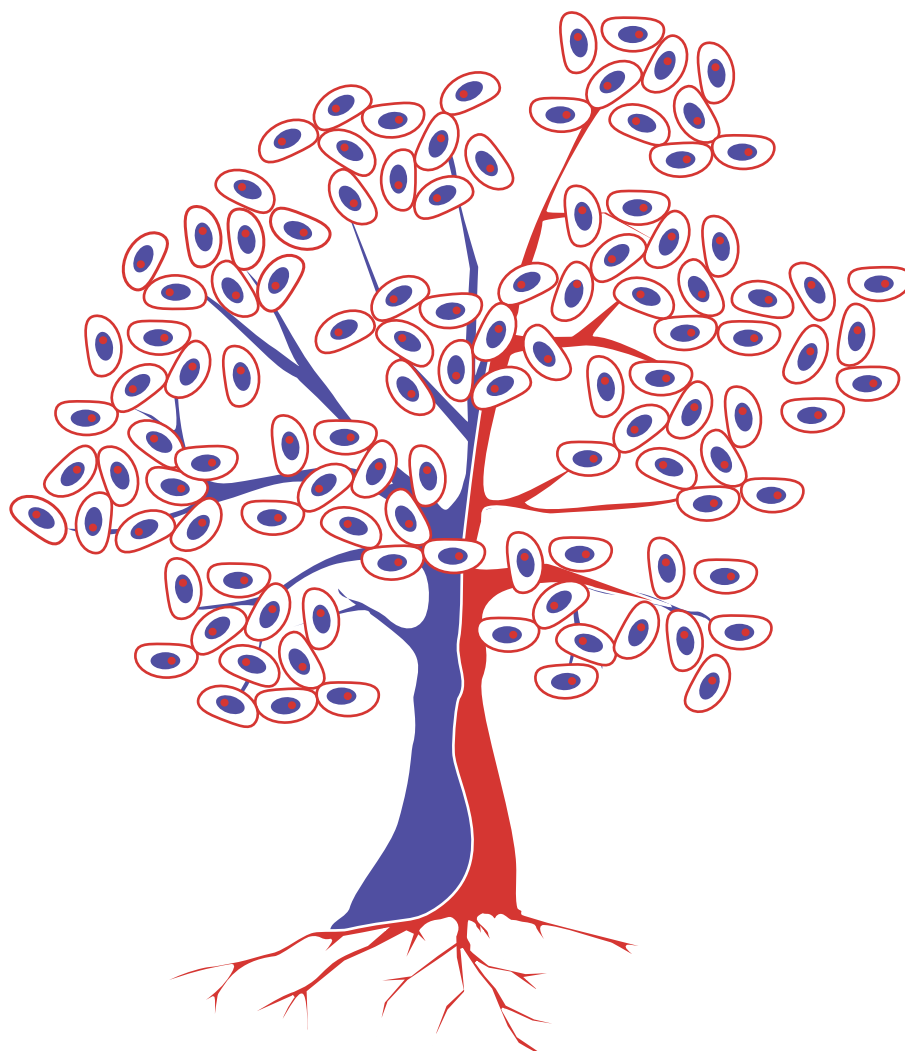


# 2020: A New Vision

## A Future for Regenerative Medicine



U.S. Department of Health and Human Services  
Washington, DC



The following document addresses a specific area of biotechnology that shows great promise for treatment and cure of life-threatening diseases. The report delineates one particular approach of how America can best maintain its preeminence in the field of biomedical engineering. The suggested timelines and endpoints are examples of a strategy that our nation can use to secure our leadership in the field of regenerative medicine.



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## EXECUTIVE SUMMARY

Regenerative medicine is the next evolution of medical treatments. Derived from the fields of tissue engineering, tissue science, biology, biochemistry, physics, chemistry, applied engineering and other fields, regenerative medicine is the first truly interdisciplinary field that utilizes and brings together nearly every field in science. This new field holds the realistic promise of regenerating damaged tissues and organs *in vivo* (in the living body) through reparative techniques that stimulate previously irreparable organs into healing themselves. Regenerative medicine also empowers scientists to grow tissues and organs *in vitro* (in the laboratory) and safely implant them when the body is unable to be prompted into healing itself.

This revolutionary technology has the potential to develop therapies for previously untreatable diseases and conditions. Examples of diseases regenerative medicine can cure include diabetes, heart disease, renal failure, osteoporosis and spinal cord injuries. Virtually any disease that results from malfunctioning, damaged, or failing tissues may be potentially cured through regenerative medicine therapies. Having these tissues available to treat sick patients creates the concept of “tissues for life.”

Beyond the obvious health benefits of regenerative medicine, this technology is desperately needed to combat rising healthcare costs. Current national healthcare costs are in excess of \$1.5 trillion annually, or 13 percent of Gross Domestic Product (GDP). The 2000 census report finds that there are 35 million Americans aged 65 or older. In 10 years, this number is expected to increase dramatically as the 56.6 million Americans who are currently aged 55-64 join the senior citizen age group. By 2040, as the last baby boomer becomes a senior citizen, the population of senior citizens over the age of 65 in the U.S. will be double today’s number, for a total of 70 million.

Accordingly, as much as 25 percent of the U.S. GDP would be devoted to healthcare by 2040. The majority of these projected costs stem from recurring treatments for diseases that arise from tissue failure commonly seen in the elderly. The baby boomer demographic is one that has seen continual medical advancement in their lifetime. This group expects the best from healthcare and will have the greatest need for regenerative medicine. Regenerative medicine therapies will help combat common diseases in the elderly such as diabetes, osteoporosis and cardiovascular disease. Baby boomers would almost certainly rally behind the efforts to advance regenerative medicine as it offers them the greatest hope for the most effective medical treatment and quality of life in their senior years.

Approximately \$4 billion has been spent to date by the U.S. private sector on regenerative medicine, with precious few products on the market. The only products to date are first generation skin and cartilage substitutes. Further innovation has been stymied by a lack of fundamental building block research in regenerative medicine. Other major scientific advancements, such as the Human Genome Project, the National Nanotechnology Initiative, and semiconductor research have seen major support from the U.S. Government, with the private sector augmenting Government driven research with great efficacy. Despite this historically proven formula for success, regenerative medicine has received more than ten times as much private funding as

Government funding. To create complex tissues and organs, Government resources and coordination are essential for driving the research effort in an efficient and swift manner.

Regenerative medicine, if driven by a cohesive Federal initiative, has the opportunity to begin producing complex skin, cartilage and bone substitutes in as little as 5 years. Tissue and organ patches, designed to help regenerate damaged tissues and organs such as the heart and kidneys are within reach in 10 years. Within 20 years, with appropriate Federal funding and direction, the goal of “tissues on demand” is realistic. Additionally, efforts to advance regenerative medicine offers the opportunity to create a tremendous new global industry led by the U.S. The current world market for replacement organ therapies is in excess of \$350 billion, and the projected U.S. market for regenerative medicine is estimated at \$100 billion. Furthering this field would create jobs and grow a new sector of the healthcare industry while creating a new generation of life-saving products.

Already, Japan, the European Union (EU), China and Australia have begun national initiatives and efforts to spur the advancement of their regenerative medicine programs. These commitments range from policy directives in the EU to extensive financial investment by the Japanese government focused on the city of Kobe and surrounding Kansai region targeted to develop a region of expertise in tissue engineering and regenerative medicine. Despite this strong foreign commitment to regenerative medicine, the U.S. presence in regenerative medicine is in danger of being eclipsed. More than 40 percent of the regenerative medicine firms founded since 2000 have been outside of the U.S., and many existing firms have had financial and technical difficulty. To remain scientifically competitive, it is essential that there be strong U.S. leadership and research in this new field.

To achieve the aggressive goal of tissues on demand within 20 years, the Federal Initiative for Regenerative Medicine (FIRM) is proposed. Appropriate annual funding is critical to the success of this initiative. In conjunction with this substantial resource commitment, FIRM would establish a guidance and governance council including all Government agencies currently involved in regenerative medicine. These agencies thus far include the Department of Health and Human Services (including the National Institutes of Health and the Food and Drug Administration), the Department of Defense (including the Defense Advanced Research Projects Agency), the Department of Commerce (including the National Institute of Standards and Technology), the White House Office of Science and Technology Policy, the National Aeronautics and Space Administration, the President’s Council of Advisors on Science and Technology, and the National Science Foundation; and would be open to any other agencies interested in furthering regenerative medicine. This council would set milestones to advance regenerative medicine and then funding and ensuring that these milestones come to fruition. Milestones will range from “pure science” techniques such as studying cellular and tissue interactions, to “challenge problems” such as curing diabetes by replacing pancreatic islets. The fruits of FIRM research will be disseminated to academia and private industry, allowing quicker product and therapy development. By adopting the formula of Government, academic and industry cooperation that has pushed



many other technological initiatives forward, FIRM will advance regenerative medicine quickly and efficiently. The Semiconductor Manufacturing Technology Consortium (SEMATECH) used this same model of government and industry cooperation and funding in the late 1980s and early 1990s. SEMATECH received about \$2 billion in Government funding and helped grow from an \$8 billion yearly U.S. semiconductor industry in 1987 to the \$170 billion, 50 percent global market share industry today. Regenerative medicine is a field primed for this same Government driven growth and success.

Without a Federal initiative, regenerative medicine as an American-driven science faces a precarious future. Although there has been strong private investment, returns thus far have been almost nonexistent. The products that the regenerative medicine industry currently produces are very simple and questionably justify the tremendous private investment to date. If private investment money ceases and there is no Government initiative, regenerative medicine will be driven by foreign efforts and companies, leaving U.S. ingenuity and influence absent from the future of regenerative medicine and increasing the cost of care to access this technology in the U.S. Even worse, without support from FIRM, regenerative medicine could take 40-50 years to be realized. The U.S. Government has always been on the forefront of new technology and regenerative medicine should be no different. It is time for the U.S. Government to embark upon an initiative that will make this technology a reality.



## INTRODUCTION

Regenerative medicine is the vanguard of 21<sup>st</sup> century healthcare. We are on the cusp of a worldwide explosion of activity in this rapidly growing field of biomedicine that will revolutionize health care treatment. Regenerative medicine will lead to the creation of fully biological or biohybrid tissues and organs that can replace or regenerate tissues and organs damaged by disease, injury, or congenital anomaly. Because of the economic potential of this industry (the worldwide market for regenerative medicine is conservatively estimated to be \$500 billion by 2010)<sup>1</sup>, initiatives to capture significant shares of this market are multiplying around the world and competition is mounting.

In the U.S., the symbiotic relationship between Government and science is vital in understanding and developing cures for disease. This relationship is an essential aspect of assuring the safety and well being of U.S. citizens. Perhaps because of the enormous medical advances fostered through Government-funded research and the public's trust in the Government's role in improvement and oversight of medical care, Americans not only embrace medical technology and medical advances, but have come to expect the best that clinical care and medical research can offer. The average American has come of age with remarkable medical advances – from the polio vaccine, to multi-organ transplants, to the real prospect of nerve regeneration. Regenerative medicine, with its promise of repairing damaged tissues and growing replacement tissues and whole organs, is the new frontier to capture the imagination and employ the famous American “can do” spirit of easing human suffering.

In the spirit of ingenuity, regenerative medicine is a collaborative effort. Leadership in this field will come from people who are willing to work across disciplinary lines and Federal and private sector boundaries. A successful regenerative medicine initiative requires the expert knowledge of scientists, engineers, physicians, researchers, and many others in a multidisciplinary effort focused through a Federal initiative that provides the framework and resources to fully realize the potential of this revolutionary new field. Other nations have already begun to realize that focused national initiatives are vital to advancing this promising science. It is now up to the U.S. to do the same and create a Federal Initiative for Regenerative Medicine (FIRM) to make this science a reality.

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<sup>1</sup> Ratner, Buddy. “What are the opportunities in the field of tissue engineering/regenerative medicine?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

## What is regenerative medicine?

### Summary

Regenerative medicine is an applied field of tissue engineering that holds the realistic promise of regenerating damaged tissues *in vivo* (in the living body) and externally creating “tissues for life” available for implantation. Through research and products developed from this field, previously untreatable diseases will become easily and routinely cured.

### How regenerative medicine works

Regenerative medicine is the application of tissue science, tissue engineering, and related biological and engineering principles that restore the structure and function of damaged tissues and organs. This new field encompasses many novel approaches to treatment of disease and restoration of biological function through the following methods:

- Using therapies that prompt the body to autonomously regenerate damaged tissues
- Using tissue engineered implants to prompt regeneration
- Direct transplantation of healthy tissues into damaged environments

Collectively, these treatments allow for two substantial advances over current medicine. The first advance is the potential to *in vivo* (*in the living body*) regenerate currently irreparably damaged tissues so that they return to full functionality. The second advance is to be able to produce tissues *in vitro* (*in the laboratory*) to be used for transplantation purposes when regeneration is not possible. This technology has the potential to cure diseases ranging from diabetes (through regeneration of islets) to the repair of cancerous tissues (by replacing the removed cancerous tissue with externally grown healthy tissue). By creating these “tissues for life,” regenerative medicine treatments will undoubtedly lead to a tremendous improvement in quality of life and healthcare.

## Why do we need Regenerative Medicine?

### Summary

Regenerative medicine is a revolutionary approach that focuses on curing conditions as opposed to treating them. Regenerative medicine empowers doctors with the ability to replace damaged tissue in patients with healthy organic tissue that is

accepted and functions like (and in some cases, is) the body’s own. These therapies will cure a variety of diseases ranging from diabetes to cancer. Regenerative medicine will lead to improved patient care while eliminating the cost of treatments such as insulin injections or dialysis.

### Regenerative Medicine is a cure, not a treatment

What truly differentiates regenerative medicine from many current therapies is that regenerative medicine has the potential to provide a cure to failing or impaired tissues. Many of today’s increasing healthcare costs stem from recurring treatments for chronic diseases and their subsequent complications. One such example is insulin therapy for type 1 diabetes, and glucose therapy for type 2 diabetes. While insulin and glucose can help patients manage diabetes, these therapies do not cure diabetes, nor do they prevent long-term complications, such as kidney failure. Despite insulin, glucose and dialysis treatments, diabetes was the underlying cause of more than 68,000 deaths and the contributing cause of death in more than another 141,000 individuals.<sup>2</sup>

Through regenerative medicine, insulin-producing pancreatic islets (in diabetics, pancreatic islets do not produce the proper insulin levels), could be regenerated *in vivo* or grown *in vitro* and implanted, creating the potential for curing the patient and completely eliminating the need for future treatments.

Other potential regenerative medical advances include the ability to improve myocardial (heart) functions, which would help combat heart failure. Regenerative medicine will enable doctors to grow new blood vessels through vascular endothelial growth factor (VEGF) techniques, and by improving myocyte growth. With these techniques, heart damage could be repaired, saving countless lives. Another benefit of regenerative medicine will be the advancement of our knowledge of the immune system as scientists

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<sup>2</sup> [National Diabetes Statistics](http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#12). National Diabetes Information Clearinghouse (NDIC). 25 September 2003 <http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#12>.

work with immunosuppression and other issues associated with implantation of organs and tissues. Such knowledge will have numerous applications in combating the HIV virus and other immune deficient conditions. These examples are but a few of the potential applications and benefits regenerative medicine will bring.

By providing tissues and organs on demand, regenerative medicine serves a dual purpose: increasing quality of life and care for patients, and reducing healthcare costs by eliminating chronic disease. This medical advance of always having tissues available for patients can be thought of as “tissues for life.”

### Regenerative medicine can combat end-organ failure

One of the greatest needs for regenerative therapy is in the field of whole organ replacement. Despite broad public education about organ donation, there remains a large and growing gap in the number of organ donors *versus* the demand for organs. In 2002 alone, there were:

- 12,800 organ donors (deceased and living)
- 24,900 life saving transplants
- 88,242 patients still on the waiting list at the end of the year
- 6,439 people who died while waiting for a transplant<sup>3</sup>

These numbers do not take into account the estimated 100,000 potential candidates who die before being placed on a waiting list.<sup>4</sup> In total, the cost of all organ replacement therapies in the U.S. is estimated to exceed \$100 billion per year.<sup>5</sup> Organ demand is a major health care issue that is growing in magnitude. Over the past 10 years,

while organ donations have increased, the waiting list has grown even more:

- In 1992, there were 28,952 patients on the transplant list and 7,092 donors
- In 1996, there were 49,381 patients on the transplant list and 9,172 donors
- In 2001, there were 81,528 patients on the transplant list and 12,607 donors<sup>6</sup>

Despite organ donation education campaigns, the rate of donations has been greatly outstripped by the increase in need. Tissue and organ failure is clearly a serious problem that will only increase as our population grows and ages.

Regenerative medicine confronts this problem from multiple fronts. First, through regenerative therapies, diseases and conditions that result from tissue failure can be stopped and healed by regenerating the damaged tissues. This regeneration is brought on by therapies that prompt the body to heal itself by recruiting the proper reparative cells *in vivo*, or by implanting small amounts of engineered tissue “patches” that prompt the damaged tissues to heal. Regenerative medicine also holds promise in transplanting and growing replacement organs. With regenerative medicine, waiting for a tissue or organ transplant will become a worry of the past.

### Regenerative medicine will dramatically alter the U.S. healthcare industry

The potential benefits of regenerative medicine – in improved health care and economic savings – are enormous. Already, the direct healthcare costs of organ replacement are about \$350 billion globally (about 8 percent of global healthcare spending). These costs arise from therapies that keep people alive (such as kidney dialysis), implanted replacement devices, and very few (due to lack of donors) organ transplants.<sup>7</sup> With a \$350 billion global industry already built on first generation tissue and organ therapy products and

<sup>3</sup> [OPTN Data](http://www.optn.org/latestData/viewDataReports.asp). The Organ Procurement and Transplantation Network. 17 September 2003 <http://www.optn.org/latestData/viewDataReports.asp>

<sup>4</sup> Gridelli, Bruno. Remuzzi, Giuseppe. “Strategies for making more organs available for transplantation.” [\*The New England Journal of Medicine\*](#). 343 (2000): 404-410

<sup>5</sup> Langer, Robert. Vacanti, Joseph P. “Tissue Engineering” [\*Science\*](#) 260 (1993): 920-926.

<sup>6</sup> [OPTN Data](http://www.optn.org/latestData/viewDataReports.asp). The Organ Procurement and Transplantation Network. 17 September 2003 <http://www.optn.org/latestData/viewDataReports.asp>.

<sup>7</sup> Lysaght, Michael J. Reyes, Joyce. “The growth of tissue engineering.” [\*Tissue Engineering\*](#) 7 (2001): 485-493

substitutes, regenerative medicine has potential to exceed \$500 billion in the next 20 years.

An example of some conditions and diseases that could be easily cured by regenerative medicine and their current cost of treatment include:

- 250,000 patients receive heart valves, at a cost of \$27 billion annually
- 950,000 people die of heart disease or stroke, at a cost of \$351 billion annually<sup>8</sup>
- 17 million patients with diabetes, at a cost of \$132 billion annually<sup>9</sup>

Regenerative medicine has the ability to prevent many of these conditions by replacing or repairing malfunctioning tissues. Currently, U.S. healthcare costs are more than \$1.5 trillion, or 13 percent of GDP.<sup>10</sup> A large fraction of these costs is attributable to tissue loss or organ failure, with approximately 8 million surgical procedures being performed annually in the U.S. to treat these disorders.<sup>11</sup> By 2040, the population of senior citizens in the U.S. will be double today's number, for a total of 70 million. As much as 25 percent of the U.S. GDP could be devoted to healthcare by 2040. Because regenerative medicine focuses on functional restoration of damaged tissues, not abatement or moderation of symptoms, this field cuts healthcare costs. Without regenerative medicine, the U.S. faces a future of rising healthcare costs and inefficient treatments.

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<sup>8</sup> Centers for Disease Control and Prevention. Preventing Heart Disease and Stroke. 2 December 2003. [http://www.cdc.gov/nccdphp/bb\\_heartdisease/index.htm](http://www.cdc.gov/nccdphp/bb_heartdisease/index.htm)

<sup>9</sup> Hogan, P., Dall, T., Nikolov, P. "Economic costs of diabetes in the U.S. in 2002." Diabetes Care 26 (2003): 917-932

<sup>10</sup> U.S. Census Bureau, Statistical Abstract of the United States. "National health expenditures by type, 1990-2000." P.92

<sup>11</sup> Niklason, Laura E. Langer, Robert. "Prospects for organ and tissue replacement." IAMA 285 (2001): 573-576

## What is the current state of regenerative medicine?

### Summary

Regenerative medicine to date has made a number of advances in the field of simple tissues such as skin, bone, and cartilage. Progress toward more complex therapies has been limited due to the reliance on private sector funding and a lack of understanding of fundamental tissue interactions. Private sector funding has led to a product-oriented approach that does not focus on research or consider the fundamental science issues in regenerative medicine. Without this fundamental research, it will be exceedingly difficult for the regenerative medicine field to develop more advanced tissues and organs. To accommodate new biomedical technology, the FDA has created the Office of Combination Products and the Office of Cellular, Tissue and Gene Therapies. These new offices solve the problem of regulating complex combination products that typically fell under two or more of the FDA's traditional offices. These changes help prepare the FDA for regenerative medicine product regulation and product approvals.

### Current technological accomplishments in regenerative medicine

Regenerative medicine research is a new science, with a many new concepts being researched and tested but few effective products are on the market. From a research standpoint, several key methods and approaches have been established including:

- Direction of cell expansion and differentiation, which explains the processes of how tissues and organ grow
- Development of techniques for assembly of cells into large, three dimensional tissue-like structures, which will lead to the physical creation of three dimensional organs
- Custom-designed biomaterials to serve as structural templates for tissue development, which helps scientists build organs

- Automated bioreactor culture vessels, which allows scientists to mass produce cells and tissues<sup>12</sup>

These techniques have allowed researchers to begin to understand at a very basic level how cells and tissues function and interact. At a functional level, regenerative medicine researchers have been able to grow heart arteries<sup>13</sup> and create artificial blood in the laboratory. Engineered bladders<sup>14</sup>, ligaments and stem cell therapies are in various stages of preclinical and clinical tests. However, the only FDA-approved and available products are much simpler tissues, such as dermal and joint substitutes, and bone marrow for orthopedics.<sup>15</sup> Many skin substitutes have been used successfully, but cartilage and bone replacement techniques have been more difficult.<sup>16</sup> As shown by the limited scope and inconsistent performance of the products available, regenerative medicine is at a very early stage of development, hampered by a lack of cohesive fundamental research to advance the field. It is this research that is needed for the science of regenerative medicine to realize its full potential of restoring even the most complex of tissues to full health.

### Current barriers to progress in regenerative medicine

There are two major barriers facing regenerative medicine. The first barrier is a lack of research

related to the fundamental “building block” areas of the science. The second barrier is the lack of interdisciplinary study, which can be attributed to the focus of private funding in the field.

Fundamental building block science is gaining the necessary understanding to manipulate the technology of a given field for a desired result. In regenerative medicine, the fundamental research focuses on cellular interactions at a micro and macro level, which can then be applied to creating and integrating tissues. Historically, primarily academia and the Government, in conjunction with private industry have performed fundamental research, and the discoveries are then applied by industry to create viable products.<sup>17</sup> The lack of a Federal funding strategy in regenerative medicine has inhibited fundamental research. While more than \$4 billion in private capital has been invested in the field (without producing a single profitable product),<sup>18</sup> cumulative Federal investment in regenerative medicine over the 13 year span from 1988 to 2001 was only about \$250 million.<sup>19</sup> This is important for two reasons. First is the obvious disparity of funding. Second, and equally important, is the type of research performed by each of these groups. Private industry research is focused on the end product, and how to get there in the quickest and most cost efficient manner. Private research also is focused around a singular field: biology, chemistry, and so on. Government research, however, tends to be in the form of grants to laboratories that are focused more on fundamental research that deepens knowledge in a field. It is because of this disparity in funding that the current situation exists: \$4 billion invested by private industry and no profitable products, and an extremely limited understanding of how

<sup>12</sup> Davison, Steven. “Where is the field of tissue engineering/regenerative medicine today?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>13</sup> Niklason, L.E. Gao, J. Abbott, W.M. Hirschl, K.K. Houser, S. Marini, R. Langer, R. “Functional arteries grown in vitro.” *Science* 284 (1999): 489-493

<sup>14</sup> Oberpenning, Frank. Meng, Jun. Yoo, James J. Atala, Anthony. “De novo reconstitution of a functional mammalian urinary bladder by tissue engineering.” *Nature Biotechnology* 17 (1999): 149-155

<sup>15</sup> Ferber, Dan. “Lab-grown organs begin to take shape.” *Science* 284 (1999): 422-425

<sup>16</sup> Hentz, Vincent R. Chang, James. “Tissue Engineering for reconstruction of the thumb.” *The New England Journal of Medicine*. 344 (2001): 1547- 1548

<sup>17</sup> Schwartz, Ketty. Vilquin, Jean-Thomas. “Building the translational highway: toward new partnerships between academia and the private sector.” *Nature Medicine* 9 (2003): 493-495

<sup>18</sup> Lysaght, Michael J. Reyes, Joyce. “The growth of tissue engineering.” *Tissue Engineering* 7 (2001): 485-493

<sup>19</sup> McIntire, Larry V. Greisler, Howard P. Griffith, Linda. Johnson, Peter C. Mooney, David J. Mrkisich, Milan. Parenteau, Nancy L. Smith, David. *WTEC panel report on tissue engineering research*. Maryland: Loyola College, 2002.

complex tissues function. This industry that has the potential economic impact of \$500 billion annually, and the Federal investment should be strategically focused.

Similar Federal investment has occurred in the past. In the late 1980s and early 1990s, the Semiconductor Manufacturing Technology consortium (SEMATECH) and National Electronics Manufacturing Initiatives served to successfully revive and then lead U.S. industries to become global market leaders in the semiconductor and electronics industries. More recent projects are just beginning to come to fruition. Treatments based on gene therapies from the Human Genome Project are beginning to arrive on the market, and the results of this project will undoubtedly have an enormous impact on the future of healthcare. A Federal initiative providing direction and resources in regenerative medicine would ensure that the U.S. would be the unquestioned pioneer and leader in this promising field.

The lack of a Government initiative has also led to the isolation of regenerative medicine research by each individual field. There is very little collaboration and communication among biologists, clinicians, engineers, biochemists, materials scientists and other related fields due to the emphasis on private, product-focused funding.<sup>20</sup> Unfortunately, regenerative medicine is a field that requires cooperation and communication among these different disciplines in order to advance the general science. Biologists and biochemists must use their knowledge of how the body works in conjunction with tissue engineers to generate products that actually function. Furthermore, all of these groups must coordinate with clinicians and the FDA to set priorities of what tissues are in highest demand and how to implant them and to ensure that they are safe for humans.<sup>21</sup> Without a Government funding initiative to pull these groups together, organizational culture issues will continue to inhibit collaboration. It is absolutely essential that

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<sup>20</sup> Boyan, Barbara. "Where is the field of tissue engineering/regenerative medicine today?" Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>21</sup> Ibid.

this coordination happen in order to expeditiously further the knowledge in the field.

### Regulatory environment

The FDA has begun working towards creating an environment that accelerates the approval of combination products. Therapies are classified by the FDA as either a device, biologic, or drug. Each classification has differing regulations and its own review Center consisting of experts in a given field. Regenerative medicine products fall under some or all of these classifications, requiring regulators to appropriately integrate different regulations to ensure adequate product safety and effectiveness. In the past, this added complexity led to combination products requiring longer approval times than standard products. To accommodate the advancements of medicine, the FDA created its Office of Combination Products (OCP). The Medical Device User Fee and Modernization Act of 2002 established this new office on December 24, 2002. Under this law, the OCP is given the power to ensure the timely review of drug-device, drug-biologic, and device-biologic combination products.<sup>22</sup> Examples of some combination products that OCP has handled include:

- Dermagraft, which uses an absorbable scaffold to deliver collagen and other skin tissues to wounds
- InFUSE Bone Graft/T-CAGE lumbar tapered fusion device, which is a treatment for a degenerative disc disease by stabilizing the spacing in the spine and then forming new bone
- Antibiotic bone cement, used for fixating prosthesis to living bone<sup>23</sup>

These products are all combinations of drug, biologic and devices. While these products are considerably simpler than organ tissues, thus far the FDA has shown that it is prepared to

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<sup>22</sup> FDA Establishes Office of Combination Products. Food and Drug Administration. 15 September 2003  
<http://www.fda.gov/bbs/topics/NEWS/2002/NEW00862.html>

<sup>23</sup> Office of Combination Products Recent Examples of Combination Products List. Food and Drug Administration. 15 September 2003  
<http://www.fda.gov/oc/combination/approval/s.html>



efficiently regulate regenerative medicine products as they become available.

The FDA has also established the Office of Cellular, Tissue and Gene Therapies (OCTGT). The OCTGT consolidates a number of regulatory programs into a single entity with a single expert staff. These consolidated groups include:

- Human tissues
- Cellular therapies
- Xenotransplantation
- Gene therapies

By creating these new offices for regulation, the FDA has begun to evolve into a more nimble approval agency capable of handling the advances of the 21<sup>st</sup> century.

To complement these new offices, the FDA has also begun collaborating with various NIH Institutes and participating in the Multi-Agency Tissue Engineering Sciences Working Group to raise awareness of FDA guidelines and procedures.

Another innovative initiative the FDA has begun in conjunction with the National Cancer Institute allows cancer researchers to link their investigational new drug (IND) applications to the FDA. This program has the goal of reducing process and submission times for researchers. If successful, this program will provide a model for IND applications in other fields, including regenerative medicine.

While the FDA has made great strides towards embracing new technologies, the private sector still views the regulatory process as somewhat difficult. FIRM will provide a cohesive framework whereby public and private funding organizations will partner with the FDA very early in the development of regenerative medicine products to facilitate transparency in the regulatory oversight process for these new products. By partnering in this manner, FIRM will set a new standard for industry and FDA cooperation that will lead to faster product approvals without sacrificing safety or efficacy.

## What is the future of regenerative medicine technology?

### Summary

Despite the availability of some first generation products, researchers know very little about the underlying science of regenerative medicine. In order to build complex tissues and organs, scientists first must understand how tissues interact with each other. To achieve the envisioned goals of regenerative medicine, a strong Federally-directed initiative is needed to ensure that this fundamental research is realized.

If a directed and well-funded research effort were to begin, regenerative medicine could begin producing results within 5 years. At the 5-year mark, complex skin, cartilage, bone, and blood vessel products would begin to reach markets. Within 10 years, organ patches that repair damaged tissues would potentially be available. Within 20 years, full organ regeneration is a strong possibility.

For these products to be regulated safely and efficiently, the FDA must continue its recent admirable moves to embrace new technology. The FDA has recognized the challenge of new medical technology and has worked to improve outreach and education about the regulation process, created a new office for handling the evaluation of combination products, and created sub-offices for handling tissue and genetic therapies. This commitment to the future is encouraging and the FDA remains involved in developments relating to regenerative medicine research.

Other countries have already embarked upon national initiatives of their own with hopes of making regenerative medicine a reality for themselves. Several members of the European Union (EU), including Great Britain, Germany, and Sweden, as well as Japan, China and Australia have all begun making strong national commitments with hopes of achieving their own advances in regenerative medicine technology. It is time for the U.S. to commit its own resources and work with these nations as a leading partner in driving this technology forward.

### Next steps for regenerative medicine

Although regenerative medicine as a field has existed for over 10 years, surprisingly little basic research has been done. In order for the field to

advance, scientists must research fundamental cellular relationships and develop techniques for cellular production and preservation. In order to eventually realize the concept of tissues on demand, interim research steps must be achieved. Examples of interim research goals that must be achieved include:

Understand the processes involved in mechanical signaling and cellular mechanotransduction, which explains how cells and systems communicate with each other<sup>24</sup>

- Improve control of organogenesis, which is the control of tissue development<sup>25</sup>
- Create tissues *in vitro* (in the laboratory) and then bringing these tissues *in situ* (in the natural environment), which teaches scientists how to integrate laboratory grown cells into actual living bodies
- Develop handling and storage procedures for regenerative medicine applications, in order to effectively manage and preserve tissue supplies<sup>26</sup>
- Increase scalability of engineered cells, that enables scientists to mass-produce engineered cells ensuring enough heart, skin, pancreas, and other needed tissues are available
- Develop tissue quality assurance procedures, to ensure tissues are safe and consistent like any mass-produced item<sup>27</sup>

Despite 10 years of study in regenerative medicine, there has been a lack of directed research. Although much has been learned on these subjects the field is still in an embryonic

stage. Without this fundamental research, the potential of fully engineered complex tissues will never be realized. If regenerative medicine researchers and clinicians are able to gain a detailed understanding of how cells interact with each other and how to mass-produce, preserve, catalogue, and build these cells, they can then apply this knowledge towards developing tissue and organ based therapies.

One example of a complex regenerative medicine issue that scientists must solve is the growth of vasculature in tissues and organs. These vascular tissues are blood vessels responsible for transporting nutrients and waste through tissue. Due to a lack of understanding of cellular interaction, scientists have not been successful in creating vasculature in tissues and organs, limiting regenerative medicine products to “two dimensional” materials, such as skin and bone, which do not require vascular tissue support.<sup>28</sup> To achieve the promise of regenerative medicine, growing vascularized tissues is a necessary next step. To do this, scientists must gain a better understanding of tissue interactions and scaffold technology. Once scientists understand these concepts, they will be able to apply this knowledge and create more advanced tissue systems.<sup>29</sup> Ultimately, the application of knowledge of cellular interactions and tissue growth will culminate in two branches of regenerative medicine research, *in vivo* cell based therapy and *in vitro* grown tissues and organs.

Cell-based therapy focuses on cellular treatments that lead to regeneration by having the body “gather” the necessary reparative cells and bring them to the damaged site. The second branch is the *in vitro* growth of tissues and organs that are then implanted within the body, either to prompt regeneration or to replace damaged tissue.<sup>30</sup> Each

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<sup>24</sup> Griffith, Linda G. Grodzinsky, Alan J. “Advances in biomedical engineering.” *JAMA* 285 (2001): 556-561

<sup>25</sup> Mitka, Mike. “Tissue engineering approaches utility.” *JAMA* 284 (2000): 2582-2583

<sup>26</sup> Bradbury, Jane. “Of tardigrades, trehalose, and tissue engineering”. *The Lancet*, August 4, 2001 358 (9279): 392

<sup>27</sup> Goldblatt, Michael. “Where is the field of tissue engineering today and what is the future?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

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<sup>28</sup> Wiesmann, William P. “What is the future of tissue engineering/regenerative medicine?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>29</sup> Zandonella, Catherine. “Tissue engineering: The beat goes on.” *Nature* 421 (2003): 884-886

<sup>30</sup> Griffith, Linda G. Naughton, Gail. “Tissue engineering – current challenges and expanding opportunities.” *Science* 295 (2002): 1005-1009

branch of research offers substantial advances over current medicine, and discoveries from one branch may be directly applicable to the other. Both of these research branches are vital for fully realizing all of the potential therapies of regenerative medicine. For example, preliminary research has shown that spinal cord regeneration through implantation of seeded scaffolds is feasible.<sup>31</sup> Seed-driven regeneration is a form of cell-driven therapy that will not require transplantation of a new tissue or organ. On the other hand, it is believed that treatment of a cancerous lung would require removing the lung and replacing it with a laboratory grown healthy lung. In the case of cancer, seeding the lung for regeneration would not work, as the cancer would still be present.

These two different applications of regenerative medicine demonstrate why it is essential to research both cellular therapies and full organ growth techniques to maximize the potential of regenerative medicine. It may be possible to use regenerative medicine to cure a diseased lung without removing it, or to cure spinal injuries through neural cell transplants. What is most important is that these two branches be investigated fully: findings from both will further our knowledge of regenerative medicine.

Fulfilling these goals will create a foundation for future regenerative medicine products and work. A cohesive effort focused on advancing the science and the field as a whole is essential.

### Projected timeline of regenerative medicine

With a cohesive Government initiative and appropriate funding, within 20 years regenerative medicine will be the standard of care for replacing all tissue/organ systems in the body in addition to extensive industrial use for pharmaceutical testing.<sup>32</sup> The ultimate goal at the end of 20 years

is to have real time mass customization of tissues on demand, *in vivo*. During those 20 years, as our knowledge of tissues grows, it is reasonable to expect to see treatments discovered along the way, roughly at the 5, 10 and 20 year marks. In 5 years the following milestones are hoped for:

- Develop multiple applications for skin, cartilage, bone, blood vessel, and some urological products<sup>33</sup>
- Develop insurance reimbursable regenerative therapies
- Establish standards for FDA regenerative medicine therapy product approvals
- Solve cell sourcing issues, giving researchers access to the materials they need to design new therapies
- Establish cost-effective means of production, paving the way for future products
- Establish specialized cell banks for tissue storage, allowing storage of viable “off the shelf” products

In 10 years, effective regenerative medicine therapies will be available for patient care and industrial research and development purposes. At this time, the following may be achieved:

- Further understand stem cell and progenitor cell biology
- Engineer smart degradable biocompatible scaffolding
- Develop microfabrication and nanofabrication technologies to produce tissues with their own complete vascular circulation<sup>34</sup>

<sup>31</sup> Teng, Yang D. Lavik, Erin B. Qu, Xianlu. Park, Kook I. Ourednik, Jitka. Zurahowski, David. Langer, Robert. Snyder, Evan Y. “Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells.” Proceedings of the National Academy of Sciences of the USA Vol. 99 (2002): 3024-3029

<sup>32</sup> Ellisseff, Jennifer “What is the future of regenerative medicine?” Workshop on Tissue

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Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>33</sup> Vacanti, Joseph P. “What is the future of regenerative medicine?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>34</sup> Vacanti, Joseph P. “What is the future of regenerative medicine?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

- Develop complex organ patches, that could repair damaged pieces of the heart or other organs<sup>35</sup>

Ultimately, within 20 years the full benefits of regenerative medicine therapies will be reached. Some of the applications of regenerative medicine could be:

- Harness regenerative medicine materials to produce *in situ* regeneration of diseased and damaged structures in many areas of the body
- Regenerate most damaged tissues and organs either *in vivo* or through implanted regeneration therapies
- Produce *in vitro* sophisticated 3-D tissues and organs that cannot be regenerated through *in vivo* techniques, such as an entire heart or lung

Without a Federal initiative supporting this research, this timeline could extend over the next 40 to 50 years. Considering the many economic and health advances this technology may bring, it is absolutely vital that regenerative medicine advance as quickly as possible.

### Future regulatory challenges and potential issues

One of the most challenging aspects of developing new medical treatments is ensuring that these treatments are safe as well as effective. What might be safe in Japan or Sweden may not be considered safe in the U.S. As with any new medical advance, regenerative medicine products will be complex and require a great deal of laboratory study in order to confirm their safety. Regenerative medicine is a new field that will pose new challenges for the FDA. In order to ensure efficient and effective regulation, it is important the FDA continue to make their review processes transparent and easy to follow so that clear expectations for product safety and quality of clinical evidence needed for approval are in place. If a researcher takes a misstep early in the complex regulatory process, a great deal of time

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<sup>35</sup> Warren, William L. "What is the current State of Regenerative Medicine?" Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

and money can be wasted.<sup>36</sup> Rigorous testing to ensure product safety is crucial. However, it is important to streamline processes where possible to foster innovation and new product development.

The most frequently cited concerns by industry are the lack of clarity about the regulatory requirements and the level of efficacy that must be demonstrated to get a product on the market. More specific criticisms include:

- Requirements for large clinical trials, which are expensive for companies to run
- Necessity for more than one efficacy trial for some products, which adds to expenses
- Shifting requirements, which confuses companies regarding the timeframes of deliverables, creating frustration about the process requirements and expectations
- Lack of direction about the regulatory pathway (drug, biologic, device), which has been largely answered by the creation of the OCP
- Level of proof needed to demonstrate effectiveness, which is used in designing clinical trials<sup>37</sup>

From the FDA's perspective, the process for approving new products is slowed by companies who delay discussions until much of the product and clinical development plan has already been established. With new technology or novel products like regenerative medicine therapies, the approval process is enhanced and expedited when the FDA is included in the discussions about product and clinical development at an early stage. This allows the FDA to provide more instructive feedback about the products and better understand the technology behind them. It is therefore critical that the FDA be involved early in

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<sup>36</sup> Heinz III, H. J. Implementing Tissue Engineering: Financial and Regulatory Guidance. Department of Engineering & Public Policy, School of Public Policy and Management and Department of Social and Decision Sciences. Carnegie Mellon University

<sup>37</sup> "A Concept Paper for A Federal Initiative in Regenerative Medicine (FIRM), Tissues for Life." Department of Health and Human Services. July 2003.

regenerative medicine research so that the regulatory scientists can learn about the technology congruently with the academic and private sectors. This understanding will ultimately lead to quicker approvals as familiarity with regenerative medicine technology increases.<sup>38</sup>

The FDA has and continues to make a strong effort to stay on the cutting edge of new technology. The most important goal of the FDA is to remain fluid in their structure and to embrace new technology by creating appropriate venues as opposed to forcing new technology into old paradigms, while upholding the necessary standards of safety and efficacy. Thus far, the FDA has performed admirably in preparing for the next generation of medicine. As long as regenerative medicine companies are willing to involve the FDA in their product design process from inception to completion, the regulatory process will be no more burdensome than is necessary to ensure product safety.

#### Foreign efforts in regenerative medicine

The U.S.' preeminence in the field of regenerative medicine is in jeopardy. A study led by the National Science Foundation and released in January 2002 noted that the U.S. lead in cross-disciplinary research is shrinking as compared to Japan and Europe, who are the next most advanced players in regenerative medicine, respectively.<sup>39</sup> In 1995, only 5 percent of companies involved in regenerative medicine research were based outside the U.S. By 2002, this percentage of non-U.S. regenerative medicine companies had increased to 46 percent.<sup>40</sup> It is apparent that regenerative medicine's promise of revolutionary curative treatments has been recognized by other nations who are now moving to embrace this technology through both private

industry and national government resource commitments.

The Japanese government has committed resources to the city of Kobe in the Kansai region of Japan. The Kobe Medical Industry Development Project aims to nurture an industry in the fields of advanced medical care and welfare to meet the new requirements of Japan's rapidly aging society.<sup>41</sup> The plan includes spending a total of ¥91 trillion (\$831 billion) by the year 2010 on assorted therapies and infrastructure to raise the standard of living of Japan's elderly. One of the key components of the Kobe Medical Industry Development program is cell therapy and regenerative medicine research.<sup>42</sup> Japan, faced with one of the largest populations of the elderly, has seen the benefits of regenerative medicine technology and appropriately embraced them.

The European Union is still working to establish an infrastructure for regenerative medicine. Currently, the Enterprise Directorate-General in the European Commission is writing the first regenerative medicine regulation for Europe and will have the responsibility to develop and organize regenerative medicine efforts in the EU.<sup>43</sup> A total of 436 tissue-engineering related companies currently exist in the EU, with 40 percent located in the United Kingdom and Germany. British firms are focusing on integration between technologies and applications, whereas German firms are focusing on vertical specializations in technologies and applications.<sup>44</sup> While the EU has a strong commercial base, their national support program is limited. However, they have taken the first step by having the

<sup>38</sup> Frey-Vasconcells, Joyce, "What regulatory, policy, economic and other obstacles confront the field of tissue engineering/regenerative medicine?" Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>39</sup> Larry V. McIntire, "What is the Current State of Regenerative Medicine?" Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>40</sup> Ibid.

<sup>41</sup> Kyoto News. "Foreign investment across Japan." Journal of Japanese Trade & Industry. September 1, 2003.

<sup>42</sup> The Kobe Medical Industry Development Project Outline. City of Kobe, Japan. 8 October 2003 [http://www.city.kobe.jp/cityoffice/06/015/iry0/contents/aramashi01\\_e.html#Project](http://www.city.kobe.jp/cityoffice/06/015/iry0/contents/aramashi01_e.html#Project)

<sup>43</sup> Mission Statement. Enterprise Directorate-General Unit F3. 8 October 2003 <http://pharmacos.eudra.org/F3/f3com/mission.htm>

<sup>44</sup> "European Competitiveness report 2001." The European Commission. P. 110

European Commission formulate a regenerative medicine strategy for the EU.

Other notable foreign efforts include Australia, which boasts a growing regenerative medicine industry, and China, which has committed a \$1 billion initial investment towards establishing regenerative medicine research.<sup>45</sup> It is very apparent that the international community views regenerative medicine as a priority over the next 20 years. In the next 15-20 years, there will be 300 foreign companies competing in the field of regenerative medicine.<sup>46</sup> It is essential that the U.S. join these efforts as a leading partner to ensure that our internal resources and expertise helps to shape this revolutionary new technology. Without direction and resources from the U.S. Government, regenerative medicine is a technology that will not be fully realized for 40 to 50 years.

## How could the United States get there?

### Summary

In order to assure that the U.S. has the most effective and comprehensive regenerative medicine program in the world, the Federal government must take a direct hand in regenerative medicine. By creating a Federal initiative focused on researching the fundamentals of regenerative medicine, the resources will be available to fill in the “research gaps” of the field and allow private industry to focus on what it does best, creating products that meet the needs of consumers.

An initiative in Regenerative Medicine would involve more than simply an allocation of funds. This initiative could be known as the Federal Initiative for Regenerative Medicine (FIRM). It would stretch beyond simply being an allocation of resources. The true strength of the program will be the funding combined with a synchronization and collaboration of the agendas of the Federal agencies already involved in

regenerative medicine research and bringing the fruits of this research to academia and private industry. Research will focus around “building block” technologies that advance the science as a whole and “challenge problems” which produce tangible results such as functional organs. In conjunction with advancing the science of regenerative medicine, FIRM will also take a strong hand in ensuring that the U.S. public is both excited about and understanding of the capabilities of regenerative medicine.

### What FIRM is and how it advances regenerative medicine

The goal of FIRM would be to advance regenerative medicine to the point of providing real time, mass-customization of tissues on demand, *in vivo*, within the next 20 years.

Following on the footsteps of past successful government initiatives, such as SEMATECH and the Human Genome Project, FIRM will provide direction through a council dedicated to reaching the goal of tissues on demand. Composed of representatives of Government agencies involved in FIRM, the governance council will be responsible for setting milestones to advance the science of regenerative medicine and empower industry to take this knowledge and technology to create effective regenerative medicine products. This centralized, coordinated effort also will allow FIRM to develop standards for cellular data, reference materials and other protocols that will enable different U.S. research teams to easily compare data with each other. This standardization could potentially extend to global efforts as well, allowing regenerative medicine research to overcome many of the protocol issues that have impaired communications between research groups in other fields.

FIRM will also take advantage of supplemental funding for regenerative medicine research. This money will be used for intramural research at Government labs (NIH, NASA, NIST, etc) as well as in the form of extramural research funding through existing Government mechanisms (NIH, DARPA). This commitment will continue over 20 years and is a flexible number: if more opportunities for research in the field are discovered, additional funds can be appropriated to take advantage of such breakthroughs. With current funding to date of only \$250 million over

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<sup>45</sup> McIntire, Larry V. Nerem, Robert M. Ratner, Buddy D. Russell, Alan J. Vacanti, Joseph P. “Letter to the President Bush “ Alliance for the Engineering of Replacement Tissues, December 13, 2002

<sup>46</sup> An Industry Emerges. Pittsburgh Tissue Engineering Institute. 10 October 2003 <http://www.ptei.org/industry/pdf/industry.pdf>

the past decade, an increase in government resources will provide the necessary commitment to make this technology a reality.

The benefits of realizing regenerative medicine will be two-fold. The first benefit will be bringing our Nation the next generation of healthcare by preventing and curing tissue and organ failure. The second will be to help grow the first new “decade defining” industry of the millennium. Past Government initiatives, such as SEMATECH, helped grow the worldwide semiconductor industry from an \$8 billion annual industry into a \$170 billion annual industry with only approximately \$2 billion in government funding. FIRM offers the chance for a similar payoff, with the end product bringing a higher quality of life to Americans as well as growing a new industry.

#### How FIRM will be structured

FIRM will crosscut the programs of a number of Federal agencies, affording opportunities for the sharing of expertise, specialized facilities, and best practices in research and research management. The current regenerative medicine stakeholders represent a multitude of organizational structures and functions. Each of these groups, such as the Department of Health and Human Services (including NIH and FDA), the Department of Defense (including DARPA), the National Aeronautics and Space Administration, Department of Commerce (including NIST), the White House Office of Science and Technology Policy, the President’s Council of Advisors on Science and Technology, and the National Science Foundation, as well as academia and industry have distinct practices and goals in implementing their regenerative medicine activities. It is important for the FDA to play an active role in the development of regenerative medicine technology. If safety and efficacy expectations are transparent, clinical studies can be designed and carried out with FDA requirements clearly understood, leading to more efficient approval processes.<sup>47</sup>

A governance council will manage FIRM. This council will include members of all participating Government agencies, with each member agency having representation on the council. Any Government agency with an interest in advancing regenerative medicine will be welcome to join. By cross-cutting multiple agencies, the council can take advantage of the strengths and expertise of each member agency. For example, NSF and NIH are principally invested in fundamental discovery, while NIST and DARPA focus on exploratory development. NASA and DOD are more specifically mission-oriented, requirement-driven organizations and thus are more focused on applied development. The strength of FIRM will be to leverage and focus the resources and strengths of these agencies to advance regenerative medicine.

The FIRM council will decide research priorities and milestones to accomplish this research through distribution of funds and Government resources. By continually monitoring the state of regenerative medicine research, setting new research goals and seeing these goals through to completion, FIRM will aggressively advance regenerative medicine. The research developed through FIRM-driven programs will be disseminated to academia and business for development of regenerative medicine therapies. Research milestones will range in scope from fundamental science issues, such as:

- Developing a greater understanding of cellular interactions in a given tissue
- Developing methods to store and preserve tissues for long periods of time
- Developing mass production techniques for a type of tissue

These research goals serve the very important goal of advancing the science of regenerative medicine leading to products and therapies. “Challenge problems” will serve to complement these research-oriented goals. These challenge problems are similar to the “Grand Challenges” of the National Nanotechnology Initiative, which include goals such as containing the entire contents of the Library of Congress on a device

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<sup>47</sup> Frey-Vasconcells, Joyce, “What regulatory, policy, economic and other obstacles confront the field of tissue engineering/regenerative medicine?” Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

no bigger than a sugar cube.<sup>48</sup> Examples of FIRM “challenge problems” are:

- Demonstrate a fully functional working organ by the year 2010
- Cure for diabetes through the successful growth and implantation of islets by the year 2015
- Cure paralysis through spinal cord treatments by the year 2020

These challenge problems serve as a powerful marketing tool that captures the imagination of end-users who will ultimately benefit from this technology. Both the research and challenge problem goals will be achieved with a combination of intramural research at Government labs, FIRM-funded centers of excellence, and externally-funded ventures. FIRM must constantly assess these goals and ensure that they are on-task and that milestones are being met. Resources will be allocated in the best interest of FIRM’s goals, taking into account the scope, payoff, and difficulty of each project. From a research standpoint, it is important that the FIRM council recognize that regenerative medicine research will focus more on breakthrough advances than incremental ones. Accordingly, funding and research must be shaped in a format that supports breakthrough style research. One such format is that seen in DARPA programs.<sup>49</sup>

The DARPA model of funding involves about 80 program managers who distribute between \$2 billion and \$2.5 billion annually. These program managers are typically experienced professionals from industry or academia. They report to one of six office directors who in turn report to the Director of DARPA. DARPA’s management structure is very lean and allows for a rapid flow of communication between layers. This funding model has shown itself to be extremely advantageous in certain situations, including:

- An advance promising a major leap, not an incremental improvement
- A capacity whose development requires substantial sustained funding
- A field or technique that is unlikely to be developed quickly by ongoing academic efforts or within industrial firms
- An emerging scientific field or technical area that lacks a natural disciplinary base<sup>50</sup>

Very clearly, regenerative medicine falls under all of these proposed categories. It would be worthwhile, in advancing this initiative, to consider disbursing at least some of FIRM’s funding through a DARPA-like model positioned out of NIH.

#### **FIRM research will be focused through theme-based centers of excellence**

To maximize the leverage of existing regenerative medicine research at NIH, FIRM will create a Center for Regenerative Medicine to bring experts from all the Institutes together under one organizational unit. In addition to this Center and existing Government laboratories, additional research will be done at “centers of excellence” which will be created through pairing Government efforts and resources with universities, research hospitals and other research centers. Each of these centers will be responsible for a particular type of regenerative medicine research, thereby creating focal points for private industry to work with in generating regenerative medicine therapies.

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<sup>48</sup> National Nanotechnology Initiative: From Vision to Implementation. Roco, M.C. National Nanotechnology Initiative. 8 October 2003 <http://www.nano.gov/nni11600/sld001.htm>

<sup>49</sup> Cook-Deegan, Robert Mullan. “Does NIH need a DARPA?” Issues in Science & Technology, Winter 1996

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<sup>50</sup> Ibid.



These centers of excellence would also focus on forming multidisciplinary teams that are vital to the advancement of regenerative medicine. Such teams bring together the following experts:

- Engineers
- Physicians
- Cell Biologists
- Computational biologists
- Nanotechnology fabrication experts
- Developmental Biologists
- Immunologists
- Materials scientists
- Economists
- Structural biologists
- Educators
- Social scientists
- Psychologists
- Ethicists
- Vascular biologists
- Chemists
- Biochemists

Some of the greatest advancements in science have grown from new discoveries in one field leading to advances in others. The invention of the steam engine, an engineering accomplishment is often credited with being the primary reason for the growth of thermodynamics. By bringing together engineers and other material scientists with biologists and other life sciences scientists, these centers will increase the spectrum of available knowledge for regenerative medicine by providing varied viewpoints that lead to a more balanced research approach.<sup>51</sup> Due to logistical issues, only a few academic and commercial laboratories have assembled such groups. With FIRM, these teams will be more commonplace, allowing FIRM researchers to take a broader and more encompassing view than has been seen thus far. These teams can then turn their collective resources towards a variety of regenerative medicine themes.

Potential themes might include:

- Tooth and Maxillo-Facial Repair and Replacement
- Cardiac Tissue Repair and Replacement
- GI and Urinary Tract Repair and Replacement
- Skin and Muscle Repair and Replacement<sup>52</sup>

Encouraging and promoting cross-center information sharing and innovative design advances, each center would provide secondary support to other themes to foster exchange of ideas. For example, the skin and muscle repair and replacement center might support the cardiac tissue repair and replacement center, as some muscle growth techniques might apply to growing muscles in the heart. These centers will ultimately become the primary source of regenerative medicine research for industry to draw upon in creating new products.

#### FIRM Funding

Proposed is an exponential change, not an incremental increase in Federal dollars allocated for regenerative medicine. An order-of-magnitude upsurge is needed to drive this field forward. Such an increase will ensure U.S. success in regenerative medicine by providing a strong underpinning, a thorough scientific-knowledge foundation, and the training for the first true generation of regenerative medicine scientists and engineers.

This money will be controlled by the FIRM council and then allocated to subsidiary agencies in accordance with the goals set by the FIRM council. Funds allocated by FIRM will be placed as a line item into member agency budgets, and the member agencies will then be responsible for accomplishing the goals set by the council. For example, DARPA (through DOD) might be assigned to research skin grafts for combat wounds. DARPA would then receive funding from the FIRM council yearly until the project is completed. The FIRM council would oversee this effort to ensure that research data is shared and the project is being managed properly. In the event that a program is not performing up to task

<sup>51</sup> Darrell J. Irvine "What Regulatory, Policy, Economic and other obstacles confront the field of tissue engineering/regenerative medicine?" Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

<sup>52</sup> Joseph Vacanti "Why should the American public support a National Tissue Engineering Initiative?" Workshop on Tissue Engineering and Regenerative Medicine. U.S. Department of Health and Human Services. 28 March 2003

or research is not being shared, the FIRM council has the power to rectify these problems in the best possible manner.

Goals along the roadmap will be monitored as milestones, and phase-out mechanisms will be included to ensure that old projects are efficiently closed down, allowing new projects to be started. Methods to measure success of specific activities need to be developed, and performance measures need to be established and continually monitored.

Choreographing a such an initiative will be challenging; however, a multi-agency framework coordinated through a FIRM council with active and strong leadership would ensure a successful utilization of resources. Implementing lessons learned from the National Nanotechnology Initiative and other complex multi-agency Government R&D efforts will also be critical. With planning and strong direction, FIRM has the power to bring regenerative medicine to the U.S. public, enhancing their welfare and leading people to live fuller, richer lives.

### Benefits of FIRM

FIRM brings two major benefits to the American public. The first is a leap to a new generation of healthcare therapies that will have countless applications towards curing an assortment of diseases and conditions. Second is an opportunity to establish a new global industry that has the potential for \$100 billion to \$500 billion in worldwide annual revenues. Both of these reasons make FIRM an essential Federal program.

Regenerative medicine has the potential to treat nearly every tissue and organ failure condition and disease that currently plagues our society. This technology is arriving at a crucial time in American healthcare. Currently, there are 35 million people over the age of 65 in the U.S.<sup>53</sup>, 12 percent of the approximate 281 million people in the U.S. However, due to the immense baby boomer population, there are about 57 million Americans aged 55-64.<sup>54</sup> Within 10 years, there will be more than 70 million Americans, more

than one-fifth of the population, over the age of 65. People in the senior citizen age group face a variety of diseases that require regenerative medicine therapies including:

- Diabetes
- Osteoporosis
- Heart Disease
- Strokes
- Cancer<sup>55</sup>

Baby boomers have watched medical technology advance substantially during their lifetime. As they age into the senior citizen category, their health is one of their top concerns, as is the desire to remain capable of leading an active lifestyle.<sup>56</sup> Regenerative medicine offers the increase of quality of healthcare that baby boomers both need and are seeking. If FIRM were to begin today, the program would be at the 10 year mark as the last baby boomer crosses into senior citizen status. At this point, regenerative medicine could potentially be offering skin, bone, and joint replacement products as well as organ patches capable of slowing or reversing organ failure and degradation. Without these regenerative medicine therapies to cure tissue failure-related diseases, healthcare costs will rise. However, with these therapies, the baby boomer population will be the first group to experience regenerative medicine's benefit to quality of life. Baby boomers will almost assuredly embrace regenerative medicine and the promises it brings them.

The second major benefit that FIRM has to offer is growing a new, multibillion-dollar global industry. While computers and semiconductors defined the 1980s, the Internet dominated the 1990s; the 2000s have seen economic challenge and thus far lack a defining cutting-edge industry. While biotechnology has offered the promise of new therapies and treatments, the biotechnology industry has yet to produce many products and even fewer profits. Government investment has led to innovation and new markets in the past.

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<sup>53</sup> Hetzel, Lisa. Smith, Annetta. "The 65 Years and Over Population: 2000" United States Census Bureau. Issued October 2001.

<sup>54</sup> Smith, Denise. "The Older Population in the United States: March 2002", United States Census Bureau. Issued April 2003

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<sup>55</sup> Seniors' Health Topic. MEDLINEplus. 23 September 2003  
<http://www.nlm.nih.gov/medlineplus/seniorshalth.html>

<sup>56</sup> Kantrowitz, Barbara. "Health for Life." Newsweek. Special Edition Fall/Winter (2001): 5-10

One story of resounding success of government-industry partnership is that of SEMATECH. In the late 1980s, to counteract the slipping performance of the \$8 billion<sup>57</sup> a year American semiconductor industry, an industry-government consortium known as SEMATECH was created, comprised of 14 U.S. semiconductor manufacturers and the U.S. Government.<sup>58</sup> Together, industry and Government leveraged common resources (including laboratories and funding), created industry roadmaps advancing technology, and shared risks to advance and raise the quality of American semiconductor technology. During the next decade, the consortium worked with a \$1.5 billion Federal commitment over 6 years in conjunction with industry manufacturing and funding to create faster, cheaper, and better chips.<sup>59</sup> By 1996, Federal funding was voluntarily stopped by SEMATECH, as the industry no longer needed the funds. The U.S. had restored its lead in the semiconductor industry. SEMATECH remains active today, mapping out future research and coordinating industry activities.<sup>60</sup> This partnership strengthened and ensured the strength of the American semiconductor industry, and had the positive effect of making the U.S. the leading nation in semiconductor technology today with \$70 billion in sales and 50 percent of global market share in 2002.<sup>61</sup> While one could rightfully argue that the global semiconductor industry would have grown to its current size today without SEMATECH, it is almost certain that

without SEMATECH the U.S. would not be the market leader in semiconductors today. Without a doubt, the SEMATECH consortium was one of the biggest and most successful partnerships between industry and Government. SEMATECH was able to right a damaged industry and reached self-sufficiency within a decade of inception. This successful story provides a powerful case study for how FIRM could potentially be structured.

Another example of successful Government-industry partnership is the hard disk storage manufacturing industry, today a \$50 billion industry. In the late 1980s Japan was poised to dominate this market. But in 1990, specifically in response to the opportunity to receive funding from the Department of Commerce, U.S. participants in this industry formed the National Storage Industry consortium and the National Science Foundation established an engineering research center on data storage. This technological investment by key government agencies led to hard drive storage densities growing at twice the pre-investment rate, and allowing the U.S. hard drive storage industry to remain competitive.<sup>62</sup>

Funding from other Government agencies has made substantial impacts as well. The Department of Energy's Office of Industrial Technologies shares the cost of developing new energy efficient technology with a number of industries (including steel, agriculture, chemicals, among others); enabling these industries to cost-efficiently develop new technologies.<sup>63</sup> This program has benefited the U.S. steel industry in particular, with new technologies that could potentially save the steel industry 70 trillion BTU/year, or about 30 percent of the industry's energy cost.<sup>64</sup>

The U.S. Government has a tremendous history of spurring forward innovation and growth of industries. Regenerative medicine is the next

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<sup>57</sup> "U.S. EQUIPMENT AND MATERIALS SUPPLIERS TO PARTICIPATE IN SEMATECH" PR Newswire. May 27, 1987

<sup>58</sup> Corporate Information: History. International Sematech. 8 October 2003 <http://www.sematech.org/public/corporate/history/history.htm>

<sup>59</sup> Auerbach, Stuart. "Chip Firms Set 5-Year Timetable Project Seen Helping U.S. Regain Its Lead." The Washington Post. May 13, 1987

<sup>60</sup> Corporate Information: History. International Sematech. 8 October 2003 <http://www.sematech.org/public/corporate/history/history.htm>

<sup>61</sup> Tuttle, Molly (Director of Communications of the Semiconductor Industry Association). Personal Interview. 8 October 2003

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<sup>62</sup> White, Robert M. "A message to Congress." MIT's Technology Review. 100 (1997): 5

<sup>63</sup> OIT Programs. Office of Industrial Technologies. 8 October 2003. <http://www.oit.doe.gov/programs.shtml#fa>

<sup>64</sup> Valenti, Michael. "A cradle for new steel technologies." Mechanical Engineering. 120 (1998): 60-65

industry waiting to be focused and grown through Government investment and leadership.

Regenerative medicine offers a field that presents the opportunity for concrete solutions to diseases through the replacement of failing tissues. If supported by the Federal government, regenerative medicine has the opportunity to become the defining industry of the 21<sup>st</sup> Century. Government initiatives and research funding have in the past been shown to lend support to industry and consumer confidence. While economic benefits from FIRM would not be realized overnight, it does provide the opportunity to lay the foundation for an industry with huge potential.

### **Increasing Public Awareness and Support**

Participants at an HHS-sponsored conference in March 2003 largely expressed disappointment that, with a few exceptions, regenerative medicine endeavors have not resulted in economically viable products and have not aroused tremendous public interest. With perception often being reality, it is important that regenerative medicine receive the appropriate attention and arouses the excitement merited from the public. It is essential that FIRM contain a large education and outreach component charged with the task of instilling enthusiasm and excitement for the initiative in American culture.

As one potential strategy to pique public interest and to attract bright researchers, the education and outreach arm of FIRM could focus on the “Challenge Problems” previously mentioned. Particularly marketable are challenge problems that involve tangible products that the public can appreciate. Examples of such “Challenge Problem” products might be:

- A retinal patch
- A living tooth
- Tissue engineered blood cells
- Tissue to repair injured or damaged hearts
- A functioning human liver
- A functioning human bladder

These challenges present an opportunity to show the public tangible accomplishments to excite them. Further, by creating milestones that build up expectations, such as first repairing heart tissue *in vivo*, then developing a heart “patch,” and finally

creating a working heart, the public has time to get accustomed and comfortable with the technology.

Equally important is the education of the public on how regenerative medicine science works and the risks of the technology. Particularly in the field of medicine, the American public is very risk adverse. In order to ensure that the technology is accepted, outreach and educational programs targeted at people of all ages should be developed and administered. The concept of therapies that repair and replace damaged organs is wondrous, but to some might be viewed as invasive. Therefore it is the FIRM’s duty to ensure that all questions are answered and that the program and its goals are transparent.

In order to achieve the proper levels of education and acceptance, FIRM must be publicly marketed and branded at a level not seen since the Apollo program. FIRM must become a part of the public school systems, have high-profile spokespeople, and have a logo as well recognized as the breast cancer ribbon or the double helix of the Human Genome Project. With all of these efforts, FIRM will become a technology whose household name ensures it is a public priority, not just a Government priority.

By integrating FIRM into the public school systems, the initiative will gain support from today’s youngsters who will grow up with regenerative medicine breakthroughs during their lives. Additionally, parents will get involved as they hear about regenerative medicine from their children. It also will serve to promote interest in the researchers of tomorrow. A high school student today could become a graduate student in 10 years who may choose to make regenerative medicine his or her life’s work. By building a foundation of people who understand and are comfortable with the technology, we can lay the foundation for future research in regenerative medicine.

By finding key spokespeople to promote FIRM, the initiative will appeal to the American public as a whole. Spokespeople can be an effective way of garnering attention and support by putting a well-known “face” to a concept. FIRM should focus on finding the appropriate celebrities who can push FIRM at public events, through public service announcements and other major venues.

Public support will dramatically affect future Government and private commitment. If the public is aware of the benefits that regenerative medicine brings, they will begin to expect and demand that this technology become a reality.



## CONCLUSION

Regenerative medicine offers the potential to cure countless fatal and debilitating conditions through therapies that spur *in vivo* regeneration and *in vitro* creation of healthy tissue for implantation. The next evolution of medical technology is now in sight, and has the potential to become reality in the next 20 years. Other nations have envisioned the opportunities that regenerative medicine will bring to society. Our Nation's private sector has seen the potential benefits, having spent \$4 billion in hopes of making regenerative medicine a reality. Despite this tremendous private investment, there is little to show in terms of viable products, due to the lack of scientific research and coordination. The U.S. Government can provide direction and resources to the regenerative medicine effort to allow private industry to focus on product development.

FIRM offers an opportunity to bring the U.S. to the forefront of regenerative medicine. With a dedicated U.S. Government investment in regenerative medicine for the next 20 years in conjunction with concise goal setting and fulfillment as directed by the FIRM council, FIRM provides the unique opportunity to leverage resources. This formula has seen success when implemented with the Human Genome Project, and is the model for the National Nanotechnology Initiative. FIRM will leverage Government labs, funding mechanisms, and financial resources to give regenerative medicine a vision and purpose, and bring this vision to the American public. While regenerative medicine is an inevitable evolution of science, without guidance the technology will take too long to mature. FIRM is required to unravel the complexities of regenerative medicine and to make this technology a reality in the next 20 years. Other nations have seen the need for national direction. Now is the U.S.' time to embrace this technology by making FIRM a framework for the next generation of healthcare. America's greatest natural resource is ingenuity. Coupled with the necessary funding and direction, our Nation can maintain its preeminence in biotechnology by paving the way to the future with the evolving world of regenerative medicine. By doing so, we can make tissue and organ failure a relic of the past by 2020.





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