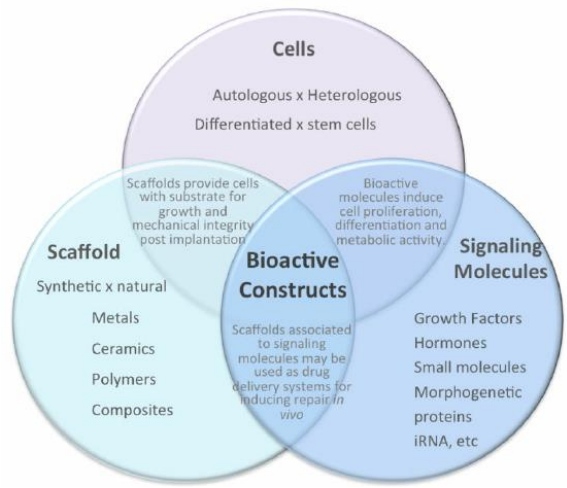
Lecture Notes on TISSUE ENGINEERING

1. INTRODUCTION:

Tissue engineering (TE) evolved from the field of biomaterials development and refers to the practice of combining scaffolds, cells, and biologically active molecules into functional tissues.

The goal of tissue engineering is to assemble functional constructs that restore, maintain, or improve damaged tissues or whole organs.



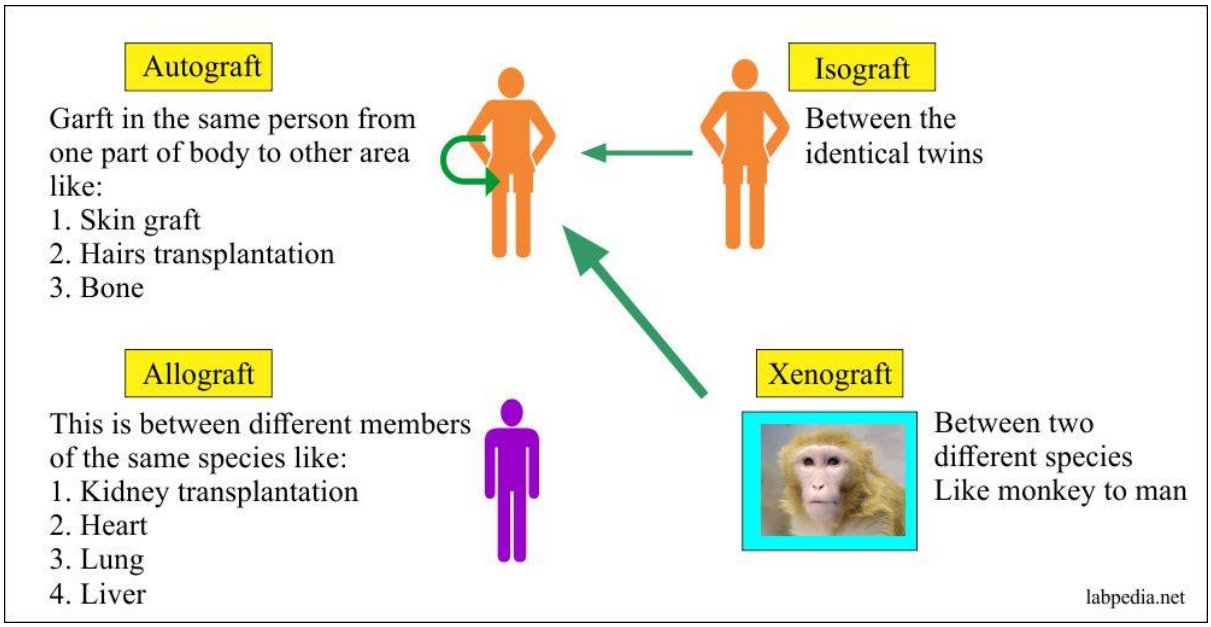
Artificial skin and cartilage are examples of engineered tissues that have been approved by the FDA; however, currently they have limited use in human patients.

Regenerative medicine is a broad field that includes tissue engineering but also incorporates research on self-healing – where the body uses its own systems, sometimes with help foreign biological material to recreate cells and rebuild tissues and organs. The terms "tissue engineering" and "regenerative medicine" have become largely interchangeable, as the field hopes to focus on cures instead of treatments for complex, often chronic, diseases.

Significance of Tissue Engineering:

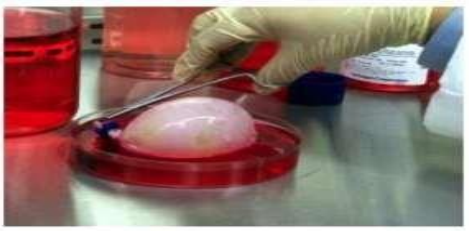
The huge increase in the demand for organ transplantation has occurred due to a surge in organ failure, illness or injury. Due to the limited availability of organ donors, and immunologic rejections associated with animal donors, tissue engineering has emerged as an effective alternative.

- **Tissue Engineering replace or facilitate the growth of diseased or damaged tissue**



Examples of tissue engineered organs:

- Bioartificial liver device
- Artificial pancreas
- Cartilage
- Doris Taylor ‘s heart in a jar
- Tissue engineered airway
- Tissue engineered vessels
- Artificial skin
- Artificial bone marrow
- Artificial bone
- Oral mucosa tissue engineering
- Foreskin



A tissue engineered bladder (left) and trachea (right) seeded with stem cells.

2. Basic principle of tissue engineering

I. **Scaffold:** Biomaterials are used to construct a scaffold

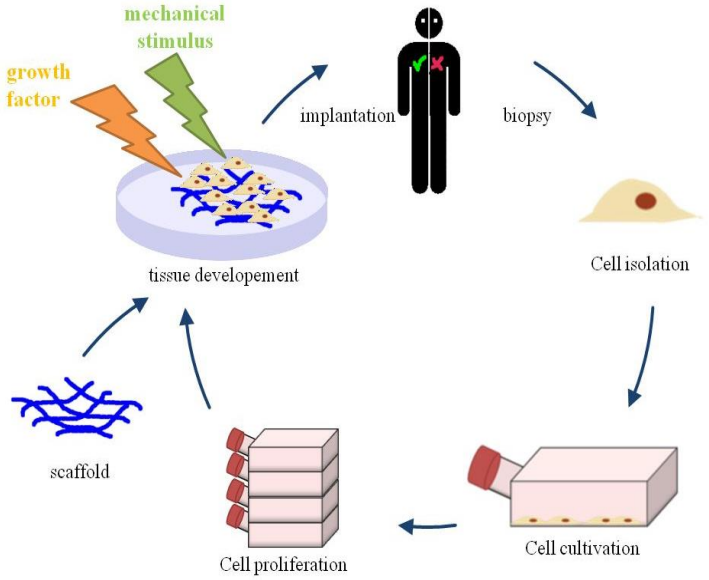
Start building material (e.g., extracellular matrix, biodegradable polymer)

II. **Stem cells** are differentiated into desired cells

- Cells are cultured on suitable scaffold

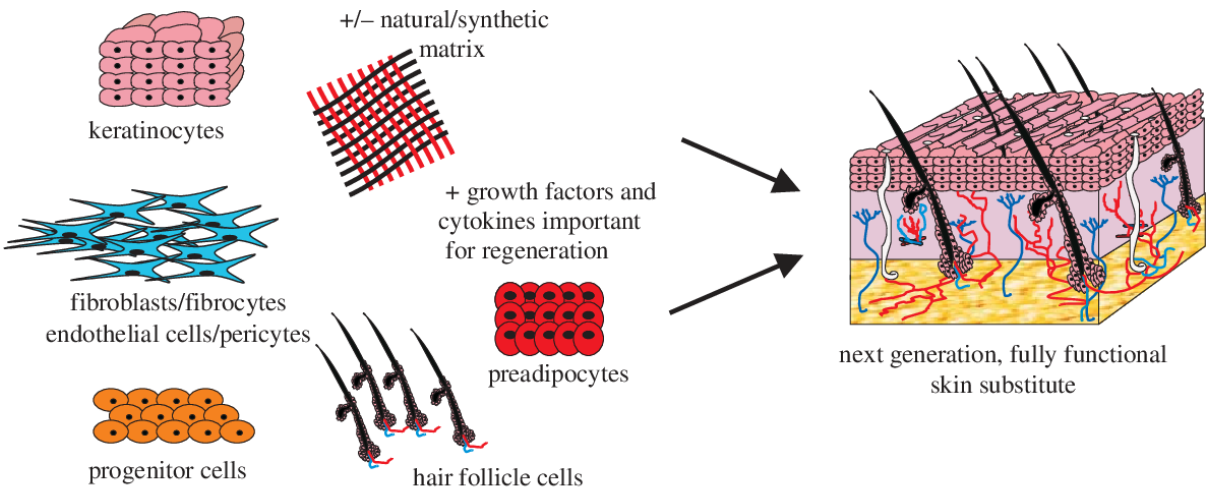
III. **Growth factors** and mechanical stimulus

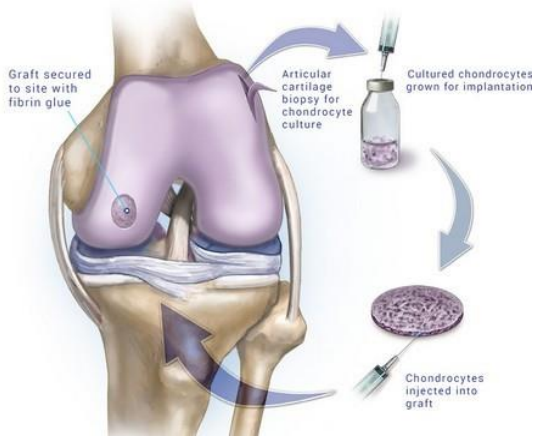
- Cells multiply & fill up the scaffold & grow into three-dimensional tissue.
- **Implanted** in the body.
- Cells recreate their intended tissue functions.
- Blood vessels attach themselves to the new tissue.
- The scaffold dissolves.
- The newly grown tissue eventually blends in with its surroundings.



2. **Cells for Tissue Engineering**

Tissue engineering utilizes living cells as engineering materials. Examples include using living fibroblasts in skin replacement or repair, cartilage repaired with living chondrocytes.





3.1 Stem cells:

A stem cell is a reserve cell that each creature has in its body. The stem cell has the ability to grow into any cell that is required by the body and to multiply, so that it can replace any and all dead or damaged adult cells.

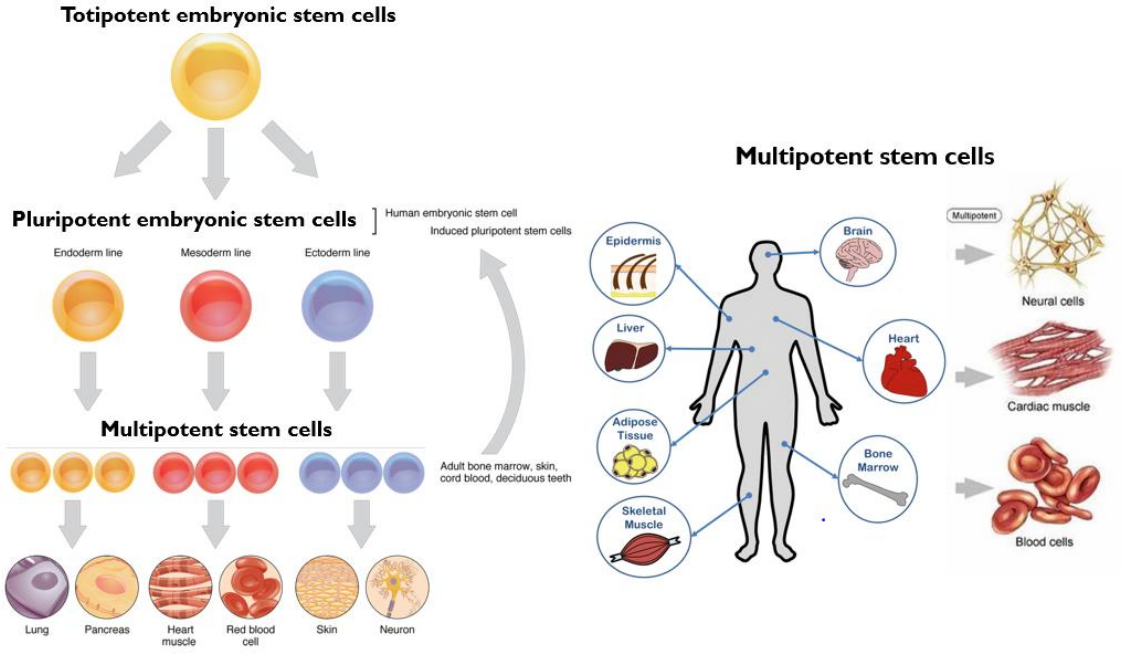
Stem Cells are different from other cells because:

1. **They can continue to divide for long periods of time:** Most cells such as skin cells cannot replicate themselves after a certain period of time. Stem cells are self-sustaining by replicating themselves for a much longer period of time.
2. **They are unspecialized:** Specialized cells have specific capabilities that allow them to perform certain tasks. For example, a red blood cell contains haemoglobin that allows

it to carry oxygen. Stem cells have unspecialized capability and do not have tissue-specific structures to perform specialized functions.

3. **They can give rise to specialized cells:** Stem cells go through a process called *differentiation* and create special types of cells (muscle, nerve, skin, etc.).

Embryonic stem cells have the ability to become a cell for any part of the body (nerve, muscle, blood, etc.). This ability to become any type of cell in the body is called **pluripotent**. The difference between totipotent and pluripotent cells is only those totipotent cells can give rise to both the placenta and the embryo. As the embryo grows these **pluripotent** cells develop into specialized, multipotent stem cells. **Multipotent** stem cells have the ability to develop specific types of cells (terminally differentiated cells). For example, a blood stem cell (multipotent) can develop into a red blood cell, white blood cell or platelets (all specialized cells). There are multipotent stem cells for all of the different types of tissue in the body.



Adult stem cells

Also known as progenitor cells or somatic stem cells, adult stem cells are located, in small quantities, throughout the body and generate specialized cells for the area they are located. These cells do not renew themselves as well as embryonic stem cells. Still, if these cells are

put in a different environment, they may produce a different type of cells from the originating cell.

Recent research indicated that multipotent stem cells from one type of tissue (blood) might actually have the ability to generate cells for a different type of tissue (nerve). Scientists are continuing to search for new sources of adult stem cells. Some of the locations where stem cells have been located include: bone marrow, skin, liver, blood, and the brain.

Some adult stem cells, which have already been used to treat illnesses, include hematopoietic stem cells and umbilical cord blood stem cells. Hematopoietic stem cells are located in the bone marrow and form blood cells. They have been successfully used to treat blood disorders for younger patients. Umbilical cord blood stem cells are located in the blood of the umbilical cord after birth. Umbilical cord stem cells are similar to hematopoietic stem cells in adults, but they are less mature and have much more potential to differentiate into various types of cells.

Stem cells summary

According to their ability to differentiate, stem cells are classified as: totipotent, pluripotent & multipotent

Totipotent cells can give rise to both the placenta and the embryo

Embryonic stem cells:

The pluripotent stem cells are always found in the embryo which can develop into specialized, multipotent stem cells

Adult stem cells or somatic stem cells are multipotent stem cells that are found in various tissues

Multipotent stem cells have the ability to develop specific types of cells (terminally differentiated cells)

For example a blood stem cell (multipotent) can develop into a red blood cell, white blood cell or platelets (all specialized cells).

Unipotent stem cells can produce only one cell type but have the property of self-renewal that distinguishes them from non-stem cells

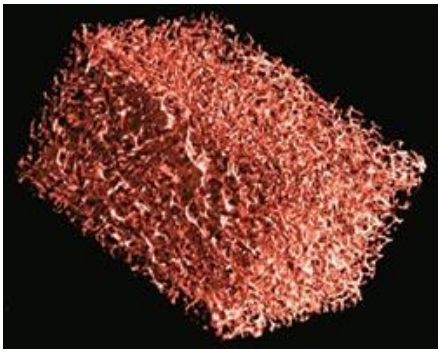
Examples of a unipotent stem cell are a germ line stem cell (producing sperm) and an epidermal stem cell (producing skin).

4. **Scaffolds:**

Cells are often implanted or 'seeded' into an **artificial structure** capable of **supporting three-dimensional tissue** formation. These structures, typically called **scaffolds**

Scaffolds usually serve at least one of the following purposes:

- Allow cell attachment and migration
- Deliver and retain cells and biochemical factors
- Enable diffusion of vital cell nutrients and expressed products
- Exert certain mechanical and biological influences to modify the behavior of the cell phase



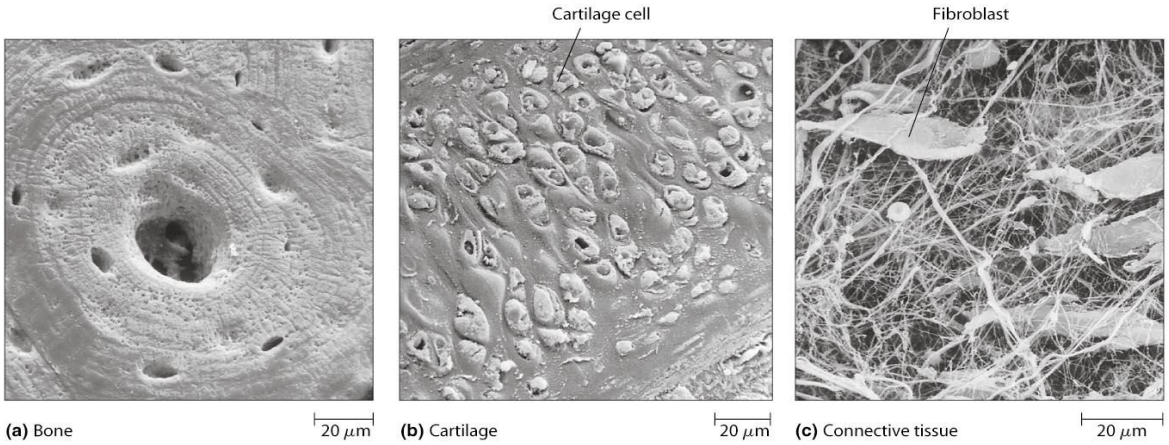
Scaffold should mimic natural ECM

Cells are intrinsically linked to other cells and to the natural extracellular matrix (ECM). They also play a role in mutual recognition of similar cell types.

The natural extracellular matrix (ECM) is the non-cellular component present within all tissues and organs, and provides not only essential physical scaffolding for the cellular constituents but also initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation and homeostasis.

- Many animal cells are intrinsically linked to other cells and to the extracellular matrix (ECM).

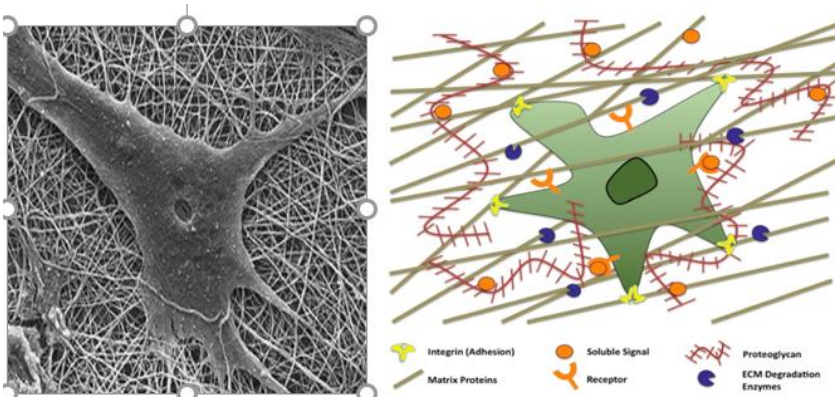
- Cell surface molecules bind to other cells, or to other components of the natural ECM. They also play a role in mutual recognition of similar cell types.
- Bone and cartilage are mostly ECM plus a very few cells. Connective tissue that surrounds glands and blood vessels, is a gelatinous matrix containing many fibroblast cells.

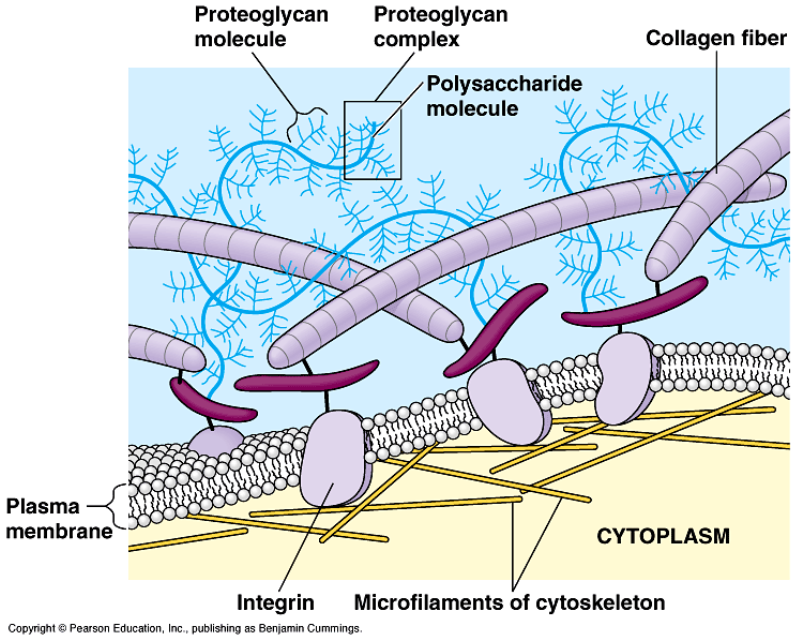


The natural ECM contains 3 classes of molecules:

- Structural proteins: Acts as physical scaffolding (collagens and elastins)
- protein-polysaccharide complexes to embed the structural proteins (proteoglycans)
- Adhesive glycoproteins: to attach cells to the matrix

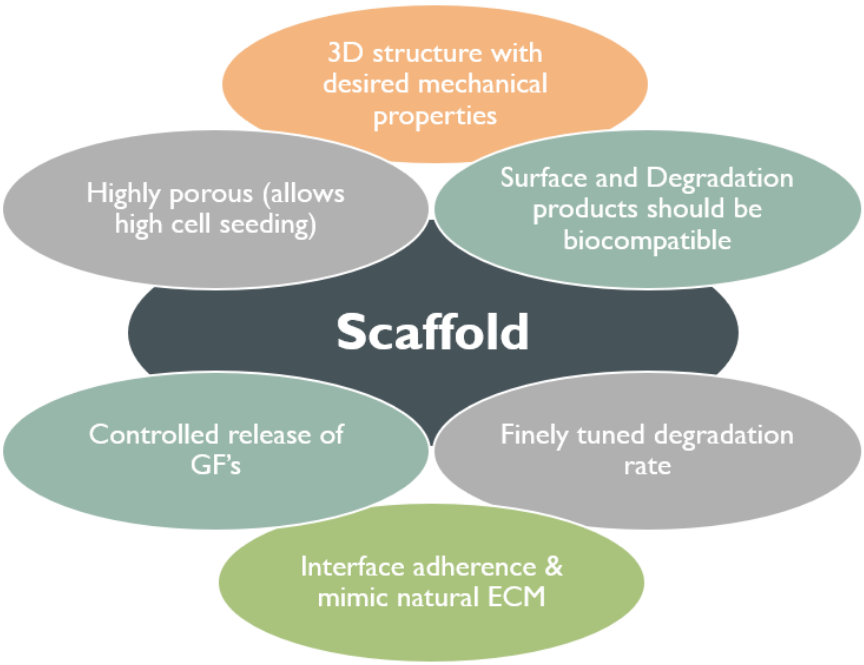
  e.g., Fibronectin and laminin





3.1 Ideal properties of scaffold

An appropriate scaffold must be capable to repair body tissues with minimum requirements, for cell growth, vascularization, proliferation, and host integration, and finally, materials should be degraded naturally during or after the healing process. However, a scaffold has specific characteristics related to the biological aspect, structure, and chemical composition.



3.2 Biological characteristics of scaffolds:

The biological aspects of scaffolds include their biocompatibility and nontoxicity properties. Cells grown in scaffolds must be able to reproduce and discriminate freely without interference to produce a new matrix. Therefore, a scaffold is considered an ideal scaffold for TE applications if it can mimic the properties of ECM of tissues for perfect and complete regeneration. However, as already mentioned, the function of the supporting cell relies on parameters, such as the selected cell line, the underlying material, the surface properties, and the scaffolding structure.

Biocompatibility allows simultaneous formation of new tissue along with the degradation of the matrix. The matrix should not be toxic so that the system can dispose of it without disturbing other members.

3.3 Structural characteristics of scaffold:

Biological tissue is an incredibly complex 3D structure with complex mechanical functions associated with mass transport characteristics. Therefore, the critical objective of TE is to abridge this structural complexity and function using biological scaffolds that provide cells, proteins, and genes for tissue reconstruction. It is clear that the biological materials and structures cannot replicate complex tissue environments, including numerous cell types that interact with a variety of cytokines to produce extracellular matrices within cells with

hierarchical properties that show mechanical function that exhibits high nonlinearity and two-phase. The development of vascularized engineering scaffolds is one of the leading challenges due to the lack of vascular insufficiency leading to the inefficient incorporation of osseo specifying that material selection affects the final physical features of the scaffold. It is often desirable that the porosity of the scaffold must improve its mechanical properties to support cell growth. Additionally, the scaffold with appropriate pore size improves cell migration and water absorption as well as promotes the high mass transfer of oxygen throughout the scaffold.

3.4 Chemical Characteristics of scaffolds and Scaffold Materials:

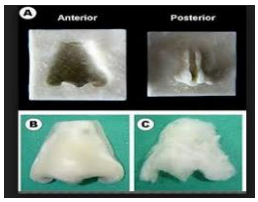
Typically, most scaffolds consist of polymers, bioceramics, and hybrid materials, whether natural or human-made. Based on the source of materials utilized for fabricating the scaffold, there are concerns related to biocompatibility, composition, and decomposition products of such matrices. Even though a wide range of materials have been evaluated for a scaffold, it has been reported that some materials do not support cell growth within scaffolds.

Polymers are of two types, natural polymers or synthetic polymers. Natural polymers, like hyaluronic acid, fibrin, chitosan, and collagen, have good biological compatibility, low immunogenicity, and osteoconductivity. However, they suffer from free degradation rates and low mechanical stability. Synthetic polymers, like polypropylene fumarate (PPF), polyanhydride, polycaprolactone (PCL), polyphosphazene, polyether ether ketone (PEEK), polylactic acid (PLA), and poly (glycolic acid) (PGA), exhibit controlled degradation rates. Additionally, they possess the ability to be fabricated into complex shapes and have improved cell attachment (negatively-charged chemical groups) and the capability to deliver soluble molecules. Furthermore, synthetic polymers can be produced at low cost, in large quantities and have a longer shelf life.

- Many different materials (natural and synthetic, biodegradable and permanent) have been investigated. Examples of the materials are collagen and some polyesters.
- New biomaterials have been engineered to have ideal properties and functional customization: injectability, biocompatibility, non-immunogenicity, transparency, nano-scale fibers, low concentration, resorption rates, etc.

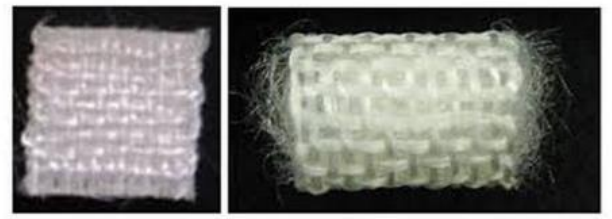
Synthetic scaffold materials	Natural Scaffold materials
Poly lactic acid (PLA)	Fibrin glue
Poly Caprolactone (PCL)	Gelatine
Poly lactic-co-glycolic acid (PLGA)	Collagen, Elastin
Hydroxyethyl methacrylate (HEMA)	Alginate
Polypropylene fumarate (PPF)	Chitosan
Poly(dioxanone)	Hyaluronic acid
Poly(trimethylene carbonate)	Mussel proteins

- A commonly used synthetic material is PLA - polylactic acid. This is a polyester which degrades within the human body to form lactic acid, a naturally occurring chemical which is easily removed from the body.



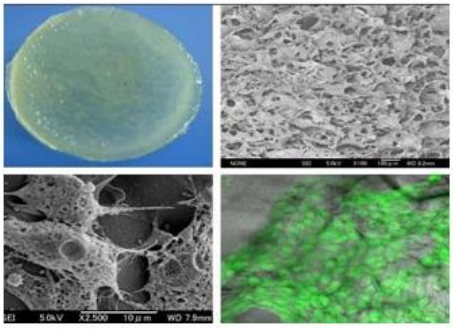
- Scaffolds may also be constructed from natural materials: in particular different derivatives of the extracellular matrix have been studied to evaluate their ability to support cell growth.
- Protein materials: collagen or fibrin
- polysaccharidic materials: chitosan or glycosaminoglycans (GAGs),
- Suitable in terms of cell compatibility, issues with potential immunogenicity still remains.
- Functionalized groups of scaffolds may be useful in the delivery of small molecules (drugs) to specific tissues.

Chitosan-HA based scaffold



Three-dimensional scaffolds fabricated with the chitosan-based HA hybrid polymer fibers: (a) cushion-type scaffold, (b) cylinder-type scaffold.

Collagen based scaffold



Depending on these considerations, the matrices closest to the natural extracellular matrix are the most promising in TE.

3.5 Methods of fabrication of tissue engineered scaffolds

In practice, the techniques of the fabrication of 3D scaffolds are subdivided into a conventional or rapid prototyping (RP) methods, each producing different scaffolds with different characteristics. Conventional techniques of scaffolding fabrication include the construction of porous polymer structures such as substrates for cell adhesion, but it is difficult to obtain complex structures with tunable microscale and macroscale using conventional methods. The RP scaffold fabrication technique provides a plethora of potential opportunities for tissue engineering. Firstly, the independent control of macroscale and microscale features allows the fabrication of multicellular structures needed for complex tissue functions. Secondly, three-dimensional vascular beds fabrication will allow support of massive tissue formation that otherwise would have been possible. Thirdly, combining clinical imaging data and 3D fabrication techniques can provide the possibility of production of customized scaffolds as well as mass production of the scaffold designs.

A) Conventional Techniques

- **Solvent Casting & Particulate Leaching (SCPL)**
- **Gas Foaming**
- **Emulsification/Freeze-drying**
- **ElectroSpinning**
- **Nanofiber Self-Assembly**

- **Textile technologies**

B) Rapid prototyping technique

- **3D Printing**

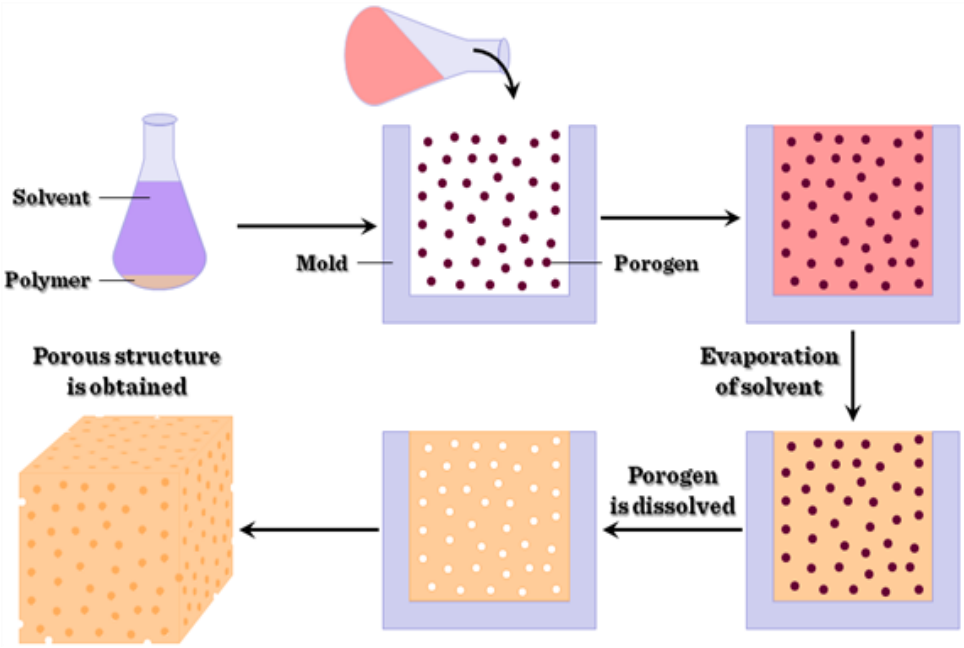
A) Conventional scaffold fabrication techniques:

A significant number of scaffolds have been developed conventionally for drug delivery, but they have subsequently been used in 3D cell culture in the context of TE [18]. The traditional techniques of scaffold fabrication like solvent casting/particulate leaching are intended to define the scaffold shape and pore size but are mostly limited to the prior the scaffold internal design or connectivity of the void space.

Solvent Casting & Particulate Leaching (SCPL)

In this technique, a solvent combined with uniformly distributed salt particles of a certain size is used to dissolve the polymer solution. The solvent evaporates leaving a matrix containing salt particles. The matrix is then submerged in water, and the salt leaches away to form a structure with high porosity. The solvent casting with particle leaching only fits thin membranes of thin wall three-dimensional specimens; otherwise, the soluble particles cannot be separated from within the polymer matrix. Scaffolds developed by this method have a porosity between 50% and 90%. This technique is relatively easy and low cost. One of the main benefits of this technique is that the produced scaffold is of high porosity and with the capability of tuning the pore size, which makes it appropriate for the development and growth of the 3D cell.

One of the drawbacks of this fabrication technique is its time consumption since it only uses thin membranes. Layers of porous sheets allow only a defined number of pore networks between them and may, therefore, limit its suitability to use because of the limited porous size. This technique applies various toxic solvents which take a lot of time to evaporate (days or weeks).



Advantages:

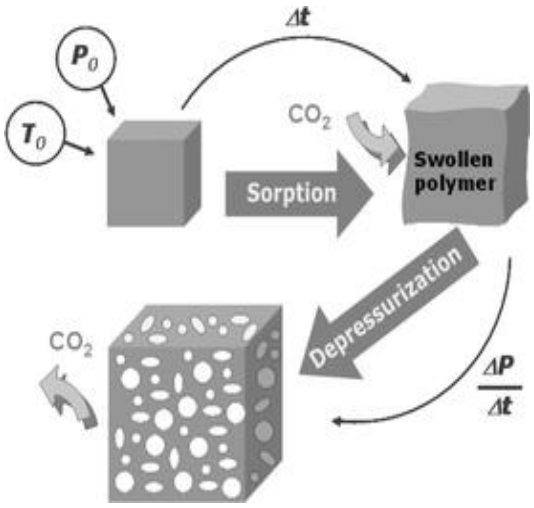
- Simple operation
- Adequate control of pore size and porosity by salt/polymer ratio and particle size of the added salt respectively.
- Pore size (0.5-2mm), Porosity 94-95%
- Desired crystallinity can be achieved
- Less amount of polymer is required to fabricate scaffold

Disadvantages

- Pore shape (cubic crystal shape of salt) and inter-pore openings are not controlled

Gas Foaming

Gas foaming technique is a technique that has been evolved to cope with using high temperature and organic cytotoxic solvents. This technique uses relatively inert gas foaming agents such as carbon dioxide or nitrogen to pressurize modelled biologically degradable polymer with water or fluoroform until they are saturated or full of gas bubbles. This technique usually produces structures like a sponge with a pore size of 30 to 700 µm and a porosity up to 85%. The drawback of this technique is that at times, the product obtained might have a closed pore structure or a solid polymeric skin.



Solid polymeric discs were formed by compression molding at high temperature

Exposed to CO2 (5.5 MPa) for 3 days and pressure is rapidly decreased to atmospheric pressure (leads to **thermodynamic instability & polymer sponges** are formed

Advantages

- No organic solvent is used, thereby reducing risk of damage caused to cells due to the solvent residues
- High temperature is not needed. Hence denaturation of GF's can be prevented.

Emulsion Freeze drying technique

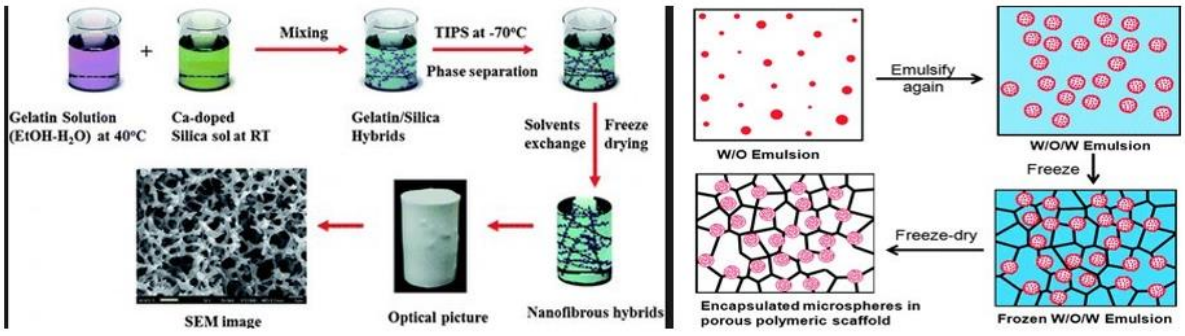
This method consists of creating an emulsion by homogenization of a polymer solution (in an organic solvent) and water mixture, rapidly cooling the emulsion to lock in the liquid state structure, and removing the solvent and water by freeze-drying

The process of freeze-drying is also known as lyophilization; it involves the use of a synthetic polymer that is first dissolved in an appropriate solvent. After dissolution, the polymer solution is cooled under the freezing point, resulting in a solid solvent that is evaporated by sublimation to leave a solid scaffold with numerous interconnected pores [11]. In this technique, when the solution is cooled to freezing point, the solutes can be separated in the ice phase resulting in a small porous structure characterized by a "fence" of matter

surrounding the ice. The scaffolds are achieved after consequent drying; by simple dissolving and freeze-drying, the macro porosity corresponds to the empty area initially occupied by ice crystals. The benefit of this technique is the capability of obviating high temperatures that could decrease the activity of integrated biological factors. Also, the pore size is manageable by controlled and changing the freezing method [26]. This method has been utilized in the fabrication of BG-collagen-phosphatidylserine scaffold with corresponding interrelated pore measuring about 300 µm. It has been shown that it is capable of forming complexes with calcium and phosphate and nucleate HA formation.

Although this technique is widely utilized in the fabrication of scaffolds, it still has several disadvantages such as high energy consumption, long-term timescale, the use of cytotoxic solvents, and the generation of small and irregular size pores (usually in the range of 15 to 35 µm)

Freeze-drying technique is a more suitable method in biomedical application because of the use of water and ice crystals instead of an organic solvent during scaffold fabrication; however, this methodology is challenged in the fabrication of hierarchical structured scaffolds such as vascular systems in biomedicine. Additionally, this method also uses cytotoxic solvents for mixing the polymer; hence, the fabricated scaffold needs to be washed repeatedly to remove the solvent and to minimize cell death.



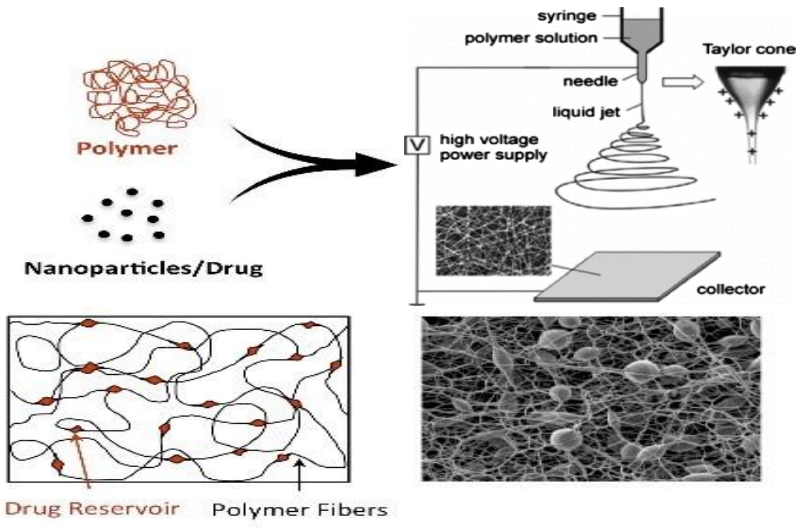
Electrospinning Technique:

Electrospinning is a fiber production method which uses electric force to draw charged threads of polymer solutions or polymer melts up to fiber diameters in the order of some hundred nanometers.

Electrospinning shares characteristics of both electrospraying and conventional solution dry spinning of fibers.

Electrospinning is known as a technique for making fibres from a solution by using electricity. This technique is vital for developing nanofibrous scaffolds in TE. Electrospinning technique involves the use of high voltage to charge the polymer solution placed within a syringe. Solution can form a droplet stabilized by its surface tension at the end of the needle tip of the syringe. However, when the applied voltage exceeds a critical value at which the electrostatic force overcomes the surface tension, a stable jet of liquid could be ejected from the droplet. Due to bending instability, the jet is subsequently stretched by many times to form much smaller polymer fibers which are collected on a grounded collector.

A standard electrospinning system consists of four main components: a spinner with a syringe pump, a metallic needle, a high-voltage power supply, and a grounded collector, as shown in Figure below. The strength of the electric field exceeds the surface tension of the droplet to produce a liquid jet that is then extended and whipped continuously by electrostatic repulsion until it is deposited on the grounded collector. The solvent evaporates in the process, and the jet is solidified to form into a nonwoven fibrous membrane

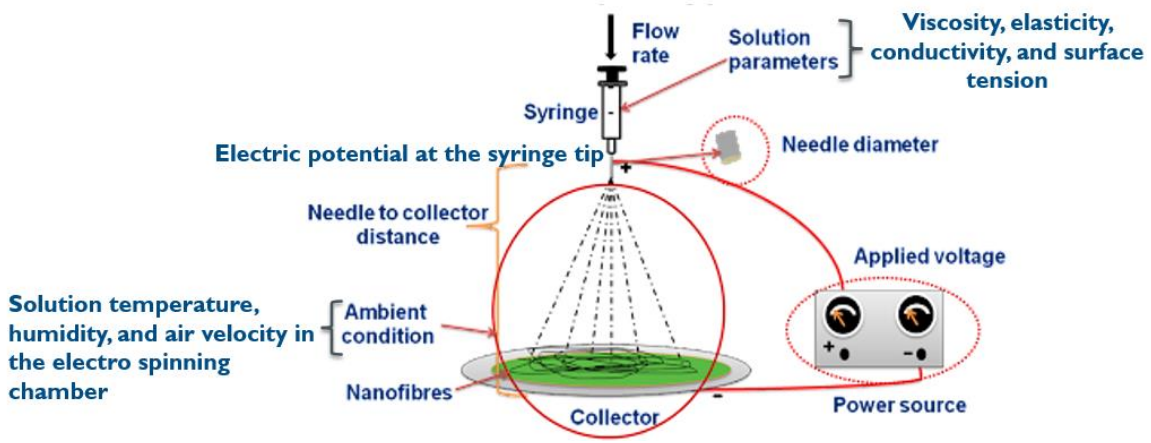


Factors influencing Electrospun fibres:

Many parameters can influence the transformation of polymer solutions into nano fibers through electro spinning. These parameters include:

(a) the solution properties such as viscosity, elasticity, conductivity, and surface tension (b) governing variables such as hydrostatic pressure in the capillary tube, electric potential at the capillary tip, and the gap (distance between the tip and the collecting screen)

(c) ambient parameters such as solution temperature, humidity, and air velocity in the electro spinning chamber



Most important quantities related with electro spinning are

i. the diameters of the fibres be consistent and controllable
ii. the fibre surface be defect-free or defect-controllable
iii. continuous single nano fibres be collectable.

However, researches so far have shown that there three targets are by no means easily achievable

Advantages :

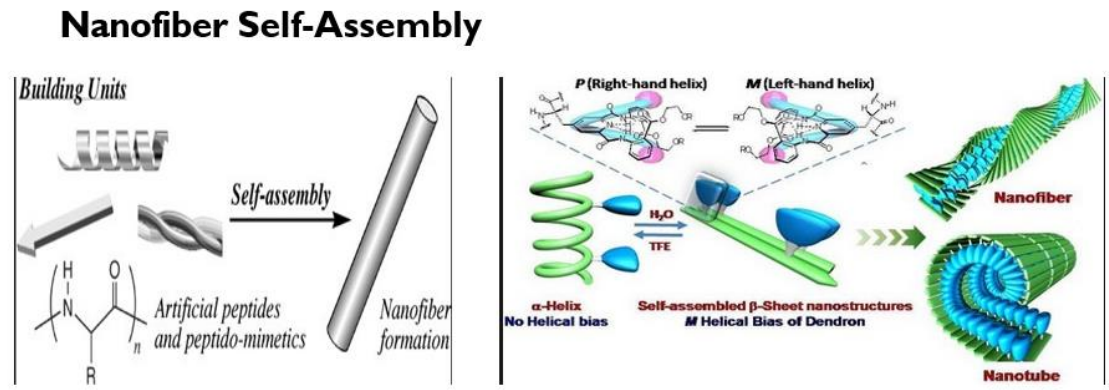
Long continuous nanofibers

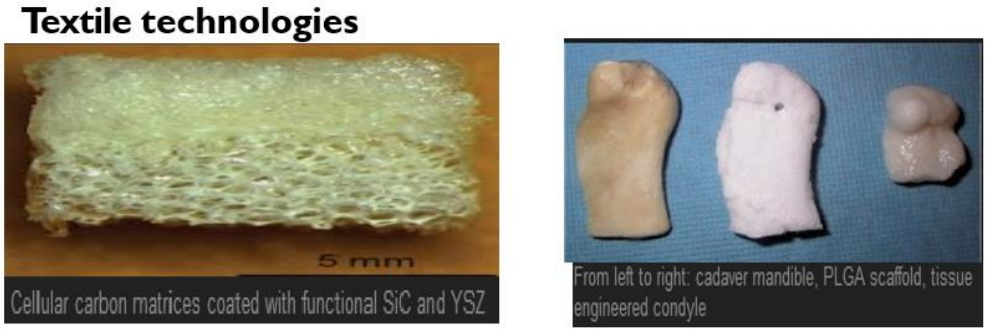
Aligned fibers

Limitation:

No control over 3D pore structure

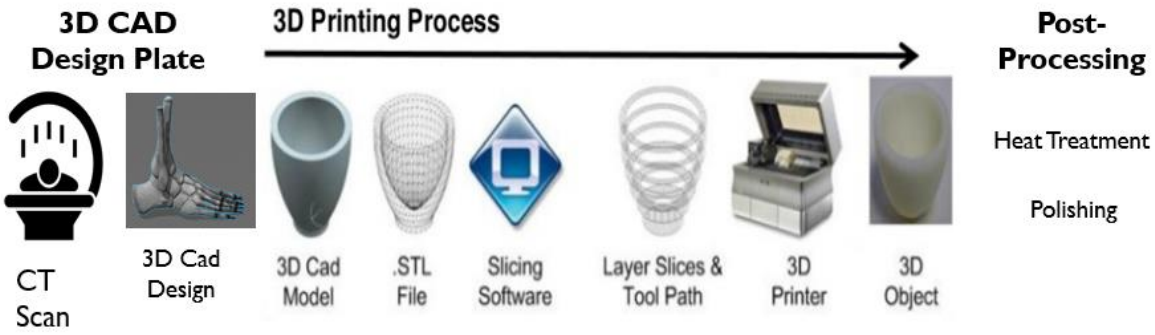
Limited strength

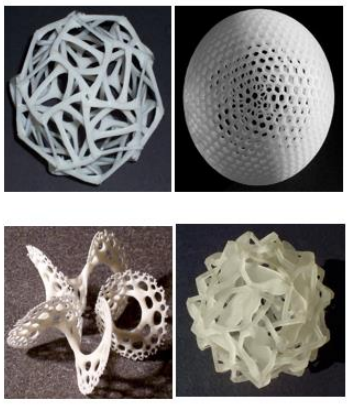




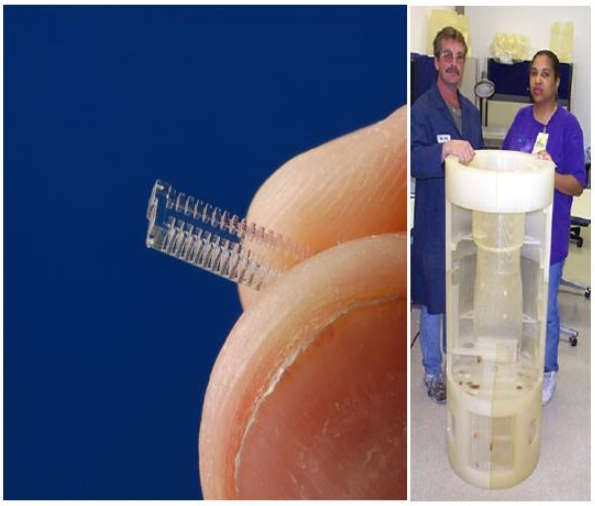
B) 3D Printing Technique:

3D printing, or additive manufacturing, is the construction of a three-dimensional object from a CAD model or a digital 3D model.





Geometric complexity is not a limitation in 3D printing



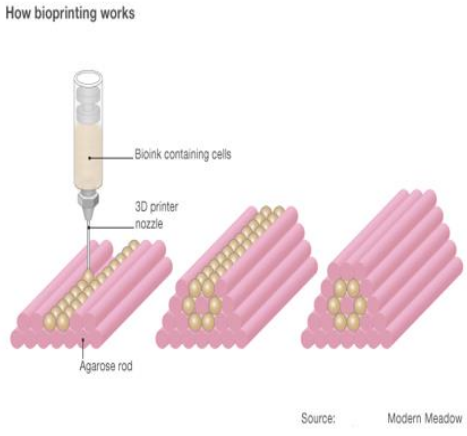
3D Printing has been used successfully to make parts of various sizes

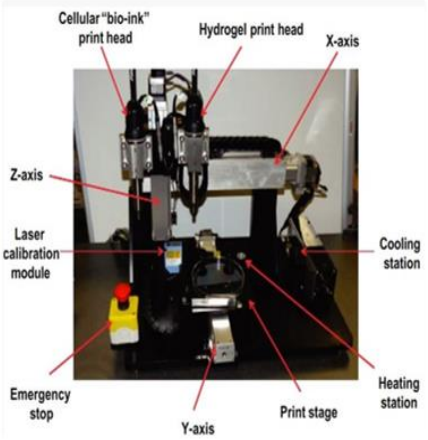
3D Printing (3DP) is a process of creating tools and functional prototype features directly from the computer models. 3DP technique is performed by applying the powdered material in layers and the selective fusion of the powder by "inkjet," where the adhesive is printed. After continuous deposition of the layers, the unbound powder is taken out, yielding a complex 3D object. This process can be utilized to make ceramic, metal, and metal/ceramic composite part. The 3DP process can directly or indirectly function in printing the actual part or a mould. 3DP is a new fabrication method for TE that can be utilized for precise control of scaffold structure at the micron level. Although its success involves the ability to strictly follow the structure of the natural tissue and the mechanical characteristics of the scaffold, the scaffolds

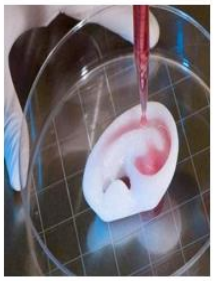
produced by 3DP technique have limited emulating of the nanoscale extracellular matrix properties of the tissue they aim to replace.

3D Bioprinting:

Bioprinting is a 3DP technique, defined as “using material transfer processes for developing a biological pattern and assembly of relevant materials, cells, molecules, tissues, and biodegradable biomaterials with a prescribed structure to achieve some biological functions”. The introduction of solvent-free, aqueous-based systems allows the direct printing of biomaterials on three-dimensional scaffolds for transplantation with/without seeded cells. In general, bioprinting enables personalized medicine by using the technical form of cell growth. Currently, the technologies of 3D bioprinting can be classified into two types, namely, acellular and cellular constructs. Using acellular bioprinting, the scaffold and biomaterial can be produced without a cell during the printing process. In comparison with cellular bioprinting, acellular bioprinting can deliver a higher accuracy and greater shape complexity because it has less restrictive fabrication conditions than methods requiring the cell viability maintenance. Cellular bioprinting integrates cells and other bioagents with the material during the production process to fabricate living tissue constructs. Therefore, the conditions and optimization of parameters in the construction of these constructs vary depending on existence or inexistence of living cells as well as biological substances.







3D Bioprinting is a form of additive manufacturing that uses cells and other biocompatible materials as "inks", also known as **bio-inks**, to print living structures **layer-by-layer** which mimic the behavior of natural living systems.

Bio-ink = Biomaterial + cells/growth factors

There are numerous different ways of 3D bioprinting, among which autonomous self-assembly, biomimicry, and minitissue building block are based on.

Currently, three major types of bioprinting techniques are most widely used methods for the deposition and patterning of biological materials.

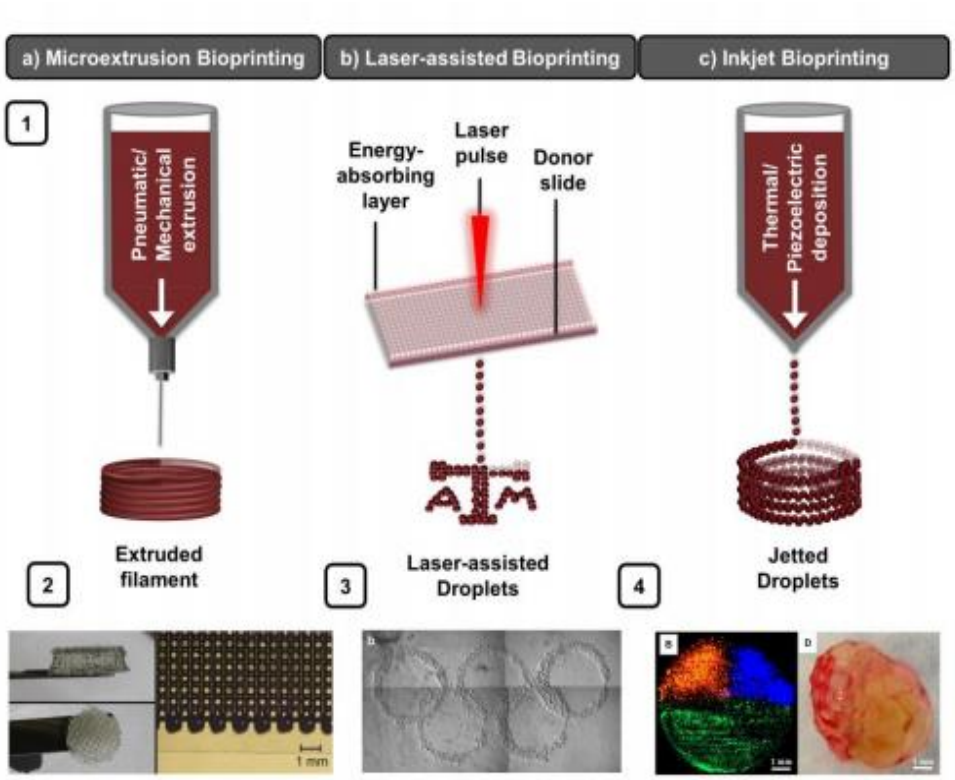
i. **Microextrusion**
ii. **laser-assisted**
iii. **inkjet printing**

i. Microextrusion bioprinting includes a temperature-managed material handling and dispensing system and stage, with either one or both being able to move along the *x*, *y*, and *z*-axes. The fiber-optic-based light source could be used to eliminate the deposition area for photoinitiator activation and photographers' activity and as a piezoelectric humidifier and a

video camera to command and control for *x*-*y*-*z*. Some systems use more than one print heads to make the serial dispensing of several materials easy without retooling. Microextrusion printers are controlled by removing robot-controlled extrusion of material deposited on a substrate using a microextrusion head. Microextrusion generates continuous material beads instead of liquid droplets. Small beads of material are deposited in 2D. Based on CAD-CAM software, the microextrusion head is moved alongside *z*-axis, and the deposited layer is the basis for the subsequent layer. Many materials correspond to microextrusion printers, among which are biodegradable copolymers hydrogels and cell spheroids

ii. **Laser-assisted bioprinting** is a technique based on laser-induced forward transfer. A typical system includes a pulsed laser beam coupled with a focusing system; a "ribbon" with donor transport support covered with a layer of gold or titanium able to absorb laser energy and a cell- and- hydrogel-containing layer of biological material; and a receiving substrate facing the ribbon. The laser-assisted bioprinter directs laser pulses on the laser-absorbing gold layer of the ribbon leading high-pressure bubble, which in turn drives the cell-containing materials to the collector substrate. One of the benefits of this method is that it has nothing to do with the problem of nozzle clogging with cells or material because it is nozzle free. Moreover, it shows compatibility with some biomaterial's viscosities (1–300 mPa/s).

ii. Inkjet bioprinting is known as a noncontact technique that uses picolitre bioink droplets to construct 2D or 3D structures layered onto a substrate. Thermal ink jetting, acoustic wave jetting, and electro-hydrodynamic jetting are typical examples of material jetting techniques. These techniques have several advantages, such as low costs because of its similarity to the structures of a commercial printer, high speed of printing with the capability of supporting parallel work mode, and high cell viability (80/90%). However, the major challenges are that the method includes the narrow material selectivity, the frequent print head clogging, and keeping the biological material in liquid form for droplet formation.



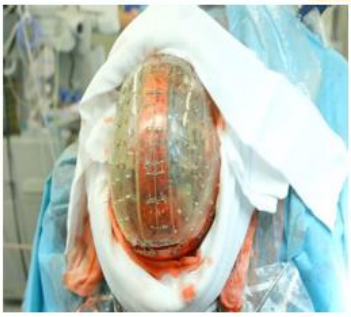
Advantages of 3D printing

- Does not require a mold as a precursor to manufacture objects
- Multiple parts can be produced in one cycle (parts integration)
- Parts of various sizes
- Complex geometries
- Mass customization
- Lab scale to industrial scale machines available
- Unique material properties (e.g. customized distribution of density)
- Combine different materials together

Limitations of 3D printing

- High cost of machine and proprietary materials especially for engineering applications
- Material choices are limited
- Rougher surface finish- resolution? tolerance?
- Sub-optimal mechanical properties due to inherent porosity?

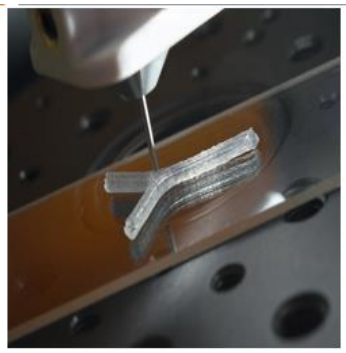
Recent developments in Tissue engineered scaffolds by 3D printing



3D Printed skull for a 22 years old woman, University Medical Centre Utrecht
http://www.wired.co.uk/news/archive/2014-03/26/3d-printed-skull

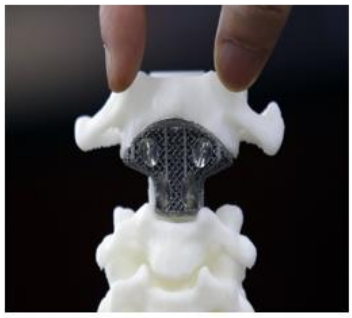
3D printed skull

3D printed windpipe (Trachea)



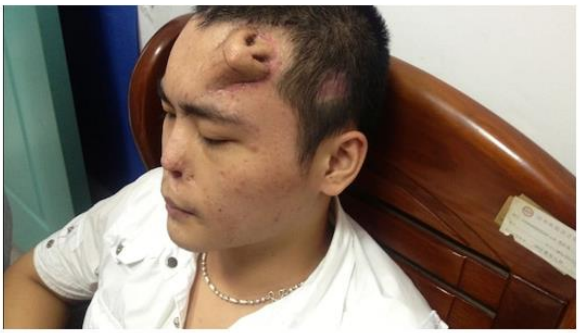
Nerve Guide

Nerve guidance channels are tubes or conduits used to bridge large-gap injuries up to 2cm

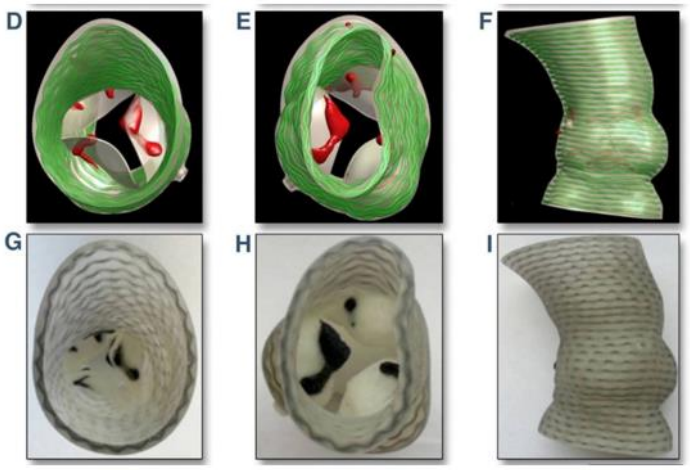


3D Titanium Vertebrae

Growing a nose on a forehead or an ear on an arm is a revolutionary approach to surgical reconstruction



3D Printed Heart Valves Improve Surgery Success Rates

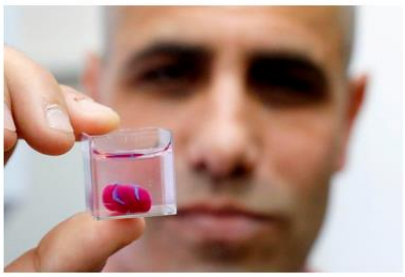


Heart valve transplants are needed in valvular dysfunction/damage where blood flow is affected within the heart

Researchers at Carnegie Mellon University recently developed a method to rebuild components of the human heart using 3D printing

3D bioprinted heart provides new tool for surgeons

- The FRESH technique of 3D bioprinting was invented in Feinberg's lab to fill an unfilled demand for 3D printed soft polymers, which lack the rigidity to stand unsupported as in a normal print
- FRESH 3D printing uses a needle to inject bioink into a bath of soft hydrogel, which supports the object as it prints
- Once finished, a simple application of heat causes the hydrogel to melt away, leaving only the 3D bioprinted object.



Summary

- Tissue engineering is a multidisciplinary study combining biology, biochemistry, clinical medicine, and engineering along with materials science to achieve clinical applications

- It has resolved the problem of organ scarcity and rejection
- Designing a proper scaffold (that mimics ECM) is a key step in achieving fully functional organ
- The scaffold must mimic the replaced organ's properties: strength, microstructure, porosity, optimal degradation and biocompatibility
- Conventional fabrication methods for scaffolds have limited control over porosity and size
- 3D Bioprinting can achieve complex microstructures with cells embedded in it
- Various fully functional organs can be developed with further developments in 3D Bioprinting techniques