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Drug Delivery Aspects for Regenerative Therapies

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ABSTRACT: The objective of regenerative medical therapy is to induce regeneration and repairing of defective and injured tissues based on the natural-healing potential of patients themselves. The success of l tissue regeneration is undoubtedly vital to create a local environment that enables cells to efficiently proliferate and differentiate, as a result of which there is natural induction of tissue regeneration. cells, biomaterials, and other factors are needed to design these constructs, but not all tissues are created equal. Below article gives an overview of the current approaches to drug delivery from scaffolds. Common methods of drug delivery, including degradable/diffusion-based, affinity-based, immobilized, and on-off drug delivery systems, are. Regenerative medicine efforts are currently in progress experimentally for virtually every type of tissue and organ within the human body. Recent progress suggests that engineered tissues may have an expanded clinical applicability in the future and may represent a viable therapeutic option for those who would benefit from the life-extending benefits of tissue replacement or repair. There are a number of key trends in healthcare today that will impact on the development of regenerative medicine, which will provide an indication of the significant role the field could play in the future of healthcare.

KEYWORDS: Regenerative Therapies; Tissue Regeneration; Drug Delivery; Scaffolds; Cells.

INTRODUCTION

Regenerative therapy is not one discipline, but covers a number of emerging and related fields. It can be defined as a therapeutic intervention which "replaces or regenerates human cells, tissues or organs, to reinstate or achieve normal function". It deploys small drug molecules, biologicals, medical devices and cell-based therapies. However, the term is more commonly used to mean advanced therapies like tissue engineering, cell based therapies, gene therapy and new biomaterials (scaffolds and matrices).[1] The objective of regenerative medical therapy is to induce regeneration and repairing of defective and injured tissues based on the natural-healing potential of patients themselves.[2] There are a number of key trends in healthcare today that will impact on the development of regenerative medicine, which provide an indication of the important role this field could play in the future of healthcare. There are strong pricing pressures from public healthcare payers globally as Governments try to reduce budget deficits. Regenerative therapies could potentially save public health bodies money by reducing the need for long-term care and reducing associated disorders, with potential benefits for the economy as a whole.[1]

Advanced surgical therapies currently available consist of reconstruction surgery and organ transplantation. Though there is no doubt that these therapies have saved and

improved countless lives, but still they have several limitations. During cases of reconstruction surgery, biomedical devices are not capable of completely substituting the biological functions like inflammation and regeneration. One of the biggest issues for organ transplantation is the shortage of donor tissues or organs. Also, the continuous and permanent use of immunosuppressive agents to prevent immunological rejection responses often causes side effects, like high possibility of carcinogenesis, bacterial infection and virus infection.

To resolve these issues, a new therapeutic solution that is clinically mild to patients, is required. In, a new therapeutic trial, where in disease healing can be achieved based on the natural healing potential of patients, this is yet to be explored. This trial is termed regenerative medical therapy where the regeneration of tissues and organs is naturally induced to therapeutically treat diseases by artificially promoting the proliferation and differentiation of cells.[3]For example, implantable scaffolds can be used to treat a variety of complications associated with the brain injury and including replacement of tissue lost due to traumatic brain injury, delivering drugs to help treat neurological diseases such as Parkinson's and Alzheimer's, as well as serving as coatings for brain-implant devices to limit inflammation. Replacement of damaged tissue with scaffolds containing drugs could help promote regeneration along with functional recovery. [4]

COMPONENT OF REGENERATIVE THERAPIES

For successful regenerative therapy, it is vital to create a local environment that enables cells to efficiently proliferate and differentiate.[5]

Considering the components consisting body tissue, there are three key factors:[5]

- Stem cells
- Bio-signaling molecules (growth factors and genes)
- Natural scaffold for cell proliferation and differentiation

Stem Cells:

Sources of stem cells:

The main sources of stem cells, cells with the ability to replicate and differentiate into other more specialized types of cells are:

- Embryonic Stem Cells: These are cells that are derived from embryos that are a few days old, at a stage lacking any anatomical organization, which have the potential to differentiate into all 200 cell types of the adult body. Such cells are termed as pluripotent cells.
- Foetal Stem Cells: These are derived from aborted human foetuses and have the potential to differentiate into many, but not all, of the adult body's cell types. These are termed as multipotent cells.
- Cord Blood and Placental Stem Cells: These are derived from umbilical cord blood and placentas. Although only able to differentiate into a limited number of cell types, such cells offer therapeutic potential and are currently used in bone-marrow replacement therapies to treat a variety of immune and blood related conditions.
- Adult Stem Cells: These are already used in a number of therapies, and are found in the vast majority of human tissue and organs. These mutipotent cells have the potential to differentiate into a limited number of cell types and are also known as "somatic stem cells".
- Induced Pluripotent Stem Cells (iPS): These are stem cells that can be derived from a variety of specialized cell types – for example adult skin cells – using genetic or biochemical manipulation. The resulting cells are pluripotent and have very similar properties to embryonic stem cells.[1]

Sources of cells for implantation include autologous cells from the patient, allogeneic cells from a human donor who is not

immunologically identical to the patient, and xenogeneic cells from a different species. [1]

2.2. Bio-signaling molecules (growth factors and genes)

Growth factors (GF) are often required to promote tissue regeneration. They can also induce angiogenesis which is required for the supply0f oxygen and nutrients for the survival of the transplanted cells. but, one cannot always expect the biological effects of growth factors to be entirely exerted because of poor in vivo stability, unless technology like growth factor delivery is applied.[6]

The materials used in the preparation of scaffolds and their details are explained in table no. 1.

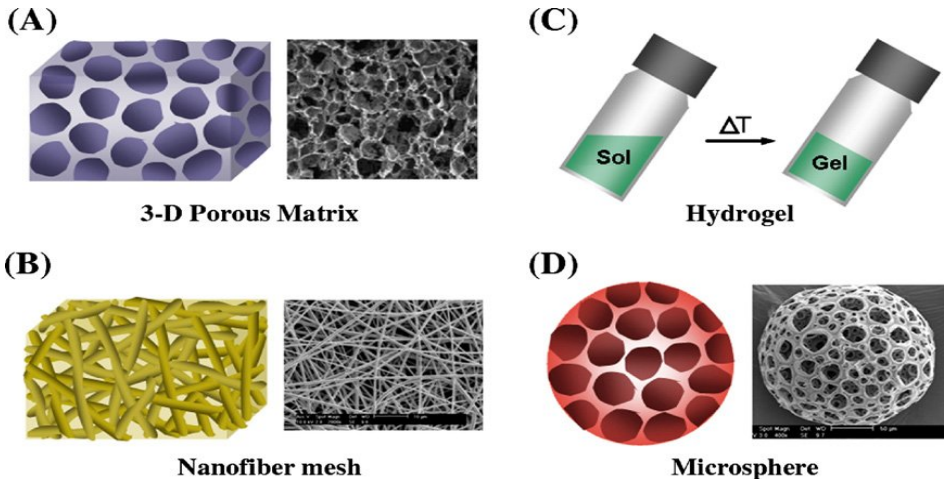

Fig 1. Different forms of polymeric scaffolds for regenerative therapies: (A) a typical 3-D porous matrix in the form of a solid foam, (B) a nano-fibrous matrix, (C) a thermo-sensitive sol–gel transition hydrogel, and (D) porous microsphere.[7]

Materials used in tissue engineering scaffolds:		
Source	**Material**	**Relevant features and application**
Naturally derived	Collagen-based scaffolds	Soft tissue repair
		Cell differentiation
		Capillary engineering
		Dermis engineering
		Vascularized adipose tissue
	Hyaluronic acid (HA) and derivatives	Regeneration of skin, cartilage
		Patterning of cell growth
	Collagen-HA gels	Control of vascular sprouting
	Chitosan	Chitosan microsphereintegrated scaffold
		Cartilage engineering
	Fibrin	Vessel engineering
		Release of fibroblasts
	Gelatin	Trachea engineering
		Bone engineering
	Alginate	Vascular engineering

Synthetic	Poly(glycolic acid) (PGA)	Musculoskeletal tissue
	Poly(lactic acid) (PLA)	Engineering
	Polylactide-co-glycolide (PLGA)	Cartilage regeneration
		Fibrovascular engineering
	Poly(ε-caprolactone) (PCL)	Skin engineering
	Polyethylene glycol (PEG)	Bone engineering
	Oligo(poly(ethylene glycol) fumarate) (OPF)	Cartilage engineering
		GF release from gelatin microspheres
Inorganic	Tricalciumphosphate (TCP)	Bone formation
	Hydroxyapatite (HA)	
Semi-synthetic	Cross-linked thiolated HA	Neurite growth and support
	Esterified hyaluronan (HYAFF derivatives)	Cartilage engineering

Table 1 Materials used in tissue engineering scaffolds:[8]

Drug selection:

Selection of an appropriate therapeutic drug or combination of drugs should be based on the type of tissue to be regenerated or the particular application of the scaffold. Caution should also be taken to make sure that the target drug retains its activity after getting incorporation into the scaffold. Following section will emphasize on some of the most commonly used drugs for neural tissue engineering.[4]

- Growth factors:
  Some of the most common growth factors used to promote neural tissue regeneration are neurotrophins which includes nerve growth factor(NGF), neurotrophin-3 (NT-3), brain derived neurotrophic factor (BNDF), etc. Other growth factors that have been studied for their ability to promote nerve regeneration include ciliary neurotrophic factor (CNTF), fibroblast growth factors, transforming growth factor β (TGF-β), and glial derived neurotrophic factor (GDNF). [4]

- Anti-inflammatory drugs:
  One of the drugs commonly used to reduce the chronic inflammation and the immune response that accompanies neural implants isa synthetic steroid, dexamethasone. Dexamethasone is commonly used to treat other inflammatory diseases such as arthritis and multiple sclerosis, It has shown promising results for neural tissue engineering applications. Another anti-inflammatory drug used is α-melanocyte stimulating hormone (αMSH).[4]

TYPES OF REGENERATIVE THERAPIES & ITS MECHANISM OF ACTION

Scaffolds with cells

The first key technology is the preparation of cells scaffold for their proliferation and differentiation for in vivo tissue regeneration. ECM is not only a physical support for the cells, but also provides a natural environment for cell proliferation and differentiation or morphogenesis, which contributes to the process of tissue regeneration and organogenesis. Generally, it is quite complicated to naturally regenerate and repair a large-size tissue defect by just supplying cells to the defective site, because cells and the ECM are both lost. , hence one way to induce tissue regeneration at the defective site, o is to artificially build a local environment for cells which is a three-dimensional scaffold of artificial ECM to initially assist their attachment and the subsequent proliferation and differentiation, inducing cell-based tissue regeneration.[3]

Limitations:

- Exposure of implanted stem cells to traumatic physical loads and high levels of locally produced inflammatory mediators and catabolic cytokines. long-term effects of such an interference with nature Is unknown .
- they are pre-specialized, i.e, blood stem cells make only blood, and brain stem cells make only brain cells.[5]

Scaffolds with cells and bio-signaling factors:

When the tissue around the defect does not have any inherent potential to regenerate, the tissue regeneration cannot be always expected only by supplying the scaffold. The scaffold should be used in combination with cells or/and bio-signaling molecules (growth factors and genes) whichas the potential to accelerate tissue regeneration. There are cases, where growth factor is required to promote tissue regeneration, but direct injection of growth factor solution into the site to be regenerated is usually ineffective, because the growth factor rapidly diffuses and is enzymatically digested or deactivated. In-order to enable the growth factor to efficiently exert its biological function, a technology or methodology is required. This is the drug delivery system (DDS), the second key technology of tissue engineering. Among the DDS technologies, the controlled release of growth factor at the site of action over an extended period is achieved by incorporating the factor into an appropriate carrier which is very important for tissue engineering (figure 2, 3).[3]

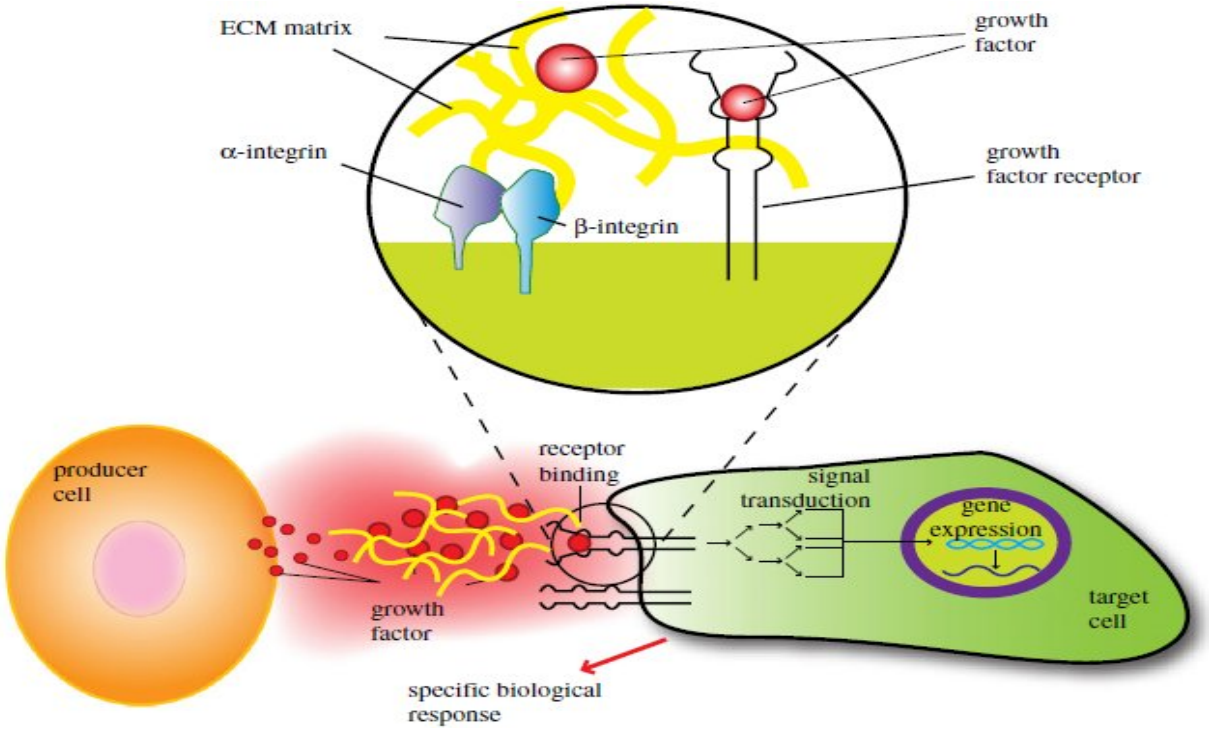

Fig 2. The producer cell secretes growth factors that bind to target cell receptors. Instructions are translated into the cell via complex signal transduction networks resulting in an explicit biological cellular response.[9]

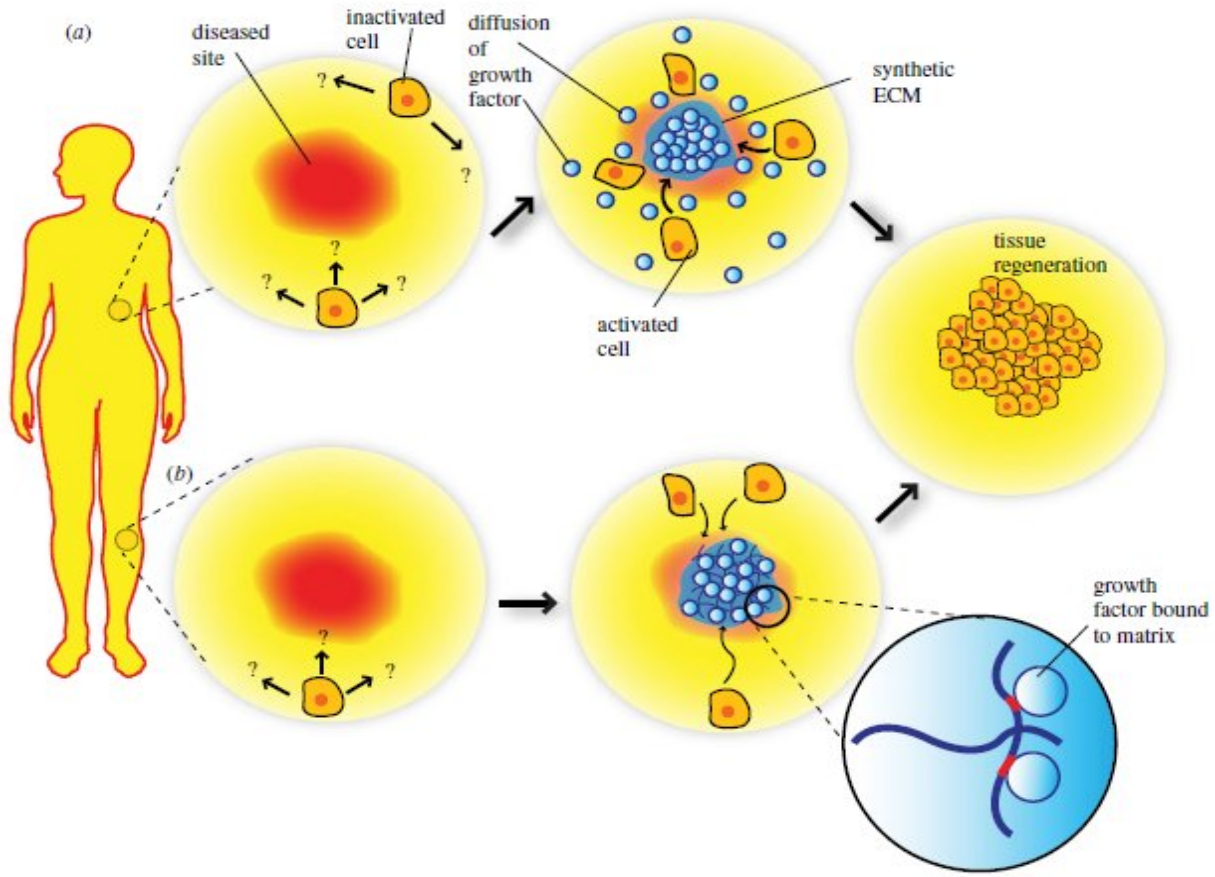

Fig 3. Tissue engineering approaches using synthetic ECMs to present growth factors to tissue. (a) Physically encapsulated bioactive factors (b) on the other hand, growth factors can be chemically bound to the material system.[9]

The scaffolds here may contain only bio-signaling molecules, if required for such a particular mode of treatment.

Limitations

The limitations of the first type also holds true here. Apart from it, few other considerations are also to be considered:

- Generally, at least a few days are required to induce and activate cell-based tissue regeneration. Consequently, it is not be expected that the regenerative therapy alone will achieve the rapid healing of wounds or diseases.[3]
- Also the functioning of bio-signaling molecules cannot be always predicted accurately for its in-vivo activity.
- The effector combination therapy which may work in a case may not work in other; hence it is very subjective and also varies from a person to person.

Physical barrier to cells:

- Yet another aspect is for a physical barrier to protect the cells transplanted and the area to be regenerated from immunological attack and fibroblast infiltration, respectively. When a body defect is generated, the defect space is occupied rapidly with the fibrous tissue produced by fibroblasts which are ubiquitously present in the body and can rapidly proliferate. To prevent the tissue in-growth, a barrier membrane is highly required to secure a space for tissue regeneration. The immune-isolation membrane used to protect the cells transplanted from the biological attacks of humoral and cellular components of the body is one such example.Therefore , it is tissue engineering that by making use of cell scaffold, barrier, and DDS technologies, biomedical technology or methodology creates an environment for the proliferation

and differentiation of cells to induce tissue regeneration.[2]

Limitations

- Based on the clinical situation, it is necessary for better medical treatment to combine the conventional therapies with the regenerative medical strategy.

Scaffolds for genetic engineering:

The forth technology is for the genetic engineering of cells. There are some cases where cells transplanted do not function well to induce cell-based tissue regeneration. one of the experiment to tackle this issue, is genetically engineered cells with biomaterials to activate the biological functions. It is necessary for genetic engineering of cells to develop the carrier of gene transfection and the cell culture system for efficient gene expression. Non-viral gene carrier of biomaterials is needed to develop from the clinical viewpoint of cell therapy because it is practically tough to use viral vectors of gene transfection clinically. This technology of gene transfection is also applicable for the basic research of stem cell biology and medicine which gives important knowledge and results for cell based therapy. Non-viral carriers for gene transfection and cell culture technologies with biomaterials are needed to induce iPS cells at higher efficiency for their clinical applications.[3]

CREATING COMPLEX ORGANS

Immense complexity can be found in the various tissues and organs targeted for replacement. Moreover, the injury or disease driving the need for tissue repair or replacement can add levels of complexity. To better understand the structural design of human tissues and organs that regenerative medicine attempts to replicate, it may be helpful to categorize them into four levels according to their increasing complexity: flat tissue structures; tubular structures; hollow, non-tubular, viscous structures; flat tissue structures, such as the cornea; tubular structures, such as the trachea; hollow, viscous structures, such as the bladder, and solid organs, such as the kidney. The complexity of a tissue engineering approach generally increases with the structure and metabolic functions of the tissue or organ targeted for repair.[10]

DRUG DELIVERY ASPECTS & TYPE OF DRUG DELIVERY SYSTEMS USED IN REGENERATIVE THERAPIES

A) Degradation/diffusion-based delivery systems:

A.1) *Scaffold based delivery systems:*

Scaffolds containing degradation/diffusion-based drug delivery systems have also been used as coatings for neural implants. Two different methods for controlled release of αMSH from nitrocellulose scaffolds, a reservoir method and a matrix method (Fig 4 A and B) were tried. For the reservoir delivery method, αMSH was evaporated directly onto the silicon electrode and then the nitrocellulose scaffold was added on top. For matrix delivery method, nitrocellulose was mixed with the αMSH and then the resulting mixture used to coat the electrodes, leading to distribution of drug throughout the scaffold. Fig 4 C shows the effect of delivery method on release over an 18 day time course.[4]

A.2) *Microsphere based delivery systems:*

Microspheres can be fabricated through a variety of techniques including solvent evaporation, spray freeze drying, etc. The rate of drug release from microspheres is regulated by diffusion and the release kinetics of the target drug can be altered by changing the polymer used, amount of protein loaded and size of the microsphere.[4]

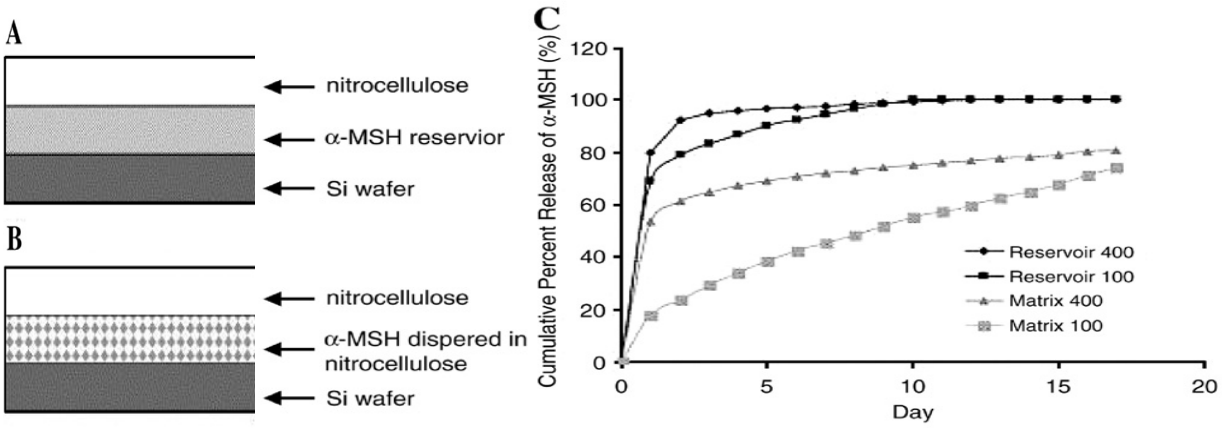

Fig 4. Comparison of two different fabrication of nitrocellulose scaffolds for delivery of αMSH. A) Schematic of the reservoir delivery method B) Schematic of the matrix delivery method C) Cumulative controlled release profile. Data shown are the average±S.E.M. (n=3). Reproduced from reference, Copyright (2005), Elsevier.[4]

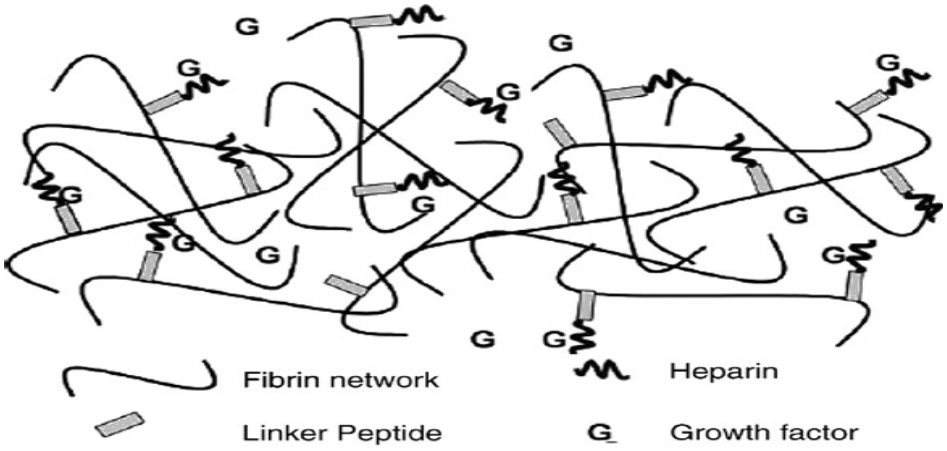

Fig 5. Schematic diagram showing the components of the heparin-binding delivery system. The bi-domain peptide is cross-linked into the fibrin gel via the transglutaminase activity of Factor XIIIa; heparin can bind to the peptide by electrostatic interactions.NT-3 can bind to the bound heparin, creating a gel-bound, non-diffusible complex.NT-3 can exist in the diffusible condition, alone, or in a complex with free heparin. Reproduced from reference, Copyright (2004), Elsevier.[4]

B) Affinity-based delivery systems:

As an alternative to relying on a material's physicalproperties to regulate release, affinity-based delivery systemsutilize non-covalent interactions between the desired drug andthe scaffold to provide controlled release. One of the mainexamples of an affinity-based delivery system is a heparinbinding delivery system (HBDS), which can be used to deliverany protein drug that binds to heparin. Such delivery systemswere initially designed to release basic fibroblast growth factor(bFGF), but recently HBDSs have been used in conjunctionwith fibrin scaffolds to treat peripheral and central nervoussystem injuries. The HBDS consists of fourcomponents, a scaffold (e.g. fibrin), a bi-domain peptide, heparin,and a growth factor as seen in Figure 5.[4]

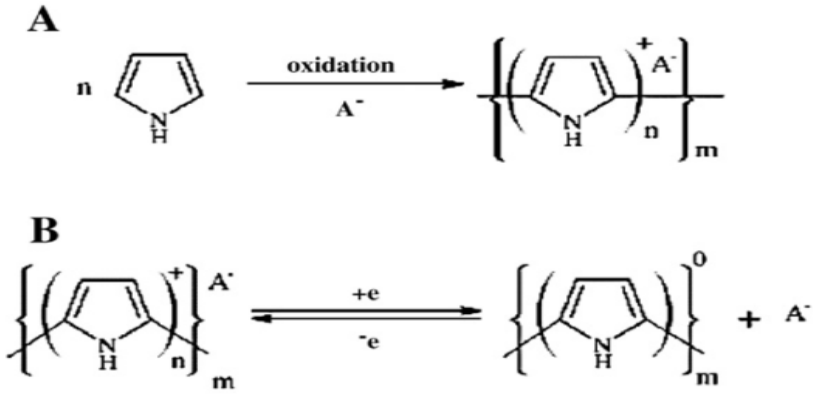

Fig 6. Schematic of chemical oxidation used to dope polypyrrole with NT-3. A) Synthesis of polypyrrole showing the incorporation of the dopant A−. (B) Release of the dopant A− during redox cycling of the polypyrrole. Copyright (2006), Elsevier.[4]

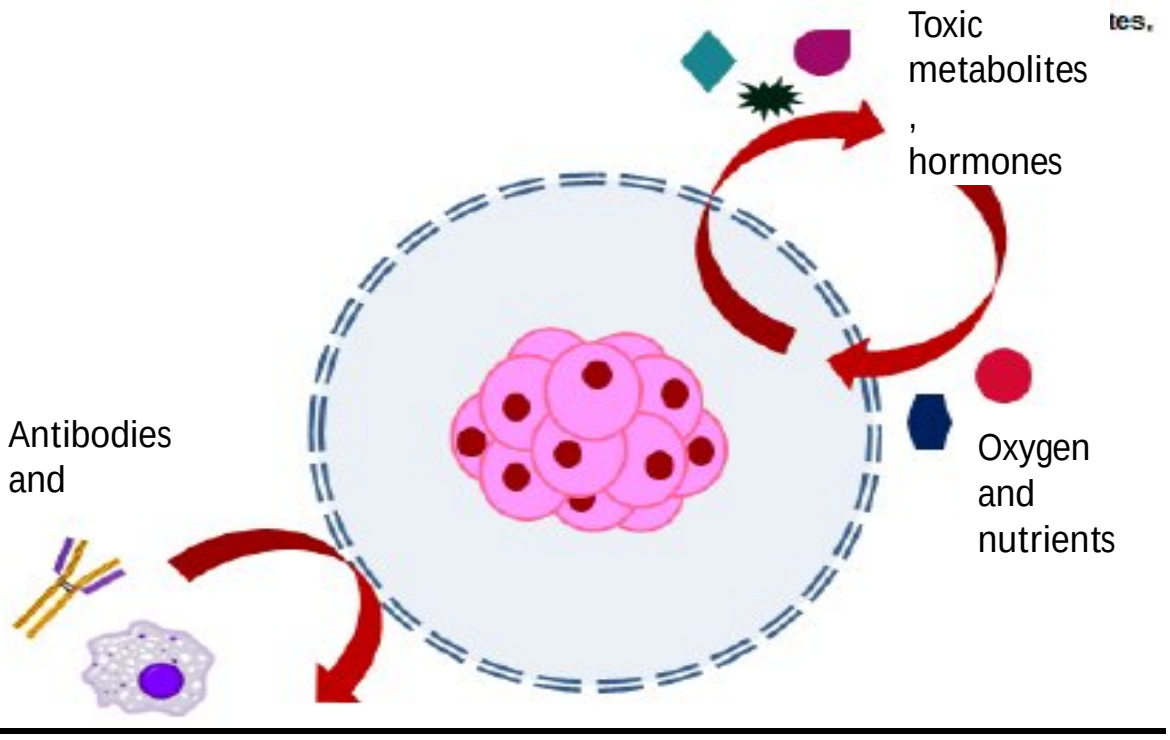

Fig 7. Schematic illustration of cell encapsulation technology. The semi-permeable membrane allows the bidirectional diffusion of nutrients, oxygen, therapeutic products and waste. At the same time this membrane avoids the entrance of immune cells and antibodies.[11]

C) Immobilized drug delivery systems:

A different approach to drug delivery involves covalently attaching the target drug into the scaffold material. In this way, drug will not be lost to diffusion and the time course of release would be comparable to the lifetime of the scaffold. A significant consideration while designing such drug delivery systems is to ensure the process of immobilizing the drug onto the scaffold does not affect the efficacy or biological activity of the target drug. Loss of activity is a result of denaturation, that blocks the receptor binding site on the drug or binds the drug to the scaffold in a manner that prevents access to the active site of enzymes various chemistry has been developed to produce immobilized drug delivery system. One way of

covalently tethering proteins to the desired scaffold is through the use of photochemistry, as shown in Fig. 6. [4]

Cell encapsulation: Cells in native tissue are embedded within a complex 3D microenvironment consisting of soluble molecules (cytokines and growth factors) and non-soluble factors (mainly ECM). The microenvironment not only provides structural integrity, but also controls numerous signal transduction processes that direct cell survival, cell cycle progression, and the expression of different phenotypes. Cell encapsulation technology is based on the immobilization of cells within a semi-permeable membrane (Figure 7). This membrane protects the inner cells from both mechanical stress and the host immune system, while allowing the bidirectional diffusion of nutrients, oxygen and waste.[11]

D) ***On–off delivery:***

Protein and peptide release can be engineered to be delivered in pulsatile mode, intended as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a pre-determined off-release interval. One way to classify pulsatile delivery systems is based on the physicochemical and biological principles that trigger the release. These devices are classified into "programmed" and "triggered" delivery systems. In programmed-delivery systems, release is completely governed by the inner mechanism of the device (for example lag-time prior to drug release in some delivery system). In triggered-delivery systems, release is governed by changes in the physiologic environment of the device (i.e. self-regulated delivery systems or biologically-triggered DDS) or by external stimuli (i.e. externally-triggered systems). In the latter case, external stimuli, such as temperature changes, electric or magnetic fields, ultrasounds and irradiation, activate drug release.[8]

D.1) ***Programmed delivery systems:***

The programmed- delivery systems are precise timed drug delivery that can be accomplished by the spontaneous hydrolysis (i.e. bulk and surface eroding systems) or enzymatic degradation of the polymer comprising device. Bulk- and surface-eroding systems may be engineered to achieve pulsed protein delivery slightly modifying the composition of the device, which can be based on PLGA, cross-linked hydrogels, polyanhydride, and all those biodegradable polymers discussed above. In case of PLGA-based microparticles, more than an effective "pulsed" drug delivery, a booster release occurring over a period of several weeks after a typical lag-phase has been realized. In perspective, the implant can enable the patterned delivery of multiple agents. Also surface eroding polymers, such as poly(anhydrides), can be of help when pointing to pulsed protein delivery. Furthermore, the load of therapeutics can be easily tailored over a broad range in the drug layers.[8]

D.2) ***Triggered delivery systems:***

Self-regulated delivery systems (i.e. biologically-regulated delivery systems) are closed-loop controlled release devices in which the release rates are adjusted by the system, in response to feedback, without any external intervention. This is the case of pH-responsive systems, which have been mainly investigated for oral protein delivery. These systems can be potentially manufactured in form of fibers, gel, sheets or microparticles to fabricate scaffolds. A great deal of interest has been focused to glucose-responsive insulin delivery since the development of pH-responsive polymeric hydrogels that swell in response to glucose. The "intelligent" system consists of immobilized glucose oxidase in a pH-responsive polymeric hydrogel, enclosing saturated insulin solution. Diffusion of glucose into the hydrogel, leads to glucoseoxidase catalyze its conversion to gluconic acid, thereby lowering pH in microenvironment of the membrane, causing swelling and insulin release. Recent progresses have been made in designing "smart" hydrogels able to specific recognize a biomolecule through molecular imprinting techniques. Contrariwise to self-regulated delivery systems, externally-regulated delivery systems are open-loop controlled devices in which drug release can be activated by an external stimuli, including temperature changes, magnetism, ultrasound,

electrical effect and irradiation. These systems make use of "smart" polymeric materials, which respond with a considerable change in their properties to small changes in their environment.[8]

E) ***Electrically controlled drug delivery systems:***

Electrically controlled drug delivery systems have been investigated for use as coatings of neural electrodes. Such systems release target drugs upon electrical stimulation, which often is used during recording via such implants. In one study, an ionic form of dexamethasone was incorporated into Polypyrrole films grown on top of gold films through the use of electro-polymerizationshows the general chemistry scheme for incorporating molecules into Polypyrrole. Controlled release of dexamethasone from the Polypyrrole films occurs after the application of a volt-ammetric stimulus. In vitro studies showed that the release of dexamethasone reduced the amount of reactive astrocytes present while having no negative effect on the viability of neurons. Additionally, the coating did not alter the impedance of the electrode. Using a similar strategy, a two-step process was used to incorporate Neurotrophin-3 into Polypyrrole coatings. In this study, the Polypyrrole was first doped using p-toulenesulphonate (pTS) to create a Polypyrrole-pTS coating on gold electrodes using galvanistic methods. A second layer was then formed using a mixture of Polypyrrole, pTS, and Neurotrophin-3 in the same fashion pulsed voltage, pulsed current and cyclic voltammetry are applied in promoting increased release of Neurotrophin-3 when compared to controls with no current applied (diffusion only). Further studies showed that these coatings promoted neurite extension in vitro, indicating that the Neurotrophin-3 retained biological activity after the polymerization process. These strategies are useful for designing coatings for neural implants and may also have applications in promoting regeneration for other injuries to the nervous system.[4]

F) **Strategies for delivery of multiple growth factors (GFs)**:

There are three frequently used strategies for the dual delivery of GFs in tissue engineering and regenerative medicine, which may have the potential to be introduced for periodontal reconstructive therapies. These strategies are direct presentation, multiphase loading, and particulate-based delivery (Fig. 8). Beyond a doubt, the simplest method to encapsulate dual/multiple GFs into a polymer matrix is to mix/ introduce these factors within the polymer directly before its gelation or solidification (Fig. 8A). However, direct entrapment methods may result in inefficient protein incorporation caused by the loss of the protein itself, its chemical activity, and/or its biological integrity during the processing steps. In addition, inefficient incorporation of GFs due to the small amounts of protein that can be attached in this manner and their unpredictable release properties render this method non-ideal. The porous supporting structure faces great difficulties in allowing the release of multiple GFs in a controlled and orchestrated fashion. Moreover, controlling the potential inter-actions among different GFs when in a scaffold is nearly impossible because of their close proximity. Accordingly, the concept of multiphase loading via the use of cross-linked microspheres embedded in different scaffold types was developed to circumvent this question, where two GFs were individually loaded into either scaffold phase or microsphere phase (Fig. 8B). Thus far, a series of microsphere/hydrogel composites have been devised to meet such criteria in which multiphase loading enables two or more GFs to be safely presented together. Two or more types of particles designed with specific release rates can then be introduced into the same scaffold, which leads to different tailored release kinetics for each type of GF (Fig. 8C)[12]

EVALUATION OF REGENERATIVE THERAPIES

A) Clinical Endpoints:

How engineered tissues are ultimately judged to be good enough for clinical application? With tissues such as kidney or bone marrow, analysis of urine or blood provides valuable information about the success or failure of the tissue in both human patients and animal models. But different methods are needed to quantitatively assess the long-term outcome of engineered connective tissues, such as cartilage, tendon, and blood vessels. Metrics used in current clinical trials of engineered cartilage, for example, are a reduction in pain, appearance of new tissue, and qualitative mechanical probing. In the absence of mechanistic models of long-term tissue repair, gene-expression changes obtained by microarray analysis, or imaging of 3D tissue structure with MRI, may be valuable alternative strategies.[14]

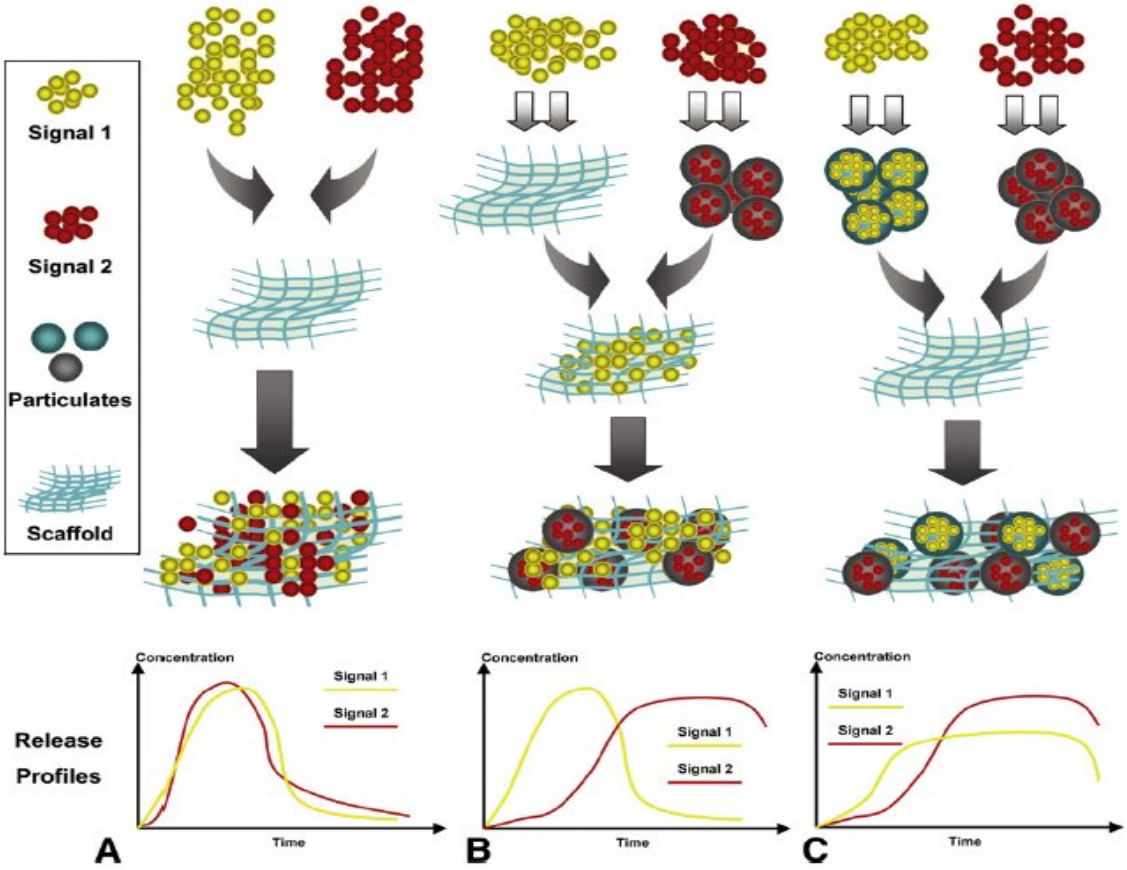

Fig 8. Schematic illustrations of two candidate strategies towards releasing endogenous growth factors (GFs) for periodontal therapeutics (illustration is not to scale). (A) Cells are modified by genes that encode GFs, using either ex vivo or in vivo gene delivery strategies (not shown), and the genetically modified cells may subsequently produce multiple endogenous GFs for therapeutics. (B) The preparation of platelet-rich plasma (PRP) or its associated formations from whole blood towards releasing multiple patient-derived GFs for therapeutics. Platelets contain high quantities of endogenous GFs. Upon activation, the platelets in the PRP may release a multitude of GFs[12]

factors can be explained as possible:

Thus, modification in the release profile of different growth

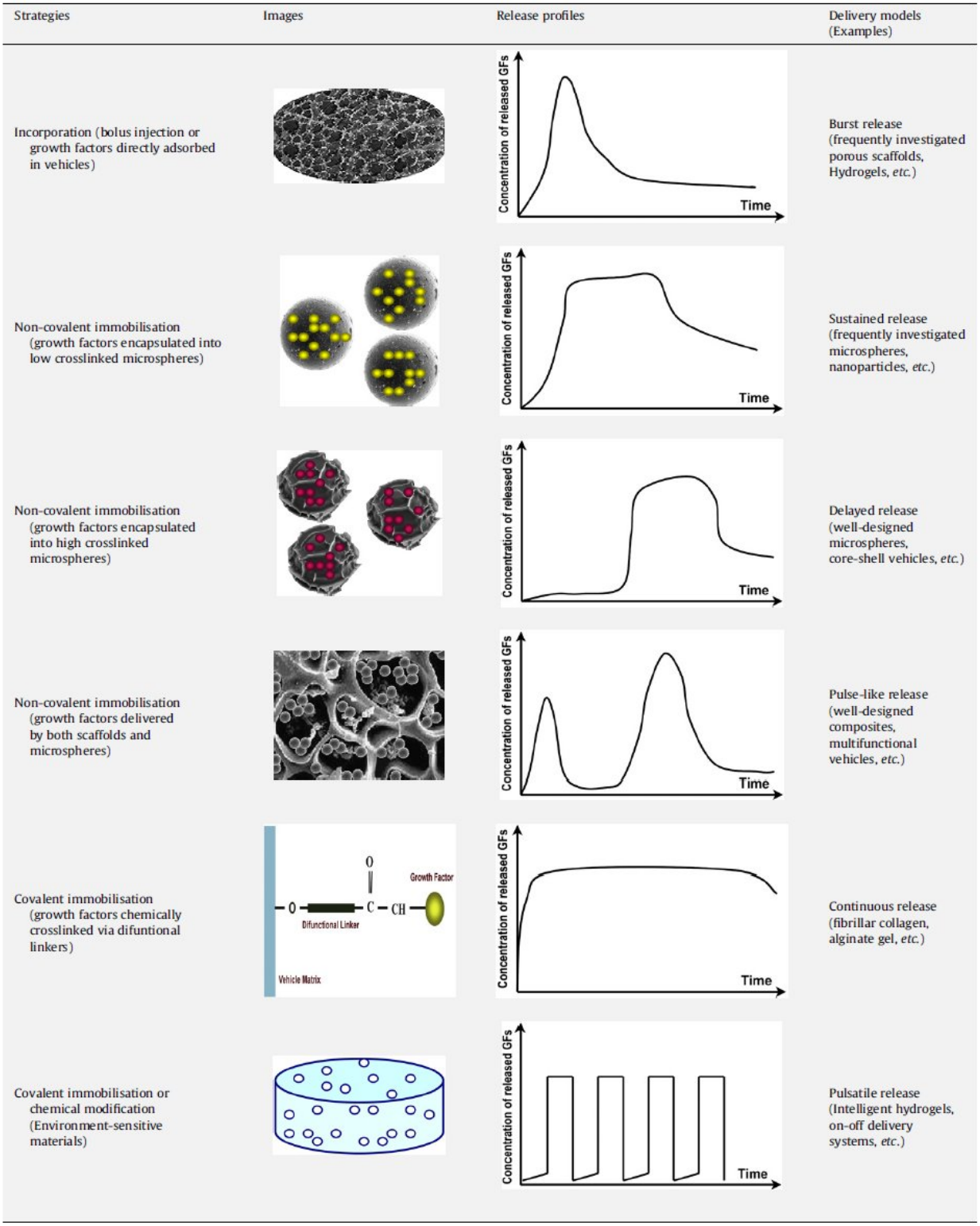

Fig 9. Schematic presentation of selected delivery strategies and their representative release profiles.[13]

B) Nanoparticle Systems for Tracking Transplanted Stem Cells (SCs):

Assuming that SCs may not trigger the immune response it is still important to consider how these cells can be guided to specific locations once they are transplanted cells are labeled ex vivo to distinguish the implanted cells from the host tissue cells to monitor and evaluate the engraftment in the host, and follow their survival, migration, differentiation and regenerative impact in living subjects. In these terms nanoparticles technology could help to track and localize transplanted cells. Nanoparticles are made with unique optical and/or magnetic properties to allow a non-invasive, accurate and real-time cell tracking. Ideally, imaging technology used for SC tracking would have single-cell sensitivity allowing quantification of exact cell numbers at any anatomic location. Evaluation can be done using drug delivery systems like, Superparamagnetic Iron Oxide Particles, fluorescence techniques, Quantum Dots, Functionalized Peptide Nanostructures and the likes.[11]

CLINICAL & REGULATORY ASPECTS

Various regulatory considerations can affect the development of tissue engineering technologies, and a clear vision of the appropriate regulatory pathway for approval or clearance of an envisioned product should be established at the onset of the technology development. In general, the regulatory complexity associated with particular tissue engineering product increases with the complexity of the product itself, for example, a synthetic, polymeric scaffold might be regulated as advice, whereas the same scaffold that delivers growth factors and contains cells might be regulated as a combination product. Consequently, the regulatory complexity and associated burden can be minimized through identification and pursuit of the simplest product sufficient to meet the desired clinical need. Additional considerations include the manufacturing consistency associated with a tissue-engineered product. As expected, manufacturing is more challenging as the complexity of the product increases, and the cost of the product will be expected to increase accordingly. Moreover, tissue-engineered products may be produced in small lot sizes, which create a challenge in establishing and maintaining inter-lot consistency. Indeed, interactions with the relevant regulatory body should be initiated at the initial stages of technology development to facilitate identification of the appropriate regulatory pathway for the envisioned technology, as well as to guide selection of suitable methods and study designs for preclinical and clinical investigations to support regulatory consideration of the technology.[10]

CHALLENGES

- To prepare vascularized organs is a big challenge even today with all the recent proceedings.
- It needs ethical considerations, at every stage.
- Therapy as such is very subjective and each and every case has to be dealt with at individual level. This causes rise in the costing of the therapy and also makes its scale-up related issues complex.
- Every organ will be different and every disorder has to be treated differently, which brings in a lot of research based work on each and every aspect related to the treatment.
- Toxicity related problems do dwell up and it is difficult to overcome them.
- Because of the use of the cells, the control on the cell based therapy in itself is a big challenge. If not taken due care then there is chances of it developing into tumor.
- It is difficult to control the therapy, if the subject is not kept under constant surveillance.
- Also, due to ever evolving field, the regulatory and clinical norms keep on changing as per requirements, so constant follow-up with the authorities is required to keep a track on it as well.
- Ability to control kinetics of polymer degradation, numerous routes of fabrication to be determined and engineering related complexities.
- Potential roles of an industry association:

- Supporting pioneer companies who lack the critical mass to address the many issues that affect them.
- Organizing promotion of both technologies push and market pulls.
- Helping to ensure sensibly drafted regulation and planning towards unified international agreement on regulations.
- Working to achieve a balance on patents and disclosure of intellectual property which encourages risk-taking entrepreneurs but does not block broad progress.
- Addressing issues of reimbursement and health insurance and the necessity of cost assessment based on the short and longer term.
- Cooperating to formulate national and international standards for terminology and technology.[15]

MARKETED PRODUCTS

Regenerative medicine is already commercially available for: tissue engineering (e.g., skin repair/wound healing), orthopedics (e.g., spinal disc and joint cartilage repair), diabetes (e.g., islet cell transplantation), oncology/hematology (e.g., stem cell transplants), ophthalmics (e.g., limbal stem cell deficiency, corneal disease, and so on), and cosmetic/aesthetic (e.g. body sculpting).[16]As on March 2011, there are some 275 therapeutic companies with about 240 different cell based therapies in place. Accordingly the data for number of products at various stages of development are as follows:[16]

Various regenerative therapy products around the world are (table no. 3.):

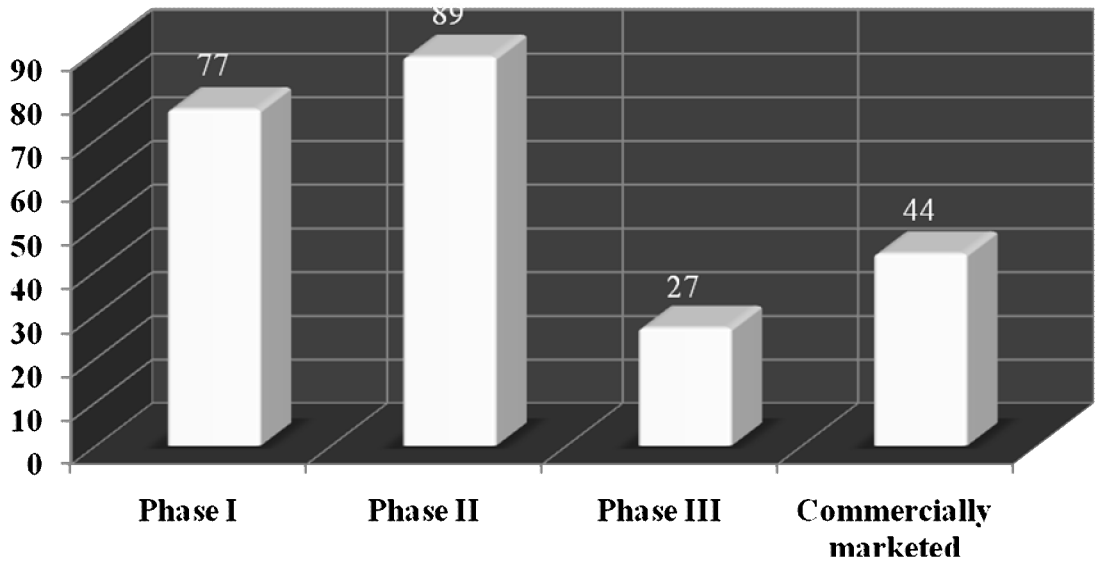

Table 3: Worldwide top 10 commercial regenerative medicine products:[16]

Worldwide top 10 commercial regenerative medicine products					
Company	**Brand Name**	**Product type**	**Therapeutic area**	**Indication**	**Launch**
Advanced biohealing	Dermagraft	Allogenetic neonatal cells with matrix	Skin	Diabetic skin ulcer	1997
Cytori	Celution	Autologous cell based product	Soft tissue (Adipose)	Reconstructive breast surgery	2008
Genzyme	Carticel	Autologous cell based product	Indication cartilage	knee repair	1995
Integra Life Science	Various	Allogenic, accellular matrix	Skin	Skin repair and replacement	2001
LifeCell	Alloderm	Allogenic, accellular matrix	Skin	Skin replacement and hernia repair	1994
Medtronic	Infuse	Growth factor with matrix	Bone	spinal, orofacial, and open tribial fractures	2002
Organogenesis	Apligraf	Allogenic, neonatal cells with matrix	Skin	Diabetic skin ulcer	1995
Osiris/Nuvasive	OS100001	Allogenic cell-based products	Bone	Fracture repair	2005
RTI	Spinal implants	Allogenica cellular matrix	Bone	Spinal fractures	1991
Stryker	OP-1	Growth factor with matrix	Bone	Spine fusion andfractures (humanitarian device exemption)	2005

CONCLUSION

Goal of regenerative medicine is to restore tissue function through the delivery of stem cells, bioactive molecules, or synthetic tissue constructs engineered in laboratory. The medical application of regenerative therapy in clinics can produce wonderful treatments to dramatically improve patient's quality of life. Regenerative medicine in the broadest sense unquestionably will affect medical practice significantly and will be routine, for primary and adjunctive therapies sooner. As an interdisciplinary endeavor, "Regenerative medicine" brings in the power of biological, chemical and physical science to real clinical problems. The combination of cell scaffold, space providing, and DDS technologies is practically promising to create an environment which enables cells to promote the proliferation and differentiation for tissue regeneration. The culturing and genetic engineering of cells are both key technologies to prepare cells clinically available for cell therapy. Every biomaterials-based technology is important not only to develop the basic research of stem cells biology and medicine, but also to comprehend the cell-based tissue regenerative therapy.

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