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Review Article

Advancing Transdisciplinary Research: The Transdisciplinary Research on Energetics and Cancer Initiative

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Abstract

Strategies for constructing and maintaining cross-disciplinary teams are in their infancy. We outline strategies to support one form, transdisciplinary research, in a major initiative of the National Cancer Institute, the Transdisciplinary Research in Energetics and Cancer 2 (TREC2) initiative. Discussion of the TREC2 sites' experiences with transdisciplinarity is structured around a conceptual model that identifies four iterative phases of transdisciplinary research. An active coordination center, regular face-to-face meetings, and input from external advisors were instrumental in moving TREC2 to the translation phase. The possibilities for advancements in the science of energetics and cancer increased as investigator ties became denser. TREC2 can be seen as a flagship effort in transdisciplinary science that provides lessons on moving ideas from development to translation.

INTRODUCTION

In recent years, efforts have been made to understand and address complex problems, such as the relationship between obesity and cancer and health disparities, by recognizing that the determinants of these problems occur at multiple levels of influence that can best be addressed in a holistic manner through cross-disciplinary approaches to research and intervention [1,2]. Yet, executing successful multilevel research depends

on the ability to visualize the multiple influences on complex phenomena. This cannot be done by a single investigator or by a single discipline. In arguing for cross-disciplinary collaboration, the Committee on Facilitating Interdisciplinary Research of the National Academies noted in 2005 that "how human societies evolve, make decisions, interact, and solve problems are all matters that call for diverse insights. Very fundamental questions are inherently complex [3]".

Cross-disciplinary collaboration has the additional challenge of accommodating new disciplines and sub-disciplines as they emerge. While there were only seven disciplines when universities were founded in the 13th century [4], there now are literally thousands, reflecting the increasing quantity and specialization of knowledge and technology. Although the specialized knowledge produced by such primary units of academic communities is critically needed to address human problems, fully capturing the complexity of these human problems requires the ability to integrate discipline-specific perspectives, theories, models, and methodologies to produce a holistic approach.

Despite increasing agreement that cross-disciplinary team-based research is valuable; methods for constructing and maintaining effective cross-disciplinary teams are in their infancy [1]. In this article, we discuss the strategies used to support one form of cross-disciplinary research (i.e., transdisciplinary research) in a major research initiative of the National Cancer Institute (NCI), the Transdisciplinary Research in Energetics and Cancer 2 (TREC2) initiative. We structure our discussion of the TREC2 sites' experiences with transdisciplinarity around a conceptual model that identifies four iterative phases of transdisciplinary research. Lastly, we use the lessons learned from these experiences to make recommendations for supporting transdisciplinary research.

A model of transdisciplinary research

Transdisciplinarity (which Rosen field defines as "research in which exchanging information, altering discipline-specific approaches, sharing resources, and integrating disciplines achieves a common scientific goal" [5]) achieves the highest degree of collaboration of any collaborative mode [6]. It relies on early agreement on research questions, methods, goals, and timelines and it may entail the development of multifaceted, broadly analytical models for investigating problems. Hall et al. [7] developed a model that identified four iterative phases of transdisciplinary team research: development, conceptualization, implementation, and translation. The model is conceptual, based on literature review, expert judgment, and input from scientists.

The primary goal of the development phase is to define the scientific or societal problem space of interest, including identifying the breadth of concepts that fall within that space and its boundaries. In this phase, critical team processes foster information sharing and integrative knowledge creation among diverse participants. The primary goals of the conceptualization phase are to develop novel research questions, hypotheses, and a research design that integrates diverse collaborators' perspectives and knowledge domains to address identified problems in innovative ways. Investigators work together to locate knowledge gaps within that space and potential novel approaches to address those gaps.

The primary goals of the implementation phase are to launch, conduct, and refine the planned transdisciplinary research. As group members become more formally involved in a project, routines are developed, such as scheduled meetings with planned agendas. Key team processes during this phase include identifying those with expertise relevant to a research project or core, assigning tasks and determining procedures, and selecting

communication methods. Conflict management and consensus building are essential to support communication to which all team members are able to contribute effectively. Another critical process is team learning, which has been defined as "a team-level property that captures the collective knowledge pool, potential synergies among team members, and unique contributions [8]". Important foci of team learning include the creation of shared terminology and an agreed upon ethic for team interactions.

Finally, the translation phase involves applying research findings to advance progress along the discovery-development-delivery continuum. Key team processes during this phase include the development of shared goals for the translation and a shared understanding of how these goals will be pursued. Dramatic differences in the perspectives of original team members and translational collaborators may result in more profound challenges than in prior phases. Although this model initially was developed to describe the processes of a single transdisciplinary research team, it also applies to multisite initiatives like TREC, which can serve as incubators by creating larger networks of investigators and providing them with space to produce novel research ideas.

The developmental phase of the TREC initiative occurred when NCI wrote the Request for Applications (RFA) (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-10-006.html>). This defined the scientific problem space for TREC as the intersection of cancer risk factors and energetics. In this sense, energetics refers to the total energy relations and transformations involved in cancer. The conceptualization phase began as grantees prepared their applications and continued after funding was awarded, when grantees refined their research studies.

A novel aspect of the TREC2 Initiative was the requirement for numerous cross-institutional activities. For example, grantees engaged in cross-center communication via semi-weekly teleconference meetings of the TREC2 Steering Committee (i.e., all site directors and co-directors) and larger, all-grantee meetings, at which topics for cross-center working groups were identified that appealed to all TREC sites, such as measuring physical activity or translating animal model discoveries into human studies. Cross-institutional initiatives enable additional research that takes advantage of high-budget infrastructure, such as high speed gene sequences, available on only a few campuses (conceptualization and implementation phases). In addition, multisite initiatives provide resources, including funding of cross-site transdisciplinary research with earmarked funds and language in funding announcements that helps grantees structure transdisciplinary pilot studies (implementation). Finally, multisite initiatives support translation of findings across centers though the fertilization of ideas across sites (translation). These activities laid the groundwork for the conceptualization of new scientific ideas.

The transdisciplinary research in energetics and cancer initiative

In the late 1990's, the NCI was reorganized to form the Division of Cancer Control and Population Sciences (DCCPS) [9], with an aim of speeding scientific discoveries across the cancer prevention continuum to implementation. A major focus of

DCCPS was to establish new transdisciplinary research initiatives in critical areas that impact cancer prevention, such as tobacco control, health disparities, obesity, and poor communication between providers and community members. Since then, NCI has launched four transdisciplinary initiatives that target these key problem areas: Transdisciplinary Tobacco Use Research Centers (TTURC) (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-012.html>); the Centers for Population Health and Health Disparities (CPHHD) (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-001.html>); Centers of Excellence in Cancer Communication Research (CECCRS) (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-004.html>); and, TREC. NIH and other funding partners offered support and collaboration [10].

The dramatic rise in obesity and its impact upon the disease development and mortality in the US population spurred the NIH to establish a Strategic Plan for Obesity Research in 2004 [10]. The NIH Obesity Task Force, of which NCI is a partner, has worked to promote a critically needed research agenda (<http://www.obesityresearch.nih.gov/about/>). The TREC initiative, along with expanded funding opportunities in energy balance research, was developed to target the public health concern represented by obesity and cancer.

The TREC2 initiative is a consortium of four research sites and a central coordination center (Figure 1) that together address the health consequences of poor energy balance and obesity, recognizing that this complex issue requires a transdisciplinary approach spanning molecular and biological research to human studies and health policy [11]. The initial primary mission of TREC2 was to foster collaboration among transdisciplinary teams of investigators to accelerate progress toward reducing cancer incidence, morbidity, and mortality related to energy balance and obesity. Its secondary mission was to provide training opportunities for early career and late career scientists to carry out integrative research on energetics and cancer risk [9].

In 2009 the NCI issued a revised RFA for the TREC2 initiative (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-001.html>), which increased the focus on conducting research among cancer survivors. Four sites were funded for the first time in the second cycle (2011 through 2016), and are located at Harvard University, the University of California San Diego, the University of Pennsylvania, and Washington University in St. Louis. The Coordination Center at the Fred Hutchinson Cancer Research Center was funded for a second cycle. In aggregate, the sites are conducting 15 interrelated projects (three animal studies, three cohort studies, four randomized controlled trials in humans, one cross-sectional study, and two modeling studies) [11]. In addition, they conduct multiple studies each year on topics developed since the original grant proposal, including those that are ancillary to the original studies or pilot studies to support new research directions. In 2012, the centers conducted ten within-center and two cross-center projects of this nature.

The development phase of TREC

The developmental phases of the four TREC sites were devoted to identifying potential investigators. At Harvard, Dr. Frank Hu and Dr. Jorge Chavarro identified a diverse group of faculty members from a variety of disciplines from seven Harvard-affiliated institutions with interests related to obesity research, energetics, and cancer. Over a course of meetings, a working group derived from the initial group coordinated and organized potential projects and cores that would constitute the proposed Harvard TREC Center.

The Director of the University of Pennsylvania TREC Survivor Center (Dr. Kathryn Schmitz) was part of the first round of TREC. During TREC2, she convened a core group of investigators from a number of disciplines pertinent to issues related to obesity and cancer to craft a submission, with an emphasis on survivorship.

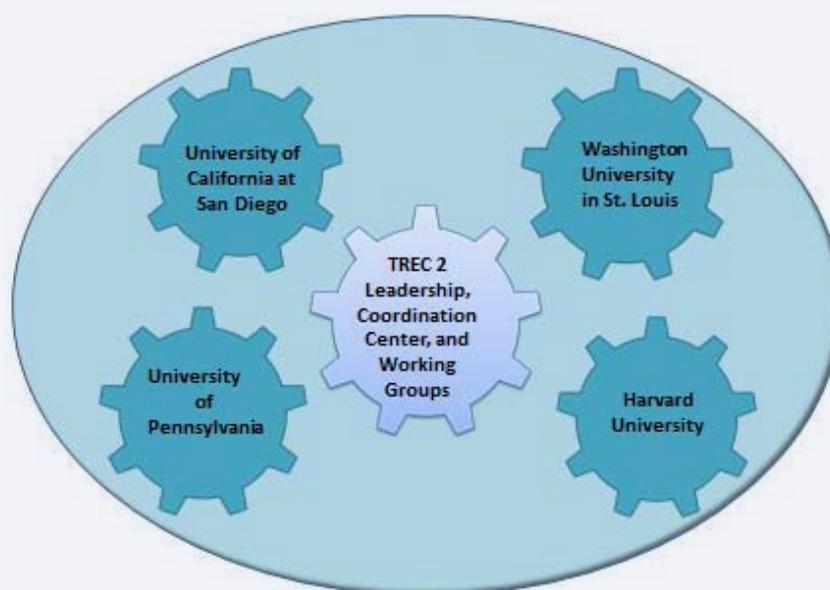


Figure 1 TREC2 Initiative.

Investigators from several departments were convened initially to explore the possibility of common goals across projects related to a murine (i.e., mouse) model of breast cancer.

The development phase at the Washington University TREC, under the direction of Dr. Graham Colditz and Dr. Sarah Gehlert, involved convening 13 investigators from within the medical school and other parts of the university who had an interest in some area of energetics or obesity and cancer. A number of research projects were proposed by the group of investigators, and four were selected for inclusion, based on the likelihood that they had the potential to mutually inform one another. The consensus of the group was that projects should cover the life course and balance discovery with translation to clinical application. As an example, a new investigator with an interest in transgenerational epigenomics and a history of working with mouse models of obesity developed a TREC project that focused on discovery. Another project focused on worksite wellness policy in the state of Missouri, thus spanning the continuum.

The TREC proposal at the University of California, San Diego (UCSD) originated with Dr. Ruth Patterson. She noted the considerable talent and experience in the School of Medicine in the area of incident breast cancer and survivorship and proposed that these outcomes would be the keystone of a UCSD TREC2 proposal. Dr. Patterson held a half-day retreat to discuss the TREC2 RFA with faculty in the multidisciplinary Population Sciences Division of the Moores Cancer Center. This retreat generated numerous ideas, including collaborations with faculty at San Diego State University (SDSU) who focused on diversity research, several randomized controlled trials, and two basic research proposals. This retreat was followed by a day-long meeting with a smaller group of faculty who helped refine the original concepts. Key staff members were included in this meeting to enhance their ownership of the proposal submission. Dr. Patterson met individually with all interested faculty to assess their commitment to the project and their capacity to meet the challenging deadline. SDSU faculty withdrew because of time constraints, one of the basic science projects was dropped because of limited collaborative potential, and a physical activity researcher with an emphasis on technology and measurement was added. Finally, the remaining team agreed that the work's focus would address the concepts of insulin resistance and inflammation in relation to cancer risk. These early meetings laid the groundwork for developing the UCSD proposal during the site's developmental phase.

The conceptualization phase of TREC

The four sites began the process of integration of projects and cores during the conceptualization phase. Through negotiation, key investigators at the Harvard site were able to agree upon four complementary and interrelated research projects, each of which addresses overlapping and distinct pieces of the determinants of obesity and the links between obesity and cancer risk and survival. As a whole, they address genetic, behavioral, and structural factors that influence obesity and the biologic mediators between obesity and cancer at multiple stages of life. They also address how these determinants interact with each other, and, ultimately, whether these biologic mediators influence cancer survival. TREC investigators at the Harvard site were assisted by an internal

Scientific Advisory Committee (SAC) that worked closely with the Executive Committee to facilitate interactions and synergy across TREC projects and cores to ensure that transdisciplinary goals were met.

While TREC investigators at the Penn site were discussing the idea of a randomized controlled energy balance study in a murine model of breast cancer survivorship, they noted that cancer biologists and researchers from Penn's Institute on Diabetes, Obesity, and Metabolism (IDOM) had a history of working together in murine models. Thus, Penn's conceptualization phase followed from its development phase when an exercise physiologist was introduced to cancer biologists to provide needed methodologic expertise. As a result of conversations with IDOM representatives, the second project was developed to translate the first project's mouse model into a human study. Finally, the investigators agreed that a third project should focus on cost-effectiveness analysis, because it became clear over the initial few meetings that cost might be an important consideration in translation from animal research to human.

Washington University's conceptualization phase was devoted to honing its four projects' research questions and selecting cores to support the projects' science, dissemination, and implementation. Shortly after initial funding, an Internal Advisory Board (IAB) was established that included WU faculty from the biological, clinical, behavioral, and social sciences who would not participate directly in TREC projects or cores. At the same time, an Executive and Leadership Committee were established to advise the director and co-director on within-site policies and procedures. In an early meeting of the IAB (i.e., during the first six months of operation), TREC projects and cores briefly described their research questions and specific aims for feedback from IAB members.

The UCSD site set up weekly meetings with investigators to share information regarding the development of their projects and cores and to identify areas for collaboration and synergism. To reduce barriers to participation, meeting locations alternated between the cancer center and the main campus. Attendance at the meetings was meant to allow subgroups of investigators to meet and leadership to rotate among members. Overall, these meetings allowed for a transdisciplinary understanding that began with individuals responsible for the projects and reached those involved at all diverse levels of the proposal development and submission.

The implementation phase of TREC

During the implementation phase at the Harvard TREC site, integrating knowledge was facilitated internally by the use of integrating themes, such as the role of sleep in obesity and energy balance, or standardizing research approaches. An example of the latter is using similar analytic strategies developed by the Director of the Bioinformatics Core across projects to foster comparisons.

Sharing information, a second critical task of Harvard's implementation phase, was facilitated by planning and promoting interactions among trainees and senior investigators and among investigators from diverse disciplines in the way of seminars send establishing a protocol for conflict resolution as a standard

for solving inevitable disagreements about the evolving research approach. The challenges of working across different institutions and from different locations were minimized by the use of a project coordinator empowered by Dr. Schmitz and university administrators to make critical decisions within the site, who serves as a critical hub, minimizing investigator burden.

Approaches for achieving TREC's goal of developing new research questions, methods, and analyses by working across disciplines included strategic use of funding to support training activities and development projects, as well as providing a variety of venues for promoting scientific interactions. Developmental pilot projects provide opportunities for junior and senior investigators to critically review data and discuss emerging scientific ideas and methodologies. An annual retreat features a keynote talk by a scientific world leader who models cells to society research as well as updates from core projects and from colleagues who present new research broadly related to TREC goals.

The shared conceptual framework, or scheme, that incorporated all of the Penn TREC projects in the same model, was clear from the outset at Penn, because of the tight linkages between projects. Multiple collaborators convened to articulate, describe, and create the visual scheme representing this framework. The first of the three projects is largely independent of the others, given that the subjects are mice, yet there was a clear expectation that it would work closely with the human project. The second and third projects are inextricably linked, with monthly joint investigator meetings held quarterly in years 2 and 3 to clarify goals and logistics, develop shared mental models, and facilitate team learning. The process of mutual information sharing was streamlined in several ways. For example, the director of the small animal laboratory core for the IDOM regularly attended meetings for the first project and began to provide valuable feedback on murine experiments to the cancer biologists running this study.

A key external component of Penn's implementation phase was the formation of an Internal Advisory Board (IAB), selected from leaders of each of the University of Pennsylvania research institutes of which the center investigators are members (e.g., Leonard Davis Institute of Health Economics and the Abramson Cancer Center). The IAB provides outside perspectives on the TREC's functioning and reviews and evaluates the TREC's activities. It also provides perspectives that, while internal to the university, come from outside of the TREC site, and therefore can be more objective in a way that TREC investigators could not be.

At Washington University, the projects and cores were implemented during the first months after funding. At first, they operated separately, with some resistance to the aims related to transdisciplinarity. Investigators expressed concern that fulfilling the TREC site's (NIH) specific aims was difficult enough without additional expectations and requirements. This concern continued through the first annual meeting with the TREC's External Advisory Board (EAB), whose members come from outside Washington University. The EAB challenged the group to create a shared conceptual model, which was developed in the next months and vetted by the TREC's own Executive Leadership Committee. This was done by a method of

externalizing cognition [7] in which maps and diagrams were generated to portray how each project, and ultimately each discipline, fit into the Washington University TREC as a whole. This conceptual model was expanded during the second IAB meeting, six months after the first, during which project leaders were asked to discuss their progress. After these updates of progress, a panel of project leaders and investigators funded during the first round of within-TREC developmental funding used an unstructured and fast paced approach to iteratively and spontaneously generate a list of possible future collaborations that they would undertake in the future. This fast-paced panel discussion was fueled by the content of earlier presentations by project leaders. This unstructured process that was used to generate the list of potential collaborations generated a number of new ideas that extended beyond the original goals of the projects.

While the WU TREC remains in its implementation phase, project and core investigators increasingly have influenced the science of one another's projects, supported by cores. As an example, the Statistical Methods and Bioinformatics Core helped the animal model project to adapt statistical regression to analyze differences in cell proliferation between two groups of mouse pups, those whose mothers were fed high calorie diets and those who were not. Using statistical regression to compare small groups, such as with rodent models, was critical to being able to compare the animal experiment with human counterparts. This adapting statistical regress, previously used in human studies, proved critical to the cross-project science of the Washington University TREC site [12]. This project had initially planned to focus on female pups, but switched its focus to male pups, based on ideas generated in collaboration with the prostate clinical project. This has the potential to extend scientific knowledge on primarily female-related cancers like breast cancer to male-related cancers like prostate. The group of TREC investigators is in the process of soliciting and selecting new developmental projects based upon shared ideas that have been generated rather than choosing projects *de novo*.

Strategic steps such as planning meeting locations to foster the sharing of ideas and integration of knowledge helped to shape the UCSD TREC's implementation phase of research question refinement. Quarterly meetings are held, so that each project leader is aware of the other projects' progress to aid in their own efforts to implement the site's shared model.

In the first year of implementation, the UCSD TREC Center met monthly to discuss issues related to communication and expectations, managing budgets, enhancing collaborations, and managing the pilot studies and the training program. After the start-up period, it was determined that quarterly meetings, supplemented with regular e-mail and phone communications and ad hoc one-to-one meetings, were sufficient to keep the Center operating efficiently and smoothly. In addition, the UCSD TREC Center held a TREC Symposium in 2012 focused on reaching out to UCSD investigators interested in breast cancer with the goal of getting them involved in the Center (via pilot studies, ancillary studies, attendance at journal club, etc.). This Symposium had a keynote address by the Moores Cancer Center director focused on the rigors of transdisciplinary research and was attended the TREC2 program officer. This TREC project

has created momentum for transdisciplinary research focused on energetics and cancer at UCSD. In particular, in the first 2 years of implementing this TREC proposal, the Center obtained a Department of Defense grant, an R01, R21, diversity supplement, and two K-awards that are directly linked to the TREC2 initiative. Finally, Dr. Patterson's department, the Department of Family & Preventive Medicine funded an Energetics and Cancer Center of Excellence. The objective of that Center was to leverage TREC2 by involving department faculty and Family Medicine clinicians in groundbreaking research in the energetics and cancer area; generating new research questions, methods, and analyses; and providing mentorship and research opportunities to post-doctoral fellows and junior faculty in energetics and cancer. All UCSD TREC investigators are invited to these research-focused meetings.

The translation phase of TREC

The Harvard site established translation phase priorities that included disseminating information and translating findings with engaged community stakeholders for purposes of informing community action or public policy. There is a strong tradition of "T4" science and multi-lateral academic and community partnerships within the TREC which facilitates public engagement through webinars, workshops, and public forums. For example, the Harvard TREC Center co-organized a community forum on sleep and obesity, which was webcasted to a national audience. Similarly, TREC has helped to launch the Obesity Prevention Source website (<http://www.hsph.harvard.edu/obesity-prevention-source/>), which aims to inform and empower health professionals, journalists, and the general public with science-based information on reducing obesity in individuals and populations [13]. The reach of this website is in the process of being evaluated by the TREC Coordination Center.

The three large projects of the University of Pennsylvania TREC are now situated between the implementation and translation phases of the four-phase model of transdisciplinary research. In addition, the TREC has successfully fostered more transdisciplinarity by naming two co-directors for each core (one from obesity and one with a cancer focus). For example, transdisciplinary science was advanced by cultivating new clinical connections between the cancer survivorship clinical program and the weight and eating disorder clinical programs, which generated new research questions for the TREC site, as well as new and close collaborations between two senior scientists (from cancer and metabolism, respectively), and two junior investigators (one from cancer, one from exercise sciences). Also, the leaders of the Education, Training, and Dissemination Core have forged a transdisciplinary training approach, based on their distinct backgrounds in clinical psychology, cancer survivorship, and health behavior, for the 10 or so trainees who regularly attend the monthly sessions. These core leaders have also developed a new transdisciplinary course entitled, "Etiology and Treatment of Contemporary Chronic Diseases in America: Focus on Obesity and Cancer," to be offered through the School of Nursing. All of these new collaborations required establishing an environment of safety in which investigators could generate shared models that incorporated all of their work. In terms of translation, Penn is in the process of developing interventions

for African-American women who develop lymphedema after breast cancer surgery and beginning to work with clinics that treat numbers of these women to implement those interventions.

The four main projects of the UCSD TREC Center are focused between the implementation and translation phases. The mouse model project is investigating the mechanisms for how EPA reduces breast cancer risk, which has the potential to lead to new pharmacologic agents. The randomized trial investigating macronutrient composition of diets in weight loss has direct application for clinical advice regarding weight loss and reducing the risk of incident breast cancer. The survivorship project aims to empower breast cancer survivors by investigating whether weight loss has the same potential influence on cancer risk as metformin. Finally, the physical activity project will provide considerable information on types and quantities of physical activity with insulin resistance and also explore obesogenic environments, which has direct applications to policy and the build environment.

The new focus of TREC2 investigators that evolved directly from the UCSD Center is a planned P01 that would study the impact of prolonged nightly fasting regimens on breast cancer risk, which would have direct application to US dietary guidelines. Results of these projects will be shared with the scientific community via publications and access to data and samples, diffused through the site's trainees to other institutions, and communicated to the public via the UCSD public relations department and websites, thereby translating this new knowledge to practical use.

The Role of the TREC Coordination Center in Fostering Transdisciplinarity

Under the direction of Dr. Mark Thornquist, the Fred Hutchinson Cancer Research Center (FHCRC) has served as the TREC Coordination Center for both cycles of TREC funding, to foster transdisciplinary collaboration across TREC Centers and the NCI. Its operations began during TREC's first grant cycle, with primary foci that included establishing a unified research consortium through scientific input, developing operational procedures and a communications infrastructure, promoting consistent data methodology, developing an evaluation plan, and assisting in the training of new transdisciplinary investigators.

Based on its experience during the first round of TREC funding, the Coordination Center was able to reference the new RFA to prepare its own infrastructure while the four sites were going through their conceptualization phases. Each of five cores (i.e., Data and Bioinformatics, Leadership and Administrative, Self-integration and Evaluation, Training, and Developmental Projects) was designed to provide the expertise and resources needed to adequately respond to the evolving individual and collective needs of the four TREC sites.

The Coordination Center was able to respond to the needs of the four sites and the initiative as a whole while the sites were going through their conceptualization, implementation, and translation phases. They routinely solicited and incorporated feedback from investigators and NCI scientists about how to better support transdisciplinary research across sites. This occurred at multiple levels and through diverse channels (e.g., Steering Committee meetings and Working Group calls). After

the Steering Committee decided to target the development of RFAs to stimulate the growth of new scientific ideas from existing projects, the Development Projects Core responded by restructuring the RFA, with input from TREC investigators.

LESSONS LEARNED AND FUTURE DIRECTIONS

As has been noted elsewhere, transdisciplinary research is not intuitive [14]. Investigators with neither prior training nor experience in transdisciplinary research almost certainly will move more slowly through the four phases of transdisciplinary team research [13]. This was the case with TREC2, whose investigators entered the initiative with varying experience in transdisciplinary research. The principal investigator at one site and co-investigator at another had led previous NCI-funded transdisciplinary initiatives. This not only gave those sites some advantage during the first three phases of their own sites' developmental cycles, by making them aware of what to expect in terms of potential obstacles to, and methods for enhancing, collaboration between investigators, but also provided guidance to the TREC initiative as a whole. This experience and guidance served to increase trust among others with little or no experience and to speed the way toward more intensive collaboration. The transdisciplinary functioning of the multisite initiative likewise was facilitated by the experience and expertise that the Coordination Center brought through its experiences with the first cycle of TREC funding. This allowed communication pathways and developmental funding mechanisms to be put in place much earlier than otherwise would have been the case.

Each of the four sites articulates unique challenges to transdisciplinary science, but more importantly, ways in which they are able to foster the flow of new scientific ideas and translate those ideas into solutions. (See Figure 2 for an overview of the facilitators of moving from development to translation on transdisciplinary teams.) The Harvard University, University of Pennsylvania, and Washington University in St. Louis sites note

that forming advisory committees from outside TREC, internal advisory committees in the case of Harvard and Pennsylvania and external and internal advisory committees at Washington University in St. Louis, help prevent them from focusing inward and goad them toward bolder and more innovative collaborations. In the absence of this external encouragement (i.e., to take a bigger picture and consider how their work contributes to the shared agenda of the enterprise as a whole), investigators tend to regress toward mono-disciplinary functioning. Advisory committees serve this function well, especially those that originate outside the universities they are advising [14].

The ability to meet at face-to-face local and national scientific meetings, although it represents additional expense, has provided TREC2 with the incubator space needed to discuss and develop new ideas and projects across sites, thus extending TREC's ability to translation discovery into public health change. A session of the third year TREC2 scientific meeting was devoted to dissemination and implementation, for example. The leader from the Dissemination and Implementation Core from one site, who is a national expert on translation, provided background on dissemination and implementation research and addressed two case studies that have been advanced to her from the Steering Committee. In this way, resources are conserved and specialized expertise can be shared across sites.

The four-phase model for transdisciplinary team science originally was developed to describe the processes of a single transdisciplinary research project. Nonetheless it is clear from a review of the TREC2 initiative that it is relevant to multisite initiatives, which generally serve as incubators for conceptualization of novel research ideas by providing opportunities for cross-site interaction within expanded networks of investigators. Cross-center activities inevitably lag behind within-center collaborations and remain in their developmental and conceptual stages by virtue of beginning later than the large projects. Monthly cross-site steering committee

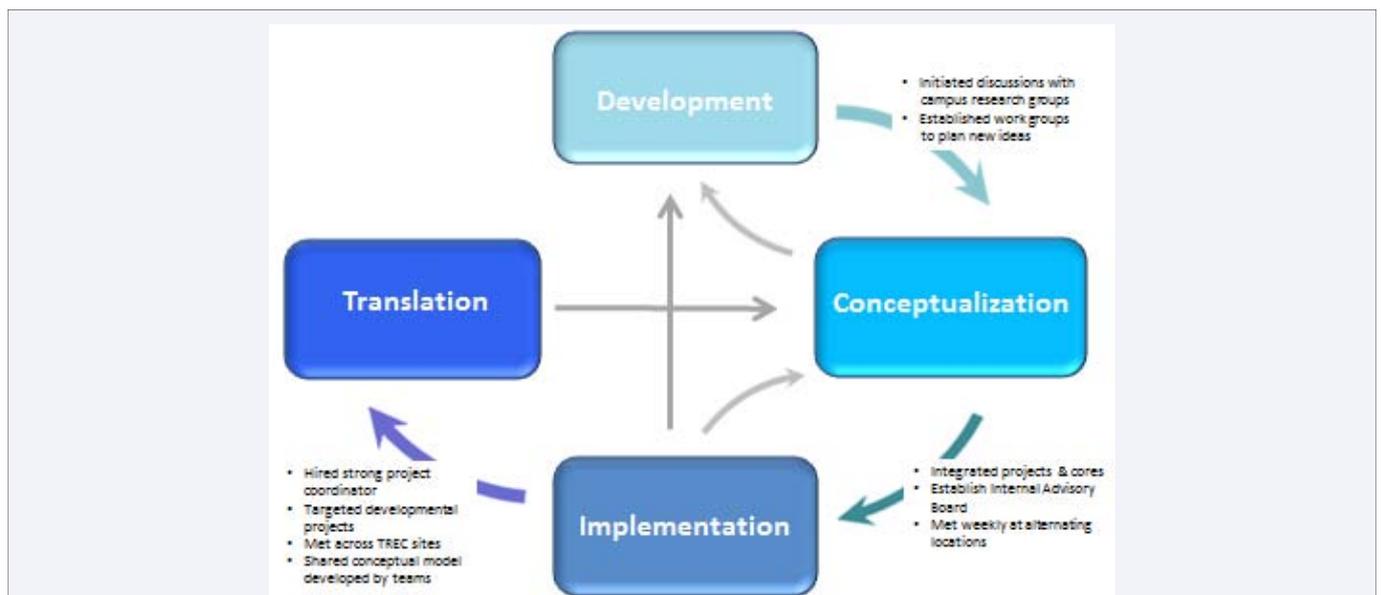


Figure 2 Facilitators of the Four Phase Model.

meetings and larger all-grantee meetings have also been instrumental in generating cross-center projects.

In research environments in which high cost infrastructure (e.g., high speed gene sequencers) may be located on only a few campuses, cross-site initiatives also enable additional research projects to be conceptualized that benefit from access to this infrastructure, when all universities on these cross-site initiatives have access to one another's resources. In addition, multisite initiatives provide resources for cross-site collaborations through funds earmarked by NIH for the purpose. Finally, multi-site initiatives support translation of findings via the cross-center fertilization of ideas. The TREC initiative provides these layers of support for within and cross-center conceptualization, implementation, and translation of transdisciplinary research.

CONCLUSION

The TREC initiative can be seen as a flagship effort in transdisciplinary science that provides important lessons on how to move ideas from development to translation.

Existing ties between investigators within TREC sites became denser through time and new investigators were added, both of which appreciably increased the possibilities for advancements in the science of energetics and cancer. In addition, in an age in which resources such as high speed gene sequences are located at a few select sites across the country, multi-site ties like those in TREC have great potential to advance our ability for scientific innovation.

A multi-site initiative essentially entails its own development as well as the development of each of its sites. Arguably, the initiative level is on its own time-scale, in which developing the mission and vision for the group of sites happens while individual sites and projects have reached their implementation phases. This is because each site must articulate its own projects, cores, and shared conceptual framework before the same process can be undertaken by the initiative as a whole. Only then can shared questions and goals be articulated across sites. Sharing across sites advances science by allowing broader questions and more ambitious goals to be addressed with the greater resources, such as facilities and investigators that are made available when universities work together. This lag, which is inevitable, was manifest in another NCI transdisciplinary initiative, the Transdisciplinary Tobacco Use Research Centers (TTURC), by an initial two-year lag in publications, when compared to single site investigations on the same topic [15]. Yet, TTURC number of publications soared above related single-site centers in subsequent years of funding. It thus seems important to build the inevitable start up time for multi-site initiatives.

Although every site in the TREC initiative moved through the four phases at a slightly different pace, certain features of individual sites clearly helped accelerate the transdisciplinary research process. These include the benefit of having a well-crafted set of external advisors to push toward greater benefits for science and society and having co-directors for projects and cores. Although the latter may have posed a threat from diffusion of responsibility, its benefits in fostering a broader perspective on energetics and cancer outweighed the costs.

The TREC experience suggests a number of new mechanisms of funding. These include appreciating the time needed to form effective collaboration at more than one level and fostering this collaboration through national meetings. It also suggests encouraging the use of external advisors and understanding the need for them to meet at least annually with investigators. This investment in fostering transdisciplinary research, based on the experiences of TREC2 and other initiatives, will allow us to convene more highly interactive, generative teams of scientists than have worked together in the past. Only then can we begin to develop the new ideas, questions, methods, and analyses needed to solve complex public health problems like energetics and cancer.

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