The Journey From Research Discovery to Optimal Heart Health for All

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TURNING FUNDAMENTAL DISCOVERIES INTO HEALTH

The tag line of the U.S. National Institutes of Health (NIH) is *Turning Discovery into Health* [1]. The phrase captures the importance of research translational steps that help turn discoveries into individual and population health impact. Without the discoveries from fundamental research in basic science to advance and expand our knowledge of the molecular, cellular, and physiological mechanisms governing health, our translational research efforts to underpin health promotion and the prevention and treatment of disease will falter. As Vannevar Bush pointed out in *Science, the Endless Frontier,* "Basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn…" [2]. This new knowledge generation through fundamental discovery science occurs not just in the biological and other natural sciences but also in the social and behavioral sciences and encompasses research conducted in humans, animals, tissues, cells, and subcellular structures [3,4].

TRANSLATIONAL RESEARCH FROM BENCH TO BEDSIDE AND BEYOND

The journey from fundamental research discovery to optimal health for individuals and populations is an arduous one. The NIH Roadmap recognized the importance of supporting basic research but also highlighted the need to "translate" basic research findings more quickly into diagnostic and therapeutic interventions to be undertaken in clinical practices in support of patient care to promote health. Re-engineering the clinical research enterprise and supporting translational research core services were just as important as new pathways to research discovery [5]. In fact, as former NIH Director Elias Zerhouni noted, "exciting basic science discoveries demand that clinical research continue and even expand, while striving to improve efficiency and better inform basic science" [5]. This was the concept of the 2 major research laboratories—bench and bedside—and the related (T1 and T2) translational steps.

In their commentary on practice-based research as the "blue highways" on the NIH Roadmap, Westfall et al. [6] emphasized that the T1 and T2 translational steps from bench to bedside and from bedside to practice in the NIH Roadmap were inadequate to capture the crux of what happens in routine clinical practices. As they eloquently stated, "What is efficacious in randomized clinical trials is not always effective in the real world of day-to-day practice" [6]. They proposed expanding the bench and bedside concept to include a third translational step (T3) involving research in ambulatory clinical practices [6]. Research generated in this third setting—practice-based research—is what Green has called for as necessary to make research relevant to the practice setting [7,8]. More recently, in alignment with the operational phases of translational research advocated by the National Academy of Medicine [9], we have built on these developments and highlighted the fourth translational step (T4), which embodies population-level outcomes research with an emphasis on implementation research outcomes (Figure 1) [10].

Collectively, what these translational research steps represent is a nonlinear, iterative process where one translational step informs as well as leverages insights from other steps through feedback loops in new knowledge generation; rigorous systematic evidence review, synthesis, and integration; clinical practice guideline development and deployment; and active dissemination and implementation research as one progresses from fundamental discovery science to population health impact. Each of these translational steps is important and features unique challenges that must be overcome to facilitate turning discoveries into health.

CHALLENGES IN EARLY-STAGE TRANSLATIONAL RESEARCH: CROSSING THE VALLEY OF DEATH

The valley of death is a well-described challenge in early translational research that spans the period after fundamental discovery and includes proof-of-concept research, product definition, prototype development and optimization, pre-clinical validation, and regulatory approval before the start of Phase I clinical trials. It refers to the proverbial challenge wherein basic research breakthroughs "languish and frequently succumb" [11] because of a lack of funding and/or expertise to turn the breakthroughs into commercially viable drugs, devices, and other products. Several current NIH initiatives provide the support necessary for proof-of-concept research, prototype building, product development and testing, and overall "de-risking" to make concepts and prototypes attractive to investors and thus help investigators and their innovations cross the valley of death [11-14].

Admittedly, the valley of death is not the only challenge faced in early translational research. As summarized by several authors [13-17], continuing cultural differences

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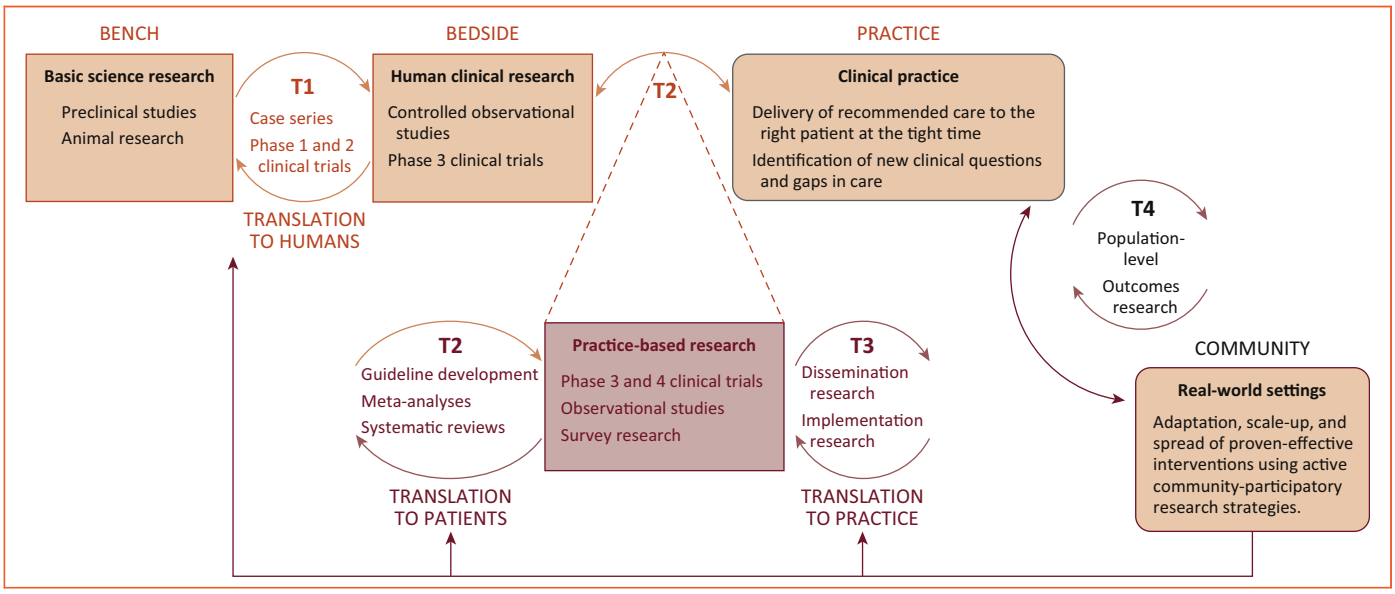

FIGURE 1. Research translation: from bench to bedside to practices to communities and back to bench research. Reproduced with permission from Westfall JM, Mensah GA. T4 translational moonshot: making cardiovascular discoveries work for everyone. Circ Res 2018;122:210-2.

between basic scientists and clinicians remain a challenge, and so do the complex regulatory environment, inadequacies in infrastructure and resource support, challenges in data access and sharing, limited training and mentoring opportunities, and inadequate numbers of trained interdisciplinary staff to support investigations throughout the early translational research spectrum. Again, there has been substantive support for early translational research, especially from the NIH, the United Kingdom's Medical Research Council and National Institute of Health Research, as well as other major research funding entities [5,9,17,18]. At the NIH, the establishment of the National Center for Advancing Translational Sciences (NCATS), with a fiscal-year 2012 budget of $575 million, is one concrete example of the commitment to "re-engineer the process of translating scientific discoveries into new drugs, diagnostics, and devices" [19,20].

CHALLENGES IN LATE-STAGE TRANSLATIONAL RESEARCH AND IMPLEMENTATION SCIENCE

Far fewer initiatives and resources exist to address the challenges in late-stage translational research. Importantly, however, this phase is when strategies to increase the adoption and sustained use of these new drugs, diagnostics, and devices to optimize health impact are explored. At the National Heart, Lung, and Blood Institute, the establishment of the Center for Translation Research and Implementation Science was an effort to focus strategic attention on the challenges inherent in this phase of the translational research pathway and to stimulate interest in T4 translation research [21,22]. The myriad late-stage translational research challenges include limited resources for rigorous systematic evidence review, evidence integration, and the development of trustworthy clinical practice guidelines; clinical, therapeutic, and knowledge translation inertia [23-25]; lack of tools and supports to facilitate guideline dissemination and effective implementation [26]; challenges in changing provider, health systems, and consumer behavior in adherence to established best practices and clinical practice guidelines [27-30]; and challenges in generating new knowledge in practice-based research to inform evidence-based practice to optimize population-level health impact [7,8,31].

Several articles in this issue of *Global Health* provide other examples of the important challenges encountered at this "tail end" of the translational research pathway in global health research and the implications they have for turning discoveries into population health impact. The examples span challenges in systematic data collection methods and data transparency [32]; importance of roadmaps that provide practical and effective solutions to improve detection, treatment, and control of hypertension and other cardiovascular risk factors [33]; context-specific health system factors that affect the patient's choices of medications and ability to adhere to dosing recommendations in the long term [34]; social and cultural conditions that vary between settings or countries and thus impact adaptation of proven interventions from one setting to another [35]; lack of relevant capacity and resource constraints [36]; and the importance of strategic partners at the local, national, continental, and global levels for the prevention, treatment, and control of cardiovascular diseases [37].

GOING ALL THE WAY

A successful journey from research discovery to optimal heart health for all can be completed when all aspects of basic science research and all translational steps in cardiovascular research are fully connected. Active engagement of key stakeholders is needed, and attention to the context in which research evidence is generated, synthesized, integrated, and used in developing implementable practice guidelines is crucial [31,38]. As Halladay et al. [39] recently observed, "engaging stakeholders in research carries the promise of enhancing the research relevance, transparency, and speed of getting findings into practice." This is particularly important in both early- and late-stage translational research [40-43]. The insights from these publications highlighting community engagement to advance translational research and the articles in this issue of *Global Heart* [32-37] convince me that we are headed in the right direction and making progress on this journey.

REFERENCES

1. National Institutes of Health. NIH: Turning Discovery into Health. NIH/Department of Health and Human Services; 2014. Available at: https://www.nih.gov/sites/default/files/about-nih/discovery-into-health/nih-turning-discovery-into-health.pdf. Accessed February 23, 2018.
2. Bush V, United States Office of Scientific Research and Development. Science, the endless frontier: A report to the President. Washington, DC: Government Printing Office; 1945.
3. Bernard HR. The science in social science. Proc Natl Acad Sci USA 2012;109:20796–9.
4. Czajkowski SM. National Institutes of Health update: translating basic behavioral science into new pediatric obesity interventions. Pediatr Clin North Am 2016;63:389–99.
5. Zerhouni E. Medicine. The NIH roadmap. Science 2003;302:63–72.
6. Westfall JM, Mold J, Fagnan L. Practice-based research—"blue highways" on the NIH roadmap. JAMA 2007;297:403–6.
7. Green LW. Making research relevant: if it is an evidence-based practice, where's the practice-based evidence? Fam Pract 2008;25 (Suppl 1):i20-4.
8. Green LW. Public health asks of systems science: to advance our evidence-based practice, can you help us get more practice-based evidence? Am J Public Health 2006;96:406–9.
9. Committee to Review the Clinical and Translational Science Awards Program at the National Center for Advancing Translational Sciences, Board on Health Sciences Policy, Institute of Medicine. The CTSA Program at NIH: Opportunities for Advancing Clinical and Translational Research. Washington, DC: National Academy of Sciences; 2013.
10. Westfall JM, Mensah GA. T4 translational moonshot: making cardiovascular discoveries work for everyone. Circ Res 2018;122:210–2.
11. Galis ZS, Black JB, Skarlatos SI. National Heart, Lung, and Blood Institute and the translation of cardiovascular discoveries into therapeutic approaches. Circ Res 2013;112:1212–8.
12. Emmert-Buck MR. An NIH intramural percubator as a model of academic-industry partnerships: from the beginning of life through the valley of death. J Transl Med 2011;9:54.
13. Coller BS, Califf RM. Traversing the valley of death: a guide to assessing prospects for translational success. Sci Transl Med 2009;1: 10cm9.
14. Butler D. Translational research: crossing the valley of death. Nature 2008;453:840–2.
15. Bayon Y, Bohner M, Eglin D, et al. Innovating in the medical device industry - challenges & opportunities ESB 2015 translational research symposium. J Mater Sci Mater Med 2016;27:144.
16. Prabhakar S. Translational research challenges: finding the right animal models. J Investig Med 2012;60:1141–6.
17. Homer-Vanniasinkam S, Tsui J. The continuing challenges of translational research: clinician-scientists' perspective. Cardiol Res Pract 2012;2012:246710.
18. Meyers FJ, Begg MD, Fleming M, Merchant C. Strengthening the career development of clinical translational scientist trainees: a consensus statement of the Clinical Translational Science Award (CTSA) Research Education and Career Development Committees. Clin Transl Sci 2012;5:132–7.
19. National Institutes of Health. NIH establishes National Center for Advancing Translational Sciences; 2011. Available at: https://www.nih.gov/news-events/news-releases/nih-establishes-national-center-advancing-translational-sciences. Accessed February 8, 2018.
20. Collins FS. Reengineering translational science: the time is right. Sci Transl Med 2011;3:90cm17.
21. Gibbons GH. Establishing the Center for Translation Research and Implementation Science (CTRIS) at NHLBI. National Heart, Lung, and Blood Institute, National Institutes of Health; 2014. Available at: http://www.nhlbi.nih.gov/about/org/ctris/. Accessed February 8, 2018.
22. National Heart, Lung, and Blood Institute. Center for Translation Research and Implementation Science (CTRIS). NIH/NHLBI/CTRIS; 2014. Available at: https://www.nhlbi.nih.gov/about/scienfic-divisions/center-translation-research-and-implementation-science. Accessed February 23, 2018.
23. Carpenter CR, Pinnock H. Starry aims to overcome knowledge translation inertia: the Standards for Reporting Implementation Studies (StaRI) guidelines. Acad Emerg Med 2017;24:1027–9.
24. Krakoff LR, Kronish IM. Guidelines, inertia, and judgment. Hypertension 2011;58:544–5.
25. Lau DC. Therapeutic inertia and nihilism. Can J Diabetes 2014;38: 290–1.
26. Mensah GA. Embracing dissemination and implementation research in cardiac critical care. Glob Heart 2014;9:363–6.
27. Lavoie KL, Rash JA, Campbell TS. Changing provider behavior in the context of chronic disease management: focus on clinical inertia. Annu Rev Pharmacol Toxicol 2017;57:263–83.
28. Mohan AV, Phillips LS. Clinical inertia and uncertainty in medicine. JAMA 2011;306:383.
29. Roumie CL, Elasy TA, Wallston KA, et al. Clinical inertia: a common barrier to changing provider prescribing behavior. Jt Comm J Qual Patient Saf 2007;33:277–85.
30. Webb D, Byrd-Bredbenner C. Overcoming consumer inertia to dietary guidance. Adv Nutr 2015;6:391–6.
31. Glasgow RE, Green LW, Taylor MV, Stange KC. An evidence integration triangle for aligning science with policy and practice. Am J Prev Med 2012;42:646–54.
32. Qu H, Lu YG, Gudbranson E, et al. Large-scale epidemiologic studies of cardiovascular diseases in China: need for improved data collection, methods, transparency, and documentation. Glob Heart 2018; 13:3–12.
33. Dudzie A, Rayner B, Ojji D, et al. Roadmap to achieve 25% hypertension control in Africa by 2025. Glob Heart 2018;13:45–59.
34. Miller V, Nambiar L, Saxena M, et al. Exploring the barriers to and facilitators of using evidence-based drugs in the secondary prevention of cardiovascular diseases: findings from a multistakeholder, qualitative analysis. Glob Heart 2018;13:27–34.
35. Nazzal C, Shea S, Castro-Diehl C, et al. Educational inequalities in cardiovascular risk factor and blood pressure control in elderly adults: comparison of MESA cohort and Chilean NHS survey outcome measures. Glob Heart 2018;13:19–26.
36. Beukes JG, Hendrikes C, Buijns SR. Lack of acute care resources to diagnose and treat acute coronary syndrome in lower-income settings. Glob Heart 2018;13:35–6.
37. Wood D, Asma S, Bettcher D, et al. Global coalition for the fight against heart disease and stroke: a global coalition for WHF Second Global Summit on Circulatory Health. Glob Heart 2018;13:37–44.
38. Chan WV, Pearson TA, Bennett GC, et al. ACC/AHA special report: clinical practice guideline implementation strategies: a summary of systematic

reviews by the NHLBI Implementation Science Work Group: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;69:1076–92.

39. Halladay JR, Donahue KE, Sleath B, et al. Community advisory boards guiding engaged research efforts within a clinical translational sciences award: key contextual factors explored. Prog Community Health Partnersh 2017;11:367–77.
40. Estape-Garrastazu ES, Noboa-Ramos C, De Jesus-Ojeda L, De Pedro-Serbia Z, Acosta-Perez E, Camacho-Feliciano DM. Clinical and translational research capacity building needs in minority medical and health science Hispanic institutions. Clin Transl Sci 2014;7:406–12.
41. Kost RG, Leinberger-Jabari A, Evering TH, et al. Helping basic scientists engage with community partners to enrich and accelerate translational research. Acad Med 2017;92:374–9.
42. Patino CM, Kubicek K, Robles M, Kiger H, Dzekov J. The community mentorship program: providing community-engagement opportunities for early-stage clinical and translational scientists to facilitate research translation. Acad Med 2017;92:209–13.
43. Shiramizu B, Shambaugh V, Petrovich H, et al. Leading by success: impact of a clinical and translational research infrastructure program to address health inequities. J Racial Ethn Health Disparities 2016;4:983–91.