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EDITOR'S PAGE

The 3 Pathways of Translational Medicine

An Evolution to a Call-and-Response Method

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Jazz music, which resulted from a necessity to disrupt previous traditions of European classical music to fully incorporate American culture, heralded in the "call and response" device, whereby 1 section of musical instruments, such as the brass section, would play a musical phrase and then be "answered" by another section, such as the saxophones. The first phrase is the *call*, the answer is the *response*, giving birth to a musical conversation that evolved into a musical revolution.

Out of necessity, translational medicine may have taken a similar path of deviation and evolution. Classically, there has been a linear path of translational medicine, by which basic science gets translated to the patient and then undergoes wide-scale distribution through clinical trials, global health initiatives, and development of clinical guidelines (the *first pathway*). However, recently there has been a distinct change to this historical model. Through technology and global databases, we now are able to observe how populations respond or do not respond to medications or procedures. Equipped with these observations from clinical trials, global health projects, and large-scale databases, researchers are now circling back with observational information that impacts patient care directly (the *second pathway*) or indirectly through basic science (the *third pathway*) (**Fig. 1**).

Thus, translational medicine no longer has a single pathway. It does not mean that the historical model is no longer relevant, but it is now bolstered by other means of getting the best care for patients. Let me provide 6 ongoing 2014 examples, 2 from each pathway, that further elucidate how these 3 pathways are already being implemented in contemporary medicine.

The *first pathway,* from which many previous generations of patient care arose, remains a vital part of the scientific process. One example relates to cholesterol-lowering therapy with statins, which may not be achieved because of compromised adherence to daily medication, intolerance to or side effects from the therapy, or insufficient lowering of low-density lipoprotein cholesterol (LDL-C) levels. An elegant basic investigation performed in a number of laboratories has shown that proprotein convertase subtilisin kexin 9 (PCSK9) binds the low-density lipoprotein receptor at the surface of hepatocytes, thereby resulting in reduced LDL-C clearance (1). Presently, PCSK9 monoclonal antibodies that inhibit its function on the low-density lipoprotein receptor are being evaluated. Thus far, evolocumab (previously AMG 145) dramatically lowered LDL-C in phase 2 clinical trials when administered subcutaneously biweekly or monthly. Similar information is evolving in phase 3 randomized studies, whereas the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study, involving 22,500 patients with atherosclerotic disease, is underway with the ambitious objective of event reduction (2).

A second contemporary example of the *first pathway* relates to an early intervention strategy during ST-segment elevation myocardial infarction (STEMI) and the evaluation of β-blockers to exert a cardioprotective capacity by decreasing reperfusion injury. Recent data from a pig model showed that the β1-selective blocker metoprolol was able to markedly reduce infarct size only when administered early and intravenously before reperfusion. The randomized METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial

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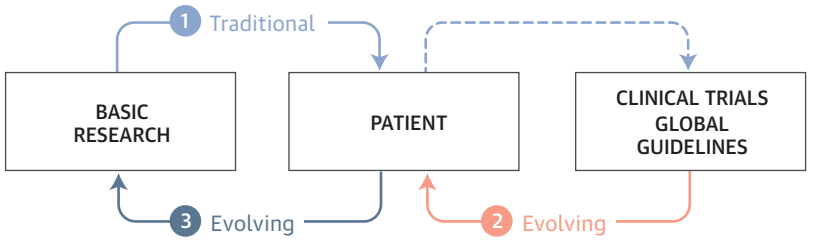

FIGURE 1 The 3 Pathways of Translational Medicine

This illustration depicts the evolutionary pathway for translational medicine, which traditionally went from basic science to global distribution, but is now finding new methods to introduce better care for patients.

Infarction) study, which applied this strategy to 270 patients with anterior STEMI, Killip class ≤II, who were undergoing primary percutaneous coronary intervention, showed that metoprolol reduced infarct size (3). This trial's results have led to the design of the MOVE ON trial, a large study of approximately 4,000 STEMI patients in 9 European countries, powered to detect differences in the primary composite endpoint of cardiac death or readmission to the hospital due to heart failure, for which recruitment is planned to start in 2015.

These 2 ongoing approaches from basic/experimental to clinical practice, with the proprotein PCSK9 and a β1-selective blocker, respectively, represent 2 examples of how the *first pathway* will continue to be a vital priority in the biomedical research arena. However, the following contemporary 4 examples of the *second* and *third pathways* corroborate that each of these approaches are also necessary to ensure the best care for our patients.

The present approach to the treatment of patients with stable complex coronary artery disease (CAD) represents a clear example of the *second pathway*. In the 1980s, based on 3 major randomized studies (CASS, VA, and European), in patients with stable CAD who had 2 out of 3 abnormal clinical variables (left ventricular dysfunction, 3-vessel disease, or significant ischemia), coronary artery bypass grafting was considered to be superior to optimal medical therapy. In the 1990s, several small studies argued the noninferiority of percutaneous coronary intervention over coronary artery bypass grafting. In the 2000s, a number of seminal clinical studies emerged that have had a significant influence on our understanding of complex coronary disease, while at the same time demonstrating that effective treatment requires an equally complex therapeutic approach (4). As a result of these recent studies, sophisticated treatment algorithms have arisen that incorporate overall anatomical complexity (SYNTAX risk score), intravascular measured presence or absence of ischemia by the fractional flow reserve (FFR) related to each individual epicardial coronary stenosis, and various clinical aspects including left ventricular dysfunction, degree of global ischemia, and comorbidities (clinical risk score). These new algorithms are now being taken directly from observations made over the last 10 years of clinical trials and practical experience and are processed into guideline-recommended treatments. This demonstrates a clear example of the *second pathway*.

Another example of the *second pathway* relates to the high global prevalence of obesity and diabetes, as well as the proven difficulties for their control through changes in lifestyle and pharmacology; the question has been raised about whether bariatric surgery could play a successful role in combating these complications. Following a few limited but promising studies addressing this question, the STAMPEDE randomized trial, involving 150 obese patients with uncontrolled type 2 diabetes, showed that intensive medical therapy plus bariatric surgery resulted in weight reduction and glycemic control in significantly more patients than did medical therapy alone (5). The benefits obtained in the bariatric surgery arm also extended to the other risk factors of the metabolic syndrome. Again, this shows research responding to the *second pathway,* whereby a potential solution to a global health problem can be translated directly to the patient through a commonly accepted procedure.

In this aging population, the burden of dementia is rising: about 25% of all people age 55 years and older have a family history of dementia, and the lifetime

risk of dementia for the family members is about 20%. In response to this global epidemic, researchers have taken a *third pathway* through both the National Alzheimer's Coordinating Center database of 5,715 autopsy cases with neuropathological and cerebrovascular evaluation (6) and the longitudinal study of more than 3,000 adults in 4 U.S. cities followed over a period of 25 years (7). Based on the information obtained from neuropathology, neurovascular imaging, and psychological testing, there is strong evolving evidence of a relationship between cardiovascular risk factors, cerebrovascular disease with microinfarcts, and dementia. Researchers are delivering this new knowledge, brought about by new imaging technologies applied at autopsy and in vivo database, back to the laboratories of basic science to see if they can discover new treatments for this confluence of diseases.

As another example of the *third pathway,* we all have become aware of the clinical and economic implications of the global problem of nonadherence, with <50% of patients with chronic conditions, such as CAD, adhering to their prescribed treatment. Across all health care categories, this accounts for about $290 billion of annual health care expenditure in the United States. In response to this global need, investigators and industry went back to the basic science laboratories to create various polypills for secondary prevention that are presently getting ready for patient use (8).

Thus, translational medicine no longer has a single pathway; there has been a distinct change in this historical model. As the early jazz musicians developed a response to each call in order to complete the musical number, investigators are utilizing 3 unique pathways to respond to the evolving needs of contemporary cardiovascular patients.

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