Redox Biology of Neurodegeneration and Cancer

Chair: Maria Clara Franco, PhD, Biochemistry and Biophysics, Oregon State University

Friday August 16, 8:30AM - 12:10PM
Redox Biology and Metabolism in a Mouse Model of Alzheimer’s Disease

Enrique Cadenas, MD, PhD

Pharmacology & Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, CA, USA

BIOGRAPHY

Enrique Cadenas is professor of Pharmacology & Pharmaceutical Sciences at the University of Southern California School of Pharmacy. He obtained a Ph.D. in Biochemistry from the University of Buenos Aires. Post-doctoral positions at the University of Dundee, Scotland (British Council Fellowship) and at the Johnson Research Foundation, University of Pennsylvania (National Institutes of Health Fogarty International Fellowship with Professor Britton Chance). Under an Alexander von Humboldt fellowship, he was research associate at the Department of Physiological Chemistry II, with Professor Helmut Sies and later associate professor of Pathology at the University of Linköping, Sweden.

Enrique Cadenas’ research addresses the impairment of oxidative metabolism due to mitochondrial dysfunction inherent in brain aging and Alzheimer’s disease. These molecular and cellular mechanisms integrate signaling and transcriptional pathways within a mitochondrion-centric approach subjected to redox regulation and nutrient-based and pharmacological interventions. This approach enables mechanistic insights on some patho-physiological states that are under the umbrella of insulin resistance: metabolic syndrome, obesity, diabetes, and neurodegenerative disorders, such as Alzheimer’s disease.

ABSTRACT

Deficits in glucose availability, mitochondrial function, and inflammatory responses are well-known hallmarks of the aging brain and are particularly accentuated in neurodegenerative disorders, such as Alzheimer’s disease. Multiple mechanisms account for the bioenergetics deficits and microglia activation as the driving forces that contribute to cognitive decline. Brain mitochondrial H₂O₂ –through thiol/disulfide exchange mechanisms– serves as a link between bioenergetics and signaling- and transcriptional pathways. The hypometabolic state inherent in a 12-month old triple transgenic mouse model of Alzheimer’s disease (3xTg-AD) was examined in a template that integrates mitochondrial function, insulin- and JNK signaling, as well as the effects
of nutraceutical interventions. Brain glucose uptake (dynamic microPET imaging) was decreased in 3xTg-AD along with the expression of insulin-sensitive neuronal GLUT4 and microvascular endothelium GLUT1 (55 kD). Impairment of energy homeostasis was accounted for by an imbalance between the PI3K/Akt pathway of insulin signaling and JNK signaling.

Diminished synaptic plasticity (long-term potentiation) was the functional outcome of the accumulating energy deficits. Conversely, 6-month old triple transgenic mice showed a hypermetabolic state (assessed by $^{13}$C-NMR). No changes in brain glucose uptake, the expression of insulin-sensitive GLUT4, and synaptic plasticity were observed in the 6-month old triple transgenic mice as compared with the age-matched non-transgenic counterpart. The hypometabolic state was rescued by treatment with lipoic acid, likely through a thiol/disulfide mechanism, which resulted largely in activation of the insulin receptor substrate and higher translocation to the membrane of the insulin-sensitive glucose transporters. In this manner, lipoic acid treatment appears to increase substrate supply; its effectiveness resulted in an increase of synaptic plasticity measured as long-term potentiation.
Redox Proteomics and Amyloid β-Peptide: Insights into Alzheimer’s Disease

D. Allan Butterfield, PhD

Department of Chemistry and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

BIOGRAPHY

With over 650 papers published from his laboratory (h-index = 102), mostly on oxidative stress and redox proteomics investigations in brain, Dr. Butterfield has demonstrated, widespread experience in neuronal oxidative stress measures and in redox proteomics methods to identify specifically oxidatively modified proteins. The latter technique, pioneered in his laboratory, was first used to identify oxidatively damaged proteins in brain of subjects with Alzheimer disease (AD) and arguably its earliest form, mild cognitive impairment (MCI). More recently, similar studies in plasma from children or adults with cancer or animal models treated with chemotherapy have revealed insights into chemotherapy induced cognitive impairment (CICI).

Many of these oxidatively dysfunctional proteins in brain or plasma are metabolic (glycolysis; TCA cycle) or mitochondrial. The Butterfield laboratory was the first to describe mTOR alterations in amnestic mild cognitive impairment and the mTOR-associated downstream pathway of autophagy alteration in PCAD and aMCI. Similar studies of mTOR alterations, with consequent insulin resistance and dysfunction of autophagy, were conducted in brains of persons with Down syndrome and DS who have transitioned to Alzheimer disease.

Dr. Butterfield is one of only 28 Fellows of the Society for Free Radical Biology and Medicine worldwide, a recipient of the 2013 Discovery Award from the SfRBM, and received the Alkmeon International Prize for Progress in Science Award from the European Brain Research Institute. Dr. Butterfield’s considerable experience with oxidative stress and redox proteomics are consistent with a demonstrated record of successful and productive research projects in an area of high relevance to oxidative stress in disease.
ABSTRACT

Alzheimer disease (AD), an age-related neurodegenerative disorder, is characterized pathologically by the presence of senile plaques (rich in amyloid beta-peptide (1-42) [Aβ(1-42)], neurofibrillary tangles (hyperphosphorylated tau), and neurite and synapse loss, and clinically by progressive loss of memory and higher executive cognitive functions, resulting in dementia. Knowledge of the underlying etiology and pathogenesis of AD is needed to effectively use agents to retard or prevent this oncoming public health crisis. Oligomeric Aβ(1-42) is neurotoxic and associated with oxidative stress in vitro and in vivo. Redox proteomics identified oxidatively dysfunctional brain proteins in oligomeric Aβ(1-42) preclinical models and human studies, including amnestic mild cognitive impairment, and familial-, preclinical-, early-, and late-AD, Down syndrome (DS), and DS with AD. These redox proteomics studies indicate oligomeric Aβ(1-42)-associated oxidative stress occurs early in AD pathogenesis, resulting in altered antioxidant and cellular detoxification defenses, decreased glucose metabolism and mitochondrial function, excitotoxicity, loss of synaptic plasticity and cell structure, neuroinflammation, impaired protein folding and degradation, and altered signal transduction.

We proposed oligomeric Aβ(1-42)-associated oxidative modification of brain glycolytic and TCA enzymes and ATP synthase leads to glucose dysmetabolism, leading to decreased ATP production, with consequent loss of neuronal cell potentials and large influx of neurotoxic Ca2+, causing necrotic and apoptotic neuronal death indexed by decreased thickness of hippocampus (memory loss) and frontal cortex (higher executive function loss). Recent neuroimaging studies on three continents involving thousands of presymptomatic persons with familial AD over 22 years prior to symptoms and three years thereafter precisely confirm the above order of events proposed by our laboratory. Redox-proteomics identified potential therapeutic targets, together with lifestyle interventions or treatments to reduce Aβ production or limit the damage caused by this neurotoxic peptide, could be beneficial in preventing or delaying the progression of this devastating dementing disorder. Support: NIH grants to DAB.
Investigating the Role of NRF2 in Mediating the Beneficial Effects of *Centella asiatica* in the Aging Brain

Nora Gray, PhD

Senior Research Associate
Department of Neurology
Oregon Health and Science University, Portland, OR, USA

**BIOGRAPHY**

Nora Gray is an assistant professor in the Neurology Department at OHSU. She graduated from Amherst College and received her PhD from the University of California Berkeley. Her research uses animal models of aging and Alzheimer’s disease to investigate how oxidative stress and mitochondrial dysfunction contribute to cognitive decline and how those pathways can be targeted for therapeutic intervention particularly with botanical compounds.

**ABSTRACT**

Nora Gray¹, Jonathan Zweig¹, Maya Caruso¹, Mikah Brandes¹, Kirsten Wright¹, Joseph Quinn¹,², Amala Soumyanath¹

¹Department of Neurology, Oregon Health and Science University, Portland, OR, USA
²Department of Neurology, Portland Veterans Affairs Medical Center, Portland, (OR), USA

*Centella asiatica* is a memory-enhancing medicinal plant the water extract of which (CAW) has been shown to improve cognitive deficits in mouse models of aging and neurodegenerative diseases. Our lab has found that CAW also increases the expression of mitochondrial and antioxidant genes in the brains of healthy aged mice and can improve mitochondrial function in isolated hippocampal neurons. Here we explore whether the antioxidant regulatory transcription factor NRF2 (nuclear factor erythroid 2-related factor 2) is necessary for the cognitive enhancing and mitochondrial effects of CAW during normal aging. Male and female NRF2 knockout (NRF2KO) and C57BL6 wild-type (WT) mice were treated with CAW in their drinking water (2g/L) beginning at 5 months of age. Learning, memory and executive function were at 6, 12 and 18
months. Hippocampal mitochondrial bioenergetics were also profiled at those same ages. No differences in cognitive performance or mitochondrial function were observed between genotypes or with CAW treatment at 6 months of age. Improvements in hippocampal mitochondrial function were seen in both male and female mice following CAW treatment beginning at 12 months of age and becoming more pronounced at 18 months. However these improvements were only observed in WT and not NRF2KO mice. CAW likewise improved age-related cognitive deficits in male and female WT animals but not NRF2KO mice. Control treated NRF2KO mice displayed exacerbated age-related cognitive and bioenergetic impairments compared to control treated WT mice. These data show that long-term CAW treatment can delay age-related declines in cognitive and mitochondrial function but only in mice that express NRF2. Because oxidative stress and mitochondrial dysfunction also accompany cognitive impairment in many neurodegenerative conditions as well, this study suggests that CAW or other NRF2 activating compounds may be broadly relevant therapeutic options beyond healthy aging.

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Pharmacological Applications of Modulators of Oxidative Stress

Luciano Saso, PhD
Faculty of Pharmacy and Medicine, Sapienza University of Rome, Rome, Italy

BIOGRAPHY

Prof. Luciano Saso is a Member of the Faculty of Pharmacy and Medicine, Sapienza University of Rome, Italy (http://en.uniroma1.it/). He is author of more than 200 original scientific articles published in peer reviewed international journals with impact factor (H-index Google Scholar = 41, H-index SCOPUS = 33, Total Impact Factor > 500) working mainly in the field of oxidative stress and antioxidants. He coordinated several international research projects and has been referee for many national and international funding agencies and international scientific journals in the last 25 years.


ABSTRACT

Oxidative stress is involved in the pathogenesis of many disorders, and modulators of oxidative stress (OS) can be of value in their treatment. The mechanisms by which OS can be modulated will be presented, including the activation or inhibition of nuclear factor erythroid 2-related factor 2 (Nrf2), the master regulator of endogenous antioxidant enzymes. Unfortunately, it is known that antioxidant treatments failed in many clinical trials and the reasons that might explain that will be illustrated. Novel approaches to redox therapies are necessary and the development of reliable biomarkers capable to predict the clinical responses is crucial.

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REFERENCES


Exploiting Redox Biology for Selectively Targeting Cancer Cells: Therapeutic Implications

Douglas R. Spitz, PhD

Free Radical and Radiation Biology Program, Department of Radiation Oncology, Holden Comprehensive Cancer Center, The University of Iowa, Iowa City, IA, USA

BIOGRAPHY

Dr. Spitz is a well-established investigator studying the role of metabolic oxidative stress in cancer biology and therapy as well as radiobiology. The impact of his work in the redox biology and medicine community is exemplified by the >225 publications he has co-authored. Among his many scientific achievements, he developed the competitive inhibition superoxide dismutase (SOD) activity assay commonly used today to discriminate between MnSOD and CuZnSOD activity in mammalian tissue homogenates. Dr. Spitz showed that acute and chronic exposure of mammalian cells in culture to both H₂O₂ (and high levels of oxygen) induced transient and stable cellular resistance through inducing genomic instability and gene amplification rendering cells cross-resistant to agents used to treat cancer. Discovering that human tumor cell mitochondria generate greater steady-state levels of superoxide and H₂O₂ relative to normal cells, Dr. Spitz has shown that glucose deprivation preferentially kills cancer vs. normal cells by metabolic oxidative stress.

Most recently, Dr. Spitz’s work with a large group of both basic and translational researchers has led to the publication of several high-profile papers and the funding of a NCI PPG as well as a grant from the Gateway Foundation. This collaborative effort is directed at implementing pharmacological ascorbate in radio-chemo-therapy protocols in both preclinical mechanistic studies as well as clinical trials to enhance anticancer responses while protecting normal tissue. These were based on fundamental alterations in oxidative metabolism in cancer versus normal cells discovered by the research team. In another exciting initiative, Dr. Spitz has been involved with both mechanistic as well as translational studies supported by Galera Therapeutics, Inc. using superoxide dismutase mimics to enhance cancer radiotherapy responses; again based on fundamental differences in oxidative metabolism between cancer versus normal cells.

Dr. Spitz serves as the director of the Free Radical and Radiation Biology Graduate Program at the University of Iowa. He is also the director of the Free Radical Metabolism and Imaging Program and the Radiation and Free Radical Research Core Laboratory in the Holden Comprehensive Cancer Center.
ABSTRACT

Relative to normal cells, cancer cells have been shown to demonstrate fundamental alterations in oxidative metabolism leading to increased steady-state levels of superoxide, hydrogen peroxide, and labile iron pools. Alterations in cancer cell oxidative metabolism in turn lead to disruptions in many redox sensitive signaling and gene expression pathways that impact cell growth, differentiation, genomic instability, and cancer progression. Cancer cells adapt to this altered metabolic state by activating many signaling and gene expression pathways that allow them to survive and continue to progress to malignancy, but preclude normal cellular differentiated function.

The current talk will discuss how pharmacological ascorbate and superoxide dismutase mimics can be used to target the oxidative metabolic frailties of cancer versus normal cells to enhance therapeutic outcomes to radio-chemo-therapies both in pre-clinical and clinical trials. The long-term goal is to utilize a detailed mechanistic understanding of alterations in cancer versus normal cell oxidative metabolism and redox biology to develop rapidly implementable new strategies that can enhance tumor responses while protecting normal tissues during standard radio-chemo-therapy protocols.

Supported by P01 CA217797, R01 CA182804, T32 CA078586
The Adaptable Antioxidant Milieu of Tumor Cells

Dr. Nadine Hempel, PhD

Department of Pharmacology,
Penn State College of Medicine
Penn State Cancer Institute

BIOGRAPHY

Dr. Nadine Hempel received her PhD in Pharmacology from the University of Queensland in Brisbane, Australia. Under the mentorship of Dr. Michael E. McManus and Dr. Masahiko Negishi from NIEHS, she studied the gene regulation of members of the SULT1A Phase II drug metabolism enzymes. During her post-doctoral training in the labs of Dr. Gerard Blob at Duke University, and Dr. J. Andres Melendez at Albany Medical College, Dr. Hempel became interested in studying the mechanisms of metastasis, focusing first on the role of the TGF-beta receptor III as a tumor suppressor in ovarian cancer at Duke University, and subsequently investigating the role of reactive oxygen species and mitochondrial superoxide dismutase Sod2 in regulating redox-signaling and cell migration with Dr. Melendez.

She started her independent lab in 2012 with a K99/R00 grant from the NCI focused on mitochondrial redox signaling at the SUNY College of Nanoscale Sciences and Engineering. Since moving to the Penn State College of Medicine in 2015 her research has been funded by the Department of Defense, Rivkin Foundation for Ovarian Cancer and the NCI. Dr. Hempel is currently an Associate Professor in Pharmacology, and Obstetrics and Gynecology, and a Member of the Penn State Cancer Institute. Her research uses a variety of molecular, cellular, imaging and in vivo techniques to focus on ovarian cancer metastasis with an emphasis on the mitochondrial antioxidant stress response, redox signaling, and mitochondrial form and function.

ABSTRACT

Nadine Hempel¹,², Yeon Soo Kim², Beth Worley², Piyushi Gupta-Vallur², Rebecca Phaeton¹, Mythreya Karthikeyan³

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The role of oxidants and their scavengers in cancer biology is complex. While oxidative stress contributes to carcinogenesis, it is now well established that tumor cells conversely adapt to overcome intrinsic and extracellular oxidant surges during tumor progression. Moreover, cancer cells evolve to utilize redox signaling to their advantage. To better understand the complex role of redox biology in cancer, our laboratory has focused on elucidating the adaptable antioxidant landscape of tumor cells, with specific emphasis on metastatic progression of ovarian cancer. Late stage ovarian cancer is marked by poor patient survival and significant metastatic spread throughout the peritoneal cavity.

During this transcoelomic spread cells must adapt to survive anchorage-independence and to cope with stress associated with matrix detachment and the new tumor environment of the ascites and peritoneal organs. We present our findings on the role and regulation of two antioxidant enzymes, the extracellular glutathione peroxidase GPX3 and the mitochondrial superoxide dismutase Sod2, which have distinct functions in aiding metastatic progression of ovarian cancer.
The Use of SOD Mimics as a Radioprotector in Prostate Cancer Therapy

Rebecca Oberley-Deegan, PhD

University of Nebraska Medical Center
Omaha, NE, USA

BIOGRAPHY

Dr. Rebecca Oberley-Deegan received her Ph.D. University of Iowa, Iowa City Iowa and did her postdoctoral training at National Jewish Health, Denver, Colorado. She joined the University of Nebraska Medical Center (UNMC) in Omaha, Nebraska in 2014 as an assistant professor and is currently an associate professor at UNMC. Dr. Oberley-Deegan’s laboratory has previously shown that a catalytically active antioxidant can protect normal prostate tissues during radiation but not prostate tumor tissues. The focus of her research is determining the mechanisms by which antioxidants can protect normal tissues from radiation while simultaneously making the tumor vulnerable to radiation damage.

Dr. Oberley-Deegan’s is focusing specifically on the role of free radical signaling to transform fibroblasts and inflammatory cells in normal tissues, which results in damage to these tissues. In the context of prostate cancer, her group is focusing on inhibiting the signaling events controlled by radiation-induced free radicals involved in tumor survival and metastasis.

ABSTRACT

S Shrishrimal ¹, EA Kosmacek ¹, A Chatterjee¹, RE Oberley-Deegan¹

¹ Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE, USA.

Prostate cancer is frequently treated with radiation therapy, which can be accompanied by damage to normal healthy tissue, resulting in fibrosis. Radiation-induced fibrosis (RIF) is caused by an increase in reactive oxygen species (ROS) and epigenetic remodeling of fibroblast cells mediated by ROS. MnTE-2-PyP (T2E), a scavenger of superoxide, prevents the development of RIF. We hypothesize that T2E prevents radiation-induced epigenetic reprogramming of fibroblast cells and expression of pro-fibrotic components.
**Results:** Animals examined 6 months post-irradiation had significantly higher collagen deposition in skin and bladder tissue after 6 months. In an *ex-vivo* experiment (2 months post-irradiation), fibroblasts isolated from animals treated with T2E were significantly less activated in comparison to radiation treatment group, measured by the collagen contraction assay. Importantly, we have identified a significant upregulation in the NRF2 signaling pathway, in T2E treated fibroblast samples. We also detected an increase in NAD+ levels and an increase in nuclear and mitochondrial sirtuin activity in cells treated with T2E as compared to controls. We have also observed a decrease in MnSOD K122 acetylation, which corresponded to increased activity of MnSOD following T2E treatment. In addition, we have also observed protection of mitochondrial function following radiation exposure with T2E treatment.

**Conclusion:** T2E inhibits radiation-induced changes in fibroblasts, by enhancing NAD+ levels, sirtuin, and MnSOD activities in these irradiated cells, which ultimately protects the mitochondria from radiation-induced damage.
Contributed Talks

Chair: Richard van Breemen, PhD, Linus Pauling Institute, Oregon State University

Friday August 16, 1:30PM - 2:50PM
Plasma Aβ as a Biomarker for Alzheimer's Disease

Scott A. Kuzdzal, PhD
Shimadzu Scientific Instruments,
Columbia, MD, USA

BIOGRAPHY

Dr. Scott Kuzdzal received a Ph.D. from the University of California at Riverside. He served as a postdoctoral fellow at the Johns Hopkins University School of Medicine, where he co-founded and directed the Johns Hopkins Center for Biomarker Discovery with Dr. Daniel Chan. Dr. Kuzdzal assisted in the completion of the Human Genome Project, working with Celera Genomics.

In addition to extensive industrial research experience, Dr. Kuzdzal has a strong medicinal and clinical chemistry background and has directed Toxicology and Therapeutic Drug Monitoring Labs at Johns Hopkins Medical Institutions. He currently serves on the editorial review board of Proteomics and on the Scientific Advisory Board for the Cannabis Science Conference. He has published protein and peptide biomarkers for pancreatic cancer (HIPAP1), Alzheimer’s disease and ovarian cancer using a wide variety of separation and detection methods. Scott has lectured at continuing medical education courses at Johns Hopkins Hospital, George Mason University/INOVA Fairfax Hospital and the NIH, as well as conferences worldwide. Scott currently serves as the Vice President of Marketing at Shimadzu Scientific Instruments.


ABSTRACT

Scott A. Kuzdzal, Masayuki Nishimura, and Yusaku Hiyoki,
Shimadzu Scientific Instruments, Columbia, MD, USA

Accurate biomarker information is necessary to facilitate clinical trials of disease-modifying therapies for Alzheimer's disease, which are expected to be most efficacious at the earliest and
mildest stages of the disease. Currently, only positron-emission tomography (PET) imaging and the measurement of amyloid-β in cerebrospinal fluid are the only validated methods for identifying amyloid-β deposition in the brain. Minimally invasive, cost-effective blood-based biomarkers are needed. Recently, Koichi Tanaka et al. (Nature. 2018 Feb 8;554(7691):249-254. doi: 10.1038/nature25456. Epub 2018 Jan 31) demonstrated the ability of amyloid-β precursor protein (APP)669-711/amyloid-β (Aβ)1-42 and Aβ1-40/Aβ1-42 ratios to predict individual brain amyloid-β-positive or -negative status.

These biomarkers showed high performance when predicting brain amyloid-β burden. The composite biomarker showed very high areas under the receiver operating characteristic curves (AUCs) in both data sets (discovery, 96.7%, n = 121 and validation, 94.1%, n = 111) with an accuracy approximately equal to 90% when using PIB-PET as a standard of truth. These test biomarkers were correlated with amyloid-β-PET burden and levels of Aβ1-42 in cerebrospinal fluid. These results demonstrate the potential clinical utility of plasma biomarkers in predicting brain amyloid-β burden at an individual level. This talk will review these biomarkers as well as describe efforts to bring reliable and accurate testing services online in North America.
Quantitative Phosphoproteomics Dereplicates Pharmacology of Leucettine Analogue L41 on the Correction of Cognitive Deficits in Down Syndrome Mouse Models

Spiros D. Garbis, PhD

California Institute of Technology, Pasadena, CA, USA

BIOGRAPHY

Dr. Garbis is engaged in the development of innovative bioanalytical mass spectrometry based methods to support the integrated multi-omics interrogation of biological specimens.

In particular, Dr. Garbis’ research interest lies in the development of blood based assays for the early diagnosis of disease. Chronic diseases, when viewed as a full spectrum disorders, share common etiologic features. For example, the multi-omics study of matched tissue, primary cell and blood specimens derived from patients with cancer, cardiovascular, and neurodegenerative disease has revealed their common causal link to deregulated insulin signalling and metabolic reprogramming. Within such a framework, the overarching theme for Dr. Garbis’ research approach envisages:

“Driving innovation in analytical chemistry and its ancillary technologies that increase biological insight with a translational impact.”

ABSTRACT

Thu Lan Nguyen¹, Arnaud Duchon¹, Antigoni Manousopoulou², Nadège Loaëc³, Benoît Villiers³, Guillaume Pani³, Laura Harsan⁴, Emmanuelle Limanton⁵, François Carreaux⁵, Spiros D. Garbis⁶, Laurent Meijer³, Yann Herault¹

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Evidence suggests the involvement of the kinase DYRK1A in the pathophysiology of Down Syndrome and Alzheimer’s disease. Quantitative and spatial phosphoproteomics demonstrated how the pharmacological inhibition of brain DYRK1A with the leucettine natural product analogue L41 was able to rectify recognition memory deficits in three DS mouse models all expressing an extra copy of *Dyrk1a*. Specifically, the accumulation of DYRK1A in the synaptic regions was reversed with L41 leading to the reduction of object cognitive impairment in these models. The study identified how the L41 treatment affected the regio-specific phosphorylation status of proteins and thus synaptic response and axonal re-organization.
From Source to Bedside: Real-world Challenges in Translational Studies of *Centella asiatica* for Alzheimer's Disease

Kirsten Wright, ND, MCR, MS

Department of Neurology
Oregon Health & Science University,
Portland, OR, USA

BIOGRAPHY

Dr. Kirsten Wright is an Assistant Professor with the Rex and Ruth H. Layton Aging and Alzheimer’s Disease Center and Department of Neurology at Oregon Health & Science University (OHSU). She focuses on translational studies of an Ayurvedic botanical, *Centella asiatica*, for neurological disorders, specifically dementia, and the impact of dietary patterns on daily function in healthy elders and those with cognitive decline.

She received her Doctorate of Naturopathic Medicine and her Master of Science in Integrative Medicine Research from the National University of Natural Medicine (NUNM; Portland, OR) in 2014. Her work focused on complex botanical medicine questions, such as herbal synergy, emphasizing the need to make botanical medicine research applicable to clinical practice. In 2018, she completed a Master of Clinical Research at OHSU through the Human Investigations Program. Prior to coming to OHSU, Dr. Wright practiced medicine in the Portland metropolitan area focused on integrative primary care, intravenous nutrient therapies, functional medicine, sports medicine and regenerative medicine.

ABSTRACT

Kirsten Wright¹, Armando Alcazar Magana²,³, Maya Caruso¹, Nora Gray¹, Donald Matthews³, Jan F. Stevens³,⁴, Claudia S. Maier²,³, Joseph Quinn¹,⁵, Amala Soumyanath¹

¹Department of Neurology, Oregon Health and Science University, Portland, OR, USA
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⁴Department of Pharmaceutical Sciences, Oregon State University, Corvallis, OR, USA
⁵Department of Neurology, Veterans Affairs Portland Health Care System, Portland, OR, USA

Alzheimer’s Disease (AD) is a debilitating form of dementia with a high global burden and unmet need for effective treatments. *Centella asiatica* (CA) is a botanical from Eastern medicine reputed to

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enhance cognition. Our preclinical studies on CA and its bioactive components strongly support its potential as a phytotherapeutic agent for aging, cognitive decline and AD through influences on antioxidant response, mitochondrial activity, tau phosphorylation and synaptic density. We have initiated Phase I clinical studies (NCT03929250) of CA based on these data, and will present our experience developing a rational phytotherapeutic product from CA for human investigation in aging and AD. Translation from preclinical models to humans, and developing an optimized, reproducible product for use in clinical trials, present particular challenges for phytotherapeutic agents compared to single chemical entities. Our robust scientific approach is an example of addressing the complexity and variability of raw botanicals and botanical extracts. Specific discussions will include approaches to identifying an optimal dose range for clinical evaluation, the analysis and characterization of phytochemical variability, contamination and adulteration of raw material, challenges in the formulation and manufacture of a stable botanical intervention and matching placebo, as well as specific considerations for botanical bioavailability studies in humans. Our studies highlight the importance of identifying active compounds of botanicals and developing sound analytical methodology for their determination in botanical extracts and animal and human samples, as these analyses are crucial to the optimization of product composition and dosage.
Quercetin Prevents Rhinovirus-Induced Progression of Lung Disease in a Mouse Model of Chronic Obstructive Pulmonary Disease

Umadevi Sajjan, PhD

Associate Professor
Department of Physiology & Thoracic Medicine and Surgery
Center for Inflammation, Translational and Clinical Lung Research
Lewis Katz Medical School, Temple University, Philadelphia, PA, USA

BIOGRAPHY

Dr. Sajjan is an eminent researcher and is interested in understanding the mechanisms of defective innate immunity of lungs that leads to development and progression of lung disease in persons with cystic fibrosis and chronic obstructive pulmonary disease. She is recognized for her work on interactions of airway epithelial cells with respiratory pathogens at the national and international levels. Another line of Dr. Sajjan’s research is to understand how quercetin, a natural polyphenol modulate innate immunity and thus inflammation. Based on the outcome of her preclinical studies, now the quercetin is being under Phase II clinical trial for the treatment of chronic obstructive pulmonary disease. One day she hopes that quercetin is useful in the treatment of other chronic inflammatory conditions. Since starting an independent career as a scientist at the Hospital for Sick Children, Toronto, Dr. Sajjan has trained several undergraduate students and post-doctoral and clinical fellows. Dr. Sajjan has also assisted senior investigators at the University of Michigan in training graduate students. Dr. Sajjan has over 80 peer reviewed publications and more than 50 conference presentations to her credit. She has written invited review articles and book chapters. Dr. Sajjan is Associate Professor in Lewis Katz Medical School, Temple University and actively participates in teaching of Medical and graduate students. She is dedicated in the training of future scientists and currently she is training three post-doctoral fellows, four undergraduate students, and rotating graduate and MD/PhD students in her research laboratory.

Since starting her career as independent investigator, Dr. Sajjan has been serving as peer reviewer for various national and international scientific journals. She also serves as a peer reviewer for various federal and non-federal grant agencies including NIH, Cystic Fibrosis Foundation, British Lung Foundation, Asthma Foundation, Agence Nationale de la Recherche, and Canadian Institutes of Health Research. While working at the Hospital for Sick Children and University of Michigan, Dr. Sajjan served as member of Annual Research Retreat committee and organized poster and oral presentation sessions. Currently, she is a member of seminar organizing committee and involved in organizing basic research seminars for CILR.
and for Department of Thoracic Medicine and Surgery. She is also a member of Faculty Recruiting committee for CILR and for Department of Thoracic Medicine and Surgery. Dr. Sajjan served as a member of University Senate while working at the University of Michigan for four years. Currently Dr. Sajjan is serving as representative of Medical School Faculty on the University Senate and is nominated for Medical School Faculty senate.

ABSTRACT

Acute exacerbations are the major cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). Rhinovirus, which causes acute exacerbations may also accelerate progression of lung disease in these patients. Current therapies reduces the respiratory symptoms and does not treat the root cause of exacerbations effectively. We hypothesized that quercetin, a potent antioxidant and anti-inflammatory agent with antiviral properties may be useful in treating rhinovirus-induced changes in COPD. Mice with COPD phenotype maintained on control or quercetin diet and normal mice were infected with sham or rhinovirus, and after 14 days mice were examined for changes in lung mechanics and lung inflammation.

Rhinovirus-infected normal mice showed no changes in lung mechanics or histology. In contrast, rhinovirus-infected mice with COPD phenotype showed reduction in elastic recoiling and increase in lung inflammation, goblet cell metaplasia, and airways cholinergic responsiveness compared to sham-infected mice. Interestingly, rhinovirus-infected mice with COPD phenotype also showed accumulation of neutrophils, CD11b+/CD11c+ macrophages and CD8+ T cells in the lungs. Quercetin supplementation attenuated rhinovirus-induced all the pathologic changes in mice with COPD phenotype. Together these results indicate that quercetin effectively mitigates rhinovirus-induced progression of lung disease in a mouse model of COPD. Therefore, quercetin may be beneficial in the treatment of rhinovirus-associated exacerbations and preventing progression of lung disease in COPD.