Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
June 27-28, 2006

Cardiovascular Program – Theme # 1: Coronary Artery Disease and Atherosclerosis

Introduction:

Despite enormous advances in prevention, diagnosis and therapy, heart disease remains the leading cause of death in the United States (929,000 cardiovascular deaths in 2002, mostly related to atherosclerosis) as well as in other industrialized nations. After obstetrical births, acute coronary syndromes represent the leading cause for hospitalization in the United States. While there are 23 Working Groups assigned to provide recommendations for NHLBI Strategic Planning, no condition is more dominant as a cause of death and disability. Thus, CAD and atherosclerosis need to be regarded as the paramount research target for the Institute.

Recommendations:

1. Define key genetic variants and the relevant "–omic" (genomic, proteomic, epigenomic, lipidomic, glycomic, metabolomic) markers/pathways and their interaction with environmental factors that confer susceptibility or protection from atherothrombotic cardiovascular disease and *define the molecular mechanisms* by which these genes and pathways confer risk or protection from atherothrombotic cardiovascular disease.

a. Explore biomarkers that emerge from the association studies to evaluate risk and individual responsiveness to interventions in populations. Moreover, novel therapeutic targets should emerge from this effort, directed by the unbiased surveys using "-omic" technologies. Large databases from these surveys should therefore be placed in the public domain in an expeditious fashion.
b. Develop and evaluate computational tools to manage and interpret large data sets and train bioinformaticians, and engineers to create computational resources appropriate for developing mathematical models to analyze complex systems. This effort will require mechanisms to support and promote the careers of individuals with core competence in computational biology.
c. Define and validate novel molecular targets for therapeutic intervention for atherothrombotic disease and its complications by promoting research that validates specific molecules as potential therapeutic targets.
d. Support the development and validation of relevant animal models that predict or recapitulate human atherosclerotic disease and that can be used to test novel therapeutics.
e. Development of improved phenotyping for genetic association studies; examples include precise categorization of cases and controls with CAD, response of fat to insulin, improved imaging of atherosclerosis, and endothelial cell-specific phenotypes, and stem cell populations.

2. Evaluate new approaches to implement proven CVD prevention/lifestyle therapies (blood pressure, lipid and weight control and smoking cessation) across the spectrum of risk (and age) and develop and test novel CVD prevention therapies and approaches. Examples include interventions that target families, that are implemented at

key life events (e.g. pregnancy, menopause), that modify intensity based on biomarkers or imaging results, and that utilize alternative systems/settings for risk management targeting both physician and patient behaviors.

a. Include physiological measures, biomarkers, molecular imaging or subclinical measurements of atherosclerosis and clinical events as outcomes.
b. Determine effects among subgroups defined by traditional demographic characteristics (sex/gender, race-ethnicity, socio-economic status, age) and genotypes.

3. Explore noninvasive imaging methods to detect and quantify atherosclerotic plaque burden and risk for rupture.

a. Compare CTA and MRI with biomarkers and other measures of atherosclerosis (such as IMT or IVUS), assess utility in clinical trials to measure progression or regression of disease determine natural history of disease and in screening asymptomatic populations (e.g. those with biomarkers of elevated risk or family history of premature atherosclerosis for disease detection)
b. Support comprehensive efforts to elucidate further the underlying pathophysiology of atherosclerosis, with an emphasis on early non-invasive detection of vulnerable plaques and patients, allowing for risk stratification, elucidation of the natural history, and appropriate preventive measures. Sex, ancestry, age, and cost effectiveness should be considered in analyzing such studies.
c. Develop molecular imaging methods to investigate atherosclerotic plaque biology, such as inflammation, including (among others) OCT and quantum-dot technology or molecular beacons.
d. Develop MRI/CT imaging to be able to evaluate microvascular perfusion.

4. Improve outcomes in acute coronary syndromes—from pluripotent stem cells to pluripotent Centers of Excellence

a. Study further cell therapy including the selection of cells, their propagation, production, dose, timing and method of administration, delivery mechanisms, adjunctive pharmacology, assessment of viability after injection, and the effect on ventricular function, remodeling, and myocardial blood flow, including microvascular perfusion.
b. Animal experiments should be carried out to examine reperfusion strategies followed by cell transplantation. These should include studies on large animals in regional shared facilities supported by NHLBI. Positive experiments should be followed closely by clinical trials, focused on STEMI patients who have sustained substantial myocardial damage. These trials should be conducted by an NHLBI-organized trial network.
c. Evaluate the feasibility of developing regional Centers of Excellence for the management of STEMI, other forms of ACS and acute stroke. These centers should be staffed to provide 365/24/7 immediate care, akin to Trauma Centers, and should accept transfer from non-designated facilities. Such Centers are differentiated from the proposed mission of Comprehensive Cardiovascular Centers---they are to be primarily focused on delivery of immediate care and expertise for patients with acute ischemic (MI, CVA) complications

d. These regional centers should also serve as a network to test new modes of circulatory support, such as the new generation of small circulatory assist devices, newer agents to combat microvascular and reperfusion induced injury and techniques to accelerate myocardial reperfusion, and determine the optimal mode of management of both acute and chronic CAD among medical therapy percutaneous intervention and surgical revascularization.

Additional Comment:
To support our 4 recommendations, we strongly endorse that additional funds be sought to support the establishment of Comprehensive Cardiovascular Centers, akin to the NCI Cancer Centers, would be in the best interest of the Institute and the research community. Such Centers would leverage their institutions and sources of philanthropy for additional support to complement NHLBI funding, and provide the necessary infrastructure to execute the principal research objectives. Further recommendations regarding Comprehensive Cardiovascular Research Centers are included in the business operations statement.

09/29/06

Business Operations
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Recommendations:

	High	Medium	Low	Priority Rank
1. Create streamlined procedures for renewing grants for established investigators, including a briefer application and greater emphasis on prior productivity	2 B 1 A 1	5 B-2	6 A 3	6 (58)
2. Funding and Award Mechanisms	8	9	1	2 (43)
3. Create incentives and mechanisms for cross-Institute and interagency funding of large projects	12	5	1	1 (32)
4. 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):	7	8	3	4 (53)
5. 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	10	7		3 (51)
6. Issues related to CSR and study sections	6	10	1	5 (54)
7. Dissemination and communication of advances and discoveries and resources made by NHLBI-Supported Investigators	7	7	8	7 (76)

Comments on EPC Business Operations Areas and Recommendations

1. There is discordance regarding support for A and B in number for EPC #1.
2. Regarding EPC #2, add K05 training to NHLBI mechanisms
3. K24 award is available for mid-career mentoring
4. Create salary=support mechanism for post K08 to K-23 (translational research)
5. Provide salary support for needed new types of expertise such as computational biologist.
6. Exercise caution regarding EPC #7 –Dissemination of NHLBI-supported advances
7. Reconsider $500K ceiling. This may be too low considering inflation
8. Increase external input into pre-approval process and decisions regarding continuance of large projects.
9. Exclude Training grants from $500K pre-approval
10. Expand number of re-submissions to three.
11. Established investigator should be anyone with an RO1: criteria to re-apply should be the same. (Re-define establish investigator)

Additional Business Operations Areas and Recommendations

1. **Develop enabling infrastructure to support research by the CV community
   a. Careful consideration should be given to creating Comprehensive Cardiovascular Centers (akin to NCI's Comprehensive Cancer Center program to foster Centers of Excellence in Cardiovascular basic and translational research and care).
   b. Development of tools to enhance cellular epidemiology; examples include methods for acquiring tissue samples, standardization of ex vivo conditions, and standardization of stimulations.
   c. Support development of novel biomarkers through a central resource. Develop a central repository of biosamples from NHLBI sponsored observational studies and clinical trials.
   d. Support recruitment of patients with rare diseases and extreme phenotypes related to atherosclerotic vascular disease to be used for genetic studies and development of novel therapeutics. Initiate a website for clinicians to report unusual patients in order to facilitate such studies.
   e. Leverage industry to access biosamples derived from large clinical trials for testing of novel biomarkers.
   f. Provide an infrastructure for critical and unbiased evaluation of novel devices for support of ischemic cardiac dysfunction, for revascularization, etc.
   g. Clinical trials should strive to include imaging substudies to provide an opportunity to validate imaging endpoints with clinical outcomes.
   h. Develop new infrastructures to include altering intramural NHLBI research facilities to enable more effective utilization of genomic/proteomic resources: e.g., siRNA libraries and associated screening technologies, small molecule libraries and synthesis capabilities, and conditionally targeted genes in the mouse.
   i. Develop a "public" library of well-characterized small molecule compounds to specific molecular targets that can be used for cell biology and animal studies. Develop high throughput assays for small molecule biological research.
   j. Development of tools to enhance cellular epidemiology; examples include methods for acquiring tissue samples.
2. Decrease percent effort on K23 to 50%. Interventional cardiologists and CT surgeons need time to maintain skills.
3. Explore cost sharing with non-profit and other private entities.
4. Reconsider 20% effort on PPG's and SCOR's. (This is too high).
5. Consider yearly updates of NHLBI–supported accomplishments.
6. Delete effort reporting and other bureaucratic tracking.

**Unanimous approval and strongly endorsed by committee.

09/29/06