The Alliance for Regenerative Medicine (ARM)'s mission is to advance regenerative medicine by representing, supporting, and engaging all stakeholders in regenerative medicine including companies, academic research institutions, patient advocacy groups, foundations, health insurers, investors, and other organizations.

ARM is a Washington, DC-based multi-stakeholder advocacy organization that promotes global initiatives necessary to facilitate access to life-giving advances in regenerative medicine.

The organization promotes legislative, regulatory reimbursement, investment, technical, and other initiatives to accelerate the development of safe and effective regenerative medicine technologies. ARM also works to increase public understanding of the field and its potential to transform human healthcare.

Prior to the formation of ARM in 2009, there was a need for more coordinated and cohesive advocacy representing the interests of the companies, research institutions, investors and patient groups that comprise the entire regenerative medicine community. Today ARM has more than 135 members and is the leading global advocacy organization in this field.
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Dear Friends and Colleagues of the Alliance for Regenerative Medicine:

On the eve of some very exciting developments in the regenerative medicine field, we are pleased to bring you the Alliance for Regenerative Medicine’s (ARM) second Regenerative Medicine Annual Report. Inside these pages you will find helpful information about scientific progress and the state of the industry today.

As our healthcare system faces an aging population and an increasing prevalence of chronic diseases, regenerative medicine will continue to play an increasingly important role in patient care, particularly where we offer therapies that deliver benefits that elude traditional drugs, devices, and surgery. Our unique ability to harness the body’s own healing processes in a safe and targeted manner means that the significance of regenerative medicine therapies will continue to intensify in the management of difficult-to-treat diseases. The potential savings from regenerative medicine treatments—for the United States alone—in terms of reducing the direct costs associated with chronic diseases have been estimated at approximately $250 billion a year.

We are at the forefront of a new era in medicine. As we stop to reflect on where the industry has come from and where it is going, we can agree that regenerative medicine has truly “come of age.” This is the result of a tenacious pursuit to translate groundbreaking research into therapeutic products, and to overcome initial setbacks that are common to any new and developing industry.

Within the following pages is a thorough overview of the regenerative medicine field, which we believe is close to reaching critical mass. Regenerative medicine is no longer an abstract concept. It is here, now, and is changing, and saving, the lives of patients around the world.

Over the past year, we have seen new products approved and released to the market, and the pipeline of therapies on the horizon continues to expand. Today, there are over 100 regenerative medicine products on the market around the world focused on diverse therapeutic areas, including oncology and the repair or regeneration of skin, soft tissue, wounds, heart tissue, cartilage, bone, and eye tissue among others. This year’s Annual Report reviews the clinical pipeline and commercially available products for several major areas.

The sector is also attracting increased attention from investors and industry partners. This past year we’ve surpassed $1 billion in annual revenue from regenerative medicine products currently on the market. We’ve also seen more than $1 billion in combined public and private investment into the sector.

Our field continues to grow by fostering the commercial expertise needed to build value for regenerative medicine products. Over the past decade, we’ve seen an acute and growing recognition of the many unique aspects required for commercial success in regenerative medicine. Major pharma, biotech and device players are also entering the field due to the value potential for this innovative therapeutic approach.

It is an exciting time to be involved with the field, and we look forward to being right there alongside all of you who are working to making regenerative medicine a reality that is helping patients today.

Best Regards,

Geoff
Regenerative medicine represents a new paradigm in human health with the potential to resolve unmet medical needs by addressing the underlying causes of disease.

The emerging field of regenerative medicine is unique in its aim to augment, repair, replace or regenerate organs and tissue that have been damaged by disease, injury or even the natural aging process. This rapidly evolving, interdisciplinary field is transforming healthcare by translating fundamental science into a variety of regenerative technologies including biologics, chemical compounds, materials and devices. It differs from other fields of medicine in the array of disciplines it brings together and in its ability to create or harness the body’s innate healing capacity.

Why is Regenerative Medicine Important to the Future of Healthcare?

Currently, the vast majority of treatments for chronic and/or life-threatening diseases are palliative. Others delay disease progression and the onset of complications associated with the underlying illness. Very few therapies in use today are capable of curing or significantly changing the course of disease. The result is a healthcare system burdened by costly treatments for an aging, increasingly ailing population, with few solutions for containing rising costs.

The best way to significantly improve the economics of our current healthcare system is to develop more effective treatments for the most burdensome diseases and conditions—diabetes, neurodegenerative disorders, stroke and cardiovascular disease, for example—to facilitate longer, healthier and more productive lives.

Regenerative medicine is uniquely capable of altering the fundamental mechanisms of disease; however, to realize its potential, we must think differently about therapeutic development and commit to investing in these transformative technologies. A more effective, sustainable healthcare system is possible through regenerative medicine, but it will require the combined efforts of patients, payers, healthcare providers, biotech and pharmaceutical companies, private investors and governments working together.

We Are on the Brink of a New Era of Medicine
A Snapshot of the Field

The field of regenerative medicine is reaching a point in its evolution where progress is not only seen in headlines but felt by thousands of patients who are receiving disease-altering therapies every day.

Regenerative Medicine Already a Commercial and Medical Reality

Even though the majority of people perceive regenerative medicine as something of the future, it is actually here and now. A significant number of regenerative medicine products are already commercially and clinically successful. In addition to over 60,000 stem cell transplants annually performed worldwide for the treatment of oncology and blood-based disorders, it is estimated by ARM that in 2012 cell therapy products distributed by biotherapeutic companies generated over $900 million with 160,000 patients receiving treatments. It is widely believed that these numbers are easily doubled when including non-cell-based regenerative medicine products such as scaffolds and other materials.

A Maturing and Increasingly Diversified Clinical Pipeline

At the same time, more products are being approved and new data are becoming available from mid-stage and late-stage regenerative medicine clinical trials. For example, in 2012, seven cell therapy products were approved by regulatory agencies around the world in contrast with five such approvals in the three previous years, and none from 2002 to 2008. Going forward, the industry expects to see multiple approvals annually.

Analysts suggest there are at least 2,500 ongoing regenerative medicine clinical trials involving tens of thousands of patients for a myriad of clinical indications. An estimated 15 percent of this is industry-sponsored, and the remainder is being sponsored by leading academic centers around the world.

This year’s Annual Industry Report will review the clinical pipeline and commercially available products for several major disease areas including cardiovascular disease, diabetes, musculoskeletal disorders, peripheral vascular disease, stroke, various neurological disorders, spinal cord injury, ocular disease, wounds and soft tissue damage, cancer and a number of debilitating autoimmune and inflammatory diseases. Over the coming years, as these new treatments continue to progress through the clinic, they will heighten public awareness of regenerative medicine and reinforce the profound impact it could have on our healthcare system.

Public and Private Investment Exceeds $1 Billion

Given that regenerative medicine has recently delivered several product approvals and over $1 billion in annual revenue, the sector is attracting increased attention from investors and industry partners. In 2012, the sector garnered over $900 million in investment from private investors and public markets, and over $300 million from grant sources totaling an approximate $1.2 billion in investment.

Governments around the world also continue to create supportive legislative and policy initiatives which include sizeable investments.
in regenerative medicine to create centers of excellence, research networks, manufacturing infrastructure, commercialization centers and economic diversification initiatives that encourage the development of regenerative medicines in their jurisdictions.

Finally, in an effort to stay ahead of the competition and embrace the future of medicine, more and more pharma companies have acquired profitable cell therapy companies or strategically invested in up-and-coming cell and advanced therapy organizations.

Cell-Based Models Accelerate Drug Discovery and Toxicity Testing
The science of stem cells and cellular biology also supports the development of more traditional medicines. Companies such as GE Healthcare and Cellular Dynamics International are mastering the science of cellular reprogramming and cellular signaling to control the fate, or differentiation, of cells for specialized functions. Because of these discoveries, scientists can now manufacture beating human heart cells, liver cells, endothelial cells and neural cells to test the safety and toxicity of newly discovered drugs, understand the biologic mechanisms of disease, as well as discover new molecules and biologics with therapeutic potential.

Payers Engage in Regenerative Medicine
Payers are beginning to recognize the encompassing potential of regenerative medicine. Further as data are released from ongoing trials, new insight into the potential cost savings from these treatments should be revealed in more sophisticated pharmacoeconomic models that measure the true impact of these technologies. Blue Cross Blue Shield Association’s recent joining of ARM is evidence of the growing payer interest in regenerative medicine.

The best way to significantly improve the economics of our current healthcare system is to develop more effective treatments for the most burdensome diseases and conditions.

The Instrumental Role of Foundations, Advocacy Groups and the Public in Moving Regenerative Medicine Forward
As patients and public supporters become increasingly aware of and educated about scientific research and clinical advancements, they are engaging more and more in policy and funding decisions that impact the development and accessibility of new therapeutics. These often personally affected and motivated individuals are working to influence government initiatives, reimbursement decisions, and investor appetite for the development of and access to new medicines. Increasingly these people are, individually or collectively, providing their own funding to drive research, development, and clinical testing of new therapeutics to address critical patient needs.

Some of these heroic advocacy efforts have led to the formation of government initiatives such as the California Institute for Regenerative Medicine and the creation of foundations and scientific centers of excellence such as The New York Stem Cell Foundation. These organizations powered by advocacy, are driving forward some of the world’s most innovative science and underfunded high-risk translational science.

ARM is grateful to these organizations and others such as the Juvenile Diabetes Research Foundation; the Parkinson’s Action Network; the Genetics Policy Institute and countless others for their stalwart support. Organizations such as these are a growing and essential segment of the ARM membership and are significant contributors to the advancement of the field.
The field of regenerative medicine has the potential to heal people and bend the health cost curve toward a more affordable long-term solution. This trend is already evident by several approved and marketed first generation regenerative medicine products that are demonstrating both clinical and cost reduction value.

Data from the Centers for Disease Control and National Center for Health Statistics show that annual healthcare expenditures in the U.S. are approximately $2.5 trillion dollars, which represents 17.4 percent of 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 heart and vascular disease, cancer, acute and chronic neurological conditions, inflammatory and immune diseases, and a range of other conditions.

As a result of these diseases and conditions associated with aging, individuals age 65 and over incur annual healthcare expenditures that are on average three to eight times greater than individuals under the age of 45.

The Healthcare Impact of Baby Boomers (1946-1964)

Increasing healthcare costs combined with staggering population demographic trends create a significant challenge for our society, especially with an aging population expected to nearly double in the next 20 years.

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 percent 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.

The Cost Impact of an Aging Population

As we age, we spend more on healthcare. Two key drivers of cost increases are:

- Increased incidence and impact of chronic disease such as: heart disease, cancer, stroke, pulmonary disease, diabetes, osteoporosis
- Significant burden associated with the seriously ill. 1% of most seriously ill account for more than 25% of total healthcare expenditures
Furthermore, according to an analysis by the Alliance for Aging Research, 83 percent 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 technologies that mitigate chronic healthcare-related costs, lessen chronic care and improve patients’ quality of life.

This challenge is exacerbated by a growing shortage of primary care physicians and clinical specialists, that along with other economic pressures will result in fewer available healthcare resources. Taken together, and if nothing else changes, these factors will unavoidably result in various forms of healthcare rationing.

Potential Economic Impact of Regenerative Medicine

Lowering healthcare costs for unmet medical needs and chronic conditions. By reducing hospital care, the need for physician, clinical and professional services, nursing and home healthcare we could substantially reduce overall healthcare expenses, since together these categories comprise 62 percent of all healthcare related expenses.

We are confident that meaningful improvements in clinical outcomes and cost reduction can be accomplished through regenerative medicine technologies. 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>Gov. 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>

Source: www.census.gov

The Cost Impact of an Aging Population

![Graph showing the cost impact of an aging population]
As a result of diseases and conditions associated with aging, individuals age 65 and over incur annual healthcare expenditures that are on average three to eight times greater than individuals under the age of 45.

Much of the dialogue around healthcare in recent years has focused on the issues of broadening access (through insurance reforms) and controlling costs through Medicare and Medicaid reimbursement reforms such as payment cuts to health providers. Clearly, reducing expenditures will be helpful, but this alone will not enable us to improve clinical outcomes and achieve enhanced patient quality of life.

We believe emerging regenerative medicine therapies will have the most significant healthcare impact on specific disease indications and chronic conditions that are currently the major drivers of healthcare costs and that represent significant areas of unmet medical need. These indications include: heart and vascular diseases, stroke, diabetes, inflammatory and immune diseases, wound healing and soft tissue regeneration, neurodegenerative diseases such as ALS, Alzheimer’s and Parkinson’s, spinal cord injury, musculoskeletal disorders and ocular disease.

The disease overviews found throughout the next section of this year’s Annual Industry Report are designed to specifically cover not only the economic impact of these diseases but to also provide a thorough overview of current regenerative medicine technologies and the therapeutic pipeline. These technologies and studies reflect a variety of product types and approaches, including the use of autologous cells (i.e. derived from the patient), allogeneic stem cells (i.e. derived from a donor), tissue-engineered products (e.g. cells plus a scaffold), gene therapies, biologics, small molecules and combination products; each of which have shown therapeutic promise.

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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)
4 Chronic Disease and Medical Innovation in an Aging Nation—The Silver Book available at http://www.silverbook.org/ (published by the Alliance for Aging Research)
As mentioned earlier, 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.

Despite the sector’s potential, there are substantial challenges, hurdles and uncertainties that have substantially impeded investment in the sector. For this reason, many countries around the world have developed national programs or strategies to help this emerging sector overcome these challenges.

In the United States, despite recent reports of progress, there remains 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. Consequently, there is no way of knowing what activities are being undertaken and funded, leading to inefficient use of existing resources. Furthermore, there is no consensus strategy about activities needed for this technology to develop.

In the United States, while there are several government and private sector projects underway, and a constructive relationship with the FDA, there is no consistent and focused opportunity for strategic interaction between the regenerative medicine community—industry, academia and patient advocates—and the government.

Other countries such as South Korea, Japan, UK, Canada and China have already made national commitments to regenerative medicine. Since regenerative medicine has the potential to address many of our most significant healthcare challenges and areas of unmet medical need, it is critical that the United States develop a national strategy given the role of the U.S. in global affairs and its high concentration of life science-focused public and private capital.

Additional challenges facing nations without a national strategy:

- Lack of clear identification and prioritization of areas of unmet medical need
- Inability to access data that could provide useful healthcare benchmarks
- Time, cost, and complexity of clinical trials
- Complexity and uncertainty of the reimbursement system
- Lack of investment capital
There is no overarching plan that will ensure this technology fulfills its promise or does so in a manner that will help the world address global and U.S. national healthcare priorities.

Elements of the Alliance for Regenerative Medicine’s Proposed U.S. Regenerative Medicine Strategy

ARM supports the creation and implementation of a multi-faceted U.S. Strategy for Regenerative Medicine, the elements of which include:

- **A strategic assessment of the U.S. current activities**: The U.S. needs a thorough, independent, strategic assessment of the current activities occurring at various federal agencies, so that we can invest limited resources more effectively. The U.S. also needs 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.

- **Designation of 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 who acts as an interface between the FDA, NIH, CMS, NCHS, other federal agencies and the private sector.

- **Creation of 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 National Biomedical Innovation Advisor (explained 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.

Other elements of a strategy could include:

- Streamlining clinical development in areas of serious unmet need
- Creating an explicitly defined list of serious unmet medical needs that represent our national priorities in healthcare
- Establishing incentives that will promote private investment in the areas we need most
- Establishing a more efficient coverage and reimbursement framework that will operate in conjunction with an accelerated clinical approval process
- Enabling better clinical trial design by broadening access and enabling more effective utilization of historical data from CMS, NCHS, CDC and other relevant agencies
- Creating a National Regenerative Medicine Clinical Trial Network focused on accelerating development of solutions in high priority disease areas

During the last Congress, ARM supported H.R.1862, the Regenerative Medicine Promotion Act, bipartisan legislation to launch a national strategy that incorporates many of these concepts. ARM expects similar legislation to be introduced this year.
ARM estimates there are more than 700 companies with a regenerative medicine focus ranging from divisions of multinational corporations to smaller organizations focused solely on the sector.

The products they are developing include several hundred cell-based therapies, small molecules, biologics, tissue-engineered cells and materials and implantable devices. Additional products use cells as drug discovery or toxicity testing tools as well as clinical tools, bioprocessing tools and platforms that include equipment, consumables, reagents and storage systems.

The field also incorporates a variety of service companies specializing in clinical trial management, manufacturing, engineering and financing among others.

Regenerative Medicine Technologies Include a Variety of Therapeutic Approaches

Regenerative medicines—the spotlight of the industry—encompass an array of technologies and therapeutic approaches including cell-based therapies, small molecules and biologics as well as synthetic and bio-based materials designed to augment, repair, replace or regenerate organs and tissues, thereby targeting the root cause of disease.

Cell-Based Therapies

Living cells, a pillar of the field, are incorporated into regenerative medicines to achieve a variety of positive effects:

- To replace damaged or diseased cells and/or tissue
- To stimulate an endogenous response that promotes the body’s own healing such as an immune response or regeneration in diseased tissue
- To deliver genetic or molecular therapies to targets

Gene Therapy

Gene therapy addresses defective or mutated genes needing either correction or improved regulation through the insertion of properly functioning genes into a patient’s cells. While the largest segment of gene therapies targets cancer, regenerative-focused gene therapies are being developed for several monogenic diseases such as cystic fibrosis, hemophilia, muscular dystrophy, thalassemia, and sickle-cell anemia. Additionally there is a significant effort to develop and test gene therapies to induce cell and tissue regeneration in cardiovascular, neurological, and ocular diseases through highly innovative regenerative gene therapies.
Biologics and Small Molecules

Biologics and small molecules can be defined as the use of chemicals and cellular components that are known to induce dormant, or edogenous cells to regain regenerative properties.

Tissue Engineering: Synthetic Materials, Biomaterials and Scaffolds

Synthetic and bio-based materials, cornerstones of the regenerative medicine field, are generally implanted in the body for reconstructive purposes, such as in joint replacement, bone repair, as artificial ligaments and tendons, dental implants, heart valves and wound repair. They work in partnership with native cells to support reconstruction and healing.

Stem Cells for Drug Discovery, Toxicity Testing and Disease Modeling

Companies are increasingly learning to leverage the use of stem cells and/or living tissue constructs to create in-vitro models to study human mechanisms of disease and the effects of drugs on a variety of cell and tissue types such as human heart, liver and brain cells. These models, built predominantly using embryonic and induced pluripotent stem cells, allow for faster and safer drug development.

Biobanking

Cell and tissue banks are responsible for collecting, storing and distributing biological materials used in regenerative medicine including adipose tissue, cord blood and birth tissues, musculoskeletal tissues, pericardium, skin, bone, vascular tissue, autologous and allogeneic cells as well as other biological samples.
Arguably the most prominent segment of the regenerative medicine industry, the cell therapy sector, is currently engaged in over 1,900 clinical trials around the world. This includes more than 300 clinical trials being sponsored by approximately 250 companies developing commercial products for almost every imaginable disease or condition.

In addition to the products commercially available and in development, cells have been used as a standard of care for decades in the medical practice of hematology and oncology. In fact, stem cell transplants have been a staple of cancer treatment since it was first introduced in the late 1960s. Stem cell transplantation continues to be routinely used in, and investigated for, an increasingly diverse and growing list of (now over 70) malignant and non-malignant diseases. Over one million stem cell transplants have been performed globally to date.

There are approximately 40 cell therapy products commercially distributed in regulated markets.¹

While no cell therapy products were approved by any regulatory agency from 2002 to 2008. In the past five years there have been 12 approvals in the United States (six), Europe (one), Canada (one), New Zealand (one), and South Korea (three).

All of the cell therapy products commercially available are for skin, wound, bone or cartilage repair with the exception of Dendreon’s Provenge, approved by the FDA in 2010 for late-stage prostate cancer. The first of these products, Apligraf, was brought to market in 1998. Collectively, these top 20 cell therapy products are estimated to have treated over 500,000 patients through the end of 2011, and approximately 140,000 patients in 2012 alone. Research conducted by ARM valued the top 20 cell therapy products based on revenue generation to total the following amounts beginning in 2010:

- $460 million (2010 estimated)
- $730 million (2011 estimated)
- $900 million (2012 estimated)

Cells are Tomorrow’s Future Therapies in Development Today

A variety of cell types including primary cells, progenitor cells, tissue-specific stem cells (adult stem cells), embryonic stem cell and now reprogrammed cells (induced pluripotent stem cells) are in various stages of development. They are being tested for almost every imaginable human condition ranging from large-scale indications like chronic heart failure, cancer and diabetes to orphan indications for which there are few available treatments.

¹ For the purposes of this report, we have restricted this data to countries with formal regulatory frameworks for this type of product, thus excluding cell therapy treatments provided in unregulated markets.
This pipeline of cell-based therapies represents a maturation of the science surrounding such products and therapeutics. As such, these next-generation products carry with them enhanced expectations of efficacy and commercial viability. Compared to the first generation of cell therapies, the products currently in clinical development must be better characterized and understood mechanistically. This in turn often requires advanced culturing techniques which may involve genetic engineering and also more targeted and effective delivery techniques. Additionally, these products often require significantly more sophisticated and scalable manufacturing technologies while also being subject to the requirements of a regulatory framework that has evolved considerably since the first products were approved.

At the same time that these therapies are targeting more complex indications and involving more sophisticated technologies, there is also concurrent pressure to significantly lower the cost of goods to improve commercial viability and support applications for reimbursement.

**Cells as Immunotherapies**

Leveraging decades of research and applying current knowledge garnered from stem cell transplantation about how to reconstitute the immune system, researchers are developing and testing a myriad of ways to manipulate (e.g., induce, enhance, or suppress) cells of the immune system as a means of employing it to battle disease—i.e., cell-based immunotherapies. There are a number of different types of immunotherapy products. Many of the first-generation products are based on interleukins, cytokines, chemokines, etc., but an emerging class are cell-based immunotherapies employing lymphocytes, macrophages, dendritic cells, T-cells, natural killer cells, cytotoxic T lymphocytes, etc. Some are autologous, others are allogeneic, some both, and some genetically modified.
FDA approval of Dendreon’s Provenge—a cell-based immunotherapy for the treatment of advanced, refractory prostate cancer—has triggered a significant resurgence in the field of immunotherapy. Furthermore, given that Provenge is an autologous cell therapy, its approval and market adoption have bolstered support for both cell-based immunotherapies and autologous cell therapies in general.

Evidence of increased market enthusiasm for autologous cell-based immunotherapies is underpinned by the exclusive global research and licensing agreement between Novartis and the University of Pennsylvania announced in August 2012. Presumably to buttress the collaboration’s efforts, Novartis announced in December that it had purchased Dendreon’s New Jersey facility. It is widely assumed that the primary driver for that purchase was to provide the kind of uniquely designed infrastructure required for autologous cell therapies, such as those expected to come out of the collaboration with Penn.

This deal is helping to demonstrate to investors that these types of therapeutics will garner interest from big pharma and heighten the competitive curiosity of other pharmaceutical companies to evaluate investment in such products or companies.

While most immunotherapies in development are currently targeting cancer, any condition where up- or down-regulation of the immune system may be beneficial is a viable target for this class of medicines. For example, Opexa Therapeutics recently launched a Phase 2b trial of its cell-based immunotherapy product, Tcelna (imilecleucel-T), for the treatment of Secondary Progressive Multiple Sclerosis. In February 2013, Merck Serono secured an option and licensing agreement for the Tcelna program in the treatment of Multiple Sclerosis.

The pipeline of cell-based immunotherapies includes products ranging from those in preclinical research to those in Phase 3 trials with the largest bucket in mid-stage development.
Gene therapy is the insertion of properly functioning genes into a patient’s cells or tissues to treat diseases that are linked to defective or mutated genes needing either correction or improved regulation. The clinical trials database hosted by *The Journal of Gene Medicine* currently reports over 1,240 open gene therapy clinical trials in 31 countries.

While the largest segment of gene therapies in development target cancer (nearly 65 percent), *The Journal of Gene Therapy* clinical trial database reports the next largest category of gene therapy trials (8.7 percent) target diseases that are believed to be the result of single-gene defects such as cystic fibrosis, haemophilia, muscular dystrophy, thalassemia, and sickle-cell anemia, as well as a plethora of other monogenic diseases. A significant amount of gene therapy research and clinical development is also targeting cardiovascular disease, neurological disease, and ocular disease, many of which are classified as regenerative gene therapies. For cardiovascular disease in particular, the expectation is that gene therapy will provide a new avenue for therapeutic angiogenesis, myocardial protection, and regeneration and repair of damaged or diseased heart tissue.

Notable Gene Therapy Commercial Milestones

**2013:** bluebird bio signs a global strategic collaboration with Celgene Corporation to discover, develop and commercialize novel disease-altering gene therapies in oncology.

### Number of Gene Therapy Clinical Trials¹

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<td>Single Subject</td>
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### Indications Addressed by Gene Therapy Clinical Trials¹

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<th>Disease Type</th>
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<tr>
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<td>Inflammatory</td>
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</tr>
<tr>
<td>Other</td>
<td>25</td>
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</table>
For Cardiovascular disease in particular, the expectation is that gene therapy will provide a new avenue for therapeutic angiogenesis, myocardial protection, and regeneration and repair of damaged or diseased heart tissue.

2012: European approval of Glybera (uniQure) for the treatment of lipoprotein lipase deficiency (LPLD).

2012: Shinya Yamanaka receives the Nobel Prize for Physiology or Medicine for the genetic reprogramming of somatic cells into an embryonic or pluripotent-like state using four retroviral vectors.

2012: Novartis and University of Pennsylvania sign a deal for gene-modified T-cell cancer immunotherapies.

2012: bluebird bio raises $60 million from experienced life science investors.

2012: Researchers at UCLA’s stem cell center identify a generic mechanism to correct mutations in human mitochondrial DNA by targeting corrective RNAs.

2010: GlaxoSmithKline licenses a cell-delivered gene therapy protocol from the Italian charity, Fondazione Telethon and Fondazione San Raffaele, for the treatment of a severe immune deficiency called ADA-SCID and six other rare diseases.

There are a variety of mechanisms (as shown in the chart above right) to deliver DNA into a patient’s cells and affect the intended genetic manipulation. Often, these vectors are introduced to the target cells in vivo but some prefer to transfect the cells ex vivo, thereby implanting the cells as carriers of the new DNA.

Sangamo Biosciences serves as a successful example of a company developing gene therapy platform technology for several monogenic diseases and HIV. The company’s zinc finger technology has been shown to modify the major co-receptor (CCR5) on the surface of cells which is used by HIV to infect cells of the immune system. Some of the patient’s T-cells are removed, genetically modified using Sangamo’s proprietary transfection technology, and then transplanted back into patients with Human Immunodeficiency Virus (HIV). This method is currently being tested in multiple clinical trials.

Vectors Used in Gene Therapy Clinical Trials¹

<table>
<thead>
<tr>
<th>Gene Types Transferred in Gene Therapy Clinical Trials¹</th>
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<tr>
<td>Adenovirus: 438</td>
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<tr>
<td>Retrovirus: 370</td>
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<tr>
<td>Naked/Plasmid DNA: 345</td>
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<tr>
<td>Vaccinia Virus: 148</td>
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<td>Lipofection: 111</td>
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<tr>
<td>Other Categories: 105</td>
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<td>Unknown: 64</td>
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Gene Types Transferred in Gene Therapy Clinical Trials¹

<table>
<thead>
<tr>
<th>Gene Types Transferred in Gene Therapy Clinical Trials¹</th>
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<tr>
<td>Antigen: 378</td>
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<td>Cytokine: 340</td>
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Tissue engineering (TE) is a multidisciplinary field that utilizes biology, medicine, and materials science to develop therapies that will restore, maintain, or improve tissue or whole organ function. These advanced therapies will revolutionize the way we improve the health and quality of life for millions of people worldwide.

These complex products are being designed and developed for a wide variety of disorders and across numerous tissue types—bone, cartilage, skeletal muscle, skin, blood vessels, nerve tissues, ocular tissues, and whole organs. In addition to having critical therapeutic utility, these technologies, through use of engineered 3D tissue models and micro-organs, have innovative diagnostic and research applications for the testing of drug absorption and metabolism, toxicity, and pathogenicity. ARM is actively tracking approximately ninety tissue engineering and biomaterials companies that meet the criteria for developing therapeutic regenerative medicine products. In researching these companies, we identified 120 products that vary in development from preclinical through marketed.

Innovation in Tissue Engineering—From Simple to Complex

Currently, the majority of the commercially available products are for wound repair, bone grafts and surgical aids. Many of these products are comparatively simple—they are comprised of minimally manipulated components. Moving to the next generation of tissue-engineered biomaterial- and scaffold-based technologies for the delivery of drugs, cells and eventually genes is far more complex with regard to design, development and ultimately commercialization.

These multifaceted products will be comprised of multiple components, in specific configurations, with unique manufacturing schemes and will be regulated as biologics or combination products requiring pre-market review, extensive safety testing and lengthy trials. From our research, the sector has a strong and growing pipeline of tissue-engineered and biomaterial-based combination products across a wide variety of tissue types and clinical applications.

By definition, these composite tissue-engineered products are comprised of multiple components (cells, scaffolds, growth factors, etc.) arranged in unique combinations for particular therapeutic applications. In general, they are built from components in the following three areas:

- **Biomaterials and Scaffolds:** These are biologic, synthetic or semi-synthetic or hybrid matrices specifically designed to direct the organization, growth, and differentiation of cells to form functional tissue by providing physical, structural, and chemical cues.

- **Cells:** Cell sources are varied and include autologous cells, allogeneic cells, xenogeneic cells, iPS cells, tissue-resident stem cells, and genetically engineered cells. Additional opportunities exist in the development of enabling methodologies for the proliferation and differentiation of these cells.

- **Biomolecules:** These include angiogenic factors, growth factors, and differentiation factors like bone morphogenic proteins currently used in various bone-promoting products.
Maturing Sector Drives Additional Commercial Opportunities

As regenerative medicine continues to grow and rely on multiple suppliers and manufacturers, additional commercial opportunities will emerge and drive overall growth. In addition to suppliers and product developers, technology and service providers that support next generation tissue-engineered products are emerging. These include the companies focused on developing technologies that support that unique assembly, manufacture, and delivery of the complex multicomponent tissue-engineered products.

In addition, we've seen growth in companies that develop 2D and 3D systems for cell expansion and tissue growth, bioreactors, vascularization methods, and cell and tissue storage and shipping (biological packaging). In addition, and specific to engineered products, is the focus on the biomechanical aspects of design including properties of native tissues, identification of minimum properties required of engineered tissues, mechanical signals regulating engineered tissues, and efficacy and safety of engineered tissues. Finally, informatics are required to support tissue-engineered products including gene and protein sequencing, gene expression analysis, protein expression and interaction analysis, quantitative cellular image analysis, quantitative tissue analysis, in silico tissue and cell modeling, digital tissue manufacturing, automated quality assurance systems, data mining tools, and clinical informatics interfaces.

TE Companies Worldwide

TE Products Commercially Available

| Bone/Spine |
| Wound Healing/Burns |
| Cartilage (Knee and Joint) |
| Soft Tissue |
| Eye |
| Cardiovascular |
| Neurosurgical |
| Non-cardiac Vascular Repair |
| Peripheral Nerve Repair |
| Degenerative Disc Disease |
| Muscle Regeneration |
| Spinal Cord Injury |
| Diabetes |
| Organ Regeneration |

TE Products in Development (Preclinical and Clinical)

| Bone/Spine |
| Wound Healing/Burns |
| Cartilage (Knee and Joint) |
| Soft Tissue |
| Eye |
| Cardiovascular |
| Non-cardiac Vascular Repair |
| Peripheral Nerve Repair |
| Degenerative Disc Disease |
| Muscle Regeneration |
| Spinal Cord Injury |
| Diabetes |
| Organ Regeneration |

TE Products by Comparison

| Synthetic Scaffolds |
| Biological Scaffolds/Tissue Grafts |
| Acellular Scaffolds |
| Decellularized Organs |
| Combination Products (Scaffold, Cells, Biologics, Gene Therapy) |
The successful and beneficial manipulation of cellular function by small molecules and biological compounds has already had a significant impact on regenerative medicine.

A number of compounds and factors have been identified that exhibit a powerful influence on stem cell behavior. These not only have the potential to help enable the development of viable cell therapies but may also be constituted as oral drugs given to patients to support endogenous cellular regeneration.

Small molecules and biologics play a pivotal role in regenerative medicine through a number of means including:

- The ex vivo expansion and maintenance of cell lines used in the production of cell-based therapies
- Companies developing and distributing small molecules and biological reagents for use in ex vivo stem cell manipulation and expansion include Akron Biotechnologies, BioLife Solutions and CellGenix, among others.

The ex vivo manipulation of cells to induce differentiation and control cell fate

- Companies developing and distributing small molecules and biologic reagents for use in ex vivo stem cell differentiation include: Life Technologies, EMD Millipore and Stemgent.

As adjuncts to cell therapies or tissue-engineered products to enhance their intended therapeutic effects

- An example of a company pursuing the development of a small molecule-based adjunct for cell therapy is Fate Therapeutics is pursuing the development of a small molecule-based adjunct for cell therapy. Fate’s technology activates hematopoietic stem cells (HSCs) using a pharmacological compound with the intent to improve engraftment in an allogeneic stem cell transplant.
As regenerative medicines which induce resident cells/tissues, through molecular signaling pathways, to be replaced, repaired or regenerated

- In this instance, small molecules and biologics are serving as epigenetic factors that control genetic pathways toward regeneration. As research continues to expand our understanding of molecular targets and pathways that control stem cell self-renewal, expansion and differentiation, we will also uncover new strategies that target the delivery of drugs to safely regenerate tissue function and avoid undesired effects such as hyperplasia, fibrosis and cancer.

- By way of example, Fate Therapeutics is leveraging its understanding of adult stem cell biology to advance its Wnt-based protein regenerative platform for muscular dystrophy and muscle degenerative disorders.

- Another example of a biological approach to regenerative medicine is Juventas Therapeutics’ stromal cell-derived factor-1 (SDF-1) therapeutic. SDF-1 is a naturally-occurring chemokine that is rapidly over-expressed in response to tissue injury. When SDF-1 is used therapeutically, it stimulates the natural healing process by recruiting endothelial progenitor cells (EPCs) to the site of injury to induce neovascularization and angiogenesis.

- iPierian is a regenerative medicine company creating cell-based screening platforms to identify therapeutic small molecules and biologics. The company recently announced that it leveraged its own iPSC disease models to identify monoclonal antibodies to treat neurodegenerative diseases by targeting the Tau protein and the Complement pathway. The disease models, which combine human cortical neurons, motor neurons, microglia and astrocytes in a dish, are used by iPierian to discover and validate novel biologic and small molecule drug candidates.

Replacement of viral vector-based reprogramming genes through the use of small molecules in order to induce pluripotency

- Recent scientific progress in the field has led to the use of molecular compounds to generate induced pluripotent cells by taking adult, somatic cells and reverse engineering them to a more immature, pluripotent state. (See reprogramming and disease modeling section of report for additional information.)

- Lastly, Cellular Dynamics International (CDI) is an example of a company using several of these molecular compounds to generate iPSCs and derivative cardiomyocytes, hepatocytes and neural cells which they commercially distribute to biopharmaceutical companies for their use in drug discovery and toxicology testing.
Drug failure due to toxicity-related attrition is a major concern for pharmaceutical development. There is a pressing need to develop more accurate tools for predicting toxicity in drug candidates earlier in the drug development pipeline, producing safer medicines.

Pharmaceutical companies worldwide have embraced the use of stem cells as drug discovery and toxicology tools.

Additionally, there has emerged a whole new class of companies, such as Cellular Dynamics International, Vistagen, California Stem Cells, Celllectis and ReproCELL, specializing in the mass manufacturing of beating heart cells (cardiomyocytes), liver cells (hepatocytes) and neurons from pluripotent stem cells for the purpose of high-throughput drug screening and toxicity testing.

These functioning “human cells in a dish” are incredibly powerful cellular assays for drug developers to more accurately model human disease and the effects of drugs on the human system. By leveraging these tools, toxic substances can be identified and eliminated during preclinical stages of development. This saves valuable resources and time while also aiding in the selection of better drug candidates that have increased probabilities of becoming marketed products.

In an effort to better predict chemical response variability in humans, pluripotent stem cell lines are now being made from a diverse population of individuals representing various genders, races, ages and disease histories. This global push is driven by the fact that there are no current methods to predict individual susceptibility to a particular drug. However, iPSCs derived from individuals with known susceptibilities or resistance to various drugs and diseases provide us the opportunity to create more personalized and predictive drug and toxicology models.

Stem Cells for Drug Discovery

Historically, biopharmaceutical companies have screened large quantities of biologics and pharmaceutical compounds in animals with certain diseases or conditions to identify those compounds with the most desired effect.

More recently, we have discovered how to create disease models using “human cells in a dish” against which we can test compounds. The use of human cells is believed to have the potential to be more accurate than animal models.

These cell lines, used as drug discovery models, are most efficiently created using pluripotent stem cells because of their expandability and plasticity, i.e. the ability to create any cell type in large quantities.
A noteworthy example of big pharma’s interest in these technologies was the December 5, 2012 announcement of the formation of StemBANCC, a $72.7 million academic-industry partnership led by Roche to create a collection of 1,500 iPSCs lines as research tools for drug discovery. Other participants include Pfizer, Sanofi, Johnson & Johnson, Eli Lilly, Merck KGaA, Novo Nordisk, Abbott Labs, Boehringer Ingelheim, Orion and 23 academic institutions.

The Major Culprits of Attrition—Heart, Liver and Neural Toxicity

The two most important human cell types for toxicity screening in preclinical drug development are hepatocytes and cardiomyocytes, as liver and heart toxicity are the leading contributors to drug attrition. Proarrhythmia is the leading cause of hospitalization for adverse drug-related events.

Liver toxicity is the second leading cause for drug failure because the physiological differences between humans and preclinical species lead to a limited understanding of how drugs will be metabolized in humans. Because drug toxicity is often the result of the way we metabolize drugs, metabolically active human hepatocytes are more predictive than animal models of what these drugs will do in patients.

The development of new and improved human neural cell lines is crucial for the efficient and reliable discovery and development of therapeutic agents for treating human nervous system diseases.

Also in December 2012, Cellular Dynamics International (CDI), a commercial producer of human iPSC lines and cell tissues, announced that GlaxoSmithKline (GSK) researchers used CDI’s commercially available iCell Neurons to model loss in human Alzheimer’s diseased brains. They accomplished this by exposing them to beta-amyloid 1-42 (Abeta1-42), a peptide known to be associated with the disease. CDI’s iCells were originally launched just one year earlier in December of 2011.

Cellular Models Go 3-D

Drug developers and advanced regenerative medicine tool providers believe that the next evolution of cell-based models is to create human-like tissue or organ structures for screening or testing drugs. While cells in a dish are comprised of mostly single cell types in an unnatural two-dimensional environment, three-dimensional tissues or organs are comprised of many cell types and even tissue types, which interact and better represent drug interactions in the human body.

By way of an industry example, Organovo, a manufacturer of functional, three-dimensional human tissues for medical research and therapeutic applications, announced a partnership with ZenBio, Inc. in February 2013. Together, they will produce three-dimensional human tissues for drug discovery and advanced tissue therapies using Organovo’s bioprinter to enable the generation of living, three-dimensional tissues that reproduce the architectural and functional features of tissues inside the human body. The resulting 3-D tissue models may lead to advances in medical research, drug discovery and development as well as direct therapies and transplantation.

These functioning “human cells in a dish” are incredibly powerful cellular assays for drug developers to more accurately model human disease and the effects of drugs on the human system.
Cellular Reprogramming
and Disease Modeling

Cellular reprogramming is a revolutionary technique that allows scientists to turn one type of cell into another, including any cell type of the body into a stem cell. The potential impact of cellular reprogramming is enormous and already changing the way we model, study, test and, in the future, treat disease.

In 1958, UK researcher, Dr. John Gurdon, demonstrated that cells could be reprogrammed into an embryonic state when he cloned a frog using nuclei from somatic cells of a tadpole. Nearly 50 years later in 2006, Kyoto University researcher, Dr. Shinya Yamanaka, expanded on those findings by expressing four proteins in mouse somatic cells to rewind their genetic clocks, converting them into embryonic-like stem cells called induced pluripotent stem cells, or iPSCs.

In 2012, Dr. John Gurdon and Dr. Shinya Yamanaka were awarded the Nobel Prize in Physiology or Medicine for discovering that mature, specialized cells can be reprogrammed to become immature cells capable of developing into all tissue of the body: formally known as iPSCs. Gurdon’s pioneering work in developmental biology, followed by Yamanaka’s groundbreaking discovery in 2006, demonstrated that specialized cells can be reprogrammed to an embryonic like state. Over the past seven years, scientists around the globe continue to build upon their work and are discovering new and more efficient methods to reprogram cells.

By taking cells derived from diseased patients and reprogramming them back to a more immature state, scientists are able to study disease progression and development in ways previously impossible.

Consequently, there is now an explosion of activity in the creation of disease-specific reprogrammed cell lines, commonly referred to as disease models, which mimic the development and manifestation of puzzling diseases such as Huntington’s, Alzheimer’s, ALS, Parkinson’s and others.

The year 2012 proved to be an exciting one for the field of cellular reprogramming as research groups consistently announced the creation of new disease models that are helping to unlock the mystery of society’s most devastating diseases. Below is a sample listing, representing just the tip of the iceberg of cellular reprogramming breakthroughs in the past 12 months.

March 2013: The California Institute for Regenerative Medicine (CIRM) awards Cellular Dynamics International (CDI) $16 million to create three iPSC lines for each of 3,000 healthy and diseased donors: a total of 9,000 disease model lines. Tissue samples will be taken from patients suffering from Alzheimer’s disease, autism spectrum disorders, liver diseases, cardiovascular diseases, neurodevelopmental disabilities such as cerebral palsy and infantile epilepsy, diseases of the eye or respiratory diseases. CDI will generate the iPSCs using the episomal, or footprint-free, reprogramming method first developed by CDI.

March 2013: Eight Parkinson’s patients ally with scientists from The Scripps Research Institute and medical professionals from Scripps Clinic to fund and participate in an investigation which involves creating patient-specific brain cells by reprogramming cells in their own bodies. The researchers have made iPSCs from all eight patients, and have turned those into the needed brain cells for two of them. The work continues for the other six.
March 2013: Researchers at the University of Minnesota’s Lillehei Heart Institute combine genetic repair with cellular reprogramming to generate stem cells capable of muscle regeneration in a mouse model for Duchenne Muscular Dystrophy.

February 2013: A research group at the Center for iPS Cell Research and Application in Japan successfully models Alzheimer’s disease (AD) using both familial and sporadic patient-derived iPSCs and revealed stress phenotypes and differential drug responsiveness associated with intracellular amyloid oligomers in AD neurons and astrocytes.

February 2013: Researchers at the University of Rochester use human iPSCs to create oligodendrocyte progenitor cells (OPCs), the source of myelin cells in the brain and spinal cord. The team also assessed the ability of the cells to make new myelin when transplanted into mice with a hereditary leukodystrophy that rendered them genetically incapable of producing myelin. They found that the OPCs spread throughout the brain and began to produce myelin.

January 2013: Researchers at the Boston University show that tissues derived from iPSCs in an experimental model are not rejected when transplanted back into genetically identical recipients. The study results suggest that using patient-specific iPSCs may one day overcome issues of immune rejection in transplantation.

January 2013: Researchers at Sanford-Burnham Medical Research Institute and Johns Hopkins University reprogram skin cells and then coax them into heart muscle cells that model the inherited heart condition known as arrhythmogenic right ventricular dysplasia/cardio-myopathy. The study was published in Nature.

January 2013: Researchers at the University of California, San Diego determine that repression of a single protein in fibroblasts is sufficient to directly convert or reprogram the cells into neurons, bypassing the need to reprogram the cells into iPSCs before differentiating them into neurons.

January 2013: Researchers at the Riken Institute in Japan succeed in efficiently regenerating T-cells capable of destroying melanoma from iPSCs, an achievement that could enhance cell-based anticancer therapy.

December 2012: Cellular Dynamics International announces the publication of research demonstrating the use of human iPSC-derived iCell Neurons to model Alzheimer’s disease and and use in high-throughput drug screening.

November 2012: Researchers at Technion-Israel Institute of Technology announce the growth of fully functional heart muscles by reprogramming skin cells from patients. They found that these reprogrammed cells can “reset” the rhythm of any unhealthy heart tissue that is placed around them.

November 2012: Researchers at the University of Wisconsin-Madison reprogram human skin cells into iPSCs and turn them into a laboratory model for an inherited type of macular degeneration.

October 2012: Researchers at the Salk Institute for Biological Studies identify a key disease mechanism in Parkinson’s by reprogramming skin cells from Parkinson’s patients with a known genetic mutation.

October 2012: Cellectis Bioresearch Inc. receives a five-year contract from the National Institutes of Health (NIH) to generate clinical-grade iPSCs.

October 2012: Scientists at the University of Maryland, School of Medicine reprogram skin cells from Gaucher’s patients into iPSCs and then differentiate them into diseased white blood cells called macrophages. A key function of macrophages in the body is to ingest and eliminate damaged or aged red blood cells. In Gaucher’s disease, the macrophages are unable to do so.

October 2012: The National Institutes of Health Center for Regenerative Medicine award Lonza Walkersville, Inc. a contract to generate iPSCs under current Good Manufacturing Practices. The production of clinical grade iPSCs is considered a critical component to realizing the therapeutic potential of pluripotent stem cells.
October 2012: Scientists at the Riken Center for Developmental Biology in Kobe announce a plan to use iPSCs in a trial among patients with macular degeneration.

October 2012: Dr. John Gurdon and Dr. Shinya Yamanaka are awarded the 2012 Nobel Prize in Physiology or Medicine for the discovery that mature, specialized cells can be reprogrammed to become immature cells capable of developing into all tissue of the body.

September 2012: Researchers at the Whitehead Institute identify four genes that are turned on very early in cellular reprogramming: Esrrb, Utf1, Lin28 and Dppa2, which control the transcription of other genes involved in pluripotency. The researchers also found that several previously proposed markers for pluripotency were active in cells that became only partially programmed, suggesting those markers would not be useful.

July 2012: Scientists at the Salk Institute for Biological Studies find a new way, using a single protein known as a transcription factor, to convert cord blood cells into neuron-like cells that may prove valuable for the treatment of a wide range of neurological conditions, including stroke, traumatic brain injury and spinal cord injury.

July 2012: A team of scientists at The New York Stem Cell Foundation Laboratory led by Dr. Scott Noggle successfully develop a cell-based model of Alzheimer’s disease by reprogramming skin cells of Alzheimer’s patients to become brain cells that are affected by the disease.

July 2012: A consortium of researchers funded by the National Institute of Neurological Disorders and Stroke reprogram skin cells from patients with genetically inherited forms of Parkinson’s. They found that the neurons derived from the individuals with distinct types of Parkinson’s showed common signs of distress and vulnerability: in particular, abnormalities in the mitochondria.

July 2012: Scientists from Imperial College London and the UCL Institute of Child Health reprogram amniotic fluid cells by adding a drug called valproic acid to the culture medium.

June 2012: Scientists at the Gladstone Institute and an international team of researchers generate a human model of Huntington’s disease by reprogramming skin cells of patients with the disease.

June 2012: Fate Therapeutics, Inc. and BD Biosciences introduce their first iPSC-related product, SMC4, resulting from the collaboration between the two companies. SMC4 is a cocktail of small molecules for improving cellular reprogramming efficiencies.

April 2012: A team of researchers from Johns Hopkins University and the National Human Genome Research Institute evaluate the whole genomic sequence of iPSCs generated from bone marrow cells and found that relatively few genetic changes occur during stem cell conversion. The findings, reported in the March issue of Cell Stem Cell were presented at the annual ISSCR meeting in June, 2012.

April 2012: Scientists at Duke University Medical Center reprogram fibroblasts (with microRNAs) to become cells resembling cardiomyocytes. The Duke team not only proved this concept in the laboratory, but also demonstrated that the cell conversion could occur inside the body of a mouse.

April 2012: Scientists at the University of Wisconsin-Madison, publish in the journal Cell Stem Cell, they have reprogrammed skin cells from patients with cystic fibrosis into iPSCs. The iPSCs were differentiated into human disease-specific functioning epithelium, the tissue that lines the airways and is the main target of the cystic fibrosis gene.
Cell and tissue banks represent a vital and rapidly evolving sector of the regenerative medicine industry. These clinically focused banks are key stakeholders in regenerative medicine and distinct from the biorepositories storing biological samples for research and testing purposes.

Cell and tissue banks are responsible for collecting biological materials including adipose tissue, cord blood and cord blood tissue, amniotic membranes, musculoskeletal tissues, pericardium, skin, bone, vascular tissue, autologous and allogeneic cells as well as other biological samples.

These banking organizations specialize in the registration, acquisition, collection, preparation, processing, handling, recovery, storage and distribution of tissue and cell samples for research and therapeutic uses.

Several ARM members are commercial-scale cell and tissue banks including AlloSource, one of the largest tissue banks in the United States. The organization provides more than 200 types of bone, skin and soft tissue allografts, including tendons, ligaments and joints to medical professionals throughout the nation: several of which are used for regenerative medicine applications.

South Texas Blood & Tissue Center is also involved in a variety of cell and tissue banking related services including a cadaveric tissue bank, public and private cord blood banking, and an independent blood center serving the South Texas region.

Blood and blood-derived cells are collected largely by blood centers. In the United States these are either independent or part of the American Red Cross. Blood Centers of America (BCA), a cooperative of over 37 independent blood centers dispersed across North America, supplies 46 percent of America's blood supply. Additionally, the cGMP-compliant organization provides services to support the sourcing and distribution of clinical-grade biological material while also providing cell processing, cell banking and tissue procurement services.

Cell and Tissue Banking Standards and Accreditation

As the field of regenerative medicine continues to mature and new therapeutic applications are realized, the number of donors, tissue allografts and cell and tissue transplants are expected to increase. To support this growth and ensure that high-quality international cell and tissue banking practices are met, industry organizations have emerged to create additional standards and accreditation programs governing the processing and storage of these critical raw materials.
For example, the American Association of Tissue Banks (AATB) has developed standards and accreditation programs for organizations banking tissues. As of March 2013, the AATB membership included 129 accredited tissue banks. In total, these banks annually recover tissue from an astonishing 30,000 donors and distribute in excess of two million allografts for more than one million tissue transplants performed each year in the United States.

Similarly the AABB, founded in 1947 as the American Association of Blood Banks, and the Foundation for the Accreditation of Cellular Therapy (FACT) accredit cord blood banking and cell processing centers. These standards and accreditation programs contribute additional safety and quality requirements to the regulatory framework established by the FDA over cell processing and banking. Combined, there are currently 199 AABB and/or FACT accredited cord blood banks in over 29 countries worldwide.

AABB and FACT Accredited Cord Blood Banks by Region

Public Banking of Cells & Tissues

Historically, tissue banking has utilized donated cadaveric tissue that is banked by public and private entities and made available on demand to physicians requiring the tissue for therapeutic use. Blood banking has been done on a similar model as well through publicly (American Red Cross) or privately (independent blood centers) collected, processed and distributed blood and blood components or derivatives to hospitals on demand.

With the emergence of science around the therapeutic potential of umbilical cord blood, public entities and governments began to invest in the public collection and storage of umbilical cord blood for use by hospitals and physicians.

In 1988, the first cord blood transplant occurred in Paris, France, to treat a six-year old boy suffering from Fanconi’s Anemia. In 1992, the New York Blood Center opened the first public cord blood bank with funding from the National Institutes of Health.

Twenty years later (2012), the National Marrow Donor Program reported over 30,000 successful cord blood transplants. Further, as of 2012, umbilical cord blood is the second most common source of stem cells for stem cell transplant therapy: peripheral blood stem cell transplants is number one.

ARM estimates there to be approximately 30 public banks and 200 collection centers throughout the United States: most at large hospitals. Nearly 600,000 cord blood units have been stored in public banks around the world.
The Regenerative Medicine Clinical Pipeline

Expected to Drive Increased Demand for Private Cell and Tissue Banking

While biobanking was originally created to supply researchers and physicians with much-needed biomaterials, the sector has now extended the value of banking to the consumer by offering personalized cell and tissue banking services for possible therapeutic use in the future.

With the current explosion of research and clinical development around cell-based regenerative medicine technologies, private cell and tissue banking businesses are becoming more and more recognized as a form of “bio-insurance.” As the number of conditions treatable with bankable cells and tissues, such as cord blood, peripheral blood or adipose tissue increases, so will public perceptions about the value of private cell and tissue banking.

Consumer, or “family” based cell and tissue banking has grown substantially since the first family private bank, the Cord Blood Registry (CBR), began operations in 1995. Recent data suggests that now over one million cord blood units have been stored in private banks in the United States alone.

Private banking companies have now extended their services to include the collection and storage of a variety of cells and tissue including adipose tissue, cord blood stem cells and cord blood tissue, placental tissue, menstrual blood, dental pulp, peripheral blood and bone marrow aspirates. For example, in 2010, the CBR was the first cord blood bank to begin offering cord tissue banking. Today, the majority of the major cord blood banks offer cord tissue and additional tissue banking options.

Private family cell and tissue banks are a growing part of the ARM membership and include companies such as CBR, the world’s, largest private cord blood and cord tissue bank; NeoStem, the first company to collect and store stem cells from adult peripheral blood and American Cryostem, a pioneer in adipose tissue banking for adults.

Cord Blood Banking Timeline

1974: Researchers propose that stem and progenitor cells are present in human cord blood
1988: First successful cord blood transplant occurs in Paris, France to treat a six-year old boy suffering from Fanconi’s Anemia
1992: New York Blood Center opens the first public cord blood bank with funding from the NIH
1995: Cord Blood Registry, the first family bank opens operations
1998: AABB accredits Cord Blood Registry
2004: Health and Human Services provides funds to create a U.S. National Cord Blood Program
2005: The Stem Cell Research and Therapeutic Act of 2005 (H.R. 2520) passes U.S. Congress to create an inventory of 150,000 cord blood samples
2006: More than 8,000 cord blood stem cell transplants are performed worldwide
2010: Cord Blood Registry is the first to offer cord tissue preservation
2011: U.S. Department of Health and Human Services posts resources on website about cord blood banking and is required to encourage healthcare professionals to provide pregnant patients with umbilical cord blood banking information
2012: More than 30,000 cord blood stem cell transplants are performed worldwide
Cardiovascular Disease

Overview

Cardiovascular disease (CVD) refers to a broad range of diseases that affect the cardiovascular system, which includes the heart and blood vessels. CVD is highly prevalent among the general population and represents the leading causes of death and disability in the United States. CVDs include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. The most recent studies completed by the American Heart Association (AHA) estimate that over one-third of Americans currently suffer from some form of CVD, and that 40,400,000 of those are over the age of 60.¹

Often there are no symptoms of underlying disease to the heart and blood vessels until the acute events or symptoms of a heart attack. Patients with these conditions and diseases frequently need life-changing treatments, ranging from daily medications to surgical interventions such as pacemakers, stents, angioplasty or heart transplants.² Patients with heart disease, especially those who have survived acute events, often suffer from long-term disabilities, loss of productivity and diminished quality of life.

Cardiovascular Disease and Regenerative Medicine

A heart attack, known formally as myocardial infarction (MI), occurs when blood supply to the heart is interrupted, causing heart cells to die from lack of oxygen. Several companies are developing regenerative medicine technologies to rescue, replace and help repair these damaged heart tissues and revascularize heart tissue in and around areas of infarct. Several ARM members are looking into using single or mixed populations of cells, both autologous (self to self) and allogeneic (other to self) to target the effects of cardiovascular disease. Other organizations are developing advanced biologics, gene therapies and small molecule approaches that focus on the cell cycle or other pathways which may allow the regeneration of lost heart cells and tissue.

Aastrom is developing an autologous ixmyelocel-T cell therapy, a patient specific, expanded multicellular therapy that selectively amplifies mesenchymal cells, monocytes and macrophages. They are currently conducting Phase 2 trials for dilated cardiomyopathy.

Amorcyte (a NeoStem company) is developing an autologous bone marrow derived, CD34 positive selected stem cell product, AMR–001, to treat damaged heart tissue following acute myocardial infarction. A Phase 2 trial has been initiated to evaluate the potential of AMR-001 to improve perfusion, preserve cardiac function and improve clinical outcomes.

Athersys Inc.’s allogeneic product, MultiStem, is a therapy that consists of a special class of stem cells obtained from bone marrow and other non-embryonic tissue sources. One year follow-up data from a Phase 1 study confirmed and extended the previous clinical observations at four months, showing a consistent safety
profile, and meaningful improvement in multiple clinical parameters.

Capricor is focusing on using cells from the heart tissue including concentrated cardiac stem and other supporting cells. Capricor successfully completed a Phase 1 clinical trial of their cardio-sphere-derived autologous stem cell product to reverse ventricular dysfunction. A second clinical study began in the fall of 2012, this time using allogeneic heart stem cells to potentially achieve myocardial regeneration.

Cytomedix is developing ALD-201, a population of autologous pluripotent stem cells isolated from the patients’ bone marrow using Cytomedix’s proprietary Bright Cell technology. In a Phase 1 ischemic heart failure clinical trial, ALD-201 was well-tolerated and the study provided initial evidence of improved blood flow and improved clinical status.

Cytori Therapeutics’ cell-based technology includes adult stem cells, endothelial progenitor cells, leukocytes, endothelial cells and vascular smooth muscle cells found in adipose tissue taken from the patient’s own body fat (known as adipose-derived stem and regenerative cells or ADRCs) to target cardiovascular disease. They are currently conducting clinical trials to evaluate the use of these ADRCs in cardiovascular disease, after pre-clinical trials showed promising signs of restoration of heart function following the use of ADRCs.

Juventas Therapeutics’ biologic product, JVS-100, utilizes stromal cell-derived factor-1 (SDF-1), a cytokine belonging to the chemokine family, which is shown to protect and repair tissue following ischemic injury by recruiting the body’s own stem cells to the injury site to prevent cell death and promote angiogenesis. JVS-100 has an ongoing Phase 2 clinical trial to test efficacy in heart failure.

Mesoblast’s technology platform is based on the use of their allogeneic mesenchymal precursor cells (MPCs) to repair tissue damaged in cardiovascular disease and induce sustainable large blood vessel formation. The company is currently working with partner Teva and the FDA on the trial design for a Phase 3 study in congestive heart failure.

Beyond cell therapy, companies such as VentriNova are developing small molecules and gene therapies that stimulate heart cells to re-enter the cell cycle, therefore regenerating lost heart tissue. VentriNova’s lead product targets the Cyclin-A2 gene to induce cellular proliferation of cardiomyocyte, and is in the preclinical stage of development. The company is hoping to receive IND approval to begin clinical trials in 2013.

Clinical progress in any of these areas could have a meaningful impact on improving clinical outcomes, cost of care and quality of life for those patients disabled by heart disease.

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**Cardiovascular Disease: Economic Impact**

**$71.2 Billion**

2005 total inpatient hospital cost for CDV care; approximately 25% of the total cost of hospital care in the United States.\(^3\)

**$316 Billion**

Overall medical cost of significant medical intervention over time, for healthcare services, medications and lost productivity of those afflicted with CDV.

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\(^1\) Heart Disease and Stroke Statistics—2012 Update: A Report from the American Heart Association available at circ.ahajournals.org/content/early/2011/12/15/CIR.0b013e31823ac046.full.pdf (published online in Circulation: Journal of the American Heart Association, December 15, 2011)

\(^2\) Mayo Clinic, “Heart Disease: Treatments and Drugs,” Mayo Clinic website, www.mayoclinic.com/health/heart-disease/DS01120/DSECTION=treatments-and-drugs

\(^3\) Heart Disease and Stroke Statistics—2008 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee available at circ.ahajournals.org/content/117/4/e25.short (published online in Circulation: Journal of the American Heart Association, December 17, 2007)
Overview

Vascular diseases are disorders that affect the extensive network of blood vessels in the body, leading to life and limb threatening disorders, such as critical limb ischemia, stroke, kidney failure, gangrene and abdominal aortic aneurysms. The disorders can affect any of the blood vessel types in the vascular system, namely arteries, veins, lymphatics and capillaries.

Peripheral vascular disease (PVD) or peripheral artery disease (PAD) affects the peripheral arteries and veins that carry blood to and from arm and leg muscles, organs in and below the stomach area, and also the arteries leading to the head.¹ When PVD occurs in the arteries outside the heart, it may be referred to as PAD. However, the terms “peripheral vascular disease” and “peripheral artery disease” are often used interchangeably.

PVD is one of the most common vascular diseases that affects one in three people over the age of 70. About eight to twelve million people are affected in the United States, with disease prevalence increasing with age.² Changes in these vessels disturb the normal flow of blood. Such changes include atherosclerosis, or the hardening of the arteries, which is caused by the buildup of fat and cholesterol depositions on their inside walls. This buildup narrows the vessels and causes ischemia, the inadequate blood (and thus oxygen) flow to the body’s tissues.³ Critical limb ischemia (CLI) is the most severe form of PVD caused by chronic inflammatory processes associated with atherosclerosis. There are estimated to be over 1 million people in the United States with CLI.⁴

PVD can also manifest itself in venous blood clots (like in deep vein thrombosis), inflammation and swelling. Venous blood clots are also a common ailment for many Americans, with 2.5 million people suffering from such clots in the leg veins every year.⁵

Lifestyle choices and heredity play large factors in the development of vascular diseases. Age, high blood pressure, smoking, obesity, high cholesterol, diabetes, family history and sedentary lifestyle are all risk factors for the diseases.⁶

Vascular Disease and Regenerative Medicine

Several cell-based regenerative medicine technologies targeting certain types of vascular disease, including PAD and CLI, are in mid- to late-stage clinical development.

Aastrom is developing an autologous ixmyelocel-T cell therapy, a patient-specific, expanded multicellular therapy that selectively amplifies mesenchymal cells, monocytes and macrophages. They are currently testing the
effectiveness of this therapy in two clinical trials for CLI. The lead trial is in Phase 3, and assessing the effect of treatment with ixmyelocel-T on amputation-free survival patients at 12 months post-injection, while the other is a Phase 2 trial to assess the safety and efficacy of the therapy.

Cytomedix is developing an autologous stem cell product ALD-301, a population of stem cells isolated from the patients' bone marrow which express high levels of the enzyme ALDH, an indicator of biological activity in heterogeneous early stage stem cells. In a Phase 1/2 trial of their product for CLI, ALD-301 demonstrated good tolerability and provided initial evidence of increased blood flow and improved clinical status for patients in the treatment group. Cytomedix is collaborating with NIH on a Phase 2 clinical study in patients with intermittent claudication (IC) which is caused by PAD.

Juventas Therapeutics' lead product JVS-100, a biologic-based regenerative therapeutic that encodes stromal cell-derived factor-1, is also targeting ischemic injury. The cytokine stimulates a number of protective anti-inflammatory pathways, causes the down regulation of pro-inflammatory mediators and can also prevent cell death. Furthermore, SDF-1 recruits stem cells to the site of tissue damage, which promotes tissue preservation and blood vessel development. The company is currently enrolling patients in a Phase 2 study for CLI patients.

Pluristem's patented PLX (Placental eXpanded) placenta-derived stem cells are being used in a multi-national study of peripheral artery disease. Pluristem completed clinical follow up in two Phase 1/2a studies in CLI that indicated that PLX-PAD was safe and potentially effective for the treatment of patients with CLI. In January 2013, the company announced it was expanding its Phase 2 study of PLX-PAD cells in patients with IC.

Tissue Genesis is developing a treatment for vascular disease using an adipose (fat)-derived stem cell-coated vascular graft. This treatment utilizes Tissue Genesis’ Cell Isolation System, a compact, automated desktop unit that utilizes liposuctioned adipose tissue to isolate millions of adult stem cells in about one hour. In April 2011, the company began enrolling patients in an FDA-approved clinical trial for PVD.

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**Vascular Disease: Economic Impact**

$164–290 Billion

Healthcare cost for Americans suffering from PAD and related conditions in 2010

$21 Billion

Vascular-related hospitalization for PAD alone in the U.S.

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1 “Peripheral Vascular Disease,” St. Luke’s Episcopal Hospital website, www.stlukeshouston.com/OurServices/HeartCareServices/Peripheral_Vascular_Disease.cfm
4 “CLI Clinical Trials: Advancing stem cell therapy to treat critical limb ischemia,” Aastrom Biosciences website, www.aastrom.com/clinical-research/cli-clinical-trials/
6 Stony Brook Medicine, “Vascular Disease,” Stony Brook University website, http://stonybrookmedicine.edu/patientcare/vasculardisease
8 University of Minnesota School of Public Health, “Peripheral artery disease continues to drive escalating health care costs in the United States,” University of Minnesota website, www.health.umn.edu/media/releases/PAD/index.htm
Overview

Chronic or non-healing wounds are wounds that have not made significant improvements after several weeks or fail to respond to medical or surgical management. They are wounds that do not undergo the normal healing process that includes inflammation, proliferation and matrix deposition and remodeling. They can be caused by diabetes, poor circulation, burns, pressure and other conditions, and are characterized by redness, warmth and pain, increased drainage or drainage with an odor, tenderness and swelling. Therefore, they can be found in patients with issues and conditions that inhibit tissue repair, including diabetic wounds, vascular insufficiency ulcers, compromised amputation sites, radiation necrosis and gas gangrene.

In the United States, approximately five to seven million people are affected. People with diabetes are especially at risk to develop chronic wounds, usually in the form of foot ulcers. The incidence of chronic wounds is highest among the eight percent of the total United States population that have diabetes, with approximately 15-25 percent of diabetic patients eventually developing them. Because the number of diabetic patients is expected to swell to 425 million people worldwide by 2030, the number of patients afflicted with chronic, non-healing wounds is also expected to increase in the coming decades.

Non-Healing Wounds

Non-Healing Wounds and Regenerative Medicine

Although traditional wound care often aids the healing process of chronic, non-healing wounds, as many as one-third of these wounds fail to heal. Regenerative medicine technologies thus have great potential to bridge the success rate gap for treatment of these ailments. The field of regenerative medicine has been focusing next generation technologies to help heal cutaneous wounds. One successful approach is the creation and use of three-dimensional scaffolds as extracellular matrix analogs that mimic the natural extracellular matrices. These scaffolds, when seeded with a range of molecules, including fibroblasts (the cells that synthesize the extracellular matrix and collagen), help foster cell adhesion, growth and differentiation to form skin functional and structural tissue. Stem cells, growth factors, chemokines, cytokines and other molecules are also being explored as regenerative medicine products to renew endogenous healing processes in chronic, non-healing wounds.

Organogenesis has commercialized a living cell-based product. Apligraf is a bi-layered cell based technology, composed of a layer of differentiated keratinocytes and a layer of fibroblasts seeded in a collagen matrix, which has been proven to close wounds faster and to reduce amputations. In 2012, the company announced that it had shipped over 500,000 units of Apligraf, making it the most widely used regenerative medicine product in the world to date. In April 2012, the product also established improved coverage from multiple healthcare contractors and payers.

Shire Regenerative Medicine’s lead product, Dermagraft, utilizes human fibroblast cells derived from newborn foreskin tissue seeded into a bioresorbable scaffold. The product is on
the market in the United States, and expected to be available in Canada in the first quarter of 2013. Another Shire Regenerative Medicine product, ABH001 (derived from neonatal dermal fibroblasts), recently initiated a Phase 3 study for patients with non-healing wounds stemming from epidermolysis bullosa (EB), a family of genetic skin fragility disorders.

Cytomedix’s product for non-healing diabetic, pressure and/or venous wounds, the AutoloGel System, utilizes autologous platelet rich plasma (PRP) to produce a gel for wound application. The PRP gel contains growth factors, cytokines and chemokines that help reestablish the body’s endogenous healing processes. In February 2013, Cytomedix announced that physicians can use AutoloGel to treat Medicare beneficiaries with chronic wounds and receive reimbursement for the product under the Coverage with Evidence Development (CED) program.

Avita Medical’s product, ReCell Spray-On Skin, is an autologous cell technology that when sprayed onto a skin wound accelerates healing, minimizes scar formation, eliminates tissue rejection and reintroduces pigmentation to the skin. The product is on the market in Europe, Canada, and Australia, and is under clinical investigation in the United States.

Cytori Therapeutics’ technology employs adult stem cells, endothelial progenitor cells, leucocytes, endothelial cells and vascular smooth muscle cells found in adipose tissue taken from the patient’s own body fat (known as adipose-derived stem and regenerative cells or ADRCs). In March 2012, the company published the favorable results of its RESTORE-2 trial, which used ADRCs in partial mastectomy patients. Cytori was recently awarded a contract valued up to $106 million by the Biomedical Advanced Research and Development Authority for preclinical and clinical development of the company’s cell therapy for the treatment of thermal burns.

Healthpoint Biotherapeutics, which was recently acquired by Smith & Nephew, is a company using acellular matrix scaffolds to treat diabetic foot ulcers. Their Oasis Wound Matrix is a matrix derived from porcine small intestinal submucosa (SIS). The SIS technology is proven to help the body repair and replace damaged tissue. The Oasis Ultra Tri-Layer Matrix is made from the same structural SIS/ECM components as the Oasis Wound Matrix, but Oasis Ultra has three layers of the SIS structure to target more problematic wounds.

Non Healing Wounds: Economic Impact

$35 Billion
The estimated cost of healthcare for individuals suffering from chronic, non-healing wounds.5

$200 Billion by 2020
Projected additional cost for treatment of diabetic foot ulcers.5

Overview

Spinal Cord Injury (SCI) is an insult to the spinal cord, resulting in temporary or permanent damage to its normal motor, sensory and autonomic function. SCI afflicts about 250,000 Americans, 82 percent of whom are male. Fifty-six percent of injuries occur between the ages of 16 and 30, and the average age of a spinal cord injury patient is 31. SCI ranges from complete injury, where function below the neurological level is lost, to incomplete injury, where some sensation or movement below the level of injury is retained. The severity of the injury in terms of functional loss is dependent on where the injury occurs and how quickly doctors can respond to it. Cervical injuries in the neck will generally result in full or partial quadriplegia, while injuries further down, at or below thoracic spinal levels and at lumbar levels, will result in paraplegia or decreased control of various functions below the point of injury. Typically, death does not result from the injury itself, but from complications, which include skin breakdown, pneumonia, osteoporosis and fractures, urinary tract infections and cardiovascular disease, among others. Treatment is currently limited to anti-inflammatory agents within eight hours of the injury, surgical implants for the stabilization of the spinal cord and intensive rehabilitation to help maintain strength.

Spinal Cord Injury and Regenerative Medicine

SCI generally results in neuron loss and demyelination of the nerve axons at and near the site of injury. It is difficult to treat effectively due to the scarring and toxic environment that also develops around the injury site.

The California Institute for Regenerative Medicine (CIRM), has been at the forefront of this research. Researchers supported by CIRM at University of California, Irvine were the first in the world to develop a method to create large amounts of high purity oligodendrocytes from hESCs. Oligodendrocytes are central nervous system specific cells that produce myelin, the material that insulates the spinal cord and nerve cells, allowing for electric conduction.

StemCells, Inc. is testing its human neural stem cell product (HuCNS-SCs) to treat SCI. In preclinical trials, these stem cells migrated to the injury site, differentiated into neurons and oligodendrocytes, which formed new myelin sheaths around the damaged nerve axons and restored motor function. In February of 2013, StemCells, Inc. announced that the first cohort of patients completed the Phase 1/2 SCI trial which demonstrated a favorable safety profile and gains in sensory motor function compared to pre-transplanted baselines.
Neuralstem’s lead cell therapy candidate, NSI-566 is a human spinal cord stem cell derived product. The cells, which are transplanted into the patient’s spinal cord are expected to integrate into the patient’s neural tissue and create new circuitry to transmit nerve signals to muscles. In preclinical work, NSI-566 made synaptic contact with the host motor neurons and expressed neurotrophic growth factors, which are protective of cells. In January of 2013, Neuralstem received FDA approval to initiate a Phase 1 human trial.

RhinoCyte Inc. is developing an adult autologous stem cell technology that repairs damage resulting from SCI. The autologous cells are cultured from the olfactory regions of the nasal passageways via outpatient surgery, which can then be transplanted into the injury site. Preclinical animal studies have demonstrated positive results. The company hopes to submit an IND in the near future.

Q Therapeutics is hoping to use their Q-cells product to treat SCI. When injected into the CNS, these cells are believed to replicate, migrate and differentiate into oligodendrocytes and astrocytes (glial support cells that provide growth and trophic factors for the oligodendrocytes and neurons). The company is currently conducting preclinical studies in disease models of SCI.

The Miami Project was the first to establish optimal laboratory methods to isolate and expand human Schwann cells, the myelin producing cells of the peripheral nervous system (PNS). They recently received FDA approval to begin a Phase 1 trial evaluating the safety of transplanting human Schwann cells to treat patients with recent SCI.

The New York Neural Stem Cell Institute (NSCI) is developing biodegradable beads that activate the dormant resident, or endogenous, CNS stem cells within the spinal cord to produce the oligodendrocytes needed to reduce CNS scarring. NSCI is hoping to progress toward clinical trials with this product.

InVivo Therapeutics is focusing on the scaffolding technology that could provide structural support and bridge the neural pathways at the site of the injury. They are currently awaiting FDA approval to commence a human clinical trial in 2013.

**Spinal Cord Injury: Economic Impact**

The cost of healthcare attributable to SCI varies greatly according to the severity of the injury, but leaves families of patients with an extremely heavy cross to bear.

- **$321,720–$985,774**
  Average yearly expenses during the first year of treatment and care (from incomplete motor function to high tetraplegia).¹

- **$39,077–$171,183**
  Average yearly expenses for each subsequent year.¹

Overview

Alzheimer’s Disease (AD) is the most common form of dementia (the general term for loss of memory and intellectual abilities) that attacks neurons in the brain, resulting in memory loss, cognitive impairment and behavioral changes. The disease disrupts the brain’s communication network, eventually destroying neuronal synapses and killing neurons altogether. There are an estimated 5.4 million Americans suffering from the disease, and the prevalence doubles every five years beyond the age of 65. As of 2010, there are 35.6 million people living with the disease, and it is the sixth-leading cause of death in the United States. While the majority of people with the disease are 65 and older, about five percent of the people afflicted have early-onset Alzheimer’s which can occur when a patient is in their 40s and 50s. AD is not a part of the normal aging process. Symptoms get progressively worse over time and can include confusion with time and place, struggles to complete familiar tasks and changes in mood and personality.

The disease is characterized by two types of abnormal lesions that build up around neurons in the brain including beta-amyloid plaques (clumps of protein fragments and cellular material) and neurofibrillary tangles (insoluble twisted fibers composed of the Tau protein). It is not certain whether these lesions cause disease or are a byproduct of it. As stated earlier, there is no cure for AD and the disease can only be officially confirmed by autopsy after a patient’s death. There are currently five FDA-approved Alzheimer’s drugs that treat the symptoms of AD, however, they do not treat the underlying causes of the disease.

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Alzheimer’s Disease and Regenerative Medicine

The creation of disease models through cellular reprogramming of patient-specific cells has allowed scientists to create human disease models of AD to study the disease in controlled laboratory conditions. Cellular reprogramming is a process when scientists reverse fully differentiated, mature cells into an embryonic state, creating disease induced pluripotent stem cell lines.

Several ARM members are highly involved in these new efforts. Scientists at The New York Stem Cell Foundation lab have developed a cell-based model of Alzheimer’s disease. In this initiative led by Scott Noggle, PhD, the researchers reprogrammed cells of early-onset patients into induced pluripotent stem cells to create cholinergic basal forebrain neurons (the cells affected in Alzheimer’s). These cells demonstrate the features of the disease on a cellular level, creating a viable disease model that will be critical for drug discovery and
testing. Preliminary results have demonstrated differences in cellular function in patients. Alzheimer’s neurons produced more of the toxic form of beta amyloid, the protein found in amyloid plaques, than healthy neurons.7

iPierian has also created disease models from patient-derived pluripotent stem cells to advance their novel drug development programs. After using the disease models to validate the therapeutic targets and mechanisms of disease, they hope to move toward using monoclonal antibodies to treat AD (and other neurodegenerative diseases) by targeting the Tau protein.7 iPierian is aiming to start human trials with their potential drugs in 2014.8

The California Institute for Regenerative Medicine (CIRM), California’s stem cell agency, is supporting the development of technologies to treat AD which includes eleven research grants.9 CIRM recently awarded StemCells, Inc. a $20 million boost for the company to collaborate with UC-Irvine’s Sue & Bill Gross Stem Cell Research Center’s neurobiologists and the Institute for Memory Impairments and Neurological Disorders (UCI MIND) to advance the company’s human neural stem cell technology in Alzheimer’s. Researchers have already reported that StemCells, Inc.’s neural stem cells restored memory and enhanced synaptic function in two animal models similar to AD. It is believed these cells provide growth factors that protect the neurons from degeneration.10

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**Alzheimer’s Disease: Economic Impact**

![Image](https://example.com/alzheimers_treatment_horizon)

**$200 Billion**

Estimated cost in 2012 to care for people with Alzheimer’s disease in the United States.11

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**$18,500–$36,000+**

Annual cost to care for an individual Alzheimer’s sufferer, depending on the stage of disease.11

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**$200 Billion → $1.1 Trillion**

Projected increase in cost to care for Alzheimer’s and other dementia sufferers by 2050. (In today’s dollars.)12

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Overview

Parkinson’s Disease (PD) is a neurodegenerative disease that afflicts more than one million people in the United States, with over 60,000 new cases being diagnosed each year. PD causes the nerve cells that generate dopamine to degenerate and die, leaving patients with limited muscle control. PD generally affects the elderly with the average onset occurring around age 60, although early onset cases do occur. Patients suffer from numerous side effects that have a strong and continued impact on their quality of life. These include uncontrollable muscle tremors and twitching, loss of facial expression, poor balance, trouble swallowing, pain and loss of movement control.

While PD is not lethal and patients can live with the disease for over 20 years, the burden on patients and their families is significant. There is currently no cure for Parkinson’s and treatments are limited to managing symptoms rather than addressing the underlying cause of the disease. Patients have to cope with frequent medication changes and side effects to manage (and not eliminate) the primary symptoms of this disease, resulting in a condition that is extraordinarily difficult to control on a chronic basis.

Parkinson’s Disease and Regenerative Medicine

Regenerative medicine technologies have the potential to shift the Parkinson’s treatment and discovery paradigm.

Currently there are two major cell-based approaches for treating PD. One approach hopes to replace the damaged or lost tissues via cell injections and several studies have shown that mesenchymal stem cells and neural stem cells can be directed into dopaminergic neurons. The second approach utilizes the trophic effect of cells to aid in the endogenous repair and rescue of the PD affected tissue.

Disease modeling is proving to be another useful tool in the research and development of PD therapies. Disease modeling allows scientists to better understand the root cause of the disease as it permits the study of the manifestation and underlying mechanisms of PD. The models are created by reprogramming adult cells from PD patients into induced pluripotent stem cells. Once the cells are reprogrammed, scientists can differentiate them into dopaminergic nerve cells that are affected by the disease. These modeled cells show distinct differences when compared to dopaminergic cells from healthy people.
Beyond disease modeling, many international groups of scientists are creating dopaminergic neurons from stem cells to replace damaged cells in people afflicted with PD. U.S.-based researcher Lorenz Studer and his colleagues at the Sloan-Kettering Cancer Center have recently succeeded in making highly efficient dopamine-producing neurons from human embryonic stem cells and have transplanted them into the brains of rats and mice with PD. The cells did not multiply abnormally and improved some symptoms. However, work is still needed before human studies begin. The scientists hope to initiate early clinical trials in 2014 or 2015. Additionally, Anne Rosser and colleagues at Cardiff University, UK are exploring ways to help transplanted nerve cells survive inside the brains of Parkinson’s patients.

Regenerative medicine is proving to play an important role in our understanding of the disease and the early development of next generation PD technologies and therapies.

While Parkinson’s Disease is not lethal and patients can live with the disease for more than 20 years, the burden on patients and their families is significant.

The California Institute for Regenerative Medicine (CIRM) grantees at Stanford University and The Parkinson’s Institute became the first research team to model Parkinson’s with reprogrammed iPSCs from a woman with a genetic form of the disease. The cells initially behaved normally, but 30–60 days later started to exhibit diseased cell traits found in PD patients. Such disease models will be useful for PD patients with a variety of genetic mutations; comparing normal and diseased models may determine commonalities and differences that advance treatments for each patient individually. CIRM is also supporting Dr. Fred H. Gage at the Salk Institute for Biological Studies. Gage has grants from CIRM to mature embryonic stem cells into neurons in order to develop new cell lines from people with the disease and more closely study the mechanisms behind Parkinson’s.

**Parkinson’s Disease: Economic Impact**

$23 Billion Annually

Estimated combined direct and indirect costs for Parkinson’s Disease patients in the U.S.\(^1\)

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\(^1\) Deborah Boland and Mark Stacy, “The Economic and Quality of Life Burden Associated with Parkinson’s Disease: A Focus on Symptoms,” *The American Journal of Managed Care* Vol. 18, September 2012, pp. 168-175 available at www.ajmc.com/publications/supplement/2012/408_12sep_Parkinsons/A408_12sep_Boland_S168to75
Overview

Musculoskeletal disorders (MSDs) occur when there are injuries to the joints and the soft tissue that helps move them. These conditions can thus affect joints, muscles, tendons, cartilage, and supporting structures of the upper and lower limbs, neck and back. They can be caused by sudden exertion or prolonged physical factors such as repetition, force, vibration and awkward posture. In essence, the tissues of these structures are working harder than they are designed to.

Common symptoms of MSDs include inflammation, redness, decreased range of motion, loss of function, pain and fatigue, among others. Arthritis, carpal tunnel syndrome, tendonitis, bursitis and epicondylitis (tennis and golfer’s elbow) and trigger finger (gamer’s finger) are some common examples of MSDs.

There are over 100 diseases that affect the joints and surrounding tissue. Arthritis alone affects around 46 million Americans. In general, more than one in four Americans has a musculoskeletal condition that requires medical attention. Though many musculoskeletal conditions can be treated by either a general practitioner or a specialist, the burden of musculoskeletal disease is expected to increase in the next 20 years.

Musculoskeletal Related Conditions and Regenerative Medicine

Several of the regenerative medicine products currently available on the market are for musculoskeletal disorders. Many ARM members are focusing on developing therapeutic products for musculoskeletal disorders with technologies including both cellular therapies and, synthetic and biomaterial-based products.

Mesoblast is developing cellular therapies using their mesenchymal precursor cell (MPC) technology platform to target several musculoskeletal disorders. By injecting MPCs into a degenerated intervertebral disc, they hope to see the replacement of the lost proteoglycan and cartilage that gives the disc its functional properties (which include cushion for stress forces and normal rotation of the spine). The company currently has several clinical studies underway for degenerative disc disease (DDD). Clinical trials for bone fracture repair and arthritis relief are also in the company’s development pipeline.

DiscGenics is using adult-derived stem cells combined with tissue-engineered technologies to treat patients with DDD. DiscGenics is isolating stem cells from disc tissue and expanding them into cell populations known as Discospheres. These cells have different properties compared to regular MSCs, but the company’s research suggests they may in fact be more effective in
their regenerative capabilities for the damaged discs. In late February of 2013, the company announced promising preclinical results, and is currently conducting additional animal studies to support the initiation of human clinical studies.

Histogenics’ products are aimed at preventing the effects of cartilage damage by regenerating healthy hyaline cartilage tissue. They are currently developing two products, NeoCart and VeriCart. NeoCart is an autologous engineered neocartilage grown outside the body and used to repair cartilage lesions. Phase 2 trials for NeoCart were recently completed, with positive data trends when compared to microfracture, and Phase 3 trials are currently ongoing. The company hopes to submit VeriCart, a collagen-based scaffold technology, for a CE mark by mid-2013 and gain regulatory approval designation by the end of the year.

ISTO Technologies is targeting orthopedic treatment with both cell-based and biomaterial-based technologies. DeNovo ET is the company’s allogeneic living cartilage implant designed to repair and regenerate damaged knee cartilage. The product uses a patented, juvenile cell-based technology which may have superior regenerative properties compared to adult cartilage cells. Isto is currently enrolling subjects in a Phase 3 trial of the product for knee repair. They are also exploring the use of these cells in the spine to combat disc damage.

MiMedix Group, Inc. is currently focusing on two musculoskeletal products. CollaFix, a product not yet approved in the U.S., functions as a scaffold that assists the body’s ability to generate new tissue. The product is also biodegradable and gradually disappears after the repair is complete. A second product, HydroFix Vas Shield, is a vessel guard made of the company’s proprietary hydrogel material to protect veins and arteries during surgery.

As mentioned earlier, many regenerative medicine products for musculoskeletal conditions are already on the market and in use by medical professionals. Genzyme Sanofi’s cell therapy product Carticel has treated thousands of patients with damaged knee cartilage and AlloSource, is developing, processing and distributing allografts (tissue grafts obtained from donors), and currently has over 200 standard and customized allograft products on the market.

## Musculoskeletal Related Conditions: Economic Impact

<table>
<thead>
<tr>
<th>132 Million MD Office Visits</th>
<th>$850 Billion</th>
<th>440 Million Days</th>
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<tr>
<td>29 Million ER Visits</td>
<td>Estimated annual direct and indirect healthcare cost for musculoskeletal related conditions.(^5)</td>
<td>Missed work days due to musculoskeletal related conditions.(^5)</td>
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<tr>
<td>15 Million Out Patient Visits</td>
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Musculoskeletal related visits per year.\(^5\)


\(^4\) The Burden of Musculoskeletal Diseases in the United States available at www.boneandjointburden.org (published by The United States Bone and Joint Initiative, 2011)

\(^5\) Penn Center for Musculoskeletal Disorders, “Overview of the Penn Center for Musculoskeletal Disorders,” Perelman School of Medicine at the University of Pennsylvania website, http://www.med.upenn.edu/pcmd/overview.shtml
Overview

Autoimmune disorders are conditions where the body produces an inappropriate response to healthy tissue and substances normally found in the body, effectively destroying them. The body's immune system is unable to tell the difference between healthy body tissues and antigens such as bacteria, viruses, toxins, cancer cells, blood or tissue from another person. It wrongly identifies the normal tissue as pathogens and attacks its own cells. This leads to the destruction of one or more types of body tissue, abnormal growth of an organ or changes in organ function. These diseases commonly affect the blood vessels, connective tissues, endocrine glands, joints, muscles, red blood cells and skin. Common diseases that are classified into the broad spectrum of autoimmune disorders include multiple sclerosis, type 1 diabetes, lupus, rheumatoid arthritis, uveitis, scleroderma, grave’s disease and chronic thyroiditis, among others. There are over 80 types of autoimmune disorders in total.¹

Around 23.5 million Americans are affected by autoimmune diseases, making it a leading cause of death and disability in the United States. Different diseases are more prevalent in certain races and ethnic groups, and 75 percent of the patients are females.²,³ What causes the inappropriate immune response in many of these disorders is still unknown, though bacteria and viruses, along with genetic factors, are thought to be involved. These diseases can strike any part of the body with widely varying symptoms, making treatment very difficult. One common form of treatment is immunosuppression, a medication which decreases the immune response in these diseases. However, this treatment also suppresses normal immunity, leaving the body at risk for infection.

Inflammation is associated with autoimmune diseases. While the inflammation can be acute, in many cases, a chronic inflammatory disorder can develop. These disorders result in abnormal inflammation and cause even more destruction of healthy tissue, as well as chronic pain, redness, swelling and immobility.

Autoimmune Disorders and Regenerative Medicine

Developing treatments for autoimmune disorders and inflammation is a significant focus in the regenerative medicine community. The mechanism of action of several of these cell based therapies is still being explored, however, data suggests immunomodulation and suppression can be achieved through cellular interaction between therapeutic cells and the patient’s immune system, including anti-inflammatory T-cell responses. Several of these technologies are based on mesenchymal stem and progenitor cell populations derived from a variety of adult
Developing treatments for autoimmune disorders and inflammation is a significant focus in the regenerative medicine community.

tissue sources. Several companies are developing regenerative medicine therapies to mitigate the adverse effects of graft-vs-host disease (GvHD), a complication of bone marrow transplantation that kills up to 80% of children affected.

Athersys, Inc. is testing its lead product, MultiStem (allogeneic adult stem cell technology), for prevention or reduction of GvHD in cases of patients undergoing allogeneic hematopoietic stem cell transplants (HSCTs) for the treatment of leukemia and related conditions. Clinical studies yielded positive results in the Phase 1 trial, potentially increasing treatment and prevention options for this autoimmune disease. Additionally, Athersys is conducting a Phase 2 clinical study with partner Pfizer to test the safety and efficacy of MultiStem in individuals suffering from Inflammatory Bowel Disease (IBD).

Celgene is commercializing placenta-derived stem cell therapies for autoimmune and inflammatory diseases. They are currently conducting several clinical studies of their product PDA-001 in autoimmune and inflammatory conditions including Phase 2 studies in both Crohn’s disease and rheumatoid arthritis and Phase 1 studies in multiple sclerosis and sarcoidosis.

NeoStem is developing a T-cell therapeutic, Athelos, which works to restore immune balance in GvHD patients by enhancing T-regulatory cell numbers and function. They are currently in a Phase 1 trial.

Osiris’s lead product, Prochymal is in Phase 3 studies in the United States for GvHD, and has been approved in Canada. The product demonstrated significant survival benefits in patients with the most severe forms of GvHD. Osiris is also testing Prochymal in Phase 2 studies for Crohn’s disease.

Tigenix, a leading European cell therapy company, is making several advancements with their adult stem cell programs targeting autoimmune and inflammatory diseases. Their stem cell platform uses allogeneic adipose tissue derived expanded stem cells (eASCs). Tigenix currently has two products in clinical studies for autoimmune and inflammatory disorders, Cx601 in Phase 3 development for Crohn’s disease and Cx611 in Phase 2 studies for rheumatoid arthritis.

Autoimmune Disorders: Economic Impact

$100 Billion Annually
NIH estimate for direct healthcare costs to treat autoimmune diseases. This figure is likely less than the total healthcare costs since isolated inflammatory disorders are not factored into this number.

3 Johns Hopkins Health System, “What is Autoimmunity?: Broad Spectrum of Autoimmune Disease,” Johns Hopkins University School of Medicine website, autoimmune.pathology.jhmi.edu/whatis_spectrum.cfm
Overview

Stroke, caused by a disruption in the flow of blood to the brain, is the third most deadly disease in the United States and the leading cause of serious disability. Someone in the U.S. has a stroke every 40 seconds, and approximately every four minutes, a life is taken due to stroke.\(^1\) When a stroke occurs, brain cells begin to die in a matter of minutes from oxygen deprivation, and over time, damage caused by inflammation and other mechanisms leaves many patients with permanent physical or cognitive disability.

The two most common types of stroke are ischemic and hemorrhagic. Ischemic strokes result from an inadequate supply of blood and oxygen to the brain due to blockage of an artery, such as by a blood clot. Hemorrhagic strokes result from rupture of a blood vessel or an abnormal vascular structure.

Unfortunately, the only non-surgical emergency treatment available for ischemic stroke (thrombolytic drugs), must be administered within three to four hours, and is only expected to help victims recover more fully, not reverse the effects of the stroke.\(^2\) Due to the narrow window of intervention, it is estimated that less than five percent of stroke victims are able to receive emergency treatment. Even with emergency treatments, stroke often leaves survivors with severe disabilities including loss of mobility, pain, numbness, memory loss, difficulty talking and impaired cognitive ability.

Stroke and Regenerative Medicine

The lack of treatment options for stroke represents an enormous gap in medical care given its high incidence and severity. As stated earlier, the treatments for stroke are currently limited to the acute phase three to four hours after a stroke event. Many of the regenerative medicine technologies in development are targeting the post-stroke rehabilitation period for which there are currently no therapies available. Stem cells from a variety of sources are being transplanted directly into the brain, and promote the repair of ischemic tissue damage by fostering neurogenesis, angiogenesis and chemotaxis, as well as anti-inflammatory action.

Athersys, Inc. is making progress on a Phase 2 trial evaluating the safety and efficacy for MultiStem, an allogeneic cell therapy product. This adult cell therapy is administered to stroke victims within 1–2 days after the stroke—broadening the treatment window available for stroke patients.

Celgene will also soon conduct a Phase 2 trial where placenta-derived stem cells are administered after ischemic stroke to assess safety, tolerability and improvement after stroke.
Cytomedix is developing an autologous stem cell product derived from the patient’s own bone marrow. They are currently expanding a Phase 2 trial in which ischemic stroke patients have these cells administered to the brain 13–19 days post stroke event in order to promote the repair of ischemic tissue damage, thus reducing patient disability.

UK-based ReNeuron is using their neural stem cell therapy, ReN001, in hopes of reversing functional deficits seen in stroke disability even when administered several weeks after the stroke event. Pre-clinical models have proven to be promising and a Phase 1 clinical study is currently underway.

Worldwide, there are several preclinical studies utilizing stem cells to enhance stroke recovery. Scientists at University of Pittsburgh Medical Center and Stanford University are working in collaboration with SanBio, a company developing genetically manipulated bone marrow stromal cells to treat a variety of neurological disorders. The cells are genetically modified to overexpress Notch, a gene that is involved in the development of infant brains.

The team at Neuralstem is also making strides in the stroke cell therapy field, having recently been approved to commence a human ischemic stroke trial. They hope to use spinal cord stem cells to treat the motor deficits, namely paralysis in the arms and legs, which occur due to ischemic stroke.

Regenerative medicine therapies currently being developed may be the best hope for the millions of stroke victims across the world faced with a lifetime of disability and impairment.

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**Stroke: Economic Impact**

Stroke victims may also lose the ability to care for themselves and require a constant caretaker or hospice care, which can be emotionally and financially draining for families. Physical therapy, extended hospitalization and long term institutional care required for many victims of stroke, represent an enormous economic and social burden.

- **$73+ Billion**
  - American Heart Association estimate of annual U.S. aggregate costs of stroke.\(^3\)

- **$140,000**
  - Mean lifetime cost of ischemic stroke in the U.S.
  - Ischemic strokes represent approximately 87% of all strokes.\(^3\)

- **800,000 Patients**
  - American Heart Association estimate of U.S. patients affected by stroke each year.\(^3\)

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Overview

Diabetes, also known as diabetes mellitus, is a group of metabolic diseases in which a person has high blood sugar either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. There are two primary types of diabetes. Type 1 diabetes, also known as insulin-dependent or juvenile diabetes, is an autoimmune disorder in which the immune system attacks and destroys the insulin-producing beta cells in the pancreas. Type 2 diabetes, known as adult onset or non-insulin dependent diabetes, is caused when either there is a deficiency in the insulin being produced, or when the cells of the body become resistant to the action of insulin. Over time, the pancreas becomes unable to make enough insulin, and glucose accumulates in the bloodstream in the same manner as in type 1 diabetes.

Diabetes is a chronic condition that requires constant monitoring and creates dangerous and debilitating secondary conditions. Long-term complications include increased risk of cardiovascular problems such as coronary artery disease, heart attack and stroke. Other complications include nerve damage in the limbs, kidney failure, blindness and nerve damage in the feet and legs that can cause diabetic foot ulcers which, if not treated properly, can lead to amputation.¹

Current treatments for type 1 diabetes include constant monitoring of blood glucose levels and insulin therapy which is time-consuming, costly and painful for many patients. Some type 2 patients also rely on insulin therapy, but the condition can often be managed with other diabetes medications, healthy eating and exercise.

Diabetes and Regenerative Medicine

There are a variety of regenerative medicine technologies in preclinical and clinical development that aim to reestablish insulin production and mediate the immune system’s attack on insulin producing beta cells. Some of the most innovative research is being funded by the Juvenile Diabetes Research Foundation (JDRF), the leading non-profit organization in the area of type 1 diabetes research. JDRF is working with several organizations including Viacyte, Osiris, researchers at the University of Florida and the National Institutes of Health among others, to develop regenerative medicine technologies for diabetes.

Athersys, Inc. is in preclinical stages of testing its MultiStem stem cell product in diabetes (as well as other autoimmune diseases). The company believes that MultiStem has the potential to regulate immune system function, and could thus work to protect the beta cells that are under attack in type 1 diabetes.
Mesoblast is using their patented human mesenchymal progenitor cells to target type 2 diabetes. In preclinical trials, the injection of a dose of MPCs into mice with diabetes resulted in a significant increase in blood insulin levels and sustained reduction in blood glucose levels during the follow-up period. Mesoblast is in the midst of a 60 patient Phase 2 clinical trial.

Osiris has completed enrollment for a Phase 2 type 1 diabetes clinical trial evaluating the efficacy and safety of their product Prochymal. Prochymal uses mesenchymal stem cells for their believed ability to delay the progression of type 1 diabetes by preserving beta cell function, and thus insulin production.

ViaCyte, a San Diego, CA-based regenerative medicine company, is developing a stem cell based technology for the treatment of type 1 and type 2 diabetes. The company is developing a combination cell therapy, medical device product, VC-01, which packages and encapsulates the PEC-01 pancreatic precursor cells derived from a human embryonic stem cell line in their ENCAPTRA drug delivery system. In animal models, the cells differentiated into insulin producing and other endocrine cells that regulated blood glucose in a manner very similar to the normal pancreas when implanted under the skin.

Researchers have also been looking at gene therapy as a means to treat diabetes. In February 2013, researchers at the Universitat Autonoma de Barcelona (UAB) claimed to have reversed all signs of type 1 diabetes in dogs using this approach with a single gene therapy session. The study showed promising signs of long-term control of diabetes in large animals.

Current Regenerative Medicine Therapies for Diabetes

In addition to these significant steps towards treating the root cause of diabetes, there are several regenerative medicine therapies currently on the market to treat diabetic foot ulcers and chronic wounds that are very common and serious comorbidities of diabetes. See ARM’s disease profile on non-healing wounds for more information on these therapies.

Diabetes: Economic Impact

As of January 2011, there are over 25 million Americans that suffer from diabetes, with 90% of the patient population being afflicted with type 2. This number is expected to increase due to a rise in obesity (obese people are more prone to develop diabetes) as well as other factors. Healthcare costs for people suffering from diabetes are 2-3 times higher than for people without the disease.

- **$174+ Billion**
  Total disease cost for diabetes care in the U.S. as of 2007.

- **24 Million → 44 Million**
  Forecast increase in number of Americans afflicted with diabetes by 2034.

- **200% → $336 Billion**
  Forecast increase in direct economic costs for diabetes care by 2034.

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Overview

Ocular diseases and anomalies affect the human eye and visual system. They cover disorders that range from infections to conditions that produce blindness and vision loss. Several systemic diseases can also affect the cornea, eyelids, retina and optic nerve head as age increases. However, the leading causes of blindness in the United States are age-related eye diseases, including age-related macular degeneration (AMD), cataracts, diabetic retinopathy and glaucoma.

- AMD afflicts more than 30 million people worldwide and is the leading cause of blindness in people over 60 in the U.S.\(^1\) An estimated 1.8 million Americans above the age of 40 are affected by AMD, with the total number expected to rise to 2.95 million by 2020.\(^2\)

- Stargardt’s disease is the most common form of inherited juvenile macular degeneration. It is usually diagnosed in people below the age of 20 if there are signs of reduced central vision.

- Glaucoma, an eye disease that causes damage to the optic nerve, affects around 50 million people worldwide and between three and four million people in the U.S.\(^2\)

- Cataracts are cloudy areas in the lens caused by a change in the chemical makeup within the lens. They cause blurred and double vision, as well as poor night vision.

- Diabetic retinopathy refers to the damage to the blood vessels of the retina caused by diabetes. The damage results in weakened and broken blood vessels that either leak fluid into the retina or cause it to swell.

Though surgery and laser treatments can be used for some ocular disorders, others remain difficult to treat. As the aging population increases in size, it is becoming more imperative to explore different treatment options for age-related eye diseases.

Ocular Diseases and Regenerative Medicine

Many of the field’s key opinion leaders consider ophthalmology to be an area where regenerative medicine will have a tremendous impact over the coming years. Promising results from animal models have been published in leading academic journals, and several companies are moving into mid-stage clinical trials for a variety of ocular disorders—especially age-related macular degeneration.

Advanced Cell Technology (ACT) is targeting degenerative retinal disease. They are focusing on commercializing human embryonic stem cell-derived retinal pigment epithelial cells (RPE). A Phase 1/2 clinical trial for AMD and Stargardt’s disease is underway with several major eye institutes, including the Wills Eye Institute in
Philadelphia to test the safety and tolerability of the hESC-derived RPEs in patients with dry AMD.

StemCells, Inc. is developing a human neural stem cell product, HuCNS-SC, for AMD. Preclinical results revealed that their product preserved the visual acuity in rats, protecting the retina from progressive degeneration. Phase 1/2 trials began in 2012. The trial will evaluate the safety and preliminary efficacy of HuCNS-SC cells as a treatment for dry AMD.

University College London’s (UCL) The London Project to Cure Blindness is also focused on using embryonic-derived RPE cells to target AMD. The scientists at UCL have established a formal collaboration with Pfizer for clinical development of a small patch of cells to cover the damaged macula, protecting the eye from age-related blindness. They have completed their preclinical safety experiments and are hoping to start clinical trials in 2013.

The RIKEN Center for Developmental Biology in Kobe, Japan, is also working toward solutions for AMD using induced pluripotent stem cells. RIKEN scientists are currently taking mature skin cells from patients, reprogramming them into stem cells, and then coaxing them into a certain type of retinal cell to be transplanted into patients’ eyes. The team, led by Masayo Takahashi, M.D., Ph.D., plans to submit an application for a clinical study to the Japanese health ministry next month, and could be recruiting patients as early as September.

Many of the field’s key opinion leaders consider ophthalmology to be an area where regenerative medicine will have a tremendous impact over the coming years.

Ocular Disease: Economic Impact

![Ocular Disease: Economic Impact](image)

$51.4 Billion
Estimated U.S. annual cost of care for those who are visually impaired or blind.\(^3\)

$570 Million
Annual portion of U.S. direct medical costs due to age-related macular degeneration.\(^3\)

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April 2013: InVivo Therapeutics announced that the Company has received approval for its request filed with the U.S. Food and Drug Administration for Humanitarian Use Device designation for its biopolymer scaffolding product. InVivo has received designation for the use of its biopolymer scaffolding for the treatment of recent complete spinal cord injury (no motor or sensory function) that does not involve penetrating injury or complete severing of the spinal cord.

February 2013: Kiadis Pharma B.V. receives the No Objection Letter from Health Canada for its new clinical study with ATIR. This study will be a Phase 2 international multi-center study with clinical sites in Canada and Belgium. ATIR is a cell-based product designed to enable stem cell transplantations from mismatched family donors.

February 2013: Gamida Cell announces the successful results of the Phase 1/2 study of its second pipeline product NiCord, and that StemEx reached its primary endpoint of improving overall survival in a Phase 2/3 study which compared the use of StemEx as part of a transplantation regimen to historical controls in the treatment of patients with hematological malignancies such as leukemia and lymphoma.

February 2013: BrainStorm Cell Therapeutics first patient began treatment in the company’s Phase 2a dose-escalating clinical trial for ALS. The trial will evaluate the safety and preliminary efficacy of BrainStorm’s NurOwn stem cell therapy candidate.

February 2013: Shire Regenerative Medicine initiates a Phase 3 study designed to evaluate the efficacy and safety of ABH001, its dermal substitute therapy, for the treatment of non-healing wounds in patients with Epidermolysis Bullosa.

January 2013: Arteriocyte receive approval from the Food and Drug Administration to initiate a Phase 1 clinical trial using its Magellan System technology in the treatment of thermal burn wounds.

January 2013: ImmunoCellular Therapeutics, Ltd. announces that the U.S. Food and Drug Administration has allowed the investigational new drug (IND) application for ICT-140, a dendritic cell vaccine targeting seven antigens that are over-expressed in ovarian cancer, as well as cancer stem cells.

January 2013: SanBio Inc. announces the successful enrollment of the second dose cohort of patients in its Phase 1/2a clinical trial testing the safety and efficacy of an allogeneic stem cell therapy product, SB623, in patients suffering from chronic deficits resulting from previous stroke injuries.
**January 2013:** Neuralstem, Inc. receives approval from the United States Food and Drug Administration to commence a Phase 1 safety trial of its lead cell therapy candidate, NSI-566, in chronic spinal cord injury patients.

**January 2013:** Mesoblast Limited announces that its Phase 2 clinical trial for lumbar spinal fusion had successfully met its safety and efficacy endpoints. These results support the progression of clinical development of NeoFuse to a Phase 3 trial in interbody lumbar fusion.

**December 2012:** Cytomedix, Inc. signs an agreement with NIH to collaborate on a Phase 2 clinical study in patients with intermittent claudication.

**November 2012:** Fate Therapeutics, Inc. initiates a randomized, controlled, Phase 2 multi-center study of its investigational hematopoietic stem cell therapy, ProHema, in adult patients undergoing double umbilical cord blood transplantation for hematologic malignancy.

**November 2012:** Cardio3BioSciences receives authorization from the Belgian Federal Agency for Medicines and Health Products (FAMHP) to begin its Congestive Heart failure Cardiopoietic Regenerative Therapy (CHART-1) European Phase 3 trial for C3BS-CQR-1 in Belgium.

**October 2012:** ISTO Technologies, Inc. initiates a Phase 2 trial to further evaluate the efficacy and safety of its NuQu cell-based therapy for the treatment of pain and disability associated with degenerated spinal discs.

**October 2012:** Histogen, Inc. presents preliminary data from the ongoing clinical trial of its Hair Stimulating Complex at the International Society of Hair Restoration Surgery Annual Meeting. Statistically significant improvement was seen across all targeted hair growth parameters in this Phase 1/2 clinical trial, with an 86% responder rate.

**October 2012:** Cytori Therapeutics announces the initiation of the FDA approved ATHENA clinical trial to investigate Cytori’s cell therapy in patients who suffer from a severe form of refractory heart failure due to chronic myocardial ischemia.

**October 2012:** NeoStem publishes evidence that AMR-001, NeoStem’s lead product candidate through its Amorcyte subsidiary, appears capable of preserving heart muscle function following a large myocardial infarction. Amorcyte demonstrated in its Phase 1 trial that AMR-001 preserved heart muscle function when a therapeutic dose of cells was administered. The new study shows that cardiac muscle function sparing effects are evident even earlier after treatment than previously shown.

**October 2012:** Calimmune received clearance from the FDA to launch its first-in-human Phase 1/2 clinical trial of the Cal-1 cell-mediated gene therapy for HIV. Cal-1 is a combination of siRNA against the CCR5 HIV co-receptor and a membrane-bound fusion inhibitor which will be delivered to both T-cells and hematopoietic stem cells. The trial will be conducted at two sites in California and will recruit a total of 12 patients.

**September 2012:** StemCells, Inc. announces that the first patient with an incomplete spinal cord injury has been enrolled in the Company’s Phase 1/2 clinical trial in chronic spinal cord injury and transplanted with the Company’s proprietary HuCNS-SC neural stem cells.

**September 2012:** Healthpoint Biotherapeutics initiates a Phase 3 clinical trial investigating the efficacy of HP802-247 for the treatment of venous leg ulcers. HP802-247 is an investigational allogeneic living cell bioformulation containing keratinocytes and fibroblasts.

**September 2012:** Shire plc announces that its lead regenerative medicine product, DERMAGRAFT, has received regulatory approval from Health Canada as a class IV medical device for the treatment of diabetic foot ulcers, a complication of diabetes.
September 2012: AlloCure, Inc. initiates a Phase 2 clinical trial of AC607, the company’s mesenchymal stem cell therapy, as a potential treatment for acute kidney injury. The randomized, double-blind, placebo-controlled, multi-center trial will enroll 200 cardiac surgery subjects at leading tertiary care centers in the United States.

August 2012: Neuralstem, Inc. completes the Phase 1 trial of its NSI-566 spinal cord neural stem cells for the treatment of ALS with the eighteenth patient treated.

August 2012: TiGenix completes patient enrollment in the Company’s Phase 2a study of Cx611, a suspension of expanded allogeneic adult stem cells, in rheumatoid arthritis. The Phase 2a clinical trial is designed to assess safety, feasibility, tolerance, and optimal dosing.

August 2012: Pluristem Therapeutics, Inc. receives approval from the Paul-Ehrlich-Institute, the medical regulatory body in Germany, to commence a Phase 1/2 randomized, double blind, placebo controlled study to assess the safety and efficacy of its PLX cells, through intramuscular injections, for the regeneration of injured gluteal musculature following total hip replacement.

July 2012: TiGenix enrolls the first patients in the ADMIRE-CD trial, its pivotal Phase 3 clinical trial with Cx601 in perianal fistulas in Crohn’s disease patients at Hospital Clínic, Barcelona, Spain.

June 2012: Harvard Bioscience, Inc. announces positive preliminary results from its ongoing clinical trial of StrataGraft, a universal human skin substitute being developed for the treatment of severe burns.
Many financial analysts now believe that regenerative medicine is at the stage of development where monoclonal antibody therapeutics were a 15 years ago—at an inflection point of clinical validation.

At the same time, pharma is in the process of retrenching and redefining its business model. Rather than build, they would rather buy and seek opportunities to acquire clinically validated novel therapeutics. According to Burrill & Company, major U.S. drug companies lost approximately $21 billion in revenue last year from lucrative medicines coming off patent (European businesses about $10 billion). At the same time, some companies significantly cut back on internal research and development programs.

The field of regenerative medicine is comprised of an estimated 120 public and 600 private companies as well as a plethora of universities. This vital community of major research institutions and companies are succeeding in advancing both the basic science and its translation into clinical testing and commercial products.

### Sector Activity

The sector delivered three $1 billion thresholds in 2012:

- Over $1.2 billion was raised through a combination of grants, public and private monies to further the field
- Sector transactions with large biopharma and device companies such as Smith & Nephew, Royal DSM and Shire totaled just under $1.1 billion in transactions
- Approved products generated approximately $1 billion in revenues
Public Company Performance

In an effort to better understand the performance of public regenerative medicine companies, ARM is working in collaboration with the Canadian Center for Commercialization of Regenerative Medicine (CCRM) to produce an unweighted stock performance index that includes 29 publicly traded regenerative medicine companies with market caps above $10 million. The corresponding table provides select performance metrics for each of the companies in the index and two trend charts comparing regenerative medicine companies against the S&P500, S&P 500 Biotech, the NASDAQ and the NASDAQ Biotech indices from March of 2012 through March of 2013.

Comparison of S&P to Unweighted Regenerative Medicine Index

![Graph showing comparison of S&P to Unweighted Regenerative Medicine Index]

Comparison of NASDAQ to Unweighted Regenerative Medicine Index

![Graph showing comparison of NASDAQ to Unweighted Regenerative Medicine Index]
More pharma companies are deciding to acquire or invest strategically in profitable or late-stage clinical regenerative medicine companies.

Companies Included in the Unweighted Regenerative Medicine Index

<table>
<thead>
<tr>
<th>Company</th>
<th>Ticker</th>
<th>Price Mar 13, 2013</th>
<th>52 Week Range</th>
<th>YTD</th>
<th>Market Cap ($ million)</th>
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<tbody>
<tr>
<td>Mesoblast Limited</td>
<td>MSB</td>
<td>$6.37</td>
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<td>Medipost Co., Ltd</td>
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<td>$4.13–$10.80</td>
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<td>$0.04</td>
<td>$0.03–$0.09</td>
<td>26.4%</td>
<td>$32</td>
</tr>
<tr>
<td>International Stem Cell Corporation</td>
<td>ISCO</td>
<td>$0.27</td>
<td>$0.17–$0.64</td>
<td>35.0%</td>
<td>$24</td>
</tr>
<tr>
<td>BioLife Solutions, Inc.</td>
<td>BLFS</td>
<td>$0.30</td>
<td>$0.07–$0.45</td>
<td>(11.8%)</td>
<td>$21</td>
</tr>
<tr>
<td>Living Cell Technologies</td>
<td>LCT</td>
<td>$0.05</td>
<td>$0.05–$0.12</td>
<td>(6.6%)</td>
<td>$17</td>
</tr>
<tr>
<td>Vistagen Therapeutics</td>
<td>VSTA</td>
<td>$0.80</td>
<td>$0.50–$2.80</td>
<td>9.6%</td>
<td>$16</td>
</tr>
<tr>
<td>Thermogenesis</td>
<td>KOOL</td>
<td>$0.83</td>
<td>$0.67–$1.29</td>
<td>(1.0%)</td>
<td>$14</td>
</tr>
</tbody>
</table>
More regenerative medicine companies are attracting investor interest

ARM and the Cell Therapy Group both report that cell therapy and cell-based regenerative medicine companies raised just over $1.2 billion in 2012. While 25 percent of this money came from grant sources, just over $900 million was raised from investors. While there is no baseline historical data to assess whether this is a milestone, most analysts and industry insiders believe this is undoubtedly an industry first.

Companies that raised $25 million or more from investors in 2012 include Fibrocell Sciences, Advanced Cell Technology, Aastrom Biosciences, Allocure, China Cord Blood Bank, Vital Therapies, Promethera Biosciences, Argos Therapeutics, Coronado Biosciences, Histogenics and bluebird bio.

Companies that raised a similar amount from grant sources include Cytori Therapeutics, Cellerant, and StemCells Inc. The first two sourced their grants from BARDA (Biomedical Advanced Research and Development Authority, within the U.S. Federal Government’s Office of the Assistant Secretary for Preparedness and Response) and the latter via two grants from CIRM (California Institute of Regenerative Medicine).

It is worth mentioning that 2012 also represented a pivotal year in CIRM’s funding focus, as it committed increased funding to regenerative medicine companies—a decision embraced by ARM and one necessary to bridge the funding gap for companies focused on clinical development for disease areas with high unmet need. In 2012, CIRM granted $80 million in funding to cell therapy companies and it is anticipated the agency will continue this trend in the coming years.

Large biopharma, device and life science companies with little previous focus in regenerative medicine are increasing their investment, licensing and acquisition activity in the sector

Since our last industry report which tracked deals through March of 2012, we’ve seen significant transaction activity in the sector from large biopharma, device and life science companies:

**April 2012:** Cook Group acquires assets of General Biotechnology

**April 2012:** Shire Pharmaceuticals acquires assets of Pervasis Therapeutics

**August 2012:** Novartis executes license and co-development deal with University of Pennsylvania

**November 2012:** Smith & Nephew acquires Healthpoint

**December 2012:** Ostuka Pharmaceutical signs license and co-development deal with Living Cell Technologies

**March 2013:** Merck Serono executes license with Opexa Therapeutics

Since March of 2012 there have been a significant number of transactions in the sector involving large pharma, device and other large life sciences firms.
March 6, 2013: Mesoblast Limited enters into agreements to raise A$170 million through an issue of new fully paid shares at A$6.30, representing a 2.2 percent discount to the stock’s last traded price of A$6.44 on March 1, 2013. The shares will be placed to a select group of existing and new global institutional investors.

February 21, 2013: University of Texas spinoff company, StemBioSys, raises $2 million to test a new technique for culturing non-embryonic, mesenchymal stem cells in its XC-marrow ECM, a proprietary three-dimensional culture system for growing stem cells from bone marrow, adipose tissue and umbilical cord blood.

February 13, 2013: ViaCyte receives more funding for diabetes stem cell therapy. JDRF, a global organization focused on type 1 diabetes (T1D) research, and the California Institute for Regenerative Medicine (CIRM) agree to provide additional funding for the development of a novel stem cell therapy by ViaCyte. JDRF and CIRM will each contribute $3 million to further advance the project.

February 4, 2013: Stem Cell Therapeutics Corp. announces the execution of a Letter of Agreement with Trillium Therapeutics Inc. (“Trillium”) of Toronto, under which Trillium would be merged into Stem Cell Therapeutics Corp. by way of a three-cornered amalgamation or plan of arrangement with a newly-created SCT subsidiary.

February 4, 2013: NewLink Genetics Corporation announces the closing of its public offering of 4,000,000 shares of common stock plus the full exercise of options by its underwriters of an additional 600,000 shares. Aggregate net proceeds to the company were approximately $49.0 million.

January 7, 2013: BioTime, Inc. and its recently formed subsidiary, BioTime Acquisition Corporation (BAC), jointly announce today that they have entered into a definitive Asset Contribution Agreement with Geron Corporation to acquire their intellectual property, including patents and patent applications, and other assets related to Geron’s human embryonic stem (hES) cell programs.

December 20, 2012: TiGenix NV announces that it has raised EUR 6.7 million through a private placement. The private placement has allowed TiGenix to place 8,629,385 new shares with a wide range of domestic and international investors at a price of EUR 0.78 per share, a 9.30 percent discount on the average closing price of the TiGenix share over the 30 day period preceding December 20, 2012.

December 17, 2012: Living Cell Technologies Limited announces the signing of an agreement with Otsuka Pharmaceutical Factory, Inc. to co-develop NTCELL for the treatment of Parkinson’s disease and other neurological disorders.
December 14, 2012: Cytori Therapeutics, Inc. announces the sale of 7,020,000 shares of its common stock in an underwritten public offering at a price to the public of $2.85 per share. The net offering proceeds to Cytori from the sale of the shares are expected to be approximately $18.5 million excluding any exercise of the underwriters’ over-allotment option.

November 28, 2012: Smith & Nephew plc announces that it is strengthening its global position in advanced wound care by entering into an agreement through its subsidiaries to acquire substantially all of the assets of Healthpoint Biotherapeutics (“Healthpoint”), a leader in bioactive debridement, dermal repair and regeneration wound care treatments, for $782 million in cash.

November 26, 2012: TCell SA announces it raised EUR 12.4 million in a third financing round. This additional capital was provided by the InnoBio fund, managed by CDC Entreprises, for EUR 6 million and by TCell’s existing shareholders Auriga Partners and Seventure Partners. Capital will be used in developing cell-based immunotherapies for the treatment of severe chronic inflammatory diseases with high unmet medical need.

November 20, 2012: Kiadis Pharma B.V. announces it has raised EUR 10 million in an equity financing round. This round was led by the company’s largest shareholder LSP (Life Sciences Partners) and supported by a large investment from DFJ-Esprit. Other investors included Alta Partners, Quest for Growth and NOM. The financing will enable Kiadis Pharma to perform a confirmatory multi-center Phase 2 proof-of-concept study with its lead product ATIR, and to prepare a pivotal Phase 2/3 study.

November 8, 2012: Fibrocell Science, Inc. announces it has entered into a securities purchase agreement for a private placement financing with a select group of institutional investors and high net worth individuals, including NRM VII Holdings I, LLC, a Third Security LLC affiliated fund. Upon the closing of the transaction, Fibrocell will receive gross proceeds of $45.0 million from the sale of 450 million shares of common stock at a price of $0.10 per share. Proceeds will be focused on commercializing LAVIV, the first and only FDA-approved person-
alized cell therapy in aesthetic dermatology, and on developing innovative autologous cell therapies for additional aesthetic, medical and scientific applications.

October 8, 2012: Cellerant Therapeutics Inc., a biotechnology company developing novel hematopoietic stem cell-based cellular therapies for blood disorders and cancer, announces that it has been awarded a Small Business Innovation Research (SBIR) Phase 1 contract and a Phase 2 option from the National Cancer Institute (NCI) valued up to $1,683,503.

October 3, 2012: Tengion, Inc. announces the pricing of a private placement of $15.0 million aggregate principal amount of Senior Secured Convertible Notes (the “Notes”), with certain investors, including Celgene Corporation, RA Capital Management LLC, Deerfield Management Company, LP, Bay City Capital and HealthCap.

September 28, 2012: Cytori Therapeutics, Inc. is awarded a contract that may be valued up to $106 million by the U.S. Department of Health and Human Service’s Biomedical Advanced Research and Development Authority (BARDA), if all contract options are executed. The contract is for preclinical and clinical development of the company’s cell therapy for the treatment of thermal burns combined with radiation injury.

September 26, 2012: StemCells, Inc. announces that the California Institute for Regenerative Medicine (CIRM) has approved an award to the Company for up to $20 million under CIRM’s Disease Team Therapy Development Award program (RFA 10-05). The award is to fund preclinical development of StemCells’ proprietary HuCNS-SC product candidate (purified human neural stem cells) in Alzheimer’s disease over a maximum four-year period, with the goal of filing an investigational new drug (IND) application for a clinical trial in that time.

September 24, 2012: Pluristem Therapeutics Inc. announces the closing of the exercise in full of the underwriters’ option to purchase an additional 1,200,000 shares of common stock of the company. The underwriters previously exercised their option to purchase 1,200,000 warrants to purchase up to 420,000 of the company’s common stock at an exercise price of $5.00 per share, at a purchase price of $0.0094 per warrant and have now also exercised their option to purchase 1,200,000 shares of common stock at $3.7506 per share. The gross proceeds to the company as a result of the exercise of this option are approximately $4.5 million.

September 19, 2012: Pluristem Therapeutics, Inc. announces the closing of its previously announced underwritten public offering of 8,000,000 units, at a purchase price of $4.00 per unit, with each unit consisting of one share of the company’s common stock and one warrant to purchase 0.35 of a share of the company’s common stock, at an exercise price of $5.00 per share. The net proceeds to the company are approximately $30 million, assuming no exercise of the warrants and after deducting underwriting commissions and discounts and estimated offering expenses payable by the Company.

September 19, 2012: Neuralstem, Inc. announces the closing of a registered direct offering of 7,000,000 shares of its common stock, offered at a price of $1.00 per share. The gross proceeds to Neuralstem from this offering were $7,000,000, before deducting the placement agent fees and other estimated offering expenses payable by Neuralstem.

September 5, 2012: Capricor, Inc. announces that the California Institute for Regenerative Medicine (CIRM) has approved an award to the company for $19.782 million to support clinical testing of its allogeneic cell therapy for heart attack patients.

August 15, 2012: Neuralstem, Inc. announces the full exercise of the over-allotment option granted to the underwriters to purchase 900,000 additional common shares, at a public offering price of $0.40 per share, in connection with its previously announced underwritten public offering of 6,000,000 shares of common stock, bringing total gross proceeds from the offering to $2,760,000.
July 26, 2012: Opexa Therapeutics, Inc. announces the closing of a private offering of convertible secured promissory notes and warrants to purchase shares of common stock for gross proceeds of approximately $4 million. Opexa expects to use proceeds from the financing to commence its planned Phase 2b clinical study of Tcelna in patients with Secondary Progressive MS (SP-MS). Participating in the financing were new investors and existing shareholders, including members of Opexa’s Board of Directors.

July 26, 2012: StemCells, Inc. announces that the California Institute for Regenerative Medicine (CIRM) has approved an award to the company and its collaborators for up to $20 million under CIRM’s Disease Team Therapy Development Award program (RFA 10-05). The award is to fund preclinical development of StemCells’ proprietary HuCNS-SC product candidate as a potential treatment for cervical spinal cord injury. The award will provide funding over a maximum four-year period, with the goal of filing an investigational new drug (IND) application to begin clinical testing in that time.

July 25, 2012: bluebird bio announces the successful completion of a $60 million Series D financing. In this round, new investors Deerfield Partners, RA Capital, Ramius Capital Group and two undisclosed blue chip public investment funds joined existing investors ARCH Venture Partners, Third Rock Ventures, TVM Capital and Forbion Capital Partners. In addition, Shire plc joined the round as a strategic investor. Proceeds will be used to support the company’s development of innovative gene therapies for severe genetic disorders.

July 24, 2012: Histogenics Corporation announces the completion of a $49 million round of financing. The syndicate was led by Sofinnova Ventures with participation from additional new investors Split Rock Partners, BioMed Ventures and FinTech GIMV Fund, L.P. Existing investors ProChon Holdings BV, Altima Partners, Foundation Medical Partners, Inflection Point Capital and Boston Millennia Partners also participated in the financing. Proceeds will be use to support the company’s commercial development of transformational cartilage repair products.

July 19, 2012: BrainStorm Cell Therapeutics Inc. announces it completed a registered public offering of 19,818,972 shares of common stock at a price per share of $0.29 and warrants to purchase 14,864,229 shares of common stock at an exercise price of $0.29 per share, representing gross proceeds of $5,747,502. The company plans to use the net proceeds from the offering for clinical trials in the United States and Israel, research and development, working capital needs, capital expenditures and other general corporate purposes.

July 16, 2012: Juventas Therapeutics announces it has closed a $22.2 million Series B financing that was co-led by Triathlon Medical Venture Partners and New Science Ventures. All previous venture firms, including Fletcher Spaght Ventures, Reservoir Venture Partners and Early Stage Partners participated in the round. Also joining the syndicate are new investors Takeda Ventures, Venture Investors, Global Cardiovascular Innovation Center, Tri-State Growth Fund, Glengary and select angel investors.

June 27, 2012: Coronado Biosciences, Inc. announces it closed its previously announced underwritten public offering of 5,750,000 shares of its common stock at a price to the public of $5.00 per share for gross proceeds to Coronado of $28.8 million. The shares include 750,000 shares of common stock sold pursuant to the over-allotment option granted by Coronado to the underwriters, which option was exercised in full. Coronado expects net proceeds of the offering will be approximately $26.5 million, after deducting underwriting commissions and other offering expenses. Proceeds will be used for the development of novel immunotherapy biologic agents for the treatment of autoimmune diseases and cancer.
May 15, 2012: Gamida Cell announces it closed a $10 million Series E financing round earmarked to support the global commercialization of the company’s lead product StemEx for leukemia and lymphoma. All major shareholders participated. The company is currently seeking a strategic partner to join in the global commercialization of StemEx.

May 3, 2012: Kensey Nash, a medical device company primarily focused on regenerative medicine, announces that it has entered into a definitive agreement with Royal DSM (DSM), under which DSM has agreed to acquire all of the common stock of Kensey Nash through a cash tender offer, followed by a merger with a subsidiary of DSM, for $38.50 per share in cash.

April 27, 2012: ReNeuron Group plc announces the company has raised gross proceeds of approximately £5.4 million by means of a placing through the issue of 134,037,500 Placing Shares at 4p per share. In addition the company provided all qualifying shareholders with the opportunity to subscribe, also at 4p per share, for an aggregate of up to 99,744,494 Open Offer Shares.

April 26, 2012: Innovacell raises EUR 8.3 million to dedicate to developing cell therapy for the treatment of stress-urinary incontinence (ICES13) and faecal incontinence. This will take effect in two tranches. The main shareholders are the financial investors Buschier, Fides, HYBAG and the private equity firm, uni venture.

April 25, 2012: Argos Therapeutics Inc. announces it has secured a $25 million Series D financing to support the commencement of its Phase 3 ADAPT study in patients with newly diagnosed, metastatic renal cell carcinoma (mRCC) in mid-2012. The financing was led by Forbion Capital and included other existing investors, TVM Capital, Lumira Capital, Intersouth Partners, and the private equity firm, uni venture.

April 12, 2012: Shire plc announces it has signed an agreement to acquire substantially all of the assets of Pervasis Therapeutics, adding a new technology platform and Phase 2 product candidate to its regenerative medicine business. Shire will provide Pervasis with an upfront payment, plus potential post-closing milestone payments that are dependent on Shire’s achievement of certain clinical development, regulatory and sales targets.

April 5, 2012: NeoStem, Inc. announces the closing of its previously announced underwritten public offering of 15,000,000 units and the exercise of the over-allotment option by the underwriter for an additional 2,000,000 units, bringing the total units offered to 17,000,000. The offering was priced at $0.40 per unit. Each unit consists of one share of common stock and a warrant to purchase one share of common.

April 2, 2012: AlloCure, Inc. announces the closing of a $25 million Series B venture financing. The round included the participation of new syndicate member Lundbeckfond Ventures, as well as previous investors SV Life Sciences and Novo A/S. Proceeds will be used on continued development of the company’s lead product for the treatment of kidney disease.

Regenerative medicines are being tested for almost every imaginable human condition ranging from large-scale indications like chronic heart failure, cancer and diabetes to orphan indications for which there are little-to-no available treatments.
Officers and Executive Committee

Geoff MacKay, Chair
President & Chief Executive Officer,
Organogenesis Inc.

Keith Murphy, Vice-Chair
Chairman & Chief Executive Officer, Organovo

Martin McGlynn, Secretary
President & Chief Executive Officer, StemCells, Inc.

Edward Field, Treasurer
Chief Operating Officer, Cytomedix, Inc.

Gil Van Bokkelen, Ex-Officio
Chairman & Chief Executive Officer, Athersys, Inc.

Anthony Atala
Director, Wake Forest Institute
for Regenerative Medicine

Christopher Calhoun
Chief Executive Officer, Cytori Therapeutics Inc.

Leanna Caron
Vice President & General Manager,
Cell Therapy & Regenerative Medicine,
Sanofi-Genzyme

Douglas Doerfler
President & Chief Executive Officer, MaxCyte

Silviu Itescu
Managing Director & Chief Executive Officer,
Mesoblast Limited

Edward Lanphier
President & Chief Executive Officer,
Sangamo BioSciences, Inc.

Robert Preti
President & Chief Scientific Officer,
Progenitor Cell Therapy

Amy Comstock-Rick
Chief Executive Officer, Parkinson’s Action Network

Robert Shaw
Commercial Director, Stem Cell Initiative,
EMD Millipore Corporation

Bernard Siegel
Executive Director, Genetics Policy Institute

Jay Siegel
Chief Biotechnology Officer, Johnson & Johnson

David Smith
Head, Cell Therapy, Lonza Group Ltd.

Devyn Smith
Chief Operating Officer, Neusentis Research Unit,
Pfizer Inc.

Susan Solomon
Chief Executive Officer,
New York Stem Cell Foundation

Matthias Steger
Global Head Research & Technology Partnering,
F. Hoffman-La Roche Ltd

Dean Tozer
Vice President, Corporate Development,
Shire Regenerative Medicine

Alan Trounson
President, California Institute
for Regenerative Medicine

Matthew Vincent
Director, Business Development,
Advanced Cell Technology, Inc.

Claudia Zylberberg
President & CEO, Akron Biotechnology, LLC
Regenerative medicine represents a new paradigm in human health with the potential to resolve unmet medical needs by addressing the underlying causes of disease.

Standing Committees

**Capital Formation and Business Development**
Chair: Edward Field, Chief Operating Officer, Cytomedix, Inc.

Timely access to capital is essential to the success of this sector and is another focal point of ARM’s activities. ARM helps its members identify prospective investors and partners in addition to non-traditional sources of capital that are essential to the successful translation and development of new technologies. We also provide unique opportunities for our pharma and large-cap biotech members to meet and interact with the top researchers, and therapeutic developers in the sector.

**Communications and Education**
Co-Chairs: Lee Buckler, Managing Director, Cell Therapy Group; Julie Meldrum, Director, Corporate Communications, Mesoblast Limited

ARM plays a vital role in making sure key stakeholders have access to consistent, accurate, and useful information about the advancements of technologies in the sector. We supply data, including analysis of clinical progress, financial information, economic impact, and technology summaries to our members and to other selected audiences. We interact regularly with the media and recommend industry and clinical experts to provide insight on major developments affecting the sector. Finally, we provide on-line resources, including interactive forums, for our members to exchange ideas with their peers and to interact with other key interest groups.

**Government Relations and Policy**
Chair: Susan Solomon, Chief Executive Officer, New York Stem Cell Foundation

Regenerative medicine and advanced therapies are high profile sectors that are the focus of healthcare investment initiatives in countries around the world. ARM is the only advocacy organization in the U.S. and operating globally working to make sure that policies and regulations affecting our sector are helpful and not an impediment.

**Operations and Governance**
Co-Chairs: Martin McGlynn, President & Chief Executive Officer, StemCells, Inc.; Keith Murphy, Chairman & Chief Executive Officer, Organovo

**Regulatory**
Chair: Kathy Tsokas, Senior Director, Regulatory Affairs, Johnson & Johnson

The ARM Regulatory Committee focuses on issues of importance to the regenerative medicines industry. Our overall objective is a clear, predictable regulatory pathway to allow safe and effective Regenerative Medicine products to reach the market as soon as possible. To achieve that objective, ARM works with its members and collaboratively with the FDA to identify obstacles to commercialization and to develop and execute regulatory strategies to address them.

Based on our work, research, and communication with FDA, ARM has identified a few significant regulatory challenges. They are: improved communication between sponsors and FDA; developing streamlined and clear market pathways for safe and effective regenerative medicine products; development and adoption of agreed-upon standards for pre-clinical issues such as animal models; and harmonization of regulatory requirements between FDA, EMA and other regulatory bodies.

The ARM Regulatory Committee impacts upon the regulatory landscape for regenerative medicine by:
1) communicating with regulators; 2) developing workshops and position papers.

**Reimbursement**
Chair: Theresa Dixon, Vice President, Government Affairs & Health Economics, Shire Regenerative Medicine

The ARM Reimbursement Committee’s objective is a reimbursement system that rewards innovation and fosters the development of regenerative medicine technologies. Achieving that objective requires a multi-faceted approach that combines education about the reimbursement process, helping payers understand regenerative medicine technologies and their potential, and public policy advocacy. To that end, the Committee’s work includes helping

continued on page 66
member organizations understand Medicare and private payer processes, developing relationships with private and public payers to further mutual understanding and to engage in education programs, working with other organizations on reimbursement models, and developing positions on important policy reimbursement issues confronting the industry. The Committee is a resource for ARM members to help them navigate reimbursement issues. The Committee also works with CMS and private insurers to help companies achieve appropriate reimbursement for their products by improving mutual understanding between the industry and payers. Moreover, the committee has engaged in public policy discussions on key issues. For example, last year, ARM developed a position paper and filed formal comments with the Patient Centered Outcomes Research Institute (PCORI) in response to PCORI’s draft report on comparative effectiveness research. In 2013 the Committee will take steps to help companies understand and prepare for these delivery and payment reforms, as well as develop position papers that explain how to ensure that innovative therapies are reimbursed appropriately under a reformed Medicare system.

Science and Technology
Co-Chairs: Dolores Baksh, Director, Research & Development, Organogenesis Inc.; Robert Deans, Executive Vice President, Regenerative Medicine, Athersys, Inc.; Robert Preti, President & Chief Scientific Officer, Progenitor Cell Therapy
The Science and Technology Committee of ARM, with more than 80 active members, is comprised of leading technical experts, engineers, and manufacturing experts who convene to address major developmental and commercialization hurdles in the sector. The Committee leads several programs dedicated to the development of standards and best practices in cell characterization, assay development, and manufacturing QC. It meets regularly with the FDA and is conducting workshops to ensure timely and productive exchange of experiences and expertise as future guidelines are established. The S&T Committee also interacts with important societies such as the ISCT, ISSCR, ASTM, FACT and others that are major contributors to this process. Finally, the S&T committee is also a forum for discussion about breakthrough drug discovery technologies involving the use of pluripotent stem cells and tissue models that are significantly improving our ability to predict how new therapies will behave in the clinic.

Tissue Engineering and Biomaterials
Co-Chairs: Michael Abecassis, Chief, Division of Transplantation, Northwestern Memorial Hospital; Jennifer Elisseeff, Professor, Ophthalmology & Biomedical Engineering, Johns Hopkins University; Robert Palay, Chief Executive Officer, Cellular Dynamics International
The TEBC’s primary mission is to develop a better understanding of the key barriers to translation and scale-up of tissue-engineered and biomaterial-based technologies, including challenges in efficient product design, pilot and scale-up manufacturing, regulation and reimbursement. Through this analysis, we hope to accelerate the development and commercialization of these novel regenerative medicine products and create a robust dialogue amongst key stakeholders: regulators, product developers, patients, physicians and investors. Presently, the Committee is focused on a detailed analysis of the tissue engineering landscape; this project, entitled Challenges in Tissue Engineering: Design to Delivery, will ultimately describe the state of the industry and the present day challenges across numerous tissues.

We need to rely on innovative solutions and technologies that mitigate chronic healthcare-related costs, lessen chronic care and improve patients’ quality of life.
Members of ARM

Companies
Aastrom Biosciences, Inc.
Aderans Research Institute
Advanced Cell & Gene Therapy, LLC
Advanced Cell Technology, Inc.
Akron Biotechnology, LLC
AlloCure, Inc.
AlloSource
American CryoStem Corporation
Amorcyte, Inc.
Athersys, Inc.
Avita Medical Ltd.
AxoGen, Inc.
Baxter International Inc.
Beckman Coulter, Inc.
Bell Biosystems, Inc.
BioLife Solutions, Inc.
BioSpherix, Ltd.
BioTime, Inc.
Blood Centers of America Inc.
bluebird bio
Brainstorm Cell Therapeutics
Calimmune
Capricor, Inc.
Celgene Corporation
Cell Line Genetics, Inc.
Cell Therapy Group
Cellerant Therapeutics, Inc.
CellGenix GmbH
Cellular Dynamics International
Cellular Technology Limited
Celsense Inc.
Circle Biologics, Inc.
Clinical Trial & Consulting Services
Cord Blood Registry
Cytomedix, Inc.
Cytori Therapeutics Inc.
DiscGenics, Inc.
EMD Millipore Corporation
Eqalix, Inc.
F. Hoffman-La Roche Ltd.
Fate Therapeutics
Fibralign Corporation
Fisher BioServices
GE Healthcare
GenVec, Inc.
Harvard Bioscience, Inc.
Healthpoint Biotherapeutics
HemoGenix
Histogenics
Humacyte, Inc.
Invitech Pty. Ltd.
InVivo Therapeutics Corporation
iPierian Inc.
ISTO Technologies
Johnson & Johnson

Membership Breakdown by Industry

<table>
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<th>Industry</th>
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<tr>
<td>Therapeutic Companies</td>
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<tr>
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<tr>
<td>Tissue Engineering, Biomaterials &amp; Devices</td>
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<tr>
<td>Academic/Research Institutions</td>
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<tr>
<td>Pharma</td>
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<td>Capital Providers/Other Financial Institutions</td>
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<tr>
<td>Banking</td>
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<tr>
<td>Third Party Payers</td>
<td>1%</td>
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<td>Total Membership</td>
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ARM Membership continued


Capital Providers/ Other Financial Institutions
Asset Management Ventures Kentucky Seed Capital Fund Novitas Capital Toucan Capital Triathlon Medical Ventures Academic/Research Institutions Johns Hopkins Translational Tissue Engineering McGowan Institute for Regenerative Medicine Northwestern University Comprehensive Transplant Center Neural Stem Cell Institute Sanford Burnham Medical Research Institute Texas Heart Institute University College London, Centre for Stem Cells & Regenerative Medicine University of Louisville, Cardiovascular Innovation Institute University of Utah, Cell Therapy & Regenerative Medicine Program Wake Forest Institute for Regenerative Medicine Patient Advocates/ Foundations/Associations Association of Clinical Research Organizations Alpha-1 Foundation ALS Association California Institute for Regenerative Medicine Californians for Cures Cell Society Centre for Commercialization of Regenerative Medicine Friends of Cancer Research Genetics Policy Institute Gift of Hope Human Organ Project, Inc. JDRF Missouri Cures Nebraska Coalition for Lifesaving Cures New York Stem Cell Foundation Parkinson's Action Network Regenerative Medicine Foundation South Texas Blood and Tissue Center Student Society for Stem Cell Research Texas Cures Education Foundation Unite 2 Fight Paralysis Affiliate Blue Cross Blue Shield Association

European Affiliates
Aposcience AG Intercytex Ltd. Pharmacel ReNeuron Group plc Sistemic Scotland Limited TiGenix NV

ARM Staff
Michael Werner Executive Director Morrie Ruffin Managing Director Bethany Kraynack Vice President, Operations Robert Margolin Vice President, Communications Luke Thorstenson Director, Membership & Advocacy Laura Parsons Director, Marketing & Events Sarah Haecker Director, TEBC