

## AUGMENTING THE EFFICIENCY OF SCAFFOLDING IN MEDICAL THERAPIES WITH THE ADVENT OF NANOTECHNOLOGY

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### Review

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### ABSTRACT

The art of manipulating materials on atomic or molecular scales that give rise to nano sized structures and devices is dynamically pioneered and instituted into the world by the name nanotechnology. The field of nanotechnology has ratified its command and is intensifying quickly with its ongoing work in the design, characterization, synthesis, and application of materials and systems by controlling shape and size at nanometer scale. Towards solving the problem of biology and medicine, many efforts have been focused in the direction of the use of nanostructures. This study starts with the main highlights of the types of Nanoscaffolds, surface modification of these scaffolds, applications of Nanoscaffolds in tissue regrowth and terminates with interaction of cells with scaffolds. We have multiple minds all around globe as a result having different perspectives of using these novel technologies in the domain of medical treatment and diagnosis. However, there are many ethics that arose with any new technology amongst supporters and opponents but now is the time to embrace the changes and not been clung to the old ways. So, let us welcome these novel technologies which pave the way for trimming down much of our problems.

**Keywords:** Nanoscaffolds, Nanostructures, Nanotechnology, Tissue Engineering, Treatment

### INTRODUCTION

A multidisciplinary approach, Tissue Engineering designed with an objective of regenerating damaged tissues by developing a substitute mimicking the biological environment for restoring, maintaining and improving the function of tissue (Langer, 2000; Atala, 2004; Bonassar and Vacanti, 1998).

Approaches for the development of engineered tissue include - scaffolds which acts a support system for the cell where cells are seeded in vitro and then the cells release matrix to produce the foundations of a tissue for transplantation. Use of scaffolds to be employed for growth factor, meaning when scaffolds are combined with growth factors, it results in the formation of tissue throughout matrix by the recruitment of body's cell at the site of scaffolds. Scaffold matrices are used to fill up the void present in between of tissue; to structurally support the tissue and to transport/deliver cells or growth factors that upon transplantation possess the ability to develop tissue (Martin *et al.*, 2004). Tissue engineering triad referred to the trio of cells, signals and scaffold which provides a standard for tissue development

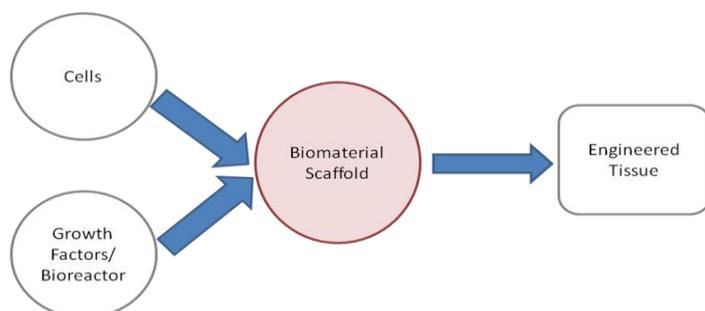


Figure 1 Tissue engineering triad

Designing of scaffold and its fabrication are the main stand back of tissue engineering and regeneration medicines, contributing significantly in the areas of biomaterial research (Langer and Vacanti,1993). Scaffolds are described as the biomaterials that are porous, act as pillar for 3-D tissue development. They are

designed in such a way that they mimic the same microenvironment as that of the native cellular tissue and go serve certain functions such as promoting interactions between the cell and biomaterial, adhesion of cell and deposition of ECM; promoting survival, proliferation and differentiation of cell by allowing sufficient amount of gases, nutrients and other regulatory factors to be transported to the cell; controlling the biodegradability date; minimizing the toxicity and inflammation rate in vivo (Langer and Tirrell,2004). For the he scaffolds to be function properly and regulate behavior the cell, it should have the same microenvironment as that of native cell (Goldberg *et al.*, 2007).

ECM surrounds the cell within tissue characterized by well-organized nanofibers (Stevens and George, 2005). Providing cell support and directing the behaviour of the cell are the important functions of this internal nano organization. Storing, releasing, activating biological factors, cell-cell interaction are the additional functions of ECM (Taipale and Keski-Oja, 1997) Thus, it's important to maintain the bifunctionality and complexity of ECM that can be possible by designing and fabricating at the nanoscale which mimic the microenvironment as that of the native ECM (Goldberg *et al.*, 2007).

### Types of Nanoscaffolds

Nanoscaffolding is extremely important in the development in tissue regrowth and regeneration. The method requires making Nanoscaffolds; a 3D microstructure of ultrafine fibers providing a microenvironment in which cells can grow, divide and recreate damage tissue. The properties of the Nanoscaffold are evidently determined by the method of fabrication of the scaffold and the material used to do this. Just like different reactions have different catalyst, the engineering of different tissues requires different Nanoscaffolds. This is due to the surface chemistry exhibited by the scaffolds (Harindi Loku Waduge, 2011). Some part of this review will have few types of Nanoscaffolds discussed along with their fabrication technique and related applications.

### Oxide Nanoscaffolds

Fabrication of oxide Nanoscaffolds takes place on the substrate of pure titanium consists of tin, chromium, and niobium; creating oxide like surface by their deposition following annealing. The most commonly used metal that serves the

purpose of devices used in load bearing like artificial hip joint stems is titanium and its alloys. Resistance to corrosive nature, biocompatibility with cell and high strength to weight ratio are some of the characteristic features of titanium that make it suitable to be used as a biomaterial (Albrektsson et al.,1981). These attractive features of titanium are due to the presence of an oxide layer that helps in creating the direct contact with the bone tissue and halts the undesirable fibrous tissue formation around the biomaterial.

**Cellulose Acetate Nanoscaffolds**

Chemical conversion of cellulose yields a product cellulose acetate. Electrospinning is one of the methods for the fabrication into structures as Nanoscaffolds (Chainoglou et al., 2016). Electrospinning cellulose acetate nanofiber has many applications that includes restricted movement of bioactive materials; cell culture; application in tissue engineering (Konwarh et al., 2013). In addition to it, integrity of calcium acetate Nanoscaffolds can be improved by binding with polymers like poly (butyl acrylate) and promote cell growth, cell interaction and electrical functionality (Baek et al., 2011) Another application of calcium acetate Nanoscaffolds is in heart valve tissue engineering where the deposition of calcium acetate Nanoscaffolds onto aortic heart valve enhances growth of cell. Use of bioactive molecules such as TGD peptides and laminins provides the biocompatibility, enhancing endothelization of heart valves and prevents thrombosis.

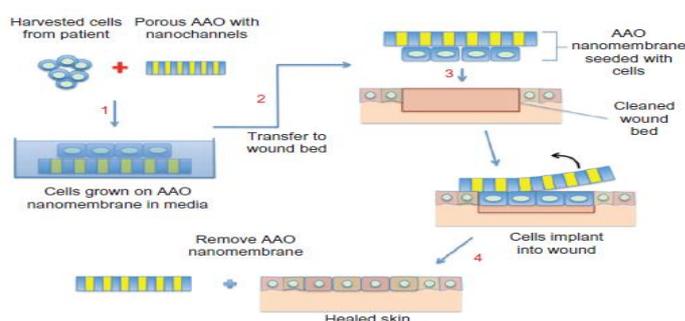
**Fibrinogen and fibrin based micro and Nanoscaffolds**

They are non-immunogenicity based Nanoscaffolds and can mimic the structure of the native tissue and can provide a perspective alternative to the tissues and organs that are damaged. Fibrinogen is a 340 kda molecular weight protein found in blood plays a significant role in coagulation and thrombogenesis. Scaffolds of Fibrinogen and Fibrin possess a high cell seeding efficiency, uniformity in cell distribution. The cells then release ECM and then proliferate, move and differentiate into specific tissues/organs. Fibrinogen provides a 3-D, structural and non- textured contact surface for the attachment of cells and their proliferation which then provides a matrix like network for cell signaling and cell- cell interactions (Sell et al., 2010). Release of ECM by Fibrinogen and Fibrin based scaffolds provides a structural based support to the connective tissues like cartilage, bones, ligament, nerves (Meinhart et al., 1999; Sahni and Francis, 2000; Park et al., 2009; Kalbermatten et al., 2008; Gorodetsky et al., 1999). Due to their easy formulation into various structural scaffolds, they are used in diverse applications of tissue engineering (Rajangam et al., 2011;

Rajangam et al., 2012; Swartz et al., 2005; Rejinold et al., 2010; Wnek et al., 2002; Rowe et al., 2007). They have an application in cancer therapy. Fibrinogen and Fibrin based Nanoscaffolds can halt the growth of the cancerous cell progression. This inhibition results by abolishing the excess of coagulation in and around cancerous tissues (Costantini and Zacharski, 1992).Other applications include orthopedic applications (bone repair/ regeneration), promoting viability and cartilage structure, wound healing activity (Patel et al., 2010; Ishimura et al., 1997; Marimuthu and Kim, 2009; Clark et al., 1982; Gailit et al., 1997).

**Aluminium Oxide Nanoscaffolds**

Aluminium oxide Nanoscaffolds involved actively in promoting the cell interactions. The skin cells initially seeded on the membrane of the Nanoscaffold, where these cells can proliferate forming a confluent layer. The confluent layer can then remove from the anodic aluminium oxide membrane and applied to wound part directly. This would have an advantage of easy exchange of gases or fluids through the bank channel and the prevention of infection caused by micro-sized bacteria. This type of Nanoscaffold used in bone implants, can conform various body shapes, skin tissue engineering (Parkinson et al., 2009).



**Figure 2** Schematic representation of the anodic Aluminum Oxide (AAO) membrane used as a 'band-aid technique' for skin tissue engineering. (Poinem G errard et al., 2011)

**Table 1** The summary depicting the distinguishing features of the types of Nanoscaffolds

Nanoscaffold material	Fabrication Technique	Strength	Porosity	Biodegradability	Application example
Oxide Nanoscaffolds	Substrate fabrication	Resistance to corrosive nature, biocompatibility with cell, high strength to weight ratio	Porous structure aid in tissue regeneration. Eg- TiO <sub>2</sub>	Biodegradable when incorporated with polymer	Neural tissue engineering
Cellulose Acetate Nanoscaffolds	Scaffold Fabrication with Electrospay Deposition System	Bio compatible with cell, exhibiting cell viability, good physicochemical morphological and non-cytotoxic properties.	Porous which makes it suitable to use in separation of some organic substances in aqueous solution.	High degree of biodegradability.	Heart Valve Tissue Engineering
Fibrinogen and fibrin-based Nanoscaffolds	Microspheres, microbeads, microfibers, nanoparticles, nanofibers, hydrogels and electrospinningmethod s	Non immunogenicity, ability to mimic the organization of native tissue, efficient cell seeding, uniformity in distribution of cells.	Pore structures can aid cell attachments, cell-matrix interactions, and nutrient/waste metabolite transport.	Biodegradable polymer carriers	Cancer therapy, Nerve tissue regeneration, Bone and cartilage tissue regeneration, Vascular tissue regeneration, Skin tissue regeneration
Anodic aluminium oxide Nanoscaffold	Al anodization	Involved actively in cell interactions.	Being able to control the pore size and porosity of the AAO scaffold structure enables the surface of material to be tailored to a specific tissue engineering application	Non-biodegradable and have to be surgically removed after use.	Used as cell culture substrate for tissue engineering application such as the bio artificial liver. Skin tissue engineering

**Surface Modification of Nanoscaffolds**

Adjusting the properties of the surface topology helps in enhancing the endothelialization and in reducing thrombosis. Some of the surface modification techniques include:

**Surface Roughening**

This technique of surface modification used to increase the surface area of implant; enhance the adhesion of cell by restricting their movement (Pavithra and Doble, 2008; Lyu et al., 1999; Curtis and Wilkinson, 1997; Meredith et

*al.*, 2003). In this modification the surface topology is done without using the chemicals (Shadpour and Allbritton, 2010). Surface roughness can be increased using oxygen of argon plasma deposition for polymers which leads to increase in cell adhesion; increases wound healing and biocompatibility by plasma deposition in SMP based stents (Pavithra and Doble, 2008; Fare *et al.*, 2005). Surface roughening can also be increased by etching, sanding, polishing and micro blasting (Martinez and Chaikof, 2011; Ikada, 1994).

### Surface Patterning

This is more efficient way of surface modification as compared to surface roughening. Patterning on nano- metal surfaces increases the attachment of endothelial cells, which leads to the increased density of cell on surface and desired healing (Martinez and Chaikof, 2011; Khang *et al.*, 2008; Ranjan and Webster, 2009). Di- block copolymer grafts can be used for patterning, forming patterns of nano size on solid surfaces by attaching (physically or chemically). Patterns are formed on the surface through the technique of photolithography which causes the surface to be exposed for photo irradiation (Nie and Kumacheva, 2008; Xu *et al.*, 2004; Kane *et al.*, 1999). Self-assembled monolayer is another technique of creating patterns which promotes cell attachment and organization, the properties needed to maintain the biocompatibility of stent (Ma *et al.*, 2007; Zhang *et al.*, 1998; Mrksich and Whitesides, 1996).

### Chemical modification of the surface

Use of chemicals to modify the surface topology but without altering its bulk properties is chemical modification. This technique attempts to enhance the performance of the material by altering it chemically. Chemical vapour deposition, plasma vapour deposition, grafting techniques are some of the methods of chemical alteration (Martinez and Chaikof, 2011; Lee *et al.*, 2007). Plasma immersion ion implantation technique for metal helps in reducing the extent of corrosion, increases hardness of the surface, slows down wear and tear using acetylene, nitrogen or oxygen (Chu, 2007). In chemical vapour deposition, a thin film is deposited onto surface of biomaterials by utilization of plasma or other bioactive chemicals rendering the surface altered (Lahann *et al.*, 2002; Favia and Dagostino, 1998). This method of chemical modification is famous for blood compatibility due to non-fouling characteristic features of the deposited film (Favia and Dagostino, 1998). Plasma vapour deposition techniques such as matrix assisted pulsed laser evaporation results in the repos of materials, either organic or biologicals onto the blood contacting surface leads to chemically alteration of the surface (Martinez and Chaikof, 2011). Self-assembled monolayers increase the hydrophobicity/hydrophobicity by the addition of functional groups to the surface.

### Interaction of Cells with Scaffolds

#### Attachment

It is the initial step in tissue development as most cells require anchorage for proliferation, migration and differentiation (Alberts *et al.*, 2002). Type 1 collagen acts as an anchor protein for many of the tissues in an early stage of development (Kadler, 2004). After that other proteins came into play where they combine with type 1 collagen forming the native ECM. Mature ECM then mediated the attachment, migration, proliferation and differentiation of cells. There is an attempt of making the artificial ECM's that mimic the native ECM structure. Fibronectin, vitronectin and laminins are some of the important attachment/anchored proteins that have the ability to adsorb to the Nanoscaffolds at levels 2.6 to 3.9 times higher than solid walled scaffolds (Woo *et al.*, 2003). Additionally, this adsorption was found to be selective and could not be explained by the surface area alone of the nano-fibrous scaffold (Woo *et al.*, 2003). In one study it has been observed that the culturing of neonatal mouse osteoblasts showed high expression of integrins that were connected with collagen, fibronectin and vitronectin as compared to solid walled scaffolds. Upregulated  $\alpha 2$  integrin expression on the Nanoscaffold in the absence of collagen fibril formation suggesting the direct cell and Nanoscaffold interaction via  $\alpha 2$  integrin (Woo *et al.*, 2007).

In order to achieve desired cell adhesion but repel unwanted attachment, surfaces of scaffold should not adhere to hyaluronan, polyethylene oxide (Liu *et al.*, 2002), PEG, Glycocalyx (Holland *et al.*, 1998), antibacterial with silver or N-alkylated poly (vinyl pyridine) coatings, and bio adhesive with RGD peptide insertion, growth factor attachment, other bioactive groups decoration, plasma etching, or other chemical modifications (Sakiyama-Elbert *et al.*, 2001). With designed patterns, the arrangement of the cells in 2-D and 3-D may be obtained (Chaikof *et al.*, 2002). Cell morphology and cellular activities can be managed by patterning as well. By creating specific patterns of surface chemistry and/or texture, cell behaviours can be confined with physical or chemical ultrastructure, which can be used to control cellular activity (Chaikof *et al.*, 2002).

### Proliferation

For tissue development, migration and proliferation of cells is required so that scaffold is fully occupied by the cells. Scar tissue formation can be reduced if the desired cell type undergoes proliferation more rapidly in vivo. It has been shown on various studies, the ability of different cell types on nano- fibrous scaffolds that have high proliferative activity as compared to normal materials (Chen *et al.*, 2006; Li *et al.*, 2003; Shih *et al.*, 2006; Schindler *et al.*, 2005; Xu *et al.*, 2004; Lee *et al.*, 2005). Culturing pre osteoblasts on nano-fibrous scaffolds showed more proliferation of cells as compared to solid-walled scaffolds and culturing chondrocytes on nanofiber for 3 weeks showed more proliferation as compared to control (Chen *et al.*, 2006; Li *et al.*, 2003).

### Differentiation

The advancement of cell from one cell type to the specialized cell type is termed as differentiation. Differentiation of neural progenitor, hepatocytes, chondrocytes, osteoblasts can be enhanced by nanofibers (Silva *et al.*, 2004; Yang *et al.*, 2004; Chua *et al.*, 2005; Semino *et al.*, 2003; Li *et al.*, 2003; Chen *et al.*, 2006; Woo *et al.*, 2007). There are markers that expressed when the undifferentiated cells get differentiated into the osteoblastic lineage. Markers like Alkaline phosphatase (early osteogenic differentiation marker); osteocalcin, bone sialoprotein (late osteogenic differentiation marker) have been reported to be upregulated on Nanoscaffolds when compared to controls in culture conditions for the time period of 3 days (in vitro) for early osteogenic markers and for 2 or more weeks for late osteogenic markers (Woo *et al.*, 2007; Li *et al.*, 2005; Chen *et al.*, 2006). Expression of osteocalcin and bone sialoprotein is 7.5 and 1.8 times more on nano fibrous scaffolds as compared to solid walled scaffolds (Chen *et al.*, 2006). Another osteogenic marker, type 1 collagen is the only marker whose expression has been shown to be down regulated on nano fibrous materials as compared to solid walled scaffolds, though type 1 collagen is highly distributed on Nanoscaffolds (Chen *et al.*, 2006; Yoshimoto *et al.*, 2003; Shin *et al.*, 2004). Accelerated maturation of ECM could be the reason for the downregulation of type 1 collagen on Nanoscaffolds. Mineralization of ECM starts as the expression of markers of differentiate bone begins by the cell. Due to the evenly distribution of minerals in Nanoscaffolds, enhanced mineralization has been found on nano fibrous scaffolds as compared to solid walled scaffolds (Chen *et al.*, 2006; Woo *et al.*, 2007; Hosseinkhani *et al.*, 2007). Thus, Nanoscaffolds can create vascularized, mineralized and embedded osteocyte like cells bone tissue.

### Integration with tissue and healing

Healing of wounds is one of the main applications in the field of tissue engineering. Many wound healing skin substitutes are available, however due to problems like wound contraction, formation of scar, and most importantly no of poor integration with host tissue, these substitutes suffer a setback. Tissue engineering is an approach which involves the development of scaffolds as ECM in three-dimensional unit that directs cell adhesion, migration, maturation and differentiation in order to develop a structural and functional tissue. These scaffolds cover the wound; provide a physical protection from external infection and acts as a template for the growth of the dermal fibroblasts and keratinocytes. Different types of materials (natural and artificially synthesized) are used in the fabrication of variety of scaffolds (Zhong *et al.*, 2010). The reason of increased mortality of diabetic patients is poor wound healing. To overcome this, Nanoscaffold based wound dressing came into existence that allows targeted drug delivery. Due to higher surface to volume ratio of the nanoparticles, the interaction with the host tissue or target has been increased and these nanoparticles penetrates the wound very easily thereby improves the wound healing process. Nanoparticles deliver drug in a sustained release manner due to which there is a continuous interaction of bioactive molecules with the target tissue which also enabled the controlled delivery of drug and thus limits the toxicity (Kim *et al.*, 2010; Krausz *et al.*, 2015). Nanoscaffold dressings are used for increasing the healing process and to reduce the total microbial load on the wound. Specifically, cellulose nanofiber dressings incorporated with the nanoparticles of silver showed the anti-microbial effects against *E. coli*, *P. aeruginosa* and *S. aureus* (Wu *et al.*, 2014).

### Application of Nanoscaffolds in Tissue Re-Growth

The ability of nano structured Nanoscaffolds in minimizing the microenvironment of the cell which leads to cytoskeleton recognition and initiating the targeted cell signaling is of the considerable effect in the field of tissue engineering and regenerative medicine. Scaffolds that behave same biochemically, mechanically and electrically as native tissue can be nano engineered so that that cell adhesion, proliferation, differentiation and maturation this improves the functionality of cell and growth of tissue (Yang *et al.*, 2014). Nano-patterning, self- assembly, electrospinning, conjugation of adhesion motifs to the matrix backbone or sulfating the matrix backbone are some of the techniques of fabricating ECM like organization (Kim *et al.*, 2010). Integration of nanomaterials such as nanowires, carbon nanotubes and nanoparticle can

easily modify the properties of ECM like organization (Dvir et al., 2011). Development of a hybrid hydrogel, electrically conductive in nature based on gold nanoparticles can boost the functions of cardiomyocytes (You et al., 2011). Surface topographical features of the Nanoscaffold provide the cell a desired surface for migration, proliferation, and differentiation thereby directing the behaviour of cell. Human mesenchymal stem cells can be differentiated towards adipocytes upon variations in these cell adhesion substrate nano surface topologies (Ahn et al., 2014). One study reported the more growth and retention of transplanted heart cells and their interaction with the target tissue after the incorporation of polyethylene glycol based Nanoscaffold in a model of rat having myocardial infarction (Kim et al., 2012). Also, the adhesion and differentiation of adipose stem cells from human enhanced after the coating of a graphene (oxide layer) on a glass slide (Kim et al., 2013). Controlled release of bioactive constituents is also one of the applications of Nanoscaffolds. Polymeric scaffolds offer many potential biological activities with the wide range of chemistry and biocompatibility due to which they are involve in organ substitution and tissue engineering applications like heart valves, arteries, skin and cartilage, pancreas, liver, bladder, corneas, nerves and other soft tissues (Dhandayuthapani et al., 2011; Mayer et al., 1997; Eaglstein and Falanga, 1998; Tziampazis and Sambanis, 1995; Mayer et al., 2000; Oberpenning et al., 1999; Germain et al., 1999; Mohammad et al., 2000; DiEdwardo et al., 1999). Funda et al., reported the use of nanoscaffolds in alveolar bone and tooth regeneration (Funda et al., 2020)

## CONCLUSION

This paper demonstrated and presented the significance of Nanoscaffolds in the field of medical treatments and therapies. The growth and many recent developments in the field of nanotechnology allow the inventions of many new materials and techniques that mimic the cell microenvironment as well as ensuring some strategies for the scaffold creation in three dimensions. However, the design and fabrication of a biodegradable scaffold that possess desirable characteristics such as surface chemistry, desired cell attachment, their proliferation and differentiation is the key challenge in the field of tissue engineering. Due to its small-scale size, the interest in modification in the principles of nanotech could be very effective in developing the implants of new design, high quality and of good performance. Although the techniques for scaffold modification are sensitive to various processing parameters (like high energy surfaces, cell density etc.). Conclusively, this review clearly briefs the multidisciplinary approach of Nanoscaffolds, their types, structure, interaction and applications in the field of tissue engineering that could lead to various innovative creations in future.

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