Perspective: **Transforming Science Into Medicine: How Clinician–Scientists Can Build Bridges Across Research's "Valley of Death"**

Scott F. Roberts, JD, Martin A. Fischhoff, Stacey A. Sakowski, PhD,
and Eva L. Feldman, MD, PhD

Abstract

Significant increases in National Institutes of Health (NIH) spending on medical research have not produced corresponding increases in new treatments and cures. Instead, laboratory discoveries remain in what has been termed the "valley of death," the gap between bench research and clinical application. Recently, there has been considerable discussion in the literature and scientific community about the causes of this phenomenon and how to bridge the abyss. In this article, the authors examine one possible explanation: Clinician–scientists' declining role in the medical research enterprise has had a dilatory effect on the successful translation of laboratory breakthroughs into new clinical applications. In recent decades, the percentage of MDs receiving NIH funding has drastically decreased compared with PhDs. The growing gap between the research and clinical enterprises has resulted in fewer scientists with a true understanding of clinical problems as well as scientists who are unable to or uninterested in gleaning new basic research hypotheses from failed clinical trials. The NIH and many U.S. medical schools have recognized the decline of the clinician–scientist as a major problem and adopted innovative programs to reverse the trend. However, more radical action may be required, including major changes to the NIH peer-review process, greater funding for translational research, and significantly more resources for the training, debt relief, and early career support of potential clinician–scientists. Such improvements are required for clinician–scientists to conduct translational research that bridges the valley of death and transforms biomedical research discoveries into tangible clinical treatments and technologies.

In this age of ever-expanding scientific discoveries and unprecedented U.S. government funding of public research, the dramatic drop in the number of new drugs and treatments being introduced for patient use should be cause for concern. The National Institutes of Health (NIH), one of the main drivers of biomedical research in the United States, invested approximately $31 billion in medical research in 2010, roughly four times the amount spent just 20 years prior.[1] However, despite increases in research funding, just 74 new drugs were approved by the U.S. Food and Drug Administration (FDA) between 2006 and 2009, fewer than half of the 157 new drugs the FDA approved between 1996 and 1999.[2] A major factor in this downward trend is the increasing isolation of the basic researchers who work in laboratories from the physicians who treat patients. This separation has resulted in a paucity of *translational research*, defined as the "process of translating discoveries in the laboratory into clinical interventions for the diagnosis, treatment, prognosis, or prevention of disease with a direct benefit of human health."[3] The growing gulf between bench research and bedside treatment has been labeled the "valley of death."[4] It is where promising scientific discoveries linger and die.

This frustrating disconnect between making scientific discoveries and developing tangible medical applications emerged relatively recently. Less than half a century ago, biomedical research was mainly carried out by clinicians. Beginning in the 1970s, however, biomedical and technological advances prompted an explosion in the number of biomedical researchers receiving PhDs focused on specialized areas of science, and physician–scientists have since become a minority.[4] The consequences of this specialization are increased competition for funding opportunities and limited career prospects for researchers with PhDs, both of which may discourage many bright, high-achieving individuals from devoting their careers to pursuing scientific discovery.[5–7] Solutions such as altering the current research environment infrastructure, improving support for young investigators, and providing support for collaboration and translational teams have been proposed or are being implemented.[8–14] However, efforts must also be made to increase the number of investigators with the potential to connect basic science and medical practice. Clinician–scientists—that is, physician–researchers with active clinical practices as well as active basic science laboratories who can understand a disease as both a scientific phenomenon and a medical problem afflicting patients—are uniquely capable of bridging this divide.

In this article, we examine the role of clinician–scientists in current medical

Mr. Roberts is an attorney, Dickinson and Wright PLLC, Bloomfield Hills, Michigan.

Mr. Fischhoff is managing director, A. Alfred Taubman Medical Research Institute, University of Michigan, Ann Arbor, Michigan.

Dr. Sakowski is research investigator, Department of Neurology, University of Michigan, Ann Arbor, Michigan.

Dr. Feldman is Russell N. DeJong Professor of Neurology and director, A. Alfred Taubman Medical Research Institute, University of Michigan, Ann Arbor, Michigan.

Correspondence should be addressed to Dr. Feldman, University of Michigan, Department of Neurology, 5017 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200; telephone: (734) 763-7274; fax: (734) 763-7275; e-mail: efeldman@umich.edu.

Acad Med. 2012;87:266–270.
First published online January 25, 2012
doi: 10.1097/ACM.0b013e3182446fa3

research enterprises. We focus on the current barriers to pursuing a career as a clinician–scientist and explore clinician–scientists' potential to conduct research that bridges the valley of death. We propose that by acknowledging the limitations presented by the current research environment and cultivating approaches to support clinician–scientists and translational research, the basic and clinical science research communities can identify ways to increase the successful translation of scientific discoveries into clinical advances for diagnosing, treating, and preventing disease.

The Basic Scientist and the Clinician–Scientist

Basic science researchers excel at identifying unanswered questions in the field of medicine and play an integral role in increasing understanding of disease pathogenesis, therapeutic mechanisms, and preclinical development. However, the fundamental questions that basic scientists answer are not always directly relevant to any prospective form of treatment or clinical advance. Even though their work offers potential new medical insights, they do not endeavor to design and execute subsequent research to apply their basic science breakthroughs toward new medical technologies, diagnostics, or treatments for clinical application.[2,4]

The problem, according to Barbara Alving, former director of the NIH's National Center for Research Resources, is that "the clinical and basic scientists don't really communicate."[4] This leads to communication barriers that promote a cultural divide between basic scientists and clinicians.[15] Physicians are under pressure to extract revenue from their clinical practices, which limits the time they have to communicate with basic scientists or to participate in research themselves.[16] Many clinicians' observations are never shared with basic scientists and, therefore, are not incorporated into the research of human disease. As a consequence, basic research often ignores the problems and complications faced by patients and their treating physicians.

Unlike basic scientists, clinician–scientists are able to bring their research from bench to bedside, and they are also uniquely capable of doing the reverse—incorporating results of clinical studies into new research and treatment approaches. Clinician–scientists use patient reactions and results of failed experiments to create new hypotheses and develop alternative avenues of treatment. They are often more heavily invested in patient well-being and more knowledgeable about clinical trials than basic scientists are—and thus they are more likely to follow up on perceived failures. Additionally, translational research performed by clinician–scientists often involves collaborations between government, industry, and private institutions, which makes it less likely that a project will be abandoned after an unsuccessful trial. Instead of leading to dead ends, such failures present clinician–scientists with opportunities to consider new approaches overlooked by previous experiments and by past research.[17]

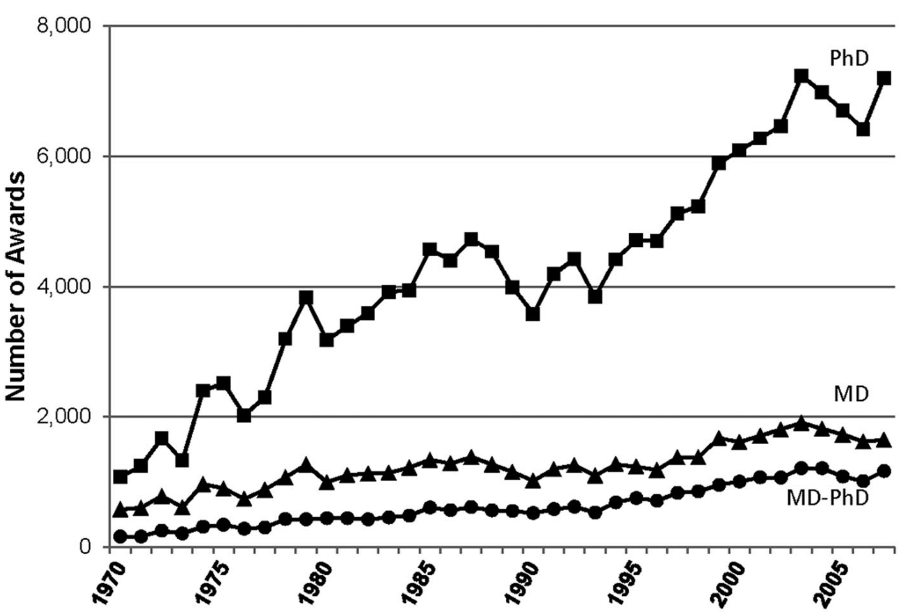

Figure 1 National Institutes of Health (NIH) research project grants by degree of principal investigator. As recently as 1970, the numbers of NIH grants to researchers with MDs and to those solely with PhDs were almost equal. By 2007, researchers with MDs received far fewer grants than those with PhDs alone. *Figure source*: Butler D. Translational research: Crossing the valley of death. Nature. 2008;453:840–842. Reprinted by permission from Macmillan Publishers Ltd.: Nature © 2008.

As noted above, the valley of death dilemma is a relatively new problem in biomedical research. Historically, basic science and clinical research were tightly linked by agencies such as the NIH,[4] and early 20th-century biomedical researchers were primarily medical doctors.[18] As biomedical research became a field of medicine in its own right in the latter half of the 20th century, clinical and basic research started to diverge and the number of clinician–scientists decreased.[4] According to the American Medical Association, the number of physician–researchers in the United States declined by 36% during an 18-year period ending in 2003.[19] Similarly, the number of physicians in academia who were competent to conduct trials declined by 25% compared with one generation ago, according to one estimate.[20] Certainly, NIH funding to clinician–scientists has not kept pace with that to PhD researchers. In 1970, the number of NIH research project grants going to MDs and PhDs was relatively equal; by 2007, the number of NIH grants to PhDs was two-and-a-half times the number to MDs or to MD-PhDs (Figure 1).[4] Even when the NIH funds purely clinical research, MDs are the principal investigators on only 36% of the grants.[21]

One of the principal problems with the divide between basic and clinical scientists is that knowledge gained from basic research is assumed to be an end in itself rather than a means to achieve better patient care through the development of breakthrough treatments. According to clinician–scientist and cancer researcher Raymond Hohl, "Colleagues tell me they're very successful getting NIH grants because their experiments are elegant and likely to yield fundamental discoveries, even if they have no prospect of producing something that helps human diseases."[2] To close this divide, translational research must build on basic research's discoveries to address the real-world problems faced by clinicians seeking patient treatments.

Barriers to Translational Research

The process of taking research from bench to beside—that is, of making a discovery, using that discovery to develop drugs or technologies, conducting preclinical testing and optimization, overcoming burdens imposed by regulatory agencies, and securing patents—presents an array of hurdles that can stop translational advances in their tracks.[13,16] In the modern era of large-scale "-omic" discoveries based on genomes or protein profiles from whole organisms, pharmaceutical companies that specialize in clearing these hurdles cannot keep up.[4] Further, patents, licensure, and increasing regulatory oversight by institutional review boards, though representing patients' well-being, can become insurmountable or discouraging obstacles to the translation of many scientific discoveries.[2,16] Additionally, translational research usually does not lead to publication in prestigious journals, which is the standard metric of professional success in basic science fields. Together, these barriers discourage most basic scientists from taking their research to the next level.[4]

Another major hurdle to translational research is securing funding: Roughly 60% of NIH research project grants support basic research compared with 30% supporting clinical research.[4] Many scientists assert that the latter percentage is artificially inflated by basic research masquerading as clinical research (e.g., research on animals).[4] The NIH peer-review process strongly favors hypothesis-driven basic research over applied research that seeks to develop clinical treatments. But even when translational research is designed to test specific hypotheses, it does not fare well against basic research in terms of scientific rigor because of ethical concerns and the complexities of designing controlled studies that involve human participants.[16] Further, basic scientists have historically dominated NIH peer-review panels. Between 1970 and 1995, the percentage of reviewers with MDs on NIH institute-specific review panels dropped from 45% to 28%.[22] A report to the Federation of American Societies for Experimental Biology summed up the situation, finding that "in an NIH peer review culture wherein basic research is given far more credence, basic research grants score better; clinical research, including translational research, often goes underfunded."[22]

Recognizing the problem, NIH director Francis Collins[13] in 2011 announced plans to establish the National Center for Advancing Translational Sciences, whose mission will be to generate innovative solutions to enhance translation. Previously, in 2006, the NIH began to establish consortia of Clinical and Translational Science Award (CTSA) sites across the country,[23] which it tasked with accelerating the pace of translating scientific discoveries into medical care. Appropriations to CTSA sites represent only 1% to 2% of NIH's annual budget, and much of this money is redirected from another clinical research program.[4] Many individuals in the medical research establishment believe, however, that the NIH continues to fund basic research at the expense of the kind of research that would turn laboratory breakthroughs into actual drugs and treatments.[2]

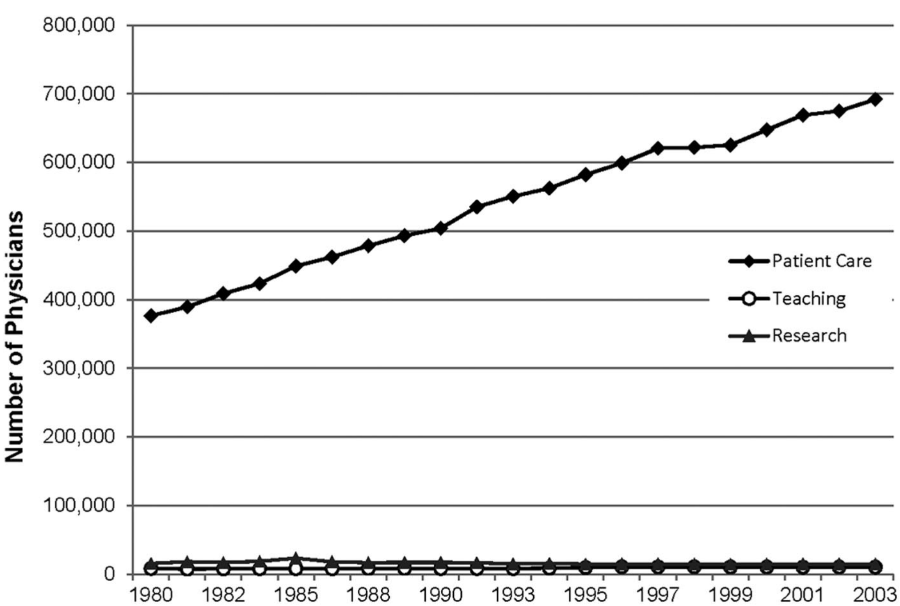

Figure 2 Number of physicians engaged in each of the three major professional activities. The number of physicians working in patient care has climbed steadily in the United States, whereas the ranks of physicians engaging in research and teaching have thinned. *Figure source*: Ley TJ, Rosenberg LE. The physician–scientist career pipeline in 2005: Build it, and they will come. JAMA. 2005;294:1343–1351. Copyright © 2005 American Medical Association. All rights reserved. Used by permission.

Barriers to Pursuing a Career as a Clinician–Scientist

Lemoine[24] writes that effective translational research "requires individuals who are fluent in two languages"—basic science and clinical medicine. In other words, it requires clinician–scientists. However, even though the number of physicians in the United States has risen steadily, the percentage of these MDs doing research declined from a peak of 4.6% in 1985 to 1.8% in 2003. Over the same period, the number of physicians involved in patient care nearly doubled (Figure 2).[19] A survey conducted in 2000 showed that the number of graduating medical students who anticipated they would have significant career involvement in research fell to 10.7% from 15.9% in 1989[25]; more recent data suggest a slight increase in interest among medical students.[19] The relatively low level of interest in research among medical students, coupled with the decline in the number of physicians actively pursuing research, reflects the obstacles clinician–scientists face today.

There are many reasons physicians may not pursue careers in research. Certainly, stifling student debt is one important deterrent. For the class of 2011, median educational debt among indebted medical students graduating from private medical schools was approximately $180,000; among their indebted public medical school peers, it was approximately $155,000.[26] Would-be physician–scientists also face an extended training period. For example, it can take neurologists who wish to pursue clinical research careers 19 years to establish themselves as independent investigators (plus another 2 years for pediatric neurologists).[20] The average age at which a researcher with an MD achieves initial R01 funding is now close to 44.[27] A recent study calculated that if the trend continues, the average age for new investigators receiving R01 funding in 2016 could be as high as 54.[28]

Many observers have called for an overhaul of the medical research funding infrastructure to create incentives for young researchers to become clinician–scientists instead of basic researchers or practicing physicians.[29] However, there are other major barriers in addition to funding, not the least of which is the growing complexity of medical research. A new drug or treatment may take 20 years to develop, without a guarantee that it will ultimately prove successful.[4] In that same time, a basic scientist could conduct numerous experiments and have many articles published. Even if the basic scientist's articles never led to new treatments or drugs, he or she could achieve some level of career success and prestige. The NIH and other institutions often reward that type of success with grants, whereas they often overlook the collaborative efforts involved in translational research.[4] For these reasons, many medical students decide to follow a more focused path—that of basic researcher or physician.

Furthermore, there is declining encouragement from academic health centers (AHCs) for their physicians to pursue research. A survey conducted by a University of California, San Francisco (UCSF) task force found that 84% of UCSF clinician–scientists did not believe that clinical research received the same "support, recognition, and credit for promotion purposes" as basic research.[30] Further, 58% of UCSF clinician–scientists reported that their balance of professional activities did not reflect their desired balance. By a wide margin, the most-often reported reason was their clinical responsibilities.[30] The driving force behind this imbalance in professional activities is AHCs' need to raise operating revenues through provision of clinical services. In 1960, a typical AHC's revenue was less than $0.5 billion, half of which came from research grants. By the end of the 20th century, the typical AHC's revenue soared to nearly $30 billion, but less than one-third came from research. The gap between AHC operating revenues and money from research grants had to be filled by insurance payments resulting from patient care.[21]

As the UCSF results suggest, those physicians who become clinician–scientists may find it challenging to conduct research and see patients. Their workloads also often include teaching, so they must juggle three time-consuming responsibilities. This may lead to an inability to be both a dedicated clinician and a focused researcher, a phenomenon dubbed Paralyzed Academic Investigator's Disease Syndrome.[31] Physician–scientists often respond by abandoning clinical practice in favor of laboratory work because it may be easier to focus on a basic research question that contains a clear-cut solution than to delve into the complex and intertwined world of combined clinical practice and translational research.[31] Nonetheless, although this condition may deter some medical students from pursuing translational research in combination with a medical career, it may also attract those students who are looking for a challenge.

Programs to Increase the Number of Clinician–Scientists

The declining ranks of clinician–scientists in the United States have prompted a variety of responses. The NIH has established awards and programs to encourage physicians to enter or remain in the research world.[19] It now funds 40 medical scientist training programs for future MD-PhDs across 45 degree-granting institutions, and 75 other medical schools privately fund their own MD-PhD programs.[32,33] Nearly all U.S. medical schools offer some sort of joint MD-PhD program.[32] Since 2002, the NIH has also created a series of loan repayment programs for scientists struggling with student loan debt. As a consequence, there has been a modest increase in the number of medical students reporting interest in research careers and an increase in the number of applications for NIH early career awards (K08 and K23) for translational and clinical research, primarily from MDs and MD-PhDs.[19] Yet, despite these efforts, the clinician–scientist population has continued to shrink and to age. Dual-degree program enrollees account for only 3% of all U.S. medical students.[33] Clearly, more aggressive debt relief and funding programs for prospective clinician–scientists are necessary to reverse this decades-long decline.[24]

Conclusions

If the valley of death is to be traversed successfully, minor changes in NIH funding will not suffice. Radical changes are required in the current NIH peer-review system that favors basic research; perhaps a separate peer-review system and funding stream for clinician–scientists could be created. Although NIH-funded CTSA sites represent a welcome first step in support for translational research, sustaining and expanding these collaborations requires more than the 1% to 2% of annual NIH funding currently allocated to such initiatives. Translational research teams—which include scientists with expertise encompassing basic and clinical science, bioinformatics, statistics, toxicology and pharmaceutical development, and trial design and regulation—must also receive support and recognition to provide comprehensive results and the required expertise to span the gap from bench to bedside.[4,29,34] Furthermore, collaborations between industry and academia could provide the expertise and funding needed to successfully navigate the complex bottlenecks that can prevent conversion of promising discoveries into medical advances.[9,13]

Most important, the U.S. government and U.S. medical schools must intensify their efforts to motivate young physicians to pursue careers in research. The NIH could reallocate resources to provide more potential clinician–scientists with training, debt relief, and early career support. Such efforts could include expanding the NIH's debt-repayment program to include more years of repayment as well as coverage for those not engaged exclusively in NIH-backed or strictly clinical research. Similarly, medical schools could encourage their top students to pursue joint degrees. Initiatives such as the Specialty Training and Advanced Research (STAR) program at the University of California, Los Angeles, are intended to persuade the most promising medical students to elect an MD-PhD course of study. The STAR program combines a clinical fellowship with postdoctoral research and, in doing so, provides a prototype that other medical schools could follow.[16,35]

The high number of applicants for loan repayment programs,[36] as well as the modest rise in applications for K08 and K23 grants, indicates that increased NIH funding for clinical and translational research and innovative joint degree programs have the potential to swell the ranks of physician–scientists. This is reflected in a heightened interest among today's medical students in becoming clinician–scientists. A majority of these students are interested in clinical topics, which could be the result of medical schools fostering an interest in research.[19] It could also reflect demographic shifts as the Millennial Generation gradually replaces its Generation X counterparts.[37,38] Whatever the cause of this interest, those responsible for medical education and training should do all in their power to advance this trend. By doing so, medical science may reap the benefits of a new generation of physician–scientists who are committed to translational research and the promise it holds for the conquest of disease.

Acknowledgments: The authors would like to thank Judith Boldt and Glen Walker for excellent administrative support during the preparation of this article.

Funding/Support: This article was funded by the A. Alfred Taubman Medical Research Institute at the University of Michigan.

Other disclosures: None.

Ethical approval: Not applicable.

References

1 National Institutes of Health. The NIH Almanac: Appropriations. http://www.nih.gov/about/almanac/appropriations/index.htm. Accessed November 20, 2011.
2 Carmichael M, Begley S. Desperately seeking cures: How the road from promising scientific breakthrough to real-world remedy has become all but a dead end. Newsweek. 2010;155(22):38–43.
3 Minna JD, Gazdar AF. Translational research comes of age. Nat Med. 1996;2:974–975.
4 Butler D. Translational research: Crossing the valley of death. Nature. 2008;453:840–842.
5 Benderly BL. The real science gap. Miller-McCune. June 14, 2010. http://www.miller-mccune.com/science/the-real-science-gap-16191/. Accessed November 23, 2011.
6 Cyranoski D, Gilbert N, Ledford H, Nayar A, Yahia M. Education: The PhD factory. Nature. 2011;472:276–279.
7 National Research Council of the National Academies. Bridges to Independence: Fostering the Independence of New Investigators in Biomedical Research. Washington, DC: National Academies Press; 2005.
8 Zerhouni EA. US biomedical research: Basic, translational, and clinical sciences. JAMA. 2005;294:1352–1358.
9 Marincola FM. The trouble with translational medicine. J Intern Med. 2011;270:123–127.
10 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.
11 Curry SH. Translational science: Past, present, and future. Biotechniques. February 2008;44:ii–viii.
12 Check E. NIH "roadmap" charts course to tackle big research issues. Nature. 2003;425: 438.
13 Collins FS. Reengineering translational science: The time is right. Sci Transl Med. 2011;3:90cm17.
14 Wadman M. Early success claimed for Zerhouni's NIH roadmap. Nature. 2004;431: 886.
15 Restifo LL, Phelan GR. The cultural divide: Exploring communication barriers between scientists and clinicians. Dis Model Mech. 2011;4:423–426.
16 Pober JS, Neuhauser CS, Pober JM. Obstacles facing translational research in academic medical centers. FASEB J. 2001;15: 2303–2313.
17 Ledford H. Translational research: The full cycle. Nature. 2008;453:843–845.
18 Wadman M. Medical research: Them and us no longer. Nature. 2006;439:779–780.
19 Ley TJ, Rosenberg LE. The physician–scientist career pipeline in 2005: Build it, and they will come. JAMA. 2005;294:1343–1351.
20 Hauser SL, McArthur JC. Saving the clinician–scientist: Report of the ANA long range planning committee. Ann Neurol. 2006;60:278–285.
21 Nathan DG. Clinical research: Perceptions, reality, and proposed solutions. National Institutes of Health Director's Panel on Clinical Research. JAMA. 1998;280:1427–1431.
22 Zemlo TR, Garrison HH, Partridge NC, Ley TJ. The physician–scientist: Career issues and challenges at the year 2000. FASEB J. 2000;14: 221–230.
23 National Institutes of Health, National Center for Research Resources. NCRR Fact Sheet: Clinical and Translational Science Awards. Summer 2011. http://www.ncrr.nih.gov/publications/pdf/ctsa_factsheet.pdf. Accessed November 23, 2011.
24 Lemoine NR. The clinician–scientist: A rare breed under threat in a hostile environment. Dis Model Mech. 2008;1:12–14.
25 Faxon DP. The chain of scientific discovery: The critical role of the physician–scientist. Circulation. 2002;105:1857–1860.
26 Association of American Medical Colleges. Medical student education: Costs, debt, and loan repayment facts. FIRST Analysis of AAMC 2011 Graduation Questionnaire (GQ) data. https://www.aamc.org/download/152968/data/debtfactcard.pdf. Accessed November 10, 2011.
27 Hauser SL, Johnston SC. Matriculating the next generation of clinician–scientists. Ann Neurol. 2007;62:A10–A11.
28 Gingras Y, Lariviere V, Macaluso B, Robitaille JP. The effects of aging on researchers' publication and citation patterns. PLoS One. 2008;3:e4048.
29 Editorial: To thwart disease, apply now. Nature. 2008;453:823.
30 The Task Force on the Future of Clinician Scientists at UCSF. The Future of Clinician Scientists: Task Force Initial Report and Recommendations. San Francisco, Calif: University of California, San Francisco, Academic Senate; 2001. http://senate.ucsf.edu/recentreports/clinicianscientistreport.html. Accessed November 23, 2011.
31 Goldstein JL, Brown MS. The clinical investigator: Bewitched, bothered, and bewildered—but still beloved. J Clin Invest. 1997;99:2803–2812.
32 National Institutes of Health, National Institute of General Medical Sciences. Medical Scientist Training Program. http://www.nigms.nih.gov/Training/InstPredoc/PredocOverview-MSTP.htm. Accessed November 20, 2011.
33 Rosenberg LE. MD/PhD programs—A call for an accounting. JAMA. 2008;300:1208–1209.
34 Disis ML, Slattery JT. The road we must take: Multidisciplinary team science. Sci Transl Med. 2010;2:22cm29.
35 University of California, Los Angeles. Specialty Training and Advanced Research (STAR) Program. http://www.star.med.ucla.edu/index.htm. Accessed November 20, 2011.
36 National Institutes of Health. Loan Repayment Programs: Reports and Statistics. http://www.lrp.nih.gov/reports_and_statistics/index.aspx. Accessed November 20, 2011.
37 Borges NJ, Manuel RS, Elam CL, Jones BJ. Differences in motives between Millennial and Generation X medical students. Med Educ. 2010;44:570–576.
38 Bickel J, Brown AJ. Generation X: Implications for faculty recruitment and development in academic health centers. Acad Med. 2005;80:205–210.