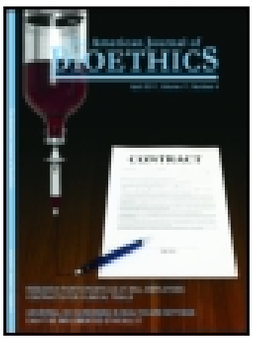

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Target Article

The Ethos and Ethics of Translational Research

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Calls for the "translation" of research from bench to bedside are increasingly demanding. What is translation, and why does it matter? We sketch the recent history of outcome-oriented translational research in the United States, with a particular focus on the Roadmap Initiative of the National Institutes of Health (Bethesda, MD). Our main example of contemporary translational research is stem cell research, which has superseded genomics as the translational object of choice. We explore the nature of and obstacles to translational research and assess the ethical and biomedical challenges of embracing a translational ethos.

Keywords: Translational science, history, National Institutes of Health, stem cell research

Translational research has become a mantra in Washington, DC, and beyond. Inspired by United States (US) congressional demands for "results," the National Institutes of Health (NIH, Bethesda, MD) issued a "Roadmap" that has marked the parade route for translational research. Groups such as the National Academies of Science (Washington, DC), medical advocacy groups, scientific professional societies, and private foundations have widely embraced the emphasis on translation and the funding that has come with it. This is bringing a new social contract for the way science works in society. Instead of implicit promissory notes about eventual results, scientists must promise specific results up front. Moreover, they must produce results sooner rather than later and more specifically targeted for particular ends rather than for general good. Finally, there is now far more guidance from public investors. The result is an ethos of translation.

It is time to examine this emerging translational ethos critically. We explore what the call for translation means, discuss stem cell research as the most revealing example of translational research, and analyze implications of the translational imperative. We probe the translational metaphor, arguing that language matters. Due to space constraints, we focus on the US, although the ethos of translation in biomedical research has become prevalent globally. We conclude by arguing that the widespread push to translation distorts the science, sometimes in indeterminate ways, and also distorts bioethical discussion.

ESTABLISHING TRANSLATIONAL RESEARCH: WHO, WHAT, WHEN, WHERE, AND WHY?

It is not the case, of course, that the term *translational research* has brought entirely new meanings to the whole biomedical research enterprise. Yet when NIH Director Elias Zerhouni issued a new Roadmap focused on translation into clinical results, the world noticed. It is worth understanding what the Roadmap envisions in order to assess its implications. The process of developing the Roadmap began in 2002 and, by 2003, concluded that:

> Ideally, basic research discoveries are quickly transformed into drugs, treatments, or methods for prevention. Such translation lies at the very heart of NIH's mission. Although NIH has historically been successful by funding medical research that has helped to transform once acute and lethal diseases into more chronic ones, it has become clear to the scientific community that our country will need to recast its entire system of clinical research if we are to remain as successful as in the past (NIH) Office of Portfolio Analysis and Strategic Initiatives [OPASI] 2008a).

Note the suggestion that the "scientific community" had already embraced this vision and that we must therefore change the way we do science and "recast the entire system." This was a broad call for change. But change in what way? It is important to examine the Roadmap language closely because it is a carefully

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negotiated political instrument that has had broad impact in shaping thinking about biomedical sciences and their applications.

Scientists have been excellent at making discoveries, with some clinical successes, the Roadmap acknowledged: "Yet the exciting discoveries we are currently making require us to conduct even more efficiently the complex clinical studies needed to make rapid medical progress, and to further inform our basic science efforts. This is undoubtedly the most challenging, but critically important, area identified through the NIH Roadmap process" (NIH OPASI 2008a). How can we move more efficiently from discovery to clinical applications? According to the Roadmap, we must develop strong new partnerships among laboratory researchers, clinical researchers, clinicians, community clinics, those developing medical delivery systems (e.g., drugs, devices), and clinical research networks; moreover, we must "fully involve and empower the public in the research process" (NIH OPASI 2008a).

It is taken for granted that: "To improve human health, scientific discoveries must be translated into practical applications (NIH OPASI 2008a)." This is a two-way process in which, "Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations" (NIH OPASI 2008a). Already, "Translational research has proven to be a powerful process that drives the clinical research engine" (NIH OPASI 2008b). Yet to carry out successful translations, the NIH claims that we need a "stronger research infrastructure" (NIH OPASI 2008b) and other enhancements (Sidebar 1). With these changes, the NIH can improve the health of the nation by promoting the translational research enterprise that will move us more quickly, effectively, and across a wider range of medical problems from bench to clinic (Pober et al. 2001).

On May 23, 2003, the NIH held a meeting in Crystal City, VA, on "Enhancing the Discipline of Clinical and Translational Sciences" to discuss the challenges (the content of Sidebar 1 was one of the key topics of discussion). To help overcome barriers to translation, part of the program was to streamline the process by which products are taken up by private companies, tested, developed, and marketed by the medical industry. For present purposes, our focus is on the translational research itself, leaving the industrial developments in the background.

The idea of translating research into clinical applications is not new; indeed, it may be coextensive with the history of biomedical research. But what is supposedly different here is an explicit recognition that translation is not easy, not inevitable, not unidirectional, and, indeed, not happening. This recognition resulted in the attempt to re-engineer health research institutions and practices so as to facilitate the bench-to-bedside translation.

ACCEPTING THE TRANSLATIONAL IMPERATIVE

By 2003, the NIH had thus issued a strong challenge to change the way scientists work, and the research and business communities had begun to respond. Often private foundations can act more quickly than large public or academic institutions, as indeed happened in this case. For example, the Bill and Melinda Gates Foundation (Seattle, WA) highlights the Grand Challenges in Global Health initiative, "a major effort to achieve scientific breakthroughs against diseases that kill millions of people each year in the world's poorest countries" (Bill and Melinda Gates Foundation 2008). As indicated in the press release accompanying the first round of grants (43 grants averaging $10 million each for research projects involving collaborations in 33 countries), "the ultimate goal of the initiative is to create 'deliverable technologies'—health tools that are not only effective, but also inexpensive to produce, easy to distribute, and simple to use in developing countries" (Bill and Melinda Gates Foundation 2008). The program began in 2003, in collaboration with the NIH, as an explicit response to the challenges of translation, though the Foundation was focusing on the side of deliverables.

Voluntary health organizations have always had mission-oriented programs explicitly emphasizing development of therapeutics for specific medical disorders, but they have also undergone transformations in the push to translation. They have felt pressures to produce results in areas ignored by major industry, and mission-oriented organizations seek urgently to do what they see as essential rebalancing of the overall funding portfolio. The feeling is that not only will such investment programs generate a greater awareness of the challenges and opportunities of translating research into action, but it will also help with workforce shortages by attracting a more diverse and deeper talent pool to the translational activities (Duyk 2003).

Additionally, NIH reactions are instructive. Earlier in 2003, in an article in *Science* (Collins et al. 2003), leaders of the National Human Genome Research Institute (Bethesda, MD) programs had announced steps for genomics research and applications. We now have the human genome, Francis Collins and his collaborators had declared happily, and so in this 50th year after the discovery of the structure of the DNA molecule, "the genomic era is now a reality" (835). They continued, noting that it was time for a new vision for genomics, as "an opportunity to explore transformative new approaches to achieve health benefits" (Collins et al. 2003, 836). The Human Genome Project had generated a vast amount of data and now, they declared, "The practical consequences of the emergence of this new field are widely apparent" (835).

Yet development of genome-based diagnostics and therapeutics does not happen on its own, and the adoption and integration of genomic tools requires appropriate stewardship: "Translating the success of the HGP into medical advances intensifies the need for proactive efforts to ensure that benefits are maximized and harms minimized in the many dimensions of human experience" (Collins et al. 2003, 836). To move forward most effectively, Collins and colleagues offered a model for the architecture of the emerging research enterprise, an elaborate multi-tiered building

constructed on the foundation of the Human Genome Project, and housing the interdependencies, challenges, and opportunities inspired by the new applied era for genomics.

The call for results—for applications of genomics data—is an obvious one, but its particular framing in their article was meant to be inspiring. If only we now take our vast store of knowledge, while of course continuing to learn more as well, then we shall have wonderful and exciting applications. If only... If only we draw on the assumptions of the traditional social contract for science articulated by Vannevar Bush following World War II (Bush 1995), then we will have exciting applications to benefit society. If only...

But what was that model of research, and to what extent was it real and really likely to yield results? Furthermore, and this is our central point: we need to consider carefully what implications the translational model of research has for scientific research in the laboratory as well as for all aspects of the research-medical-industrial enterprise. It is, after all, quite possible that much will be lost in translation.

SOME HISTORY

Standard assumptions about the usefulness of science date at least from Francis Bacon in the 17th century. If we observe the world, we can discover patterns and learn to make predictions and explanations. Then we can use the knowledge through technology. Therefore, we should begin with "basic" science and then generate "applied" results. Pour the investment into the research, and the results will come — inevitably. Eventually, we will get all the results we want and need, or think we need.

In 1945, as Director of the Office of Scientific Research and Development, Vannevar Bush extended this model for scientific research with his *Science The Endless Frontier* (Bush 1945). There he argued strongly for government investment in scientific research. We must fund scientific discovery, he argued, so that results can follow. Indeed progress in basic scientific research that requires government investment is necessary for national security, which was a primary concern just after the war as it is now. Investment in science would provide jobs for scientists, which would produce a productive career path for those returning from the military. And the overall result would be improvement in public welfare, including the medical condition of the American people.

Bush called for much greater investment in medical research, and also the development of a new basic research foundation. The latter became the National Science Foundation (NSF, Arlington, VA), founded in 1950 by an act of Congress with the mission "To promote the progress of science; to advance the national health, prosperity, and welfare; to secure the national defense; and for other purposes" (NSF 2008). The social contract implicit in this act was clear: the public would invest in science, and they would get results to make their lives better. The scientific contract was clear, too: give scientists money to do the basic science that they wished to pursue in their decentralized, independent laboratories spread across the country, and they would produce important results with widespread implications. While their research would be judged by standards within science, the assumption was that the enterprise as a whole would produce publicly useful outcomes. Bush's extremely influential report gave us a research model that "works"—at least according to some metrics (Sarewitz 2000). It has been accepted, invested in, and it has produced results of a sort. Yet in recent decades, the public has begun to question whether they have gotten the expected results. The current push to translational research is one expression of that concern.

The 1970s had already begun to bring public criticism of the traditional research model, when dissidents challenged public investment in particular sorts of science. Nuclear weapons and power, recombinant DNA, pesticides, and even some foods and drugs were targets of criticism. But this challenge really addressed whether public investment should be constrained in some ways; it did not suggest that the research enterprise as a whole had problems. Then with the rise of AIDS and activists for a number of diseases with low incidence but serious consequence, critics began to argue that public investment in research was not producing products for *their* particular disease. The concept of "orphan drugs" arose, as it became clear that the pharmaceutical industry was not investing in some drugs for some diseases that mattered to real people, because the markets were too small or the targets too complex. Groups of critics began to demand that perhaps we needed to rethink the research–industrial complex.

The late 1970s and 1980s brought challenges on a new front. Members of Congress, long advocates for NIH and NSF funding, began to ask whether their investment was paying off. Was the public getting what they expected? The Republican Congress also brought a climate increasingly friendly to private industry and development. The 1980 Bayh–Dole Act explicitly encouraged universities, which were largely fueled by government funding, to move research into product development by smoothing the legal and economic requirements to do so. Assumptions about government investment in research were shifting. Perhaps it is not enough to give money to independent university researchers through peer-reviewed individual grants and then expect knowledge that will automatically (or even ever) turn into anything useful. Rather, we need to encourage development through government-private partnerships to grease the pipeline from investigator to market.

A few years later, swept in under the "Contract With America," US House of Representatives Speaker Newt Gingrich expressed his enthusiasm for science, but also demanded results from government investment. Under his leadership, the Congress passed the Government Performance and Results Act (GPRA) in 1993 and fine-tuned it thereafter. Every government agency had to develop its response, explaining how it would turn funding into results and what assessment strategy would be used to guarantee success (Office of Management and Budget 2008).

Scientists largely accepted the changing agreement, without serious dissent. The NSF accepted the challenge to rethink their evaluation standards and added what is

known as "Criterion 2." As then-NSF Director Rita Colwell explained in a widely circulated letter, to satisfy Criterion 2 ("What are the broader impacts of the proposed activity?"), investigators had to move beyond curiosity-driven, discovery-oriented research and explain the significance of their research more broadly:

> They must ask: How well does the activity advance discovery and understanding while promoting teaching, training, and learning? How well does the proposed activity broaden the participation of underrepresented groups (e.g., gender, ethnicity, disability, geographic, etc.)? To what extent will it enhance the infrastructure for research and education, such as facilities, instrumentation, networks, and partnerships? Will the results be disseminated broadly to enhance scientific and technological understanding? What are the benefits to society? (<NSF Office of the Director 1999).

Many agreed that this was a valuable addition, and that thinking outside the cloistered academy would serve science well in the end.

Donald Stokes, Professor and Dean of the Woodrow Wilson School of Public and International Affairs at Princeton University (Princeton, NJ), reflected the growing national discussion with his *Pasteur's Quadrant* (Stokes 1997). Although not great history, this essay created considerable flurry as university administrators around the country picked up the discussion of the "quadrant," supposedly representative of Louis Pasteur, of "pure basic," "pure applied," "curiosity-driven," and finally "use-inspired basic research." It is this latter category that created the interest, since it seemed to respond to the changing social contract and, in turn, undoubtedly fed the ethos of translation. What is wrong, after all, with being mission-driven and doing public good rather than just following one's own whims, on the public's dime?

Similarly, many embraced the NIH's emphasis on translation. If we can double the NIH budget, as leading members of Congress began to insist they would do, then surely it was fair for the public to expect, and for scientists to be expected to deliver, results. Results are good. But who decides what count as results? And who decides which science will best get us the results desired? Who decides what to translate, how to do the translation, and when something counts as having been successfully translated? And on what basis (justifiable or not) are any of these decisions made?

By 2007, we clearly had an established ethos of translation, with the implicit value that science that can be translated into results is the best science, and everything else is second-tier. Only slowly has the research community begun to see possible distortions in the integrity of the scientific process that this translational ethos brings with it. We are not claiming that only curiosity-driven research has integrity—far from it. *All* research must be assessed for its integrity and significance, or lack thereof. But the idea that good research must necessarily translate into what some evaluating parties interpret as 'results' is problematic, since the nature of the results actually matters. It matters scientifically, it matters ethically, and it matters socially. The problem is not with translation as such, but in determining the legitimate *languages* from which and into which translation takes place. From the perspectives of science, ethics, and society, not all 'languages' are equally desirable, valid, or appropriate.

INTERROGATING TRANSLATION

What are the implications of this translational model? In an excellent reflective summary article in *Science*, Geoffrey Duyk notes that one result has been that rather than valuing primarily hypothesis-driven research or even discovery-driven science,

> ...there is recognition of the necessity for redefinition of what constitutes technical progress or demonstrates legitimate scholarship. In this context, it is not surprising that there is interest in expanding the depth and breadth of activities as well as know-how expected of life scientists, and that these changes should also be reflected in their research programs" (603).

But, alas, just how to do that remains unclear.

If scientists and clinicians are to pursue truly translational research, with robust interactions of laboratory research and clinical results, Duyk (2003) suggests, we need a new way of doing science. The existing model relies on decentralized, independent researchers each pursuing an individual line of work. But to be truly translational, the academic community must ask: "What are the central issues confronting therapeutic discovery and development today? What types of investments will have the greatest impact on the process?" *Attrition*, defined as the failure to develop drugs, keeps science from actually getting to products. This is the central problem, Duyk argues, and gaining greater "predictability" from basic research by joining knowledge gleaned from research in physiology and genetics is the area needing the most attention. This is an important point, and one that goes beyond the NIH's apparent attention mainly to matters of process as distinct from the substance of the science.

We may know much about genetics, but if there are no focused programs—and no intellectual incentives—to cause researchers to link genetics knowledge to knowledge of physiology, the research will not often yield medical results. This is not just about the failure of genetics to connect with physiology as such, but "The villain in this story is the inherent lack of predictability of our available models for complex biological processes and the inability of our current life science paradigm to provide an effective road map for improvement" (Duyk 2003, 604). We end up failing to integrate across specialties and therefore fail to develop new therapies for the diseases that continue to ail us.

This failure to integrate and therefore to understand the complexity of life will be deadly for a translational program in biology, Duyk concludes, because "It is ultimately the deficits in this domain that deny translational research—despite its appearance of rationality and technological sophistication—a legacy of cost-effectiveness, reliability, and consistent success" (Duyk 2003, 604). We must train scientists to carry out the integrative, whole organism

biology that allows predictions about health on the basis of our scientific knowledge if we are to succeed with the translational program.

But, again, note that these suggestions are relevant regardless of the NIH's commitment to re-engineering the *process* of translational research, largely because Duyk (2003) is here focusing as well on the *substance* of translational research - not just the recipe, but also the ingredients; not just the Roadmap and infrastructure, but also the landscape, the culture, the place, the people, and, of course, the languages they use.

SOME MORE HISTORY

The enthusiasm for stem cell research is an excellent case of the risks and potential benefits of endorsing a translational model. While the Human Genome Project, and its promises for translation of genetics and genomics into diagnostics and therapeutics, has buoyed public enthusiasm about biomedical translation, it is stem cell science that is currently at center stage and that best illuminates what is at issue. To understand why, we offer a bit of context for stem cell research and then focus on research today. History illuminates the shift in ethos from traditional bench research to translational research.

What is stem cell research, how has it developed, and how has it been influenced by demands for translation? We argue that contemporary stem cell research is being shaped by the translational ethos precisely because the research is developing at the same time as the demand for results. There is no longer the possibility of "pure" or "curiosity-driven" exploration of stem cell science because of the nature of nonfederal government funding accompanied by exalted expectations for results. We return to this point, but first lay out what history illustrates about the transition from basic to translational science.

Stem cell research actually began in the late 19th century, in plants, and in the early 20th century, in animals. Stem cells have been defined as those cells that are as yet undifferentiated and that have two capacities: to become differentiated in diverse ways and also to continue multiplying and generating more stem cells. That, at least, is the understanding of pluripotent stem cells of the sort that are found in blastocysts. Until recently, however, the term *stem cell* was often used with a descriptor explaining what the cell would become or its source: *neural stem cell; epithelial stem cell; mesenchymal stem cell*. Today we have a muddle of usages, including what are called *pluripotent cells, precursor cells,* and*progenitor cells*, each more delimited than the previous one.

Ross Harrison (1907) did not call them *stem cells* at all when he extracted neuroblast cells, which were known to give rise to nerve fibers, and transplanted them into a medium of frog lymph. This was the first tissue culture ever, carried out in 1907 and improved in 1910 with the help of bacteriological culture techniques (Maienschein 1991). What Harrison showed, and tissue culture researchers soon realized, was that it is possible to culture some cells for medical uses. Most of these cells do just what they do in normal organisms, and they are either already differentiated or follow their usual developmental path. But in the 1950s, it became clear that some cells retain the capacity to develop in diverse ways. Hematopoietic stem cells, taken from people's bone marrow, have the ability to become a variety of different kinds of cells. Most importantly for the medical purposes at hand, they can become blood cells. First discovered for use with burn victims, the technique of transplanting stem cells gained use with leukemia patients and in a few other cases. This was a matter of transplanting particular kinds of what are now referred to as "adult stem cells" because they are taken from born individuals rather than embryos or fetuses. After transplantation, under select conditions, these stem cells then multiply and also differentiate into other cell types, though of limited variety.

These successes came from cells that were in many ways unlike the cells in embryos. But it seemed logical to carry out stem cell research in embryos too. There was no way to do this in humans, where until 1978 (with the development of *in vitro* fertilization) the embryos remained secured inside the bodies of the women carrying them. But mice are enough like humans that they seemed to provide a model for studying human developmental processes. In the 1970s, mouse embryological research attracted considerable attention within the biological research community, though little attention beyond.

In 1953, Leroy Stevens was studying cancer in mice. Working at the Jackson Laboratory in Bar Harbor, Maine, he was funded by tobacco companies to examine the effects of tobacco and cigarette papers on mice. His research led him to techniques that produced teratomas of abnormal disorganized jumbles of cartilage, teeth, and hair inside the testicles. Why were some germ cells becoming differentiated? Furthermore, why were they becoming specific, selected cell types rather than whole embryos? By 1970, Stevens had identified what he labeled "pluripotent stem cells" that could become some types of cells but that did not have the capacity to become whole organisms (Lewis 2000).

These stem cells quickly gained attention among developmental biologists. What is it that gives them the capacity to become some, but not all, of the kinds of cells of a body? What determines which kinds of cells they become? Could researchers learn to "tame" these cells by engineering them to become specified kinds of cells for medical uses? They were quite aware of this possibility, but also realized that the cells were intriguing precisely because of their unpredictability and undifferentiated status (Robert et al. 2006). Good embryologists knew also that much research would have to be done to discover the fundamental factors causing differentiation and therefore to get from basic science to any sort of medical application.

As Robert Edwards noted, he was working in his laboratory pursing such stem cell basic research when Patrick Steptoe persuaded him to join the effort to develop what came to be called*in vitro* fertilization (Edwards and Steptoe

1980). Clearly, the science of stem cells and the science of differentiation and embryo development were seen as related. The questions concerned how. Mouse embryonic stem cell research continued.

Only in 1998 did *human* embryonic stem cell research leap to public attention, when both James Thomson (Thomson et al. 1998), working with human embryos, and John Gearhart (Gearhart 1998), working with human fetal tissue, discovered the pluripotent stem cells in humans that Stevens had nearly thirty years earlier identified in mice (Shamblott et al. 1998). Commentators have speculated that this discovery probably would have received a much different response had the public not learned about the cloning of Dolly, the sheep, just the year before. Stem cell research, immediately following cloning, fell into the same furor of bioethical debate and immediately the solid details of the science became much less important than the prospects—or fears—for application. Simultaneously with the possibility of carrying out basic developmental study of human pluripotent stem cells, it became necessary also to address both calls for biomedical translation and political/religious/ethical demands for limitations on embryo research. It is this concurrence of science and application that makes human stem cell research the prime example of the impacts of the translational ethos in contemporary America.

STEM CELL RESEARCH AS EXEMPLARY OF THE TRANSLATIONAL ETHOS

Stem cell research is a poster child for translational research. Many researchers ground their claims for funding in terms of claimed concrete clinical applications. Researchers make claims that we are experiencing "a new era in biology and medicine" (Keller 2005, 1129), where changes in our understanding of fundamental biological concepts have resulted in altered expectations about what can be brought into the clinic, and how fast. Stem cell research outcomes may well set the agenda for future funding initiatives and change the ways in which translational research is understood, by both scientists and the public.

Here we focus on human stem cell research, setting aside studies of mice and other organisms, even though they are also impacted by the current translational demands. We take the term *stem cell research* to include studies of the full range of things that have been labeled "stem cells." These include *multipotent stem cells*, meaning those cells with the capacity to 1) multiply indefinitely in cultured cell lines, 2) self-renew, and 3) differentiate into region, or organ specific cell types. These multipotent cells can be isolated from various regions of the body (e.g., brain, eye, blood, muscle) in both prenatal and adult tissue. In contrast, *embryonic stem cells* are isolated from embryos at the blastocyst stage, and are distinguished by their ability to generate all the various cell types found in an adult. In addition, like adult stem cells, they can self-renew and multiply in culture.

Stem cell research has captured the public's attention. Celebrity support, political campaigns (particularly those surrounding the California referendum and US federal funding decisions), and moral debates (especially regarding sources of stem cells and the status of the embryo) have converged to produce a "stem cell circus" (e.g., Vergano 2004). Some have called for closer examination of the 'hype' surrounding stem cell research, particularly with regard to false public expectations being created both by the popular media and by researchers themselves (Daley et al. 2003). Critics writing for both scientific and lay audiences worry that this hype promotes unrealistic expectations about which disease conditions are likely to be treatable and on what timelines.

We take a different approach by placing such claims in the wider context of translational research: while the public may not recognize the term *translation* in this context, it captures the basis for hopes about what stem cell research might achieve, how it might travel from the bench to people's everyday bedsides. Although public attention typically focuses on what might be viewed as ethical and political issues, we contend that we need to look more closely at the impacts of repeated claims about the translational imperatives for research.

Scientists' understanding of stem cells, and of heredity and development more broadly, has altered our views about biology and what might be possible in the way of applications. We are beginning to have different conceptions from those of even a few years ago about what can be controlled and modified in development and its biomedical applications. Stem cell research is "widely touted as a new treatment modality" (Daley et al. 2003, 398). Stem cells are now thought to be different from other sorts of cells in that they are plastic and can be "reprogrammed" to behave in a variety of desirable ways. They thus may allow new types of therapies, oftentimes for disease conditions with few available treatment options. Stem cell technologies (combined with genomics) may also allow for individualized therapies, to avoid immunological rejection.

But in order to make these promises realizable, we need considerably more knowledge about how basic development and cell interactions work (Robert et al. 2006). Some basic biologists fear that the pressures to ask particular kinds of questions that will help us understand stem cell development are undercutting their abilities to study other kinds of fundamental developmental processes without the direct connections to stem cells and therapies. Clinicians are often caricatured as wanting to rush into the clinic, even before the science is ready, but in the case of stem cells it is the demand for translation itself that is driving the clinical studies, while careful benchside study is often being ignored. Yet it is the fundamental research in the lab and in the clinic on which we will need to rely. We are, in effect, translating from sadly incomplete benchside and bedside source languages, languages with unknown grammar, unknown syntax, and few if any native speakers.

In the end, translation may prove extremely difficult to achieve for stem cells in part because we do not know enough of the basic underlying science. Of course, some basic discoveries may be made along the way, but perhaps

incidentally and incompletely. At some point, we must address the tensions created within science by the rush to translation. Stem cell research raises questions about relationships between basic biological research, clinical research, and medical therapies. It suggests that the push for translational research may actually transform the participating disciplines.

Separate research fields often share goals. For example, both basic developmental biology and certain subfields of clinical medicine want to find ways to repair or regenerate compromised systems using stem cells, while basic toxicology and clinical pharmacology ask how stem cell lines might serve as assays for testing new drugs. Shared goals encourage making connections across disciplines to promote conceptual unification and efficiency (economic and otherwise). The agenda for translational research encourages such connections (and perhaps also more interdisciplinary or multidisciplinary research) yet also raises questions about how they can be more than superficial.

Skeptics might note that, although stem cell researchers often invoke the rhetoric of translation, and even provide evidence of their commitment to it by having research teams with both basic and clinical researchers, actual practices of such interdisciplinary translational research teams have not been adequately documented or scrutinized (Wainwright et al. 2006). The excitement surrounding stem cells has brought together an unusual range of research programs, both within and across disciplines. Underneath the surface of what often are presented as unified goals lay different fundamental concepts: some researchers are searching for "stemness" and examining how stem cell development works, in detail and in order to understand the processes themselves. Others have turned to stem cells because they appear to provide the most promising approach to questions previously asked within different contexts (e.g., clinical researchers interested in neural degenerative diseases). Questions remain about how these different approaches can best work together and what difference it makes when they do.

Furthermore, the institutional contexts where stem cell research is done have changed dramatically: there are institutes devoted to stem cell research (often termed *regenerative medicine*) ,which include researchers from different fields and explicit discussion of translation in their mandates. New biotech enterprises are arising with a range of promises and proposals to promote stem cell science and results. How these changing institutional contexts affect the science and influence the likelihood of "success" remains unclear.

LESSONS FOR SCIENCE, LESSONS FOR ETHICS

Science policy decisions are typically shaped by powerful political forces with particular assumptions, and often policy is driven primarily by funding interests. Scientists lobby for increased funding; patient advocacy groups push for more funding (and presumed results) while also raising funds and investing in translational projects; and other advocacy lobbyists push their own set of values that influence the funding. As we accept a translational model for research, including the expectation of applied payouts, what are the consequences? What are the effects for scientists? For societal expectations? What are the policy implications? The ethical implications?

We can, as usual, bring ethical considerations to bear in assessing particular research protocols. But how does that change if we are assessing both the research and its expected translational results at the same time? If we are indeed entering a new social contract, we have much to learn about how it will work and the implications for scientists, for the scientific enterprise, and for scientific institutions as well as for the public.

Stem cell science reveals new ideas about the 'right way' to do science. Although we have seen historical examples of "mission-driven science," such as the push to build atomic bombs, reach the moon, or sequence the human genome, this case is different. In this case, scientists are not the main experts for deciding how their mission is to be accomplished. Rather, those considered relevant "experts" have expanded dramatically, to include not only politicians but also bureaucrats, members of voluntary health organizations, ethicists (and would-be ethicists), clinicians, and even celebrities. Public, political, and industrial demands, particularly with regard to what the products of the research should be, shape the landscape within which the research trajectory is determined, and that landscape is dominated by various demands for translation. Where the Vannevar Bush model emphasized purity of science in its own right (even when it could also have worthy applications), today's translational research builds certain (and sometimes dubious) end goals into the research from the start. One lesson is that *assuming* outcomes (however well-intentioned) alters the research endeavor.

In addition, the translational ethos can lead to distorted ethical results. For example, some ethical discussion surrounding stem cell science has addressed how science might offer a technical "solution" to ethical problems associated with embryonic stem cells (Snyder et al. 2006). In particular William Hurlbut has suggested altered nuclear transfer as a technological end-run around some ethical problems posed by harvesting embryonic stem cells (Hurlbut 2005). Altered nuclear transfer involves manipulating the genome of eggs prior to fusion with somatic cells, in order to prevent the resultant embryos from developing normally beyond the blastocyst stage, thereby rendering the non-viable and supposedly solving all ethical problems associated with their procurement.

We are concerned that this proposal has an important negative effect on the ethical discourse about stem cell research. It distorts the discourse by taking the desire for translating science into results as given, then asserts that technology can determine when life begins and what life is and thereby purportedly solve the ethical problems while preserving the translational objectives. Yet technology and translational assumptions cannot solve a highly contentious

issue with a long, rich and complicated history (Maienschein 2003). Furthermore, this approach suggests that the *only* ethical problem with stem cell research is the "when life begins" issue, thereby highlighting the "potential person" or "viability" problem at the expense of the many other ethical issues raised by embryonic stem cell research (e.g., Baylis and Downie 2005; Lysaght et al. 2006; Giacomini et al. 2007)—including those raised by embryonic stem cell research as translational research (Robert et al. 2006). Moreover, such putative "solutions" risk derailing stem cell research from more scientifically sound paths, inappropriately delaying potential clinical applications while contributing nothing to our basic understanding of development or of the clinical potential of human embryonic stem cells. The problem is taking the translation as an unquestioned desirable goal and trying to make the ethics fit. This distorts the ethical discussion as well as the science.

What about the impact of the translational ethos on our notions of science and scientific change? Does all the rhetoric about translation and the requirement that scientists make their translational outcomes clear and of first priority actually bring more than a new model for scientific research? Does it actually change the science done, and if so in what way is it truly new? And what difference does that make? Does a translational model demand a different role for individual scientists in doing science, such that they are now driven by the need for translation and must choose particular kinds of scientific questions or methods or organisms? If so, is the translational model actually a stable strategy for scientific research? Or by pushing so much emphasis on development and results does this approach, in fact, distort the generation of scientific knowledge? Here, we have aimed to show that distortion is indeed occurring in the case of stem cell science both within the basic science and in the surrounding ethical discussions. This case leads us to wonder how other areas of biomedical research might be similarly affected and leads to this call for further analysis.

It is not the case that reflecting on outcomes is always problematic, of course. Although assuming (and imposing) the expectation of meeting particular outcomes can be problematic as a guide for the scientific research enterprise, openly and collaboratively *negotiating* outcomes for scientific research may nonetheless be entirely desirable. Crafting tools for undertaking such negotiations is a fraught task, but an important one to foster connections between scientific research and valuable social goals - especially but not exclusively where the research is publicly funded (Sarewitz 2000; Guston 2004; Pirtle 2006; see also Kitcher 2001). The problem with the translational ethos is not translation as such, but rather the nature of the source language and certain presumptions about outcomes. We all want results from our science, but too many questions—what will count as results, who will certify these, and who is left out as a result of the choices—remain wide open. It should be simultaneously possible to protect the integrity of the source language, generate new understanding through "translation," and negotiate frankly and responsibly about the desirability of particular outcomes. That is a task to which historians and philosophers of science, ethicists, and policy scholars should turn their sustained and focused attention.

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Sidebar 1. Institutional changes in process required to engineer translational research, according to the United States National Institutes of Health (NIH)

Re-engineering the clinical and translational sciences requires the NIH to:

- Provide institutions with an academic home and integrated resources needed to advance the new intellectual discipline of clinical and translational sciences;
- Create and nurture robust clinical research teams;
- Establish or expand degree granting programs in clinical research;
- Consolidate, integrate, and strengthen infrastructure resources to synergize clinical research and develop interdisciplinary talent;
- Reduce barriers that impede the transfer of laboratory discoveries into clinical trials;
- Enhance and integrate clinical informatics support; and
- Advance the health of the nation by transforming patient observations and basic discovery research into clinical practice.

Data from: http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp (accessed July 22, 2005). This material is now available at: http://im.org/AAIM/PublicPolicy/MERLIN/2005/May/05-13-05.htm (accessed April 4, 2007).