Journal of the American College of Cardiology Vol. 55, No. 12, 2010

Published by Elsevier Inc.
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.11.055

# News from the NHLBI

## The National Heart, Lung, and Blood Institute Bench to Bassinet Program: A New Paradigm for Translational Research

Jonathan R. Kaltman, MD, Charlene Schramm, PhD, Gail D. Pearson, MD, ScD
*Bethesda, Maryland*

Congenital heart disease (CHD) is the most common birth defect and is a significant source of morbidity and mortality in children. Despite considerable recent progress in the clinical arena, we have a lot yet to learn about the causes of CHD and the genetic modifiers of clinical outcome. It is our hope that an improved understanding of the etiology of CHD will lead to improved care for the patient with this disease. To accelerate discovery in these areas, the National Heart, Lung, and Blood Institute (NHLBI) launched a novel translational research program in pediatric cardiovascular disease, the Bench to Bassinet program, in September 2009 (http://www.benchtobassinet.com).

The Bench to Bassinet program is designed to accelerate the pace of discovery and the translation of basic research into clinical studies through large-scale collaborations at all levels, with a nimble interactive structure to provide for seamless integration of findings from 1 research stream into another. The Cardiovascular Development Consortium (CvDC) comprises 4 research centers (Table 1) that will use various techniques and animal models to elucidate the regulatory and developmental derangements that cause CHD. The Pediatric Cardiac Genomics Consortium (PCGC) involves 5 research centers (Table 1) whose goals are to delineate the genetic underpinnings of CHD through the use of genome-wide analytic techniques and high-throughput sequencing. The CvDC and the PCGC will share an administrative coordinating center. These new programs will align and interact with an existing NHLBI-funded clinical research network, the Pediatric Heart Network (PHN) (1) and its data coordinating center.

From the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
Manuscript received November 5, 2009; accepted November 10, 2009.

### CvDC

Development of a fully formed and functional cardiovascular system is the outcome of an exquisite network of interacting molecular pathways at the levels of molecule, cell, tissue, organ, and organism. Numerous pathways and components of this network have been identified, but they fail to explain fully the emergence of a complex structure such as the heart (2,3). The field of cardiovascular development now has the necessary elements (i.e., basic research, investigators, technology, and so forth) to move beyond analysis of single steps within pathways to compiling existing and new data in an effort to understand the overall regulatory network architecture (4). To do so, however, requires large-scale team science and sophisticated informatics tools. The CvDC brings together state-of-the-art research teams and resources capable of executing this scientific paradigm shift in a flexible environment in which investigators can react quickly to new scientific or technical opportunities.

The participating research centers of the CvDC will use a variety of genome-wide approaches to build a higher-order cardiac development network model. High-throughput sequencing technology will shed light on global transcriptional and epigenetic regulation, ribonucleic acid (RNA) expression, and microRNA feedback mechanisms. Forward genetic screening in mice will expand the number of mutant

mouse lines that display phenotypes at the stages most relevant for human heart defects. Selected candidate molecules identified by the high-throughput techniques will be functionally validated by perturbation studies and subsequent characterization. The CvDC will use a variety of species models including mouse, chick, and zebrafish; and through interactions with its sister groups in the Bench to Bassinet program, will identify and pursue those basic discoveries with the greatest potential to translate to clinical applications.

The genetic underpinning of CHD is demonstrated by the occurrence of familial clustering of certain types of heart defects (5), the documented association of human genetic syndromes with CHD (6), and the link between single gene mutations and CHD in animal models (2). Painstaking work in each of these areas has helped uncover monogenic mutations and alterations of genetic regions that cause CHD. Many of the monogenic mutations are found in genes that encode transcription factors. One of the goals of the CvDC will be to assemble these transcription factors with upstream and downstream components to fully flesh out the complex regulatory networks that affect cardiac development.

## PCGC

Despite the compelling evidence of a genetic etiology for CHD, only a minority of cases of human CHD can be explained by an identified genetic defect. Barriers to gene discovery in the setting of CHD include the sporadic and sometimes lethal nature of the disease, the numerous genes that affect cardiac development (7), and the imprecise correlation of genotype and phenotype (8).

**Table 1** Institutions and Project Titles of the Cardiovascular Development and Pediatric Cardiac Genomics Consortia

| Institution | Project Title |
|---|---|
| Cardiovascular Development Consortium | |
| Gladstone Institutes | The Epigenetic Landscape of Heart Development |
| Harvard University | Mapping Transcriptional Networks in Cardiac Development |
| University of Pittsburgh | Modeling the Genetic Basis for Human Congenital Heart Disease in Mice |
| University of Utah | Genome-wide Analysis of Cardiac Development in Zebrafish |
| Pediatric Cardiac Genomics Consortium | |
| Children's Hospital Boston/Brigham and Women's Hospital | Copy Number Variants for Discovery of Congenital Heart Genes |
| Children's Hospital of Philadelphia | The Genetic Basis of Conotruncal Defects |
| Columbia University | Molecular Approaches to Gene Identification in Congenital Heart Disease |
| Mount Sinai School of Medicine | Genomic Studies of Secundum Atrial Septal Defects |
| Yale University | Genetic Determinants of Human Heterotaxy and Aortic Arch Malformation |

**Abbreviations and Acronyms**

**CHD** = congenital heart disease

**CvDC** = Cardiovascular Development Consortium

**NHLBI** = National Heart, Lung, and Blood Institute

**PCGC** = Pediatric Cardiac Genomics Consortium

**PHN** = Pediatric Heart Network

The participating research centers of the PCGC will use recent advances in large-scale genetic techniques developed in response to the sequencing of the human genome to overcome the barriers to identification of genetic causes of CHD (9). These advances include genome-wide interrogation of single nucleotide polymorphisms and structural variations, array technologies, and high-throughput sequencing. Using a genome-wide strategy is an inherently unbiased approach to detecting associations between genetic variation and phenotype, such as CHD diagnosis. By casting the net broadly, the limits of a candidate gene approach are overcome. Associations are detected by comparing cases with an unrelated control population or with unaffected family members, and thus obviate the need for multigenerational affected families as is required for traditional linkage analysis.

Genomic studies require large populations to detect true positive findings (10). It is here that the power of the consortium will be brought to bear. Approximately 40,000 infants are born with CHD each year and, of these, ≈15,000 have complex defects. While single centers have access to only a limited number of patients, the Consortium will be able to recruit a significant subset of this population. Recruiting and phenotyping protocols will be developed by the centers of the PCGC so that clinical data and biospecimens can be shared to meet the individual needs of the research centers. Bioinformatics technology will further enhance efficiency and promote sharing of data, analyses, and ideas.

## Aligning With the PHN

The CvDC and PCGC will align with and interact with the PHN (11). Established in 2001 with funding from the NHLBI, the PHN is a collaborative network of 8 primary sites that perform clinical trials and studies in patients with pediatric cardiovascular disease (1). Recent studies have included a randomized surgical trial comparing 2 surgical strategies for palliation of hypoplastic left heart syndrome (12) and a randomized, placebo-controlled trial of angiotensin-converting enzyme inhibitors in patients with single-ventricle physiology (13).

The PHN's established track record in recruiting patients with CHD will be invaluable as the PCGC develops and

then implements its recruiting and phenotyping protocols. The PHN and PCGC will share the same coordinating center, the New England Research Institutes, so this experience and expertise can be readily brought to bear for the PCGC. The PHN clinical sites offer a logical means of extending the reach of the PCGC through expanded recruitment. Finally, with its existing clinical trials/research infrastructure, the PHN is poised to rapidly translate any promising findings from either the CvDC or the PCGC to the clinical world (the bassinet) as a primary study or as an ancillary study to an ongoing protocol. The PHN has already demonstrated that it can quickly take a concept from promising preliminary animal data to trial recruitment (14).

## New Paradigm for Translational Research

Translational research describes the continuum from basic science discovery to clinical application—from bench to bedside, or in the case of a newborn with complex CHD, from bench to bassinet. The central tenets of early translational research are delineated by the first goal of the NHLBI's Strategic Plan: "To improve understanding of the molecular and physiological basis of health and disease, and to use that understanding to develop improved approaches to disease diagnosis, treatment, and prevention" (15).

The conventional model for funding translational research has been to create a multidisciplinary team of researchers, typically at a single institution or a few institutions. The expectation was that communication and cooperation between basic scientists and clinical researchers would allow knowledge to flow seamlessly from the laboratory to the clinic and back again. While such an arrangement may have enhanced collaboration between groups that often do not interact, it may have been overly optimistic to anticipate that the findings from an individual laboratory would be applicable to the patient population at that same institution within a single funding cycle.

The Bench to Bassinet program will employ a novel approach to the barriers and opportunities of translational research. The program will create a critical mass of collaborative research at each stage of discovery with open lines of communication across the paradigm. Multiple groups will focus on decoding the regulatory pathways that underlie cardiac development. Simultaneously, a consortium of researchers will attempt to evaluate the association of genetic variation with the etiology and outcome of CHD, with the ultimate goal of discovering critical causative genes. These groups will work in parallel but with close communication so that important discoveries by 1 consortium can be evaluated and tested by the disciplines and technologies of the other. In addition, the Consortia will employ high-throughput technologies, which will produce reams of data. An important requirement of both Consortia is rapid sharing of data with the larger scientific community. This aggressive sharing plan will further amplify the collaborative process and maximize the opportunity for identifying translatable knowledge.

The PHN, with its ongoing patient recruitment and clinical studies activities, represents the clinical end of the translational spectrum. The established infrastructure of the PHN will allow for efficient adaptation of important findings from the CvDC or PCGC into an appropriate clinical study. Elucidation of a regulatory transcriptional pathway may suggest a novel target for drug therapy or identification of a genetic variant that is significantly associated with a clinical outcome may inform stratification for a clinical trial. An important aspect of translational research is that the flow of knowledge along the continuum is in both directions. Thus, observations from ongoing clinical trials may suggest potential areas of inquiry for the developmental and genetic researchers, and assist in prioritizing aspects of the animal studies that have the most clinical relevance.

We are very excited about the initiation of the Bench to Bassinet program. Our goal for the program is that it will accelerate the pace of discovery of the cause of CHD. In so doing, we hope the organizational paradigm of the Consortia may serve as a model that will improve efficiency and enhance collaboration of the translational research process. Most importantly, we hope and anticipate that the research efforts of the Consortia will translate into improved health and care for the infant with CHD who lies asleep in her bassinet . . . waiting.

**Reprint requests and correspondence:** Dr. Jonathan R. Kaltman, Heart Development and Structural Diseases Branch, Division of Cardiovascular Sciences, NHLBI/NIH, 6701 Rockledge Drive, Room 8222, Bethesda, Maryland 20892. E-mail: kaltmanj@nhlbi.nih.gov.

## REFERENCES

1. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27:191–8.
2. Bruneau BG. The developmental genetics of congenital heart disease. Nature 2008;451:943–8.
3. Olson EN. Gene regulatory networks in the evolution and development of the heart. Science 2006;313:1922–7.
4. Busser BW, Bulyk ML, Michelson AM. Toward a systems-level understanding of developmental regulatory networks. Curr Opin Genet Dev 2008;18:521–9.
5. Oyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PK, Melbye M. Recurrence of congenital heart defects in families. Circulation 2009; 120:295–301.
6. Pierpont ME, Basson CT, Benson DW Jr., et al. Genetic basis for congenital heart defects: current knowledge. A scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007;115:3015–38.
7. Kile BT, Hentges KE, Clark AT, et al. Functional genetic analysis of mouse chromosome 11. Nature 2003;425:81–6.

8. Benson DW. Advances in cardiovascular genetics and embryology: role of transcription factors in congenital heart disease. Curr Opin Pediatr 2000;12:497–500.
9. Altshuler D, Daly MJ, Lander ES. Genetic mapping in human disease. Science 2008;322:881–8.
10. Manolio TA, Collins FS. The HapMap and genome-wide association studies in diagnosis and therapy. Annu Rev Med 2009;60:443–56.
11. Pediatric Heart Network. Available at: http://www.pediatricheartnetwork.org/. Accessed September 28, 2009.
12. Ohye RG, Gaynor JW, Ghanayem NS, et al. Design and rationale of a randomized trial comparing the Blalock-Taussig and right ventricle-pulmonary artery shunts in the Norwood procedure. J Thorac Cardiovasc Surg 2008;136:968–75.
13. Hsu DT, Mital S, Ravishankar C, et al. Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle. Am Heart J 2009;157:37–45.
14. Lacro RV, Dietz HC, Wruck LM, et al. Rationale and design of a randomized clinical trial of beta-blocker therapy (atenolol) versus angiotensin II receptor blocker therapy (losartan) in individuals with Marfan syndrome. Am Heart J 2007;154:624–31.
15. National Heart, Lung, and Blood Institute. NHLBI Strategic Plan. Available at: http://www.nhlbi.nih.gov/about/strategicplan/index.htm. Accessed September 28, 2009.

**Key Words:** congenital heart disease ■ cardiac development ■ genomics.