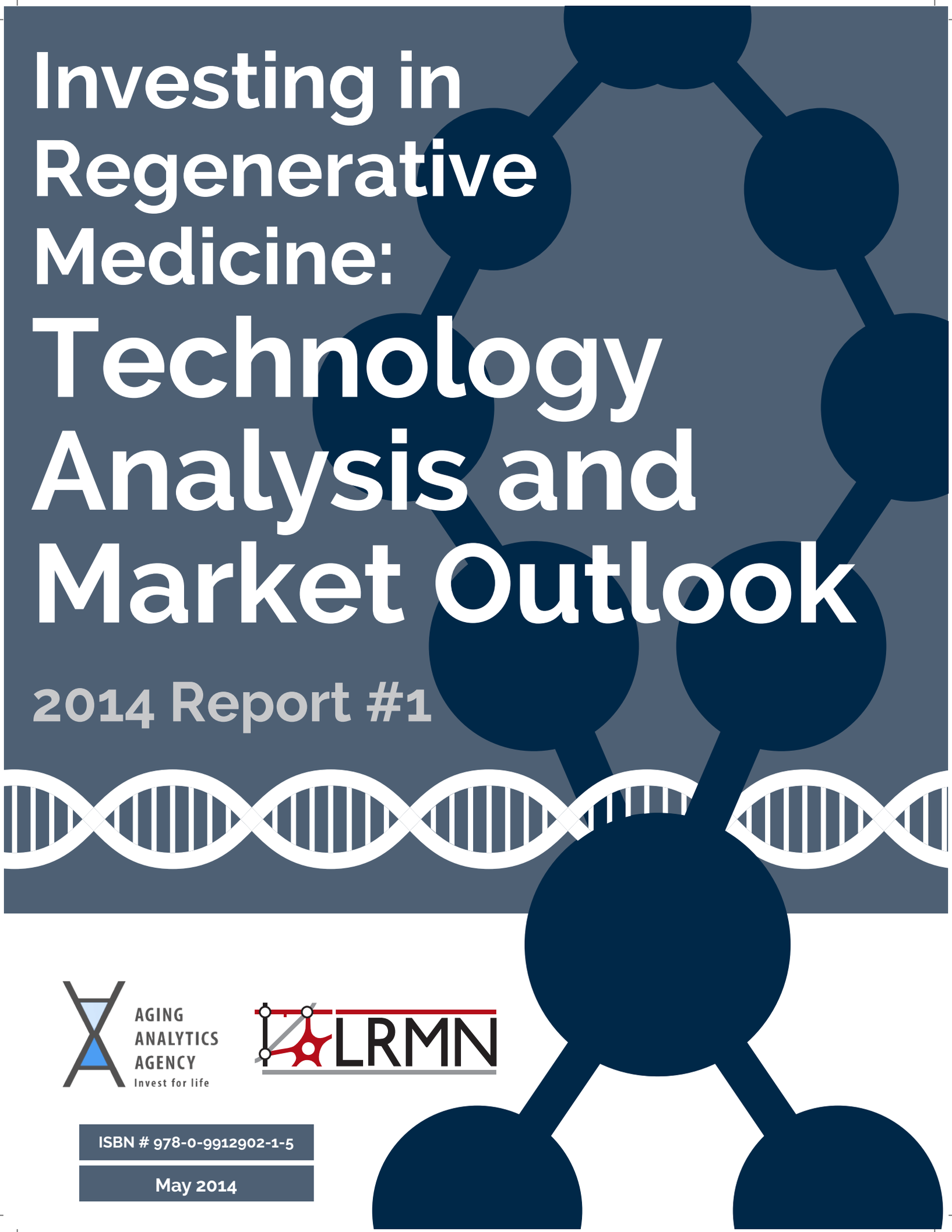
Investing in Regenerative Medicine: Technology Analysis and Market Outlook

2014 Report #1



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LRMN

ISBN # 978-0-9912902-1-5

May 2014

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Glossary

3D-bioprinting: layer-by-layer approach to create tissue and organ architecture using bio-ink and structure materials.

Bio-ink: multicellular building blocks for bioprinting.

Adult stem cells: multipotent stem cells that can be found in juvenile and adult organism.

Allogeneic: taken from the same species but genetically different.

Autologous: taken from the same organism.

Biomaterial: biocompatible material interacting with the body to improve biological functions and replace faulty cellular structures.

Cells: basic structural, functional and biological unit of all living organisms except viruses.

Cell therapy: administration of cells into the body in order to treat a disease or improve the function of the existing cells.

Clinical trial: stage of medical research that gives information of safety and efficacy for health interventions in humans (drugs, therapy protocols, diagnostics etc.).

Phase 0 trial: first in-human trials in small groups of patients to investigate the response of a new intervention in humans (e.g. drug pharmacodynamics and pharmacokinetics).

Phase 1 trial: trials in a small group of patients to screen the method of intervention for safety.

Phase 2 trial: experimental treatment of larger groups of people to investigate the safety and effectiveness of new intervention against a placebo.

Phase 3 trial: final confirmation of the safety and efficacy for a new intervention.

Phase 4 trial: post-marketing studies of the risks and benefits of the new intervention as well as the determination of optimal usage for the intervention.

Embryonic stem cells (ES cells): pluripotent stem cells derived from an early-stage embryo.

Implant: non-biological medical device designed to improve or replace a biological structure.

Expression: realization of information from a gene within the cell.

Extracellular matrix: tissue material between cells.

Ex vivo: outside the living organism.

In silico: performed on a computer or via computer simulation.

In vitro: performed in laboratory conditions rather than within a living organism.

In vivo: within the living organism.

Induced pluripotent stem cells (iPSC or iPS cells): pluripotent stem cells derived from non-pluripotent cells by reprogramming of genes.

Isogenic: taken from another organism but genetically identical.

Gene therapy: introduction of genetic material into cells to treat a disease.

Genetic vector: DNA or RNA molecule used for the introduction of foreign genetic material into the cells for research or medical treatment.

Medical Tourism: the practice of a patient traveling from one country to another to receive medical treatment that is not available or not approved in their country of origin.

Multipotent stem cells: stem cells that can differentiate into a family of related cells.

Oligopotent stem cells: stem cells that can differentiate into a few cell types.

Plasmid vector: small circular double-stranded bacterial DNA that can replicate independently within of the chromosomal DNA in a cell.

Glossary (cont'd.)

Pluripotent stem cells: stem cells that can differentiate into all cells except embryonic cells.

Regenerative medicine: field of medicine referring to approaches for replacing or regenerating human cells, tissues or organs to improve or restore biological functions.

Reprogramming: deriving less differentiated cells from more differentiated ones by forced expression of specific genes.

Scaffold: artificial structure capable of supporting the formation of a three-dimensional tissue.

Stem cells: undifferentiated biological cells that have ability for self-renewal and a capacity to differentiate into specialized cell types.

Tissue: group of similar cells from the same origin that together carry out specific function in the body.

Totipotent stem cells: stem cells that can differentiate into all embryonic and extra embryonic cell types.

Tissue engineering: use of cells, engineering, materials, factors and methods to manufacture tissues and organs ex vivo in order to improve or replace biological functions.

Transcription: copying of DNA into RNA by the enzyme RNA polymerase.

Transcription factor: protein that specifically binds to a known DNA sequence in the gene and controls the transcription of genes.

Translation: The process of protein synthesis by ribosomes, using the code from the RNA sequence within the cell.

Transplant: biological material placed into recipient organism to improve or replace a biological structure.

Viral vector: genetically engineered viruses carrying noninfectious modified viral DNA or RNA.

Retroviral vector: RNA-containing viral vectors that can integrate only into the genome of dividing cells.

Lentiviral vector: RNA-containing viral vectors that can integrate into genome of non-dividing and dividing cells.

Adenoviral vector: DNA-containing viral vector that does not integrate into the genome and does not replicate during cell division.

Xenogenic: originating from foreign substance.

Introduction

The field of regenerative medicine encompasses many areas of scientific research and clinical applications. While many attempts have been made to compare various companies, research organizations, and research projects, few models account for the whole industry supply chain and the fact that many companies participate in multiple industry segments.

For example, some of the companies supply reagents, equipment, and cells and may have a conservative growth projection, being less risky from the cash flow and clinical trials perspectives, and may also have basic research or translational medicine projects that may serve as major sources of growth.

Likewise, companies engaged in "high risk / high reward" projects that are not publicly known may have research divisions working on novel research projects that may be out-licensed to other industry participants and provide stable sources of funding.

There are a vast number of biotechnology companies and healthcare organizations which are not classically classified as players in the regenerative medicine field, but are either providing services to the industry acting as suppliers or deploying regenerative medicine technologies in the clinic, thereby contributing to the creation of demand.

Some of the large biopharmaceutical companies often have research or translational medicine divisions that occupy leadership positions in certain industry segments. These divisions are insignificant compared to the rest of the company, but have leadership positions in certain industry segments.

To address these issues, we developed a comprehensive **Analytical Regenerative Medicine Industry Framework (ARMIF)**, which incorporates many segments of the regenerative medicine industry and includes services, enabling technologies, technologies for manipulation at the cellular and tissue level, and diseases. ARMIF highlights the focus on the level of organismal organization such as cells, tissue, and organs.

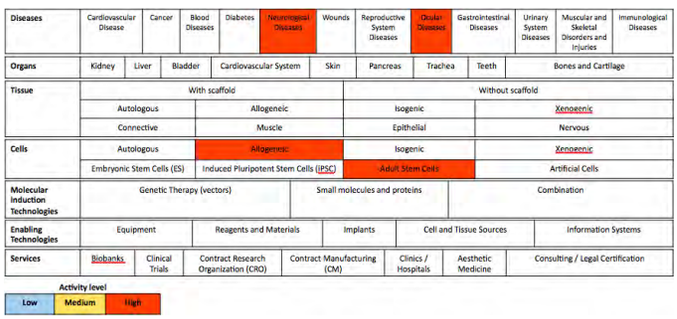
The presence of an individual company and that company's level of activity in each market segment is visualized using color codes for low, medium, and high.

For example, if the company's main business is supplying reagents and cells, the appropriate segments are highlighted in red. If the company is engaged in research of multiple cell types, but is mostly focusing on autologous cells, but it also has projects using allogeneic cells and is just starting the induced stem cell program, each one of these fields will be color coded by the company's level of activity in each field.

To facilitate an effective analysis and comparison of the companies and projects in regenerative medicine, we created an advanced knowledge management system called **AgingAnalytics.com**.

The system tracks over 150 public and private companies engaged in the regenerative medicine industry and uses the ARMIF model to analyze and compare these companies. In addition to the color codes, the AgingAnalytics system allows for each segment to be evaluated using multiple parameters of competition, growth, growth potential, technology risk, legal risk, and other factors. These parameters can then be used to evaluate and compare industry segments and companies, along with clinical and research organizations, as well as specific projects.

While ARMIF is currently limited in both granularity and scale, it is one of the most



Sample ARMIF diagram. Refer to page 85 for full page diagrams and industry segment analyis.

comprehensive models for analyzing the organizations and projects in the field of regenerative medicine. The system not only allows us to analyze a company's positioning, but also to evaluate the company's level of industry participation and to track multiple parameters in each market or research segment.

It is a scalable and flexible platform that allows for new parameters to be added as the industry develops to produce new innovations and new applications.

Regenerative Medicine Landscape

Viewed comprehensively, the Regenerative Medicine industry includes a diverse range of suppliers, specialist contract research organisations and hospitals. The makeup of the industry includes not only the primary companies involved directly in the regenerative medicine business, but also the services industry. Also associated are diverse fields like bioengineering, the chemical industry, and the pharmaceutical industry, as well as clinics and hospitals involved in trials.

We have developed a map which can help one to understand the regenerative medicine industry landscape. The projection of this map is in the form of a table, which is divided into several levels (horizontal rows). Each level in this table represents a separate part of the regenerative medicine industry, but some of these levels are strongly connected. There may be some segments in a level which describe specific technologies or services.

This table can also be used for the description of the companies working in regenerative medicine. Each company's table has its own representation of its presence and activities in the industry. If a company develops a particular technology or provides a particular service, the respective table cell will be marked with a color code. Otherwise, it will remain white.

The first two levels in this table are represented as 'Services' and 'Enabling technologies.' Services form a vital part of any industry, and Enabling technologies provide an innovative thrust for future developments in the field of regenerative medicine.

The next four levels in the table are very similar to the levels of the biological organization in humans.

Molecular induction technologies are a very important part of regenerative medicine. The molecular level of the organization of the body is the simplest one, but it is not less important than the others.

The cellular level of the organization in the body has a higher complexity than the molecular level. Cells form the traditional basis of regenerative medicine, as they are the primary unit involved in the regenerative process. A large number of current treatment modalities in the field of regenerative medicine are based on cells or cell-derived products.

The organization at a tissue level is strongly connected to the cellular level. The source of cells and tissues can be classified into four different groups based on the source of the cell/tissue material and the cells' immunogenic capacity:

1. **Autologous:** Cells and/or tissues derived from the same person who is undergoing a treatment. Autologous cells/tissues have a very low probability of rejection after transplantation.
2. **Allogeneic:** Cells and/or tissues derived from a person, for the treatment of another person. Allogeneic cells/tissues have a large probability of rejection after transplantation.

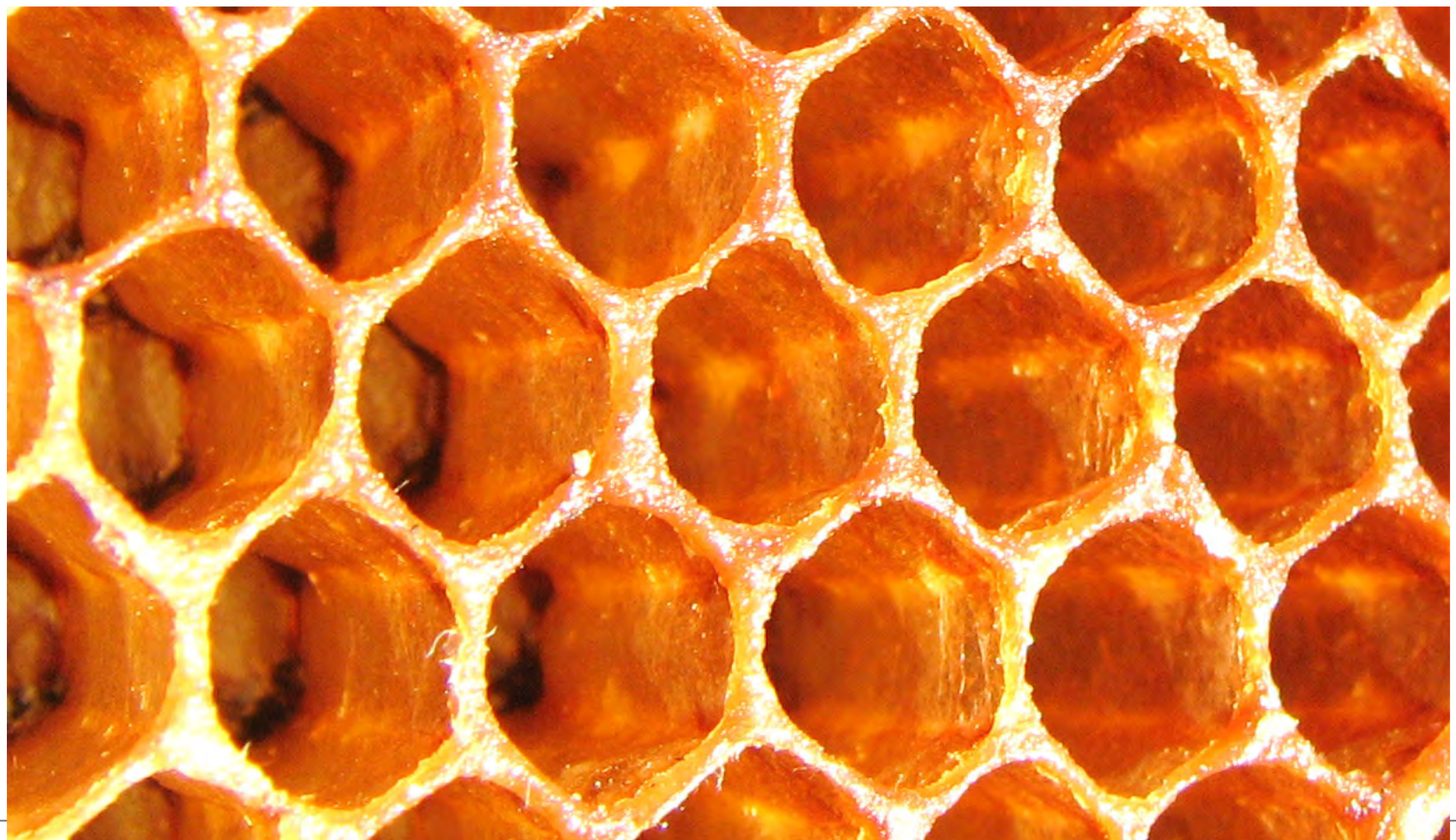
3. **Isogenic:** Cells and/or tissues derived from a person with the same genetic make-up as the patient (for example, from a twin). Isogenic cells and tissues also have a rather low probability of rejection after transplantation.
4. **Xenogenic:** Cells and/or tissues derived from an animal and intended for the treatment of a person. Xenogenic cells and tissues have a large probability of rejection after transplantation.

The next level of complexity in an organism is organization on the organ level. Each organ consists of different types of tissues, which in turn are composed of different cell types. Bio-engineered organs have already been produced, and some of them have already been successfully transplanted.

And the final level is the level of diseases, where some particular treatments are discussed.

Every table cell is described in the next chapter, which is called Segmentation.

Industry Segmentation



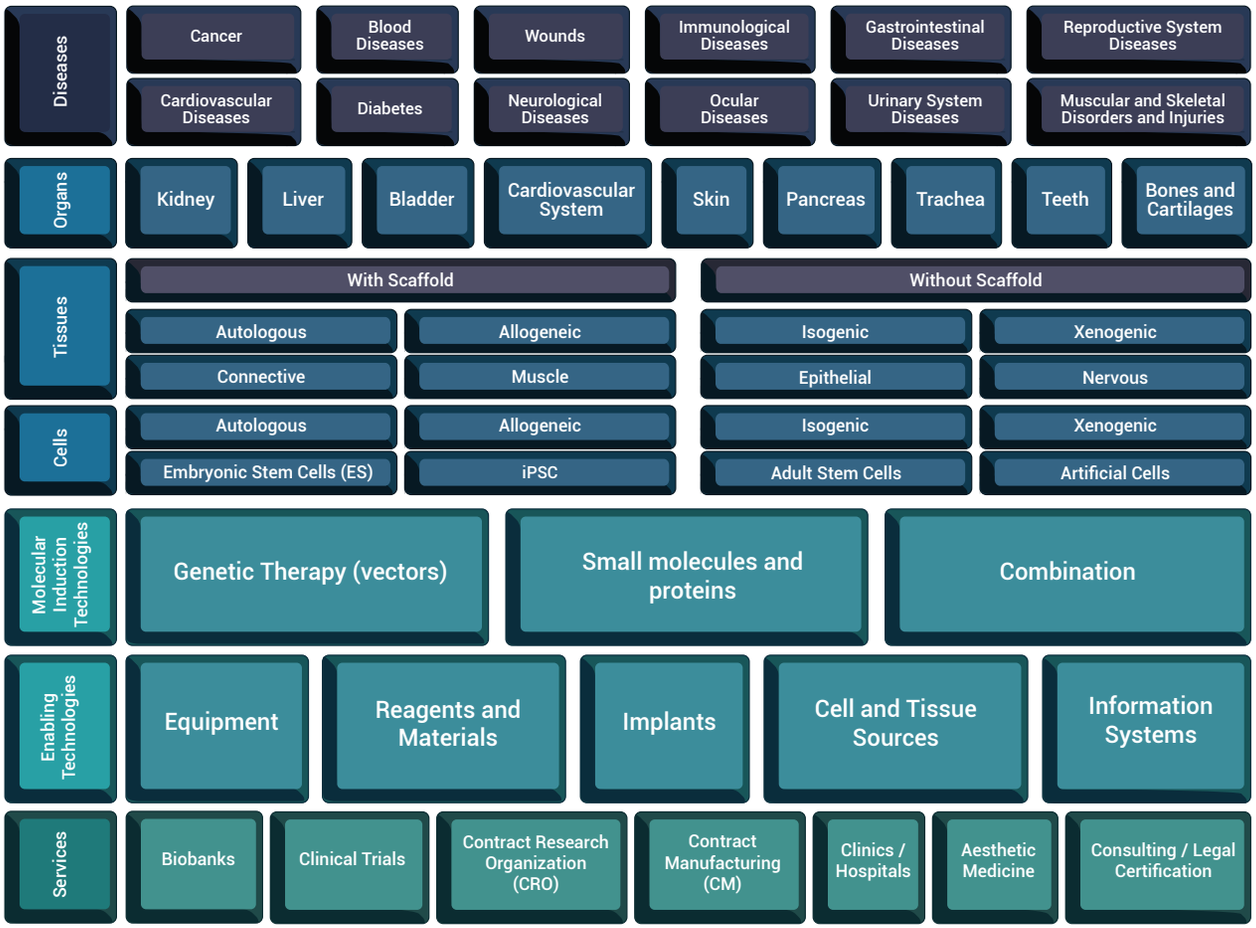


Table 1 : Segmentation of the Regenerative Medicine Industry

Segment 1. Services

Services form an important part of any industry. In the field of regenerative medicine, their role can hardly be overstated because it is a new area, and all stakeholders face pressure from the industry. A well-organized services sector supporting the regenerative medicine industry can undoubtedly make a great contribution to the development of the field. Some of the associated service providers cater to the needs of companies, while others provide services to the final consumers.

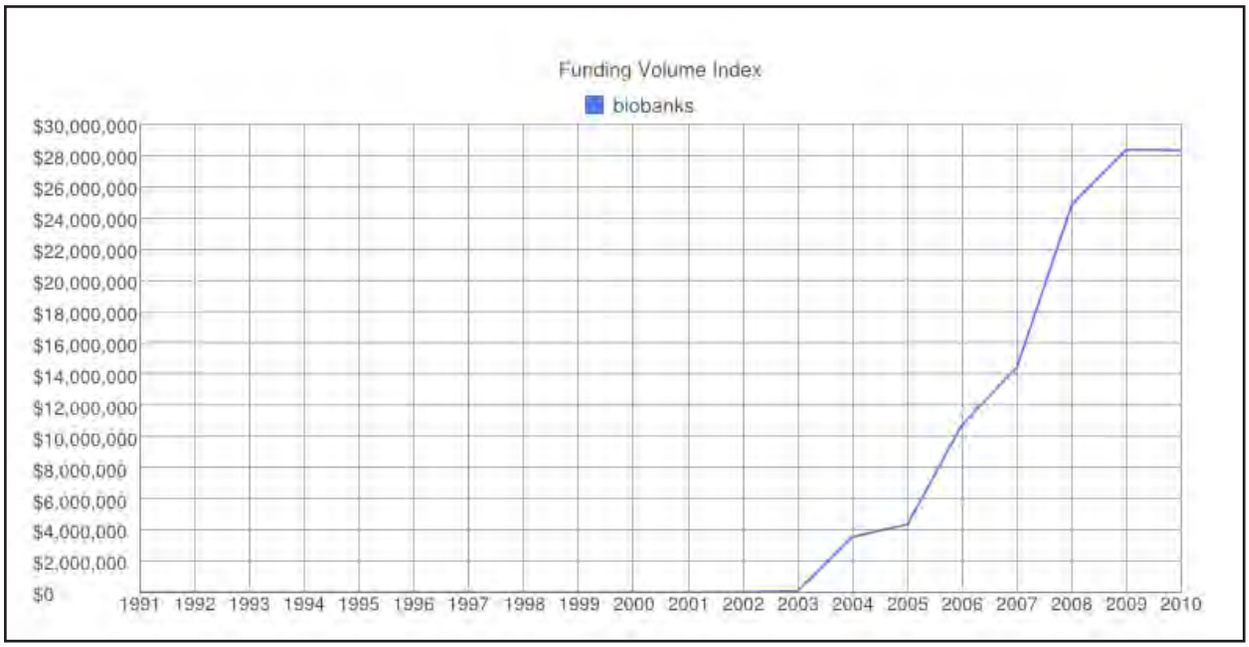
A. Biobanks

A biobank is a repository of different biological materials such as blood, umbilical cords, cells, and tissues, where these materials are collected, processed, and stored. The bio-specimens can be used for different purposes such as scientific research and transplantation. In this section, we shall cover biobanks which are focused on storage of different cells and tissues for future transplantation, as they are of significant relevance in the regenerative medicine industry.

Present day technology makes it possible to collect a large number of different cell and tissue types from the human body. For example, collected material can be adipose tissue, cord blood, amniotic stem cells and skin, and so on.

Biobanks can be publicly or privately controlled. Public banks collect cells and tissues and make them available for anyone who needs a transplantation. In such cases, donors are not assured that their donated

Chart 1:
Funding received by Biobanks.



specimens will be available to them in future, such as in the case of a donor contracting a disease. Public banks are non-profit organizations.

Private biobanks are commercial organizations which offer their clients a possibility to store their tissues and cells for potential use in the future at a cost.

Cord blood banks are an example of the most successful biobanks. According to the Alliance for Regenerative Medicine (URL Ref. 1), More than 30,000 cord blood transplants have been performed leading up to the year 2012. The popularity of private cord blood banks is rising sharply, but there is a strong opinion that the average probability of usage of the transplant material by its donor is too low, giving an advantage to the public banks in terms of the potential for developing research and real-world transplant studies.

According to FundingTrends.org, funding of biobanks has risen sharply since the year 2003, and reached a plateau in 2009.

B. Clinical trials

Clinical trials are an extremely important, but cost- and time-intensive step towards bringing a research product to the market once its safety and efficacy can be evaluated. The process of conducting clinical trials can face many challenges, and this is the precise reason that small scale companies engaged in the development of therapeutics prefer to use the services provided by companies specialized in getting approvals for and conducting clinical trials. One example is multinational Contract Research Organization PAREXEL, with a corporate presence across several continents. According to Yahoo Finance, this company's market cap is currently about 2.84 billion dollars.

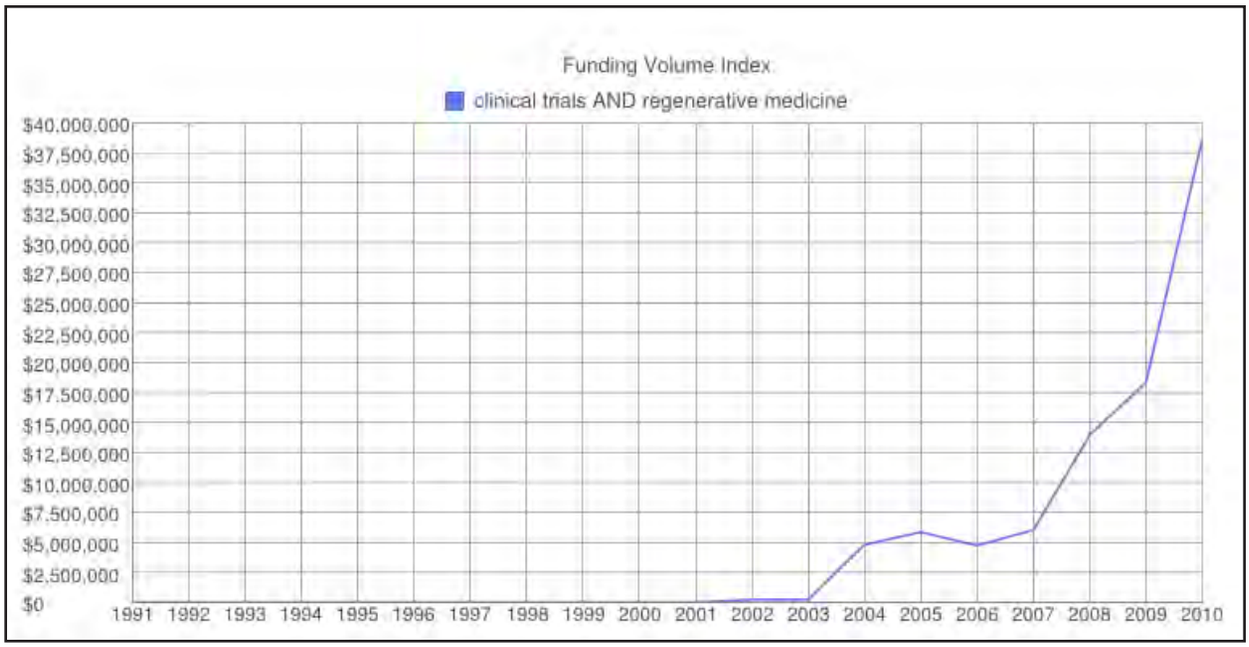
Such specialized companies provide services that can be helpful for the development of the regenerative medicine field, as a large number of small companies, incapable of conducting such trials independently, can use the expertise and know-how of the companies engaged primarily in clinical trial development. FundingTrends.org cites that the funding of clinical trials related to the regenerative medicine field has sharply increased since 2003,

Contract Research Organizations (CROs)

A Contract Research Organization is an organization which provides different research services to the pharmaceutical and biotechnological companies on a contract basis. For example, services provided can come in the form of biological assays, preclinical trials, etc.

These CROs have a strong connection with the regenerative medicine field. Firstly, their

Chart 2: Funding for clinical trials in regenerative medicine.



services can be very helpful for the companies which are focused on development of a particular regenerative technology. Secondly, these CROs are often the first clients to test new models developed by the regenerative medicine industry, one example being the new 3D tissue models that are gaining popularity in the field of drug testing.

The annual growth of the CRO segment of the market in the United States is 12.1 % and annual revenue is about $15 billion (URL Ref. 2).

C. Contract Manufacturing (CM)

A Contract Manufacturer is an organization which manufactures a product on a contract basis. Of the diverse assortment of manufacturers across the biomedical industry, some contract manufacturers provide specialized manufacturing services for the regenerative medicine industry. Again, as mentioned in the case of CROs, CM can be beneficial for small innovative companies which may have a breakthrough product but do not have the manufacturing capabilities. The list of products which can be produced by such organizations is rather extensive. It includes different reagents, vectors for gene therapy, induced pluripotent stem cells, and the list goes on.

D. Clinics and Hospitals

Clinics and hospitals are considerable stakeholders in the regenerative medicine industry. In any case, all clinical trials and fully developed therapies are connected with eventual clinical and medical applications. These institutions can also participate in the development of different regenerative technologies, as they have their own research facilities and real world data to collect.

In the future, the role of clinics shall be increasingly important as it is often easier to produce stem cell products onsite in a hospital rather than in a separate laboratory. The delivery of any stem cell product is a complex process involving considerable regulation. Moreover, some products have to be used immediately after preparation, as they have a short shelf life and may be subjected to damage upon storage and/or transportation. Hospitals and clinics can be a valuable source of the donor material and at the same time provide the most appropriate facilities to deliver the product to the recipient. Hence, in the future, big hospitals and clinics are expected to play major roles in the field of regenerative medicine.

E. Aesthetic Medicine

The technologies of regenerative medicine can make a serious contribution to aesthetic medicine. Regeneration and protection of the skin is one of the most important aims of cosmetic procedures. Several technologies

which are currently used for the treatment of connective tissue and skin related problems are also relevant for cosmetic purposes. For example, the company Anika Therapeutics manufactures and markets products which can be used for correction of facial wrinkles, scar remediation, and lip augmentation (URL Ref. 3).

F. Consulting and Legal Certification

Consulting and legal certification is an extremely important part of the services sector benefitting regenerative medicine. The rules and regulations covering products and services in regenerative medicine differ between national jurisdictions. Moreover, the regulations are often not easy to interpret, and the innovator often requires professional legal and regulatory personnel to get through the process of legal certifications and regulatory boards.

Consulting and analytics are also important, as regenerative medicine is a very dynamic industry and stakeholders need to keep apprised of industry events to inform decision-making.

Segment 2. Enabling Technologies

Enabling Technology, as the name suggests, is a driving innovation or technology that can radically change existing capabilities, to the benefit of service providers and the end user. These organizations may not be directly involved in the development of a specific treatment using the standard approaches of regenerative medicine.

A. Equipment Suppliers

This group of companies is specialized in the production of equipment for cell and tissue culturing. The range of necessary equipment is rather wide. It includes cell culture hoods, incubators, microscopes, centrifuges, refrigerators, freezers, etc. As an example, the laminar flow hoods provide an aseptic work area, which is necessary for the process of carrying out manipulations with cells and tissues. Incubators are needed for maintaining special conditions (gas composition, temperature, etc.) for proper cell growth. Moreover, some incubators contain special microscopes which allow real time imaging of cell development and to correct it when it is needed.
(URL Ref. 4)

Refrigerators are used for storage of some reagents. Freezers can be used for different purposes. There are three types of them (-20˚C, -80˚C, and liquid nitrogen freezers with the temperature of -196˚C). The first two are primarily used for storage of reagents, but the third is used for the preservation of biomaterials (cells, tissues, etc.).

Other equipment (centrifuges, shakers, pipettes, etc.) is used for different manipulations with cells and tissues.

B. Reagents and Materials

Another segment of enabling technologies is the production of different reagents and materials. The reagents used in regenerative medicine are varied and diverse. The list includes cell culture media, different solutions, growth factors, cytokines, antibodies, and other chemical compounds. Companies such as Life Technologies Corporation, STEMCELL Technologies, Inc., and others provide a wide range of such reagents.

Another important part of the market is production of different biomaterials. These materials are used for tissue engineering and provide proper environments for cell growth and differentiation. They also have special mechanical properties depending on their purpose.

C. Implants

A medical implant is a device introduced into the body to replace a missing biological structure, and/or to support or enhance the function of a damaged biological structure. Implants as defined by regenerative medicine are composed of biomaterials, but they should be described separately due to their

importance. Surgeons have used different mechanical implants for a long time. However, these implants do not mimic human tissues as the materials used have properties that are different from biological material. At present, it is possible to construct implants from materials foreign to the human body which can be used as a scaffold for the attachment and growth of human cells. It has now became possible to combine stem cells and foreign material implants to derive a cell-based implant with mechanical properties that is better than the mechanical implant alone. These implants are also less susceptible to rejection by an organism (Smith et al, 2012).

D. Cell and Tissue Sources

The sourcing of donor cells, specimens, and other biological material is a necessary factor in the development of regenerative medicine products. Companies specialized in providing reliable biological material which is well characterized and meets the required regulatory standards form the foundation of the Enabling Technologies classification. These characterized biomaterials can be used for different purposes, such as clinical and scientific research or pharmaceutical assays. The list of common bio-specimens includes donor cells, cell lines, frozen tissue, etc. All biological samples should be well-characterized and obtained from reliable sources.

E. Information Systems

In the present-day Life Science industry, information systems play a vital role. For example, the modern field of bioinformatics could not exist without such systems. Regenerative medicine is not an exception to this rule. Handling of large scale data regarding gene sequences, signaling pathways, and mechanisms of actions of drugs on specific pathways all utilize the resources of information systems to comprehend and study valuable data. Companies involved with the management and interpretation of large volumes of such data related to biological processes are an extremely important component for the development of regenerative medicine. Information systems help integrate and update the research on biological processes, which then forms the basis of research and development for new products in the Life Science industry.

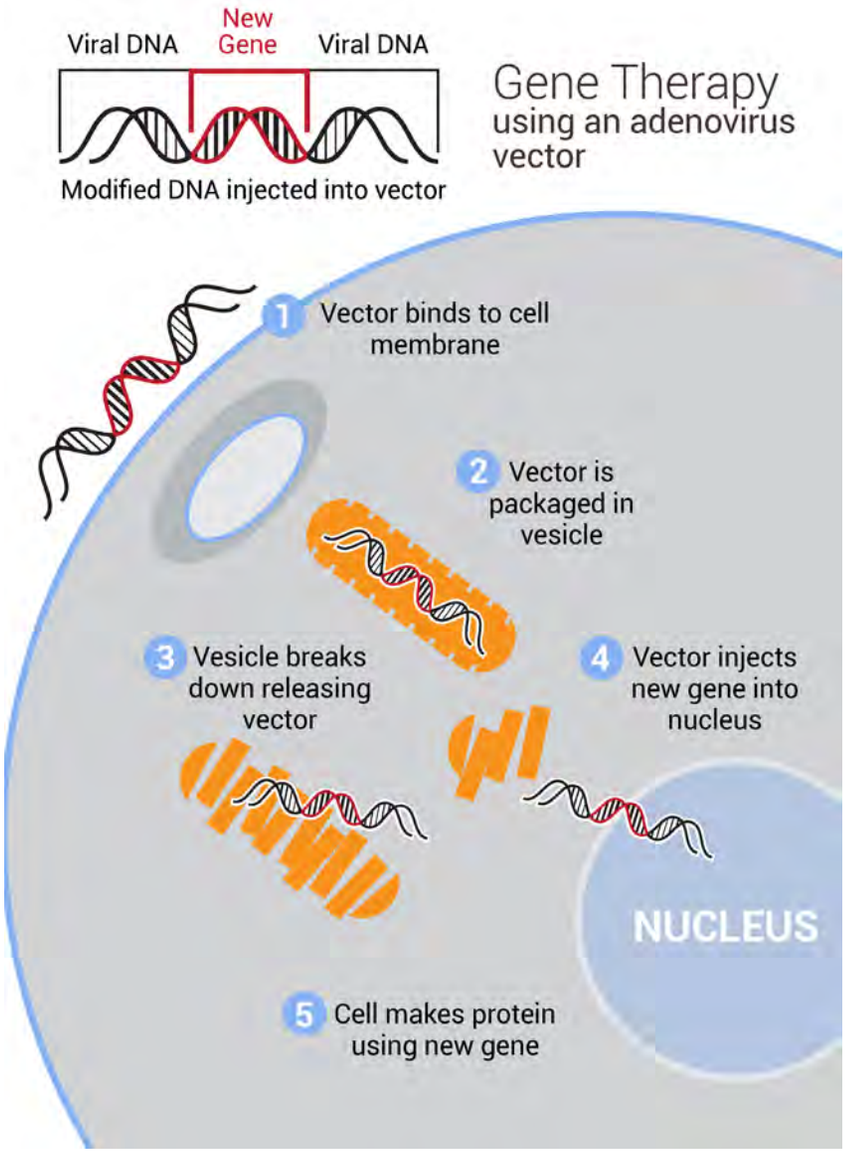
Segment 3. Molecular Induction Technologies

One possibility for the regeneration of damaged human cells in case of a disease is to transform them to circumvent this damage. For example, if a cell produces a faulty protein which results in a specific disease type, we can inject the gene coding to produce the correct protein. Another possibility is to transform stem cells from a patient's own body and allow them to differentiate into a specific subtype, replacing the damaged cells. In this chapter, we shall discuss different factors that can be used to induce the transformation of damaged or diseased cells.

All transforming factors can be divided into two groups. The first group is that of the different vectors used in gene therapy. The second group is classified as the small molecules and different biological proteins which can be introduced into the cells, resulting in a specific transformation.

A. Gene Therapy (Vectors)

Gene therapy addresses the correction or an improved regulation of a mutated or defective gene by introducing nucleic acids (DNA or RNA) as therapeutic molecules for the correction of a specific defect. Gene therapy can be used to add a new gene to a human genome or to replace, correct or knock out a damaged gene. Nucleic acids, which are used as therapeutic agents, should be packaged within a specialized carrier, called a vector, in order to reach the cell nucleus and express a desired protein product. Finally, all delivered DNA and RNA transform into functional proteins or RNA which can change behaviors of the treated cells.



There are several types of vectors which can be classified into two subtypes: **Viral Vectors and Non-Viral Vectors.**

a. Viral Vectors

The first possibility to deliver nucleic acids into a cell is through the use of different viruses. Viruses can penetrate into the cell and nucleic membrane and deliver genetic material which is then expressed by the cell. If a part of a viral genome is replaced with a gene of interest, this gene will be expressed by the cells, instead of the viral genes. Different types of viruses such as adenoviruses, retroviruses, and lentiviruses are widely used for human gene therapy.

b. Non-Viral Vectors

Non-viral vectors are comprised of small molecules including naked DNA, liposomes, inorganic nanoparticles, and other structures, such as dendrimers. The efficiency of these methods has been enhanced since they were first discovered, and their main advantage lies in low immunogenicity and an ease of large scale production.

Their therapy can be classified as somatic cell gene therapy, where only somatic cells in the body are manipulated, and the gene defect is still passed on to the future generations.

The second type is germ line gene therapy, where human germ cells are modified, the genetic defect is corrected, and the corrected gene is passed on to future generations. Unfortunately, germ line gene therapy has not yet been completely validated for safety and remains forbidden in several countries.

Gene therapy is suited for diseases caused by single-gene defects. There are at the present time a large number of gene therapy trials targeting cancer and hereditary diseases. Targeting genetic defects resulting from a combination of several faulty genes is still deemed difficult and has not been widely investigated.

Until 2012, more than 1800 clinical trials involving gene therapy have been successfully completed (Ginn, Alexander, Edelstein, Abedi, & Wixon, 2013) in more than 31 countries. There are also a number of ongoing clinical trials evaluating the potential of gene therapy methods (URL Ref. 5). For example, the first gene therapy trial was conducted on a 4 year old girl at the NIH center in the USA on 14 September 1990 for the treatment of adenosine deaminase deficiency (URL Ref. 6).

Although there are a number of clinical trials reporting success, the method has some serious disadvantages. The efficacy of many

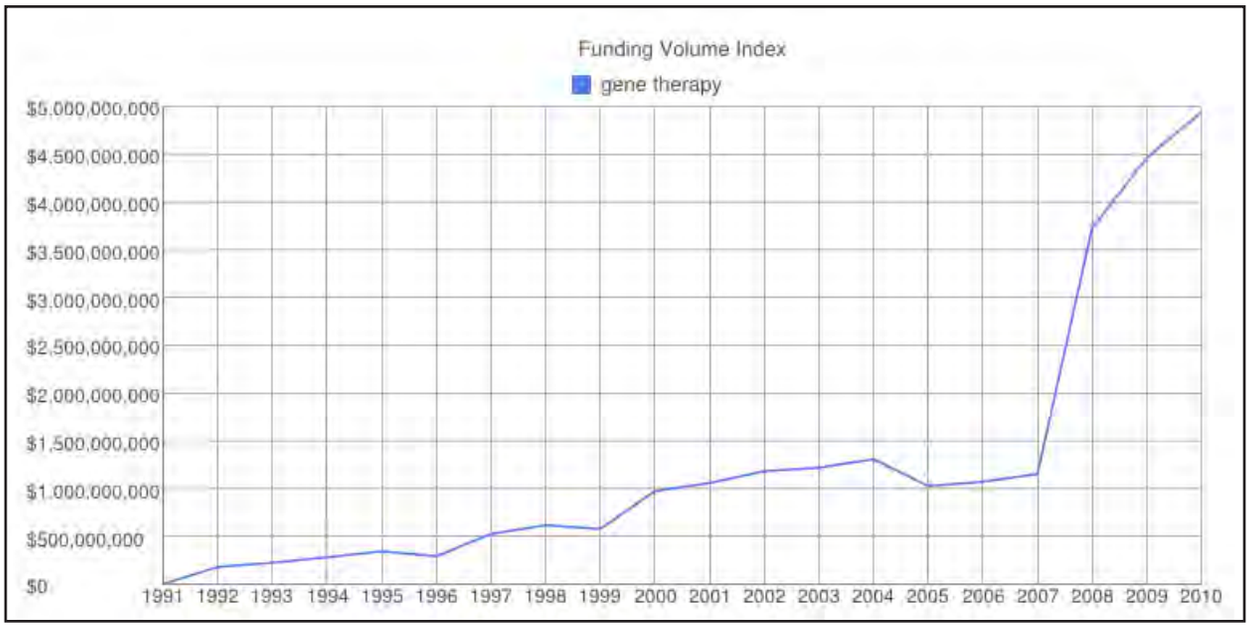


Chart 3: Funding for projects in gene therapy.

gene therapies is not long-lasting, especially for somatic cell gene therapy. The second disadvantage is the immune response to the treated cells, as they carry fragments of DNA which are recognized by the host as 'non-self.' Furthermore, the use of viruses can also elicit an immune response, at times incapacitating the mode of delivery. The use of integrating viruses, which integrate the DNA into the host DNA, can be tumorigenic, as the site of DNA integration is unpredictable, and might affect the normal cellular processes and functioning of cells. Several strategies to overcome these potential disadvantages are currently being investigated.

The funding of projects to study and test gene therapy has seen a sharp increase since the year 2007, and the funding reached almost $5 billion for the year 2010. (URL Ref. 7)

B. Small Molecules and Proteins

Another promising approach for the treatment of diseases is to introduce small molecules such as growth factors or other specific proteins in the body to allow for the regeneration of a damaged or diseased tissue. Different proteins and small molecules can be

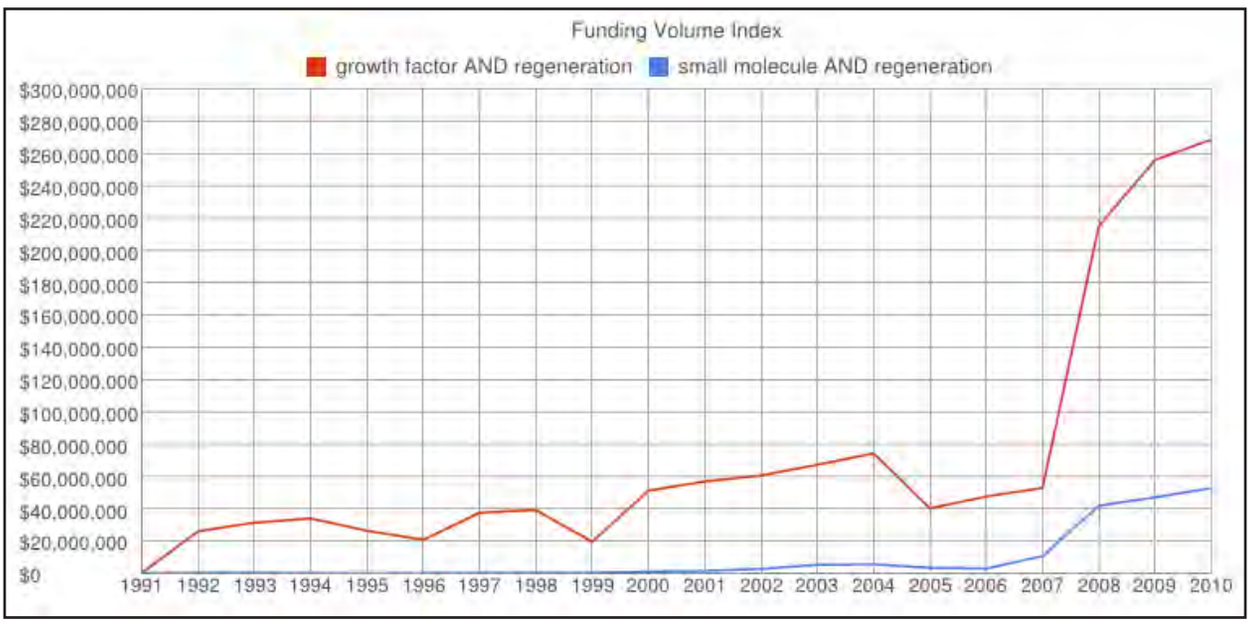
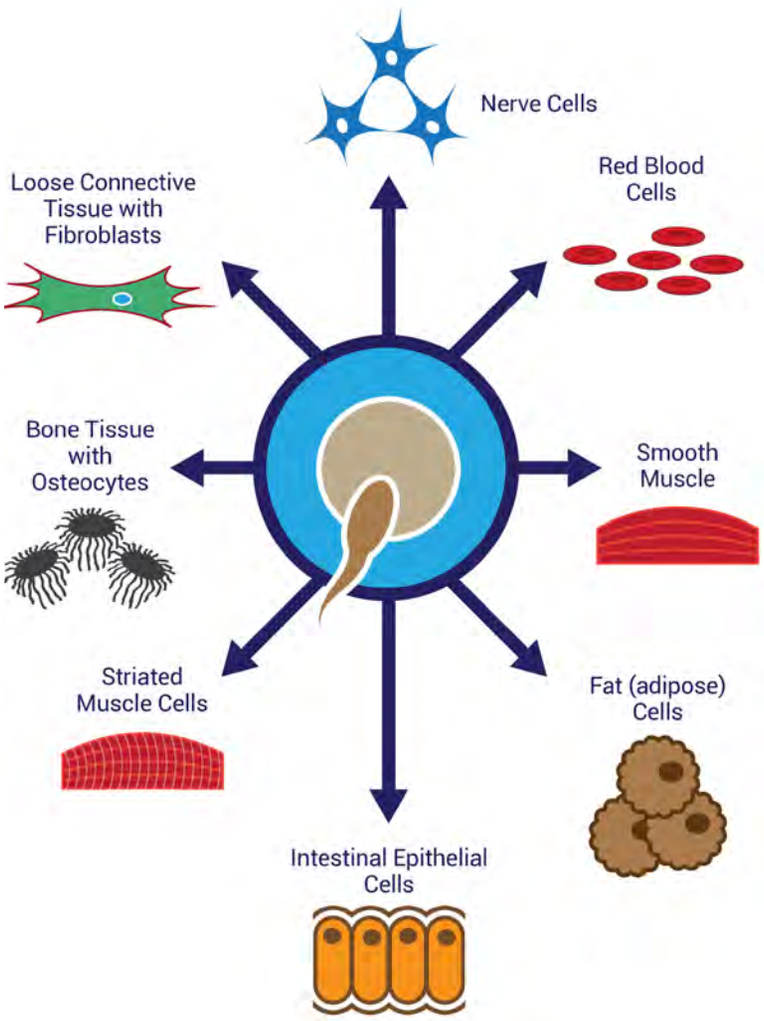


Chart 4: Funding received by projects in regenerative medicine exploring growth factors and small molecules.



used for these purposes.

For example, Platelet Growth Factor (biological protein which is contained in platelets) can be used for treatment of non-healing wounds and for regeneration of bones (Burnouf et al, 2013). Small molecules have also been used for the regeneration of bones (Lo, Ashe, Kan, & Laurencin, 2012). Recently, scientists have discovered that small molecules and proteins can be used to reprogram mature cells into stem cells. These stem cells are called induced pluripotent stem cells (iPSCs) and have the potential to revolutionize the field of regenerative medicine. These will be discussed separately.

The funding of projects on regeneration which use small molecules and growth factors has also seen a sharp rise since 2007. However, the funding for projects which use small molecules for regeneration is much less than those using growth factors. (URL Ref. 8)

C. Combination of Gene Therapy and Small Molecules and/or Proteins

Combining gene therapy with small molecules or protein therapy can reduce the side effects of gene therapy alone and improve its efficacy. For example, when adenoviruses are used as vectors, they have a strong hepatic tropism, strongly reducing the safety and efficacy of the therapy. Recently, scientists have discovered several small molecules which can circumvent this side effect and make the therapy safer (Duffy et al, 2013). This approach is very promising and will probably have widespread applications in the future.

Segment 4. Cells

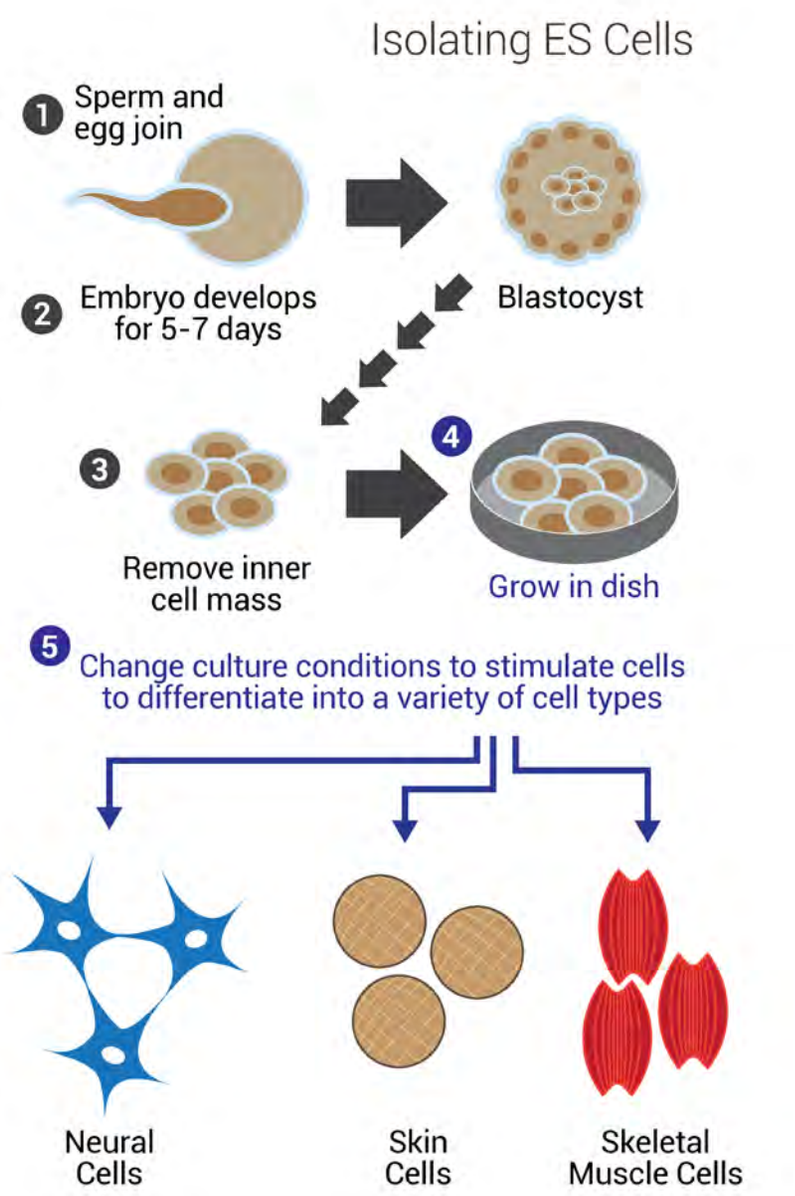
The human body consists of more than 10^{13} (10,000,000,000,000) cells of several different types. These differences in different cell types are both morphological and functional.

Different cell types display stark differences in the pathways used for cell signaling, though they may have structurally similar compositions.

All cells in a human body are derived from a single fertilized egg cell. Most of the cells in an adult human body are mature cells without the capacity to proliferate, but can perform a specialized function in the body.

After a certain number of cell cycles, a mature cell cannot divide any further and hence, is unable to regenerate when afflicted by damage or disease. Stem cells have two main features that make them suitable to replenish the lost adult cells. Stem cells can proliferate and generate a large number of identical daughter cells, making them suitable to be used for regenerative purposes.

Secondly, stem cells are capable of being transformed into many specialized cell types.



Stem cells in general can also be classified into several subtypes depending on their lineage. For example, mesenchymal stem cells, cardiac stem cells, embryonic stem cells, and so on. Each subtype of stem cells has its own set of advantages and disadvantages, which will be discussed in later sections. The regenerative capacity of stem cells, as employed in cell therapy, undoubtedly makes them the most important factor in the field of regenerative medicine, as they have enormous medical and economic potential.

A. Embryonic stem cells (ESCs)

As was mentioned before, cells in a human body are derived from the zygote, formed after fertilization of an egg and a sperm. After fertilization, the zygote divides to form an embryo. At this stage, the embryonic cells can form all cell subtypes found in a human body, along with the cells forming the placenta, for the attachment of the embryo to the mother's uterus. After several days, the cells in an embryo divide and form a blastocyst. At this stage, the embryo consists of a trophoblast and an embryoblast. The trophoblast is an outer layer of ancillary cells which provide nutrients and form the placenta.

The embryoblast or the inner cell mass contains cells which are capable of differentiating into all cell subtypes in a human body.

Due to their potential to differentiate, these cells are called Embryonic Stem Cells (ESCs), and they are valuable because they can help to restore any type of human cells.

In order to get ESCs, the blastocyst is destroyed, and the inner cell mass is extracted. Thereafter, the cells are cultivated to generate a stable cell line.

The process of cultivating stem cells is rather difficult and time intensive, and often, additional cells are added into the medium to support the growth of these ESCs. These additional cells can be of a xenogenic origin and thus, the clinical usage of derived ESCs is limited because of a high risk of rejection.

In order to get specifically differentiated cells (for example fibroblasts), the ESCs are placed into a special medium containing chemicals which help the ESCs differentiate into the necessary cell types.

As ESCs are pluripotent i.e. they can transform into any type of human cells, they are promising for clinical purposes. They can be transformed into cells such as cardiomyocytes, fibroblasts, chondrocytes, hepatocytes, etc., paving the way for treatment of diseases such as cardiovascular diseases, diabetes, neurological diseases, etc. The FDA approved

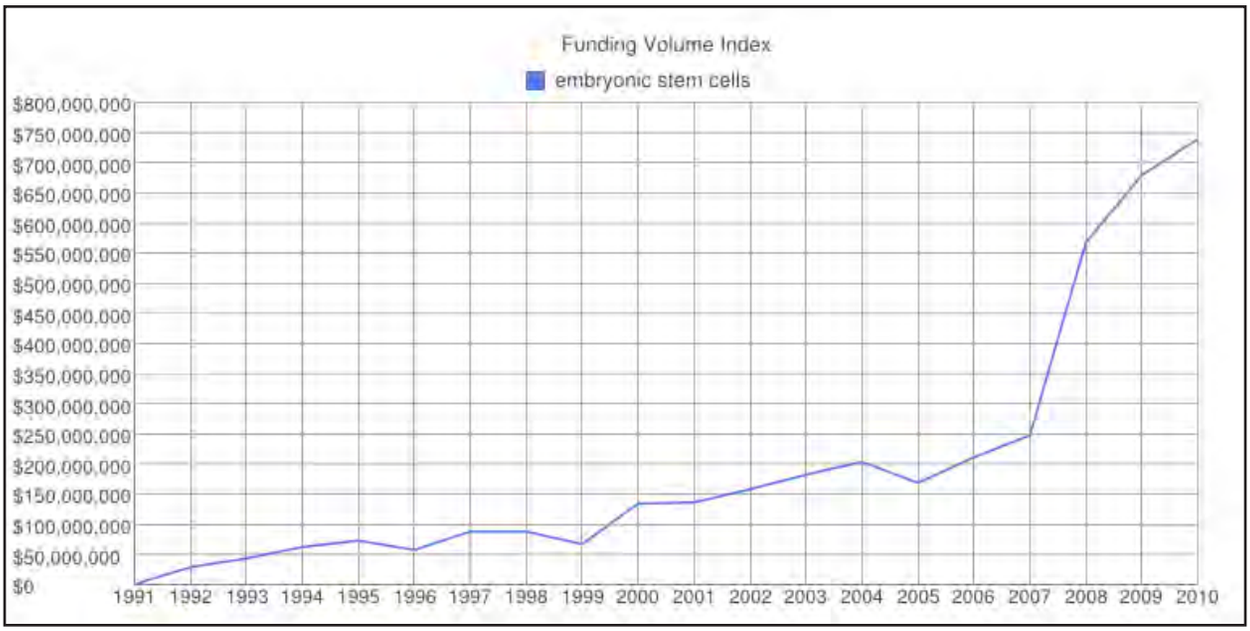


Chart 5: Funding received by projects dealing with embryonic stem cells.

the first clinical trial of ESCs in 2009 for the treatment of spinal cord injury, a treatment developed by Geron Corporation (Falco, 2009). The company declined to schedule subsequent trial stages because of an internal change in strategy.

Although ESCs are promising, there are several technical and ethical issues related to the development of stem cell therapies. In previous times, a scientist had to destroy an embryo to retrieve ESCs, and thusly, their usage for research has raised a number of ethical and legal questions. In some countries, stem cell research using human embryos is forbidden.

However, there is now a way to get ESCs without destruction of an embryo, and this new method can help to solve most of the ethical and legal problems encountered thus far. Earlier, xenogenic components were used during the cultivation of ESCs, which could result in a rejection of the induced stem cells, and at the same time, was a risk for transmission of diseases from a foreign animal source. However, it is now possible to generate ESCs without the use of xenogenic elements.

The third major problem associated with the use of ESCs is the development of tumors in the patients, as not all the cells introduced into the body have been specifically differentiated and the non-differentiated cells result in the formation of tumors. New methods of ESC cultivation and clinical use of ESCs are underway, and a breakthrough is expected in the near future.

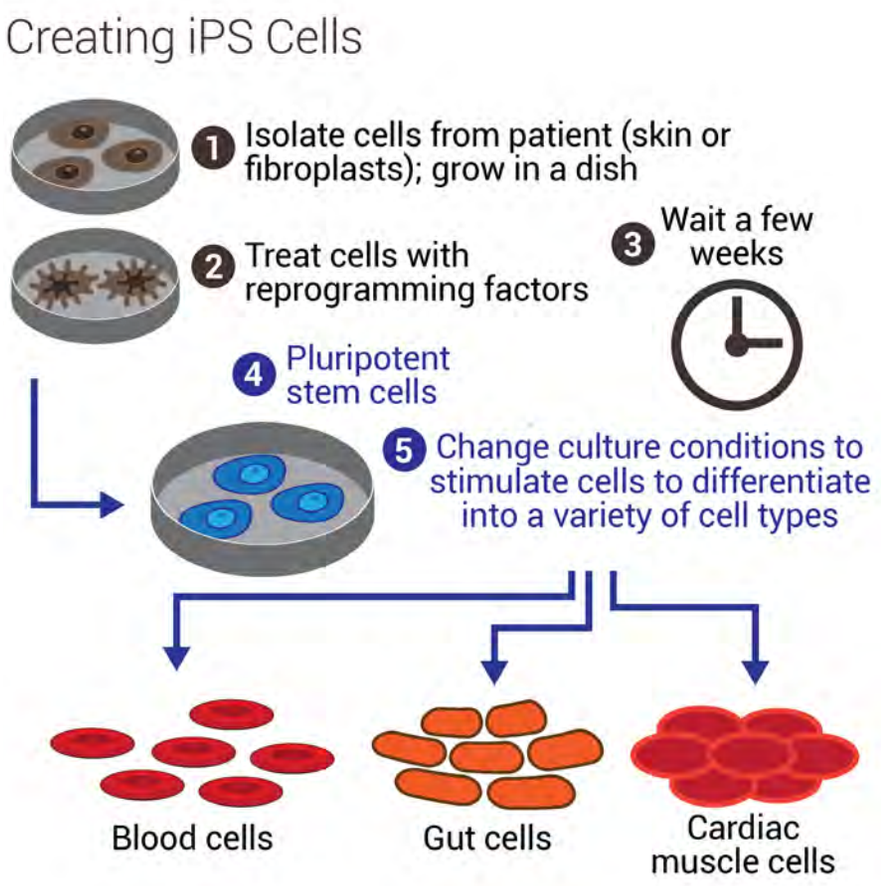
According to FundingTrends.org, the funding of projects using ESCs sharply increased since 2007.
(URL Ref. 9)

B. Induced Pluripotent Stem Cells (iPSCs)

Induced Pluripotent Stem Cells are stem cells artificially derived from mature human cells by inducing an overexpression of several specific genes. The possibility of transforming mature somatic cells into stem cells was demonstrated by Shinya Yamanaka and his team in 2006, and they managed to produce human iPSCs in 2007. In 2012, Shinya Yamanaka was awarded the Nobel Prize in Physiology or Medicine for his discovery.

iPSCs are produced from somatic cells, and the new discovery paves the way for a novel method of deriving stem cells without destroying an embryo. This method therefore doesn't raise any ethical issues. Another important aspect of iPSCs lies in the fact that they can be directly derived from a patient's own cells, and consequently, the chances of rejection after transplantation is unlikely.

The process of reprogramming mature cells to derive iPSCs initially was reported using

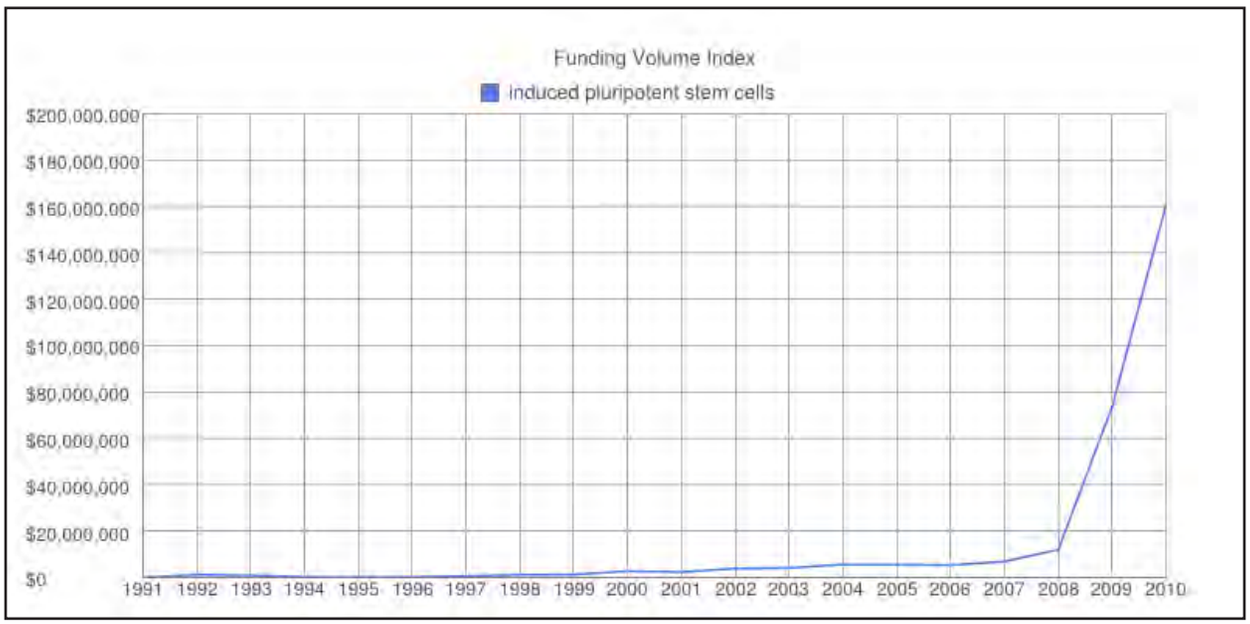


four specific genes. It has now been shown that all of these four genes may not be required for successful reprogramming. This finding is extremely significant, as some of the genes reported are oncogenes and could cause cancer.

There are several ways to start the transformation process, with each of the methods having its own advantages and disadvantages. First of all, different types of vectors can be used to deliver the genes for reprogramming. A vector delivers the necessary genes into a cell and makes it transform into a stem cell. Some of the delivered genes can be oncogenes, and this is why usage of such iPSCs in real world applications is considered dangerous. Moreover, some of the vectors used (such as plasmids and retroviruses) can integrate into the human genome and result in unpredictable mutations.

Another approach is to use microRNAs, which are small RNA molecules with an ability to bind

Chart 6: Funding volume index for induced pluripotent stem cells.



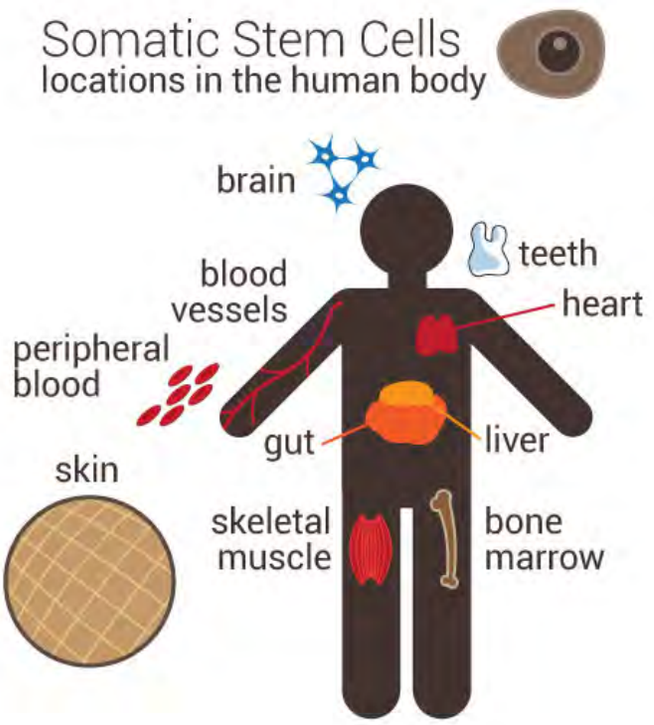
to specific mRNA sequences, primarily at the 3' end, and thus regulate gene expression (Bao et al, 2013), along with the assistance of proteins and small molecules (Science daily, 2009; Cyranoski, 2013). These methods for reprogramming are relatively safer, as there is no modification of the genome, and as a result, mutations are unlikely. Moreover, the efficacy of these methods can be similar or higher than that reported for the other methods.

iPSCs have properties very similar to embryonic stem cells (although there are some differences). For example, if one replaces the embryonic stem cells in a mouse embryo with iPSCs, the embryo grows into a normal mouse.

This implies that iPSCs can be used to derive cells of a specific subtype, i.e. for the treatment of cardiovascular diseases, diabetes, neurological diseases and a number of other diseases with any type of damaged cells.

The first clinical trial of iPSCs was approved in Japan on 19 July 2013 (Cyranoski, 2013).

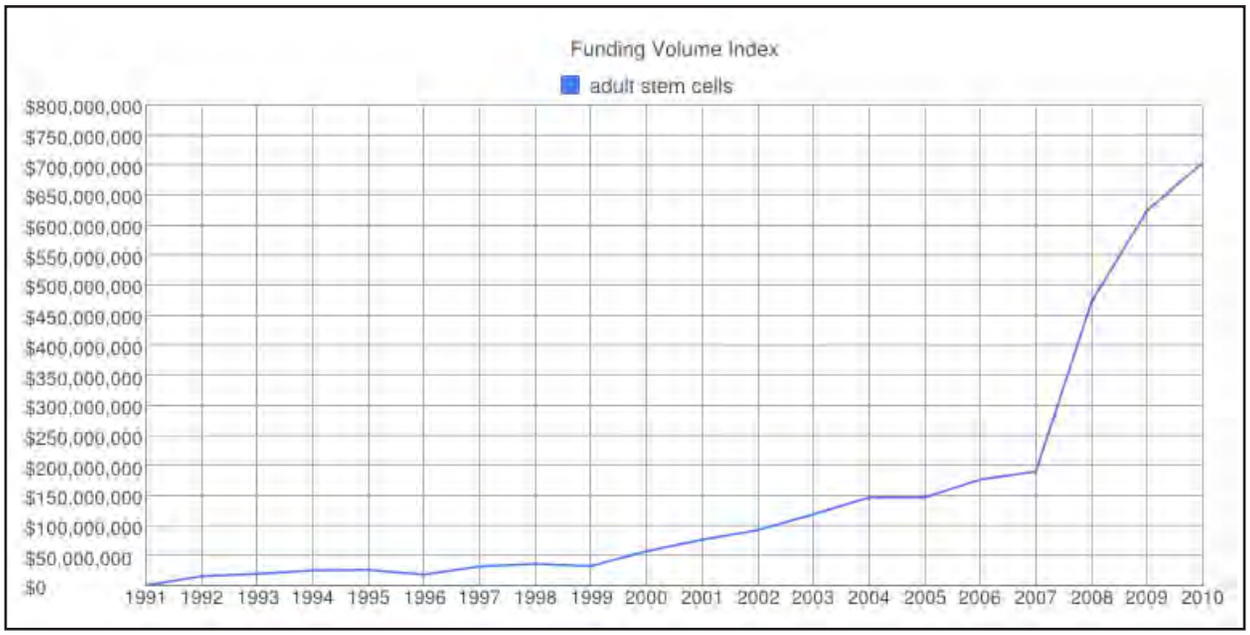
Presently underway, the investigation shall be transforming human cells from the skin into retinal pigment epithelial cells to be used for the treatment of age-related macular degeneration.



Although iPSCs hold a promise for the future of regenerative medicine, there is a high risk of developing mutations and cancer with them. The efficacy of reprogramming adult cells into iPSCs is rather low. The process of transformation is rather difficult and can sometimes result in an incomplete gene expression.

According to FundingTrends.org, funding of projects using iPSCs has dramatically

Chart 7: Funding volume index for adult stem cells.



increased since the year 2007.

C. Adult Stem Cells (ASCs)

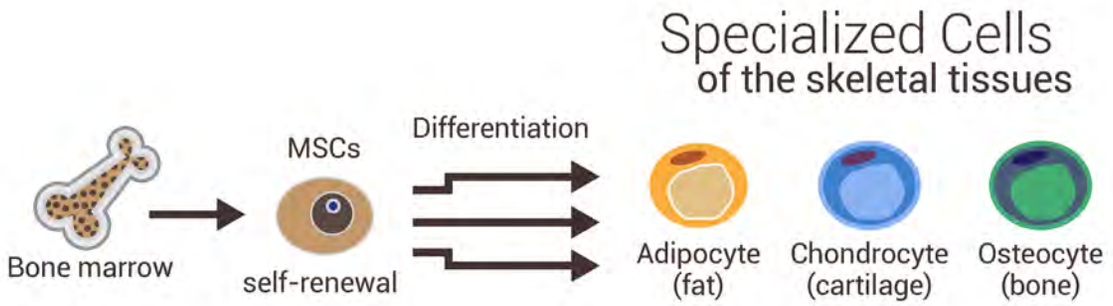
Adult Stem Cells (or Somatic Stem Cells) are stem cells found in a juvenile or an adult human body.

These cells are multipotent with a capacity to differentiate into a limited number of cell types, rather than all types of human cells. Usually they differentiate into the cells of the same germ layer. Sometimes, they can transform into the cells of another germ layer. This phenomenon is referred to as Trans-Differentiation or Plasticity.

The function of ASCs in the body is to regenerate specific tissues (they regenerate the tissue where they are presented). They are classified into different types of ASCs, i.e. hematopoietic stem cells, umbilical cord blood stem cells, intestinal stem cells, mesenchymal stem cells, neural stem cells, olfactory adult stem cells, and others. Some are widely used in clinics, while others are at present being evaluated for safety and efficacy of usage. The most important types of adult stem cells will be discussed in later sections.

Most ASCs are rare, and therefore, it is difficult to isolate them. Moreover, cultivating ASCs in the laboratory has proven to be rather difficult. Another drawback is that the method of obtaining these stem cells often involves serious damage to the organs and tissues (for example, isolation of heart stem cells).

It is possible to transplant ASCs from one individual to another, but it is obligatory to use immunosuppressive therapy in order to avoid rejection.



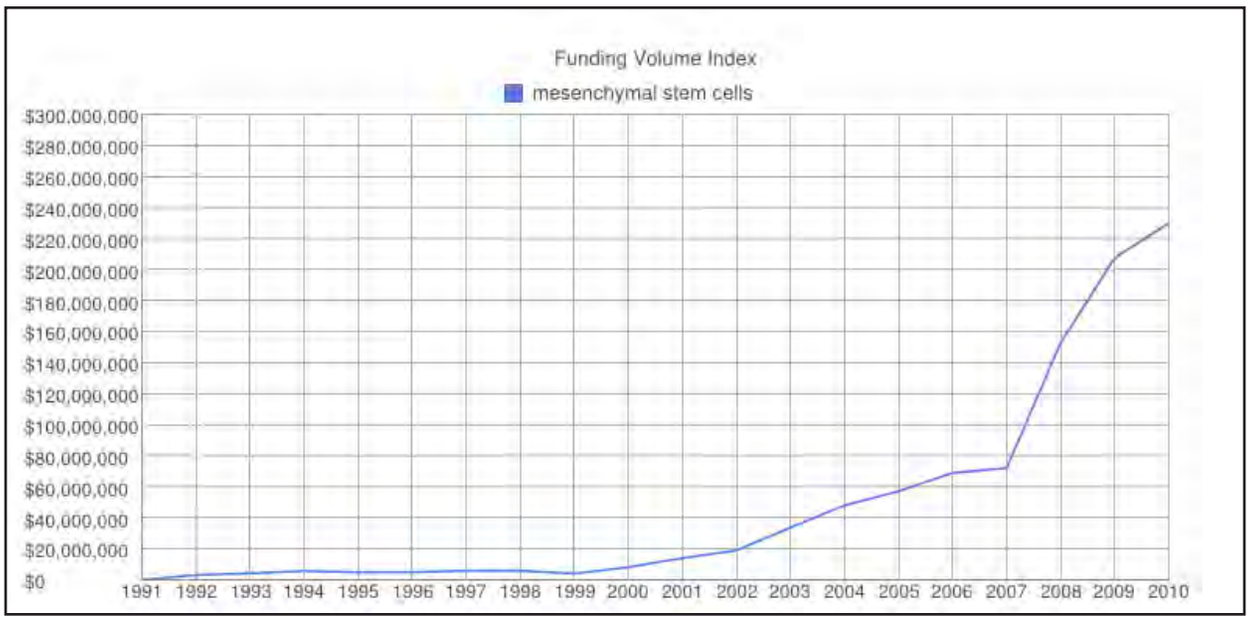


Chart 8: Funding of projects on mesenchymal stem cells (MSCs)

According to FundingTrends.org, funding of projects using ASCs has sharply increased since 2007.

a. Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) were originally found in the bone marrow. Thereafter, they were also isolated from the fat tissue, muscle tissue, and other places. However, there is no evidence that the cells from other sources are similar to the cells from bone marrow.

Bone marrow is a source of several different cell types (amongst them are the Hematopoietic Stem Cells which shall be discussed later), but only 0.001-0.01% of them qualify as MSCs, making their isolation process time intensive and difficult.

MSCs from the bone marrow can differentiate only into three cell types i.e. adipocytes (fat), chondrocytes (cartilages), and osteocytes (bones). Differentiation of MSCs into other cell types is not validated or the derived cells are often non-functional.

MSCs can be used in treatment of local skeletal defects. They also have the potential to repair cartilages. Another area where MSCs can be helpful is treatment of heart and blood vessels. MSCs can induce neovascularization, which is the process of forming new blood vessels. MSCs themselves do not form new vessels, but they activate the precursors of endothelial cells, which form the inner layer of all blood vessels.

There are a number of early stage clinical trials validating the ability of MSCs to induce neovascularization. There are also some reports indicating that MSCs can be transplanted from one patient to another without any risk of rejection, and moreover, it has been demonstrated that MSCs can be used as an immunosuppressant. All of these reported studies are in the preliminary stages and require further evidence to prove the efficacy of MSCs.

According to FundingTrends.org, funding of projects using MSCs considerably increased since 2007.

b. Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) have the capacity to form all types of blood cells. The population of hematopoietic stem cells contain different cells, some of which are multipotent, and some of which are oligopotent and unipotent. The main source of hematopoietic stem cells is the bone marrow. HSCs can also be harvested from umbilical cord blood, peripheral blood, and amniotic fluid. HSCs can be frozen and stored for years in special cryofreezers.

Hematopoietic stem cells are used for

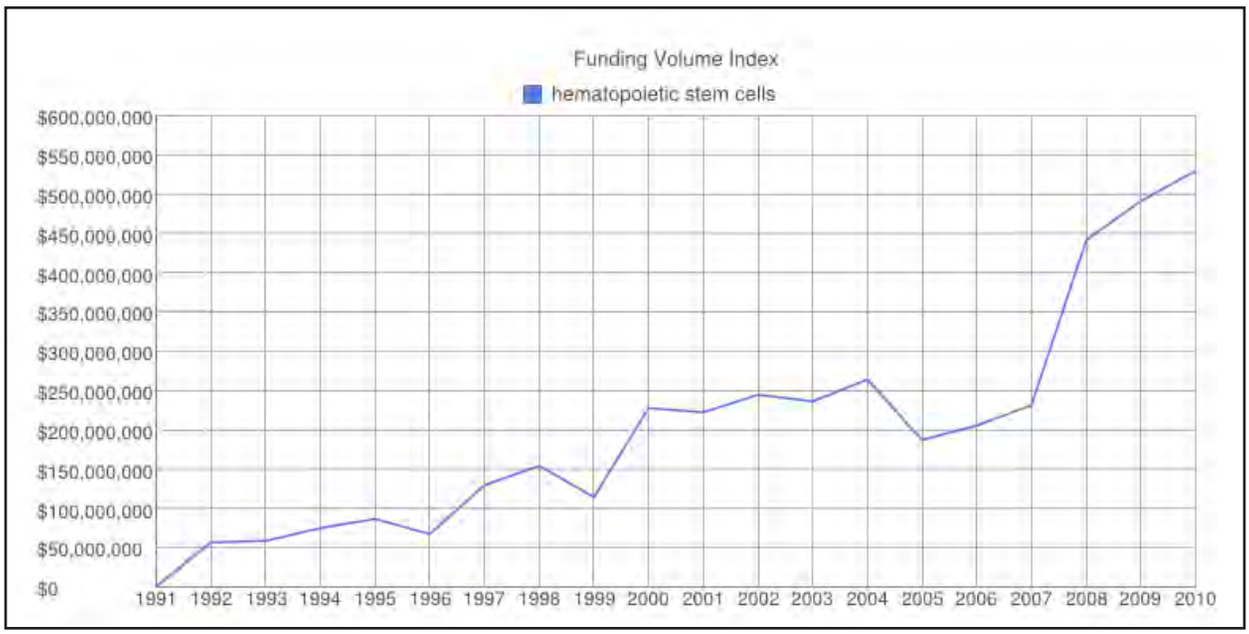
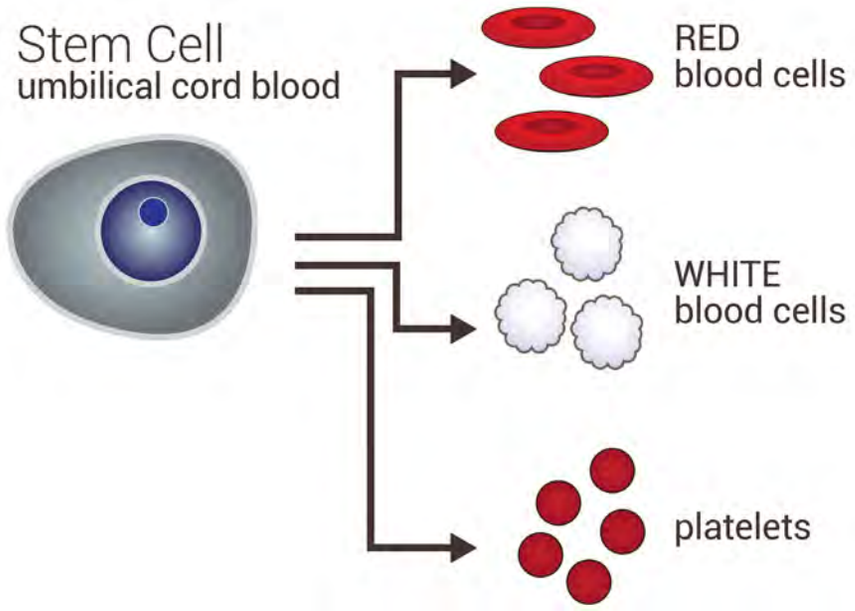


Chart 9: Funding for hematopoietic stem cells

transplantation. This procedure is often performed on patients with cancer of the blood or bone marrow. Before transplantation, radiation and chemotherapy are used to weaken the immune system of a recipient in order to avoid rejection, and to kill malignant cells.



The graft can be autologous or allogeneic. In case of an autologous graft, HSCs are collected from the patient before complete or partial weakening of his bone marrow, and then the transplantation is performed. The advantage of this method is a low risk of rejection, but the risk of relapse (as the graft can contain malignant cells) rises.

The allogeneic graft can be safer in some cases, but is associated with issues such as the graft-versus-host disease, which is when the immune cells of the graft begin to attack the implanted tissues. It is also difficult to find a suitable donor with similar human leucocyte antigen (HLA). HLA is a molecule expressed on a cell surface (also referred to as the major histocompatibility complex MHC). The HLA of the donor and HLA of the recipient should be similar in order to avoid immune conflict.

More than 50,000 hematopoietic stem cell transplantations (HSCTs) are performed annually, of which more than half are autologous. Other are allogeneic and the total number of HSCTs continues to increase at a rate of 10-20% every year (Perumbeti, 2013).

Although HSCTs are common, they have been associated with a risk of infection and graft-versus-host disease. They are commonly used only for the treatment of life-threatening diseases such as leukemia. Improved outcomes have been attributed to better safety standards and a reduction in the number of infections and other negative outcomes.

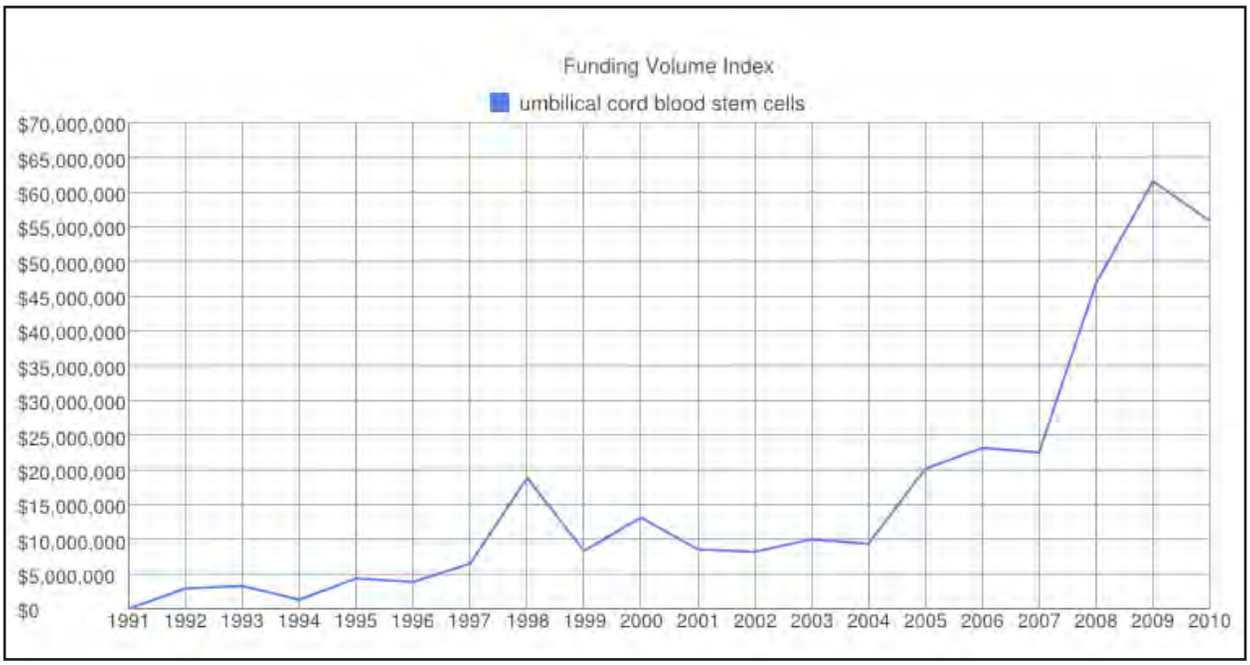


Chart 10: Funding in the field of umbilical cord blood stem cells.

According to FundingTrends.org, funding of projects using HSCs steadily grew since 1991 up to 2010.

c. Umbilical Cord Blood Stem Cells

Umbilical Cord Blood Stem Cells (UCBSC) are derived from the blood in the umbilical cord and placenta after a baby is born. They can be easily collected, with no risk to the baby or mother.

Cord blood contains hematopoietic stem cells, along with other types of stem cells, but additional studies are required to confirm this finding.

Although the process of collecting from an umbilical cord is rather easy, the amount of blood harvested from the cord is rather small. Usually, this amount is enough to treat a child, but not enough to threat an adult person. To solve this problem, it is possible to harvest cells from multiple umbilical cords or from the placenta. There is also an opportunity to cultivate UCBSCs in vitro.

Cord blood is used to treat different types of blood cancer or to treat genetic blood diseases like Fanconi Anemia. About 20,000 umbilical cord blood transplants have been performed up until 2013 (Gupta, 2012). Several attempts to use UCBSCs in the treatment of other diseases have not been successful. For example, a clinical trial studying cord blood treatment for diabetes failed to show any improvements. At

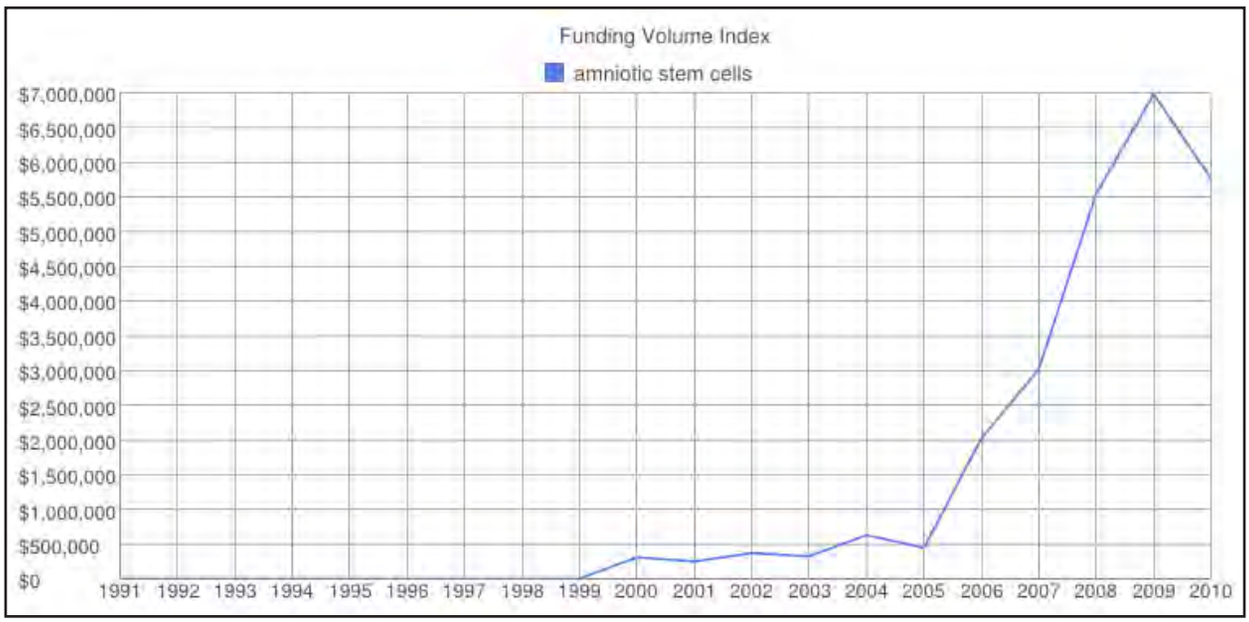


Chart 11: Funding for amniotic stem cells.

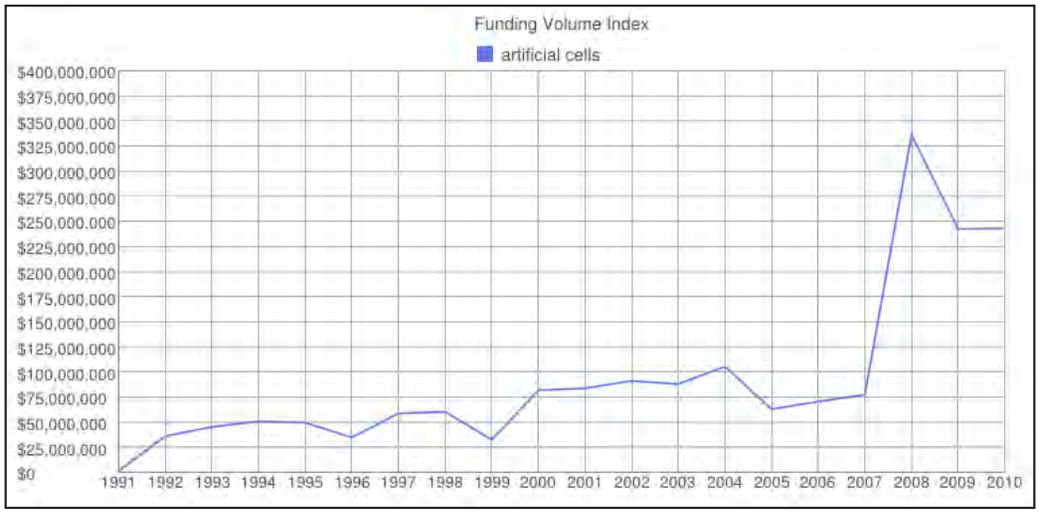
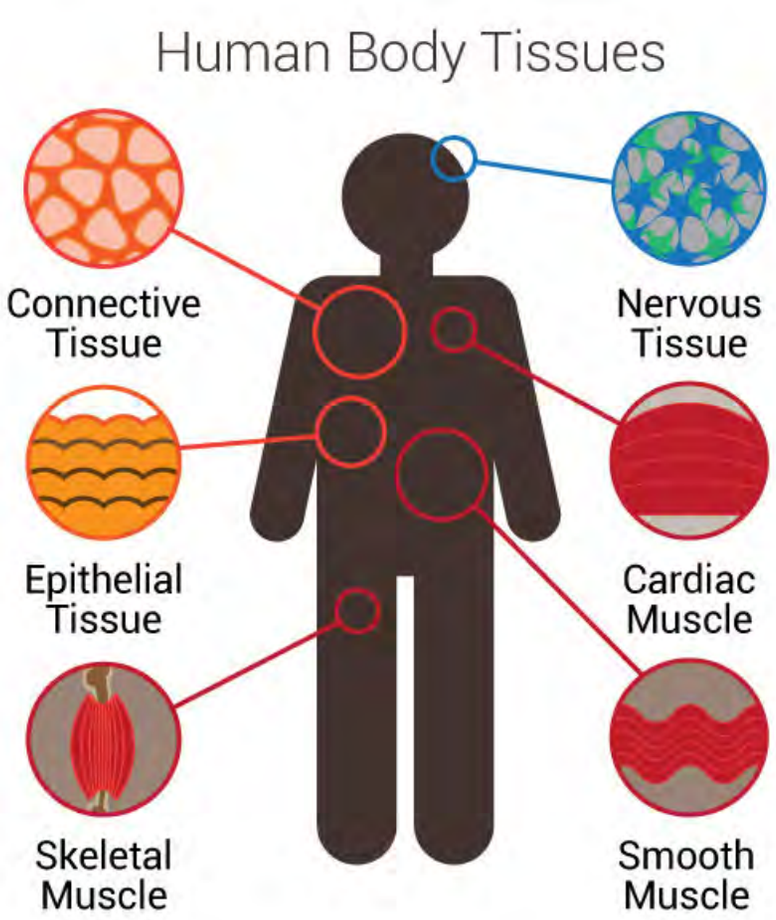


Chart 12: Funding related to artificial cells.

present, there is an active clinical trial exploring the benefits of UCBSCs in the treatment of child brain disorders and traumatic brain injury, but the results have proven controversial.

Cord blood banks provide the facilities to freeze and store the umbilical cord blood over long periods of time. There are two types of cord blood banks: public and private. Public cord blood banks work for the benefit of the general public, while the private cord blood banks are usually profit-making organizations, and cord blood stored in these banks is used exclusively by the client donors or the donor's relatives. The benefit of a private cord blood bank is a controversial issue because the probability of the original donor ever using their own cord blood is often very low.

According to FundingTrends.org, funding of projects using UCBSC reached a peak in 2009.



d. Amniotic Stem Cells

Amniotic Stem Cells are derived from the amniotic fluid. Amniotic fluid is a protective liquid surrounding a fetus. Amniotic stem cells are primarily composed of mesenchymal stem cells with a capacity to differentiate into various types of human cells.

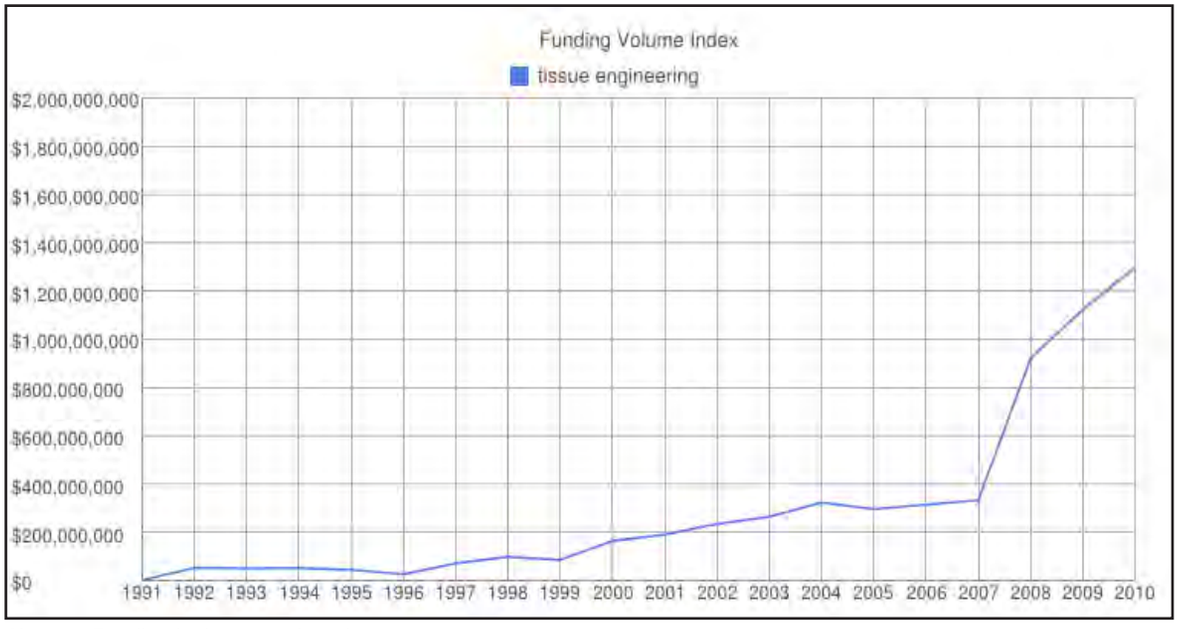


Chart 12: Funding in tissue engineering.

Amniotic stem cells can be collected without destroying an embryo, but there is a very small risk of pregnancy loss. Overall, the use of amniotic stem cells has not been associated with any ethical problems. Many banks now provide the facility to store amniotic stem cells.

According to FundingTrends.org, funding of projects using amniotic stem cells reached a peak in 2009.

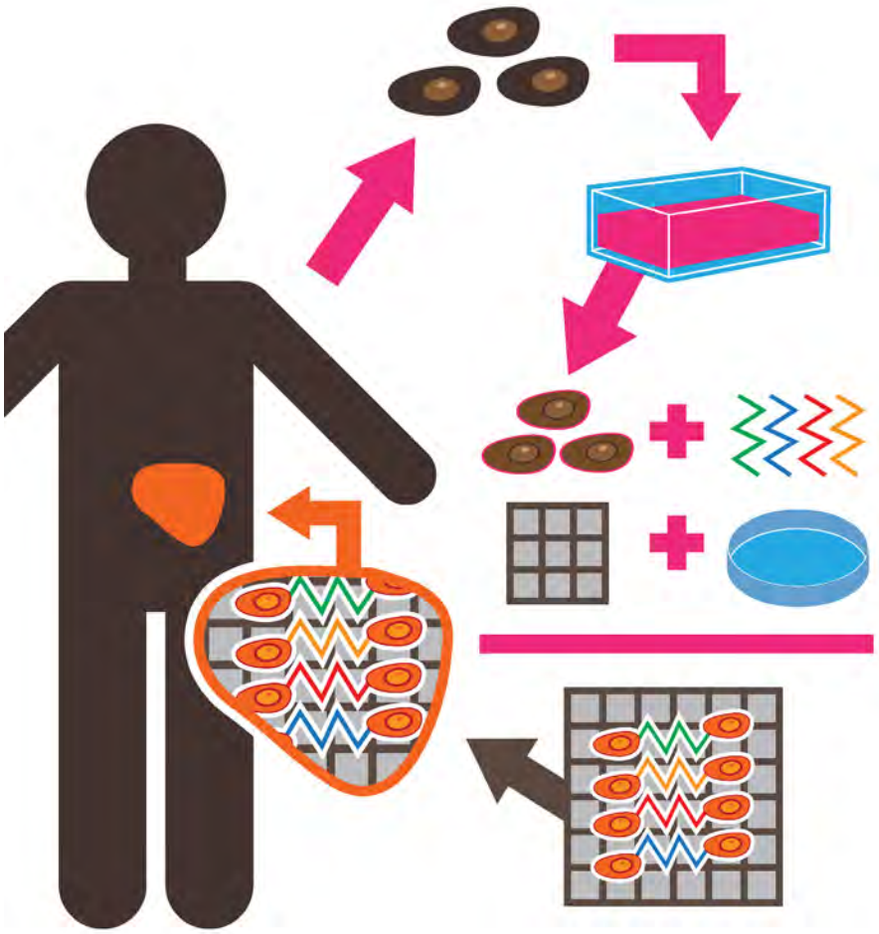
e. Artificial Cells (ACs)

Artificial Cells are engineered constructs which mimic some cell functions and are non-living

entities. An example of an artificial cell is a liposome. Liposomes have a lipid membrane like living cells and can be used to mimic cells and deliver molecules such as nucleic acids, proteins, and small molecules.

As the surface of these artificial cells lacks antigens, they can be useful where immunogenicity is a problem. They can help to avoid immune system rejection. For example, it is possible to encapsulate stem cells into artificial cells and use them as carriers. Artificial cells can also be used for transporting different drugs and nucleic acids (DNA and RNA).

According to FundingTrends.org funding of projects using artificial cells reached a peak in 2008.



Segment 5. Tissues

Tissue is the next level of organization of our body after cells. Every tissue consists of a group of specialized cells and an extracellular matrix supporting these cells in a 3-dimensional structure. The extracellular matrix is produced by the cells and plays a very important role in cell communication, nutrition, and special mechanical features of the tissue.

All tissues are classified into four types, i.e. the connective tissue, the muscle tissue, the epithelial tissue, and the nervous tissue.

Regeneration of tissues is an important and challenging issue, as one has to recover not only cells, but also the extracellular matrix. Today it is possible to regenerate bones, cartilages, skin, muscles, and other tissues.

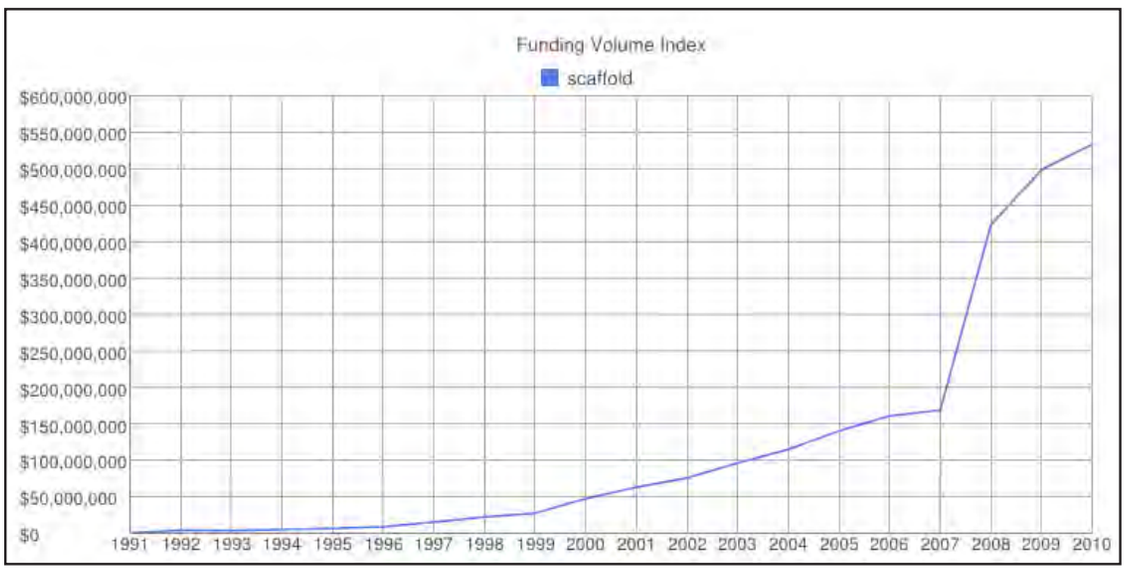


Chart 13: Funding for projects using the scaffold technique.

There are several approaches to tissue engineering which shall be discussed in later sections.

According to FundingTrends.org, funding of projects

for tissue engineering has risen considerably since 2007.

A. With Scaffold

The most popular technique used in tissue engineering is scaffold-based tissue regeneration. There are three main components to this approach. The first one is a scaffold. A scaffold is defined as a biologic, synthetic or semi-synthetic matrix with special mechanical properties. It provides a necessary microenvironment for cell growth and differentiation. The second component is the stem cell cluster, and the third component is formed by different molecular induction factors which are necessary for cell growth and differentiation.

The process of regeneration of any tissue consists of several stages.

1. Harvesting of stem cells from a donor. (It can also be induced pluripotent stem cells.)
2. Cultivating of the derived stem cells.
3. Combining of the scaffold, stem cells, and induction factors.
4. Tissue organization.
5. Transplanting of the graft.

There are some modifications of this method. For example, tissue can be formed in vivo rather than ex vivo. One can introduce a scaffold in the place where regeneration is required and treat it with stem cells and induction factors, and the tissue grows inside the body.

The results of this technique are promising and probably will be widely used in future applications.

Another modification of the scaffold-based method is 3D bioprinting. This technique utilizes special 3D printers to form the tissues from biomaterials and cells. At present, scientists are developing 3D bioprinting facilities aimed at printing whole organs rather than tissues.

According to FundingTrends.org, funding of projects using the scaffold technique increased in 2007.

B. Without scaffold

There is an alternative method to 3D printing without the use of scaffolds. In this method, small bio blocks are used as three-dimensional pixels. These blocks consist of different cells derived from a donor, and their composition can be precisely controlled.

Once they are put together, they fuse to form a new tissue (Mironov et al, 2009).

Segment 6. Organs

The Organ level is the next level of organization in the human body. Every organ consists of different tissues and has a higher level of structural complexity than observed at a tissue level. Due to a higher level of complexity in organization, regeneration of whole organs is a much more complicated task than regeneration of tissues. There are a number of promising results on animal experiments relating to tissue engineering of complete organs, and this field is believed to contribute to the growth of regenerative medicine in the future.

A. Kidney

At present, there is no data on a complete lab-grown human kidney, but scientists have attempted to combine conventional renal filters with bioreactors seeded with renal cells. Renal epithelial cells have the ability to provide metabolic, endocrine, and immune functions, and the renal filters produce urine. Stem cells can have a significant role in compiling an artificial kidney as an unlimited source of renal cells (Tasnim et al, 2010).

Animal experiments have also shown promising results in experiments attempting to create a new kidney using decellularized kidneys from a xenogenic source or a donor (Yong, 2013). This process encompasses the stripping of cells from a donor kidney using

specialized detergents to get a connective tissue scaffold. The decellularized scaffold is then seeded with human umbilical cord blood stem cells (for the development of vessels) and with the kidney cells from newborn rats. The transplant can grow in a special incubator and was shown to be functional after transplantation, although not as efficiently as a normal kidney.

B. Liver

A lab-grown human liver has made considerable progress using decellularized scaffolds and stem cells, as described in the previous section (Uygun & Yarmush, 2013). In a recent study, scientists created a vascularized and functional human liver using iPSCs to derive specific hepatic cells, human umbilical endothelial cells (for development of vessels), and human mesenchymal stem cells (for the development of connective tissue matrices). All of these cells were combined in a dish, where they self-organized into macroscopic cell clusters. Upon transplantation, these clusters were functional and showed good vascularization (Takebe et al, 2013).

C. Bladder

A bio-engineered bladder has already been created and successfully transplanted using a biodegradable scaffold and cells from the bladder, along with muscle cells to generate a new bladder (Khamsi, 2006). However, there are several problems concerning the functionality of the transplanted bladder that are currently being worked on (Horst et al, 2013).

D. Cardiovascular System

In successful experiments on rats, scientists used decellularized hearts as scaffolds (Maher, 2013). In order to construct a new heart, one needs at least two types of cells. These are endothelial precursor cells (for the development of vessels) and heart muscle precursor cells. In the experiments, these cells were derived from iPSCs. The engineered hearts were shown to be functional but their efficacy was too low for a successful transplantation. At present, it is also possible to construct blood vessels and heart valves using decellularized scaffolds.

E. Skin

Tissue-engineered skin is already available and widely used in clinics, for example, for the treatment of non-healing wounds. These transplants can mimic all layers of the skin or just one of the layers, as desired. They can be cellular or acellular. Some of them are derived from autologous sources while others are of allogeneic or even xenogenic origin.

F. Pancreas

Recent experiments on animals to produce a lab-grown pancreas are promising (Science daily, 2012). Researchers have succeeded in growing small functional parts of a pancreas with the ability to produce insulin after transplantation. They used special scaffolds and pancreatic cells from a healthy donor. They also used umbilical cord blood cells for the development of vessels. It was found from these studies that vascularization is a key to a successful transplantation of the pancreatic tissue.

G. Trachea

The first bio-engineered trachea has already been constructed and successfully transplanted. It was performed by Paolo Macchiarini in 2008 using adult stem cells from bone marrow, which were transformed into cartilage cells. A decellularized segment of a cadaveric trachea was used as a scaffold in these experiments. In these experiments, the vascularization of the trachea was observed as early as one month after transplantation.

H. Teeth

Usage of stem cells for the regeneration of teeth is a relatively new approach, but currently, there are some advances in this field. For example, studies on animal models are being conducted in order to understand the mechanism of the regeneration of teeth (Wu et al, 2013). Most likely, in the future, this research would help the development of a translational therapy for humans. At present, the most interesting experiments on teeth regeneration

are aimed at using induced pluripotent stem cells (iPSCs) (Cai et al, 2013). Usage of iPSCs is not connected with any ethical issues or with problems of rejection, making the approach attractive for many investigators.

I. Bones and Cartilages

Different types of grafts are already in use in clinics, the main types are allografts and autografts. Special scaffolds and adult stem cells are used for these purposes. These days, scientists are trying to create entire bones using 3D bioprinters.

A. Cardiovascular Diseases

Cardiovascular diseases (CDVs) are diseases which affect the cardiovascular system, including the heart and blood vessels. The list of cardiovascular diseases includes coronary heart disease, cerebrovascular disease, rheumatic heart disease, and congenital heart diseases, amongst many others.

According to the World Health Organization, cardiovascular diseases are the leading cause of death in the world, and it is estimated that by the year 2030, more than 23 million people will die of cardiovascular diseases annually (URL Ref. 10).

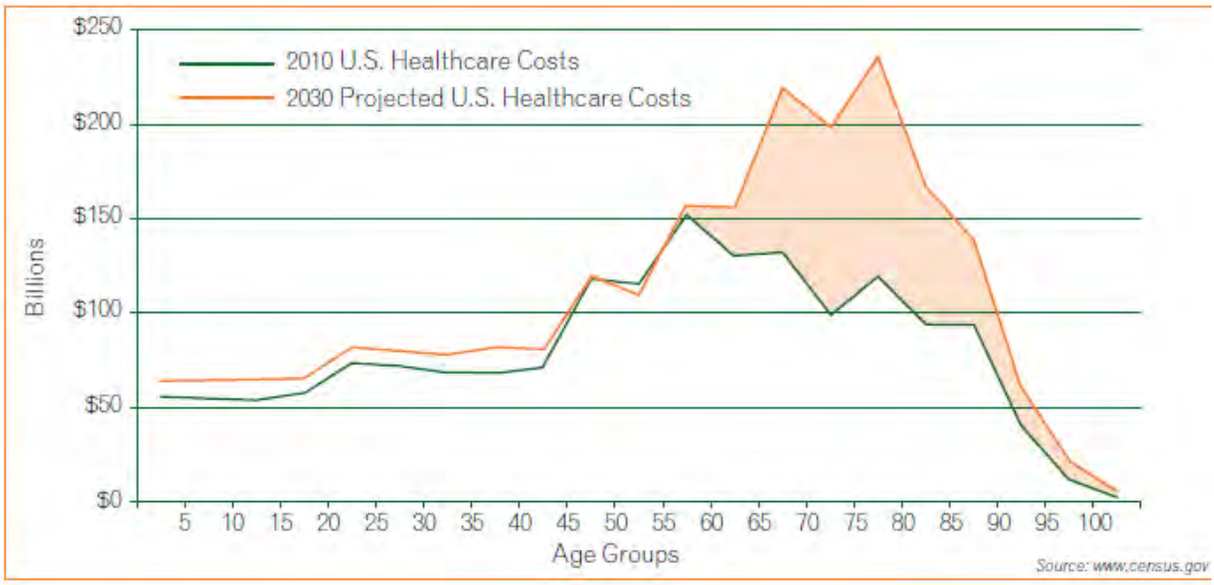


Chart 14: Projected U.S. Healthcare Costs by age group

Segment 7. Diseases

The main goal of regenerative medicine is to treat different diseases, some of which are extremely severe and can seriously affect a patient's life. An effective treatment of such diseases can bring benefits not only to patients, but also to global economics, as it can seriously reduce healthcare costs. According to the Alliance for Regenerative Medicine, healthcare costs in the USA alone are expected to increase tremendously by 2030, especially for the elderly population. In this chapter, we highlight several important diseases and the role of regenerative medicine in their treatment.

Often, there are no symptoms associated with cardiovascular diseases until the occurrence of acute events (for example, a heart attack). After such events, patients need life-changing treatment, such as a surgical operation. After the treatment, a number of patients suffer from long-term disabilities, loss of productivity, and a low quality of life.

Regenerative medicine can bring plenty of benefits to the treatment of cardiovascular diseases, and there are a number of regenerative products in the market catering to cardiovascular treatments.

Some available products:

1. Amorcyte (a NeoStem company) is an

autologous bone marrow derived stem cell product designed for the treatment of damaged heart tissue following acute myocardial infarction. A Phase 2 clinical trial of the product has already begun.

2. The company VentriNova uses small molecules and gene therapy to induce heart cells and to make them repair the damaged heart tissue. Their lead product, which targets the Cyclin-A2 gene is currently in the preclinical stage of development.

According to the Alliance for Regenerative Medicine, total inpatient hospital costs in the USA for CDVs care were $71.2 billion in 2005. Overall medical costs, which include medical interventions, healthcare services, medications, and lost productivity of the patients was reported to be $316 billion.
(URL Ref. 11)

B. Cancer

The term "Cancer" comprises a large group of diseases, which are characterized by an uncontrollable cell growth. They invade and damage nearby tissues and can spread or metastasize to distant parts of the body, forming secondary tumors. According to the World Health Organization, cancer is the third leading cause of death in the world.

Transplantation of hematopoietic stem cells is widely used in clinics for the treatment of blood cancer. Scientists are also trying to use adult stem cells for the regeneration of lost tissue after a surgical resection of tumor. There are also a large number of gene therapies at a preclinical or clinical testing stage for different types of cancers.

Cancer is associated with huge economic burdens to society. According to the American Cancer Society in the USA, overall annual costs of cancer were $201.5 billion in the year 2008. Direct medical costs were estimated to be $77.4 billion and indirect costs (cost of loss in productivity because of premature death) were $124 billion.

C. Blood Diseases

Blood diseases include different types of anemia, cytopenias, coagulopathies, and other associated diseases of the blood. Regenerative medicine has a huge potential in the treatment of different blood diseases, as all blood cell types originate from a single progenitor, the pluripotent hematopoietic stem cell. These cells have been widely used in clinics for some time. For example, bone marrow transplantation is used for the treatment of several forms of anemia.

D. Wounds

Application of regenerative medicine for wound healing forms a large part of the regenerative medicine industry. Non-healing wounds are a focus of attention in regenerative medicine, as these wounds do not undergo the normal healing process. These wounds can be caused by burns or are often associated with the presence of other medical conditions such as diabetes. Conventional methods for the treatment of such wounds are often ineffective, and regenerative medicine can bring considerable benefits.

Some available products:

1. Organogenesis has developed a cellular product which is called Apligraf. It is a bi-layered graft composed of a layer of mature keratinocytes and a layer of fibroblasts in a collagen matrix. The efficacy of Apligraf has been proven, and in 2012, the company sold more than 500,000 units.

2. Avita Medical has developed a product which is called ReCell Spray-On Skin. It is an autologous cell technology where the product can be sprayed onto a wound. This product is proven to accelerate the healing process and minimize scar formation. It is already available in Europe, Canada, and Australia.

According to the Alliance for Regenerative Medicine in the USA, the annual costs associated with the treatment of non-healing wounds is about $35 billion, which is expected to increase to $200 billion by 2020.

E. Reproductive System Diseases

Stem cell therapy has a huge potential in reproductive medicine, as it was discovered that ovaries contain stem cells, which can differentiate into new oocytes. Previously, it was believed that ovaries contain a limited number of oocytes. Extraction and cultivation of ovarian stem cells can be used for the treatment of infertility, and there have also been attempts to use bone marrow-derived stem cells for the regeneration of endometrium tissue (Duke & Taylor, 2013).

F. Neurological Diseases

Neurological diseases encompass diseases which affect various parts of the nervous system. Often, these diseases are hard to cure and very expensive for the health care system. The list of neurological diseases includes Alzheimer's disease, Parkinson's disease, spinal cord injuries, etc. Regenerative medicine could significantly improve the lives of patients suffering from neurological diseases.

Alzheimer's disease (AD) is the most common disease associated with the loss of memory and intellectual abilities. The majority of patients are above 65 years of age. Scientists have managed to create a human disease model of AD using reprogrammed donor cells. This model could help to find clues for the treatment of this disease.

According to the Alliance for Regenerative Medicine in the USA, annual costs associated with providing care for people with AD are about $200 billion, and these costs are expected to increase to $1.1 trillion by 2050.

Parkinson's Disease (PD) is a neurodegenerative disease associated with the degeneration and death of neurons. Patients with PD suffer from tremors, poor balance, and loss of movement control. Although this disease is not lethal, it seriously affects the quality of life of the patients and their families. Scientists succeeded in constructing a model of PD, and now they are trying to use regenerative technologies to replace the dying neurons and to improve the tropism of healthy neurons.

According to the Alliance for Regenerative Medicine in the USA, annual combined direct and indirect costs associated with PD are about $23 billion.

Spinal cord injuries often lead to quadriplegia or paraplegia and have a strong negative impact on the life of the patient. At present, there are several commercial products which could help with the treatment of spinal cord injuries. Some of them are based on the use of stem cells, which can differentiate into the various cells of the nervous system; others use special scaffolds to provide appropriate conditions for the regeneration of spinal cord nervous tissue.

According to the Alliance for Regenerative Medicine in the USA, annual costs for the treatment of one patient after a spinal cord injury is more than $320,000 for the first year after the injury, and more than $39,000 for subsequent years.

G. Ocular Diseases

Ocular diseases affect the human vision system and include diseases such as age-related macular degeneration (AMD), cataracts, and glaucoma, amongst others. Some of these diseases can be treated by conventional methods, but regenerative medicine can bring a lot of benefits into this field. There are a number of promising animal experiments which can lead to future treatment of the diseases which cannot be treated now.

Some available products:

1. Advanced Cell Technology has developed a treatment for degenerative retinal disease. This technology uses retinal pigment epithelial cells derived from human embryonic stem cells.

2. StemCells Inc. has developed a product which can preserve the visual acuity and protect the retina from progressive degeneration in rats. This product uses neural stem cells. Phase 1/2 of clinical trials of this product began in 2012.

According to the Alliance for Regenerative Medicine in the USA, annual cost of care

for patients suffering from different ocular diseases is about $51.4 billion.

H. Gastrointestinal Diseases

A number of regenerative technologies are aimed at the treatment of different parts of the digestive tract. Some of these are associated with the regeneration of large parts of our gastrointestinal system, such as the liver and the pancreas. Others are targeted towards the treatment of different intestinal diseases such as Familial Adenomatous Polyposis (FAP) and Crohn's disease.

I. Urinary System Diseases

There has been some research on technologies for regeneration of different parts of the urinary system. For example, scientists have already succeeded in the synthesis and transplantation of a bio-engineered bladder (Khamsi, 2006). Presently, there are several companies aimed at treatment of urological diseases. For instance, the company Tengion has a technology for the treatment of patients after removal of the bladder. They have also developed a stem cell technology for augmenting and repairing the kidneys. (URL Ref. 12)

J. Muscular and Skeletal Disorders and Injuries

Musculoskeletal disorders (MSDs) result from injuries of joints, tendons, bones, cartilages, and muscles. They are generally a result of a sudden trauma or various prolonged physical factors. Common symptoms of MSDs are pain, inflammation, and stiffness. The list of MSDs includes such diseases as arthritis, tendonitis, bursitis, etc. According to the Centers for Disease Control and Prevention in the USA, more than 20 million people suffer from arthritis.

Some available products for musculoskeletal disorders include:

1. The company Mesoblast has developed a treatment for degenerative disc disease using mesenchymal precursor cells. The company is currently testing its technology in clinic.
2. MiMedix Group, Inc. has developed a product which acts as a scaffold, assisting the body in the generation of new tissue. Unfortunately, this product has not yet been approved in the USA.

According to Alliance for Regenerative Medicine in the USA, annual healthcare costs of MSDs are about $850 billion.

K. Diabetes

Diabetes is a group of metabolic diseases in which a patient suffers from high blood sugar levels accompanied with several secondary factors. It is a chronic condition which can lead to many different complications. For example, it can lead to cardiovascular problems, nerve damage, kidney failure, blindness, and diabetic ulcers.

Diabetes is classified into two types:

Type 1 (or insulin-dependent) diabetes is caused by insufficient insulin production resulting in elevated levels of blood glucose. Insulin is a hormone which regulates the level of glucose in the blood and is produced by special cells in the pancreas. If a patient has type 1 diabetes, these cells are attacked by a patient's immune system, and as a result, are non-functional. A decrease in the number of insulin producing cells results in insufficient production of insulin, resulting in increased levels of blood glucose. Currently this type of diabetes is treated by injections of insulin.

Type 2 (or noninsulin-dependent) diabetes is characterized by insulin resistance and relative insulin deficiency. Type 2 diabetes is treated by injecting insulin and by some other medications. Balanced diet and regular exercise have been shown to have a positive impact in alleviating this condition.

Regenerative medicine can offer a more radical treatment of diabetes. Some technologies are aimed at the regeneration of insulin producing cells, while others try to mediate the immune system and prevent its attack on the insulin-producing pancreatic cells. Gene therapy can also be helpful in the treatment of diabetes.

Some available products targeting diabetes include:

1. Athersys Inc. has launched a preclinical trial of their product, which is called MultiStem. This product should mediate the immune system and protect pancreatic cells.
2. Mesoblast has developed a product derived from mesenchymal progenitor cells. This product can be helpful in both type 1 and type 2 diabetes. Mesoblast is currently in a Phase 2 clinical trial of their product.

According to the Alliance for regenerative medicine in the USA, annual costs of caring for patients suffering from diabetes was more than $174 billion in 2007 and is expected to increase to $336 billion by 2034.

L. Immunological diseases

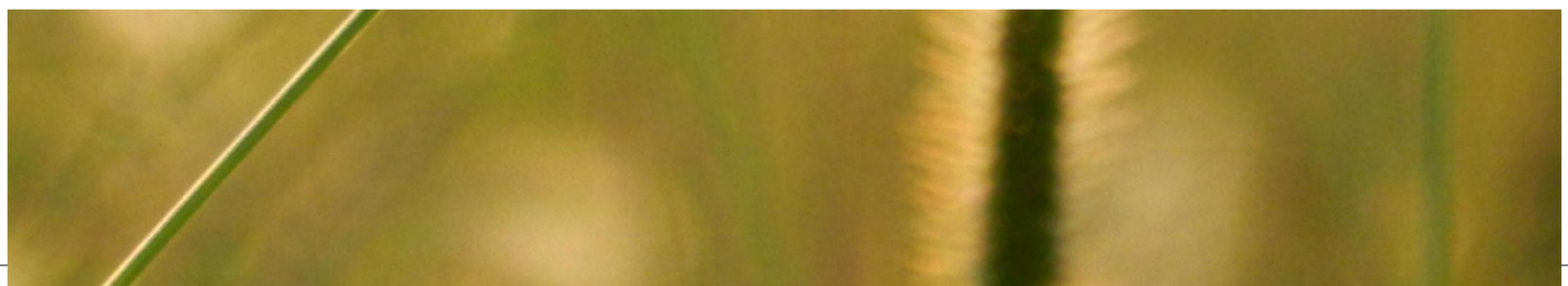
The list of immunological diseases is huge and includes several autoimmune disorders, host versus graft disease, etc. Autoimmune disorders occur when a previously healthy immune system begins to attack healthy tissues and destroy them, resulting in an inflammatory response. Usually, the immune system attacks the connective tissues, blood vessels, joints, muscles, and endocrine glands. The list of autoimmune disorders includes lupus, rheumatoid arthritis, thyroiditis, and type 1 diabetes, amongst many others. The causes of autoimmune disorders are unknown. There are some technologies using stem cells which can prevent such conditions.

Some available products:

1. Celgene has developed a product aimed at the treatment of different autoimmune disorders. Placenta-derived stem cells are used in this technology. The company has already launched a Phase 2 clinical trial of their product for the treatment of Crohn's disease and rheumatoid arthritis. They also plan Phase 1 clinical trials for their products targeting multiple sclerosis and sarcoidosis.
2. Tigenix has two products derived from adipose tissue stem cells, which are designed for the treatment of autoimmune disorders. The first product, Cx601, is for the treatment of Crohn's disease. This product is currently in the Phase 3 trial. The second product, Cx611, is targeted for the treatment of rheumatoid arthritis and is in a Phase 2 trial.

According to the Alliance for regenerative medicine in the USA, annual direct costs for treatment of autoimmune disorders are about $100 billion.

Highlights of 2013



Collaborations Partnerships & Alliances

January 3, 2013

Cellular Dynamics International, WI, USA (www.cellulardynamics.com) announced an agreement with **AstraZeneca Company** (www.astrazeneca.com) to accelerate the pace of drug discovery through the use of human induced pluripotent stem (iPS) cell lines and tissue cells.

March 4, 2013

VistaGen Therapeutics, CA, USA (www.vistagen.com) and **Celsis In Vitro Technologies, MD, USA** (www.celsisivt.com) have agreed to collaborate on characterizing and functionally benchmarking VistaGen's human liver cell platform, LiverSafe 3D™, with Celsis products for studying and predicting human liver drug metabolism.

June 17, 2013

VistaGen Therapeutics, CA, USA (www.vistagen.com), a biotechnology company dealing with development of stem cell technology for drug rescue, predictive toxicology, and drug metabolism screening, presented key developments involving its CardioSafe 3D™ and LiverSafe 3D™ bioassay systems.

March 6, 2013

BioLamina, Sweden (www.biolamina.com) and **Roche, Switzerland** (www. roche.com) signed a research and development agreement to jointly develop new cell culture systems for various applications. The collaboration will focus on assessing laminin-based in vitro cell culture matrixes offering highly physiological microenvironments for living cells. Under the terms, Roche will provide R&D funding and scientific expertise to BioLamina company.

March 28, 2013

The Bellvitge Biomedical Research Institute (IDIBELL), Spain (www.idibell.cat) has signed a licensing agreement with the Spanish biotech company **Histocell** (www. histocell.com/en) to make use of a patent for the treatment of acute pulmonary diseases with mesenchymal stem cells (MSCs). MSCs could be administered intravenously and have the ability to go directly to the damaged lungs, acting as a 'smart drug' without any risk of rejection. To enhance the effect, researchers have modified these cells by genetic engineering to secrete IL-33.

March 4, 2013

Life Technologies, CA, USA (www.lifetechnologies.com) signed a research and license agreement with **Harvard University, MA, USA** (www.harvard.edu), under which the firm has acquired exclusive rights to develop a panel of characterization assays designed to rapidly evaluate human pluripotent stem cells for their utility in a variety of discovery and translational research applications. The panel will be offered on the company's semiconductor sequencing and PCR-based genetic analysis platforms.

April 25, 2013

Stemedica Asia, a wholly-owned subsidiary of **Stemedica Cell Technologies, CA, USA** (www. stemedica.com), has entered into a definitive licensing agreement with the **Stem Cell and Cancer Institute, a division of PT Kalbe Farma Tbk, Indonesia** (www. kalbe.co.id), the largest publicly listed pharmaceutical company in southeast Asia. Under the terms of the agreement Kalbe shall be the exclusive licensor of Stemedica's ischemia-tolerant adult allogeneic mesenchymal and neural stem cells for use in clinical trials in Indonesia, Thailand, and the Philippines. Kalbe's Stem Cell and Cancer

Institute will be responsible for organizing and funding clinical trials in southeast Asia.

May 27, 2013

Epistem, UK (www.epistem.co.uk) and **ScandiDerma, Norway** (www.scandiderma.com) aim to develop together a new in vitro human living skin-equivalent model for testing inflammatory responses. Epistem's expertise is in the regulation of adult stem cells in epithelial tissue, which includes the skin, hair follicles, GI tract, breast, and prostate. ScandiDerma is focused on developing new dermatological products from existing organic cells.

The collaboration is made possible through the UK's innovation agency, the **Technology Strategy Board** (www.innovateuk.org), and **Innovation Norway** (http://innovasjonnorge.no), following a successful application for funding in the Sustainable High-Value Chemical Manufacture Through Industrial Biotechnology competition.

June 13, 2013

Stemedica Cell Technologies, CA, USA (www.stemedica.com) have entered into a global distribution agreement with **Life Technologies, CA, USA** (www.lifetech.com). Under the terms of this agreement, Life Technologies will exclusively offer Stemedica's ischemic tolerant allogeneic adult mesenchymal stem cells and neural stem cells for worldwide sale. Stemedica stem cell lines will be sold under the brand name Gibco® and are available to purchase for research works beginning of the second quarter of 2013.

June 17, 2013

NGM Biopharmaceuticals, CA, USA (www.ngmbio.com) and **MedImmune, CA, USA** (www.medimmune.com) have entered into an exclusive agreement to discover, develop, and commercialize novel therapeutics from NGM's enteroendocrine cell program for the treatment of Type 2 diabetes and obesity.

July 1, 2013

Fibrocell Science, PA, USA (www.fibrocellscience.com) and **Intrexon, VA, USA** (www.dna.com) have expanded their partnership. Fibrocell is known for its FDA-approved product LAVIV®, a wrinkle treatment that involves extracting, multiplying and injecting a patient's own fibroblasts.

The new agreement broadens the existing collaboration to include potential treatments based on engineered autologous fibroblast cells for the localized treatment of autoimmune and inflammatory disorders. This could lead to developing a potentially new class of therapeutics.

July 15, 2013

Neostem, NY, USA (www.neostem.com) and the **University of California, San Francisco, CA, USA** (www.ucsf.edu) have agreed to collaborate on the development of human regulatory T-cells for the treatment of Type 1 diabetes, steroidresistant asthma, and organ transplant rejection.

August 6, 2013

Cardium Therapeutics, CA, USA (www. cardiumthx.com) has entered into an agreement with **Orbsen Therapeutics, Ireland** (www.orbsentherapeutics.com) and the **National University of Ireland, Galway, Ireland** (www.nuigalway.ie) to utilize Cardium's **Excellagen®** (www.excellagen.com) pharmaceutically formulated 2.6% fibrillar type I bovine collagen gel as a delivery agent for Orbsen's proprietary stromal cell therapy in preclinical studies for the potential treatment of diabetic foot ulcers.

August 12, 2013

Cardium Therapeutics, CA, USA (www.cardiumthx.com) and **Boston Children's Hospital, MA, USA** (www.childrenshospital.org) have entered research collaboration to assess the medical utility of Excellagen as a delivery scaffold to seed autologous mesenchymal fetal stem cells for ex vivo engineering of tissue grafts for transplantation into infants to repair prenatally diagnosed birth defects.

September 6, 2013

Novartis, Switzerland (www.novartis.com) has entered into an exclusive global licensing and research collaboration agreement with **Regenerex, KY, USA** (www.regenerex.com) for use of the Company's novel Facilitating Cell Therapy platform.

Facilitating Cell Therapy is a novel allogeneic hematopoietic stem cell-based therapy platform that also contains facilitating cells derived from a donor. The platform supports the development of tolerance, or 'bone marrow chimerism,' in transplant recipients, providing a better side-effect profile than current human hematopoietic stem cell transplantation protocols. Chimerism may eventually render the recipient tolerant to cell, tissue, or organ transplants from the same donor, thereby enabling transplant patients to discontinue immunosuppressive medications after building stable immunological tolerance.

Results from a Phase II study in 15 kidney transplant recipients are encouraging, with six patients fully withdrawn from immunosuppression without loss of engraftment, and a further two with planned full withdrawal at 1 year. Currently, solid organ transplant recipients must take immunosuppressive drugs for life to prevent rejection. This approach may also allow for treatment of inherited metabolic diseases.

October 1, 2013

MiMedx Group, GA, USA (www.mimedx. com), developer, manufacturer, and marketer of patent-protected regenerative biomaterials and bioimplants processed from human amniotic membrane, has entered into a distribution agreement with **Medtronic, MN, USA** (www.medtronic.com) and **SpinalGraft Technologies, TN, USA,** a wholly-owned subsidiary of Medtronic.

Through the agreement, MiMedx will provide its PURION® processed allograft products to Medtronic to be marketed by SpinalGraft Technologies for spinal applications. The MiMedx allografts produced from the company's proprietary PURION Process for amniotic membrane tissue can be stored at room temperature for 5 years without the need for refrigeration or freezing. The grafts can be utilized right out of the package without a complicated thawing process.

December 9, 2013

The Hamner Institutes, NC, USA (www.thehamner.org) and **Cellular Dynamics, WI, USA** (www.cellulardynamics.com) collaborate to develop In Vitro Assays using human iPS cell-derived hepatocytes. The Hamner Institutes for Health Sciences today announced a collaborative agreement with Cellular Dynamics International (CDI) to develop predictive in vitro screening assays for chemical, environmental, and pharmaceutical toxicology assessments that utilize CDI's human induced pluripotent stem (iPS) cell-derived hepatocytes.

Next: Launching New Projects, Products, & Services (p. 37)

Launching New Projects Products & Services

January 8, 2013

Thermo Fisher Scientific, MA, USA (www.thermofisher.com) has expanded its suite of cryopreservation reagents with the introduction of the Thermo Scientific HyClone HyCryo™ and HyCryoSTEM™ cryopreservation media. HyCryo™ is a medium for cryogenic preservation and storage of standard cell lines, and HyCryoSTEM™ a medium for stem cell applications.

January 28, 2013

Royan Stem Cell Technology, Iran (www.rsct.ir/en) has established an umbilical cord blood bank office in Erbil, Iraq.

January 29, 2013

InSphero, Switzerland (www.insphero.com) launched a new service for testing embryonic stem cell toxicity. The mouse embryonic stem cell-based easyEST™ is now available as a service.

February 19, 2013

NeuroInDx, CA, USA (www.neuroindx.com) presented an innovative new cell and tissue microdissection instrument Kuiqpick™. Kuiqpick costs less than US$30,000 per device, or approximately a quarter of the cost of existing laser-assisted microdissection systems.

It has the additional capacity to collect cells from tissues and cultures without affecting their viability. This means the collected cells can then be cultured in the laboratory. Kuiqpick can be attached to an inverted microscope to dissect tissue slices at the cellular resolution and collect individual cells from various cell cultures.

March 1, 2013

Osiris Therapeutics, MD, USA (www.osiris.com) introduced a proprietary, direct sales force for Grafix, a cellular repair matrix for serious wounds including diabetic foot ulcers. In 2012, Osiris had received transitional pass-through status from the **Center for Medicare & Medicaid Services (MD, USA)** with C-Codes being designated for Grafix. Osiris medical affairs staff and a team of stem cell scientists will lend support for representatives.

April 30, 2013 EMD

Millipore (www.emdmillipore.com), the Life Science division of **Merck, Germany** (http://www.emdgroup.com), and **Plasticell, UK** (www.plasticell.co.uk) announced the availability of OsteoMAX-XF™, the xeno-free medium for the differentiation of human mesenchymal stem cells into osteocytes. Mineralization can be detected in less than 1 week.

April 30, 2013

RepliCel Life Sciences, BC, Canada (www.replicel.com) started the clinical development of a new autologous cell therapy for the treatment of a variety of chronic tendon injuries. Preclinical research and published clinical Phase I data indicates that the engraftment of collagen-producing fibroblasts from the dermal sheath of a hair follicle can repair microtears and promote the regeneration of damaged tendons associated with chronic tendinosis. Phase I work in humans, using fibroblast cells derived from adipose tissue, produced statistically significant

improvements in function and pain. RepliCel is planning a Phase II Achilles tendinosis trial using a new source of cells, fibroblasts isolated from nonbulbar dermal sheath cells of a hair follicle. This tendon technology, named RepliCel Tendon-01 (RCT-01), will be tested in approximately 90-120 subjects in a Phase II trial anticipated to commence in late 2013.

April 30, 2013

StemCell Technologies, BC, Canada (www.stemcell.com) has signed an agreement to license induced pluripotent stem cell technologies from **iPS Academia Japan** (www.ips-cell.net). This agreement will enable StemCell Technologies to develop media for optimization of cell reprogramming.

May 20, 2013

Cord Blood America, NV, USA (www.cordblood-america.com) launched a new service CordMatrix™ offering the storage of mesenchymal stem cells from umbilical cords as both a stand-alone service and in combination with the storage of umbilical cord blood, through its wholly owned subsidiary **CorCell Companies, NV, USA** (www.corcell.com).

June 5, 2013

Cellular Dynamics International, WI, USA (www.cellulardynamics.com) company is actively working on expanding its disease model offering, currently working on additional disease models for neurodegenerative disorders and drug-induced liver injury. Now it offers through its MyCel® product line access to a number of disease models, including cardiomyopathies and arrhythmias, vision disorders, neurological disorders, and muscular dystrophies.

June 25, 2013

AMSBio, UK (www.amsbio.com) has introduced a new range of 96-well format 3D Spheroid Cell Proliferation/Viability Assays, providing a new tool to allow cell-based assays to be carried out in 3D. The assay offers an in-vitro, standardized, 3D, high-content format for inducing multicellular tumor spheroid formation and quantitating cell viability within the spheroids in response to pharmacological treatment. Uniform spheroid size and physiology is determined through cell seeding, providing a robust and reproducible assay format for drug screening or pathway analysis.

August 1, 2013

ReNeuron, UK (www.reneuron.com), which announced that they received regulatory and ethical approval to commence a Phase I clinical trial in the UK with its ReN009 stem cell therapy program targeting the major unmet medical need of critical limb ischemia, has been awarded two separate grants, totaling US$1.86 million, from the UK Biomedical Catalyst to pursue further development of two of its core stem cell therapy candidates.

Also following a further positive assessment from the independent data safety monitoring board for the study, the final dose cohort in the ongoing PISCES Phase I clinical trial with ReN001 in stroke therapy has now been treated and the final patient dosed in the study has been discharged from hospital.

ReNeuron and the **UK Center of Translational Excellence Catapult** (http://ct.catapult.org.uk/) signed an agreement to work together on ReNeuron's lead CTX stem cell line. Catapult will contribute US$2.0 million into the collaboration, to be provided in the form of expert knowledge, plus state-of-the-art laboratories, equipment, and services, while ReNeuron will also provide facilities, staff, and relevant expertise.

September 20, 2013

STEMSOFT Software, BC, Canada (www.stemsoft.com) released a new cord banking software STEMSOFT CORD. The STEMSOFT CORD software is designed to track all operational and manufacturing details in one location while assisting with accreditation compliance, ensuring processing standardization and increasing access to data.

September 26, 2013

Cell Medica, UK (www.cellmedica.co.uk) opened a commercial manufacturing facility

at the **Max Delbruck Center for Molecular Medicine** (www.mdc-berlin.de) within the biotechnology park of Campus Berlin-Buch in Germany. This state-of-the-art facility for the cGMP production of cell and gene therapies includes approximately 350 sq. meters clean room space. Initial manufacturing will focus on Cytovir™ CMV – an innovative treatment that uses the immune cells of a healthy donor to restore viral immunity against cytomegalovirus infections in patients who are immunocompromised following allogeneic bone marrow hematopoietic stem cell transplant. The commercial launch of this product is planned in early 2014.

October 10, 2013

Scientists at **Genea Biocells** have achieved an Australian first by producing human skeletal muscle from stem cells – a breakthrough expected to aid in the treatment of muscular dystrophies.

October 15, 2013

Rainbow Scientific, CT, USA (www.rainbowscientific.com) offers advanced research products for human mesenchymal stem cell and human embryonic stem cell culture from **Biological Industries, Israel** (www.bioind.com). The company claims that these chemically-defined, non-animal origin culture media can provide superior growth and maintenance of mesenchymal stem cells and human embryonic stem cell lines.

October 15, 2013

Life Technologies Corporation, CA, USA (www.lifetechnologies.com) has extended its collaborative agreement with Japanese firm **DNAVEC Corp.** (www.dnavec.co.jp/en) to launch the CytoTune™-iPS 2.0 Sendai Reprogramming Kit, the next-generation technology that enables an efficient method for developing iPSC from human somatic cells.

November 13, 2013

Pluristem Therapeutics, Israel (www.pluristem.com) receives regulatory approval to extend Phase II Study of PLX-PAD cells in the treatment of intermittent claudication, a subset of peripheral artery disease, to South Korea.

Next: Accomplishments (p. 40)

Accomplishments

January 17, 2013

Cellular Dynamics International, WI, USA (www.cellulardynamics.com) announced that it is producing human iPSC master cell banks from five individual donors under cGMP, enabling their possible use within a clinical setting.

January 24, 2013

Genea Stem Cells, Australia (www.geneastemcells.com.au) announced that 25 of its disease-specific human embryonic stem cell lines have been placed on the US NIH human stem cell registry. All of these cell lines are genetically unmodified and have been derived in compliance with international regulatory and ethical guidelines.

Genea Stem Cells is planning to work with drug developers globally to make disease-specific cell lines for application from in-vitro research.

March 4, 2013

Cerapedics, CO, USA (www.cerapedics.com) has announced that more than 10,000 patients have been treated with its product i-FACTOR™ worldwide since the product became available outside the USA in late 2008. i-FACTOR Peptide Enhanced Bone Graft incorporates Cerapedics' proprietary anorganic bone mineral and synthetic small peptide (P-15™) technologies for use in a wide variety of spine, trauma, and orthopedic surgical procedures.

i-FACTOR is not commercially available in the USA, where it is, as an investigational device, limited by federal law to investigational use only.

April 30, 2013

Harvard Bioscience, MA, USA (HBIO) (www.harvardbioscience.com) announced that the InBreath tracheal scaffold and bioreactor system manufactured by **Harvard Apparatus Regenerative Technology, Inc., MA, USA** (www.harvardapparatus.com), its wholly owned regenerative medicine technology subsidiary, were used in the first successful transplant of a regenerated trachea in the USA. The recipient of the implant was a 2-year-old girl.

May 7, 2013

Researchers at **Duke University, NC, USA** (www.duke.edu) combined **Vista-Gen's (CA, USA)** (www.vistagen.com) human stem cell-derived heart cells with innovative tissue engineering and cardiac electrophysiology technologies to grow what is being called a 'heart patch,' which mimics the natural functions of native human heart tissue .

This heart patch technology is being developed for better understanding of the biology critical to cardiac tissue engineering, for applications in regenerative cell therapy for heart disease, and as predictive in-vitro assays for drug rescue and development.

August 19, 2013

A **University of California, Los Angeles, CA, USA** collaborative study demonstrated a potential mechanism for converting research-grade adult skin cells into clinical grade iPSCs using two fibroblast lines from **Fibrocell Science, PA, USA** (www.fibrocellscience.com)

Next:
Capital Market Deals (p. 41)

Capital Market Deals

February 1, 2013

Opexa Therapeutics, TX, USA (www. opexatherapeutics.com) granted **Merck Serono, Switzerland** (www.merckserono.com) an option for exclusive license to develop and commercialize Tcelna™, an investigational personalized autologous T-cell therapy for patients with multiple sclerosis. The potential first-in-class therapy has received the FDA's Fast Track designation, and is now in an ongoing Phase IIb clinical trial in patients with secondary progressive multiple sclerosis.

March 21, 2013

Coriell Institute, NJ, USA (http://ccr.coriell.org) was awarded about US$10 million to set up and biobank storage of the iPS cell lines, of which Cellular Dynamics will be the primary subcontractor. Coriell Institute will establish a biorepository with proven methods for managing sample collection, tracking, and safe storage capabilities for worldwide distribution of iPS cells generated by Cellular Dynamics.

March 21, 2013

California Institute for Regenerative Medicine, CA, USA (www.cirm.ca.gov) awarded **Cellular Dynamics International, WI, USA** (www.cellulardynamics.com) US$16 million to create three iPS cell lines for each of their 3000 healthy and diseased donors.

Tissue samples will be taken from patients suffering from Alzheimer's disease, autism spectrum disorders, neurodevelopmental disabilities, cardiovascular diseases, liver diseases, and diseases of the eye or respiratory diseases. Cellular Dynamics will generate the iPS cell lines with the help of the episomal or footprint-free reprogramming method they developed.

July 31, 2013

Stratatech, WI, USA (www.stratatech.com) has been awarded a contract valued at up to US$47.2 million by the US Department of Health and Human Service's Biomedical Advanced Research and Development Authority. The contract is for the advanced clinical and manufacturing development of StrataGraft skin tissue, the Company's skin replacement product, as a medical countermeasure to treat patients with severe thermal burns.

The total award will support the preclinical, clinical, regulatory, and technology development activities needed to complete the FDA approval process for use of StrataGraft skin tissue to treat thermal burn injury.

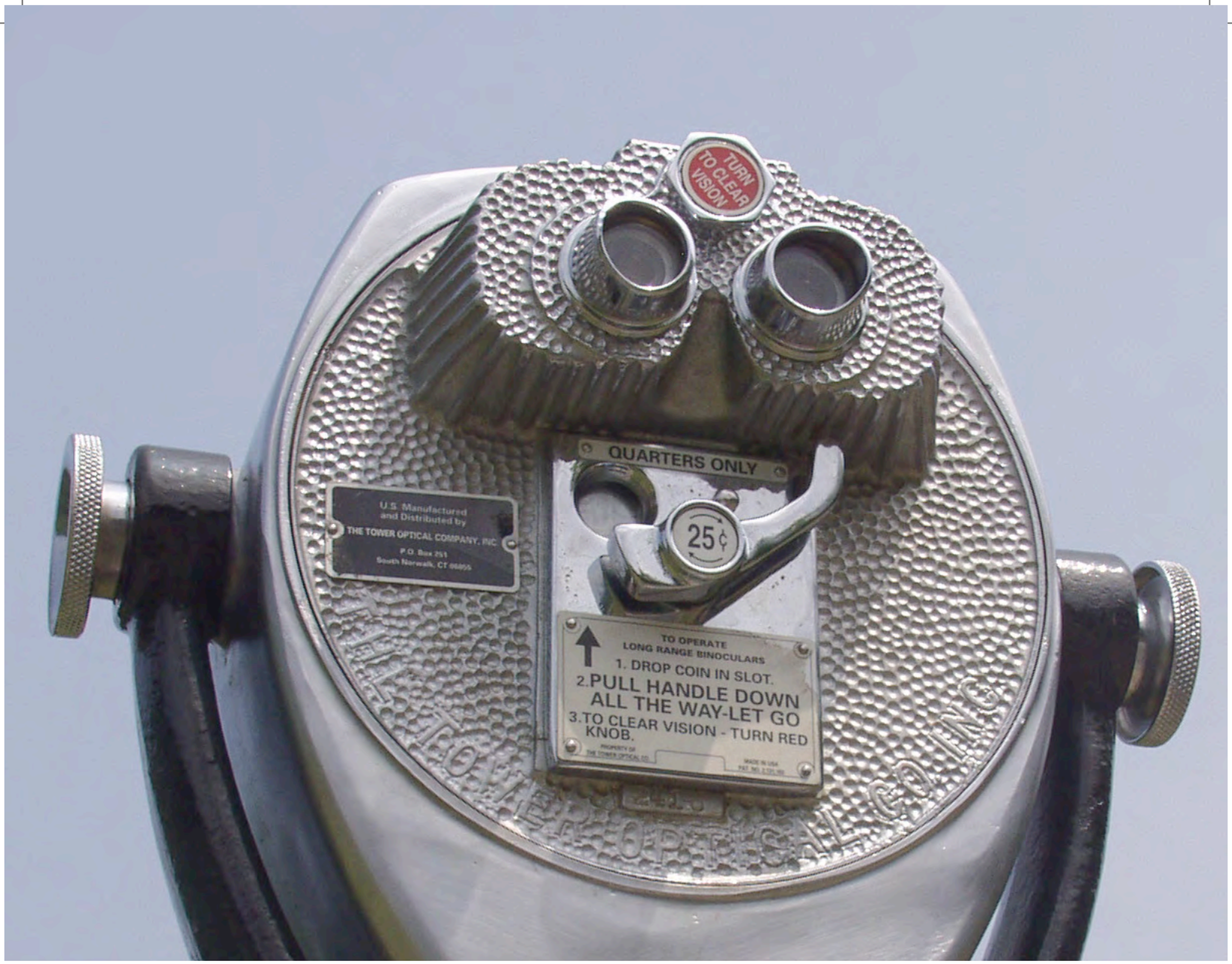
October 10, 2013

Osiris Therapeutics announced an agreement with **Mesoblast Limited** for the sale of a culture-expanded mesenchymal stem cell platform. The transaction amounted to US$100M in initial consideration and milestone payments. Also, Osiris will receive royalty payments on sales of Prochymal and other products using Osiris's MSC technology.

December 11, 2013

BrainStorm Cell Therapeutics, Israel (www.brainstorm-cell.com) was awarded a US$800,000 grant from Israel's Office of the Chief Scientist for the year 2013. The grant is intended to support BrainStorm's research and development program for its proprietary NurOwn™ technology for the propagation and differentiation of autologous MSCs into neurotrophic factor-secreting cells.

Also, BrainStrom has signed an agreement with **Octane Biotech, ON, Canada** (www.octaneco.com) to jointly develop a proprietary bioreactor for production of the NurOwn stem cell therapy candidate.



Industry Landscape

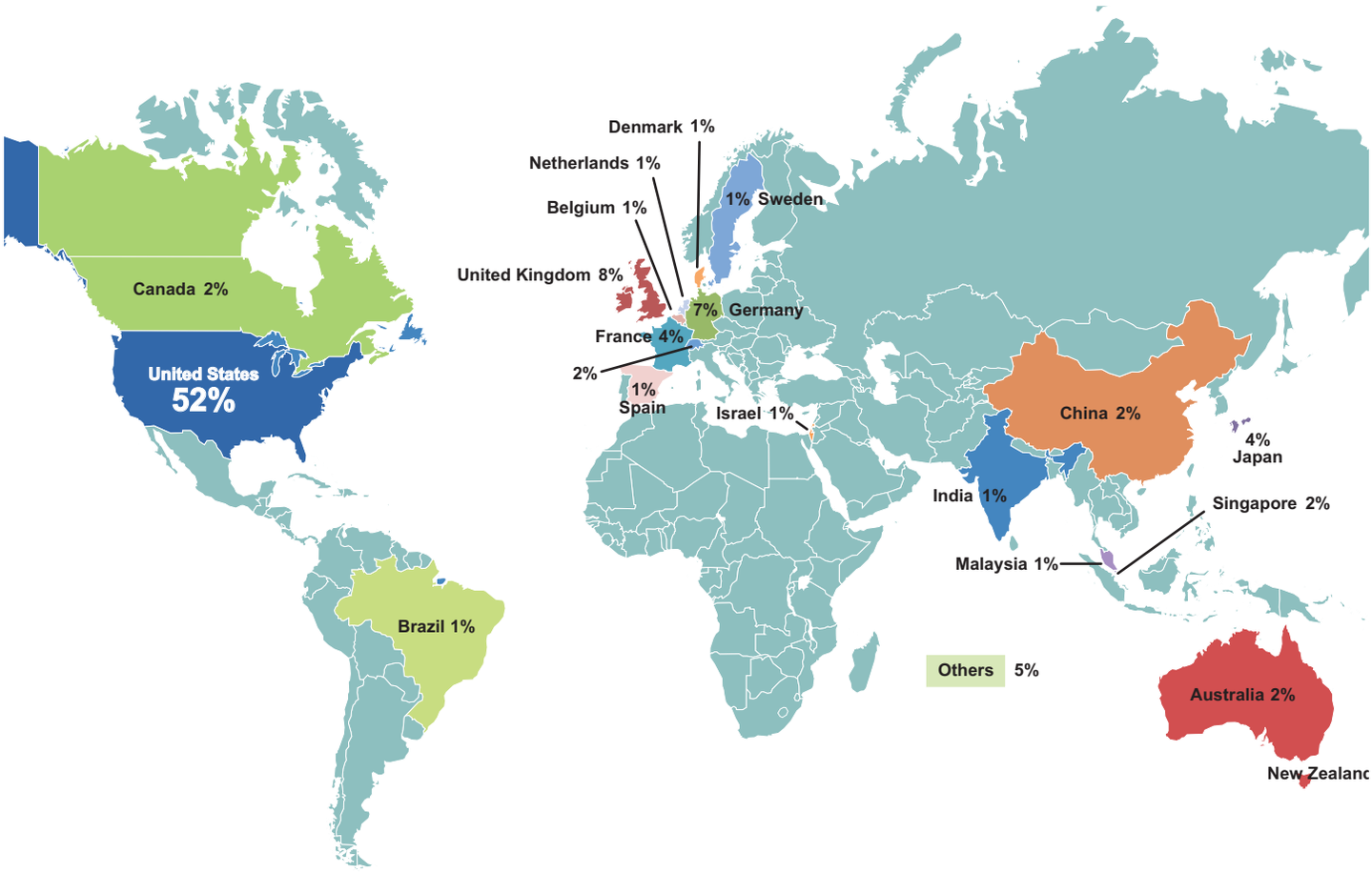
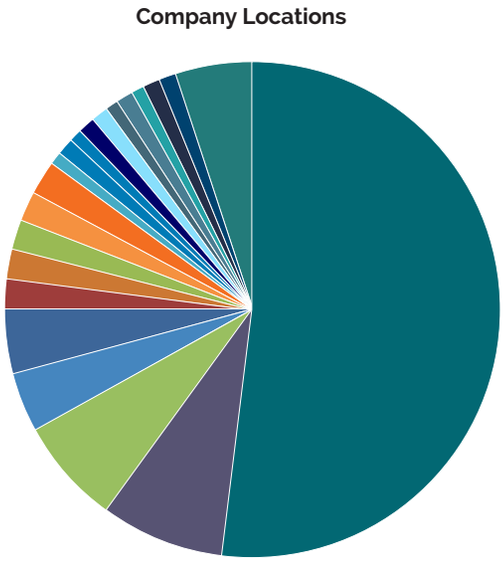


Chart 1: Company Locations

In our database, we are presently tracking more than 500 companies. Looking at the geographic distribution of these companies, approximately 52%, representing more than half of the organizations working in Regenerative Medicine worldwide, are registered in the United States. Another 38 companies, representing 8%, are working from the UK, and 33 companies, representing 7%, are based in Germany. Despite the size of biotech market in China, very little information is publicly available on regenerative medicine companies. The following countries, represented in the "other" category, are characterized by the lowest ratios of companies working towards RM or Stem Cell innovations. Argentina, Cyprus, Ireland, the Republic of Korea (South Korea), South Africa, Thailand, Poland, Slovenia, and South Africa each have only one company qualifying for our

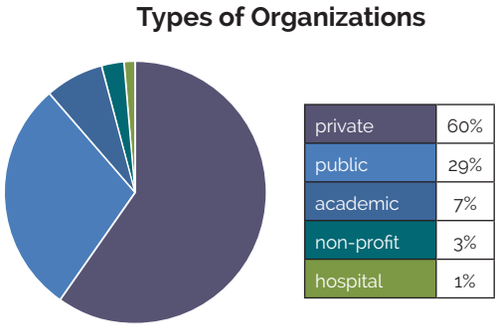


United States	52%
United Kingdom	8%
Germany	7%
Japan	4%
France	4%
China	2%
Switzerland	2%
Australia	2%
Canada	2%
Singapore	2%
India	1%
Israel	1%
Sweden	1%
Spain	1%
Brazil	1%
Malaysia	1%
New Zealand	1%
Denmark	1%
Netherlands	1%
Belgium	1%
Others	5%

database.North Korea and Panama each have two companies in our database, while Austria, Finland, and Italy have 3 each.

Chart 2: Organization Types

Looking at our companies based on their type of organization and funding status, we find that the majority are privately held, about 59.9%, with no stock offerings as of yet, where another 28.9% are publicly held, with existing stock options. Of the remaining, 7.1% are classified as Academic, including University research centers and Institutes, while non-profit organizations make up 2.8%. The non-profits consist of charity organizations, trial networks, interest groups, and foundations. We track certain unique organizations within the category "Hospitals," and clinical stage research participant groups make up 1.2%.



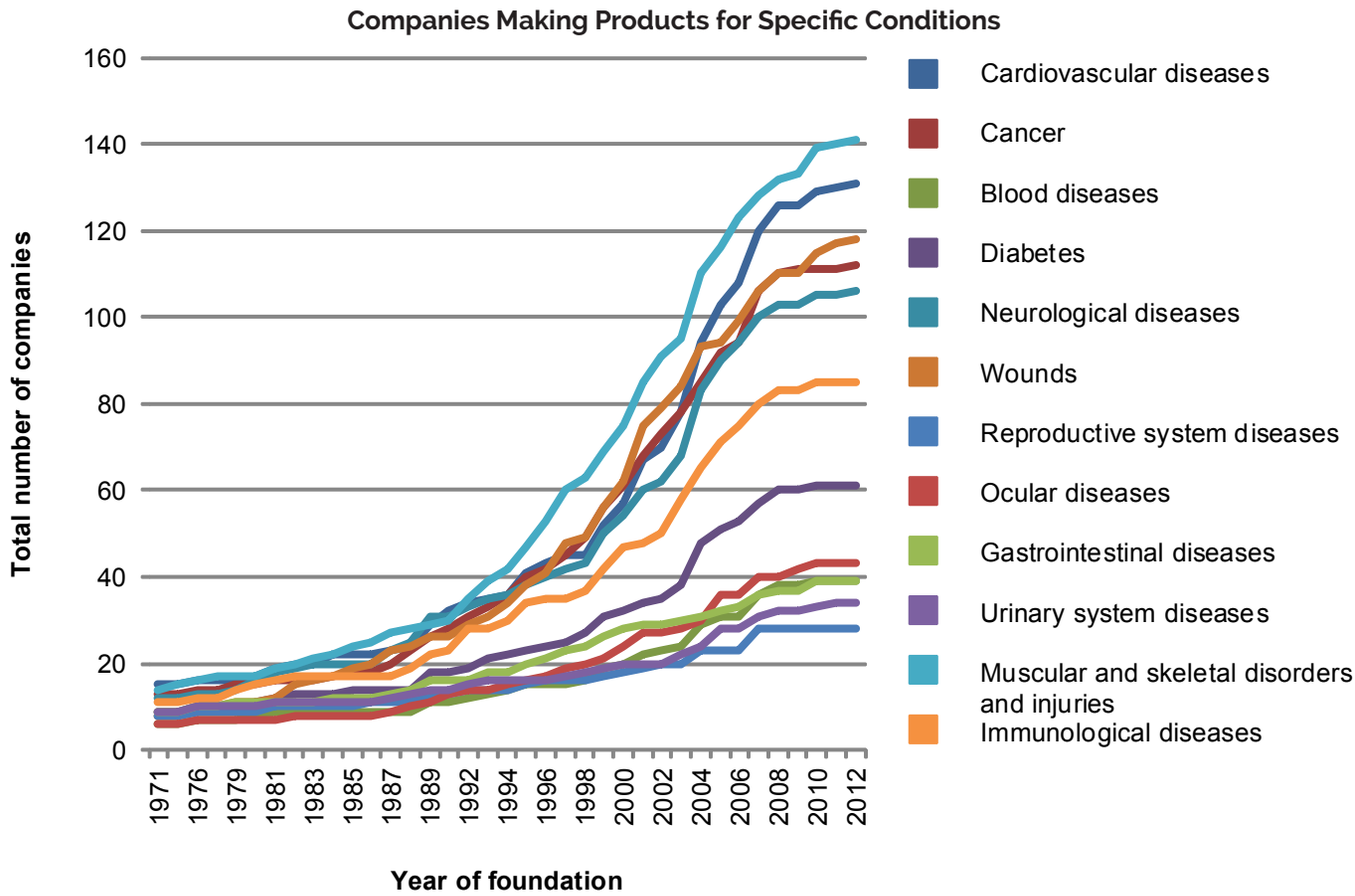


Chart 3: Products for Specific Conditions

Since the introduction of Stem Cell and Regenerative Medicine in the 1970s and into the 21st century, many of the companies in our database have focused on developing products to address specific conditions. The majority of fully developed and marketable products have come from specific areas, with treatments for musculoskeletal disorders, cardiovascular diseases, wounds, cancer, and neurological diseases achieving the best

measurable treatment results and the most success in the market.

Into the 21st century, our database indicates that by 2012, a total of 141 Regenerative Medicine companies were working with an interest in advanced therapies for musculoskeletal disorders, while only 28 companies are focusing on treatments for reproductive system diseases, indicating that this area of interest may have significant room to grow in coming years.

Regenerative Medicine Supply Lines, 1971 - 2012

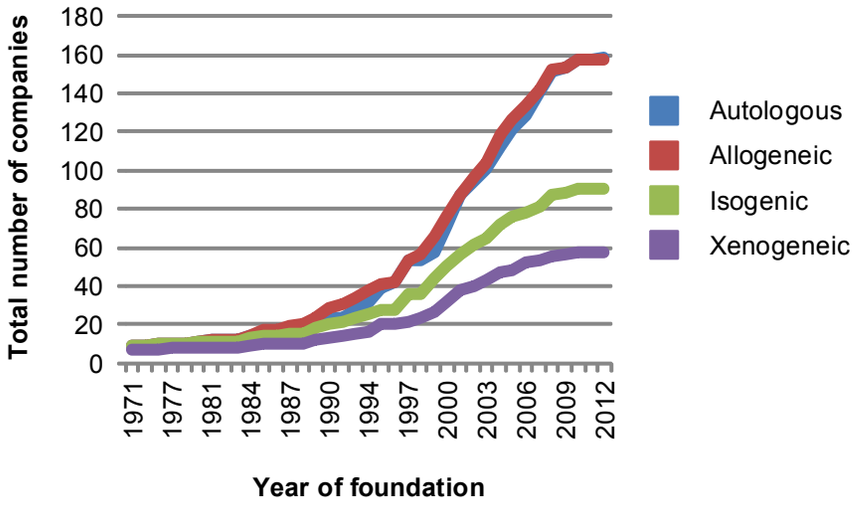


Chart 4: Supply Lines

Since 1971, the industry has focused on developing specific types of engineered cells for transplants and cellular therapy procedures. Autologous and allogeneic cell supply lines represent (and have always represented) similar presence in the market, and one can clearly see a dramatic rise in the number of companies developing both types of cells around the year 2000. Compared to the first two sub-fields, the number of companies developing Xenogenic and Isogenic technologies represent similar, though slightly less prevalent, portions of the market prior to 2000, with a relatively smaller boom since 2000, a "boom" that is relatively large, nonetheless, when compared to pre-millenial levels.

Stem Cell Companies Specialties, 1971 - 2012

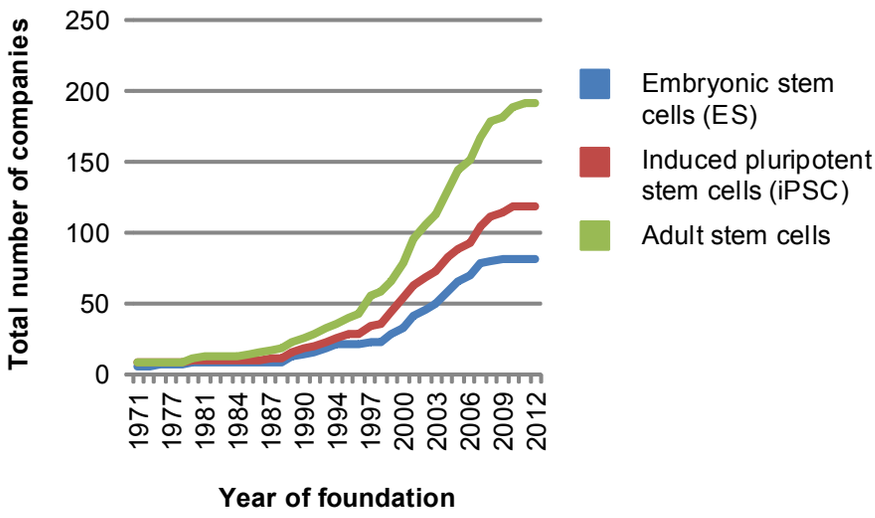


Chart 5: Company Specialties, 1971-2012

Of the wide range of specialized Regenerative Medicine companies, many focus on various specific types of stem cells. Companies working with Adult stem cells saw an influx of new companies starting in the mid-1990s, bringing about noticeable change in that specific part of the industry. It is important to recognize that the iPSC (induced pluripotent stem cell) technology is relatively new in comparison, and many older, more established companies have recently jumped on the iPSC bandwagon, transforming the specialization into a comparatively booming industry moving forward into the 21st century.

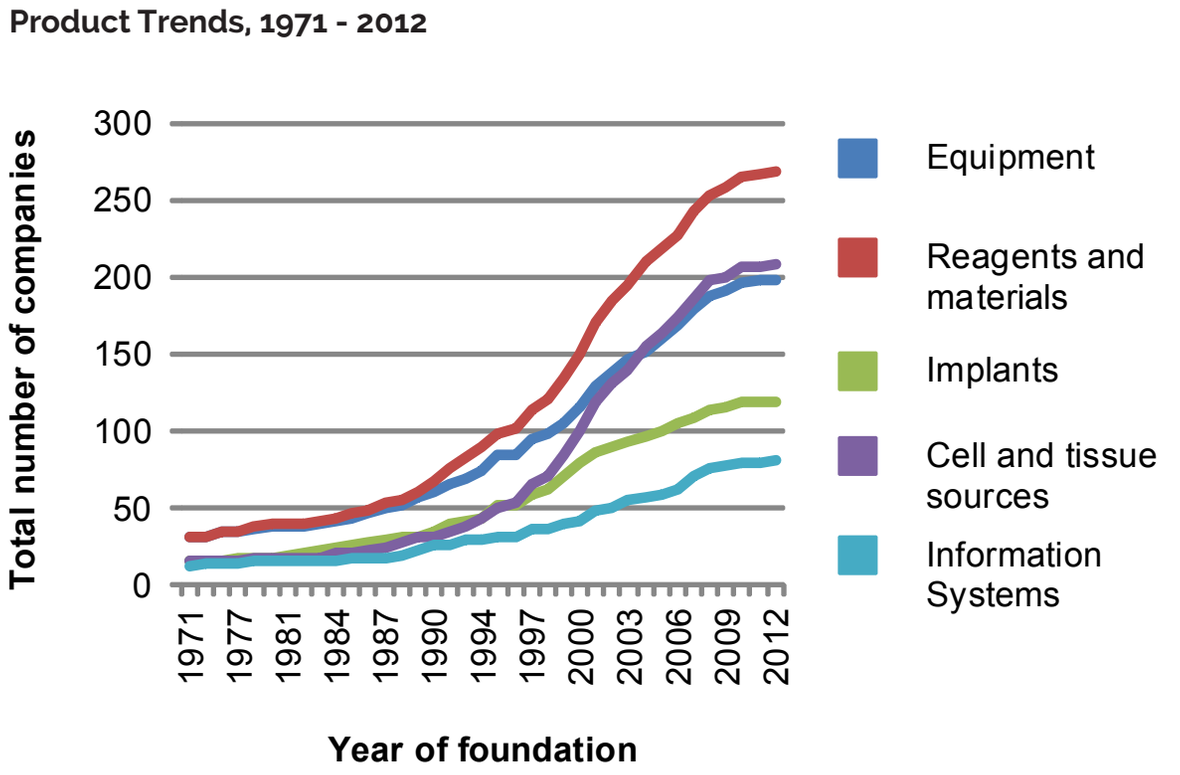


Chart 6: Product Trends

In terms of new product development, one observes that the development of implants and information systems do not appear to show a significant rise compared to other technologies. For many organizations, Reagents and Materials, Equipment, and Cell and Tissue sources appear to be the most attractive specialty fields at this time. Many of the new organizations that came on board around the turn of the century did so to develop products in these areas.

It is imperative to state that the rise in Cell and Tissue Sources lagged behind the development of Equipment and Reagents. In the 21st century, though, the pace quickly picked up for Cell and Tissue products. From our database records, a reported 208 organizations focus on Cells and Tissue today, compared to the 108 focusing on equipment. There appears to be steady interest in the area of Information Systems, though growth in this segment occurs at a slower pace compared to other areas.

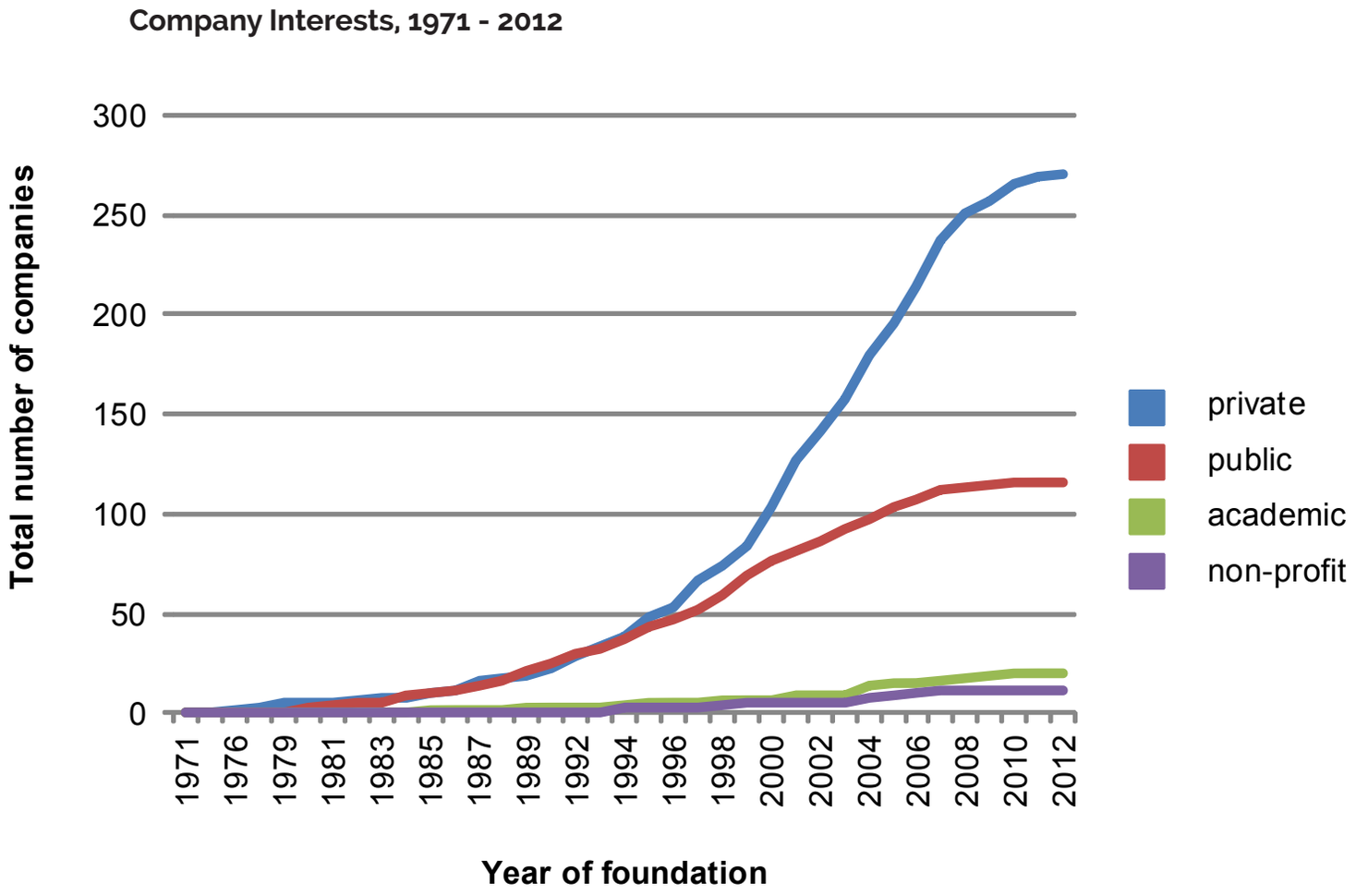
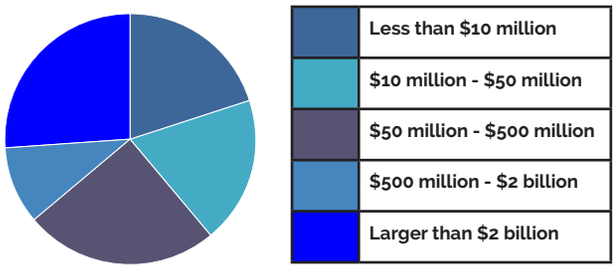


Chart 7: Company Interests

The mid-1990s signified a clear increase in the number of both private and publicly held companies. The dawn of the 21st century brought about an exponentially faster rise in the number of private companies, along with a comparatively sized rise in the number of public companies. The numbers of non-profit and academic organizations continue to rise steadily, though at a slower pace than companies engaged in the open market. It is noteworthy to state that non-profits were the first type of organization on the scene, starting in 1971, while private and public companies came into the field starting in 1973 and 1979, respectively.

Chart 8: Market Cap

Company Distribution based on Market Capitalization



Today, the companies we track vary in Market Capitalization from less than $10 million to larger than $2 billion, according to data gathered from Yahoo finance. While some mid-cap companies have a market capitalization greater than $2 billion, at 26% of the market, micro-cap companies make up 25% of the market, with market caps between $50 million and $500 million. Another 20% of the companies represent less than $10 million in market capitalization. 19% hold between $10 million to $50 million of share capitalization, and the remaining 10% of companies have a market capitalization of $500 million to $2 billion.

Deals and Partnerships

Looking at deals and partnerships in regenerative medicine and stem cells, well over 570 deals have been established since 2009, based on Current Agreements' Life Science Deals and Alliances Database.

A noticeable development is huge interest from many high ranking pharmaceutical companies. This interest arises from anticipation that regenerative medicine and stem cell technology will produce viable, mass market treatment solutions for many conditions that were previously untreatable or can be treated better with RM and stem cells.

Pfizer leads the group of interested Big Pharma companies with 9 partnerships. They are followed by Sanofi, which has 7 partnerships, and GlaxoSmithKline and Roche, which have 3 partnerships each.

The main goals of these regenerative medicine and stem cell partnerships are of important significance. Oncology ranks as the top area of interest, with 159 inter-company deals. A far second is cardiovascular treatment, with 74 partnerships, then hospital care, with 58 partnerships, followed by central nervous system treatment with 57 partnerships, and metabolic diseases, with 49 partnerships.

Regenerative medicine and stem cell partnerships represent a sharply rising and stimulating development of new treatments and technology, where the industry as a whole is coming together to produce compatible, standardized treatment options for the mass market, and from this environment, even

Figure 1: Established deals in Regenerative Medicine and Stem since 2009
Source: Current Agreements, 2013

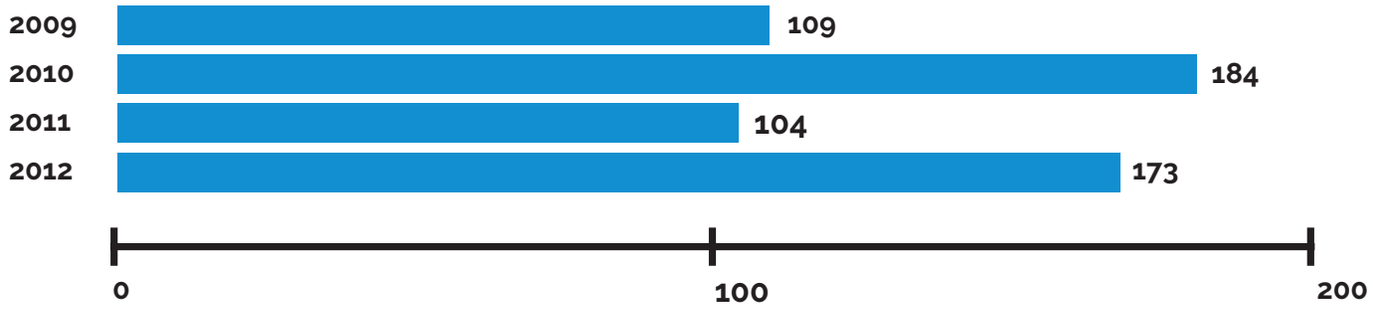
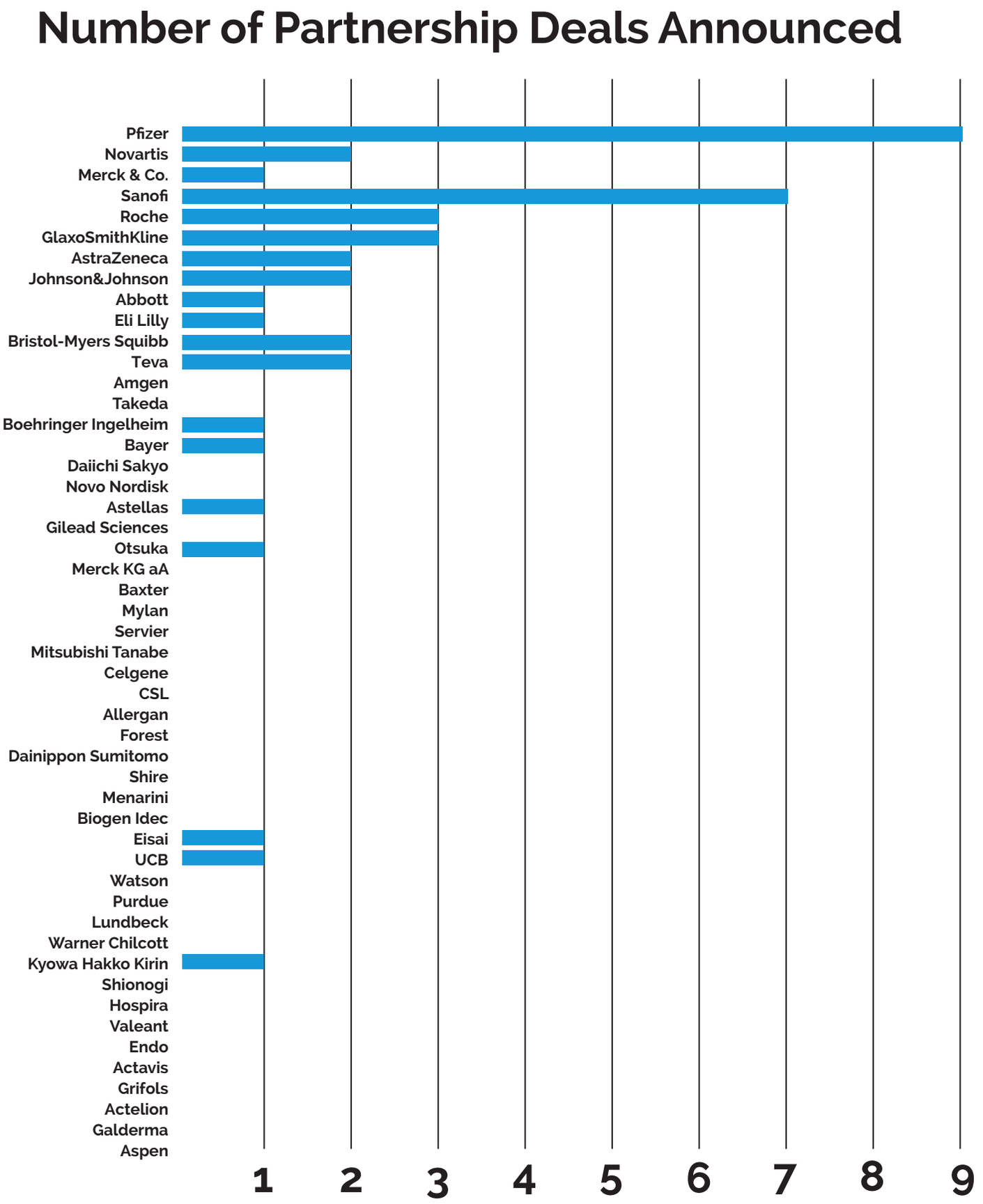


Figure 2: Partnership deals among pharmaceutical companies in regenerative medicine and stem cells since 2009
Source: Current Agreements, 2013



a small investment can eventually yield large returns. Characterized by lucrative and profitable ventures, these areas of interest provide opportunities for hefty rewards. The industry presently rises above the billion dollar level and is just now starting to produce new products for an emerging market. Now is the time to get involved, learn about, and gain an understanding of the regenerative medicine and stem cell industries.

Today is the day to get started.

This industry, the next big thing in bioscience and industrial medicine for many years into the future, can provide more than just a financial reward, but also a path to improving the lives of many people.

Partnerships by Therapy Area

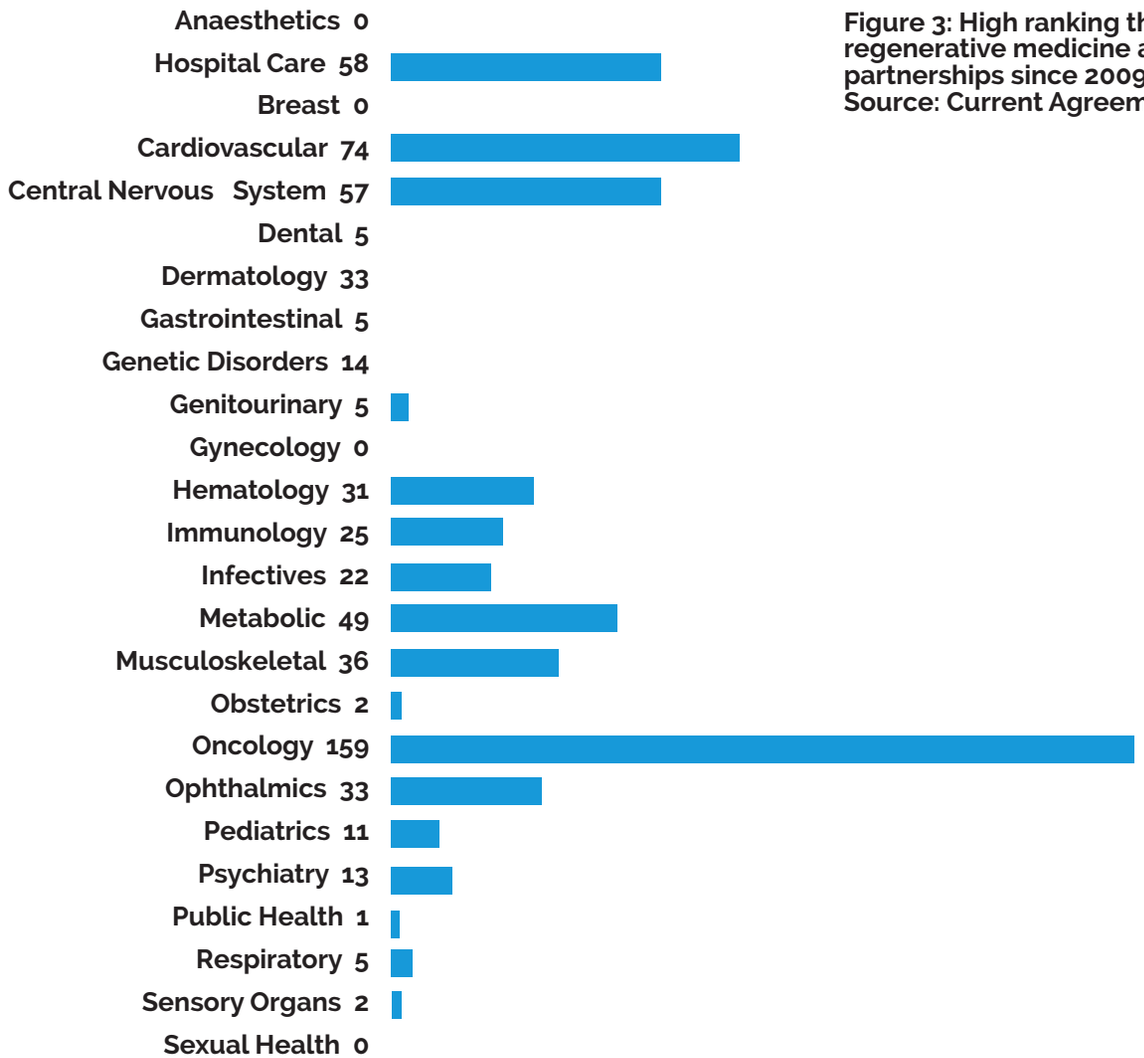
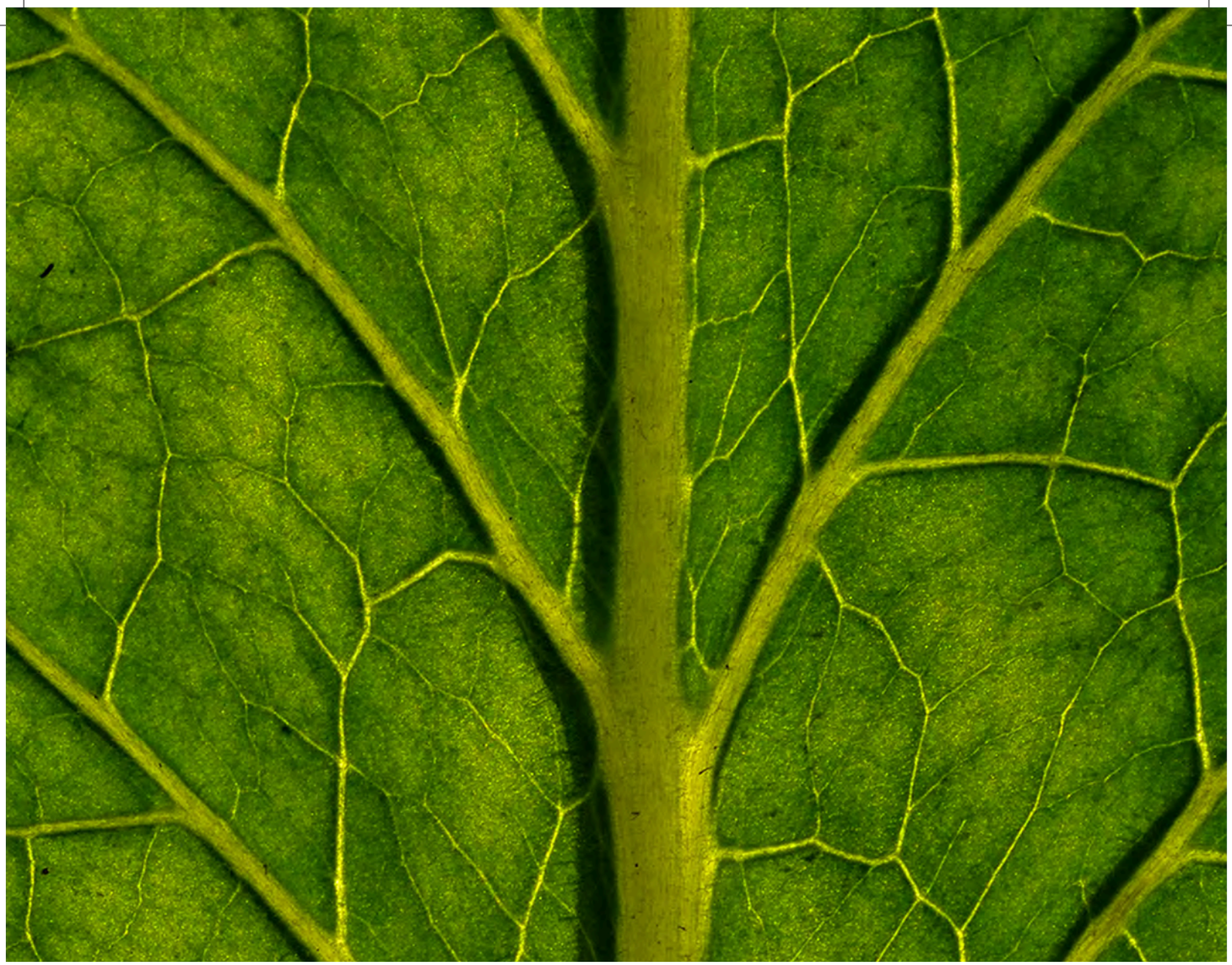


Figure 3: High ranking therapy areas for regenerative medicine and stem cells partnerships since 2009
Source: Current Agreements, 2013



Trends

Regenerative Medicine, still an emerging field of specialized medicine, has enormous potential, spanning stem cell transplantation, cell reprogramming, synthetic organ creation through tissue engineering, and nanotechnology. TechNavio's analysts forecast the Regenerative Medicine market in the US to grow at a CAGR of 15.83 percent from 2012 to 2016. One of the key factors contributing to this market growth is an increasing number of degenerative diseases.

However, despite the progress of the past 10 years, it is still uncertain how regenerative medicine will develop in the future. Currently, effective and safe regenerative therapies beyond bone marrow transplants remain elusive and expensive.

The ability to maintain sustainable investment in research, coupled with widespread ethical concerns, could hamper the speed of progress and implementation. In this section, we cover several interesting trends and novel technological vectors defining the industry.

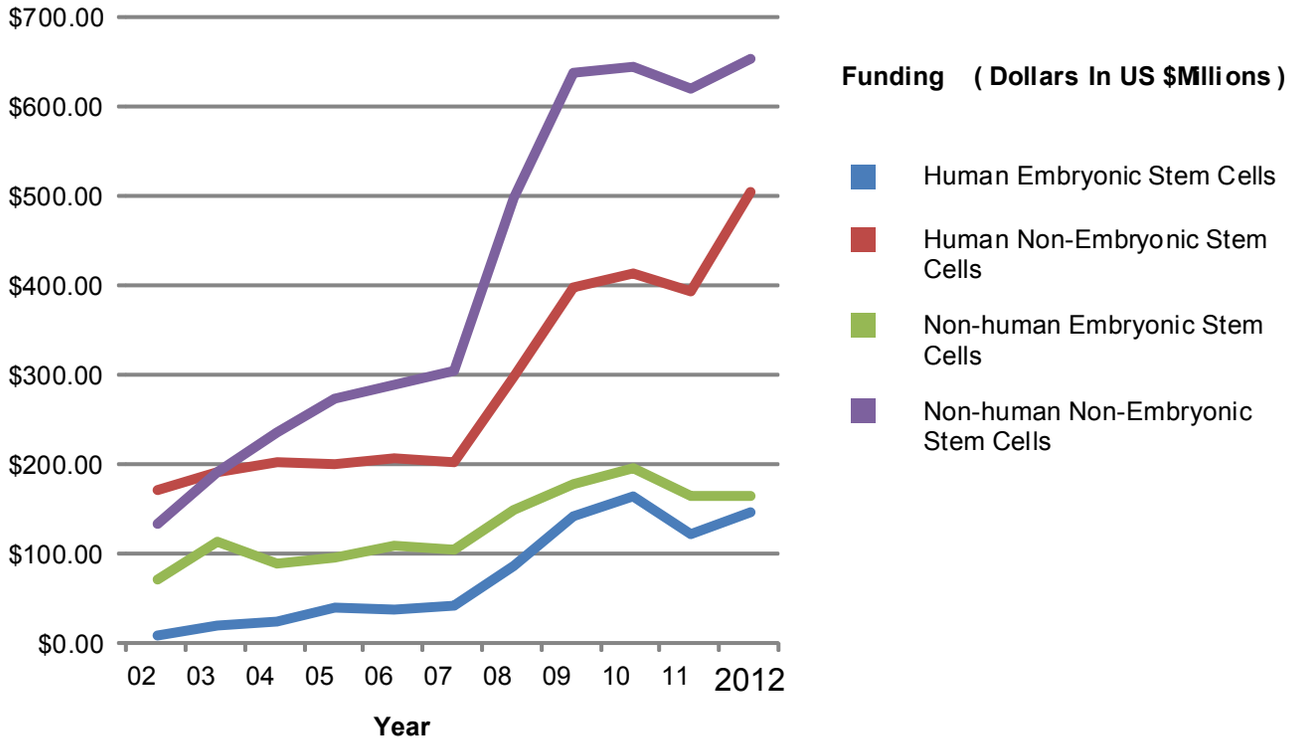
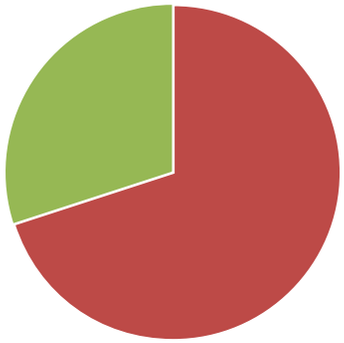


Chart: NIH Stem Cell Research Funding, FY 2002 - 2012 (Dollars in millions) Source: http://stemcells.nih.gov/

Growing Stem Cell Research

According to a new market report published by Transparency Market Research (TMR 2013), the market for stem cells was valued at USD $26.23 billion in 2011 and is expected to reach an estimated value of USD $119.51 billion in 2018, growing at a CAGR of 24.2% from 2012 to 2018. This market growth is attributed to therapeutic research activities led by government support worldwide, in large response to the growing number of patients

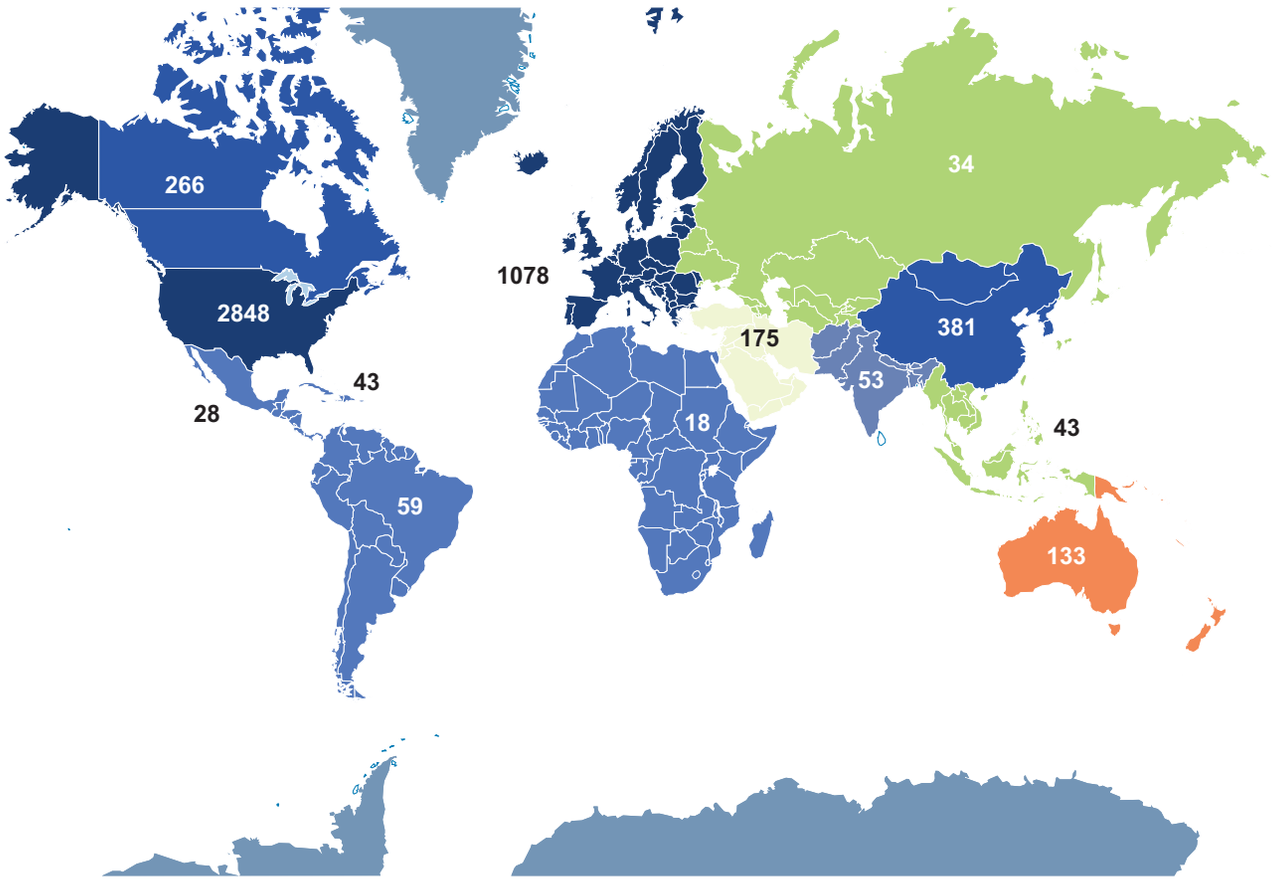
Chart: Number of academic ("Non-profit") and commercial ("For profit") entities sponsored by CIRM. Source: http://www.cirm.ca.gov/



For Profit	21
Non-Profit	49

Total Number of Stem Cells Clinical Trials, as of September 2013.

Source: http://www.ipscell.com/2013/09/maps-of-global-stem-cell-clinical-trial-trends/



around the globe with chronic diseases. In many countries, the government is a major source of funding for the stem cell and regenerative medicine fields.

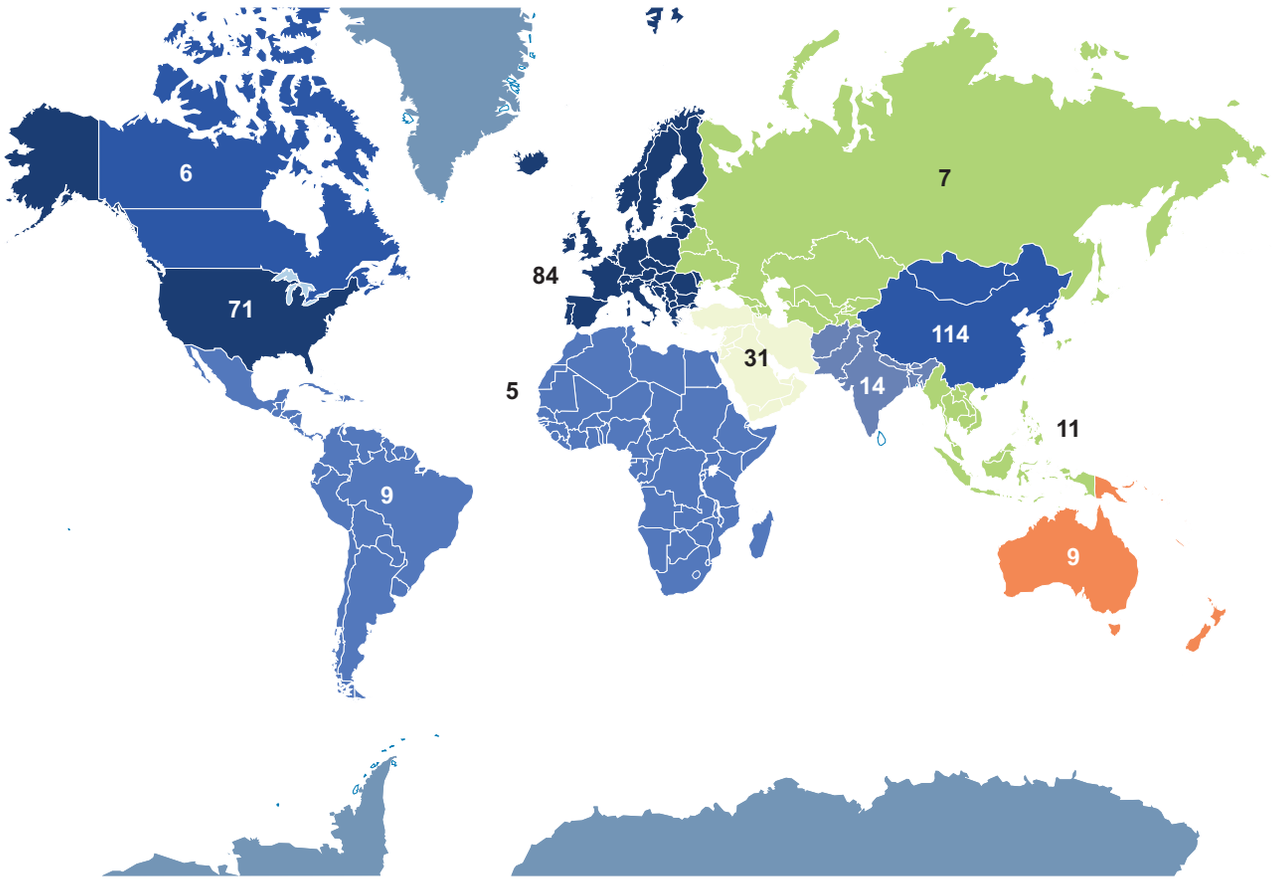
For instance, if we look at the National Institutes of Health (NIH) and the California Institute for Regenerative Medicine (CIRM), these two institutions fund by far the majority of academic translational stem cell research and regenerative medicine development in the US.

Official data clearly shows the dynamic increase of NIH government funding for academic stem cell research since 2002.

In turn, and in addition to academic organizations, CIRM also funds different commercial entities allocated in California. Those include companies like ViaCyte, Capricor, Stem Cells, Inc., Biotime, Cellular Dynamics International, and others. Since its foundation in 2004, CIRM has given away more than $1.7bn worth of grants.

Total Number of Mesenchymal Stem Cells Clinical Trials, as of September 2013.

Source: http://www.ipscell.com/2013/09/maps-of-global-stem-cell-clinical-trial-trends/



Another illustration of this trend is the growing number of stem cell clinical trials.

According to the Knoepfler Lab Stem Cell Blog (URL Ref. 13), the number of clinical trials associated with stem cells is growing very rapidly. In the study, Knoepfler Lab tracked all stem cell-based clinical trials registered from December 2012 to September 2013. It has been shown that in these 10 months, the total number of clinical trials increased by 10.6% from 4,316 to 4,775. Most of the clinical trials were registered in the US, followed by the European Union, China, and Canada.

Even more astonishing is the dynamic of MSC-associated clinical trials. The total number of MSC trials increased by 26% during this time, from 281 to 354. This increase suggests that the rate of growth for MSC research is substantially faster than that of the overall stem cell research being conducted. In terms of numbers, the global leader of MSC clinical trials is China, followed by the European Union and the United States.

Point-Of-Care Cell Therapy

In Glossary: ADRC - adipose-derived regenerative cells

Point-of-care (POC) cell therapy is a medical procedure where the patient is treated with tissues or cells produced from cells native to the patient's body. The therapy consists of several steps, including collection of native cells, processing, and administering new cell structures. The procedure is comparatively fast and can take from 1 to 30 hours. POC cell therapy is already being used for the treatment of multiple conditions covering soft tissue disorders, neurological diseases, dermal wounds, and spine injuries.

Using the patient's own cells via POC cell therapy represents a far safer and cheaper approach than allogeneic transplantation. Another advantage of POC cell therapy is the possibility of creating custom combinations of different cell types to treat complex diseases. Nevertheless, there are a number of issues doctors must take into account, such as the source and dose of the cells, a patient's age and health status, possible side effects of device implants, and environmental factors effecting new tissues. Despite the complexity of manufacturing and logistics, POC cell therapy has far fewer issues with quality control and approval than other conventional cell therapies requiring GMP processing and obligatory IND clinical trials. Of course, certain companies work around the presently loose FDA regulations and market their devices without any FDA clearance whatsoever. The lack of strict FDA regulations, combined with limited clinical trial data and treatment protocols still being developed, represent issues for the future of POC cell therapy.

Currently, there are around 20 companies developing and commercializing POC cell therapies. In 2007, one of the frontrunners in the field of POC cell therapy, Cytori Therapeutics, entered the POC market and presented its FDA-approved Autologous Fat Transfer (AFT) System. In July 2013, ThermoGenesis and TotipotentRx (TotiRx) merged in an all-stock deal to create one public company, Cesca Therapeutics. With the combined clinically-validated cell therapy protocols and cell therapy kits of TotiRx and the cell-processing devices of ThermoGenesis, Cesca Therapeutics might become one the strongest players in the POC cell therapy market. In August 2013, Cytori Therapeutics received notice from the Australian Therapeutic Goods Administration (TGA) that the Celution System was approved for commercial use for autologous re-implantation and re-infusion of a patient's own ADRCs. This approval enables physicians to treat critical unmet medical needs with point-of-care cell therapies and to conduct important clinical research in promising areas of therapeutics.

3D-Bioprinting

3D-Bioprinting is a technology derived from additive manufacturing activities that consist of printing, layer by layer in 3D, the biologically relevant materials (such as cells, tissues, or biodegradable biomaterials) that will accomplish one or more biological functions. This technology covers a wide range of applications, from drug discovery and assays to in vitro diagnostics, cell therapy, and tissue engineering, as well as the production of biomolecules. This year, we have already witnessed many cutting-edge developments and big steps in terms of new 3D printing innovations.

In September 2012, At the University of

Missouri, Columbia, researchers have 3D-printed viable, functional blood vessels and sheets of beating heart muscle.

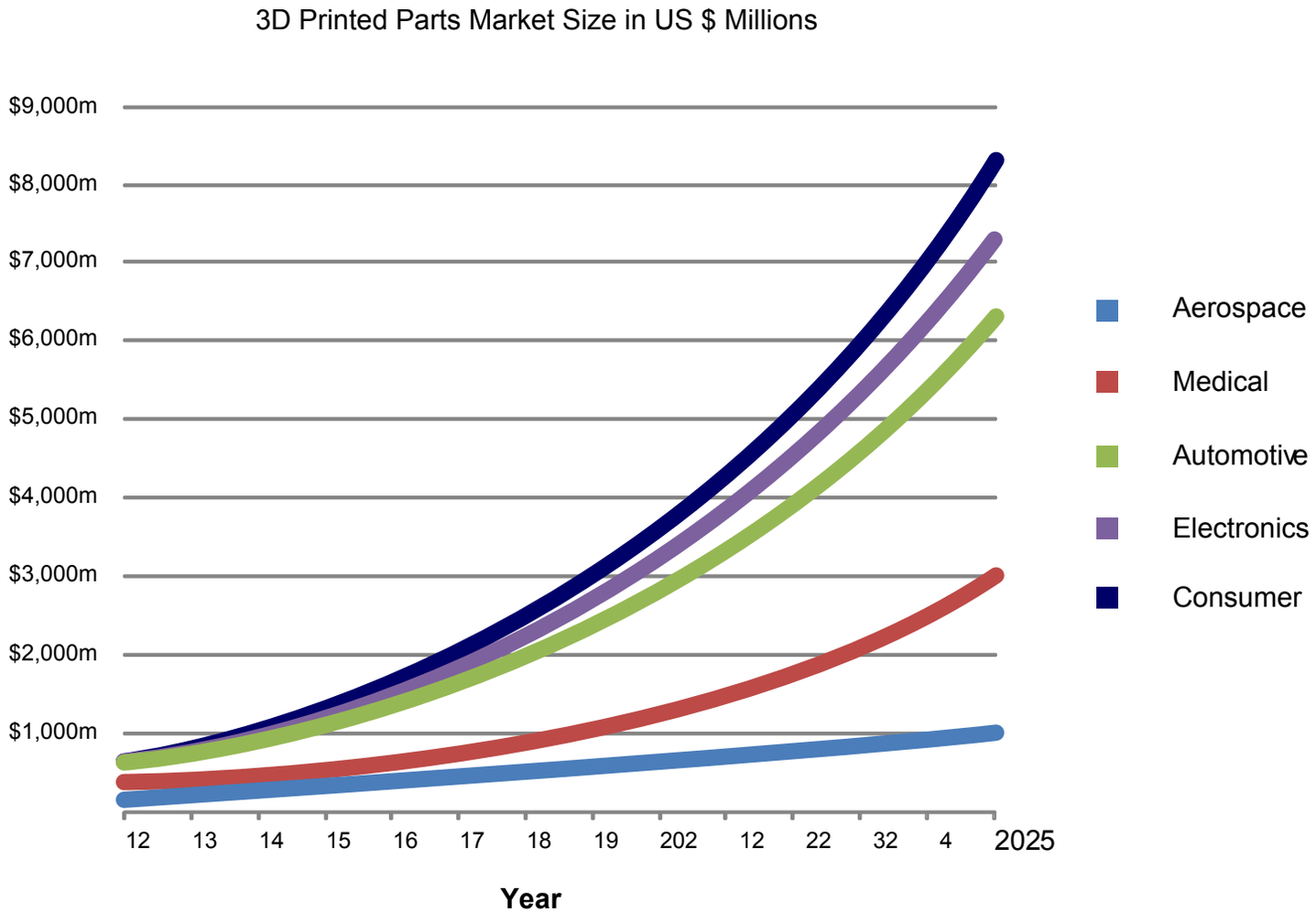
In February 2013, Dr. Will Shu and his colleagues at Heriot-Watt's Biomedical Microengineering Group were the first to print more delicate embryonic cell cultures, which have an ability to replicate indefinitely and differentiate into almost any cell type in the human body (URL Ref. 14).

In February 2013, Larry Bonassar, Cornell Associate Professor of Mechanical Engineering, and his research team developed a 3D printing method to produce a precisely-modeled replacement human ear. (URL Ref. 15)In July 2013, scientists at Wake Forest University's Military Research Center developed a method to 3D print new skin cells directly onto burn wounds. (URL Ref. 16)

China is also keeping the pace. In August 2013, researchers at Hangzhou-based Dianzi University using a biomaterial 3D printer called "Regenovo" successfully printed out small-scaled human body parts, like an ear and a nose (URL Ref. 17).

The aforementioned organizations engaged in 3D bioprinting currently focus solely on the research, but there are several commercial companies moving forward with research and development, hoping to extract some profit in the near future. The world's first commercial bioprinter, the NovoGen MMX Bioprinter, was put on the market in 2009 by a company called Organovo. Organovo uses bioink made up of various human cells and places them in a precise manner using its NovoGen MMX Bioprinter into microplates or other form factors. Because these cells are placed in a certain architecture and are fed with nutrients, they begin to signal to each other to behave naturally, catalyzing the formation of tissue.

Organovo's competitor in the bioprinting



market is TeVido BioDevices. TeVido BioDevices is an early-stage life science and biotech company using 3D bioprinting of live cells to build custom implants and grafts for breast cancer-effected tissue reconstruction. In 2013, nearly 300,000 women in the US will be diagnosed with breast cancer, with 50-60% of them choosing a lumpectomy as part of the treatment. Longer term, TeVido's solution for lumpectomies could expand to the broader and more lucrative market for breast augmentation, which is estimated at $10 Billion in the U.S. According to TeVido, this application will take seven more years of R&D and approximately $40million of funding.

So what is the global 3D printing picture at the moment? According to a report from Boston-based Lux Research, the overall 3D printing market had a $777 million base in 2012, with 3D printed prototype parts in aerospace and automotive applications totaling $315 million and $428 million, respectively, accounting for more than 95% of aggregate sales. The market for 3D printing is expected to grow to $8.4bn by 2025. Bioprinting's contribution will be negligible, and most of the medical industry's $1.9 billion share of the market (rising from a modest $11 million in 2012) will come from 3D printed medical devices and orthopedic parts.

Basically, biotech firms in this emerging field are not yet profitable, as they still have very low revenue coupled with high R&D expenses. For instance, Organovo's revenues doubled to $1.2m between 2010 and 2012, but losses increased nearly eight-fold to $9.3m in the same time period (URL Ref. 18).

All of the companies engaged in the 3D bioprinting field are facing the same regulatory difficulties. At the moment, their services will only be available for drug and other medical research. In the short term, they can increase their revenue by providing products to aid in academic and pharmaceutical research. It may be years before tissue-engineered products are actually available and approved for widespread application to the human body. Yet, the companies continue their research to create valuable patents. At the moment, the main source of dividends for investors in this specialized field are potential buyouts from larger pharma companies.

Company	Ticker	Number of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca	AZN	5	11790.93	58955
GlaxoSmithKline	GSK	10	8170.81	81708
Sanofi	SNY	8	7909.26	63274
Roche Holding AG	RHHBY	11	7803.77	85841
Pfizer PFE Inc.	PFE	14	7727.03	108178
Johnson & Johnson	JNJ	15	5885.65	88285
Eli Lilly & Co.	LLY	11	4577.04	50347
Abbott Laboratories	ABT	8	4496.21	35970
Merck & Co Inc	MRK	16	4209.99	67360
Bristol-Myers Squibb Co.	BMY	11	4152.26	45675
Novartis AG	NVS	21	3983.13	83646
Amgen Inc.	AMGN	9	3692.14	33229

Table. Research Spending Per New Drug. Source: http://www.forbes.com

Why Should "Big Pharma" Be Interested?

According to a Forbes's article by Matthew Herper (URL Ref. 19), the top 12 pharmaceutical companies spent **$802.5 billion on research and development** between 1997 and 2011 on their way to 139 drug approvals. This means that in average, a single company spent an astounding $5.77 billion per each approved drug. Several perspective in silico methods for drug discovery have even been proposed (Zhavoronkov 2014).

One of the biggest problems during drug discovery is accurately assessing the drug's toxicity to human cells, particularly liver toxicity. Approximately 25% of all drugs that were withdrawn from the market or failed a phase 3 trial between 1990 and 2010 were yanked due to liver toxicities (URL Ref. 20). 3D bioprinting companies can help Big Pharma companies increase their efficiency by more accurately predicting liver toxicities.

Earlier this year, Organovo published data on its 3D bioprinted liver model and found that the liver tissue lasts much longer than 2D cell cultures. And even before the data was published, Organovo established agreements with Pfizer and United Therapeutics to use its technology for drug discovery.

In January 2013, the company signed an agreement with Knight Cancer Institute at Oregon Health & Science University to develop more clinically predictive in vitro 3D cancer models to advance discovery of novel cancer therapeutics, along with signaling pathway analysis (Buzdin 2014) - these models could be useful for researching new oncology compounds and developing personalized medicine applications. The first results from several studies are expected to be published after the second half of next year, after which a path to commercial application can be formulated.

Organovo is also working on the development of tissue-engineered therapies to replace damaged or diseased tissue, but creating a fully functional organ is a very difficult task for researchers at present, and it may take years before the ability to produce one becomes a reality. Once it is created, it may require up to a decade to complete the necessary trials to release it for medical application.

Medical Tourism

'Medical Tourism' refers to the practice by patients of travelling to a different country for an urgent or elective medical procedure that is either not approved or too costly in their home country. The practice is fast becoming a worldwide, multibillion dollar industry. According to United Nations statistics, the median age of the world's population will be growing over the next 50 years in all major regions of the world. Biomedical progress has already been suggested as one of the future key economical factors for these age groups (Zhavoronkov 2013). And, in turn, the increase of the median age of population will bring an increasing flow of potential customers interested in medical tourism.

Medical tourism is an emerging global industry, with a range of key stakeholders and commercial interests including brokers, healthcare providers, insurance providers, website providers, networking providers, and media services. According to a new market report published by Transparency Market Research, "Medical Tourism Market (India, Thailand,Singapore, Malaysia, Mexico, Brazil, Taiwan, Turkey, South Korea, Costa Rica, Poland, Dubai and Philippines) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019," the global medical

tourism market was valued at USD $10.5 billion in 2012 and is estimated to reach a market valuation of USD $32.5 billion in 2019 at a CAGR of 17.9% from 2013 to 2019.

The rise in healthcare costs in developed countries coupled with the availability of high quality medical services at a low cost in developing countries have given a boost to the medical tourism industry. These medical services range from elective procedures such as cosmetic surgeries to complicated surgeries such as cardiac procedures, orthopedics, neurosurgery, and others. Significant growth in this industry is due to economic developments in developing countries that in turn has led to the growth in the medical industry and the quality of medical services. Biomedical progress has been already suggested as one of the future key economical factors (Zhavoronkov 2012).

The rise in healthcare expenditures in developed countries coupled with a growing elderly population has also contributed to the growth of medical tourism around the globe. The recent economic crisis in the U.S. has increased the number of the uninsured population, consequently further triggering the growth of this market.

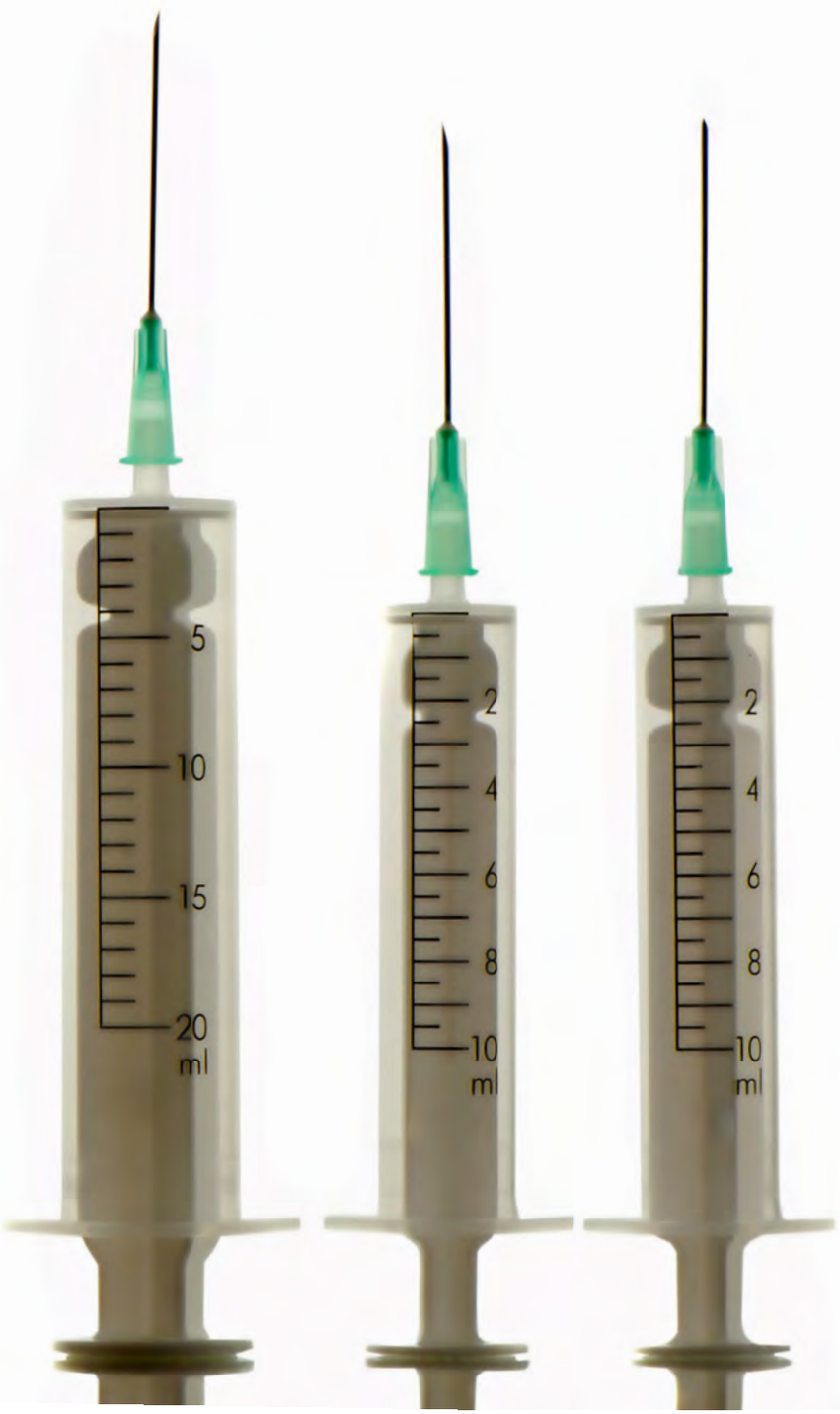
Among this giant industry, there are a small number of regenerative medicine solutions. So-called "stem cell tourism" has already become an emerging trend, at the same time raising quite a bit of concern. Due to the slow drug approval procedures in the U.S. and the growing number of already ill and desperate people, patients often go to other countries looking for non-approved stem cell treatment. Some people are even exploring the newly appeared option of personalized science (Zhavoronkov 2014).

Some countries have less strict regulations concerning drugs and medical innovation, and stem cell therapy remains uncontrolled (or even encouraged) in these parts of the world. According to the National Center for Biotechnology Information, over 700 companies and clinics around the world offer stem cell therapy services. Many experts, as well as the International Society of Stem Cell Research and the FDA, discourage people from traveling overseas for such treatments, saying the treatments are unsafe and unproven. Patients and physicians ought to distinguish between clinically-proven stem cell treatment, non-approved stem cell therapy in competent clinics, and fraudulent stem cell therapy with no scientific basis whatsoever.

In August 2013, ISCT published Patient Advisory for Stem Cell Therapy and Medical Tourism. In this document, ISCT emphasized the key points that physicians, patients, and family members should carefully consider before starting any stem cell-based treatment. ISCT is the only group focused on pre-clinical and translational aspects of developing cell therapy products. As such, ISCT helps academic, government, and biotech/pharma sectors transform research into practice and product. In September 2013, the International Society for Stem Cell Research (ISSCR) has urged medical licensing bodies, legal authorities, patient advocacy organizations, clinics, and physicians to exercise their power in discouraging commercial treatments of unproven stem cell therapies outside of clinical trials.

Clinical Trials

Here, we overview international clinical trial databases via the WHO Search Portal. We have tracked trials in cell therapy and tissue engineering registered from Jan.1, 2013 to Dec.31, 2013.



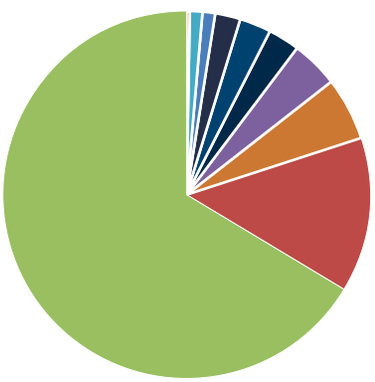
Cell Therapy Clinical Trials

We tracked trials by following the search terms: "cell therapy" and "stem cells." At this stage, we have excluded trials related to tissue engineering, gene therapy, growth factor therapy, and platelet-rich plasma use. We will describe these aspects of the regenerative medicine field in the next stages of our research and publications.

We have also excluded research efforts related to the use of stem cells for diagnostic purposes, like stem cell phenotyping for cancer research, as well as data related to supportive manipulations around stem therapy, like antibiotic indications during allogeneic stem therapy for immunosuppressive conditions and the complications related to the therapy.

We have included all trials assessing the use of stem hematopoietic and other blood cells in blood malignances. We took data about trial ID, country of origin, phase of research, indication, cell type, donor type, type of sponsorship, company-sponsor name, and product identification from each trial's description. To date, we have tracked 184 trials for the calendar year 2013.

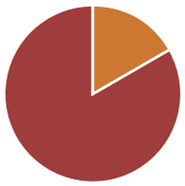
Database Representation



Cell Therapy: Databases

South Korea	KCT	1
Deutch	DRK	2
India	CTRI	2
Iran	IRCT	4
International	ISRCTN	5
Australia	ACTRN	5
China	ChiCTR	8
Europe	EUCTR	10
Japan	JPRN	25
USA	NCT	122

Sponsorship

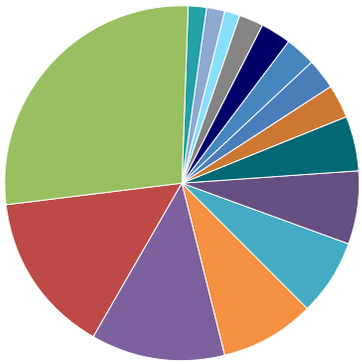


Cell Therapy: Sponsorship

Academic	153
Commercial	31

All trials were divided into 2 categories - "Academic" or "Commercial." "Academic" trials are supported by non-profit organizations, and "Commercial" trials are sponsored by profit-seeking agencies.

Demographics

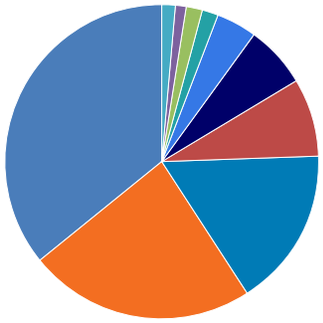


Cell Therapy: Countries

France	3
Russia	3
UK	3
Brazil	4
Italy	5
Australia	5
Germany	5
Iran	6
Spain	9
Others	12
South Korea	13
India	16
China	22
Japan	27
USA	51

"Other Countries" include Sweden, Switzerland, Poland, Mexico, Taiwan, Panama, and Egypt. The number of trials registered in these countries during 2013 was smaller, registering at 1 or 2 per country.

Cell Types



ES+fetal	3
Neuronal Precursor	2
Cardiac Precursor	3
iPSC	3
Other Adult	8
Cord Blood SC	12
ADSC	15
Hematopoietic	31
Adult Immune	44
Bone Marrow Derived SC	67

Cell Therapy: Cell Types

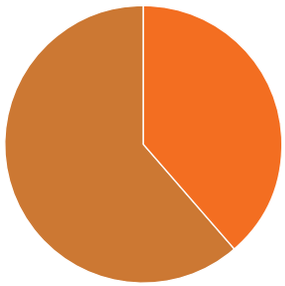
The number of cell types mentioned is 188, because some trials act on an assortment of cell types, rather than a single cell type. For example, the cell type category "MSC Cells" can include bone marrow, adipose tissue, and cord blood. Our classification system is partly tissue-oriented, because hematopoietic cells can also be derived from the above-mentioned tissues and organs, and cellular therapy can be based on many types of stem and progenitor cells derived from a single source.

We have subdivided the cell types used for cell therapy into the following categories:

- "ES and fetal": fetal fibroblasts, fetal neuronal cells, placenta-derived cells.
- "iPSC": induced Pluripotent Stem Cells.
- "Adult, Adult Stem, and Progenitor Cells": neuronal (including adult olfactory mucosa), cardiac (including cardiosphere-derived cells), pancreatic progenitors cells, chondrocytes, osteoblasts.
- "Adipose-Derived Stem Cells": cells derived from adipose tissue, also called SVF, or Stromal Vascular Fraction.
- "Cord Blood Cells": includes all types of cells derived from umbilical cord blood.
- "Hematopoietic": mobilised peripheral blood stem cells, including adult endothelial CD 34+ progenitors.
- "Adult Immune" includes cytokine-induced killer cells, T-lymphocytes, NK-cells, and dendritic cell vaccines.
- "Bone-Marrow Derived Stem Cells" is related to the mononuclear part of bone-marrow derived stem cells and separate fractions of it like mesenchymal SC, endothelium, and blood progenitors.

Cell Donor Type

Allogeneic	75
Autologous	119



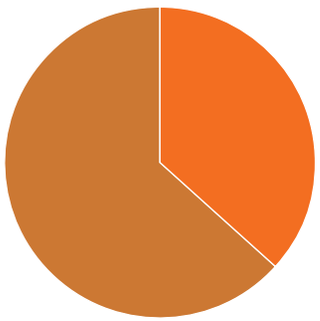
Cell Therapy: Source of Donor Cells

The number of cell types we are mentioning is 194, because 5 trials assessed the use of both autologous and allogeneic cells.

These diagrams represent the distribution of autologous and allogeneic donorship between commercial and academic trials.

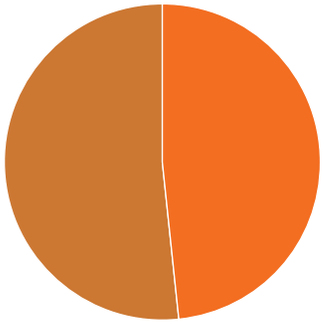
Distribution of Donor Type in Academic Trials

Academic Allogeneic	60
Academic Autologous	103



Distribution of Donor Type in Commercial Trials

Commercial Allogeneic	16
Commercial Autologous	15



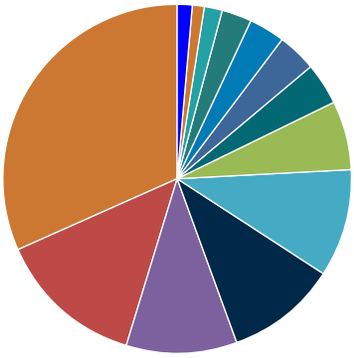
Companies And Products Acting In Cellular Therapy

Name of Company	Product(s)	Indication	Phase	Country
Angioblast Systems	Stro3 – allogeneic bone marrow derived MSC	Acute Myocardial Infarction	Phase 2	USA
Antria	Autologous adipose-derived MSC	Facial fat grafting, cosmetic surgery	Phase 1	USA
Bioheart, Inc	Autologous adipose-derived MSC	Dry Age-related macular degeneration	Phase 1/2	USA
Bone Therapeutics S.A.	PREOB® - autologous osteoblastic cell product	Fractures, osteonecrosis	Phase 2b/3	Netherlands
Brainstorm-Cell Therapeutics	MSC-NTF Cells technology: technology for the propagation and differentiation of autologous Mesenchymal Stem Cells (MSCs) into NeuroTrophic Factor (NTF)-secreting cells	Amyotrophic Lateral Sclerosis	Phase 2	USA
California Stem Cell, Inc.	Autologous Dendritic Cell-Tumor Cell Immunotherapy	Stage IV Melanoma Stage III Melanoma	Phase 3	USA
Celgene Corporation	PDA002 – allogeneic human placenta-derived cells	Peripheral Arterial Disease Diabetic Foot	Phase 1	USA
Cell Surgical Network Inc	Autologous adipose-derived MSC	Neurodegenerative Diseases Osteoarthritis Erectile Dysfunction Autoimmune Diseases Cardiomyopathies Emphysema	Phase 1	USA
Cellular Biomedicine Group Ltd.	Autologous adipose-derived MSC	Osteoarthritis	Phase 1/2	China
Citospin	MSV® - Allogeneic bone marrow derived MSC	Degenerative disc disease	Phase 2	Spain
Dong-A Pharmaceutical Co., Ltd.	Collaborator for Medipost Co Ltd CARTISTEM® trial.			Republic of Korea
FCB-PHARMICELL CO.	Autologous bone marrow derived MSC	Alcoholic liver cirrhosis	Phase 2	USA
Fondren Orthopedic Group L.L.P.	Autologous adipose-derived MSC	Microfracture surgery, cartilage regeneration	Phase 1/2	USA
InGeneron, Inc.	InGeneron's Transpose RT™ System is a system for the preparation of autologous regenerative cells from human lipoaspirate. Collaborator for Fondren Orthopedic Group L.L.P's trial.			USA
Gamida Cell ltd	NiCord® - allogeneic umbilical cord blood-derived Ex Vivo Expanded Stem and Progenitor Cells	Hematological Malignancies Acute Lymphoblastic Leukemia (ALL) Acute Myeloid Leukemia (AML) Myelodysplastic Syndrome (MDS)	Phase 1/2	Israel
Medipost Co Ltd	PNEUMOSTEM® CARTISTEM® Both are allogeneic umbilical cord blood derived MSC.	Bronchopulmonary Dysplasia Degenerative Osteoarthritis Defect of Articular Cartilage	Phase 2 (PNEUMOSTEM) Phase 3 (CARTISTEM)	Republic of Korea
Mesoblast, Ltd.	Allogeneic bone marrow derived MSC	Rheumatoid arthritis Diabetic nephropathy	Phase 1/2	USA
Miltenyl biotech	CliniMACS® Cytokine Capture System The CliniMACS® Cytokine Capture System (IFN-gamma) – Product Line is comprised of the CliniMACS IFN-gamma Catchmatrix Reagent, consisting of CD45 antibodies conjugated to IFN-gamma specific antibodies, and the CliniMACS IFN-gamma Enrichment Reagent.	Adenovirus infection	Phase 1/2	Switzerland
Neuralstem Inc.	Human spinal cord stem cells	Spinal Cord Injury	Phase 1	USA
RNL Bio Company Ltd.	Autologous Adipose Tissue derived MSC	Spinal Cord Injury	Phase1/2	Republic of Korea
Stemedica Cell Technologies, Inc.	Allogeneic Mesenchymal Bone Marrow-derived MSC	Intrinsic Aging of Skin Chronic Effect of Ultraviolet Radiation on Normal Skin (Photo-aging) Dermatologic Disorders, ST Segment Elevation Myocardial Infarction (STEMI)	Phase 1/2 Phase 2 (STEMI)	USA

SYZ Cell Therapies Co	MASCT That Expresses Multiple Antigens Specific Cellular Therapy, Autologous Immune Cytotoxic of T-lymphocytes(CTL) Induced by Dendritic Cell(DC) Loaded With Multiple Antigens	Treatment of hepatocellular carcinoma	Phase 2	China
Tianhe Stem Cell Biotechnologies, Inc	Stem Cell Educator therapy: cord-blood stem cells that can control autoimmune responses by altering Tregs and human islet b cell-specific T cell clones	Diabetes mellitus type 1	Phase 1/2	China
Translational Biosciences	Autologous Adipose Tissue derived MSC	Rheumatoid Arthritis	Phase 1/2	Panama

*Repeated companies are not included.

Indications



Cell Therapy: Indications

Reproductive System Diseases	3
Aesthetic Medicine	2
Aging	3
Ophthalmology	5
Diabetes	6
Respiratory	7
Unhealing Wounds	7
Other	12
Cardiovascular	18
Immune Disorders	19
Musculoskeletal Disorders	19
Neurological Diseases	25
Cancer	58

- "Neurological Disorders": spinal cord and brain injury, Parkinson's disease, stroke, cerebellar ataxia, chronic paraplegia, mental retardation, amyotrophic lateral sclerosis, multiple sclerosis, muscular atrophy type IV, Huntington's Chorea.

- "Cardiovascular Disorders" are related to acute myocardial infarction, other ischemic disorders excluding ischemic limbs disease (because the main problem for these patients is unhealing ulcers, and this is a cause for intervention), vascular insufficiency in terms of angiogenesis evaluation, defective development like hypoplasia of left ventricle, arterial hypertension, atherosclerotic stenosis of arteries, dilated cardiomyopathy.

- "Musculosceletal Disorders": fractures, injuries, chondropathies, arthropathies, osteonecrosis, Duchenne's muscular dystrophy,

- "Diabetes": conditions related to type 1 and type 2 diabetes.

- "Immune Disorders": graft-versus-host disease, autoimmune diseases like rheumatoid arthritis, scleroderma, congenital immune deficiency, GATA2-deficiency, Crohn's disease, and other inflammatory bowel disease.

- "Ophthalmology": glaucoma, age-related macular degeneration, retinitis pigmentosa, optic nerve disease.

- "Respiratory Disorders": bronchopleural fistula, idiopathic pulmonary fibrosis, acute respiratory-distress syndrome, bronchopulmonary dysplasia, pulmonary emphysema.

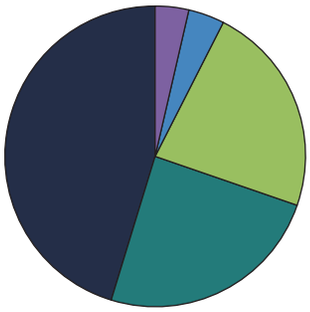
- "Reproductive System Diseases": Ashermann syndrome (adhesions inside the womb after childbirth) and premature ovarian failure, azoospermia.

- "Aging": cutaneous photoaging, skin aging.

- "Other" included fecal incontinence, liver cirrhosis, chronic renal failure, adenovirus infection, amyloidosis, sickle cell disease, adenovirus infection.

- "Aestetic Medicine": cosmetic surgery, skin aging.

Phases Of Clinical Trials



Cell Therapy: Phases of Clinical Trials

Phase 3	7
Phase 4	7
Phase 2	42
Phase 1	45
Phase 1/2	83

Phase 1/2 trials combine a Phase 1 and a Phase 2 trial of the same treatment into a single protocol. First, the Phase 1 part of the trial determines the Maximum Tolerable Dose (MTD), and further evaluation of safety and/or efficacy can be done in the Phase 2 portion of the study.

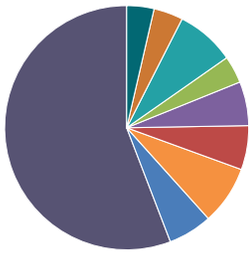
Tissue Engineering Clinical Trials

We tracked Tissue Engineering trials by following the search terms "tissue engineering, scaffold, matrix, transplant, and implant."

We have excluded from our search results the data related to synthetic implants such as metal and silicone implants, allogeneic organ transplants like kidney or liver transplantation, xenogenic valves for cardiological needs, and drug-eluting vascular stents.

We took data about trial ID, country, phase, type of replaced tissue, presence of cellular and acellular(scaffold) components in grafts, indication, donor type, type of sponsorship, name of company-sponsor, and product from each trial's description. The total number of trials tracked is 52.

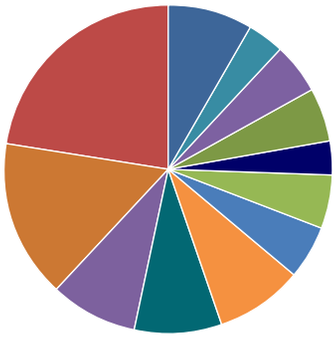
Database Representation



Tissue Engineering: Databases

Dutch	NTR	2
International	ISRCTN	2
Australia	ACTRN	4
Dutch	DRK	2
India	CTRI	3
Iran	IRCT	3
Japan	JPRN	4
China	ChiCTR	3
USA	NCT	29

Tissue Engineering: Demography



Tissue Engineering: Countries

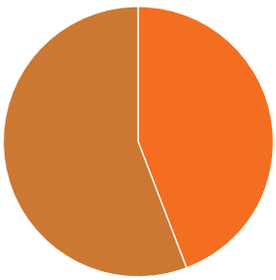
Australia	5
Brazil	2
India	3
Netherlands	3
South Korea	2
Germany	3
Italy	3
France	5
Japan	5
Iran	5
Others	9
USA	13

The category "Other" includes Belgium, Switzerland, Azerbaijan, Hong Kong, Singapore, Denmark, Israel, and Spain with 1 tissue engineering trial registered in 2013. The number of countries tracked is 58, because some trials are international.

Tissue Engineering: Sponsorship

Tissue Engineering: Sponsors

Commercial	23
Academic	29

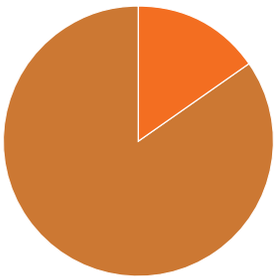


All trials were divided into 2 categories - "Academic" or "Commercial." "Academic" trials are supported by non-profit organizations, and "Commercial" trials are sponsored by profit-seeking agencies..

Tissue Engineering: Materials

Tissue Engineering: Materials

Cellular	8
Acellular (only scaffold)	44



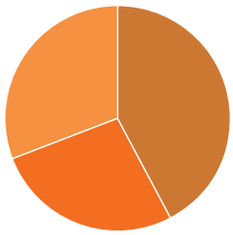
"Acellular" includes tissue enjineering trials not involving any cells. "Cellular" clinical trials could investigate the use of cells, cells and scafford, or tissues in tissue engineering. Acellular materials are more abundant between tissue engineering products. Investigation of acellular matrixes for needs of dental, reconstructive, and traumatic surgery is frequent between non-commercial and industrial trials. Interestingly, all commercial trials are related to investigation of allogeneic or xenegeneic acellular matrixes and scaffolds in different approaches.

Trials which use cellular components include:

1. transplantation of pancreatic islets for treatment of diabetes mellitus, type 1 and benign pancreatic neoplasms (after partial pancreatectomy);
2. autologous transplantation of cultured fibroblast on amniotic membrane in patients with epidermolysis bullosa;
3. transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets in preventing formation of strictures after endoscopic submucosal dissection for esophageal cancer;
4. transplantation of tissue-engineered autologous skin sheets in wound healing or burn treatment:
5. treatment of nonunion of long bone fracture using mononuclear stem cells from the iliac wing within a 3-D tissue engineered scaffold;

Tissue Engineering: Tissue Type

Connective	22
Epithelial	14
Other	16

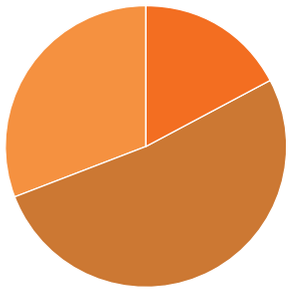


The category "connective tissue" includes material for bone, cartilage (intervertebral disks), tendon, and loose connective tissue reconstruction. Products for recovery and remodeling of mucosal, conjunctival, and also endocrine epithelium are observed under the term "epithelial." "Other" is a group of materials like vascular stents and hemostatic materials.

Tissue Engineering: Source Of Donor Material

Tissue engineering: source of donor material

Autologous	9
Xenogenic	27
Allogeneic	16

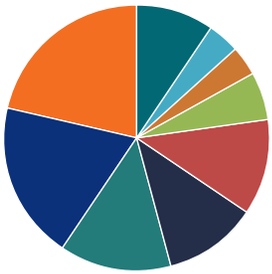


Companies And Products Acting In Tissue Engineering

Name of company	Product(s)	Indication	Phase	Country
Abbott Vascular	Absorb™ BVS, Bioresorbable Vascular drug-eluting Scaffold	Coronary Artery Disease, myocardial ischaemia	Phase 1/2 Phase 1	Japan, Netherlands
Allergan Medical	SERI® xenogenic surgical scaffold	breast cancer, reconstruction surgery	Phase 4 Phase 1	Israel USA
Biosensors International Ltd	BioMatrix™ xenogenic biodegradable polymer arterial stents	Coronary artery disease	Phase 1/2	India
Celxcel Pty Ltd	CardioCel® allogeneic acellular tissue matrix	congenital heart disease	Phase 1/2	Australia
Elixir Medical Corporation	DESolve® Novolimus eluting bioresorbable coronary scaffold	Coronary artery disease	Phase 4	USA
Geistlich Pharma AG	Geistlich Bio-Oss® - allogeneic bone mineral matrix	Dental Surgery	Phase 4	Switzerland
Kensey Nash Corporation	Meso BioMatrix Device, allogeneic acellular matrix	breast cancer, reconstruction surgery	Phase 1/2	USA
Keystone dental	DynaMatrix® allogeneic non-biodegradable acellular matrix	Dental Surgery	Phase 1/2	USA
LifeCell	Device: Strattice™ allogeneic acellular dermal tissue Matrix	breast cancer, reconstruction surgery	Phase 1/2	Italy
Luitpold Pharmaceuticals	As collaborator	Dental Surgery	Phase 4	USA
Osteohealth®	Mucograft® Allogeneic Acellular Collagen Matrix EQUIMATRIX® - allogeneic bone mineral matrix	Dental Surgery	Phase 2 Phase 4	USA
Otr3	CACICOL20®, single-dose eye drops for corneal healing prescribed for chronic corneal lesions.	Corneal ulcers and dystrophy	Phase 2	France
Perio Health Professionals™	Xenogenic Collagen Matrix	Dental Surgery	Phase 2	USA
PolyNovoBiomaterials Pty Ltd	NovoSorbTM Biodegradable Temporising Matrix (BTM)	Burn treatment	Phase 1	Australia
TEI Biosciences Inc	SurgiMend, allogeneic acellular dermal biodegradable matrix	breast cancer, reconstruction surgery	Phase 1/2	USA, UK
Tornier, Inc	BioFiber™ Absorbable Biologic Scaffold for Soft Tissue Repair and Reinforcement	Cuff, Rotator	Phase 4	France, USA
Zimmer Dental Inc	Puros - allogeneic bone mineral matrix	Dental Surgery	Phase 4	USA

Indications

Tissue engineering: Indications



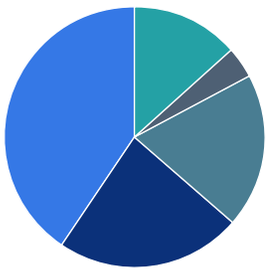
Wound Healing	5
Diabetes	2
Hemostasis	2
Other	3
Musculoskeletal Disorders	6
Cosmetic Surgery	6
Ophthalmology	7
Cardiovascular Diseases	10
Stomatology	11

- "Wound healing": epidermolisys bullosa.
- "Diabetes": diabetes mellitus 1 type.
- "Hemostasis": treatment of haemorrage during operations, coagulopathies.
- "Musculoskeletal disorders": cuff rotator, degenerative disk disease, osteonecrosis, non-union of fracture.
- "Cosmetic surgery": breast reconstruction after mastectomy.
- "Ophthalmology": pterigium, open-angled glaucoma, cataract, corneal traums.
- "Cardiovascular Diseases": ischemic heart disease, IM treatment, congenital heart disease.
- "Stomatology": dental surgery is the most frequent indication for tissue-engineered products. Implants and scaffolds are used for soft tissue replacement, sinus augmentation, treatment of keratinized mucosa, chronic periodontitis and edentulism, and for gingiva transplantation.
- "Other" indications include giant pigmential nevi, ovarian cysts, esophageal cancer.

Phases Of Clinical Trial

Tissue engineering: Phases of Clinical Trials

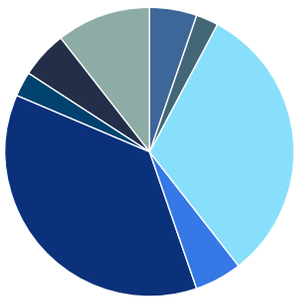
Phase 1	7
Phase 3	2
Phase 4	10
Phase 1/2	12
Phase 2	21



Platelet-Rich Plasma Clinical Trials

We tracked trials by the search term "platelet rich plasma" registered at the WHO clinical trials database since 01/01/2013 to 31/12/2013. The number of trials tracked is 38. According to the WHO database, all trials registered during this period are academic, except one trial, sponsored by Anthrex, Inc, although some regenerative medicine companies develop technologies of platelet-rich plasma derivation or products based on it.

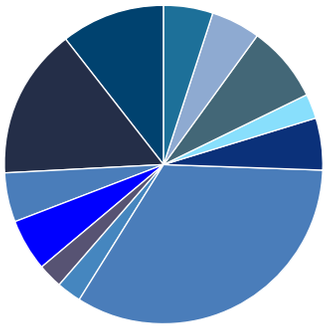
Platelet-Rich Plasma: Databases



Platelet-Rich Plasma: Databases

Australian	ACTRN	2
Indian	CTRI	1
Iranian	IRCT	12
International	ISRCTN	2
USA	NCT	14
Dutch	NTR	1
EU	EUCTR	2
Japan	JPRN	4

Platelet-Rich Plasma: Countries

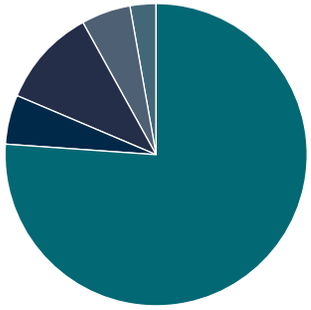


Platelet-Rich Plasma: Countries

Australia	1
Bahrain	2
Canada	3
Finland	1
India	2
Iran	13
Netherlands	1
Qatar	1
Spain	2
UK	2
USA	6
Japan	4

The number of countries tracked is 39, because some trials are multi-centered and involve more than one country.

Platelet-Rich Plasma: Indications



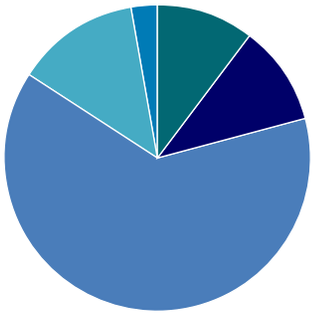
Platelet-Rich Plasma: Indications

Musculoskeletal Disorders	29
Dental Surgery	2
Alopecia	4
Wound Healing	2
Aging	1

Platelet-Rich Plasma: Clinical Trial Phases

Platelet-Rich Plasma: Clinical Trial Phases

Phase 1	4
Phase 1/2	4
Phase 2	24
Phase 3	5
Phase 4	1



The most frequent indication for platelet-rich plasma uses are musculoskeletal disorders, like inflammatory or dystrophic joint and muscle lesions.

Three clinical trials are dedicated to the treatment of male alopecia.

Two clinical trials investigate the use of platelet-rich plasma in dental surgery.

One clinical trial investigates the role of platelet-rich plasma in skin aging.

Platelet-rich plasma is used for pain management, improving ligament and muscle regeneration, treatment of unhealing wounds, and ortopaedic injuries. Autologic platelets are injected in high concentration into an injured tendon, ligament, or muscle. The platelets contain growth factors which promote healing. Some clinical trials investigated this problem had successfully finished in 2013.

A Phase 1 clinical trial held in Iran investigating the effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis showed that intra-articular knee injection of platelet-rich plasma can decrease joint pain and stiffness, and improve patients' quality of life (URL Ref. 21). A double-blind, prospective, multicenter, controlled trial of 230 patients in the USA demonstrated that platelet-rich plasma significantly improves clinical outcomes in patients with chronic tennis elbow compared to the active control group (URL Ref. 22).

According to Dori and colleagues (URL Ref. 23), PRP has not been shown to be more effective for fracture treatment than enamel matrix derivative and natural bone mineral.

These results indicate that platelet-rich plasma is significantly effective compared to placebo, but its advantages over other medicines are to be properly investigated.

However, some regenerative medicine companies have developed techniques of PRP preparation or medicines based on it and actively work with them.

At the end of 2012, Cytomedix, Inc received FDA clearance for the use of its Angel Concentrated Platelet-Rich Plasma System for processing a small sample of blood or a mixture of blood and bone marrow aspirate. Another FDA-approved product of this company, the AutoloGel™ System, is used in clinics for the treatment of chronic, non-healing wounds.

Name of Company	Product(s)	Indication	Phase	Country
Anthrex, Inc, sponsor of trial	The Arthrex ACP® Double Syringe System	Patellar tendinopathy	Phase 2	Trial - Canada Company - USA

Gene Therapy Clinical Trials

We tracked Gene Therapy trials by following the search terms "gene therapy, genetic therapy, lentivirus, lentiviral, retrovirus, retroviral, adenovirus, adenoviral, adeno-associated, vaccinia, antisense, miRNA, siRNA, shRNA, cDNA, electroporation, lypofection, and herpes simplex virus" and manually excluded trials not related to gene therapy .

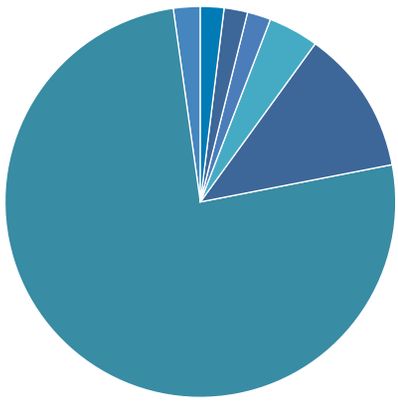
We have excluded trials related to use of viral vaccines for homologous use, like treatment of adenovirus respiratory infections with adenoviral vaccine, and also to peptide vaccines. We have excluded research related to use of nucleic acids for diagnostic purposes like tumor phenotyping in cancer.

We took data about trial ID, country, phase, indication, vector, donor type, material delivered into macroorganism, type of sponsorship, name of company-sponsor, and product from each trial's description. The number of trials tracked is 50.

Database Representation

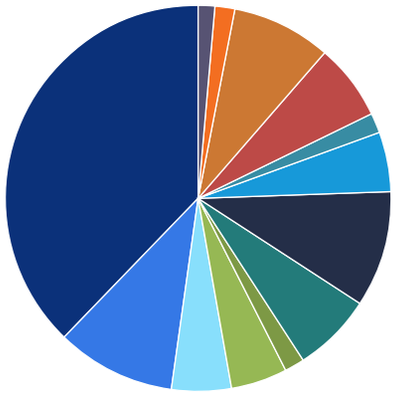
Gene Therapy: Databases

Dutch	NTR	1
Australian	ACNTRN	1
Chinese	ChiCTR	1
International	ISRCTN	2
Japanese	JPRN	6
US	NCT	38
African	PACTR	1



Demographics

GeneTherapy : Demography



Australia	1
Canada	1
China	5
France	4
Germany	1
Italy	3
Japan	6
Netherlands	4
South Africa	1
Spain	3
Sweden	3
UK	6
USA	23

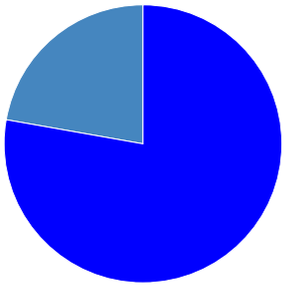
Number of countries mentioned is 61, because some trials are multi-centered.

Sponsorship

All trials were divided into 2 categories - "Academic" or "Commercial." "Academic" trials are supported by non-profit organizations, and "Commercial" trials are sponsored by profit-seeking agencies.

GeneTherapy: Type of Sponsorship

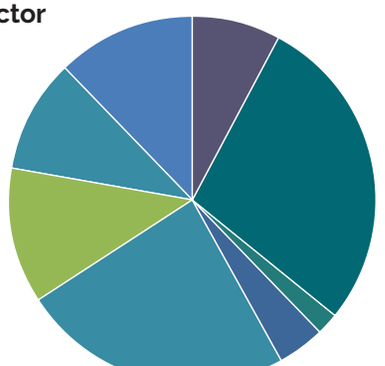
Academic	39
Commercial	11



Genetic Vector's Type

GeneTherapy : Type of vector

Adeno-Associated Virus	4
Adenovirus	14
DNA	1
Herpes Simplex Virus Type 1	2
Lentivirus	12
RNA	6
Retrovirus	5
Vaccinia Virus	6



"Vector" is a vehicle used to deliver artificial nucleic acid into a recipient cell. We were able to identify several vector types applied for genetic material delivery in clinical trials registered in the WHO database.

"Adenovirus" refers to adenoviral vectors. Adenoviral vectors are double-strand DNA-based vectors which are used for genetic delivery into epithelial cells. Genetic material is transcribed together with a host genome, but not incorporated into it. According to WHO database data, these vectors are used for cancer treatment as oncolytic adenoviruses, the means for immune cell modification.

"Adeno-Associated Virus" is a type of viral vector that has some typical features. These double-strand DNA-based vectors cause very mild immune response. Some of them integrate into a known locus of a genome, and the modified AAV lost the ability to integrate into a host's genome at all. Tracked trials referred to AAV coding antibodies at HIV/AIDS, ARSA gene for metachromatic leucodystrophy, genetic modifications of immune cells, and DNA coding small hairpin RNA for Hepatitis C treatment.

One trial assessed use of direct DNA delivery into host cells in vivo by electroporation.

Two trials used herpes simplex virus type 1 vectors with oncolytic activity.

Twelve clinical trials were based on lentiviral vectors. These integrating RNA-vectors can affect both dividing and non-dividing cells. Usually, such integrating vectors are used for in vitro modification of immune cells, but one trial investigated in vivo gene delivery in treatment of retinitis pigmentosa.

Direct delivery of microRNA, small interfering RNA, or antisense RNA for inducing RNA-interference-mediated destruction of pathological RNA was used in 6 trials.

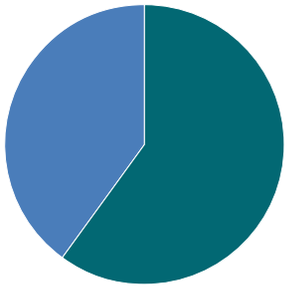
5 trials referred to use of retroviral vectors. Application of these integrating and replicating RNA vectors is limited because of possible insertional mutagenesis. However, we tracked trials assessing use of these vectors for in vitro modification of host cells for treatment of cancer, HIV/AIDS, and X-linked Chronic Granulomatous Disease.

6 trials used Vaccinia Virusesor Modified Vaccinia Ankara Virus viruses for safe delivery of genetic material for in vivo treatment of HIV/AIDS. One trial was dedicated to application of Modified Vaccinia Ankara virus for oncolytic purposes.

Approach To Modification

GeneTherapy : Approach to modification

In Vivo	30
In Vitro	20



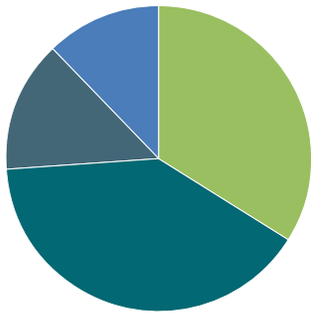
"In vivo" use of a genetic vector means it is delivered into the bloodstream, into solid tumor mass, or into eye tissues.

"In vitro" use of genetic vectors refers to genetic modifications of cells in vitro conditions with subsequent transfer of these cells into a host organism.

Gene Therapy: Type Of Material Delivered Into Cells

GeneTherapy : Material Delivered

Gene	17
Genetically Modified Cells	20
Oncolytic Virus	7
siRNA / miRNA / shRNA / antisense RNA	6



By "genes" here, we tracked trials assessing in vivo delivery of genetic material into a host organism.

We mark out "genetically modified cells" because delivery of necessary genes in vitro into immune or cancer cells is a frequent approach in gene therapy.

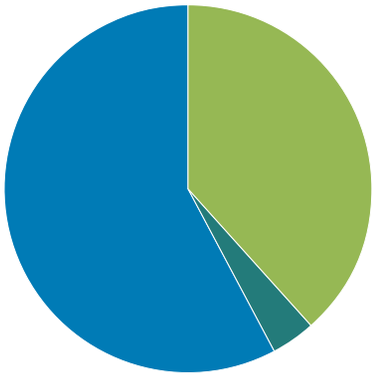
Seven trials used vectors for oncolytic purposes.

Six trials were based on direct or indirect delivery of RNAs acting on RNA interference process in vivo conditions.

Source Of Donorship

GeneTherapy : Source of Donorship

Autologous	20
Allogeneic	2
Non-Cellular	30



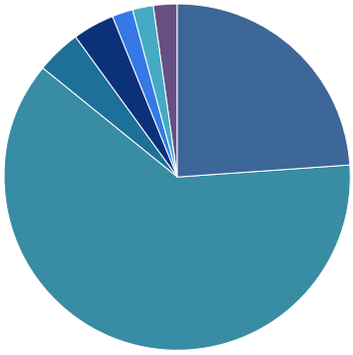
The number of mentioned approaches is 52, because two trials assessed use of both allogeneic and autologous cells.

"Non-cellular" refers to direct use in vivo of viral vectors.

"Autologous" means use of autologous cells for genetic modifications in vitro conditions.

"Allogeneic" is related to two trials comparing use of autologous and allogeneic cells for genetic modification.

Indications



Gene Therapy: Indications

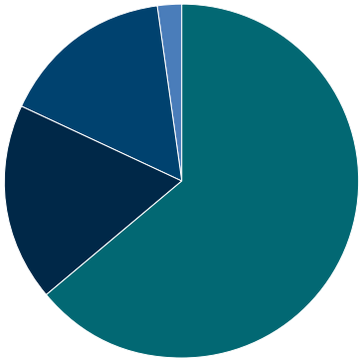
Immune Disorders	12
Cancer	31
Neurological Disorders	2
Hapatic Disorders	2
Cardiovascular	1
Opthamological	1
Diabetes	1

- "Immune Disorders" includes HIV/AIDS, ADA immunodeficiency, and X-linked chronic granulomatous disease.
- "Neurological Disorders" includes metachromatic leukodystrophy and cerebral adrenoleucodystrophy.
- "Hepatic Disorders" refers to liver fibrosis and hepatitis C treatment.
- "Cardiovascular Disorders" assesses use of genetic vectors for ischemic heart disease treatment.
- "Ophtalmological Disorders" includes one trial dedicated to retinitis pigmentosa treatment.
- "Diabetes" refers to one trial related to diabetes mellitus type 2 treatment.

Phases Of Clinical Trials

Gene Therapy: Phases of Clinical Trials

Phase 1	32
Phase 1/2	9
Phase 2	8
Phase 2/3	1



Only one trial registered during 2013 and several clinical trials are currently at phase 2/3.

We searched for all available results of clinical trials finished or published in 2013 and related to stem cell therapy, gene therapy, and tissue engineering in terms of the ARMIF model. We subdivided all these results into groups according to phase of clinical trial and mentioned them in chronological order.

Companies And Products Acting In Gene Therapy

Name of company	Product(s)	Indication	Phase	Country
Bluebird bio	Lenti-D product candidate, based on lentiviral vector, involves the ex vivo insertion of a functional copy of the ABCD1 gene into a patient's own hematopoietic stem cells.	Cerebral adrenoleucodystrophy	Phase 2/3	USA
EnGeneIC Ltd	An EnGeneIC Delivery Vehicle (EDV) is an anucleate bacterially derived minicell. EDVs can be loaded with chemotherapy, in this case either cytotoxic drug or siRNA or miRNA. The EDV is coated with EGFR antibodies to enable it to attach to cancer cells.	Advanced Solid Tumors	Phase 1	Australia
Genelux corporation	GL-ONC1 is a genetically stable oncolytic virus based on modified vaccinia virus (Lister strain).	Cancer, malignant tumor effusion	Phase 1	USA
Genethon	Lentiviral vector containing XCGD gene (restores NADPH oxidase function)	X-linked chronic granulomatous disease	Phase 1/2	France
Ichor Medical Systems, Inc	TriGrid™ Delivery System for DNA drugs	HIV/AIDS	Phase 1	USA
Isis Pharmaceuticals	ISIS-GCCRRx, an RNA antisense glucocorticoid receptor antagonist	Diabetes mellitus, type 2	Phase 2	Canada
Mirna Therapeutics, Inc	MRX34, MicroRNA miR-RX34 Liposome Injectable Suspension	Primary liver cancer, liver metastases.	Phase 1	USA
Motomaro-gene, Inc	Ad5-SGE-REIC/Dkk3, adenovirus vector that is a transport mechanism to infuse the REIC protein into the cell providing a temporary transfusion of protein that induces apoptosis in target cancer cells.	Prostate cancer	Phase 1/2	USA
Nitto Denco Corporation	ND-L02-s020, a Vitamin A-Coupled Lipid Nanoparticle Containing siRNA Against HSP47	Liver fibrosis	Phase 1	USA
Profectus Biosciences, Inc	GeneVax® DNA vaccines	HIV/AIDS	Phase 1	USA
Tacere Therapeutics, Inc	TT-034 is a DNA construct that codes shRNA which which targets three highly-conserved regions of the Hepatitis C Virus (HCV). It is introduced in living cells via AAV vector.	Hepatitis C	Phase 1/2	USA
Ziopharm	AD-RTS-IL12, adenovirus Vector Engineered to Express hIL-12 (INXN-2001)	Glioblastoma	Phase 1	USA

Results of Clinical Trials

Results of Phase I/IIa trials

On January 16, 2013 – **Stratatech Corp.** announced results from its proof-of-concept clinical trial of **StrataGraft®**, a universal human skin substitute based on the **NIKS®** human keratinocyte progenitor cell line and being developed for the treatment of severe burns. 19 of 20 patients avoided the need for autograft surgery and regrafting at their StrataGraft-treated sites because of complete wound closure within 3 months. In addition, no StrataGraft tissue residual DNA was observed after 3 months.

(URL Ref. 24)

On February 14, 2013, **Gamida Cell** reported the successful results of the Phase I/II study of its product **NiCord**, umbilical cord-derived stem cells expanded using the company's proprietary **NAM** technology. Eleven patients, ages 21-61, with high-risk hematological malignancies received NiCord and an un-manipulated graft of umbilical cord blood. Eight patients engrafted with NiCord. The median time to neutrophil engraftment was 10.5 (7-18) days for those engrafting with NiCord. Two patients engrafted with the un-manipulated UCB and one patient experienced primary graft failure. There were no cases of Grade III/IV acute GvHD. No safety concerns surrounding the use of NiCord were raised. With a median follow-up of 8 months, the progression-free and overall survival are both 90%.

(URL Ref. 25)

On March 13, 2013, **Isis Pharmaceuticals, Inc**. announced results of Phase 1 trial of **ISIS-CRP$_{Rx}$** that selectively reduced severe elevations in C-reactive protein (CRP) in healthy humans without changes in other immune modulators. ISIS-CRP$_{Rx}$ is currently being evaluated in a Phase 2 study in patients with rheumatoid arthritis. ISIS-CRP$_{Rx}$ is an antisense drug that is designed to inhibit the production of C-reactive protein.

(URL Ref. 26)

On March 21, 2013, **BrainStorm Cell Therapeutics**, a developer of adult stem cell technologies for neurodegenerative diseases reported some of the final results from a clinical study evaluating the company's **NurOwn™** technology in 12 ALS patients. All patients demonstrated significantly slower decline in respiratory function and clinical condition. The trial proved the safety of cell therapy, and the company is currently conducting a Phase IIa dose-escalating trial. NurOwn™ technology is treatment based on autologous bone marrow-derived stem cells differentiated into neuron-supporting cells.

(URL Ref. 27)

In May 2013, **ReNeuron** published interim results from the first nine patients treated in the Phase I **PISCES** study. The results were presented by the clinical team from Glasgow's Southern General Hospital at the 22nd European Stroke Conference in London, proving the safety of ReNeuron's **ReN001** stem cell therapy in treatment of ischaemic stroke.

(URL Ref. 28)

Cancer vaccine company **DCPrime** on May 28, 2013 announced the successful completion of its Phase I/IIa study in acute myeloid leukemia (AML). The study establishes the safety and feasibility of vaccination with DCPrime's lead product **DCP-001**, and shows clear evidence of a positive vaccination-induced immune response. Several patients from 12 studies demonstrated prolonged survival compared to historic expectations.

(URL Ref. 29)

In June 2013, the Journal of Translational Medicine published an article demonstrating results of **Stempeutics Research Company's** clinical trial. A double blind. randomized placebo-controlled phase I/II study indicated the safety and efficacy of allogeneic bone marrow-derived mesenchymal stem cells in critical limb ischemia.

(URL Ref. 30)

In June 2013, the journal Transplantation published an article dedicated to a pilot study by **Citospin**. The pilot trial was aimed at evaluating the feasibility and safety of osteoarthritis treatment with mesenchymal stromal cells in 12 patients. The trial confirmed the safety of intervention and demonstrated significant improvement in patients' condition, examination, and testing results.

(URL Ref. 31)

On July 9, 2013, an article reporting the results of a Phase I/II clinical trial, organized by **Tianhe Stem Cell Biotechnologies**, was published in the journal BMC Medicine. Clinical findings indicate that type 2 diabetes patients achieved improved metabolic control and reduced inflammation markers after receiving **Stem Cell Educator** therapy. Stem Cell Educator therapy supposes circulation of patients' blood in a closed-loop system that separates mononuclear cells and promotes their contact with adherent allogeneic cord blood cells. The study also demonstrated improvement of insulin resistance and beta-cell function after Stem Cell Educator therapy.

(URL Ref. 32)

Stemedica Cell Technologies, Inc. announced on July 10, 2013 the completion of enrollment and treatment of patients suffering from ischemic stroke in a Phase I study with Stemedica's lead product **Stemedyne-MSC.** The trial involved 15 patients and demonstrated the safety of the company's product, allowing trial to proceed to approval for Phase II.

(URL Ref. 33)

On September 11, 2013, **Kiadis Pharma** published positive results of a completed five-year follow-up of its **Phase I/II Clinical Study with Blood Cancer Product ATIR™** that proved the safety, effectiveness, and high 5-years survival rate of graft recipients. **ATIR™** is a cell-based medicinal product enabling stem cell transplantations using partially mismatched (haploidentical) family members as donors for patients suffering from blood malignancies without causing acute GvHD.

(URL Ref. 34)

On September 19, 2013, **Isis Pharmaceuticals, Inc.** reported follow-up preliminary data from a single-dose, open-label Phase 1 study of **ISIS-SMN$_{Rx}$** in children with spinal muscular atrophy (SMA). Results showed that most SMA children receiving the two highest doses of the drug (6 mg and 9 mg) continued to show improvements in muscle function tests up to 14 months after a single injection. Positive results on Phase 1 trial were published in March of 2013. **ISIS-SMN$_{Rx}$** is an antisense drug designed to alter the splicing of the SMN2 gene and to increase production of fully functional SMN protein. SMN2 is a gene closely related to SMN1, in which a defect leads to a decrease in the survival motor neuron (SMN) protein and death of spinal motoneurons.

(URL Ref. 35)

(URL Ref. 36)

On September 20, 2013, **Cytori Therapeutics** announced positive early data of a safety classification from a study evaluating Cytori's cell therapy as a potential treatment for scleroderma. 12 patients received Cytori's cell therapy (autologous adipose-derived stem cells) in the form of finger injections. The trial has safety approval for manipulation and has demonstrated significant improvement in hand function.

(URL Ref. 37)

On September 26, 2013, **Bioheart, Inc.,** a biotechnology company, announced preliminary results of a Phase I trial investigating the safety and efficacy of **AdipoCell™**, adipose-derived stem cells, in patients with congestive heart failure. The trial evaluated safety and functional cardiovascular system tests at time points of 0, 3, 6, and 12 months post-stem-cell injection. Significant functional improvement of cardiovascular system was observed in patients at 3 months after injection.

(URL Ref. 38)

On September 26, 2013, **Celladon Corporation** announced the full, three-year long-term follow-up results from Phase 2a of the **CUPID 1** trial. Patients treated with the company's product, **MYDICAR** (adenoassociated viral vector coding endoplasmatic reticulum enzyme SERCA1), demonstrated stable lower levels of cardiovascular and terminal complications of advanced heart failure. Now, the company moves forward to Phase 2b trial. Results are anticipated in the first half of 2015.

(URL Ref. 39)

On October 21, 2013, **StemCells, Inc.** announced results of a long-term follow-up study in Batten Disease (neuronal ceroid lipofuscinosis). Results of the four-year observation of NCL patients had been involved in a Phase I study. The data provides long-term evidence of safety, up to five years post transplantation, for the surgical transplantation of the **HuCNS-SC** cells into multiple sites in the brain, and at doses of up to one billion cells.

(URL Ref. 40)

On October 21, 2013, **Tissue Regenix Group plc** announced full trial results into the effectiveness of **DermaPure™** in healing treatment-resistant chronic wounds. The results show that patients who had chronic wounds for an average of 4½ years and who were treated with a single application of **Tissue Regenix's dCELL® Dermis**, saw an average 87% reduction in the size of all wounds, while 60% of patients were completely healed, with virtually no recurrences. DermaPure is an acellular dermis matrix.

(URL Ref. 41)

Living Cell Technologies Limited on November 1, 2013 announced the findings of DIA-09-a Phase I/IIa clinical trial of **DIABECELL®**, therapeutic porcine cell implants in patients with type 1 diabetes. The non-randomised, open label study was conducted at the Hospital Eva Perón, Buenos Aires, Argentina. Significant positive clinical and laboratory test results demonstrated the effectiveness and safety of the company's product.

(URL Ref. 42)

On November 1, 2013, **Cellular Biomedicine Group** announced completion of patient treatment for a Phase I/IIa clinical trial for treatment of knee osteoarthritis with **ReJoin™**, a human adipose-derived mesenchymal precursor cell. Patients had a clinically meaningful reduction in pain and an increase in mobility, with a significant improvement ($P<0.05$) from the baseline in some clinical scores, and no serious adverse events were reported for the duration of the trial.

(URL Ref. 43)

On December 2, 2013, **Biom'Up**, a manufacturer of absorbable medical implants, announced the results of a clinical study in pediatric cardiac surgery. The Phase I study in 36 patients aimed to evaluate the use of **COVATM+**, a collagen membrane preventing the formation of postoperative adherences. The trial proved the safety of the company's product and simplified surgical interventions.

(URL Ref. 44)

On December 7, 2013, **ZIOPHARM Oncology, Inc.** announced positive interim results from its ongoing Phase 1/2 study of **Ad-RTS-IL-12**, a novel DNA-based therapeutic candidate that is being evaluated with the oral activator, **Veledimex**, in patients with advanced melanoma. In this study, 21 patients with unresectable, recurrent stage III/IV melanoma have been treated with intratumoral injections of Ad-RTS-IL-12 and the oral activator Veledimex. The oral activator controls IL-12 mRNA with an on-off mechanism, supposing return of IL-12 mRNA expression to baseline after stopping of Veledimex administration. Observable adverse effects were pyrexia, hypotension, mental status changes, and cytokine release syndrome. In June of 2013, the company published positive results of a phase 1 trial that accessed use of Ad-RTS-IL-12 trial in 7 patients with grade III/IV melanoma.

(URL Ref. 45)

(URL Ref. 46)

On December 9, 2013, biotechnology company

MOLOGEN AG finished the treatment phase of the clinical trial phase I for **MGN1703**. In terms of safety and tolerability, no significant clinical events were observed to date. MOLOGEN expects that first results will become available in early 2014. MGN1703 is based on **dSLIM® (**"double Stem Loop Immunomodulator"), a DNA-based TLR9 agonist developed by MOLOGEN.

(URL Ref. 47)

On December 18, 2013, **Targazyme, Inc.**, previously named America Stem Cell, Inc., published results of Phase I/IIa trial of Targazyme's lead product, **TZ101**, an enzyme-based treatment for use in cell transplants. It is comprised of a recombinant enzyme, α1,3 fucosyltransferase VI (FTVI), and its substrate, GDP-fucose. TZ101 is designed to add a sugar (fucose) to the surface of stem cells thus improving homing to bone marrow in patients receiving hematopoietic stem cell transplantation. The study evaluated the safety and efficacy of TZ101 together with cord blood transplantation in patients with hematologic malignancies and myelodysplastic syndrome. TZ101 significantly improved engraftment of neutrophils and platelets in bone marrow.

(URL Ref. 48)

On December 18, 2013, **California Stem Cell, Inc**. announced the successful completion of a Phase I clinical trial investigating the safety of a cancer stem cell-based therapy in patients with Stage IV hepatocellular carcinoma. **DC-TC** treatment is based on directing dendrytic cells to recognize cancer stem cells of a patient in vitro conditions with subsequent transplantation of cells into a patient organism.

(URL Ref. 49)

Results of Phase II and IIb trials

On February 2, 2013, **Innocoll, Inc**. announced that the following series of three articles presenting Phase 2 clinical data for its bupivacaine-collagen implant, **XaraColl®**, have recently been published in the Journal of Pain Research (JPR). XaraColl is currently in Phase 3 development for postoperative analgesia, and the three articles present the safety and efficacy data from two Phase 2 studies performed in patients undergoing hernia repair by open laparotomy, another study in patients undergoing open gynecological surgery, and a feasibility study in patients undergoing laparoscopic hernia repair.

On April 22, 2013, **Mesoblast Limited** reported positive interim results in a phase 2 trial of allogeneic Mesenchymal Precursor Cells (MPC,) adult stem cells for intervertebral disc repair. A single low-dose injection of MPCs resulted in significantly greater reduction in low back pain, significantly greater improvement in function, and significantly greater treatment success compared with controls. The complete results of phase 2 trial covering 100 patients were expected to be published in late 2013.

(URL Ref. 50)

(URL Ref. 51)

On April 22, 2013, **Transgene SA** published information about final data of the Phase 2 HCVac trial of **TG4040** for the treatment of genotype 1 chronic hepatitis C (CHC). The control arm was treated with a combination of ribavirin(R) and PegIFNα2a(P), while arm B patients got injections of TG4040 after R+P therapy and arm C patients were pre-treated with TG4040. The positive effect of TG4040 was seen with pre-treatment of TG4040 with a complete early viral response (cEVR) of 64% as compared to 30% in the control arm. TG4040 immunotherapeutic product is a recombinant vector based on the modified vaccinia virus carrying and expressing three of the major non-structural proteins (NS3, NS4 and NS5B) of the hepatitis C virus.

(URL Ref. 52)

On July 22, 2013, **Oxford BioMedica**, a gene-based biopharmaceutical company, announces that analyses of a **TroVax®** plus chemotherapy drug **Docetaxel** (**Taxotere®**) versus Docetaxel alone Phase II study in patients with castration-resistant prostate cancer (CRPC) have been accepted for publication in the peer-reviewed medical journal Cancer Immunology and Immunotherapy, the official journal of the Association for Cancer Immunotherapy. The

study enrolled 25 patients with CRPC. TroVax® was well-tolerated in all the patients, while patients treated with TroVax plus Docetaxel showed a greater median-progression free surval of 9.67 months compared to 5.10 months for patients treated with Docetaxel only. TroVax® (MVA-5T4) is a therapeutic cancer vaccine containing modified vaccinia virus Ankara (MVA) vector, encoding the 5T4 antigen.

(URL Ref. 53)

(URL Ref. 54)

On September 3, 2013, **Transgene SA** announced that **TRAVERSE**, a randomized Phase 2b study of **Pexa-Vec** in second-line, advanced liver cancer patients. failed to meet its primary endpoint of overall survival for Pexa-Vec plus best supportive care (BSC) compared to BSC. The company is waiting for results of ongoing clinical trials of Pexa-Vec for kidney, colorectal, and ovarian cancer. Pexa-Vec is a modified vaccinia virus modified with GM-CSF, which promotes immune response.

(URL Ref. 55)

On November 18, 2013, **Biocardia, Inc.** published positive 12-month results for the randomized **Transendocardial Autologous Cells (MSC or BMC)** in an Ischemic Heart Failure Trial (TAC-HFT). The phase II trial demonstrated the safety of trans-endocardial, autologous, culture-expanded mesenchymal cells (MSCs) and autologous bone marrow mononuclear cells (BMCs) delivered by the company's **Helical Infusion Catheter System™** in the treatment of chronic ischemic cardiomyopathy (ICM). Significant quality of life improvement was observed in patients treated with this procedure. Statistical difference between therapy and placebo was observed in part of the functional tests and ultrasound measurements.

(URL Ref. 56)

On November 18, 2013, **Isis Pharmaceuticals, Inc** reported a fifth positive Phase 2 data set for use of **ISIS-APOCIII$_{Rx}$** as a monotherapy in patients with very high to severely high triglycerides that demonstrated significant reduction in triglyceride and ApoC-III levels. In September 2013, the company announced data from a Phase 2 study of ISIS-APOCIII$_{Rx}$ used as a monotherapy in patients with familial chylomicronemia syndrome. Results showed substantial reductions of triglycerides and Apoc-III levels. In July 2013, the company published results of a Phase 2 trial on ISIS-APOCIII$_{Rx}$ that demonstrated significant reductions of ApoC-III and triglycerides in patients with high triglycerides taking fibrates. In June 2013, the company announced Phase 2 Data on ISIS-APOCIII$_{Rx}$ in patients with high triglycerides and Type 2 Diabetes. Results showed significant reductions in triglycerides and APOC-III and improvements in glucose control and insulin sensitivity. ISIS-APOCIII$_{Rx}$ is an antisense drug that inhibits APOC-III, a protein that regulates triglyceride metabolism in blood.

(URL Ref. 57)

(URL Ref. 58)

(URL Ref. 59)

(URL Ref. 60)

On December 4, 2013, regenerative medicine company **Mesoblast Limited** announced top-line results from the Phase 2 trial of its proprietary **Mesenchymal Precursor Cells (MPCs)** in subjects with type 2 diabetes. The results of the trial support the safety and tolerability of a single intravenous infusion of MPCs in type 2 diabetes.

(URL Ref. 61)

On December 12, 2013, **Integra LifeSciences** announces the **NeuraGen®** Clinical Study published in the Journal of Hand Surgery. A two-year follow-up of a controlled, randomized, blind multi-center study of peripheral nerve repair, comparing NeuraGen® Nerve Guide to the conventional method of direct suture repair in patients who had complete traumatic nerve injuries to the median and/or ulnar nerves. Results from 32 patients completed within a two-year postoperative period demonstrated equivalent effectiveness of the company's product in the repair of major mixed motor and sensory

nerves comparing to the "gold standards" of surgical repair.

(URL Ref. 62)

On December 18, 2013, **Osiris Therapeutics, Inc.** announced data published in the December issue of Ostomy Wound Management. Results show that the use of **Grafix®** on a variety of chronic wounds resulted in an overall closure rate of 76% by 12 weeks, including 68% of Venous Leg Ulcers (VLUs) and 85% of Diabetic Foot Ulcers (DFUs) treated. Grafix is a human cellular matrix containing living stem cells for acute and chronic wounds.

(URL Ref. 63)

Results of Phase II/III and III trials

On February 4, 2013, **Gamida Cell's StemEx®** announced achievement of a primary endpoint in a Phase II/III clinical study which compared the use of StemEx as part of a transplantation regimen to historical controls in the treatment of patients with hematological malignancies such as leukemia and lymphoma. The primary endpoint is defined as the rate of mortality (%) within 100 days after transplantation. The analysis shows 15.8% mortality in the StemEx group and 24.5% in the control group (p=0.034). The study also demonstrated increased number of patients with early hematopoietic recovery and shortened time of neutrophil and platelet engraftment. But the survival advantage was not statistically significant by day 180, with mortality of 32.7% in the StemEx® group and 34.7% in the control group (p=0.39) and the same frequency of severe acute graft versus host disease was observed in both groups.

(URL Ref. 64)

(URL Ref. 65)

Merck Serono, a division of Merck, Darmstadt, Germany, on May 16, 2013 announced detailed results from the randomized Phase III START trial of its investigational MUC1 antigen-specific cancer vaccine **L-BLP25** in patients with unresectable, locally-advanced Stage III non-small cell lung cancer (NSCLC). **Tecemotide** is being developed by Merck under a license agreement with **Oncothyreon**. Overall, a survival rate of 30,8 (after Tecemotide treatment) months comparing with 20,6 months (placebo) was observed, although a primal endpoint of survival extension was not met.

(URL Ref. 66)

(URL Ref. 67)

GlaxoSmithKline (GSK) and **Prosensa** on September 20, 2013 announced that GSK's Phase III clinical study of **Drisapersen**, an antisense oligonucleotide, for the treatment of Duchenne Muscular Dystrophy patients with an amenable mutation, did not meet the primary endpoint of a statistically significant improvement in tests compared to placebo.

(URL Ref. 68)

Market Approvals

Market approval allows high-risk medicine or intervention to be involved in marketing. To receive such an approval, the manufacturing company must demonstrate that its devices provide a reasonable assurance of safety and effectiveness. Special agencies are responsible for regulation and supervision of these processes. We analyzed information related to stem cell, gene therapies, and tissue engineering approval by the following organizations:

Food And Drug Administration (USA)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

National Health Surveillance Agency (Brazil)

Marketed Health Products Directorate (Canada)

European Medicines Agency (EU)

Pharmaceuticals and Medical Devices Agency (Japan)

Federal Commission for the Protection Against Sanitary Risk (Mexico)

Medicines and Healthcare Products Regulatory Agency (UK)

Australian Therapeutic Drug Administration (Australia) ANZTPA

Drug Controller General of India

FDA Approvals

FDA regulates market approval of new drugs in the USA. Cell, gene therapy, and tissue engineering are classified as "biologics" by the FDA.

In 2013, the FDA approved two biological interventions and one tissue-engineered implant:

HPC, Cord Blood;

Allocord;

Juvéderm Voluma XC - P11003

Name	Description	Indication	Manufacturer	Country
HPC, Cord Blood	Cord blood, allogeneic cord blood hematopoietic progenitor cell therapy	hematopoietic and immunologic reconstitution	LifeSouth Community Blood Centers, Inc.	USA
Allocord	Cord blood, allogeneic cord blood hematopoietic progenitor cell therapy	hematopoietic and immunologic reconstitution	SSM Cardinal Glennon Children's Medical Center	USA
Juvéderm Voluma XC - P110033	Sterile, biodegradable, viscoelastic gel implant. It consists of crosslinked hyaluronic acid produced by Streptococcus equi bacteria	Cosmetic surgery, age-related skin changes	Allergan	Juvéderm Voluma XC

(URL Ref. 69)

(URL Ref. 70)

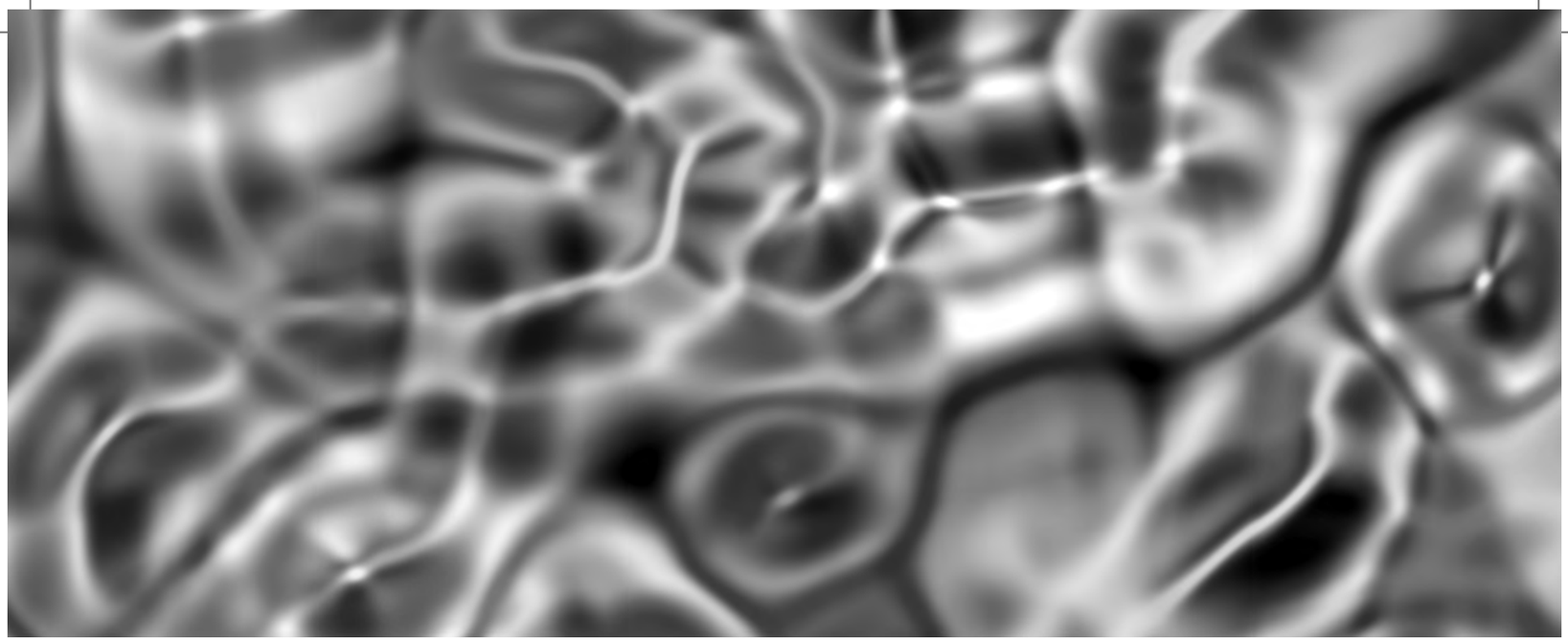
European Medicines Agency Approvals

The European Medicines Agency evaluates new drugs for market approval in the European Union. Gene-therapy medicines, somatic-cell therapy medicines, tissue-engineered medicines, and combined advanced-therapy medicines are classified as "advanced therapies" by this agency.

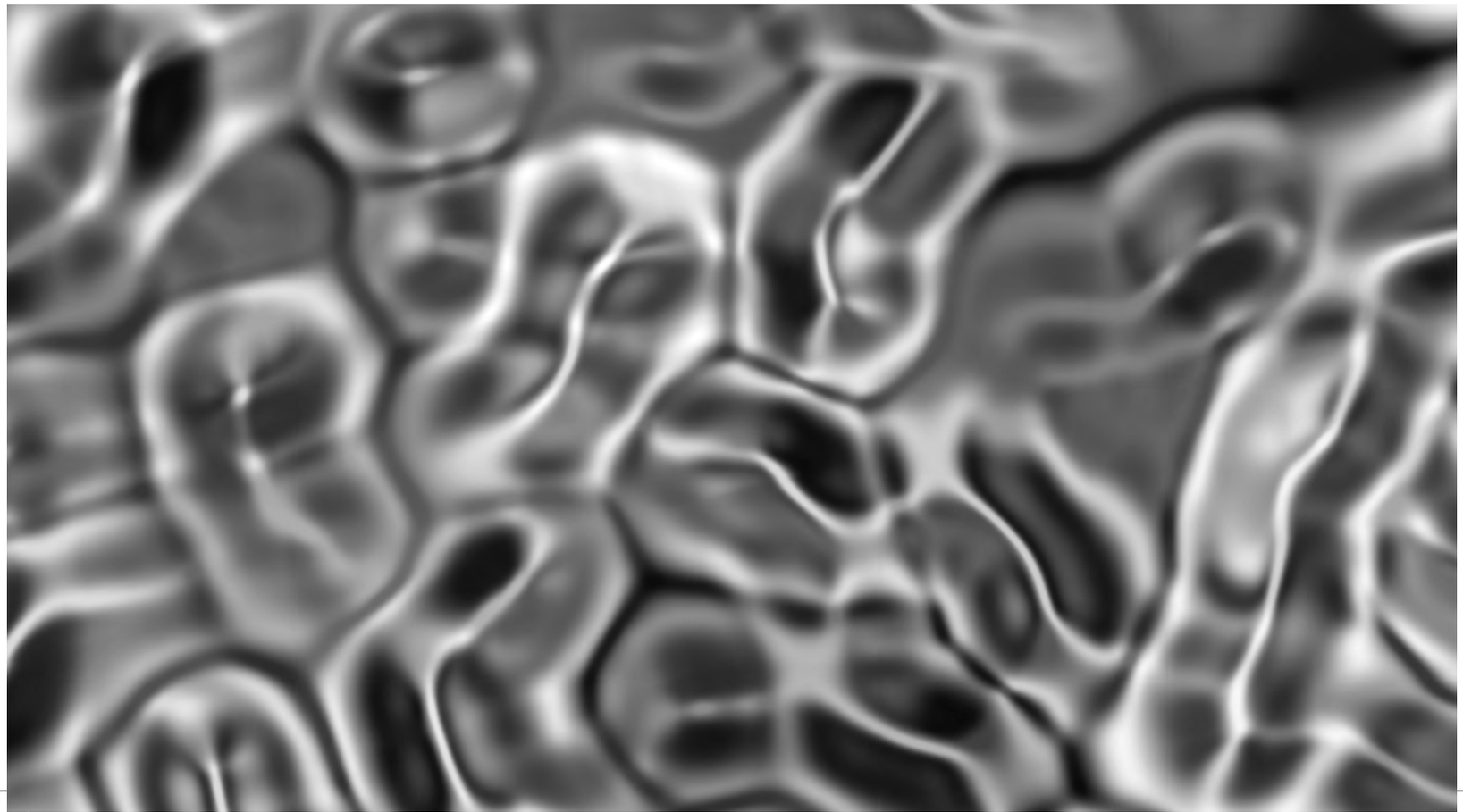
Name	Description	Indication	Manufacturer	Country
Provenge	PROVENGE® (SIPULEUCEL-T) cellular immunotherapy made by autologous immune cells with a recombinant prostate-specific antigen PAP-GM-CSF. It activates T cells to target and attack prostate cancer cells.	Asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer in male adults	Dendrion	USA
MACI ("Matrix-induced autologous chondrocyte implantation)	Tissue-engineered product made of matrix-induced autologous chondrocytes. Matrix is formed of porcine collagen.	Repair of damaged cartilage	Sanofi Biosurgery, Genzyme	USA

(URL Ref. 71)

(URL Ref. 72)



Notable Public Companies



BioTime, Inc.

Ticker symbol: BTX
Year of foundation: 1990
Address: 1301 Harbor Bay Parkway, Suite 100, Alameda, CA 94502, United States
Phone number: +1-510-521-3390
Fax number: +1-510-521-3389
Web-site: http://www.biotimeinc.com/

Profile: BioTime is an internationally operating biotechnology company focused on the emerging field of regenerative medicine. Leading products of BioTime include blood plasma volume expander Hextend, PureStem™ cell lines, HyStem® hydrogels, culture media, and differentiation kits.

Through its specialized subsidiaries, the company develops and markets products based on human embryonic stem cell and induced pluripotent stem cell technology. BioTime's subsidiary Cell Cure Neurosciences Ltd. is involved with the development of products derived from stem cells for the treatment of retinal and neural degenerative diseases. OrthoCyte Corporation is a BioTime subsidiary, developing stem cell based therapeutic solutions to treat orthopedic diseases and injuries. Another subsidiary, OncoCyte Corporation, focuses on the diagnostic and therapeutic applications of stem cell technology in cancer and includes the diagnostic product PanC-Dx™, currently being developed for the detection of cancer in blood samples.

One of the major BioTime subsidiaries, ReCyte Therapeutics, Inc., is developing products based on induced pluripotent stem cell technology to reverse the developmental aging of human cells and to treat cardiovascular and blood cell diseases. ReCyte Therapeutics owns the license to use ACTCellerate technology, developed by Advanced Cell Technology, Inc. (ACT,) to produce and market its human embryonic progenitor cells (hEPCs), called PureStem cell lines. Commercial distribution of PureStem hEPCs is realized through LifeMap Sciences, Inc. (LifeMap Sciences). LifeMap Sciences, Inc. also markets GeneCards, the leading human gene database and MalaCards, the human disease database.

Source: Yahoo Finance

Another subsidiary, ES Cell International Pte. Ltd (ESI), has developed and markets hES cell lines. ESI has agreements with the California Institute of Regenerative Medicine (CIRM) and the University of California to distribute its hES cell lines to research institutes in California.

In September 2012, BioTime established Asterias Biotherapeutics, Inc. (formerly known as BioTime Acquisition Corporation ("BAC"), a subsidiary created to acquire the stem cell assets of Geron Corporation (NASDAQ: GERN). In October and November 2012, Asterias Biotherapeutics,

Inc. approached Geron with two consecutive proposals, and in July 2013, Asterias Biotherapeutics, Inc. entered into a definitive Asset Contribution Agreement with Geron to acquire the intellectual property, including over 400 hES-related patents and patent applications; biological materials and reagents; lab equipment, and other assets related to Geron's human embryonic stem (hES) cell programs, including the Phase I clinical trial of human embryonic stem (hES) cell-derived oligodendrocytes in patients with acute spinal cord injury, and an autologous cellular immunotherapy program and the Phase II trial of the therapy in acute myeloid leukemia (as well as the related INDs for both).

Geron will own 21.4% of Asterias Biotherapeutics, Inc. (BioTime owns the majority, 71.6%, and a private investor, the rest) will receive a 4% royalty. Separately, BioTime is contributing to Asterias Biotherapeutics, Inc. $5mm in cash, 8.9mm of its common stock (valued at $30mm), five-year warrants to buy 8mm shares for $5, rights to use certain clinical-grade hES cell lines, a nonexclusive global sublicense on stem cell differentiation patents, and minority stakes, 10% and 6%, in two of its subsidiaries, OrthoCyte and Cell Cure Neurosciences, respectively. Asterias Biotherapeutics, Inc. also received $5mm from the private investor. The company has a commercial license and option agreement with Wisconsin Alumni Research Foundation (WARF) to use 140 patents and patent pending technology belonging to WARF, as well as certain stem cell materials. The company also has a license agreement with Cornell University for the worldwide development and commercialization of technology developed at Weill Cornell Medical College for the differentiation of hES cells into vascular endothelial cells.

At the moment, the company owns or licenses more than 400 US patents and US patent applications. The major customers of BioTime, Inc. are Hospira, Inc.; CJ CheilJedang Corp.; and Summit Pharmaceuticals International Corporation.

Top management:

Michael D West, PhD, Pres. & CEO

Robert W Peabody, SVP, COO & CFO

Hal Sternberg, PhD, VP, Research

William. P. Tew, PhD, VP, Bus. Dev. & Chief Commercial Officer

Diseases	Cardiovascular Disease	Cancer	Blood Diseases	Diabetes	Neurological Diseases	Wounds	Reproductive System Diseases	Ocular Diseases	Gastrointestinal Diseases	Urinary System Diseases	Muscular and Skeletal Disorders and Injuries	Immunological Diseases
Organs	Kidney	Liver	Bladder	Cardiovascular System		Skin	Pancreas	Trachea	Teeth	Bones and Cartilage		
Tissue	With scaffold					Without scaffold						
	Autologous		Allogeneic			Isogenic		Xenogenic				
	Connective		Muscle			Epithelial		Nervous				
Cells	Autologous		Allogeneic			Isogenic		Xenogenic				
	Embryonic Stem Cells (ES)		Induced Pluripotent Stem Cells (iPSC)			Adult Stem Cells		Artificial Cells				
Molecular Induction Technologies	Genetic Therapy (vectors)					Small molecules and proteins			Combination			
Enabling Technologies	Equipment			Reagents and Materials		Implants		Cell and Tissue Sources			Information Systems	
Services	Biobanks	Clinical Trials	Contract Research Organization (CRO)		Contract Manufacturing (CM)		Clinics / Hospitals	Aesthetic Medicine		Consulting / Legal Certification		

Activity level

Low	Medium	High

Biotime, Inc. ARMIF

Osiris Therapeutics, Inc.

Ticker symbol: OSIR
Year of foundation: 1990
Address: 7015 Albert Einstein Drive, Columbia, MD 21046-1707, United States
Phone number: +1-510-521-3390
Fax number: +1-510-521-3389
Web-site: http://www.osiris.com/

Profile:

Osiris Therapeutics is a biotechnology company that develops and commercializes products to treat medical conditions in inflammatory, cardiovascular, orthopedic, and wound healing markets.

Osiris operates in two main segments: therapeutics and biosurgery. The therapeutics segment offers biologic stem cell drug candidates from bone marrow derived MSCs.

Osiris Therapeutics was the first company to receive marketing clearance for its stem cell drug Prochymal for the treatment of acute graft-vs.-host disease (GvHD) in children. It was the world's first regulatory approval of a manufactured stem cell product, and the first therapy approved for GvHD. Osiris partnered with the Juvenile Diabetes Research Foundation (JDRF) for the development of Prochymal as a treatment for patients with newly diagnosed type 1 diabetes mellitus. and also joined JCR Pharmaceutical Corporation to produce and market Prochymal in Japan. Another product in the therapeutic segment is called Chondrogen and is aimed at osteoarthritis and cartilage protection.

Source: Yahoo Finance

The biosurgery segment develops, manufactures, and markets products for orthopedic, wound healing, and surgical procedures. The three-dimensional cellular repair matrix Grafix was developed for the treatment of acute and chronic wounds, including diabetic foot ulcers and burns. It demonstrated a very high efficacy in the recent multicenter, randomized, controlled clinical trial comparing the safety and effectiveness of Grafix to the standard of care in patients with chronic diabetic foot ulcers.

Another product manufactured in this segment, named Ovation, is a cellular repair matrix designed for bone repair.

In October 2013, Mesoblast LTD acquired Osiris' culture-expanded mesenchymal stem cell (ceMSC) business, including Prochymal, in a transaction worth up to $100mm in initial consideration and milestone payments. Additionally, Osiris will receive royalty payments on sales of Prochymal and other products utilizing the acquired ceMSC technology.

At the moment, Osiris has an extensive intellectual property portfolio, including 162 foreign

patents, 45 issued U.S. patents and 13 filed U.S. patent applications.

Top management.

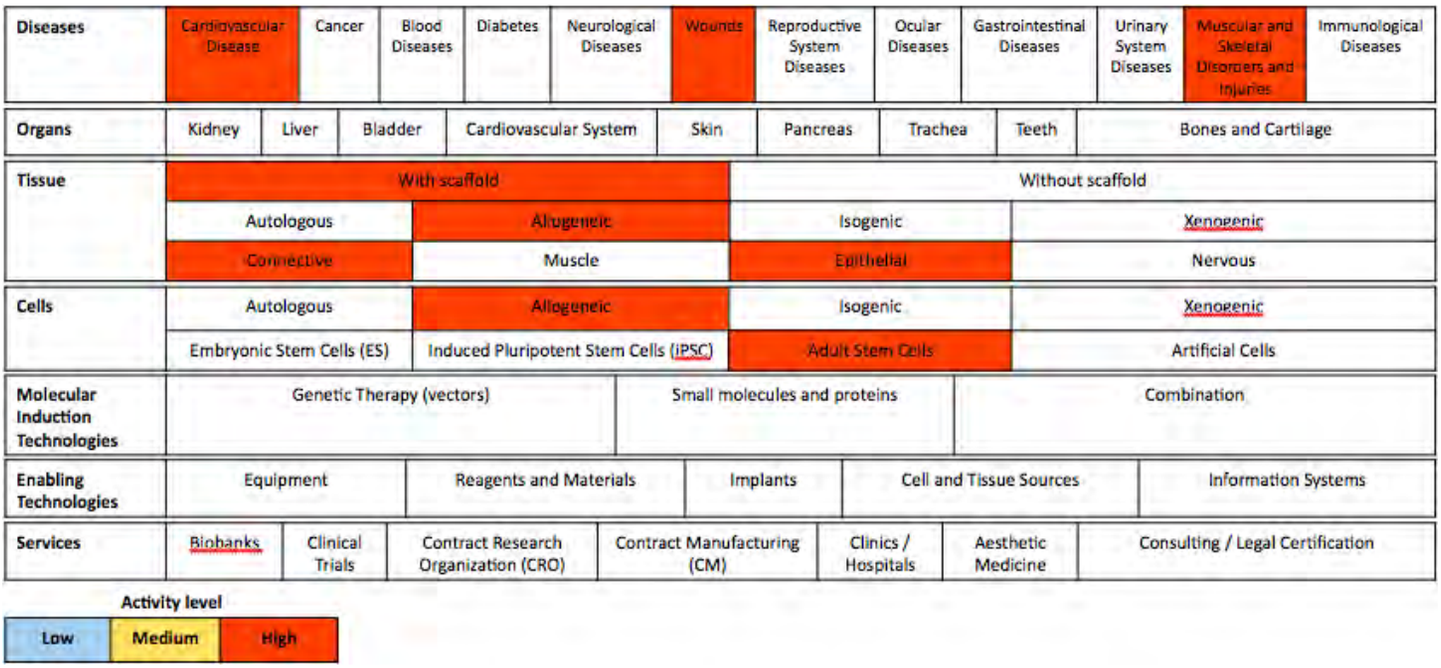
Lode Debrabandere, PhD, Pres. & CEO

Philip R Jacoby, CFO

Peter Friedli, Chairman of the Board

Michelle LeRoux Williams, PhD, CSO

Stephen W Potter, SVP, Ops. & Corp. Dev



Osiris Therapeutics, Inc. ARMIF

Cytori Therapeutics, Inc.

Ticker symbol: CYTX
Year of foundation: 1996
Address: 3020 Callan Road, San Diego, CA 92121, United States
Phone: +1-858-4580900
Fax: +1-858-4580994
Web-site: http://www.cytori.com/

Profile:

Cytori Therapeutics, Inc. is an internationally operating biotechnology company that develops and commercializes cell therapies based on autologous adipose-derived stem and regenerative cells to treat cardiovascular disease and repair soft tissue injuries.

Source: Yahoo Finance

Cytori has developed the Celution(R) System device technology for processing a mixture of adult stem cells from adipose tissue. In the U.S., the company focuses on developing therapeutic applications for the treatment of refractory heart failure and thermal/radiation injuries.

In Japan, Cytori sells its products mainly to researchers at hospitals and medical institutes. In September 2012, Cytori signed a contract with the Biomedical Advanced Research and Development Authority (BARDA), a segment of the U.S. Department of Health & Human Services, to develop cellular therapies for the treatment of thermal and radiation-induced wounds.

The company is currently conducting several clinical trials, including a U.S. safety and feasibility trial of ATHENA for refractory heart failure treatment and a European trial, ADVANCE, for acute myocardial infarction.

Cytori has completed enrollment and reported data from two European safety and feasibility trials, the APOLLO and PRECISE trials, in the areas of acute heart attack and chronic myocardial ischemia, respectively. The company also has completed the RESTORE 2 trial using autologous fat grafts enriched with the patient's own adipose-derived stem and regenerative cells (ADRCs) in partial mastectomy patients. In February 2013, Cytori received CE Mark approval in Europe for Intravase, a reagent designed to be used with Cytori's Celution System for preparing safe and optimized adipose-derived stem and regenerative cells (ADRCs) for intravascular delivery into the same patient.

The company's intellectual portfolio consists of over 100 U.S. and internationally issued patents and patent applications.

Top management:

Christopher J. Calhoun, CEO, Director

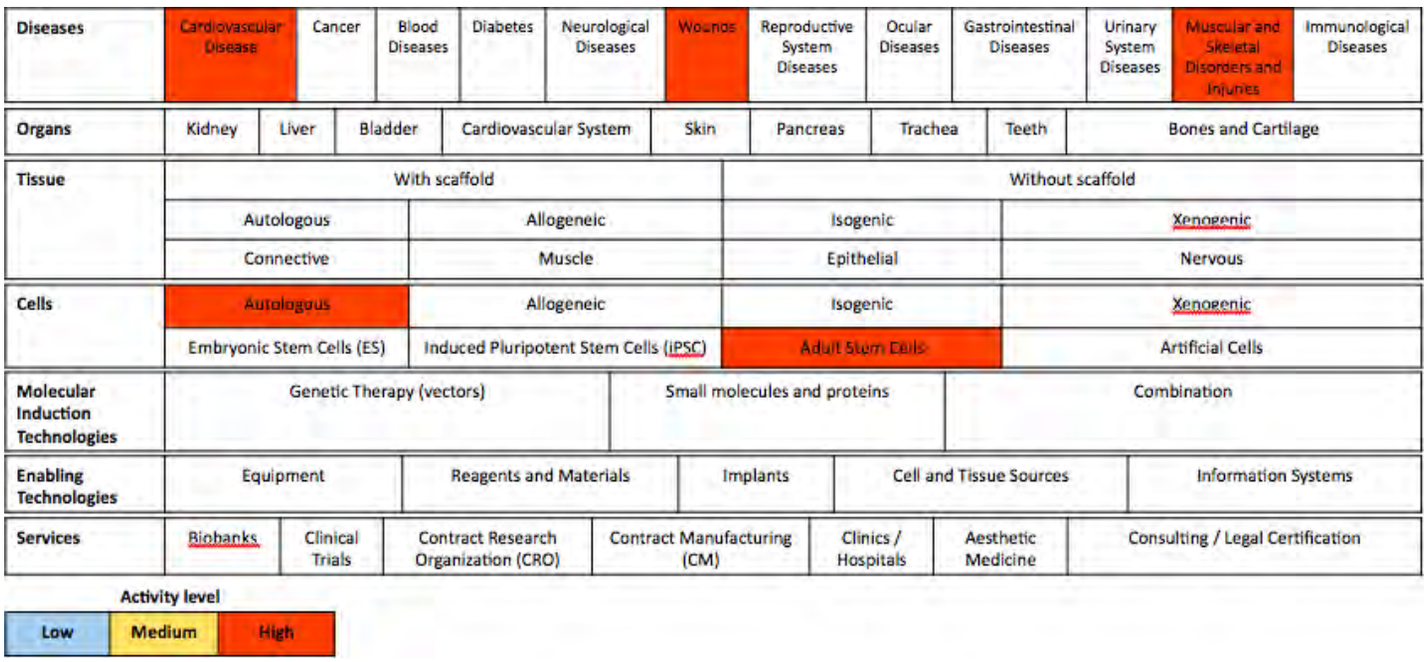
Mark E. Saad, CFO

David M. Rickey, Independent Chairman of the Board

Marc H. Hedrick M.D., President, Director

Seijiro N. Shirahama, President , Asia Pacific

Clyde W. Shores, EVP - Marketing & Sales



Cytori Therapeutics, Inc. ARMIF

Mesoblast, Ltd.

Ticker symbol: MBLTY
Year of foundation: 2004
Address: 55 Collins St., Level 39, Melbourne, Victoria 3000, Australia
Phone number: +61-3-9639-6036
Fax number: +61-3-9639-6030
Web-site: http://www.mesoblast.com

Profile:

Source: Yahoo Finance

Mesoblast Ltd. is a biotechnology company developing stem cell based technologies for various medical conditions. Mesoblast's cell-based core technologies include its lead Mesenchymal Precursor Cell (MPC) technology platform, currently used to develop products derived from bone marrow and adipose tissue sources, its Dental Pulp Stem Cells (DPSCs), and expanded Hematopoietic Stem Cells (HSCs).

The Company's MPC products are currently being evaluated in patients with congestive heart failure, acute myocardial infarction, type 2 diabetes and kidney disease, rheumatoid arthritis, inflammatory lung diseases, and intervertebral disc disease. In addition, Mesoblast is developing certain biotherapeutics based on protein factors derived from its proprietary cellular platforms.

The Company operates through its wholly owned subsidiaries Mesoblast, Inc., Mesoblast International SA, Mesoblast Australia Pty Ltd., and Mesoblast UK Limited. In December 2010, Mesoblast partnered with Teva Pharmaceutical Industries Ltd. for the development and commercialization of its Mesenchymal Precursor Cell (MPC) products in a number of fields, including cardiovascular diseases (in particular, congestive heart failure) and neurologic conditions.

This strategic partnership provides Mesoblast with a partner who has Phase 3 clinical and regulatory expertise, proven capability to bring products to market, and global distribution strength.

In September 2011, Mesoblast and Lonza Group (SWS: LONN), a world leader in biologic manufacturing, entered into a strategic alliance for clinical and long-term commercial production of Mesoblast's off-the-shelf (allogeneic) adult stem cell products. Other commercial benefits include the ability to reduce cost of goods (COGS) and to provide research support for optimized second generation products.

This alliance provides Mesoblast with significant commercial advantages, including certainty of

capacity to meet long-term global supply of its proprietary MPC products, exclusive access to Lonza's cell therapy facilities in Singapore, and the potential for a purpose-built manufacturing facility to be built by Lonza to meet Mesoblast's long-term commercial objectives. In March 2013, Mesoblast raised $174mm by selling 27mm shares at $A6.30, a 3% discount, to first-time US inventors and global institutional funds (including M&G Investment Management and Capital Research) and returning institutional buyers.

The money will be used for a Phase III trial of NeoFuse (consisting of allogeneic mesenchymal precursor cells (MPCs) in minimally invasive lumbar spinal fusion surgery; Phase II studies of IV formulations of MPCs for systemic inflammatory indications; optimizing MPC manufacturing methods and increasing inventory; and for hiring more employees.

In October 2013, Mesoblast LTD acquired Osiris' culture-expanded mesenchymal stem cell (ceMSC) business, including Prochymal, in a transaction worth up to $100mm in initial consideration and milestone payments. Additionally, Osiris will receive royalty payments on sales of Prochymal and other products utilizing the acquired ceMSC technology.

The company's intellectual property portfolio comprises around 20 US and international patents and patent applications.

Top management:

Silviu Itescu, CEO

Jenni Pilcher, CFO

James T Ryaby, PhD, VP, Rsch. & Clinical Affairs

Diseases	Cardiovascular Disease	Cancer	Blood Diseases	Diabetes	Neurological Diseases	Wounds	Reproductive System Diseases	Ocular Diseases	Gastrointestinal Diseases	Urinary System Diseases	Muscular and Skeletal Disorders and Injuries	Immunological Diseases
Organs	Kidney	Liver	Bladder	Cardiovascular System		Skin	Pancreas	Trachea	Teeth	Bones and Cartilage		
Tissue	With scaffold					Without scaffold						
	Autologous		Allogeneic			Isogenic			Xenogenic			
	Connective		Muscle			Epithelial			Nervous			
Cells	Autologous		Allogeneic			Isogenic			Xenogenic			
	Embryonic Stem Cells (ES)		Induced Pluripotent Stem Cells (iPSC)			Adult Stem Cells			Artificial Cells			
Molecular Induction Technologies	Genetic Therapy (vectors)					Small molecules and proteins			Combination			
Enabling Technologies	Equipment			Reagents and Materials		Implants		Cell and Tissue Sources			Information Systems	
Services	Biobanks	Clinical Trials	Contract Research Organization (CRO)		Contract Manufacturing (CM)		Clinics / Hospitals	Aesthetic Medicine	Consulting / Legal Certification			

Activity level

Low	Medium	High

Mesoblast, Ltd. ARMIF

Neostem, Inc.

Ticker symbol: NBS
Year of foundation: 2006
Address: 405 Eagleview Boulevard, Exton, PA 19341, United States
Phone number: +1-212-5844180
Fax number: +1-646-5147787
Web-site: http://www.neostem.com

Profile:

Neostem, Inc. is an internationally operating biopharmaceutical company focused on developing cell therapy products. The company's business model includes the development of novel proprietary cell therapy products, as well as operating a contract development and manufacturing organization (CDMO) providing services to others in the regenerative medicine industry. Since 2007, NeoStem has been engaged in research and development of new therapies and adult stem cell technology based on human very small embryonic-like stem cells, or VSELTM Technology, with the University of Louisville Research Foundation and other academic partners. In October 2011, Neostem acquired Amorcyte, LLC (Amorcyte), a development stage cell therapy company focusing on novel treatments for cardiovascular disease.

Currently, the company is in a phase 2 of the PreSERVE clinical trial Amorcyte's proprietary chemotactic hematopoietic stem cell product AMR-001 is being evaluated for the preservation of heart function after a severe heart attack.

Neostem's wholly-owned subsidiary, Progenitor Cell Therapy, LLC (PCT), was acquired in January 2011 and is a CDMO in the cellular therapy industry with manufacturing, regulatory, and commercialization expertise for therapeutics development.

In January 2011, Neostem acquired an 80% ownership of Athelos, a company developing a T-cell therapeutic with potential for a range of auto-immune conditions including graft vs. host disease, type 1 diabetes, steroid resistant asthma, lupus, multiple sclerosis, and solid organ transplant rejection. Neostem's intellectual portfolio includes 31 US and internationally issued patents and 54 pending patent applications, including composition of

Source: Yahoo Finance

matter and method claims, and a geographic breadth of filings.

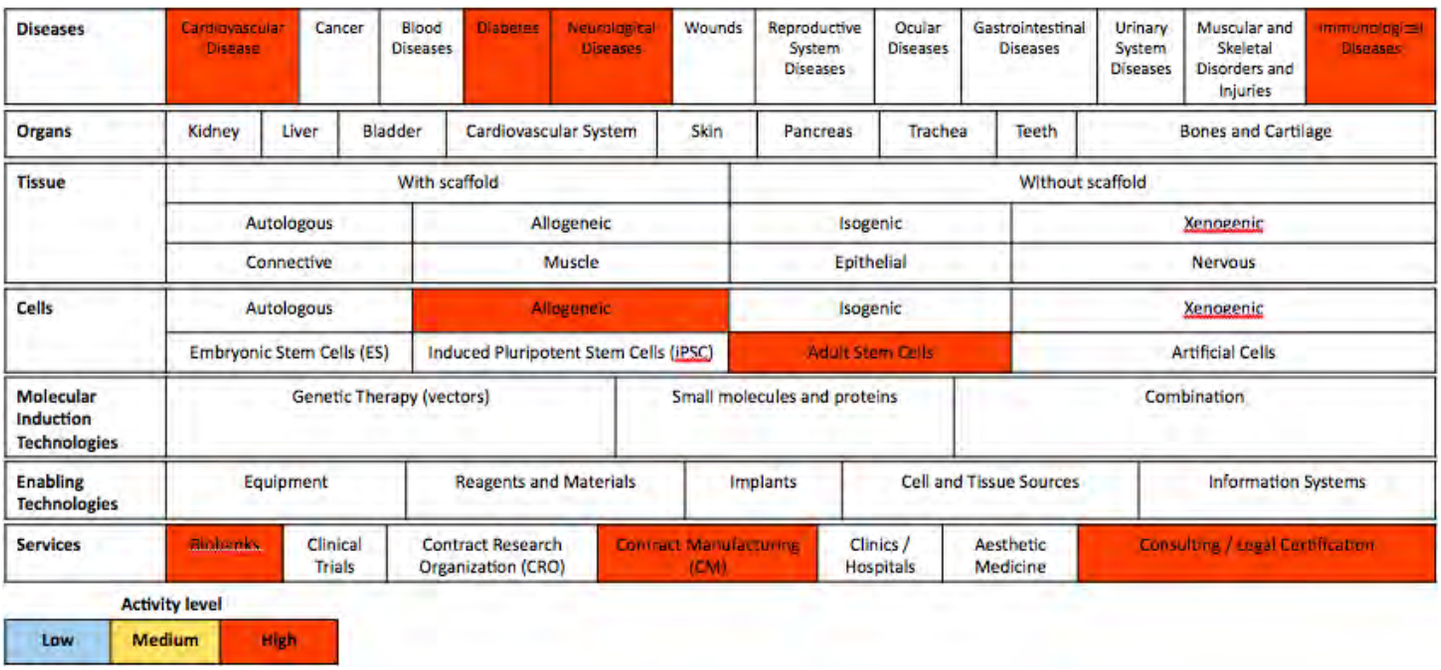
Top management:

Robin L Smith, MD, Chmn. & CEO

Larry A May, CFO

Martin E Schmieg, VP, Corp. Dev.

Andrew L Pecora, MD, CMO



Neostem, Inc. ARMIF

Advanced Cell Technology, Inc.

Ticker symbol: ACTC
Year of foundation: 1994
Address: 149 Commonwealth Dr., Menlo Park, CA 94025, United States
Phone number: +1-508-756-1212
Fax number: +1-508-229-2333
Web-site: http://www.advancedcell.com

Profile:

Advanced Cell Technology is a biotechnology company operating in the United States and internationally. It develops and commercializes products and services based on the human embrionic, induced pluripotent and adult stem technology.

Source: Yahoo Finance

The company focuses on the development of proprietary methods to generate new cells to replace malfunctioning or damaged cells.

Being focused on clinical-staged technologies, the company owns or licenses more than 200 patents and patent applications in the field of regenerative medicine and stem cell therapy. Currently, the company's patent portfolio covers broad intellectual property (IP) holdings around its embryo-safe single-cell blastomere technique and a variety of applications including stem cell-based methods for production of retinal pigment epithelium (RPE) cells, myoblast stem cells, and hemangioblasts.

To fine tune the manufacturing process of human embryonic stem cell lines using it's embryo-safe single-cell blastomere technique, in 2011 ACT established a partnership with Roslin Cells LTD of Scotland.

Top management:

Michael T. Heffernan, Chmn.

Edward H. Myles CPA, Interim Pres., CFO, EVP - Corporate Development

Eddy Anglade M.D., EVP - Clinical Development

Robert P. Lanza M.D., CSO

Diseases	Cardiovascular Disease	Cancer	Blood Diseases	Diabetes	Neurological Diseases	Wounds	Reproductive System Diseases	Ocular Diseases	Gastrointestinal Diseases	Urinary System Diseases	Muscular and Skeletal Disorders and Injuries	Immunological Diseases
Organs	Kidney	Liver	Bladder	Cardiovascular System		Skin	Pancreas	Trachea	Teeth	Bones and Cartilage		
Tissue	With scaffold					Without scaffold						
	Autologous		Allogeneic			Isogenic			Xenogenic			
	Connective		Muscle			Epithelial			Nervous			
Cells	Autologous		Allogeneic			Isogenic			Xenogenic			
	Embryonic Stem Cells (ES)		Induced Pluripotent Stem Cells (iPSC)			Adult Stem Cells			Artificial Cells			
Molecular Induction Technologies	Genetic Therapy (vectors)				Small molecules and proteins			Combination				
Enabling Technologies	Equipment			Reagents and Materials			Implants		Cell and Tissue Sources		Information Systems	
Services	Biobanks	Clinical Trials		Contract Research Organization (CRO)		Contract Manufacturing (CM)		Clinics / Hospitals	Aesthetic Medicine		Consulting / Legal Certification	

Activity level

Low	Medium	High

Advanced Cell Technology, Inc. ARMIF

Organovo, Inc.

Ticker symbol: ONVO
Year of foundation: 2007
Address: 6275 Nancy Ridge Drive, Suite 110, San Diego, CA 92121, United States
Phone number: +1-858-550-9994
Web-site: http://www.organovo.com/

Profile:

Organovo Holdings, Inc. develops and commercializes functional, three-dimensional human tissues for medical research and therapeutic applications.

The main focus of the company lies on the development of three-dimensional models of human tissue for regenerative medicine solutions (i.e. bio-printed blood vessels and nerve grafts), drug discovery, and development.

The company designed the NovoGen MMX Bioprinter to create 3D tissue constructs using cellular bio-ink, biocompatible hydrogel, or a mixture of the two. These technologies enable the fabrication of various tissue architectures.

Source: Yahoo Finance

In April 2013, Organovo announced the production of the first fully cellular 3D bioprinted liver tissue. To manufacture its NovoGen MMX Bioprinter, Organovo partnered with a third party manufacturer, Invetech Pty., of Melbourne, Australia.

The company actively collaborates with several major companies and institutes. In 2010, Organovo Holdings established a collaborative research agreement with Pfizer, Inc. to develop tissue based drug discovery assays utilizing its NovoGen MMX Bioprinter technology. In 2011, the company entered into a research agreement with United Therapeutics Corporation to conduct a research program to discover treatments for pulmonary hypertension. In January 2013, Organovo and OHSU Knight Cancer Institute established a collaboration for cancer research.

In August 2013, Organovo netted $43.8mm through the public sale of 10.4mm common shares (including the overallotment) at $4.50. In September 2013, Organovo Holdings, Inc. has entered into an agreement with The Michael J. Fox Foundation for Parkinson's Research to develop tissues for drug discovery. Organovo Holdings, Inc. was founded in 2007 with an IP portfolio obtained

from the University of Missouri and Clemson University. To date, Organovo Holdings, Inc. has filed 8 U.S. and foreign patent applications.

Top management:

Keith Murphy, CEO, Chmn., Pres.

Barry D. Michaels, CFO, Corporate Secretary

Sharon Collins Presnell Ph.D., EVP - Research and Development, Chief Technology Officer

Michael Renard, EVP - Commercial Operations

Eric Michael David Ph.D., Chief Strategy Officer

Richard Heyman Ph.D., Director

Diseases	Cardiovascular Disease	Cancer	Blood Diseases	Diabetes	Neurological Diseases	Wounds	Reproductive System Diseases	Ocular Diseases	Gastrointestinal Diseases	Urinary System Diseases	Muscular and Skeletal Disorders and Injuries	Immunological Diseases
Organs	Kidney	Liver	Bladder	Cardiovascular System	Skin	Pancreas	Trachea	Teeth	Bones and Cartilage			
Tissue	With scaffold					Without scaffold						
	Autologous		Allogeneic			Isogenic			Xenogenic			
	Connective		Muscle			Epithelial			Nervous			
Cells	Autologous		Allogeneic			Isogenic			Xenogenic			
	Embryonic Stem Cells (ES)		Induced Pluripotent Stem Cells (iPSC)			Adult Stem Cells			Artificial Cells			
Molecular Induction Technologies	Genetic Therapy (vectors)				Small molecules and proteins				Combination			
Enabling Technologies	Equipment		Reagents and Materials			Implants		Cell and Tissue Sources			Information Systems	
Services	Biobanks	Clinical Trials	Contract Research Organization (CRO)		Contract Manufacturing (CM)		Clinics / Hospitals	Aesthetic Medicine	Consulting / Legal Certification			

Activity level

Low	Medium	High

Organovo, Inc. ARMIF

ReNeuron
pioneering stem cell therapeutics

Reneuron Group, Plc.

Ticker symbol: RENE.L
Year of foundation: 1997
Address: 10 Nugent Rd, Surrey Research Park, Guildford, Surrey, GU2 7AF, UK
Phone number: +44-0-1483-302560
Fax number: +44-0-1483-534864
Web-site: http://www.reneuron.com

Profile:

ReNeuron Group, Plc. Develops and commercializes stem cell-based therapies for a range of neurodegenerative diseases, Type 1 diabetes, Parkinson's disease, and various ocular diseases.

The company's therapeutic product pipeline includes ReN001, a pre-clinical development stage therapy for disabled stroke patients. The company's other therapeutic and non-therapeutic programs in pre-clinical trials comprise ReN002 for diabetes, ReN003 for retinal diseases, ReN004 for Parkinson's disease, and ReN005 for Huntington's disease.

ReNeuron Group also works as a supplier, by marketing its proprietary neural stem cell lines such as ReNcell VM and ReNcell CX.

Top management:

Bryan Morton, Non-Executive Chmn.

Michael Hunt, CEO

John Sinden Ph.D, CSO

Source: Yahoo Finance

Diseases	Cardiovascular Disease	Cancer	Blood Diseases	Diabetes	Neurological Diseases	Wounds	Reproductive System Diseases	Ocular Diseases	Gastrointestinal Diseases	Urinary System Diseases	Muscular and Skeletal Disorders and Injuries	Immunological Diseases
Organs	Kidney	Liver	Bladder	Cardiovascular System	Skin	Pancreas	Trachea	Teeth	Bones and Cartilage			
Tissue	With scaffold				Without scaffold							
	Autologous		Allogeneic		Isogenic		Xenogenic					
	Connective		Muscle		Epithelial		Nervous					
Cells	Autologous		Allogeneic		Isogenic		Xenogenic					
	Embryonic Stem Cells (ES)		Induced Pluripotent Stem Cells (iPSC)		Adult Stem Cells		Artificial Cells					
Molecular Induction Technologies	Genetic Therapy (vectors)				Small molecules and proteins				Combination			
Enabling Technologies	Equipment			Reagents and Materials		Implants		Cell and Tissue Sources			Information Systems	
Services	Biobanks	Clinical Trials		Contract Research Organization (CRO)		Contract Manufacturing (CM)		Clinics / Hospitals	Aesthetic Medicine		Consulting / Legal Certification	

Activity level: Low | Medium | High

Reneuron Group, Plc. ARMIF

Stem Cells, Inc.

Ticker symbol: STEM
Year of foundation: 1994
Address: 7707 Gateway Blvd., Suite 140 Newark, CA 94560, United States
Phone number: +1-510-456-4000
Fax number: +1-510-456-4001
Web-site: http://www.stemcellsciences.com

Source: Yahoo Finance

Profile:

StemCells, Inc. is a clinical-stage biotechnology company focused on the discovery, development, and commercialization of cell-based therapeutics to treat diseases of the central nervous system and liver. They seek to address unmet medical needs through the development of stem cells as therapeutic agents to treat damage or degeneration of major organ systems. Stem Cells, Inc. product development programs seek to repair or repopulate CNS and liver tissue that has been damaged or lost as a result of disease or injury.

Stem Cells, Inc. has pioneered the discovery and development of HuCNS-SC® cells, its highly purified, expandable population of human neural stem cells. Stem Cells has completed a six patient Phase I clinical trial of its proprietary HuCNS-SC product candidate as a treatment for neuronal ceroid lipofuscinosis (NCL), a rare and fatal neurodegenerative disease that affects infants and young children.

Stem Cells has also received approval from the U.S. Food and Drug Administration (FDA) to initiate a Phase I clinical trial of the HuCNS-SC cells to treat Pelizaeus-Merzbacher Disease (PMD), also a rare and fatal brain disorder that mainly affects young children. Stem Cells, Inc. owns or has exclusive rights to approximately 50 issued or allowed U.S. patents and more than 150 granted or allowed non-U.S. patents. Stem Cells Sciences, Plc was acquired by Stem Cells, Inc in 2009. As a result, StemCells has acquired proprietary cell technologies relating to embryonic stem cells, induced pluripotent stem (iPS) cells, and tissue-derived (adult) stem cells; expertise and infrastructure for providing cell-based assays for drug discovery; the SC Proven® media formulation and reagent business; an intellectual property portfolio with claims relevant to cell processing, reprogramming, and manipulation, as well as to gene targeting and insertion; and existing business and license relationships with several major life science companies, such as Merck and Millipore.

Top management:

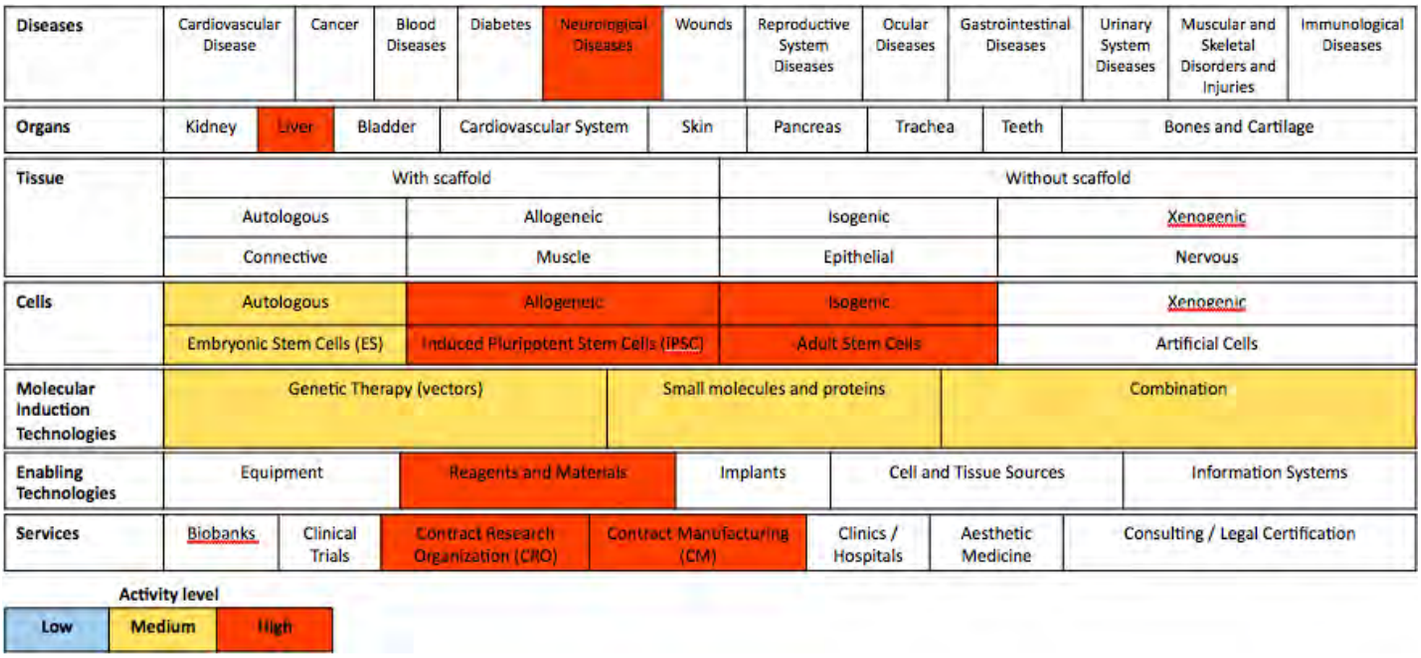
John J. Schwartz Ph.D., Indep. Chmn.

Martin M. McGlynn, CEO, Pres., Director

Gregory T. Schiffman, CFO, EVP - Finance

Stewart Craig Ph.D., EVP - Development / Operations

Ann Tsukamoto Ph.D., EVP - Scientific and Strategic Alliances



Stem Cells, Inc. ARMIF

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