

# 2005 DHLRI THEMATIC PROGRAMS: SCIENTIFIC AND FINANCIAL PLAN

Original Investment Area title: INFLAMMATION AND FIBROSIS  
New Title (if applicable):

Program Director: **CLAY MARSH, M.D.**  
Program Co-Directors: **MARK WEWERS, M.D.; MIKE OSTROWSKI, PH.D.**  
Clinical/Translational Assoc-directors: **DAREN KNOELL, PHARM.D.; SUSHEELA TRIDANDIPANI, PH.D.**

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

**The underlying goals of this research focus are to discover the basic mechanisms that regulate lung inflammation and fibrosis and the host responses to infectious challenges with the ultimate goal to develop therapies that will alleviate the diseases associated with these conditions.** This DHLRI focus area has three major specific areas of directed research. The first is to analyze the injury and repair processes that contribute to lung fibrosis in both animal models and human disease. The second is to utilize the active program in critical care to model the inflammatory and tissue injury pathways involved in sepsis and lung infections. The last which readily interacts with the first two programs will analyze the role of mitochondrial function in health and disease. All programs will have a strong immunology/inflammation focus with particular attention to the function of mononuclear phagocytes as regulators of the processes.

The guiding principles underlying this scientific plan are to use the resources provided by this thematic program 1) to provide an infrastructure that will support the scientific programs of the members (this would include seed grant support for young investigators, grant reviews for members, grant preparation support, mentorship, and an environment that promotes clinical and basic science interaction; and 2) to organize and support program project plans (one in lung fibrosis, one in mitochondrial biology and one in human sepsis).

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
Clay Marsh	Pulm.	PI
Mark Wewers	Pulm.	PI
Mike Ostrowski	MVIMG	PI
<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>		
SusheelaTridandipani	Pulmonary	Co-I
Daren Knoell	Pharmacy/Pulm.	Co-I
Elliott Crouser	Pulmonary	Co-I
Andrea Doseff	Pulmonary	Co-I
Larry Schlesinger	Infectious Dis/CMIB	Co-I
John Sheridan	Dental School	Co-I
Chandan Sen	DHLRI/Surgery	Co-I
Terry Elton	DHLRI/Pharmacy	Co-I
Doug Pfeiffer	Pulmonary	Co-I
Periannan Kuppusamy	DHLRI	Co-I
Yong Xia	DHLRI	Co-I
Art Strauch	DHLRI	Co-I
David Brigstock	Children's/Cell	Co-I
John Gunn	MVIMG/Infectious Dis.	Co-I
Wolfgang Sadee	Pharmacology	Co-I
Phil Diaz	Pulmonary	Co-I
James O'Brien	Pulmonary	Co-I
Ruairi Fahy	Pulmonary	Co-I
John Mastronarde	Pulmonary	Co-I
Mark W. Hall	Children's/ Critical Care	Co-I

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
Chris Baran	Pulmonary	
Mikhail Gavrilin	Pulmonary	
Tim Eubank	Pulmonary	
Melissa Hunter	Pulmonary	
Anasuya Sarkar	Pulmonary	
Narasimham Parinandi	Pulmonary	
Hee-Jung Kim	Pulmonary	
Matt Exline	Pulmonary	

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
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**Further details:**

**Faculty recruitment objectives:** Although new faculty recruitment will be a major goal of the Inflammation/Fibrosis Cornerstone, the funds will not be directly utilized for new faculty hires but to promote programs that will seed new faculty recruitments by virtue of the programmatic strengths.

**Development of junior faculty and clinical translational projects:** Substantial funds will be set aside for seed grants for junior faculty over the first 3 years. One time grants of \$50,000 will be reviewed by a committee of Cornerstone faculty and 4 will be funded each year of the first three years of the support.

**Mentorship and faculty development:** Mentorship for junior faculty will be provided by a grant review process and by subgroup meetings directed by the program project committees.

**Short term programmatic goals:** Programmatic goals are to seed focused interest groups in lung inflammation, lung fibrosis, human response to sepsis and the role of the mitochondria in host diseases. These programs are highlighted as the most likely to develop into NIH PPG support and to lead to individual RO1 funding.

**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 program is to understand the principles and mechanism involved in diseases of the lung (fibrotic and destructive), diseases as a response to host infections and diseases that affect the function of mitochondria.**

*Specific Research Objectives*

1. *To determine the mechanisms responsible for the development of lung fibrosis with particular focus on idiopathic pulmonary fibrosis.*
2. *To determine the mechanisms responsible for the sepsis response and multiple organ failure that accompanies severe sepsis.*
3. *To understand the role of mitochondrial injury in the host response to stress as related to sepsis, infectious challenges, aging and tissue repair.*

These programmatic efforts fit well into the overall mission of the Davis Heart and Lung Research Institute because they direct specific focused efforts toward understanding processes important in the day to day function of the lung and heart as it pertains to host responses to external insults. These projects are interdisciplinary and provide opportunities to bring basic and clinical science investigators together to work toward not only understanding the basic principle but also providing unique opportunities to test the principles in patient populations studied within the jurisdiction of the clinical faculty of the DHLRI. Finally, these programs offer the direct opportunity to generate novel therapeutic approaches to these disorders.

*Specific Training and Faculty Development Objectives*

There are two major mechanisms that will directly affect the training and faculty development of the Cornerstone members. The first is the support provided for startup grants within this initiative. These grants will be reviewed by senior faculty within the program with the intent of not only providing grantsmanship direction but more importantly research guidance and support. This formalized process will guarantee senior/junior faculty interactions and as a byproduct will introduce junior faculty projects to senior faculty in such a way that larger projects will also be supported. The second mechanism of training will be provided by participation in the program project development part of this cornerstone. The process of development will give junior faculty a front row seat in the mechanics of research with on the job exposure to the science, planning, evolution and political aspects of project development.

*Cross-over to other programmatic themes.*

These projects will provide interprogrammatic strengths for other cornerstone initiatives. For example, the program on regenerative medicine will be highly relevant and supportive of the planned work in lung fibrosis. The program on ischemia and metabolism has direct links to the interests here of response to septic shock and to the regulation of mitochondrial biology. It is highly probable that projects developed within this cornerstone initiative will partner with other cornerstones in RO1 and PO1 projects.

**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)**

The program exists within the Pulmonary, Critical Care and Sleep Medicine Division that is dedicated to the development of clinical and translational research efforts. Twice monthly research conferences are dedicated to promoting the interaction of clinicians and basic investigators toward the common goal of developing new therapies and new diagnostic tools to assist in the treatment of diseases of the lung. This cornerstone project will be intimately linked to University Hospital's initiative to develop a signature program in critical care which interconnects the goals of study in mitochondrial biology and sepsis'.

**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).**

The teaching mission of this thematic program will be centered upon inflammatory biology in specifics with focus on macrophage biology, aspects of fibrosis and the role of the mitochondria in disease. The program is designed to foster the growth and mentoring of junior faculty by both providing startup support for their related projects and formalized review of their projects by senior investigators.

In addition, individual programs (designed to foster PPG development) will be meeting on a monthly basis to review the literature and critique ongoing research projects. This is the ultimate process of science and will provide intellectual stimulation and review for both junior and senior faculty involved in the Lung Inflammation and Fibrosis Program.

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

Support will be provided to the three major programs to foster the generation of fundable program project grants. These efforts will be directed by the individual scientific leaders of each PPG whose task it will be to bring together a functioning group of collaborators who have the

background, track record and continuing support needed to package a successful PPG or SCCOR proposal to the NIH (or equivalent external support mechanism). This directed support will provided a more flexible but coordinated effort in that it will depend largely upon the leadership of the director to keep the program on track with a tangible goal in mind, the successful funding of a large programmatic grant.

**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).**

Funds are to be used to promote support for new faculty recruits but not as solely supported by this Cornerstone project. The current need is to enhance the ability to generate animal models of disease with particular emphasis upon genetic models. Other areas of need that are relevant to this project include expertise in human genetics.

**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)**

See attached spreadsheet which outlines the time table for the outlay and expected returns for this project.

**Budget –3 years** (see attached spreadsheet).

### **Accomplishments and Related Metrics**

We anticipate that this program will result in 6 new RO1's and the funding of a minimum of one PPG. The indirects generated by this accomplishment will repay the investment made in the research efforts supported by this project.