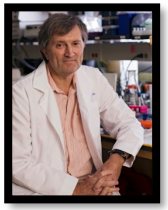
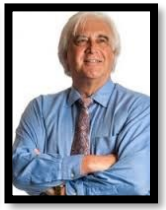
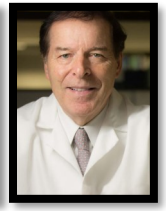
COBRE Core Directors




1) **Lauren Ball, PhD**
Associate Professor of Cell & Molecular Pharmacology & Experimental Therapeutics
Director of Core B: Proteomics Core
2) **Craig Beeson, PhD**
Professor of Pharmaceutical and Biomedical Sciences
Director of Core C: Bioenergetics Profiling Core
3) **John J. Lemasters, MD, PhD**
Professor and GlaxoSmithKlein
Distinguished Endowed Chair of Drug Discovery and Biomedical Sciences
Professor of Biochemistry and Molecular Biology
Director of Core D: Cell and Molecular Imaging Core
4) **Danyelle Townsend, PhD**
Associate Professor of Drug Discovery & Biomedical Science
Director of Core E: Analytical Redox Biology Core

COBRE Executive Board 2017


1) **Kenneth D. Tew, PhD, DSc**
Medical University of South Carolina MUSC
2) **Franklin G. Berger, PhD**
University of South Carolina
3) **Yvonne Janssen-Heininger, PhD**
The University of Vermont
4) **Dean P. Jones, PhD**
Emory University of Medicine
5) **Garth Powis, D. Phil**
Sanford Burnham Prebys Medical Discovery Institute
6) **Peter J. van Bladeren, PhD**
Nestlé : Retired Vice President of Regulatory & Scientific Affairs

COBRE Spring 2017

SC COBRE in Oxidants, Redox Balance and Stress Signaling

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

Tuesday
7th of March 2017
8am-3:30pm
Bulls Bay Golf Club
955 Bulls Bay Boulevard
Awendaw, SC 29429
www.bullsbaygolf.com

About COBRE...

After successfully competing for Phase II funding, the COBRE program is now entering the second stage of its development. For funding years 6 – 10 we continue to bring together junior investigators with interests and expertise in oxidants, redox balance and stress signaling at the Medical University of South Carolina. During the first year of Phase II (2016-2017) we have supported four individuals and successfully integrated a fourth scientific core facility. Building the core infrastructure is a prerequisite for facilitating longer-term plan of developing a viable Phase III application that focuses only on facilities support for the Center. Our plan continues to be to develop in South Carolina a Center of Excellence in the scientific discipline of redox biology.

Existing infrastructure has provided a successful mentoring environment for target faculty members with research interests that span a number of human pathologies. RO1 successes of some of our recent graduates in addiction (Uys) and neurodegenerative disorders (Pehar) now leave us with four investigators with interests in cancer (Wang; Dolloff), cardiovascular disease (Angel), neurodegenerative disorders (Boger). In each instance, the interface of these diseases with oxidant stress, redox homeostasis and stress signaling provides the fundamentals for the programmatic development of the Center. Their projects provide interdisciplinary opportunities and are supported by four scientific cores in Proteomics, Bioenergetics, Cell and Molecular Imaging and Analytical Redox. Our central hypothesis continues to be that redox regulated pathways impact significantly on the pathobiology of diseases such as cancer, aging, diabetes, inflammation and neurodegeneration. We anticipate releasing an RFA for new junior investigators in the third quarter of 2017.

The administrative core facilitates many functions including business management, faculty development, mentoring, program planning and sustainability. We have appointed oversight committees to include Steering, Internal Advisors and External Advisors. Since last year, Dr. Banarjee has retired from the EAB and has been replaced by Dr. Frank Berger from USC. He brings extensive experience having run a COBRE program for the previous 15 years. His expertise in evolving our core components into a successful Phase III application will be extremely valuable. Our advisory groups contain individuals who have broad scientific expertise in chosen disciplines and also considerable mentoring experience. Future development of the program at MUSC is also presently served by existing financial commitments from the Deans of Medicine and Pharmacy and the Provost Office. As we move forward with additional faculty recruitments, our goals will continue to include attainment of peer review support and continued development of the core facilities. We have had a very successful year.

Gavin Wang, MD, PhD

COBRE Project Director

Assistant Professor of Pathology
and Laboratory Medicine

Targeting Cancer Stem Cells for Breast Cancer Treatment

Despite recent advances in the treatment of breast cancer, drug resistance and metastatic progression remain a significant hurdle in clinical practice. Cancer stem cells (CSCs), also known as tumor initiating cells, are thought to be responsible for driving tumor initiation, growth, maintenance, recurrence and metastasis. Increasing evidence has shown that CSCs are resistant to traditional therapies and thus may account for tumor recurrence and metastasis by regenerating new tumors. Therefore, there is a critical need to discover and develop new drugs that can effectively eliminate drug-resistant CSCs. Our recent studies have demonstrated that C1572, a small-molecule, naturally occurring phenanthrofuran, selectively kills CSCs in a dose-dependent fashion in various human triple-negative breast cancer (TNBC) cell lines. Mechanistically, we found that nanomolar concentrations of C1572 reduced expression and function of c-Myc (MYC) via a proteasome-dependent mechanism. Knockdown of MYC recapitulates the CSC killing effect of C1572. Treatment with C1572 leads to a 28-fold decrease of TNBC CSCs. Together, these results identify C1572 as a promising first-in-class lead compound that depletes drug-resistant CSCs in TNBC via targeting the MYC oncoprotein. These new findings prompt us to hypothesize that targeted inhibition of MYC by C1572 or its analogues can be exploited as an innovative therapeutic strategy to eliminate drug-resistant CSCs and thus improve the clinical outcome of TNBC treatment.

To gain new insights into the mechanisms by which CSCs are resistant to chemotherapy and radiation, we investigated reactive oxygen species (ROS) levels in CSCs compared with non-stem tumor cells (NSCs). Surprisingly, we found that CSCs show marked lower levels of ROS than NSCs do, suggesting a role for redox signaling in CSC drug resistance. In agreement with this idea, our recent studies have revealed that pharmacological activation of Nrf2 attenuates ionizing radiation (IR)-induced cell killing in TNBC CSCs, whereas knockdown of Nrf2 sensitizes CSCs to radiation therapy. These results strongly support the hypothesis that the redox signaling pathways may play a critical role in modulating the response of CSCs to radiation-induced oxidative stress. We will vigorously test this hypothesis by pursuing the following three Specific Aims: Aim 1 will elucidate the mechanisms whereby CSCs maintain a lower level of ROS, Aim 2 will investigate the role of Nrf2 in regulating redox balance and therapy resistance in TNBC CSCs, and Aim 3 will determine if targeting of selective redox signaling pathways enhances the therapeutic efficacy of TNBC treatment.

Nathan Dolloff, PhD

COBRE Project Director

Assistant Professor of Cell and Molecular Pharmacology and Experimental Therapeutics

Altered redox and cellular bioenergetics drive Velcade resistance in multiple myeloma

Multiple Myeloma (MM) is a plasma cell dyscrasia and the second most common hematological malignancy in the U.S. Patient survival has significantly improved due to treatment advances, such as the development of the proteasome inhibitor bortezomib (Btz). Despite the clinical success of Btz, therapeutic resistance invariably emerges, thus marking the incurable nature of the disease. New molecular targeted treatment strategies are therefore needed, particularly those that enhance the activity of existing drugs like Btz.

Redox signaling is a particularly attractive target in the treatment of MM and other plasma cell disorders for multiple reasons. Plasma cells are the effector cells of the humoral immune response and are tasked with synthesizing and secreting immunoglobulins. The process of mass-producing bulk amounts of protein generates equimolar amounts of reactive oxygen species (ROS), making these cells vulnerable to even the slightest alterations in redox homeostasis. Secondly, the most prevalent genetic abnormality in plasma cell disorders is a chromosomal translocation involving the immunoglobulin heavy chain gene (IgH) and a region of chromosome 11q13. This translocation induces the up-regulation of 11q13 genes, one of which is glutathione S-transferase pi (GSTP), an important regulator of the cellular redox state.

Further evidence comes from drug screening studies that were conducted by our group to identify chemical structures that restore Btz sensitivity to resistant cells. Interestingly, the screening hits were enriched for redox-modulating compounds (4 out of 7), suggesting that disrupting redox signaling reverses proteasome inhibitor resistance. Taken together, the redox pathway is a promising target for the treatment of plasma cell malignancies, and may be an effective therapeutic approach to combating drug resistant MM.

Overview of the Day...

CONTINENTAL BREAKFAST
- 7:30am- 8:00am

OPENING REMARKS
CHAIR: KENNETH D. TEW, PHD, DSC
- 8:00am- 8:15am

Peggi Angel, PhD —*COBRE Project Director*
- 8:15am- 8:50am
- 8:50am– 9:00am *DISCUSSION*

Craig Beeson, PhD —*Director of Core C*
- 9:00am– 9:15am
- 9:15am– 9:25am —*DISCUSSION*

BREAK –10 MINUTES

Heather Boger, PhD —*COBRE Project Director*
- 9:35am—10:10am
- 10:10am–10:20am —*DISCUSSION*

Lauren Ball, PhD —*Director of Core B*
- 10:20am–10:35am
- 10:35am–10:45am —*DISCUSSION*

Nathan Dolloff, PhD —*COBRE Project Director*
- 10:45am-11:20am
- 11:20am–11:30am *DISCUSSION*

LUNCH –45 MINUTES
- 11:30am–12:15pm

KEYNOTE SPEAKER:
PETER J. VAN BLADEREN, PHD
Retired Vice President of Regulatory & Scientific Affairs
Nestlé Switzerland
TITLE: *Innovation at Nestlé and in Europe*
- 12:15pm– 1:15pm

John Lemasters, MD, PhD —*Director of Core D*
- 1:15pm– 1:30pm
- 1:30pm– 1:40pm —*DISCUSSION*

Gavin Wang, MD, PhD —*COBRE Project Director*
- 1:40pm– 2:15pm
- 2:15pm– 2:25pm *DISCUSSION*

Danyelle Townsend, PhD —*Director of Core E*
- 2:25pm– 2:40pm
- 2:40pm– 2:50pm —*DISCUSSION*

CLOSING REMARKS
CHAIR: KENNETH D. TEW, PHD, DSC
- 2:50pm-3:00pm

EXECUTIVE BOARD MEETING
- 3:00pm-3:30pm

Peggi Angel, PhD

COBRE Project Director

Assistant Professor of Cell and Molecular Pharmacology and Experimental Therapeutics

Systems-based analysis of redox activity in aortic valve stenosis

Oxidative stress plays a key but unknown role in fibrocalcific aortic valve stenosis (FAVS). FAVS is a disease of aortic valve (AV), where leaflets progressively stiffen and eventually calcify, causing cardiac malfunction. The only treatment is surgical valve replacement. Increased oxidative stress due to redox imbalance is believed to be an initiating factor for end point calcification of the aortic valve (AV) leaflets, but redox status during FAVS remains undefined. Our current data shows that oxidative stress is increased in a very young adult mouse model of aortic valve stiffening, concomitant with extracellular matrix remodeling, implicating that redox mechanisms play a much earlier role in FAVS than previously described. We hypothesize that early redox imbalances are associated with the ECM disorganization that results in valvular stiffening. To delineate redox mechanisms, Aim 1 will define redox status in bulk, whole mount and histological cross sectional measurements of the AV leaflet during early sequential aortic valve stiffening. Physiological measurements of heart function and biomechanical properties of the AV will be used to define levels of AV stiffening parallel with redox status. Aim 2 will utilize proteomic techniques on extracts from decellularized valve leaflets to identify redox sensitive cellular pathways and protein interaction networks (PINs) during sequential valve stiffening. Bioinformatic approaches will be used to assess PINs regulated during valve stiffening, earmarking new candidates of FAVs. Extracellular matrix (ECM) from the decellularized valve structure will be interrogated by proteomics and immunoblotting to report on ECM changes correlating to increased oxidative stress. Bioinformatics tools and immunoblotting techniques will be used to report on oxidative stress induced post translational modifications. Aim 3 will delineate regulation in protein interaction networks coinciding with increased oxidative stress in de-identified normal and FAVS clinical specimens. A combination of immunohistochemistry, immunoblotting, and proteomics will be used to define the redox status of normal AV compared to FAVS at a cellular level and assess overall contribution to valve structure phenotype. Candidates from the murine model of early valve stiffening will be evaluated for contribution to FAVS in clinical specimens. This investigation relies on the unique resources of the Medical University of South Carolina's COBRE in Oxidants, Redox Balance and Stress Signaling and would not be accomplished without use of these resources. This study will allow us to define the role of redox balance and affected protein expression during the early stages of valve stiffening in FAVS, identifying new therapeutic targets that might inhibit disease progression, improve quality of life and decrease mortality.

Heather Boger, PhD

COBRE Project Director

Assistant Professor of Neurosciences

Novel Therapeutic Strategy for Parkinson's Disease

Individuals with Parkinson's disease (PD) not only have an accelerated decline in substantia nigra dopamine (SN-DA) neurons and locus coeruleus norepinephrine (LC-NA) neurons; they also have reduced SN BDNF levels and increased oxidative stress. Preliminary studies from our laboratory show that chronic vagus nerve stimulation (VNS) retains the number of DAergic and NAergic neurons, improves locomotor activity, and increases BDNF in the brain. Preclinical studies have shown that VNS exerts its protective effects via brainstem nuclei, such as the LC. The use of vagus nerve stimulation (VNS) has already been implemented for the clinical use of treatment-resistant depression and epilepsy.

To date, no studies have assessed the effects of VNS on PD pathology and motor dysfunction VNS models have shown increased NAergic levels and brain-derived neurotrophic factor (BDNF) expression in LC target regions via PPARγ activation. In addition VNS has been shown to exert anti-oxidant effects in various peripheral and central nervous system models. Based on these findings we want to further explore the use of VNS as a treatment strategy for PD. In addition, we want to determine a potential mechanism by which VNS is exerting is neuroprotective effects, specifically, if VNS has anti-oxidant and neuroprotective signaling effects in a double lesion model of PD. Our overall hypothesis is that chronic vagus nerve stimulation will alleviate PD-like pathology and motor dysfunction as a result of combined DAergic/NAergic degeneration via PPARγ activation: 1) as an antioxidant to reduce oxidative stress and 2) as a transcription factor to increase BDNF expression.

To address this hypothesis, two aims were formulated: Aim 1) Chronic vagus nerve stimulation reduces oxidative stress via activation of PPARγ, resulting in attenuation of motor impairment and DAergic/NAergic degeneration; and Aim 2) Chronic vagus nerve stimulation abrogates DAergic/NAergic degeneration by increasing BDNF expression and activation of the BDNF receptor, TrkB. Findings from these studies will provide insight into the mechanism by which VNS alleviates neuronal damage as a result of PD. Furthermore, these studies will provide information on novel treatment strategies, VNS and the systemic administration of PPARγ agonists, to be implemented in clinics for PD patients.