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Regenerative Medicine: A Scaffold Therapy in Heart Regeneration Through Tissue Engineering.

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ABSTRACT

- Organ and tissue loss through any injury motivate to formulate or develop new techniques that can generate tissues and decrease the dependency of transplantation. Regenerative medicine is an interdisciplinary field that solely depends on the principle of engineering and life science. These techniques used to fabricate cell sheets on biomaterials and then grafted it on host tissues to heal injury. Regenerative medicine involves use of substrate such a bioreactors and growth factors with cells and scaffold, which shows increase in the regenerative capacity of host tissues by using cell injection or immune modulation. Object of the present research is to reprograming of somatic cells to pluripotent cells that holds huge potential of regenerative medicine. Tissues are grafting in 3D construction by different techniques in tissue engineering. Bio-printing is an enabling technology of tissue engineering that promises to fabricate highly mimicked organs with a digital control. It gives the understanding of biomaterials and stem cell biology to integrate various printing mechanism for multi-phase tissue engineering.

Keywords: Regenerative medicine, Tissue engineering, Scaffold, Bio-materials, 3D Bio-printing, Cardiac regeneration.

INTRODUCTION

Heart failure – Dilated cardiomyopathy is a leading cause of mortality worldwide, accounting 9 million death per year. Increases in the number of scar tissues in heart result into loss of contractibility and blood circulation deficiency; that progressively leads to fatal heart failure followed by fibrosis, loss of myocardium tissue, cardiac dysfunction and dilatation. Myocardial infarction is the main cause behind damaging of heart muscles. It defined as heart attack, which decreases in blood flow in arteries. It is accompanied by signs such as sweating, nausea, chest pain and fainting. It may arise when heart tissues are occluded, resulting in deprivation of adequate oxygen supply at tissues. The healthy human left ventricle (LV) is about 1 cm thick, and changes may occur to the shape, size and structure of it as of severity of disease4.

The different types of Cardiovascular diseases include Cerebrovascular disease, Rheumatic heart disease, Congenital heart disease, Peripheral arterial disease, Coronary artery disease and Deep vein thrombosis while the cardiac disease include Angina, Coronary artery disease, Congenital heart disease, Arrythmia, Heart attack, Heart failure, Dilated cardiomyopathy, Mitral regurgitation, Hypertrophic cardiomyopathy and Aortic stenosis.

Myocardial Infarction

Symptoms and risk factors of Myocardial Infarction

The symptoms of Myocardial Infarction are High pressure, Irregular breathing rhythm, Dizziness, Fatigue, Nausea and Discomfort to jaw, neck or arms. The risk factors include Hypertension, Obesity, Stress, Smoking, Atherosclerosis, Physical inactivity, Excessive alcohol consumption and Poor sleep hygiene.

Diagnosis and process of healing of Myocardial Infarction

The myocardial infarction can be diagnosed by Blood test, chest x-ray, electrocardiogram, echocardiogram, CT scan, MRI and myocardial biopsy. The healing of myocardial infarction occurs in the flow as shown in (Figure 1).

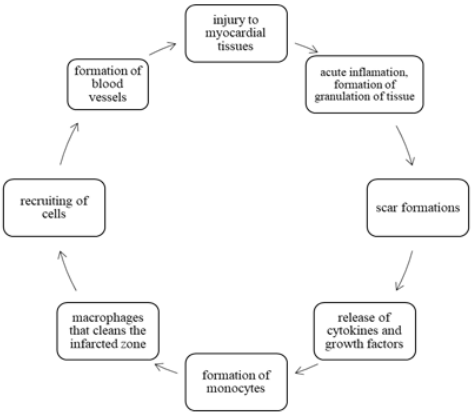

Figure 1: The process of healing of Myocardial Infarction.

Traditional therapies to treat myocardial infarction and its limitations

Existence of Cardiovascular diseases or myocardial infarction or heart disease causes millions of deaths of cardiomyocytes which triggers the remodelling of heart and at the end leads to chronic heart failure. Recent public research data indicates that renewal rate of cardiomyocytes reaches 1% at age of 20 and it decrease down to 0.4% at age of 70. The conventional approaches used for the treatment of myocardial infarction includes Fibrinolytics, Aspirin, ACE inhibitors, β- Blockers, ARB blockers, Surgery and Heart transplant. Traditional therapies as only cures the disease in some extent, despite unable to regenerate healthy heart cells. Traditional therapies cannot be able to decrease the severity of ischemia, leads to reperfusion- associated condition which may lead to death. Reconstruction of left ventricular has not been found an accepted treatment in medical era. Conventional therapeutic strategies can only be able to delay the disease instead of reversing or stopping of disease occurrence. Heart transplantation is the only curative approach in current therapies.Due to the higher rate of disease occurrence and higher cost of medical care systems it claims for novel approach over the conventional health care system. End stage cardiac disease may become refractory to therapy. Synthetic grafting material may be used in place of natural cells, which may show decrease in activity performance of tissues. Synthetic materials may prone to thrombosis and deposition of calcium, that lack the ability of tissue to grow [1].

Regenerative medicine – A concept

Organ transplantation is the only backbone, which decreases the morbidity of heart failure. Though, difficulty in immune suppression and insufficiency of donors limits the application of its medical era. Dependency on organ transplant may resulted into waiting list of patients requiring donated organs and supply cannot meet up with demand. Use of direct seeding of cells or implantation of growth factors has shown less effect and limited cost - effectiveness as short half-life of growth factor directly affects the activity of growth factors.Myocardial contraction activity can be improved by ventricular assisted device, but it may cause complications such as bleeding, right ventricular failure, blood clotting or infection to the vessels connected with heart. Hence, generation of abundant supply of tissues and organs is the challenging task in the current life. Many inventions have been conducted to decrease the shortage of donors and increase the use of donated organs with high efficacy. As a result, alternative medical therapies are in interest to reverse the disease condition. Regenerative medicine is an interdisciplinary branch which works on the principles of engineering and life science to promote regeneration and subsequently decreases potential of disease. Regenerative medicine is "a branch of transitional research in tissue engineering and molecular biology which deals with process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal functions". It is a promising tool that has the ability to reconstruct the injured tissues and organs by stimulating the body's healing mechanism[30]. It includes the concept of formation of tissues and organs in laboratory and then injected them when body rejects to heal itself [2].

Regenerative medicine is a group of biomedical approaches that involves use of stem cells such as immune modulation therapy, cell therapies (stem cells injection or progenitor injection) and tissue engineering. Regenerative medicine concept has given promising results for the reconstruction and replacement of different types of tissues and organs including heart, skin, kidney and liver.System often involved mechanical and structural properties of tissues for proper functioning which is performed by artificial -created system. The system has the capacity to enhancing regenerative capacity of host by changing in environment. It holds the promise to treated genetic disease. Repairing or replacing the damaged tissue involves combining active molecules, cells, and scaffolds into new and functional tissue. Here scientist grows tissues outside the body to replace damaged tissues. Current

examples of this process are artificial cartilage and skin (tissue engineering). It helps to trigger the regenerative capacity of body to treat untreatable injuries and helps to cure faster with more efficiency [3].

A pain-free future

Living with chronic pain makes the routine life very challenging. No longer the effect of medications make a person frustrated and high dose of medication and its side effects makes the person miserable. While physical therapy works in a slower rate of healing. Platelet rich plasma or stem cell therapy or artificial organ transplantation are the examples of fast recovery from chronic pains. Regenerative medicine concept decreases the side effect of medications as well. It also helps in reverse devasting of damaged organs such as heart, brain disorders, and lung disorders.

Types of regenerative medicines

Four focusing field exist within the branch of regenerative medicine. These include:

Cellular Therapy: Natural healing mechanism is existing within the body. Presence of stem cells in the body has the ability to heal the damaged tissues or organs. Stem cells are implanted or injected within the injured area of tissues or organs using different approaches. Stem cells to be taken for regeneration may of the same person or of other persons who have same capacity as that of patient. Stem cells are proliferated outside the body in laboratory with the base of scaffolds and growth factors or bioreactors. Induced pluripotent or stem cells are used. hCMPCs and hiPSC-CMs are popular choices for 3D bioprinting [4].

Tissue Engineering: The main goal of regenerative medicine is to cure patients without transplantation of whole new organ. There is no guarantee of body whether it accepts the donor organs or not and the availability of organs. Development of a new heart with use of regenerative medicine is preferable rather than heart transplantation.

Artificial Organs: Improvement within the field, it makes possible to form or generate a new organ in the laboratory using patient's own cells or by replacing it with other biomaterials. This approach directly responded to the crisis of donor organs, as it decreases the unavailability of new organs and also decreases the organ rejection.

Clinical Translation: Though not widely used at the present time, clinical translation is a form of regenerative medicine that has the ability to cure heart disease, diabetes, stroke, and a number of other serious health conditions. In these cases, clinicians use healthy cells from the patient's own body as the cure. CRN currently concentrates in the area of providing regenerative medicine physicians with cellular therapy and tissue engineering products, because we believe these areas currently offer the broadest and most immediate promise [5].

Regenerative medicine in heart repairing

Humans heart has no capacity to regenerate or reconstruct the adult cardiomyocytes as it cannot proliferate after injury[4]. Cardiac organ or tissue transplantation may perform in foreign countries with the influence of money. Human myocardium has limited cell division capacity and less capacity to heal itself. Cardiac regenerative medicine is a progressing tool which mainly focuses on the mechanism of cardiomyocytes differentiation. To decrease the morbidity of heart failing, researchers focuses on an approach to induce the heart regeneration. Different types of cells are present in heart; cardiac regenerative medicine presents many unique challenges. The donor cells must have to be compatible with the area of heart where it is grafted and to be compatible with the physiological and electro-physiological characteristics to avoid any dysfunction or arrythmia. Grafted material not only contains cardiomyocytes but vascular network is also attached with cells to meet up with oxygen supply and nutrition. The research was initialized with first generation cell-based therapy, involved translation and transplantation of non-cardiac cells that includes skeletal tissues-expected to give good contractibility to heart, bone marrow-derived cells and mesenchymal stem cells with expected results shows carcinogenic potential.Next generation cell-based therapy used cardiac cells having same property as of stem cells .Another approach involved incubation of functional cardiomyocytes in *vitro* and then transferred into damaged heart through injection. Cell free approaches reprogrammed which focusing on converting cardiac fibroblasts cells to a cardiomyocyte [1].

Challenges comes in regenerative medicine:

The materials used in a combination of growth factors, scaffolds must have the capacity to replace the injured tissues and be able to work with same

efficiency as that of origin tissue. Cells should be taken from the same patient or from another person (allogenic) having same capacity of tissues. Cells used in regenerative medicines are stem cells, fibroblasts, chondrocytes and keratinocytes.

Tissue engineering in heart

Why to go for it

Progression of drug and biologics from concept to market required various clinical testing, dozens of and entails an average cost ranging from $802 million to $2.6 billion per drug. Non-cellular products such as acellular metrics in contrast to medical devices, reaches in market within 3-7 years of development and may undergo an expedited process if they are demonstrated to be similar to pre-existing devices. As such, acellular products may be preferable from a regulatory and development perspective, compared with cell-based products, due to the less arduous approval process. Tissue engineering is a promising therapy for the patients suffering from severe cardiac arrest. Tissue engineering is an approach of regenerative medicine, has the capability to replace the deconstructed organs or tissues by supplying functional cells, supporting scaffolds, growth promoting cells and DNA in the area of heart. Tissue engineering is a field of coding of cell transplantation in combination with various scaffolds. Tissue engineering is a promising approach that restructured the conventional therapies for irreversible myocardial damage, cardiac arrest and enhance the quality of life of millions.

In conventional treatment, mechanical and biological prosthetic valves are used in valve replacement therapy. As mechanical valves have high durability, thrombogeneses or clotting of valve is major concern. Hence, blood-thinning medication shall be prescribed to the patients. On the other hand, in biological prosthetic valves, allografts and xenografts may lead to degeneration of valve over the period of years, may generate immune rejection and blood clotting takes place, in some cases autograft may lead to complicated surgery with possibility of reoperation [5].

Strategy to regenerate heart tissues

Cellular therapy is a revolutionized approach to generate heart muscle and vascular tissues to treat heart disease . It can be classified in to two; in *vitro* generation of tissues in cultured dish and in situ generation.

In *vitro* tissue generation includes the following steps:

- Generation of cardiac graft using cell seeded scaffold.
- Formation of cardiac graft from biomaterial gel.
- Printing of cell film using cardiac cells and biomaterials.

In *vivo* tissue engineering is:

- Cell transplantation.
- Injected cell seeded scaffold.
- Recreation of endogenous cells by imbibing unseeded scaffolds.
- Injectable formulation containing scaffolds with or without cells.
- Healing process take place by active moiety.

Cellular repairing steps include:

- Direct transferring of cells into damaged environment,
- Development of replaced tissues by tissues engineering techniques,
- Regeneration of damaged heart by using different therapies (Figure 2).

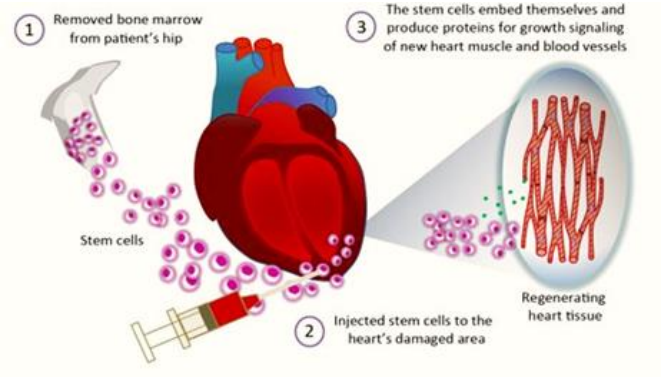

Figure 2: **Cellular Repairing steps.**

The classic tissue engineering strategy is to isolate specific cells through a biopsy from a patient, to isolate them on a three-dimensional (3D) biomimetic scaffold under precisely controlled culture conditions, to deliver the construct to the desired site in the patient's body, and to direct new tissue formation into the scaffold that can be degraded over time[42] (Figure 3).

Cardiac graft

The cardiac grafting focuses on four issues namely:

- scaffold material selection
- scaffold material production
- cell selection; and
- *In-vitro* cell culture.

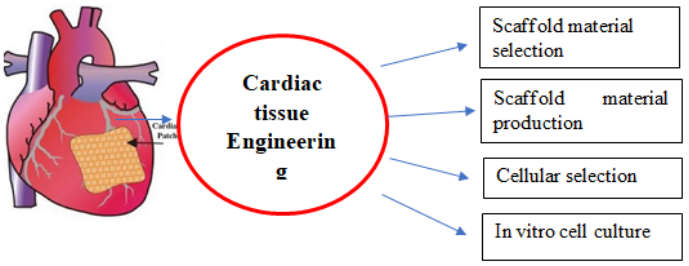

Figure 3: Cardiac graft engineering techniques.

Current achievements in cardiac tissue engineering

The in-*vitro* formulation of heart muscles shows:

- Good contractibility
- Electro-physiologically stable
- Mechanically robust but yet flexible
- Quickly vascularized after transplantation of scaffold.
- Bioreactors: They attribute to enhance the mechanical strength of cells and scaffolds transplantation of tissues constructed to repair heart defects.

Limitation of the conventional tissue engineering approaches

The conventional tissue engineering approaches fail to generate thick, complex and vascularized tissues due to the following limitations

- The effectiveness of cell seeding and penetration to the biomaterial scaffold is still limited.
- Organs with complex structure are usually composed by multiple cell types and biological factors. Precise delivery of cells and biological factors to the desired 3D positions is still far from being resolved.
- Thick tissues possess complex vascular system, which should be enabled within the scaffold. However, the conventional tissue engineering approach has difficulties to construct vascular system within the pre-formed 3D scaffold [2].

Delivery strategies of tissue engineering

Growth factor infused delivery: Growth factors are mixed with cell culture and poured directly on scaffold by manually (seeded scaffold- hydrogel) or mechanically (Bioreactors).

- Scaffold seeding method is widely used in tissue engineering field. Quantified amount of growth factors is mixed with cell culture medium. Poor penetration data decreases the use of drop-seeding method in delivery[246566].
- Bioreactors used in the method to increase the nutrient transport in tissue engineering. commonly used bioreactors are spinner flask, rotating walls and perfusion system which shows improvement in cell viability, proliferation and differentiation[246768]. Because bioreactors having a tendency to infuse GF and nutrients within the scaffold, this type of delivery has proved useful in tissues that naturally lack blood supply or where the vessel ingrowth is challenging.

Programmed delivery

It involves pH- responsive, molecular recognition and triggered delivery[24].

Scaffold immobilization

Scaffold immobilization is a strategy widely employed in TE to protect GF from denaturation conditions such as high-temperature exposure. The incorporation of GF within scaffolds can be classified by their encapsulation method as (i) Chemical encapsulation or (ii) Physical encapsulation.

Micro-encapsulation

Different techniques of tissue engineering

Myocardial tissue engineering by layering cell sheets

In myocardial tissue engineering, various biomaterials such as poly (glycolic acid) (PGA), gelatin, alginate and collagen have been used as prefabricated biodegradable scaffolds. For the repair of damaged cardiac muscle, two strategies have been applied to incorporate cells into the scaffolding materials. One method is to seed cells into prefabricated, highly porous scaffolds the transplantation of tissue-engineered cardiacgrafts using gelatin scaffolds could replace myocardial scars and right ventricular outflow track defects (Figure 4).

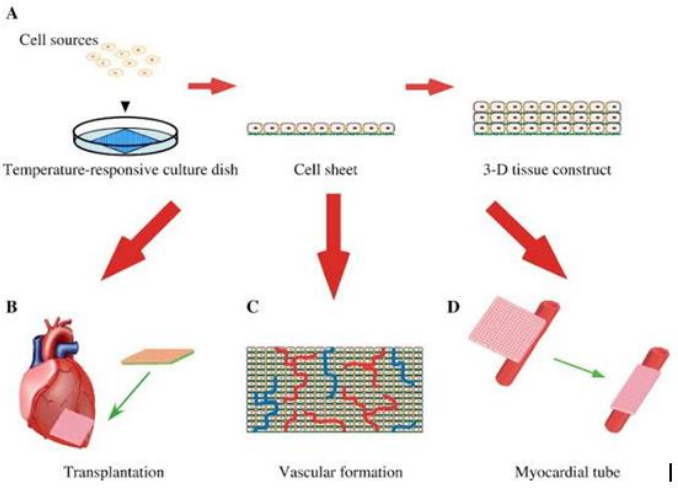

Figure 4: Future views of myocardial tissue reconstruction by using cell sheet engineering.

- 3-D myocardial tissue generated by using cell sheets. As candidates for the source 4. Problems and future perspective of myocardial tissue engineering
- Transplantation of the layered cell sheet constructs directly to impaired hearts.
- Thick cardiomyocyte grafts with well-organized microvascular networks.

- Myocardial tubes as independent cardiac assist devices.

Preparation of cell sheet

- Pouring of stem cells or keratinocytes onto a temperature-responsive culture dish, incubate the cultured cells at 37°cin a carbon dioxide incubator for few days to produce a coalescent culture.
- Critical step- period for the formation of cell sheets and seeded cells are highly depends on type of cells used.
- Transfer of coalescent culture into a separate co2, incubate it the culture at 20°c to set a cell sheet. Cell sheet can be detached after 60 minutes.

Fabrication of 3D tissues

It is done by layering cell sheets using simple pipetting method or using a hydrogel coated plunger-like manipulator.

Simple pipetting method

- Detaching of cell sheet through a tip of pipette
- Transfer the cell sheet into another culture medium
- Pull out remaining culture medium and incubate the cell sheet at 37°c for 30-60 min in a CO_2 medium to evoke adhesion n between cell sheet and culture medium surface.
- Transfer the dish in another incubator and incubate it at 20°c to detach other layer.
- Transfer second layer sheet on first layer cell sheet.
- Removing of excess of culture medium and incubate it again at 30°c to generate an adhesion between two cell sheet layers.
- Repeat the steps to construct a 3D structure of cells (Figure 5).

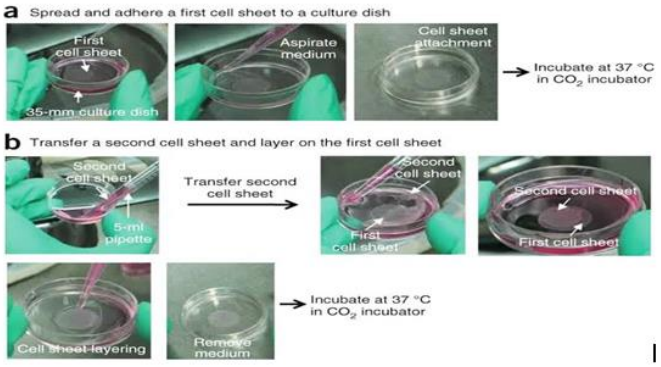

Figure 5: fabrication of 3D tissue with simple pipetting method.

Fabrication of 3D cell-dense tissue using a manipulator

- Apply hydrogel on plunger- like manipulator and silicone molds. Remove the excess of hydrogel using needle.
- Remove the culture medium from temperature responsive culture dish and prepared coalescent cells. Place the plunger with hydrogel over the dish.
- Incubate the medium in CO_2 at 20°C (Detachment of cells from culture dish)
- Lift up the plunger that holding cell sheet.
- Place the plunger on the other cell sheet and incubate it at 37°c.
- Fibrin gel has been used.
- Stack the cell sheets to make a multilayer construction (Figure 6).

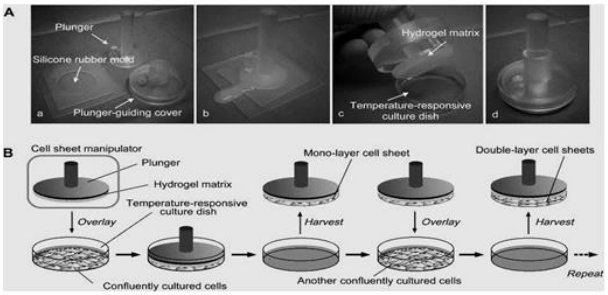

Figure 6: Preparation of a hydrogel-coated, plunger-like manipulator and cell sheet manipulation.

3D bioprinting

3D bioprinting is the combined field of material science, cell biology, and tissue engineering. In order to mimic human tissue, 3D bioprinting must be able to capture the complex structure of the extracellular matrix (ECM) and the different cells present in different tissues. Major advance and innovations are being made in the fields of tissue engineering and regenerative medicine and have a huge impact on three-dimensional bioprinting (3D bioprinting) of tissues and organs. Hydrogel is used as a natural scaffold to graft cells. The different steps of 3D bio-printing are as shown in (Figure 7).

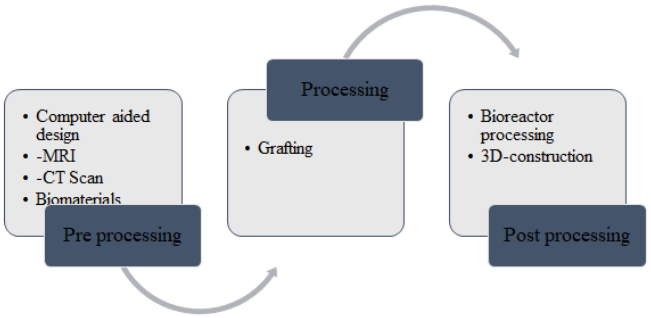

Figure 7: Steps in 3D bioprinting.

Different techniques of bioprinting

Laser-assisted bioprinting

- This process uses laser energy to pattern cell sheet bioinks in a three-dimensional arrangement with the help of computer aided design and manufacturing. With the features of high resolution and reproducibility, the process is more widely used in biomedical science such as cell printing.
- The instrument is made up of laser source, laser transparent printing ribbon coated with a sheet of cell-laden bio-ink and a substate. The process includes laser -induced forward transfer, absorbing film assisted laser induced forward transfer and LG DW. as the process is non-contact process, it results into high post printing cell viability. Existence of nozzle free approach, clogging problem is eliminated (Figure 8).

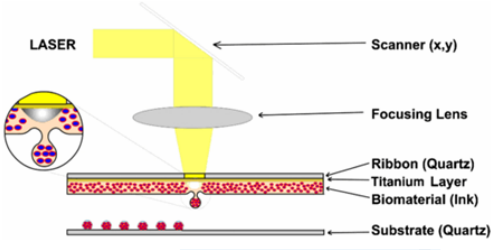

Figure 8: lase based bioprinting.

Droplet based bioprinting

The method involving eject of cell in form of droplets. The process is further classified into inkjet bioprinting and piezoelectric, electro-hydrodynamic jetting and microwave-based printing (Figure 9).

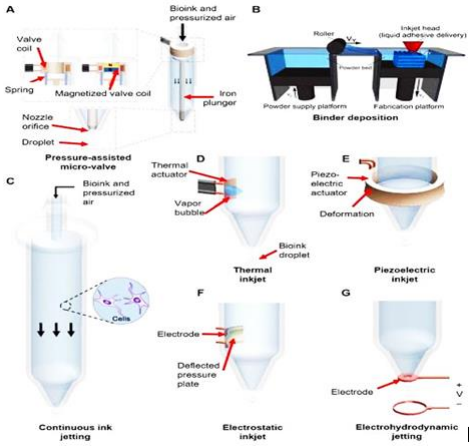

Figure 9: Droplet based bioprinting.

Extrusion based bioprinting

The bioink is extruded out of the nozzle using pneumatic pressure or mechanical force by means of a piston or screw. Extrusion-based bioprinting had been used to bioprint cells, tissues, organ modules, and organ-on-a-chip devices, for tissue engineering, cancer research, drug testing, and transplantation (Figure 10).

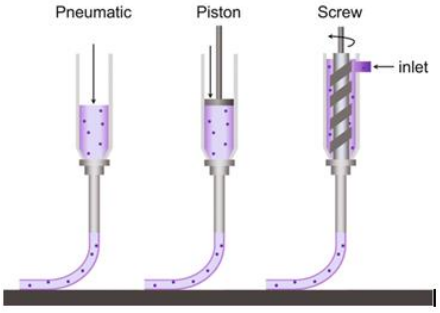

Figure 10: extrusion based bioprinting.

Stereo lithography

Stereolithography bioprinting shows the highest resolution (~6 μm) among other bioprinting methods. With the advent of two-photon polymerization based stereolithography, very high resolution in nanometre scale (~200 nm) could be obtained. As it is a nozzle free technique, clogging problem can be avoided even with the use of high cell concentration.

4D Bioprinting

4D- bioprinting approach has the ability in which an object can change their structure in the presence of stimuli such as cell-fusion or self-assembly takes place (14 cross 101). As 4D bioprinting has ability to promote dynamic, structural and cellular changes with time, it also overcomes the static nature of 3D bioprinting (14 cross 102, 03).

Application of Bio-Materials

To make the regenerative medicine concept successful, materials used in combinations of scaffolds, stem cells and growth factors, must able to stimulate regeneration of original tissue. Materials used in the bioprinting of cells shall be non-cytotoxic, biodegradable, printable, grafted, good adhesive property with tissues within body. Ideal biomaterials have the capacity to enhance the tissue formation in host and avoiding secondary surgery removal. It should also possess properties that promote cell adhesion, migration, maturation, proliferation and differentiation.

- Natural polymers: it includes gelatine, collagen, alginate, chitosan, hyaluronic acid and agarose.

- Collagen is a derived component of ECM printed at lower temperature and form a solidify gel at body temperature.
- Hyaluronic is used in the regeneration of cartilages.
- Encapsulated alginate and gelatin composition with cardiomyocyte are used in the generation of cardiac tissues.
- Porosity of chitosan is important for the cell replication and integration. A multi-layered porous scaffold of chitosan-gelatin hydrogel used in cardiac repair.
- chitosan-hyaluronan/silk fibroin patch shows reduction in LV dilatation and improve heart function[73]. Non-adherent property of chitosan may be improved by combining with lower compressive moduli which increase tissue integration and mechanical stability for heart regeneration.
- alginate has good gelation capacity and non-thrombogenic property
- synthetic polymers: such as Poly(ethylene) glycol, calcium phosphate, hydroxyapatite, poly lactic acid, poly glycolic acid as well as poly-caprolactone are widely used in bioprinting (Table 1).

Biomaterials	**Advantages**	**Limitation**
Collagen	Excellent biocompatibility and biodegradability	Low elastic modulation
Chitosan	Porosity, high elastic modulation	Non-cell adherent
Alginate	Gelation capacity, non-thrombogenic property	Lack of integration with cardiac cells
Synthetic materials	Improved mechanical properties, excellent strength and durability, lower risk of infection	Toxicity, low biocompatibility

Table 1: Advantages and limitations of biomaterials.

Cardiac patch

The heart muscle patches is of about 100-µm-thick tissues, implanted on the epithelialized surface of damaged heart. Several reasons may account for it (Figure 11).

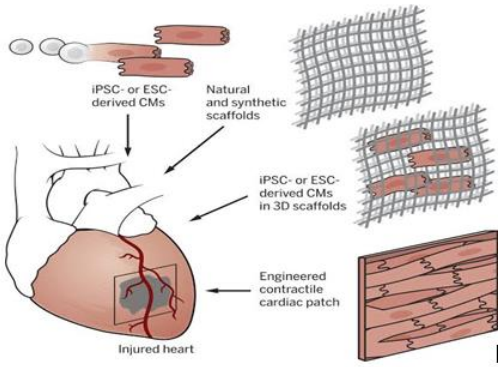

Figure 11: Implanting stem cell–derived cardiomyocytes for regeneration.

Challenges in application of myocardial tissue engineering

The various challenges involved in implementation of myocardial tissue engineering is as indicated in (Figure 12).

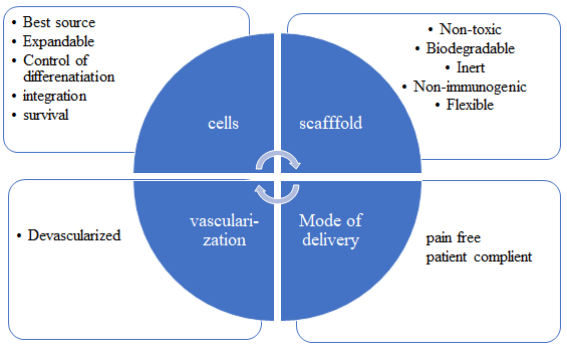

Figure 12: Challenges in application of myocardial tissue engineering.

Advantages of bioprinting

3D bioprinting is widely used approach over other tissue engineering field and shows great potential due to its controllable morphology and high resolution. use of bioprinting is increased in engineering of biomimetic heart valves as it shows accurate replication of complex biomimetic structure, fabricate mechanically heterogenic structure and have the ability to control the over proliferation of cells. Bioprinting functional cardiac patches could help in the treatment of patients with myocardial infarction, and bio printed blood vessels in the valve-replacement surgeries. Focussed efforts on bringing bio printed valves (from patient's own cells) to the clinical practice are necessary to replace the mechanical and bioprosthetic valves currently in the market. Avenues to use iPSCs also should be explored further, given the limited availability of primary cells. Formulating an ideal 'cardiac bio-ink' with appropriate stiffness and cell microenvironment is still a challenge, and development of in situ cross linkable bio-inks with spatially and temporally controllable crosslink rate and degree is an interesting future direction. Though the macrostructure of the whole heart could be printed and partially functional cardiac tissues could be bio printed, bioprinting (organ printing) of a fully functional heart is still very far from reality.

Future direction in the perspective of heart regeneration

Achievement in material sciences, tissue engineering and nanotechnology has led to an explosion in the variety of frameworks available for tissue grafting in heart tissue regeneration. Many ideal biomaterial-cell combinations are in the pipeline to decrease the obstacles. Current individual biomaterials have less capacity to meet elasticity as of native myocardium and encapsulated cells. Since the electrophysiological characteristic is essential in heart as the largest bioelectrical source, synthesizing conductive materials may facilitate the beating of cardiomyocytes. It enhances the link in-between transplanted patch and host myocardium. Another challenge in this process is to select selected cells and biomaterials with ability to exchange gases, nutrients and metabolic products within normal organ and 3D patches. In near future, development of in *vitro* heart regeneration has the ability to completely mimic the use of donor organs, which increase the effect of health care medicines as well as improves the quality of life too.

Regulation of regenerative medicine in India

India has its own separate guidelines for some regenerative medicine subsectors, governed by ICMR, while other fields have no written regulations and guidelines. social science research has demonstrated the key role that regulation plays in constituting emerging technological domains by stabilizing markets through establishing common standards, creating professional norms and building consumer confidence. For the stem cells, following previous revisions of 2007 guidelines in 2013, the ICMR and the DBT have issued new guidelines in October 2017. A key change from 2007 is that the guidelines dispense with the potentially misleading reference to 'therapy' in the original title, preferring the simpler *"Guidelines for Stem Cell Research"*. The above change was commended by the ISSCR. As per guidelines research in stem cell is classified into three categories, namely: permitted; restricted; and prohibited. For instance, research on the human germ line and reproductive cloning is prohibited. However, research on *in vitro* studies on embryonic stem cells or induced pluripotent stem cells or somatic cells, intended to enhance understanding in basic stem cell biology, and may be permitted with prior approval of the Institutional Committee for Stem Cell Research. The 2013 guidelines clearly stated that "stem cells are still not a part of standard of care; hence there can be no guidelines for therapy until efficacy is proven. These guidelines are meant that covers only stem cell research, both basic and translational, and not therapy. It clearly defines that the used of stem cells in patients other than that for hematopoietic cells for approval are in investigational steps. Use of any stem cells in patients can be only done by approval of clinicians and continuous monitoring of clinical trials with the intent to advance science and medicine, and not offering it as therapy". The 2017 guidelines reiterated the same. Those guidelines, therefore, strongly discouraged any therapeutic applications of stem cells, other than hematopoietic stem cells in patients. However, some commentators on the draft 2017 stem cell guidelines have argued that the current section 8 of the guidelines (section 7 in the final guidelines) is controversial by "defines level of stem cell manipulation as minimum and major which is absolutely unnecessary and gives clear escape route to push unapproved stem cell for therapy by the clinicians". In particular they argue that: "sometimes patients are not ready to understand the terminology and argue with clinicians. Clinicians use adipose-derived stromal cells or bone marrow cells that do not require any clinical trials." The ISSCR has also expressed concerns over the use of stem cell derived from bone marrow. In addition, research guidelines cannot compel clinicians to follow its mandates, as the ICMR has no jurisdiction over their professional conduct. It is up to the Medical Council of India to take action against unethical practice as stem cell treatments still fall within the purview of clinical practice. Though there are a few reported cases of adverse effects linked to stem cell treatments, scientists, social scientists and policymakers are concerned that such episodes damage the reputation of their field and stifle innovation. The 2013/2017 ICMR-DBT guidelines spotlight regulations formulated by the CDSCO for collection, processing, testing, storage, banking and release of umbilical cord blood. Recently, the National Apex Committee for Stem Cell Research and Therapy has taken initiatives against fraudulent advertisements by some companies with the help of the Advertising Standards Council of India. However, as noted previously, tax support for private blood banking contradicts this objective of regulatory control. For the use of stem cells in tissue engineering and scaffolds, the ICMR-DBT recommends ASTM International standards related to biomaterial scaffolds, including US FDA guidelines. In gene therapy, the ICMR has formulated dedicated ethical guidelines, which strongly recommend only somatic cell gene therapy in a situation

where all other options have been exhausted. For the enhancement of genetic characteristic, gene therapy is not permitted.

CONCLUSION

Fabrication of new heart can be achieved through tissue engineering-regenerative medicine technique. Rejection of organs is decreased as cells are taken from patient. Crisis of organs can be decreased as availability of tissue engineered organs are available. Cost of artificial pacemaker or artificial heart is high, can be decreased. Increased accuracy of disease model may improve the efficacy of regenerative medicine strategies and enhance translation of clinical promising approaches.

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