Welcome from the Chair of the Local Organizing Committee for the Canadian Oxidative Stress Consortium

On behalf of the Local Organizing Committee (LOC), I am honoured to welcome you to Ottawa for the 8th Meeting of the Canadian Oxidative Stress Consortium (COSC) held at Carleton University June 11th to 13th, 2014.

The LOC and Executive Committee for the COSC has put together an outstanding scientific program that brings together today's leading Canadian researchers in the field of oxidative stress. The Ottawa COSC 2014 Meeting has four symposia: 1) Oxidative Stress and Aging, 2) Oxidative Stress and Cardiovascular Disease, 3) Oxidative Stress and Neurodegeneration and 4) Oxidative Stress, the Environment and Health and Nutrition. As well, the Meeting will have a Graduate Trainee Symposium/Competition and Postdoctoral Trainee Symposium organized from the submitted abstracts. There will be poster sessions and travel awards presented at the Meeting Banquet. Commercial exhibits and workshops will be an integral part of our conference. The conference will be held at the newly built River Building overlooking the Rideau River with a large outdoor terrace.

We look forward to you joining us for a meeting filled with opportunities for discussion and rich scientific exchange. In addition, we hope that you will take the opportunity to experience Canada's beautiful capital city where one can visit the downtown area and Byward Market, the historic Parliament Hill, the National Arts Centre, twelve national museums, the Experimental Farm and restaurants in Ottawa and Hull (Gatineau). As well, there are canal tours, bicycling and strolling along the Rideau Canal.

I personally look forward to meeting you all at COSC 2014 in June.

Sincerely,

Bill Willmore

Bill Willmore
COSC 2014 Meeting LOC Chair

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Program at a Glance

Day 1	Wednesday, June 11, 2014	Location (All Events are in the River Building)	Session
8:00 AM	On-Site Registration	Atrium	
8:30 AM	Opening Remarks	Theatre 2200	
8:40 AM	Symposium I	Theatre 2200	Oxidative Stress and Aging **Sponsored by CIHR Institute of Aging**
10:00 AM	Coffee & Tea Break	Atrium	
10:30 AM	Symposium I	Theatre 2200	Oxidative Stress and Aging *(continues)* **Sponsored by CIHR Institute of Aging**
11:50 AM	Lunch/ Exhibitors/Open Poster viewing I	Atrium & Conf. Room	
2:00 PM	Keynote Lecture	Theatre 2200	**Seigfried Hekimi**
3:00 PM	Symposium II	Theatre 2200	Oxidative Stress and Cardiovascular Disease
4:20 PM	Coffee & Tea Break	Atrium & Conf. Room	
4:50 PM	Symposium II	Theatre 2200	Oxidative Stress and Cardiovascular Disease *(continues)*
6:30 PM	Reception	Atrium	Cash Bar
Day 2	**Thursday, June 12, 2014**	**Location**	**Session**
8:00 AM	Opening Remarks	Theatre 2200	
8:30 AM	Symposium III	Theatre 2200	Graduate Student Trainees
9:45 AM	Coffee & Tea Break	Atrium & Conf. Room	
10:15 AM	Symposium IV	Theatre 2200	Postdoctoral Fellow Trainees
11:45 PM	Lunch/ Exhibitors/Open Poster viewing II	Atrium & Conf. Room	
1:30 PM	Keynote Lecture	Theatre 2200	**Rafael Radi** **Sponsored by the Society of Free Radical Biology & Medicine**
2:30 PM	Symposium V	Theatre 2200	Oxidative Stress, the Environment & Health &Nutrition (Session 1)
3:50 PM	Coffee & Tea Break	Atrium & Conf. Room	
4:20 PM	Symposium V	Theatre 2200	Oxidative Stress, the Environment & Health & Nutrition (Session 1) *(continues)*
7:15 PM	Banquet	Hellenic Centre	1315 Prince of Wales Drive Ottawa, Ontario, K2C 1N2 **(Bus leaving from Carleton University at 7:00 PM)** **Please arrive 15 minutes before departure time**
Day 3	**Friday, June 13, 2014**	**Location**	**Session**
8:00 AM	Opening Remarks	Theatre 2200	
8:30 AM	Symposium VI	Theatre 2200	Oxidative Stress and Neurodegeneration **Sponsored by CIHR Institute of Neurosciences, Mental Health and Addiction**
9:30 AM	Coffee & Tea Break	Atrium	
10:00 AM	Symposium VI	Theatre 2200	Oxidative Stress and Neurodegeneration *(continues)* **Sponsored by CIHR Institute of Neurosciences, Mental Health and Addiction**
11:00 AM	Keynote Lecture	Theatre 2200	**Richard Schulz**
12:00 PM	Lunch	Atrium	
	COSC Executive Meeting	Boardroom 2211	
1:00 PM	Symposium VII	Theatre 2200	Oxidative Stress, the Environment & Health & Nutrition (Session 2)
3:00 PM	Coffee & Tea Break	Atrium	
3:30 PM	Symposium VII	Theatre 2200	Oxidative Stress, the Environment & Health & Nutrition (Session 2) *(continues)*
4:50 PM	End of COSC 8th Meeting	Theatre 2200	Closing Remarks/Conference Evaluation/Wrap-Up

Canadian Oxidative Stress Consortium
Executive Committee

Dr. Richard Austin
McMaster University
Department of Medicine
RAUSTIN@thrombosis.hhscr.org

Dr. Diana Averill-Bates
Université du Québec à Montréal
Departmente du Sciences biologiques
averill.diana@uqam.ca

Dr. Brian Hasinoff
University of Manitoba
Department of Medicinal Chemistry
B_Hasinoff@UManitoba.ca

Dr. Neelam Khaper
Lakehead University
Department of Chemistry
nkhaper@nosm.ca

Dr. Peter O'Brien
University of Toronto
Graduate Department of Pharmaceutical Sciences
peter.obrien@utoronto.ca

Dr. Richard Schulz
University of Alberta
Departments of Paediatrics and Pharmacology
rschulz@ualberta.ca

Dr. Pawan Singal
St. Boniface Hospital Research Centre
University of Manitoba
Institute of Cardiovascular Sciences
psingal@sbrc.ca

Dr. Arno Siraki
University of Alberta
Department of Pharmacy & Pharmaceutical Sciences
siraki@ualberta.ca

Dr. William Willmore
Carleton University
Department of Biochemistry
Bill_Willmore@carleton.ca

COSC 8th Meeting
Local Organizing Committee

Dr. William Willmore
Chair of 8th Meeting of COSC
Carleton University
Department of Biochemistry
Bill_Willmore@carleton.ca

Dr. Steffany Bennett
University of Ottawa
Department of Biochemistry, Microbiology, and Immunology
sbennet@Uottawa.ca

Dr. Mary-Ellen Harper
University of Ottawa
Department of Biochemistry, Microbiology and Immunology
mharper@uottawa.ca

Dr. Chet Holterman
Ottawa Hospital Research Institute
Kidney Research Centre
cholterm@uottawa.ca

Dr. Farah Hosseinian
Carleton University
Department of Chemistry
farah.hosseinian@carleton.ca

Dr. Xiaolei (Dawn) Jin
Toxicology Research Division, Health Products and Food Bureau, Health Canada
Dawn_Jin@hc-sc.gc.ca

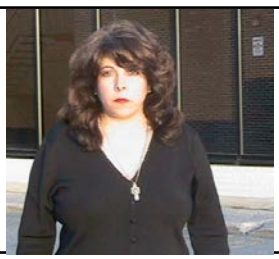
Dr. Prem Kumarathasan
Environmental and Occupational Toxicology Division,
Environmental Health Directorate,
Health Canada
Premkumari.Kumarathasan@hc-sc.gc.ca

Dr. Derek A. Pratt
University of Ottawa
Department of Chemistry,
dpratt@uOttawa.ca

Dr. Apollinaire Tsopmo
Carleton University
Department of Chemistry
Apollinaire.Tsopmo@carleton.ca

Dr. Renaud Vincent
Health Canada
Renaud.Vincent@hc-sc.gc.ca

COSC Conference Organizer
Mrs. Wafaa H. Antonious
c/o Rofail Conference and Management Services
17 Dossetter Way
Ottawa, ON K1G 4S3 Canada
Tel: (613) 421-7229 **Fax:** (613) 421-9811
Email: cosc2014@carleton.ca



Carleton UNIVERSITY CAMPUS MAP

River Building (RB)
All COSC 8th Meeting Events will take place in the River Building

Frontenac House (FR)
Delegates residence

Leeds House (LE)
Delegates residence

Parking lot 9 (P_9)
(Levels 2 & 3)

- Hourly rate: $3.50
- Daily rate: $13.00

Wireless Code
(Select CU Wireless)

Username: wirelessguest
Password: Ravens.2014

Exhibitors

Please visit our exhibits

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Workshop

Luoxis is an in-vitro diagnostics company focused on the development and global commercialization of **RedoxSYS™**. This novel, diagnostic platform is comprised of a first-in-class, point-of-care device and disposable, testing strips that together measure the presence of oxidative stress and antioxidant reserves. **RedoxSYS™** is the only in-vitro diagnostic platform that measures human **Oxidation-Reduction Potential (ORP)**, an important, complete measure of oxidative stress that is implicated in both critical and chronic illnesses. As demonstrated over decades in multiple, peer-reviewed publications. ORP is an important marker in the assessment of patient morbidity across a wide range of diseases and conditions. There are numerous clinical applications for this oxidative stress marker for which there is no currently available diagnostic test. Visit them at **luoxis.com**.

8th Meeting of the COSC 2014
Scientific Program

Wednesday – June 11, 2014 **All Events are located in the River Building**

8:00 – 8:20 AM **Theatre Atrium**	**On-Site Registration**
8:20 – 8:40 AM **Theatre 2200**	**Opening Ceremonies and Welcome** *By: Dr. William Willmore, Carleton University, Ottawa, ON*
8:40 – 10:00 AM **Theatre 2200**	**SYMPOSIUM I: Oxidative Stress and Aging** **Sponsored by CIHR Institute of Aging** ***Chairs:*** William Willmore and Rania Agil, Carleton University **8:40 – 9:00 AM** **Redox activities of flavonoids at the membrane interface: Implications for mitochondrial oxidative stress** Brian Bandy, University of Saskatchewan, Saskatoon, SK **9:00 – 9:20 AM** **Mitochondrial H_2O_2 signalling involving heme transfer between proteins** Ann English, Concordia University, Montréal, QC **9:20 – 9:40 AM** **Increased DNA double strand break repair as a consequence of exposure to oxidative stress** Louise Winn, Queen's University, Kingston, ON **9:40 – 10:00 AM** **Oxidative stress in oncodynamics**
10:00 – 10:30 AM **Atrium**	*Coffee and Tea Break*
10:30 – 11:50 AM **Theatre 2200**	**10:30 – 10:50 AM** **Testing the sulfhydration of peptides and proteins with sulphide** Bulent Mutus, University of Windsor, Windsor, ON **10:50 – 11:10 AM** **The role of ROS in autophagy in cancer** Spencer Gibson, University of Manitoba, Winnipeg, MB **11:10 – 11:30 AM** **The impact of vitamin C on the premature aging disorder Werner syndrome** Michel Lebel, Université Laval, Québec City, QC **11:30 – 11:50 AM** **Cancer cells exploit hypoxia-activated eIF4E2-directed protein synthesis to drive tumor progression** **New Investigator:** Jim Uniacke, University of Guelph, Guelph, ON

11:50 AM – 2:00 PM **Atrium & Conf. Room**	**Lunch/ Exhibits/ Open Poster Viewing I**
2:00 – 3:00 PM **Theatre 2200**	**Keynote Lecture** *Chair*: William Willmore, Carleton University **Pro-longevity mitochondrial ROS signaling** **Seigfried Hekimi**, McGill University, Montréal, QC
3:00 – 4:20 PM **Theatre 2200**	**SYMPOSIUM II: Oxidative Stress and Cardiovascular Disease** ***Chairs:*** William Willmore, Carleton University and Xiaolei (Dawn) Jin, Health Canada **3:00 – 3:20 PM** **TDAG51 as a modulator of oxidative stress in atherosclerosis** Richard Austin, McMaster University, Hamilton, ON **3:20 – 3:40 PM** **Oxidative stress and cytokines in heart failure** Pawan Singal, St-Boniface Hospital Research, Winnipeg, MB **3:40 – 4:00 PM** **Complex stabilization and destabilization of cytokines mRNA by NADPH oxidase production of O_2^-** Sheldon Magder, McGill University, Montréal, QC **4:00 – 4:20 PM** **Distinct roles high and low molecular weight FGF-2 in heart pathology; an overview** Elissavet Kardami, University of Manitoba, Winnipeg, MB
4:20 – 4:50 AM **Atrium & Conf. Room**	*Coffee and Tea Break*
4:50 – 6:30 PM **Theatre 2200**	**4:50 – 5:10 PM** **Differential influence of fatty acids on ischemic reperfusion injury in cardiomyocytes** Grant Pierce, St-Boniface Hospital Research, Winnipeg, MB **5:10 – 5:30 PM** **Changes in *Drosophila* mito proteome during aging and following chaperone-mediated lifespan extension** Robert Tanguay, Université Laval, Québec City, QC **5:30 – 5:50 PM** **Examining the interaction between Nox5 and the AngII/AT1R pathway in podocytes** Chet Holterman, Ottawa Hospital Research Institute, Ottawa, ON **5:50 – 6:10 PM** **Altered mitochondrial bioenergetics and cellular redox conditions link high fat diets to the etiology of skeletal muscle insulin resistance** **New Investigator:** Christopher Perry, York University, Toronto, ON **6:10 – 6:30 PM** **S-Glutathionylation reactions are essential for the control of mitochondrial function** **New Investigator:** Ryan Mailloux, Carleton University, Ottawa ON
6:30 – 8:00 PM **Atrium**	*Reception* (**Cash Bar**)

Thursday – June 12, 2014

All Events are located in the River Building

8:00 – 8:30 AM **Theatre 2200**	**Opening Remarks** *By: Dr. William Willmore, Carleton University, Ottawa, ON*
8:30 – 9:45 AM **Theatre 2200**	**SYMPOSIUM III: Graduate Student Trainees** ***Chairs:*** William Willmore, Carleton University and Steffany Bennett, University of Ottawa **8:30 – 8:45 AM** **Lipid peroxidation-linked mitochondrial facets of neuronal aging in an invertebrate model of normal aging** Jonathon Lee, University of Calgary, Calgary, AB **8:45 – 9:00 AM** **Protection by ascorbate and catechin against myocardial ischemia-reperfusion injury in an isolated rat heart model** Ahmed Abou Hadeed, University of Saskatchewan, Saskatoon, SK **9:00 – 9:15 AM** **Free radical trapping agents as adjunct therapy to antipsychotic drugs for the treatment of schizophrenia** Ritesh Daya, McMaster University, Hamilton, ON **9:15 – 9:30 AM** **Enzyme-specific inhibition of recombinant human glutathione transferases by naphthalene analogues of 1-chloro-2,4-dinitrobenzene** Hilary Groom, University of Guelph, Guelph, ON **9:30 – 9:45 AM** **Possible role for superoxide dismutase in phenylbutazone cytotoxicity in HT-29 colorectal cancer cells** Naif Aljuhani, University of Alberta, Edmonton, AB
9:45 – 10:15 AM **Atrium & Conf. Room**	*Coffee and Tea Break*

10:15 – 11:45 AM **Theatre 2200**	**SYMPOSIUM IV: Postdoctoral Fellow Trainees** ***Chairs:*** William Willmore, Carleton University and Steffany Bennett, University of Ottawa **10:15 – 10:30 AM** **Differential role of toll-like receptors in the elicitation of cardiac innate response to IL-10** Ashim Bagchi, St-Boniface Hospital Research, Winnipeg, MB **10:30 – 10:45 AM** **FGF-2 isoforms and doxorubicin-induced cardiac dysfunction** Navid Koleini, St-Boniface Hospital Research, Winnipeg, MB **10:45 – 11:00 AM** **A comparison of transient transfection methods to enhance eNOS expression in human endothelial progenitor cells (EPCs)** Maria Florian, Ottawa Hospital Research Institute, Ottawa, ON **11:00 – 11:15 AM** **Systemic oxidative stress induction leads to brain edema in hyperammonemic portacaval-shunted rats** Cristina Bosoi, CRCHUM, Montreal University, Montréal, QC **11:15 – 11:30 AM** **Effects of caloric and non-caloric soft drink intake on consumption of nutrients and lipoperoxidation in rats fed the cafeteria diet** Martine Hagen, Universidade Federal do Rio Grande do Sul and Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil **11:30 – 11:45 AM** **Skeletal Muscle Mitochondrial Respiration and ROS production is Increased in Obese Diet Sensitive Compared to Obese Diet Resistant Women** Brianne Thrush, University of Ottawa, Ottawa, ON
11:45 AM – 1:30 PM **Atrium & Conf. Room**	**Lunch/ Exhibits/ Open Poster Viewing II**
1:30 – 2:30 PM **Theatre 2200**	**Keynote Lecture** *Chair*: William Willmore, Carleton University ***Sponsored by the Society of Free Radical Biology and Medicine*** **Nitroxidative stress: molecular mechanisms and biological consequences** **Rafael Radi**, Universidad de la República, Montevideo, PA Uruguay

2:30 – 3:50 PM **Theatre 2200**	**SYMPOSIUM V: Oxidative Stress, the Environment and Health and Nutrition (Session 1)** ***Chairs:*** Farah Hosseinian and Shana Cameron, Carleton University **2:30 – 2:50 PM** **Bioactive dietary fibre and phenolics in flaxseed are carriers of antioxidants- an essential physiological function in oxidative stress** Farah Hosseinian, Carleton University, Ottawa, ON **2:50 – 3:10 PM** **Ascorbylperoxide generated in parenteral nutrition induces oxidative stress and loss of alveoli in the lung of newborn guinea pig, a characteristic of human bronchopulmonary dysplasia** Jean-Claude Lavoie, Université de Montréal, Montréal, QC **3:10 – 3:30 PM** **RedoxSYS™ Diagnostic Systems: The first and only clinical test to provide a complete measure of redox in a biological system.** Alessandro Orlando, MPH Clinical Research Epidemiologist **3:30 – 3:50 PM** **Induction of ER stress and apoptosis by acrolein, a lipid peroxidation-derived aldehyde** Diana Averill-Bates, Université du Québec à Montréal, Montréal, QC
3:50 – 4:20 PM **Atrium & Conf. Room**	*Coffee and Tea Break*
4:20 – 6:00 PM **Theatre 2200**	**4:20 – 4:40 PM** **Bioactive molecules in oat and their relation to oxidative stress** Apollinaire Tsopmo, Carleton University, Ottawa, ON **4:40 – 5:00 PM** **Understanding oxidative stress in pregnancy** Sandeep Raha, McMaster University, Hamilton, ON **5:00 – 5:20 PM** **Teratogens induce oxidative and embryonic stress responses in the organogenesis-stage embryo** Barbara Hales, McGill University, Montréal, QC **5:20 – 5:40 PM** **NADPH-oxidase dependent mechanisms that determine the fate of the innate immune response to respiratory viruses** Nathalie Grandvaux, Université de Montréal, Montréal, QC **5:40 – 6:00 PM** **Oxidative stress and the marine environment - "radical" management** Kenneth Storey, Carleton University, Ottawa ON
7:15 – 11:00 PM **In front of River Building**	**Banquet: Hellenic Centre** ***(Bus leaving from Carleton University at 7:00 PM)*** **Please arrive 15 minutes before departure time**

Friday – June 13, 2014

All Events are located in the River Building

8:00 – 8:30 AM **Theatre 2200**	**Opening Remarks** *By: Dr. William Willmore, Carleton University, Ottawa, ON*
8:30 – 9:30 AM **Theatre 2200**	**SYMPOSIUM VI: Oxidative Stress and Neurodegeneration** **Sponsored by CIHR Institute of Neurosciences, Mental Health and Addiction** ***Chairs:*** Steffany Bennett, University of Ottawa and Yichen Du, Carleton University **8:30 – 8:50 AM** **Anti-psychotic drug induced oxidative stress involves translocation of apoptosis inducing factor** Ram Mishra, McMaster University, Hamilton, ON **8:50 – 9:10 AM** **The role of oxidative stress in the pathogenesis of hepatic encephalopathy** Christopher Rose, Université de Montréal, Montréal, QC **9:10 – 9:30 AM** **Embryonic and fetal reactive oxygen species formation, oxidative DNA damage and repair and nuclear factor-E2-related factor 2 (Nrf2) in teratogenesis and postnatal neurodevelopmental deficits** Peter Wells, University of Toronto, Toronto, ON
9:30 – 10:00 AM **Atrium**	*Coffee and Tea Break*
10:00 – 11:00 AM **Theatre 2200**	**10:00 – 10:20 AM** **Mechanisms of natural products antioxidants: a case study with garlic-derived organosulfur compounds** Derek Pratt, University of Ottawa, Ottawa, ON **10:20 – 10:40 AM** ***Lymnaea stagnalis*: a platform for system-wide investigations of neuronal aging and age-associated memory impairment – lipid peroxidation and PLA2 activation as instruments of age-associated memory impairment** Willem Wildering, University of Calgary Calgary, AB **10:40 – 11:00 AM** **NO-problem, Oxidative stress in a stem cell model of Parkinson's Disease** **New Investigator:** Scott Ryan, University of Guelph, Guelph, ON

<table>
<tr><td>11:00 AM – 12:00 PM
Theatre 2200</td><td colspan="2">Keynote Lecture
Chair: William Willmore, Carleton University
Why inhibitors of matrix metalloproteinase-2 (MMP-2) are next generation drugs to treat diseases of oxidative stress injury
Richard Schulz, University of Alberta, Edmonton, AB</td></tr>
<tr><td>12:00 – 1:00 PM</td><td>Lunch
River Building Atrium</td><td>COSC Executive Meeting
River Building Boardroom 2211</td></tr>
<tr><td>1:00 – 3:00 PM
Theatre 2200</td><td colspan="2">SYMPOSIUM VII: Oxidative Stress, the Environment and Health and Nutrition (Session 2)
Chairs: Derek Pratt, University of Ottawa and Magdalena Bugno, Carleton University

1:00 – 1:20 PM
The transcription factor Nrf3 (NFE2L3): role in detoxification and cancer
Volker Blank, McGill University, Montréal, QC

1:20 – 1:40 PM
Impact of air pollutant exposure on oxidative stress and endothelial dysfunction
Premkumari Kumarathasan, Health Canada, Ottawa, ON

1:40 – 2:00 PM
Novel interventions in the resuscitation of asphyxiated neonates: combating oxidative stress
Po-Yin Cheung, University of Alberta, Edmonton, AB

2:00 – 2:20 PM
Proteomic changes in response to arylamine free radical formation in HL-60 cells
Arno Siraki, University of Alberta, Edmonton, AB

2:20 – 2:50 PM
Oxidative stress in sepsis: necessary or Injurious?
Alison Fox-Robichaud, McMaster University, Hamilton ON

2:50 – 3:00 PM
Glutathione-dependent metabolism of xenobiotics
David Josephy, University of Guelph, Guelph, ON</td></tr>
</table>

3:00 – 3:30 PM **Atrium & Conf. Room**	*Coffee and Tea Break*
3:30 – 4:50 PM **Theatre 2200**	**SYMPOSIUM VII: Oxidative Stress, the Environment and Health and Nutrition (Session 2)** ***(continues)*** ***Chairs:*** Derek Pratt, University of Ottawa and Magdalena Bugno, Carleton University **3:30 – 3:50 PM** **Iron and complementary feeding of breast-fed infants** James Friel, University of Manitoba, Winnipeg, MB **3:50 – 4:10 PM** **Redox balance and non-alcoholic fatty liver disease and non-alcoholic steatohepatitis** Xiaolei (Dawn) Jin, Health Canada, Ottawa, ON **4:10 – 4:30 PM** **Tyrosine nitration in membranes: role of lipid-derived radicals and modulatory action of tocopherols** Silvina Bartesaghi, Facultad de Medicina-Uruguay, Montevideo, Uruguay **4:30 – 4:50 PM** **Toxicogenomics analysis of the potent carcinogen dibenzo[def,p]chrysene (DBC) provides mechanistic and quantitative insights into its immunotoxicity** **New Investigator:** Nikolai Chepelev, Health Canada, Ottawa, ON
4:50 – 5:00 PM	**Closing Remarks** **Conference Evaluation** **Wrap-Up** *Thank you for joining us!*

Keynote Lecture:

Dr. Seigfried Hekimi, McGill University Montréal, QC

Wednesday, June 11, 2014 @ 2:00 PM

Siegfried Hekimi was born in Zürich and obtained his undergraduate degree in Biology at the University of Geneva in 1980. He did not immediately pursue graduate studies but instead engaged in a full-time career as a cyclist, first as a member of the amateur Swiss National Team and then as a professional in various teams in Switzerland and Italy. He was selected for the World Championships four times and participated in such well known races as the Tour de France and the Giro d'Italia. After this adventure he renewed with his true calling by completing a PhD in Neurobiology in 1988 with Professor Michael O'Shea, again at the University of Geneva. His thesis focused on the biosynthesis of neuropeptides, which was poorly understood at the time. It was to tackle this problem that he first developed an interest in using invertebrate models to study evolutionarily conserved processes. This approach led him to study the cardiac bodies of locusts, a pair of endocrine glands almost completely dedicated to the production of the peptidic adipokinetic hormones. He then moved to the famed Laboratory of Molecular Biology (LMB) of the Medical Research Council in Cambridge, UK, to collaborate with Dr J.J. White as a post-doctoral fellow of the Swiss National Science Fund. It is at the LMB that Sydney Brenner developed the nematode *Caenorhabditis elegans* as one of the premier research tools in genetics, and where Hekimi developed his interest for using 'the worm' for translational studies in the biology of aging. It is also in Cambridge that he identified the first mutants that helped to demonstrate that aging could be manipulated genetically and that inducing mild mitochondrial dysfunction could in fact slow down the aging process of animals. After three years in Cambridge, Hekimi joined the Department of Biology at McGill University. He became a Canadian and remained at McGill where he is a full professor since 2004. He has continued his research on the aging process, extending his reach to include mouse models of aging and of age-dependent diseases, as well as drug discovery through the medium of a spin-off company, Chronogen, which closed in 2007 when its assets were acquired by larger entities. His research at McGill University has been principally funded by the Canadian Institute of Health Research and the Canadian Fund for Innovation, and also by the National Science and Engineering Council, by the Canadian Cancer Society Research Institute, industrial partners, and McGill University. He holds two endowed chairs, the Strathcona Chair of Zoology (since 2004), and the newly created Robert Archibald & Catherine Louise Campbell Chair in Developmental Biology (since 2007). In 2010 he became a Fellow of the Royal Society of Canada and two years later was awarded the Flavelle Medal of the RSC for outstanding contribution to biological science. Hekimi has published more than 80 highly-cited peer-reviewed publications, has several patent applications, has given over 100 invited lectures and conferences presentations, and has supervised 67 graduate students and post-doctoral fellows. He is also a populariser who is regularly interviewed by radio and television broadcasters and the written press to explain the meaning of new findings in the biology of aging, including his own, for human aging and human health.

ABSTRACT

Pro-Longevity Mitochondrial ROS Signaling

Seigfried Hekimi, Department of Biology, McGill University Montréal, QC

The oxidative stress theory of aging postulates that aging results from the accumulation of molecular damage caused by mitochondrial reactive oxygen species (ROS) generated during normal metabolism. In the nematode C. elegans several mutations in mitochondrial proteins lead to a substantial increase in longevity. Example include isp-1 and nuo-6, which encode subunits of mitochondrial respiratory chain complexes, and sod-2, which encodes the main mitochondrial superoxide dismutase. We have investigated the involvement of ROS metabolism in the mechanisms of longevity of these mutants. Our findings indicate that the longevity of these mutants is not the result of lower accumulation of oxidative damage. Rather we find that their mitochondria display an enhanced generation of superoxide, a property that we find to be necessary and sufficient for their increased longevity. We propose a general model that suggests that the level of ROS generation increases with aging because the signalling function of ROS is protective and is stimulated by age-dependent damage and cellular dysfunction. We have investigated the signal transduction mechanisms by which mitochondrial ROS (mtROS) induce longevity. We find the mtROS signal is relayed by the conserved, mitochondria-associated, intrinsic apoptosis signalling pathway, in a manner completely independent of apoptosis per se. In vertebrates, mtROS stimulate apoptosis through the intrinsic pathway to protect from severely damaged cells. Our observations in nematodes demonstrate that sensing of mtROS by the apoptotic pathway can, independently of apoptosis, elicit protective mechanisms that keep the organism alive under stressful conditions. This results in extended longevity when mtROS generation is inappropriately elevated, as in the mitochondrial mutants we have been studying. We believe our findings help to clarify the relationships between mitochondria, ROS, apoptosis, and aging.

Keynote Lecture:

Dr. Rafael Radi, Universidad de la República, Montevideo, PA Uruguay

Thursday, June 12, 2014 @ 1:30 PM

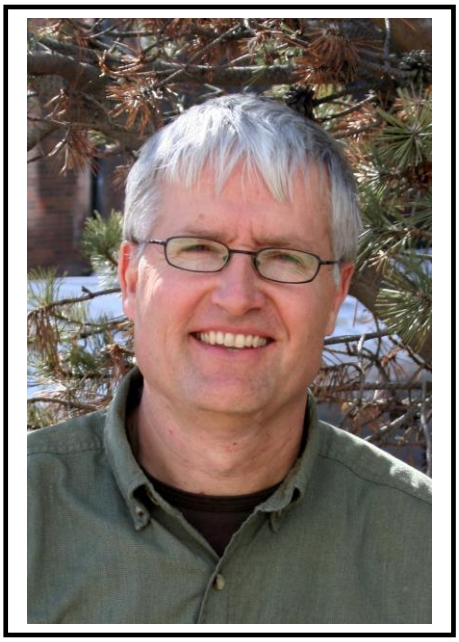
Rafael Radi, MD, PhD was born in Montevideo, Uruguay. He studied Medicine and Biochemistry at Universidad de la República, Uruguay, obtaining the degrees in 1989 and 1991, respectively. As a postdoctoral fellow at the University of Alabama at Birminghan (USA) in the early nineties in Bruce A. Freeman's lab, he played a key role on the discovery of peroxynitrite and the biochemical characterization of oxidizing and nitrating species derived from nitric oxide in biological systems. Upon returning to Uruguay, he advanced through all the academic ranks to the currently position as Professor and Chairman of Biochemistry and Director of the Center for Free Radical and Biomedical Research, Facultad de Medicina, Universidad de la República, Uruguay. Some of his honours include the Leloir Award to International Cooperation (2012), Discovery Award of the Society for Free Radical Biology and Medicine (SFRBM, 2011), Alexander Von Humboldt Senior Award (2010) and the National Prize in Science and Technology (2007), among many others. He was a Howard Hughes International Research Scholar (2000-2011). He is the President-Elect of the Society for Free Radical Research International and Past-President of the Society for Free Radical Biology and Medicine. Founding Member and Secretary of Academia de Ciencias del Uruguay and foreign member of the Academy of Sciences of Argentina, Brazil, The Developing World and Latin America. He is Adjunct Professor at the University of Buenos Aires, Pittsburgh, Alabama at Birmingham, and Vanderbilt University. He is currently Associate Editor of Free Radical Research and Free Radical Biology and Medicine. He has played an important role in the development of research infrastructure and science policy at the national and international levels. His current research interests include the biological chemistry and pharmacology of peroxynitrite and nitrating species, structural biology of oxidized proteins, redox control of microbial invasion to mammalian cells, role of mitochondrial dysfunction in disease progression and development and testing of redox-sensitive probes and redox-based therapeutics.

ABSTRACT

Nitroxidative Stress: Molecular Mechanisms and Biological Consequences

Rafael Radi[1,2]
[1]Departamento de Bioquímica and [2]Center for Free Radical and Biomedical Research, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

Excess production of nitric oxide ($^{\bullet}NO$) in the presence of reactive oxygen species and/or transition metal-containing centers lead to the formation of $^{\bullet}NO$-derived oxidants. For instance, the diffusion-controlled reaction of $^{\bullet}NO$ with superoxide radical ($O_2^{\bullet-}$) yields peroxynitrite anion ($ONOO^-$), while the reactions of hydrogen peroxide (H_2O_2) and nitrite (NO_2^-) with hemeperoxidases lead to the formation of nitrogen dioxide ($^{\bullet}NO_2$). Nitric oxide-derived oxidants promote oxidation, nitration and nitrosation of biomolecules, chemical modifications that can result in changes of their structure and function and cause alteration of cell homeostasis *via* "nitroxidative stress". In the presentation, I will 1) analyze our current understanding of the molecular mechanisms that lead to nitroxidative stress, with a focus in protein modifications, and 2) provide evidence for a causative link of excess $^{\bullet}NO$-derived oxidants levels with biological responses related to physiology and pathophysiology. A comprehensive understanding of the biochemical basis of nitroxidative stress is facilitating the development of pharmacological- and genetic engineering-based interventions of prospective therapeutic value.



Keynote Lecture:
Dr. Richard Schulz, University of Alberta, Edmonton, AB
Friday, June 13, 2014 @ 11:00 AM

The Schulz lab has expertise in cardiovascular pharmacology and pathophysiology, particularly in relation to oxidative stress. Many cardiovascular diseases involve an increase in oxidative stress to the heart and blood vessels, causing damage to these tissues and contributing to acute heart failure. Our lab investigates the role of some specific molecules in contributing to this oxidative stress damage. Specifically, we are interested in the roles of nitric oxide, superoxide and peroxynitrite in cardiac and vascular injury relating to the activation of the immune system as well as in myocardial ischemia and reperfusion injury. We have discovered that some of these molecules may mediate their damaging effects through activation of a protein enzyme called matrix metalloproteinase-2 (MMP-2) within the cardiac myocyte. Although MMP-2 was previously thought to act only on extracellular targets, our lab has discovered that MMP-2 also targets (and subsequently damages) intracellular proteins. Our short-term objective is to understand the contribution of each of these molecules in the development of acute heart failure. Our long-term objective is to develop and test specific pharmacological treatments to protect the heart from oxidative stress injury (e.g. matrix metalloproteinase or nitric oxide synthase inhibitors, superoxide or peroxynitrite scavengers.

ABSTRACT

Why inhibitors of matrix metalloproteinase-2 (MMP-2) are next generation drugs to treat diseases of oxidative stress injury

Richard Schulz, PhD FBPharmacolS. Departments of Pediatrics & Pharmacology, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada. richard.schulz@ualberta.ca.

Matrix metalloproteinases may be best known for their biological actions to proteolyse extracellular matrix proteins to affect tissue remodeling, both physiological and pathological, however it is now understood that they have several intracellular functions. My lab discovered that MMP-2, found in almost every cell type, also localizes to specific subcellular organelles and has unique susceptible protein targets inside the cardiac myocyte. We recently found that a combination of MMP-2 signal sequence quality, as well as its splicing, dictate its distribution between the cytosol and the secretory pathway. MMP-2 is activated directly by oxidative stress (in the form of peroxynitrite) to a S-glutathiolated Cys derivative which is catalytically active and distinct from the secreted form. It is an integral sarcomeric protein localized to thin, thick and intermediate (titin) filaments, most prominently at the Z-line, and is also found in nuclei, mitochondria, the mitochondrial associated membrane, and caveolae. During oxidative stress injury of the heart MMP-2 is rapidly activated and cleaves specific sarcomeric and cytoskeletal targets including troponin I, alpha-actinin, myosin light chain-1, glycogen synthase kinase-3beta and titin. The cleavage of these sarcomeric proteins results in the rapid loss of contractile function. MMP inhibitor drugs prevent the cleavage of these targets and protect the heart from oxidative stress injury by preventing inefficient contractile function. Such drugs, including doxycycline, which possesses MMP inhibitory properties distinct from its antibacterial actions, are promising drugs for the treatment of ischemic heart disease and heart failure. Post-translational modifications of intracellular MMP-2, including S-glutathiolation and its phosphorylation, will allow the development of inhibitors specifically targeting intracellular but not extracellular MMP-2, and should be useful in treating diseases caused by oxidative stress in the body.