

The Stem Cells Landscape

Cancun Stem Cell Clinic

<http://www.cancunstemcellclinic.com>

The purpose of this white paper is to review the landscape and present some key trends as they are emerging in the stem cells marketplace. A stem cell is an extraordinary type of cell that has the ability to self-renew for long periods of time and to differentiate into specialized cells under appropriate physiological or experimental conditions. Traditionally, stem cells have been classified as either embryonic or adult (tissue-specific) stem cells. Embryonic stem cells (ESCs) are derived from [are outgrowths of] the inner cell mass of the blastocyst stage embryo. They possess an unlimited capacity for self-renewal and have the potential to develop into any cell type found in the three primary germ layers of the embryo (endoderm, mesoderm, and ectoderm), as well as germ cells and extra-embryonic cells. In contrast, adult stem cells are found in differentiated tissues, have limited self-renewal capability, and generally can only differentiate into specialized (mature) cell types of the tissue in which they reside.

Basic Properties of Stem Cells are:

- Self Renewal—Potentially unlimited rounds of replication
- Pluripotency—Capable of generating all the mature cell types found in the adult. hESCs are pluripotent stem cells capable of forming all tissues of the human body

Recent understanding of stem cell biology may provide new approaches for the treatment of a number of diseases as well as tissue/organ injuries, including cardiovascular disease, neurological disease, musculoskeletal disease, diabetes, and hematopoietic disorders. These approaches could involve cell replacement therapy and/or drug treatment to stimulate the body's own regenerative capabilities by promoting survival, migration/homing, proliferation and differentiation of endogenous stem/progenitor cells. Essential to these pursuits is the identification of renewable sources of engraftable functional cells, an improved ability to manipulate stem cell proliferation and differentiation and a better understanding of the signaling pathways that control stem cell fate. In addition, there is a growing body of evidence supporting the notion that tumors are initiated and maintained by a small number of cancer cells with stem-like features: normal and cancer stem cells share similar self-renewal mechanisms; deregulation of signaling pathways involved in stem cell self-renewal is associated with oncogenesis; cancer stem cells may arise from normal stem cells or through transformations of progenitor cells. A better understanding of stem cell biology may also contribute to development of improved therapies for cancers.

The Various Sources of Human Stem Cells are:

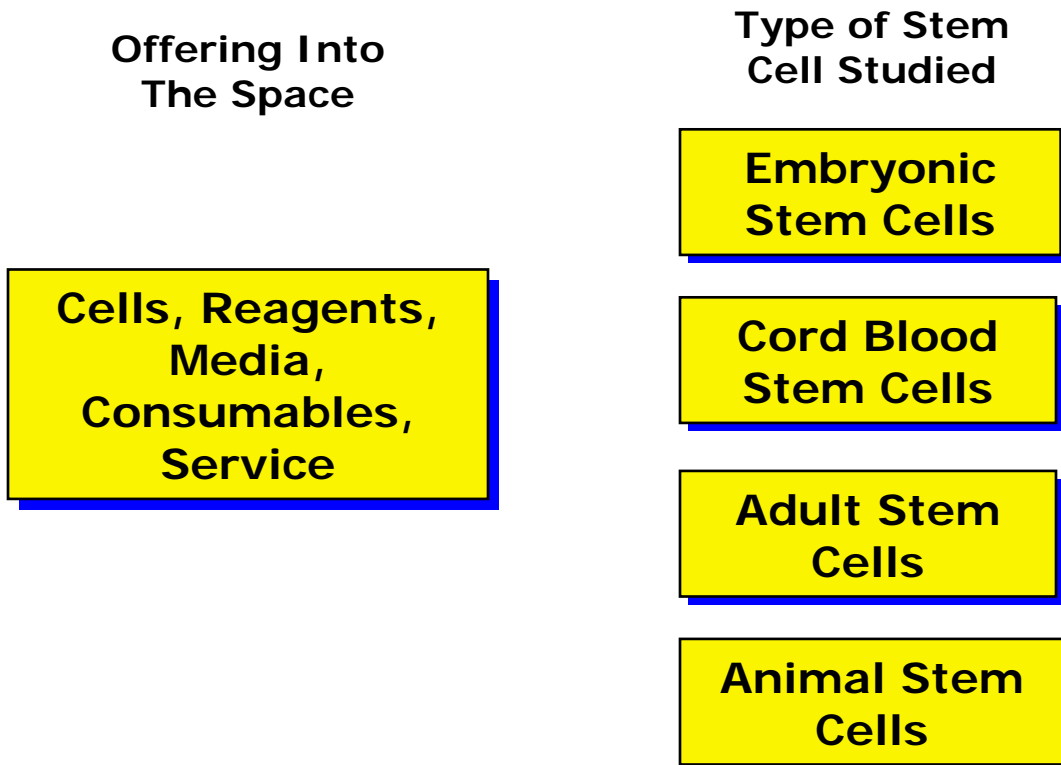
- Embryonic stem cells (ES cells; hESCs). Derived from fetal tissue and embryos.

- Stem or progenitor cells from developing tissues (such as umbilical cord blood stem cells). Derived from cord blood and placenta.
- Stem, progenitor or precursor cells from mature tissues in the adult (Adult Stem Cells; ASCs). Derived from adult tissue such as hematopoietic stem cells, mesenchymal stem cells, neural stem cells, muscle-derived stem cells, pancreatic stem cells, hepatic stem cells, epithelial stem cells.
- Immortalized cell lines. Derived from cells grown in culture.

Stem cell fate is determined by both intrinsic regulators and the extra-cellular environment (niche), and their expansion and differentiation *ex vivo* are generally controlled by growing them in a specific configuration (monolayer or three-dimensional culture) with cocktails of growth factors and signaling molecules, as well as genetic manipulations. However, most of these conditions are either incompletely defined, or non-specific in regulating the desired cellular process. It is these media and additives that are a large fraction of the total industry revenues generated by this marketplace.

Most interesting to the research community today are the various market segments that define the stem cells space and the opportunities that exist in each of these market segments—ie., how to identify growth areas and value drivers in each of these growth areas.

The following frames the key market segments within the stem cells space:

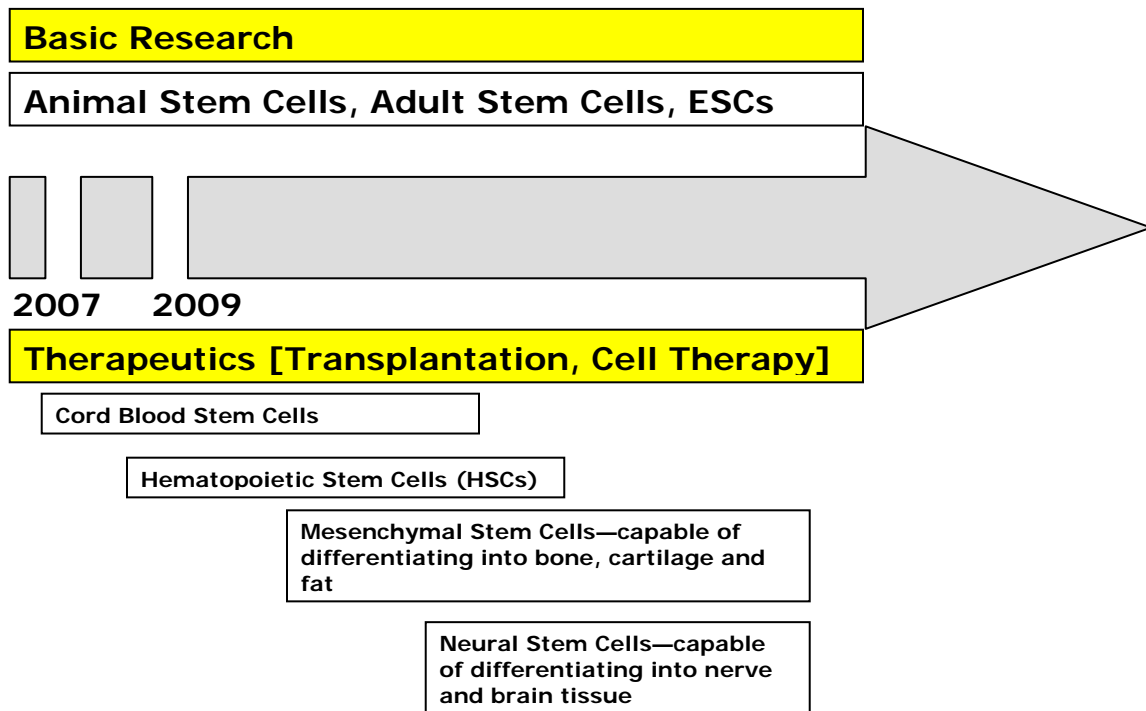


We have been tracking each of these above market segments and each has an associated set of challenges/barriers to entry, end-user base and set of applications, and associated market opportunity.

The unique feature of the stem cells marketplace is the large number of potential applications—and therefore market segments—that can be carved-out using the plasticity of various types of stem cells. The following bulleted list presents some of the potential applications that are gaining traction in the research and therapeutics development communities:

- Umbilical cord blood banking—harvesting and saving cord-blood at the time of delivery for potential autologous or allogeneic transplantation in the future.
- Replacement cell therapy [stem cells as therapeutic entities] in a number of therapeutic/disease areas.
- Research tool to model neurodegenerative and other diseases.
- A tool for drug discovery and drug development—toxicity screening in the pharmaceutical industry is an example.
- Model for understanding and targeting the stem cells of cancer—cancer stem cells.
- Studying autoimmune diseases.
- Understanding embryonic development.

Note that each of these applications has an associated timeline and we have been tracking the market impact of many of these applications—a summary of the applications and the expected timeline for market impact is presented below:



Summary of Challenges and Opportunities in the Stem Cells Space

The following presents some of the challenges and opportunities that we have assessed based on our continuing tracking of this marketplace and various end-user interviews:

- ESCs are developmental cells that come from a place in the organism where their role is to create the entire organism. Because of this, when you inject an ESC into an animal, it forms a teratoma—a type of tumor composed of various distinct cell types. Extensive differentiation is needed to prevent that malignancy from forming.
- To put the challenge in perspective, to inject ESCs into an individual for cardiac therapy, first you must make an ESC that's not rejected by the recipient, growing up those cells, differentiating them into heart cells, injecting them in vivo and then relying on differentiation to prevent them from forming a teratoma.
- ESCs do offer some key opportunities: They appear to be the only cells that can differentiate into all cells and tissues in the body, and can renew themselves indefinitely in the undifferentiated state
- hESCs express huge amounts of telomerase enzyme (key to cellular immortality), are scalable (ie., can be grown *ex vivo* in an undifferentiated state), and are a renewable source. Therefore, hESCs are amenable to production scale-up and manufacturing—a scalable business model.
- In the longer term, it is the ESCs that offer the most potential as therapeutic entities. At the present time, only ESCs have been shown to have the full developmental potential and lifespan of an adult.
- A number of companies in the 1990s developed business plans based upon autologous (ie., from the patient themselves) stem cells, but found it was virtually impossible to purify and expand them to the extent required for cell therapy. A more viable near-term business opportunity is to develop cell therapies using allogeneic cord blood or adult stem cells—this is a focus of many companies in the stem cells therapeutics [cell therapy] space.
- Adult stem cells lack the surface proteins (the histo-compatibility antigens) that trigger an immune response, therefore they can be used in allogeneic cell therapy.
- Adult stem cells are involved in tissue repair and therefore will either repair damaged tissue or be absorbed into the body.
- Adult stem cells work by more than just differentiation. They make growth factors, including vascular endothelial growth factor (VEGF) and the anti-apoptotic hepatocyte growth factor (HGF). Because of this, when they are injected at an injury site, they trigger the re-growth of injured tissues as needed
- A lot of the autologous stem cell transplants/research that have been performed could not be reliably delivered with every patient. These approaches suffice well for doing research or illustrating the capabilities of the cells, but are not amenable to scale-up and delivery as a product
- *Ex vivo* expanded allogeneic stem cells (either cord-blood derived or adult) are currently the most promising route forward and the nearest market opportunity.
- hESCs are a more longer-term potentially higher-value proposition: A future market opportunity.
- Value capture today from stem cells space is in life science research consumables, reagents, cells, media, and services.

- If therapeutics are approved, this will drive the research market also, as more commercial entities [Pharma, Biotech] will finance research into the cell therapy spaces.
- The current early entrants into the therapeutics space are providing much needed hope for patients who can find benefit with stem cell treatment options.
- We at Cancun Stem Cell Clinic urge you to peruse the materials on our website, ask questions, and thereby make informed healthcare decisions. We are always available to provide more information to you and address your specific questions.