Translation of Highly Promising Basic Science Research into Clinical Applications

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PURPOSE: To evaluate the predictors of and time taken for the translation of highly promising basic research into clinical experimentation and use.

METHODS: We identified 101 articles, published between 1979 and 1983 in six major basic science journals, which clearly stated that the technology studied had novel therapeutic or preventive promises. Each case was evaluated for whether the promising finding resulted in relevant randomized controlled trials and clinical use. Main outcomes included the time to published trials, time to published trials with favorable results ("positive" trials), and licensed clinical use.

RESULTS: By October 2002, 27 of the promising technologies had resulted in at least one published randomized trial, 19 of which had led to the publication of at least one positive randomized trial. Five basic science findings are currently licensed for clinical use, but only one has been used extensively for the licensed indications. Promising technologies that did not lead to a published human study within 10 to 12 years were unlikely to be tested in humans subsequently. Some form of industry involvement in the basic science publication was the strongest predictor of clinical experimentation, accelerating the process by about eightfold (95% confidence interval: 3 to 19) when an author had industry affiliations.

CONCLUSION: Even the most promising findings of basic research take a long time to translate into clinical experimentation, and adoption in clinical practice is rare. **Am J Med. 2003; 114:477–484.** ©2003 by Excerpta Medica Inc.

Medical progress is highly dependent on the products of basic research (1), which occasionally lead to discoveries that have clinical promise. However, it is not known how often and how fast original basic research findings translate into clinical development and use, as well as what are the predictors of and obstacles to realization of these findings. To address these questions, we evaluated a sample of basic research publications in highly cited journals that had presented findings showing a clear clinical promise, and studied whether the original expectations materialized over a period of 20 years.

METHODS

Inclusion Criteria

We searched PubMed for articles published from 1979 to 1983 in six highly cited basic science journals: *Science, Nature, Cell*, the *Journal of Experimental Medicine*, and the *Journal of Clinical Investigation*, which had the highest impact factors in 2000, and the *Journal of Biological Chemistry*, which receives the most citations. We identified all articles that contained the word *therapy*, *therapies*, *therapeutic*, *therapeutical*, *prevention*, *preventive*, *vaccine*, *vaccines*, or *clinical*. From these articles, we retained all original publications that clearly stated that the studied technology might have future clinical therapeutic or preventive application. The 5-year period (1979 to 1983) allowed a meaningful time of approximately 20 years to elapse for examining the translation of basic science research into clinical research and practice. Eligible technologies included substances, antibodies, vaccines, gene therapies, technical devices and other nonpharmacologic interventions, combination therapies, or novel techniques for production of the above technologies. We only considered technologies that were still at an experimental stage (molecular, cellular, animal, and early nonrandomized human studies) that did not have prior application in humans for the specific promise. We also included articles that focused on a novel application (different disease or indication) of a technology already in use in humans or on a novel strategy combining technologies already in use. We excluded articles that did not describe a clear clinical promise in the abstract; editorials; commentaries; reviews; news articles; articles that focused on mechanisms of action, pathophysiology, or diagnosis; and articles on agricultural or veterinary applications. Initial

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screening was based on the title and abstract. Two reviewers screened the full texts of potentially eligible articles, discussed the rules for selection, and independently screened articles for eligibility. Discrepancies were resolved by consensus.

Data Extraction

The following information was collected from each eligible publication: author name, publication year, journal name, study design, promising technology, whether a specific technology or a category of technologies was involved, anticipated application (therapeutic, preventive, or both), and disease target (single disease/condition vs. broader disease category). We also noted if there was involvement by the biotechnology or pharmaceutical industry, defined as reported industry affiliation by an author, financial support, or provision of the technology studied.

Outcomes

For each promising technology, we noted if any randomized controlled trials had been published, and whether the technology had shown favorable results ("positive" trial), including statistically significant superiority ($P < 0.05$) to placebo, no treatment, or established interventions; or stated equivalence compared with established interventions. We also determined whether any published research was performed in humans for any application (general human study) or for the specific application described in the basic science publication (specific human study).

Identification of Human Studies and Trials

We searched PubMed (to October 2002) using strategies that considered all alternative names of the experimental technology, including drug class and chemical substance, if applicable. Alternative names were identified by reviewing the full text and references of the basic science publication, the medical subject heading in PubMed, abstracts of related articles (including subheadings), relevant publications by the same authors, relevant basic and clinical science textbooks, electronic books available from the National Center for Biotechnology Information (National Library of Medicine, Bethesda, Maryland), and drug reference guides. For antibodies and vaccines, we ascertained that the same technology discussed in the basic science publication was used for production of these substances. For identification of human studies, we restricted the search to the "human study" group. For identification of randomized controlled trials, we restricted the search by using the terms *randomized controlled trial*, *randomized clinical trial*, *controlled clinical trial*, *random allocation*, *double blind*, and *single blind*. Additional terms were used to focus the search on articles on prevention or therapy, if applicable. Disease-related terms were used when the promising technology pertained to a specific disease or disease category. Abstracts and full articles were examined to ascertain the study design and pertinence of the retrieved studies. When the targeted search did not retrieve relevant articles, we used unrestricted search strategies.

Determination of Current Clinical Use and Development Status

For technologies that reached at least the stage of specific human study, we searched the most recent editions of the British National Formulary (2) and the Physician's Desk Reference (3). We performed an extensive PubMed search for trials, meta-analyses, guidelines, reviews, and other articles about the current development status of the technology. For technical devices, we searched the list of approved devices in the database of the Center for Devices and Radiological Health, U.S. Food and Drug Administration (4).

Statistical Analysis

Kaplan-Meier curves were constructed for the time to publication of the first randomized and positive trials. We also examined which characteristics of the basic science article affected the publication rate. Comparisons were made using Cox proportional hazards models. Multivariate models considered all variables with $P < 0.1$ on univariate models and used a backward elimination approach for final selection. There was no overt violation of the proportionality assumption. All analyses were performed with SPSS 10.0 (Chicago, Illinois). *P* values are two-tailed.

RESULTS

Of the 25,190 articles published from 1979 to 1983 in the six basic science journals, 562 contained the selected key words (Figure 1). Of those, 101 were original articles that clearly stated future clinical therapeutic or preventive applications in humans for the studied technologies (Table 1). None of the 101 articles were published in *Cell*, and only four were published in the *Journal of Biological Chemistry*, which likely reflects the focus of those journals on basic molecular rather than preclinical research, as compared with the other journals.

Translation into Clinical Research

Except for one outlier (n = 26,840 articles), two to 7715 articles (median, 183 articles) were retrieved for screening each of the 101 promising technologies. By October 2002, 27 promising technologies had resulted in at least one published trial, 19 of which had at least one published positive trial (Table 1). Ten years after the initial basic science report, the probability of having a relevant publication was 48% for a general human study, 37% for a specific human study, 18% for a randomized trial, and 12% for a positive trial; at 20 years, the rates were 54%,

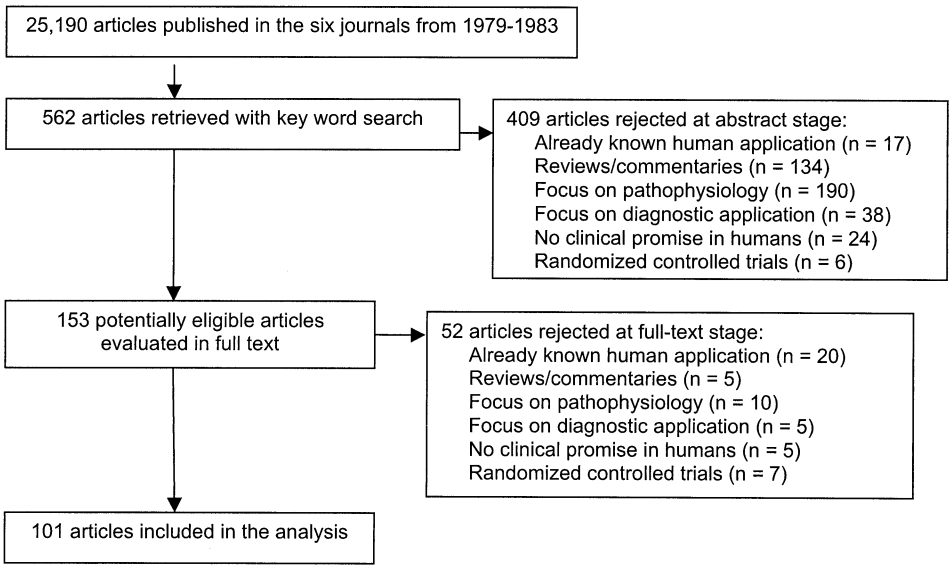

Figure 1. Selection of basic science publications with promising therapeutic or preventive applications.

45%, 27%, and 19% (Figure 2). When no human study was published 10 to 12 years from the index basic science publication, it was unlikely that one would be published subsequently. The likelihood of having a published randomized trial or positive trial also decreased after 12 to 15 years (Figure 2).

Factors Associated with Publication

The rate at which the first randomized (or first positive) trial was published was considerably faster when there was industry involvement (Table 2). Having an author affiliated with the pharmaceutical or biotechnology industry was associated with an eight- to 10-fold accelerated process, whereas commercial financial support or provision of the tested technology had a lesser effect. Promises of a vaccine were somewhat more likely to have a published positive trial, and more recent basic science findings were somewhat less likely to have a published positive trial. Multivariate models yielded similar results for author affiliations with the industry for published randomized trials (rate ratio [RR] = 5.7; 95% confidence interval [CI]: 2.6 to 13) and for published positive trials (RR = 8.3; 95% CI: 3.1 to 22). Similarly, after multivariate adjustment, more recent basic science articles were less likely to have published randomized trials (RR = 0.8 per year of publication; 95% CI: 0.6 to 1.0) and published positive trials (RR = 0.5; 95% CI: 0.3 to 0.8), whereas vaccine studies were more likely to have published positive trials (RR = 3.7; 95% CI: 1.3 to 11).

Current Status

Of the 27 technologies with at least one published randomized trial (Table 3), only five are licensed for clinical use (2,3). Of them, four had at least one positive trial during their development. Only one—angiotensin-converting enzyme inhibitors (N-carboxymethyl dipeptides)—has shown extensive clinical advantages with expanding indications (5). Pergolide mesylate is used as adjunctive treatment to reduce the dose of levodopa in patients with Parkinson's disease (3,6). Recombinant interleukin 2 is licensed in the United Kingdom for the treatment of metastatic renal cell carcinoma, with expanding indications in the United States (2). However, it is toxic; tumor shrinkage occurs only in few patients; and survival benefits are limited (2). Alpha-1 antitrypsin treatment and naloxone (for shock) are licensed in the United States (3), but there are questions about their efficacy (7,8).

Four other technologies had limited clinical use (Table 3). The rotavirus vaccine was licensed in the United States in 1998 (9), but it was subsequently withdrawn because of adverse effects (intussusception). The acyl-enzyme anistreplase, which showed no clear advantages over other thrombolytic agents, is no longer available (2). Eflornithine (difluoronethylornithine) may be used to treat trypanosomiasis on special request, but the drug has only been tested in nonrandomized studies for this indication (10). Finally, there is no licensed subunit vaccine with the F glycoprotein of respiratory syncytial virus (paramyxovirus F glycoprotein). Monoclonal antibodies against this glycoprotein were licensed in the United States (3,11), but cost-effectiveness of the therapy is questioned in the United Kingdom (12).

Ten technologies that had at least one published randomized trial are still in development, with some continuing to show promise, although use is still limited to research purposes (Table 3). Eight have had at least one

Table 1. Characteristics of the Eligible Basic Science Publications*

	Total (n = 101)	Promising Technology Leading to Publication of: Randomized Trial (n = 27)	Positive Trial (n = 19)
	Number		
Journal			
Science	47	11	9
Nature	21	8	5
Journal of Clinical Investigation	18	4	2
Journal of Biological Chemistry	4	1	0
Journal of Experimental Medicine	11	3	3
Cell	0	0	0
Year			
1979	11	5	5
1980	28	7	6
1981	21	7	3
1982	22	4	3
1983	19	4	2
Industry involvement			
Author affiliation	16	11	9
Financial support†	5	1	1
Provision of technology†	11	5	3
None reported	69	10	6
Type of study			
Molecular	6	1	1
Cellular	22	7	4
Animal	64	16	12
Human	9	3	2
Promising technology			
Substance	69	20	12
Antibody	9	1	1
Vaccine	12	6	6
Other‡	11	0	0
Type of promising technology			
Specific	70	21	16
General	31	6	3
Implication			
Therapy	73	15	9
Prevention	10	4	2
Vaccine	13	7	7
Both therapy and prevention	5	1	1
Target of potential application			
Single disease/condition	62	19	13
Broader disease category	39	8	6

* Supplementary information on the 101 publications can be obtained from the authors.
† Without reported author affiliation with the industry.
‡ Combination of therapeutic interventions, including nonpharmacologic interventions (n = 7), technical devices (n = 1), and gene therapy (n = 3).

published positive trial, three of which had the first positive trial published after at least 12 years.

Eight additional technologies that had at least one published randomized trial have had mostly discouraging overall results (Table 3). N-acetylcysteine pretreatment for doxorubicin cardiotoxicity (13), naloxone for spinal cord injury (14), relaxin (recombinant human relaxin) for dystocia (15), and vitamin D metabolites for leukemia (16) never had published positive trials, and their randomized trials suggest they are unlikely to be effective.

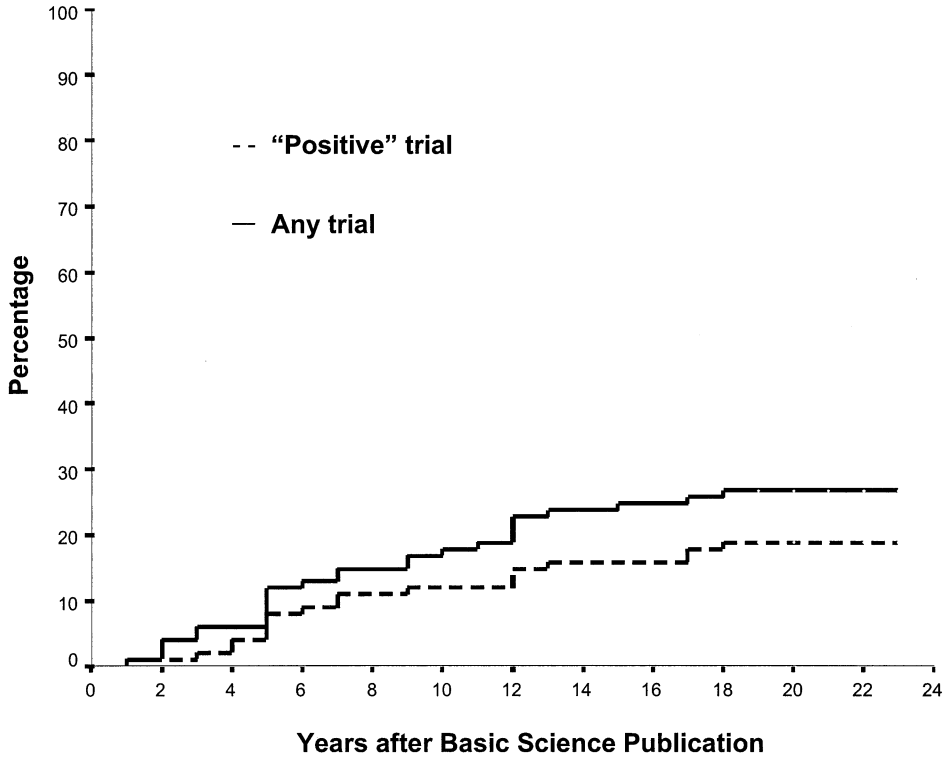

Figure 2. Proportion of promising technologies that were evaluated in at least one published randomized controlled trial and at least one published positive trial, by time since the index basic science publication.

Even in the case of the other four technologies with at least one positive trial, most evidence has been unfavorable. Preventive treatment with vitamin A analogs showed promise in decreasing mortality from mesothelioma (17), but larger trials reported poor rates for lung cancer (18). Similarly, thiorphan, which decreased postmyelography headache in a small trial (19), has not been used since evidence suggested that it does not affect spinal pain control (20). Aspirin, which was similar to ursodeoxycholic acid in prevention of gallstone and crystal for-

Table 2. Factors Associated with Publication of Randomized Controlled Trials and Positive Trials

Variable	Rate Ratio* (95% Confidence Interval)	
	Randomized Trial (n = 27)	Positive Trial (n = 19)
Year of basic science article (per year)	0.8 (0.6–1.1)	0.7 (0.5–1.0)
Industry involvement in basic science article		
Author affiliation	8.0 (3.4–19)	9.9 (3.5–28)
Financial support/provision of technology	2.9 (1.0–7.9)	2.9 (0.81–10)
None reported	1.00	1.00
Basic science article on humans or animals	0.9 (0.4–2.1)	1.1 (0.4–3.0)
Promising technology		
Substance	1.00	1.00
Antibody	0.3 (0.04–2.5)	0.6 (0.08–4.6)
Vaccine	1.9 (0.7–4.6)	3.3 (1.2–8.9)
Other	Undefined†	Undefined†
Specific promising technology	1.6 (0.7–4.0)	2.5 (0.7–8.7)
Preventive application proposed	2.1 (0.96–4.6)	2.5 (0.99–6.2)
Specific disease target proposed	1.6 (0.7–3.6)	1.4 (0.5–3.6)

* A rate ratio >1 indicates a faster publication.
† None of the 11 other technologies had a published randomized trial.

Table 3. Characteristics of Promising Technologies in Basic Science Publications That Were Eventually Tested in At Least One Randomized Trial

Technology/Implication for Use (Year)	Year of First Trial Any (Positive)	Endpoint of First Positive Trial	Development Stage (In October 2002)
Naloxone (opiate antagonist)/shock (1979)	1984 (1984)	Hemodynamics, amines	In licensed use
Thymopoietin pentapeptide 32-36 analog/immunodeficiency (1979)	1982 (1983)	Atopic dermatitis	In development
Native type III group B *Streptococcus* polysaccharide/vaccine (1979)	1996 (1996)	Immunogenicity	In development
Pergolide mesylate/dopamine deficiency disorders (1979)	1981 (1983*)	Prolactin levels	In licensed use
Bovine rotavirus/rotavirus vaccine (1979)	1984 (1984)	Rotavirus diarrhea	Withdrawn
Difluoromethylornithine/parasitic diseases (1980)	1992 (–)		Use on request
Paramyxovirus F glycoprotein/paramyxovirus vaccine (1980)	1993 (1993)	Respiratory syncytial virus	Antibody in use
Synthetic vitamin A analog/occupational lung cancer (1980)	1995 (1998)	Mesothelioma mortality	Discouraging
N-carboxymethyl dipeptide (ACE inhibitor)/hypertension (1980)	1981 (1981)	Blood pressure	In licensed use
Gonadotropin-releasing hormone antagonists/male contraception (1980)	1992 (1992)	Hormone levels	In development
Thiorphan/pain control (1980)	1983 (1983)	Postmyelography headache	Discouraging
Interleukin 2/diseases involving T lymphocytes (1980)	1992 (1992)	Natural killer cells	In licensed use
Classic antidepressants plus α-adrenergic antagonists/depression (1981)	1986 (–)		In development
N-acetylcysteine pretreatment/doxorubicin toxicity prevention (1981)	1983 (–)		Discouraging
Naloxone (opiate antagonist)/spinal cord injury (1981)	1990 (–)		Discouraging
Alpha-1 antitrypsin/substitution in emphysema (1981)	1999 (–)		In licensed use
Aspirin, NSAIDs/gallstone formation prevention (1981)	1983 (1988*)	Gallstone/crystal formation	Discouraging
Cyclosporin A/autoimmune uveitis (1981)	1986 (1988)	Visual acuity	In development
Acyl-enzymes/fibrinolysis (1981)	1986 (1986)	Indices of infarct size	Not available
Ibuprofen/septic shock (1982)	1991 (1999)	Mortality rate	In development
Avian-human influenza A reassortant virus/influenza A vaccine (1982)	1988 (1988*)	Influenza	Discouraging
Free radical scavengers*/prevention of insulin-dependent diabetes (1982)	1993 (–)		In development
Herpesvirus glycoprotein D gene sequenced/herpesvirus vaccine (1982)	1994 (1994)	Genital herpes recurrence	In development
Escherichia coli–recombinant sporozoite surface antigen gene/malaria vaccine (1983)	1990 (1992)	Malaria	In development
Recombinant human relaxin/dystocia (1983)	1993 (–)		Discouraging
Vitamin D_3 dihydroxymetabolite/leukemia (1983)	1990 (–)		Discouraging
Recombinant cholera with mutant ctxA gene/live cholera vaccine (1983)	1988 (1988)	Cholera	In development

* Showed no difference from other effective interventions (equivalence or no superiority).
ACE = angiotensin-converting enzyme; NSAID = nonsteroidal anti-inflammatory drug.

mation in one trial (21), had no association with the development of gallstones in larger epidemiologic studies (22). Avian-human influenza A reassortant virus initially tested favorably as a candidate influenza vaccine (23), but subsequent research suggested that the avian virus was not a suitable donor for attenuation of wild-type influenza virus (24).

Twenty-four technologies have been tested in specific human studies without having had published randomized trials. Only sodium benzoate is licensed for use in

rare metabolic conditions (2). No randomized trials were conducted to support its use because of the uncommonness of these diseases; the indication is based on case series. None of the 50 technologies without a published specific human study have been licensed.

DISCUSSION

In our study, only one in four promising technologies resulted in a published randomized trial and fewer than one in 10 entered routine clinical use within 20 years of the index basic science publication, supporting the notion that basic science research rarely translates into clinical research and clinical practice, even when they seem highly promising. Furthermore, only one technology has had a major clinical impact to date. Indeed, several factors may hinder the clinical development process. Findings may have been refuted in early phases of development by other biological or clinical evidence, and randomization may have been considered unethical. Even though nonrandomized studies may have merits (25,26), randomized trials are difficult to replace with other designs to achieve licensure for technologies that reach the stage of human experimentation. Moreover, an approved technology may be shown to be harmful or less effective than its competitors and thus be discontinued. In fact, the strongest predictor of having a published randomized trial was industry involvement in the original basic science publication. Scientists without industry support rarely saw their discoveries materialize.

We also found that there were considerable delays in the transition from basic research to clinical research and practice, regardless of the type of original study, promising technology, and therapeutic and preventive implication. Basic science promises are lost, refuted, or neglected at all stages of the clinical development process. Although it is difficult to state what constitutes a "good" rate of translation of basic research, current rates appear to be somewhat slow, and the process of rejecting or adopting new research findings should be accelerated. At the same time, caution should be exercised to avoid the implementation of faulty ideas that may stem from hastiness.

Only one in six of the promising technologies were "validated" in at least one published positive trial. Still, having a positive trial does not necessarily warrant adoption in clinical practice. "Negative" trials that report adverse effects or demonstrate irreproducibility of experiments should also be considered. We identified technologies that were not approved for licensed clinical use despite continued promise and published positive trials. In three cases, the first published positive trial was at least 12 years old, suggesting either a very slow development or a lack of reliability in results (27).

Our study has several limitations. Our estimates of the rate of translation of basic research into clinical applications are probably optimistic. We selected top journals that were most likely to attract submissions on major basic science breakthroughs. We used strict eligibility criteria to ensure that only promising technologies with a clear therapeutic or preventive implication were included. Our search algorithm limited subjective selection, yielding a reproducible sample of basic science promises. Moreover, basic research often leads to subsequent clinical breakthroughs simply by answering fundamental questions instead of targeting specific clinical problems (1,28). Hence, our eligibility criteria selected cases where translation into clinical application would have been most imminent. The study's retrospective design and its dependence on computer searches were other limitations. Since some human studies and randomized trials, especially those with negative results, may have remained unpublished, our data pertain to the time of published evidence rather than to the time of the conduct of the study. Nevertheless, unpublished studies or studies in less prominent journals are unlikely to make major contributions towards the clinical adoption of a basic science promise. Finally, although it is unknown whether very recent basic research would translate faster into clinical experimentation and use in the near future, our data suggest that more recent promises in the period 1979–1983 were actually less likely to result in positive trials.

The gap between basic and clinical research needs to be narrowed. Promoting more interdisciplinary training will be challenging, given the demands of clinical practice, the changing health environment in research-oriented countries (29–32), the rapid pace of basic and technological research, and the competing resources for funding (33–37). Despite major improvements (38) since clinical investigators were called an "endangered species" (39), there is still a dearth of well-trained clinical researchers. Furthermore, outside of governmental funding, clinical research is often conducted by or for the pharmaceutical and biotechnology industry. Our data suggest that investigators without links to the industry may have difficulties realizing their discoveries. The private sector is the major producer of therapies and preventive measures, and scientific merit and human needs may not always coincide with corporate profit (40). There is room for improvement in the translation of important basic research into clinical applications, and leaders in academic medicine and industry must develop strategies to enhance interdisciplinary work (41–43).

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The application of science to the development of new medical technologies holds promise for eradicating diseases and personalizing health care. Effective translation from bench to bedside, however, requires that our major engines of biomedical researchâ€”the academic medical centers funded by the U.S. National Institutes of Health (NIH)â€”work effectively with industry (1).Â , Translation of highly promising basic science research into clinical applications.Am. J. Med.114, 477â€“484 (2003).doi:10.1016/S0002-9343(03)00013-5pmid:12731504. OpenUrl CrossRef PubMed Web of Science Google Scholar. PURPOSE: To evaluate the predictors of and time taken for the translation of highly promising basic research into clinical experimentation and use. METHODS: We identified 101 articles, published between 1979 and 1983 in six major basic science journals, which clearly stated that the technology studied had novel therapeutic or preventive promises. Each case was evaluated for whether the promising finding resulted in relevant randomized controlled trials and clinical use.Â Some form of industry involvement in the basic science publication was the strongest predictor of clinical experimentation, accelerating the process by about eightfold (95% confidence interval: 3 to 19) when an author had industry affiliations. Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Greece. Purpose : To evaluate the predictors of and time taken for the translation of highly promising basic research into clinical experimentation and use. Methods : We identified 101 articles, published between 1979 and 1983 in six major basic science journals, which clearly stated that the technology studied had novel therapeutic or preventive promises. Each case was evaluated for whether the promising finding resulted in relevant randomized controlled trials