



IN THIS ISSUE

President's Message.....	2
Next FRS Webinar.....	3
2011 Discovery Award.....	5
Annual Meeting.....	6-7
Social Media Tools.....	8
Research Spotlight.....	9
Literature Review.....	10
Foundation Honor Roll.....	10

UPCOMING EVENTS

FREE RADICAL SCHOOL WEBINAR

Oxygen and Gene Expression
November 3, 2011



18TH ANNUAL MEETING

November 16 - 20, 2011
Sheraton Atlanta Hotel
Atlanta, GA USA

SFRBM HEADQUARTERS

8365 Keystone Crossing
Suite 107
Indianapolis, IN 46240
317/205-9482
fax: 317/205-9481
info@sfrbm.org
www.sfrbm.org

THE RADICAL VIEW

Mike Murphy, Ph.D.

DOT: Tell us a little about your background and current passions in your professional life.

When I was growing up in Dublin I was always interested in science, so I never really thought of being anything other than a scientist. Biochemistry and molecular biology interested me most, but I figured it was important to learn the physical sciences first, so I did an undergraduate degree in chemistry at Trinity College, Dublin. After that I shifted to biochemistry for a PhD at Cambridge supervised by Martin Brand. There, I first started working on mitochondria, which has continued ever since. After my PhD, I spent some time as a teacher in Zimbabwe and then went back to Dublin to lecture in biochemistry for a couple of years before moving to the University of Otago in New Zealand, where I was on the faculty from 1992 to 2001. Over this time I dabbled in many different areas of mitochondrial biology, before focusing on the interactions of reactive oxygen species with mitochondrial function in health and disease. By then, the Medical Research Council (MRC) Dunn Human Nutrition Unit in Cambridge, UK had appointed the Nobel laureate John Walker as its Director, and he set about recruiting group leaders with mitochondrial interests, which led to me joining the Unit and moving back to Cambridge in 2001. The Unit has since been renamed the MRC Mitochondrial Biology Unit and is now a leading center of mitochondrial research with a number of notable recent achievements, such as the structure of respiratory Complex I by Leo Sazanov's group.



Mike Murphy, Ph.D.
MRC Mitochondrial
Biology Unit
Cambridge, UK

The areas of mitochondrial biology that interest me most are those that relate to the damage caused by redox events and the potential for these events to be biologically relevant signals. In this, I like to work at the chemistry/biology interface and two areas in particular are of current interest. The first is the design of small, mitochondria-targeted molecules that we can use to detoxify or report on mitochondrial reactive species. The second general area is trying to understand the role of redox changes to mitochondrial protein thiols in response to oxidative damage and redox signaling, mainly using proteomic approaches. In all these areas, I am most interested in understanding and measuring the levels of changes in these species in vivo. My view is that our understanding of the roles of mitochondrial redox changes in biology is limited because of the difficulty of quantifying these changes in vivo. While we can often identify a redox change in biological systems, without quantification it is often unclear whether these modifications have a biological impact.

DOT: What do you feel were the most important factors that shaped your career?

Mainly luck! There certainly wasn't a career plan. I was interested in the chemistry/biology interface but had no clear idea of how best to pursue this. I chose to do a PhD on mitochondrial bioenergetics because it seemed interesting. This turned out to be fortunate because the many

SFRBM COUNCIL

President

Harry Ischiropoulos, Ph.D.
*Children's Hospital of Philadelphia
 Research Institute
 University of Pennsylvania*

**Vice President of Research & Scientific Development (President-Elect)**

Henry Forman, Ph.D.
University of California - Merced

Vice President of Finance

Margaret Briehl, Ph.D.
University of Arizona

Vice President of Education & Professional Development

Paul Brookes, Ph.D.
University of Rochester

Vice President of Membership

Sally Nelson, Ph.D.
SomaLogic, Inc.

Vice President of Communications

Chris Kevil, Ph.D.
LSU Health Sciences Center

Past President

Victor-Darley-Usmar, Ph.D.
University of Alabama - Birmingham

Executive Director

Kent Lindeman, CMP

Council Members

Marcie Cole, Ph.D.
 Brian Day, Ph.D.
 Rick Domann, Ph.D.
 Neil Hogg, Ph.D.
 Eric Kelley, Ph.D.
 Alicia Kowaltowski, Ph.D.
 Aimee Landar, Ph.D.
 Francisco Laurindo, MD
 Lee Ann MacMillan-Crow, Ph.D.
 Lin Mantell, MD, Ph.D.
 Andre Melendez, Ph.D.
 Bulent Mutus, Ph.D.
 Tim Oury, MD, Ph.D.
 Homero Rubbo, Ph.D.
 Sruti Shiva, Ph.D.
 Daret St. Clair, Ph.D.
 Albert van der Vliet, Ph.D.

Internal Marketing Committee

Dot Editor: Lee Ann MacMillan-Crow, Ph.D.
 Tak Yee Aw, Ph.D.
 Ines Batinic-Haberle, Ph.D.
 Christian Schöneich, Ph.D.
 Matthew Zimmerman, Ph.D.

PRESIDENT'S MESSAGE:

Harry Ischiropoulos, Ph.D.



Harry Ischiropoulos

Only 8 weeks remain until SFRBM's 18th Annual Meeting in Atlanta.

The program committee has started to review and organize the submitted abstracts into oral and poster presentations. Specific assignments will be announced and communicated at the end of the first week of October. Remember that the meeting is always a great venue for both young and established investigators to share exciting new results in all areas of free radical chemistry, redox biology and antioxidants. I look forward to seeing many of you at SFRBM 2011.

Here are some of the other projects that SFRBM has been working on over the past few months:

- 1. Development of a SFRBM App.** We have partnered with XCube, a worldwide leader in mobile applications development, to create a SFRBM-specific app that can be used on your iPhone, iPad, Android, Windows Mobile, Blackberry or any other hand-held device. By early 2012, SFRBM members will be able to access the latest journal articles, view virtual seminars, browse meeting abstracts and access our research collaboration database – all from your phone or tablet. We are excited to be at the forefront of application development for scientific societies.
- 2. Rolling out the SFRBM Research Forum.** The Website Committee will be circulating a series of posts between now and the Annual Meeting aimed at initiating discussions with members about methods, techniques or general questions. The Research Forum categories are Aging & Disease; Antioxidants and Novel Therapeutics; Generation, Action and Metabolism of Reactive Species and Cell/Systems Biology. When you receive the emails with the posts, please log onto the Research Forum and post your replies or comments. Remember that the Forum will only be as good as the people that contribute to it.
- 3. Established a presence on Facebook.** Thanks to the efforts of Neil Hogg and the Marketing External Committee, SFRBM now has a Facebook page. Type "Society for Free Radical Biology and Medicine" into the Search bar in Facebook and hit "Like" to add it to your personal list. This committee is currently exploring a social media strategy, which would integrate a series of YouTube videos to promote SFRBM.
- 4. Selected Seattle for our 2014 Annual Meeting location.** We will be returning to the Emerald City for SFRBM 2014. Seattle was the site of one of our most successful meetings (SFRBM 2003), which drew over 750 scientists.
- 5. Revamped the criteria for Young Investigator Award Judging.** The Awards – Junior Committee has changed the way that Young Investigator Awards will be judged for the 2011 Annual Meeting and beyond. Each student or postdoc candidate will receive 3 scores from judges at the meeting plus a 4th score taken from the double-blinded abstract evaluations that occur prior to the meeting. Judges must have at

continued on page 3

least 2 published papers in the past 3 years that relate to the abstract area in which they volunteer to judge and the committee will invite selected members to encourage diversity (areas of interest, gender and geography). Each individual score will be comprised of the following 3 areas:

- ACCURACY (max of 10 points)
 - **Quality of data presentation and discussion** (major criterion)
 - Use of adequate / state-of-the-art methods
 - Technical excellence
- IMPACT / INCREMENTAL CONTRIBUTION (max of 10 points)
 - **Originality and extent of conceptual novelty** (major criterion)
 - Degree of advance over previous knowledge
 - Relevance
 - **Strength of mechanistic insights** (major criterion)
 - Completeness
 - Potential implications for other fields
- PRESENTER (max of 10 points)
 - **Critical thinking on results and related work** (major criterion)
 - Knowledge level
 - Quality, clarity and depth of presentation and ability to answer questions

For additional details, please visit the SFRBM website.

As always, please let me know if you have any questions, comments or feedback about SFRBM. I can be reached at ischirop@mail.med.upenn.edu or phone at (215) 590-5320. Thanks for your continued participation in SFRBM.

VOLUNTEERS NEEDED

The SFRBM Marketing-Internal Committee is seeking volunteers who would be interested in writing articles and literature reviews for future issues of the *Dot*. The *Dot* is published quarterly in March, June, September and December. If you are interested in assisting with any future issues, please contact Lee Ann MacMillan-Crow at lmcrow@uams.edu.

FREE RADICAL SCHOOL VIRTUAL SEMINAR SERIES



Oxygen and Gene Expression

Thursday, November 3, 2011

1:00 pm Eastern (17:00 GMT/UTC)

Speaker: Phyllis Dennerly, MD

Children's Hospital of Philadelphia

Cost: FREE for SFRBM members

PROGRAM OVERVIEW

- Consequences of high or low oxygen exposure in the lung
- How oxygen change impacts gene regulation with relation to:
 - HIF1- α
 - NF- $\kappa\beta$
 - Genes that are regulated through the Nrf2 pathway
- Overview of the effects of high/low oxygen (hyperoxia and hypoxia) on regulation of factors sensitive to oxygen concentration
- Downstream consequences on cells & tissues associated with the lung

ABOUT THE SPEAKER

Phyllis Dennerly, MD, FAAP, is chief of the Division of Neonatology and Newborn Service at The Children's Hospital of Philadelphia and the University of Pennsylvania Health System. Her area of basic science research is in the regulation of lung gene expression in oxidative stress, in particular the role of heme oxygenase, the rate-limiting enzyme in bilirubin production.

She is the author of more than 100 publications including manuscripts, book chapters, editorials and abstracts and holds several grants from the National Institutes of Health. Dr. Dennerly is an active member of many professional and scientific societies, including SFRBM and is an Associate Editor for Free Radical Biology and Medicine.

Cost:

There is no cost for SFRBM members to participate. The webinar is open to SFRBM members only. Visit <http://sfrbm.org/sections/virtualfreeradicalschooll.php> to register or to view past archived sessions.

LATEST ARCHIVED WEBINAR

Glutathione: Protective Roles and Regulation of its Synthesis
Henry Jay Forman, Ph.D.
University of California - Merced
Presented July 27, 2011

Visit the Members Only area at www.sfrbm.org.

Radical View *continued from page 1*

ways in which mitochondrial biology has developed in the intervening years meant I could dabble in a range of different areas from chemistry to medicine. It also opened up many opportunities to apply chemical approaches to mitochondrial problems and made the study of redox and free radical processes central to my work. The other factor that helped my career was the people I have been lucky enough to work with. I was influenced by many mentors over the years, including John Kelly in Dublin when I was an undergraduate and particularly by Martin Brand when I was in his lab for my PhD. After I moved to New Zealand I established a close and ongoing collaboration with Rob Smith, who synthesises many of the mitochondria-targeted compounds we have used, and with Ken Taylor who has led the drive to bring these developments to patients as new pharmaceuticals. These interactions have been critical for what my lab and collaborators have been able to achieve. I also spent time during my sabbatical year with Jeff Schatz in Basel from whom I learned a great deal about how to do science. Later the same year, I spent four critical months with Victor Darley-Usmar and Joe Beckman in Alabama which was an exciting time during which I learned about nitric oxide and free radical biology in general. Since returning to Cambridge, it has been tremendously stimulating to be part of a Unit focusing on mitochondrial biology and to interact with my colleagues here. I have also been involved in a number of fruitful collaborations, notably those with Linda Partridge, Richard Hartley, Paul Brookes and Thomas Krieg, which are all leading to interesting new insights. Finally, I have been lucky to have a large number of excellent students, technicians and post-docs in my lab over the years - I won't name them for fear of forgetting someone.

DOT: What was your most exciting discovery in research?

Hopefully it's the stuff we're working on now! More generally, from the late 1990s onwards, myself and Rob Smith starting working on targeting small molecules to mitochondria by conjugation to lipophilic cations. Initially, we saw this as a limited approach to assess mitochondrial thiols. However, the project subsequently took off and it turned out that we could use this approach to target a wide range of bioactive molecules to mitochondria. The most widely used of these is the mitochondria-targeted antioxidant MitoQ, which has since gone on to show efficacy in a wide range of animal studies and in phase II clinical trials. Since then we have also used this approach to target nitric oxide donors to mitochondria (ie MitoSNO) which has been shown to be cardioprotective in vivo. This was recently extended to develop a mitochondria-targeted boronic acid peroxide sensor (MitoB) that we have used in conjunction with mass spectrometry to estimate mitochondrial hydrogen peroxide levels in vivo. Since then, we and many others have shown that it is possible to target many pharmacophores to mitochondria in vivo. When we started this work mitochondria were a neglected drug target but this work has led to the growing realization that mitochondria are an important therapeutic target for the many diseases involving mitochondrial dysfunction. Now many groups are developing further mitochondrial therapies and probes.

DOT: Your training involved working in numerous countries, was this by choice, if so, why?

This was not really by choice, I just took the jobs I was offered. However, it has been interesting as I have now worked in six different countries. I went from Ireland to England to do my PhD and then after some time in New York and Zimbabwe, I ended up in New Zealand for 9 years which was a great place to live. During that time, I spent significant sabbaticals in Switzerland and the US, before returning to Cambridge when a job came up there. So, as with the rest of my career there was no real plan, I just took opportunities as they came up. Looking back, it was a great opportunity to see how different labs operated and to work with a wide range of colleagues.

DOT: What advice would you give to young researchers entering the field?

For better or worse, I don't think I listened much to advice when I was young. However, I do remember a point that I read by Peter Medawar saying that no matter how elegant a favorite idea or hypothesis may be, it can still be completely wrong and you should be prepared to abandon it – easier said than done of course. Anyway, some of the things that have worked for me have been to try and do your own thing and not to follow the crowd so that you have something unique to offer as a collaborator. I have found that collaborating with others with complementary expertise to be a great way to make progress and also exposes you to new ways of viewing problems. Through my collaborations, I have been involved in a range of areas from clinical trials through to basic chemistry, all of which has been fun. More specifically, to those entering the free radical and redox field I suggest that you should be continually sceptical about what seems to be established, even if it is published in top journals, or repeated in numerous mini-reviews. Our field is technically very tricky, and it's easy to mislead yourself - and others.

Article submitted by Dr. Lee Ann Macmillan-Crow

2011 ANNUAL MEETING SUPPORT

Thank you to the generous supporters of SFRBM's 18th Annual Meeting.



Seahorse Bioscience



molecular probes[®]
by life technologies™

IKARIA[®]
ADVANCING CRITICAL CARE



Albany Medical College
Office of Medical Education

DIONEX
Part of Thermo Fisher Scientific

BIOLINK LifeSciences

Cayman CHEMICAL
curacyte health sciences

RADI SELECTED AS 2011 DISCOVERY AWARD RECIPIENT



SFRBM's Senior Awards Committee has announced Rafael Radi, MD, PhD of the Universidad de la República – Uruguay as the 2011 recipient of the Discovery Award.

Dr. Radi's research activities have focused on the biochemistry, cell biology and relevance to disease states and therapeutics of free radicals, oxidants and antioxidant systems. In particular, he has contributed to clarify the mechanisms of nitric oxide-dependent toxicity through its interaction with superoxide

and the formation of peroxynitrite. Radi has extensively characterized the biological chemistry of peroxynitrite, including the discovery of novel free radical-dependent and independent reaction pathways, its impact in mitochondrial dysfunction and apoptosis *via* oxidation and nitration reactions and its role in pathology. He has helped to create the concept that an oxidizing environment can "shift" the physiological actions of nitric oxide towards pathophysiology and has facilitated the development, testing and chemical characterization of antioxidants that serve as peroxynitrite decomposition catalysts. Radi has shown that peroxynitrite plays an important role in cellular immune responses against pathogens such as the causative agent of Chagas disease, *Trypanosoma cruzi*, and how microbial antioxidant systems constitute virulent factors. These observations provide the foundation for future anti-parasitic drug developments and therapeutic discovery.

Radi is widely known in the international scientific community and served as SFRBM President in 2007 - 2008. Currently, Dr. Radi serves as the Professor and Chair of the Department of Biochemistry at the Universidad de la República in Montevideo, Uruguay while also serving as the Director of the Center for Free Radical and Biomedical Research. Radi holds appointments as First Level Researcher in Biology and Chemistry of the Uruguayan National Research System and as Honorary Professor of the University of Buenos Aires (Argentina) and Adjunct Professor of the Universities of Alabama at Birmingham, Pittsburgh and Vanderbilt University (USA).

Radi will be a featured speaker at SFRBM 2011 in Atlanta, Georgia where he will present Biological Chemistry of Peroxynitrite: Relevance to Molecular Mechanisms of Disease and Therapeutics on Friday, November 18, 2011. He will also be presented with a \$2,500 cash award, be recognized during the awards banquet and receive an invitation to publish a review article in *Free Radical Biology & Medicine*, SFRBM's Journal.

18TH ANNUAL MEETING OF THE SOCIETY FOR FREE RADICAL BIOLOGY AND MEDICINE

Plan to join us during SFRBM's Annual Meeting to be held
November 16 - 20 in Atlanta, Georgia, USA.



FEATURED SESSIONS

- ▶ Redox Regulation by Epigenetics
- ▶ Oxidative Stress in Neurodegenerative Diseases
- ▶ Mitochondria, Redox Metabolism and Cancer Biology
- ▶ Crosstalk Between NO and H₂S Signaling
- ▶ Lipid Oxidation: An Overview of Methods, Products, and Functional Effects In Vivo
- ▶ Sunrise Free Radical School

ORAL PRESENTATIONS & POSTER SYMPOSIA

- | | |
|--|---|
| <ul style="list-style-type: none"> ▶ Adaptative Responses ▶ Biological Formation of Reactive Species ▶ Biological Regulation by Reactive Oxygen Species ▶ Cancer, Cell Proliferation and Death ▶ Cardiovascular Redox Biology and Pathology ▶ Chemotherapy ▶ DNA Damage and its Consequences ▶ Free Radical Chemistry and Biochemistry ▶ Hydrogen Sulfide Chemistry and Biology ▶ Inflammatory Oxidative Signaling and Injury ▶ Lipids In Redox Biology ▶ Macromolecule Modification | <ul style="list-style-type: none"> ▶ Mitochondria and Cell Proliferation ▶ Nitric Oxide Chemistry, Biology and Physiology ▶ Novel Therapeutics ▶ Protective Enzymes ▶ Redox Imaging ▶ Redox Signaling ▶ Redox Reaction Mechanisms ▶ Signal Transduction and Gene Expression ▶ Superoxide and Superoxide Dismutases ▶ Targeted Antioxidants ▶ UV Effects and Atmospheric Pollutants |
|--|---|

For further details regarding SFRBM 2011, please visit www.sfrbm.org and click on the SFRBM 2011 meeting logo. Questions about SFRBM 2011 can be directed to SFRBM via phone (317) 205-9482, fax (317)205-9481 or e-mail at info@sfrbm.org.



SFRBM 2011 PRE-MEETING WORKSHOP

SFRBM's 18th Annual Meeting in Atlanta, will kick-off with a Pre-Meeting Workshop on Lipid Oxidation: An Overview of Methods, Products, and Functional Effects In Vivo. This workshop will focus on methods to assess lipid oxidation in vivo and in vitro, in addition to focusing on their application in biology and medicine. This program will include laboratory-based protocols used for methods described by the speakers. Registration for this workshop is \$175 per person for SFRBM members and \$200 for non-members. Fees for this workshop include lunch and course materials and are not included in the annual meeting tuition.

Featured Sessions and Speakers

- **Lipid Oxidation in Biology: An Overview**
Garry Buettner, Ph.D., The University of Iowa
- **Measurement of Lipid Oxidation in vitro and in vivo: Pitfalls and Disasters**
Kevin Moore, MD, Ph.D., University College London, UK
- **Measurement of F2-Isoprostanes and Isofurans**
Ginger Milne, MD, Vanderbilt University
- **Identification of Lipid Oxidation Adducts and Functional Analysis as Receptor Ligands**
Koji Uchida, Ph.D., Nagoya University
- **Analysis of Phospholipid and Neutral Lipid Oxidation Products Formed in vitro and in vivo**
Robert Murphy, Ph.D., University of Colorado – Denver
- **Nitrated Lipids: How to Make Them, How to Measure Them and Avoiding Artifact**
Bruce Freeman, Ph.D., University of Pittsburgh
- **Analytical Strategies for Characterization of Bile Acid and Oxysterol Metabolomes**
William Griffiths, BSc, Ph.D., CChem, MRSC, Institute of Mass Spectrometry, UK
- **Chlorinated Lipids in Cardiovascular Disease: An Introduction to Myocardial Lipidomics**
David Ford, Ph.D., St. Louis University
- **Novel Lipid Mediators and Resolution Mechanisms in Acute Inflammation**
Karsten Gronert, Ph.D., University of California, Berkeley
- **The Lipid Whisker Model of Oxidized Cell Membranes**
Stan Hazen, MD, Ph.D., Cleveland Clinic Foundation
- **Interesting Things about PAF and PAF acetyl-hydrolase That You Never Knew**
Tom McIntyre, Ph.D., Cleveland Clinic
- **Generation and Biological Effects of γ -ketoaldehydes (isoketals)**
Jack Roberts, II, MD, Vanderbilt University

OPENING DOORS: THE ART OF LEADERSHIP IN SCIENCE

The 9th Annual Opening Doors Event, entitled "The Art of Leadership in Science," will provide SFRBM members at all career levels an opportunity to review and discuss the general attributes of a good leader and how we can all effectively incorporate these skills into our daily lives in order to achieve our professional and personal goals. Scientific careers have become extremely specialized and greater emphasis is being placed on interdisciplinary research. As a result, the Opening Doors event will be highlighting the art of effectively leading groups of individuals. The event will take place on Thursday, November 17, 2011. Cost is \$25 for students and postdocs and \$35 for senior investigators.



SFRBM IMPLEMENTS SOCIAL MEDIA TOOLS

As a way to promote the visibility of SFRBM to current and potential members, the society has been busy rolling out a new research forum, creating a social media platform, and developing a mobile app. The implementation of these new resources will help in the exchange of information to the scientific community.

- **Research Forum** – Currently in its introductory stage, SFRBM's Research Forum is a way for members to post comments about methods, techniques or general questions for which they are looking for input from colleagues. The Research Forum categories are:
 - Aging & Disease
 - Antioxidants & Novel Therapeutics
 - Generation, Action and Metabolism of Reactive Species
 - Cell & Systems Biology

The Website Committee is currently circulating posts to spur discussions on various topics. To stay up-to-date, sign up for the SFRBM Research Forum Digest which summarizes daily posts and replies within a single email. SFRBM members can access the Research Forum by logging in to the Members Only section of the SFRBM website and clicking on SFRBM Research Forum.

- **Facebook** – Have a Facebook account? Make sure to search for Society for Free Radical Biology and Medicine and click "Like." On our page, you'll find important information regarding the Annual Meeting as well as information about upcoming webinars. This social media platform is another way for SFRBM to promote scientific excellence with redox researchers across the world.
- **Mobile App** – Work is currently underway to develop a cross platform SFRBM app for both Android and Apple users that will allow members to effortlessly keep up with the latest scientific developments as well as their colleagues and friends. The app will feature numerous unique functions and tools for members such as directory listing of member research specialties and contact information, links and RSS feeds from the society journal, access to the DOT and webinar materials, and key information on the Annual Society meeting such as calendar of events, speaker information, abstracts and other cutting edge late breaking information. These unique and useful tools will significantly aid members with their research and program development while increasing the value and voice of SFRBM membership. Launch of the app is slated for late 2011/early 2012 and will be highlighted at the 2011 Annual Meeting.



We want to keep you connected! Make sure to login in to the Research Forum to post your comments and suggestions and like us on Facebook. Use your mobile device to scan the QR code to the right to be taken directly to the SFRBM Facebook page.



GORDON RESEARCH CONFERENCE - OXYGEN RADICALS February 5 - 10, 2012 • Ventura Beach Marriott • Ventura, CA

The Oxygen Radicals Conference is designed to provide chemists, biologists, biochemists, cell biologists, clinicians, and other biomedical scientists with state-of-the-art knowledge on reactive oxygen species in the context of human pathophysiology. An honorary lecture at the end of this conference will be presented by SFRBM's past president, Victor Darley-Usmar, Ph.D. Chairs of this conference are Neil Hogg and Valerie O'Donnell and Vice Chairs are Ronald Mason and Alicia Kowaltowski. For more information, visit <http://www.grc.org/programs.aspx?year=2012&program=oxygen>.

RESEARCH SPOTLIGHT: SFRBM YOUNG INVESTIGATORS

SFRBM will be announcing Travel Award Winners and poster presenters for the 2011 Annual Meeting in Atlanta the week of October 5.

One of SFRBM's 2010 Travel Awards was given to **Leena Chaudhuri**, a student from the University of Iowa, to present her research "Manganese superoxide dismutase (SOD2) 3'-untranslated region: a novel molecular sensor for environmental stress." Leena was awarded \$500 for being selected.



"Our study shows that the 3'-untranslated region (UTR) of MnSOD regulates its expression during transitions between quiescent and proliferating cycle as well as radiation. Preferential increase in the levels of the 1.5 kb MnSOD transcript was observed in quiescent cells as well as in irradiated cells. However, the longer 4.2 kb transcript showed direct correlation with percent S-phase cells, in proliferating normal and cancer cells. This abundance of the shorter 4.2 kb transcript correlated with lower MnSOD protein levels in proliferating cells. Deletion and reporter assays showed decrease in reporter activity in constructs carrying multiple AU-rich sequences in the 3' UTR of the longer transcript. This observation was further validated when overexpression of the MnSOD 3' UTR of the longer transcript could act as an exogenous 'decoy' to titrate trans-factors from binding to the endogenous transcript. Overexpression of the longer MnSOD 3' UTR not only increased the MnSOD mRNA and protein levels but also slower proliferation. Thus, this novel role of transcript selection and the 3' UTR adds a new level of complexity to MnSOD expression. We hypothesize that such a complex mode of transcript selection is necessary to fine-tune the cellular redox environment during transitions through the cell cycle."



Siobhan Craige, a post-doctoral fellow from the University of Massachusetts, also received a travel award for her research "NADPH oxidase 4 promotes endothelial angiogenesis."

"My research focuses on the function of NADPH oxidase 4 (Nox4), an enzyme that produces reactive oxygen species (ROS), in the endothelium. ROS accumulate in conditions of low oxygen (hypoxia), and tissues respond by forming new blood vessels (angiogenesis). This work uncovered a previously unrecognized function for Nox4 in the response to tissue injury, in which tissue hypoxia increases the expression of Nox4, resulting in ROS production and the induction of angiogenesis."

Kasia Broniowska, a post-doctoral fellow at the Medical College of Wisconsin, received a Young Investigator Award at the 2010 Annual Meeting in Orlando for work poster on "The effects of nitrosating agent, S-nitroso-L-cysteine, on the bioenergetics of breast cancer cells." Kasia received a \$500 stipend in recognition for her work as well as a free meeting registration to a future Annual Meeting.



"It is emerging that modulation of cancer metabolism is a viable therapeutic strategy for the treatment of many malignancies. Since multiple metabolic enzymes are inhibited by S-nitrosation (e.g. GAPDH, Complex I), we have focused on the impact of nitrosative stress on cancer cell bioenergetics. Using the intracellular nitrosating agent S-nitroso-L-cysteine (L-CysNO) to initiate protein S-nitrosation, we showed that basal respiration, reserve respiratory capacity, ATP levels, and GAPDH activity are decreased after treatment with L-CysNO in breast cancer cells. In addition, we demonstrated that thiol groups of the pyruvate transporter, MCT4, are modified after L-CysNO exposure, and this resulted in inhibition of pyruvate uptake. Taken together, our findings may have important implications for the regulation of cancer cell metabolism by reactive nitrogen species."

Travel Award and Young Investigator Award Winners will be given their awards at the SFRBM 2011 Awards Banquet on November 19. They will also receive a free meeting registration for the 2012 SFRBM Annual Meeting in San Diego, CA or the 2013 Annual Meeting in San Antonio, TX.

LITERATURE REVIEW

Putting bioactivation reactions to work: Targeting antioxidants to mitochondria. *Anders MW, Chemico-Biological Interactions 192 (2011) 8–13.* Considering that mitochondria are the major cellular source of reactive oxygen species, there is a growing interest in targeting antioxidants to mitochondria, in an attempt to alleviate oxidative stress. Strategies for targeting antioxidants to mitochondria are based either on biophysical properties of mitochondria, particularly the highly negative membrane potential, or on the unique mitochondrial localization of enzymes that catalyze the release of drugs from prodrugs once the prodrug enters mitochondria. Former strategy is exemplified by the successful optimization of the redox active cationic compounds: (1) phenolic ubiquinone resulting in mitochondrially targeted MitoQ and (2) lipophilic metal complexes, Mn(III) *N*-alkylpyridylporphyrins. Anders examines herein the latter approach, focusing on the mitochondrial biotransformation of prodrugs, ω -(phenoxy)alkanoates, 3-(phenoxy)acrylates, and ω -(1-methyl-1*H*-imidazol-2-ylthio)alkanoates by the mitochondrial β -oxidation pathway, releasing phenolic antioxidants and methimazole. The observed cytoprotective effect in the hypoxia-reoxygenation model in rat cardiomyocytes demonstrates the potential of thia- and oxaalkanoate-based prodrugs to target antioxidants to mitochondria and mitigate the oxidative damage associated with ischemic–reperfusion injury. The transporters and enzymes that make up the mitochondrial fatty acid β -oxidation pathway for short- and medium-chain fatty acids are found only in mitochondria, indicating the feasibility of exploiting these bioactivation reactions for targeted mitochondrial drug delivery. Moreover, the prodrugs described above or analogous compounds may prove to be orally available, provided that they are processed by the transporters involved in the uptake of dietary fatty acids from the intestine. *Reviewed by Tin Weitner and Ines Batinic-Haberle, Duke University Medical Center.*

Tumor-induced endothelial cell apoptosis: roles of NAD(P)H oxidase-derived reactive oxygen species. *Lin RZ, Wang TP, Hung RJ, Chuang YJ, Chien CC, Chang HY. J Cell Physiol. 2011;226:1750-62.*

Metastasis contributes largely to the mortality of cancer patients and remains major challenge in the development of anticancer modalities. Attachment of the cancer cell to the endothelium and its penetration through the vascular barrier, while it is circulating, is considered to be of critical importance in metastatic process. Reactive oxygen species (ROS) are documented to have a decisive involvement in cancer metastasis. However, the major molecular mechanisms regulating tumor cell extravasation have not yet been completely understood, and need further elucidation. Herein, the authors nicely demonstrated that certain solid tumor cells can induce endothelial cell apoptosis to facilitate their escape from the circulation. The apoptosis of endothelial cells (EC) is triggered by elevated intracellular ROS levels as a result of their direct contacts with tumor cell. The antioxidants, such as ascorbate and *N*-acetyl-L-cysteine (NAC), and a glutathione precursor, glutathione ethylester were able to rescue the ECs from tumor-induced apoptosis and reduce the number of tumor cells migrating across endothelial barriers. NAD(P)H oxidase was identified as the major ROS producer in the event, since inhibitors and small interference RNA specific to the enzyme could abrogate the tumor-induced ROS production and hence EC death. This study also provides evidence that the interaction between tumor and EC increases intracellular Ca^{2+} concentration and activates protein kinase C (PKC) activity, which leads to NAD(P)H oxidase activation through the serine-phosphorylation of p47(phox) subunit. These findings suggest that blocking the tumor-induced EC apoptosis is a potential way to prevent tumor metastasis and development of such strategies may benefit for anticancer therapies. *Reviewed by Artak Tovmasyan and Ines Batinic-Haberle, Duke University Medical Center.*

SFRBM FOUNDATION HONOR ROLL

We would like to thank the following members who made donations to the SFRBM Foundation during the second quarter of 2011:

PLATINUM (\$500 or more)

Margaret M. Tarpey, *University of Pittsburgh*

SILVER (\$100 - \$249)

Douglas Thomas, *University of Illinois - Chicago*

BRONZE (\$25 - \$99)

Paul R.S. Baker, *University of Pittsburgh*

Garry Buettner, *University of Iowa*

Peter Gutierrez

To make a tax-deductible donation to the Foundation, please visit <http://sfrbm.org/sections/sfrbmfoundation.php>.