From the bench to bedside to babies: translational medicine made possible by funding multidisciplinary team science

Teresa K. Woodruff

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Abstract

Purpose In 2005, The National Institutes of Health (NIH) called upon the scientific community to identify the most intractable problems in science and medicine and describe how we would solve these problems using teams.

Methods Our group was one of 8 research communities awarded an ‘interdisciplinary research consortium (IRC) grant.’ Using the infrastructure of this large, multi-institute grant and a team science approach, we set out to solve the problem of fertility loss in young female cancer patients—work that was not easily funded through other mechanisms.

Results The word ‘oncofertility’ was coined specifically for the IRC to reflect the intimate partnership between oncology care and fertility care for these patients—two disciplines that would no longer function at arms’ length, but as an integrated unit. Catalyzed by the IRC funding mechanism, interdisciplinary teams worked together in unique ways to create a ‘bench to bedside to baby’ outcome.

Conclusions The grant has now ended, and remarkably, so have the most intractable parts of the original problem. As we look back on what worked and look forward to tackling the next set of fertility-related questions, we are confident that this very special NIH funding mechanism made a meaningful difference in the lives of women and their future children. NIH and the public would be well-served by supporting clinical problem-based, multidisciplinary team science approaches to catalyze fundamental biomedical breakthroughs and create new intellectual environments in which changes in clinical practice and standard of care can be implemented.

Keywords Cancer · Oncology · Fertility · Research funding · Multidisciplinary

Introduction

In 2005, The National Institutes of Health (NIH) called upon the scientific community to identify the most intractable problems in science and medicine and describe how we would solve these problems using teams. Our group was one of 8 research communities awarded an ‘interdisciplinary research consortium (IRC) grant.’ Using the infrastructure of this grant and a team science approach, we formed the multi-institute Oncofertility Consortium to solve the problem of fertility loss in young female cancer patients—work that was not easily funded through other mechanisms. The word ‘oncofertility’ was coined specifically for the IRC to reflect the intimate partnership between oncology care and fertility care for these patients—two disciplines that would no longer function at arms’ length, but as an integrated unit. The Oncofertility Consortium brought together a diverse group of investigators from the biomedical, social science, and medical communities (Table 1) [1]. The IRC was a unique mechanism that linked ‘ordinary’ R01s, P01s, T-, and K-grants together in an extraordinary way to catalyze the work of multidisciplinary teams and the translation of discovery into practical patient care—from the bench to bedside to baby.

The unmet need

The emergence of oncofertility was driven by the increasing number of young female cancer patients who survived their disease but found themselves sterilized by their cancer treatment. These cancer survivors experienced profound menopausal symptoms, had few reproductive cycles, and unexpectedly entered reproductive senescence [2]. While men and

Capsule Funding multidisciplinary research can catalyze biomedical breakthroughs and rapidly advance the translation of scientific research to improve clinical care.

T. K. Woodruff (✉)
Department of Obstetrics and Gynecology, Feinberg School
of Medicine, Northwestern University, Chicago, IL 60611, USA
e-mail: tkw@northwestern.edu

Table 1 Projects linked by the IRC grant to create the Oncofertility Consortium

Grant number	Title	PI	Location
UL1DE019587	Administrative Core	<i>Principal Investigator:</i> Teresa K. Woodruff, PhD	Northwestern University
RL1HD058293	Novel Method for Cryopreservation and Recovery of Female Follicles	<i>Principal Investigator:</i> Mary B. Zelinski, PhD <i>Co-Investigator:</i> Richard R. Yeoman, PhD	Oregon National Primate Research Center
RL1HD058294	Bioengineering Primate Follicles: From Immature Eggs to Live Births	<i>Principal Investigator:</i> Richard L. Stouffer, PhD <i>Co-Investigators:</i> Mary B. Zelinski, PhD, David M. Lee, MD	Oregon National Primate Research Center
RL1HD058295	Preservation and Growth of Human Follicles	<i>Principal Investigator:</i> Teresa K. Woodruff, PhD	Northwestern University
RL1HD058296	An Interdisciplinary Perspective: A Social Science & Humanities Examination of Oncofertility	<i>Principal Investigator:</i> Linda Emanuel, PhD	Northwestern University
PL1EB008542	Biomaterials Core	<i>Principal Investigator:</i> Lonnie D. Shea, PhD	Northwestern University
PL1CA133835	National Physicians Cooperative to Preserve Fertility for Female Cancer Patients	<i>Principal Investigator:</i> R. Jeffrey Chang, MD <i>Co-Investigator:</i> H. Irene Su, MD	University of California at San Diego
RL5CA133836	Learning Modules in Oncofertility	<i>Principal Investigator:</i> Kemi Jona, PhD	Northwestern University
TL1CA133837	Training the Globally Ready Scholar	<i>Principal Investigator:</i> Christos Coutifaris, MD, PhD	University of Pennsylvania
RL9CA133838			
KL1CA133839	Measures of Fertility in Young Cancer Patients	<i>Principal Investigator:</i> Clarisa Gracia, MD	University of Pennsylvania

pubertal boys were being offered sperm banking before starting cancer treatment, young women and girls—who had the same hope for survival—were being told that they should focus on treating the cancer rather than thinking about fertility [3, 4]. Providers' attitudes included the belief that patients who were single probably weren't interested in discussing fertility, that it would take too much time for the patient to find fertility care, or that patients could worry about their fertility later [5].

To link the areas of oncology and fertility, we had to understand the interests of female cancer patients and the barriers for providers. Though patients' interest in fertility preservation was documented in social media and through advocacy groups, in 2005, few female cancer patients were referred to fertility care and most had to seek out their own treatments, often while being discouraged by their oncologists. Reproductive endocrinologists and infertility (REI) specialists who saw cancer patients made special accommodations based on the compressed timeframe for fertility treatment, but there were no practice guidelines or field-wide mechanisms for patient care. These problems were large and pervasive, and included issues of insurance and reimbursement, ethics, legal considerations, and religious interpretation of fertility interventions [6].

The clinical opportunity

The primary clinical challenge we faced was how to facilitate patient access to existing and emerging reproductive technologies in an 'emergency medicine' setting. We needed to

engage oncologists who may not be well versed in all of the fertility options available and may feel uncomfortable talking with their patients about fertility issues [7]. Oncologists needed to know that there were fertility preservation options for their patients that would allow the patient to return quickly to cancer care. Even though rapid stimulation cycles and emergency IVF were available when the Oncofertility Consortium was formed, the lack of communication between oncology and reproductive medicine meant that few referrals were being made. Because infertility is not a life-threatening condition, REI practices are set up to manage patients in groups rather than individually, and doctors, nurses, embryologists, and other support staff work on a well-established schedule [8]. REI practitioners were being asked to accommodate and care for a significant number of urgently ill patients who may have ill-timed cycles or who may be at unknown stages of their cycle and may have any number of medicines in their system, relative infertility (independent of the cancer), and unclear partner status. The typical REI patient is a highly knowledgeable consumer of medical information while the average young cancer patient may know relatively little about these things. Therefore, the conversation that the REI practitioner has with the oncofertility patient differs substantially from the discussion they would have in a typical consultation [9].

To build the necessary bridges between oncology and REI providers and patients, the Oncofertility Consortium created a number of tools, including multilingual iPhone Apps, websites, and age-based decision aids, and established a national fertility preservation hotline and dedicated patient navigator. Annual Oncofertility Consortium conferences bring together providers across disciplines to discuss clinical issues

and needs and disseminate data. Monthly Virtual Grand Rounds provide the global community with opportunities for continuing medical education. Because physicians cannot always attend in person, webcasts and video archives extend the reach of this information. Supported by this connectivity, oncofertility has emerged as a cohesive discipline, moving from a fragmented set of practitioners and researchers to an active organization that is catalyzing patient care (Fig. 1).

The Oncofertility Consortium also built the National Physicians Cooperative (NPC) as a coordinated national presence; creating a network of collaborating clinicians is difficult to support through standard NIH funding. The NPC now includes 55 clinical reproductive endocrinology sites, 10 oncology or ‘allied sites,’ and 10 global partners. The NPC definitively demonstrated that when oncologists and REI specialists work together to ensure readiness of REI practices for cancer patients, clinicians are more likely to recognize that, for many patients, there is time to provide conventional fertility treatments before the start of cancer therapy. The members of the NPC share their cases and outcomes in a way that continues to move the field of oncofertility forward. For this reason, the NPC is one of the most important and enduring achievements of the work supported by the IRC grant.

The cooperation between oncology and fertility medicine represents a paradigm shift in medical practice, creating a new ‘standard of therapy’ for young female cancer

patients. We can quantitate the changes that have occurred in oncofertility patient care in a number of ways, but the most impressive is the number of female cancer patients referred to REI in 2005 versus 2013 at Northwestern Memorial Hospital, which rose from 0 % to 85 %, with nearly 90 % of patients able to undergo traditional IVF. In addition, hundreds of patients have stored tissue for later use in a domestic national tissue repository as well as in centralized labs around the globe [10]. I predict that the changes experienced in fertility management in the cancer care setting will soon be as routine a part of the conversation as genetic counseling.

The bench breakthroughs

The most recent advances in oncofertility have been in the technique of encapsulated in vitro follicle growth (eIVFG), which uses biomaterial support matrices to maintain ovarian follicle function in vitro [11]. eIVFG can now be used to support all stages of folliculogenesis—including the mechanical processes of ovulation and luteinization—in large mammalian species for extended lengths of time. Thus far, live births have been recorded in mice [12] and embryos have been created in non-human primates [13–15] using eggs grown following eIVFG. This system has also led to many breakthroughs and new ideas in ovarian biology, including follicle preservation and activation, pathways for oocyte cell death and chromosomal fidelity, fertility-aware chemotherapy design and delivery, vitrification methods, and human ovarian tissue transplant.

To date, eggs developed to the meiosis II (MII) stage have been derived from human tissue [16], bringing us to the very edge of research that can be performed under NIH authorization. For these efforts to continue, either the rules of egg activation through parthenogenesis or embryo research for reproductive applications must be modified at the federal level [17]. Without this research, we will lack fundamental knowledge of the biology of the human egg and embryo and have limited means to pre-clinically test egg and embryo quality in emerging assisted reproductive technologies in the United States. Laboratories around the globe—particularly in countries where governing boards permit licensed labs to work with human embryos to improve human health—will likely take the next steps in this field [18].

Through the adaptation of existing technologies and introduction of emerging technologies, there is now a continuum of fertility preservation options for women diagnosed with cancer [19]. These options are open to women from birth through later reproductive age (39 years), and provide the starting point for discussions with young cancer patients about fertility and the possibility of a future family.

Fig. 1 The emergence of a new field. Metrics of team science were evaluated for ‘fertility preservation,’ ‘cancer,’ and ‘oncofertility,’ and in-depth surveys were completed by members of these communities. Four conclusions were reached about the nature of team science in these areas: (1) there was minimal work published in this field in 2000; (2) by 2005, the field began emerging (e.g., larger teams with groups of researchers published articles together); (3) by 2010, many research groups had formed with increasing collaboration across cliques; and (4) in 2012, strong networks connected oncofertility researchers, clinical practitioners, patients, students, humanists, and patient advocates. Contractor and Uzzi, unpublished results, used with permission

The public policy front

The NIH rarely funds research in the humanities; however, if we limited our work to basic or clinical science, we risked missing the complexity of the patient environment and removing the science from its implications. The IRC mechanism provided us with a full R01 in order to examine ethical issues [20], religious perspectives, financing and reimbursement hurdles [21], legal challenges [22], patient empowerment challenges [23], and communication strategies [24]. We recognized the need to ask hard questions about financing of reproductive technologies, which have reached a cost ceiling, and whether this makes cancer patients prey to abrupt economic choices. We continue to wrestle with the question of how to provide options under financial constraints and to discuss the ethical issues that arise when considering the risk of infertility vs. the risk of death vs. the risk of intervention [20]. We engaged in advocating for insurance and reimbursement for patients facing a sterilizing treatment, examining faith-based attitudes about cancer and fertility, identifying legal issues that might emerge over time, debating the ethics of the work, and implementing the most thoughtful approaches to the issue of tissue acquisition, especially in the case of minors [6]. Incorporating health law, ethics, religious concerns, patient costs, and practitioner reimbursements in a comprehensive health care discussion has changed standard practice and is a critical reason for the success of the Oncofertility Consortium.

Sustainability

We recognized from the beginning that the Oncofertility Consortium had to outlast NIH funding. Network analysis of the Oncofertility Consortium (Fig. 1) found that while publications increased with time, more importantly, a network was formed that could outlast a singular funding source and sustain a critical area of work. We placed an emphasis on education as a major area of sustainability, and developed programs geared to middle school, high school, and college/medical school students as well as scientists and clinicians, patients, and the public. Educating through the lens of oncofertility, we provided opportunities for high school girls to participate in a laboratory setting and feel the excitement of discovery research, where scientists and clinicians learn and share new technologies with each other [25]. These students are the future of science and medicine who will work in multidisciplinary teams to solve the next generation of intractable biomedical problems.

The legacy

In the past 6 years, we have increased awareness among providers of their young cancer patients' interest in fertility,

collected data on the kinds of treatments that threaten fertility, and created a mechanism for patient navigation to ensure that existing technology could be used and new options developed. As the Oncofertility Consortium filled gaps in knowledge, data, practice management plans, and fertility preservation options, we have changed the care and clinical experience of young women with a cancer diagnosis. Funded by the IRC mechanism, the Oncofertility Consortium has had a profound impact on creating and sustaining an entirely new area of research, and continues to make a meaningful difference in the lives of women today and their children yet to come.

There is more to do, but we now have a system in place where previously there was none. We have produced a new generation of interdisciplinary scientists, clinicians, and scholars across all disciplines of the academy, and created a global collaboration network that is moving ideas and data in an altruistic and patient/results-focused manner. While the IRC grant funding to the Oncofertility Consortium is now completed, the legacy of 'bench to bedside to babies' will continue for generations to come.

By funding science through ordinary grant mechanisms linked together in extraordinary ways and by providing space for physician development programs and non-hypothesis-driven humanities research, the NIH Common Fund can support discovery that will ultimately change lives. NIH and the public would be well-served by continuing support of clinical problem-based, multidisciplinary team science approaches to catalyze fundamental biomedical breakthroughs and create new intellectual environments in which changes in clinical practice and standard of care can be implemented.

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