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PRECONDITIONING: IN BIOLOGY AND MEDICINE

ADAPTIVE RESPONSES/ PRECONDITIONING

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ABSTRACT BOOK

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University of Massachusetts, Amherst, MA

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Plenary Session

Hormesis: Its Impact on Biology, Toxicology, and Medicine
Walter J. Kozumbo, *Hormesis Project, University of Massachusetts, Amherst, MA*

Radiation Hormesis: Its Significance and Applications
Douglas R. Boreham, *Northern Ontario School of Medicine, Sudbury, Ontario, Canada*

Cancer as a Metabolic Disease
Thomas Seyfried, *Biology Department, Boston College, Chestnut Hill, MA*

Transposable Elements, Genomic Instability and Radiation; Barbara McClintock's Legacy in Modern Radiobiology
Carmel Mothersill, Andrej Rusin, and Colin Seymour, *McMaster University, Hamilton, Ontario, Canada*

Radiation Hormesis: Its Significance and Applications.

Douglas R. Boreham, *Northern Ontario School of Medicine Sudbury, Ontario, Canada*

Radiation-induced hormesis has been known for decades. The ability of cells and organisms to adapt to environmental changes or stress is a biologically normal process. Radiation exposure causes damage to biomolecules and produces oxidative stress which subsequently induces molecular pathways to process the insults while concomitantly eliciting a hormetic phenotype. Our understanding of the complex pathways involved in hormesis have allowed us to manipulate risk outcome and provide health benefits to organisms. Radiation induced hormetic responses can be used to significantly reduced mutation and neoplastic transformation caused by exposure to carcinogens. It can reduce oxidative damage to cardiovascular systems and stimulate the immune systems to fight infection and eliminate precancerous cells. Overall, low doses of radiation can be beneficial and perhaps required as part of normal life on this planet. Consequently, it is plausible that the absence of low dose radiation might be detrimental. Our work in ultra-low dose background environments will test this hypothesis.

Presenting Author: Douglas R. Boreham

Transposable Elements, Genomic Instability and Radiation; Barbara McClintock's Legacy in Modern Radiobiology

Carmel Mothersill, Andrej Rusin, and Colin Seymour, *McMaster University, Hamilton, Ontario, Canada*

Barbara McClintock's pioneering work in the 1940s preceded the discovery of the structure of DNA and how inheritance worked. She not only discovered mobile elements in DNA but also elucidated how interacting loci in DNA could destabilise previously stable mutations. Her work was highly controversial and she was not believed by many of her fellow scientists. However her work was really the first demonstration of what we now call genomic instability (GI) – i.e. the increased tolerance for mutation, in stressed systems. In more recent times GI and associated signalling effects have been recognised as important long-term consequences of low dose radiation exposure. Considerable thought has gone into determining the potential impacts of GI on radiation risk with arguments for increased risk due to increased instability or decreased risk due to the potential at the population level for selection of fitter (that is "adapted") genomes through hormetic or other protective mechanisms .

This presentation will discuss some of Barbara McClintock's major discoveries in the light of modern low dose radiation biology and will suggest that revisiting some of the concepts and ideas proposed by McClintock, could help us understand the mechanistic basis and the consequences of induced GI in radiation protection.

Digitizing Physical Activity Dose: Step Counting and Cadence Tracking

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Physical activity is a health-related behavior that can be widely studied as an independent, dependent, confounding, moderating, or modifying variable. Therefore, there is an almost universal need to facilitate translation by quantifying physical activity in a standardized manner across research studies. Digitizing physical activity dose is simplified by the contemporary ubiquity of wearable technologies that detect bipedal locomotion as step events. Step counting informs accumulated steps/day and cadence (steps/min) tracking is a proxy indicator for metabolic intensity. A graduated step/day index has been developed and refined to rank order dose relative to descriptors of highly physically active or ≥10,000 steps/day, physically active or 7,500-9,999 steps/day, insufficiently physically active or 5,000-7,499 steps/say, and sedentary or <5,000 steps/day, this latter category further split into subdivisions of limited or 2,500-4,999 steps/day and basal activity or < 2,500 steps/day. Data is emerging that continues to clarify doses associated with various health outcomes including mental, metabolic, and cardiorespiratory health. Sufficient evidence is also now available to inform expected (i.e., normative or reference) values, including change values due to intervention (approximately 2,000-2,500 steps/day). Heuristic cadence-based threshold values are taking shape indicative of absolutely-defined moderate (approximately 100 steps/min) and vigorous (approximately 130 steps/min) intensity across the lifespan. Preliminary evidence suggests the walk-to-run transitions takes place at approximately 140 steps/min. Novel indices (e.g., peak 30-min cadence; the average value for the highest 30 minutes in a day) offer opportunities to digitize dose beyond simple engagement in exercise (yes/no) and toward a more nuanced presentation using step-based metrics to quantify volume and intensity as well as persistence and regularity of day-to-day "best effort" performances. Digitizing physical activity dose with step counting and cadence tracking can illuminate and aid translation of science across the spectrum of researchers, practitioners, and the general public.

Session II: INTERMITTENT FASTING

Harnessing the Benefits of Intermittent Fasting by Targeting Lysosomes
Abhinav Diwan, *Department of Internal Medicine, Washington University, St. Louis. MO*

Prolonged Fasting Regulates Human CD4+ T Effector Cell Activation Via Novel Transcriptional Networks
Michael N. Sack, Kim Han, and Komudi Singh, *Laboratory of Mitochondrial Biology and Metabolism, NHLBI, Bethesda, MD*

Prolonged Fasting Regulates Human CD4+ T Effector Cell Activation Via Novel Transcriptional Networks

Michael N. Sack, Kim Han, and Komudi Singh, *Laboratory of Mitochondrial Biology and Metabolism, NHLBI, Bethesda, MD*

Fasting and caloric restriction as hormetic stressors confer beneficial effects against caloric excess linked disease risks, including evidence of anti-inflammatory effects. However, the mechanisms underpinning fasting and fasting mimetic diet mediated reduction in inflammatory biomarkers and inflammatory diseases are poorly characterized. To delineate how fasting mediates immune regulation, we performed, flow cytometry, RNA-seq, bioinformatics and biochemical/genetic validation studies on peripheral blood mononuclear cells (PBMCs) extracted from 21 human subjects in response to a 24-hr fast and 3 hrs. refeeding. High-dimensional flow cytometry showed decreased Th1, Th17 populations, diminished activated monocytes, and a increased Treg and Th2 cells in the fasted state. Bioinformatic cell-type enrichment and ClusterProfiler RNA-seq analysis further support that T cell activation pathways are blunted in fasting compared to the refed state. For functional validation we analyzed $CD4^+$ T cell cytokine release by PBMCs stimulation in response to PMA and ionomycin and by $CD4^+$ T cell activation in response to anti-CD3 and anti-CD28 stimulation. Both triggers induced Th1 and Th17 cytokines to a greater extent in refeeding versus the fasted state. Weighted Gene Co-expression Network Analysis (WGCNA) revealed that PU.1 and two novel nutrient-level dependent transcription factor (TF) networks were significantly differentially expressed between fasted and refed states. We confirmed that these TF levels were differentially regulated in CD4+T cells isolated from the fasted and refed states and that gain- and loss- of-function experiments targeting these TFs in human T cell derived H9 cells showed that these TF's differentially modulate T cell activation. These data identify that nutrient signaling can prime adaptive CD4+ T cell via novel transcriptional regulatory networks.

Session III: ENHANCING RESILIENCE

Extending Biological Resilience by Modifying Both the Temporal and Spatial Dimensions of Hormesis/Conditioning
Rehana K. Leak, *Duquesne University, Graduate School of Pharmaceutical Sciences Pittsburgh, PA*
Edward J. Calabrese, *School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA*
Walter Kozumbo, *Hormesis Project, University of Massachusetts, Amherst, MA*

Remote Ischemic Conditioning: Trials, Tribulations and Clinical Translation
Karin Przyklenk, *Cardiovascular Research Institute and Departments of Physiology & Emergency Medicine, Wayne State University School of Medicine, Detroit, MI*
Peter Whittaker, *Cardiovascular Research Institute and Department of Emergency Medicine, Wayne State University School of Medicine, Detroit, MI*

Remote Ischemic Conditioning for Acute Stroke and VCID
David C. Hess, Mohammad B. Khan, Babak Baban, and Krishnan Dhandapani, *Department of Neurology, Medical College of Georgia, Augusta, GA*

Pharmacological Induction of ER Stress to Model Sporadic ALS. Future Therapeutic Perspectives
Danilo B. Medinas and Claudio Hetz, *Biomedical Neuroscience Institute, University of Chile, Santiago, Chile*

Biomarker Development for Aerobic Exercise: Applications for Assessing Performance and Pathology
Michel Modo, *University of Pittsburgh, Pittsburgh, PA*
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Stress Inducible Evolution from Bacteria to Cancer
Susan M. Rosenberg, *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX*

Remote Ischemic Conditioning: Trials, Tribulations and Clinical Translation

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The development of novel interventions capable of reducing damage to the heart by acute myocardial infarction (MI) or 'heart attack' remains a major, unmet clinical need. A wealth of preclinical evidence obtained in multiple models and species has established that benign episodes of ischemia applied in a remote tissue or organ can render the heart resistant to infarction – a phenomenon termed 'remote ischemic conditioning' (RIC). However, despite the preclinical consensus that RIC is cardioprotective, investigation of RIC in Phase II clinical trials has yielded mixed results and the outcomes of Phase III trials have, to date, not demonstrated significant benefit. Many potential explanations have been proposed to reconcile this apparent paradox, including (but not limited to) our lack of understanding of the fundamental molecular mechanisms responsible for RIC-induced cardioprotection, together with reports that clinically relevant comorbidities (including diabetes and aging) undermine the infarct-sparing effect of RIC. Accordingly, successful clinical translation of RIC is critically dependent upon gaining greater insight into both the mechanisms of RIC and the effects of comorbidities on the 'conditioned' phenotype.

Presenting author: Karin Przyklenk

Pharmacological Induction of ER Stress to Model Sporadic ALS. Future Therapeutic Perspectives

Danilo B. Medinas and Claudio Hetz, *Biomedical Neuroscience Institute, University of Chile, Santiago, Chile*

Mutations in superoxide dismutase 1 (SOD1) cause familial amyotrophic lateral sclerosis (fALS) due to proteostasis alterations. Despite previous evidence implicating wild-type SOD1 ($SOD1^{WT}$) misfolding in sporadic ALS (sALS), no molecular or cellular pathways interfering with $SOD1^{WT}$ processing had been identified *in vivo*. We undertook a systematic approach looking at $SOD1^{WT}$ misfolding and aggregation in young, middle-age and old transgenic mice and found that disulfide-crosslinked $SOD1^{WT}$ aggregates accumulate first during aging. The formation of these species occurs in the endoplasmic reticulum (ER), and overexpression of ER chaperones decreased $SOD1^{WT}$ aggregation. Relevantly, we observed that such aggregates and ER chaperones were augmented in spinal cord tissue of sALS patients, prompting us to investigate the relationship between ER stress and $SOD1^{WT}$ aggregation. To this end, we established different pharmacological paradigms of ER stress in mice through administration of tunicamycin (Tm), an inhibitor of N-glycosylation. While acute Tm doses markedly activated apoptotic cascade, chronic Tm delivery favored induction of ER chaperones. The chronic, but not acute, ER stress regimen triggered disulfide-dependent $SOD1^{WT}$ aggregation associated with activation of astrocytes in the spinal cord of transgenic mice, thus recapitulating key features of sALS pathology. Indeed, ER stress has been proposed as an early and transversal pathological mechanism in ALS. Our data support a feed-forward cycle of ER stress and $SOD1^{WT}$ aggregation contributing to the etiology of sALS. We reason that low-level administration of ER toxins may activate adaptive mechanisms affording neuroprotection in ALS and other neurodegenerative diseases.

Presenting author: Danilo B. Medinas

Stress Inducible Evolution from Bacteria to Cancer

Susan M. Rosenberg, *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX*

If you would like a copy of Dr. Rosenberg's abstract, please email her at smr.bcm.bcm@gmail.com

Non-Targeted Effects of Environmental Radiation Exposure in Insects and Mammals

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Characterizing the Radio-adaptive Response in The Human Colon Cancer HCT116 $p53^{+/+}$ Cells

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Attenuation of Liver Injury with Hypothermic Conditioning in Acute Hepatotoxicity

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Re-Evaluation of a Low Dose Radiogenic Cancer Database

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Using the database described in the "Database of Radiogenic Cancer in Experimental Animals Exposed to Low Doses of Ionizing Radiation" by Duport, et al a secondary analysis was conducted to assess the number of individual dose responses within the 800 dataset database that exhibited an increased tumor response and number that exhibited a reduced tumor response. A new database, which allowed for a 10% increase in tumor incidence from control, included study information and tumor responses for 391 data sets from 70 different experiments. The new database was analyzed for the diversity in studies (radiation type, cancer type, species used, etc.) and percent decrease in tumor responses for dose responses below control. This new database was also analyzed relative to the top cancer sites of the studies and relative to the proportion of tumor incidence in control groups. Analysis was then conducted from a secondary refinement of original 800 data sets, allowing for up to a 20% and up to a 30% increase in tumor incidence from control. Tumor responses from the 20% and 30% increase were analyzed relative to the proportion of tumor incidence in control groups. This data, like with the 10% increase from control tumor incidence, was assessed for changes in tumor response relative to corresponding control incidence of tumors. Across all analysis parameters, it was found that there was a higher percentage of decreased tumor responses than increased tumor responses.
Presenting Author: Maureen A. Cottrell

Reproductive Cell Death Following Low-Dose Ionizing Radiation is Exacerbated by Serotonin in Human Colon Carcinoma Cells

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The underlying mechanisms that mediate cell death following low-dose radiation (LDR) exposure are not well-understood and are complicated by non-targeted effects such as the radiation-induced bystander effect. Serotonin (5-HT) has been shown to exacerbate reproductive cell death in certain cell types, however, the mechanisms that facilitate these effects have yet to be fully consolidated. We hypothesized that sensitivity to 5-HT in the amplification of cell death following LDR exposure would reflect the expression of 5-HT_{2A} and 5-HT_3 receptors. Human colon carcinoma HCT116 and human keratinocyte HaCaT cells were exposed to a wide range of 5-HT concentrations (0.001-100 μM) and clonogenic survival was assessed following exposure to direct irradiation and irradiated cell condition medium (ICCM). In addition, we examined the effect of the selective 5-HT receptor antagonists ketanserin (5-HT_{2A}) and ondansetron (5-HT_3). The expression of 5-HT_{2A} and 5-HT_3 receptors were measured in both cell types using western blotting. Herein, we report highly significant 5-HT concentration-dependent reductions in cell survival following direct LDR exposure in both cell types. Ondansetron significantly attenuated these effects, while ketanserin only significantly attenuated death in HCT116 cells. Both the production of and response to ICCM radiation damage signals in HCT116 cells were significantly augmented by 5-HT. Both receptor antagonists abolished death in ICCM-recipient HCT116 cells when present during irradiation. HaCaT cells lack the expression of 5-HT_{2A} receptors, while HCT116 cells express both receptor types. We have established 5-HT as a biomarker for the exacerbation of multiple mechanisms of LDR-induced cell death in human colon carcinoma cells. Moreover, we have identified 5-HT_{2A} and 5-HT_3 receptors as potential therapeutic targets for ameliorating LDR cell death. Evidence from this study suggests that the 5-HT_{2A} receptor may be a prerequisite for cells to elicit non-targeted 5-HT-augmented cell damage.

Presenting Author: Jacob J. Curtis

The Effects of Low Dose Ionizing Radiation on HUVEC Exosome Cargo

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It is well known that high doses of ionizing radiation (IR) have deterministic effects that may lead to measurable injuries and even death. However, the stochastic effects from low doses of radiation remain as an enigma. During low dose exposure, non-targeted effects have been documented, due to a process known as radiation induced bystander effect (RIBE). Studies from previous nuclear disasters, tell us that even some of the smallest doses may have deleterious effects. In vitro, we can see that low doses can affect transcription, translation, proliferation, apoptosis, and other cellular processes. Most cells will communicate these effects through gap junctions. However, research has now shown that exosomes produced by the affected cells are able to elicit non-targeted effects in naive cells. Previous literature on the topic has looked at higher doses that are rarely seen throughout one's life time or only look for specific miRNA, proteins, or mRNA. In this study, exosomes were isolated from HUVECs, in order to determine the full proteomic *fingerprint* via Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and DAVID Bioinformatics Resources. The proteins and pathways identified suggest that lower doses of IR may play a role in the development of Alzheimer's disease, Type 2 Diabetes, and various forms of cancer. Furthermore, signs of ER stress, ECM remodelling proteins, and neurodegenerative related proteins were also identified. Lastly, there was an increase in iron transport, secretion, and metabolism related proteins. Previous work by Shen et al, indicated that dysregulation in iron metabolism may be one of the driving mechanisms behind alzheimer's, osteoporosis and various cancers. This study, alongside previous work, furthers our understanding of the driving mechanism behind RIBE. Future studies should look at the effects of low dose ionizing radiation and its role in the progression of type 2 diabetes and neurodegenerative diseases.

voles of Chernobyl, there is evidence of genomic instability caused by the historic dose to the progenitor organisms from the characteristic steady increase of mutation levels throughout increasing generations. The fruit flies did not seem to show this relationship. This may have been due to the low number of tested generations. In all testing, adaptive responses were seen within the characteristic dose ranges from evident plateau regions.

Attenuation of Liver Injury with Hypothermic Conditioning in Acute Hepatotoxicity

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Introduction
The problem of hepatotoxicity has been prevalent and distressing, especially when the liver is frequently exposed to drugs, herbs or toxicants and many may pose a risk to liver injury. Furthermore, its early asymptomatic manifestation may impede timely treatment, thereby escalating deterioration and worsens outcome. Hence, therapeutic hypothermia has been explored in this study as a potentially simple and effective drug-free approach to preserve liver functions. Hitherto the concept of hypothermia for toxicity management has been contentious and we aim to debunk the conflict with a systematic investigation of hypothermic effects in an acetaminophen (APAP)-induced liver injury model.

Methods
Transforming growth factor-α mouse hepatocytes (TAMH) were incubated in moderate hypothermic condition, at 32 °C for 24 h, during the exposure to cytotoxic level of APAP (5mM) which induced acute liver injury. Thereafter, the extent of cytoprotective effects was investigated in parallel with an evaluation on the functional aspects of hepatocytes following cooling and upon rewarming of cells back to 37 °C for 24 h. In addition, we attempt to elucidate its protective mechanism through an examination of basic oxidative stress and autophagy markers.

Results
Moderate hypothermia could promote liver preservation, with comparable cytoprotective outcomes as the gold standard of APAP intoxication rescue therapy, N-acetylcysteine. Furthermore, the increased cell viability and reduced cell death continued for 24 h after temperature restoration. Transcriptional expressions, activities and inducibilities of key drugmetabolizing enzymes varied in their response to hypothermia while there was unremarkable change in the clearance capacity of TAMH. Mechanistically, moderate hypothermia could induce autophagy upon cooling and promote anti-oxidative effects for cytoprotection.

An Examination of Low Doses of Arsenic Trioxide on Human Keratinocytes with Implications for Homeopathy

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Homeopathy is an alternative therapeutic treatment strategy in which it is believed that extremely high dilutions of substances, when prepared in accordance with the homeopathic method, yield greater medicinal benefits. Uncertainty exists with regards to the recognition of homeopathy as a plausible facet of healthcare, despite efforts being made to demonstrate the efficacy of the field through empirical research. The lack of proven explanatory mechanisms for homeopathic successes, inconsistencies in replication of trials, as well as discordance between homeopathic beliefs and laws of physical sciences, have functioned as objections for the notion that homeopathic remedies may elicit more success in treatment than a placebo. However, toxicological research suggests that exposure to low doses of metals may induce protective effects. The current study seeks to expand upon the analysis of ultra-low dose effects of toxic metals on human health by examining human HaCaT keratinocytes in response to a range of increasingly low concentrations of As_2O_3. To accomplish this, we prepared serial dilutions of an arsenic stock solution using homeopathic tenets as well as classic scientific protocols. Cellular proliferation was monitored using the Trypan Blue Exclusion Method to analyze and compare the two groups. This area of research is important in toxicology and may provide new insights into the relationship between homeopathic treatment and conventional therapy.

Effects of Lead Exposure on Radiation Response in Human Colon Tumor Cells

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Previous research has shown that lead exposure alone can impair neurological development in children and can cause various detrimental health effects in adults. Radiation is commonly used in medicine to aid in diagnosing and treating medical conditions. However, the effect of lead and radiation coexposure in humans is poorly understood. Recent studies have reported higher than recommended levels of lead in drinking water among homes and schools across North America. With increased chronic exposure to lead, undergoing medical imaging or treatment requiring radiation may pose a risk to the health of patients. In this study, we investigate the effects chronic exposure of lead may have towards gamma radiation responses in human colorectal carcinoma cells. To study this, clonogenic cell survival of HCT116 p53 wild-type ($HCT116^{+/+}$) cell cultures treated with media containing lead acetate will be assessed following gamma ray exposure from a Cs-137 source. Media will have lead concentrations ranging from 0.1-100 μM. Cell cultures will be exposed to gamma radiation doses ranging from 5mGy-5Gy. The findings from this study will provide insight on the effects of lead and radiation coexposure in human cells.

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