TBM

ESSAY

Transdisciplinary translational behavioral (TDTB) research: opportunities, barriers, and innovations

Susan M Czajkowski, Ph.D,[1] Minda R Lynch, Ph.D,[2] Kara L Hall, Ph.D,[1] Brooke A Stipelman, Ph.D,[1] Lynne Haverkos, MD, MPH,[3] Harold Perl, Ph.D,[4] Marcia S Scott, Ph.D,[5] Mariela C. Shirley, Ph.D[5]

[1]National Cancer Institute, National Institutes of Health, Rockville, MD, USA

[2]National Institute on Drug Abuse, National Institute of Health, Rockville, MD, USA

[3]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD, USA

[4]Independent Consultant, Arroyo Seco, NM; Formerly with National Institution of Drug Abuse, National Institutes of Health, Rockville, MD, USA

[5]National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD, USA

Correspondence to: S Czajkowski
Susan.Czajkowski@nih.gov

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Abstract

The translation of basic behavioral science discoveries into practical strategies represents a promising approach to developing more effective preventive interventions to improve health. Since translational research inevitably involves making use of diverse perspectives from multiple disciplines, it is best conducted as a transdisciplinary enterprise. In this paper, we discuss current strategies used by NIH to support transdisciplinary translational behavioral (TDTB) research, summarize successful efforts, and highlight challenges encountered in conducting such work (ranging from conceptual to organizational to methodological). Using examples from NIH-funded projects we illustrate the potential benefits of, and barriers to, pursuing this type of research and discuss next steps and potential future directions for NIH-supported TDTB research.

Keywords

Transdisciplinary, Translational, Behavioral, NIH

The views expressed in this article are those of the authors and do not necessarily reflect the view of the National Institutes of Health (NIH) or the U.S. Department of Health and Human Services.

Implications

Policy: Funders, reviewers, editors and others who wish to promote and support TDTB research can use the highlighted exemplars funded by NIH to inform the development of structures and systems that better support TDTB research.

Research: Examples provided highlight concrete ways in which TDTB projects, research programs, and initiatives can be designed and implemented at all phases of the translational spectrum.

Practice: Investigators and translational partners engaged in TDTB research can leverage the recommendations proposed in this paper to advance and promote the area of TDTB research.

INTRODUCTION

The translation of basic behavioral science discoveries into practical strategies to improve health is a promising pathway for bolstering the impact of prevention science research on health outcomes. A translational approach to identifying, optimizing, and implementing preventive behavioral interventions is consistent with the mission of the National Institutes of Health (NIH), which is to seek "fundamental knowledge about the nature *and behavior* of living systems *and the application of that knowledge* to enhance health, lengthen life, and reduce illness and disability."

Translational research is defined by the NIH as: (1) "the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans," and (2) "research aimed at enhancing the adoption of best practices in the community." The first area is often referred to as T1 and the second as T2 research. The translational spectrum applied to prevention research can be further broken down into additional categories, resulting in an interactive and dynamic set of research phases as illustrated in Table 1 [1]. As depicted in Table 1, the translational spectrum in prevention research begins with "type zero" or T0, characterized by basic discovery science and the movement of basic science findings to the next logical step along the translational continuum (e.g., findings on basic principles, mechanisms, and processes in animal models validated with human subjects in field or laboratory settings); continues through T1 (bench to bedside), which involves early stage intervention development and testing; to efficacy and effectiveness (T2) testing; and culminates in the dissemination, adoption and implementation of proven interventions in clinical and community settings (T4), and ultimately at a global level (T3-T5).

This depiction of the translational spectrum is meant to be heuristic only, since there are many ways to portray how research may progress from more basic/mechanistic stages to clinical and public health application, including less linear, more multi-directional or circular approaches and those that allow for combinations of stages (e.g., integration of efficacy/effectiveness research into a "hybrid" of the two).

Table 1 | Full translational spectrum of prevention science: research stages

Type	Type 0 Translation (T0)	Type 1 Translation (T1)	Type 2 Translation (T2)
Definition	The fundamental process of discovery, where findings from the social, behavioral, and biomedical sciences (animal and human) are translated into applied research with human subjects. Includes study of analogous processes and phenomena via field or lab-based investigations using human subjects that could be applied to preventive intervention.	Moving the research from bench to bedside location. Includes the translation of applied theory to development of methods (measures, analysis) and programs.	Moving from bedside to practice. Involves the translation of program development to implementation (i.e., efficacy trials with emphasis on internal validity and effectiveness trials with emphasis on internal and external validity).
Example	A parallel study with forward- and back-translation to understand the impact of early environmental adversity on brain development and mechanisms that subsequently confer risk.	Development of measures, methodologies, and interventions that focuses on self-regulatory processes subserved by prefrontal-limbic connections. Includes the initial development of the Good Behavior Game and Promoting Alternative THinking Strategies (PATHS).	Randomized clinical trials of preventive interventions to establish the size of outcomes that can be attributed to the programs (controlling for alternative influences), followed by rigorous testing with well-defined populations.
Type	Type 3 (Translation) (T3)	Type 4 Translation (T4)	Type 5 Translation (T5)
Definition	The practice-oriented phase involving research to test the degree to which efficacy and effectiveness trial outcomes can be replicated under real world settings. Focuses on adoption, adaptation, and dissemination.	Research focused on 'scaling-up.' Wide-scale implementation, adoption, and institutionalization of new guidelines, practices, and policies.	Translation for application in global communities. Involves fundamental and universal change in attitudes, policies, and social systems.
Example	Study of parameters of adaptation of highly replicated programs and interventions with strong positive effects across time and context.	Research on scaling of the evidence-based programs in multiple school districts within and across counties.	Policies based on acceptance of science-based practices such as laws instituting juvenile justice reforms and programs providing wide-scale educational innovations.

Table developed by Fishbein et al. [1] as framework to be used by all articles in this Special Issue

The translation of basic behavioral science findings into behavioral interventions has been an under-recognized area of research, with relatively fewer resources devoted to the early phases of behavioral translation (T1) than to similar biomedically oriented research and to later phases (e.g., T2–T5) of behavioral research. Given the strong evidence for a significant behavioral contribution to morbidity and mortality [2, 3], the potential impact of accelerating the translation of basic behavioral science findings into health-related preventive interventions is increasingly being recognized as an important area of need. Basic behavioral and social science discoveries in areas as diverse as behavioral neuroscience, cognitive, and emotional processes (e.g., self-regulation, stress reactivity), interpersonal relationships and dynamics, formation of change in social norms, and influence of the social and built environment, are more frequently being used to guide the development of interventions for behavioral risk factors such as smoking, obesity, and non-adherence to medical regimens.

The processes underlying behavior change are complex and require a transdisciplinary approach at the individual project [4], program of research ([5]–see below) and center or initiative levels [6]. Transdisciplinary research refers to the most integrative form of cross-disciplinary collaboration. In this type of research, investigators typically transcend their disciplines and engage in a collaborative process to develop a shared conceptual framework that integrates and extends beyond each member's unique disciplinary perspectives [6]. Transdisciplinary research brings together perspectives from different disciplines, stakeholders, and/or levels of analysis to generate new breakthroughs–novel findings based on new conceptual models, methods, and approaches that may yield greater sustained effects over time. For instance, in a program of research spanning two decades, Lerman and colleagues have conducted innovative

translational behavioral science research that bridges neuroscience, pharmacology, and genetics, creating novel lines of investigation, including the behavioral epidemiology of cancer susceptibility testing, pharmacogenetic approaches to the treatment of nicotine dependence, and the neurobehavioral substrates of cancer risk behaviors such as tobacco use and overweight/obesity [7]. Furthermore, a series of discoveries by Lerman et al. converged on the importance of working memory-related brain activity in smoking cessation, culminating in an fMRI-based predictive model of smoking relapse [8] and identification of a novel neuro-therapeutic target for behavior change interventions [9].

Translational research benefits from collaboration between experts with diverse scientific perspectives and methodological approaches. For this reason, we focus on *Transdisciplinary Translational Behavioral* (*TDTB*) *Research* and use this term to refer to transdisciplinary behavioral research across the translational spectrum. TDTB research encompasses early-stage studies translating basic biological and behavioral science into behavioral interventions (e.g., Epstein et al.'s work translating research on habituation into novel approaches to improving dietary intake in obese children and their families [10]). In addition, it includes later-stage research that investigates how proven interventions can be effectively scaled up, implemented, disseminated and adopted within clinical and community settings–utilizing multiple areas of expertise–and thereby transcending disciplinary boundaries. As presented herein, TDTB research is relevant to primary, secondary, and tertiary prevention as well as other prevention systems such as the one described by Gordon [11], which includes universal interventions applied to the general population, regardless of risk; selective interventions targeting groups at increased risk because of a particular common factor; and indicated interventions that target individuals or groups with signs and symptoms that foreshadow disorder onset [12].

In this paper, we highlight current efforts as well as challenges and strategies for engaging in TDTB research. We do so by using examples from NIH-funded initiatives and projects to illustrate the potential benefits of, barriers to, and future opportunities in pursuing this type of research, describing next steps and potential future directions for TDTB research at NIH.

Conceptual and definitional issues in TDTB research

Defining TDTB research

While the present issue sets forth definitions for a TDTB spectrum, considerable variation still exists within and across fields regarding the way in which TDTB research is defined and conceptualized. In biomedical research, translation from basic biological science to clinical application (T1 or bench to bedside) is based on a well-defined, phased model guided by regulatory requirements developed for drug development research [13, 14]. In behavioral research, there has been a lack of consensus regarding an analogous framework to be used for developing and testing preventive and therapeutic behavioral interventions. However, the NIH has served an important role in stimulating the development of several models to better define and guide TDTB research (see Table 2 for a summary of selected examples).

An early example is the Stage Model of Treatment Development, originally a three-stage model for developing treatments in mental health and substance abuse [15] that has been revised to encompass six stages of intervention development and testing [16], beginning with basic science (Stage 0), proceeding to generation and refinement of behavioral interventions (Stage 1), and continuing through efficacy testing in research settings (Stage 2), efficacy testing in community settings (Stage 3), effectiveness research (Stage 4) and implementation and dissemination research (Stage 5).

More recently, the NIH has supported development of the ORBIT model (*Obesity-Related Behavioral Intervention Trials*, www.nihorbit.org) [17], which focuses exclusively on the early-phase (pre-efficacy) development of behavioral treatments, primarily for *chronic physical diseases*. The ORBIT framework encompasses two overarching phases of intervention development, entitled "Phase I" (Intervention Design) and "Phase II" (Preliminary Testing) and each includes two distinct sub-phases. In Phase Ia, treatment targets and components are initially defined, including the degree of change in the treatment target needed to demonstrate a clinically meaningful effect in the ultimate health outcome. In Phase Ib, these components are tested and refined to achieve a well-defined treatment "package." Phase IIa involves "proof-of-concept" testing which aims to determine if the treatment package can achieve a clinically significant degree of change in the pre-specified treatment target; Phase IIb involves further pilot testing using larger samples, randomized designs and a determination of feasibility. The ORBIT model, like the Stage model, acknowledges the important contribution of basic research and is interactive (allowing for interaction across and between phases) and iterative. However, the ORBIT model is based explicitly on the drug development process (e.g., Phase I and II research). In addition, the ORBIT model focuses less on incorporating and understanding mechanisms of action and more on achieving clinically meaningful changes in behavioral treatment targets to prevent or mitigate disease risk and outcomes.

Congruent with both of these frameworks, the NIH Common Fund *Science of Behavior Change Program* (SOBC, https://commonfund.nih.gov/behaviorchange/index) supports the application of an "experimental medicine approach" to the development of mechanistically-based interventions for preventing and treating unhealthy behaviors that promote development of disease. This experimental medicine approach

Table 2 | Selected examples of TDTB models

Model/framework	Primary focus	Translational phases included
Greenwald and Cullen [19]	Five-stage model to guide *cancer control* research	Includes all phases from hypothesis development (Phase I) through D&I (Phase V) research
Flay [20]	Eight-phase framework for development of *health promotion* programs	Includes all phases from basic research (Phase I) through demonstration studies (Phase VIII)
Rounsaville et al. [15]; Onken et al. [16] Stage Model	Three-stage model, updated in 2014 to include six stages, with a focus on developing psychological treatments for *mental health, substance use/abuse disorders*	Includes all phases from basic research (Stage 0) to D&I (Stage V)
Medical Research Council (MRC), 2008	Proposes a four-phase cyclical framework for developing and evaluating *complex interventions*	Includes all phases from intervention development through implementation
ORBIT model [17]	Two-phase model for developing behavioral interventions with a focus on preventing and treating *chronic physical diseases*	Focuses on pre-efficacy phases (Phases I and II)

includes four main steps: (1) identifying a set of putative targets within a psychological or behavioral domain that is implicated in health behavior; (2) leveraging existing or developing new experimental or intervention approaches to *engage* the targets; (3) identifying or developing appropriate assays (measures) to permit verification of target engagement; and (4) testing the degree to which engaging the targets produces a desired change in health behaviors leading to clinically significant outcomes or endpoints. Essentially, this approach provides a detailed set of steps for identifying and validating treatment targets, and is thus well-aligned with and can be used to achieve the goals of Phase Ia in the ORBIT model and Stage I in the Stage model.

A larger number of models or frameworks have been developed to define later phases of the translational research spectrum–for example, some researchers estimate at least 61 models have been created to guide Dissemination and Implementation (D&I) research [18]. Many of these models are based on Greenwald and Cullen's [19] description of 5 phases of cancer control research and Flay's [20] eight-stage model, both of which include efficacy and effectiveness phases. A number of models such as Glasgow's RE-AIM framework (http://www.re-aim.hnfe.vt.edu/index.html) deviate from this linear, sequential approach to D&I research, emphasizing the need to incorporate aspects of the practice environment in the development and testing of interventions to enable successful translation of preventive interventions from research to practice. This reflects more of a public health approach as opposed to the more clinically oriented models used to define early-stage translational research.

Conceptual challenges in TDTB research

Although the NIH has played an important role in the TDTB arena by helping to better define the process of developing, testing and implementing behavioral interventions, the use of these models to define T1 research, in particular, is not yet as common and widespread as the nearly universal adoption (within the biomedical community) of the drug development model to guide early-phase translational biomedical research. In addition, although the authors of the present issue have agreed on a set of definitions for the translational continuum (Table 1), considerable variation still persists within and across fields regarding the way in which translation is defined and conceptualized. Likewise, transdisciplinary research is defined in many different ways in the literature and in practice [21].

The lack of consensus regarding terminology, definitions, concepts, and models across evolving typologies, especially those used in TDTB research, may confuse some researchers and the lay public. Research suggests that the process between scientific discovery and translation to clinical practice is a long and slow process, sometimes taking 17 to 24 years [22, 23] and lack of conceptual clarity may limit appropriate evaluation of translational research as a step in this process.

For Type 0 TDTB research, there are unique definitional and conceptual challenges, especially in the area of animal to human translation. While animal models are needed to investigate aspects of behavior not readily amenable to human investigation, challenges include in variation in behavioral measurement and difficulties in cross-species comparisons. These translational challenges have been the topic of several expert panels and symposia sponsored by NIH's Basic Behavioral and Social Sciences Research Opportunity Network–OppNet (http://oppnet.nih.gov/–for example see http://oppnet.nih.gov/news-102810.asp for the "Model Animals, Human Applications" roundtable, and http://oppnet.nih.gov/news-07232012.asp for the "Improving Animal Models of Human Behavioral and Social Processes" meeting). These meetings represent efforts to highlight and address ongoing T0 conceptual challenges.

Variation in translational research definitions and concepts is not unique to the behavioral sciences: there are many definitions and frameworks used in translational research (especially T2–T5 research) within the biomedical arena as well. Since there are no regulatory requirements for behavioral research that require the use of a specific framework (paralleling drug development requirements), it may be that multiple approaches and models will in fact facilitate TDTB efforts. Can the various behavioral translational models co-exist, and perhaps be used for different purposes or goals (e.g., the Stage model focusing on mental health and substance abuse, the ORBIT model focused on behavioral treatments for physical health conditions, the Medical Research Council (MRC) model more useful for multi-level public health-oriented interventions)? Or, is it necessary for TDTB researchers to come to consensus on a single model or framework? More research and experience with these models is needed to clarify whether the use of multiple approaches facilitates or hinders the ultimate success of TDTB research.

Given that different models or frameworks are being used and consensus on a single model may not be possible or desirable, harmonization might be important for clarifying some of the terminology being used within the various models and to permit comparability across studies. For example, is Type 4 translation research, which involves "scaling-up" and wide-scale implementation of scientific discoveries, adoption and institutionalization of new guidelines, practices and policies, the same as or different than D&I research?

Regardless of the framework or model used, clarification is required for many of the features of TDTB research. Although the field is approaching consensus on the dynamic nature of TDTB research among all phases of the translational spectrum, there remains disagreement on key features in the process of translation. For example, what are the most critical or necessary steps in the translational process? Where does one phase in the process start and the next begin? What methods can be used to define "milestones" or criteria for moving from one translational phase to another? What are the study designs and methods that can or should be used at different phases of the translational spectrum [24]?

As we work to deconstruct the research process into specific stages, we need to ensure that such parsing does not create new unintended consequences. For example, failure to take into account the contexts in which interventions will eventually be implemented during earlier phases of the translational continuum may lead to lower success rates in effectiveness trials [25]. Keeping the full continuum in perspective during research development and testing, and utilizing concepts such as "designing for dissemination" [26] in which stakeholders are engaged early in the process of intervention development, can help ensure the success of interventions at later stages of the continuum. This transdisciplinary process, which encourages participation of community or patient representatives, practioners, and intervention specialists throughout the research continuum, is likely to increase uptake and ensure consideration of real world concerns and constraints.

Next steps for addressing definitional and conceptual issues in TDTB research

- Increase the dissemination and use of TDTB intervention development and testing models to help guide behavioral translational research at all phases of the spectrum.
- Foster research experiences that expose experts trained in different scientific perspectives and at different levels of the TDTB spectrum, to each other's scientific culture, including definitions, concepts, languages, paradigms, metrics, and experimental approaches.
- Increase stakeholder (e.g., patient, provider) engagement throughout the research process to help ensure stakeholder perspectives and needs are incorporated across the behavioral translational spectrum.

Review and funding of TDTB research

Challenges in reviewing and funding TDTB research

The present NIH organizational structure, where individual Institutes solicit and support mission-relevant research, creates research silos that have made it difficult to find a "home" for research that crosses diseases, disorders, and conditions. In addition, the current grant structure is such that there are few mechanisms in place to fund research that spans the translational continuum within a single project or even over a series of projects initiated by one investigator or a team.

In the biomedical sciences, both NIH and industry funding is available to support T1 translational research, whereas industry support is not as available for T1 TDTB research. Currently, there are few avenues for Investigator-initiated NIH funding of early-phase, high-risk/high-reward and developmental TDTB research. While the R21 mechanism is intended to fund exploratory/developmental grants, it provides only short term support (limited to 2 years) and has funding limits ($275,000 direct costs over a 2-year period) that preclude the use of this mechanism for long term behavioral intervention programs that extend beyond the earliest T0–T1 phases.

An important potential barrier for funding Investigator-initiated TDTB research exists at the level of the NIH review structure, where study sections and review panels often fail to adequately represent TDTB

interests or understand TDTB approaches. For example, review groups are often not familiar with, nor structured specifically to review, early-phase behavioral intervention development research outside of the R21 context.

NIH role in supporting TDTB research

Few NIH funding mechanisms are explicitly designed to support Investigator-initiated TDTB research. One mechanism being increasingly used to support early, developmental phases of TDTB research is NIH's Exploratory/Developmental Phased Innovation grant mechanism (R21/R33). This hybrid mechanism provides support for up to 2 years (R21 phase) for research planning activities and feasibility studies, followed by possible transition of up to 4 years of expanded research support (R33 phase). The application delineates specific and tangible milestones that must be met during the R21 phase in order for the R33 portion to be awarded; therefore not all R21 recipients will necessarily move on to the R33 phase. A parent announcement for this mechanism does not exist; instead, individual ICs issue a Funding Opportunity Announcement (FOA) in a specific field of inquiry when appropriate. (Two recent examples from the National Institute on Drug Abuse, NIDA, and the National Cancer Institute, NCI, can be found at http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-13-001.html and http://grants.nih.gov/grants/guide/pa-files/PAR-14-321.html).

Another approach for stimulating research interaction and collaborations at early TDTB stages has been the P20 Exploratory Grant. NIDA has used this funding mechanism to encourage animal to human translation (research) with *Exploratory Centers for Translation on the Clinical Neurobiology of Drug Addiction* (http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-09-012.html).

Several efforts to stimulate TDTB research in the area of prevention through targeted FOAs have been successful. Prior examples include the NIDA prevention FOAs on: "*Using Basic Science to Develop New Directions in Drug Abuse Prevention Research*" (http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-02-010.html) and "*Brain Imaging Drug Use Prevention Messages*" (http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-07-007.html). Recently NIDA issued an FOA on "*Drug Abuse Prevention Intervention Research*" to encourage research on cognitive, behavioral, and social processes as they relate to the development of novel prevention approaches; efficacy and effectiveness of prevention interventions or programs; processes that optimize the selection, integration, implementation, and sustainability of science-based prevention (including systems-level and health economic factors); and methodologies appropriate for studying complex aspects of prevention science (http://grants.nih.gov/grants/guide/pa-files/PA-15-082.html).

In 2011, the NIH spent over $350 million to fund 55 research centers with Clinical and Translational Science Awards (CTSA). Research supported by these centers addresses the need for research to determine what works, for whom, under which circumstances, and why interventions work or do not work. However, the CTSA program has not typically supported behavioral research at the T0–T1 phase. This may change with a recent focus on supporting stage T1–T4 research efforts from a recent U01 program issued by NIH's National Center for Advancing Translational Sciences (NCATS). This FOA invites applications for collaborative investigations between three or more CTSA sites into improvements of the methods of translational research at any step along the spectrum from T1 to T4. Projects will be supported to develop new technologies, methods or approaches to address roadblocks in science or in operations that limit the efficiency and effectiveness of translation. Also of interest are innovative approaches to training or community/patient engagement that focus on improving translation (http://grants2.nih.gov/grants/guide/pa-files/PAR-15-172.html).

Programs of support from the NIH Office of the Director, such as the Common Fund (https://commonfund.nih.gov/about), Neuroscience Blueprint (http://neuroscienceblueprint.nih.gov/) and OppNet (see url above) encourage and support research that spans the interests of many different Institutes. NIH also supports research to develop tools, technologies and methods that can be applied across many of the institutes' missions–e.g., PROMIS http://www.nihpromis.org, the NIH Toolbox http://www.nihtoolbox.org and the NCI's Grid-Enabled Measures Database, (GEM), https://www.gem-measures.org/Public/Home.aspx. Some of these programs support research in common processes and mechanisms that may underlie multiple disease processes and health problems (e.g., SOBC, https://commonfund.nih.gov/behaviorchange/index).

Large-scale transdisciplinary center-based initiatives have also been developed by individual Institutes to support TDTB research. For example, the NCI has developed several Centers programs in which transdisciplinary teams of basic and clinically oriented behavioral and biological scientists work to develop and test interventions for cancer-related risk factors such as smoking and obesity. The *Transdisciplinary Tobacco Use Research Centers* program (TTURC; see http://cancercontrol.cancer.gov/brp/tcrb/tturc/about.html) was a ten-year initiative funded by NCI in partnership with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and NIDA, which had as its goal the facilitation of a transdisciplinary approach to the full spectrum of basic and applied research on tobacco use to reduce the disease burden of tobacco use. Among the goals of the TTURC program was increasing the number of investigators participating in transdisciplinary teams; post hoc analyses of this program found increases in productivity, collaboration [27], scientific impact, and dissemination reach [28] across the transdisciplinary center grants as compared to matched investigator-initiated grants [6].

More recently, NCI's *Transdisciplinary Research on Energetics and Cancer* (*TREC*) program (https://www.trecscience.org/trec/default.aspx) aims to integrate diverse disciplines to find effective interventions across the lifespan to reduce the burden of obesity and cancer and to improve population health by building teams that can create sustainable solutions to address complex problems. TREC has been shown to have importance attitudinal, collaborative, scientific, institutional, and career impacts and to foster strategies that have facilitated its transdisciplinary and translational aims [29].

The National Heart, Lung, and Blood Institute (NHLBI) has developed several programs of TDTB research focused on the early-phase development of interventions. The first such program was the "*Translational Behavioral Science Research Consortia*" (*TBSRC*), http://grants.nih.gov/grants/guide/notice-files/NOT-HL-02-005.html, initiated in 2002, which funded two programs of research to translate basic behavioral science theory and findings into interventions for heart, lung, and blood diseases and disorders. A subsequent NHLBI-initiated TDTB-focused program on "*Translating Basic Behavioral and Social Science Discoveries into Interventions to Reduce Obesity*: *Centers for Behavioral Intervention Development*" (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-013.html) was launched in 2009 in partnership with NCI, NIDDK, the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD,) and OBSSR. The objective was to translate findings from basic research on human behavior to develop more effective interventions for reducing obesity and improving obesity-related health behaviors. The resulting program–"The ORBIT Consortium" (www.nihorbit.org)–consists of seven research centers and a Resource and Coordination Unit to facilitate cross-study activities. Each research center supports interdisciplinary project teams of basic and applied biological, clinical, behavioral and social scientists who are developing novel obesity-related interventions through formative and experimental research, early phase trials and pilot studies.

The orbit initiative served as a model for another trans-NIH program. The ORBIT initiative which was developed by NIH's Office of Behavioral and Social Sciences Research (OBSSR). This FOA, entitled "*Translating Basic Behavioral and Social Science Research Discoveries into Interventions to Improve Health-Related Behaviors*" resulted in 17 funded grants focusing on translation of basic behavioral science findings into preventive and therapeutic interventions for diseases and disorders from hypertension, cardiovascular disease and cancer to obesity and diabetes (http://grants.nih.gov/grants/guide/pa-files/PA-11-063.html).

The NIAAA and NIDA are attempting to facilitate translational efforts that will lead to implementable prevention programming by supporting R34 ("Pilot and Feasibility Studies in Preparation for Drug and Alcohol Abuse Prevention Trials") grants to pilot and/or feasibility test novel prevention interventions based on, and informed by, translation of basic science findings. (http://grants.nih.gov/grants/guide/pa-files/PA-15-177.html). The National Institute of Mental Health (NIMH) has similarly promoted TDTB-oriented Program Announcements such as "Pilot Intervention and Services Research Grants" (http://grants2.nih.gov/grants/guide/pa-files/PAR-12-279.html), which encourage research on the development and/or pilot testing of new or adapted interventions and adaptation and/or pilot testing of interventions with demonstrated efficacy for use in broader scale effectiveness trials.

NIH has supported TDTB research across the lifespan, from translational projects in children and families and in older adults. An example of the former is the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD) "Work, Family & Health Network," which supports research across the translational spectrum–from pilot studies through full-scale randomized trials and implementation studies in workplace settings–focused on workplace structures, systems and policies that lead to better individual and family well-being and health (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-04-017.html and http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-07-101.html). (For an example, see http://projects.iq.harvard.edu/wfhn/home). Exemplar TDTB projects in older adults include the "Roybal Centers for Translational Research on Aging" (http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-14-004.html). The Roybal Centers' objectives are to develop and test new and innovative ideas for early stage and late stage translation of basic behavioral and social research findings about established or hypothesized mechanisms of action, at the individual or population level, into programs and practices that will improve the lives of older people and the capacity of institutions to adapt to societal aging. This program has been highly successful and 13 Roybal Centers are currently supported by the National Institute on Aging (NIA).

NIH has been particularly successful in stimulating research in the later-phases of TDTB research (i.e., Phases T2–T5). Late-stage translational behavioral research has been highly visible and widely promoted through a series of FOAs in D&I science that include dedicated review groups (see e.g., http://grants.nih.gov/grants/guide/PA-files/PAR-13-055.html); a funding mechanism that is specifically geared toward D&I research (R18); a standing study section in D&I Research in Health (http://public.csr.nih.gov/StudySections/IntegratedReviewGroups/HDMIRG/DIRH/Pages/default.aspx); special, NIH-supported training opportunities (e.g., the yearly "Training Institute in Dissemination & Implementation Science"–http://public.csr.nih.gov/StudySections/

IntegratedReviewGroups/HDMIRG/DIRH/Pages/default.aspx); conferences on D&I Science (http://www.academyhealth.org/Events/events.cfm?ItemNumber=13518&navItemNumber=13668); and journals dedicated to D&I research (e.g., *Implementation Science*, *Translational Behavioral Medicine*).

NIH activities have also emphasized the importance of these later stages of translation, including T4 and T5. Examples of this focus include NHLBI's new "*Center for Translation Research and Implementation Science" (CTRIS),* which supports programs of research to understand the multi-level processes and factors that are associated with successful integration of evidence-based interventions within specific clinical and public health settings such as worksites, communities, and schools. CTRIS is particularly interested in the T4 phase of research, as well as health inequities research, both nationally and globally–thus, it includes an emphasis on T5, or global D&I research, as well (see http://www.nhlbi.nih.gov/about/org/ctris).

The recent NIH emphasis on supporting later-phase translational research–through both investigator-initiated and Institute-initiated programs (FOAs)–demonstrates the important role NIH can play in advancing TDTB research, resulting in improvements in the dissemination, implementation and adoption of proven preventive and therapeutic interventions, both behavioral and biomedical. Facilitating a similar set of T0–T1 research will likely require of dedicated funding and review activities as those devoted to later phase TDTB research.

Next Steps for improving review and funding of TDTB research at NIH

- Conduct a portfolio analyses to identify the proportion of research supported by NIH in various phases of the TDTB process to identify gaps and suggest strategies for correcting deficits (such an analysis, for example, has been conducted for the area of cancer genetics [30]).
- Solicit and support earlier phase TDTB research, with FOAs and specialized grant review panels.
- Integrate support across translational phases at the individual project level.
- Develop new grant mechanisms that allow for the development of interventions using existing intervention development models (ORBIT, Stage, SOBC Models).
- Forge partnerships between Federal agencies–NIH, NSF, USDA, CDC, or AHRQ–as well as with industry, to leverage funding and create new streams of financial support for TDTB research.
- Orient reviewers in TDTB research concepts, models and methods and create a standing review group specifically for T0/T1 TDTB research.
- Design mechanisms for continuing to foster collaborations between basic behavioral and social scientists and clinical researchers to solve problems related to clinical care.

Promoting an organizational and scientific culture conducive to TDTB research

Challenges in developing a supportive culture for TDTB research

Much has been written about the barriers to transdisciplinary research and collaborations within the academic environment [29, 31, 32]. Key barriers include lack of a tradition of treatment development in the behavioral sciences (e.g., the high-risk nature of early-phase translational research in particular, coupled with low funding paylines, that mean investigators on soft money are less likely to pursue high-risk topics); housing of different disciplines at academic institutions in ways that hinder ease of crossing disciplinary boundaries; and incentives for academic advancement that favor the single, independent investigator over teams.

Along with organizational and structural challenges associated with conducting TDTB research, TDTB researchers are also faced with challenges produced by different disciplinary-specific values, terminology, research methods, paradigms, and approaches [29]. For example, relatively few experts have knowledge of and can speak about topics outside their own discipline; e.g., behavioral interventionists frequently do not understand the language of genetics or pharmacology, and basic science experts are often not familiar with, nor do they speak about issues relevant to patient care, community engagement, or other later-phase translational science phases. These issues are especially acute for those working in TDTB research which, unlike translational research in the biomedical arena, is less oriented to the "clinician-scientist" model as a basis for early-phase translational efforts.

Finally, a challenge for all phases of TDTB research is the limited number of publication venues available for publishing cross-disciplinary and translational behavioral research. While progress has been made and more journals are available for publishing TDTB research than in the past, many scientific journals remain discipline specific and researchers are incentivized to publish in high-impact journals focused on uni-disciplinary research areas in their disciplines rather than those that support TDTB findings. In an effort to accelerate the speed of research synthesis across disciplines, publications based on interdisciplinary research often are limited to newer low-impact, open access journals.

NIH role in promoting TDTB-supportive culture

Several early NIH efforts were instrumental in promoting a "culture" in which TDTB research is valued, collaborations across basic-clinical research arenas are encouraged, and the capacity for TDTB research in the extramural behavioral science community is stimulated. For example, beginning in the 1990s, NIDA instituted a set of initiatives to describe and address barriers to early stage (T1) translation, resulting in development of the Stage Model (described above)

and several key FOAs to promote T1 behavioral science related to drug abuse and mental health issues as part of its "*Behavioral Therapies Development Program.*" NIDA also hosted a series of workshops devoted to bridging basic behavioral and clinical science. In these early meetings researchers specializing in basic behavioral research in the neurosciences, emotion, cognition, social processes, and other areas were paired with clinical researchers with the goal of highlighting opportunities for translation of basic behavioral science findings into novel mental health and substance abuse interventions. NIDA's efforts were critical in stimulating researchers to work in cross-disciplinary teams transcend traditional basic/clinical research silos, and thus build capacity among researchers for conducting TDTB research.

Similarly, the NCI, NHLB,I and other large-scale Centers programs described earlier (e.g., TTURCs, TREC, TBSRC and ORBIT) have, by supporting TDTB efforts, served to promote a culture within the behavioral science community in which both transdisciplinary and translational approaches to research are disseminated and the value of these approaches are highlighted. This "culture change" has occurred through implementation of the funded research programs themselves, as well as through workshops and scientific meetings, often associated with these programs that provide important vehicles for communicating TDTB concepts, models, methods, research exemplars and "lessons learned." Additional NIDA supported efforts to promote TDTB acceptance and support, specifically in the area of prevention research, have included meetings such as the 2000 Annual Meeting of the College of Problems on Drug Dependence (CPDD) session on "*Bridging Biological, Behavioral Science and Drug Abuse Prevention: Intervention and Insult Along a Developmental Continuum*", a 2001 Society for Prevention Research Satellite Meeting on "*Bridging Neurobiological, Behavioral and Prevention Science*", a 2005 CPDD Conference Satellite entitled "*Translating Research from Neural, Behavioral and Social Sciences to Prevention: Challenges and Opportunities*", 2013 American Psychological Association symposium on "*Using Neuroscience to Inform Prevention in Drug Abuse.*"

OBSSR has also supported TDTB workshops to highlight scientific gaps and to suggest future directions for NIH investments. For example, a workshop in 2011 was convened to address issues in *Harmonization Strategies for Behavioral, Social Science, and Genetic Research* to foster translation between different scientific approaches and disciplines. Also at the level of trans-institute collaborations, in 2006 an NIH-wide coordinating committee led by the National Human Genome Research Institute (NHGRI) and the National Institute of Environmental Health Sciences (NIEHS) created a "Genes, Environment and Health Initiative" (http://www.genome.gov/19518663) to support research leading to the understanding of genetic contributions and gene-by-environment interactions in common diseases. The focus of one GEI program–the "*Exposure Biology Program*" (http://www.niehs.nih.gov/research/supported/dert/programs/exposure/)–was to determine how environmental exposures including drug use, diet, and physical activity contribute to human disease by supporting TDTB teams to develop new technology to measure psychosocial stress responses.

Additionally, in 1999, NIH launched "*Bench to Bedside*" research programs to encourage intramural collaborations between basic and clinical researchers. This program challenges investigators to consider cross-institute projects that have potential to speed laboratory discoveries into new treatments (http://obssr.od.nih.gov/scientific_areas/translation/index.aspx). Between 2006 and 2013, four percent of these investments supported behavioral and social sciences research with the OBSSR providing over one million dollars to this program.

In an attempt to encourage institutional infrastructures and a culture that is supportive of TDTB research, NIH has supported several trans-NIH Roadmap and Common Fund investments. One example is the NIH "*Roadmap Program on Interdisciplinary Research Consortia*" (http://www.nih.gov/news/pr/sep2007/od-06.htm). Launched in 2007, the purpose of this program was to dissolve academic departmental boundaries and support the integration of different disciplines to address health challenges that have been resistant to traditional research approaches. In these consortia, teams of scientists from basic to clinical experts, across levels of analyses from basic genetic, molecular and cellular approaches through animal behavior and neurobiology, to human laboratory based investigation and treatment intervention development collaborated on research focused upon a single scientific question (for an example, see the Yale School of Medicine "*Stress, Self-Control and Addiction Consortium*", http://medicine.yale.edu/stress/projects.aspx). These consortia supported training and career development to provide experience in the process of conducting team science, and in developing and implementing educational programs that cross-train students and junior faculty in multiple disciplines.

Other examples of trans-institute programs at NIH focusing on early-phase TDTB research include the Science of Behavior Change (SOBC) Common Fund program, which seeks to implement a mechanisms-focused approach to behavior change research and to develop the tools required to implement such an approach at eight research sites and a Resource and Coordinating Center. (see http://commonfund.nih.gov/behaivorchange/index) Several OppNet efforts and activities, such as the R13 Conference grant program (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-10-017.html), contain translational components as well. Through this program an R13 was awarded to Dr. Diana Fishbein (Principal Investigator) for meetings on "*Advancing Transdisciplinary Translation for Prevention of High-Risk Behaviors*", resulting in the current special issue on *The Full Translational Spectrum of Prevention Science.*

Next Steps for promoting a TDTB-supportive research culture

- Raise awareness about TDTB research in the behavioral science community by:
  - Disseminating information about T1 TDTB to familiarize the scientific community with the best concepts, models, and methods to be used–e.g., through case study webinars, workshops, seminar and speaker series, pre-conference symposia.
  - Publishing white papers and viewpoint articles focusing on TDTB research, including T0–T1 behavioral science frameworks, methods, and findings.
  - Creating additional translation journals as venues for TDTB research, especially for early phase TDTB research.
- Develop and disseminate tools to help researchers collaborate more effectively:
  - Disseminate the "Team Science Toolkit", an interactive website developed by NCI that provides resources to help individuals manage, support, and conduct team-based research, https://www.teamsciencetoolkit.cancer.gov/Public/Home.aspx.
  - Emphasize pushing early TDTB research efforts toward later phases of development (efficacy and effectiveness trials), ultimately to benefit patients by developing clinically directed and meaningful preventive and treatment approaches.
  - Develop strategies to recognize collaborative roles and contributions; e.g., (a) investigators serving as brokers to facilitate the inclusion and integration of diverse stakeholder and disciplinary perspectives or (b) development of collaborative products such as shared datasets, pre-authorship documentation.

TDTB methods and training

Challenges in TDTB methods and training

Unlike the biomedical sciences, most behavioral and social science academic and career research programs do not employ a "clinician-scientist" training model. As a result, behavioral science training programs often do not include didactic instruction at the intersection of basic and clinical research, and curricula do not include many of the methodologies most useful for TDTB research–from intervention development to D&I research methods. Therefore, a major barrier to TDTB research is lack of knowledge and acceptance in the behavioral science research community of appropriate methods useful in both early-phase intervention development (e.g., "small-N" and non-randomized trials, adaptive designs) and later-phase translational research (e.g., cluster-randomized trials, quasi-experimental research), illustrating a need to incorporate training in these methodologies at all levels from graduate level through continuing education (e.g., with use of the NIH R25 mechanism,http://grants.nih.gov/grants/funding/funding_program.htm%23). Resource, which funds short courses and programs, such as Summer Institutes, in areas of special need).

A major methodological challenge faced by T1 TDTB researchers specifically is lack of training in approaches for early-phase development of behavioral interventions. This is especially notable in the area of animal to human translation, and in 2014, in response to this need, OppNet created a Career Development Program to provide research experience at the intersection of animal models and human investigation, to begin building a cadre of TDTB experts at the T0 level ("Short-term Mentored Career Enhancement Awards in the Basic Behavioral and Social Sciences: Cross-training at the Intersection of Animal Models and Human Investigation", http://grants1.nih.gov/grants/guide/rfa-files/RFA-DA-14-002.html). This program can provide a model for other training mechanisms, especially those focusing on T1 behavioral research involving research on human subjects, for which few structured training programs currently exist.

The complexity of behavioral constructs (e.g., impulsivity, motivation, and cognition), the multi-level nature of many behaviorally based interventions that span individual, social, and environmental levels of analyses, and the need to account for the dynamic nature of behavior over time, requires development of new methods that incorporate this complexity into the design and testing of behavioral interventions. Advances have been made in this regard in terms of the development and utilization of techniques such as adaptive intervention designs [33], fractional factorial designs [34] and other methods based on engineering models [35]. Additionally, agent-based and other modeling methods can be used to identify intervention targets and time-points for successful intervention. These techniques are becoming better known but many in the behavioral research community are still unaware of the appropriate use of many newer designs for intervention development and testing. A recent NIH-sponsored Workshop, "Innovative Methods in Developing, Testing and Implementing Behavioral Interventions to Improve Health," held in Bethesda in April of 2014, highlighted many of these new study designs and methods (see www.nihorbit.org for agenda and slide sets from this workshop). However, there still remains a need for wider dissemination of existing methods used in TDTB research, as well as a need for development of new methods to measure and increase our understanding of timing, dosage and intensity of behavioral interventional components and exposures needed for maximum effect.

Next steps for enhancing TDTB methods development and training

- Fund training and research in new methods, study designs and analytic techniques for use in TDTB research by:
  - Creating methods workshops and short courses, including R25 resource grants/Summer Institute and mini-training sessions; and use K18s or other later-career sabbaticals and mentoring programs aimed at developing capacity for TDTB research.
  - Using one or more of these mechanisms to promote learning of new methods and study designs for research at all phases of TDTB research, from intervention development through dissemination and implementation studies–some of which might be focused especially at the new investigator level.
  - Developing methods allowing for "deeper" behavioral phenotyping to enable more precise prediction and better environmental measurement/characterization of influences.
  - Encouraging training and familiarization with methods appropriate to early phase intervention development, (e.g., "small-N" studies, micro-trials [36], non-randomized designs); as well as with later-phase methods for T2–T5 TDTB (e.g., cluster-randomized trials). This includes training in adaptive intervention designs [33] and personalized interventions that tailor approaches to specific individual characteristics (e.g., genotype, attributions, gender, motives, temperament/personality factors, psychiatric comorbidity, etc., or clusters of risk factors) and contextual characteristics (e.g., precipitating event, environmental context).
  - Sponsoring working groups to explore best practices in methods useful for TDTB research–e.g., "small-N" or "N-of-1" studies, signal detection methods, systems science and modeling, qualitative designs, pilot studies, cluster-randomized and quasi-experimental designs useful for both early and later-phase TDTB research.
  - Integrating TDTB research into studies that are part of existing large-scale translational initiatives, such as the NIH Health Care System Research Collaboratory (https://www.nihcollaboratory.org/about-us/Pages/default.aspx).
  - Developing comprehensive approaches to allow comparisons across studies that use overlapping constructs.
  - Developing well-validated measures and items that facilitate creation of integrative multidimensional models.

CONCLUSION

The NIH has been at the forefront of promoting translational research in the biomedical arena, and is now poised to lead in developing and implementing translational research programs in the behavioral and social sciences. Similarly, transdisciplinary research, exemplified by "team science" approaches, is being increasingly appreciated and applied across both the biomedical and behavioral research spheres. In this paper, we've highlighted both the challenges inherent in TDTB research as well as examples of NIH-supported programs that are attempting to address these challenges and advance this important area. In particular, we recommend the use of frameworks capable of guiding TDTB research at all phases of the translational spectrum; encourage the creation of structures and systems that support TDTB research at the NIH and within academic institutions; and suggest the need for development of training programs and methods for early-through-late stage TDTB research.

Compliance with ethical standards: This paper does not involve the use of human subjects or animals. As such, no informed consent was necessary.

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