# Value-Engineered Translation for Regenerative Medicine: Meeting the Needs of Health Systems

**Tania Bubela[1,*] and Christopher McCabe[2]**

## ABSTRACT

Despite high expectations of economic returns, large investments in regenerative medicine technology have yet to materialize, partly due to a lack of proven business and investment models, regulatory hurdles, and a greater focus on cost-effectiveness for reimbursement decisions by payors. Adoption of new economic modeling methods will better link investment decisions to value-based criteria of health systems.

In spite of ongoing challenges, a substantial volume of stem cell therapies are moving into late-stage clinical development.

Regenerative medicine aims to harness stem cells, biomaterials, and molecules to repair, regenerate, or replace diseased cells, tissues, and organs. Internationally, policy-based estimates of economic return from the creation of a regenerative medicine industry range over orders of magnitude from tens of millions to billions of dollars, while predicted employment gains vary from tens of thousands to hundreds of thousands of jobs [1,2]. Jurisdictions as disparate as India, China, Japan, Singapore, the United Kingdom, Australia, and Canada all signal intense competition for economic advantage, each declaring a bid for preeminence in regenerative medicine. U.S. states such as California, Massachusetts, and Texas have committed significant funds and legislative support to stem cell research based on this expectation of rapid economic and health returns.

In contrast with this expectation, however, large-scale corporate investment in the field has been slow to materialize largely because of the complexity of cell- and tissue-based therapies compared with small molecules and even other biologics; a cautious and evolving regulatory pathway; and the lack of proven business and investment models [3–5]. Here, we first discuss business models that are emerging for regenerative medicine. We then call for investment decisions along research and development pipelines for complex biologics and combination products to consider likely market access hurdles. The largest markets will be health systems that have adopted methods for health technology assessment to ensure that novel therapies are more cost effective than the ones they replace within limited healthcare budgets. Given the personalized nature of many intended applications for regenerative medicine, as well as manufacturing costs, which may exceed even those for biopharmaceuticals, cell- and tissue-based therapies will likely need to be close to curative to be cost effective compared with current therapies. Alternatively, they must target diseases for which there are limited or no treatment options, to which standard value criteria are less stringently applied [6].

In spite of ongoing challenges, a substantial volume of stem cell therapies are moving into late-stage clinical development [7–9]. The stem cell field has gone global, with increasing numbers of trials outside of North America and Europe. We conducted a comprehensive analysis of 4,102 stem cell clinical trials published up to the end of 2012 in ClinicalTrials.gov and the WHO *meta*Register of Controlled Trials [10]. We classified 860 as novel stem cell clinical trials. Our definition of novel excluded trials that were observational in nature; involved an established stem cell therapy for an established indication, such as hematopoietic stem cell transplantation for leukemia; or investigated supportive measures surrounding a stem cell therapy

[1] School of Public Health, and
[2] Department of Emergency Medicine Research, University of Alberta, Edmonton, Canada.
*(Correspondence: tbubela@ualberta.ca)

such as antibiotics to prevent infection in hematopoietic stem cell recipients.

While the majority of trials remain early-stage academic center trials that use hematopoietic stem cells to treat hematopoietic cancers and anemias, 25% of novel trials reported industry as either principal sponsor or collaborator, testing products and systems for autologous or allogeneic use. The majority of companies engaged in clinical trials were small to medium in size and privately held biotechnology companies. Many were engaged in testing stem cell products for allogeneic use in a broad range of conditions. Some firms, such as Athersys, Osiris, and Medipost, were engaged in trials for multiple, unrelated conditions. Others with allogeneic products, such as Advanced Cell Technology and Mesoblast, were more targeted. Larger pharmaceutical companies (e.g., Pfizer and Takeda Italia Farmacutici) were testing small-molecule drugs for stem cell mobilization and/or derivation, as well as entering into joint ventures with biotechnology companies for allogeneic SC products. The engagement of pharmaceutical companies in the stem cell space remains largely focused on product development for broad-based use. Indeed, one product, Prochymal, has received a notice of compliance with conditions in Canada for the treatment of pediatric steroid-refractory graft-versus-host disease. This is the first stem cell biologic licensed by a national regulatory agency [101]. Prochymal is also being evaluated in phase III clinical trials for graft-versus-host disease and Crohn's disease and is the only stem cell product currently designated by the U.S. Food and Drug Administration as both an orphan drug and a fast track product [102].

From our analysis, it is evident that a number of business models are emerging for regenerative medicine. The models most closely aligned with conventional clinical applications are (i) drugs that act on stem cells by promoting stem cell recruitment, mobilization, or reprogramming; (ii) the orphan disease model, which incentivizes the development of subsidized, high-cost therapies for extremely rare diseases with no other treatment options; (iii) the bone marrow transplant (BMT) model, for standard and novel indications, such as autoimmune disorders, including multiple sclerosis and diabetes (the BMT model involves on-site collection, processing, and transplantation of autologous stem cells); and (iv) the development of allogeneic products for allogeneic, mass-produced, and distributed stem cell products, which is analogous to the current Pharma model. Beyond clinical applications, other models with lower regulatory burdens are also apparent. These are largely supportive of research and development, such as reagent and equipment supply; use of specific disease stem cells as tools for traditional drug discovery or screening; clinical trial management; and the development of centralized, clinical-grade cell-processing or device manufacture with distribution to clinical centers. This model currently supplies clinical-grade material for trials. One model of manufacturing adopts an off-the-shelf approach [3,5], using standardized therapies that allow for scaled manufacturing and bulk production, similar to current biopharmaceuticals. A second model is off-site processing of cells for autologous transplantation with GMP standard facilities [5]. A number of publicly funded initiatives currently support product development and manufacturing through the provision of clinical-grade cell-based material for clinical trials [11]. For example, the National Heart Lung and Blood Institute supports the production assistance for cellular therapies and its five cGMP facilities in the United States. Finally, of less interest to health systems, some companies are developing cosmetic and veterinary applications, and there is a market for private stem cell banks.

The commercial environment in which cell-based therapies will launch, regardless of business model, is increasingly challenging. Price and value for money are now explicit determinants of whether and for which patients healthcare payers, the largest market for stem cell therapies, will approve reimbursement [12–15]. Innovative technologies, such as stem cell technologies, must travel through many stages to become a healthcare product available to patients, where a series of institutional, structural, regulatory, behavioral, financial, and political factors contribute to the probability of success. This is a challenging environment for conventional therapies, and considerably more so for regenerative medicine, where the science itself is complex [9], and where many products will be combination products, engaging multiple developers across the associated technologies and multiple regulatory pathways [16]. For example, tissue engineering combines cells with bioscaffolds, which may also be combined with small molecules to encourage endogenous recruitment of cells. Cell therapies may also be combined with medical devices or encapsulated to avoid immune system attack. The failure of any one of the combined technologies within the regulatory pathway may mean failure for all. Even when all constituent technologies navigate regulatory pathways successfully, failure to coordinate the translational processes may still impose significant costs.

The historical model for the clinical translation of basic science research may be defined as technology-push via traditional commercialization pathways [17,18]. These pathways comprise a series of distinct translational steps supported by silos of research activity. While meeting the evaluative targets for each step of the translational pathway is necessary, it does not determine whether the next stage of translation represents a good investment, from either a commercial or a health system perspective. As a result, some technologies that have pushed through to regulatory approval are not paid for, as the considerations that determine each of the microtranslations (from preclinical to clinical development, early clinical studies to late clinical studies) are only indirectly related to the criteria that determine reimbursement. Furthermore, the current reality of limited health budgets means that healthcare payers are increasingly specific about what they will pay for.

What is currently missing from development decisions for new regenerative medicine technologies is a realistic appraisal

of whether a piece of new knowledge can be translated into a marketable healthcare product. Most importantly, this requires an assessment of whether a healthcare payer will reimburse the technology at a price sufficient to generate a competitive return. Developers can no longer assume that technologies that make it to the market will be adopted and paid for; rather, they must respond to the pull of the market.

Developers in the field of regenerative medicine must therefore pay more attention to market needs, necessitating a shift toward a market-pull model of translation. In this model, technology developers must understand and target the evidence requirements of healthcare budget holders (both public and private) throughout the translation process, ensuring the existence of a "reimbursable evidence dossier" by the time of product launch [19]. The largest market for regenerative medicine therapies will be healthcare systems, focused on providing sustainable and comprehensive healthcare for defined populations. The implications of an inadequate evidence base for regenerative medicine technologies include limited patient access, substantial price discounts, and a degree of withholding reimbursement awaiting further research.

In response to the shift to a market-pull model, some payers are abandoning the historical "price-taker" approach in favor of value-based pricing as a model for incentivizing the development of technologies that meet the needs of healthcare systems [14]. Over the last decade there has been a number of advances in the methods for assessing the value of investing in the development of evidence on the safety and effectiveness of innovative technologies, often referred to as value-of-information analysis [20–25]. Unlike conventional hypothesis-driven research, value-of-information analysis recognizes that reimbursement decisions are based upon expected values rather than tests of statistical significance and inference [26]. In this context, research has value to the decision maker to the extent that it reduces the risk of making the wrong decision—that is, paying for a technology that is not good value for money or failing to pay for one that is good value. The return on investment in research can be characterized by quantifying its expected impact on the probability the technology will be adopted by a healthcare system or systems. For the manufacturer, the adoption decision generates revenue from sales. For the healthcare payer, the value is generated from the reduced risk that the technology fails to deliver the predicted health benefits and thus costs more than it produces [27,28].

Further supporting the market-pull model is the central role of social values, which has led to an expanding body of work to identify the values that should inform reimbursement decisions [29]. Social values may include higher values for orphan indications, but the evidence for this is currently limited. Studies on the characteristics of legitimate or fair healthcare reimbursement processes are, however, supporting the development of infrastructures that hardwire population and patient inputs into the development of decision-making criteria [30,31,103,104]. This increasing focus on the value of health gain, combined with the ability of healthcare systems to pay for health, is prompting interest in the explicit linkage of investment in research in innovative technologies to the return on that investment, in terms of population health from the payer perspective [27,32,33] and sales revenues from the perspective of health technology developers [34,35].

Finally, from the perspective of allogeneic product development and even autologous cell processing, the two most prominent business models in the growing translational research space, lessons may be learned from biopharmaceuticals. The key lesson is that substantial manufacturing costs can have significant commercial implications. High manufacturing costs translate into higher prices, delaying market access, and reducing the scope of the reimbursed population below those for whom there is evidence of clinical benefit [36]. Biopharmaceuticals may have been victims of a change in the reimbursement environment that took place while they were still in development. Many of the investments in these products might not have been made if they had been assessed against the reimbursement criteria the technologies subsequently faced. However, since value-based market access criteria are increasingly mature, these can now be reliably incorporated into frameworks for appraising alternative investment strategies for bringing novel regenerative medicine therapies to market. Regulation of both the evidence base to support licensing and reimbursement, and manufacture and logistics processes are substantial cost drivers that need to be incorporated into these considerations [105].

In conclusion, immediate attention needs to be paid to applying novel economic modeling methods, in general, and value-of-information analyses, in particular, to better

### Brief Synopsis

- Large investments in regenerative medicine technology have yet to materialize.
- There is a mismatch between criteria for regulatory approval and criteria healthcare payers use to determine reimbursement.
- Regenerative medical technology developers must respond to market needs by adopting a market-pull model of translation.
- Within the market-pull model there is a focus on the explicit link between investment in innovative technologies and return on investment for healthcare payers and developers.
- Adopting novel economic modeling methods, specifically value-of-information analyses, to guide investment decisions in regenerative medicine could also inform emerging regulatory frameworks.
- Value-engineered translation of regenerative therapies is necessary to set regulatory frameworks, policy, and tie investment decisions to value-based criteria of health systems.



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inform investment decisions in regenerative medicine. These models must include the costs of manufacturing and cell processing. An added benefit is that such analyses may still inform emerging regulatory frameworks. If the regulatory burden is too high, it may drive the costs of regenerative medicine out of the range of most health systems. In other words, what is required is not simply translation of therapies, but value-engineered translation of regenerative medicine therapies to set regulatory frameworks, policy, and tie investment decisions to the value-based criteria of health systems.

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## Author disclosure statement

The authors declare that no competing financial interests exist.

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