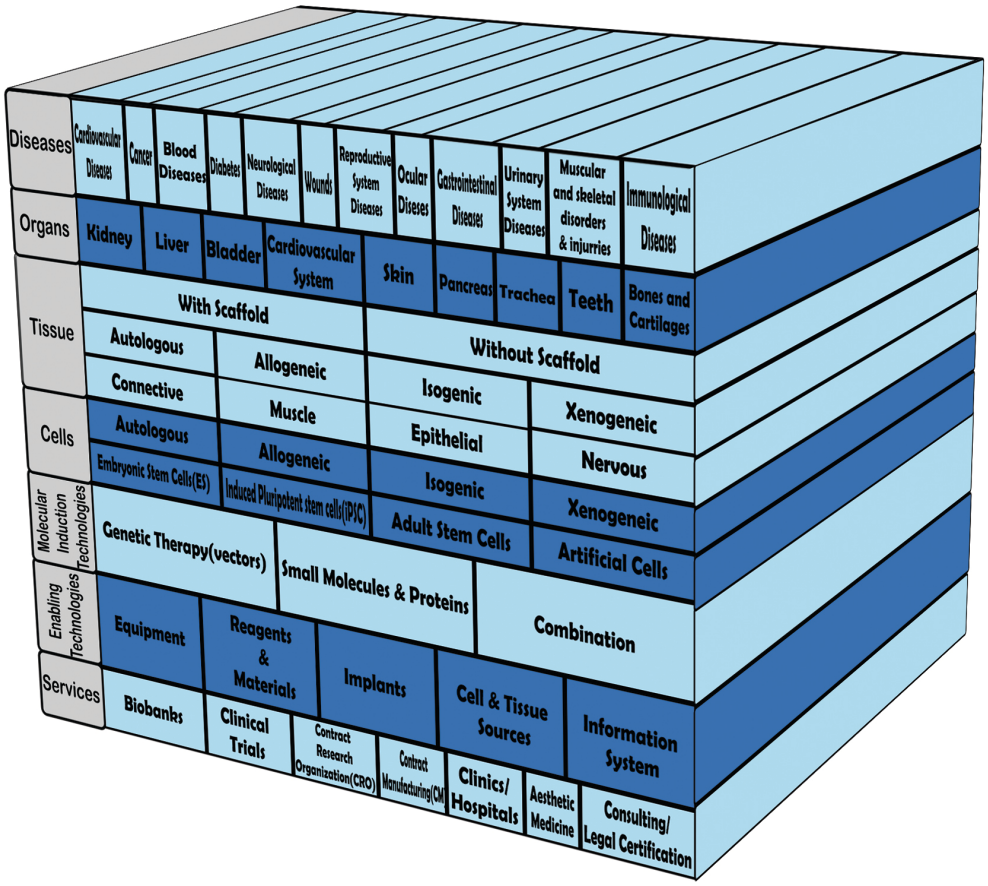

Analytical Regenerative Medicine Industry Framework

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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.
Allogenic: 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 (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 destined 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.

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Medical tourism: movement of patients from one country to another to access medical care facilities.
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.
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.

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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 and are less risky from the cash flow and clinical trials perspective, may also have basic research or translational medicine projects that may serve as major sources of growth. Likewise, companies engaged in lengthy, expensive and risky clinical trials 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 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, diseases and highlights the focus on the level of organismal organization such as cells, tissue and organs.

The presence of the company and level of activity in each segment is visualized using the color codes: 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 allogenic cells and is just starting the induced stem cell program, each one of these fields will be color coded by the level of activity in the field.

While ARMIF is currently limited in both, granularity and scale, it is one of the most comprehensive models for analyzing the organizations and projects in regenerative medicine that not only allows to analyze the positioning, but also evaluate the level of participation and track multiple parameters in each segment. It is a scalable and flexible platform that allows for new parameters to be added.

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REGENERATIVE MEDICINE LANDSCAPE

Regenerative medicine is rather big industry with an extremely complex structure due to the involvement of not only the primary companies involved directly in the regenerative medicine business, but also the services industry associated with diverse fields like bioengineering, chemical industry, pharmaceutical industry as well as clinics and hospitals involve in trials. We have developed a map which can help understand what regenerative medicine is. 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 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 shall have its own copy of the table. 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 the '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 level of the organization of the body is the simplest one but it is not less important than the others. Molecular induction technologies are a very important part of regenerative medicine.

Cellular level of the organization in the body has a higher complexity than a molecular level. Cells are a part of this level form the 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.

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Table 1 : Segmentation of regenerative medicine industry

Diseases	Cardiovascular diseases	Cancer	Blood diseases	Diabetes	Neurological diseases	Wounds	Reproductive system diseases	Ocular diseases	Gastrointestinal diseases	Urinary system diseases	Muscular and skeletal disorders and injures	Immunological diseases
Organs	Kidney	Liver	Bladder	Cardiovascular system	Skin	Pancreas	Trachea	Teeth	Bones and cartilages			
Tissue	With scaffold				Without scaffold							
	Autologous		Allogeneic		Isogenic		Xenogeneic					
	Connective		Muscle		Epithelial		Nervous					
Cells	Autologous		Allogeneic		Isogenic		Xenogeneic					
	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		

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 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. Allogenic-Cells and/or tissues derived from a person for treatment another person. Allogenic 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. Xenogenic cells and tissues have a large probability of rejection after transplantation.

The next level of complexity in an organism is the organ level organization. Each organ consists of different types of tissues, which in turn are composed of different cell types. Bio-engineered

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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.

SEGMENTATION

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 a lot of problems. 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 services industry caters to the needs of the companies while other provide services to the final consumers.

A. BIOBANKS

Biobank is a repository of different biological materials such as blood, umbilical cord, 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.
The present day technology makes it possible to collect a large number of different cell and tissue types from the human body. For example it can be adipose tissue, cord blood, amniotic stem cells, and skin and so on.
Biobanks can be public and 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 specimens will be available to them in future, in a case of 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 private use at a cost.
Cord blood banks are an example of the most successful biobanks. According to the Alliance for regenerative medicine (http://alliancerm.org/), more than 30000 cord blood transplants have been performed until the year 2012. The popularity of private cord blood banks is rising sharply but there is a strong opinion that the probability of usage of the transplant material by its donor is too low, giving an advantage to the public banks are better.

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

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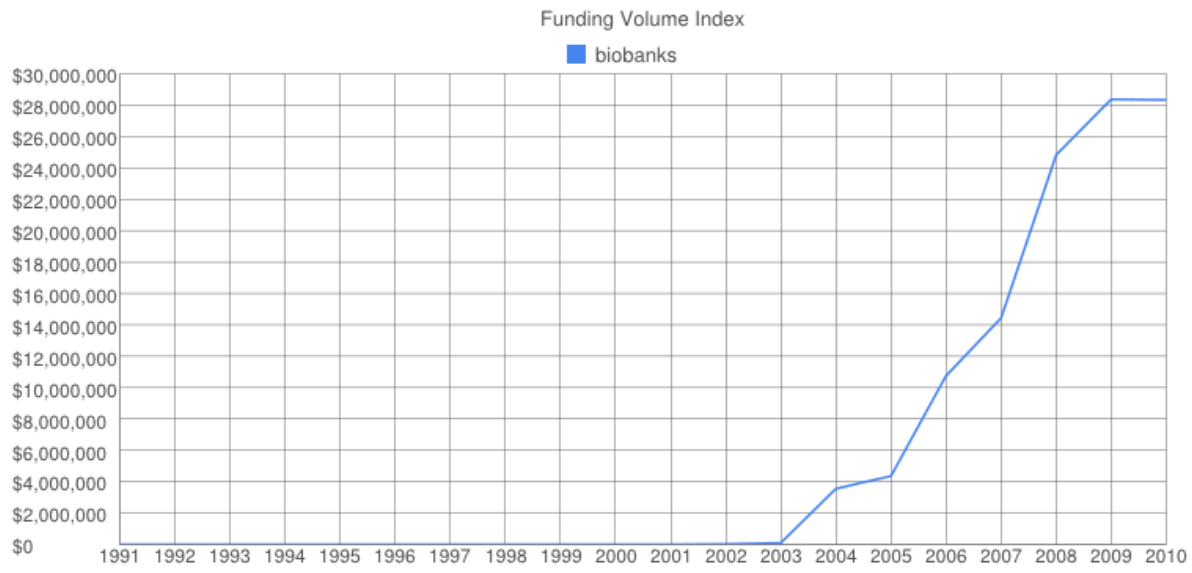

Chart 1: Funding* received by Biobanks.

B. CLINICAL TRIALS

Clinical trials are an extremely important but cost and time intensive step towards bringing a research product into the market and to evaluate its safety and efficacy. The process of conducting clinical trials can face many challenges that 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 of such a company is PAREXEL, with its presence across continents. According to Yahoo Finance (http://finance.yahoo.com/) market cap of this company is about 2.84 billion dollars.

Such specialized companies provide services that can be very helpful for development of 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 professional companies specialized in clinical trials. FundingTrends.org cites that the funding of clinical trials related to the regenerative medicine field has sharply increased since 2003.

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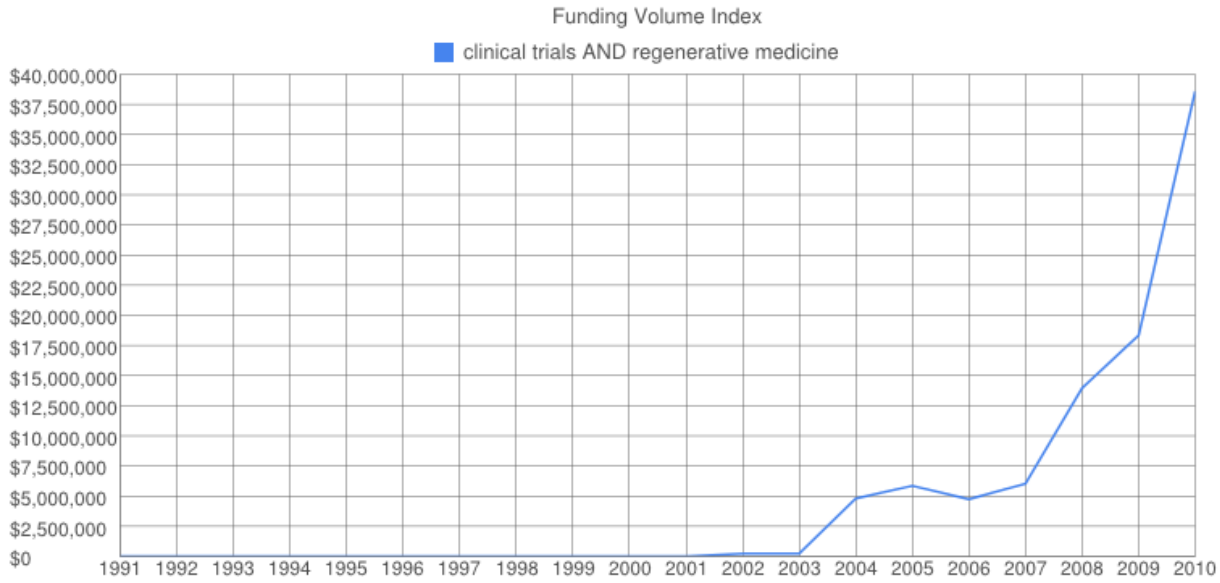

Chart 2: Funding* for clinical trials in regenerative medicine.

C. CONTRACT RESEARCH ORGANIZATIONS (CROS)

Contract research organization is an organization which provides different research services to the pharmaceutical and biotechnological companies on a contract basis. For example, it can be biological assays, preclinical trials etc. These CROs have a strong connection with the regenerative medicine field. Firstly, their 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 using the models developed by the regenerative medicine industry. For instance, the new 3D tissue models are gaining popularity in the field of drug testing.
The annual growth of this segment of the market in the Unites States is 12.1 % and the revenue is about $15 billion (http://www.ibisworld.com/industry/contract-research-organizations.html).

D. CONTRACT MANUFACTURING (CM)

Contract manufacturer is an organization which manufactures a product on a contract basis. Of the many manufacturers in biomedical industry, some contract manufacturers provide specialized manufacturing services for the regenerative medicine industry. Again, as mentioned in the case of Cos, CM can be beneficial for small innovative companies which may have a breakthrough product but do not have the manufacturing facilities. 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 etc.

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E. CLINICS/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 them. They also participate in the development of different regenerative technologies as they have their own research facilities. In future, the role of clinics shall be increasingly important as it is often easier to produce stem cell products in hospitals rather than in separate laboratories. The delivery of a stem cell product is a complex process involving legal restrictions. 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 used as a source of the material from the donors and at the same time provide facilities to deliver the product to the recipient. Hence, in future, big hospitals and clinics are expected to play a major role in regenerative medicine.

F. 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 manufacture and market some products which can be used for correction of facial wrinkles, scar remediation and lip augmentation (http://www.anikatherapeutics.com/products/dermal/index.html).

G. CONSULTING/LEGAL CERTIFICATION

Consulting and legal certification is an extremely important part of services in regenerative medicine. The rules and regulations for products as well as services in regenerative medicine are different depending on the country. 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 all stakeholders need up-to-date information about all events in the field for the decision making process.

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2. ENABLING TECHNOLOGIES

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

A. EQUIPMENT SUPPLIERS

There is a group of companies which are specialized in the production of equipment for cells and tissues culturing. The range of necessary equipment is rather wide. It includes cell culture hoods, incubators, microscopes, centrifuges, refrigerators, freezers, etc. The laminar flow hoods provide 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 (http://www.olympusamerica.com/seg_section/seg_presscenter_headline.asp?pressNo=750).
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 ones are primary used for storage of reagents but the third one is used for 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. There are a lot of reagents used in regenerative medicine. The list of them 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 environment 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 are composed of biomaterials but they should be described separately due to their importance. Surgeons have used different metal implants for a long time. However, these implants do not

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mimic human tissues as metals have properties that are different from biological material. At present, it is possible to construct metal implants 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 metal implants to derive an implant with mechanical properties that are better than the metal implant alone. These implants are also less susceptible to rejected by an organism (Smith et al, 2012).

D. Cell and tissue sources

The source of donor cells, specimens and other biological material is a necessary tool used in the development of regenerative medicine products. Companies specialized in providing reliable biological material which is well characterized and meets the required regulatory standards also form a part of enabling technologies. These characterized biomaterials can be used for different purposes such as clinical and scientific research or pharmaceutical assays. The list of the 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 present day life science industry, information systems play a vital role. For example, the whole branch 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 knowledge of information systems to comprehend this 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.

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 for the correct protein. Another possibility is to transform the 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/diseased cells. All transforming factors can be divided into two groups. The first group is that of the different vectors used in gene

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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 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 as the 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 behavior of the treated cells.

There are several types of vectors which can be classified into two subtypes: the viral vectors and the 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 then expressed. If a part of viral genome is replaced with a gene of interest, this gene will be expressed in cells instead of viral genes. Different types of viruses such as the adenoviruses, retroviruses and lentiviruses are widely used for human gene therapy.

b. Non-viral vectors

Non-viral vectors comprises of small molecules including naked DNA, liposomes, inorganic nanoparticles and other structures such as the 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.

There 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 the germ line gene therapy where the human germ cells are modified and the genetic defect is corrected and the corrected gene is passed on to the 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 a large number of gene therapy trials targeting cancer and hereditary diseases. Targeting genetic defects resulting from several faulty genes is still deemed difficult and has not been widely investigated.

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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 a number of ongoing clinical trials evaluating the potential of gene therapy methods (http://www.genetherapynet.com/clinical-trials.html). 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 (http://history.nih.gov/exhibits/genetics/sect4.htm). Although there are a number of clinical trials reporting success, the method has some serious disadvantages. The efficacy of many 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 as 'non-self' by the host. The Furthermore, the use of viruses can also elicit an immune response, at times making the mode of delivery incapacitated. 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.

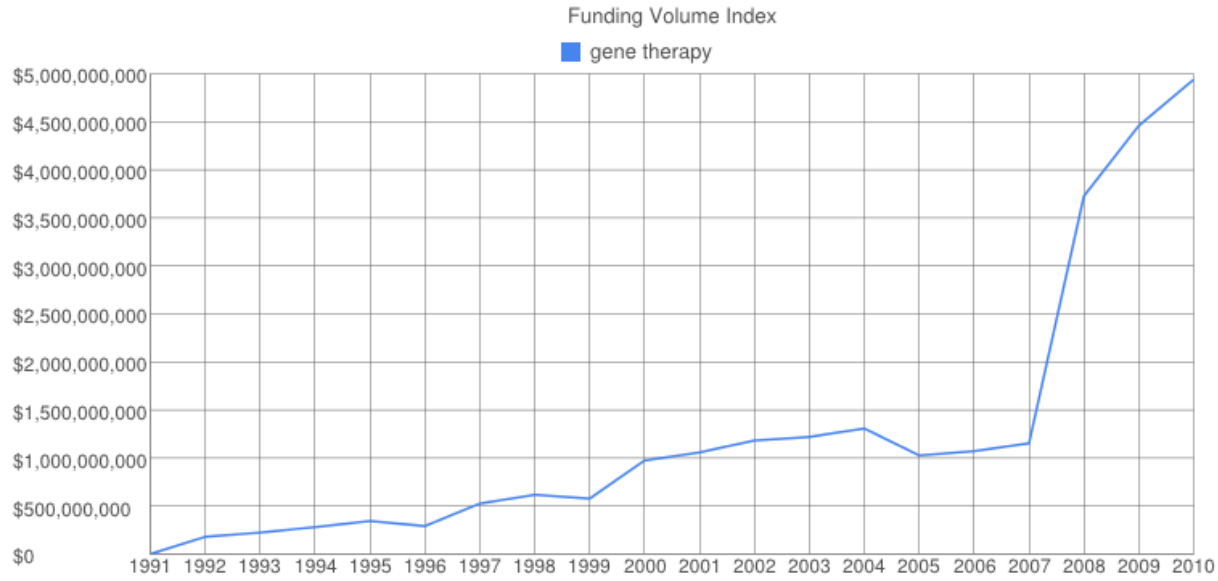

Chart 3: Funding* for projects in gene therapy.

The funding of projects on gene therapy has seen a sharp increase since the year 2007 and the funding reached almost $ 5 billion for the year 2010 (http://www.fundingtrends.org/?keywords=gene+therapy).

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 used for these purposes.

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For example platelet growth factor (biological protein which is contained in platelets) can be used for treatment 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, 201 2). 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 and shall be discussed separately.

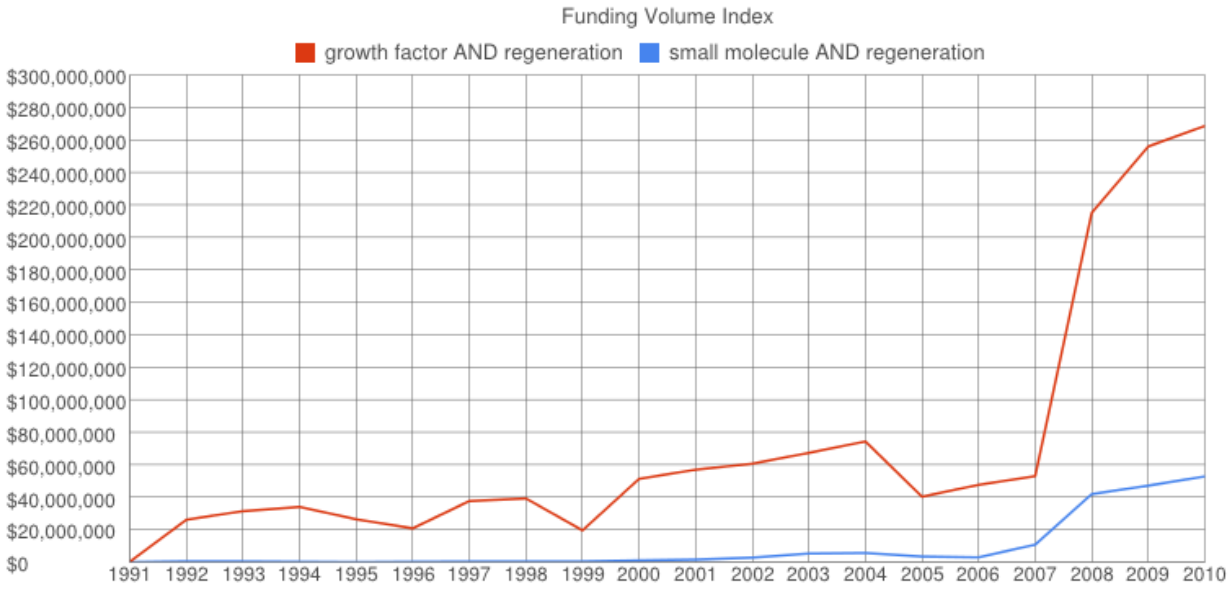

Chart 4: Funding* received by projects in regenerative medicine exploring growth factors and small molecules.

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 (http://www.fundingtrends.org/?keywords=+growth+factors%2C+small+molecules).

C. Combination of gene therapy and small molecules and/or proteins

Combination of gene therapy and small molecules or proteins can reduce the side effects of the first one 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.

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4. CELLS

The human body consists of more than 10^{13} cells of several different types. These differences in different cell types are both, morphological and functional. Different cell types have stark differences in cell signaling pathways although they have a structurally identical composition. All cells in a human body are derived from a single fertilized egg cells. 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 the 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 advantages and disadvantages which will be discussed in later sections. The regenerative capacity of cell therapy using stem cells undoubtedly makes them the most important field in regenerative medicine as they have enormous medical and economic potential.

A. EMBRYONIC STEM CELLS (ESCS)

As is 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 as the Embryonic Stem Cells (ESCs) and they are very 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 cell 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 type.

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 way for treatment of diseases such as cardiovascular diseases, diabetes, neurological diseases, etc. FDA approved the first clinical trial of ESCs in

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2009 for the treatment of spinal cord injury developed by Geron Corporation. Unfortunately, the company had to stop the trial due to financial problems (Falco, 2009).

Although ESCs are promising, there are several technical and ethical issues related to the development of stem cell therapies. As one has to destroy an embryo to retrieve ESCs, their usage for research raises a number of ethical and legal problems. In some countries, stem cell research using human embryos is forbidden. However now there is a way to get ESCs without destruction of an embryo and it can help to solve such kind of problems. 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 cultivation of ESCs and clinical use of ESCs are underway and a breakthrough is expected in near future.

According to FundingTrends.org, the funding of projects using ESCs sharply increased since 2007 (http://www.fundingtrends.org/?keywords=embryonic+stem+cells).

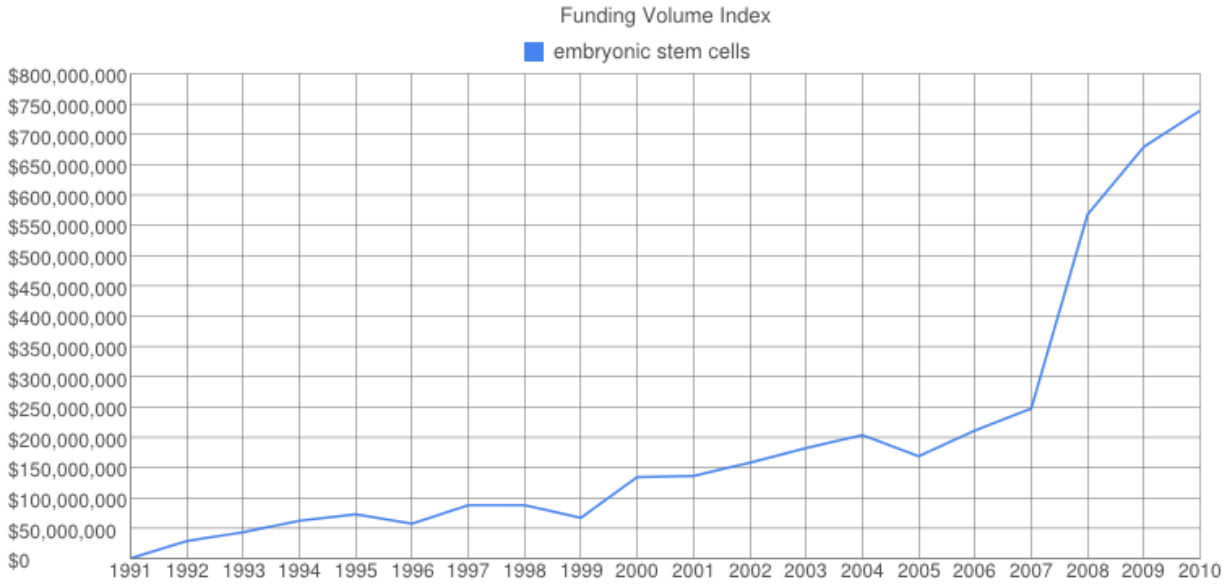

Chart 5: Funding* received by projects dealing with embryonic stem cells.

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 it paves way for a novel method of deriving stem cells without destroying an embryo. This method therefore doesn't raise any ethical issues. Another important of iPSCs lies in the

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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 of mature cells to derive iPSCs initially was reported using four genes. It has now been shown that all the 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 delivered genes can be oncogenes and that's why usage of such iPSCs in clinic is 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 to specific mRNA sequences, primarily at the 3' end and thus regulate gene expression (Bao et al, 2013) or 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). The investigators 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 and the process of transformation is rather difficult and can sometimes result in an incomplete

According to FundingTrends.org, funding of projects using iPSCs has dramatically increased since the year 2007.

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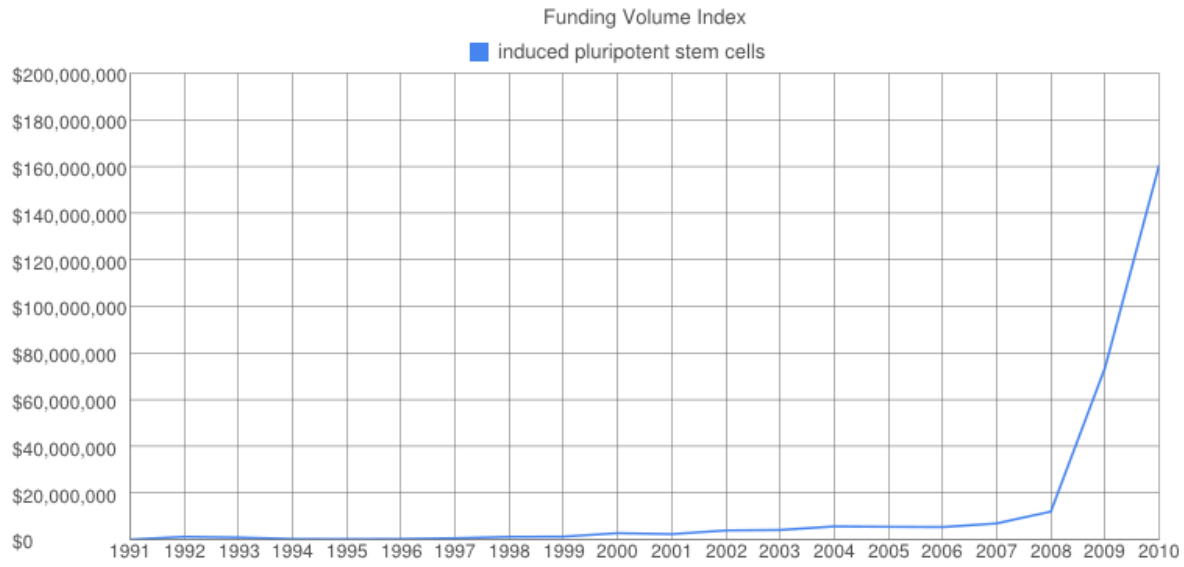

Chart 6: Funding* volume index for induced pluripotent stem cells.

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 limited number of cell types, rather than all types of human cells. Usually they differentiate into the cells of the same germ layer. But 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). There are a 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 clinic 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 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.

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

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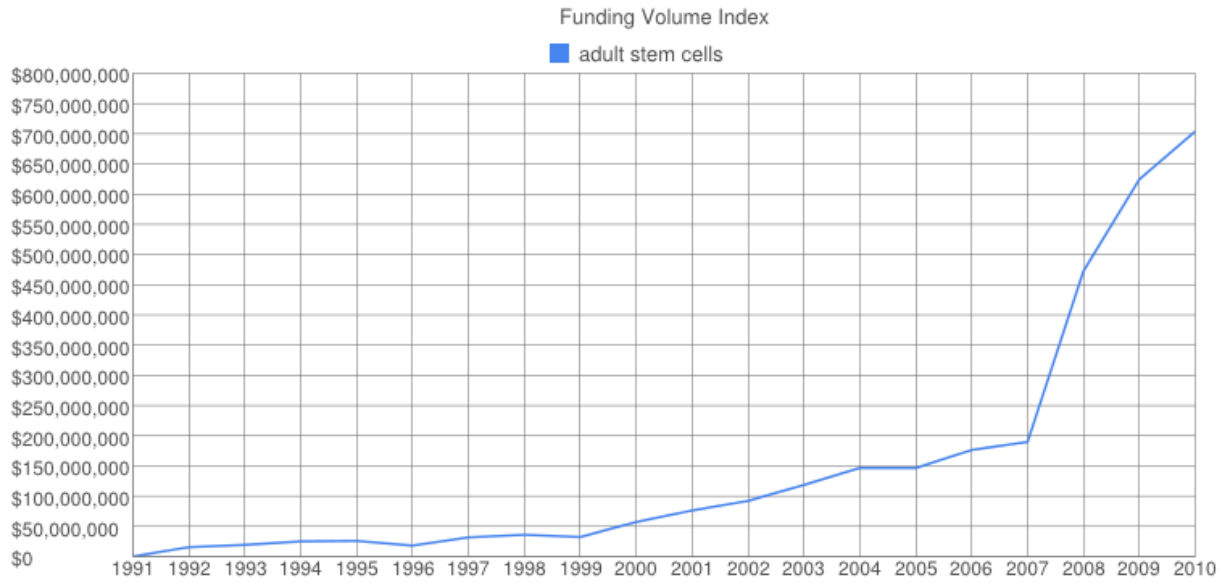

Chart 7: Funding* volume index for adult stem cells.

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 are 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 formation of new 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 immunosuppressant. All 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.

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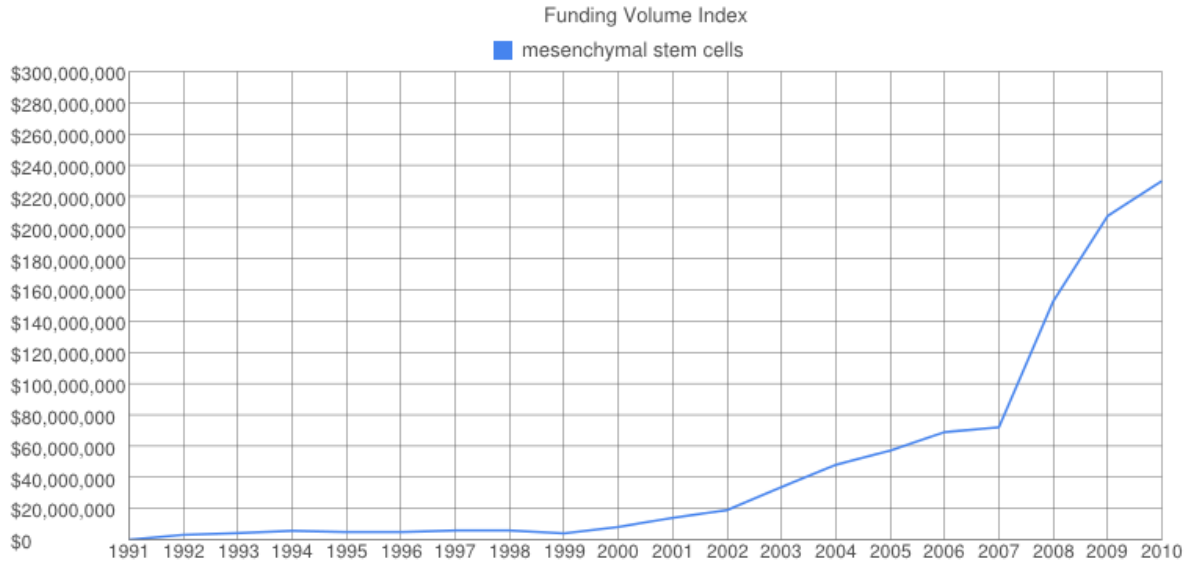

Chart 8: Funding* of projects on mesenchymal stem cells (MSCs)

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 others are oligopotent and unipotent. The main source of hematopoietic stem cells is the bone marrow. HSCs can be also 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 transplantation. This procedure often performed on patients with cancer of blood or bone marrow. Before transplantation, radiation and chemotherapy are used to destroy the immune system of a recipient (in order to avoid rejection) and to kill malignant cells. The graft can be autologous or allogenic. In case of an autologous graft, HSCs are collected from the patient before complete or partial destruction 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 allogenic graft can be safer in some cases but is associated with issues such as the graft-versus-host disease when the immune cells of the graft begin to attack donor's tissues. It's also difficult to find a suitable donor with similar human leucocyte antigen (HLA). HLA is a molecule expressed on cell surface (also referred to as the major histocompatibility complex MHC). HLA of the donor and HLA of recipient should be similar in order to avoid immune conflict.
More than 50000 hematopoietic stem cell transplantations (HSCTs) are performed annually, of which more than half are autologous and others are allogenic and the number of HSCTs continues to increase at a rate of 10-20% every year (Perumbeti , 2013).
Although HSCTs are common, they are 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

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

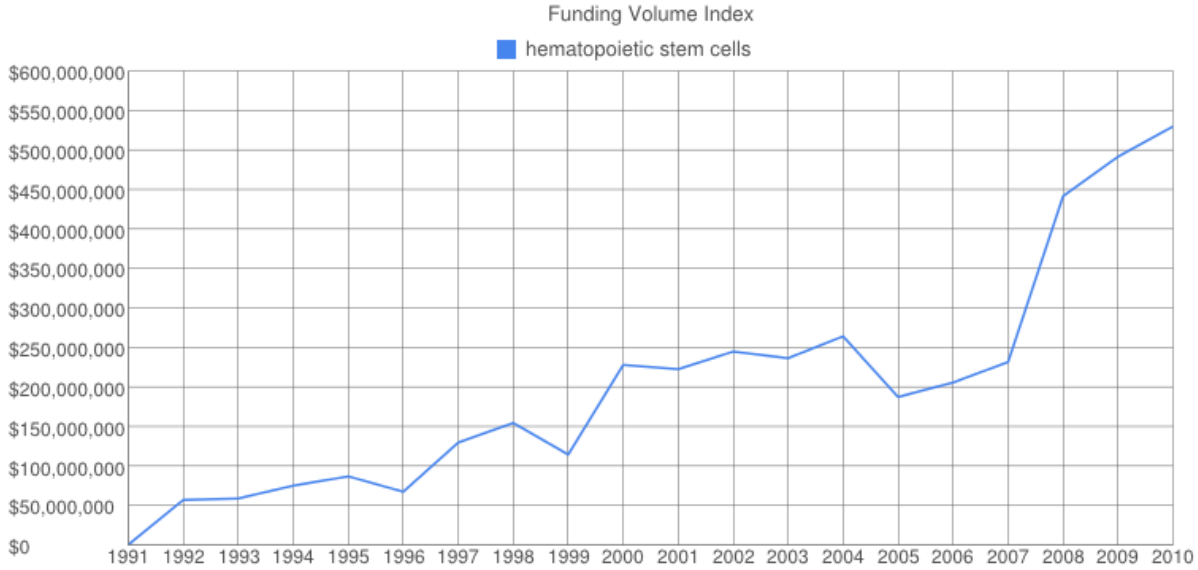

Chart 9: Funding* for hematopoietic stem cells

c. Umbilical cord blood stem cells

Umbilical cord blood stem cells (UCBSC) are derived from the cord blood in the umbilical cord and placenta after a baby is born. It 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 an umbilical cord is rather easy, the amount of blood harvested from the cord is small. Usually this amount is enough to threat a child but not enough to threat an adult person. To solve this problem, it is possible harvest cells from two umbilical cords or from the placenta. There is also an opportunity to cultivate UCBSCs in vitro.

Cord blood is used to treat with different types of blood cancer or with genetic blood diseases like Fanconi anemia. About 20000 umbilical cord blood transplants have been performed 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 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 been controversial.

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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 donor or donor's relatives. The benefits of private cord blood banks is a controversial issue because the probability of using cord blood by the donor is too low. According to FundingTrends.org, funding of projects using UCBSC reached a peak in 2009.

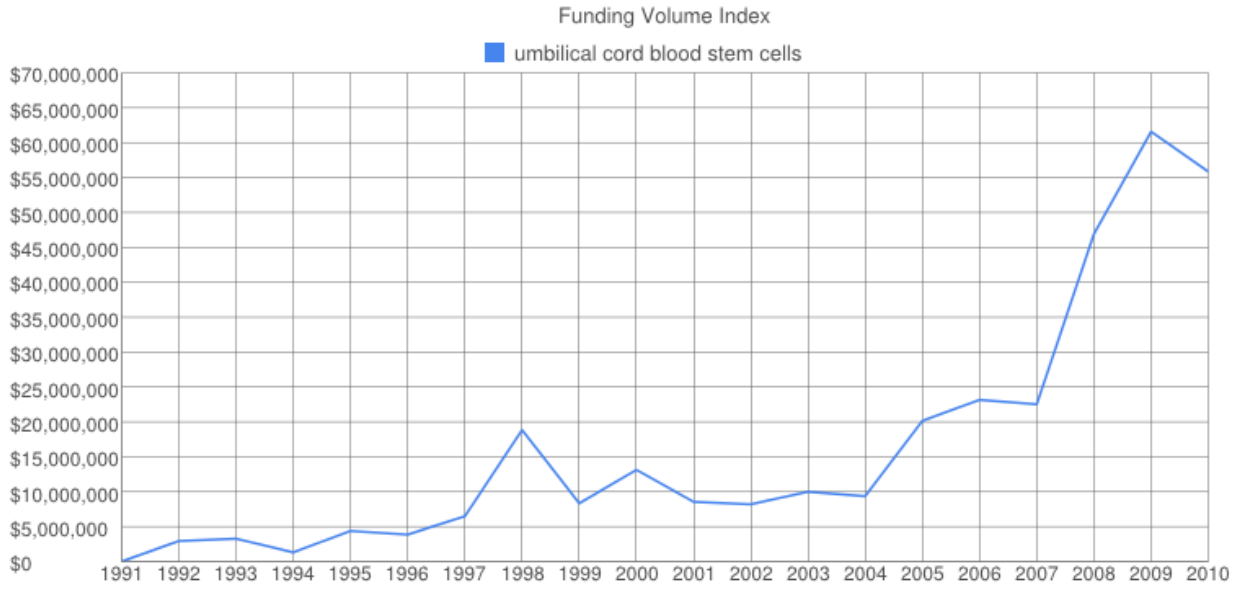

Chart 10: Funding* in the field of umbilical cord blood stem cells.

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.

Amniotic stem cells can be collected without destroying an embryo but there is a very little 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.

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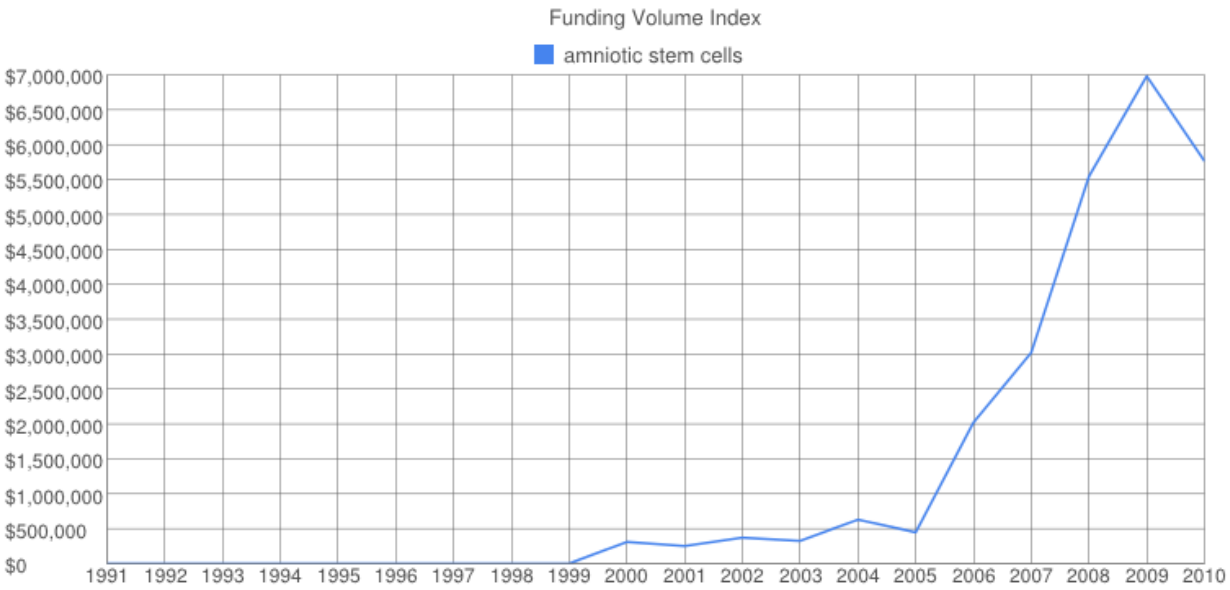

Chart 11: Funding* for amniotic stem cells.

D. 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.

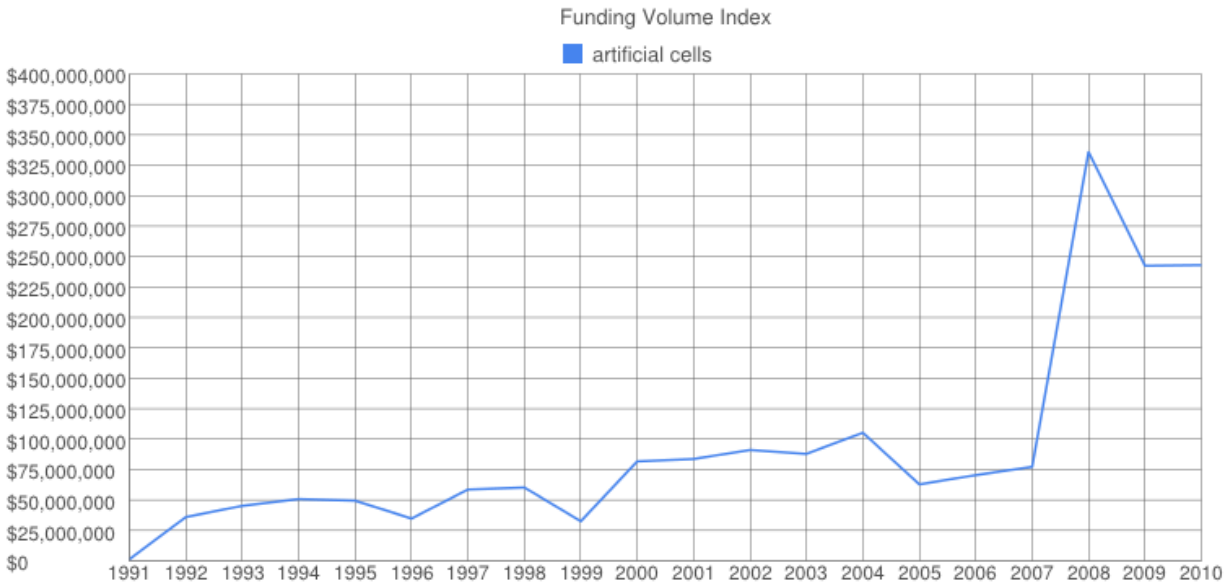

Chart 7: Funding* related to artificial cells.

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As the surface of these artificial cells lacks antigens, they can be useful where immunogenicity is a problem the can help to avoid immune respond. 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.

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. Extracellular matrix is produced by the cells and plays a very important role providing cell communication, nutrition and special mechanical features to 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. There are several approaches to tissue engineering which shall be discussed in later sections.

According to FundingTrends.org funding of projects on tissue engineering considerable grew since 2007.

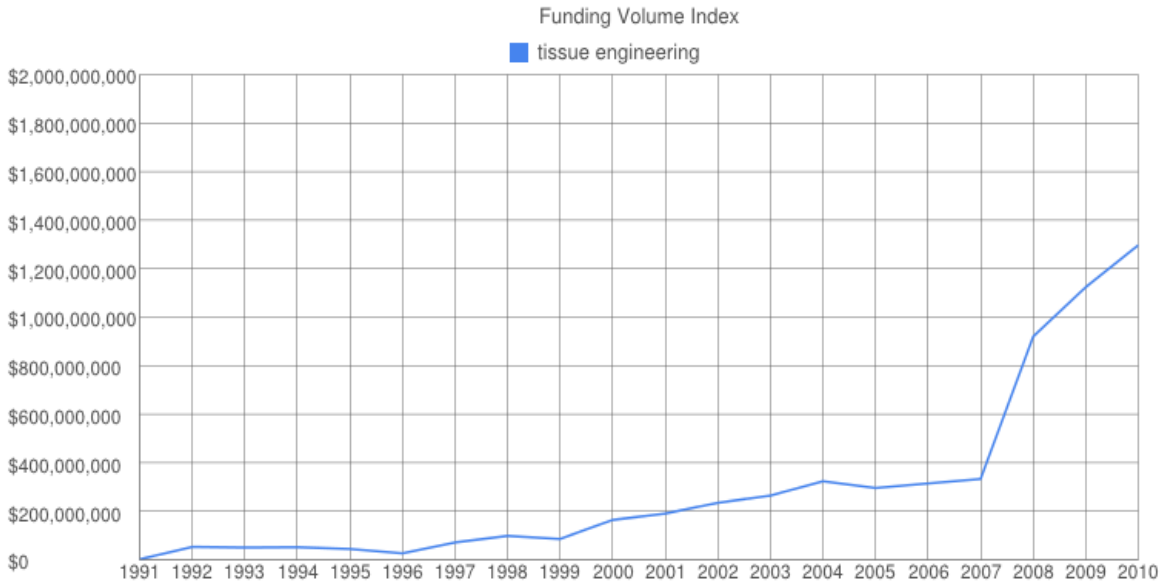

Chart 8: Funding* in tissue engineering.

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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. Scaffold is defined as a biologic, synthetic or semi-synthetic matrix with special mechanical properties and provides a necessary microenvironment for cell growth and differentiation. The second component is the stem cells 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 also can 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. The tissue grows inside the body and the results of this technique are very promising and probably will be widely used in future.

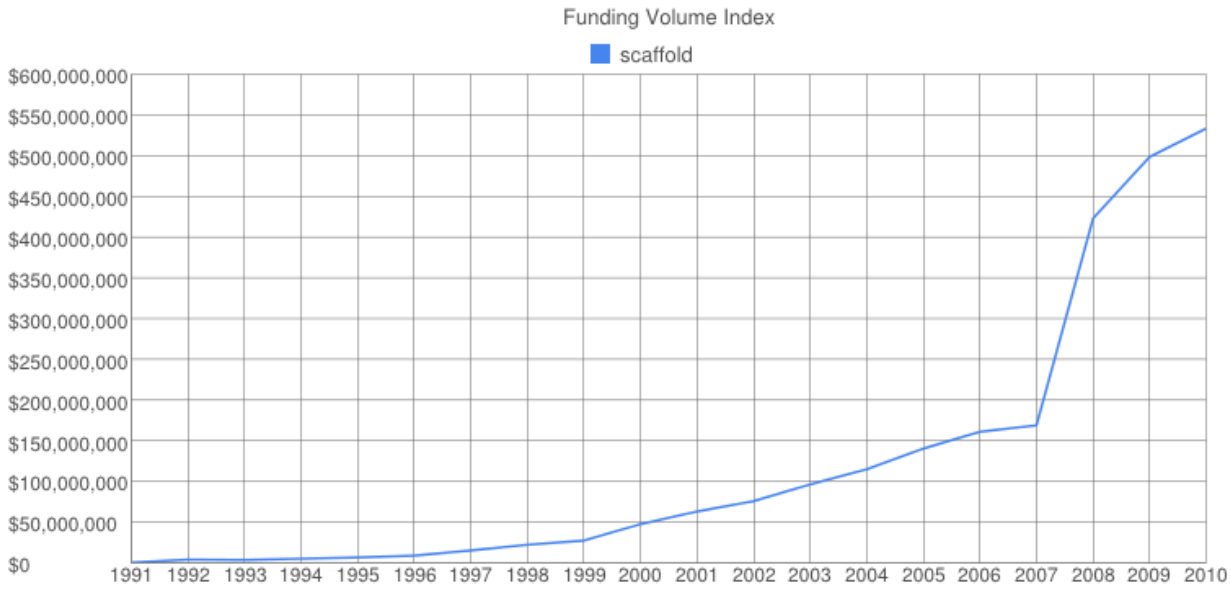

Chart 9: Funding* in the field of scaffolds.

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Another modification of 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 scaffolds 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).

6. ORGANS

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 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.

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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 these cells were combined in a dish and they self-organized into macroscopic cell clusters. Upon transplantation, these clusters were functional and showed good vascularization (Takebe et al, 2013).

C. BLADDER

Bio-engineered bladder has already been created and successfully transplanted using a biodegradable scaffold and cells from the bladder and 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 upon (Horst et al, 2013).

D. CARDIOVASCULAR SYSTEM

In successful rat experiments scientists used decellularized hearts as scaffolds (Maher, 2013). In these experiments. 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 clinic, 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 allogenic or even xenogenic origin.

F. PANCREAS

Animal experiments on lab-grown pancreas are rather promising (Science daily, 2012). Researchers have succeeded in growing small functional parts of 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.

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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 one month after transplantation.

H. TEETH

Usage of stem cells for the regeneration of teeth is 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 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 and with problems of rejection, making the approach extremely attractive for many investigators.

I. BONES AND CARTILAGES

Different types of grafts are already used in clinic. It can be allografts or autografts. Special scaffolds and adult stem cells are used for these purposes. Nowadays scientists try to create the whole bones using 3D bioprinters.

7. DISEASES

The main goal of regenerative medicine is to treat different diseases, some of some of which are extremely severe and seriously affect patients' 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 cost. According to the Alliance for regenerative medicine, healthcare cost in the USA alone is 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.

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A. CARDIOVASCULAR DISEASES

Cardiovascular diseases (CDVs) are diseases which affect 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 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 (http://www.who.int/cardiovascular_diseases/en/). 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 a lot of benefits in treatment of cardiovascular diseases and there are a number of products in the market catering to the branch of cardiovascular diseases.

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 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 (http://alliancerm.org/disease/cardiovascular-and-regenerative-medicine).

B. CANCER

Cancer is comprises of 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 World Health Organization cancer is the third cause of death in the world.

Transplantation of hematopoietic stem cells is widely used in clinic for the treatment of blood cancer. Scientists also try 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.

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Cancer is associated with huge economic burden to the 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 dingle progenitor, the pluripotent hematopoietic stem cell. These cells have been widely used in clinic. 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 the regenerative medicine as these wounds do not undergo the normal healing process. They can be caused by burns or are 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 500000 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 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 the 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

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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 (Duke & Taylor, 2013).

F. NEUROLOGICAL DISEASES

Neurological diseases encompass diseases which affect various parts of 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 life of the 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 patients. At present, there are several commercial products which could help in treatment of spinal cord injuries. Some of them are based on the use of stem cells, which can differentiate into the cells of nervous system; others use special scaffolds to provide appropriate conditions for the regeneration of spinal cord. 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 are affect 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

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field. There are a number of promising animal experiments which can lead to treatment of the diseases which cannot be treated now.

Some available products:

1. Advanced Cell Technology has developed a treatment of 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 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 digestive tract. Some of them 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 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 the patients after removal of bladder. They have also developed a stem cell technology for augmenting and repairing the kidneys (http://www.tengion.com/pipeline/kidneys.cfm).

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 by the action of 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 Centers for Disease Control and prevention In the USA more than 20 million people suffer from arthritis.

Some available products for musculoskeletal disorders include:

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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 act 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 pancreas. If a patient has type 1 diabetes, these cells are attacked by 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 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 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 Phase 2 clinical trial of their product.

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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 are conditions when immune system begin 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, 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 treatment of different autoimmune disorders. Placenta-derived stem cells are used in this technology. The company has already launched a Phase 2 clinical trials 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 the 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 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.

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EXAMPLES OF ANALYTICS USING ARMIF

1. BIOTIME, INC.

Ticker symbol: BTX
Year of foundation: 1990
Address: 1301 Harbor Bay Parkway, Suite 100, Alameda, CA 94502, United States
Phone number: (510) 521-3390
Fax number: (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 cells 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 subsidiary 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. Another subsidiary, ES Cell International Pte. Ltd (ESI), has develops and markets hES cell lines. ESI has agreements 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

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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

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Company's ARMIF

Diseases	Cardiovascular diseases	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 cartilages			
Tissue	With scaffold				Without scaffold							
	Autologous		Allogeneic		Isogenic		Xenogeneic					
	Connective		Muscle		Epithelial		Nervous					
Cells	Autologous		Allogeneic		Isogenic		Xenogeneic					
	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

High	Medium	Low

Source: ***Yahoo Finance (http://biz.yahoo.com/e/130809/btx10-q.html)***

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2. OSIRIS THERAPEUTICS, INC.

Ticker symbol: OSIR
Year of foundation: 1990
Address: 7015 Albert Einstein Drive, Columbia, MD 21046-1707, United States
Phone number: (510) 521-3390
Fax number: (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 company joined JCR Pharmaceutical Corporation to produce and market Prochymal in Japan. Another product in the therapeutic segment is called Chondrogen and aimed at osteoarthritis and cartilage protection.
Biosurgery segment develops, manufactures and markets products orthopedic, wound healing, and surgical procedures. 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 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.
C. Randal Mills, PhD, Pres. & CEO
Philip R Jacoby, CFO
Michelle LeRoux Williams, PhD, CSO
Lode Debrabandere, PhD, COO
Stephen W Potter, SVP, Ops. & Corp. Dev.

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Company's ARMIF

Diseases	Cardiovascular diseases	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 cartilages			
Tissue	With scaffold				Without scaffold							
	Autologous		Allogeneic		Isogenic		Xenogeneic					
	Connective		Muscle		Epithelial		Nervous					
Cells	Autologous		Allogeneic		Isogenic		Xenogeneic					
	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

High	Medium	Low

Source: *Yahoo Finance (http://finance.yahoo.com/q?s=OSIR)*

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3. STRATATECH, INC.

Ticker symbol: **private**
Year of foundation: 2000
Address: 505 South Rosa Road, Suite 169, Madison, WI 53719, United States
Phone: (608) 441-2750
Fax: (608) 441-2757
Web-site: www.stratatechcorp.com

Profile:

The company is using this progenitor cell line to create a portfolio of therapeutic skin substitutes to treat severe burns, non-healing ulcers, and other complex skin defects, as well as create novel three dimensional cellular models that researchers can use as an alternative to animal testing to evaluate the effects of new chemicals and compounds on human skin. The company was founded in 2000 to commercialize the discovery of NIKS cells - a human keratinocyte cell line that produces living tissue nearly identical to native human skin-made at the University of Wisconsin-Madison. Its proprietary product StrataGraft tissue, is a viable, full-thickness human skin substitute being developed as a treatment for severe burns and other complex skin defects. In June 2012, StrataGraft was designated an orphan drug by the U.S. Food and Drug Administration for the treatment of partial and full thickness skin burns. In January 2013, the Company has successfully finished proof-of-concept clinical trial of StrataGraft in severe burns. And in July 2013, Stratatech was awarded a contract valued at up to $47.2 million by the U.S. Department of Health and Human Service's Biomedical Advanced Research and Development Authority (BARDA) for the advanced clinical and manufacturing development of StrataGraft skin tissue.

The company is also developing another class of products called ExpressGraft, which is genetically enhanced tissues that produce elevated levels of natural wound healing and anti-microbial factors. Clinical development for ExpressGraft products will focus on large, underserved markets in chronic, non-healing ulcers, including diabetic foot ulcers, venous leg ulcers and sclerotic digital ulcers. It is anticipated that the ExpressGraft antimicrobial product will enter a Phase I clinical study in diabetic foot ulcers in late 2013.

Company's intellectual property portfolio comprises nearly 50 US and international patents and patent applications.

Top management:
B. Lynn Allen-Hoffmann, PhD, CEO & CSO
Russell R. Smestad, President
Robert T. Barnard, CPA, VP & Treasurer
Allen R. Comer, PhD, Director, R&D

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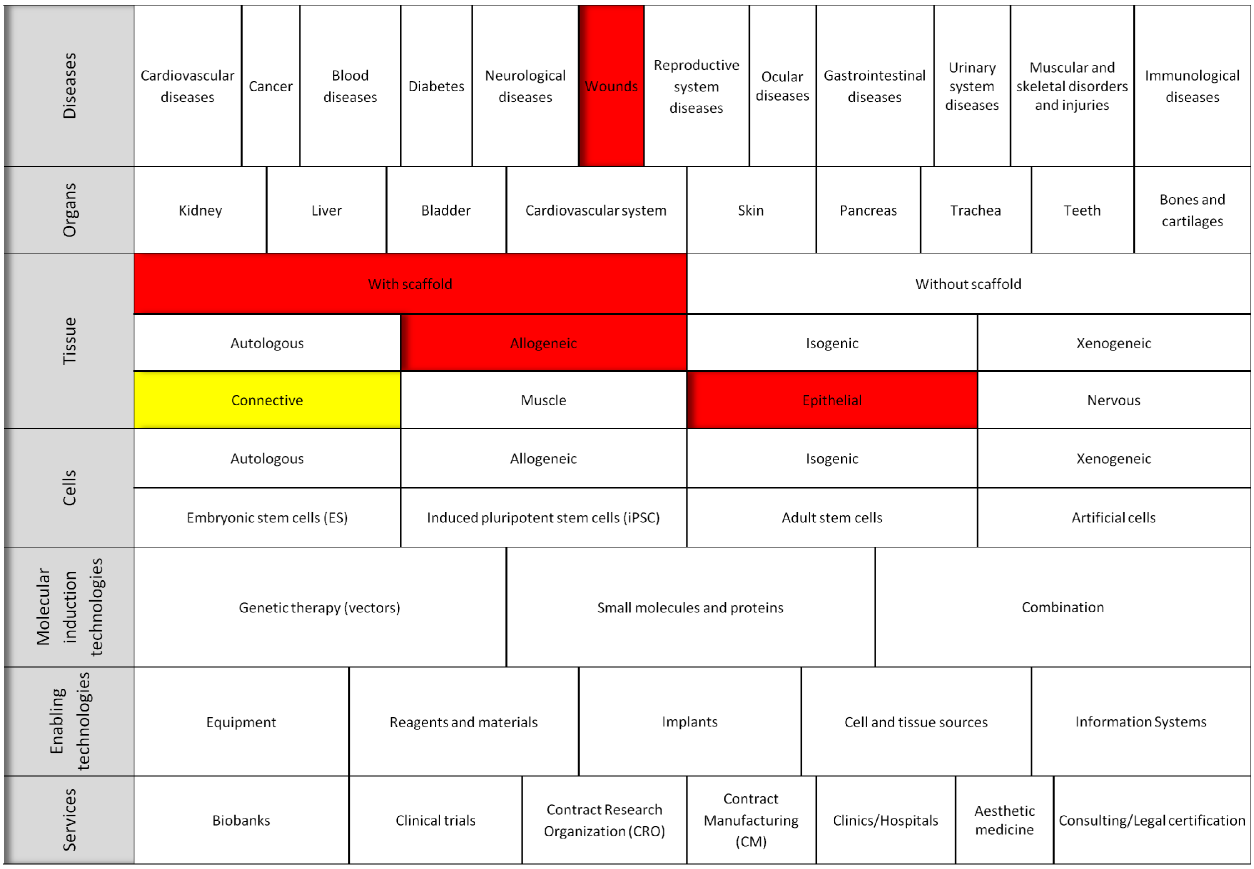
Company's ARMIF



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