom-up method, Top-down method, Zebrafish

### **Ultraviolet-A photoemission from cells upon $\beta$ -irradiation and consequent bystander effects**

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Following the observation of significant ultraviolet-A (UVA) photon emission from irradiated human keratinocyte (HaCaT) cells, it became evident that investigating biological endpoints would be important in determining the biological implications of this secondary luminescence. Photons were quantified using a single photon counting apparatus; a photomultiplier tube (PMT) and an interference band filter centered at  $340 \pm 5$  nm were used. Living HaCaT cell cultures were directly treated with various activities of tritiated water ( $^3\text{H}$ , beta emitter). Reporter flasks containing clonogenic densities were placed directly above the petri plate containing  $^3\text{H}$ -irradiated cells; these were concurrently incubated in this configuration at  $37^\circ\text{C}$  for 24 hours. Photosensitizer (20  $\mu\text{M}$  lomefloxacin, fluoroquinolone antibiotic) and photoprotectant (10 mg/L melanin) treatments were also added to reporter flasks, directly irradiated petri dishes, or both in order to confirm the role of photons in the production of an effect in reporter cells. This irradiation configuration resulted in a dose-dependent reduction of clonogenic survival in reporter cells. The demonstrated pattern of clonogenic survival was strongly correlated with the photon emission measured at corresponding doses ( $r=0.977$ ,  $p<0.01$ ). Reporter flasks treated with lomefloxacin while in the field of petri dishes irradiated with 85.75  $\mu\text{Ci}$  (0.05 Gy), 171.5  $\mu\text{Ci}$  (0.1 Gy) and 857.7  $\mu\text{Ci}$  (0.5 Gy) experienced further reductions in clonogenic survival from untreated irradiated flasks by 9, 11 and 14 percent. Reporter flasks that were treated with melanin while placed above 85.75  $\mu\text{Ci}$ , 171.5  $\mu\text{Ci}$  and 857.7  $\mu\text{Ci}$  irradiated petri dishes experienced survival that was 6, 5.8 and 30 percent greater than those that were untreated. Treatment of directly irradiated petri dish cultures with lomefloxacin and melanin resulted in reduction of photoemission intensity and corresponding increases in reporter cell survival. Observed modifications in clonogenic survival upon treatment with photosensitizing/photoprotecting substrates supports the role of UVA as a physical bystander mechanism.

### **Physiological Conditioning Hormesis Improves Post-Irradiation Performance in Young and Aging Fruit Flies**

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Oxidative stress can be triggered by an array of environmental stressors, and increases in oxidative stress and damage can affect sexual performance and strongly impact mating success, organismal performance, and immunity; among other life history traits. Using gamma irradiation to induce oxidative stress, we have found that female flies prefer to mate with males that have lower levels of free radical damage. This is due to the fact that oxidative damage to lipids, proteins, and DNA affect male performance by reducing flight ability, mating competitiveness, and longevity. We have previously found that an hour-long treatment of anoxia (complete oxygen depletion) was not life-threatening to the flies, but also boosted their total antioxidant levels. Thus, we wanted to explore the potential of physiological conditioning hormesis at reducing post-irradiation oxidative damage and improving male performance. To this end, we used one hour anoxia treatment prior to irradiation, as well as, performing irradiation in an oxygen-free environment. We hypothesize that this combination would reduce oxidative damage and improve post-irradiation performance. Here we present evidence that this antioxidant boost associated with anoxia, lowered post-irradiation oxidative damage to lipids and proteins. The lower levels of oxidative damage were then correlated with improved flight ability and mating success at a young age (1 to 10 days old). Additionally, we found that this hormetic approach improved longevity and mating success in older flies (30+ days old). Our data reinforces that physiological conditioning hormesis can be used to reduce/prevent oxidative stress and improve performance in youth and advanced age.

**Communication of Protective Signals from Fish Sub-Lethally Challenged with *Vibrio anguillarum* VIB1 to Naïve Fish**

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Salmonid fish were exposed to a sublethal dose of *Vibrio anguillarum* VIB1 and allowed to recover. After 7 days, naïve fish, which had never been exposed were introduced to the tank. These swam with the recovered fish for 7 days before both groups and a control group were exposed to a lethal dose of the pathogen. Mortality records were 100% in the control group, 47% in the adapted group and 60% in the unchallenged “bystander” group, which swam with the adapted group. This inter animal communication of signals has previously been documented for fish and other species exposed to ionizing radiation. Assays of tissues from control, challenged and “bystander” fish showed that a signal similar to that seen in bystanders to irradiated fish was produced. This signal caused a sharp and transient increase in intra-cellular calcium and a decrease in clonogenicity in a well characterized reporter assay, suggesting a similar mechanism may be induced by a pathogenic stress as is induced by radiation stress. These results clearly have major importance in fish pathology and in efforts to develop natural vaccines. They also may be important in evolutionary biology as taken with the radiation data, they point to a potential general pre-conditioning mechanism underlying population level control of environmental stressors.

**Pre-Operative Stress Conditioning: Role for Hyperbaric Oxygen Therapy**

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Invasive surgical procedures expose patients to periods of severe tissue stress and detract from clinical outcomes. Surgical stresses are largely due to acute ischemia-reperfusion injury and subsequent systemic inflammation. Elective surgical procedures can be planned for and thus readily targeted for preconditioning protocols. Many translational models have demonstrated the ability of a brief stress, (heat shock or ischemia) to confer a state of cytoprotection that will allow tissues and whole organisms to survive lethal degrees of acute ischemia and reperfusion. Gene expression profiles associated with this cytoprotected phenotype has been studied in many models and consistently demonstrate up-regulation of the family of cytoprotective genes known as molecular chaperones. These genetic changes provide a plausible mechanism of action whereby a brief stress confers protection to subsequent potentially lethal stressful events. Human application awaits a clinically relevant manner by which to induce these genetic changes (stress condition) in patients prior to major surgical interventions. Whole body hyperthermia and ischemic preconditioning are effective but not clinically practical. Hyperbaric oxygen therapy is becoming more widely available in medical centers due to its ability to enhance wound healing. Patients, especially those with cardiopulmonary disease, safely tolerate exposures to hyperbaric oxygen. We have recently tested the hypothesis that hyperbaric oxygen (2.4 ATA as hyperbaric oxygen) pretreatment of human microvascular endothelial cells will result in the development of resistance to oxidant injury in vitro. This cytoprotected phenotype is associated the acute changes in the expression of over 8,000 genes based on a genome-wide microarray analysis. Changes in gene expression are dominated by genes regulating the cytoprotective chaperones as well as those regulating pro-proliferative and anti-oxidant functions. Hyperbaric oxygen is an attractive clinical tool that may permit human trials of stress conditioning to be designed.

### **Assessing Predictive Factors and Radiation-Induced Non-Targeted Effects in Blood Serum from Cancer Patients**

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Clastogenic effects, radiation-induced bystander effects (RIBE), and adaptive responses are readily classified as non-targeted radiation effects. To assess human subjects' response to radiation treatments, a blood serum *in vivo* colony-forming assay was used. The cancer patients underwent fractionated high dose rate (HDR) intraluminal brachytherapy (ILBT). Ethics approval was obtained from the Hamilton Health Sciences Faculty of Health Sciences (HHS/FHS) research ethics board. The study objective was to determine whether a blood based colony forming assay could be used to detect trace levels of bystander signals being generated following brachytherapy. The results revealed that blood sera exposed to HPV-G reporters at baseline, after treatment 1, after treatment 2, and after treatment 3 had no statistical difference in cloning efficiency percentage ( $p=0.129$ ). These findings suggest that reporters treated with blood sera post-treatment show no indication of a protective response throughout fractionated brachytherapy. A multitude of factors were also assessed to determine whether these characteristics may be influencing cell communicating signals and affecting the growth of non-irradiated cells. Statistically significant findings were revealed at the first fraction of brachytherapy for samples collected immediately following the treatment (adjusted  $R^2=0.864$ ,  $p=0.007$ ). However, age, gender, cancer stage, and metastatic status were poor predictors for this model at treatments 2 and 3. These results suggest that other influential factors, that were not accounted for or

controlled during the study, may be playing a role in the HPV-G reporters' cloning ability during later stages of treatment. A follow-up study has been undertaken with a target sample size of 50 cancer patients and 15 healthy patients. This work will provide further insight on whether non-targeted radiation effects have relevance in brachytherapy. In conclusion, this simple blood based assay may have future applications as a biological dosimeter used to predict treatment outcome based upon certain patient characteristics.



**The Effects of Chronic Exposure to Low Levels of Alpha-Emitting Radionuclides on the Health and Reproductive Fitness of Mammals**

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Uranium mines and mills release radionuclide waste, mainly as alpha-emitting radionuclides. The ability of alpha particles to produce internal biological damage in non-human biota living in environments surrounding uranium mines has rarely been studied. The objective of the study was to assess whether environmentally relevant levels (0.01, 0.1, 1.0, 10.0 Bq/L) of alpha radiation (ingested as Ra-226 in drinking water) affected the health and reproductive fitness of mammal models, when exposed over four generations. No decreases in reproductive fitness were observed with increased Ra-226 exposure in all four generations. Statistically significant variation in body weights between the control and treatment groups were observed in the second and third generations in the 0.01 Bq/L and 10.0 Bq/L groups. However, overall, we conclude that the health and reproductive fitness of mammals was not negatively affected with low levels of alpha radiation. These data are preliminary and further investigation will be necessary. However, the results suggest that further environmental protection and development initiatives may be crucial to preserve the health of non-human biota in alpha radiation contaminated areas.