Advancing Cardiovascular Research

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Over the past 50 years, we have seen dramatic changes in cardiovascular science and clinical care, accompanied by marked declines in the morbidity and mortality. Nonetheless, cardiovascular disease remains the leading cause of death and disability in the world, and its nature is changing as Americans become older, fatter, and ethnically more diverse. Instead of young or middle-aged men with ST-segment elevation myocardial infarction, the “typical” cardiac patient now presents with acute coronary syndrome or with complications related to chronic hypertension or ischemic heart disease, including heart failure, sudden death, and atrial fibrillation. Analogously, structural heart disease is now dominated by degenerative valve or congenital disease, far more common than rheumatic disease. The changing clinical scene presents cardiovascular scientists with a number of opportunities and challenges, including taking advantage of high-throughput technologies to elucidate complex disease mechanisms, accelerating development and implementation of evidence-based strategies, assessing evolving technologies of unclear value, addressing a global epidemic of cardiovascular disease, and maintaining high levels of innovation in a time of budgetary constraint and economic turmoil.

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Abbreviations: miRNA = microRNA; NHLBI = National Heart, Lung, and Blood Institute

Twenty-six years ago, as a medical resident, I admitted a 55-year-old man with a large anterior-wall myocardial infarction. He had been previously “healthy,” although he had smoked one pack of cigarettes a day for 30 years. We treated him with lidocaine and nitroglycerine. On his eighth hospital day, he died suddenly of an autopsy-proven myocardial rupture.

Five years ago, as an attending cardiologist, I admitted a 76-year-old woman with a non-ST segment elevation myocardial infarction. She was overweight and had well-controlled hypertension, but she did not have diabetes. Given elevated levels of troponin T, we arranged coronary angiography, which showed a

thrombus-laden lesion in her proximal circumflex artery, where my interventional colleague placed a stent. An echocardiogram showed left ventricular hypertrophy, preserved systolic function, impaired diastolic function, and moderate aortic stenosis. She was discharged on aspirin, clopidogrel, metoprolol, enalapril, and atorvastatin, and was referred to cardiac rehabilitation. Her outpatient physicians planned to focus on adherence and to monitor for other cardiac problems, as she was at risk for developing heart failure (with preserved ejection fraction), symptomatic aortic stenosis, and atrial fibrillation.

These two stories are indicative of the “cardiac revolution,” reflecting the accomplishments and challenges of modern cardiovascular medicine. During the past few decades, we have seen dramatic declines in the incidence of cardiovascular death¹ and myocardial infarction.² Supported by government and industry, countless teams of basic, translational, clinical, and population scientists developed new paradigms for predicting, preventing, and treating disease. Meanwhile, Americans are getting older, fatter, and ethnically more diverse. Rheumatic heart disease and ST-elevation myocardial infarction are “giving way” to heart failure, degenerative valve disease, and atrial fibrillation.

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Despite successes, heart disease remains the leading cause of death in the United States and is already the leading cause of death in the world.³ Science can rightfully claim credit for reshaping the cardiovascular landscape, but there is much to learn.

CONTEMPORARY CHALLENGES

Shortly after becoming National Institutes of Health Director, Francis Collins outlined five opportunities for biomedical research: high-throughput technologies, translational medicine, science to inform health-care reform, global health, and reinvigoration of the biomedical research enterprise.⁴ We can use Collins' framework to consider how to address cardiovascular challenges: elucidating complex disease pathways, accelerating development and implementation of evidence-based strategies, assessing rapidly evolving technologies of unclear value, addressing a global epidemic of cardiovascular disease, and maintaining high levels of innovation in a time of budgetary constraint and economic turmoil.

MECHANISMS OF DISEASE: APPLICATION OF HIGH-THROUGHPUT TECHNOLOGIES

Over the past 10 to 20 years, we have come to appreciate the pathophysiologic roles of inflammation, fibrosis, hypertrophy, apoptosis, autophagy, electrical remodeling, cellular proliferation, endothelial dysfunction, and angiogenesis in the progression of cardiovascular disease. Advances in genomics, epigenetics, proteomics, metabolomics, nanotechnology, systems biology, and bioinformatics have enabled scientists to elucidate complex, interwoven pathways, some which present novel targets for therapy. Among the most exciting recent developments include discoveries of: unsuspected genetic predictors,⁵ genomic guides to pharmacologic responses,⁶ microRNA (miRNA) in posttranscriptional modification,⁷⁻⁹ Mendelian randomization to clarify causality of putative biomarkers,¹⁰ induced pluripotent stem cells to model human disease,¹¹ and intestinal microflora as producers of toxic metabolites.¹²

In 2007, two groups performed genome-wide association studies and found a strong link between a noncoding sequence polymorphism on chromosome 9p21 and risk of coronary disease.^{13,14} Other groups found that the 9p21 polymorphism predicts peripheral arterial disease, stroke, and aneurysms of the abdominal aorta and intracranial arteries.⁵ The 9p21 locus is near to genes that code for cyclin-dependent kinase inhibitors that are known tumor suppressors.¹⁵ Visel et al¹⁶ found two mouse orthologs on chromo-

some 4 and examined the phenotype of a model in which both genes were deleted. Mutant mice had higher mortality rates; their aortic smooth muscle cells had higher degrees of proliferation and lower rates of senescence. Harismendy et al¹⁷ used population sequencing and cellular assays to show that 9p21 sits within a region densely packed with enhancers, one of which is tightly linked with inflammation and interferon signaling. These findings underpin a genomic basis for atherosclerotic disease, offering new possible therapeutic strategies.¹⁵ However, genome-wide association studies have only identified a small proportion of the heritability of atherosclerosis. Some investigators believe that this unresolved problem will be addressed by application of newer techniques in rare variant sequencing, epigenetics, proteomics, and metabolomics.⁵

Genomics offers opportunities to examine new approaches to existing treatment paradigms. It is now well established that statins, by reducing low-density lipoprotein cholesterol, can prevent major cardiovascular events in people with and without established disease.¹⁸ Cohen and colleagues¹⁹ genotyped healthy adults in the National Heart, Lung, and Blood Institute (NHLBI)-funded Atherosclerosis Risk in Communities (ARIC) study and found that variations in the proprotein convertase subtilisin/kexin type 9 serine protease gene are associated with dramatic reductions in low-density lipoprotein-cholesterol levels and in risk of coronary disease. Inhibition of proprotein convertase subtilisin/kexin type 9 serine protease may offer a wholly different approach to preventing cardiovascular events.

Genomics holds promise as a way to personalize therapy, identifying patients who are more likely to respond to candidate therapies. Lynch et al⁶ found that polymorphisms of the atrial natriuretic peptide precursor A gene predicts relative benefits from diuretics or calcium blockers in patients with hypertension. However, for complex polygenic conditions with relatively low event rates, it is difficult to find clinically meaningful drug-gene interactions. Florez et al²⁰ demonstrated that the transcription factor 7-like 2 gene predicts risk of diabetes, but did not predict clinical response to drug or lifestyle interventions. Similarly, the hepatic CYP2C19 gene has been linked to platelet resistance and to poor clinical outcomes.⁵ The value of routine CYP2C19 testing in clinical care has been challenged though; in large-scale trials, clopidogrel yielded clinical benefits irrespective of genotype status.²¹

miRNA consists of small single-nucleotide strands that bind to complementary segments of transcriptional mRNA.⁷ Under conditions of hemodynamic stress, miRNA-208 stimulates increased expression of the β form of the myosin heavy chain, stimulating

hypertrophy and tissue fibrosis.²² miRNA overexpression may affect other pathways, including cell proliferation, apoptosis, electrical remodeling, leukocyte adherence, smooth muscle cell remodeling, and angiogenesis.^{8,9} It is not clear whether miRNA genes are viable therapeutic targets.^{7,23}

Biomarkers are being increasingly used and promoted to stratify risk and plan therapies. Three leading “novel” biomarkers in cardiovascular medicine are high-sensitivity C-reactive protein, cardiac troponin, and B-natriuretic peptide.²⁴ The associations between biomarkers and clinical outcomes are epidemiologic and cannot be used to establish causality. However, investigators have taken advantage of random distribution of alleles at conception, or “Mendelian randomization,” as a tool to determine whether biomarkers are causative links to disease. If a gene leads to increased levels of a biomarker and to higher risk of disease, one can conclude that the biomarker is likely to cause disease and, therefore, is a viable therapeutic target.⁵ If the gene does not predict disease risk, the biomarker is more likely to be just that, a “marker” for disease, but nothing more. Recently, investigators used Mendelian randomization methods to show that high-sensitivity C-reactive protein probably does not cause coronary disease,¹⁰ whereas lipoprotein(a) probably does.²⁵

Traditionally, cardiovascular scientists have relied on animal models to identify and develop new diagnostics and therapeutics. With the advent of induced pluripotent stem cells, it is now possible to create human cellular models that can serve as platforms for pharmacological experiments. Moretti et al¹¹ took dermal fibroblasts from two people with characterized genetic long QT syndrome and used transcription factor--encoded retroviral vectors to generate pluripotent stem cells, which were then directed to differentiate into cardiomyocytes. The newly created cardiomyocytes appeared to fully reproduce the patients' phenotypes, with prolonged action potentials, abnormal potassium channel activity, and susceptibility to catecholamine induced ventricular tachyarrhythmias.

We have come to appreciate that the intestinal microflora (“microbiome”) may play a critical role in predisposing people to obesity, metabolic syndrome, and diabetes. Wang et al¹² found that trimethylamine N-oxide, a derivative of dietary phosphatidylcholine, was associated with increased risk of coronary disease. In order for the body to synthesize trimethylamine N-oxide, it requires gut flora to transform choline to trimethylamine. Based on clinical observations, Wang et al performed a series of experiments in atherosclerosis-prone mice, finding an obligatory role of gut flora in enabling phosphatidylcholine-induced atherosclerosis. The findings raise the poten-

tial that manipulation of the microbiome could prevent or ameliorate disease.

NEXT-GENERATION CARDIOVASCULAR TRANSLATION

Translation is a “hot topic” in science news, particularly as the National Institutes of Health moves to fund its second cycle of clinical translational science awards and to form a proposed National Center for Advancing Translational Sciences.²⁶ We recognize that there are numerous logistical, regulatory, economic, legal, commercial, and philosophical challenges as we seek to realize the potential benefits of regenerative medicine, stem cell biology, tissue engineering, nanotechnology, and -omics discoveries.²⁷ Cardiovascular medicine is particularly problematic as leading pharmaceutical companies have chosen to scale back their research programs.²⁸

We have described elsewhere NHLBI's approach to fostering cardiovascular translational research.²⁷ Our efforts include programs in heart failure therapeutics, pediatric heart disease, progenitor cells, and cell therapy,²⁹ and a program to assist investigators in developing preclinical and clinical-grade production and testing of biologics, nonbiologics, and small molecules. We are about to launch a program designed to stimulate rapid early translation of diagnostics and therapeutics for peripheral vascular disease. While no one has found a “magic bullet” for assuring translation, we are focusing on multidisciplinary environments that support a large number of short-duration projects.

The other end of translation is assuring that robust clinical research findings are disseminated into practice. We have seen some successes; after the Women's Health Initiative trial results were published, doctors wrote fewer postmenopausal hormone prescriptions.³⁰ After implementation research identified successful approaches to reducing door-to-balloon times, national door-to-balloon times dramatically improved.³¹ On the other hand, after the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)³² and Occluded Artery Trial (OAT)³³ findings were published, physicians did not materially change their practice.^{34,35}

With the advent of the newly created Patient-Centered Outcomes Research Institute (PCORI),³⁶ there is increasing focus on engaging stakeholders in prioritizing, designing, implementing, and disseminating comparative effectiveness research. It is not clear whether this kind of engagement will lead to better adoption of research findings. In both the ALLHAT and OAT cases, powerful market, legal, and cultural forces may have created difficult-to-surmount conditions for overutilization of medical treatments.³⁷

RAPIDLY EVOLVING TECHNOLOGIES: SCIENCE TO INFORM HEALTH CARE REFORM

Over the past 25 years, we have seen dizzying transformations of cardiovascular technologies and paradigms. For coronary disease, bypass surgery appears to be giving way to bare metal and drug-eluting stents.³⁸ For heart failure, drug therapy is now accompanied by implantable defibrillators and cardiac resynchronization therapy.³⁹ For atrial fibrillation, catheter ablation of arrhythmogenic foci near the pulmonary vein ostia is emerging as a possible long-term treatment,⁴⁰ while warfarin anticoagulation may be supplanted by direct thrombin inhibitors.⁴¹ For aortic stenosis, percutaneous valve replacement appears to be a viable alternative to open heart surgery.⁴² We have also seen rapid growth of diagnostics and imaging, including circulating biomarkers, genomic tests, perfusion imaging, PET scan, MRI, coronary calcium detection and quantification, and CT scan angiography. Imaging procedures and diagnostic tests are the two leading growth services among patients insured by Medicare.⁴³

For some of the newer technologies and strategies, there is strong evidence of meaningful benefit. In appropriate patients, defibrillators, cardiac resynchronization therapy, and coronary stents save lives. However, there are serious questions about the value of other commonly used technologies. Recent trials have shown that aggressive management of blood glucose,⁴⁴ BP,⁴⁵ and triglycerides⁴⁶ does not improve outcomes in patients with complex diabetes. We do not know whether doctors improve clinical outcomes when they implant stents in patients with stable angina, when they perform catheter ablation in patients with atrial fibrillation, or when they order advanced imaging studies in patients with suspected coronary disease. NHLBI will soon launch a comparative effectiveness trial which will compare medical and angiographic strategies in patients with documented ischemia. NHLBI is launching major trials to test new paradigms including: the Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial,⁴⁷ which is testing whether atrial fibrillation ablation reduces mortality; a trial of methotrexate, a powerful antiinflammatory agent, in patients with established high-risk cardiovascular disease; and two trials which are assessing whether CT scan angiography improves clinical outcomes.^{48,49}

Cardiovascular medicine is deeply steeped in application of evidence-based technologies, yet a recent survey found that only 11% of current practice guidelines are based on high-level evidence (well done randomized trials).⁵⁰ While we clearly need to support large-scale comparative effectiveness trials of unproven technologies, we often find it difficult to enroll patients

and to complete trials on time.⁵¹ Our impressions are not unique. The National Cancer Institute ran into stiff resistance when it attempted a trial of helical CT scan for lung cancer screening⁵²; ironically, the trial was positive, demonstrating the ability of the technology to save lives.⁵³ One of our most important challenges over the next few years will be to work closely with academic, physician, industry, and patient groups to reinvigorate cardiovascular trials.

THE GLOBAL EPIDEMIC OF CARDIOVASCULAR DISEASE

The world is going through a period of epidemiologic transition with a greater proportion of deaths occurring in older people and with more deaths due to noncommunicable diseases.³ By recent projections, ischemic heart disease and cerebrovascular disease are the two leading causes of death in the world and will continue to be for many decades.^{54,55}

Both government and industry are already engaged in global cardiovascular research. In partnership with United Healthcare, NHLBI is funding seven global centers of excellence that are overseeing prevention and epidemiology studies as well as training young investigators. Industry is shifting some clinical trial operations to developing countries, where costs and regulatory requirements are less. Some have expressed concern that the “outsourcing” of clinical trials may fail to improve American cardiovascular health, while failing to materially benefit populations in the developing world.⁵⁶ Along with reinvigorating clinical research in the United States, an equally important and related challenge will be to assure that clinical research resources are appropriately allocated to improve health in both developed and developing countries.

ENHANCING CARDIOVASCULAR RESEARCH DURING CHALLENGING TIMES

In *The Wisdom of the Sands*, French author and aviator Antoine de Saint-Exupéry wrote, “As for the Future, your task is not to foresee, but to enable it.”⁵⁷ Enabling a vigorous future in cardiovascular research is inevitably going to be increasingly challenging as government science funding shrinks and as industry shifts to different priorities.²⁸ While beyond the scope of this essay, it is clear that we will need to wholly rethink our business paradigms.⁵⁸ In the future, it will be equally important to think about how we do science as it will be to think about what science to do. We have every right to be proud of the advances brought by the cardiac revolution and of the many exciting new avenues of research, some discussed here, that basic, translational, and clinical scientists are

pursuing. But if we fail to use the current fiscal crisis as an opportunity to work smarter, a future “Ahead of the Curve” essay may not have much new to say.

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