I. STEM CELLS

Stem Cells and Regenerative Medicine

In general terms, stem cells are cells that can duplicate themselves and differentiate into cell types found in the body. However, stem cells are not all equal. Embryonic stem (ES) cells can transform into any cell type found in the body and this gives rise to the term, “pluripotent” cells. Human ES cells are obtained from pre-implantation embryos, created using in vitro fertilization. Completely different pluripotent stem cells can be derived from fully differentiated cells. These pluripotent cells are called induced pluripotent stem cells (iPSC). There are yet other cell types that only differentiate into specific cell types, e.g. mesenchymal adult cells from bone marrow, which differentiate into cartilage and other connective tissues. It is not the purpose here to provide a detailed background on stem cells and their biology, but rather to describe the challenges of conducting well-controlled clinical trials with these cell types. Detailed explanations on the background of stem cell physiology can be found in numerous reviews.1

Contemporary research has demonstrated the ability to harvest and transform specific cells from adults back into pluripotent stem cells. This technology has transformed the use of stem cells in clinical research, and also removed much of the earlier controversy surrounding research on embryonic stem cells.2 Nevertheless, the debate on research using embryonic stem cells continues and it is important to be cognizant of the issues, both from scientific and ethical perspectives. However, the current discussion is not whether research should be conducted, but on how research using these cells should be conducted.3,4

Given the properties of stem cells to differentiate into specific cell types, it comes as no surprise that these cells are the focus of multiple investigational uses in medicine. With properties that give stem cells the potential to repair and renew damaged tissue, they have the potential for use in multiple medical conditions. Furthermore, by placing stem cells on, or in, biological scaffold constructs, it might be possible to generate new organs that can be used in transplants or to augment damaged cellular activity. Such combination products and artificial organs are just the tip of the iceberg in terms of where stem cell biology could transform life science. Stem cells and medicine appear to have come of age.
Stem Cells, Metabolomics, Proteomics and Gene Therapy

Of course, the use of stem cells in medicine is not a static science. Advances in our understanding of gene therapy, metabolomics and proteomics have merged many scientific disciplines into one. When we discuss stem cells, we need to be mindful that the field is dynamic and all these scientific advances might be involved.

The confluence of stem cell science with other scientific disciplines is most obvious in preclinical activities where stem cells can be used to evaluate toxic properties of potential drugs intended for use in humans. Specific reviews on this topic can be found in a number of publications.

The Structure of Scientific Revolution

With all new biological discoveries and technologies comes promise and disappointment. The expectation that stem cells will one day transform medicine seems reasonable. Unfortunately, in many instances, enthusiasm has taken the place of reality and the use of stem cells has not lived up to the hype of transformational therapies. However, over the last decade, which is littered with disappointments in stem cell therapy, we have learned a great deal. Now this exciting therapeutic space seems primed for clinical development – but clinical development that must be conducted in a well-controlled unbiased manner, not only with solid scientific rationale, but also with excellence in operational execution. If we can combine these two attributes, science and operational execution, we should be confident that the potential of stem cells will live up to the nature of scientific revolution.

Sources of Stem Cells for Clinical Trials

In the drug development world, small molecules and biologics intended for medical investigation are controlled tightly by good manufacturing practices (GMPs). This ensures purity of the product and consistent quality across manufactured batches. This has not always been the case with stem cell research. While this is perhaps not surprising given the many early experiments conducted in small independent laboratories, there is still an issue of ensuring not only the source of cells, but also the conditions under which they are harvested. Furthermore, the concept of GMPs, also referred to as Good Tissue Practices when applied to stem cells, applies to both autologous and allogeneic derived stem cells.

Proving Effective Therapy – Robust Clinical Research

Interestingly, much of the activities that pertain to conducting a robust clinical trial with stem cells are identical to those conducted for small molecules and other biologics. For example, data capture, blinding, randomization and monitoring are common to almost every Phase I through Phase III clinical study. However, when considering the differences between traditional clinical trials and stem cell clinical trials, approximately 25-30% of activities will be different. If not performed correctly, this 25-30% differential will be more than enough to cause failure and ultimate rejection of the product by regulatory authorities. Over the last decade there have been a number of failures in clinical studies using stem cells. For autologous stem cells used in cardiac repair studies it has been suggested that a number of factors are responsible. These include poor definition of cell types, diversity in handling techniques and functional variability. Other failures have been self-induced with hype and false promises. However, regardless of the reasons for clinical trial failures with these “first generation” stem cells, there is great optimism and enthusiasm for “next generation” stem cells, especially with regard to the application of, and absolute necessity for, robust clinical research.
Figure 1 delineates the differences in clinical trial operations between traditional drugs and next generation medicines. Two differences seem particularly worthy of mention: first, the intersection of GMPs with good clinical practices (GCPs); and, second, the difference in monitoring the safety aspects of the clinical study. In terms of delivering viable cells to the patient, there are several logistical challenges – temperature control (sometimes -196°C/-321°F), cell viability and preparation prior to administration and documentation. It might not seem so difficult to transport these cells across the hospital grounds, or even across town, but it is a little more challenging to transport these cells across the country in multicenter randomized clinical studies! And once these cells are administered to the patient enrolled in the clinical study, how do you monitor safety? There are numerous guidances from regulatory agencies on this subject for traditional drugs and biologics, but for next generation medicines, it is much more complex. For example: for how long do you monitor patients? How often do you collect safety data? Are patient registries the way to move forward for the required long follow-up periods, or are guidelines for other advanced therapies the answer? This is a new therapeutic space – ICH guidelines, most of which are themselves now more than 20 years old, will not all be applicable to new generation therapies!

Aside from the challenges of monitoring safety and tolerability in clinical trials, there will also be issues related to some efficacy measures in well-controlled clinical studies. While many clinical endpoints will be related to current acceptable norms, e.g. ejection fraction in congestive heart failure, there is also a need to develop new biomarkers. These biomarkers will require validation and robust evaluation that satisfies regulatory agency review. A clear understanding of biomarkers and biomarker development as it applies to commercialization of a product will often be the difference between success and failure.

Informed Consent – The Same but Different

Many of the elements of informed consent for subjects enrolling in clinical studies involving stem cells are identical to standard clinical trials using investigational products. However, there are differences in informed consent processes for clinical trials involving allogeneic stem cells. Not only is the informed consent of the patient required, but also the informed consent of the cell donor. Given the discussion around the use of stem cells in clinical research, the double informed consent is an issue not to be overlooked.14
Global Differences – No Harmonization in Sight

There is, of course, much debate across geographical boundaries on the correct methodology to conduct clinical research with stem cells. Unfortunately, there are differences between countries in their view of stem cell research. Spending millions of dollars to conduct clinical studies in the United States does not help patients in Europe if the source of the stem cells is not acceptable in both regions. A global view toward development strategy and early clinical operations for clinical trials with stem cells can avoid many of these issues.

Marketing Approval – Identifying Regulatory Pathways

Clinical studies with stem cells are usually directed at life-saving therapies. Consequently, many of the registration pathways in place to expedite marketing authorizations will apply to stem cells. For example, fast-track designations, breakthrough therapy designations and expedited reviews might well get a stem cell product on the market quickly – this is especially so with a well-thought-out clinical development plan (CDP). However, not all stem cell therapies will qualify for these pathways and care should be taken to fully understand these regulatory mechanisms.

Global regulatory agencies have created reviewing divisions and processes to keep pace with this rapidly changing field. The FDA, EMA and PMDA are all positioned to provide guidance early in the development process to clarify the pathway for registration (Table 1). We have learned from traditional drug development the importance of regulatory agency interactions in maximizing the probability of success; this will be especially true for next generation therapies.\(^{15,16}\)

Table 1: Divisions at Regulatory Agencies Where Next Generation Therapies, Including Stem Cells, are Evaluated

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<thead>
<tr>
<th>Regulatory Agency</th>
<th>Evaluation Processes</th>
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<tbody>
<tr>
<td>Food &amp; Drug Administration (FDA)</td>
<td>Office of Cellular, Tissue, and Gene Therapy – OCTGT (CBER) Division of Therapeutic Proteins – DTP (CDER)</td>
</tr>
<tr>
<td>European Medicines Agency (EMA)</td>
<td>Processes for Advanced Therapy Medicinal Products (ATMPs) Committee for Advanced Therapies (CAT)</td>
</tr>
<tr>
<td>Japan Pharmaceuticals and Medical &amp; Devices Agency (PMDA)</td>
<td>Office of Cellular and Tissue-Based Products</td>
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Finally, as health care costs increase, governments have taken steps to control costs of drugs and biologics. The issue of reimbursement is new with regard to stem cells. How do you price a one-time treatment that might be life-saving? Reimbursement and payers are two areas requiring serious considerations early in the process of designing a comprehensive CDP.
A New Era in Clinical Trials with Stem Cells

The last decade has seen many advances in the basic biology of stem cells. As we move into the early part of the 21st century, it has become clear that the initial promise of stem cell therapy is on the verge of therapeutic success. Part of that success must be adoption of well-controlled clinical trials to prove the therapeutic benefit. With well-designed clinical development plans, clarity of registration pathways and logistical expertise to conduct these complex trials, we will surely see the promise of stem cell therapy become a reality.

Covance’s Next Generation Therapies Group combines scientific solutions with excellence in clinical trial execution. The Next Generation Therapies Group is comprised of highly experienced drug development professionals from across Covance. The group has experience in academia, pharma, biotech and the CRO industry – they understand the importance of time and flexibility in approach. The goal of the Next Generation Therapies Group is to maximize the probability of success, create value and provide excellence in developing advanced therapies.

Multidisciplinary and Seamless Execution

- Molecule Development Group
- Global Regulatory Strategy
- Early Clinical Development
- Pharmacovigilance/Safety
- Clinical Trial Logistics and Start-Up
- Physicians/Science Group Providing Specific Therapeutic Expertise

If you would like to discuss whether Covance’s Next Generation Therapies Group can create value for your project, please contact Richard N. Williams, PhD, J.D., richard.williams@covance.com.