

2005 DHLRI THEMATIC PROGRAMS: SCIENTIFIC AND FINANCIAL PLAN

Original Investment Area title: ISCHEMIA and METABOLISM
New Title (if applicable):

Program Director: **JAY ZWEIER, M.D.**

Program Co-Director: **THOMAS CLANTON, PH.D.**

Clinical/Translational Assoc-directors: **MARK ANGELOS, M.D., BEN SUN, M.D., GLEN COOKE, M.D.**

ABSTRACT (Please limit to the size of the text box)

The goal of this research focus is to understand the underlying mechanisms of tissue injury associated with periods of ischemia/reperfusion and to determine new approaches of preventing and reversing post-ischemic tissue damage.

Particular focus will be placed on understanding these mechanisms in the heart and its vasculature. Special focus will also be on approaches to precondition or chemoprotect the heart. Investment will also be used to promote more basic investigations regarding how cells sense, respond and adapt to various forms of hypoxia, the role of reactive oxygen and nitrogen intermediates and the responses of the brain, vascular wall and other relevant organs and tissues to hypoxia and ischemia. The action plan for this theme includes 1) regular meetings and study groups to develop a community of scholars in this area, 2) provisions for financial opportunities and incentives for young investigators and clinical translational seed projects, 3) active recruitment of new faculty to round out projected future program projects and new research vectors and 4) ongoing development of collaborative research in the form of program projects and other center grants. 5) support of the development of a training grant in this area 6) support of national / international scholars in residence to facilitate building world leading research in ischemia and metabolism.

Faculty recruitment objectives: A Search Committee of 5 active members of this programmatic area will oversee the faculty recruitment efforts with the final decision made by the Program Director and approval of the DEC.

Development of junior faculty and clinical translational projects: Funds will be set aside for seed grants for junior faculty, with support of developing translational and clinically oriented projects highly encouraged.

Mentorship and faculty development: Junior faculty focusing in this area will be provided intensive mentorship from teams of investigators who will assist them in career development, grant writing and encouragement of creative new ideas.

Short term programmatic goals: Three program projects have been outlined by the group with the first in "cardiac ischemia/myocardial salvage" with a goal of the first submission being in the spring or fall of 2006.

1. Projected Faculty Participation

Key Personnel (P.I. status/ HLRI Members) who will actively participate in this Program (use additional rows as necessary).

Name	Dept./Div.	Role in the Development Plan
Jay Zweier	Cardiol.	Director
Tom Clanton	Pulm.	Co-Director
Mark Angelos	Emer.Med	Clinical Assoc-Director
Glen Cooke	Cardiol.	Clinical Assoc-Director
Ben Sun	Thor. Surg.	Clinical Assoc-Director
<i>Note: The following faculty will play a variety of roles as possible team leaders of program project grants, co-investigators, consultants or simply interested parties. Their individual roles have not been determined at this time.</i>		
Agarwal, Sudha	Dental School	
Alevriadou, Rita	Cardiology	
Bauer, John	Children's Research	
Billman, George	Physiology & Cell Biology	
Binkley, Philip	IM/Cardiology	
Bonagura, John	Veterinary Clinical Science	
AJ Cardounel	Pharmacology	
Carnes, Cynthia	Pharmacology	
Chen, Yeong-Ren	Cardiology	
Clanton, Thomas	Biophysics	
Crouser, Elliott	Pulmonary	
Elton, Terry	Pharmacy	
Gerhardt, Mark	Anesthesiology	
Gyorke, Sandor	Cardiology	
Hassanain, Hamdy	CT Surgery	
He, Guanglong	Cardiology DHLRI	
Hille, Russ	M&C Biochemistry	
Hoyt, Dale	Pharmacology	
Ilangovan, Govindasamy	Cardiology DHLRI	
Janssen, Paul	Physiology & Cell Biology	
Khrantsov, Valery	Pulmonary	
Kuppusamy, Periannan	Cardiology DHLRI	
Li, Yunbo	Cardiology	
Liu, Xiaoping	Cardiology DHLRI	
Liu, Zhenguo	Cardiology	
Magalang, Ulysses	Pulmonary	
Mehta, Kamal	M&C Biochemistry	
Moldovan, Leni	Cardiology	
Moldovan, Nicanor	Cardiology	
Parinandi, Narasimham	Pulmonary	
Roy, Sashwati	Surgery	
Sadee, Wolfgang	Pharmacology	
Saltz, Joel	Biomedical Informatics	
Samouilov, Alex	Cardiology DHLRI	
Sen, Chandan	Surgery	
Villamena, Frederick	Cardiology DHLRI	
Xia, Yong	Cardiology DHLRI	
Ziolo, Mark	Physiology & Cell Biology	
Zweier, Jay	Cardiology, DHLRI	

Other Personnel (Faculty status/ HLRI Members) who are likely to collaborate or directly benefit from the Program.

Name	Dept./Div.	Role in the Development Plan
NA		

List of Current Active and submitted funding of Key Personnel and its relationship to this project:

P.I. Last Name	Source/ Grant Number	Yrs	Grant Title
Zweier	See attached list		
Clanton	NHLBI-533333-10	2006-2011	“Redox mechanisms of respiratory muscle stress adaptation”
Angelos			
Cooke			
Sun			

Further details:

Faculty recruitment objectives: A Search Committee of 5 active members of this programmatic area will oversee the faculty recruitment efforts with the final decision made by the Program Director and approval of the DEC. Initial discussions have set the goal of bringing in one or more nationally funded leaders who can provide crossover expertise into at least 2 other thematic programs. Discussions thus far have centered on candidates with the following descriptions: a) an outstanding clinical and/or translational scientist who will bring substantial and proven abilities to link the basic research in the ischemic heart to human or to relevant whole animal models; b) a basic scientist with expertise in NMR spectroscopy, related to metabolic control in the ischemic, stunned or hibernating myocardium, c) expertise in the control of post-ischemic myocardial inflammation and tissue repair and d) expertise in the use of stem cell or gene replacement methodologies for post-ischemic myocardial repair & regeneration.

Development of junior faculty and clinical translational projects: Substantial funds will be set aside for seed grants for junior faculty over the first 2 years. Seed grants for developing translational and clinically oriented projects will be highly encouraged. Considerable care will be given to ensure tracking of research funds, sustained productivity and accountability.

Mentorship and faculty development: Junior faculty focusing in this area will be provided intensive mentorship from teams of investigators who will assist them in career development, grant writing and encouragement of creative new ideas.

Short term programmatic goals: Three to four program projects have been outlined by the group. It was generally decided that the first program project will be in “cardiac ischemia” with a goal of the first submission being in the spring or fall of 2006. A second goal is a response to an NIH RFA from the NHLBI on “Systems Biology.” The goal will be to develop the equivalent of 2-linked RO-1/R-21’s in the area of “modeling the redox environment in the myocardium in both of these projects take advantage of current strengths and interests within existing faculty and provide an avenue for future growth and collaboration with other thematic programs.

2. Overall Objectives of the Thematic Program, how they fit with the DHLRI Mission and how they resonate with national research priorities. (Limit 2 pages).

Overall Objective

The goal of this research focus is to understand the underlying mechanisms of tissue injury associated with prolonged periods of ischemia and to determine new approaches of preventing and reversing progressive tissue damage in the post-ischemic/ recovery phase.

Specific Research Objectives

1. To determine the underlying mechanisms responsible for long term myocardial tissue injury, post ischemia. Sub categories of potential investment and focus include the following:
 - a. The influence of the local cellular and tissue environments during and after ischemia on downstream events that result in organ injury and cell death.
 - b. The influence of ischemic events in triggering later inflammatory cell migration and activation in the ischemic region.
 - c. The mechanisms by which healthy cardiac tissue resists ischemic injury by oxygen or energy sensing mechanisms and how these mechanisms may be compromised with aging, local environmental factors, diabetes, sleep apnea, etc.
 - d. The role of redox state and nitric oxide metabolism in responses of the myocardium and vasculature to ischemic insult.
 - e. Calcium regulation and calcium-induced damage in the post ischemic state.
 - f. Mechanisms of altered mitochondrial function and permeability transition in the ischemic myocardium.
 - g. Measurement and imaging of cardiac bioenergetics
 - h. In vivo imaging of cellular viability, function, calcium, oxygen or redox state
2. To effectively develop and test strategies for limiting damage and promoting recovery of the post-ischemic myocardium and vasculature.
 - a. To develop a rational strategy for post-ischemic metabolic treatment that maximizes the rapid return toward metabolic homeostasis.
 - b. To determine whether antioxidants, nitroxides or other redox sensitive agents can substantially influence the damaging events in the post-ischemic phase.
 - c. To investigate potential strategies for recovery and regeneration of lost or hibernating tissue following prolonged ischemia.
 - d. To develop new methods of prevention of progression to heart failure following severe myocardial infarction.
3. To develop modeling/hypothesis-generating computational system for understanding the redox and calcium-regulating microenvironment of the ischemic myocardium.

4. To achieve a basic understanding of how cells respond naturally to conditions of hypoxia and to integrate this understanding into disordered end-organ function in patients with systemic hypoxia in the clinical environment.
5. To understand the alterations in nitric oxide synthesis and metabolism that occur during and following ischemia in the heart and in the brain.

These aims fit well into the overall mission of the Davis Heart & Lung Research Institute in that they are directly centered on the treatment, prevention and further development of our understanding of myocardial infarction, probably the most common form of heart disease in the U.S. The area of "Arrhythmias, ischemia and sudden cardiac death" is also a major subdivision of the NHLBI, Division of Heart and Cardiovascular Disease. There are a number of new research initiatives in stroke and many long term research initiatives in areas related to myocardial ischemia. The area of "oxygen sensing" is one of the most rapidly growing areas of biology, at both a molecular and physiological level and the DHLRI is currently the center of world-wide research in the role of oxidants, NO and related redox sensitive systems in the heart.

Specific Training and Faculty Development Objectives

1. To provide resources and support for junior faculty to develop their own independent research along the lines of this programmatic theme.
2. To provide new avenues for faculty to play collaborative roles in this programmatic theme that take advantage of their individual strengths as independent investigators and provide substantial benefits to support their research program.
3. To provide resources and support for clinical faculty to lay the groundwork for translational projects related to this theme.
4. To provide a more intense senior mentoring program to ensure the individual success of investigators and their trainees working in this area of research.

Cross-over to other programmatic themes.

1) One of the frontiers of research in this area is to understand the signals that arise from the damaged myocardium that are responsible for recruitment and retention of inflammatory cells, which are believed to contribute to the long term damage. Therefore, there are strong ties to the thematic area related to **Inflammation**.

2) A particular emphasis will be paid to therapeutic strategies for repair and salvage of the myocardium following ischemic injury. This area greatly overlaps the thematic area of **tissue regeneration**.

3) Since much of the focus in this area is related to the myocardium, the area also overlaps strongly with **myocyte biology**. In particular, one of the principle problems in the post-ischemic myocardium is in calcium regulation, which is a major interest of many investigators in this area.

3. Describe plans for integration of the basic science aspects of the program with existing clinical or translational research in heart and lung disease. (limit 1 page)

One of our primary areas of recruitment is targeting faculty working in the area of the ischemic myocardium who can provide leadership in translational research, large animal research and in aligning the clinical enterprise with this research area. We will work closely with several clinical

departments to find the appropriate match for this area, including the Division of Cardiology, Physiology and Cell Biology, Emergency Medicine and Thoracic Surgery.

We have chosen Dr. Mark Angelos to help us in making this translational effort with the Emergency Room and Emergency Department personnel. Ben Sun will assist us in interaction with the Thoracic Surgery Division and Glen Cooke will provide the contact with the Cardiology Division. We will work closely with these investigators to find ways to bring members of their respective departments and Divisions into this research effort. We hope to recruit young faculty, fellows and residents within their programs to be attracted to this area of research and we need their help in communicating what we can do for their respective departments/divisions with respect to translational research support.

By having a pool of resources *specifically* reserved for promotion of clinical and translational research in this area, we feel we will provide the incentive for collaborative work between our clinical and basic science investigators. Special efforts will be made to ask clinical investigators to attend our meetings, workshops, study groups and seminars. We will also make every effort to “team” a clinical investigator or group of investigators with specific basic scientist or group of scientists who could cross-fertilize.

With regard to the types of clinical projects or areas, there are many opportunities in the OR for research in ischemia and myocardial protection, particularly with regard to successful bypass surgery and transplant, myocyte preconditioning before surgery and graft patency. In the cath. lab various translational projects related to the vascular wall would be appropriate and to the treatment and salvage of myocardium after removal of coronary blockage, etc. In the Emergency room there are many translational areas that could be pursued, particularly with respect to recovery of the heart, brain and other organs after cardiac arrest.

4. Describe how the Thematic Program will be used to facilitate the success of junior clinical and basic science faculty and how support will facilitate participation in the mentoring and teaching missions of the DHLRI. (limit ½ page).

We have specifically designated \$500,000 for seed grants to promote support basic scientists and for translational scientists to collect preliminary data in this thematic program. Approximately \$250,000 will be proportioned for promoting clinical research and the same for promoting basic research. The application process will be spread across two years of the initial period with the potential for additional resources being allocated at a later date. Applicants will be required to submit independent proposals within 1 year to national and local funding agencies that address the same topic, relevant to the thematic program. Faculty with existing training grants or grants in aid from charitable sources will be encouraged to apply and the proposed funding may be in the form of “matching funds” for these relevant, funded projects.

Our mentorship program will be highly focused and will integrate with existing mentorship programs within the DHLRI, the Divisions of Internal Medicine and the various Departments involved in order to not be redundant. Essentially, we will assign or agree to a proposal of 3 senior faculty mentors who will meet with junior faculty and postdocs on a semiannual basis. Formal evaluations and recommendation will be provided to the individual and his/or her academic unit.

A study Group in this area will be initiated in which we will couple translational and basic scientists working in the same area to present on the same day. These will be used to encourage translational research activities, etc.

5. Discuss how you intend to utilize support to leverage other specific programmatic funding opportunities, e.g. SCOR, PPG, BRTT, etc. (limit ½ page).

Our first PPG application will be related to “Myocardial Protection in the Setting of Acute Myocardial Infarction.” The players for this proposal are under the process of review. Much of our efforts for recruitment, education and planning will be oriented toward filling the needs of this direction. Although the Ischemic Myocardium is a major direction of support by the NHLBI, there are upcoming deadlines for a SCCOR in this area. There is a planned SCCOR announcement in stroke and brain ischemia which would be an interesting area to develop within the Institute. DHLRI investigators such as Sashwati Roy and Chandan Sen could play a key role in developing this potential area.

A second area of programmatic development is to respond to an RFA from the NHLBI which involves development of a Systems Biology approach to a problem related to the mission of the NHLBI. We wish to coordinate our Institute with the Mathematical Biosciences Institute, our own DHLRI Bioinformatics Core Laboratory and a number of chemists and modelers within the University. The proposed title of the project will be “Modeling the redox environment in the myocardium in silico.” This will actually be the joint effort of a team of DHLRI scientists and is in the form of two major grants, linked together by a common theme. Another related application will be in response to an RFA from the NIH entitled that is designed to meet the future direction of the “NIH RoadMap, entitled, “Training for an Interdisciplinary Work Force.” We will basically utilize this same theme to develop a graduate training program in redox biology that is in response this NIH request.

6. Provide a priority list of the categories and specialties (if known, specific names can be provided) of faculty recruits anticipated for support. Include a brief justification. (limit 1 page).

- a) An outstanding clinical and/or translational scientist who will bring substantial and proven abilities to link the basic research in the ischemic heart to human or to relevant whole animal models.
- b) A basic scientist with expertise in NMR spectroscopy and imaging, related to metabolic control in the ischemic, stunned or hibernating myocardium,
- c) An Investigator experienced in the control of post-ischemic myocardial inflammation and tissue repair.
- d) An investigator experienced in the use of stem cell or gene replacement methodologies for post-ischemic myocardial repair and regeneration.
- e) A biologist and mathematician who can help develop modeling and bioinformatics approaches to this area of research.
- f) A medical geneticist who specializes in cardiovascular and pulmonary diseases.

7. Timetable and Milestones: Generate a detailed timetable for projected expenditures and accomplishments over two years. Discuss how you expect to be evaluated and by what metrics. (limit 1 page)

Budget – 2 years

- 1) \$1,500,000- to recruit 2 or 3 faculty
- 2) \$250,000 support of the development of programmatic grants of or equivalent to 2 PPG's
- 3) \$75,000 bridging fellow support linking investigators working on critical areas of PPG development linking two independent investigator groups
- 4) \$50,000 programmatic equipment
- 5) \$500,000 seed grants
- 6) \$50,000 visiting faculty
- 7) \$30,000 fellow/faculty meeting support
- 8) \$25,000 administrative support for training grant
- 9) \$20,000 educational programs and lectures

Accomplishments and Related Metrics

We will evaluate the return on these investments in terms of the grants generated both individual and programmatic. The financial goal is for the investments to regenerate the funds utilized within 4 years.

We expect 3 new R01 grants from new faculty within 2 years and 1 new R01 per year from existing faculty. We expect 1 PPG grant within two years and a second within 4 years. We expect a training grant in place within two years.