The Application of Regenerative Medicine Products and Technologies Toward Areas of Significant Medical Need – Improving Clinical Outcomes & Reducing Costs

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Why the US Needs a National Strategy and What It Should Include

Summary

Increasing healthcare costs combined with demographic trends create a significant challenge for our society as the impact of a rapidly expanding aging population is expected to increase dramatically in coming years. Current medical treatments for most chronic diseases merely treat symptoms or provide palliative care. Better and more cost-effective therapeutic options are the key to improving clinical outcomes for patients, improving their quality of life, and the quality of their family’s lives. The field of regenerative medicine has the potential to provide many such solutions through the use of innovative, disease-altering treatments and at the same time bend the healthcare cost curve in a meaningful way. Regenerative medicine products already on the market have demonstrated their clinical and cost reduction value. Moreover, there are over 200 regenerative medicine products currently in clinical development for major medical challenges such as heart and vascular diseases, stroke, diabetes, inflammatory and immune diseases and other conditions. The rationale for developing a National Strategy to address these areas is presented in this white paper along with a description of primary hurdles and challenges.

Regenerative medicine represents healthcare related technologies that translate the fundamental knowledge in biology, chemistry and physics into materials, devices and systems through a variety of therapeutic strategies that augment, repair, replace or regenerate organs and tissues. This rapidly evolving, interdisciplinary field in healthcare is poised to transform the practice of medicine through medical innovation and the development of safer and more effective treatments.

There are currently more than 600 companies in this space developing products that include cell-based therapies, small molecules, biologics, tissue-engineered biomaterials, scaffolds and implantable devices. Additional products include research tools such as equipment, consumables, software, cells as drug discovery or toxicity testing tools, as well as clinical tools, bioprocessing tools, reagents and storage systems. The creation of a national strategy for regenerative medicine will accelerate the development and
application of these technologies – thus lowering healthcare costs and delivering patients better, safer medicines and improving their quality of life.

Data from the Centers for Disease Control (CDC) and National Center for Health Statistics (NCHS) shows that annual healthcare expenditures in the U.S. are approximately $2.5 trillion dollars, which represents 17.4% of the GDP. Demographic analysis of healthcare expenditures shows that average per capita healthcare expenses increase significantly with age, particularly for individuals beyond the age of 65 who are more susceptible to a wide-range of conditions and diseases, including heart and vascular disease, cancer, acute and chronic neurological conditions, inflammatory and immune diseases and a host of other illnesses. Primarily as a result of these aging-associated diseases and conditions, individuals age 65 and over incur annual healthcare expenditures on average that are 3 to 8 times greater than individuals under the age of 45.

Another major demographic trend in healthcare is the aging of the “baby boom” generation, which is causing a dramatic increase in the number of individuals over the age of 65. According to U.S. Census data and projections, the segment of the population that is over age 65 will increase by more than 80% between the years 2010 and 2030, (i.e. from 40.2 million people in 2010, to more than 72 million people in 2030). It’s no secret that this unprecedented demographic shift will create enormous pressure on the healthcare system in the years ahead. This challenge is exacerbated by a growing shortage of primary care physicians and clinical specialists (e.g. cardiology, oncology, general surgery) that, along with other economic pressures will result in fewer available healthcare resources. Taken together, if nothing else changes, these factors will unavoidably result in various forms of healthcare rationing.

According to an analysis by the Alliance for Aging Research, 83% of healthcare spending is associated with treating chronic diseases and conditions. These statistics reflect a longstanding emphasis of the healthcare infrastructure on triage and palliative care. Given the unavoidable pressures created by the demographic shift now occurring, we need to rely on innovative solutions and new technologies if we seek to achieve the goals of improving clinical outcomes, enhancing patient (and family) quality of life, reducing costs and supporting the goal of achieving broader access with a finite pool of financial and human resources.

Much of the dialogue around healthcare in recent years has focused on the issues of broadening access (through insurance reforms) and controlling costs through regulatory means such as payment cuts to health providers. Increased access and cost containment are worthwhile objectives. However, it is important to note that cost reduction does not fundamentally result in improved clinical outcomes, and could be a conflicting objective, since spending less could reduce the quantity and/or quality of care. Clearly, reducing expenditures will be helpful, but will not enable us to improve clinical outcomes and

1 Health, United States, 2011 available at http://www.cdc.gov/nchs/data/hus/hus11.pdf (published by the Department of health and Human Services and the National Center for Health Statistics, and the Centers for Disease Control and Prevention
3 See “Physician shortage projected to soar to more than 91,000 in a decade” at http://www.ama-assn.org/amednews/2010/10/11/prsb1011.htm
4 Chronic Disease and Medical Innovation in an Aging Nation – the Silver Book available at http://www.silverbook.org/SilverBook.pdf (published by the Alliance for Aging Research)
achieve enhanced patient quality of life. Holding aggregate spending constant while broadening access at the margin could enable improved care for those individuals previously without care, but in reality this represents a shift of resources from one group to another, and represents form of rationing.

Understanding exactly where healthcare dollars are spent, and are likely to be spent in the future, is critical to understanding how we can strategically invest (as a nation), to address the challenges we face. To critically evaluate how we can improve care and reduce costs, we can begin by examining the largest categories of healthcare expense, both by category of activity, and disease area. Recent data shows the following:


<table>
<thead>
<tr>
<th>Expense Category</th>
<th>2009 Impact ($ Billions)</th>
<th>% of Overall Healthcare Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Care</td>
<td>759.1</td>
<td>30.5%</td>
</tr>
<tr>
<td>Physician, Clinical &amp; Professional Services</td>
<td>572.7</td>
<td>23.0%</td>
</tr>
<tr>
<td>Nursing Home &amp; Home Healthcare</td>
<td>205.3</td>
<td>8.3%</td>
</tr>
<tr>
<td>Prescription Drugs*</td>
<td>250.0</td>
<td>10.0%</td>
</tr>
<tr>
<td>Government Administration, Public Health &amp; Health Insurance</td>
<td>240.2</td>
<td>9.7%</td>
</tr>
<tr>
<td>Research &amp; Capital Investment</td>
<td>156.2</td>
<td>6.3%</td>
</tr>
<tr>
<td>Other (e.g. dental, durable equipment, etc.)</td>
<td>303.0</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

*Approximately 70% of prescriptions are for generics (which accounts for ~20% of total prescription drug costs)

Improving healthcare and clinical outcomes should ideally result in fewer hospital admissions (and readmissions), and less time in the hospital, especially in an intensive care environment. In addition, for many patients, reducing the need for full-time institutional care such as long-term hospital care or a nursing home, and reducing the need for professional home care would represent meaningful improvements in quality of life. Reducing hospital care, the need for physician, clinical and professional services and nursing and home healthcare would also have a meaningful impact on reducing overall healthcare expenses, since together these categories comprise 62% of all healthcare related expenses.

Meaningful improvements in clinical outcomes and cost reduction can be accomplished through innovations that advance standards of care and enhance efficiency, such as regenerative medicine. To understand how we can achieve these goals, we must first identify the greatest areas of unmet medical need, examine where (and how) current treatment approaches are inadequate, and understand how successful development of regenerative medicine and related therapies could improve clinical outcomes and reduce costs.

Currently there are several regenerative medicine products (largely comprised of cell and biomaterial-based therapies) that have been approved by the FDA (and other regulatory agencies) in clinical use. In addition, several hundred clinical trials are being conducted in the U.S. that utilize various stem cell and regenerative medicine approaches and technologies. This clinical activity encompasses a broad range of indications and therapeutic areas, including cardiovascular disease, neurological conditions and injury, inflammatory and immune conditions, diabetes, transplant support, orthopedics, hematological...
conditions, pulmonary conditions and a range of others. These studies also reflect a variety of product types and approaches, including the use of autologous cells (derived from the patient), allogeneic stem cells (derived from a donor), tissue-engineered products (e.g. scaffolds and biomaterials), gene therapies, biologics, small molecules and combination products – all of which have shown therapeutic promise pre-clinically and clinically.

To understand where and how emerging regenerative medicine therapies can have an impact, it’s useful to examine a few specific areas that are major drivers of healthcare costs and that represent significant areas of unmet medical need. Much of the historical focus on stem cell clinical trials has concentrated on oncology related indications such as bone marrow transplantation or the use of hematopoietic stem cells or peripheral blood stem cells. These approaches represent important advances in medicine and longstanding clinical practices that have improved medical outcomes for many patients. They are excluded from further discussion here, however, since these approaches are routinely used in current clinical practice and provide substantial benefit to many patients. The focus in this white paper is on emerging applications of regenerative medicine that have the potential to address substantial areas of unmet medical need, especially those that are major healthcare cost drivers. Note that this analysis does not explicitly consider certain forms of tissue engineering or certain other treatments, such as in the area of orthopedics, which could be covered in a separate white paper.

**Heart and Vascular Disease**

Cardiovascular disease, according to the American Heart Association (AHA), represents the leading cause of death in the U.S., is a leading cause of morbidity and disability and is responsible for 17% of all healthcare related costs. By 2030 the AHA projects that over 40 million people will suffer from some form of heart disease in the U.S. Due in large measure to an aging population, by 2030 direct medical costs for cardiovascular disease (measured in 2008 dollars) will exceed $818 billion annually, more than triple current levels. Indirect costs will contribute an additional $275 billion in annual impact, resulting in nearly $1.1 trillion in annual costs and economic impact. When adjusted for inflation that could occur over a 20-year time frame, the actual impact is expected to be far greater.

Major forms of cardiovascular disease include acute myocardial infarction (heart attack), chronic ischemia (e.g. congestive heart failure) and peripheral vascular or arterial disease (e.g. intermittent claudication and critical limb ischemia (CLI), which are significant causes of disability and in the case of CLI can result in the need for surgical amputation of the ischemic digit or limbs to remove necrotic and chronically painful tissue). While survival rates among patients suffering a heart attack are meaningfully higher than they were 30 years ago thanks to better interventional techniques and the emergence of thrombolytics, the impact of chronic heart and vascular disease has also increased.

Extensive research over the past decade has shown that stem cell and regenerative medicine therapy could have a substantial impact on treating cardiovascular disease, and could provide meaningful benefits through multiple important mechanisms⁵, including:

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⁵ For recent example reviews and opinions describing various approaches how cell therapies can provide a benefit through expression of paracrine factors, see the following examples: (1) “Stem and progenitor cell-based therapy in ischaemic heart disease: promise, uncertainties, and challenges.” European Heart Journal (2011) 32, 1197–1206; (2) “Novel Avenues for Cell Therapy in Acute Myocardial Infarction.” Circulation Research (2012), 110:195-197; (3)
- Reducing the loss of heart muscle tissue (e.g. by reducing apoptotic cell death in the ischemic area);
- Promoting angiogenesis in regions of ischemia;
- Reducing inflammatory mediated tissue loss and scarring;
- Promoting the repair and regeneration of muscle tissue;
- Recruitment of other cell types into regions of chronic injury to enhance repair and recovery; and
- Replacing lost muscle tissue.

As of December 2012, there were approximately 80 open clinical trials registered on Clinicaltrials.Gov in the cardiovascular area involving administration of stem cells as the therapeutic intervention for heart and vascular disease (excluding stroke). Of these, ~83% (64 studies) were listed as actively enrolling patients, whereas the remainder had not yet initiated enrollment; roughly one-third of the studies were sponsored either fully or in part by industry.

It’s worth noting that most of the trials being conducted are focused on the treatment of cardiovascular conditions that are serious areas of unmet medical need and are inadequately addressed by current approaches. In terms of specific therapeutic indications, most of the trials are focused on treating damage from congestive heart failure & chronic ischemia in the heart (~40%), promoting more effective recovery in patients that have suffered a myocardial infarction (~27%) and treating advanced vascular or arterial disease, such as critical limb ischemia or other serious forms of peripheral arterial or vascular disease (~15%).

Some examples of more advanced clinical programs to treat acute or chronic heart and vascular disease include the following:

- **Mesoblast’s planned 1,700 patient Phase 3 trial involving administration of Revascor, an “off-the-shelf” allogeneic mesenchymal progenitor cell therapy, to patients suffering from congestive heart failure (partnered with Teva pharmaceuticals), which is anticipated to initiate in 2013.** Data from prior clinical and preclinical work suggests that Revascor can promote angiogenesis and enhance recovery in areas of chronic ischemic injury. Previous clinical data suggests that this could translate to reduced mortality, morbidity and hospitalization;
- **Aastrom’s ongoing ~100 patient Phase 2 trial involving the treatment of Ischemic Dilated Cardiomyopathy (IDCM).** Prior preclinical and clinical work suggests that treatment can enhance angiogenesis in areas of heart tissue damage, enhancing tissue repair and reducing long term complications;
- **Baxter’s ongoing ~440 patient Phase 3 study evaluating autologous CD34+ stem cells to treat patients suffering from refractory angina;**
- **Cytori’s active ~260 patient Phase 2 trial using autologous adipose derived stem cells to treat patients that have suffered damage from an acute myocardial infarction; and**
- **Neostem’s trial enrolling 160 patient Phase 2 study exploring the use of autologous CD34+ stem cells to treat damage from acute myocardial infarction;**

Athensys has FDA authorization for a 150 patient Phase 2 clinical trial to evaluated MultiStem, an allogeneic “off-the-shelf” cell therapy treatment to treat damage from acute myocardial infarction.

In addition to these advanced clinical programs, a robust number of early stage technologies are expected be entering the clinical pipeline. Representative examples include:

- 3-D Matrix Medical Technology is developing a medical device to treat myocardial infarction using technology based on a biocompatible, and bioabsorbable extracellular matrix.
- VentriNova is developing small molecules and gene therapies that stimulate heart cells to re-enter the cell cycle, therefore regenerating lost heart tissue.

Clinical progress in any of these areas could have a meaningful impact on improving clinical outcomes and improved quality of life for those patients disabled by heart disease, such as by more effectively rescuing injured or ischemic tissue, improving heart function and improving vascularization. Such approaches could also substantially reduce overall costs associated with treating heart and vascular disease by reducing hospitalizations (e.g. admissions, length of stay, and time in intensive care), procedural interventions (e.g. reducing the number of treatments for patients suffering from congestive heart failure or other chronic ischemic conditions), as well as reducing mortality, morbidity, pain and disability. These would reflect meaningful advances in clinical outcomes, patient quality of life and reduce healthcare costs.

Neurological Injury and Conditions

Acute and chronic neurological conditions are also leading causes of serious long-term disability. Numerous conditions have a substantial impact on patient quality of life and require substantial healthcare resources in the form of clinical intervention and support, full time institutional care and professional home care. In particular, stroke, Alzheimer’s disease and Parkinson’s disease, are primary causes of chronic disability among the older portion of the population as well as leading causes of mortality. Traumatic Brain Injury (TBI) and spinal cord injury are leading causes of serious disability among younger segments of the population.

In terms of aggregate economic impact, these neurological injuries and conditions are estimated to be responsible for more than $200 billion in annual healthcare and institutional care costs. A 2009 analysis published by the Alliance for Aging Research estimates that the direct and indirect economic impact of Parkinson’s disease and Alzheimer’s disease alone to be as much as $175 Billion per year.

While there has been meaningful progress in some areas, traditional interventional procedures and pharmaceutical approaches have done very little to improve the standard of care for patients suffering

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6 See for example the CDC’s website on Traumatic Brain Injury at http://www.cdc.gov/traumaticbraininjury/statistics.html, and on Spinal Cord Injury at http://www.cdc.gov/injury/Publications/FactBook/ and the Christopher and Dana Reeves Foundation report

from these or other neurological conditions (e.g. orphan neurological conditions, chronic progressive Multiple Sclerosis, spinal cord injury). In recent years, extensive preclinical work has demonstrated how cell therapy approaches could provide effective new treatments for neurological damage and injury in multiple ways\(^8\), such as acting through the following types of mechanisms:

- Reducing the loss of neuronal tissue following stroke or acute injury (e.g. TBI), by reducing inflammatory mediated tissue loss and scarring;
- Promoting formation of new blood vessels (angiogenesis) in regions of ischemic injury;
- Promoting repair and regeneration of damaged neuronal tissue by production of neurotrophic factors and through stimulation of reparative immune response pathways;
- Stimulating recruitment or activity of reparative cell populations in regions of acute or chronic injury to enhance recovery; and
- Replacing lost neuronal tissue.

In contrast to traditional pharmaceuticals and biologics, which by design typically convey one specific effect, and exhibit a single, precise activity, cells are dynamic, living entities that are frequently capable of exerting multiple benefits in parallel. Depending on the cell type and the approach being taken, many of the observed effects are not achieved through permanent engraftment of cell therapy-based products, but rather through the dynamically regulated production of multiple “trophic factors” (e.g. secreted proteins, chemokines, cytokines) that can promote healing and tissue repair. Research shows that administered cells may dynamically interact with endogenous populations of cells that play an important role in various processes central to healing and tissue repair. This includes down-regulation of certain cell types and processes that can cause tissue loss and scarring (e.g. active inflammatory cells) and up-regulation of other cell types involved in tissue repair and rebuilding (e.g. regulatory T cells, non-inflammatory macrophages, tissue-specific stem cells).

Currently there are more than 80 clinical trials involving the use of stem cells or cell therapy to treat acute or chronic neurological disease or injury, with approximately 60 open and active studies. Of these, more than one-third are focused on treating acute, sub-acute or chronic damage from ischemic stroke (24 active studies), while one-quarter are focused on treating damage from orphan neurological conditions and severe developmental disorders, such as lysosomal storage disorders, cerebral palsy and neonatal hypoxic ischemia (14 active studies), chronic neurological conditions such as Multiple Sclerosis, Parkinson’s or Alzheimer’s Disease (13 active studies) and severely debilitating and invariably lethal conditions such as Amyotrophic Lateral Sclerosis, more commonly referred to as Lou Gehrig’s disease or ALS, (1 open study). Other active areas of interest include treating damage from

\(^8\) There are a wide range of references that describe the range of regenerative medicine approaches being used to treat neurological diseases and conditions, including various cell types and biological mechanisms of action - see for example: (1) “Adult Bone Marrow: Which Stem Cells for Cellular Therapy Protocols in Neurodegenerative Disorders?” *Journal of Biomedicine and Biotechnology* Volume 2012, Article ID 601560; (2) “The potential benefit of stem cell therapy after stroke: An update” *Vascular Health and Risk Management* 2012:8 569–580, and (3) “Neurorestoration Induced by Mesenchymal Stem Cells: Potential Therapeutic Mechanisms for Clinical Trials” *Yonsei Med J* 53(6):1059-1067, 2012
Traumatic Brain Injury (TBI) and spinal cord injury, which are leading causes of death and serious long-term disability among young people (3 active studies). Each of these conditions can have a substantial, long term impact on patients (and their families), and pose significant clinical and institutional care costs and challenges.

Examples of clinical studies currently being conducted to evaluate the impact of cell therapy on treating acute or chronic neurological conditions include the following:

- **Athersys’ ongoing ~140 patient Phase 2 clinical trial to treat victims of ischemic stroke involving intravenous administration of an allogeneic cell therapy product (MultiStem) 1-2 days after the stroke has occurred, which would meaningfully extend the current treatment window beyond the current standard of care, with tPA (which must be administered within 4.5 hours of the stroke);**
- **Cytomedix’ (Aldagen) active ~100 patient study involving intracarotid administration of autologous bone marrow cells in patients that have recently suffered a recent ischemic stroke, which could further extend the treatment window to ~3 weeks;**
- **Georgia Health Sciences University ongoing ~40 patient Phase1/2 study involving administration of umbilical cord blood stem cells to neonates and children suffering from cerebral palsy;**
- **The University of Texas Health Sciences Center in Houston’s trial evaluating administration of autologous bone marrow mononuclear cells to treat patients that have suffered a traumatic brain injury (TBI);**
- **Reneuron’s Phase 1 study exploring the administration of genetically modified neuronal stem cells to treat patients with chronic stroke damage (i.e. treatment 6 months to 5 years post stroke);**
- **Stem Cells, Inc.’s Phase 1/2 study evaluating administration of HuCNS-SC (neural stem cells) in patients that have suffered a spinal cord injury, as well as an ongoing trial in age-related macular degeneration, and recently reported trial results in Pelizaeus Merzbacher Disease; and**
- **The Mayo Clinic’s ongoing Phase 1 clinical trial to evaluate autologous mesenchymal stem cells in patients that are diagnosed with ALS;**

Further, preclinical studies that have produced favorable data and will likely begin human trials in the next 12 months include:

- **InVivo Therapeutics, who has submitted and Investigational Device Exemption (IDE) to the FDA to begin human studies to test its biopolymer scaffolding for the treatment of acute spinal cord injury.**
- **iPierian who has created disease models from patient-derived induced pluripotent stem cells (iPSC) to advance their novel drug development programs, and is aiming to start human trials with their potential drugs to treat Alzheimer’s Disease and others in 2014.**

Successful development of cell therapy and regenerative medicine treatments could have a significant impact on improving clinical outcomes and quality of life for patients that have suffered an acute neurological injury that causes long term effects, especially those that occur during early development. These and other conditions can have a long lasting impact, such as chronic progressive diseases that
tend to occur with greater frequency in an aging population. Effective treatments would improve clinical outcomes, reduce or eliminate disability and pain, and thereby enhance patient quality of life (and family quality of life where there is a home care burden). However, such treatments could also meaningfully reduce healthcare costs by minimizing hospitalization or shortening length of stay (particularly in an intensive care or full-time hospital care environment), reducing rehabilitation, physical therapy and occupational therapy needs and costs, and shortening (or in some cases eliminating) the need for long term/full time institutional care (e.g. nursing or convalescent home care) or significant home care support.

**Wound Healing, Inflammatory and Immune Disease, Diabetes & Other Indications**

There are already more than a dozen cell therapy products that have been approved by the FDA and other regulatory agencies that are in regular clinical use for certain orthopedic applications, and the treatment of chronic wounds. Notable examples include *Apligraf*, an allogeneic cell therapy product that is approved by the FDA for treating venous leg ulcers and diabetic foot ulcers, and *Gintuit* for treating certain oral conditions, both of which were developed by Organogenesis, Inc. Similarly, *Dermagraft*, also approved by the FDA, is used for the treatment of full thickness diabetic foot ulcers, and is marketed by Shire Regenerative Medicine (after being successfully developed by Advanced BioHealing, Inc.).

Chronic inflammatory and immune diseases also pose a significant healthcare burden. While there are numerous anti-inflammatory drugs and treatment options available, for chronic and significantly debilitating conditions many forms of intervention may provide only temporary relief, or may provide no meaningful or durable therapeutic benefits.

A growing body of pre-clinical research produced over the past decade has shown promising signs that various cell therapy approaches may be able to help achieve more meaningful and durable relief in a range of inflammatory and immune diseases. This is believed to be possible because cell therapy-based approaches may result in a more durable resetting of the immune system (i.e. achieve durable immunological homeostasis) without causing significant immunosuppression that could result in increased susceptibility to infection or malignant neoplasm.

Currently there are 27 clinical trials involving the use of cell therapy treatments for inflammatory and immune conditions such as Inflammatory Bowel Disease (13 active studies), Multiple Sclerosis (5 active studies), Lupus (1 active study) and Scleroderma (1 active study). There are also 13 active trials for diabetes, 10 active trials for rheumatoid or osteoarthritis and 9 studies involving administration of non-hematopoietic stem cells for transplant related procedures, such as prevention or treatment of GVHD.

Examples of pre-clinical and commercially sponsored clinical studies in these disease areas include:

- Osiris’ ongoing 270 patient Phase 3 study involving intravenous administration of Prochymal, an allogeneic Mesenchymal Stem Cell therapy, to patients suffering from Crohn’s disease;
- Pfizer’s (Athersys) ongoing ~130 patient Phase 2 trial involving intravenous administration of MultiStem, an allogeneic cell therapy to patients suffering moderate to severe Ulcerative colitis;
- Mesoblast’s ongoing 60 patient Phase 2 trial involving administration of allogeneic mesenchymal precursor cells (MPC’s) in patients suffering from type 2 diabetes;
Tigenix's (Cellerix) ongoing 50 patient Phase 2 study involving administration of autologous adipose derived stem cells to patients suffering from anal fistulas;

ViaCyte is focused on developing innovative cell encapsulation technologies for use in modern cell therapy combination products, including the company's PEC-01 cells for the treatment of type-1 diabetes; and

Other companies, such as Harvard Biosciences, manufacturer of bioreactors and Nanofiber Solutions, manufacturer of 3D nanofiber scaffolds, have combined their technologies to create and treat 2 patients with the first synthetic laryngotracheal scaffolds seeded with cells take from the patient's bone marrow.

There are numerous other areas of significant unmet medical need where regenerative medicine technologies could meaningfully improve clinical care, ameliorate disability and also reduce healthcare costs. These include trials to evaluate the application of cell therapy and regenerative medicine approaches to treat orthopedic conditions, blindness and other conditions. Examples of other programs include the following:

Mesoblast's ongoing Phase 2 study exploring administration of mesenchymal precursor cells (MPC's) to patients suffering from chronic low back pain due to degenerative disc disease (DDD). In contrast to more invasive approaches using discectomy, this approach relies on minimally invasive local injection of cells to help rebuild and restore the integrity of disc tissue;

DiscGenics recently published positive preclinical data using a combination of adult-derived stem cells and tissue-engineered scaffolds to treat patients with DDD. The company plans to begin human trials in early 2014;

Advanced Cell Technologies ongoing clinical trials using an allogeneic cell therapy approach to treat Macular Degeneration (a leading cause of blindness in the elderly) and Stargardt’s Macular Dystrophy. According to recent analysis conducted by the Alliance for Aging research, more than 38 million Americans age 40 and older suffer from an age related eye disease, are visually impaired, or legally blind. The annual economic cost of adult vision loss is estimated to exceed $51 billion annually; and

Currently there are 13 active clinical trials exploring the use of cell therapy to treat chronic liver disease – all of which are being conducted at clinical institutions outside the U.S., and none of which are commercially sponsored.

**Application of iPSC Cells and Other Platforms for Disease Characterization, Novel Clinical Diagnostics, More Effective Drug Screening, and Personalized Medicine**

Another area where regenerative medicine will have a substantial impact relates to the use of induced pluripotent stem cell technology that enables isolation of cells from healthy and diseased tissues to conduct comparative analysis of the underlying molecular causes of disease. The ability to efficiently create panels of differentiated cell types (e.g. heart muscle cells, neural tissue, liver cells) derived from both healthy individuals and those suffering from specific types of disease will enable researchers to definitively establish the molecular causes of disease, and as a result, will enable the development of novel and more precise diagnostic technologies. These will ultimately enable faster, more accurate, and

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less expensive diagnosis of a range of conditions, as well as lead to development of safer and more effective interventions that can be tailored to the specific needs of the patient. Faster, more accurate diagnosis and safer, more effective treatments will reduce overall healthcare costs, and substantially enhance patient quality of life.

**Identifying and Addressing the Hurdles and Critical gaps**

As described above, regenerative medicine has the potential to impact many different areas of unmet medical need. Many of these conditions pose a substantial clinical, human and economic burden on patients, their families and society in general. However, there are a number of substantial challenges, hurdles and uncertainties that have substantially impeded investment in the area. These include the following:

- **The Absence of a National Strategy** – Currently there is a lack of communication, effective coordination and prioritization among various federal agencies that have an interest in supporting regenerative medicine and cell therapy-based treatments. There is no overarching plan that will ensure this technology fulfills its promise, or do so in a manner that will help us address our national healthcare priorities. This means we don’t accurately know what activities are being undertaken and funded; leading to inefficient use of existing resources and that there is no consensus strategy about activities needed for this technology to develop. Other countries such as South Korea, UK, Canada and China have already made national commitments to regenerative medicine. Since our biggest healthcare challenges relate to addressing the areas of unmet medical need described above, we must have a national strategy designed to address these challenges in a more systematic and efficient manner.

- **Lack of Coordination Between the Government and Private Sector** -- In addition to lack of coordination among federal agencies, there is no coordination between the federal government and the private sector. While there are individual projects underway, there is no consistent and focused opportunity for strategic interaction between the regenerative medicine community -- industry, academia and patient advocates -- and the government.

- **Lack of Clear Identification and Prioritization of Areas of Unmet Medical Need** – Our biggest healthcare challenges are fairly obvious -- an aging population, which results in increased incidence/prevalence of heart and vascular disease, stroke, chronic neurological conditions and a host other conditions that are expensive to deal with and have a huge quality of life impact. Furthermore, the substantial increase in obesity and diabetes also increases the risk or impact of many of these conditions, as well as others that have a significant impact on Medicare and overall healthcare costs. In contrast to traditional approaches, regenerative medicine and cell therapy has shown potential to address many of these areas of unmet need. However, we have never established a clear list of healthcare priorities that explicitly focuses on areas of unmet medical needs. These can and should become imperatives for the NIH, FDA, CMS and any other federal agencies that can focus greater effort and emphasis on the development of innovative solutions.

- **Inability to Access Data that Could Provide Useful Healthcare Benchmarks and Enable More Efficient Clinical Trials** – Currently there is an enormous amount of data that is resident within CMS, CDC, the VA hospital system, the National Center for Health Statistics and certain other federal agencies about the cost of caring for patients with particular diseases. However, it is very difficult and very expensive for small innovative companies that are committed to
developing advanced therapies and healthcare solutions to access or use this data. By providing easier and more transparent access to information that could help companies design smarter and more efficient clinical trials, it will speed development and encourage investment. It will also allow us to benchmark more effectively against current standards of care and outcomes. This doesn’t require new government infrastructure, it requires using our current infrastructure more efficiently.

**The Cost, Time and Complexity of Clinical Trials** – As a result of FDASIA and PDUFA-V, we now have new opportunities to prioritize areas of unmet medical need, and help speed clinical development while protecting patient safety. Initiatives such as the broadened accelerated approval pathway, breakthrough therapies designation and other actions will help create a more efficient and transparent regulatory landscape – but we need to see these initiatives are properly funded and implemented. By establishing a more transparent and efficient regulatory landscape, while ensuring patient safety, this will also encourage investment and speed the development of innovative new solutions. Furthermore, although this legislation is clearly a positive step forward, there are other bottlenecks that significantly impede clinical development, such as a lack of centralized Institutional Review Boards (IRB’s) and standardization in other areas. These substantially delay the initiation and completion of clinical trials, adding greatly to the time and cost of development.

**Complexity and Uncertainty of the Coverage and Reimbursement System** – Even when the FDA has approved a product, in order to be utilized clinically, coverage and reimbursement needs to be in place. For the emerging field of cell therapy and other forms of regenerative medicine, there are few if any relevant precedents, including coverage codes and reimbursement mechanisms that can enable new medicines to be implemented clinically in an efficient, rational manner.

**Lack of Investment Capital** – From an investor perspective the field of regenerative medicine is viewed as having transformational potential, but is also viewed as high risk for multiple reasons, including the perceived high degree of technical risk, regulatory and reimbursement uncertainty and other factors. As long as significant uncertainties exist around these and other issues, investors will continue to underinvest, making capital scarce and slowing innovation. However, development of a national strategy that includes specific steps designed to reduce uncertainty in these and other areas and increase the efficiency of development, and will result in greater investor confidence and an increase in capital investment.

**Proposed Elements of a National Strategy for Regenerative Medicine**

There are practical solutions for these challenges and obstacles. The Alliance for Regenerative Medicine (ARM) believes that the right way to address them is the creation and implementation of a multi-faceted National Strategy for Regenerative Medicine, outlined below. The first six components are rapid and actionable steps that would demonstrate the Administration’s support for regenerative medicine, as well as other medical innovative technologies that can meet unmet medical needs.

- **Conduct a strategic assessment of our current activities to achieve better coordination of federal activity** – In order to effectively map out where we want to go, we first need to take a hard look at where we are. This should start with a thorough strategic assessment of the current activities occurring at various federal agencies, so that we can invest limited resources more effectively. We need to perform a gap analysis as well as identify areas of redundant
activity. The outcome should be a report with findings and recommendations for policies and actions to spur the field. We have previously recommended that GAO perform this analysis. An independent and comprehensive study will send a strong positive signal to the field.

- **Designate a National Biomedical Innovation Advisor** -- Given the impact on the population and our long-term national finances, solving our biggest healthcare challenges should be a national priority. ARM believes there needs to be a clear point of contact in the White House that is focused on promoting biomedical innovation as a way to help address these issues, and that should be their ONLY focus. Acting as an interface between the FDA, NIH, CMS, NCHS, other federal agencies and the private sector will be a huge job, and it deserves someone that is truly empowered and singularly focused on solving bottlenecks and accelerating progress in a cost-effective and rational way.

- **Create a multi-agency task force with senior agency officials and representatives from industry** -- The task force should include senior staff from key federal agencies, as well as select members of industry and the clinical community, which will be chaired by the Biomedical Innovation Advisor (above). This group should develop a plan, based on the strategic assessment and other actions, to promote regenerative medicine in ways that effectively address our biggest healthcare priorities. It should include recommendations for regulatory, reimbursement, research and other federal policies needed to foster research and product development.

- **Streamline clinical development in areas of serious unmet need** - While always ensuring the protection of patient safety, we need to accelerate and improve the efficiency of clinical trials, particularly in areas where there is a serious unmet medical need. As noted above, we've already taken some important first steps in the right direction. Recent legislation (FDASIA and PDUFA V) included important provisions designed to help speed clinical development in areas of serious medical need. This legislation, which was passed in a bipartisan manner by Congress, and signed by the President, helps establish a framework for an expanded “Accelerated Approval Pathway” and a “Breakthrough Therapies” category. While the precise operational framework around these designations remains to be defined, as a component of a national strategy we can act now to explicitly identify the areas that we want to prioritize solutions for, and then establish an operational framework that will allow us to implement these solutions in a meaningful way.

- **Create an explicitly defined list of serious unmet medical needs that represent our national priorities in healthcare** – We know what the major areas of burden are in our healthcare system, and we know approximately how big an impact these conditions will have in the years and decades ahead. By defining a clear list of priorities, we can implement a series of steps that will better enable us to develop more effective solutions. This will be an important step in the establishment of the new Accelerated Approval process (noted above), and will help us move towards the ultimate goal of improving clinical outcomes, enhancing patient quality of life and reducing overall costs.

Other elements of a strategy are more complex, though necessary to provide critical support for the field.

- **Establish incentives that will promote private investment in the areas we need most** – Funding for emerging companies that are doing the most innovative research is sparse. Furthermore, with the impact of sequestration and the future prospect of tax reform looming, it
creates uncertainty in the economic and investment climate. By creating meaningful incentives that promote targeted investment in defined areas of significant unmet medical need, it could catalyze a meaningful investment in the areas we need most. This could accelerate the development of innovative and cost-effective solutions, and also spur economic activity at a time when we really need it. Ultimately the biggest payoff would be for patients and their enhanced quality of life, but the economic impact on productivity and reducing our national healthcare bill could be enormous.

- **Establish a more efficient coverage and reimbursement framework that will operate in conjunction with an accelerated clinical approval framework** – If companies are successful at developing innovative solutions, and ultimately obtain regulatory approval through an accelerated pathway, the implementation of the new therapies will be substantially delayed if they don’t have a path to coverage and reimbursement. If we want to get the most from a more efficient regulatory framework, we need to take steps on the coverage and reimbursement side as well, including the creation of reimbursement mechanisms that will address therapies that are approved under the accelerated approval, breakthrough therapies, fast track or other designations.

- **Enable better clinical trial design by broadening access and enabling more effective utilization of historical data from CMS, NCHS, CDC and other relevant agencies** – Much of the innovative translational research is occurring at smaller (i.e. biotech) companies. But small companies are at a disadvantage in terms of access to capital, and frequently they have to run smaller, less informative clinical studies due to significant resource constraints. One way to enable companies to design more powerful studies would be to enable them to access and analyze more data from NCHS, CMS, CDC and perhaps other federal agencies, so that clinical trials can be designed more efficiently and effectively. These agencies can and should provide access to data without charge to innovative organizations that are committed to developing therapies designed to address serious unmet needs (i.e. our list of national healthcare priorities). This data could help with trial endpoint selection, understanding and modeling the frequency of clinically relevant events, establishing benchmarks and also help in establishing sensible reimbursement for products that are ultimately approved. Obviously such analysis must be done in a manner that never compromises patient identity – but this type of analysis is already done, so those types of safeguards exist and can be applied.

- **Create a National Regenerative Medicine Clinical Trial Network focused on accelerating development of solutions in high priority disease areas** - By first encouraging and enabling the establishment of regional (e.g. statewide) Clinical Trial Networks (CTN), we can ultimately link them to establish national Clinical Trial Network(s) that enable faster initiation of clinical trials through the use of centralized Institutional Review Boards and standardized contracting (both of which are huge impediments that delay and significantly increase the cost of clinical trials). These CTN’s will expand patient access and participation in active studies, speed trial enrollment and accelerate the development of innovative therapies while reducing costs.\(^{10}\)

\(^{10}\) Note that we are not suggesting completely redefining how institutional IRB’s work, which would be a complicated process. However, there are some recent State initiatives (e.g. Ohio) that are focused on making it easier for clinical institutions and patients to jointly participate in clinical trials through the use of common IRB mechanisms and regional IRB frameworks. For a description of this initiative in Ohio see [http://healthnews.uc.edu/news/?/20772/](http://healthnews.uc.edu/news/?/20772/).
Summary

There are a broad range of diseases and conditions that are inadequately addressed by current medical interventions and available forms of treatment. Emerging forms of cell therapy and regenerative medicine are already showing promising impact across many areas, and emerging technologies (e.g. induced pluripotent stem cell technology, tissue engineering and other approaches) promise to do even more. In contrast to traditional interventional or pharmacological approaches, which in many areas are palliative, regenerative medicine and cell therapies represent a unique and promising way to address the underlying cause of pathology in many conditions, and collectively represent a way to improve clinical outcomes in areas of unmet medical need, enhance patient quality of life by reducing disability and reduce overall healthcare costs by minimizing the impact of acute and chronic conditions and reducing hospitalization, interventional procedures by physicians and other healthcare professionals and mitigating the need for full-time, long term institutional care or professional home care.

Achieving these goals will require a commitment from both the public and private sectors. Other countries have already recognized the potential of regenerative medicine and cellular therapies. Now is the time for the U.S. to take the necessary steps to establish a national strategy for regenerative medicine so this technology's promise can become a reality.