STEM CELLS TRANSLATIONAL MEDICINE™

PERSPECTIVES

Steering a New Course for Stem Cell Research: NIH's Intramural Center for Regenerative Medicine

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SUMMARY

The phenomenal progress made in stem cell biology in the past few years has infused the field of regenerative medicine with a great deal of scientific enthusiasm. However, along with the excitement of discovery comes a new sense of translational urgency. The prospect of using embryonic and induced pluripotent stem cell tools and technologies to produce cell-based therapies and other treatments is no longer a distant dream; it is a very real opportunity that demands our attention today. As with most new fields, regenerative medicine has experienced some significant growing pains, and we have identified a number of key obstacles to progress. Given our role as the lead U.S. biomedical research agency and the world's largest supporter of medical research, the National Institutes of Health (NIH) has a responsibility to find ways to reduce or remove many of these obstacles and, consequently, has—and continues—to respond to these challenges in a variety of ways. In this brief essay, we will review our progress and highlight a new development: the founding of a Center for Regenerative Medicine on the NIH campus.

A Short History of Stem Cell Funding

The first NIH funding for research involving human embryonic stem cells (hESCs) was authorized more than a decade ago by President George W. Bush, but that decision only allowed the use of cell lines for which derivation had begun before the President's decision date of August 9, 2001 [1]. Ultimately, only 21 cell lines were available for distribution, and, as science moved forward, it became clear that this arbitrary time stamp was inhibiting the field significantly. Still, despite such constraints, the NIH strongly supported the regenerative medicine field and, since fiscal year 2008, has allocated approximately $1.5 billion to human stem cell-related research, with about $396 million going to hESC research and $1.1 billion going to human adult stem cell research, which includes $213 million for human induced pluripotent stem cell research [2].

Another seismic shift occurred about 5 years ago, when, in an unexpected breakthrough, Takahashi and Yamanaka showed that it is possible to take adult cells and reprogram them to produce induced pluripotent cells (iPSCs) that appear very similar to embryonic stem cells [3]. The initial methods that employed viral vectors for overexpressing transcription factors represented a barrier to therapeutic utility of the iPSCs because of the risk of insertional mutagenesis [4] and immunogenic response [5]. However, the rapid pace of discovery brought nonintegrative reprogramming strategies [6, 7] and highly efficient protocols for directed differentiation [8]. Together, these advances have made the idea of clinical applications more realistic. Although some have argued that hESC research is no longer needed, comparisons between iPSCs and hESCs continue to be critical for progress. The two types of stem cells are not identical, and hESCs remain the scientific gold standard.

Less than 3 months after taking office in 2009, President Barack Obama issued an Executive Order stating that the Secretary of Health and Human Services, through the Director of the NIH, may support and conduct responsible, scientifically worthy human stem cell research, including hESC research to the extent permitted by law [9]. This order asked the NIH to review existing guidelines and issue new guidelines for human stem cell research. After careful analysis of more than 49,000 comments, the NIH published final guidelines that allow federal funding for research involving cell lines derived from embryos that were created using in vitro fertilization for reproductive purposes and no longer needed for that purpose; that were donated for research by individuals who sought reproductive treatment; and for which donors gave voluntary written consent [10].

Since then, based on careful ethical review involving either rigorous review by NIH staff or by a working group of primarily outside experts and the Advisory Committee to the Director, the NIH has approved 136 ESC lines for use in NIH-funded research [11]. This action has fueled a rapid expansion of effort and progress in a broad range of research areas, including studies aimed at improving stem cell technologies, comparing different types of stem cells, and developing cell types for use in treating debilitating conditions such as diabetes, cardiovascular disorders, and neurodegenerative diseases.

More recently, the Obama administration has vigorously—and successfully—defended a legal challenge to continued federal support of human embryonic stem cell research. The July 27, 2011, favorable ruling by the U.S. District Court for the District of Columbia, in *Sherley v. Sebelius*, should help to ensure this groundbreaking research can continue to move forward as the litigation wends its way through the courts [12].

One New Intramural Center, Many New Possibilities

Although basic science advances occur almost weekly in stem cell research, there is a great desire to explore clinical applications, along with an equally strong desire not to have those applications delayed by the absence of appropriate interdisciplinary centers of excellence. Such centers need to include facilities for the con-

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duct of cutting edge, first-in-human clinical research. The largest such research hospital in the world is the Clinical Center at NIH [13]. Just recognized with a 2011 Lasker–Bloomberg Award for Public Service [14], the Clinical Center is where the cures for childhood leukemia, Hodgkin's disease, and Gaucher disease were developed, and where the first human gene therapy trials were conducted.

In early 2010, drawing upon resources in the NIH Director's Common Fund, the NIH established its own intramural center to develop new therapies using stem cell approaches [15]. Originally dubbed the NIH Induced Pluripotent Stem Cell Center (NiPC), it was recently renamed the NIH Center for Regenerative Medicine (NIH-CRM) to recognize its broader scope, which includes new therapeutic possibilities, such as adult stem cells and transdifferentiated cells, as well as to reflect the fact that the translational use of iPSCs will require diverse research expertise (Box 1).

The NIH-CRM will not operate in isolation. Rather, it will draw upon the investment in staff, buildings, and equipment that the NIH already has in place to take things from the bench to the bedside. In particular, the NIH-CRM plans to interact closely with the NIH Center for Translational Therapeutics (NCTT) [16] and the NIH Clinical Center, both of which are widely recognized as state-of-the-art, best-in-class centers. For example, the NIH-CRM might work with a clinical researcher who sees patients with a rare disorder to generate iPSC lines, which the NCTT could then use in high-throughput screening assays to identify small molecules or other compounds that may have therapeutic potential for the disease. In addition, NIH-CRM researchers, working within the Clinical Center's Good Manufacturing Practice environment, could use genetic engineering techniques to rescue or repair cell lines derived from the patients and then return them to the patients in early-stage clinical trials. The NIH-CRM will also work hand-in-glove with the NIH's proposed National Center for Advancing Translational Sciences [17], the NIH Stem Cell Unit [18], and the NIH Bone Marrow Stromal Stem Cell Transplantation Center [19], all of which will position the Center to make rapid, clinically relevant advances in this pioneering field.

Administered by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the NIH-CRM will also serve as a resource for the wider NIH scientific community, providing stem cells along with the supporting protocols and standard operating procedures used to derive, culture, and differentiate them into different cell types. Thus, the NIH-CRM will operate in a transparent manner, share information swiftly, and create resources that will benefit the broad scientific community. It is important to note that the NIH Bone Marrow Stromal Stem Cell Transplantation Center already has worked with the Clinical Center to file Investigational New Drug applications for clinical trials using adult stem cells and expects to submit several more soon.

As a government entity, the NIH-CRM is ideally positioned to use the infrastructure and resources of the NIH to facilitate the rapid translation of highly promising therapies to the clinic. This broadly collaborative effort will tap into the respective strengths of many different NIH Institutes and Centers and draw upon the considerable expertise that exists within both the intramural and extramural arms of the NIH.

Furthermore, the NIH-CRM is well situated to interact with other federal agencies, such as the Food and Drug Administration (FDA), in ways that may inform efforts to address thorny issues affecting the entire stem cell research community (Table 1). Consider the matter of stem cell standards or, more precisely, the disturbing lack thereof. The need for a standardized control test has become even more urgent in recent years with the explosive growth in the number of iPSC lines, which now far surpasses the number of ESC lines. One of the NIH-CRM's first undertakings will be the development of off-the-shelf control cell lines that can be used as a comparator to evaluate newly generated cell lines, as well as for testing and developing validated assays. This will not be a simple task given the cells will need to be free from use constraints so they can be widely distributed throughout the stem cell research community.

Moving into the Medical Mainstream

Clearly, many details still remain to be put in place at the NIH-CRM, and uncertainties remain regarding the future course of the entire field of stem cell research. Right now, no one can predict which cell type will prove to have the most therapeutic promise, what conditions will be most amenable to cell-based approaches, and whether scientists, regulators, and policy makers will develop the ability to work effectively together to move these new therapies from the microscope to the marketplace.

Table 1. Current Roadblocks to Stem Cell Therapy

1.	Periods of limited government involvement due to legal, political and ethical issues
2.	Lack of mature regulatory policy
3.	Absence of uniform regulations and activity across countries
4.	Absence of uniform global patent interpretations on pluripotent stem cells
5.	Absence of standards and controls
6.	Lack of successful business models thus far for autologous therapy
7.	Limited availability of investment in new business models
8.	Issues of consent and sourcing related to cell-based manufacture
9.	Limited expertise in scaled-up cell manufacturing
10.	Issues of risk management, reimbursement, and long-term follow-up in cell-based therapy trials.

Obstacles to translation of novel findings to cell-based therapy. The NIH Center for Regenerative Medicine may be able to assist, as an unbiased arbiter, to resolve some of these issues.

The Early Days

Although the NIH-CRM did not gain a permanent Director until August 2011, the fledgling Center has been far from idle over the past 1.5 years. Under the guidance of Acting Director John O'Shea of NIAMS, the NIH-CRM has supported 24 intramural pilot projects that will facilitate the clinical translation of iPSCs. Those projects include the maintenance of pluripotency, the development of preclinical animal models, and the methodology for gene correction and insertion. In July 2011, the NIH-CRM and the NIH Stem Cell Interest Group cosponsored an inaugural stem cell research symposium, attended by more than 400 people, to provide a platform for NIH-CRM-funded investigators to present their latest findings, as well as to help build a collaborative community of investigators. In a related effort to jump-start the intramural program's stem cell capabilities, the NIH-CRM has sponsored several training courses in mouse and human iPSC generation and culture.

What we do know is that many hurdles listed in Table 1 are already becoming less of a challenge. Creative researchers have shown that particular models of delivery of cell-based therapy can work and, equally importantly, that others do not. Technical advances, such as integration-free iPSC reprogramming, will overcome some issues. The expertise of the regulatory authorities has increased as they gain more experience approving such therapies and efforts to harmonize standards begin to bear fruit. Although research budgets are very tight, federal funding for stem cell research in the United States and abroad has increased in recent years, and this, coupled with state funding, has served to advance the field. Pharmaceutical companies also have begun to invest in this area. Importantly, public support for stem cell research remains strong, thanks to the realization that such work offers hope to millions of people who suffer from debilitating diseases and incurable conditions.

From our vantage point, it appears that the field of regenerative medicine has moved out of the rocky shallows and is rapidly sailing towards the therapeutic mainstream. As it has for so many other translational advances in the past, the NIH stands ready and willing to steer.

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