TISSUE ENGINEERING: Part B
Volume 23, Number 2, 2017

DOI: 10.1089/ten.teb.2016.0292

termis
Tissue Engineering
& Regenerative Medicine
International Society

REVIEW ARTICLE

How Regenerative Medicine Stakeholders Adapt to Ever-Changing Technology and Regulatory Challenges? Snapshots from the World TERMIS Industry Symposium (September 10, 2015, Boston)

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Regenerative medicine (RM) is a fascinating area of research and innovation. The huge potential of the field has been fairly underexploited so far. Both TERMIS-AM and TERMIS-EU Industry Committees are committed to mentoring and training young entrepreneurs for more successful commercial translation of upstream research. With this objective in mind, the two entities jointly organized an industry symposium during the past TERMIS World Congress (Boston, September 8–11, 2015) and invited senior managers of the RM industry for lectures and panel discussions. One of the two sessions of the symposium—How to overcome obstacles encountered when bringing products to the commercial phase?—aimed to share the inside, real experiences of leaders from TEI Biosciences (an Integra Company), Vericel (formerly Aastrom; acquirer of Genzyme Regenerative Medicine assets), RegenMedTX (formerly Tengion), Mindset Rx, ViThera Pharmaceuticals, and L'Oreal Research & Innovation. The symposium provided practical recommendations for RM product development, for remaining critical and objective when reviewing progress, for keeping solutions simple, and for remaining relevant and persistent.

Keywords: regenerative medicine, commercial translation, tissue engineering, business management, recommendations

Introduction/Background

The TERMIS-AM Industry Committee (IC) recently completed its 5-year plan for investigating, communicating, and educating the research community about topics that are most relevant to TERMIS members in relation to the commercialization of tissue engineering/regenerative medicine (TERM) products. The IC conducted an initial survey, published in 2011,[1] and held the first of several workshops to disseminate the results and offer opportunities to promote better understanding of the issues identified in the survey. The IC further engaged the research community through additional workshops at the TERMIS-AM annual conferences in 2013 and 2014, at the TERMIS World Congress in 2015, and through additional publications.[2–9] During this time, it became evident that there was a strong interest within the TERMIS membership for information and insights into commercial processes and regulatory guidelines, as well as a desire for dissemination of emerging and established best practices. To address this, TERMIS-AM and TERMIS-EU ICs cosponsored the session titled ''How Regenerative Medicine Stakeholders Adapt to the Ever Changing Technology and Regulatory Challenges?'' at the 2015 World Congress meeting held in Boston, MA, on

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September 10, 2015. The symposium consisted of two parts, both featuring a distinguished group of speakers and panelists who shared their expertise and discussed their perspectives. The first session focused on evaluating the past and current situation of regenerative medicine (RM) and the five major drivers for successful translation of RM solutions. This article provides a synopsis of the second session entitled ''How to overcome obstacles encountered when bringing products to the commercial phase.'' A series of speakers with a variety of RM backgrounds (i.e., cell therapies, tissue engineering, small molecules, tissue graft, and collagen scaffolds) shared their experiences in bringing technologies through the different phases of development to the market. Most were early players in TERM technologies, and all experienced growing pains and the consequences of an evolving regulatory approach to their novel products. Their brief lectures were followed up with a panel, driven by a series of questions as follows:

- How to overcome—clinical, technical, financial, and regulatory…—obstacles encountered when bringing products to the commercial phase?
- What has been learned from past failures? What can we learn from on-going commercial translation of TE/RM?
- What are the success stories? What are the contributions from the technology, the clinics, and the business models?
- From these experiences, how should a compelling story be written to support the key development stages of RM/TE solutions; what are the value propositions for TE/RM to be successful in the future?

Speaker Summaries

Robert Buelher (VP Manufacturing and Quality; TEI BioSciences) shared his past and current experiences at both Organogenesis and TEI Biosciences, concerning the development of tissue-engineered skin, collagen scaffolds, and xenografts. He emphasized the importance of clearly defining the product from design, processing, regulatory, and reimbursement perspectives. For example, the manufacturability should be carefully evaluated from the very preliminary product development stages with particular attention to (1) safe, reliable, and sustainable sourcing and supply of raw materials, especially for biological components, and (2) the economic viability of the product to be developed, which will be determined by the standard cost of production. Although this may seem intuitive for all medical products, troubleshooting during later stages of preclinical and early clinical development in TERM technologies can often lead to slight changes that are initially deemed to be of minor consequence but which may have amplified effects on the resulting biology. Moreover, regulatory agencies pay attention to such small changes and require information to evaluate potential patient risk. This may lead to the full reassessment of the biocompatibility and safety profile of the product, jeopardizing commercial development of the product because of extra costs (e.g., up to millions USD) and extended time to market (e.g., up to a couple of years).

Ross Tubo, formerly of Genzyme Tissue Repair and current Chief Scientific Officer at Vericel, offered the perspective of a cell and gene therapy company. Given the potential complexity of cell and gene therapies as well as the perceived and actual risks posed to patients, the U.S. Food and Drug Administration (FDA) is understandably thorough in their dealings with such products. There can be a myriad of safety questions related to cell and gene therapy treatments and, in today's regulatory, medical, and reimbursement environment, efficacy must also be taken into account. Essentially every product—and its application—is different. Therefore, even when the development team is highly experienced, new questions can be raised by the FDA that will impact timelines and cost. Dr. Tubo stressed early engagement with the FDA as a means to mitigate this stress. Successful implementation of preinvestigative new drug meetings with regulators, and even the use of ''presubmission'' meetings, can be used to share early research findings and solicit FDA feedback on the most appropriate pathway to pursue.

Tim Bertram, Chief Executive Officer of RegenMedTX, shared his experience with Tengion, a company that had been at the forefront of urological RM product development for more than a decade. Tengion raised more than $350M in investment capital, a notable accomplishment for a start-up company in the RM space. They were also able to attract a highly experienced and complementary management team, an attribute stressed by Dr. Bertram as invaluable, although not without limitations. Despite knowledgeable directors, an evolving regulatory landscape placed significant challenges on Tengion. He further emphasized the importance of setting manufacturing processes and standards early in the product development life cycle, and the importance of a robust fit between potential products and accepted medical practice. On the business management side, Dr. Bertram discussed the important need to manage investor expectations for RM technologies, as product development cycles can be much longer than traditional medical products. It is also important that there is a clear value proposition communicated to all stakeholders, as many RM products, particularly engineered tissues, are anticipated to have a high per-unit cost basis.

On another note, Dr. Bertram recommended carefully managing the depth of the product candidate portfolio as ''chasing too many rabbits may result in getting neither one.'' This is particularly important because of limited technical and financial resources as well as the high complexity of RM solutions. Tengion had a mixed experience with a broad portfolio of product candidates, intended to be used for all the indications, urologic, renal, gastrointestinal, and vascular surgeries. As a consequence, the company went into bankruptcy. It resuscitated as RegenMedTX, focusing now on the development of autologous cell-based therapies for the treatment of chronic renal disease only. The selection of this disease condition was motivated by its commonality and impact on millions of people every year in the United States, the severe associated loss of quality of life, particularly in its most advanced stages, and the absence of effective solutions stopping the course of the disease.

Bernard Malfroy-Camine is the current President and CEO of MindSet Rx (formerly Eukarion, Inc.), and ViThera Laboratories, an early stage drug company focused on treatments for inflammatory bowel disease. Dr. Malfroy-Camine talked about his experience in founding and directing Eukarion, Inc. (now Mindset Rx). Eukarion, Inc. aimed to treat neurodegenerative disorders using synthetic

enzymes that mitigate the effects of oxidative stress. He talked about how early preclinical success does not always translate into a viable commercialization pathway. Oxidative stress plays a significant role in the pathology of many diseases, and targeting degeneration rather than regeneration as a therapeutic strategy has several advantages. However, although Eukarion's enzymes had many potential disease targets such as in inflammation (chronic inflammation in colitis, inflammatory bowel disease, etc.), fibrosis, and radiation-induced dermatitis, this did not guarantee commercial success. It is critical that earlier studies produce clinically relevant data so that a target product profile can be generated. Such profiles greatly enhance the chance of commercial success. In parallel, the FDA must be engaged early on to obtain input on essential preclinical studies. However, it is worth noting that the time frame for the development path of this type of product can consume a significant portion of the patent protection period and thereby diminish investment interest.

This last comment by Bernard Malfroy-Camine raises important questions about best practices for the intellectual property management of RM solutions. There are no easy or fit-to-all answers. There are only critical questions for patent applications such as (1) when to file, (2) how to file, and (3) what to protect. Panelists recommended a balance between secrecy and patent protection that considers the potential value of first-to-market advantages relative to the cost of market approval hurdles and the existing patent landscape.

A large company perspective was provided by Michelle Rathman, R&D Director, from L'Oréal, a company not normally associated with RM. Dr. Rathman shared the background surrounding L'Oréal's decades-long effort to produce physiologically functional engineered human skin, to be used in the safety and performance testing of cosmetics and other skin care products. For example, aged skin and functionalized epidermis with a modified cutaneous barrier—made of filaggrin knockout cells—have been engineered as disease models. Another direction that is being explored is the personalization of engineered skin models by using individual cells of different phenotypes to better represent human physiology and pathogenicity variety (e.g., models reconstructed with skin cells of patients suffering from xeroderma pigmentosum). Although not strictly considered a medical treatment, the company's efforts nevertheless fall under the purview of the Food, Drug, and Cosmetic Act in the United States and other regulations worldwide. Therefore, L'Oréal shares many of the same considerations facing tissue engineering companies. L'Oréal's decision to forgo animal testing for its product development has not only placed additional constraints on their product development plans but has also led them to pursue alternative and innovative solutions. Dr. Rathman discussed how L'Oréal gained valuable technology and expertise through strategic acquisitions and how these acquisitions accelerated technology development timelines. She acknowledged that this method is typically not possible for small start-up companies. However, she also highlighted L'Oréal's success in accumulating expertise and other resources by working collaboratively with other organizations. For example, she mentioned recent work by L'Oréal to develop grafts for burn patients and potential treatments for xeroderma pigmentosum.

Key Learnings

The panel discussion focused on the early stages of technology development, and lessons learned from the experience of each speaker that were instrumental in their success. The speakers agreed that finding and pursuing the right technology are an essential first step. This requires careful and objective evaluation early in the process to determine whether a product development effort is justified. Such considerations include not only the safety and efficacy of a product in an appropriate and profitable application but also the resources it will take to get there, manufacturing considerations, regulatory path, intellectual property positions, market and reimbursement issues, and adoption into mainstream medical practice. Recruiting individuals with the experience and expertise to conduct such evaluations is essential. The panel also stressed the need to be flexible and to pursue flexible strategies given potential changes in the regulatory environment. Flexibility and adaptation increase the chance for success. Simple technologies are favored, but the panel acknowledged that this ideal is not always possible in the field of RM. In light of this, it is critical to identify key components of the product early. That is, early determination of the mode of action, product potency, and the ability to apply this knowledge to manufacturing processes and regulatory activities is critical.

In sum, RM has huge but mostly unexploited potential. Pursuing RM is a good choice, despite its complexity, but requires heeding the following recommendations: (1) excellence in operations, (2) developing RM solutions/products using a robust risk-based approach, (3) elucidating the mechanism of action for products/solutions, (4) recognizing that you cannot develop everything on your own and that you should collaborate with external experts, and (5) being stubborn and focused.

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Received: July 14, 2016
Accepted: October 7, 2016
Online Publication Date: November 21, 2016