Bench-to-Bedside; Clinical and Translational Research; Personalized Medicine; Precision Medicine—What's in a Name?

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Anyone who has followed the popular television serial "Mad Men" knows that a product's name is an important focus of Madison Avenue. A bad outcome can tarnish a good name (e.g., the Chevrolet Corvair) while a bad name can tarnish a potentially good product (e.g., the Ford Edsel). Appealing names attached to excellent products can becomes iconic in the minds of the public and become inculcated into common language – examples being the Mustang and the Corvette. So what do automobiles have to do with science? I would argue that the translational science community has done a poor job of marketing our signature research program—translational science—and thus have confused the public, potential investors, donors, Congress and most importantly the next generation of physician-scientists. We would therefore do well to take a lesson from Madison Avenue and agree upon a single moniker for research that is focused on improving the health of our population.

In May 1968, the Editor of the New England Journal of Medicine used the term "Bench-Bedside Interface" to describe two papers published in the issue that demonstrated for the first time that chronic granulomatous disease of childhood could occur in females.[1] The concept that scientists, and in particular physician scientists, would try to understand the biology of clinical observations by pursuing studies in their laboratories or that they would identify new therapeutic targets or biomarkers in the laboratory which could then be evaluated in the clinic was not new. William Osler had built the School of Medicine at Johns Hopkins on the foundation that the clinics and the laboratories had to be inextricably linked and Lewellys Barker, Osler's successor as Director of Medicine at Hopkins, established the concept of the laboratory as a place where the underlying biology of disease could be determined and where new treatments could be developed. The concept that both physicians (clinical scientists) and basic scientists could produce important findings while working at the interface between basic science and clinical medicine persisted through the 20th century—but it lacked a name.

In 1999 the NIH first established a funding mechanism for what they described as "bench-to-bedside" projects through the creation of what they referred to as "B2B" programs. (www.cc.nih.gov/ccc/btb/) Established by the Director of the Clinical Center, the B2B awards incentivized intramural basic scientists to collaborate with intramural clinical researchers in order to speed the **translation** of laboratory discoveries into new therapeutics. In 2006, the program was expanded to include partnerships between intramural and extramural clinical researchers: a large step for the NIH as it was the first time that a single award funded both intramural and extramural investigators. In 2004, a panel chaired by Edward J. Benz and Joseph L. Goldstein reported that: "The Bench-to-Bedside Awards program serves as a superb example of a highly successful program that fosters collaborations among intramural scientists and clinicians in areas of research that have the potential for improving understanding of an important disease process or for leading to a new therapeutic intervention."[2] However, the awards remained largely seed funding and the program modest with only 10 of 127 applications funded in 2013. Thus, the term "B2B" gained little attention or traction.

With the human genome project well underway, scientists in the late 1990's began to conceptualize how completion of the project would lead to the ability to "personalize" medical regimens for individual patients based on either their own genotype (pharmacogenomics)[3] or the genotype of their tumor.[4] The completion of the human genome project in 2003 provided the scientific platform that would allow investigators to identify genetic causes for both rare and common diseases, understand the molecular basis of human diseases, identify molecular markers of risk and/or disease severity, uncover new therapeutic targets for either small molecules, biologics or gene therapy, and elucidate methods to individualize therapy based on an individual's genotype—the essence of "personalized medicine." The use of "personalized medicine" to define a field of research continued to be used in the literature, but like B2B, it did not receive a great deal of attention from the public or from Congress. In fact, it wasn't until a 2010 Perspective in the *New England Journal of Medicine* entitled "The Path to Personalized Medicine," by Margaret Hamburg, Director of the Food and Drug Administration and Francis Collins, Director of the NiH, that specific plans to enhance personalized medicine and to overcome the inherent obstacles needed to move personalized medicine from an esoteric vision to a reality were conceptualized.[5] They pledged to "invest in advancing ***translational and regulatory science***, better define regulatory pathways for coordinated approval of co-developed diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make information about tests readily available." Importantly, the central concept of their perspective was translation. Perhaps the failure of the term "personalized medicine" to gain traction has been attributable in part to the fact that genetic heterogeneity

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makes using genetic tests to predict disease occurrence imperfect, molecular diagnostics and biomarkers have been associated with false positives as well as false negatives, and results of gene therapy have been disappointing.[6,7]

In 2005, research focused on human disease gained another new moniker with the announcement by Elias Zerhouni, the new Director of the NIH, of the creation of the Institutional Clinical and Translational Science Awards (CTSAs) program.[8] It was designed to "foster productive collaboration among experts in different fields, lower barriers between disciplines, and encourage creative, new approaches that will help us solve complex medical mysteries" leading to improved human health." Unlike past NIH funding programs, the CTSAs were multidimensional and multidisciplinary as they incorporated the concept of "team science." Translational medicine brought together basic scientists, physician scientists, biostatisticians, epidemiologists, nonphysician health care providers, computational biologists, informaticians, health care economists, healthcare economics and policy experts, biomedical engineers, ethicists, volunteers and regulators. These large teams of scientists also incorporated the talents of volunteers, educators, women's health groups, faith-based groups, community housing organizations, federally qualified health centers as well as behavioral scientists, sociologists, and health care attorneys. Thus, entire communities became involved in translational medicine. With a critical part of a CTSA being focused on education, the next generation of clinical and translational scientists became apostles of the new term "translational science."

The term "translational medicine" was not initially embraced by either academia or the lay public, but four events moved it into the basic language of medicine: (1) Steven Reis, Director of the Clinical and Translational Institute at the University of Pittsburgh, published an iconic figure that clearly defined translational medicine; (2) numerous journals were created in order to publish clinical and translational science including this journal and the highly prestigious Science Translational Medicine and at least 5 other new journals with "translational" in their names; (3) funding for CTSAs increased with nearly half of America's medical schools having CTSAs and even academic medical centers without CTSA funding creating "Centers for Translational Medicine" or "Clinical and Translational Science Institutes; and (4) translational medicine became a required component of the curriculum of U.S. medical schools. LCME Standard 7.3 (Scientific Method/Clinical/Translational Research) of the Liaison Committee on Medical Education, states: "The faculty of a medical school ensure that the medical curriculum includes instruction in the scientific method (including hands-on or simulated exercises in which medical students collect or use data to test and/or verify hypotheses or address questions about biomedical phenomena) and in the basic scientific and ethical principles of **clinical and translational research**. Thus, the concept of translational medicine has become inculcated into the psyche of American medical research and medical education. In fact, a Pubmed search using the key words "translational medicine" yields nearly 50,000 citations.

But a new terminology has now entered medical research in the U.S—"Precision Medicine." Unlike nomenclature that was introduced by leading physician-scientists, precision medicine was introduced to the public by President Obama in his State of the Union Address, January 20, 2015 when he announced that: "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier."[9]

In the press briefing that accompanied the announcement, the President posited that: "Most medical treatments have been designed for the 'average patient.' As a result of this 'one-size-fits-all-approach,' treatments can be very successful for some patients but not for others. This is changing with the emergence of precision medicine, an innovative approach to disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles. Precision medicine gives clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective." According to The White House, precision medicine would leverage advances in informatics, computational biology and a coordinated national effort as well as the enrollment of a million or more volunteers to develop new and more precise treatment strategies.

Will "Precision Medicine" become an icon of American medicine or will it be this year's Edsel? I would argue that it should not be added to the medical lexicon for the following reasons. First, the term "precision medicine" implies that physicians do not currently provide patients with precise care. This is the wrong message to give the public and our students. We should be pointing out how research has already led us to be precise in our care: implanting a cardiac defibrillator in a patient with Brugada's syndrome, placing a coated stent after an angioplasty of a coronary lesion, or providing genetic counseling for a patient with a family history of breast and/or ovarian cancer and a BRCA1 or BRCA2 mutation. Second, the President has failed to address the bottlenecks that inhibit the delivery of "precise care" to a significant segment or our population when precise treatments are available: the high cost of many of the new targeted medications. Take for instance the new molecularly targeted drugs Imbruvica for mantle cell lymphoma, Lenyima for differentiated thyroid cancer or Zykadia for non–small cell lung cancer—all priced at nearly $140,000 per year. Third, the concept of gathering genetic, socioeconomic, ethnic, gender, activity and dietary data from a large cohort of voluntary subjects through smartphones and other high technology devices is intriguing and certainly has the potential for changing the way we look at disease—but there is no mention of the fact that underserved minorities have extremely low participation rates in clinical research and the elderly are challenged by devices. Therefore, great care must be taken to insure that we don't increase already existing disparities in healthcare. Fourth, the program fails to address the fact that big pharmaceutical companies have no interest in collecting genomic, proteomic or metabolomics data from large clinical trials because it is far more economical to show that a drug is effective in a large population of patients than to demonstrate that a drug is effective in only a defined subset of patients—and thus a small market. Finally, and most importantly, the President has committed an investment of only $215 million that will be shared across the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Office of the National Coordinator for Health Information Technology (ONC). In fact, only $70 million will be allocated to the National Cancer Institute to scale up efforts to identify genomic drivers in cancer and to apply that knowledge to the development of new approaches for the treatment of cancer. By contrast, commercial development of a single new drug or biologic costs nearly $1 billion. Thus, even an initiative that is

focused only on cancer will have little chance of success when such a paltry sum is invested.

In a recent perspective, Francis Collins and Harold Varmus supported the concept of Precision Medicine and opined that by taking advantage of research tools including proteomics, metabolomics, and genomics, smart phones and social media to collect data on patient outcomes and disease progression and computational biology and data analytics to collate and interpret large data sets we achieve a health care system in which we use "prevention and treatment strategies that take individual variability into account."[10] I certainly can't argue with their vision, but I would argue that what they are really describing is the **translation** of data acquired from the research bench, from individual patients, or from large data sets to the development of new diagnostics and treatment strategies for both individuals and populations—an area that for over a decade we have referred to as "Translational Medicine." The term translational medicine is widely accepted, clearly defined and substantial financial supported has been directed towards translational medicine programs by the NIH and from private sources. In fact, translational scientists spend each day trying to make the care of patients more precise. Therefore, it would serve science and education best if we retained clinical and translational science as what we do and respectfully suggest to the President that he focus his efforts on significantly increasing the NIH budget and not on labeling fields of research efforts. **CTS**

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