Commentary

Cancer Prevention Research

Toward a Modern Science of Obesity at Washington University: How We Do It and What is the Payoff?

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Abstract

In our Cancer Prevention Program at Washington University in Saint Louis (WUSTL), we have made extraordinary efforts to create the kind of cancer prevention and control program that is both translational and transdisciplinary in nature, to accelerate the march from basic discoveries to population change. Here we present an overview of our obesity-related research currently ongoing in our Center, paying particular attention to both the translational– transdisciplinary process and to community-based participatory research. We end with our future directions for improving obesity-related cancer outcomes research. *Cancer Prev Res; 9(7); 503–8. ©2016 AACR.*

Changing Population Health Outcomes Requires Extraordinary Means

The NIH Roadmap (1) has been a driver of a paradigm shift in health-related research over the past decade. The catalyst behind this shift has been a call to action to address the documented lag from basic research discoveries to application and dissemination, leading to an eventual population health benefit, called translation. The median time from the initial publication of a basic scientific discovery to the publication of its use for health benefit is 24 years (2). Accelerating this translational process entails finding ways to shorten the delays in communicating and acting on results from different disciplines.

In our Cancer Prevention and Control Program at Washington University in Saint Louis (WUSTL), we have made extraordinary efforts to create the kind of cancer prevention and control program that is both translational and transdisciplinary in nature, to accelerate the march from basic discoveries to population change. Through the study of exposures at multiple levels of influence across the life course, understanding inefficiencies in cancer prevention diagnosis and treatment, we aim to identify options for high-impact and cost-effective translation in life course interventions at multiple levels to counter the burden of cancer in Missouri and elsewhere. In this article, we articulate the elements of our research program, and how they link together across the phases of transdisciplinary research across disciplines.

Overview of Translational Research

Translational research (3) moves through four stages, labeled T1 through T4 (4), as shown in Fig. 1. T1 research is essentially the identification and characterization of basic processes of human functioning and is the largest research area funded by NIH (5, 6). T2 research is the study of the utility of potential applications of basic science findings to clinical or public health practice, such as the U.S. Guide to Clinical Preventive Services or the Community Guide (7, 8). T3 research is defined as research that adapts and tests guidelines and best practices identified through T2 research into real world settings. Here one of the great debates in the field is regarding the appropriate times to move forward with "enough" evidence or appropriate evidence (9, 10). Systematic review and meta-analysis can guide us here, but even these methods have gaps and flaws which do not fit into every situation (11, 12). T4 research involves evaluation of practices, once they have been implemented in the community or with the general public (13).

Disciplines Needed for Obesity Prevention

The disciplines that are needed to conduct research in obesity at the population level are multiple, spanning all of the biomedical sciences but also social and environmental sciences, systems science, and political and cultural studies as well (14). Our long-term goal is to reduce the burden of cancer in Missouri. As a comprehensive cancer center with accountability for regional cancer incidence and mortality, Siteman Cancer Center and WUSTL sit in St. Louis between excess total cancer mortality in Southern Missouri and similar excess mortality in Southern Illinois. These areas have higher rates of poverty and added distance for travel to for risk factor reduction, for and for

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doi: 10.1158/1940-6207.CAPR-15-0060

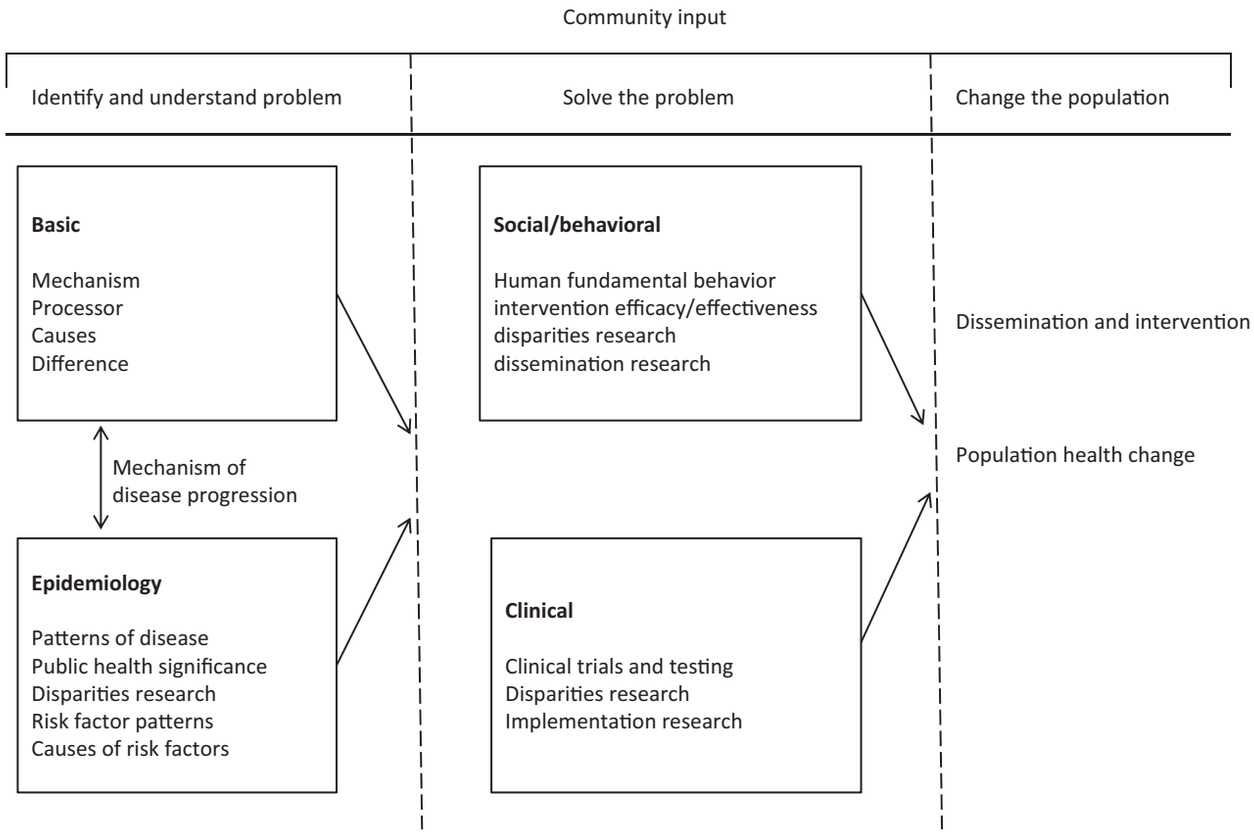

Figure 1.
Overarching model of cancer prevention and obesity, guiding TREC at WUSTL.

follow-up of positive screening tests and referral care. The entire TREC effort is infused with a lifespan perspective, as in, for example, efforts to understand the role of socioeconomic status currently, but also earlier in life (i.e., generational socioeconomic status) in obesity. In addition, a lifespan perspective must take into account how as aging of the population contributes to obesity, in the St. Louis region as well as nationally (15).

Overview of TREC Research at WUSTL

A strong example of basic science that has potential for translation into human research is our TREC Project 1. The objective of TREC Project 1 is to investigate the effect of maternal high-fat diet and changes in metabolic bioenergetics on prostate gland development and susceptibility to prostate cancer in the male offspring. We hypothesize that a high-fat maternal diet prior to and throughout pregnancy alters epigenomic marks leading to abnormal expression of key genes involved in the development of the prostate gland, which predispose the offspring to develop prostate cancer. Our rationale is that if maternal diet and metabolic bioenergetics alter the process of tumor development and progression in the prostate, then further studies exploring the mechanism of this process may elucidate new therapies and recommendations for the prevention and treatment of prostate cancer.

One of our TREC projects, TREC Project 4, is a powerful example of when traditional epidemiologic methods are combined with community-based participatory research methods to produce an understanding of cancer risk. Project 4 is group model building with stakeholder engagement, focusing on understanding the role that social determinants play in the link between obesity and cancer at the population level across the lifespan by developing a multicohort computer simulation model of obesity and non-Hodgkin lymphoma (NHL). This project is generating a systems model of obesity causation, identified through group model building (16) with community members and other stakeholders that will guide selection of policies and programs to address social determinants. This project is also synthesizing findings from other TREC projects in both animals and humans to identify existing social determinants of obesity that might play a role in NHL population level incidence, treatment toxicity, and survival trends. This includes the lifespan perspective from our animal work, the clinical perspective from our human survivorship work, and the environmental perspective from our workplace studies. The underlying population structure and obesity levels inform trade-offs over time projecting future cancer burden in an aging population. The interplay of all the projects will be integrated into this final project, which serves as a laboratory for testing new causal ideas about obesity in modeling its role in NHL and systematically evaluating the consequences of uncertainty on policy, program, and research decisions.

A strong example of transdisciplinary research is the research on breast cancer conducted by investigators at the Center for Interdisciplinary Health Disparities Research (17). The fundamental question posed by this group is: given that White women are more likely to be diagnosed with breast cancer, why is it that Black women are more likely to die from it? The research brings together human and animal work to investigate the biobehavioral mechanisms of sporadic breast cancers in Black women. The animal model findings of the role of social interactions, isolation, and genetic transformation (18) in the intermediate outcomes leading to breast cancer risk have driven the human studies trying to measure and quantify these risks in humans using the same intermediate markers. These biomarkers include both stress and inflammatory markers, but also obesogenic markers, to understand the interplay between stress, obesity, reproduction, and cancer risk in Black women (17, 19). This is also a good example of how translational research does not need to move along the standard continuum in an ordinal fashion, but can lead to research questions from an "earlier" stage as well as progress forward. The same finding may uncover a mechanism that must be addressed, as well as lead us to an optimal intervention.

An example of the kind of research that is leading to a clinical trial among patients is our TREC Project 2, a longitudinal study of the role of physical activity in prostate cancer outcomes. Specifically, we will examine whether physical activity and obesity, individually and jointly, influence sexual and urinary function outcomes in men with clinically localized prostate cancer undergoing radical prostatectomy. We will explore whether these associations vary by race. Finally, we will investigate whether postsurgical change in physical activity and weight are associated with urinary and sexual function. These findings may be directly translated into interventions to assist men undergoing radical prostatectomy with changes in functioning and effects on obesity and activity. Related research is addressing approaches to engaging African American men in physical activity programs after surgery for prostate cancer as participation by this high-risk group is essential to any dissemination and implementation of findings.

Interactions during our first Internal Advisory Board (IAB) meeting moved our basic science work from male gender emphasis, to add female outcomes of the effects of dietary factors instead of disposing of them. During the planning meetings developing our TREC response to the RFA, one group initially proposed to investigate epigenetic changes and obesity among pups after mothers' exposure to a high-density caloric diet. After hearing the aims and methods of the second TREC project on prostate cancer, the basic science team shifted its focus to proliferation of prostate cells among male pups. In this case and others, exposure to each other's ways of viewing the science of obesity bred a combining of ideas and methods that would not have happened in isolation.

Dissemination research is the final step in this area, to identify methods of moving successful interventions into public use. A specific example of this work can be found in our TREC Project 3, a survey of employees across the state of Missouri, to determine the role of workplace policy in shaping the obesogenic behaviors of employees. This project will translate into the identification of new and stronger policies to create workplaces that promote healthful behavioral patterns. It also sets the stage for intervention research that allows for testing of new hypotheses about the role of policy in health behavior change.

The final phase described in Fig. 1 is to see changes that have been found through this research process in place and working to change overall health outcomes. Both clinical and population changes must occur in the population to improve overall population health levels in any measurable way. Eliminating disparities in all of the phases is key in changing population health levels as well, as disparities are found at any phase of research and can be addressed throughout the process. Also, as shown in Fig. 1, community input will help guide disparities research, but as shown in this figure, can also guide all research questions, help to interpret answers, and guide all implementation decisions, using principles of community-based participatory research (20, 21)

Evaluation of Transdisciplinary Research at WUSTL

We evaluate the process of transdisciplinary science in our TREC project through surveys and interviews of faculty, trainees, and staff involved in TREC, both at baseline and during the process of conducting the TREC projects. For example, we asked all TREC participants about who they work with and how they work with people with differing types of training and backgrounds. We applied a social network method to these data, to graphically display the interactions among the investigators at multiple sites. Figure 2 presents baseline and interim data from our social network analysis of the national connections among TREC investigators as they implement their proposed studies and data from the third year of operation (2013). Each of the nodes in Fig. 2 represents a TREC investigator at one of the five TREC sites, and each line a collaboration (self-reported joint grant proposals, publications and presentations, or mentorship opportunities) between two people. In this figure, the denser the number of lines connecting sites, the more interactions are occurring. We would hypothesize that the connections will become denser over time, with continued collaboration, and that more nodes will become connected with collaborative lines over time. This is significant, because denser networks suggest faster propagation of information and greater group cohesion (22). Also, individuals who conduct more information tend to be more productive in terms of research goals and objectives (23).

To date, we have found that collaborations have increased across sites as investigators become familiar with one another's work and begin to leverage resources across sites to form cross-site developmental projects fostered and funded by the TREC initiative as a whole. In 2011, 15.66% of all collaborations between investigators were cross-site. This increased to 34.48% by 2013. This type of analysis, which will occur annually during the current phase of funding, will help us track our collaborative process in transdisciplinary research and will allow us to compare ourselves to more traditional research centers that likely have less dense connections. It likewise will guide our training efforts to increase interactions among investigators, which is associated with more rapid flow of information (24).

Evaluation of Translational Work at WUSTL

Engagement of an experienced basic science research team in the study of obesity (25–27) in our TREC proposal provided a starting point for translation to occur. This team had never

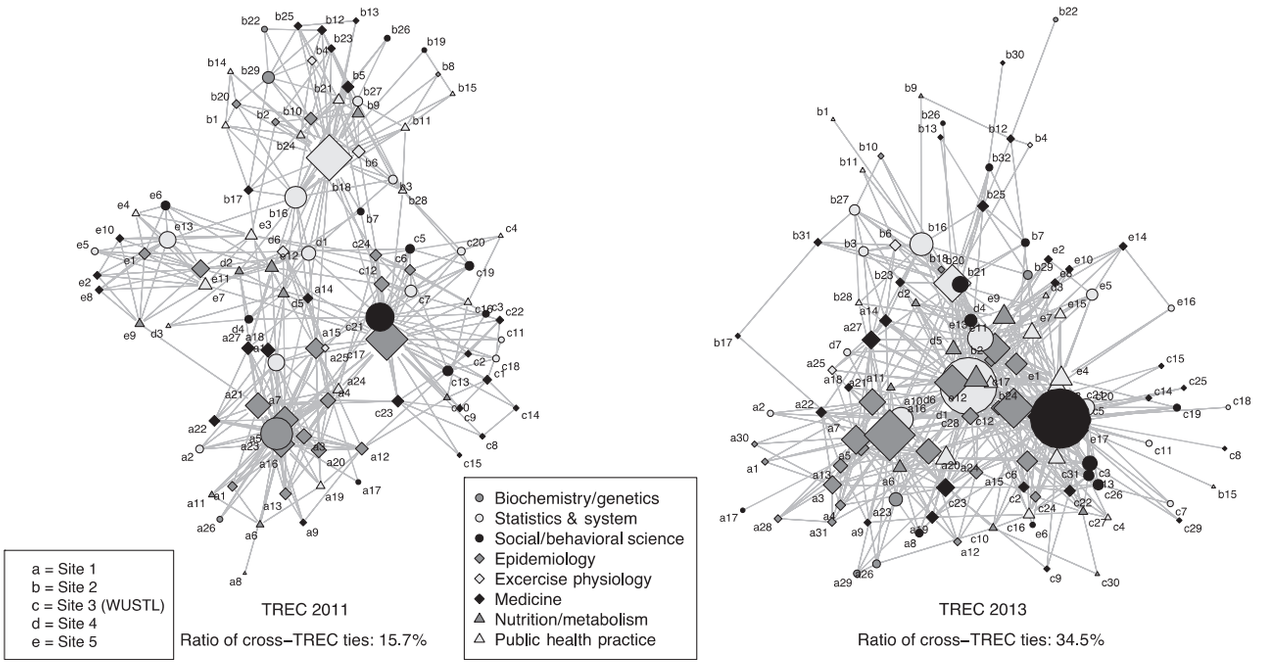

Figure 2.
Network plot of the five TREC sites in 2011 and 2013.

conducted work with any sort of cancer outcome prior to this application with TREC. We found through initial discussions with the group that the more basic research into the exposures of pregnant mothers to differing dietary and other conditions might have relevance to the development of early intermediate changes in the pups of rats through *in utero* exposure. Project 1 (Transgenerational animal models of nutritional impact on cancer predisposition) was the result of this transformation. Classic statistical tests (*t* tests and ANOVA) were not identifying any significant differences in the data. The Statistical Methods and Bioinformatics Core was thus designed to address the aims of other human-focused TREC projects by the basic researchers and the lead biostatistician from the Core, who thought he could create a "modeling system" to evaluate the dataset. The biostatistician pushed past this and used a generalized linear model (GLM) with a Poisson (log-linear) link function to associate the expected counts on the left-hand side of the model with the standard linear-additive right-hand side treatment of the covariates: $yi = \exp(Xi\beta) + \varrho i$, where β is the estimated set of regression parameters and ϱi is the *i*th residual. He ran the Poisson GLM in R 10 times with the 10 imputed datasets and averaged the results. This allowed for significant findings to emerge in the study of hyperplasia in the mouse pups differentially exposed to high-fat diets *in utero* through the mother. These were presented at AACR in spring 2013 and subsequently published (24).

Another example of TREC as a driver of transdisciplinary opportunity is the current focus on life course of obesity now built into each of the TREC research projects. At an IAB meeting, the TREC investigators invited a health economist who studies the generational pathway of obesity to present her data (28) due to the interest in the mother and pup research. Because of the data presented, all of the projects decided to include a multigenerational approach and have extended their data gathering efforts to earlier and younger generations.

Vision for Research on the Obesity/Cancer Link

Here are some gaps or areas for improvement in research conducted around the country on cancer control, that we think would help to translate basic science into population science and to usable practice in clinical and public health settings. In some ways, this list could function as a to-do list for the field to insure that we make progress toward population level change.

- Tie good epidemiologic methods together with mechanistic basic science studies. In 2012, the Epidemiology and Genomics Research Program (EGRP) at the NCI initiated a longitudinal conversation in the scientific community to examine the current state of epidemiology and identify goals for the future of the field. The set of recommendations assembled from this effort has been published (29) and contains several that are transdisciplinary in nature. One deals with including studies of mechanisms of disease development together with the application of population health surveillance methods to understand behavioral patterns and biologic risk factors as related to disease outcomes. We applaud this and encourage investigators to support this and other more innovative research directions. At WUSTL, we are bringing mouse models of myeloma (including MGUS as a precursor), Veterans Administration outcomes data (Carson, submitted), and novel imaging (30) together to better understand pathways and exposures across the life course that can build into a transdisciplinary multi-investigator project.

- Engage more basic scientists in gaining an understanding of cancer-related changes. This is a complicated area to enhance, as it is often difficult for basic scientists to see value in more applied scientific efforts, especially as the incentive for transdisciplinary research are not directly supported by the field. Our pilot study funds have supported basic scientists to continue and extend the conduct of translational research related to obesity. For example, two of our most recently funded pilots went to study lipidomic profiling of energetics-associated cancer models in mice and the transgenerational effect of maternal diet on methylation of cancer-related genes. These investments in new research will hopefully lead to new studies in humans along the translational pathway. With attention to these issues of translation in our internal pilot funding request for proposals, we can further harness early findings and encourage translation to clinical and public health applications.
- Make intervention research accountable to change population health. Dissemination and implementation research is a growing area of funding and research activity and needs to be further enhanced to enable us to understand and bring about population health changes. Most intervention researchers have a shelf full of interventions that are all published in journals but are not used in practice. One simple reason is that we do not know how to change population health outcomes in many cases. Planning for dissemination and implementation while testing for efficacy must become the norm if we hope to change population levels of obesity.

In considering dissemination as the final outcome of a successful intervention, we need to invest in elements of change that can be expected to have population impact. The increase in rates of bariatric surgery nationally coupled with decreases in prices and increases in eligibility for potential patients is in stark contrast to the consideration of this method as a population health intervention. For individuals at high risk of chronic disease who have tried and failed at other methods and are morbidly obese, bariatric surgery may be an option. However, as a public health strategy, it is inadequate at best and dangerous at worst. Similar resources need to be spent on interventions that shift obesity distributions in the population and can safely be used on entire populations. We have spent the past 25 years or more constructing an obesogenic society. We should expect that dismantling this will require similar commitment and investments over the next 25 years.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Grant Support

This work was supported by NCI U54 CA 155496 and P30 CA091842, both to G.A. Colditz.

Received February 17, 2015; revised March 3, 2016; accepted March 21, 2016; published OnlineFirst April 8, 2016.

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