Circulation: Genomic and Precision Medicine

PERSPECTIVE

1986 American Heart Association Bugher Program Pivotal to Current Management and Research of Heart Disease

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In 1961, philanthropist Fred Bugher, under the guidance of his lawyer Nelson Adams, established the Henriette B. and Frederick H. Bugher Foundation, dedicated to funding cardiovascular research within the District of Columbia. On Fred's passing, Adams—an inaugural trustee of the Foundation—saw to it that much of his fortune was allocated to his family's organization. With the foundation's resources drastically increased, the Board of Trustees decided the scope should be increased as well. Rather than being limited to the nation's capital, they contacted the American Heart Association (AHA) to seek guidance on how best to contribute to the fight against heart disease. In response to this request, the AHA, led by Dr Howard Morgan, took a refreshing view that would, in part, change the direction of cardiovascular research and management of heart disease in this country and internationally for decades to come. The AHA traditionally funds cardiovascular research selected by the peer review committees from applications submitted by investigators. In general, less than one third of the research applications can be funded. The usual response to a donor was to accept financial contributions to maintain this level of funding for the ongoing research portfolio. However, the Bugher Foundation wanted something novel and more engaging on a sustained basis. This stimulated Howard Morgan and his AHA colleagues to think outside the box. There was on the horizon the techniques of molecular biology and recombinant DNA. These techniques appeared to offer significant advantage over conventional techniques and were being embraced in the basic research disciplines and to a minor extent in cancer research. The cancer research community recognizing these techniques are DNA-based knew they would be essential to the core of cancer research, namely, the pursuit of abnormal cell growth.

The cardiovascular community, particularly adult cardiology, had neither the training nor education to embrace these techniques. Trainees in cardiovascular medicine were already overburdened with the time requirements to become proficient in the skills demanded for invasive and noninvasive clinical technologies. The diagnostic cardiac catheterization laboratory was transitioning to include therapeutic procedures because of the blossoming of percutaneous coronary interventions, such as angioplasty for coronary artery disease (CAD) and catheter-based therapeutic interventions for the treatment of arrhythmias. There was also a fundamental barrier, namely, the heart, a terminally differentiated organ does not proliferate which raised concern as to whether these molecular techniques, primarily applicable to cell growth, would be appropriate to advance cardiac research. Last, there was the practical point of view as to whether trainees would further increase the duration of their training for procedures which may not have clinical application. Nevertheless, the AHA was convinced that these techniques had be a part of the future armamentarium necessary in the fight against cardiovascular disease. The trustees of the Bugher Foundation were ecstatic at the suggestion of

Key Words: American Heart Association ■ cardiovascular diseases ■ coronary artery disease ■ financial management ■ research personnel

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setting up centers to train cardiologists and scientists in applying the techniques of molecular biology to cardiovascular disorders. The centers were referred to as the AHA-Bugher Centers for Molecular Biology in the Cardiovascular System. The first 3 centers were funded in 1986 and 3 more centers added in 1991.[1] Funding for the centers was >$9 million which enabled the training of 120 fellows in the new research of cardiovascular molecular biology. This effort produced many of the future leaders of today. Molecular cardiology received national and international recognition with the establishment in 1989 of the first of a series of Keystone Symposia devoted to molecular cardiology.[2] This was followed by annual symposia at the national cardiovascular meetings, including AHA, American College of Cardiology, and European Society of Cardiology. In 1993, the first textbook, *Molecular Basis of Cardiology*, was published, authored by investigators from the Bugher Centers.[3]

It was soon appreciated that these techniques of molecular biology were essential in our pursuit to understand physiology and pathophysiology. After all, the heart replaces itself every 3 to 4 weeks (eg, myosin, the main contractile element of the heart, has a half-life of 3–5 days and accounts for 36% of the weight of the heart). Cardiac hypertrophy is the normal compensatory growth response of the heart to most forms of stress, such as hypertension or myocardial infarction. All forms of growth, whether maintenance or compensatory, are initiated and directed by DNA, hence a prerequisite to their understanding is the application of these techniques.

The recombinant DNA techniques initiated the genetic engineering of the first genetic recombinant cardiac drug, tissue-type plasminogen activator. This drug revolutionized the treatment of myocardial infarction, reducing its acute mortality to 4% to 5%.[4] Discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9)[5] and identification of a family with a mutation in PCSK9 associated with familial hyperlipidemia led to the development and approval[6] by Food and Drug Administration of a new class of drugs referred to as PCSK9 inhibitors.[7] This potent and novel therapy markedly decreases plasma low-density lipoprotein cholesterol and reduces cardiac morbidity and mortality.[8]

A low lying fruit was genetics, which led to the chromosomal mapping of the first gene responsible for familial hypertrophic cardiomyopathy[8,9] and cloning of the gene in 1990.[10] This ushered in a golden age for cardiovascular single-gene disorders, including atrial fibrillation, dilated cardiomyopathies, arrhythmogenic right ventricular cardiomyopathy, and Wolff–Parkinson–White Syndrome.[11,12] Most of these single-gene disorders are autosomal dominant, with only one half of the offspring having the mutant gene. The clinical application is almost self-evident; genetic screening would immediately exclude half of the offspring from the need for periodic cardiac follow-up and would also assure these individuals that they could not pass on the mutant gene to their children. Individuals with the gene and the potential to develop the disease are also better managed.

In 2007, these techniques enabled the discovery of the first genetic risk variant (9p21) for a cardiovascular polygenic disorder, namely, CAD, the number one killer in the world.[13,14] Currently, >90 genetic risk variants have been discovered that predispose to CAD.[15] We know from these studies that genetic risk for CAD is directly related to the number of risk variants rather than the intensity of any one risk variant. Second, only one third of these genetic risk variants mediate their risk for CAD through known conventional risk factors, such as cholesterol or hypertension, indicating that there are other mechanisms contributing to the pathogenesis of CAD. Third, genetic risk stratification for CAD is mostly independent of conventional risk factors and more discriminatory than conventional risk factors.[16,17] Fourth, the genetic risk score is independent of age, and because one's DNA does not change in one's lifetime, risk stratification for CAD can be determined at any time throughout one's lifetime. The latter feature could induce a paradigm shift in primary prevention based on genetic risk stratification of asymptomatic individuals.[18]

Discovery of genetic variants mediating risk for CAD makes possible the widespread use of the power of Mendelian randomization. Using this technique, it is possible to assess the causality, safety, and to some extent efficacy of a lifetime exposure to a particular genetic risk variant without confounding factors. In a large Case Control Association Study, a genetic variant associated with increased plasma high-density lipoprotein cholesterol did not protect against heart disease.[19] The lack of protection from CAD of plasma high-density lipoprotein cholesterol has now been confirmed in several studies.[20] The average time for a cardiovascular drug from concept to market is ≈12 years, and the cost is >$2 billion.[21] Application of this technique has the potential to reduce both the time and cost required for approval of a new drug. Using Mendelian randomization, one can determine a priori whether the drugs' target is indeed causal of the disease. An example of the application of Mendelian randomization in determining a drug target was recently illustrated for the drugs varespladib (Anthera Pharmaceuticals) and darapladib (GlaxoSmithKline), inhibitors of secretory phospholipase A2 and lipoprotein-associated PL A2, respectively.[22–24] It was observed that secretory phospholipase A2 and lipoprotein-associated PL A2are consistently present in coronary atheromatous plaques, and hence their inhibition would potentially be beneficial. Three clinical trials, costing millions of dollars, were performed, and

all were negative. A Mendelian randomization study performed before the completion of the third clinical trial showed that phospholipase A2 is only a marker and not causative of coronary plaques. The Mendelian randomization study predicted the clinical trial should show no benefit.[25–27] Selection of a drug target proven to be causative by Mendelian randomization should significantly decrease the time and cost required to develop and evaluate cardiovascular drugs. A large part of the cost is the high efficacy failure rate because of selection of targets associated with the disease but not causative.

A major research and therapeutic thrust of the 21st century is the administration of pluripotent stem cells to regenerate the human myocardium—regenerative medicine. A decade of basic and clinical research[28] has led to the successful delivery of human stem cells to the heart, proving that cell therapy is feasible and safe. However, incorporation and proliferation of these cells have not been achieved and remain a future goal. The success or failure to regenerate the human heart is likely to be a distinguishing feature of the 21st century. As we conquer more diseases, such as CAD, regenerating organs such as the heart will become an even greater barrier to improving the quality of life and prolonging one's lifespan.

The techniques of molecular biology have become routine in cardiovascular research laboratories throughout the world. The impact of their application on the management of cardiac patients is particularly evident in drug development, the management of inherited disorders, and prevention and treatment of CAD. The future application of genetic risk stratification for prevention and treatment of CAD together with utilization of the genetic risk variants as drug targets for development of novel therapy is likely to markedly attenuate the pandemic of CAD.

The AHA is to be congratulated on their 1986 decision and the dominant role it has played in the past 3 decades.

ARTICLE INFORMATION

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Acknowledgments

I acknowledge Arlene Guadalupe Campillo, MPH, for her support in preparation of the manuscript.

Disclosures

Dr Roberts is a consultant to Cumberland Pharmaceuticals and confirms no conflicts.

REFERENCES

1. Morgan HE, et al. American Heart Association-Bugher Foundation Centers for molecular biology in the cardiovascular system. *Circulation*. 1995;91:487–493.
2. UCLA Symposia. Molecular biology of the cardiovascular system. *Cell*. 1998;55.
3. Roberts R. *Molecular Basis of Cardiology*. Hamden, CT: Blackwell Scientific Publications; 1992:1–518.
4. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I findings. *N Engl J Med*. 1985;312:932–936. DOI: 10.1056/NEJM198504043121437.
5. Seidah NG, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. *Proc Natl Acad Sci USA*. 2003;100:928–933. doi: 10.1073/pnas.0335507100.
6. Abifadel M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154–156. doi: 10.1038/ng1161.
7. Roberts R. PCSK9 inhibition–a new thrust in the prevention of heart disease: genetics does it again. *Can J Cardiol*. 2013;29:899–901. doi: 10.1016/j.cjca.2013.04.014.
8. Jarcho JA, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *N Engl J Med*. 1989;321:1372–1378. doi: 10.1056/NEJM198911163212005.
9. Hejtmancik JF, et al. Localization of gene for familial hypertrophic cardiomyopathy to chromosome 14q1 in a diverse US population. *Circulation*. 1991;83:1592–1597.
10. Geisterfer-Lowrance AA, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell*. 1990;62:999–1006.
11. Marian AJ, et al. Genetics and genomics of single-gene cardiovascular diseases: common hereditary cardiomyopathies as prototypes of single-gene disorders. *J Am Coll Cardiol*. 2016;68:2831–2849. doi: 10.1016/j.jacc.2016.09.968.
12. Burke MA, et al. Clinical and mechanistic insights into the genetics of cardiomyopathy. *J Am Coll Cardiol*. 2016;68:2871–2886. doi: 10.1016/j.jacc.2016.08.079.
13. McPherson R, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science*. 2007;316:1488–1491. doi: 10.1126/science.1142447.
14. Helgadottir A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–1493. doi: 10.1126/science.1142842.
15. Howson JMM, et al; CARDIoGRAMplusC4D; EPIC-CVD. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet*. 2017;49:1113–1119. doi: 10.1038/ng.3874.
16. Natarajan P, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. *Circulation*. 2017;135:2091–2101. doi: 10.1161/CIRCULATIONAHA.116.024436.
17. Roberts R. Genetic risk stratification and prevention of CAD: an idea whose time is now. *Clin Chem*. 2017;63:1821–1823. doi: 10.1373/clinchem.2017.278895.
18. Roberts R. A breakthrough in genetics and prevention of coronary artery disease and its relevance to prevention in low and middle income countries. *Glob Heart*. 2017:12: 247–257.
19. Voight BF, et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet*. 2012;380:572–580. doi: 10.1016/S0140-6736(12)60312-2.
20. Assimes TL, et al. Genetics: implications for prevention and management of coronary artery disease. *J Am Coll Cardiol*. 2016;68:2797–2818. doi: 10.1016/j.jacc.2016.10.039.
21. Mullin R. Tufts study finds big rise 'in cost of drug development'. *Chemical and Engineering News*. 2014;92. http://cen.acs.org/articles/92/web/2014/11/Tufts-Study-Finds-Big-Rise.html. Accessed: November 1, 2018.
22. Nicholls SJ, et al; VISTA-16 Investigators. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA-16 randomized clinical trial. *JAMA*. 2014;311:252–262. doi: 10.1001/jama.2013.282836.
23. O'Donoghue ML, et al; SOLID-TIMI 52 Investigators. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA*. 2014;312:1006–1015. doi: 10.1001/jama.2014.11061.
24. White HD, et al; STABILITY Investigators. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med*. 2014;370:1702–1711. doi: 10.1056/NEJMoa1315878.

25. Holmes MV, et al. Secretory phospholipase A(2)-IIA and cardiovascular disease: a Mendelian randomization study. *J Am Coll Cardiol*. 2013;62:1966–1976. doi: 10.1016/j.jacc.2013.06.044.
26. Holmes MV, et al; CARDIoGRAM Consortium. Novel genetic approach to investigate the role of plasma secretory phospholipase A2 (sPLA2)-V isoenzyme in coronary heart disease: modified Mendelian randomization analysis using PLA2G5 expression levels. *Circ Cardiovasc Genet*. 2014;7:144–150. doi: 10.1161/CIRCGENETICS.113.000271.
27. Lee RT, et al. The future of cardiovascular regenerative medicine. *Circulation*. 2016;133:2618–2625. doi: 10.1161/CIRCULATIONAHA.115.019214.
28. Dimmeler S, et al. Translational strategies and challenges in regenerative medicine. *Nat Med*. 2014;20:814–821. doi: 10.1038/nm.3627.

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Circ Genom Precis Med. 2018;11:
doi: 10.1161/CIRCGEN.118.002222
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1942-325X. Online ISSN: 1942-3268