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

Cardiovascular Program – Theme # 5: Valvular and Congenital Heart Diseases

Introduction:

Valvular and congenital heart diseases affect over 15 million Americans, and the number is increasing. As advances in surgical management have dramatically improved early survival, chronic morbidity and premature mortality are emerging as public health concerns. Few data are available to guide key treatment decisions for these disorders. Knowledge of valve development and degeneration is limited. Recent research in heart development and myocardial biology and technological advances in imaging and interventions create compelling opportunities for translational and clinical research in valvular and congenital heart diseases. More research is needed to understand cardiogenesis, valve formation/maintenance, and myocardial function under normal and abnormal conditions. Identification of genetic and environmental predisposition to this spectrum of heart disease is essential for future intervention and prevention. Multi-disciplinary research will advance knowledge, create new therapies, and improve public health. The following research priorities are not hierarchically ranked.

Recommendations:

1. Problem: Many key factors control cardiac biology, but mechanisms are not understood because targets of signaling and transcriptional pathways are not known and thus impact on cardiac development and valvular and myocardial cellular function is unclear.

Opportunity: New tools to discover targets and cellular function are available. Morphogenetic pathways are re-used in disease processes so knowledge of key targets will be applicable to most areas of cardiac biology.

Recommendation: **Develop research network to systematically identify DNA targets of key signaling and transcriptional pathways involved in morphogenesis and remodeling in normal and pathologic states.**

- Recruit experts to do genome-wide target approaches, such as chromatin immunoprecipitation (ChIP), by standardized protocols for key regulatory proteins (~200).
- Perform microarray or sequencing approaches to analyze output of target screens in standardized manner.
- Centralize bioinformatics analyses of all data for network and systems analyses.

2. Problem: Improvement in survival of patients with valvular and congenital heart disease has created a growing population with ongoing morbidity and premature mortality.

Opportunity: Use the successful model of collaboration and interdisciplinary research of the Pediatric Heart Network to develop and test novel multi-disciplinary approaches.

Recommendation: **Promote innovative and interdisciplinary strategies to improve long-term outcomes and quality of life in patients with valvular and congenital heart disease.**

- Develop image-based computational methods and software for planning interventions in valvular and congenital heart disease (e.g., predictive modeling of flow dynamics, structure-fluid interaction, cardiac electrophysiology).
- Determine appropriate timing of interventions for valvular and congenital heart disease.
- Develop validated endpoints reflective of morbidity and quality of life.
- Support integrated and flexible infrastructures (e.g., networks, registries, databanks, tissue repositories) for clinical research to test new procedures and therapies; include "small n" clinical trials that have a high-degree of operator and institution dependence.
- Support funding mechanisms to foster interdisciplinary interaction and training.

3. Problem: Predisposition to valvular and congenital heart disease and genetic influence on clinical outcomes are unknown.

Opportunity: New genomic and biomarker tools will allow analysis of genetic risk/influence.

Recommendation: **Promote elucidation of genetic/epigenetic predisposition to valvular and congenital heart disease and genetic background effects on short and long-term clinical outcomes by developing:**

- Multi-center bio-bank networks, including appropriate phenotypic characterization, with peer-reviewed access to materials and data.
- Databases of environmental exposures and other epidemiologic data.
- Genomic, biomarker, and bioinformatic tools and methods to analyze populations.

4. Problem: Large and small animal models developed for study of valvular and congenital heart disease do not adequately mimic clinical conditions.

Opportunity: Sophisticated genetic tools are available to manipulate gene expression in spatial and temporal-specific fashion and to study the effect of physical forces on gene expression and disease progression. Furthermore, surgical and other models that affect structure and physical forces can be developed.

Recommendation: **Promote development of more relevant animal clinical models of valvular and congenital heart disease that will facilitate translational research:**

- Support development of late fetal and early neonatal models
- Support development of chronic and degenerative valve disease models
- Support systematic phenotyping of animal models.
- Develop high-throughput methods for generating and characterizing animal models
- Develop tools to study small animal and fetal physiology

5. Problem: Lack of new therapies for valvular and congenital heart disease.

Opportunity: Emerging technologies and knowledge may be applied to develop novel therapies based on pathobiology and mechanisms of valvular and congenital heart disease.

Recommendation: **Develop and evaluate by clinical trials new therapies for valvular and congenital heart disease.**

- With new approaches in imaging, genomics, proteomics and cell biology, investigate mechanisms of initiation, progression and potential reversal of valvular and congenital heart disease.
- Define the molecular, cellular and organ-wide myocardial and concomitant vascular consequences of valve and congenital lesions.
- Establish imaging and biomarker measures of pathophysiology and outcome.
- Stimulate development of new molecular, cellular and other tissue targets for drug therapy.
- Investigate new treatments based on biomaterial, nanotechnology, tissue engineering, gene and cell therapies with pharmacological, percutaneous and surgical approaches.
- Further investigate fetal interventions, including development of better imaging tools, instruments, and evaluation of impact of interventions on disease progression.
- Validate principles developed through basic and applied research through clinical trials.

6. Problem: The evidence to guide practice in valvular and congenital heart diseases is limited.

Opportunity: Clinical networks allow development of patient registries, clinical cohorts, tissue repositories, family genetic studies, standardized clinical protocols, and multi-center trials.

Recommendations: **Create a clinical research network for valvular heart disease involving community and academic participation, and expand the existing Pediatric Heart Network:**

- To provide information on practice, care and outcomes using:
    - Clinical and population-based cohorts with longitudinal data
    - Genetic background and exposures linked to clinical outcome
- To create a tissue and DNA repository for multidisciplinary studies.
- To conduct multicenter randomized clinical trials regarding efficacy and safety of valvular disease treatments.
- To train the next generation of valvular and congenital heart disease investigators.

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Business Operations
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Recommendations:

The Working Group reviewed and discussed business operations areas and developed the following recommendations and comments:

1. Promote a culture of research among the public
NHLBI should use its resources to "sell" the benefits of research to the general public through its web site and the media. This would include not only highlighting important research findings, but also educating the public about the role of research in improving public health. Partnering with the AHA and ACC to achieve this goal should be considered.

2. Bolster research infrastructure
The network approach to translational and clinical research is successful and should be expanded to additional areas of science. There is also a need for biobanks coupled with good phenotype information for NHLBI and other NIH studies. Funding for such biobanks should be at a level sufficient to support the time-consuming and expensive collection of detailed patient data to afford optimal integration of the biological specimens and patient data. Biobanks could be organized in a complementary fashion to the network model.

3. Streamline administrative processes
Consideration should be given to decreasing the length of the research plan in R01s using both word and page limits. Although this would require a change in NIH policy, it could be applied now to grants reviewed internally by NHLBI peer review groups.

Reduce obstacles to evaluation of novel ideas and therapeutic techniques by, for example, working to simplify the regulatory environment and establishing central IRBs. Tools such as electronic adverse event reporting, protocol design templates, consent form templates, and succinct clinical research educational materials should be developed for NHLBI studies.

Shorten the time from grant submission to funding, at least for grants reviewed by NHLBI. This could be accomplished by reducing the time from grant receipt to study section formation and the time from review to funding decision.

4. Expand MERIT awards to afford senior investigators more latitude in continuing their work.

5. Foster collaboration
NHLBI should develop incentives for multi-disciplinary research to foster collaboration among basic, translational, and clinical researchers. The BRP and K25 mechanisms partly serve this role, but further incentives such as more generous pay lines for this type of research and more widespread adoption of the multiple PI policy are also needed. Another strategy to foster collaboration is to provide more information on the NHLBI web site about ongoing large studies.

NHLBI should provide funding and mechanisms to allow greater use of the CMS database to answer questions that arise from the development of new therapies and diagnostic modalities, and also to facilitate developing areas of study for NIH grantees.

NHLBI should consider grants or mechanisms for improving the integration of clinical information systems (i.e., clinical and clinical/translational IT, linking systems with clinical operations).

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