KINETICOS LIFE SCIENCES

A Primer on Regenerative Medicine

Introduction

Scientific advances in regenerative medicine research continue to fuel the pharmaceutical industry in developing treatments for a variety of diseases. Regenerative medicine rebuilds the patient, harnessing pluripotent stem cells, DNA/RNA, and other mechanisms to regenerate, replace, and supplement the body's natural physiological system during a diseased state. For example, stem cells can be used to repair the heart after a severe heart attack, restoring its full function. While these new treatments have the potential to offset substantial medical costs, especially in aging populations, regenerative medicine has proven to improve the overall quality of life for both the patients and their families.

As an emerging and innovative area, regenerative medicine still relies heavily on partnerships within industry and with academia. Much of the research and early clinical trials require teamwork between multiple companies and hospital systems. Additionally, the funding sources for developing these therapies are both public and private, further contributing to the complex and collaborative nature of this work. Although there is a lack of established business models, pharma is beginning to establish the innovative business models these novel therapies require, and companies that pursue these avenues must be able to navigate in an uncertain, shifting, high risk/high reward environment with strategic plans that make good assumptions and can adapt to unexpected challenges. However, the inherent uncertainties associated with life cycle management in an emerging, high cost, and scientifically demanding industry make it extremely difficult to establish successful business models. Due to regenerative medicine's individualized style of care, clinical outcomes are highly variable between each patient. Thus, companies that are able to pull together the right data, expertise, and educated assumptions in a cohesive and adaptable strategy plan will be the ones to succeed.

The two most groundbreaking and fastest-growing areas of regenerative medicine are cell and gene therapies, with small molecules and biologics, tissue-engineered biomaterials and scaffolds, and implantable devices representing the majority of other sub-areas. Cell therapies utilize fully differentiated cells and/or progenitor cells to repair diseased tissue and overall body systems, either through an autologous or allogenic pathway. Moreover, the immune properties of these cells can be used as an immunological treatment against pathogens and cancer.

The relevance of these therapies is illustrated by the fact that, according to a study conducted by BIS Research in 2018, cell therapies have had the fastest compound annual growth rate out of any other regenerative treatment methods.[1] This is primarily due to increase in cancer and chronic diseases, which

[1] Global Cell and Gene Therapy Market: Focus on Products, Applications, Regions, and Competitive Landscape – Analysis and Forecast, 2019-2025. https://bisresearch.com/industry-report/cell-gene-therapy-market.html?gclid=Cj0KCQjwzozsBRCNARIsAEM9kBNwt-lP5n9TmjB44PomsR9D2LS_SdxCQ88pGzEu4--T-F1Qlow_tsgaAuOXEALw_wcB. Accessed September 15, 2019.

increases the overall diversity of diseases that require cellular therapy, which can be seen in Figure 1. According the Alliance for Regenerative Medicine, 2018 saw the most financing for clinical trials involving cellular-based therapy. Moreover, major companies such as GSK and Spark Therapeutics continue to release new cellular treatments fix mutations involving blindness and cancer.[2]
In addition to cell therapies, gene therapies are an equally strong and slightly newer investment for diseases that have limited treatment options such as metabolic diseases. Gene therapies act on the molecular level, utilizing DNA/RNA molecules to fix mutated genes, influence healthy growth and function, and ultimately cure genetic disorders. The investment we are now seeing in cell and gene therapies is shown in a study done by Grand View Research, where in 2018 there were more than 950 different gene therapies in the pipeline.[3]

Although the challenges associated with regenerative medicine and bringing it to market are vast and unique even within the biopharmaceutical industry, the potential of these transformative therapies is unprecedented. For example, advances in regenerative wound healing are already providing clinical outcomes that were unimaginable ten years ago to everyone but the ambitious and altruistic pioneers who saw the possibilities presented by cell therapy and made them the reality that is benefiting wound sufferers all over the world today. Most of the progress in regenerative medicine is at a much more mature stage than that of 2013, with more biopharmaceutical companies focusing on musculoskeletal, oncological, and cardiovascular diseases.[4] However, few therapeutic areas have the potential to offer long-term returns, with the gap between potential therapies in the pipeline and current therapies still looms large.

Yet, the scale of investment for regenerative medicine will very soon be a $39 billion industry by 2026, with big pharma fully involved with more public financial support.[5] The next decade promises revolutionary breakthroughs in areas of intense research such as ocular disease, musculoskeletal

diseases, neurodegeneration, oncology, vascular and cardiac disease, and metabolic disorders as a myriad of smaller pharmaceutical and biotech companies follow big pharma.
Although there is very little in regenerative medicine that can be considered low-hanging fruit, there is potential to tap into an enormous market of revolutionary medicine, given substantial investment and high risk. One particular field involves cardiovascular and neurodegenerative diseases: as an illustration of the potential in some key areas of investment in cell and gene therapies, Figure 2 shows the projected increase in global disease burdens for deaths due to cardiovascular disease and incidence of dementia

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[2] Why It's the Best Time to Be in Cell and Gene Therapy. https://www.labiotech.eu/interviews/cell-gene-therapy-biotech/. Accessed September 15, 2019.

[3] Regenerative Medicine Market Size, Share & Trends Analysis By Product (Primary Cell-based, Stem & Progenitor Cell-Based), by Therapeutic Category (Dermatology, Oncology), and Segment Forecasts, 2019-2025). https://www.grandviewresearch.com/industry-analysis/regenerative-medicine-market?utm_source=google&utm_medium=cpc&utm_campaign=AdWords_Regenerative-Medicine-Market_Type3_Healthcare&gclid=Cj0KCQjwzozsBRCNARIsAEM9kBOYxLU5hMz9blN5y3JkXn9V9oMswaBTs8szXU_85DNJi-RcJ1cZ4qsaAi2CEALw_wcB. Accessed September 15, 2019.

[4] Grand View Research et al.

[5] Regenerative Medicine Market by Type [Cell-Based Immunotherapy & Cell Therapy (Allogeneic & Autologous Products), Tissue Engineering, Gene Therapy], Applications (Wounds & Dermal, Musculoskeletal, Oncology), Region - Global Forecast to 2024. https://www.marketsandmarkets.com/Market-Reports/regenerative-medicine-market-65442579.html?gclid=Cj0KCQjwzozsBRCNARIsAEM9kBPam0V_Z99k77UAkQvOOrHpVGhekBEPwv2FYnQ2Fie3VgLbCeYzCXcaAjgBEALw_wcB. Accessed September 15, 2019.

(primarily Alzheimer's Disease). Cardiovascular disease is a particularly intense area of research, with companies constantly developing new strains of pluripotent stem cells and progenitor cells to heal damaged cardiac tissue after a heart attack. Additionally, when looking at cardiovascular disease, the Health Metrics Association predicts that from 2016 to 2035, the overall domestic cost of cardiovascular disease will increase from $555 billion to $1.1 trillion.[6] With its individualized approach, cell-based therapy has the potential to reduce that cost, reverse the adverse outcomes of the disease, and ultimately change lives.

Strategic Plans for Life Cycle Management

In traditional pharma, especially when it is based on the delivery of small biologic compounds, the path from R&D to market is rigorous but predictable. Once a compound is synthesized and reliably produced with consistent clinical outcomes that follow established protocols, the delivery systems can be designed based on one of the many accepted established vehicles. The area of largest variation is during clinical trials; however, the nature and size of small molecules allows for easy modification and future planning throughout the life cycle management. Although clinical trials often present a set of unknown variables due to differences between patients, the life cycle management can be mapped out and planned. Moreover, it draws on established expertise and personnel in the field, and most often uses existing production facilities and proven delivery methods.

In contrast, the transition from laboratory development to successful clinical trials for regenerative medicine is unique, complex, and often peppered with variability. Cell and gene therapy represent the highest level of biological engineering, where companies are producing tissues de novo and manipulating the biological instructions of a patient. Every patient has a different genome, with different relationships between their genes and tissues, thus cell and gene therapies not only require carefully controlled clinical testing, but also requires evolving expertise, access to personnel, and specialized production facilities. Moreover, the effects of cell and gene therapies carry into patient care, with the administration often a clinical procedure. Thus, the delivery procedures and results must be reproducible, with the infrastructure for the procedure evolving within pre-existing pharma. The chances for unforeseen complications (expenses/adverse clinical outcomes) are high with this type of therapy, but so are the rewards if planned and administered consistently and with a stable, reliable protocol. A sound strategic plan for taking these therapies from basic research to the pharmaceutical marketplace must be designed to adapt to these hurdles without sacrificing scientific integrity or commercial viability.

Secondly, scalability for a small molecule or even most biologics requires the transformation of laboratory bench production to large-scale automated production with the associated manufacturing, quality control, and storage requirements. Although this process presents its own challenges, it is an established one and these challenges pale in comparison to those presented by, for example, transforming the process of carefully culturing progenitor cells in a laboratory setting to industrial production and distribution. In fact, cell and gene therapies in particular call for manufacturing processes and facilities of a type previously reserved for research institutions but on a scale that is aligned with a commercial plan. These delicate cell lines require supplies, very specific environmental conditions, and

[6] Cardiovascular Disease: A Costly Burden for America, Projections Through 2035. https://healthmetrics.heart.org/wp-content/uploads/2017/10/Cardiovascular-Disease-A-Costly-Burden.pdf. Accessed on September 15, 2019.

careful handling in order to prevent damage and alter their effects on the patient. Thus, not only does the commercial production process need to be designed and developed with the same conditions and protocol as a laboratory, but appropriate facilities may simply be unavailable and need to be built or refurbished.

The expertise and talent required for cell and gene therapies has increased the past few years, with more individuals focusing on cancer, cardiovascular, and musculoskeletal-related treatments in academia. However, regenerative medicine still remains to be an immature market, thus there is very little established expertise outside academia and other research institutions. Successful clinical trials cannot be implemented into a more labor-intensive production process without the necessary expertise at the lead. It is crucial that this expertise understands the unique nature of cell and gene therapy, its storage, maintenance, and administration requirements in the clinic and how those requirements can be translated into a smooth manufacturing process. The methods used by clinical trials must be expanded to the scale of a complex and demanding production and delivery infrastructure, with an understanding of the challenges, familiarity with the requirements, and an ability to tease apart the process and focus on key steps. Gaining the appropriate expertise is paramount for success in the cell and gene therapy industry. As new cancer isoforms and genetic disorders are discovered, the competition for talent is expected to increase as well, populating the field with sources for a successful transition from the clinic to commercial environment. Ultimately, competition is a crucial variable for cell and gene therapy.

A factor as basic as cost of goods, which is largely negligible for most small-molecule pharmaceutical production, can make up a non-negligible portion of production expenses for complex biological or whole cell therapies. Growing cells in culture and maintaining them during transport and testing involves a complex life cycle management and must be included in the overall cost analysis of the treatment. Certain cell lines, such as human pluripotent stem cells, are quite costly due to their versatility in tissue development and are highly susceptible to death during transport. The inclusion of finer cost-related details in regenerative medicine cannot be overlooked, especially since the production and maintenance of the necessary materials inflates the overall cost of goods for each unit of therapy.

Regulatory pathways for these new classes of therapies are currently uncertain, especially on a global scale. Although regulatory expertise is a strength of most pharmaceutical companies and many biotechs, it often remains uncertain how extensively an emerging therapy will be commercially viable in late adopter markets where approval and reimbursement of novel or controversial therapies is likely to be delayed or more difficult. One of the benefits for astute companies at the forefront of shaping the regenerative medicine environment is that they can not only stay abreast of regulatory development, but also contribute to ensuring that the interests of all parties involved are considered as it takes shape. However, until the regulatory environment becomes clearer, it is critical that companies engaged in regenerative medicine continue to monitor and adapt to changes as they occur, especially in major markets such as North America and Europe. Regenerative treatments involve a high level of variability between each patient; thus this inconsistency can be a direct cause of the changes in said major North American and European markets.

Finally, and overlaying all the other factors that must be considered in a thorough and viable strategic plan, designing costs and pricing algorithms and establishing a sound business model and a viable commercial plan in this high risk/high reward sector requires courage, ambition, and astute decisions in acquiring the right expertise and taking well-informed acceptable risks. Failure to make the correct choices early, for example in considering pursuit of a flexible “off-the-shelf” allogeneic cell therapy versus a more challenging autologous one, can have a disastrous effect when rash assumptions ultimately threaten the business model. If a company were to invest highly in a cell culture that resulted in an adverse immune reaction in clinical trials, the overall model for treatment must be restarted.

Although the reimbursement environment for these therapies is uncertain, the potential for unparalleled clinical benefit, often for conditions without any alternative treatments currently available, will allow providers to command high prices. However, even in the more established areas of regenerative medicine such as wound healing, balancing costs and pricing in a successful commercial model remains an issue as third-party payers demand clinical results that match the high cost. Many of the therapies currently in the pipeline or under preliminary investigation may need to set price points at an unprecedented level to offset development and manufacturing costs, such that knowledge of the marketplace and a comprehensive evaluation of commercial viability are essential components of a successful strategic plan. It is crucial that companies participate in pricing discussions, as well as those pertaining to industry standards and the regulatory framework, in order to ensure that the outcomes of these are fair, balanced, and realistic.

Commercialization Challenges

Although some aspects of strategic planning for cell and gene therapy development follow a familiar pattern, albeit often at more demanding levels of cost, time, and complexity, there are others that can present unique and unexpected challenges. It is in planning for the circumstances that these present that a sound and informed strategic plan can make the difference between either being able to adapt and adjust with commercial viability still intact or seeing years of work and possibly millions of dollars of investments crumble along with the viability of the therapy.

One example of a challenge that is unique to cell and gene therapies in both scope and scale is the process of taking a therapy from the R&D laboratory to commercially viable industrial production. It is one thing to, for example, carefully culture a therapeutic cell line in a bench setting or even conduct carefully designed small-scale early clinical trials, but quite another to manufacture therapeutic doses on an industrial scale at a manageable cost. For example, if a company develops a gene therapy that uses RNA molecules to upregulate protein production in cells to treat a musculoskeletal disorder, that treatment could have different effects in each patient due to the genetic manipulation. The treatment could potentially result in adverse results, be ineffective in others, or require different doses depending on the severity. Even if manufacturing proves scalable and the path to successful production seems clear, most of these therapies have a very limited viability window within which they must be administered, even under ideal storage and transport conditions. In light of this, it is also imperative to strategically place production facilities and design a storage and transport infrastructure that can deliver the therapy at the point of care.

At one end of this scaling process, we find the research scientists and clinicians and at the other, we find the company executives who seek a product that is consistent and manufactured at a cost that aligns with the market value. This brings into play two perspectives and sets of priorities that are vastly different and must be reconciled for the commercial application of a therapy to succeed. From the bottom up, researchers and clinicians will look for production, storage, transport, and delivery processes that

protect the integrity and fragile efficacy of the therapy, ideally seeking to scale their rigorous laboratory standards wherever possible. In contrast, the top-down perspective of executives seeking to take the product to market is one where the cost and efficiency of these processes is weighed in balancing clinical efficacy and regulatory requirements against financial realities. If a development plan fails to align these bottom-up and top-down processes, the strategic plan fails, and the viability of the therapy is jeopardized. Both sides need to be considered in detail, such that they come together to yield a production-through-delivery model that meets therapeutic and regulatory standards while falling in line with the cost requirements of the commercial model.

Although pharma is well equipped to work within and adapt to an uncertain and evolving regulatory framework, a greater concern is the lack of industry standards and the resulting danger of inconsistency across products, even within narrow therapy types such as wound healing. The companies that are successful in the regenerative medicine arena will be the ones who are leaders in the push for industry standards, not followers. A successful company will make informed decisions about cell lines and certain diseases to focus on and understand the current market trends and treatability for certain genetic diseases. Failure to align a product with the industry standards against which it will ultimately be measured could prove to be a disastrous or even fatal setback, especially since cell and gene therapies have the potential to butterfly if a mistake is made. It is therefore crucial for a forward-thinking company to be proactive in using the best information from both clinical and economic experts in a position to monitor and follow these industry standards as they emerge as they map out their path to commercialize the therapies to market.

Another area that is proving unexpectedly challenging in regenerative medicine development in general and scientifically demanding areas in particular is availability of the necessary expertise and competent personnel. As with any emerging scientific field, this is to be expected as industry skills catch up with those of the academic and other research specialists, but the dearth of the necessary skill sets in areas such as cell and gene therapies is compounded by the demanding and specialized nature of the skills required. As these therapeutic areas such as musculoskeletal and neurodegenerative mature, the availability of these competencies will become less of a problem. However, competition for the best talent is currently fierce, because a holistic understanding of the human genome and its relationship between each body system is seldom found. Thus, companies are presently faced with the need to grow their own talent or partner with academia, research institutions, or (in the case of pharma) biotechs. Ultimately, a long-term strategic plan must address the need to acquire the necessary expertise early because it might otherwise simply not be available when it becomes needed.

Finally, an additional unique challenge facing regenerative medicine as the leading companies move from early clinical trials into efficacy and dosing evaluations is potency assay validation. Dosages and effects can very between patients, sometimes to potentially severe effects during clinical trials. While issues such as cell characterization and therapy administration vehicles are less problematic than previously, it is a requirement from both clinical and regulatory standpoints that a therapy has predictable and preferably also quantifiable effects. For example, when growing new heart tissue after a heart attack, the tissue must be able to be adequately perfused and contract in-rhythm with the rest of the heart, consistently. With cell therapies, clinical outcomes are extremely difficult to evaluate and any company venturing into this area must be prepared for a process that is not only more tortuous than that in traditional pharma, but also presents unique challenges that require ambitious and innovative trials under the guidance of the right experts.

Summary

Overall, with the sheer scale of regenerative medicine investment in the past few years, the future is now for these therapies. However, it will take more than courage and ambition to be successful in the field. Delivering reproducibility and scalability on an industrial scale for these therapies requires innovation paired with a detailed understanding of critical life cycle management elements, such as cellular longevity and maintenance. The process of bringing the therapies to market requires critical thinking and the humility to acknowledge that no amount of expertise in traditional pharma, biotechnology, or regenerative therapeutics alone is enough to be successful. Regenerative medicine is a collaborative effort amongst companies of differing expertise, and today's regenerative medicine pioneers are acknowledging that strategic partners are essential to the effective and efficient use of company

resources where they are most needed. Success in the regenerative medicine arena is predicated on strategic plans that deliver sound business models based on a combination of innovative critical thinking, making the right assumptions but allowing for a great deal of inherent uncertainty with patient outcomes, and – not least – drawing on the expertise of those who understand both the pharmaceutical industry in general and the science behind cell and gene therapies. Success in developing regenerative medicine therapies requires agility and innovation but, even when paired with expertise and experience in the pharmaceutical arena, these are necessary but not sufficient. Life cycle management is complicated but possible to control given enough research and good market predictions. The ultimate goal of to plan for these therapies is to anticipate and define the steps involved, fully understand the intricacies and variables of each, and then reassemble them into a fully aligned and comprehensive strategic plan. Only with such a plan in place can a company confidently move forward with a viable financial model and a clear commercially consistent clinical model for a cell or gene therapy within this rapidly-evolving industry.

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Figure 1

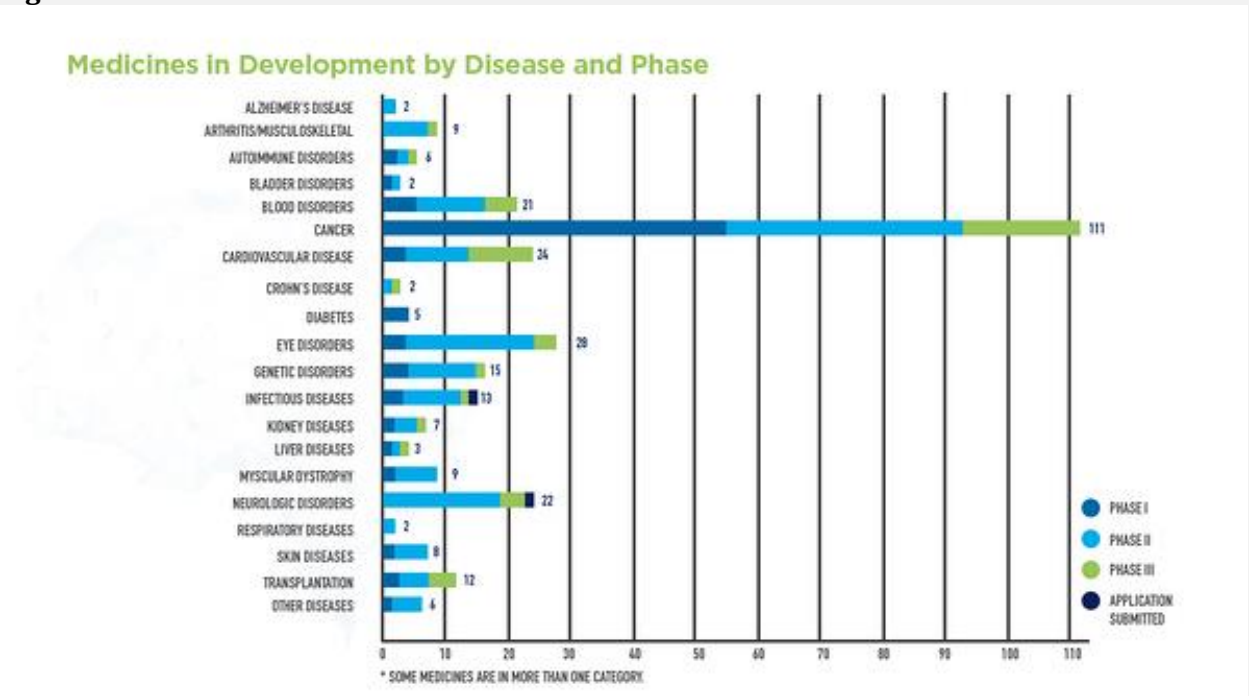

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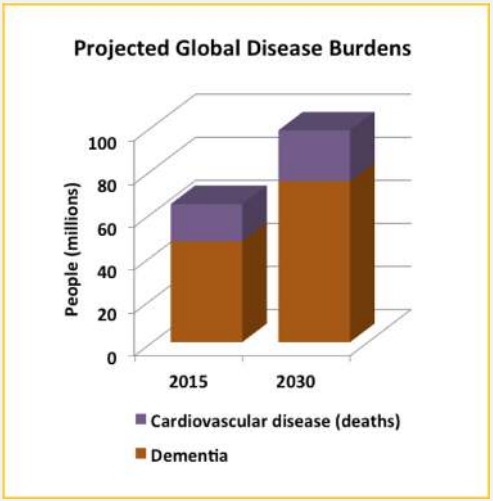
Figure 2



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