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HORMESIS AND ITS POTENTIAL IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY

Kenneth I. Maynard, PhD, FAHA, Sanofi-aventis, US, Inc., Project Direction, Neurology, BX2-3-309A, 200 Crossing Blvd, Bridgewater, NJ 08807, Tel: 908-304-6352, Fax: 908-304-6730, Email: Kenneth.maynard@sanofi-aventis.com

Hormesis is a dose-response phenomenon characterized by low dose stimulation and high dose inhibition, resulting in for example, a J-shaped or an inverted U-shaped dose response. It is a concept that is known in the field of toxicology, and although its mechanism of action is not well understood it is exemplified by a pollutant or toxin exhibiting the opposite effect in small doses versus large doses.

Numerous scientific publications over the past decade suggest that hormesis has much wider application outside of the field of toxicology with potential for fundamental impact in the conduct of basic and applied sciences.

This presentation will review some examples of hormesis in biological sciences outside of the field of toxicology and discuss its potential impact on drug discovery and development in the pharmaceutical industry.

ADAPTIVE RESPONSES AND RISK – YEAST TO THE CLINIC

Douglas R. Boreham, McMaster University, Medical Physics and Applied Radiation Sciences, Hamilton, Ontario, Canada, L8S 4K1, Tel: 905-525-9140 ext 27538, Email: boreham@mcmaster.ca

It has been known for decades that low dose radiation can induce an adaptive response in cells and whole organisms. Our early work with yeast showed that sub-lethal exposures to ionizing radiation could induce resistance to killing by higher challenge doses of radiation. This adaptive response also conferred resistance to a number of other agents including chemical carcinogens. Several pathways that control this mechanism have been identified and homologous recombinational repair has a major role. Subsequent work in mammalian cells and animals has demonstrated similar protective adaptive responses. One interesting observation is that a single low dose exposure to low LET radiation can increase the latency period of cancer progression in cancer prone animals. We are currently studying the effects of medical diagnostic radiation (CT and PET scans) on cancer risk in animals. We have shown that a single CT or PET scan can induced an adaptive response and modify the response of cells to subsequent exposures. Similar work has been performed in the clinic were we have shown that CT and PET scans in patients induce adaptive responses in their cells. Patients undergoing radiation therapy also show adaptive responses during the course of the treatment and systemic changes in non targeted cells have been observed. Radiation therapy can also cause perturbation to the gastro-intestinal system whereby gut motility, gastric emptying, nausea, and vomiting can occur after some types of radiation treatments. In animal models, we have shown that these GI related impacts can be reduced by prior low dose adaptive exposures. Overall, the highly conserved and reproducible effect of low dose radiation exposures seems to have beneficial effects at all levels of biological organization.

ADAPTIVE RESPONSES TO OXIDATIVE STRESS: PARTICULARLY THE RCAN1 GENE

Kelvin J. A. Davies, University of Southern California, Andrus Gerontology Center of the Davis School of Gerontology, and Division of Molecular & Computational Biology of the USC College, Los Angeles, California 90089-0191, U.S.A., Tel: 213-740-4200, Fax: 213-740-6462, Email: kelvin@usc.edu

Adaptive responses are essential components of cellular defenses against environmental stresses. During adaptation to oxidative stress, the expression of at least 35 genes is significantly increased, while other genes are downregulated. In the first stages of oxidative stress responses, in dividing mammalian cells, three growth-arrest-inducing genes are expressed: gadd45, gadd153, and adapt15. The ensuing 4-5 hours of growth-arrest provide significant stress-protection. Over the next 13-14 hours, mammalian cells exhibit four distinct "waves" of transcription and translation until, at approximately 18 hours after initial stress exposure, maximal stress resistance is attained. Importantly, stress-resistance gradually fades over the next 18 hours so that, by about 36 hours after initial stress exposure, all induced resistance is lost. Cells can actually be made to undergo repeated rounds of adaptation and de-adaptation, an important survival skill, which also demonstrates that the experimenter is not simply selecting for a pre-existing naturally resistant sub-population. The roles of several adaptive genes will be discussed, with particular emphasis on the RCAN1, Regulator of Calcineurin 1, gene (previously called DSCR1 or Adapt78) and its protein product, RCAN1. Stress-induced transcription/translation of RCAN1 raises cellular RCAN1 levels and activity, causing significant inhibition of calcineurin. Since calcineurin is a serine/threonine phosphatase which acts as an "off switch" for many of the kinases that are essential to stress-adaptation, transient induction of RCAN1 allows a full stress response to be mounted. Cells that fail to mount a suitable stress adaptation may enter a state of permanent growth-arrest, or may die by either apoptosis or by necrosis. Unfortunately, chronic overexpression of RCAN1 (due to chronic inflammation or gene dysregulation) can be extremely harmful, and is associated with diseases such as Down syndrome, and Alzheimer disease. Similarly, chronic under-expression of RCAN1 is also undesirable and has now been linked with Huntington disease.

THREE BARRIERS BLOCK DAMAGE FROM LOW-DOSE IRRADIATION

Ludwig E. Feinendegen, Heinrich-Heine-University Düsseldorf. Germany; and Brookhaven National Laboratory, Upton, NY, USA, Email: feinendegen@gmx.net
Myron Pollycove, School of Medicine, University of California San Francisco, San Francisco, CA, USA, Email: pollycove@comcast.net
Ronald D. Neumann, Radiology and Imaging Sciences, Clinical Center, The National Institutes of Health, Bethesda, MD, USA, Email: RNeumann@cc.nih.gov

Organisms keep integrity through signaling at and between hierarchical levels of molecules, cells, tissue-organs and the whole body. Ionizing radiation primarily perturbs the basic molecular level proportional to dose, with potential damage amplification to higher levels. - Each level exhibits three types of physiological defenses against perturbations and damage propagation to higher levels, a physical-static one and two metabolic-dynamic ones usually involving enzymes under genetic control. The first defense operates at each level deterministically with a threshold of impact below which there is no response. The first metabolic-dynamic defense acts immediately and non-linearly with dose against perturbation and damage propagation and includes: - scavenging of toxins at the molecular level; - molecular repair, especially of DNA, at the cellular level; - removal of damage carrying cells at the tissue-organ level either by apoptosis, differentiation-senescence, or by immune responses, also involving replacement of lost elements. The second metabolic-dynamic defense arises delayed by up-regulating components of the immediately responding defense. This adaptive response may last beyond a year and create temporary protection against renewed potentially toxic impacts also from non-radiogenic endogenous sources. Effectiveness of adaptive protection reaches a maximum after a single tissue absorbed dose below about 150 mSv and disappears with higher doses. For low dose rates, maximum protection is likely at lower cell doses delivered repetitively at optimal time intervals. - Therefore, low-dose and low dose rate irradiation can exert a dual response, one of damage and the other of protection largely against endogenous damage. Indeed, protection preventing only about 2 – 3 % of endogenous life-time cancer risk, would fully balance a calculated induced cancer risk of about 100 mSv. Epidemiology agrees with risk of low-doses and dose rates not to follow a linear function of dose but have a dose threshold, or even show hormesis with clinical benefit.

BIOMEDICAL SESSION

STIMULATING HORMETIC SIGNALING PATHWAYS TO IMPROVE BRAIN HEALTH

Mark P. Mattson, National Institute on Aging Intramural Research Program, Baltimore, MD

VITAGENES, CELLULAR STRESS RESPONSE AND ACETYLCARNITINE: RELEVANCE TO HORMESIS

Vittorio Calabrese, Department of Chemistry, University of Catania, Catania, Italy
Carolin Cornelius Department of Chemistry, University of Catania, Catania, Italy
Albena T. Dinkova-Kostova, University of Dundee, Scotland, UK
Edward J. Calabrese, University of Massachusetts, Amherst, Massachusetts

HORMETIC IMMUNE SIGNALING INITIATES NEUROLOGICAL PREVENTATIVE HEALTH

Richard P. Kraig, The University of Chicago Medical Center, Chicago, IL
Heidi Mitchell, The University of Chicago Medical Center, Chicago, IL
Barbara Christie-Pope, Cornell College, Mt. Vernon, IA
David M. White, The University of Chicago Medical Center, Chicago, IL
Phillip E. Kunkler, The University of Chicago Medical Center, Chicago, IL

THE RATIONAL DESIGN OF THERAPEUTIC ANTIOXIDANTS: FREE RADICAL TRAPPING ACTIVITY AND THE DOSE-RESPONSE RELATIONSHIP

James J. Ley, Univeristy of Miami, Miami, FL

MIMETICS OF HORMETIC AGENTS OFFER INTERVENTIONS IN AGING, DISEASE, AND TRAUMA

Joan Smith Sonneborn, Ph.D., University of Wyoming, Laramie, WY

RESVERATROL, A POLYPHENOLIC ANTIOXIDANT PRESENT IN RED WINE, IS DOSE-DEPENDENT IN DELIVERING CARDIOPROTECTION

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Subvendu Mukherjee, University of Connecticut Health Center, Farmington, CT
Dipak K. Das, University of Connecticut Health Center, Farmington, CT

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Ying-Ying Huang MD, Massachusetts General Hospital; Harvard Medical School; and Guangxi Medical University, Nanning, Guangxi, China
Aaron C-H Chen MS, Massachusetts General Hospital; and Boston University School of Medicine, Boston, MA
Michael R Hamblin, PhD, Massachusetts General Hospital; Harvard Medical School; and Harvard-MIT Division of Health Science and Technology, Boston, MA

METHYLENE BLUE DOSE-RESPONSE: IMPLICATIONS FOR TOXICOLOGY AND MEDICINE

F. Gonzalez-Lima, University of Texas at Austin, Austin, TX
Aleksandra K. Bruchey, University of Texas at Austin, Austin, TX

IMPLICATIONS FOR DRUG DEVELOPMENT OF THE U-SHAPED DOSE RESPONSE CURVE FREQUENTLY OBSERVED WITH ANTI-ANGIOGENIC DRUGS
Andrew P. Mazar, Attenuon, LLC, Evanston, IL

THE HORMETIC MORPHOGEN THEORY OF CURVATURE AND THE MORPHOGENESIS AND PATHOLOGY OF TUBULAR AND OTHER CURVED STRUCTURES
Egil Fosslien, University of Illinois at Chicago, Chicago, IL

INHIBITORS OF ANGIOGENESIS CAN EXHIBIT BELL-SHAPED OR U-SHAPED DOSE-RESPONSE CURVES: RELEVANCE FOR CANCER THERAPY
Andrew R. Reynolds, Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London, UK
Jim C. Norman, Integrin Cell Biology Laboratory, Beatson Institute for Cancer Research, Glasgow, Scotland
Gordon C. Tucker Institut de Recherches Servier (IdRS), Cancer Drug Discovery Division, Croissy-sur-Seine, France
Kairbaan M. Hodivala-Dilke, The Adhesion and Angiogenesis Laboratory, Centre for Tumour Biology, Barts & The London School Of Medicine & Dentistry, London, UK

STIMULATING HORMETIC SIGNALING PATHWAYS TO IMPROVE BRAIN HEALTH

Mark P. Mattson, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, 251 Bayview Boulevard, Baltimore, MD 21224, Tel: 410 558-8463, Fax: 410 558-8465, Email: mattsonma@mail.nih.gov

Regular exercise, dietary energy restriction and intellectual challenges may protect neurons in the brain against age-related degenerative disorders including Alzheimer's and Parkinson's diseases and stroke. Data from this and other laboratories suggest that all three of the lifestyle factors protect neurons by a hormetic mechanism that involves the activation of adaptive cellular stress response pathways. The pathways stimulate the production of neuroprotective proteins such as neurotrophic factors (BDNF, bFGF and GDNF), protein chaperones (HSP70 and GRP78) and antioxidant enzymes (HO-1), while suppressing the production of pro-inflammatory cytokines (TNFalpha, IL-6 and IL-1beta). Based upon the hypothesis that some of these same adaptive stress response pathways naturally occurring "toxins", we have established bioassays to screen a panel of botanical pesticides to identify those that (at low subtoxic doses) activate one or more neuroprotective pathways including those involving the transcription factors Nrf-2, NF-kB, FOXO and CREB. These screens resulted in the identification and further characterization of lead "neurohormetic phytochemicals" which we are testing for their potential to reduce neuronal degeneration and improve function in animal models of neurodegenerative disorders. The long-term goal of this hormesis-centric approach to neuroprotection is to develop novel preventative and therapeutic interventions for humans that improve their brain health and protect them against neurodegenerative disorders.

VITAGENES, CELLULAR STRESS RESPONSE AND ACETYLCARNITINE: RELEVANCE TO HORMESIS

Vittorio Calabrese, Department of Chemistry, University of Catania, Via Andrea Doria, 95100 Catania, Italy, calabres@unict.it
Carolin Cornelius Department of Chemistry, University of Catania, Via Andrea Doria, 95100 Catania, Italy, Email: carolin.Cornelius@receptura.de
Albena T. Dinkova-Kostova, The Biomedical Research Institute, University of Dundee, Scotland, UK, Dundee DD1 9SY, and Division of Clinical Pharmacology, Departments of Medicine and Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, Email: A.DinkovaKostova@dundee.ac.uk
Edward J. Calabrese Environmental Health Sciences Division, School of Public Health, University of Massachusetts, Amherst, Massachusetts, USA. Email: edwardc@schoolph.umass.edu

Protein thiols play a key role in redox sensing, and regulation of cellular redox state is crucial mediator of multiple metabolic, signalling and transcriptional processes[1-4]. Under optimal conditions long-term health protection is accomplished by protein homeostasis, a highly complex network of molecular interactions that balances protein biosynthesis, folding, translocation, assembly/disassembly, and clearance. Efficient functioning of these mechanisms is accomplished by a complex network of mechanisms under control of different genes termed vitagenes[5]. The term vitagenes refers to a group of genes which are strictly involved in preserving cellular homeostasis during stressful conditions. The vitagene family is actually composed of the heat shock proteins (Hsp) Hsp32, Hsp70, the thioredoxin system and the sirtuin system[2]. Dietary antioxidants have recently been demonstrated to be neuroprotective through the activation of hormetic pathways, including vitagenes. Over the past decade there has been a remarkable increase of interest in hormesis as a result of more significance being given to low dose effects and the use of more powerful study designs which have enabled to identify rational approaches to detect hormetic biphasic dose responses in the low dose zone[5]. The hormetic dose–response has the challenging potential to affect significantly the design of pre-clinical studies and clinical trials as well as strategies for optimal patient dosing in the treatment of numerous diseases. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing stress responses. Here, we will present and discuss the most current and up to date understanding of the possible signaling mechanisms by which acetylcarnitine by activating vitagenes can differentially modulate signal transduction cascades inducing apoptosis/cell death in abnormal cancer cells but at the same time enhancing defensive enzymes to protect against carcinogenesis and neurodegeneration in normal cells.

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HORMETIC IMMUNE SIGNALING INITIATES NEUROLOGICAL PREVENTATIVE HEALTH

Richard P. Kraig, Department of Neurology, The University of Chicago Medical Center, 5841 South Maryland Avenue, Chicago, IL 60637, Tel: 773-702-0802, Fax: 773-702-5175, Email: rkraig@neurology.bsd.uchicago.edu
Heidi Mitchell, Department of Neurology, The University of Chicago Medical Center, 5841 South Maryland Avenue, Chicago, IL 60637, Tel: 773-702-9141, Fax: 773-702-5175, Email: hmitchel@neurology.bsd.uchicago.edu
Barbara Christie-Pope, Department of Biology, Cornell College, Mt. Vernon, Iowa 52314, Tel: 319-895-4350, Fax: 319-895-5764, bchristie-pope@cornellcollege.edu
David M. White, The University of Chicago Medical Center, 5841 South Maryland Avenue, Chicago, IL 60637, Tel: 773-702-9141, Fax: 773-702-5175, Email: dwhite@neurology.bsd.uchicago.edu
Phillip E. Kunkler, Department of Neurology, The University of Chicago Medical Center, 5841 South Maryland Avenue, Chicago, IL 60637, Tel: 773-702-9141, Fax: 773-702-5175, Email: golgi61@aol.com

Brain is unique among organ structures since it alters its regional, cellular and molecular structure and function in response to neural activity. This ability is evidenced by the Hebbian synaptic plasticity and extends to environmental enrichment (i.e., increased intellectual, social, and physical activity). Importantly, environmental enrichment prompts brain to become more resilient against neurodegernative diseases including stroke, epilepsy, migraine, Alzheimer's disease and Parkinson's disease. Increasing evidence indicates that activation of the immune system including low-level signals that only "irritate" the brain is involved. This irritation is not enough to kill, but prompts the brain to adapt, and so it becomes stronger, consistent with the principles of hormesis.

For example, monomeric immunoglobin G (IgG) is regarded as quiescent and only poised to initiate injurious inflammatory reactions via immune complex formation associated with phagocytosis and tumor necrosis factor alpha (TNF-α) production in response to disease. Instead, we show IgG has hormetic signaling function in normal brain which triggers neuroprotection against subsequent brain injury at physiological levels (but not at non-physiologically low or high levels of IgG). This IgG effect requires TNF-α, which also follows an analogous pattern of hormesis and takes time to develop. Furthermore, TNF-α is involved in neuroprotection from spreading depression, long-term potentiation (i.e., a cellular model of learning) and environmental enrichment.

Brain and immune signaling are known to be closely interrelated but are most often examined in relation to neurological disease associated with high-level immune reactions. We hypothesize that brain utilizes these same peripheral and central immune signaling systems (i.e., innate and adaptive immunity) to evoke low-level (and likely phasic) irritative immune signaling in the absence of disease to trigger the adaptive neural changes that account for neuroprotection due to increased brain activity.

THE RATIONAL DESIGN OF THERAPEUTIC ANTIOXIDANTS: FREE RADICAL TRAPPING ACTIVITY AND THE DOSE-RESPONSE RELATIONSHIP

James J. Ley, Univeristy of Miami, Miller School of Medicine, 1501 NW 9th Avenue, Miami, Florida, 33136, Tel: 305-776-9839, Email: jley02@hotmail.com

Extensive experimental evidence has demonstrated the ubiquitous role of oxidative stress in diverse diseases, suggesting a role for antioxidant therapy to help fulfill the large, unmet need for the effective treatment of devastating conditions such as cardiovascular diseases and neurodegenerative diseases. Unfortunately, in large placebo-controlled trials, antioxidants have failed to demonstrate clinical benefit. Consequently, many suggestions, including greater consideration of the therapeutic dose, have been advanced to improve the clinical trials, to better discern favorable outcomes. However, in addition, the experimental results of the *in vitro* and *in vivo* free radical trapping activity and the dose-response relationship of antioxidants may be useful to design improved antioxidant molecules with greater therapeutic efficacy. This presentation reviews the correlations between molecular structure and antioxidant potency that have been successfully exploited to design more potent free radical scavengers. The bell shaped dose-response curves seen with various antioxidants is also reviewed. Clinical benefit may be limited if the maximal or therapeutic effect is only attainable within a narrow dose range. This prompts consideration of whether the dose-response curve might be amenable to modification by means of changes to the molecular structure in order to prepare an antioxidant with greater therapeutic efficacy.

MIMETICS OF HORMETIC AGENTS OFFER INTERVENTIONS IN AGING, DISEASE, AND TRAUMA

Joan Smith Sonneborn, Ph.D. Professor Emeritus, Zoology Department, University of Wyoming, 1226 E Curtis Street, Laramie, WY 82072, Tel: 307-742-4728, Fax: 307-745-3139, Email: cancun@uwyo.edu

Mimetics of hormetic agents offer a novel approach to adjust dose to minimize the risk of toxic response, and maximize the benefit of induction of at least partial physiological conditioning. Since species-survival requires living long enough to reproduce and the ability to withstand physical and chemical environmental challenge, Nature selected and preserved those organisms and triggers that promote tolerance to stress. Examples of known stresses include radiation, heat, cold, over exercise, hunger, infectious-agents, as well as chemicals that are oxidizing or otherwise poisonous. The induced tolerance not only serves to resist that challenge, but also can repair previous age, disease, and trauma damage to provide a more youthful response to other stresses. The associated physiological conditioning and rejuvenation benefits may include youthful restoration of DNA repair, resistance to oxidizing pollutants, protein structure and function repair, improved immunity, tissue remodeling, adjustments in central and peripheral nervous systems, and altered metabolism. By elucidating common pathways activated by hormetic agent's mimetics, new strategies for intervention in aging, disease, and trauma emerge. Hormetic mimetics have intervention potential in cancer, diabetes, age-related diseases, infectious diseases, heart and kidney failure, cardiovascular diseases, and Alzheimer's disease. Examples of hormetic mimetics exist in pathways activated in primitive organisms and are latent in humans. Peptides, oligonucleotides, and hormones are among the mimetics that promoter resistance to radiation, physical endurance, strength, and immunity. The triggers are effective both as pre and post exposure physiological conditioners to tolerate stress. Preservation of native protein cytoskeleton structures and activation of latent longevity assurance loci by hormesis mimetics offer powerful intervention strategies for health and stress survival. Combinations of several mimetics may more closely elicit the beneficial stimulation of multiple stress resistance pathways found at the low dose hormetic dose response threshold.

RESVERATROL, A POLYPHENOLIC ANTIOXIDANT PRESENT IN RED WINE, IS DOSE-DEPENDENT IN DELIVERING CARDIOPROTECTION

Jocelyn I. Dudley, Department of Surgery Room #L1086, University of Connecticut Health Center, 263 Farmington Avenue Farmington, CT 06030, Tel: 860-679-1861, Fax: 860-679-4606, Email: jocelyn.dudley@uconn.edu
Subvendu Mukherjee, Department of Surgery Room #L1072, University of Connecticut Health Center, 263 Farmington Avenue Farmington, CT 06030, Tel: 860-679-7907, Fax: 860-679-4606, Email: smukherjee@uchc.edu
Dipak K. Das, Department of Surgery Room #L1076, University of Connecticut Health Center, 263 Farmington Avenue Farmington, CT 06030, Tel: 860-679-3687, Fax: 860-679-4606, Email: ddas@neuron.uchc.edu

Recent studies have demonstrated cardioprotective abilities of resveratrol, a polyphenolic antioxidant present in red wine. Studies have shown that resveratrol not only provides cardioprotection at lower doses, but can kill cancer cells at relatively higher doses by exerting a death signal. We reasoned that resveratrol might possess the ability to protect the cells at lower doses as observed during pharmacological preconditioning of the heart, while at higher doses cause cell death as found for cancer cells. To test this hypothesis, rats were randomly fed for 14 days by gavaging any of the four doses of resveratrol - 2.5, 5.0, 25 or 50 mg/kg/day - while vehicle-fed animals served as placebo control. The rats fed either 2.5 or 5 mg/kg dose of resveratrol for 14 days provided cardioprotection as evidenced by improved post-ischemic ventricular recovery and reduction of myocardial infarct size and cardiomyocyte apoptosis compared to control. In contrast, both groups of hearts of either 25 or 50 mg/kg dose of resveratrol depressed cardiac function and increased myocardial infarct size and number of apoptotic cells. The results for Western blots and RT-PCR demonstrated an increase of protein and RNA transcripts of redox proteins including thioredoxin (Trx)-1, Trx-2, glutaredoxin (Grx)-1, Grx-2, redox factor Ref-1 as well as redox-sensitive transcription factor NFkappaB, and survival factors such as phosphorylated-Akt (p-Akt), and Bcl-2 in the animals fed lower doses (2.5 and 5 mg/kg) of resveratrol, while the reverse was true for the animals fed higher doses (25 and 50 mg/kg) of resveratrol. The results of this study revealed that resveratrol provides cardioprotection only at lower doses by enhancing genes and proteins of survival pathway that include Akt and Bcl-2, while at higher doses (>25 mg/kg), it potentiates a death signal by down-regulating redox proteins and up-regulating pro-apoptotic proteins.

BIPHASIC DOSE RESPONSE IN LOW-LEVEL LIGHT THERAPY

Ying-Ying Huang MD, Wellman Center for Photomedicine, Massachusetts General Hospital; Department of Dermatology, Harvard Medical School; and Aesthetic Plastic Laser Center, Guangxi Medical University, Nanning, Guangxi, China
Aaron C-H Chen MS, Wellman Center for Photomedicine, Massachusetts General Hospital; and Graduate Medical Sciences, Boston University School of Medicine
Michael R Hamblin, PhD, Wellman Center for Photomedicine, Massachusetts General Hospital; Department of Dermatology, Harvard Medical School; and Harvard-MIT Division of Health Science and Technology, BAR 414, 40 Blossom Street, Boston, MA 02114, Tel: 617-726-6182, Fax: 617-726-8566, Email hamblin@helix.mgh.harvard.edu

The use of low levels of visible or near infrared light for reducing pain, inflammation and edema, promoting healing of wounds, deeper tissues and nerves, and preventing cell death and tissue damage has been known for over forty years since the invention of lasers. Originally thought to be a peculiar property of laser light (soft or cold lasers), the subject has now broadened to include photobiomodulation and photobiostimulation using non-coherent light. Despite many reports of positive findings from experiments conducted in vitro, in animal models and in randomized controlled clinical trials, LLLT remains controversial. This likely is due to two main reasons; firstly the biochemical mechanisms underlying the positive effects are incompletely understood, and secondly the complexity of rationally choosing amongst a large number of illumination parameters such as wavelength, fluence, power density, pulse structure and treatment timing has led to the publication of a number of negative studies as well as many positive ones. In particular a biphasic dose response has been frequently observed where low levels of light have a much better effect on stimulating and repairing tissues than higher levels of light. Many reports refer to stimulation of biological processes at relatively low levels of energy density or power density, and that the positive effect diminishes as the dose is increased, and eventually inhibitory effects predominate leading to worsening of clinical conditions. The so-called Arndt-Schulz curve is frequently used to describe this biphasic dose response. This presentation will review these studies and describe some of our recent results in vitro and in vivo that provide scientific explanations for this observation.

METHYLENE BLUE DOSE-RESPONSE: IMPLICATIONS FOR TOXICOLOGY AND MEDICINE

F. Gonzalez-Lima, University of Texas at Austin, Departments of Psychology, Pharmacology and Toxicology, 1 University Station A8000,
Austin, TX 78712-0187, Tel: 512-471-5895, Fax 512-471-4728. Email: gonzalez-lima@mail.utexas.edu
Aleksandra K. Bruchey, University of Texas at Austin, Department of Psychology, 1 University Station A8000, Austin, TX 78712-0187, Tel: 512-471-5895, Fax: 512-471-4728. Email: aleksandra@mail.utexas.edu

Methylene blue (MB) is a remarkable compound in the history of pharmacology that is characterized by hormetic behavior for a wide range of effects. MB was the first phenothiazine developed and the first synthetic chemical tested in human patients, which Ehrlich demonstrated in 1891 as effective in malaria treatment. MB's pharmacological properties have been under investigation for over 120 years in numerous therapeutic applications, from microbiology to psychiatry. Our recent research on MB's neurobehavioral actions suggests that MB has powerful metabolic enhancing and antioxidant effects that facilitate memory and promote neuroprotection. In this presentation we address the question of what is unique about MB that could account for its wide applicability and hormetic behavior as a drug. At doses spanning its hormetic zone, MB can increase select behavioral, physiological and biochemical responses until they are 130-160% of control. For example, low doses of MB produce maximum behavioral and biochemical responses with averages of approximately 140% of control. As MB dose is raised outside the hormetic zone the response decreases below the control response, as exemplified by MB's ability to increase cytochrome oxidase activity at intermediate doses, while decreasing cytochrome oxidase activity at higher doses. A key chemical property of MB is that it is an autoxidizable dye. That is, MB is a reducible dye with a reduction-oxidation capacity for electron cycling. MB will be reduced by accepting electrons from a reduced electron transport donor and it will in turn transfer electrons to oxygen to form water. Therefore, MB's autoxidizable property provides a chemical mechanism for electron transfer to oxygen, but MB does not gain any stoichiometric or net reduction. We propose that MB's autoxidizable chemical property may be responsible for its unique pharmacological action as both a metabolic energy enhancer and antioxidant that is frequently characterized by hormetic dose-response relationships.

IMPLICATIONS FOR DRUG DEVELOPMENT OF THE U-SHAPED DOSE RESPONSE CURVE FREQUENTLY OBSERVED WITH ANTI-ANGIOGENIC DRUGS

Andrew P. Mazar, Attenuon, LLC, 825 Chicago Ave., Suite E2, Evanston, IL 60202, Tel: 847-570-0640, Fax: 847-570-0641, Email: mazar@attenuon.com

The development of anti-angiogenic drugs (those that inhibit blood vessel formation) is an area of intense effort in oncology, diabetes, and ophthalmology. Unlike traditional cytotoxic drugs developed historically in oncology, anti-angiogenic drugs often do not achieve a Maximally Toleretad Dose (MTD) either in pre-clinical animal tumor models or clinically in cancer patients. Since this allows dosing to continue well-above the optimal active dose of a particular compound (in contrast to cytotoxic drugs which typically work at or near the MTD), this has led to the observation that many of these compounds exhibit U-shaped dose responses. Despite initial skepticism by cancer drug developers, this phenomenon appears to be very prevalent for anti-angiogenic drugs and may in fact be a universal characteristic for this class of compounds. Unfortunately, the presence of a U-shaped dose response has led to significant challenges to the development of these drugs and attempts have been made to overcome some of these challenges using recent advances in technology to evaluate biomarkers of the optimal dose of these anti-angiogenic compounds. These challenges will be discussed in the context of several relevant examples of anti-angiogenic drugs that have now reached phase II of human testing.

THE HORMETIC MORPHOGEN THEORY OF CURVATURE AND THE MORPHOGENESIS AND PATHOLOGY OF TUBULAR AND OTHER CURVED STRUCTURES

Egil Fosslien, College of Medicine, University of Illinois at Chicago, Chicago, IL, Mail: 502 Fairview Avenue, Glen Ellyn, IL, Tel: 630-469-6824, Email: efosslie@uic.edu

The hormetic morphogen theory proposes that curvature formation in biology is determined by tissue gradients of hormetic morphogens such as transforming growth factor beta (TGF-β) in mammals and auxin in plants that down- and up-regulate basic growth rates at high and low concentrations respectively. At high morphogen concentrations close to a gradient source, cell growth is reduced. With increasing distance from the source, growth inhibition lessens until a point is reached beyond which cell growth gradually increases as morphogen concentration declines. These opposite effects on growth along the gradients are responsible for curving the tissue. The morphogen gradient source concentration and slope determine the radius of curvature and diameter of tubular, cystic, domed, and other curved biological structures. At very high concentrations, morphogens such as TGF-β induce apoptosis, which enables cavity formation during morphogenesis of hollow structures. Hormetic morphogens control growth rates and thereby curvature along their gradients by amplitude modulation of cellular generation of adenosine triphosphate (ATP), the limiting growth regulator in mammals and plants. The hormetic morphogen theory applies to regulation of curvature during developmental morphogenesis, tissue remodeling and repair of injury. Aberrant hormetic morphogen signaling is associated with developmental abnormalities and tumor formation in man, animals, and plants.

INHIBITORS OF ANGIOGENESIS CAN EXHIBIT BELL-SHAPED OR U-SHAPED DOSE-RESPONSE CURVES: RELEVANCE FOR CANCER THERAPY

Andrew R. Reynolds, Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK, Tel: +44 (0)207 153 5330, Fax: +44 (0)207 153 5340, Email: andrew.reynolds@icr.ac.uk
Jim C. Norman, Integrin Cell Biology Laboratory, Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Glasgow, G61 1BD, UK, Tel: +44(0)141 330 3953, Fax: +44(0)141 942 6521, Email: j.norman@beatson.gla.ac.uk
Gordon C. Tucker Institut de Recherches Servier (IdRS), Cancer Drug Discovery Division, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, France, Tel: +33(0)155722748, Fax: +33(0)155722810, Email: gordon.tucker@fr.netgrs.com
Kairbaan M. Hodivala-Dilke, The Adhesion and Angiogenesis Laboratory, Centre for Tumour Biology, Barts & The London School Of Medicine & Dentistry, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK, Tel: +44(0)207 014 0406, Fax: +44(0)207 014 0401, Email: Kairbaan.Hodivala-Dilke@cancer.org.uk

Angiogenesis is thought to be essential for the growth of tumors and inhibitors of angiogenesis can slow tumor growth in pre-clinical models. However, the translation of angiogenesis inhibitors to the clinic has not been straightforward. For example, although inhibitors of VEGF signaling (e.g. bevacizumab, sunitinib) have shown promising results in some cancer patients, inhibitors of integrins (e.g. cilengitide, vitaxin) have performed poorly. The reasons for these problems are largely unknown. We have recently investigated why integrin inhibitors may be ineffective as anti-cancer agents. Surprisingly, we observed that low (nanomolar) concentrations of integrin inhibitors actually can stimulate tumor growth and tumor angiogenesis *in vivo*. Further studies showed that the dose-response to these drugs is bell-shaped: integrin inhibitors stimulate angiogenesis at low doses and inhibit angiogenesis at high doses. By way of mechanism, we show that low doses of integrin inhibitors enhance angiogenesis by promoting endothelial cell migration. Growing evidence suggests that cell migration is dependent on the intracellular recycling of integrins and growth factor receptors. We found that low doses of integrin inhibitors promote the intracellular recycling of αvβ3-integrin and VEGF receptor 2 and that this is the mechanism through which integrin inhibitors promote endothelial cell migration and angiogenesis. This phenomenon could be clinically relevant, since circulating levels of integrin inhibitors fall to nanomolar concentrations hours after administration. We speculate that during this 'low dose window,' tumor angiogenesis could conceivably be stimulated in patients. These data provide insight into a novel form of therapy-resistance, which could seriously compromise the efficacy of integrin inhibitors in patients. Moreover, we discuss other angiogenesis inhibitors that exhibit bell-shaped or U-shaped dose-response curves and discuss the relevance of these phenomenon for cancer therapy.

TOXICOLOGY SESSION

SELENIUM, APOPTOSIS, AND DNA DAMAGE: DEFINING THE OPTIMAL SELENIUM DOSE FOR HUMAN PROSTATE CANCER PREVENTION

David J. Waters, Purdue University, West Lafayette, IN
Shuren Shen, The Gerald P. Murphy Cancer Foundation, West Lafayette, IN
Seema S. Kengeri, The Gerald P. Murphy Cancer Foundation, West Lafayette, IN
Emily C. Chiang, Purdue University Interdepartmental Nutrition Program; and The Gerald P. Murphy Cancer Foundation, West Lafayette, IN
Huiping Xu, Purdue University, Department of Statistics, West Lafayette, IN
Gerald F. Combs, Jr., Grand Forks Human Nutrition Research Center, USDA, ARS Grand Forks, ND
J. Steven Morris, University of Missouri-Columbia Research Reactor Center, Columbia, MO
David G. Bostwick, Bostwick Laboratories, Richmond, VA

PREDICTING LOW DOSE EFFECTS FOR CHEMICALS IN HIGH THROUGH-PUT STUDIES

Edward J. Stanek III, University of Massachusetts, Amherst, MA
Edward J. Calabrese, University of Massachusetts, Amherst, MA

HORMESIS AND RADIATION-INDUCED NEOPLASTIC TRANSFORMATION IN VITRO: THE ROLE OF RADIATION DOSE-RATE

J. Leslie Redpath, University of California Irvine, Irvine, CA

TRANSLATIONALLY CONTROLLED TUMOR PROTEIN (TCTP) PARTICIPATES IN THE PROTECTIVE EFFECTS OF LOW DOSE γ-RAYS

Jie Zhang, Department of Radiology, New Jersey Medical School Cancer Center, Newark, NJ; and Fourth Military Medical University, Xian, China
Sonia M. de Toledo, New Jersey Medical School Cancer Center, Newark, NJ
Guozheng Guo, Fourth Military Medical University, Xian, China
Edouard I. Azzam, New Jersey Medical School Cancer Center, Newark, NJ

SYSTEMS BIOLOGY AND NON-TARGETED EFFECTS OF RADIATION AND CHEMICALS – FROM THE GENE TO THE STREAM

Carmel Mothersill and Colin Seymour, McMaster University, ON, Canada

FEEDBACK/FEEDFORWARD HOMEOSTATIC CONTROL AND HORMESIS

Qiang Zhang, The Hamner Institutes for Health Sciences, Research Triangle Park, NC
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ON THE DEATH OF THRESHOLD

Janet E. Kester, PhD, DABT, NewFields, Wentzville, MO

SURVEY RESULTS FOR A HORMESIS KNOWLEDGE AND OPINION SURVEY ADMINISTERED TO RISK ASSESSMENT AND TOXICOLOGY PROFESSIONALS

Amy C. Jones, University of Massachusetts, Amherst, MA
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SELENIUM, APOPTOSIS, AND DNA DAMAGE: DEFINING THE OPTIMAL SELENIUM DOSE FOR HUMAN PROSTATE CANCER PREVENTION

David J. Waters, Purdue University, Department of Veterinary Clinical Sciences, Center on Aging and the Life Course; and The Gerald P. Murphy Cancer Foundation, West Lafayette, IN 47906 USA, Tel: 765-494-9271, Fax: 765-775-1006, Email: waters@purdue.edu
Shuren Shen, The Gerald P. Murphy Cancer Foundation, West Lafayette, IN, USA
Seema S. Kengeri, The Gerald P. Murphy Cancer Foundation, West Lafayette, IN, USA
Emily C. Chiang, Purdue University Interdepartmental Nutrition Program; and The Gerald P. Murphy Cancer Foundation, West Lafayette, IN, USA
Huiping Xu, Purdue University, Department of Statistics, West Lafayette, IN, USA
Gerald F. Combs, Jr. Grand Forks Human Nutrition Research Center, USDA, ARS Grand Forks, ND, USA
J. Steven Morris, University of Missouri-Columbia Research Reactor Center, Columbia, MO, USA
David G. Bostwick, Bostwick Laboratories, Richmond, VA, USA

Our work in dogs has revealed an intriguing U-shaped dose response between selenium (Se) status and prostatic DNA damage that remarkably parallels the relationship between dietary Se and prostate cancer risk in men, suggesting that more Se is not necessarily better. Herein, we extend this work to test the hypothesis that the Se dose that minimizes prostatic DNA damage upregulates apoptosis in prostatic epithelial cells. In a randomized feeding trial, 62 elderly beagle dogs (equivalent to 65 year-old men) received nutritionally adequate or supranutritional levels of Se for 7 months to mimic the range of dietary Se intake in U.S. men. Prostatic DNA damage (alkaline Comet assay) and apoptosis (TUNEL staining of formalin-fixed prostate tissues collected at necropsy) and Se status (neutron activation analysis of toenails) were measured. The extent of epithelial cell apoptosis was compared between dogs with low Se status (<.67 ppm in toenails, the level above which selenoenzymes like glutathione peroxidases are maximally expressed), moderate Se status (.67-.92 ppm), and high Se status (>.92 ppm, which exceeds one s.d. above the mean Se level of U.S. men). Dogs with moderate Se status were 84% less likely to have high prostatic DNA damage than dogs in the low Se group (OR, 95% CI = 0.16, 0.04-0.63); prostatic damage in the low and high Se groups was not significantly different. Apoptosis was higher in dogs with moderate Se status than in dogs with low Se (average of 2.6 versus 1.0 apoptotic cells/200X field, p=.025). Foci of intense apoptosis ("hot spots" with >30 apoptotic cells/200X field) were seen 4.1X (95% CI, 1.1-15.3) more often in the moderate Se group than in the low Se group. Moreover, this association strengthened (OR=5.3) in multivariate analysis including age, body weight change, serum testosterone, and sensitivity of PBLs to oxidative stress. Consistent with the concept of a U-shaped dose-response between Se intake and apoptosis, there was no significant difference between the frequency of apoptotic hot spots in the high and low Se groups. We conclude the dose range of .67-.92 ppm Se in toenails that minimizes prostatic DNA damage also maximizes prostatic epithelial cell apoptosis. These data support the notion that the triggering of apoptosis in prostatic cells by Se is an important determinant of the U-shaped dose-response between Se and DNA damage, and moves us closer to defining the optimal dose of Se for human prostate cancer prevention.

PREDICTING LOW DOSE EFFECTS FOR CHEMICALS IN HIGH THROUGH-PUT STUDIES

Edward J. Stanek III, University of Massachusetts, Division of Biostatistics and Epidemiology, 401 Arnold House, 715 N. Pleasant Street, Amherst, MA 01003, Tel: 413-545-3812, Fax: 413-545-1645, Email: stanek@schoolph.umass.edu
Edward J. Calabrese, University of Massachusetts, Environmental Health Sciences Division, Morrill I, N344, Amherst, MA 01003, Tel: 413-545-3164, Fax: 413-545-0964, Email: edwardc@schoolph.umass.edu

High through-put studies are commonly used to screen large numbers of chemicals, with typical analysis objectives aimed at identifying toxicity of a particular organism, such as yeast, e-coli, or tumor cell lines. The studies can be characterized by automated systems using 96-well plates in which multiple chemicals are tested at multiple doses using log-2 dose increments on a single plate after a suitable incubation period. There are typically few (ranging from five to eleven) doses on each chemical, and occasionally plate replications of the dose-response studies. Although the target endpoint for such studies is typically the LD50, for some chemicals, there may be multiple doses below a threshold where response falls below control response. We discuss how mixed models with random chemical effects can be used to predict average response for chemicals with doses below a specified bench mark dose. Using data from a high throughput study of 2189 chemicals on yeast, we describe the features of a stochastic model that includes a random effect for chemicals, and review how mixed model methods lead to best linear unbiased predictors (BLUPs) of chemical effects. Of particular relevance is interpretation of these effects, and their connection to realized chemicals. Although limited data are available for any individual chemical below the benchmark dose, we discuss how construction of multiple confidence intervals for response below the benchmark dose, along with a plot of expected response if there is no low-dose effect, can provide an informative summary of low dose response patterns. We conclude with a discussion of interpretation of such an analysis strategy, as well as the strengths and limitations of the approach.

HORMESIS AND RADIATION-INDUCED NEOPLASTIC TRANSFORMATION IN VITRO: THE ROLE OF RADIATION DOSE-RATE

J. Leslie Redpath, Department of Radiation Oncology, University of California Irvine, Irvine, CA, 92697, Tel: 949-824-7395, Fax: 949-824-3566, Email: jlredpat@uci.edu

Low doses (< 10 to 20 cGy) of low-LET radiation delivered at high dose-rate have been consistently shown to suppress the frequency of neoplastic transformation in vitro to levels below those seen spontaneously. When such radiation is delivered at low dose-rates suppressive effects have been demonstrated out to doses as high as 100 cGy. Furthermore, these cells that have been adapted to a low dose-rate environment are more resistant to a high challenge dose (e.g. 3 Gy). These observations will be discussed in terms of mechanistic aspects as well as be compared to data on cancer induction at low dose-rates from the in vivo and epidemiologic literature.

TRANSLATIONALLY CONTROLLED TUMOR PROTEIN (TCTP) PARTICIPATES IN THE PROTECTIVE EFFECTS OF LOW DOSE Γ-RAYS

Jie Zhang, Department of Radiology, UMDNJ-New Jersey Medical School Cancer Center, Newark, NJ 07103, and Department of Radiation Medicine, Fourth Military Medical University, Xian, P. R. China, Email: zhangjie78@gmail.com
Sonia M. de Toledo, Department of Radiology, UMDNJ-New Jersey Medical School Cancer Center, Newark, NJ 07103, Email: detolesm@umdnj.edu
Guozheng Guo, Department of Radiation Medicine, Fourth Military Medical University, Xian, P. R. China, Email: guozhen@fmmu.edu.cn
Edouard I. Azzam, Department of Radiology, UMDNJ-New Jersey Medical School Cancer Center, Newark, NJ 07103, Tel: 973-972 5323, Fax: 973-972 6474, Email: azzamei@umdnj.edu

We have previously shown that exposure to low dose γ-rays induces significant adaptive responses in normal human and rodent cells. Exposure to doses in the range of 0.1 to 10 cGy delivered at low dose rates reduced micronucleus frequency to levels similar or lower than occurs spontaneously in normal human fibroblasts, and reduced the frequency of neoplastic transformation by 3- to 4-fold from the spontaneous level in mouse embryo fibroblasts. Thus, a single low dose of low linear energy transfer radiation, in the background, occupational or diagnostic dose range, can induce biological processes, which reduce, rather than increase, detrimental effects. To gain deeper insight into the mechanisms underlying low dose radiation effects, we used amine-specific isobaric tags for relative and absolute quantitation (iTRAQ)-based approach to identify induced proteolytic events. The Translationally Controlled Tumor Protein (TCTP) was significantly up-regulated after 10cGy exposure, but not after 400 cGy in several normal human fibroblast strains. TCTP is a highly conserved protein that is abundantly expressed in many eukaryotes. Whereas low dose radiation stabilized TCTP, high doses enhanced its degradation. TCTP levels were increased by 3-fold in proteins extracted from whole cells that were exposed to 1 cGy. Cell fractionation studies showed that in nuclei, TCTP is increased by 9.5-folds. Strikingly, knockdown of TCTP expression by siRNA approach abolished the low dose γ-ray-induced adaptive responses against chromosomal damage, and suggested a role for TCTP in DNA repair and regulation of the radiation-induced G_1 checkpoint. In low dose-exposed si-*tpt1/*TCTP cells, knockdown of TCTP expression was associated with significant decrease in p53. In contrast, in high dose-irradiated cell cultures, down-regulation of TCTP did not interfere with repair of chromosomal damage or p53 expression. We show that regulation of TCTP by low dose γ-rays is ATM- and DNA-PK-dependent, but p53-independent. (*Supported by Grant DE-FG02-07ER64344 from the U.S. Department of Energy, Low Dose Radiation Research Program*)

SYSTEMS BIOLOGY AND NON-TARGETED EFFECTS OF RADIATION AND CHEMICALS – FROM THE GENE TO THE STREAM

Carmel Mothersill and Colin Seymour, McMaster University, Hamilton, Ontario, Canada

This paper will consider the implications for environmental health and sustainability of new developments in radiobiology and ecotoxicology. Specifically it will discuss how the newly appreciated non-targeted effects of low doses of radiation, not only mirror similar effects from low doses of chemical stressors but may actually lead to unpredictable emergent effects at higher hierarchical levels. The position is argued that non-targeted effects are mechanistically important in coordinating phased hierarchical transitions. The field of multiple stressors (both radiation and chemical) is highly complex. By definition, particulate radiation is always a multiple stressor. Agents can interact in an additive, antagonist or synergistic manner. The outcome following low dose multiple stressor exposure also is impacted by the context in which the stressors are received, perceived or communicated by the organism or tissue. Modern biology has given us very sensitive tools to examine change following stressor interaction with biological systems at several levels of organization but the effect-harm-risk relationship remains difficult to resolve. Since multiple stressor exposure is the norm in the environment, it is essential to move away from single stressor based protection and to develop tools, including legal instruments, which will enable us to use response based risk assessment. Radiation protection in the context of multiple stressors includes consideration of humans and non-humans as separate groups requiring separate assessment frameworks. This is because for humans, individual survival and prevention of cancer are paramount but for animals, it is considered sufficient to protect populations and cancer is not of concern. The need to revisit this position is discussed not only from the environmental perspective but also from the human health perspective because the importance of "pollution" (a generic term for multiple environmental stressors) as a cause of non-cancer disease is increasingly being recognized. Finally a way forward involving experimental assessment of biomarker performance to lead to a theoretical framework allowing modeling is suggested.

FEEDBACK/FEEDFORWARD HOMEOSTATIC CONTROL AND HORMESIS

Qiang Zhang, The Hamner Institutes for Health Sciences, Division of Computational Biology, 6 Davis Dr., Research Triangle Park, NC, 27709-2137, Tel: 919-558-1337, Fax: 919-558-1300, Email: qzhang@thehamner.org
Jingbo Pi, The Hamner Institutes for Health Sciences, Division of Translational Biology, 6 Davis Dr., Research Triangle Park, NC, 27709-2137, Tel: 919-558-1395, Fax: 919-558-1300, Email: jpi@thehamner.org
Courtney G. Woods, The Hamner Institutes for Health Sciences, Division of Computational Biology, 6 Davis Dr., Research Triangle Park, NC, 27709-2137, Tel: 919-558-1337, Fax: 919-558-1300, Email: cwoods@thehamner.org
Melvin E. Andersen, The Hamner Institutes for Health Sciences, Division of Computational Biology, 6 Davis Dr., Research Triangle Park, NC, 27709-2137, Tel: 919-558-1205, Fax: 919-558-1300, Email: mandersen@thehamner.org

Hormesis represents a significant set of nonmonotonic dose response behaviors observed in biological systems exposed to external stressors. One generic mechanism for hormesis is believed to arise as a consequence of overcompensation by adaptive, homeostatic mechanisms operating in biological systems. For hormesis to gain widespread support, it is crucially important to convert this verbal argument into a defensible formalism, by understanding (1) the molecular and cellular networks that underlie adaptation and homeostasis at all levels of biological organizations, and (2) the manner in which these pathways may overcorrect at low stressor doses, resulting in hormesis. Our work has focused on negative feedback and feedforward control circuits, which are network structures usually found in biological systems for homeostatic operation in the face of perturbations. Our theoretical analyses and computer simulations indicate that although the steady-state dose response mediated by negative feedback control is inherently nonlinear, steady-state hormesis does not arise from such a control scheme. Negative feedback does generate conditioning hormesis, where initial low doses reduce the response to the subsequent large stressor doses. More importantly, feedforward control does create steady-state hormesis, and it is also capable of producing conditioning hormesis. The role of ultrasensitive signaling motifs in these circuits is discussed. Our analyses emphasize that one important focus of hormesis research should be examining cellular and molecular circuits that form potential feedforward homeostatic controls in biological systems.

ON THE DEATH OF THRESHOLD

Janet E. Kester, PhD, DABT, NewFields, 155 Cedar Lake Drive, Wentzville, MO 63385, Tel: 636-327-3776, Email: jkester@newfields.com

First set forth in the 1983 "Red Book," the four basic steps of health risk assessment – hazard identification, dose-response assessment (together composing "toxicity assessment"), exposure assessment, and risk characterization – have been retained in all elaborations of the process to date. Central to the risk assessment paradigm, as to toxicology itself, is the dose-response relationship. A peculiarity of toxicity assessment, especially in the U.S., has been an artificial distinction between the dose-response characteristics of cancer vs. non-cancer endpoints. That is, in the absence of specific information to the contrary, carcinogenic effects have been assumed to exhibit (1) no threshold, and (2) low-dose linearity, while adverse non-carcinogenic effects have been assumed to occur only at doses greater than a threshold. For carcinogens, population risk has been quantified as the product of estimated dose and a cancer potency of slope factor derived from a modeled low dose-response curve (in units of incremental cancer risk per unit dose). The absence of a threshold for carcinogenic effects has fostered the notion that "there is no safe dose for carcinogens." The risk of non-carcinogenic effects has been quantified as the non-probabilistic hazard quotient – ratio of estimated dose to a reference dose "likely to be without appreciable risk of deleterious effects." These fundamental differences in dose-response assumptions are reflected not only in the disparate toxicity criteria and risk characterization methods developed for carcinogenic and non-carcinogenic effects, but also in the imbalance in perceived health significance and societal resources accorded to them. Tremendous advances in comprehension of biological mechanisms since the 1980s have enabled greater definition of dose-response relationships, including the rediscovery of hormesis, and support commensurate evolution of toxicity and risk assessment. This talk surveys recent international efforts to harmonize cancer and non-cancer dose-response assessment, and questions whether rumors regarding the death of threshold are exaggerated.

SURVEY RESULTS FOR A HORMESIS KNOWLEDGE AND OPINION SURVEY ADMINISTERED TO RISK ASSESSMENT AND TOXICOLOGY PROFESSIONALS

Amy C. Jones, University of Massachusetts, Environmental Health Science, N233 Morrill Science Center, 639 N. N. Pleasant Street, Amherst, Massachusetts 01003, Tel: 301-758-0547, Fax: 301-548-2235, Email: amyn@schoolph.umass.edu
Douglas L. Anderton, University of Massachusetts, Social and Demographic Research Institute, W34A Machmer Hall, 240 Hicks Way 01003, Tel: 413-545-5973, Fax: 413-545-0746, Email: dla@umass.edu
Edward J. Stanek, University of Massachusetts, School of Public Health Biostatistics, 408 Arnold House, 745 N. Pleasant Street, Amherst, Massachusetts 01003, Tel: 413-545-3812, Email: stanek@schoolph.umass.edu
Edward J. Calabrese, University of Massachusetts, Environmental Health Science, N233 Morrill Science Center, 639 N. Pleasant Street, Amherst, Massachusetts 01003, Tel: 413-545-3164 Email: edwardc@schoolph.umass.edu

Background: Studies and review articles on the topic of hormesis are being published at an increasing rate by researchers from a variety of disciplines. Due to this increased publication interest in hormesis, we conducted an opinion survey to assess knowledge and attitudes about the dose response. Specific research objectives were to 1) evaluate the respondent's general knowledge about dose response models, including hormesis, 2) determine the characteristics of people who would, if allowed by the regulatory framework, take hormesis into account when designing or interpreting risk assessments, and 3) compare characteristics of those who would consider hormesis to those who would not by identifying variables affecting acceptance/rejection.

Methods: The survey consisted of 44 questions covering basic demographics, knowledge and attitudes about dose response, including hormesis, and knowledge and attitudes about risk assessment. The survey was pre-tested and pilot tested by 25 esteemed toxicologists and risk assessors representing diverse backgrounds and distributed via email to 9,500 potential respondents, all of whom were a member of either the Society of Toxicology or the Society for Risk Analysis.

Results: The survey had a response rate of 17% (n= 1,197) and a completion rate of 73%. The results of detailed analysis identified the characteristics of those who would employ hormesis in a risk assessment and those who would not. In general, respondents were evenly divided as to whether sufficient data exists to suggest hormesis occurs in a wide range of species and chemicals. The only demographic characteristic that distinguished respondents on this question was gender. Males were slightly more likely than females to accept hormesis broadly across all species and stressors. Several questions asked about the use of hormesis in Risk Assessment. Overall, respondents were open to hormesis as a scientific concept that should be applied to risk assessment. Over 60% thought risk assessment should be modified to obtain potential benefits associated with hormesis and 65% thought hormesis justifies a change in hazard assessment protocols.