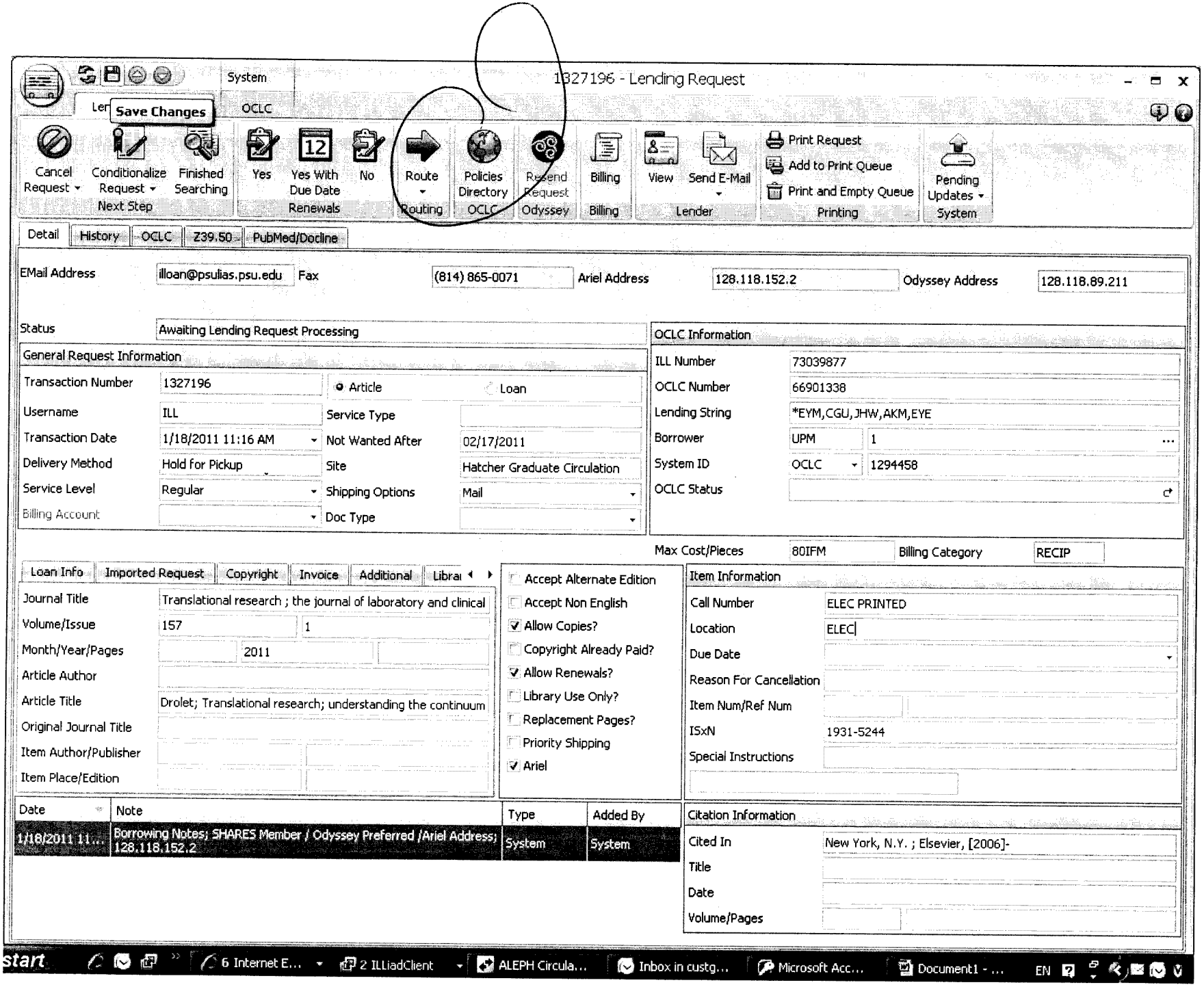
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REVIEW ARTICLE

Translational research: understanding the continuum from bench to bedside

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The process of translating basic scientific discoveries to clinical applications, and ultimately to public health improvements, has emerged as an important, but difficult, objective in biomedical research. The process is best described as a "translation continuum" because various resources and actions are involved in this progression of knowledge, which advances discoveries from the bench to the bedside. The current model of this continuum focuses primarily on translational research, which is merely one component of the overall translation process. This approach is ineffective. A revised model to address the entire continuum would provide a methodology to identify and describe all translational activities (eg, implementation, adoption translational research, etc) as well their place within the continuum. This manuscript reviews and synthesizes the literature to provide an overview of the current terminology and model for translation. A modification of the existing model is proposed to create a framework called the Biomedical Research Translation Continuum, which defines the translation process and describes the progression of knowledge from laboratory to health gains. This framework clarifies translation for readers who have not followed the evolving and complicated models currently described. Authors and researchers may use the continuum to understand and describe their research better as well as the translational activities within a conceptual framework. Additionally, the framework may increase the advancement of knowledge by refining discussions of translation and allowing more precise identification of barriers to progress. (Translational Research 2011;157:1–5)

Abbreviations: CTSA = Clinical and Translational Science Awards; IOM = Institute of Medicine; MI = myocardial infarction; NIH = National Institutes of Health; TR = translational research

The gap between what we know and what we do in public health is lethal to Americans, if not the world.

— David Satcher MD, PhD
Former U.S. Surgeon General

The advancement of scientific knowledge from "bench to bedside"[1] occurs through a process called translation. This term, translation, describes the transformation of knowledge through successive fields of research from a basic science discovery to public health

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impact—a complex process that requires both research (eg, bench-work and clinical trials) and nonresearch activities (eg, implementation). The order of such translational activities occurs along a "continuum," which can be used as a model for accurately describing the entire translation process. Our purpose is to review, synthesize, and clarify the current models and terminology of translation and translational research (TR). We propose a novel model called The Biomedical Translation Continuum to describe and understand the process of taking basic science findings to public health interventions. Understanding this continuum is necessary for effective translation to occur, which is vital to increasing the public health impact of basic science discoveries.

IMPORTANCE OF TRANSLATION

Although translation has been discussed for more than 30 years,[1] the process recently has become a major focus in biomedical research. In the 2001 *Crossing the Quality Chasm* report, the Institute of Medicine (IOM) identified the importance and difficulty of translating basic scientific knowledge to patient care.[2] In that same year, the editors of *The Journal of the American Medical Association* published a call for papers discussing TR, identifying this work as vital to the progress of biomedical research.[3] Likewise, the 2003 National Institutes of Health (NIH) Roadmap identified translation as a vital component of research and health-care improvement.[4] The NIH also endorsed the importance of translation with the foundation of Clinical and Translational Science Awards (CTSAs) in 2005. These grants were created to stimulate progress from scientific innovation to health improvement and will have an estimated $500 million annual budget by 2012.[5,6] It is clear in both the literature and the funding of biomedical research that translation is now recognized as a necessary process to reach health improvements from basic science research.

Although improved health is the common objective of basic science and biomedical research, this goal has not been achieved as often as desired or needed. The NIH funded nearly $15 billion of basic science research in 2009, but the rate of translation of this work into clinical practice will be low and slow. One well-designed study found that less than 25% of highly promising biomedical discoveries resulted in a published randomized clinical trial and less than 10% were established in clinical practice within 20 years.[7] Moreover, even when demonstrated to have positive health benefits, medications and treatments are not administered universally when appropriate in clinical practice. Well-known examples include the administration of beta blockers after myocardial infarction (MI) or lipid screening and cholesterol-lowering agents in coronary artery disease.[8,9] Why is this happening? What are the consequences?

The response to the first question revolves around difficult or unknown processes of moving basic science research into a translation mode (eg, nonbasic research that is an entirely different type of investigation). No clear model of translation is available to describe these processes that move basic science into translation. The lack of adequate framework prevents the identification of steps during which research and knowledge are "lost in translation" and therefore do not reach public health gains. Understanding and defining the continuum from the laboratory to public health is vital to improving successful translation of research. Without a framework to identify steps in the translation process where knowledge is lost, it is difficult or impossible to bridges these gaps. For the second question, the ramifications of poor translation and adherence to guidelines are 2-fold. First, billions of research dollars are "lost in translation" along the path from bench to bedside as previously discussed. More importantly, potentially significant public health gains may be lost in this process as well.

THE TRANSLATION LEXICON

To discuss translation, it is necessary to understand a new lexicon that has developed in the literature and may be difficult to interpret without the appropriate background. The IOM Clinical Research Roundtable first described the current terminology and model of TR in 2003. They described a 2-phase process of research progressing from (1) basic science to clinical science, then (2) from clinical science to public health impact. In their framework, they identified "translational blocks" between these steps that are obstacles to research progress and represent major challenge areas for reaching health improvements from basic sciences.[10] The second phase of translation later was subdivided creating a model of the following translational phases: (T1) basic science to clinical science, to (T2) clinical practice, and to (T3) health improvements.[11] The authors of this model use the terms T1, T2, and T3 to describe the 3 periods of translation in respective order but, interestingly, do not discuss these terms in their manuscript.[11] Whether intentional or not, this "T terminology" has become standard, though no explicit description is given to date. Thus, it is not surprising that we have found varying usage and meaning of these "Ts" in the literature.

The most current translation model in the literature expounds the 3 translation periods—basic science translated to clinical efficacy (T1); efficacy translated to clinical effectiveness (T2); and finally effectiveness translated

to health-care delivery (T3).[12] Although this model improved on those prior with greater detail, the terminology remains indistinct to both researchers and physicians.[13,14] We found in numerous references that the T terms (ie, T1, T2, and T3) are used indiscriminately to describe translation obstacles,[10] translation steps,[11] translational activities,[12] or TR.[13-15] An unambiguous framework to define and solidify the concepts and terminology of translation would be useful, particularly for practicing physicians and other researchers not following the ever-changing literature on translation.

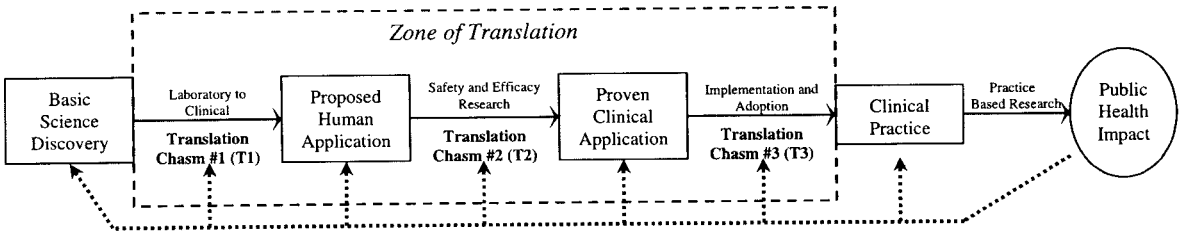
THE BIOMEDICAL RESEARCH TRANSLATION CONTINUUM

We reviewed the evolution of translation through a detailed evaluation of the published literature. This review begins with an editorial from the *New England Journal of Medicine* in 1974, progresses to the first workable definition by Dr. Thomas A. Waldmann in the early 1990s, and ends with the current model from Blue Highways and the "3 T's" Road Map.[1,11,12,16] Noting that obscurity exists in the current terminology and model of translation, we then created a framework to describe the process of translation fully, which incorporates the most important features of 3 previous translation models with several modifications for improved clarity and simplicity.[10-13]

We call our model the Biomedical Research Translation Continuum (Fig 1). This figure represents the entire translation process from basic science knowledge to improved public health. This model has 4 practical landmarks in the progression of knowledge, which are separated by gaps corresponding to the previously described "T-terminology" (T1–T3).[12] However, we have called these gaps "translation chasms" to represent periods during which translation activities will bridge between the 4 stages of research progress. For example, to bridge the first translation chasm (T1), interpretation must occur of a basic science discovery in the context of a potential medical application. If the scientific discovery is genetic or biochemical, then continued *in vitro* laboratory investigation and animal models may be necessary to bridge T1 and to create a potential clinical use. Therefore, T1 translation activities will have similar goals (to interpret basic science to human application) but will be unique for each discovery entering the translation continuum. The same is true for each of the subsequent translation chasms and bridging activities. After a potential human application is identified, large animal models and human studies (clinical trials) are necessary to evaluate the safety and efficacy of interventions. These trials bridge the T2 chasm to an accepted clinical application. Finally, T3 is bridged when clinical practices and guidelines are implemented and adopted ultimately to yield public health changes.

To see a complete picture of the translation continuum, consider the example of aspirin administration after MI, which has been demonstrated to decrease morbidity and mortality.[17] In retrospect, we could examine the entire translation continuum for aspirin in this specific medical application. From the outset, basic science discoveries must be translated from laboratory discoveries and knowledge (*acetylsalicylic acid inhibits prostaglandin synthesis*), to accepted clinical practice (*aspirin administered after MI*), and ultimately to health gains (*decreased mortality*). The "zone of translation" represents the sum of activities that must occur to reach health impact. This process begins with crossing the first translational chasm (T1), which requires the interpretation of basic science to medicine. Activities to bridge T1 involve identifying potential human applications (*Does aspirin decrease platelet aggregation in vivo via inhibition of prostaglandin synthesis?)* as well as continued laboratory investigations to examine how biochemical findings are applied *in vivo*. On the development of a potential human application (*Can aspirin inhibited platelet aggregation be used to prevent post-MI thrombosis?*), translational clinical research (ie, clinical trials) occurs to examine safety and efficacy. If an effective clinical application is found (*Aspirin effectively decreases thrombosis and decreases mortality in individual patients*), then it must be implemented and adopted in clinical practice before public health gains can be made—bridging T3. Then the public health impact is studied via practice-based research (*Does use of aspirin after MI decrease morbidity and mortality in the population?*). Finally, a process of reciprocal translation is needed, which is a feedback loop to promote a cycle of continual improvement (eg, reevaluate T3—why are clinicians not administering acetylsalicylic acid post-MI?).

Our model advances prior models in several ways. First, we define and clarify the standard "translation" terminology within a simple, conceptual framework for the process of translation. We distinguish a "zone of translation," which separates basic science discoveries from accepted clinical practice and ultimately from positive health impact. To reach this destination, several checkpoints are encountered along the way, which are separated by translational chasms in research progression (T1–T3 previously described). Second, our model explicitly defines "translational research" as activities bridging these chasms, for example, advancing proposed human applications (ideas) to proven clinical treatments (practices). However, translation of research occurs along the entire continuum as knowledge progress to public health gains. This is an important



	Pathway	*Inquiry* and Action
Basic Science Discovery	Beta-adrenergic stimulation increases cardiac automaticity and conduction velocity	*Does beta-blockade decrease chronotropy and ionotropy?*
T1	**Translation of basic science to humans**	**Evaluation of biochemical findings in animals, proposal of a potential medical application**
Proposed Human Application	Beta-blockade decreases cardiac work and oxygen demand	*Can beta-blocking drugs be used to prevent further ischemic injury following myocardial infarction?*
T2	**Translation to clinical treatment (e.g. drug development)**	**Evaluation of safety and efficacy (i.e. clinical trials)**
Effective Clinical Application	Beta-blockers are cardioprotective; safely decreasing post-MI ischemic injury	*How do we get physicians to use beta-blockers in practice?*
T3	**Translation to practice**	**Implementation and Adoption**
Clinical Practice	Beta-blocker administration following myocardial infarction	*In true clinical setting, does beta-blocker administration decrease morbidity and mortality?*
**	**Practice Based Research**	**Practice-based research networks; patient registries; cohort and case-control studies; meta-analysis**
Public Health Impact	Beta-blockers decrease post-MI mortality; established standard of care	*Can we improve how any part of our treatment pathway (e.g. improved pharmacology, greater adoption, etc)?*
**	***Continual practice improvement***	**Findings in any stage feedback to previous research stages (dotted line) for further examination and action**

Fig 1. Biomedical research translation continuum.

distinction because the term TR is used broadly in the literature to describe the process of translation, whereas it more accurately describes research activities within the translation continuum. Finally, our model is the first to identify implementation and adoption in the translation process to reaching accepted clinical practices.

In our model, we have chosen the term "translation chasms" to represent the "black boxes" in which activities of translation remain vague. Although TR-like clinical trials are well established to bridge T2, the resources and actions to bridge T1 and T3 remain more vague. Many researchers are involved in basic science or clinical research, but we need to bridge T1 and bring laboratory findings to human applications. Likewise, many proven clinical applications never find the way to clinical practice.[7] As a result, bridging these T-chasms may be a greater barrier along the continuum than adequately funding TR studies. Our model may help better identify areas in which research and knowledge is "lost in translation."

CONCLUSIONS

The loss of scientific discoveries along the Biomedical Research Translation Continuum is a major public health problem. Despite multibillion dollar research funding and considerable laboratory productivity, only a fraction of promising basic science discoveries result in applied clinical practices and health gains.[7] As a result, immense research budgets, a wealth of scientific knowledge, and significant public health benefits are lost in translation. Therefore, it is vital that we understand how knowledge progresses to health gains.

The study of translation and translational science recently has come to the forefront of research priorities. A descriptive model for translation with well-defined terminology is evolving, and until this description is well established, confusion will persist for researchers and clinicians.[14] To understand the complicated translation process, we must have a clear framework and terminology.

In developing such a framework, we first define checkpoints along the continuum according to the real-world progression of research from basic science discovery to proposed human application, to effective clinical treatment, to clinical practice, and finally, to public health impact. We redefined T1–T3 as "translation chasms" to represent gaps that must be bridged by interpretation, TR, and implementation efforts for research and knowledge to progress effectively. Although we have proposed general descriptions for activities of each T-chasm (eg, clinical trials occur in T2), bridging still represents the most poorly described and

formidable obstacle in knowledge utilization. Understanding how to bridge these chasms or to shorten their span could greatly increase the translation of scientific research to improved public health.

The terminology of our model may be used to describe where research has progressed or stalled (eg, a human application proposed early in T2 or clinical application delayed in T3). Likewise, researchers hoping to improve translation (eg, CTSA applicants) may describe the aim of their investigation more clearly along the research continuum with our model and terms. Finally, the simplifications of previous models to realistic and pragmatic research practices should clarify the processes of translation for practicing physicians interested in improved public health but not actively in research.

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