Provocative Idea:
Challenges of T3 and T4 Translational Research

Charles J. Vukotich, Jr.
School of Medicine, University of Pittsburgh
Pittsburgh, PA, UNITED STATES
charlesv@pitt.edu

Abstract

Translational research is a new and important way of thinking about research. It is a major priority of the National Institutes of Health (NIH) in the United States. NIH has created the Clinical and Translational Science Awards to promote this priority. NIH has defined T1 and T2 phases of translational research in the medical field, in order to bring the benefits of scientific results into communities. Current discussions focus on clarifying the subsequent phases of translational research necessary to achieve the intended social impact of research. This article suggests that T3 translational research could aim at getting research out of the highly controlled environment of the academic health center and into the real world. Likewise, it suggests T4 translational research could aim at policy development through policy analysis and evaluation, cost-benefit analysis, and surveillance studies. Translational research has challenges beyond definitions. Translational research is incomplete at any level unless appropriate steps are taken to communicate the results to relevant stakeholders. It appears that communication is currently suboptimal at all levels of translation. Translational research also faced challenges in research funding and training of researchers. Translational thinking should be a key part of research policy and research practice at all levels.

Index Terms: translational research; medical research; public health; research application; research education

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1. Current Thinking

Translational research, at its core, builds on previous research to create broader applications of science, ultimately reaching the general public, finding general acceptance and influencing public policy decisions. It brings basic science out of the lab and creates practical advances for the good of society. Since translational research originated in medicine, and the author is in this field, this article is written in the context of medicine, but the concepts herein are widely applicable. Translational research is an important way of thinking for all investigators. (In this article, the author uses the term *translational research*. The term *translational science* can also be found in the literature. The two terms should be considered interchangeable.)

The concept of translational research started with the National Institutes of Health (NIH), United States, but has implications across all disciplines. NIH created the idea of translational research with the formation of the Clinical and Translational Science Awards. NIH explains:

> Under NCATS' leadership, the Clinical and Translational Science Awards (CTSA) Program supports a national network of medical research institutions—called hubs—that work together to improve the translational research process to get more treatments to more patients more quickly. The hubs collaborate locally and regionally to catalyze innovation in training, research tools and processes.
>
> CTSA Program support enables research teams including scientists, patient advocacy organizations and community members to tackle system-wide scientific and operational problems in clinical and translational research that no one team can overcome. Program goals are to:
>
> - Train and cultivate the translational science workforce;
> - Engage patients and communities in every phase of the translational process;
> - Promote the integration of special and underserved populations in translational research across the human lifespan;
> - Innovate processes to increase the quality and efficiency of translational research, particularly of multisite trials; and
> - Advance the use of cutting-edge informatics.
>
> ("About the CTSA Program," 2016)

The need for this approach is self-evident. Westfall, Mold, and Fagnan (2007) have estimated that, in the medical field, it takes 17 years for 14% of new scientific discoveries to enter routine clinical practice. In a study over a 15-year period, Contopoulos-Ioannidis, Ntzani, and Ioannidis (2003) showed that only 5% of "highly promising" basic science was licensed for clinical use and only 1% was actually used for the licensed therapeutic or preventive intervention. Dougherty and Conway (2008), Khoury et al. (2007), Szilagyi (2009) and Westfall, Mold, and Fagnan (2007) have made detailed arguments about how few scientific advances are finding their way into improving the health of individuals and the general population; these arguments won't be repeated here.

NIH created definitions for *T1* and *T2* phases of translational research in 2004 with the *NIH Roadmap for Medical Research* (National Institutes of Health, 2008). *T1* is defined as the translation of research from "bench to bedside." It involves taking research from the laboratory and applying it to treatment of patients, often through clinical trials, and experimental procedures. *T1* is usually the first application of a treatment to humans. *T2* is the translation of research from "bedside to practice," where *T1* research has demonstrated efficacy in a controlled and limited trial, and it is being tested in a broader, but still highly controlled environment, such as an academic health center.

There has since been an effort to build on the NIH framework for translational research. Westfall, Mold, and Fagnan (2007) suggested a *T3* phase of translational research focused on day-to-day clinical practice, done in an ambulatory care setting or doctor's office, where patients receive most of their care. Dougherty and Conway (2008) expanded this definition, suggesting an ever broader base for *T3*, which includes "policy changes necessary to foster attempts to improve health outcomes" (p. 2319). Szilagyi (2009) extended the phases of translational research to include *T4*, which encompasses the policy level. Both Khoury et al. (2007) and Khoury, Gwinn, and Ioannidis (2010) also suggested *T4*, focused on the translation of research from clinical practice to population health impact, including policy development.

The purpose of this article is to advance the discussion by suggesting a definition of *T3* and *T4* within the framework of *T1* and *T2*, using some real, illustrative examples. In addition, the article discusses some of the challenges and barriers associated with translational research. All of this is done to help reach consensus and move forward toward the goal of translational research: bringing scientific results into communities.

2. T3 and T4 Translational Research: Proposed Definitions and Examples

T1 and *T2* translational research brings scientific discoveries out of the laboratory and into clinical practice, but not fully into the real world. *T3* translational research takes the next step and brings research into communities in order to test if the new treatments and interventions based on scientific research would work in less controlled conditions. *T4* takes this process forward to determine if the research can benefit communities through appropriate public health policies and programs. This finds resonance in the work of Khoury, Gwinn, and Ioannidis (2010) who indicate the importance of epidemiology to translational research, drawing attention to the public health dimension of medical research. Accordingly, the author proposes the following definitions of the T3 and T4 phases of translational research.

2.1. Proposed Definitions of T3 and T4 Translational Research

T3: Practice to Community. *T3* research moves out of the controlled environment (e.g., an academic health center) and into the community—the real world—where it is subject to random and uncontrollable effects. *T3* often involves strategies and interventions which were successful on a small scale in a controlled environment and determines if these can be scaled up to a larger population, being implemented in primary care practices, ambulatory care centers, and community clinics. Examples of *T3* research includes community-based participatory research (CBPR) and Phase IV clinical trials.

Israel, Schulz, Parker, and Becker (1998) define CBPR is a partnership approach to research

that involves community members, organizational representatives, and researchers equitably in all aspects of the research process and in which all partners contribute expertise and share decision making and ownership. The aim of CBPR is to increase knowledge of a given phenomenon and integrate the knowledge gained with interventions and policy to improve the quality of life of community members.

Phase IV clinical trials are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

T4: Community to Public Health. *T4* research evaluates the implementation and efficacy of policies and accepted medical practices, as they impact individual and public health outcomes. *T4* research may include cost–benefit analysis, policy analysis, surveillance studies, and program evaluation.

2.2. Examples of T3 and T4 Translational Research

2.2.1. Vaccine Development

Vaccine development is an excellent example of the effective implementation of translational research. At the *T1* level, basic research is conducted to determine if a vaccine can be created. This is done in the laboratory, with animals and limited human trials. At the *T2* level, highly controlled trials are run to determine both the safety and efficacy of the vaccine. At the *T3* level, in the United States, the US Food and Drug Administration (FDA) authorizes the general use of the vaccine. FDA and US Centers for Disease Control and Prevention (CDC) would monitor adverse reactions through their existing reporting system. CDC would track the progression of disease to evaluate the community-wide efficacy of the vaccine. Finally, CDC's Advisory Committee on Immunization Practices (ACIP) would evaluate data and create a policy for use in clinical and community settings. The vaccine may be recommended for use within a set immunization schedule or suggested as optional.

ACIP, FDA, and CDC continuously monitor effectiveness of the vaccine as well as its adverse reactions, if any. This is *T4* translational research. At all levels, scientific results are communicated through existing networks, from FDA announcements, scholarly journals, *Morbidity and Mortality Weekly Review*, and press releases to the general public. Such pronouncements receive wide publicity in the general news media. Weinberg and Szilagyi (2010) have also explained *T1-T4* phases of translational research using a vaccine example, specifically the rotavirus vaccine.

2.2.2. Drug Development

Drug development is another example. There has been substantial progress in treating certain types of leukemia, especially Chronic Lymphocytic Leukemia (CLL). Basic science found that kinase (enzymes that catalyze certain cellular processes) played a role in the proliferation and survival of abnormal white blood cells (leukemia cells). At the *T1* level, research was done to determine the mechanism of this reaction and investigate drugs to inhibit kinase to stop the reaction. Existing drugs used to treat leukemia were not very effective with this disease. At the *T2* level, Eichhorst et al. (2013) showed that existing drugs used to treat CLL had toxic effects on older people. Phase III studies by Goede et al. (Goede, Fischer, Busch et al., 2014; Goede,

Fischer, Engelke et al., 2015) and Hillmen et al. (2015) showed that the addition of drugs related to ibrutinib to existing therapies showed improvement in reduction of disease progression and patient survival. Bringing all these results together at the *T3* level, 269 patients over 65 years old were treated with ibrutinib as a frontline drug. Burger et al. (2015) reported that 90% were progression free at the 18-month endpoint, with minimal adverse reactions. Research showed that ibrutinib could inhibit kinase in this environment. *T3* Research continues to determine the long term efficacy of this drug—84% of the patients in the trial are still alive and the disease has not progressed in this group. *T4* research now continues to investigate the efficacy of ibrutinib and other similar drugs to inhibit CLL and other cancers. Finally, there is thinking that some forms of cancer are indeed chronic diseases. *T4* research will assess the correctness of this thinking, if ibrutinib is effective in prolonging their survival indefinitely. This would change people's perception of cancer, in general, and specifically CLL/leukemia, encouraging people to think of this as just another chronic disease for which they should be screened.

2.2.3. Influenza Prevention

A third example to illustrate *T3* and *T4* translational research comes from public health. The Pittsburgh Influenza Prevention Project (PIPP) was a prospective, controlled, cluster-randomized design to test the effectiveness of a suite of multi-layered, non-pharmaceutical interventions (NPIs) in controlling influenza in elementary schools. At the *T1* level, it is now accepted as fact that soap and alcohol based hand sanitizers kill germs. Stebbins, Stark, and Vukotich (2010) found six *T2* studies that demonstrated school children could adopt NPIs and obtain a positive outcome. PIPP built on the *T2* studies and created a large scale NPI intervention, a *T3* translation. Stebbins, Cummings et al. (2011) found that the intervention was effective in reducing influenza A by 52% and absenteeism by 26%. PIPP extended this research into *T4* by disseminating the results to schools in the region for the NPIs to be adopted as school-wide policy. The full implementation of a *T4* research effort would have included the evaluation of schools adopting the intervention policy, but PIPP was not able to do this fully.

3. Challenges of Translational Research

While the first challenge is to come to a widespread agreement on what translation research is, there are additional issues which must be addressed before the research community can become more successful in bringing the benefits of research to the world.

In order for research to be useful, its results and implications must be communicated to potential users. The *T1* and *T2* phases may be the easiest in this regard. *T1* and *T2* are reported in peer-reviewed journals, which are readily accessed by investigators monitoring the literature. *T1* and T2 research may be well documented through conference presentations and other collegial interactions. *T1* and *T2* research are often shared with colleagues who are working at the same academic medical center. But, even here, all presupposed communication does not occur. Szilagyi (2009) found that many factors hinder communication, including "research silos," a desire to prolong studies to maintain funding, and regulatory obstacles. Finally, communication does not ensure use.

Community-based practitioners do not have the time, inclination, or resources to monitor this peer-reviewed literature. Community and government leaders do not read the medical literature,

and they are not colleagues of those doing the investigations. The people who might use research do not attend the same conferences as the researchers.

In a survey of 292 policymakers by Sorian and Baugh (2002), 89% said that they want to know what the researcher sees as the policy implications or recommendations. These authors quoted one respondent as characteristic of the general sentiment: "I may not follow the researcher's advice, but I want to know what they think" (Sorian & Baugh, 2002, p. 271).

Mirvis (2009) examined the extent to which research findings, both basic and clinical, are applied to design public policies that promote health. He concluded that, in spite of the desire, and the obvious value of data-driven policy making, research is not commonly used in setting policy. Kon (2008) also made a similar observation and emphasized the importance of communication.

Feinstein (1999) suggested that there is also much less written at the *T3* and *T4* levels, as most funding is focused on the basic science level. Szilagyi (2009) found that more than 90% of funding is focused on *T1* research, although it is difficult to determine the exact amount of funding, since funding is not categorized that way. He concluded that very little research funding has a *T3* or *T4* focus.

Writing on the mission of the journal *Clinical and Translational Science*, Feldman (2008) identified another problem. He suggested that translational research requires a multidisciplinary approach, but there is a "paucity of well-trained multi- and inter-disciplinary investigative teams" (p. 1) that limits the ability to apply new knowledge.

Accordingly, the academic community should be educating scientists on the principles of translational research. The author has found little evidence of this. With the importance of NIH in the medical community, medical schools should be at the forefront. Feldman (2015) congratulated the Association of American Medical Colleges (AAMC) that it has included translational research instruction into its accreditation standards. However, he cites that this is "[u]nrecognized by most translational scientists and by leaders of clinical and translational science institutes" (p. 267). In addition, "the AAMC has left it up to individual schools of medicine to create the programs that will provide students with the requisite experience in CTS [clinical and translational research]" (p. 268). He concludes that there is an important need to create a standard curriculum on clinical and translational research.

4. Discussion and Conclusions

It is obvious that the translation of research into practical applications is important. The effort to define translational research may seem pedantic, but it is important for investigators to consider how their work could advance to the next step of research application. Thus, it is important that we consider the subject of translational research so that we make it a part of the entire research process, not just an afterthought.

This article has focused on defining translational research as four distinctive nodes, *T1-T2-T3-T4*. Others suggest more complex models. Dougherty and Conway (2008), Khoury et al. (2007), and Szilagyi (2009) suggest that it is a continuum. Mata and Davis (2012) have suggested that translational research involves a complex feedback loop. This is a matter for future consideration and refinement of translational research thinking and practice.

The scientific community also needs to consider how to promote translational research. Communication with multiple stakeholders is critical. Scientific work is usually disseminated in peer-reviewed journals, without regard to who might see it. Translational research directs us to disseminate our scientific research to those in a position to do additional research, utilize it in practice or community, make policy which can affect public health, and use it to make personal health decisions. But professional journals can be silos in which those outside the field are not engaged. We have to begin to consider how to break down barriers to the flow of knowledge beyond our own disciplines. Investigators should be thinking of the applicability of their research and how the results will be communicated, as part of their overall project design. Funders and Institutional Review Boards could make this a formal part of their process.

Finally, translational research should be part of the education and development of all researchers. It is hoped that increased recognition of the breadth and depth of translational research will lead to more funding and development of *T3 and T4 translational* research.

Acknowledgments

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