Regenerative Medicine and Health Technology Assessment: Vision and Challenges

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Received: 06-30-2016
Accepted: 08-01-2016
Published: 08-08-2016
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Abstract

Cell sheet engineering technology, a form of regenerative medicine that uses tissue regeneration technology to cure or reduce disease in patients, has the potential to dramatically improve health outcomes worldwide. Cell sheet engineering therapy represents a potential cure, with possibly high one-time costs of cell sheet manipulation but improved health outcomes versus the long-term costs of many traditional ongoing symptom-management therapies. Research is increasing into clinical applications of cultured cell products as well as into the automation of multi-disciplinary integrated processes of manufacturing and distributing living cell sheets to treat large numbers of patients. Because this technology is neither pharmaceutical nor a traditionally-defined medical treatment, issues of regulation, value, reimbursement, investment, and global access must be addressed as clinical research continues. Comparative research showing the technology’s value compared to standard of care will become increasingly important for acceptance into budgets, guidelines, and policies. Patent issues, which vary widely from country to country, must be addressed internationally, requiring experts trained in regenerative medicine intellectual property rights. Pricing and payment decisions must balance development, manufacturing, and delivery costs with affordability, encourage and reward innovation, and provide access for countries with fewer resources. With cell sheet engineering technology still in early stages of development, now is the appropriate time to begin addressing these issues, and these discussions must include government, industry, clinical, and patient representatives on an international level. In addition, these discussions may help define acceptance paths for future innovations in regenerative medicine.

Keywords: Health Technology Assessment; Regulatory; Health Economics; Cost-Effectiveness Analysis; Regenerative medicine; Cell Sheet Engineering Technology; Reimbursement; Pricing

**Key Points**

- Regenerative medicine technology often represents a one-time cure, both comparative effectiveness data and cost-effectiveness data versus standard of care (often long-term symptom management) will be essential to show benefit in an industry increasingly averse to adding coverage for innovative technologies within limited budgets.

- International forums consisting of government, industry, clinical, and patient representatives should continue to work together on complex international patent issues as well as standardization issues in technology, automated manufacturing procedures, and global access.

**Introduction: Regenerative Medicine and Cell Sheet Engineering Technology**

To advance the discussion of regenerative medicine and its future challenges and opportunities, the Third Annual Health Technology Assessment International Symposium and a one-day advisory panel meeting were convened at the University of Tokyo, September 15-16, 2014, addressing the topic from scientific, economic, and regulatory perspectives. This article presents highlights from that event.

Regenerative medicine is the development and application of tissue regeneration technology, materials, and strategies to cure or reduce disease that is not controlled by drugs, surgery or other traditional interventions. A broad definition of regenerative medicine refers to any approach to restore normal tissue or organ functions [1]. Within the framework of our symposium our focus was the generation of target cells from autologous or allogeneic cells, which are used to replace, repair, or augment tissues or organs within the body [2,3].

Regenerative medicine is already in use today, with over 60,000 stem cell transplants performed annually worldwide to treat oncology and blood-based disorders [1]. In cell sheet engineering technology, another form of regenerative medicine developed by Professor Teruo Okano of Tokyo Women’s Medical University and his collaborators, a cell sheet maintains its own adhesive protein that adheres to and integrates with the surface of organs or tissue. Investigation into potential applications for cell sheet engineering technology is increasing, and initial studies are showing potential success when compared with standards of care in areas such as esophageal cancer [4-7]; knee cartilage repair [8,9]; corneal [10,11], heart [12], and periodontal disease [13]; and pearl tumors of the middle ear[14].

The U.S. Department of Health and Human Services calls regenerative medicine “the next evolution of medical treatments,” adding, “This revolutionary technology has the potential to develop therapies for previously untreated diseases and conditions [15].” As research into regenerative medicine grows, governments and other payers are being asked to evaluate and modify existing regulations and policies to address regenerative medicine, which is neither a pharmaceutical nor a traditionally defined medical treatment. Significant questions must be answered before governments and payers can fully incorporate regenerative medicine into health care regulations, including: 1) How do we calculate value? 2) How do we encourage innovation? 3) How do we ensure reimbursement? 4) How do we make this technology available globally? [Figure 1]

**Figure 1.** Major Challenges to Bring Regenerative Medicine to the Marketplace.

**Beyond RCTs— A Growing Need for Value Data**

During early stages of research, development, and diffusion, most new technologies are expensive. Research, trial, manufacturing, laboratory, delivery, training, and implementation costs are still high. But initial high costs are not necessarily an impediment if data justify costs in terms of improved outcomes or savings. Gathering outcomes and comparative data on regenerative technologies and producing a reliable health technology assessment (HTA), then, is critical to advancing the technology.

With any new product, payers want to know if it is safe, efficacious, and has a valuable effect on outcomes, costs, or both. The first two questions are answered during traditional randomized controlled trials (RCTs). But RCTs are only required to show safety and efficacy, not effectiveness or value when the product is used in clinical practice. In general, comparative effectiveness data showing results and costs in target populations cannot be analyzed until the product has been used in the market for some time. Ironically, the lack of such effectiveness data at launch can discourage payers from covering the new technology, keeping it out of the reach of...
patients and delaying the accumulation of real world data.

Overcoming this dilemma and amassing strong comparative effectiveness data will be essential for the advancement of regenerative medicine. Unlike therapies that manage symptoms of an ongoing disease, regenerative medicine’s goal is often a cure. That means the value of a cure-oriented technology, with its one-time cost, may differ greatly from the value of symptom management therapies for the same disease, which spreads costs over a longer timeframe. A recent example of this occurred in the hepatitis C market with sofosbuvir’s introduction [16].

Comparative effectiveness research examines the technology’s impact on health care (benefits or quality-adjusted life years gained, for example) and/or its costs, then compares those benefits and/or costs to existing alternatives. Although the process sounds straightforward, in reality it will be anything but. Because the value for a cancer cure is different from the value of a knee cartilage repair, for example, regenerative medicine’s value may be calculated separately for different applications of the technology in different diseases, and potentially within different stages of a single disease. In addition, limited data on the standard of care for some targeted diseases makes comparisons challenging. Furthermore, the governments and payers may hold biases against real-world data and observational studies because of the inconsistent nature of past reports. In fact, HTA is not fully utilized in Japan yet, and various policies limit its use by Medicare in the U.S. However, the development of “personalized medicine” may expand the focus from evidence gathered during RCTs for pre-market authorization to include evidence gathered from post-market observational studies.

The Global Complexity of Patents and Regulations

Once a rich evidence base has been developed for assessing health technology, the next challenge is to get that assessment approved by governmental organizations and incorporated into regulations and policies, and to protect intellectual property. Regulations and patent laws vary widely from country to country, making global availability a complex issue.

Health care systems are often designed to accommodate pharmaceuticals and traditionally defined medical treatments, but regenerative medicine does not fit neatly into either category. In the U.S., therapies are classified as a device, biologic, or drug (determined by the mechanism of action), and each classification has its own pathway for regulatory review and approval by the U.S. Food and Drug Administration (FDA). However, regenerative medicine may fall into more than one classification, complicating pathways and possibly requiring integration, duplication, or the development of new approaches to achieve regulatory approval. In the U.S., in 2010, the Regenerative Medicine Promotion Act was introduced to support regenerative medicine with increased funding for research, commercial development, and development of a regulatory environment to enable rapid approval of safe and effective regenerative medicine products [17]. The bill was rejected. A similar bill re-introduced in 2014 is still under review by a subcommittee, [18] demonstrating how long the process of changing regulations can take.

In May 2013, Japan’s Promotion Act of Regenerative Medicine was enacted, and in November 2014, Japan’s Pharmaceutical and Medical Device Act (PMA) and Regenerative Medicine Safety Law were enacted, creating a more appropriate system to ensure the safety and effectiveness of therapies [19]. These laws created a new category for regenerative medicine products, establishing a conditional and time-limited approval system for such products to secure earlier access for patients. The law requires mandatory outcome reports and encourages cost-effectiveness analysis to promote wide access and innovation, although it does not define how those goals will be achieved or measured. Japan appears to be on a faster track towards support for the research and development of regenerative medicine than the U.S. and many other countries; their approach may offer a model for other countries.

Regenerative medicine also raises questions of intellectual property rights. Within each country, decisions must be made on what is being patented, who owns the patent, and whether a single patent is awarded for the technology’s use in all applications or for individual applications. As the technology progresses, standardized cell culture methodology and treatment protocols will be potential areas of cost reduction, but will introduce more patent issues to resolve. Additionally, medical treatments can be claimed as intellectual property rights in the U.S. and, to some extent, in some E.U. countries, but not in Japan and Asia. Regenerative medicine also raises ethical concerns, such as whether a company can patent human allogeneic cells.

Faced with complex patent issues, industry and academic representatives are engaging in global collaborations to address technology and manufacturing standardization issues. By focusing on standardization consensus rather than patent competition, such international forums may be key to the development and acceptance of regenerative medicine.

Reimbursement Issues

After regulatory issues are addressed in a given country, reimbursement support from public (governmental) and private (commercial) payers must be sought. Every year, new products are introduced into an already crowded market, but budget limits make payers less likely to replace existing products with new technologies. With regenerative medicine, the pharmaceutical industry is cautiously watching whether payers will be willing to trade higher one-time costs for potential cures.
Assuming payers become convinced that cell sheet engineering technology shows value for their populations, pricing becomes the next step. Costs of developing and delivering a new technology are incurred during three stages: research and development, manufacturing, and delivery (which includes marketing, distribution, provider handling, and treatment). Under cost-based pricing and reimbursement, the product’s price is determined by the cost of manufacturing and delivering the product to the consumer. Under value-based pricing, price is determined by the product’s perceived or expected value, which may be measured as quality-adjusted life-years (QALYs), for example. With value-based pricing, the value of cell sheet engineering technology could vary not just between diseases, but at different stages of a single disease. However, current pricing systems are not nuanced enough to pay for different values of the same pill, for example, in different stages of the same disease. Also, few health care systems’ databases measure and track patient records adequately enough to make such indication-based value pricing feasible [20].

There are clearly opportunities here for future research in further pharmacoeconomic methodological development [21,22]. In addition, many countries do not use HTA in decision making and do not use value-based pricing and reimbursement, although such policy changes are being discussed. Japan may be unique in developing its own HTA regulations including cost-based and partially value-based pricing (called a premium rule), [23] and its government is moving towards implementing pharmacoeconomic requirements as a new policy beginning April 2016, which will employ standard methods to assess cost-effectiveness of new technologies. Another challenge arises in countries such as the U.S. that apply an administered pricing model for hospital procedures, charging a fixed price for all services provided for a single medical event. Fortunately, unlike pills that are identical in every case, the cell sheet generation procedure varies by application, which may help differentiate value.

Payers need objective and verifiable evidence from well-designed, rigorous cost-effectiveness studies to create policies ensuring better health outcomes within controlled budgets. Where real-world evidence is limited, modeling can provide data for initial value projections, which can be refined later as real-world evidence is accumulated. With these projections, manufacturers, providers, and payers can work together to develop flexible policies, incorporating concepts such as performance-based agreements (also called risk-sharing agreements) that tie evidence to price, gaining early reimbursement coverage with agreements to measure subsequent performance and modify policies accordingly. However, there can be resistance to cost-effectiveness evidence. Some opponents argue that governments and payers should not interfere with provider and patient decisions based on cost. In addition, observers raise ethical questions, such as whether cost-effectiveness evidence discriminates against disabled patients, would not give priority to the sickest or most vulnerable patients, and whether it is better to provide small benefits to many patients or provide large benefits to fewer patients [24].

Adaptive licensing may lend itself well to regenerative medicine. Adaptive licensing, also called adaptive pathways, integrates regulatory and payer needs into medical technology development, potentially accelerating patient access to vital therapies more cost-effectively [25,26]. An important issue in pricing and reimbursement is the concept of encouraging and rewarding innovation. In cost-based pricing, price is determined by costs of manufacturing and delivering the therapy. Research and development costs are not considered, although those can represent the bulk of the developer’s investment. Historically, innovative medical technologies were developed primarily in the U.S. or Europe, so cost-based systems make economic sense in countries that only import such products. Japanese cost-based pricing is different since it incorporates research and development costs, although those costs must be claimed according to the government’s rules and equations.

Now that newly emerging developed countries are developing innovative medical technologies, their lack of experience in evaluating innovative products and considering development costs could have serious ramifications. Systems which allow value-based pricing and patent protection, reward innovation by letting developers recoup at least some of the investment for products that reach the market before other companies produce generic versions and undercut their return on investment. Patent protection can even encourage companies to develop products that target smaller patient populations, by ensuring a longer timeframe for recouping costs. The U.S.’s system may better reward so-called “blockbuster” drugs, which can provide a pharmaceutical company enough capital to finance innovative research into other technologies, even if those never reach the market [27]. However, one downside to this system is that the U.S. does not provide universal health care. In contrast, Japan is seeking a balance between universal health coverage and medical innovation. Under Prime Minister Shinzo Abe’s global competition strategic initiative, Japan is encouraging more innovation-friendly approaches to health care development, while still maintaining universal health care, although how to measure and encourage innovation must still be determined with input from government, academia, and other sources [28].

The E.U. faces additional issues as a result of comprising 28 countries at different stages of economic development and per capita income, with varying abilities to pay for health care and innovation. E.U. countries need cost-effectiveness evidence to help them allocate limited resources for their...
The 3rd HTA International Symposium held September 15-16, 2014, in Tokyo, Japan, was planned and presented by the Graduate School of Public Policy, The University of Tokyo, in association with the Cannon Institute for Global Studies under the auspices of the Cell Sheet Tissue Engineering Center of Tokyo Women's Medical University (Regenerative Medicine Research project sponsored by MEXT Japan). The authors would also like to thank Takashi Sugimoto, Project Fellow, The University of Tokyo, for his assistance with and contributions to the preparatory meetings and Amy Sainski-Nguyen and Kelley J. P. Lindberg for their assistance in the editing and preparation of this manuscript.

Acknowledgements

The 3rd HTA International Symposium and its preparatory meeting held September 15-16, 2014, in Tokyo, Japan, were sponsored by MEXT Japan. Financial support for the transcription and editing of this manuscript was provided by Japan Science & Technology Agency (JST) Research Institute of Science and Technology for Society (RISTEX).

Sources of Financial Support

Content for this report is based on presentations, panel discussions, and a closed preparatory meeting of speakers at the 3rd HTA International Symposium held September 15-16, 2014, in Tokyo, Japan. The Symposium and its preparatory meeting were presented by the Graduate School of Public Policy, The University of Tokyo, in association with the Cannon Institute for Global Studies under the auspices of the Cell Sheet Tissue Engineering Center of Tokyo Women's Medical University (Regenerative Medicine Research project sponsored by MEXT Japan). Financial support for the transcription and editing of this manuscript was provided by Japan Science & Technology Agency (JST) Research Institute of Science and Technology for Society (RISTEX).

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