REGENERATIVE MEDICINE

a paradigm shift in healthcare

The regenerative medicine market offers phenomenal opportunities for growth in the next few decades. However, there are still major issues to be addressed to enable this nascent industry to truly flourish, especially with regard to investment and the attitudes of regulatory agencies and reimbursement bodies in an area which is relatively new to them.

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Traditional pharmacological approaches to medicine and healthcare have been highly successful in developing treatments for many acute and chronic disease and disorders. With these discoveries also came scientific advances in understanding the underlying mechanisms of disease, leading to innovative therapies that focus on addressing the causes of the disease instead of just treating symptoms.

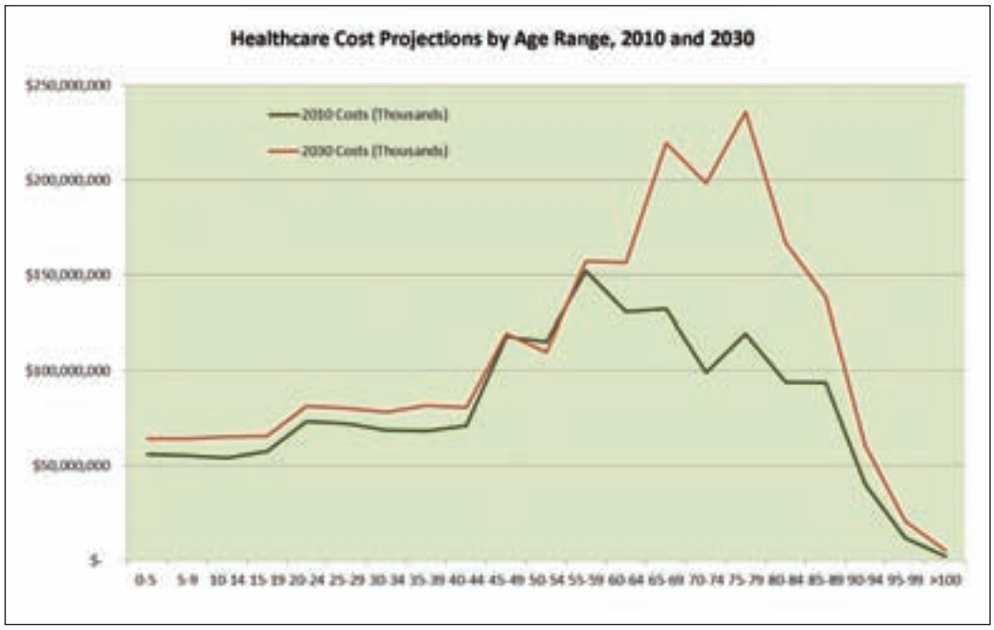
Unfortunately, far too many patients suffer from diseases for which there is no treatment. Regenerative medicine (RM) represents a paradigm shift in healthcare therapies and treatment by focusing on the underlying causes of disease by repairing, replacing, or regenerating damaged cells in the body. By focusing on problems at a cellular level, these therapies have the potential to cure or significantly reduce the disease burden for some of the most common chronic and acute conditions including stroke, heart disease, progressive neurological conditions, autoimmune diseases and trauma. Successful development of novel stem cell and regenerative medicine therapies could greatly improve the quality of life for millions of patients living with these debilitating diseases and conditions. Regenerative medicine is also important from a national healthcare perspective, as these technologies have the potential to create less costly and more effective therapies for some of the most expensive and devastating conditions plaguing our society.

This potential is already being realised by the multiple regenerative medicine products on the market, with many more promising products and technologies in mid- and late-stage clinical trials for common conditions including stroke, diabetes, Parkinson's disease and heart disease. As the population ages and the need for these innovative therapies grow, however, numerous commercial, financial and regulatory obstacles continue to hinder the advancement of the field. The industry, working with other stakeholders, is now taking steps to collectively address the greatest barriers to widescale clinical success.

Shifting demographics are creating higher burden of chronic disease

The market for RM products – as well as the potential economic impact of the industry – is growing. The populations of developed countries are ageing rapidly, and with this demographic shift we will see an increased number of the elderly living longer and spending more on healthcare. According to the latest census, the percentage of the US population that is over the age of 65 is projected to increase from 13% to 19% from

Figure 1



2010 to 2030[1]. This means there will be nearly 32 million more elderly people in the US in 2030 than there are today. With this change in demographics, markets in indications common among older populations will grow. These include heart disease, cancer, stroke, pulmonary disease, diabetes and osteoporosis – diseases which favour a cell-based approach to renew, repair or replace damaged tissue and where regenerative medicine could contribute to vastly improved standards of care. Further, many of these diseases and disorders are associated with secondary conditions that are also strong candidates for new regenerative medicine therapies and represent large markets, such as diabetic foot ulcers and chemotherapy-induced neutropenia.

As the elderly population increases in both percentage and real terms, healthcare costs are expected to rise both as a percentage of the federal budget as well as on a per capita basis. Annual healthcare costs for people 65-74 is more than $10,000, a figure which is nearly four times greater than those in the 19-44 age range[1]. The aggregate cost impact of these two indicators will create substantial stress on the economy and personal finances, even before adjusting for inflation (**Figure 1**). Such population changes create a huge demand for therapies for chronic conditions, especially innovative treatments that improve the standard of care, reduce the physical disease burden and shift the cost curve.

Even without future projections, the current market opportunity calculations for key regenerative medicine therapies are substantial. The direct costs associated with chronic diseases that could be addressed by regenerative medicine treatments in the US – late-stage Parkinson's disease, new cases of spinal cord industry, heart failure, stroke and insulin-dependent diabetes –is approximately $250 billion a year[2]. The newest numbers released by the American Heart Association on heart failure and stroke paint a similar picture. Not only is heart disease the leading cause of death in the US, but it is also responsible for 17% of national healthcare expenditures. When future estimates of disease incidence are included, the direct costs of all heart disease are projected to increase from $273 billion in 2010 to $818 billion in 2030[3]. For heart failure and stroke – both central in regenerative medicine research programmes – real medical costs are expected to increase by 200% and 238%, respectively, over the next 20 years[4]. These looming costs create both incentives and opportunities for public and private investment in cell-based medicine as the sector that has the strongest potential to shift long-term costs for such serious acute and chronic conditions.

Numerous companies are poised to deliver effective therapies to this growing patient need. According to analysis done by the Cell Therapy Group, there are currently 275 therapeutic companies with 240 cell-based therapies in clinical development or on the market. These numbers include 44 commercial products and 27 candidates in

Phase III clinical trials[5]. There are 23 regenerative medicine trials in heart failure alone, attempting to tap a market anticipated to reach $80 million in costs by 2030[6]. In addition to the promising therapies in the pipeline, there are already multiple successful regenerative medicine products on the market. More than 300,000 patients have been treated with regenerative medicine products to date – the bulk having received Apligraft (Organogenesis) or Dermagraft (Advanced BioHealing) for foot and leg ulcers. With these sales the regenerative medicine cell therapy market was valued between $100-$200 million in 2010[7].

A nascent industry takes off

Given the forecasted market growth and impressive product pipeline, there is a growing perception in the biotech and pharmaceutical industries, the research community, among policy makers and some parts of the investment community that regenerative medicine is poised for significant breakthroughs in the next few years and could represent the next major leap forward in medical innovation. This view in part is due to several major developments in 2010.

First, and perhaps most importantly, the sector performed quite well in 2010. The top 20 public regenerative medicine companies experienced 40% growth in their market capitalisation[8]. This compares with 23% growth in the BioCentury 100 index of public biotech stocks, 17% for Nasdaq, and 13% growth for the S&P 500. If Dendreon, which makes the autologous immunotherapy PROVENGE®, had been included in the regenerative medicine performance index, the sector's performance would have been even better. In addition, there are a large number of private regenerative medicine companies, several with products on the market, which are attracting the interest of investors, prospective partners or acquirers, or are candidates for initial public offerings. Advanced BioHealing filed an initial public offering in February 2011 in hopes of raising $200 million[9]. There are also numerous orthobiologic companies focused on bone regeneration and cartilage repair which remain private but have captured the interest of investors and the medical device companies. Finally, there are a very large number of profitable tool and service companies developing the enabling technology platforms that are indispensible to the research community and critical to the success of the regenerative medicine industry. Other areas of great potential are drug discovery and cell modulation. Large pharmaceutical companies such as AstraZeneca, GlaxoSmithKline and Roche are all showing interest in using stem cell-based assays for safety and efficacy screening for traditional small molecules. Boutique regenerative medicine firms such as iPierian are pioneering work in this field. Such assays could potentially cut costs and reduce uncertainty in diagnosis and treatment by providing vital information about biological interaction early on in the development process. Many of these companies also experienced significant growth in 2010.

One event that signalled a major advancement in cell-based therapies during 2010 was the approval in April of Dendreon's autologous immunotherapy, PROVENGE®, for the treatment of asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer. PROVENGE® is derived from white blood cells taken from the patient and incubated with a fusion protein comprised of prostatic acid phosphatase (PAP) and GM-CSF before being shipped back to the infusion centre for administration to the patient. Dendreon's facilities should be fully operational by mid-2011 and sales in the US could surpass $1 billion. Their market capitalisation has increased 10-fold from March 2009, when it stood at $412.44 million, to its current capitalisation of $4.74 billion. This was one of the largest increases in valuation of any company in the biotech sector in the past few years. Dendreon's success is significant in that it represents the first approval of an autologous cell product and highlights the potential for the multiple autologous and allogeneic cell therapies in the clinical pipeline. Many of these treatments are being developed for major unmet medical needs such as spinal cord injury, diabetes and critical limb ischaemia, which represent huge market potential. As these products progress through clinical trials and reach the marketplace, the regenerative medicine sector could be poised for significant growth.

Another major development in 2010 that indicated a growing interest in the RM sector among pharmaceutical companies and large-cap biotech firms was the $1.7 billion deal announced in December between Mesoblast and Cephalon. Cephalon received a 19.99% equity stake in Mesoblast for $220 million and global rights to their mesenchymal precursor stem cell platform for cardiovascular disease, stroke and various neurodegenerative indications. The deal also included an upfront payment of $130 million. This was one of the largest biotech deals of 2010 and revealed a strategic shift into regenerative medicine by a

more traditional small molecule pharmaceutical company that recognised the growth potential of this field. Other pharmaceutical companies are making similar strategic investments, which suggests that as regenerative medicine companies continue to progress, there could be multiple options for strategic partnerships downstream.

Despite these positive developments, the traditional venture community has been slow to invest in regenerative medicine. They still view the sector as extremely risky with uncertain regulatory and reimbursement prospects and very long development timelines. Moreover, the VC community is facing its own challenges as many of them are addressing underperforming portfolios, anxious limited partners and limited prospects for raising new funds[10]. Therefore, the cost of funding discovery and early clinical development of regenerative medicine products is being born disproportionately by small-mid size companies funded primarily by federal and private research grants and a small amount of private investment capital. Pharmaceutical firms are beginning to invest more in this field, but it is still early and the amount of funding available has thus far been crowded out by their near-term revenue priorities. If the industry is to sustain the progress it is making in regenerative medicine, careful consideration should be given to new funding models and tax incentives that will attract new sources of capital to this vitally important sector.

Getting the regulatory house in order

Despite the growing market and impressive pipeline for regenerative medicine technologies, tools and therapies, there are still many regulatory roadblocks that need to be addressed to ensure that safe and effective products reach patients quickly. A key component to the industry's broader commercialisation strategy is the reduction of regulatory risk.

The current regulatory barriers to commercialisation are recognised by both industry and regulators. Both groups understand the need for a predictable, efficient and swift review and approval process and are working together to address these issues. These efforts require engagement and co-ordination among many groups, including the FDA and NIH; Congress; industry stakeholders; research institutions and organisations; and the patient advocacy community. The Alliance for Regenerative Medicine (the Alliance) is bringing these stakeholders together to define and achieve actionable steps toward improvements in the regulatory process.

The Alliance is currently working with the FDA and others to address the key regulatory issues currently impacting regulatory risk. Key issues for discussion are: FDA processes; development of standards and consensus best practices in the regenerative medicine community; the need for cross-agency co-ordination; and improving the regulatory science base at the FDA.

FDA processes

Unclear regulatory pathways are one of key issues that affect the risk perception for regenerative medicine companies, both from a product development and investment viewpoint. Clearer rules regarding co-ordination between CBER and CDRH on product review are needed. Even after a product is assigned to one division to lead the review, questions remain as to how the divisions will co-ordinate on key issues. This creates uncertainty for companies as they work toward a regulatory filing in terms of what data will be needed for endpoints, understanding of the timetable for review and other matters. This is a particular challenge in the cross-disciplinary field of regenerative medicine as many products are comprised of both biologic and medical device components and may require expert review from multiple FDA divisions. Discussions with agency regulators earlier on in the development process could help ease some of this uncertainty by providing clarification on agency viewpoints of complex products, especially those that can be considered medical devices or biologics.

Additionally, regulatory approval of regenerative medicine products is impeded by the lack of consensus standards surrounding important scientific issues related to the regulatory process for regenerative medicine products including: cell characterisation; quality control; and animal models. The lack of standards makes comparability across studies (and products) difficult, slows the regulatory process, and contributes to uncertainty in the development process. Development of standards, especially on pre-clinical topics such as those listed above is critical to inform regulatory assessments and analyses of new products. The Alliance has convened an expert working group of scientists from industry, research organisations, and universities to begin work on these standardisation issues with an initial focus on cell potency assay development. Workshops with participation from all these organisations as well as patient advocacy groups and FDA will also be important information sharing opportunities.

References

1 Vincent, Grayson K and Velkoff, Victoria A. The Next Four Decades, The Older Population in the United States: 2010 to 2050. U.S. Census Bureau. May 2010. www.census.gov. http://www.census.gov/prod/2010pubs/p25-1138.pdf. Accessed 14 Mar. 2011.

2 Mason, Chris. The strong financial case for regenerative medicine and the regen industry. Regen Med (2008) 3 (3), 351-363.

3 Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement from the American Heart Association. Journal of the American Heart Association. Circulation. 2011; 123.

4 Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement from the American Heart Association. Journal of the American Heart Association. Circulation. 2011; 123.

5 Buckler, Lee. Cell Therapy Industry Overview: Products And Applications. Cell Manufacturing 2010 Symposium, October 13, 2010.

6 Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement from the American Heart Association. Journal of the American Heart Association. Circulation. 2011; 123.

7 Mason, C, Manzotti, E. Regenerative Medicine cell therapies: numbers of units manufactured and patents treated between 1998 and 2010. Regen. Med.(2010) 5(3), 307-13.

8 Stem Cell – Analysis and Market Forecasts. RRY Publications, LLC. February 2011.

9 Advanced BioHealing files for IPO of $200 mln. Reuters. February 25, 2011.

10 Duff, Wilson. Patent Woes Threaten Drug Firms. NY Times. March 6, 2011.

Cross-agency co-ordination

Increased co-ordination between the FDA and NIH on regenerative medicine related issues is critical to identifying and rolling out new methods to facilitate translation of scientific discoveries into products for patients and to support regulatory science research. The FDA-NIH Leadership Council could address these issues. The Council was created in 2010 to facilitate research and product development through agency co-operation. The Alliance has recommended the creation of a sub-committee to focus on regenerative medicine with the active participation of representatives from the regenerative medicine community. At the least, the Council should create an advisory board for the sub-committee comprised of representatives from industry, patient advocacy groups, research organisations and universities that has ongoing interaction with the subcommittee and Council. Creating an institutionalised mechanism for input will ensure that information is shared across sectors and that policies developed by the agencies are guided by the experience and expertise of people working in the relevant fields.

Regulatory science

The agency needs increased funding to perform regulatory research, so that FDA can become better equipped with scientific expertise needed to regulate new products in regenerative medicine and to define regulatory pathways. This research should be performed not only at FDA but also through public-private partnerships, such as consortia of industry, academia and others. The regenerative medicine community – industry, patient advocacy groups, non-profit research organisations and universities and researchers – should participate in the setting of regulatory research priorities. NIH should participate as well and help fund this research. Since regenerative medicine research is occurring throughout the world, efforts should also be made to ensure co-ordination among various government regulatory bodies.

All of these issues are being addressed by the Alliance through meetings and discussions between agency decision-makers and leaders from industry and other stakeholders. Additionally, Congress has entered the debate through the introduction last year of the Regenerative Medicine Promotion Act (HR 6173). The legislation contained provisions designed to develop a regulatory system that would enable speedy approval of safe and effective regenerative medicine products. Specifically, the legislation called for an assessment of current federal actions and policies on regenerative medicine; created a new national Regenerative Medicine Co-ordinating Council to include senior officials from all federal agencies that fund or regulate regenerative medicine research or products to co-ordinate federal funding and regulatory policies; and authorised funding for the FDA to conduct regulatory research in regenerative medicine.

The Alliance is working with a bi-partisan group of Congressmen and Senators in 2011 to reintroduce the bill this year. DDW

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