Editorial

What Constitutes Translational Research? Implications for the Scope of *Translational Vision Science and Technology*

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"I have been impressed with the urgency of doing. Knowing is not enough; we must apply."

Leonardo da Vinci

Overview

- The conceptualization of translational research has expanded since the inception of *Translational Vision Science and Technology* (*TVST*).
- The expanded scope of translational research necessitates that we likewise expand the scope of the journal.
- *TVST* will publish work that fits into phases T1 through T4 translational research. Some examples are as follows:
  - T1: Development and validation of animal models, preclinical drug studies, development of clinically relevant technologies, and phase 1 and 2 clinical studies ("bench to bedside" research).
  - T2: Phase 3 clinical trials (including comparative effectiveness trials), phase 4 clinical research, and development of clinical guidelines ("bedside to practice" research).
  - T3: Research focused on implementation and dissemination of phase 3 and 4 clinical research results (dissemination and implementation research).
  - T4: Research focused on outcomes and effectiveness in populations, including assessment of benefit to communities through public health policies and programs, as well as adoption of proven interventions' best practices in communities (diffusion research), and cost-benefit analyses.
- This classification scheme is best conceived as a continuum, a natural progression of investigative activity, rather than as a series of clearly defined categories.
- As a result of the change in scope, the number and diversity of publications accepted by the journal is likely to increase compared with past years.
- ARVO's commitment to this expanded scope will enable *TVST* to better represent the diversity of research that is already represented in platform and poster presentations at the annual ARVO meeting.
- This scope change will enable ARVO to represent the interests of its members and to advance the development and assessment of treatments for blinding diseases worldwide.

Defining Translational Research

TVST was established to provide a venue for multidisciplinary research that bridges the gap between basic research and clinical care. Although the journal's focus may have been unique in the vision science community at the time of its inception, the concept of translational research was not.

In 1945, the Director of the National Science Foundation described the nexus between basic and applied research:

Basic research is performed without thought of practical ends. It results in general knowledge and an understanding of nature and its laws. This general knowledge provides the means of answering a large number of important practical problems, though it may not give a complete specific answer to any one of them. The function of applied research is to provide such complete answers…

One of the peculiarities of basic science is the variety of paths, which lead to productive advance. Many of the most important discoveries have come as a result of experiments undertaken with very different purposes in mind. Statistically it is certain that important and

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highly useful discoveries will result from some fraction of the undertakings in basic science; but the results of any one particular investigation cannot be predicted with accuracy.

Basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn. New products and new processes do not appear full-grown. They are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science.

Today, it is truer than ever that basic research is the pacemaker of technological progress. (https://www.nsf.gov/about/history/nsf50/vbush1945_content.jsp)

Nonetheless, the distinction between basic and early stage translational research is not always clear, nor is the distinction between late stage translational research and research focused on clinical practice. Some investigators envision translational research as development of laboratory discoveries for clinical application. Public health agencies, however, envision a different role in which translational research establishes the evidence that not only validates the incorporation of these applications into clinical practice but also demonstrates benefit at a population level (vs. the artificial environment of a clinical trial). This ambiguity may underlie the numerous attempts to define translational research.[1–6] An emerging consensus of what defines translational research exists,[7] and I believe the ARVO journals should reflect this consensus.

Importance of Translational Research

In one study of 101 very promising claims of scientific discoveries with unambiguous clinical potential published in major science journals between 1979 and 1983, only five resulted in interventions with licensed clinical use by 2003.[8] Estimates of the median time required for new scientific discoveries to result in successfully completed clinical trials or entrance into clinical practice range from 17 to 24 years.[9,10] These facts are a matter of great concern to policy makers and have led to significant efforts to identify and resolve the obstacles impeding the translation of basic science discoveries into clinical studies and clinical practice.[1] The purpose of *TVST* is to highlight translational research in vision science, and in so doing to accelerate our progress toward developing and assessing treatments for blinding diseases. During the past decade, the scope of translational research has been expanded.[1–7] *TVST* should reflect this broader definition of translational research in its published manuscripts.

Current Classification of Translational Research: Phases T1, T2, T3, and T4

Translational Research Phase	Description	Examples
T1	Development of concepts and discoveries from basic research through early phase clinical trials	Drug development Diagnostic device development Phase 1 and 2 clinical trials
T2	Establishment of efficacy in humans and clinical guidelines	Phase 3 clinical trial Comparative effectiveness trial Phase 4 clinical trial
T3	Implementation and dissemination of phase T2 research results	Dissemination research Implementation research
T4	Assessment of outcomes and effectiveness of clinical interventions in populations	Diffusion research Assessment of public health policy and programs on communities

Phase T1 translational research involves work that develops concepts and discoveries from basic research through early phase clinical trials in humans.[7] Drug development, some studies of disease mechanisms, including proteomics, genomics, genetics, metabolomics, and animal models, are examples of T1 phase translational research. Other examples include development of diagnostic devices and modalities, application of artificial intelligence to identify ocular or systemic disease using ocular imaging technology, development of treatment technologies (e.g., sustained drug delivery systems), and phase 1 and 2 clinical trials. Phase T1 translational research typically is described as "bench to bedside."

Phase T2 translational research refers to work that establishes efficacy in humans, as well as clinical guidelines.[7] Phase 3 clinical trials, development of clinical guidelines, and assessment of whether treatments that have proved effective in the highly controlled environment of registration trials are effective in less controlled

conditions (external validity) are examples of phase T2 research. Phase 4 clinical studies are an example of T2-phase translational research, as they enable assessment of a drug or treatment's effectiveness in diverse populations, as well as the incidence of infrequent but important off-target effects.[5] Comparative effectiveness trials (e.g., CATT,[11] Protocol T[12]) are classified as T2 activity by some authors and as T3 phase translational research by others. Phase T2 translational research has been described as "bedside to practice."[5]

Phase T3 translational research refers to work that is focused on implementation and dissemination of phase T2 research results.[7] Phase T3 research involves studies that aim to spread knowledge regarding evidence-based interventions (dissemination research) and integrate interventions into existing programs (implementation research).[6,10] Some authorities classify phase 4 clinical trials as phase T3 translational research.[6]

Phase T4 translational research is focused on outcomes and effectiveness in populations[7] and involves studies that assess the benefit to communities through public health policies and programs, as well as adoption of proven interventions' best practices in communities (diffusion research).[13] Cost-benefit analyses, surveillance studies, and program evaluations are examples of T4 phase translational research.[5] Thus epidemiology plays an important role in translational research.[14]

Areas of overlap in this classification scheme demonstrate that the different phases of translational research are best conceived as a continuum, a natural progression of investigative activity, rather than as a series of clearly defined categories.

Although translational research as defined in phases T1 through T4 includes a broad spectrum of work, its boundaries are finite. Observational studies, such as case reports or case series, for example, generally would not qualify as translational research. Quality of life studies or comparative treatment studies involving patient cohorts in which there is no adequate control group would have limited translational value due to limitations in study design.

The Virtuous Cycle

The transition from basic to translational research is not unidirectional. The results of phase T3 and T4 translational research can be hypothesis-generating and stimulate additional basic research. Limitations in the clinical effectiveness of anti-vascular endothelial growth factor therapy in patients with the neovascular complications of age-related macular degeneration, for example, have stimulated additional research into the pathophysiology of this condition and resulted in the development of drugs modulating different pathways, and in which preclinical experiments and early phase trials suggest efficacy.[15,16]

Implications for the Scope of *TVST*

Currently, *TVST* emphasizes multidisciplinary research that bridges the gap between basic research and clinical care. The scope includes a broad spectrum of work, for example, refinement of data analysis algorithms to improve in vivo imaging technology, nanoengineering to improve virus-based gene delivery, nanoengineering of artificial extracellular matrices, development of new animal models of human disease, applications of stem cell technology for regenerative medicine, development of surgical technology, results of phase 1 clinical trials, and reverse translational ("bedside to bench") research. Short updates on new developments and controversies and summaries of symposia are considered on an individual basis.

The conceptualization of translational research has expanded since the inception of *TVST*. The expanded scope of translational research necessitates that we likewise expand the scope of the journal, while we maintain high standards regarding study design, method of data analysis, and impact in evaluating submitted research. *TVST* will publish work that fits into phase T1 to T4 translational research, as defined earlier. As a result, the number and diversity of clinical publications accepted by the journal is likely to increase compared with past years. This commitment will enable the journal to better represent the diversity of research that is accepted for platform and poster presentations at the annual ARVO meeting. It will thus better enable ARVO to represent the interests of its members, and to advance the development and assessment of treatments for blinding diseases worldwide.

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