A vertical strip on the left side of the page features a microscopic image of several yellow, spherical cells. The cells have a textured, porous surface and are set against a dark green background. The central cell is in sharp focus, while others are blurred in the foreground and background.

Alliance for Regenerative Medicine

Annual Industry Report
2012

ALLIANCE_{for}
Regenerative Medicine

A Letter from the Chairman



Gil Van Bokkelen, Ph.D.

Chairman and CEO, Athersys, Inc.
Chairman, Alliance for Regenerative Medicine

Dear Friends and Colleagues of the Alliance:
I am delighted to state that the Alliance for Regenerative Medicine's *2012 Annual Industry Report* is our first such effort. I invite you to browse its pages for valuable and exciting information about advancements in regenerative medicine, the state of the industry and progress made by the Alliance in our many initiatives to promote a thriving industry and a new future for healthcare.

The common bond that ties together members of the Alliance is our unwavering commitment to revolutionizing medicine as we know it. We envision a future where cell therapy, tissue engineering and other forms of regenerative medicine will be used to treat, or even cure, diseases and conditions that are currently untreatable or resistant to current therapies. We know regenerative medicine technologies have the potential to redefine diseases that most burden our healthcare systems and our very way of life: heart disease, stroke and other neurological conditions, inflammatory and immune disease, diabetes, kidney disease and traumatic injury, as well as major surgeries and other areas that traditional medicine has failed to address.

We are confronted with a rapidly aging population, extraordinary increases in chronic and serious disease and increasingly serious resource constraints. If nothing changes, we face a future of limited healthcare resources,

dependent care challenges we cannot effectively manage and ultimately rationing or other limits on healthcare.

Few people have the desire or will to take on challenges so enormous they could fundamentally change the world for the better, and fewer still have the opportunity to actually do it. The Alliance for Regenerative Medicine represents an industry with the will and the opportunity to change human health. We share an unshakable belief in the transformational power of the technologies we are developing and a tenacious commitment to seeing our vision become a reality for patients around the world.

With innovative cell therapy and regenerative medicine technologies that improve clinical outcomes, enhance patient quality of life and reduce healthcare costs, we can achieve the future we envision. While there will be the inevitable disappointments along the way, we are making steady, and in some cases dramatic, progress towards achieving our goals.

Defining ways in which we can work together as members and supporters of the Alliance is critical—and advocating for regenerative medicine is among the most important. Together we can make a difference, and I'm proud to represent and be part of the Alliance. Thanks again for your support.

Best regards,



We are on the Brink of a New Era of Medicine

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

Regenerative medicine research translates fundamental knowledge in biology, chemistry and physics into materials, devices, systems and a variety of therapeutic strategies which augment, repair, replace or regenerate organs and tissues. This rapidly evolving, interdisciplinary field in healthcare is transforming the practice of medicine, medical innovation and the production of medical devices and therapies.

Why Is Regenerative Medicine So 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—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.

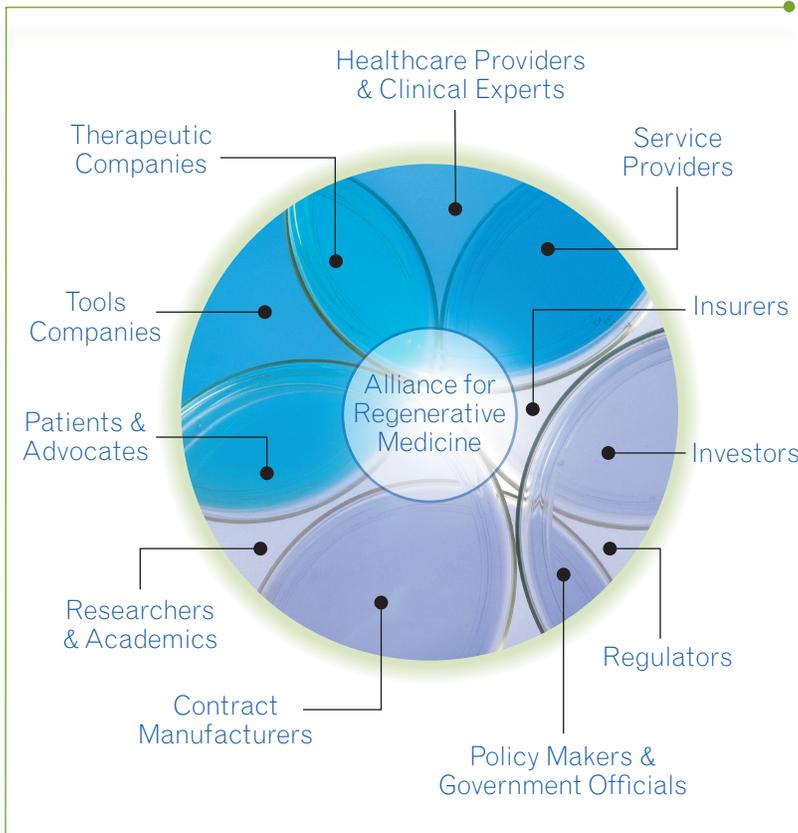
Stakeholder Coordination—A Critical Factor for Success

Delivering cures through regenerative medicine requires coordination amongst a broad range of stakeholder groups from industry, academia, government, healthcare professionals, the investment community and consumer advocates. The Alliance for Regenerative Medicine is the voice for these groups, drawing them together to create an influential and unified community that is paving the way for a healthier future with many new life saving therapies.

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. At the same time, new data are becoming available from late-stage clinical trials of regenerative medicines to treat cardiovascular disease, stroke, ALS, critical limb ischemia, cancer and a number of debilitating autoimmune diseases. As these results become known, they will dramatically heighten

Regenerative Medicine Stakeholders



awareness around regenerative medicine and reinforced the profound impact it could have on our healthcare system.

Additionally, companies such as GE Healthcare and Cellular Dynamics International—the Gold winner of the 2011 Wall Street Journal’s Technology Awards Contest—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.

Recent advancements at the federal level include bipartisan congressional support for the Regenerative Medicine Promotion Act (HR 1862), the first national initiative to support regenerative medicine. The National Institute of Standards and Technology received funding in the 2012 Appropriations bill and encouragement from the House to conduct research addressing standards and measurement for regenerative medicine technologies. Additionally, the National Institutes of Health established a Center for Regenerative Medicine to advance translational research. At the state level, the California Institute for Regenerative Medicine formed twelve international agency partnerships to fund cutting-edge translational research. We are energized by these developments and see them as building blocks toward the establishment of a coordinated national strategy for regenerative medicine. This will be a key focus of our advocacy efforts in 2012 and beyond.

Payers are beginning to recognize the encompassing potential of regenerative medicine. Further, as data are released from the late-, mid- and early-stage clinical trials that have enrolled more than 17,000 patients, significant advancements will be seen in pharmacoeconomic models reflecting the breadth and depth of economic transformation through regenerative medicine.

Patients and advocates of regenerative medicine continue to inspire and urge us on each day. We are grateful to organizations such as the New York Stem Cell Foundation, which recently received *Time* magazine’s scientific discovery of the year award; the Juvenile Diabetes Research Foundation; the Parkinson’s Action Network; and the Genetics Policy Institute. Thanks to organizations like these, the patient advocacy community continues to remain unified and fund critical translational research.

Industry Overview



The Alliance estimates the industry to include more than 700 companies focused on regenerative medicine technologies and services.

With 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.

Including 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 healing and regeneration in diseased tissue
- To deliver small molecule therapies to targeted areas

Small Molecules and Biologics

The use of chemicals and cellular components that are known to induce dormant cells to regain regenerative properties.

And 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.

An Expansive and Growing Industry

The regenerative medicine industry represents a vast network of interdisciplinary companies working in biology, chemistry, engineering and physical sciences. These companies are developing some of the world's most advanced therapies, tools and services in medicine today, and addressing many unmet medical needs.

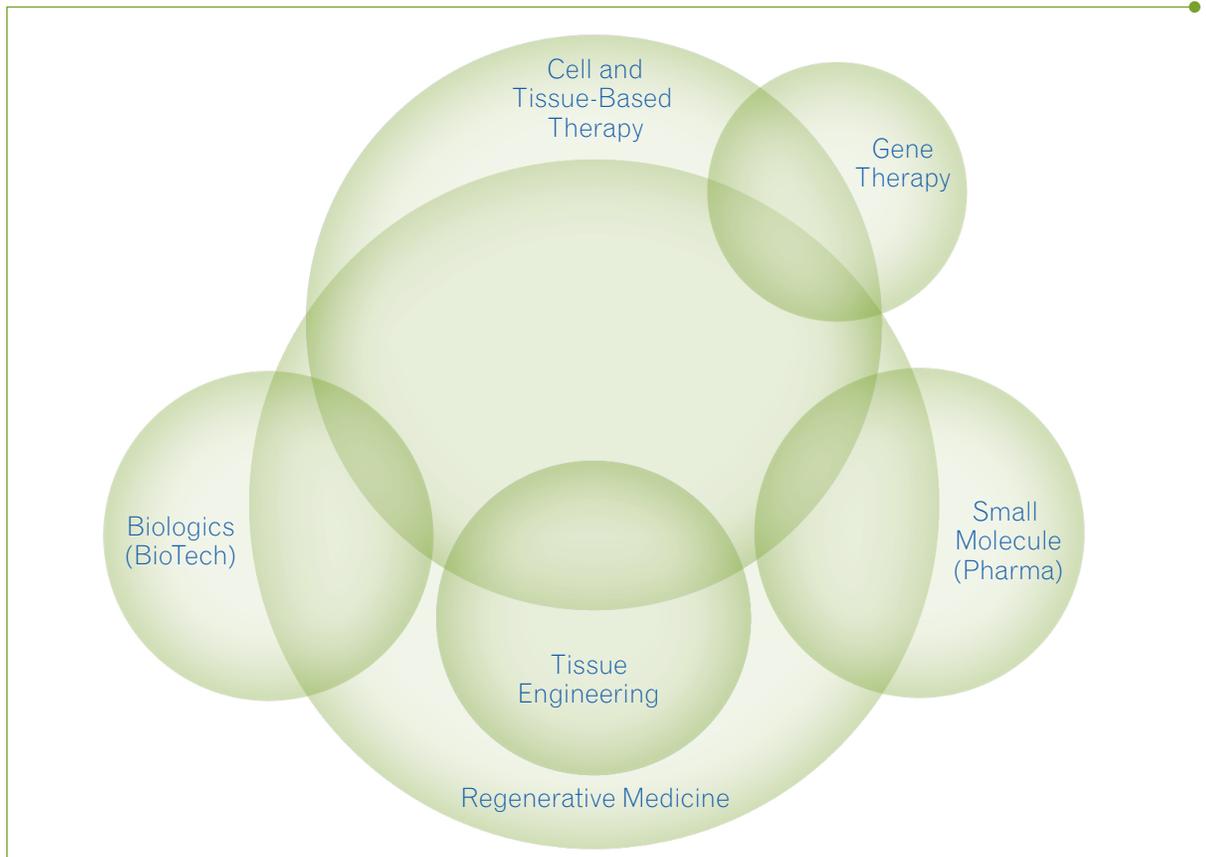
As of 2012, the Alliance estimates the industry to include more than 700 companies ranging from divisions of multinational corporations to smaller organizations focused solely on regenerative medicine technologies.

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

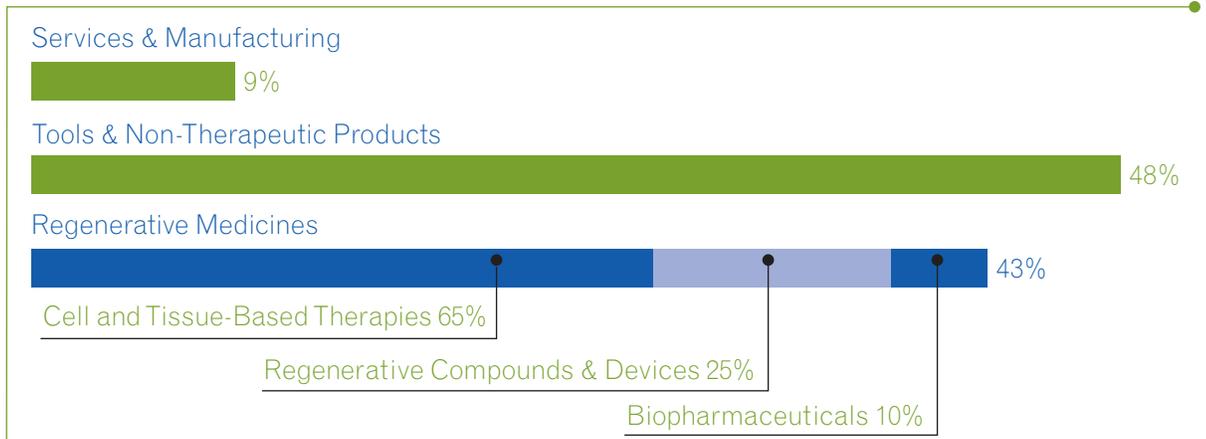
The field also incorporates a variety of service companies specializing in clinical trial management, manufacturing, engineering and financing among others.

Delivering cures through regenerative medicine requires coordination amongst a broad range of stakeholder groups from industry, academia, government, healthcare professionals, the investment community and consumer advocates.

Regenerative Medicine Industry Sectors



Regenerative Medicine Industry Sectors



Cell and Tissue-Based Therapies

Cell and tissue-based therapies are being sold or tested for almost every imaginable disease or condition.

Cell and Tissue-Based Segment

25%: Percentage of cell and tissue companies which are publicly traded.

A Global Look at the Cell and Tissue-Based Therapeutic Sector

Arguably the most prominent segment of the regenerative medicine industry, this sector includes more than 250 companies developing therapies for almost every imaginable disease or condition.

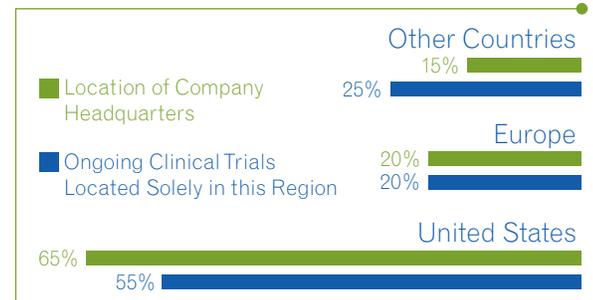
There are approximately 300 cell and tissue-based therapeutics commercially available or in clinical development around the world, 55 of which are described and marketed as regenerative medicine products.*

Research conducted by the Alliance valued the top 15 regenerative medicine products, based on revenue generation, to total the following amounts beginning in 2010:

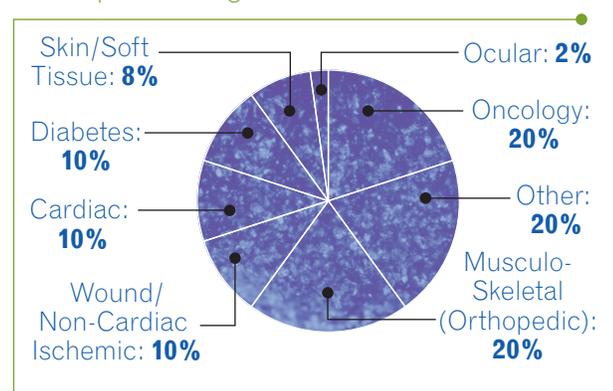
\$460 million 2010 (estimated)	\$730 million 2011 (estimated)	\$900 million 2012 (projected)
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All but one of these 15 products is for skin, wound, bone or cartilage repair with the exception of Dendreon's Provenge, approved by the FDA in 2010 for late-stage prostate cancer. The first of these products was brought to market in 1998 and collectively these products have treated over 500,000 patients through the end of 2011.

Companies and Trials by Location

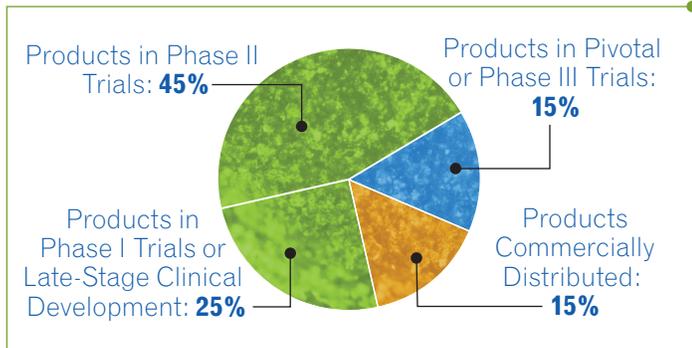


Therapies Being Sold or Tested

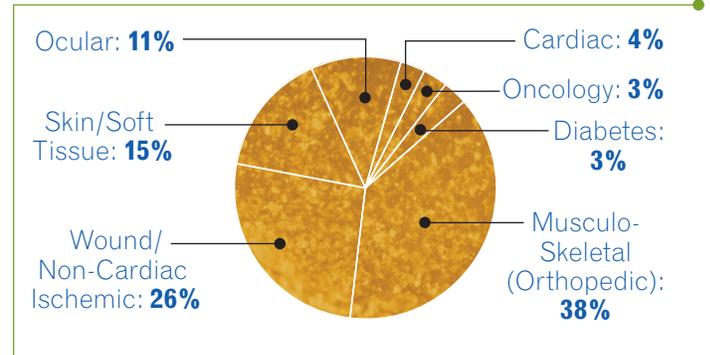


* For the purposes of this report we have restricted this data to countries with formal regulatory frameworks for this type of product, thus excluding cell therapy treatments provided in unregulated markets.

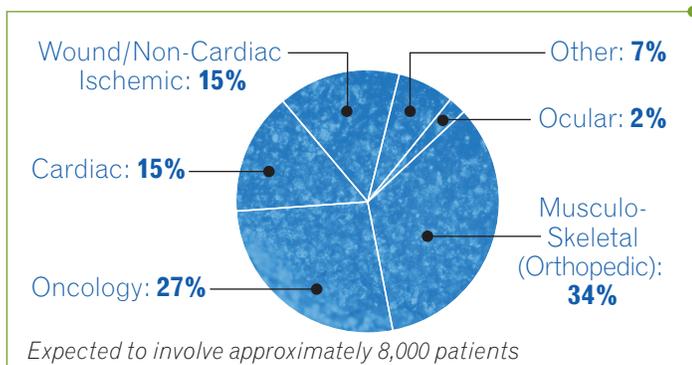
Clinical Trial Overview



Products Commercially Available



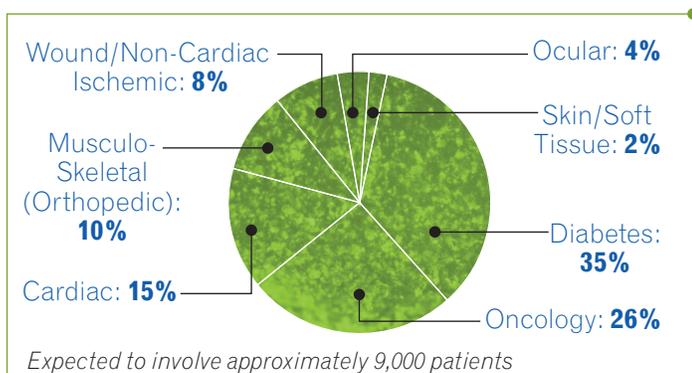
Currently in Late Stage Trials [Phase II/III, III, pivotal]



A Sampling of Leading Commercial Cell Therapy Products

Company	Product
Advanced Biohealing, a Shire company	Dermagraft
Allosource distributed by NuVasive	OsteoCel
Alphatec Spine	PureGen
Altrika	MySkin
Altrika	Cryoskin
Avita Medical	ReCell
BioDlogics (distributed by Amedica)	BioDfactor
BioDlogics (distributed by Amedica)	BioDfence
Dendreon	Provenge
Fibrocell	laViv
Genzyme, a Sanofi company	Carticel
Genzyme, a Sanofi company	Epicel
Genzyme, a Sanofi company	MACI
NuTech	NuCel
Organogenesis	Apligraf
Organogenesis	GINTUIT
Orthofix	Trinity / Trinity Evolution
Osiris Therapeutics	Grafix
TiGenix	ChondroCelect
Zimmer and ISTO Technologies	DeNovo NT

Currently in Early-to-Mid Stage Trials [Phase I, I/II, II]



Clinical Milestones in the News



March 2012: [Organogenesis Inc.](#), announces U.S. FDA approval of GINTUIT™, a cell-based product that generates new and aesthetically appealing oral gum tissue. GINTUIT™ is a cellular sheet that contains human fibroblasts, keratinocytes, human extracellular matrix proteins and bovine collagen. GINTUIT™ is the first approval of an allogeneic cell product via the Center for Biologics Evaluation and Research (CBER) arm of the FDA, and the first cell-based technology that is FDA-approved for use in the dental market.

February 2012: [Aastrom Biosciences, Inc.](#) initiates patient enrollment in the REVIVE Phase III clinical trial to assess the efficacy and safety of ixmyelocel-T in the treatment of patients with critical limb ischemia (CLI). The study is the largest randomized, double blind, placebo-controlled, multicenter trial ever conducted, with more than 80 sites in the U.S. including 594 CLI patients who have no option for revascularization. The trial's primary endpoint is amputation-free survival at 12 months.

February 2012: [Baxter International Inc.](#) announces the initiation of a Phase III pivotal clinical trial to evaluate the efficacy and safety of adult autologous CD34+ stem cells to increase exercise capacity in patients with chronic myocardial ischemia (CMI). Progenator Cell

Therapy, LLC is Baxter's manufacturing partner for this trial. The study is enrolling approximately 450 patients across 50 clinical sites in the U.S.

February 2012: [StemCells, Inc.](#) announces the FDA has authorized the initiation of a Phase I/II clinical trial of the company's proprietary HuCNS-SC® product candidate (purified human neural stem cells) in dry age-related macular degeneration (AMD), the most common form of AMD. The company's human neural stem cell platform is now being studied for all three elements of the central nervous system: the brain, spinal cord and eye. The trial is an open-label, dose-escalation study, and is expected to enroll a total of 16 patients. Preclinical data submitted as part of the company's IND application demonstrated that HuCNS-SC cells protect host photoreceptors and preserve vision in a well-established animal model of retinal disease that is relevant to dry AMD.

February 2012: [Zimmer Holdings, Inc.](#) and [ISTO Technologies, Inc.](#), announce a Phase III clinical study to evaluate DeNovo® ET Engineered Tissue Graft, an engineered cartilage implant for the repair of cartilage defects in the knee. DeNovo ET Graft is being developed under a collaborative relationship between ISTO and Zimmer. The Phase III study comprises a randomized, controlled clinical trial involving 225 patients at up to 25 centers in the U.S. The program is designed to demonstrate superiority over the current standard of care (microfracture) for articular cartilage defects.

January 2012: [Advanced Cell Technology, Inc.](#) (ACT) announces Phase I/II clinical data published in *The Lancet* demonstrating the safety of ACT's human embryonic stem cell (hESC)-derived retinal pigment epithelium cells for the treatment of Stargardt's macular dystrophy and dry age-related macular degeneration. Results were reported for two

patients, the first in each of the Phase I/II clinical trials. In addition to showing no adverse safety issues, structural evidence confirmed that the hESC-derived cells survived and continued to persist during the study period reported. Both patients had measurable improvements in their vision that persisted for more than four months.

January 2012: [Amorcyte, LLC](#), a [NeoStem, Inc.](#) company, announces the enrollment of the first patient in the Amorcyte PreSERVE Phase II trial for acute myocardial infarction. The study is a multicenter, randomized, double blind, placebo-controlled clinical trial to evaluate the safety and efficacy of infarct-related artery infusion of AMR-001, an autologous bone marrow derived cell therapy enriched for CD34+ cells. Approximately 160 subjects, age 18 and older, will be enrolled. Progenitor Cell Therapy, also a NeoStem company, is supporting the manufacturing, product supply and logistics for the trial.

January 2012: [AxoGen, Inc.](#) reports that the Avance® Nerve Graft is achieving meaningful recovery in 87 percent of patients with peripheral nerve injuries. The study is being conducted at 12 leading U.S. surgical sites and led by the Buncke Clinic in San Francisco. It is also the first multi-center clinical trial on processed nerve allografts. A summary of the findings have been published in the January 2012 issue of *Microsurgery*.

January 2012: [Cytori Therapeutics](#) receives an Investigational Device Exemption (IDE) approval from the U.S. FDA to begin the ATHENA trial to investigate the use of the Celution® System, a medical device to prepare adipose-derived stem and regenerative cells (ADRCs) to treat chronic myocardial ischemia (CMI). The trial is enrolling up to 45 patients who have limited therapeutic options. The study is evaluating clinical and

functional outcomes, including safety, peak oxygen consumption (mVO₂) and clinical outcomes at 12 months.

January 2012: [Sangamo BioSciences, Inc.](#) announces the initiation of two new Phase II clinical studies in its program to develop a “functional cure” for HIV/AIDS. Sangamo’s ZFP Therapeutic® approach generates T-cells that are resistant to HIV infection using its zinc finger nuclease technology to permanently disrupt the DNA sequence encoding CCR5, a co-receptor used by HIV to enter cells. In Sangamo’s Phase I trial, the viral load of an SB-728-T treated-subject decreased to undetectable levels during a scheduled treatment interruption. The research and pre-IND work is supported through a collaboration with scientists at City of Hope and the University of Southern California, under a \$14.5 million CIRM Disease Team Research Award.

November 2011: [Harvard Bioscience, Inc.](#), a developer of tools to advance regenerative medicine, announces that its “InBreath” bioreactor was used for the world’s second successful transplantation of a synthetic tissue-engineered windpipe at the Karolinska University Hospital in Stockholm, Sweden—the tracheas in both procedures were grown in Harvard Bioscience’s bioreactors. Patient-derived cells were grown on the scaffold inside the bioreactor for two days before transplantation.



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.

November 2011: [Mesoblast's](#) Phase II 60-patient clinical trial results show that Revascor™ increases blood supply to damaged heart muscle. After one year of treatment Revascor™ reduces the rate of major adverse events including heart attack, cardiac death and need for artery clearing procedures by 78% when compared with patients who received the current standard of care.

September 2011: [ReNeuron](#) announces that the Pilot Investigation of Stem Cells in Stroke (PISCES) trial's independent Data Safety Monitoring Board recommends that the ReN001 stem cell therapy trial for disabled stroke patients advance to the evaluation of a higher dose of cells based on safety data from the first dose cohort of three patients treated with ReN001. In this Phase I single administration, dose escalation study, ReNeuron's stem cell therapy is being administered to a total of 12 stroke patients who have been left disabled by an ischemic stroke. The PISCES study is the world's first fully regulated clinical trial of a neural stem cell therapy for disabled stroke patients.

August 2011: [Healthpoint Biotherapeutics](#) announces positive top line results for its Phase IIb clinical trial investigating the efficacy of HP802-247 in venous leg ulcers. HP802-247 is an investigational allogeneic living cell suspension containing keratinocytes and fibroblasts. Overall, HP802-247 is achieving statistical significance, as compared with control plus standard care, with the safety profile of the active groups being similar to placebo.

May 2011: [Aldagen, Inc.](#) announces Phase I/II clinical trial results for ALD-301, a stem cell therapy being developed as a treatment for critical limb ischemia. The Phase I/II study is a multi-center study and includes Cardiology PC, Duke University, Texas Heart Institute and St. Joseph's Research Institute. The Phase I/II double-blind study includes a total of 21 subjects. The primary objective of the trial is to

evaluate the safety of ALD-301. Overall, ALD-301 is showing to be well tolerated, with no therapy-related adverse events and also shows significant improvements in three efficacy endpoints compared to baseline at 12 weeks.

April 2011: [Juventas Therapeutics](#) announces completion of its Phase I clinical trial evaluating the safety and preliminary efficacy of JVS-100 for treatment of patients with heart failure. The trial included 17 NYHA Class III heart failure patients. Results from several pre-clinical studies demonstrated cardiac repair following a myocardial infarction through activation of natural stem-cell repair pathways, promotion of new blood vessel formation and prevention of ongoing cell death.

March 2011: [Athersys, Inc.](#) announces the initiation of patient enrollment, and dosing of the first patient for a Phase II clinical trial evaluating the safety and efficacy of administration of MultiStem®, Athersys' allogeneic cell therapy product for the treatment of ulcerative colitis. This Phase II clinical trial is part of a strategic global collaboration between Athersys and Pfizer Inc. to investigate MultiStem for the treatment of inflammatory bowel disease. The trial is being conducted at multiple clinical sites in North America and Europe, and will include up to approximately 126 patients.

March 2011: [StemCells, Inc.](#) announces the initiation of a Phase I/II clinical trial of its proprietary HuCNS-SC® human neural stem cells in chronic spinal cord injury. The trial is enrolling 12 patients with thoracic (chest-level) spinal cord injury who have a neurological injury level of T2-T11, and will include both complete and incomplete injuries as classified by the American Spinal Injury Association (ASIA) Impairment Scale. The trial is being conducted in Switzerland at the Balgrist University Hospital at the University of Zurich, a world leading medical center for spinal cord injury and rehabilitation.



Size and Pace of Deals Continues to Accelerate

Acquisitions and Partnerships

May 2011: Shire plc acquires [Advanced BioHealing, Inc.](#), whose lead product is Dermagraft, a bio-engineered skin substitute used to treat diabetic foot ulcers. The purchase price of \$750 million in cash was announced one day before the biotechnology company was to go public. The acquisition combines Advanced BioHealing's world-class experience and commercial capability in regenerative medicine with Shire's strengths and expertise in human cell biological manufacturing. Shire's purchase valued Advanced BioHealing at 5.1 times last year's sales of \$146.7 million.

April 2011: [Terumo Americas Holding](#), a U.S. subsidiary of Japan's [Terumo](#), acquires all outstanding shares of [Harvest Technologies](#), a biotechnology developer of point-of-care technologies that allows physicians to derive autologous, adult stem cells from their patients, for \$70 million.

February 2011: [Sanofi](#) and [Genzyme Corporation](#) enter into a definitive agreement under which Sanofi acquires Genzyme for \$74.00 per share in cash, or approximately \$20.1 billion. Through the acquisition Sanofi retains Genzyme's BioSurgery Unit and creates a global Cell Therapy and Regenerative Medicine Division.

January 2011: [NeoStem, Inc.](#) acquires [Progenitor Cell Therapy LLC](#), a cell therapy and regenerative medicine service and manufacturing specialist with cGMP state-of-the-art cell therapy manufacturing, processing and storage facilities.

December 2010: [Mesoblast Limited](#) and [Cephalon, Inc.](#) enter into a strategic alliance to develop and commercialize adult stem cell therapeutics for degenerative conditions of the central nervous and cardiovascular systems. These conditions include Parkinson's disease, Alzheimer's Disease, Congestive Heart Failure and Acute Myocardial Infarction. The strategic alliance provides Mesoblast an up front fee of \$130 million and up to \$1.7 billion in milestone payments. Cephalon receives exclusive worldwide commercialization rights to selected Mesoblast products and makes an equity investment, purchasing a 19.99% stake in Mesoblast at \$4.35 per share, totaling approximately \$220 million.

Noteworthy Financings

April 2012: [AlloCure, Inc.](#), announces the closing of a \$25 million Series B venture financing. The round includes the participation of new syndicate member Lundbeckfond Ventures, as well as previous investors SV Life Sciences and Novo A/S. Allocure's lead product, AC607, comprises allogeneic bone marrow-derived mesenchymal stem cells that are harvested from healthy adult donors and then expanded via a state-of-the-art manufacturing process for the treatment of kidney disease.

March 2012: [Athersys, Inc.](#) raises \$9 million in a private placement to support ongoing clinical trials evaluating MultiStem,[®] a stem cell therapy for the treatment of cardiovascular disease, neurological conditions and inflammatory and immune conditions.

Strategic corporate investors have over the last 18 months shown a growing interest in the sector with several significant partnerships and acquisitions.

March 2012: [Promethera Biosciences](#), a cell therapy company operating in the field of liver diseases, raises \$31.4 million funding to advance a Phase I/II study of its lead stem cell therapy, Hepastem, for the repair of severe liver defects and liver disease. New investors include the venture arms of pharmaceutical industry leaders Boehringer Ingelheim and Shire, Japanese investment fund Mitsui Global Investment, U.S. company ATMI and Belgian venture capital fund Sambrinvest.

February 2012: [InVivo Therapeutics Holdings Corp.](#), a developer of biomaterials and medical devices for the treatment of spinal cord injuries, announced that it raised \$17.4 million in a secondary offering to support the company's research, pre-clinical and clinical trial activities.

February–March 2012: [Organovo Holdings Inc.](#), a Delaware Corporation and [Organovo, Inc.](#), a bioprinting company, merged to create [Organovo](#). As part of the transaction, the company raised \$15.2 million in private placement financing and announced that Organovo will trade on the OTC-QB (over the counter) market under the symbol ONVO.

February 2012: [Cytomedix, Inc.](#) acquires [Aldagen, Inc.](#), which is developing regenerative cell therapies based on its proprietary ALDH bright cell technology. Under the terms of the deal, Cytomedix issues \$16 million in preferred shares and will issue additional common stock to Aldagen shareholders upon attainment of certain clinical milestones associated with Aldagen's Phase II trial in post-acute ischemic stroke. As a result of the transaction, Aldagen shareholders will own approximately 17.3% of Cytomedix common shares outstanding

May 2011: [Takeda Pharmaceutical Company Limited](#) and [Fate Therapeutics, Inc.](#) jointly announce that Takeda's corporate venture arm, [Takeda Ventures, Inc.](#), made an equity investment in Fate Therapeutics, Inc. The investment is consistent with the stated intention of Takeda to develop a stronger foundation in regenerative medicines. Other investors behind Fate include Arch Venture Partners, OVP Venture Partners, Venrock, Polaris Venture Partners, Astellas Venture Management, Genzyme Ventures, and a third unnamed corporate venture investment group.

April 2011: [Cellular Dynamics International, Inc.](#), a manufacturer of human induced pluripotent stem cells (iPSCs) and tissue cells, closes a \$30 million private equity round. This Series B Preferred Stock financing was led by an entity affiliated with Tactics II Stem Cell Ventures. Other investors include Sam Zell's Equity Group Investments LLC, Sixth Floor Investors LP and G Force Investments LLC. This financing enables the company to launch new iCell® iPSC lines as well as iCell Endothelial Cells, iCell Neurons, iCell Cardiomyocytes and iCell Hepatocytes lines for biomedical and pharmaceutical drug development and safety research.

December 2010: [Cytori Therapeutics](#) and [Astellas Pharma Inc.](#) enter a strategic equity agreement to evaluate the potential of adipose derived stem and regenerative cells for the treatment of several illnesses for which there is no fundamental treatment. Astellas will purchase approximately 1.4 million unregistered shares of Cytori common stock at \$7.00 per share for net proceeds to Cytori of \$10 million.

Alliance for Regenerative Medicine Reports

Image courtesy of the Australian Stem Cell Centre



Industry and Capital Formation Overview

One of the biggest challenges facing regenerative medicine is the lack of risk capital available to fund pre-clinical and early clinical development.

Despite the enormous therapeutic potential of many of these technologies, few traditional venture investors are patient enough to fund a 7–12 year development cycle with all of the regulatory and reimbursement risks inherent in the process. As a result, most early-stage companies in the field of regenerative medicine must look to alternative sources of funding—pharmaceutical firms, disease foundations, individual investors, state and federal sources. Strategic corporate investors have over the last 18 months shown a growing interest in the sector with significant partnerships and acquisitions: Cephalon's \$1.8 billion investment in Mesoblast and Shire's \$750 million acquisition of Advanced BioHealing are two notable examples. Strategic investors have also participated in recent financings of early-stage companies providing funding for Phase I and Phase II clinical trials. Shire and Boehringer Ingelheim's investment in Promethera in March 2012 and the Lundbeck Foundation's investment in Allocure, also in March 2012, are significant

examples of strategic investments by mid-tier pharmaceutical firms in regenerative medicine.

Though recent, this growing interest from strategic investors suggests that companies which are able to access sufficient resources to fund laboratory, preclinical and perhaps early stages of clinical research may discover a "silk road" to development partnerships to fund later stage pivotal trials. It is clear that the success of regenerative medicine in the U.S., indeed globally, will largely depend on the ability of companies to fund and achieve early clinical proof of concept so they can attract additional financing. In recognition of the critical importance of continued access to capital for all of its member companies and organizations, the Alliance is taking the unusual step, through its Capital Formation Committee, of leading outreach efforts to a variety of potential financing resources—institutional, retail and non-traditional. This effort also involves leveraging clinical experts and other key opinion leaders to facilitate broader understanding of the commercial opportunities inherent in regenerative medicine products. □

Industry-Sponsored Active Cell Therapy Trials

	2007	2012
Phase I	77	52
Phase I/II & II	89	148
Phase II/II & III	32	41
Total	198	241
Commercial revenue from cell therapies	<\$100 million	>\$1 billion

"Cell therapy" is defined as therapeutic products containing live cells. "Active" trials includes trials not yet open for recruiting and trials ongoing but recruiting complete. This data excludes trials of non-proprietary cell transplant procedures (e.g. trials sponsored solely by academia).



Policy and Legislation Overview

In late 2010 and again in early in 2011, the Alliance worked with congressional leaders to introduce legislation that would launch the first national initiative to support regenerative medicine.

The Regenerative Medicine Promotion Act of 2011 (HR 1862) was introduced in the U.S. House of Representatives in April 2011, and has bi-partisan support. Reps. Brian Bilbray (R-CA) and Diana DeGette (D-CO) are the lead sponsors and have been joined by 15 other Members of Congress. Major provisions of the bill include:

- requiring that the U.S. Government Accountability Office (USGAO) be responsible for strategic assessment of all federal agency activities related to regenerative medicine
- creating a multi-agency Regenerative Medicine Coordinating Council within the Department of Health and Human Services (HHS)
- establishing grant programs to accelerate the availability of life-saving regenerative medicine therapies and research tools
- funding of critical regulatory research at the FDA.

Supporting HR 1862 and its provisions is a major legislative focus of the Alliance for 2012 and beyond.

In addition, in September 2011 the U.S. House of Representatives Tri-Caucus (comprised of the Congressional Black Caucus, the Congressional Hispanic Caucus and the Congressional Asian Pacific American Caucus) hosted a briefing for Alliance leaders. The focus of the briefing was for the Alliance to educate congressional offices about the potential of regenerative medicine to treat currently unmet medical needs. Several congressional offices represented at the briefing have since become co-sponsors of HR 1862.

Regenerative medicine achieved a major milestone concerning federal funding of human embryonic stem cell (hESC) research when, in the spring of 2011, the U.S. Court of Appeals overturned an August 2010 preliminary injunction that, by a vote of 2-1, prohibited the federal government from funding research involving human embryonic stem cells. The court held that funding such research is not prohibited by a statute (known as the Dickey-Wicker Amendment) that prohibits federal funding of “research in which a human embryo or embryos are destroyed.” The court also held—contrary to the lower court—that enjoining hESC research would cause harm to the government significantly greater than the harm that the plaintiffs would suffer without an injunction. Thus, since that time, the NIH developed funding guidelines for researcher-grantees.

Supporting increased funding for the National Institute for Standards and Technology (NIST) regenerative medicine programs and the FDA are also legislative priorities for the Alliance. Positive news occurred in July 2011, when the House encouraged NIST to consider supporting standards and measurement work in

regenerative medicine technologies under the Scientific and Technical Research and Services budget, which was increased by \$10 million from 2011 to 2012. Additionally, the FDA received a \$50 million budget increase in FY 2012.

Moreover, in August 2011 the National Institutes of Health appointed the esteemed human embryonic stem cell scientist Dr. Mahendra Rao as Director of the new Intramural Center for Regenerative Medicine (NIH-CRM). The NIH-CRM is an initiative to create a world-class center of excellence in stem cell technology on the NIH campus. Research at NIH-CRM will include induced pluripotent stem cells (iPSC), which have potential applications in many systems and organs of the body. A major goal for the center is to build upon existing NIH investments in stem cell research to advance translational studies and, ultimately, cell-based therapies in the NIH Clinical Center. The center will also serve as a resource for the scientific community, providing stem cells, as well as the supporting protocols and standard operating procedures used to derive, culture and differentiate them into different cell types for research and potential regenerative therapies. □

Regulatory Overview

A major priority for the Alliance is to assist in creating clear and predictable regulatory pathways that facilitate rapid approval of safe and effective regenerative medicine products.

The Alliance has a robust regulatory agenda designed to achieve this goal, and has developed a collaborative working relationship with FDA. Commencing in May 2010 at a meeting with Commissioner Hamburg, center directors and senior agency staff, the Alliance began a series

of productive meetings and interactions with the agency, and will continue to have regular meetings with senior FDA officials in the coming weeks and months. Specific regulatory initiatives resulting from these exchanges include:

Standards: After conversations with regulatory officials, it was clear that a review and analysis of scientific standards initiatives was necessary. In response, the Alliance performed a thorough gap analysis of existing standards that was shared with FDA. The analysis focused on standards related to cell potency assay development and validation, which are crucial to regenerative medicine product development and regulatory approval. The Alliance additionally formed working groups to identify key regulatory issues as well as provide information and support to product developers and the agency.

Improved Communication: Improved communication between sponsors and FDA is critical to support regulatory approval of regenerative medicine products, as evidenced by the high number of cell therapy INDs put on hold. The Alliance is developing a paper for publication that will outline best practices for commercial sponsors to communicate with the FDA during clinical development, from pre-IND through post-market.

Presentations at FDA Public Meetings: The Alliance presented at multiple FDA-sponsored public meetings to discuss efforts and best practices for translating scientific discoveries into innovative products for patients.

Submissions: The Alliance regularly takes advantage of FDA requests for public comment on topics germane to regenerative medicine. To date, the Alliance has publicly addressed: unmet needs for clinical translation of cell-based therapies; the FDA-NIH Leadership Council; improving regulation and regulatory review; and parallel review of medical products.



International Regulatory Harmonization:

Global consistency of regulatory policy, where possible, will facilitate more rapid and efficient introduction of regenerative medicine products. The Alliance has formed a working group to develop policies that will improve international regulatory harmonization. □

Reimbursement Overview

The Alliance is committed to ensuring that the U.S. reimbursement system rewards innovation and value, and recognizes that a new paradigm is needed to recognize the value of regenerative medicine products to the health system.

The Alliance has a strong reimbursement agenda to accomplish this goal.

Engage the Center for Medicare and Medicaid Services (CMS)

The Alliance has met with senior CMS officials to discuss how best to work together to ensure regenerative medicine products are covered by Medicare and receive appropriate reimbursement. Further, CMS and the Alliance have discussed methods to measure cost, quality and outcomes in order to compare regenerative

medicine products with current therapies. We plan to continue discussions through a newly formed collaborative relationship.

Engage Private Payers

The Alliance will be working with the Blue Cross Blue Shield Association as well as the National Association of Managed Care Physicians to educate them about regenerative medicine and begin developing models for proper reimbursement. The Alliance will also identify pharmacoeconomic and clinical data needs for regenerative medicine in order to assure proper coding, insurance coverage and satisfactory pricing.

Engage the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI)

These federal agencies will be performing comparative effectiveness research. The Alliance has met with both agencies to discuss the potential of regenerative medicine to improve clinical outcomes and reduce health system costs.

Member Education and Support

In 2011, the Alliance released a publication that provided a description of the coding, coverage and payment components of the U.S. reimbursement system. This guide for CEOs and executives also contained a “decision-tree” to help company executives ask the proper questions to payers and design clinical programs that are best suited for reimbursement discussions. Further to these efforts, in 2012 the Alliance expects to publish a paper that outlines the pharmacoeconomic benefits of regenerative medicine products. □

Economics of Regenerative Medicine

The promise of regenerative medicine is that altering the course of disease will eliminate the need for daily therapies, reduce hospitalizations and avert expensive medical procedures, thus enabling patients to lead healthier and more productive lives.

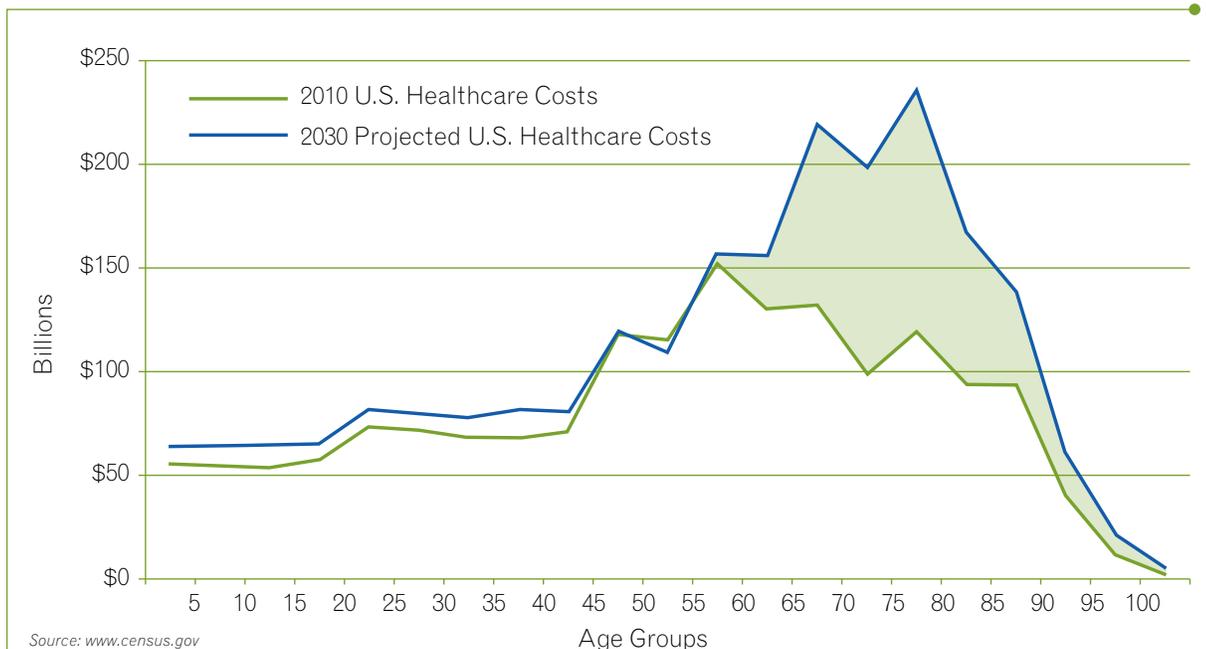
In turn, analysts estimate that the availability of regenerative medicines will decrease overall healthcare costs for patients and create positive economic impacts through increased productivity and healthcare effectiveness.

Regenerative medicine is not just a future hope, it is a reality today. Cell-based therapies and products are on the market now and, as highlighted elsewhere in this report, many more are in advanced stages of being tested in patients. These products provide insight

into what the future holds in terms of patient health and economic impact.

Cell-based replacement skin products from two companies, Advanced BioHealing (now owned by Shire) and Organogenesis have been available for several years to treat diabetic foot ulcers. Over 18 million patients suffer from diabetes in the U.S. alone, and each year nearly 140,000 of those patients will see a wound care specialist for a diabetic foot ulcer that results from poor circulation. The consequences of not effectively managing the wound include chronic infections, laborious cleaning of the wound and in the worst cases, amputation of the foot. While there are drugs to fight infection, no drug available today will help the skin to grow back. Engineered skin products, Dermagraft and Apligraf, are the only therapies that actually accelerate healing, effectively closing the wound and preventing infection and other dire consequences. □

The Cost Impact of an Aging Population





Understanding and Measuring the Potential Economic Benefit

Throughout the health care system, the growing question is whether our society can afford innovative medical advances.

Clearly, it will be the responsibility of clinical researchers, payer organizations and companies to demonstrate clinical and economic value for new therapies. The discipline of understanding the cost-benefit trade-offs associated with new treatment alternatives is known as pharmacoeconomics. For example, a patient with diabetes that pricks her finger eight or more times a day and must endure multiple insulin injections to maintain proper blood sugar levels may one day be treated with beta cells that replace her own dysfunctional pancreas. Pharmacoeconomic analysis will determine which of these approaches is most clinically and economically effective, capturing such factors as the downstream costs associated with managing heart disease, kidney disease, loss of sight and limb amputations that result from poor control of blood sugar. Taking this logic one step further, analysts assess the downstream impact of a new treatment on patient quality of life and compare it with the incremental cost of treatment over time. For

example, living with reduced vision, kidney disease or an amputated limb would all significantly reduce the quality of life value for a diabetic patient. While determining intermediate values to represent states of partial health is necessarily an approximation, the methodology allows comparison of different treatment approaches and different diseases. When such data are available, it is possible to develop a reliable set of outcomes and economic scenarios, consider trade-offs and make better decisions regarding the value of a novel therapy.

Emphasis on economic justification for patient care is evident across all aspects of healthcare, from reimbursement decisions by CMS, to payers demanding data that support treatment pathways, to large payer systems that collect and analyze their own data. Companies are incorporating pharmacoeconomic assessment tools and decision analysis processes earlier in product development. More frequently pivotal clinical studies are designed to capture cost data as well as clinical outcomes. Every advanced cellular therapy developed today will undergo some level of pharmacoeconomic analysis. □

Cellular Therapies Cost-Benefit Arguments

By applying increasingly sophisticated pharmacoeconomic tools, the cost-benefit of cellular therapies can be assessed, validated and justified.

The advantages of these therapies are clear as long as pharmacoeconomic benefits are adequately detailed. For example:

[Complete Solution For Complex Physiologic Processes](#): Heart tissue damaged by

atherosclerosis, chronic ischemia or a heart attack is weak and ineffective. Drugs can make the heart beat stronger and can reduce workload by controlling blood pressure, but even our best tools are frequently overwhelmed, and patient health declines quickly. Neither is a heart transplant the perfect solution, given the necessary immunosuppressive regimens required to prevent rejection, the high cost of complicated surgery and the limited supply of donor organs. However, cell-based therapies that rescue and heal infarcted heart tissue could adequately address the multifactorial demands on a compromised cardiovascular system and prevent the decline in functional capacity resulting from the loss of heart tissue.

Dramatically Reduced Morbidity In Chronic Diseases: Complications from poor control of blood sugar leads to extensive morbidity in diabetes patients. Testing methods have improved and better forms of insulin have contributed to a higher life expectancy, but adverse consequences are a major risk for a large number of Type 1 and Type 2 diabetes patients. Studies show that a cellular approach may allow for near-natural response to peaks and troughs of insulin demand, providing better glycemic control and dramatically reducing the downstream consequences of chronic diabetes. Additionally, cell-based therapies are proving effective treatments for diabetes complications such as diabetic foot ulcers, an ischemic disease that often leads to amputation.

Improved Quality Of Life: Promising clinical research of retinal cells is underway that has potential to restore sight to those with age-related macular degeneration (AMD) and other incurable disorders of the eye. It is possible through pharmacoeconomic tools to compare the cost benefit of scenarios in which a patient is either limited by blindness or experiences restored vision. In such cases, quality of life

is viscerally understood and one can easily imagine a favorable evaluation of a therapy capable of restoring vision.

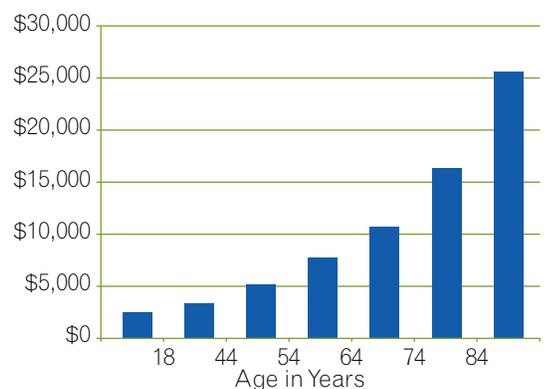
Cell-based therapies have the potential to deliver dramatic clinical benefits and address important unmet medical needs. It is possible to translate clinical improvement into a robust assessment of the economic benefit derived from superior clinical outcomes. With pharmacoeconomic analysis, companies, payers and policy makers will be able to accurately assess long-range cost benefit trade-offs for regenerative medicine products compared to traditional therapies, providing a level playing field for overcoming concerns about affording innovation. □

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 seriously ill. 1% of most seriously ill account for more than 25% of total healthcare expenditures

Annual Healthcare Cost per Capita by Age Group



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Acknowledgments: Special thanks to Lee Buckler of the the Cell Therapy Group for the tremendous market research effort and support in gathering industry related data and materials, and Skip Irving of Health Advances, LLC for contributing the Economics of Regenerative Medicine section to this year's report. This publication would not be possible without these meaningful contributions—thank you.

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ALLIANCE_{for}
Regenerative Medicine

525 Second Street, NE
Washington, DC 20002
(202) 568-6240
www.alliancerm.org