

*A Private Investor Guide to Regenerative Medicine:
Unique Opportunities in an Emerging Field*

Introduction

The field of regenerative medicine remains at the forefront of personalized medicine and healthcare innovation. Regenerative medicine is broad in scope, multidisciplinary in execution, and incorporates many unique elements that play out on an international stage.

Regenerative medicine is attractive in that it has the potential to disrupt current expensive therapies that are limited in their capacity to restore fully functioning organs and processes, in some cases without the need for lifelong immunosuppressant medication. Regenerative medicine also addresses larger societal issues such as the cost of the healthcare, access to healthcare, and it holds the promise of creating dramatic new possibilities around the quality and duration of life.

This white paper examines the key elements and dynamics relating to the commercialization of a cell-based or tissue-engineered technology into a patient therapy and a viable business. The strategic topics addressed in the white paper include:

1. Therapies and Technologies
2. Understanding the Market and Market Drivers
3. The Value Chain and Business Models
4. Commercialization Issues

Regenerative medicine is an emerging field, and the vision of creating new, functioning human tissue and organs must be balanced with the realities of bringing those therapies to patients in a model that encourages investment at each step in the value chain.

The Investor Role in Translation of Therapies from Bench To Beside

Investors have a keen eye for business opportunities. Not only for those opportunities that are presented to them in the business plan or the pitch, but those embedded in, or adjacent to, the original concept. Investors make a unique contribution by bringing the management expertise and network of resources to draw out, examine and refine commercial potential. Given the complexities of regenerative medicine commercialization, the investor contribution has even greater relevance to ensure success.

The investment community provides a critical component to scientific founders who may lack the financial means, manufacturing and marketing experience, or even the desire to create a therapy platform and sustainable business around their own area of expertise.

Investors surround the scientific founder with a strong board of directors and management team, to help determine a defensible intellectual property position, a viable business model, and opportunities for near-term revenue that reduce the risk of bringing the core technology to market. Driven by an exit strategy and risk/return metrics,

investors provide the ideal complement to the scientific founders, creating a team approach around realistic costs and timeframes.

The process of due diligence introduces the critical questions for completing the translation of the research:

- Is this therapy a “game changer”?
- Can it be brought to the clinic in a reasonable timeframe?
- Is the market for this therapy large enough?
- Is this solution a single product play or part of a larger platform?
- Is the intellectual property defensible?
- Are there strategic partners identified that will share in the development costs?
- Are there potential licensees or acquirers of this therapy with the ability to manufacture it on a large scale and deliver it through existing marketing channels?

Investor considerations bring discipline and further refinement to the original ideas that arise in basic and pre-clinical research, and it will ultimately be the engagement of the investment community that provides a key catalyst for advancing the field.

1. Therapies and Technologies

After a period of close to 30 years, the field of regenerative medicine encompasses a broad range of commercialization is occurring in cell therapies, tissues and organ development, biomaterial advances, drug discovery and other enabling technologies. A multidisciplinary field that not only includes biology, physics and chemistry, it incorporates unique engineering applications and combines existing commercial treatments across biologics, medical devices and diagnostics.

Regenerative medicine holds out the promise of addressing chronic diseases and conditions including Alzheimer’s, Parkinson’s, diabetes, heart disease and renal failure. While original treatments involved prosthetic devices and surgical manipulation of tissues, the therapies are far-ranging to include bone, cardiac and liver tissue, corneal tissue, wound healing, and blood vessels.

Regenerative medicine products can be comprised of a scaffold or matrix material on its own, cells, or a combination of scaffold with cells to create the desired effect and therapeutic model. Cells are either derived from the patient (Autologous) or from a donor (Allogenic). Cell research can be found along the entire spectrum, from discovering new cell sources, to differentiating those cells into differing cell types, to tissue and organ engineering, as well as the biomaterials and enabling technologies that support each method of action.

In terms of the largest market opportunities, the current forecast is that commercial products will come first in orthopedics, cardiology, skin and wound healing, diabetes and central nervous system disorders. With initiatives like the Armed Forces Institute for Regenerative Medicine (AFIRM), the acceleration of therapy development for the

treatment of wounded warriors could create more rapid adoption for general patient populations due to the significant clinical research dollars and highly-collaborative nature of the AFIRM program.

2. Understanding Market Size and Market Drivers

Overall demographics make a compelling case for examination of regenerative medicine as a field of the future. The demands of an aging population places ever increasing demands on healthcare delivery requirements and cost, and most prominently shows up as in the dramatic percentage of GDP spending on healthcare. The U.S. alone spent an estimated \$2.2T, or 16% of GDP, on healthcare in 2006, a figure that is expected to reach \$4.1T by 2016. By 2040, the senior citizen population will double in the U.S. to about 70 million and about 25% of GDP could be devoted to healthcare by that time.

The current market for regenerative medicine is approaching \$4B, and with estimates of the market size by 2010 in the range of \$15B to \$20B, with a cumulative annual growth rate exceeding 25%.

Proteus Ventures cites worldwide funding for research increasing from \$1.5B in 2009 to \$14B in 10 Years, with over 900 clinical trials currently, 400 commercial products on the market (mostly skin, tools and devices) and another 600 products in development.

As with any emerging field, everything is subject to additional refinement and standardization of metrics and sources. There is just not enough data to draw from, a gap that the regenerative medicine field is attempting to address at the policy and institutional level.

Regenerative medicine can also capitalize on the trends surrounding cost containment. As healthcare costs rise, there has been a similar boost in efforts to limit expenses by employers, payers and the government. If regenerative medicine therapies can provide a cost-effective alternative to current treatments, physicians and hospitals might have an incentive to more readily adopt them. Again, the need for baseline clinical and cost data, and more comprehensive studies, is as critical as the funding the research itself.

3. The Value Chain and Business Models

While the market size and dynamics may prove to be compelling, the next investment filter involves an understanding of the business models. To balance the high cost of therapy development compared with what the market will bear has been challenging, and there is as much innovation creating viable business models as there is in creating the therapies themselves.

Some companies are looking to leverage their research across multiple product lines, while others are focusing specifically on the tools side of the business, where market share and revenue opportunities are more likely to exist in the near-term. Given high hurdles for product development in the traditional sense, including incredibly complex intellectual property and manufacturing scale-up challenges, some are opting for a service model approach.

Unlike traditional medical device and drug development business models, which have established pathways and parameters, tissue-engineered and cell-based biological business products are unique in a number of ways. There are no “fast track” programs for regulatory or reimbursement approval, and in fact, many times the therapies are so novel that the regulators and payers are being educated by the companies seeking approval in a series of early discussion meetings and disclosure of the scientific underpinnings of the products. In some instances, a regenerative medicine product may be regulated as a medical device and reimbursed as a biologic, depending on the country where it is being sold.

In absence of common scientific understanding, pathways and metrics, the regenerative medicine field is driven to develop creative alliances to address the complexities and current gaps of data and expertise. The complexities are creating an even greater environment of collaboration. This is happening internally within individual companies, in collaborations between companies, and more recently in broader coalitions. One such collaboration is the Alliance for Regenerative Medicine, a Washington, DC-based public policy group formed in 2009 that now has over 40 members from the academia, patient advocacy and both large and small companies, addressing critical issues in regulatory, reimbursement and capital formation arenas.

Beyond domestic considerations, there are a multitude of international business model issues for companies to address. There is great interest in harmonization of regulatory and reimbursement guidelines, and also in the refinement of manufacturing and marketing channels. Regenerative medicine has been predominantly global from inception, and does have an advantage in its engagement of an open environment of international interaction around key research and development initiatives.

4. Commercialization Issues

Given that regenerative medicine is an emerging field, the number of investors and management teams with deep domain experience is limited. The compelling technologies and market opportunities have attracted individuals and management teams from related industries in drug discovery and development, medical devices, diagnostics and medical equipment, who bring high-level functional expertise as well as the skills and networks to execute quickly on the entire range of commercialization issues, and build infrastructure where it has been lacking.

The following checklist provides a summary of the key aspects of commercialization and elements that are potentially unique to regenerative medicine.

Public Policy Climate

The field is now engaged formally in educating policy makers and the general public about the benefits to patients and the prospect of economic growth through technology-based ventures. Addressing patient safety, healthcare cost concerns and the ethical implications of these therapies up front, can lead to a public policy climate that is conducive to entrepreneurial and commercial development,

especially where unclear regulatory and reimbursement guideline can forestall investment and company growth.

Intellectual Property

Driven by the increase in federal funding and related regenerative medicine initiatives, the number of patents in the field is growing, and is one of the most important considerations for investors. Proteus Ventures cites an annual patent filing growth rate in excess of 25% since 2000, with no single company owning more than 3% of granted patents. To avoid litigation and allow freedom to operate, the patent “thicket” must be acknowledged and cleared.

Regulatory Issues

The innovative and complex nature of regenerative medicine has created challenges in commercialization. Regenerative medicine products can be considered a biologic, a medical device, and in the case where the biologic and device are combined, the FDA has a special office to determine the primary method of action and the appropriate regulatory pathway. Regulation is less stringent when autologous (patient) cells are used, although the company must still follow GMP (Good Manufacturing Practice) or GTP (Good Tissue Practice) protocols. Clinical trial design has become of greater importance, as well as early and frequent interaction with the FDA and international regulatory agencies.

Reimbursement

While a company’s reimbursement and regulatory strategies should be aligned, it is possible to have a product regulated as a medical device and reimbursed as a cell therapy, within one country, and multiple reimbursement categories from each country where you sell your product. In the United States, the Centers for Medicare and Medicaid (CMS), and private insurers are important partners in the reducing market risk. Investigating the reimbursement pathway early on with these potential payers is critical, as coding for novel therapies can take several years for approval, and physicians are not fully-reimbursed for miscellaneous coding, leading to slower adoption. Organized industry efforts to provide health economic data and prove comparative effectiveness of regenerative medicine therapies will be essential as individual companies examine future revenue streams and valuations.

Scale-Up and Manufacturing

It’s not enough to demonstrate the ability to make 15 or 150 of a cell or tissue-based product. Companies must show that they can manufacture multiples of thousands and tens of thousands in product runs, in consistent lots, and in the case of many of these “live” products without any kind of terminal sterilization or bar-coding of the tissue or organ. While research, regulatory and reimbursement issues rule the day, key areas like cost-of-good-sold, quality assurance, supply chain and the workforce become the dominant factors as the company moves into production mode. What was once unique must now be made and delivered according to strict standards, without variance. Process automation must be designed and developed to support characterization and control. With the promise of life-long therapeutic value comes the accountability that these cells, tissues and organs are produced in a profitable manner in accordance with their promise.

Clinical Adoption

How do you sell a product that nobody's ever seen before, let alone used? Adoption in the clinic can be one of the greatest challenge for new venture, where the physician is at the nexus of the patient, the hospital or clinic and the reimbursement channel (revenue). If the therapies can be adapted easily, are seen to provide substantial improvement in quality of life, reduced hospital stays, recovery and return visits, at a reasonable cost, then adoption can accelerate. Integration is key to adoption, and should be considered as much as the technology itself. In addition to cost containment, the successful therapies will be the ones that can be stored and delivered easily, don't require elaborate preparation of resources, and don't require the physician to learn a radically different procedure.

Conclusion

Opportunities in regenerative medicine are complex, and they will require unique collaborations of researchers, investors and management, all played out against a larger landscape of public policy, healthcare innovation and restructuring.

Near-term opportunities exist in the enabling technologies and tools segments, as well as in complementary therapies that can be manufactured at scale, easily adopted by physicians and reimbursed under current pricing models.

Longer-term, more disruptive prospects exist, but will require consistent and large investment in scientific research funding, sorting out complicated intellectual property issues, and most importantly, solving the manufacturing dilemma of producing these products safely at large-scale and at a costs that the market will bear.

Advancing regenerative medicine and investment in the field will require a classic "high-low" strategy of engaging public policy and large biotech interests to create the greater ecosystem and infrastructure, while at the same time becoming fervent at the individual level of understanding the costs and dynamics of delivery to patients.