REJUVENATION RESEARCH
Volume 14, Number 6, 2011

DOI: 10.1089/rej.2011.1292

MEETING REPORT

Steady Advance of Stem Cell Therapies: Report from the 2011 World Stem Cell Summit, Pasadena, California, October 3–5

Melanie Swan

Abstract

Stem cell research and related therapies (including regenerative medicine and cellular therapies) could have a significant near-term impact on worldwide public health and aging. One reason is the industry's strong linkage between policy, science, industry, and patient advocacy, as was clear in the attendance and programming at the 7th annual World Stem Cell Summit held in Pasadena, California, October 3–5, 2011. A special conference session sponsored by the SENS Foundation discussed how stem cell therapies are being used to extend healthy life span. Stem cells are useful not only in cell-replacement therapies, but also in disease modeling, drug discovery, and drug toxicity screening. Stem cell therapies are currently being applied to over 50 diseases, including heart, lung, neurodegenerative, and eye disease, cancer, and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Dozens of companies are developing therapeutic solutions that are in different stages of clinical use and clinical trials. Some high-profile therapies include Dendreon's Provenge for prostate cancer, Geron's first-ever embryonic stem cell trials for spinal cord injury, Fibrocell's laViv cellular therapy for wrinkles, and well-established commercial skin substitutes (Organogenesis' Apligraf and Advanced BioHealing's Dermagraft). Stem cell policy issues under consideration include medical tourism, standards for large-scale stem cell manufacturing, and lingering ethical debates over the use of embryonic stem cells. Contemporary stem cell science advances include a focus on techniques for the direct reprogramming of cells from one lineage to another without returning to pluripotency as an intermediary step, improved means of generating and characterizing induced pluripotent cells, and progress in approaches to neurodegenerative disease.

Introduction

Stem cell therapies—treatments that involve the transplantation of stem cells, organs, or other cells into patients to improve the function of diseased or damaged tissues or organs—is a field that has been steadily advancing. Perhaps more than any other industry, stem cell therapies are poised to make a significant near-term impact on worldwide public health and aging, and many individuals living today may experience stem cell-related therapies. The most obvious use of stem cells is in cell-replacement therapies, but they are also valuable in disease modeling, drug discovery, and drug toxicity assessment.

The first reason for the progress in stem cell therapies is the industry's multidisciplinary integration of policy, science, industry, and patient advocacy, as was clear from the programming and attendance at the 7th annual World Stem Cell Summit, held October 3–5, 2011 in Pasadena, California. The 1,000–1,100 person attendance was on par with that of the last two year's conferences in Baltimore (2009) and Detroit (2010), and the conference was supported by 200–300 sponsors and exhibitors. Although the interdisciplinary nature of the stem cell industry may have been built more out of necessity than design, due to a strong regulatory environment, the ensuing model involves a broader swath of society than many science fields. This has allowed more expedient progress as diverse groups feel comfortable and knowledgeable in decision-making, particularly funders and investors. Other science-driven fields such as synthetic biology, nanomedicine, and aging might hasten progress by cultivating a more multidisciplinary approach.

A second indication of the growing strength of the stem cell therapies industry is the wide range of diseases that is

MS Futures Group, Palo Alto, California.

being targeted—over 50. There are dozens of stem cell treatments in different stages of development ranging from clinical availability to early-stage testing. Some of the disease focal areas include: Leukemia; human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS); AIDS lymphoma; rare blood disorders like Fanconi anemia and sickle cell disease; cancers like hematological malignancy, glioblastoma, and solid tumors; neurological and central nervous system diseases like Parkinson disease, Alzheimer disease, Huntington disease, Canavan disease, amyotrophic lateral sclerosis, autism, spinal cord injury, traumatic brain injury, stroke, and spinal cord injury; eye disease like macular degeneration and retinitis pigmentosa; and heart disease, acute myocardial infarction, heart failure, liver failure, and ischemic stroke. These research efforts are corroborated by the 189,996 "stem cell" papers listed in PubMed and 3,732 clinical trials listed in the U.S.-based www.ClinicalTrials.gov database as of October, 2011.

A third sign of the maturity of the stem cell therapies industry is the contemporary focus on commercialization and the mechanics of putting stem cell therapies into clinical practice. Both areas will certainly be multiyear projects, but the fact that the industry is focusing on these next steps indicates progress. Manufacturing is an important challenge; the large-scale industrialized production of human stem cells in tightly controlled conditions is required. It appears possible to deliver stem cell therapies through the current public health infrastructure, although clinics specifically devoted to stem cell treatments may arise over time.

Public Health and Drug Development Model Is Broken

On the other hand, stem cell research is a nascent field with expensive therapies that are challenging to commercialize, for example, $93,000 for the prostate cancer therapy Provenge. Translation is slow, with few eligible patients actually receiving stem cell therapies, and widespread clinical implementation could be 10–20 years away. The timing for cellular therapies could be off as overloaded public health systems are forced to address higher-priority issues.

New models for health care delivery are necessary as costs continue to rise, worldwide populations age, and physician shortages are expected. It is estimated that 75% of health care spending is on chronic conditions, and that many older individuals have multiple chronic conditions. Simultaneously, the cost to bring a new drug to market has soared to $1.5 billion, and there are fewer drugs seeking approval (in 2011, the U.S. Food and Drug Administration [FDA] had only 23 new drugs applications as compared with 45 in 1996[1]). Also, new classes of drugs, such as cellular and gene therapies, are even more costly and complicated than today's already expensive small-molecule drugs and biologics. These collective uncertainties have given rise to a reticence to invest in biotechnology by both industry and financial investors.[1] At the national public health level, there could be a bleak period of care rationing.

However, despite the potential challenges, the momentum of stem cell therapies may prove unstoppable, and they could find a nice fit within public health landscapes to ease costs and provide effective disease treatment. Even if a few of the 50 therapies currently in development were to be successful, the impact could be substantial in both improving patient outcomes and reducing health care costs.

Stem Cells and Aging: SENS Foundation-Sponsored Session

Stem cell therapies and regenerative medicine will be important for overcoming age-related deterioration. A special conference session addressed advances in this area, Unleashing Regenerative Medicine to Extend the Healthy Lifespan: Technological Issues and Commercial, sponsored by the SENS Foundation (www.SENS.org).

Michael West, CEO of BioTime (Alameda, CA), discussed the company's diverse stem cell-based technology platform with six human embryonic stem cell (hESC) lines. The hESCs have been used to differentiate 200 downstream cell types such as kidney, smooth muscle, and skeletal muscle cells. Early in the process, cells are exposed to growth factors to facilitate differentiation specificity, for example, osteogenic and chondrogenic (cartilage-generating) growth factors. Similarly, hESCs were differentiated into retinal pigment epithelium (RPE) stem cells[2] and applied commercially in a treatment for macular degeneration.[3] BioTime's subsidiary ReCyte Therapeutics is specifically focused on therapies to reverse the developmental aging of human cells, using hESC-derived therapies for age-related vascular and blood disorders, such as coronary disease and heart failure.[4] Other research is investigating hyaluronate restoration through stem-cell generated extracellular matrices, and resetting telomere length back to before the Hayflick limit through induced pluripotent stem cell (iPSC) reprogramming.[5]

Xianmin Zeng, a researcher at the Buck Institute for Aging Research (Novato, CA), presented advances in addressing Parkinson disease. The current treatments, levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, and deep brain stimulation, are not particularly effective and do not cure the disease. Cell replacement therapies might be a solution for combatting the death of nigral dopaminergic neurons that occurs as the disease progresses. Clinically compliant stem cell lines capable of differentiating into midbrain neurons were selected, and iPSCs were used to generate committed neuronal stem cells, which were then further differentiated into dopaminergic neurons.[6] The stability and fidelity of the dopaminergic neurons has been confirmed and the next step is scaling up production for clinical trials. This looks feasible because life sciences product manufacturer Lonza is developing dopaminergic neuron products with these methods. A readily available supply of iPSC-derived dopaminergic neurons could facilitate research in other neurodegenerative diseases such as Alzheimer disease, Huntington disease, and amyotrophic lateral sclerosis.[7]

Stephen Minger, head of GE Healthcare's Cell Technologies group (Cardiff, UK), discussed the company's stem cell-based platform for drug toxicity screening. Drug development costs are high in part due to the withdrawal of drugs for previously undetected toxicity; 45% of withdrawals are due to cardiotoxicity and 37% are due to hepatotoxicity. Some recent cardiotoxicity-related withdrawals are sibutramine (an appetite suppressant), rosiglitazone (an

antidiabetic), and terfenadine (an antihistamine). Stem cell assays could be used to analyze compounds predictively before they are tested in animals. GE developed cardiomyocytes from an approved hESC line with current at-scale production of 5–10 billion cells per batch for cardiotoxicity and hepatotoxicity testing.[8] Another interesting preclinical biomarker test measures the influence of a compound on cardiac action potential, indicating potential toxicity if the action potential is prolonged upon exposure.[9]

Policy and Regulation of Stem Cell Therapies

Four current policy concerns have to do with the use of ESCs, iPSC manufacture, cellular therapy approval and access, and medical tourism. While a regulatory ban was lifted in 2009 in the United States that previously limited the ESC lines that could be used in federally funded research, debate about the use of embryos continues. Approximately 48,000 *in vitro* fertilization babies are born each year in the United States.[10] In the process, typically 10 blastocysts are created, only one of which is implanted into the prospective mother. The rest are frozen, discarded, or donated to research. Ethical debate about the appropriate use of the unused blastocysts remains unresolved, although not limited legally. A second policy issue has to do with the understandable need for manufacturing standards as the industry scales up in the production of stem cell therapies, particularly with regard to iPSC-derived products.[11] Consistent output, quality control, process reproducibility, and safety testing, within clinical time constraints, are some of the points outlined for regulation. Other cellular therapy-related policy concerns include the issue that therapies may not fit into the current FDA approval phases and may require alternative processes (*e.g.*, testing Phase I and II safety and efficacy together), and that current loopholes by which physicians administer drugs to patients (*e.g.*, access to investigational programs and off-label prescribing) may not be appropriate for cellular therapies.[12]

The fourth contemporary policy issue is medical tourism, which has considerable discussion and opinion both in the popular press and from scientists. Although scientifically rigorous stem cell therapies are slowly progressing through regulatory approval, numerous companies in the United States and abroad have begun to offer stem cell therapies that many scientists denounce as unproven. Responses range from the outright dismissal of such treatments as quackery and 21st century snake oil to wondering how a better job can be done to deliver effective therapies through the traditional public health system. The issue is compounded by some recent high-profile individuals obtaining overseas stem cell treatments that apparently did not work, for example, those received by professional football player Peyton Manning[13] and Texas governor Rick Perry.[14] There is a call for the stronger international regulation of stem cell therapies, with an emphasis on establishing accountability and efficacy and the suggestion that other countries adopt regulatory frameworks similar to those used in the United States and the United Kingdom.[15] One resource for information about clinics outside of the United States is the International Society for Stem Cell Research (www.ISSCR.org). Although at present few Americans are traveling for medical tourism (mainly orthopedic, cardiac, and cosmetic procedures),[16] demand could increase and it may be difficult for laypersons to assess treatment appropriateness and efficacy.

Science of Stem Cell Therapies

Different kinds of stem cells and current status of advances in stem cell generation

The least contentious type of stem cell is adult stem cells, which have been in medical use for over 40 years. The main form of adult stem cells used is the two types found in the bone marrow—hematopoietic stem cells (HSCs), which form all types of blood cells, and mesenchymal or bone marrow stromal stem cells (MSCs), which form bone, cartilage, fat, and fibrous connective tissue.[17] One limitation of adult stem cells is that they can only further differentiate into cells within their own tissue type. Therefore, ESCs became attractive because they can differentiate into any cell type, although their use is more contentious as previously discussed. Another kind of stem cell was developed, the iPSCs, by retrovirally introducing genes to encode four transcription factors (Oct4, Sox2, Klf4, and c-Myc) to reprogram somatic (*e.g.*, non-germ line) cells such as skin cells back to a pluripotent stage, where they can then be differentiated into any cell type. A landmark paper was published in 2006,[18] with ongoing advances from the same lab including the recent direct reprogramming of one mature cell lineage to another. Adult dermal fibroblasts were transformed into functional neurons with a combination of a microRNA (miR-124) and two transcription factors (Myt1l and Brn2).[19] One of the first tests that scientists conduct after generating iPSCs is whether they are the functional equivalent of ESCs.

There are some problematic aspects in working with both ESCs and iPSCs; for example, incomplete differentiation may lead to teratoma (tumor) formation or the buildup of other unusable extra cells. Also, it may be difficult to identify and separate fully differentiated cells in culture for *in vivo* transfer. There are issues related to iPSC generation, such as problems with the retroviral delivery method and the transcription factors. Rigorous analysis has found that iPS-generated cells may not be functionally and molecularly equivalent to ESCs, because aberrant gene silencing[20] and point mutations may occur. One study found that iPS reprogramming in 22 cell lines using five different methods resulted in an average of five point mutations in the regions sampled.[21] Other recent work examined the extensive regulatory process that accompanies dedifferentiation and redifferentiation, and how the epigenetic landscape may be reset in iPSCs as some cells upregulate and downregulate more quickly than others when transcription factors are applied.[22] A better understanding of the mechanics of reprogramming to pluripotency might help in the direct reprogramming of one lineage to another without having to induce pluripotency.

Other techniques for generating iPSCs are under investigation, including replacing the transcription factors with small molecules and some recent promise in the targeted genetic engineering of human pluripotent cells. Nucleases (DNA-cleaving enzymes) have shown some success in directed genetic programming, for some time with zinc-finger nucleases (ZFNs) and more recently with transcription activator-like effector nucleases (TALENs).[23]

Area of particular promise: Neurodegenerative disease

Stem cells may be able to aid in disease conditions that do not have effective current treatments, particularly neurodegenerative disease, which has a paucity of clinical therapies for conditions such as Parkinson disease, Alzheimer disease, Huntington disease, and amyotrophic lateral sclerosis (ALS). It is difficult to test hypotheses on live cells, but scientists are using iPSCs to develop patient-specific disease models, for example, in Alzheimer disease.[24] Using stem cells in disease modeling has also been helpful in Parkinson disease in recent work linking genetics and pathology. Synuclein (soluble proteins expressed in the brain) gene mutations (E46K and A53T) may lead to early-onset Parkinson disease, because they cause the build-up of Lewy bodies that impair nigral dopaminergic neurons.[25]

In the case of ALS, the best drug, riluzole, is only estimated to extend life 3–4 months, and it does not change the progression of the disease, generally 3–5 years to death after diagnosis, as motor neuron capability is lost. It may not be appropriate or feasible to implant new motor neurons into the body because they are very long and wired all over the body. In an alternative approach, scientists have been examining the cause of motor neuron death, finding that it may be triggered by a mutation in the superoxide dismutase 1 (SOD1) gene, and that disease progression slowed in mice when there was elevated dismutase (*e.g.*, a certain enzyme) activity in Schwann cells.[26] Another solution for ALS is underway in clinical trials at Neuralstem (Rockville, MD). Positive Phase I safety data for the company's neural stem cell lumbar transplantation trials was presented on the first 12 patients in September, 2011.[27] The trial began in January, 2010.

Industry View of Stem Cell Therapies and Cellular Therapies

Dozens of companies are developing a variety of therapeutic solutions using MSCs, ESCs, and iPSCs, assiduously working through clinical trials and regulatory approval processes. The early-stage industry has been advancing quickly since the U.S. hESC ban was lifted, and is starting to attract interest from Big Pharma in both developing therapies in-house and acquiring startups. Some of the most interesting studies with the potential for near-term high-impact results are discussed below.

MSCs for heart, lung, and islet cell repair

Prochymal, an MSC product from Osiris Therapeutics (Columbia, MD) is in FDA Phase III clinical trials for the treatment of acute graft-versus-host disease (GvHD) and Crohn disease, and in Phase II clinical trials for acute myocardial infarction (repair of heart tissue), diabetes (protection of pancreatic islet cells), and pulmonary disease (repair of lung tissue). Another product, Chondrogen, is being developed for treating osteoarthritis of the knee. These solutions are based on research work finding that pericytes (connective tissue cell occurring around small blood vessels) may behave as stem cells throughout the body,[28] harnessing the capabilities of MSCs in secreting bioactive molecules such as growth factors, cytokines, and chemokines.[29]

Cellular immunotherapy treatment for prostate cancer

For the treatment of certain kinds of prostate cancer, Provenge from Dendreon (Seattle, WA) was approved in April, 2010. It is an autologous (derived from the same individual's body) cellular immunotherapy.[30] Provenge introduces a protein to a patient's own immune cells that acts as an antigen for prostate cancer, which causes the body to activate an immune response against the cancer cells. The company estimated having the capacity to treat 2,000 patients in the first year and opened a third U.S. manufacturing facility in August, 2011.

Dermal substitutes

Two of the most-widely used cellular therapies are dermal substitutes: Dermagraft from Advanced BioHealing (Westport, CT) and Apligraf from Organogenesis (Canton, MA), where an epidermis is formed in a 20-day manufacturing process. Apligraf is the first allogeneic (*e.g.*, developed with one person's cells for transfer to another person, using cell types that do not elicit immune response) cell-based product approved by the FDA and has had over 250,000 patient applications.

Cell therapy for wrinkles

LaViv (azficel-T) is a therapy from Fibrocell Science (Exton, PA) approved in June, 2011. Collagen-producing fibroblasts are biopsied from behind the ear and cultured for 90 days, then injected into smile line wrinkles around the nose and mouth.[31] Apparently, the treatment is longer-lasting than the absorbable fillers used by competitors.

Spinal cord injury

Geron (Menlo Park, CA) has the first-ever ESC clinical trials underway for spinal cord injury with two enrolled patients as of June, 2011,[32] to investigate the use of hESC-derived oligodendrocyte progenitor cells, GRNOPC1, in the treatment of paralysis.[33]

HIV cure

HIV is an example where anti-HIV drugs suppress the virus but do not cure patients. It has been discovered that individuals with a certain genetic mutation, homozygous for the CCR5-delta32 allele, are virtually resistant. Sangamo BioSciences (Richmond CA) helped to design zinc finger nucleases that knock out the CCR5-receptor gene and generate CCR5-negative immune cells that would be permanently protected against HIV. The stem cells were then transplanted successfully into the "Berlin patient" who was declared to be cured of HIV after remaining off retroviral therapy for over 3 years.[34,35]

References

1. Hsu, J. Fear of risk threatens medical innovation. Innovation News Daily, June 29, 2011. Available at www.innovationnewsdaily.com/medical-innovation-pharmaceutical-drugs-2090/. Accessed October 9, 2011.
2. Idelson M, Alper R, Obolensky A, Ben-Shushan E, Hemo I, Yachimovich-Cohen N, Khaner H, Smith Y, Wiser O, Gropp M, Cohen MA, Even-Ram S, Berman-Zaken Y, Matzrafi L, Rechavi G, Banin E, Reubinoff B. Directed differentiation of

human embryonic stem cells into functional retinal pigment epithelium cells. Cell Stem Cell 2009;5:396–408.
3. Sharma, A. Cell Cure partner Teva to develop OpRegen. Pharma Age October 11, 2010. Available at www.pharmaage.com/2010/10/11/cell-cure-partner-teva-to-develop-opregen/. Accessed October 9, 2011.
4. Segall, J. Company plans near-term commercialization of iPS cell banking services that reverse the developmental aging of human cells. Company press release. January 3, 2011. Available at www.b2i.us/profiles/investor/ResLibraryView.asp?ResLibraryID=42754&GoTopage=1&Category=1802&BzID=1152/. Accessed October 9, 2011.
5. West MD, Vaziri H. Back to immortality: The restoration of embryonic telomere length during induced pluripotency. Regen Med 2010;5:485–488.
6. Swistowski A, Peng J, Liu Q, Mali P, Rao MS, Cheng L, Zeng X. Efficient generation of functional dopaminergic neurons from human induced pluripotent stem cells under defined conditions. Stem Cells 2010;28:1893–1904.
7. Peng J, Zeng X. The role of induced pluripotent stem cells in regenerative medicine: neurodegenerative diseases. Stem Cell Res Ther 2011;2:32.
8. McKechnie, C. GE Healthcare launches human cardiomyocytes for predictive toxicity testing. Company press release. October 4, 2010. Available at www.genewscenter.com/content/detailEmail.aspx?NewsAreaID=2&ReleaseID=11106&AddPreview=False and http://www.gelifesciences.com/aptrix/upp01077.nsf/content/drug-safety-screening/. Accessed October 9, 2011.
9. Peng S, Lacerda AE, Kirsch GE, Brown AM, Bruening-Wright A. The action potential and comparative pharmacology of stem cell-derived human cardiomyocytes. J Pharmacol Toxicol Methods 2010;61:277–286.
10. BabyCenter Medical Advisory Board. Fertility treatment: In vitro fertilization (IVF). Online text from BabyCenter. 2011. Available at www.babycenter.com/0_fertility-treatment-in-vitro-fertilization-ivf_4094.bc/. Accessed October 9, 2011.
11. Carpenter MK, Couture LA. Regulatory considerations for the development of autologous induced pluripotent stem cell therapies. Regen Med 2010;5:569–579.
12. Hyun I. Allowing innovative stem cell-based therapies outside of clinical trials: Ethical and policy challenges. J Law Med Ethics 2010;38:277–285.
13. Childs, D. Peyton Manning's stem cell hail Mary. ABC News. September 12, 2011. Available at http://abcnews.go.com/blogs/health/2011/09/19/peyton-mannings-stem-cell-hail-mary/. Accessed October 9, 2011.
14. Brown, E. Rick Perry's stem cell surgery worries some doctors. Los Angeles Times. August 19, 2011. Available at http://articles.latimes.com/2011/aug/19/news/la-heb-rick-perry-stem-cell-back-surgery-20110819/. Accessed October 9, 2011.
15. Cohen CB, Cohen PJ. International stem cell tourism and the need for effective regulation. Part II: Developing sound oversight measures and effective patient support. Kennedy Inst Ethics J 2010;20:207–230.
16. Alleman BW, Luger T, Reisinger HS, Martin R, Horowitz MD, Cram P. Medical tourism services available to residents of the United States. J Gen Intern Med 2011;26:492–497.
17. U.S. National Institutes of Health. Stem Cell Basics. Stem Cell Information. Available at http://stemcells.nih.gov/info/basics/basics4.asp/. Accessed October 9, 2011.
18. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–676.
19. Ambasudhan R, Talantova M, Coleman R, Yuan X, Zhu S, Lipton SA, Ding S. Direct reprogramming of adult human fibroblasts to functional neurons under defined conditions. Cell Stem Cell 2011;9:113–118.
20. Stadtfeld M, Apostolou E, Akutsu H, Fukuda A, Follett P, Natesan S, Kono T, Shioda T, Hochedlinger K. Aberrant silencing of imprinted genes on chromosome 12qF1 in mouse induced pluripotent stem cells. Nature. 2010;465:175–181.
21. Gore A, Li Z, Fung HL, Young JE, Agarwal S, Antosiewicz-Bourget J, Canto I, Giorgetti A, Israel MA, Kiskinis E, Lee JH, Loh YH, Manos PD, Montserrat N, Panopoulos AD, Ruiz S, Wilbert ML, Yu J, Kirkness EF, Izpisua Belmonte JC, Rossi DJ, Thomson JA, Eggan K, Daley GQ, Goldstein LS, Zhang K. Somatic coding mutations in human induced pluripotent stem cells. Nature 2011;471:63–67.
22. Papp B, Plath K. Reprogramming to pluripotency: stepwise resetting of the epigenetic landscape. Cell Res 2011;21:486–501.
23. Hockemeyer D, Wang H, Kiani S, Lai CS, Gao Q, Cassady JP, Cost GJ, Zhang L, Santiago Y, Miller JC, Zeitler B, Cherone JM, Meng X, Hinkley SJ, Rebar EJ, Gregory PD, Urnov FD, Jaenisch R. Genetic engineering of human pluripotent cells using TALE nucleases. Nat Biotechnol 2011;29:731–734.
24. Israel MA, Goldstein LS. Capturing Alzheimer's disease genomes with induced pluripotent stem cells: Prospects and challenges. Genome Med 2011;3:49.
25. Comellas G, Lemkau LR, Nieuwkoop AJ, Kloepper KD, Ladror DT, Ebisu R, Woods WS, Lipton AS, George JM, Rienstra CM. Structured regions of a-synuclein fibrils include the early-onset Parkinson's disease mutation sites. J Mol Biol 2011;411:881–895.
26. Lobsiger CS, Boillee S, McAlonis-Downes M, Khan AM, Feltri ML, Yamanaka K, Cleveland DW. Schwann cells expressing dismutase active mutant SOD1 unexpectedly slow disease progression in ALS mice. Proc Natl Acad Sci USA 2009;106:4465–4470.
27. Neuralstem, Inc. Dr. Eva Feldman, Principal Investigator, presents interim data on Neuralstem ALS trial. Company press release. September 27, 2011. Available at http://investor.neuralstem.com/phoenix.zhtml?c=203908&p=irol-newsArticle&ID=1610372&highlight=/. Accessed October 9, 2011.
28. Meirelles Lda S, Nardi NB. Methodology, biology and clinical applications of mesenchymal stem cells. Front Biosci 2009;14:4281–4298.
29. Caplan AI, Correa D. The MSC: An injury drugstore. Cell Stem Cell 2011;9:11–15.
30. Burgess, S. FDA approves a cellular immunotherapy for men with advanced prostate cancer. U.S. Food and Drug Administration press release. April 29, 2010. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210174.htm/. Accessed October 9, 2011.
31. Schmidt C. FDA approves first cell therapy for wrinkle-free visage. Nat Biotechnol 2011;29:674–675.
32. Geron Corporation. Geron presents data from GRNOPC1 trial at international conferences on spinal cord medicine and rehabilitation. Company press release. June 7, 2011. Available at www.geron.com/media/pressview.aspx?id=1271/. Accessed October 10, 2011.
33. Keirstead HS, Nistor G, Bernal G, Totoiu M, Cloutier F, Sharp K, Steward O. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and

restore locomotion after spinal cord injury. J Neurosci 2005;25:4694–4705.
34. Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, Allers K, Schneider T, Hofmann J, Kücherer C, Blau O, Blau IW, Hofmann WK, Thiel E. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 2009;360:692–698.
35. Barre-Sinoussi, F. Toward an H.I.V. cure. New York Times. June 3, 2011. Available at www.nytimes.com/2011/06/04/opinion/04iht-edsinoussi04.html/. Accessed October 9, 2011.

Address correspondence to:
Melanie Swan
MS Futures Group
P.O. Box 61258
Palo Alto, CA 94306

E-mail: m@melanieswan.com