

2005 DHLRI THEMATIC PROGRAMS: SCIENTIFIC AND FINANCIAL PLAN

Original Investment Area title: Myocyte Biology and Disease
New Title (if applicable):

Program Director: Muthu Periasamy
Program Co-Director: Sandor Gyorke
Clinical/Translational Co-director: William T Abraham

ABSTRACT

The overall mission of the Myocyte Biology and Disease program is to enhance basic and translational research in heart failure and identify relevant targets towards drug development and heart failure treatment. The Myocyte Biology and Disease program will build upon existing strengths at OSU, and will have direct relevance to the clinical mission of the OSU-Ross Heart Hospital towards treating heart disease, in particular heart failure. The goals of the Myocyte Biology and Disease Research Program include: 1) promote and coordinate interdisciplinary research in heart failure, 2) provide expertise to other thematic programs of the DHLRI, including ischemic heart disease and Cardiac regeneration, 3) to develop training opportunities for fellows, junior scientists and clinician scientists, and 4) to involve basic scientists and clinicians in programmatic research.

Relevance to mission of the DHLRI and Ross Heart Hospital:

The Myocyte Biology and Disease program will continue to expand its research in understanding molecular and cellular mechanisms that lead to heart failure and build strength in translational research towards developing Therapeutics. Targeted growth areas will include:

- Calcium Homeostasis and its role in heart disease
- Signaling mechanisms in cardiac hypertrophy and Heart failure
- Translational research and novel targets in treating heart failure

The Program will invest its valuable resources 1) to expand its current faculty, 2) to promote collaboration and interdisciplinary research among faculty through a variety of mechanisms, and 3) towards building Programs of excellence and submission of one or more program projects as a successful return of investment.

Our long range goal is to promote an outstanding scientific environment and excellence in myocyte biology and disease. We will encourage in particular, interaction between clinical and basic science faculty through selected investment where necessary. One of the highest priorities would be the development of "a critical mass" of scientists and resources in the medical center enabling us to become an internationally recognized leader in heart failure research. The program will also seek opportunities to interact and collaborate with other sister programs. These principles will also optimize the opportunity for researchers to compete for the extramural funds targeted to cardiovascular research as individual RO1s and program projects sponsored through NHLBI.

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
William Abraham		Co-Director
Muthu Periasamy		Principle Investigator and Director
Sandor Gyorke		Co-Director
Mark Ziolo		
Paul Janssen		
George Billman		
Cynthia Carnes		
Jack Rall		

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
Subha Raman		
Kuppusamy		
Chandan Sen		
Phil Binkley		
Robert Hamlin		
Art Strauch		
Jay L Zweier		

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
Periasamy	NIH		
Gyorke	NIH		
Billman	NIH		
Janssen	NIH		
Abraham	NIH		
Ziolo	NIH		
Zweier	AHA		

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).*

The overall mission of the Myocyte Biology and Disease Program is to develop a first rate research program in heart failure. Ultimately, a strong research component will contribute to better understanding of the disease and may potentially identify new targets towards drug development and heart failure treatment. The Myocyte Biology and Disease program will promote the DHLRI mission and will be aligned with initiatives of the College of Medicine, the Heart Signature program led by Bill Abraham will have direct relevance to the clinical mission of the Ross Heart Hospital in applying fundamental research and its knowledge towards treating heart failure patients. The goals of the Myocyte Biology and Disease Research Program include: 1) to promote and coordinate interdisciplinary research in heart failure and support cardiac research including ischemic heart disease, cardiac regenerative therapy and cardiac transplantation on the OSU campus. Thus, the overall priorities of this program are well aligned with the goals of the DHLRI and the College of Medicine and resonate well with the national research priorities which is to study and treat heart failure, a common cause of mortality in elderly patients.

Thematic focus areas, relevance to mission of the Ross Heart Hospital and DHLRI.

The Myocyte Biology and Disease Program will continue to expand its research in understanding molecular and cellular mechanisms that lead to heart failure and build strength in translational research towards developing therapeutics. Targeted growth areas will include:

- Calcium Homeostasis and its role in heart disease
- Signaling mechanisms in cardiac hypertrophy and heart failure
- Translational research and novel targets in treating heart failure

The Program will invest its resources 1) to expand its current faculty, 2) to promote collaboration and interdisciplinary research through a variety of mechanisms, and 3) towards Program development that will lead to successful return of investment

Specific Goals:

- 1) Faculty recruitment**
- 2) Seed grants to promote collaborative interdisciplinary research**
- 3) Support for Program Grant Proposals**
- 4) Investment in multi-user Animal Models**
- 5) Investment in shared equipment/resources**
- 6) Support for Fellows and students (Travel grants)**
- 7) Invited speakers/consultants for the program**

a. Faculty Recruitment:

Recruitment has already begun and we anticipate that a new faculty will be hired in 2006, with joint appointments between Cardiology, DHLRI and the Department of

PCB. We anticipate hiring one additional faculty during 2007. We anticipate that these hires will represent a mixed portfolio in rank. (Assistant Professor with a salary range \$75,000-\$80,000; Associate \$100,000-\$120,000 range). Start up costs should range from \$400,000-\$600,000.

- b. Seed Grant Program for junior faculty (\$25K for 1 year; 2 grants per year)
Goal: Facilitate the success of junior faculty at Research- and Tenure-Track level.
Mechanism: Grants in AHA Grant-in-Aid format submitted by a once a year deadline; evaluated by a programmatic review panel (Set up by the Program) using AHA criteria.
 - c. Start up funds for junior investigators linked to receiving extramural grant support (\$25)
Goal: Facilitate the success of junior investigators (who have not received start-up funds) at receiving independent grant support and establishing independent research.
Mechanism: Awarded automatically on obtaining an extramural career development or research grant.
 - d. Basic science lab rotations for clinical fellows (\$5-10K for 3-6 months; 2 per year)
Costs for procuring shared instrumentation (up to \$10,000 Cost sharing Basis)
 - e. Support toward using DHLRI Core facilities for junior investigators (\$5-10K)
Goal: Facilitate the success of junior investigators in establishing independent research
Mechanism: Application evaluated by a programmatic committee and director of the core.
 - f. Involvement of external advisers/consultants (\$20K/yr)
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 Myocyte Biology Disease program has a strong translational component to understand heart failure and modalities of treatment in human as well using animal models. The studies being conducted by Drs Billman, Carnes, Hamlin and Gyorke use large animal models to explore potential targets for treating cardiac arrhythmia and Heart Failure. Recent data from these labs have established that Ryanodine receptor a major Ca²⁺ handling protein could be a novel target for HF therapy. A major effort is focused on developing novel strategies to treat and prevent cardiac disease. Several other research components resonate similar approaches towards understanding molecular defects in failing /hypertrophied myocardium. Our goal is to build on existing strengths in basic myocyte biology (Periasamy, Gyorke, Janssen, Ziolo,) translational /clinical research in the area of heart failure (application and development of new tools /therapies including CRT for evaluation and treatment of Heart failure led by Abraham,

Binkley, Gary Haas, Subha Raman) and implementing clinically relevant animal models of cardiac disease (Periasamy, Hamlin, Carnes, Billman).

Specific directions:

- a. Elucidate the mechanisms of the beneficial effects of beta blockers and cardiac re-synchronization therapies in order to optimize these approaches to treat HF. In this regard collaboration was established to understand how CRT therapy in patients affects cardiac remodeling and gene expression gene expression. (on going collaboration between Abraham and Periasamy).
 - b. Determine the therapeutic potentials of targeting of calcium-cycling proteins (include ca²⁺ handling proteins, SERCA-phospholamban and ryanodine receptor complexes) and calcium-sensitizing agents.
 - c. Novel drugs for cardiac Arrhythmia
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).

Specific programs/initiatives:

- a. Seed Grant Program for junior faculty (\$25K for 1 year; 2 grants per year)
Goal: Facilitate the success of junior faculty at Research- and Tenure-Track level.
Mechanism: Grants in AHA Grant-in-Aid format submitted by a once a year deadline; evaluated by a programmatic review panel (Set up by the Program) using AHA criteria.
- b. Start up funds for junior investigators linked to receiving extramural grant support (\$25). Provide costs for procuring shared instrumentation (5-10K)
Goal: Facilitate the success of junior investigators (who have not received start-up funds) at receiving independent grant support and establishing independent research.
Mechanism: Awarded automatically on obtaining an extramural carrier development or research grant.
- c. Basic science lab rotations for clinical fellows (\$5-10K for 3-6 months; 4 per year)
- d. Support toward using DHLRI Core facilities for junior investigators (\$5-10K)
Goal: Facilitate the success of junior investigators in establishing independent research
Mechanism: Application evaluated by a programmatic committee and director of the core.

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

It is anticipated that the funds will directly support generation of 2 PPGs. The following investment components will contribute to this goal: It is anticipated that developing junior faculty, investing in animal models (Transgenic and HF dog models) should provide novel data leading to new grant submissions.

Programmatic expansion via recruitment of scientists in new key areas (Cellular Imaging, Biology of Heart Failure) (Assistant \$75,000-\$80,000 range; Associate \$100,000-\$120,000 range). Start up costs should range from \$400,000-\$600,000.

Development/maintenance of shared use animal models (emphasis on large animal models and genetic models) of cardiac disease (up to \$100K/yr)

Support of inter- and intraprogrammatic collaborations through a Seed grant program (\$25K/yr X 2 per yr)

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).*

Two main areas for recruitment are identified as specified below. These recruitments are intended to fill thematic gaps and complement existing strengths in the Myocyte Biology/Heart failure program. Recruitment efforts in these areas are conducted in conjunction with the faculty search by the Department of Physiology and Cell Biology.

Area 1: Biology of Heart Failure. Recruitment in this area will bring expertise in the area of signaling mechanisms involved in cardiac hypertrophy and remodeling

Area 2: Myocyte Biology /imaging. Recruitment in this area will bring expertise in new technology including novel imaging techniques for visualization of intracellular signaling process and protein-protein interactions inside living cells.

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.*

EXPENDITURES:

Expansion/recruitment:

(Assistant \$75,000-\$80,000 range; Associate \$100,000-\$120,000 range). Start up costs should range from \$400,000-\$600,000. Total \$~1, 700,000)

Inner development:

Support of inter- and intraprogrammatic collaborations through Seed grants (\$100K/yr)

Development of animal models of cardiac disease - \$ 50-100K/yr

Investment into shared instruments and core facilities - \$60K/yr

Support of junior research and clinical faculty (\$100k/yr)

Administrative costs (\$20K/yr)

External consultant/advisory costs (\$25k/yr)

PROJECTED ACCOMPLISHMENTS:

Year 1-2:

1. One new senior faculty with 2R01 or equivalent grants is recruited
2. Seed Grant Program for collaborative program development is implemented
3. Support mechanisms (seed grants, fellowship etc) for junior investigators is implemented
4. One PPG project is submitted
5. A major shared-user instrument is acquired
6. Two shared-user animal models are established

Year 2-4:

1. One new senior faculty with 2R01 or equivalent grants is recruited
2. A new PPG initiative is started
3. 2-3 collaborative RO1 grants (or equivalent) are submitted
4. Programmatic support mechanisms are refined