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National Institutes of Health: A Catalyst in Advancing Regenerative Medicine Science Into Practice

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Abstract

The stem cell domain of the regenerative medicine field has seen fundamental changes initiated by seminal discoveries in cell biology, genetic engineering, and whole genome sequencing. Many of these discoveries were funded in part by the National Institutes of Health (NIH), and the NIH remains a leader in supporting research in the United States. However, as the field has developed, the NIH has responded proactively to identify roadblocks and to develop solutions that will accelerate translation of basic discoveries to the clinical setting. These activities range from organizing specialized workshops and coordinating activities among international organizations and the different arms of the government to funding small-scale industry. In addition, the NIH has been a key driver in providing needed infrastructure in areas in which the private sector has been unable to, or does not believe it can, invest. These activities of the NIH are as important as its traditional funding role, and I believe they have contributed to the innovation and rapid pace of discovery in this field.

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THE NIH AND ITS ROLE IN ADVANCING REGENERATIVE MEDICINE SCIENCE INTO PRACTICE

As the largest provider of research dollars in the Unites States, the NIH plays an important role in funding research and, as with any other field, has played a leading role in supporting regenerative medicine research. The dollar amount invested in research is substantial (Figure), and approximately a billion dollars a year are invested directly into stem cell research.[1] However, funding is not the only important function of a government agency. As in any new area, the government's role is larger than simply providing research dollars (Table 1). To be responsive to the community it serves, the NIH must be able to identify trends, anticipate change, develop programs, and be prepared to respond to these anticipated challenges.[2] In the subsequent sections, I provide an overview of where I see the field moving and how I see the NIH responding to these challenges.

IDENTIFYING TRENDS AND ROADBLOCKS

Trends that I see in the field are summarized in Table 2. These trends, I believe, have shaped the way the field has grown. They affect the choice of cells researchers use, the regulatory pathways investigators follow, the type of manufacturing paradigm they utilize, how they obtain funding for the development process to generate a regulated product, and how they market the product. Because the NIH is the premier source of funding in the United States, it is perhaps only reasonable to assume that NIH funding decisions contributed to these trends, and I have no doubt that ongoing allocation efforts by the NIH will continue to shape the field. What the NIH recognized and what none of the other funding agencies anticipated was the rapid translation of these fundamental discoveries to

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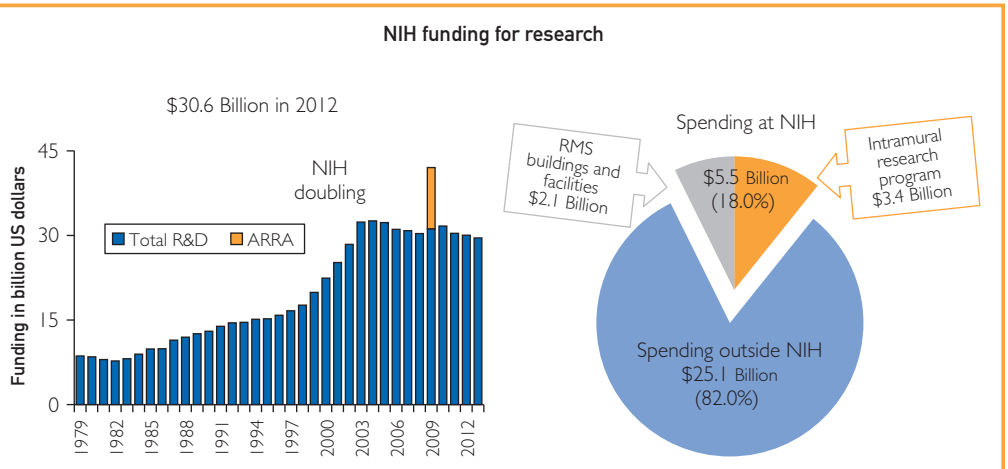

FIGURE. National Institutes of Health (NIH) funding for research has doubled over the past 10 years and has remained at this high level over the past 5 years. ARRA = American Recovery & Reinvestment Act; R&D = research and development; RMS = Research Management and Support.

clinical practice and how quickly the NIH must respond if it wishes to remain proactive rather than reactive.

In hindsight, perhaps one could have anticipated this acceleration. The change has been rapid because the field could take advantage of independent discoveries that were being made by scientists in other domains and apply these solutions to current problems in the regenerative medicine field. For example, the award-winning work on pluripotency by Gurdon and Byrne[3] and Takahashi et al[4] enabled investigators to apply the Nobel Prize–winning work of Capecchi and Thomas[5,6] on homologous recombination to human stem cells. These new results and discoveries were further accelerated by the advances in genetic engineering made by other groups working in fields as diverse as plant biology.[7] These new engineering techniques in turn could be readily refined as the embryonic stem cell (ESC) and induced pluripotent stem cell (IPSC) discoveries enabled researchers to test tissues rapidly in large panels of lines whose culture conditions had been standardized and whose properties we understand in detail thanks to the advances in next-generation sequencing.[8,9] Table 2 highlights discoveries or developments that have contributed to this rapid acceleration. Although no list can be comprehensive, the following breakthroughs have contributed to the accelerating pace of change and contributed to the birth of entire industries.

TABLE 1. Possible Roles of the National Institutes of Health in Translating Research Discoveries to Therapy

Identify trends and roadblocks
Fund efforts likely to succeed
Decrease the risks of translational efforts
Provide the infrastructure to enable innovation
Ensure that appropriate regulations exist
Help establish rules and regulations
Coordinate activity
Monitor the field
Showcase or provide examples

Each of the breakthroughs I have identified has had a fundamental effect on the field, although some at first blush may sound trivial. The ability to freeze cells and ship them, for example, has led to the development of a tissue banking service that includes storage and shipping of organs for transplant, providing bone marrow and apheresis products, and banking of cord blood and other newer cell types now being considered for therapy. More than 150 cord blood storage companies exist worldwide, and bone marrow transplant is the standard of care with tissue routinely being shipped from one country to another for transplant.

Next-generation sequencing companies abound, and in addition to providing services to the academic community, they provide sequencing services to the medical community and have made testing for a large number of

TABLE 2. Major Trends Shaping the Field of Regenerative Medicine[a]
Rapid technological advances in PSC technology
Ability to manufacture, freeze, and ship cells on a large scale
Decreasing cost of next-generation sequencing
Breakthroughs in gene engineering technologies
Ability to make 3-dimensional structures
Regulations defining what is a product vs practice of medicine
The changing patent landscape
Changes in the funding landscape
The pharmaceutical business model is undergoing revamping
New business models for autologous therapy
Hospitals and academic institutions taking the lead in personalized medicine
The drug reimbursement model is changing
Health care delivery and cost containment models are being reevaluated

[a]PSC = pluripotent stem cell.

familial diseases feasible. It is now possible to design a breast cancer screen or a familial Parkinson disease screen to look at all sequence variations in a subset of genes to determine risk and perform preventive medical procedures. Sequencing in individuals with undiagnosed diseases has already yielded dividends for those individuals or families. The Beerys' story on identifying the sequence variations that led to a diagnosis and an off-the-shelf treatment[10] or the story of Lilly Grossman[11] are illustrative of the power of this methodology. High-profile stories and the direct marketing of tests to patients have changed the field in unexpected ways.[12,13]

The ability to obtain cells from well-characterized, well-annotated parent populations and differentiate them from cells that were difficult to obtain in any other way, and to do so in numbers that are sufficient for screening and therapy, has caused a sea change in the field. One obvious example is the number of companies that are being established to consider cell-based therapy. Several of the companies that have somatic cell products have now successfully navigated the regulatory pathway to have commercial products. These companies range from mesenchymal stem cell companies and cord blood–based services to skin- and cartilage-based product providers. Companies using other cell types have products in late-stage trials, and such companies include neural stem cell–based companies, ESC-derived retinal cell– and islet cell–based companies, and more recently, IPSC-derived product–based companies.

Although there are not as many companies in the screening and toxicology field, it is perhaps important to note that the screening world and in particular the toxicology screening world is undergoing a change as a result of the advances in our ability to generate specific types of stem cells. Perhaps the earliest example of change was the adoption of the ESC test for toxicology by the European Center for Validation of Alternate Methods. More recently, the availability of cardiomyocytes from human pluripotent cells on a large scale from a number of companies and the demonstration that human cardiomyocytes are a better predictor of cardiotoxicity than cardiomyocytes from other species has led to widespread adoption of this test in early-stage drug screening.[14,15] Thanks to the advances in bioreactor technology, the availability of other cell types in bulk cultures will further accelerate adoption. Equally important has been the work of several investigators documenting the utility of pluripotent stem cell–derived cells in screening for new therapeutics and their utility for screening in orphan and rare disorders. These new findings have led to the availability of novel screening services and the establishment of public-private partnerships to identify compounds using panels of ESC- and PSC-derived cells.

The NIH interprets these trends to allocate resources and guide its budget decisions and to identify experts, think tanks, and societies that can help provide feedback on how best to move forward.[16] Equally important, the NIH has tried to understand what roadblocks need to be resolved first to enable the rapid pace of change to continue.

DESPITE POSITIVE TRENDS, ROADBLOCKS EXIST AND NEED TO BE RESOLVED

The NIH has identified several major roadblocks that hamper translational science (Table 3), ranging from the obvious, such as the reduction in funding from federal sources, to the less obvious practical issues, such as the lack of appropriate consent documents. Although space constraints limit a detailed discussion, I will discuss some examples of the types of efforts undertaken by the NIH to resolve some of these roadblocks.

To obtain the best return on scarce research dollars, the NIH, in addition to its direct research support, has partnered with other government

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TABLE 3. Translational Science Roadblocks and NIH Solutions

Roadblocks	NIH solutions
Difficulties in procuring cells	Develop consent documents, identify tissue sourcing agencies, identify and fund storage and banking groups and enable them to distribute tissue
Difficulty in navigating the patent landscape	Develop landscape documents, develop a UBMTA, establish standardized LULLS for engineering technologies
Lack of infrastructure to manufacture cells	Develop PACT centers, enable companies, identify CMOs, resolve roadblocks to academic-industry collaborations with service providers
No coordinating activity	NIHCRM, CNRM, work with ATCC on testing, help coordinate FDA harmonization efforts, work with international repositories, develop controls and standards, identify biorepositories and ensure distribution of cells, work with NIEHS on cell panels, annual meeting with pharmaceutical firms to coordinate and establish public-private partnerships
Limited funding for translational efforts	PO1, SBIR, STTR, cofunding with other funding agencies, establish public-private partnerships
No regulatory clarity	NIH-FDA meetings, international harmonization, work with societies and other stakeholders
Lack of screening programs	NCATS, NIH funding for screening centers, public-private partnerships
Lack of clarity for the cell therapy process	NIH-FDA meetings, develop intramural capability, NIH Clinical Center for orphan and rare diseases, CTSAs

ATTC = American Type Culture Collection; CMO = contact manufacturing organization; CNRM = Center for Neuroscience and Regenerative Medicine; CTSA = Clinical and Translational Sciences Award; FDA = Food and Drug Administration; LULLS = limited-use label licenses; NCATS = National Center for Advancing Translational Science; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NIHCRM = NIH Center for Regenerative Medicine; PACT = Production Assistance for Cellular Therapies; PO1 = Research Program Project grant; SBIR = Small Business Innovation Research program; STTR = Small Business Technology Transfer program; UBMTA = uniform biological material transfer agreement.

agencies such as the Defense Advanced Research Projects Agency, the Department of Defense, the Department of Veterans Affairs, the National Institute of Science and Technology, and the Environmental Protection Agency to help coordinate funding efforts and has begun to develop common data sets of information. The NIH has noted that funding for this activity has come from other sources as well, including private foundations, state governments, and industry, and the NIH has worked hard to help coordinate such activity and develop public-private partnerships.[17] Important components of the public-private partnership that have been the cornerstones of innovation in biotechnology are the Small Business Innovation Research program, the Small Business Technology Transfer program, and advanced technology funding programs. The NIH has encouraged stem cell companies to register and apply for these grants and has worked at the institutional level to ensure that companies could access the requisite technology to be competitive in the bidding process (http://oamp.od.nih.gov/contracts/contract.htm).

The NIH realized that current funding programs may not be suited for translational research and that necessary infrastructure would need to be developed to allow for successful translation. As the NIH engaged in discussion with stakeholders, there existed a need to modify the standard Research Project Grant (R01) program and introduce longer-term grants and larger project grants with larger dollar amounts to enable preclinical studies to be performed by academic investigators.[16]

Three major initiatives introduced by Dr Francis S. Collins, director of the NIH, deserve special mention. The National Center for Advancing Translational Science was established to meet the tasks of accelerating translational science, including work with stem cells in screening and toxicology, and helping bridge the gap that exists because of a dearth of funding from traditional investing sources. The NIH has identified the NIH Clinical Center as an invaluable resource and developed plans to allow access to NIH-funded investigators worldwide. Dr John I. Gallin, the director of the Clinical Center, has identified different ways researchers can work with the center,[18] including work on stem cells. More recently, Dr Collins established the NIH Center for Regenerative Medicine to help identify the roadblocks that exist for this field and to develop creative solutions to resolve such roadblocks.

In an attempt to develop synergy and enhance the ability of investigators to move their results to the next step on the translation path, the NIH has developed model consent forms and material transfer agreements, identified patent issues, and negotiated appropriate limited-use label licenses to enable researchers to distribute their results widely and access services from service providers. To further ensure access to key reagents, the NIH Center for Regenerative Medicine generated IPSC lines including engineered reporter lines, deposited them with repositories, and ensured that these repositories could distribute cell lines worldwide with minimal restrictions at a reasonable cost. The NIH has also developed Program Assistance for Cellular Therapeutics centers for manufacturing clinical-grade cells and university-based screening centers to allow investigators access to resources that would be difficult to generate for any individual group. The NIH has also transferred expertise and reagents to service providers so that such technology would be widely disseminated and allow individual investigators to focus on key questions rather than having to develop and standardize protocols themselves.

To reduce the cost of access to clinically compliant lines that will be required for therapy and to make preclinical studies easier, the NIH funded the development of an ESC bank at a Current Good Manufacturing Practices (CGMP) site and the generation of a set of IPSC lines from healthy donors using commercial contract manufacturing organizations. In addition, it funded the development of reporter cell line subclones in these CGMP-compliant lines. Because the government bore the initial costs, obtaining a matched research-grade stock of the cells will cost individual investigators much less and, more importantly, will save them time while providing some security that lines made with a similar process will behave similarly. The reporter cell line subclones will make biodistribution and other required safety studies much easier to assess, and because they will be closely related to the CGMP line, it will likely mean fewer concerns about interpreting the results. A criterion for these reporter cell lines was that they be available to both commercial and noncommercial groups. This stipulation was important because it meant that as research transitioned from an academic to a more applied approach, investigators would not have to go back and remake lines (or develop new constructs) or negotiate licenses at a later and more expensive stage.

It is hoped that while each initiative may have only a small effect, the cumulative effect of resolving roadblocks along the entire path may be synergistic. It is further hoped that any investigator armed with the appropriate consent forms, material transfer agreements, and licenses and with access to standardized cell lines and controls (that can be obtained at a reasonable cost by a single phone call) can readily develop a screening or therapeutic intervention protocol. Further development of the novel protocol can be funded via novel granting mechanisms or with the assistance of the National Center for Advancing Translational Science, the NIH Clinical Center, or university-funded screening and cell manufacturing centers, enabling rapid development that can then be disseminated widely via service providers, small businesses, and pharmaceutical partners who in turn are funded by specialized granting programs or public-private partnerships to permit widespread access to cell-based therapy.

THE NIH MUST DEVELOP NEW WAYS TO SUPPORT NEW BUSINESS MODELS

Although the NIH believes that the aforementioned efforts will play an important role in accelerating the development of cell-based therapeutic interventions, it recognizes that many of the old models of drug delivery may not work, and new business models will have to be supported. In examining the field, the new efforts can be broadly divided into 3 different groups: engineered cells, hospital-based services, and "homegrown" tissues.

Engineered Cells

As discussed previously, major advances have been made in engineering of cells and continuous improvements in vector design, delivery, and development of self-inactivating vectors or integration-free gene delivery technologies. Gene therapy companies have begun to adopt these techniques, and companies have initiated clinical trials with such therapies. Three different approaches are being adopted: (1) the use of cells as delivery vehicles whereby the product is inserted into a "safe harbor" site using vectors that allow conditional

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delivery that is not epigenomically silenced for the lifetime of the individual, (2) a knockout strategy in which the abnormal product is deleted using precision excision methods, and (3) a repair strategy in which the specific defect is corrected. Individual groups and companies are exploring these technologies for therapy in diseases such as cancer, human immunodeficiency virus infection, and lysosomal storage disorders.[19,20]

Hospital-Based Services

Two trends in practice in some medical centers are changing treatment paradigms. The first is the development of personalized medicine strategies based on current technology. These strategies include diagnostic panels with which evermore customized tests can be performed and developed relatively rapidly. The second is personalized therapy such as testing drugs on tumor cells from an individual patient's tumor to develop the right "cocktail" of effective drugs for treatment of that patient.[21-24]

Homegrown Tissue

Several hospital- and institute-based services have begun to adopt biomaterial engineering services and combine them with cell culture techniques to build 3-dimensional structures. These innovations include structures such as the trachea, the esophagus, valves, the bladder, and sheets of cells. Companies that provide specialized bioreactors to enable this sort of growth have emerged, and novel methodologies to image the growing tissue have been developed.[25-27]

Potential Solutions

It is hard to imagine fitting these efforts into the centralized manufacture and global distribution model that the pharmaceutical industry has used effectively to deliver small-molecule products or even biologics. Novel models, however, mean novel infrastructure, novel players, and higher risk, which in turn means that our metrics from funding need to change, our information dissemination needs to target a different audience, and our partnership program models need to evolve.[28-31] It is still the early days of this new era, and so far no successful model has been developed. However, the NIH has continued to experiment with providing CGMP-grade cells to multiple users, developing banks of IPSCs, and providing royalty-free licenses. Time will tell what is the best method moving forward, but it is important to note that the NIH understands the need and is proactively attempting to develop a solution.

THE NIH NEEDS TO ANTICIPATE AND SUPPORT TOMORROW'S BREAKTHROUGHS

As with any prediction, it is far more likely that I will be wrong than right, but nevertheless, I can perhaps make some cautious predictions, summarized in Table 4. It seems to me that the genetic engineering breakthroughs coupled with the ability to make differentiated cells of various kinds will allow for functional cures. Perhaps the earliest success will come in the hematopoietic system or in the retina, where viral delivery of a missing gene product has already had success. Using safe harbor technologies and strategies to prevent silencing and regulating gene expression in immune-matched cells that are differentiated into a tissue or organ phenotype will allow controlled and regulated therapy. Another breakthrough that I believe will change the field is the ability to make more complex 3-dimensional structures. Currently, we have been limited by our inability to construct a true vasculature that will allow nutrient delivery in synthetic constructs that are more than 8 or 10 cell layers thick. Keeping organ structures alive while a vasculature develops has been difficult as well. Current work in angiogenesis, the ability to print organs layer by layer, and the isolation of endothelial cells in large numbers suggest that we are close. A third breakthrough that builds on the work on IPSCs is the idea of direct transdifferentiation using readily available sources of adult cells and directing their differentiation into a difficult to obtain cell type.

TABLE 4. New Breakthroughs That May Change the Field of Cell Therapy

Ability to expand HSC or make HSC from PSC
Developing a cost-effective model to resolve the immune rejection issue
Accelerating maturation of PSC-derived cells
Somatic cell engineering
Directed differentiation without a stable PSC stage
Developing a way to vascularize tissue
In vivo directed differentiation

HSC = hematopoietic stem cells; PSC = pluripotent stem cells.

The NIH has recognized that funding such innovation is key and will continue to focus on funding the best science. However, it also recognizes that novel discoveries may render earlier efforts obsolete and that it needs to constantly evaluate its priorities and allocations to remain responsive. This is all the more crucial in this field that is moving far faster than we had anticipated. The NIH will continue its efforts to gather information and obtain feedback and encourages readers to write or respond to the Requests for Information that the NIH publishes.

CONCLUSION

The NIH sees the stem cell field as a broad area that has many subfields with investigators at various stages of progress on the translational pathway. The NIH believes that its role in accelerating translation includes not just funding the field but also identifying trends, anticipating challenges, and proactively developing novel solutions to enable researchers' efforts. These solutions include resolving issues related to access to tissues and cells, providing clarification on regulations, reducing costs, and enabling access to key reagents and resources that are not easily obtained elsewhere. Equally important, the NIH realizes that it cannot do it alone and that it needs to help develop public-private interactions to ensure that progress continues. The NIH encourages feedback and looks forward to developing novel programs and novel solutions based on such interactions.

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The opinions expressed in this article reflect my personal view and do not in any way represent or indicate the views of the NIH.

Abbreviations and Acronyms: **CGMP** = Current Good Manufacturing Practices; **ESC** = embryonic stem cell; **IPSC** = induced pluripotent stem cell; **NIH** = National Institutes of Health

Correspondence: Address to Mahendra Rao, MD, New York Stem Cell Foundation, 1995 Broadway, Ste 600, New York, NY 10023 (mrao@qthera.com). Individual reprints of this article and a bound reprint of the entire Symposium on Regenerative Medicine will be available for purchase from our Web site www.mayoclinicproceedings.org.

The end of the Symposium on Regenerative Medicine.

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