Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
May 24-25, 2006

Cardiovascular Program – Theme # 2: Heart Failure and Cardiomyopathy

Introduction:

Despite improvements in survival following the onset of heart failure, HF remains highly lethal; in the 1990s, 59% of men and 45% of women were dead 5 years after diagnosis. Because HF is such a profoundly costly condition, both in human and fiscal terms, it is important to understand its incidence, prevalence and mortality, and study the effects of treatment on disease outcomes. Such knowledge will help project future needs both in terms of health care resources and research priorities. Expanding our understanding of the relations of heart failure risk factors and the underlying cellular processes to the development of heart failure will provide insight into approaches for the primary prevention and treatment of this dreaded disease. In order to achieve improved diagnosis and treatment for patients with heart failure the NHLBI should: 1) develop Heart Failure Consortiums to maximize the benefit forthcoming from exciting and novel science aimed at understanding and treating heart failure; 2) establish a public education program (e.g. a "War on Heart Failure").

Recommendations:

1. Develop new tools for studying heart failure. There is an urgent need to develop novel tools, reagents, and platforms that can be widely used to achieve new understandings of HF mechanisms, to improve diagnosis and ultimately to prevent HF. Needed tools include cardiomyocyte cell lines, organ cultures and multi-organ models (e.g. heart and kidney, heart and brain) that can be used to test hypotheses concerning cardiovascular failure. (A highly innovative discovery program that incorporates nanotechnology to make physiological measurements, biomarkers to track function, in vivo imaging at subcellular and systemic levels, and probes for metabolic state should be established to identify novel markers/metrics in individuals with very early perturbations of cardiac structure or function that encompass the full spectrum of HF triggers, and adaptive or maladaptive responses. Importantly, gender and ethnic disparities are to be considered in all studies since HF outcomes differ with race and gender. The NHLBI should develop shared databases and virtual platforms to enable diverse investigators to integrate information about HF triggers and myocardial responses.

2. Explore mechanisms of heart failure at the molecular, cellular, organ and systemic levels. Use new tools to achieve novel mechanistic insights as to the causes of heart failure - triggers and modifiers - at cellular, organ, and systemic levels (e.g. cardio-renal dysregulation, which affects over 25% of heart failure patients - can be systematic study of molecular, neurohormonal, and renal responses to volume loading in animal models and humans with hypertension, cardiac hypertrophy, asymptomatic and symptomatic heart failure with both normal and reduced ejection fraction, cross-connections with NIDDK and NIA would be particularly fruitful). Study animal and human responses to cardiotoxic drugs inhibiting cancer growth, to elucidate new pathways of cardiac response and adaptation amenable to intervention. Genetic: contributions of genetic variation to HF susceptibility and progression - including ethnic and gender differences. Cellular: define signaling pathways

that control cardiomyocyte function and identify defects in these pathways that cause HF. Organ: examine maladaptive interactions between components in the heart and vasculature (e.g. fibroblasts and cardiomyocytes, smooth muscle and endothelial cells) in HF. Systemic: study the responses to stress and reversibility of these responses in the cardiovascular system and determine how these systemic responses contribute to HF progression (e.g how cancer drugs that modify tyrosine kinase receptor pathways influence cardiac adaptation to injury).

3. Study the progression and re-compensation of right and left ventricular dysfunction. Despite current pharmacologic and device therapies, heart failure remains a progressive syndrome resulting in huge morbidity and mortality. We propose an innovative feasible approach to examine the events from HF to *re-compensation* (reversal of remodeling – in its broadest interpretation), irrespective of the mechanism by which re-compensation/ recovery occurs, to identify novel pathways, mechanisms, and bio-molecular markers that reflect the recovery processes. At each stage, identification of the marker profile best predictive of progression and regression (genomic / proteomic profiles and dynamic markers of disease progression/regression) that are responsive to intervention would allow targeted intervention as well as understanding of biologic events determining progression or regression. The underlying premise is that this would be a model easy to identify, to study, would centrally inform studies regarding progression of heart failure, and would identify strategic points for inhibition of progression. This approach would be equally applicable to HF with or without preserved systolic function, as well to basic science and clinical studies.

4. Advance gene-based and regenerative therapy for heart failure. Given the considerable advances and promise of gene-based and regenerative therapy and recognizing multifaceted technical and ethical challenges, investment by NHLBI is essential. 1) Gene-based strategies should incorporate non-vector methodologies (e.g., oligonucleotide-based approaches for exon skipping, termination suppression, gene correction) and newer vector-based strategies. 2) Cell-based strategies should emphasize preclinical discovery of fundamental biology and mechanisms for regeneration. Development and validation of effective strategies will be facilitated by broad availability of well-characterized cells (resident and non-resident precursor cells), standardized procurement, culture, and differentiation protocols, identification of cell extrinsic mechanisms, and incorporation of tissue engineering approaches. Lifting of the NIH moratorium on human ES cells will hasten the success of cell-based therapies in human heart failure. Opportune investigations include whether regenerative potential is amplified by combining gene and cell-based strategies, whether genetically modified cells are useful for cardiac delivery of gene products, development of optimal heart delivery systems, definition of criteria to assess long-term efficacy and safety that includes in vivo imaging and assays (biochemical/molecular/cellular) for gene and heart response, identification of patients who are appropriate for cell and gene based therapies, and eventually rigorous clinical trials to test efficacy. Strategies that support cross-institute investigation are needed.

5. Explore Heart Failure with Preserved Ejection Fraction: *The Other Heart Failure.* Nearly half of all patients presenting with heart failure have non-dilated hearts and an ejection fraction exceeding 50%. Patients with this syndrome have very high re-hospitalization rates, and a poor overall prognosis. Lack of adequate detailed physiologic and clinical phenotyping, particularly in broad, community based populations, is a central problem that has prevented development of basic mechanism insights and effective therapies. To address this problem we propose to characterize the human physiologic

phenotype of heart failure with preserved EF (HFPEF) by a prospective cohort study to obtain data from HFPEF patients in acute decompensated as well as in the subsequent compensated state. These data would provide detailed phenotypic data in broad, diverse and representative populations of patients with HFPEF and comparators (heart failure with reduced EF) and controls (demographically similar patients), examine cardiac, vascular, renal and stress (exercise) pathophysiology, with a particular focus on cardio-renal interactions, and identify and develop novel biomarkers, including genomic based strategies. Results would inform future cellular and molecular pathophysiology studies, development of appropriate animal models, and clinical trial design. To facilitate representative data collection, we recommend strong support of phenotyping and genotyping sub-studies relevant ongoing and planned HFPEF studies sponsored by the NIH and if possible by industry. As HFPEF patients are often cared for in the community rather than in major academic centers, it is important that research initiatives be extended to partnerships within the community. In addition, cross fertilization with NIH agencies concentrating on metabolic and renal disease (e.g. Kaiser, NIDDK, and NIA).

6. Support population-based and outcomes research. A prerequisite to the understanding and valid monitoring of the heart failure epidemic requires agreement at the national level on the nomenclature, including definition and classification of heart failure. Ongoing population surveillance is required to evaluate the effectiveness of strategies aiming at reducing the public health burden of heart failure and to measure trends in incidence, prevalence, patterns of practice and mortality of heart failure. Patient-centric outcomes measures (health status) should be included. Understanding heart failure at the population level requires characterization of the phenotype of heart failure in prospective population-based cohorts, designed to ensure generalizability to diverse populations. Such cohorts should be assembled for comprehensive characterization of heart failure, including imaging and biomarkers and the creation of population-based biobanks of subjects with overt heart failure and asymptomatic left ventricular dysfunction. These cohorts also would constitute a source population for recruitment in clinical trials. Among disease-free individuals, investigations should leverage existing resources of ongoing population-based studies. These studies need to be complemented by less comprehensive but more generalizable studies that assess the psychological, social, environmental and clinical (including patterns of care) factors that affect biological responses and patient outcomes. In addition, there is an urgent need to characterize and address the bottlenecks in translation to address the poor outcomes that accrue because efficacious strategies are not provided consistently in actual practice because little information exists about the best strategies to use in understudied subpopulations. Also, there is a need to develop, test and disseminate non-pharmacologic interventions that have potential to improve outcomes at a reasonable cost. These may include interventions targeted at patients, health care providers, the health care system, or some combination in disease management strategies.

09/29/06

Business Operations
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
May 24-25, 2006

Cardiovascular Program – Theme # 2: Heart Failure and Cardiomyopathy

Recommendations:

Urge development of uniform NHLBI input on IRB and HIPPA rules for protocols, currently the individual discrepancies in interpretation of human subjects and privacy requirements in both initial approval and continuing review pose one of the largest single time burdens for clinical investigation, including the acquisition and sharing of blood and tissue samples for genomic and proteomic analysis. Propose shorten time between peer review and funding. There is a need for new infrastructure including NHLBI searchable databases that will enhance integrating diverse data. Training opportunities need to be linked to each strategic innovation in heart failure. There should be a "War on heart failure" - public education - what is heart failure? Targeted information should be emailed from NHLBI to all funded investigators to alert them about opportunities for networking – e.g. RO1 holders should be informed about clinical trials and clinical trialists should be emailed lists of all NHLBI funded RO1s on heart failure. The following are additional specific proposed improvements to the NHLBI business practices.

1. Funding and Award Mechanisms: Increase funding opportunities for junior faculty after the K-award stage, including the current practice of providing 5- and 10-point advantages in the funding payline, greater utilization of the R21 mechanism, and other ideas. Develop mechanisms to provide funding and expedited review for mechanistic substudies and collect genomic and biomarker information within large studies funded by NHLBI and by other non-profit and corporate sponsors.

2. Dissemination and communication of advances and discoveries and resources made by NHLBI-Supported Investigators: Dissemination is critical in order to get public support for research. Strategies recommended are: 1) all NHLBI funded investigators should be encouraged to submit brief progress reports each time they make a significant discovery (publish an important paper) via a web site. These reports will be reviewed by NHLBI staff, edited if needed, and posted on a web site that is open to the public and advertised widely; 2) all press releases from NHLBI funded investigators about discoveries should be posted on the NHLBI web site open to the public and clearly advertised on the home page of the NHLBI; 3) the NHLBI web site should list a top discoveries funded by the NHLBI web page that summarizes in lay terms important advances in combating diseases similar to one that the AHA posts;4) a news letter interviewing NHLBI funded scientists should be published on the NHLBI web site featuring a different scientist each month discussing her or his recent discoveries and how they are leading to improved care of patients;5) NHLBI staff should identify key NHLBI funded investigators and encourage them to write letters, commentaries, editorials etc in the lay press highlighting advances in diagnosis and treatment of cardiovascular diseases. The NHLBI should provide access to consultants/freelance writers who for a modest fee (supported by NIH grants) can help scientists translate their discoveries into lay language that is powerful and informative.6) Hold more meetings in Wash DC to highlight NHLBI research and meet with Congress and NHLBI staff.

3. Overhaul CSR and study sections: Include more senior, established investigators with proven productivity as reviewers; alter the frequency and/or structure of the review process to allow reviewers to participate from a distance by video-conferencing or related approaches; avoid the excessive workload that characterizes the experience for reviewers at present.

4. Create incentives and mechanisms for cross-Institute and interagency funding of large projects: Partner with other agencies (in and out of NIH and government) and pharmaceutical industry to fund large-scale projects.

5. Review the NHLBI pre-approval process for investigator-initiated grants with direct costs >$500K in any year and the process for Institute-initiated programs (RFAs, RFPs): For applications which exceed the PPG cap, NHLBI should consider having some external review process up front, instead of waiting until the final council step.

6. Create a mechanism to provide infrastructure support for large observational studies to facilitate addition of ancillary studies. Create mechanisms to assure that the data and samples from the core studies are made available to the wider scientific community as a resource for further research. Can other organizations (CDC) conduct some of these studies?

09/29/06