# Periodontal Regeneration-Recent concepts

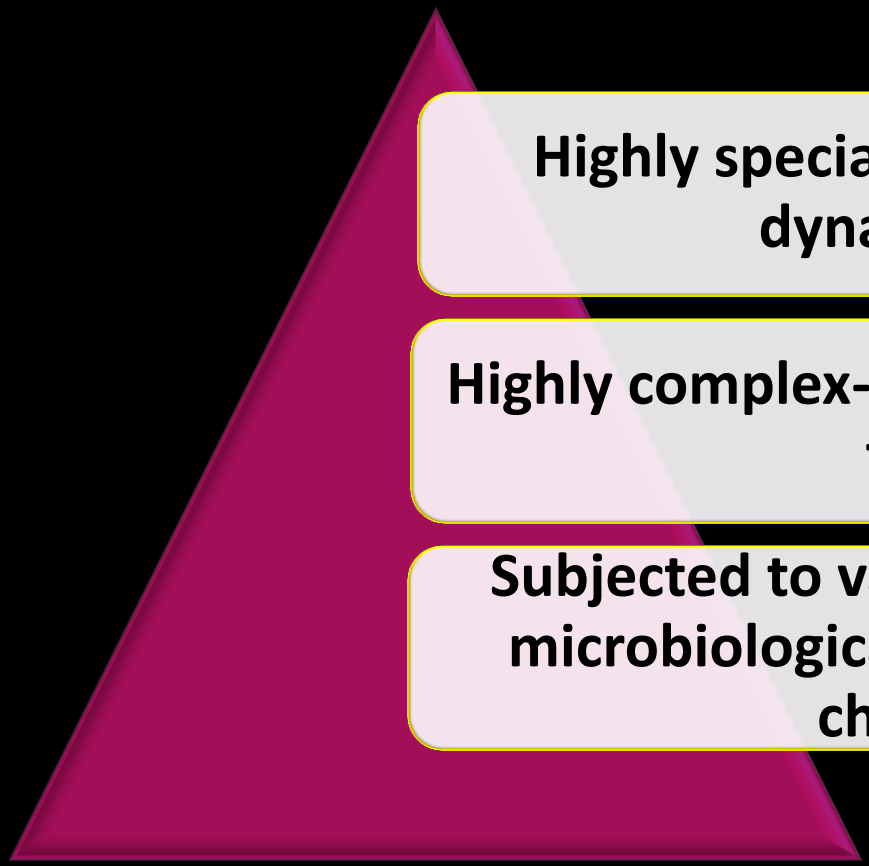
Dr. Kanchan Jagtap

# ABOUT REGENERATION….

- It’s a natural continuous process happening in any living tissue
- It’s a part of healing process after any injury or destruction wherein complete architecture and function of lost tissue is restored

**Periodontal regeneration is defined as the restoration of lost periodontium which includes formation of new alv.bone , cementum and functionally oriented periodontal ligament resulting in new attacment**

# Periodontium is Unique…

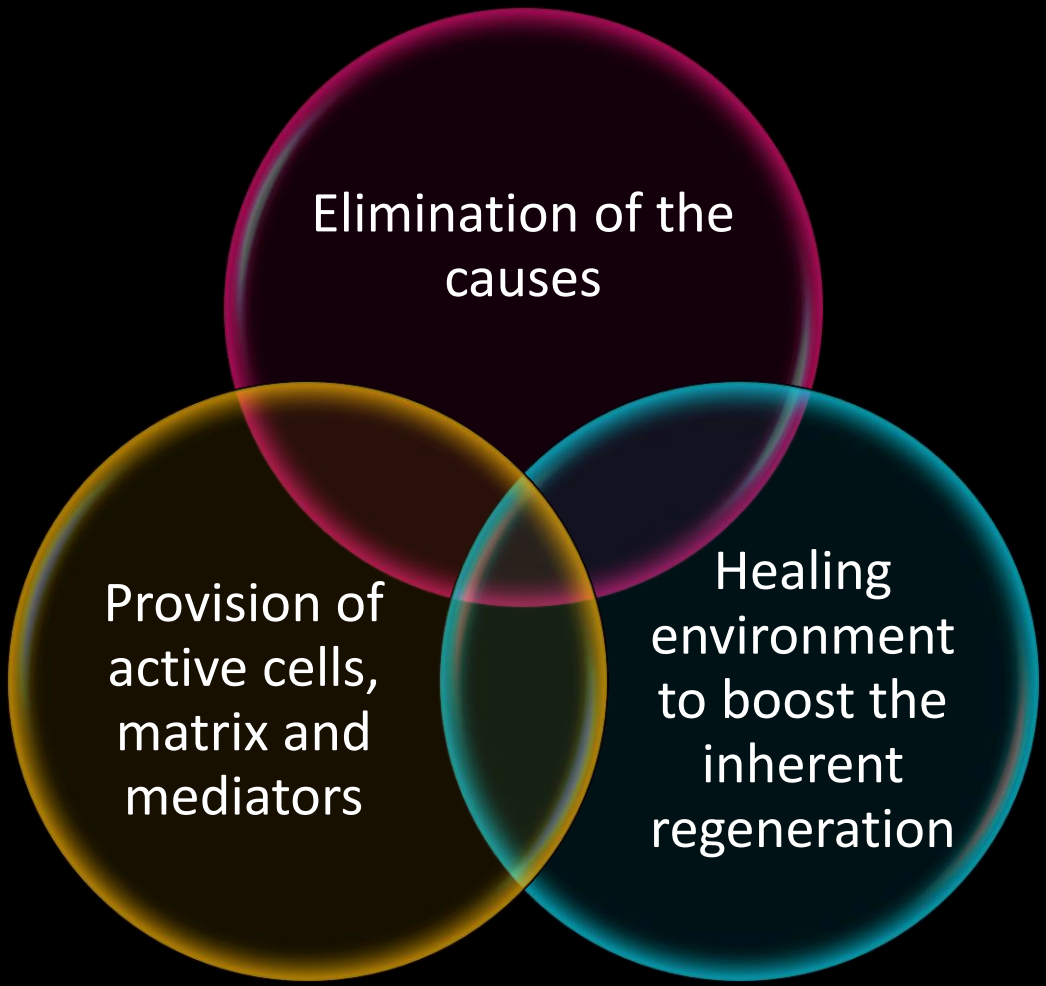


**Highly specialized, adaptive and dynamic tissue**

**Highly complex-Four different types of tissues**

**Subjected to variety of mechanical, microbiological and inflammatory challanges**

# HOW TO ATTAIN REGENERATION?



# Conventional Periodontal Surgery

Goals - Provide Critical access to debride the root surface
- Establish Improved periodontal form & architecture.

Limitation - Gives only repair
- Limited potential in restoring or reconstructing the periodontal tissues.

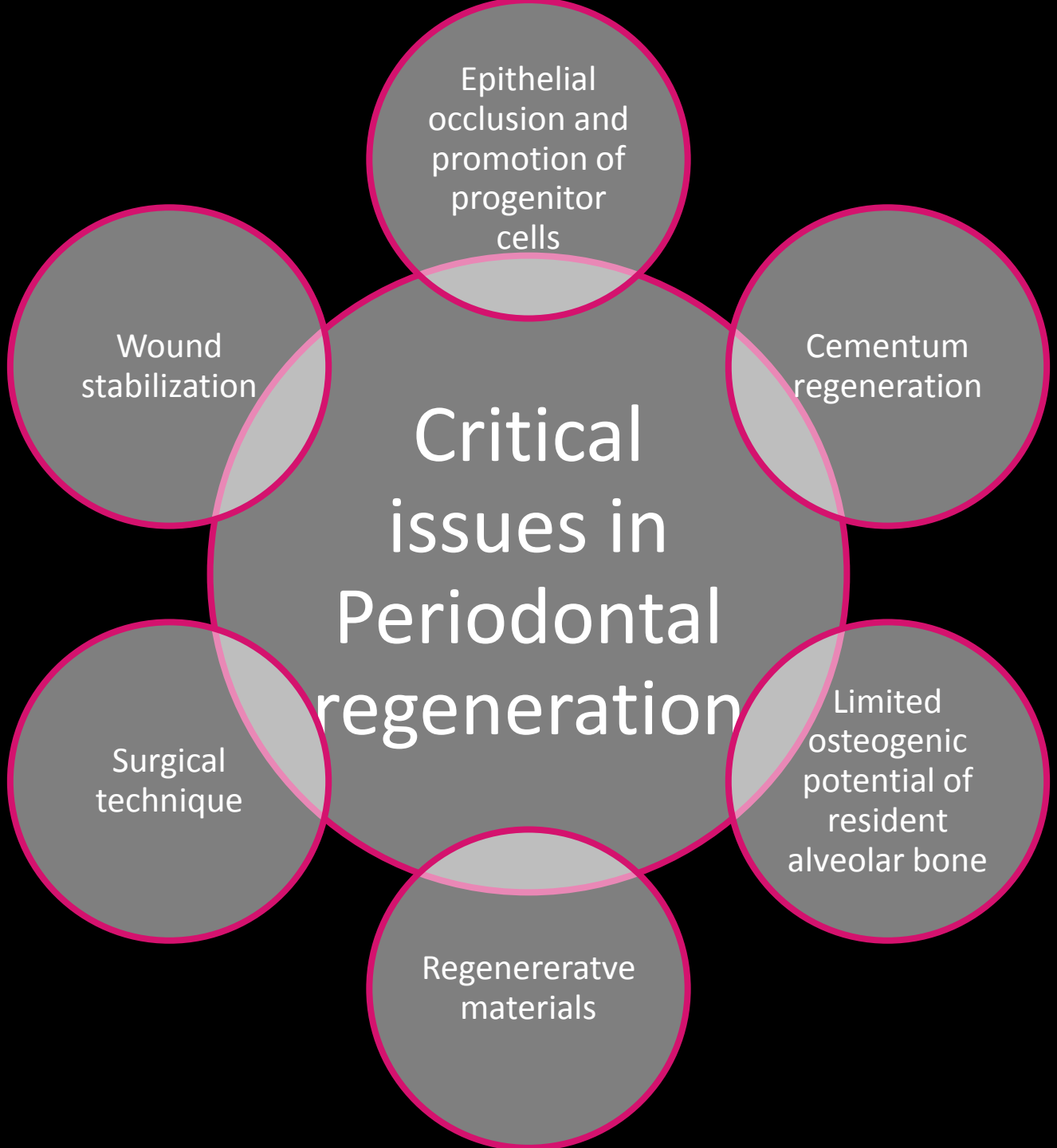
# Periodontal Regeneration is Challenging – Why?

- The need for Regeneration of not one but four tissues.

- It involves Significant Communication between all the Cellular and matrix Components of the periodontium to induce inherent regeneration capability of the tissues.

- To achieve complete tissue regeneration it is necessary to recapitulate the process of embryogenesis & morphogenesis.

- The etio pathogenic factors may not have been completely eliminated


Epithelial occlusion and promotion of progenitor cells
Wound stabilization
Cementum regeneration
Critical issues in Periodontal regeneration
Surgical technique
Limited osteogenic potential of resident alveolar bone
Regenereratve materials

# SUCCESS OF PERIODONTAL REGENERATION DEPENDS ON.....

- Patient related– oral hygiene, systemic heaith, habits, genetics
- Tooth related- hypermobility, endodontic status
- Defect related- Number of walls, defect angle, grade of furcation defects
- Surgical technique
- Regenerative material

# Regenerative Therapeutics-Various methods

- Conductive therapeutics
- Inductive therapeutics
- Cell based therapeutics
- Gene based therapeutics
- RNA based therapeutics

# Conductive Therapeutics

Basis - Bio compatible Scaffold that guide the regeneration of the tissue by passively allowing the attachment & growth of vascular elements and progenitor stem cells that reside in the tissue defect.

# Conductive Therapeutics-Examples

- Cortical autogenous bone grafts,
- FDBA,
- Alloplasts- hydroxyapatite, tricalcium phosphate Calcium Salfate etc.
- GTR
- Peptide Coated biomaterials-Various Cell binding peptide Sequence of Cell adhesion.

# How do they work?

- They provide a structural frame work for clot development, maturation and remodeling

- They provide structure and surface topography that permit cellular attachment , proliferation and migration

**Limitations**

- Regenerative potential is limited due to lack of biologically active factors and sufficient progenitor Cells within the defect.

# INDUCTIVE THERAPEUTICS

Basis - Biocompatible Scaffold that guides and induces the regeneration by carrying one or more biologically active factors that recruit vascular elements & progenitor Stem cells from the immediate vicinity to the defects.

# Inductive Therapeutics-Examples

- DFDBA,
- Biomaterials carrying osteoinductive recombinant Protein such as PDGF, IGF,TGF β , Rh BMP – 2, BMP-3,6,7,12,14

**Limitation**
- Short half lives (Minutes to few hours)
- Proteolytic break down
- limited bioavailability due to difficulty in reaching the desired site
- Receptor binding Problem
- Dependent on the Stability of the Carrier

# Cell based Therapeutics

- **Basis-** Cell based therapeutic is a biocompatible scaffold that contains progenitor stem cells or differentiated Cells
- **Examples.**
- Cancellous or marrow derived autogeneous graft
- Cell sheet technology
- Stem cell based therapy

# Cell based therapeutics

- Cancellous or marrow derived autogeneous graft

Limitations- Survival of the cells are not Predictable
-Can regenerate bone – Not entire Periodontium
-Root resorption & ankylosis

- Cell sheet technology

Limitation - require substantial volume of donor tissue.

- Stem cell based therapy

Limitation - Ethical issues (For embryonic stem cells)
- Scarce availability of cells & technical difficulties .(Adult stem cell)

# Gene based Therapeutics

Basis - A biocompatible scaffold carrying single or multiple genes that transform the non progenitor cells already Present within the tissue defect into both Progenitor and mature tissue Specific cells.

- One or more genes encoding for growth factors or transcriptional regulators may be delivered - simultaneously or sequentially .
The Vectors used are viral or non viral

Adv: Potentially mimicking the complex natural process of tissue formation.

•

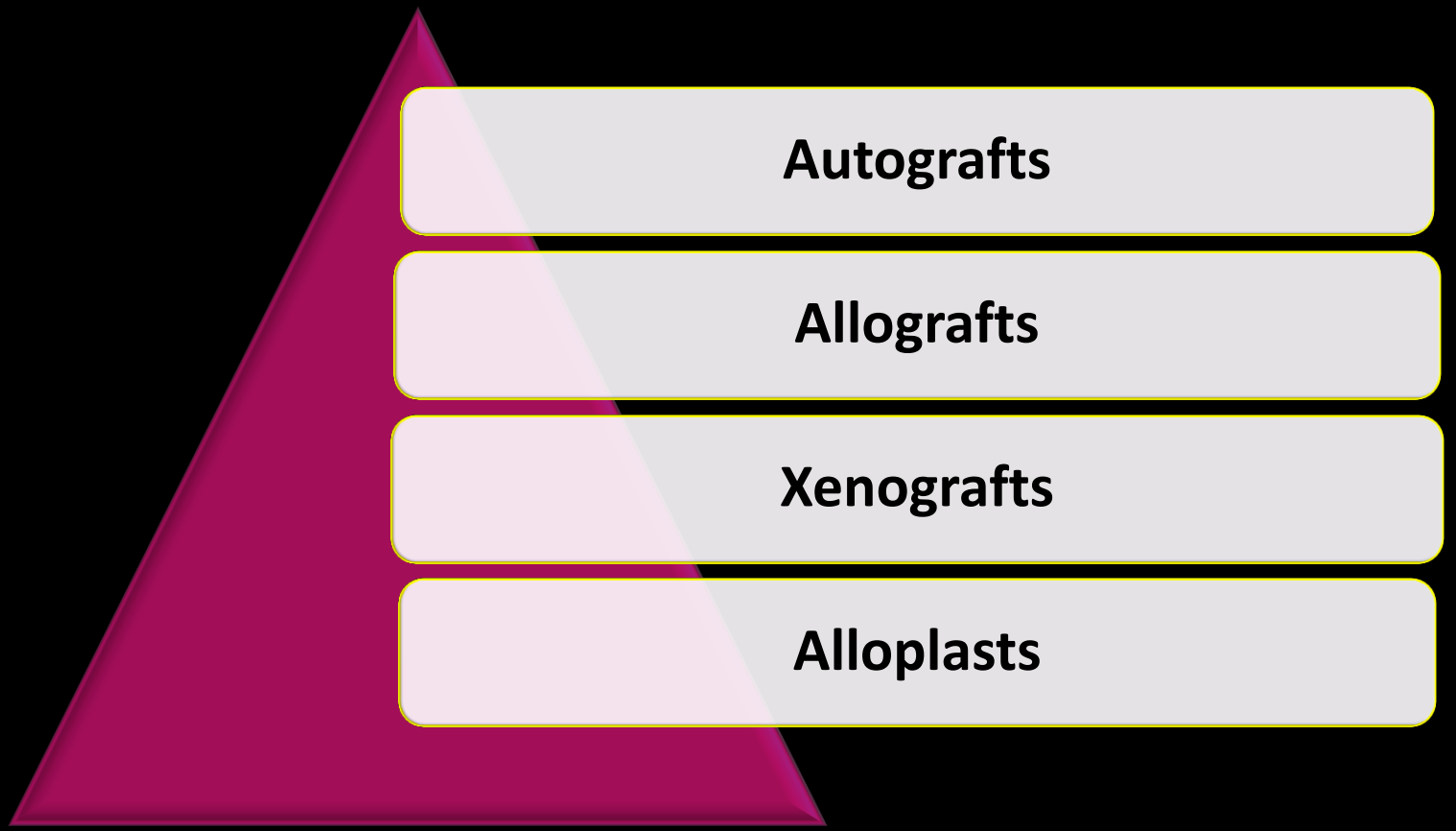
# RNA Based Therapeutics

Basis : RNA Mediated Silencing process (RNA interference works through small RNAs(20-30 nucleotides) that guide the degradation of complimentary or semi complementary in mRNAs (Post Transcriptional Silencing) or interfere with the expression of gene at the promoter level(Transcriptional gene silencing)

Introducing mRNA directly to cytoplasm thereby facilitating particular protein translation

# CONDUCTIVE & INDUCTIVE THERAPEUTICS

# Bone Grafts



# Autografts

Advantages; No immunogenicity,  Can be osteogenic, osteo inductive and osteo conductive

Limitations; Second surgical site, Graft volume, Increased surgical time, High morbidity, Graft replacement rate is unpredictable

# Allografts

Types- FFBA,FDBA,DFDBA

Advantages; Less morbidity, Large quantity, Osteoconductive and DFDBA is osteoinductive

Limitations;  FFBA has the risk of disease transmission and immune rejection,

# Xenoografts

Types; Bovine. Porcine, Equine orgin

Advantages; Less morbidity, Good osteo conductivity, Slow resorption process

Limitations; No osteogenic osteo inductive property, Disease transmission through Prions, Very slow resorption

# Alloplasts

**Advantages and limitations;**

Easily available, biocompatible, osteoconductive, no morbidity

HA acts only as a filler and doesnot contribute to bone formation and very slow resorption rate,

Beta TCP is osteo conductive and resorbed in 6-9 months

Bioglass is osteo conductive but hardly resorbed

Ann Periodontol

# The Efficacy of Bone Replacement Grafts in the Treatment of Periodontal Osseous Defects. A Systematic Review

Mark A. Reynolds, Mary Elizabeth Aichelmann-Reidy, Grishondra L. Branch-Mays, and John C. Gunsolley

*Department of Periodontics, Baltimore College of Dental Surgery, University of Maryland, Baltimore, Maryland.*

## Reviewers' Conclusions

1. With respect to the treatment of intrabony defects, the results of meta-analysis supported the following conclusions: 1) bone grafts increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing depth compared to open flap debridement (OFD) procedures; 2) No differences in clinical outcome measures emerge between particulate bone allograft and calcium phosphate (hydroxyapatite) ceramic grafts; and 3) bone grafts in combination with barrier membranes increase clinical attachment level and reduce probing depth compared to graft alone.

2. With respect to the treatment of furcation defects, 15 controlled studies provided data on clinical outcomes. Insufficient studies of comparable design were available to submit data to meta-analysis. Nonetheless, outcome data from these studies generally indicated positive clinical benefits with the use of grafts in the treatment of Class II furcations.

Ann Periodontol

# The Efficacy of Bone Replacement Grafts in the Treatment of Periodontal Osseous Defects. A Systematic Review

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*Department of Periodontics, Baltimore College of Dental Surgery, University of Maryland, Baltimore, Maryland.*

With respect to histological outcome parameters, 2 randomised controlled studies provide evidence that **DFDBA** supports the **formation of a new attachment apparatus.**

- Consistent histological evidence show that **autogenous** and **demineralized allogenic bone grafts** support the **formation of new attachment.**

- **Limited data** also suggest **that xenogenic bone grafts** can support the **formation of a new attachment**.

- All available data indicate that **alloplastic grafts** support ***periodontal repair*** **rather than regeneration**.

Periodontology 2000

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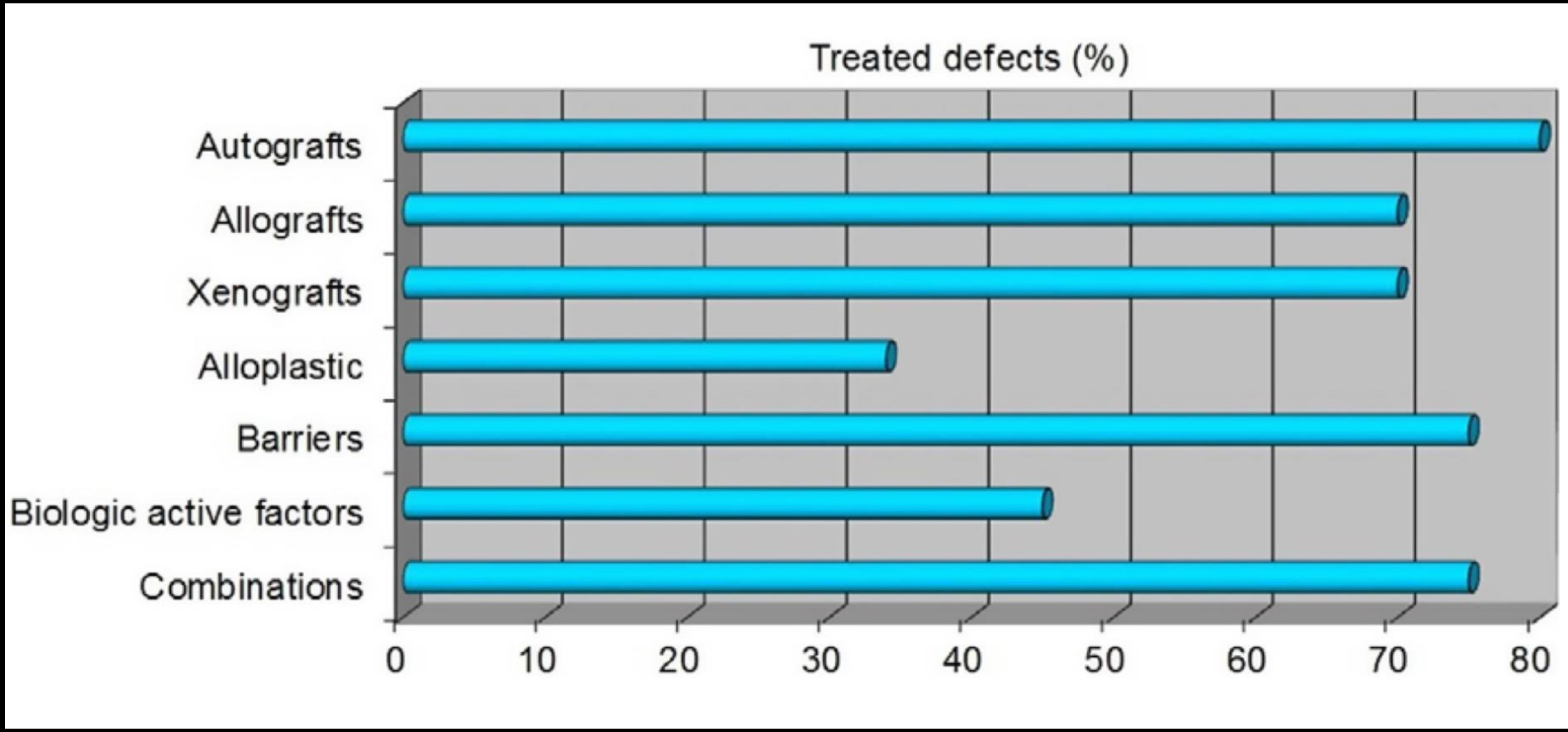
PERIODONTOLOGY 2000

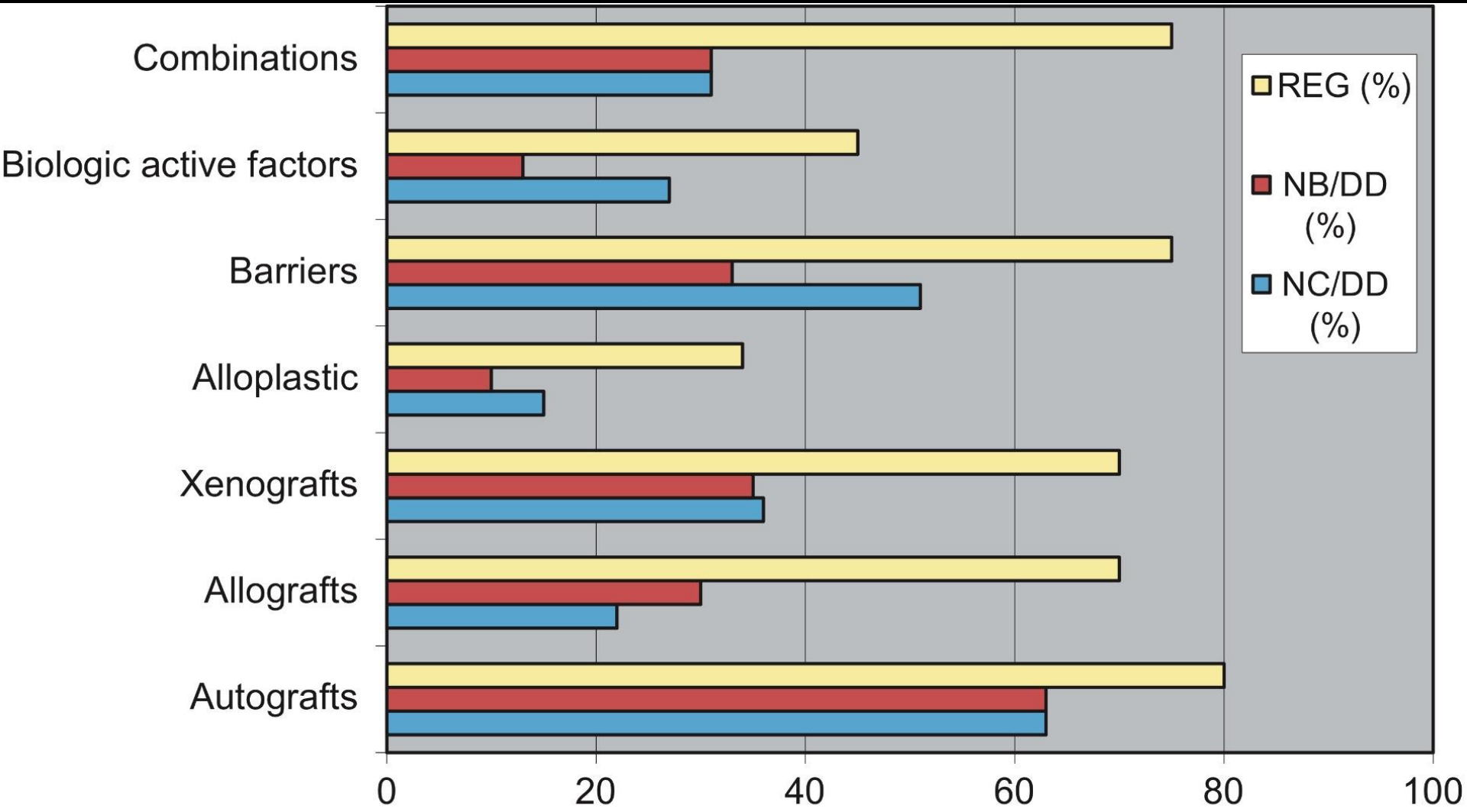
# Biomaterials for promoting periodontal regeneration in human intrabony defects: a systematic review

Anton Sculean*, Dimitris Nikolidakis*, George Nikou, Aleksandar Ivanovic, Iain L. C. Chapple & Andreas Stavropoulos

# Histologic Evidence of Regeneration



# Histologic Evidence of Regeneration



# Important observations from SR

- The amount of periodontal regeneration (i.e. new cementum with inserting fibers functionally oriented and new bone) was rather similar among the various treatments (the average values ranged from 1.3 to 2.3 mm), except for alloplastic materials and biological factors used as monotherapies, which showed limited amounts of periodontal regeneration (the average values were 0.4 and 0.6 mm, respectively despite the large range (3-6.6mm) on defrct depth

# Important observations from SR

- The amount of new cementum formation ( in terms of height) was  larger than or equal to that of new bone
- Long junctional epithelium was not necessarily formed in non guided tissue regeneration cases
- Majority of available bone grafts and substitute materials are merely osteocompatible than osteoconductive

# Guided Tissue Regeneration

- **Basis- Melcher's concept**
- **FUNCTIONS**
- **CELL OCCLUSIVE:** To predictably isolate and protect the defect space.
- **SPACE MAKING:** To create and maintain space in which clot can form and regeneration can occur.
- **EPITHELIAL INHIBITION**: To prevent deep pocketing and interference with regeneration beneath the material.
- **CLOT STABILIZATION**: To enhance healing through incorporation of material with the surrounding tissues.

# GTR-TYPES

**First generation-Non resorbable**

**Second generation-Resorbable**

**Third Generation- Tissue engineering membranes**

# First Generation GTR

Primary objective –Cell occlusivity

Examples-Cellulose Acetate(Millipore)

ePTFE –Pore size 5-20 microns

dPTFE- Pore size 0.3 micron

Titanium reinforced membranes-Space maintenance

Limitations- Need for second surgery

higher membrane exposure rate

# Second generation

**Natural or Synthetic**

Natural- Collagen, Chitosan, silk fibrin

Mechanical property of collagen can be improved by cross linking

Synthetic- Poly glycolic acid(PGA),Poly lactic aci(PLA)

Adv.- Resorbable

Disadv.-Variability and lack of control of degradation of membranes,

Tissue reaction during the absorption of membranes

Journal of Clinical Periodontology

Official Journal of The European Federation of Periodontology

Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2008; 35 (Suppl. 8): 106–116 doi: 10.1111/j.1600-051X.2008.01263.x

Journal of Clinical Periodontology

# Regeneration of periodontal tissues: combinations of barrier membranes and grafting materials – biological foundation and preclinical evidence

## A systematic review

**Anton Sculean[1], Dimitris Nikolidakis[1] and Frank Schwarz[2]**

[1]Department of Periodontology Radboud University Medical Center, Nijmegen, The Netherlands; [2]Department of Oral Surgery, Heinrich Heine University, Düsseldorf, Germany

(a) The combination of barrier membranes and grafting materials may result in histological evidence of periodontal regeneration, predominantly bone repair.

# Guided tissue regeneration for periodontal infra-bony defects (Review)

Needleman I, Worthington HV, Giedrys-Leeper E, Tucker R

## Authors' conclusions

GTR has a greater effect on probing measures of periodontal treatment than open flap debridement, including improved attachment gain, reduced pocket depth, less increase in gingival recession and more gain in hard tissue probing at re-entry surgery. However there is marked variability between studies and the clinical relevance of these changes is unknown. As a result, it is difficult to draw general conclusions about the clinical benefit of GTR. Whilst there is evidence that GTR can demonstrate a significant improvement over

# Third Generation GTR

These are membranes with a **Functional layer**

1. Membranes Releasing Antimicrobials
2. Membranes Releasing Growth factors
3. Membrane with Calcium Phosphate
4. Cell transferred membranes

Other membranes used as GTR

1.PRF

2.Amniotic membrane

# Membranes with Zone dependent bioactivity

1.Electrospinning membranes-By Electrospinning we can make biocompatible and degradable natural synthetic polymers or blends, and resembles the arrangement of the native ECM

2.Multilayer membranes with a functionally graded structure-This consists of a core layer and two functional surface layers one facing bone and other facing epithelium

# Protein/Peptide therapy

**Commercially available products**

Enamel Matrix derivative(EMD)

Recombinant human Platelet derived growth factor-BB(rhPDGF-BB)

Synthetic peptide binding protein P-15

Recombinant BMP-2

**Materials in trial**

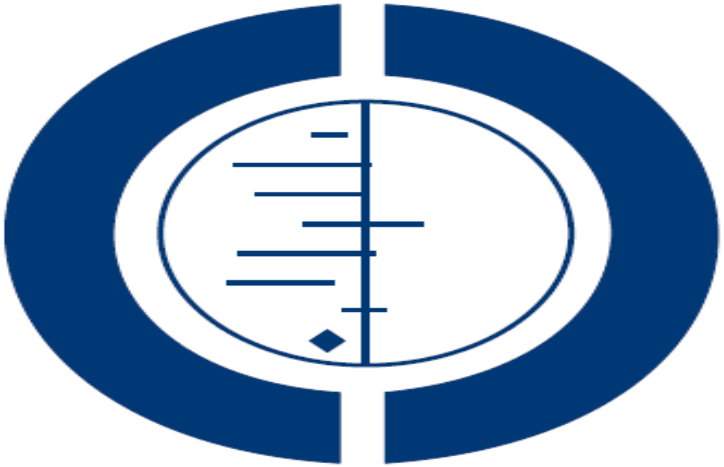
Recombinant human fibroblast growth factor

BMP-6,7,12

PTH(teriperatide),SOST(Sclerostin) antibodies

# Enamel matrix derivative (Emdogain®) for periodontal tissue regeneration in intrabony defects (Review)

Esposito M, Coulthard P, Worthington HV



## Main results

No difference in tooth loss was observed. A meta-analysis including eight trials showed that Emdogain treated sites displayed statistically significant PAL improvements (mean difference 1.3 mm, 95%CI: 0.8 to 1.8) and PPD reduction (1 mm, 95%CI: 0.5 to 1.4) when compared to flap surgery. Comparing Emdogain with GTR (six trials), GTR showed a statistically significant reduction of PPD (0.6 mm) and increase of REC (0.5 mm). No difference in postoperative infections was observed.

J Clin Periodontol 2014; 41: 377–386 doi: 10.1111/jcpe.12218

Journal of Clinical Periodontology

Systematic Review

# Does enamel matrix derivative application provide additional clinical benefits in residual periodontal pockets associated with suprabony defects? A systematic review and meta-analysis of randomized clinical trials

Filippo Graziani[1,2], Stefano Gennai[1,2], Silvia Cei[1], Francesco Ducci[1], Nicola Discepoli[2], Alessandro Carmignani[1] and Maurizio Tonetti[3]

[1]Department of Surgical, Medicine, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [2]University Hospital of Pisa, Sub-Unit of Periodontology and Periodontal Medicine, Pisa, Italy; [3]European Research Group on Periodontology, Genova, Italy

ducted. The primary outcome measures were tooth survival (TS) and clinical attachment level (CAL) gain. Pocket probing depth (PPD) reduction and recession (REC) increase were secondary outcome measures. Information concerning clinical and radiological bone gain was also collected.

**Results:** The search identified 1170 studies, three articles reporting on (99 subjects/358 teeth) met the inclusion criteria and were included. No tooth was lost during follow-up (8–12 months). The adjunctive mean benefit of EMD was: 1.2 mm for CAL gain [confidence interval (CI): (0.9, 1.4), $p < 0.00001$, $I^2 = 66\%$], 1.2 mm for the PPD reduction (CI: [0.8, 1.5], $p < 0.0001$, $I^2 = 0\%$), −0.5 mm for the REC increase (CI: [−0.8, −0.2], $p = 0.003$, $I^2 = 0\%$). Potential risk of bias was identified.

**Conclusions:** No differences were noted in TS but EMD application resulted in clinical and radiographic additional benefits compared to OFD alone. Nevertheless, the paucity of data, the risk of methodological and potential publication bias suggests caution in interpreting these results while supporting multicenter studies for this specific application.

# Platelet concentrates in Regeneration

Rationale

Types

Advantages & disadvantages

Current Evidences

Volume 82 • Number 8

# Is Platelet Concentrate Advantageous for the Surgical Treatment of Periodontal Diseases? A Systematic Review and Meta-Analysis

Massimo Del Fabbro,* Monica Bortolin,* Silvio Taschieri,* and Roberto Weinstein*

**Conclusions:** PRP may exert a positive adjunctive effect when used in combination with graft materials, but not with GTR, for the treatment of intrabony defects. No significant benefit of platelet concentrates was found for the treatment of gingival recession. *J Periodontol 2011;82:1100-1111.*

Cochrane Library

Cochrane Database of Systematic Reviews

# Autologous platelet concentrates for treating periodontal infrabony defects (Review)

Del Fabbro M, Karanxha L, Panda S, Bucchi C, Nadathur Doraiswamy J, Sankari M, Ramamoorthi S, Varghese S, Taschieri S

-Platelet-rich fibrin (PRF) has a significant additive effect when used along with OFD.

-Platelet-rich plasma (PRP) has a significant additive effect when used along with bone grafts.

-Conversely, PRP was found to be ineffective when used in combination with GTR procedures.

-Platelet-rich plasma may be used advantageously as an adjunct to grafting materials, but not in combination with GTR, for treatment of intrabony defects.

International Journal of
*Molecular Sciences*

MDPI

*Review*

# Autologous Platelet Concentrates in Treatment of Furcation Defects—A Systematic Review and Meta-Analysis

Sourav Panda [1,2], Lorena Karanxha [1], Funda Goker [1], Anurag Satpathy [2], Silvio Taschieri [1,3], Luca Francetti [1,3], Abhaya Chandra Das [2], Manoj Kumar [2], Sital Panda [4] and Massimo Del Fabbro [1,3,*]

one study was found. Conclusion: For the treatment of furcation defects APCs may be beneficial as an adjunct to open flap debridement alone and bone grafting, while limited evidence of an effect of APCs when used in combination with GTR was found.

# CELL BASED THERAPEUTICS

# Cell- Based therapy

**Two primary  mechanisms by which it works**

1, Cells as carriers to deliver regenerative signals including cytokines/growth factors/chemokines

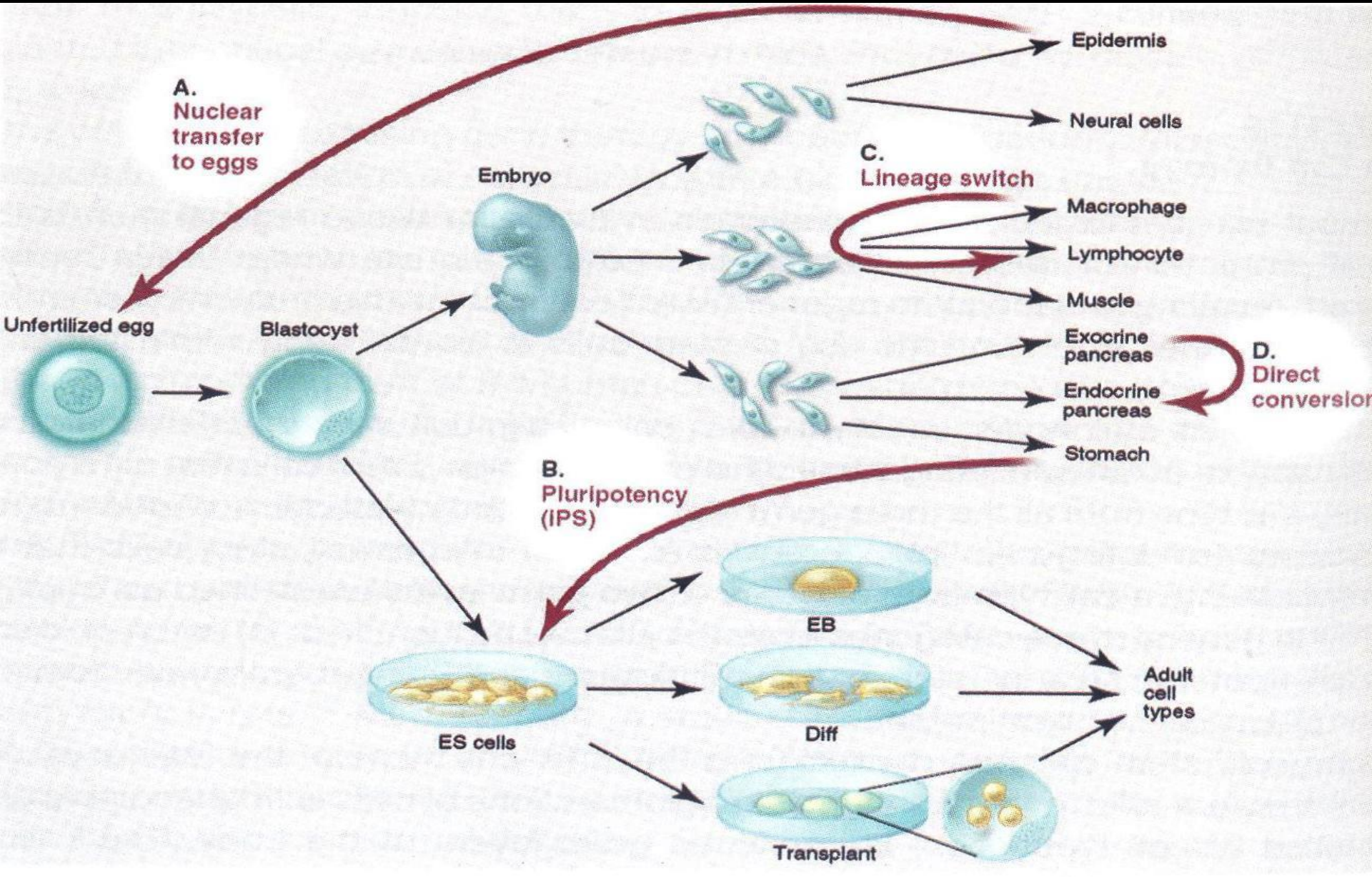
2,Provision of stem cells that able to differentiate to multiple cell typesto promote regeneration

# Stem Cell Based Therapy

Stem Cells can be divided into

1. Embryonic Stem cell(Pluripotent)
   (From inner Cell mass of blastocyst)
2. Adult Stem Cells (multi potent)
   (Bone marrow, epithelium, adipose tissue, liver, Pdl, pulp)
3. Reprogrammed Stem Cells(Either Pluripotent or multipotent)
   -Whose genetic program has been substituted or modified to induce switch from one cell phenotype to another phenotype

# Reprogrammed Stem Cells



Limitation - Ethical issues (For embryonic stem cells)

- Scarce availability of cells & technical difficulties .(Adult stem cell)

Challenges - identifying unique PDLSC markers which allows selection of pure PDLSC population

- Appropriate delivery system for engineering an efficient cell based therapeutic tool for Periodontal regeneration.

# Cells Able to Differentiate Into Periodontal Tissues

| Cell Type | Origin | Advantages | Disadvantages |
|---|---|---|---|
| BMSC (autogenous) | Bone marrow | Relatively easy accessibility, multipotency, no immune rejection, no carcinogenesis | Invasive technique to harvest cells, slow proliferation rate, limited cell source |
| PDL progenitor cell | PDL | Multipotency, no immune rejection, no carcinogenesis | Relatively low accessibility, slow proliferation rate, limited cell resource, depends on cell banking and cannot "harvest when needed" |
| BMSC (allogenous) | Allogenous bone graft | Relatively easy accessibility, multipotency, no carcinogenesis | Small cell number, immune response, risk of contamination of pathogens from donors, amount and quality of stem cell may vary between donors |
| Adipose-derived stem cell | Adipose tissue | Easy accessibility, multipotency, no immune rejection, no carcinogenesis | Slow proliferation rate, limited cell source, less potential to osteogenic differentiation |
| iPS cell–derived MSC | Differentiate from iPS cell | Multipotency, no immune rejection, abundant cell source | Possible carcinogenesis, difficulty in cell purification |
| ES cell | Inner cell mass of the blastocyst | Pluripotency, potential resource from abandoned in vitro fertilization embryos, immortal and fast proliferation rate | Immune rejection, potential carcinogenesis, differentiation into unwanted cell types after implantation, relatively rare cell source, migration to distant organs |
| iPS cell | Induced from somatic cells by ectopic gene expression or small molecules | induced from any somatic cells, easy accessibility, pluripotency, abundant cell source, immortal, fast proliferation rate, lack of immune rejection | Differentiation into unwanted cell types after implantation, migration to distant organs, potential carcinogenesis |

# TISSUE ENGINEERING

# Periodontal Tissue Engineering

Tissue engineering involves using techniques for fabrication of tissue outside the body for implantation into the body to regenerate the lost biological function of that respective tissue

Tissue Engineering combines conductive therapeutics, Inductive therapeutics, Cell based therapeutics and genetics to stimulate regeneration of tissues or organs by either implanting biomaterials in vivo regeneration or by constructing substitutes in vitro

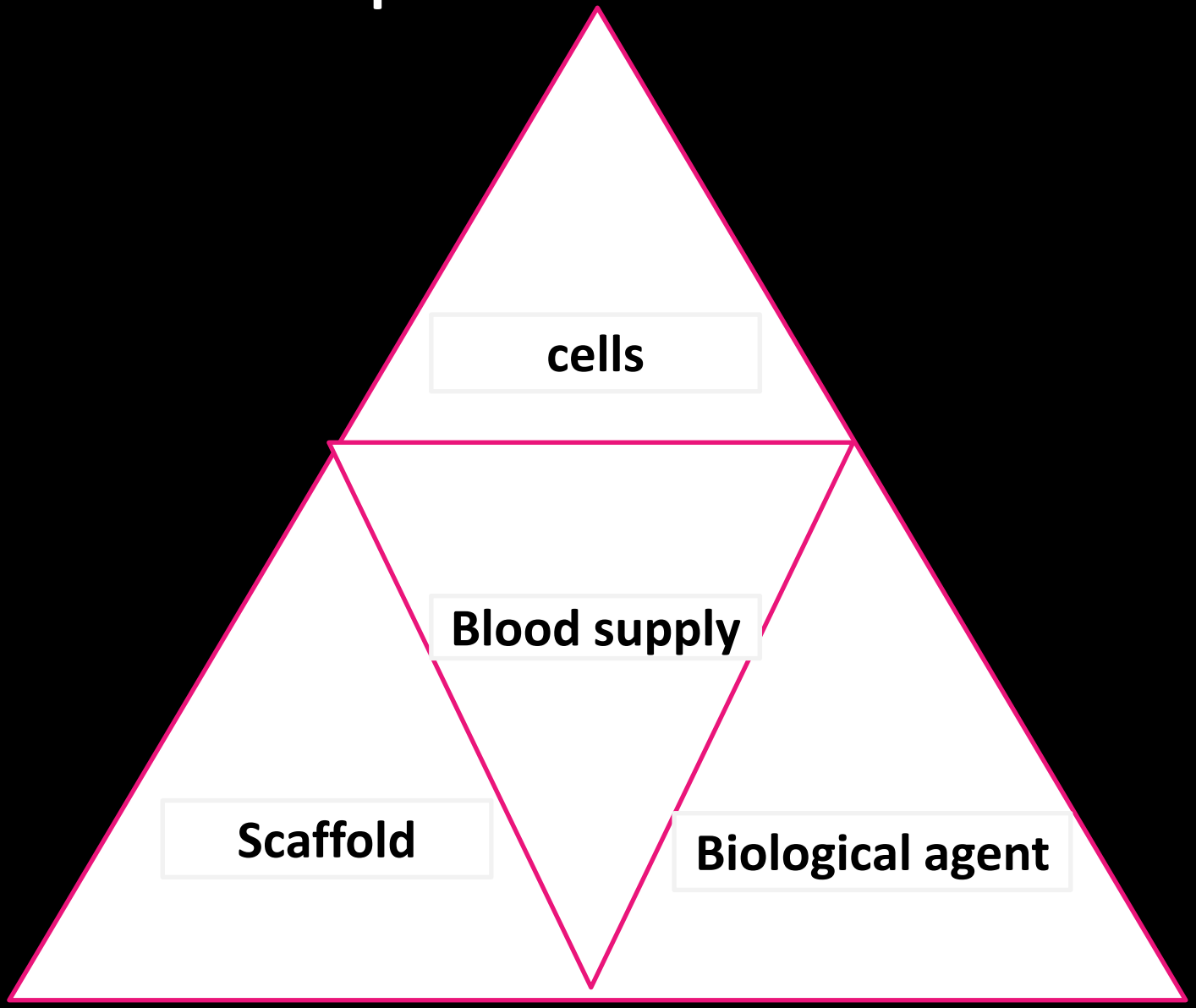
# Important Principles of TE

1. Engineered tissue have to have sufficient biomechanical strength, architectural properties and space maintaining abilities

2. The engineered tissue has to maintain space for in growth of alv. Bone, but it also has to be exclusionary with respect to epithelial tissue

3. It has to have appropriate biologic function to allow cellular recruitment and proliferation, vascularisation and delivery of the appropriate biologic factors

# The Requirements for TE



# TE-Scaffolds

**Various Requirements of Scaffold**

Support the cell colonization, migration, growth & differentiation

Provide sufficient initial mechanical strength and stiffness

Should have a porous interconnected network

Biocompatible

Controlled biodegradability

# Scaffolds- For soft tissue augmentation

## Allogenic

- ADM
- HAM

## Xenogenic

- Collagen matrx (bilayered or volume stable)
- XenogenicADM
- ECM from sub mucosa of intestine

## Alloplastic

- Natural Polymers( from Proteins,Poly sacharides, Polynucleiotides)
- Synthetic ( PLA,PCL,PLGA)

# TE-Cells

**The types of cells used**

Autologous- difficulty in harvesting, Cell expansion is time consuming

Allogenic- Best suited owing to the powerful secretion of growth factors

Xenogenic- least safe

# TE-Cell sheets

Cell sheet technology is based on the formation of an adherent monolayer of cells that allows cells to preserve cell to cell junctions, cell antigens, and proteins from the extra cellular matrix

Major steps

Identification and isolation of cells required for periodontal regeneration

Growing of cells on a temperature sensitive sheets (Poly –N-isopropylacrimide(PIPA-Am)) in culture plate

Detachment of cells from temperature sensitive sheet by decreasing the temperature

# CAD/CAM in TE

Application

- To prepare anatomically precise  scaffold with flexible properties
- Bio fabrication of scaffolds with multiphase compartments (bone compartment, PDL compartment etc)
- 3D bio printing to reconstruct  the spatio temporal orientation PDL fibers

# Nanotechnology in TE

Biomaterials with nanoscale features with the ability to form ideal interaction with tissues is having very good potential in tissue engineering

Nanotechnology provides a new frontier to create self assembling systems that are wholly biocompatible for TE

# Nano composite Electrospun fibers in Periodontal regeneration

- Nano composite blended with polymeric matrix- both natural and synthetic polymers
- Nano composite with inorganic components (Ca P, CA-Si, Ceramics)
- Nano composite with Carbon based components
- Nano composite with metal components
- Nano compsite  blended with drugs, growth factors and proteins

# Challenges in TE

**Controlled and Efficient delivery of growth factors**

**Short half life of growth factors**

**Limitations of Scaffold- Biodegradabilitry, Inflammatory reaction, Immune rejection**

# GENE & RNA BASED THERAPEUTICS

# Gene based therapy

**Rationale- To overcome the limited duration of action and lack of stability of growth factors and limited solubility of delivery vehicle gene therapy is developed**

**It gives directed, sustained and regulated protein expression**

**Advanages**

Greater sustainability

Relatively low cost

Easier than protein manufacturing

**Techniques to carry genes to cells**

1, Viral vectors- Longer gene expression

2,Non viral vectors- Low transduction efficiency

# **Viral vectors-**Transduction

The Vectors used are adenovirus adeno associated virus, retro virus, lenti virus .

Adv: Higher transduction efficiency, Prolonged transgene expression

Disadv - Virus vectors can elicit immune reaction

- transgene expression is quiet brief (adeno virus as it does not integrate)
- Difficult to construct (adeno associated virus as it need helper virus)
- serious adverse effect due to mutagenesis (Retro Virus)
- Continuous expression of the transgene (lenti Virus)

(Not suitable for temporary regenerative process)

# **Non viral vectors**- Transfection

Naked oligomeric DNA or plasmid DNA is used

**Gene delivery can be done by**

**Physical methods-** Electroporation ,sonoporation, magnetofection, electric field induced molecular vibration, optical transfection, particle gins, micro injection , lipofection

**Chemical methods-** Carriers such as dextranas, proteins, artificial lipids, calcium phosphate and other plymers as vectors

# **Non viral vectors**- Transfection

Advantages

Low cost, Proven safety, less mutagenesis high DNA carrying capacity and possibility of producing artificial vectors according to the specific need

Limitations

Low transfection efficiency, transient expression, and non selective cell targeting

# Exosomes as vectors

Exosomes are extra cellular vesicles of endocytic origin secreted by cells that carry macromolecules including nucleic acids mainly RNA

Advantages; They are rapidly taken up by target cells and the exosomal membrane protect the RNA from degradation

Mechanisms

1. Exosomes can selectively bind the cell surface receptors and initiate intra cellular signaling
2. Exosmes can directly transfer the intra exosomal content by fusion with cell membrane

# Route of gene delivery; Ex vivo vs In vivo

**In Vivo**

- One step process
- Low transduction efficiency
- Possibility of immune/ infammatory response
- Difficulty in targetting the cell population of interest

**Ex Vivo**

- Complex process
- More safer
- More labor intensive
- Significant cost

# Gene Activated Matrix(GAM)

A direct gene transfer strategy blending tissue engineering and local gene delivery systems

GAM serve as a bioreactor with therapeutic gene expression and provides a structural template to fill the lesion defect for cell adhesion, proliferation, and synthesis of extra cellular matrix

# RNA based therapeutics

- Scope in regeneration – Delivery of mRNA instead of gene can be altrernate approach for protein translation
- RNA based gene delivery is having a better safety profile as it needs to enter only cytoplasm and no nuclear integration is required
- It is suitable where transient expression of protein is required
- RNA Silencing-Through the silencing of the genes that negatively control cell Proliferation and cell differentiation or genes that induce inflammation or apoptosis it can favor tissue regeneration

# Role of Epigenetics in periodontal regeneration

- DNA methylation, histone modifications, and non coding RNAs might have a role in periodontal destruction

- Epi-drugs (DNA methyl transferase inhibitors and histone deacetylase inhibitors) can be used to counteract bone resorption

# Endogenous Regenerative medicine

**Basis- Endogenous cell homing and mobilization of resident stem cells.**

Periodontal regeneration is facilitated at the defect by using biomolecules which coax the recruitement of endogenous stem cells from their niche.

**Agents used**

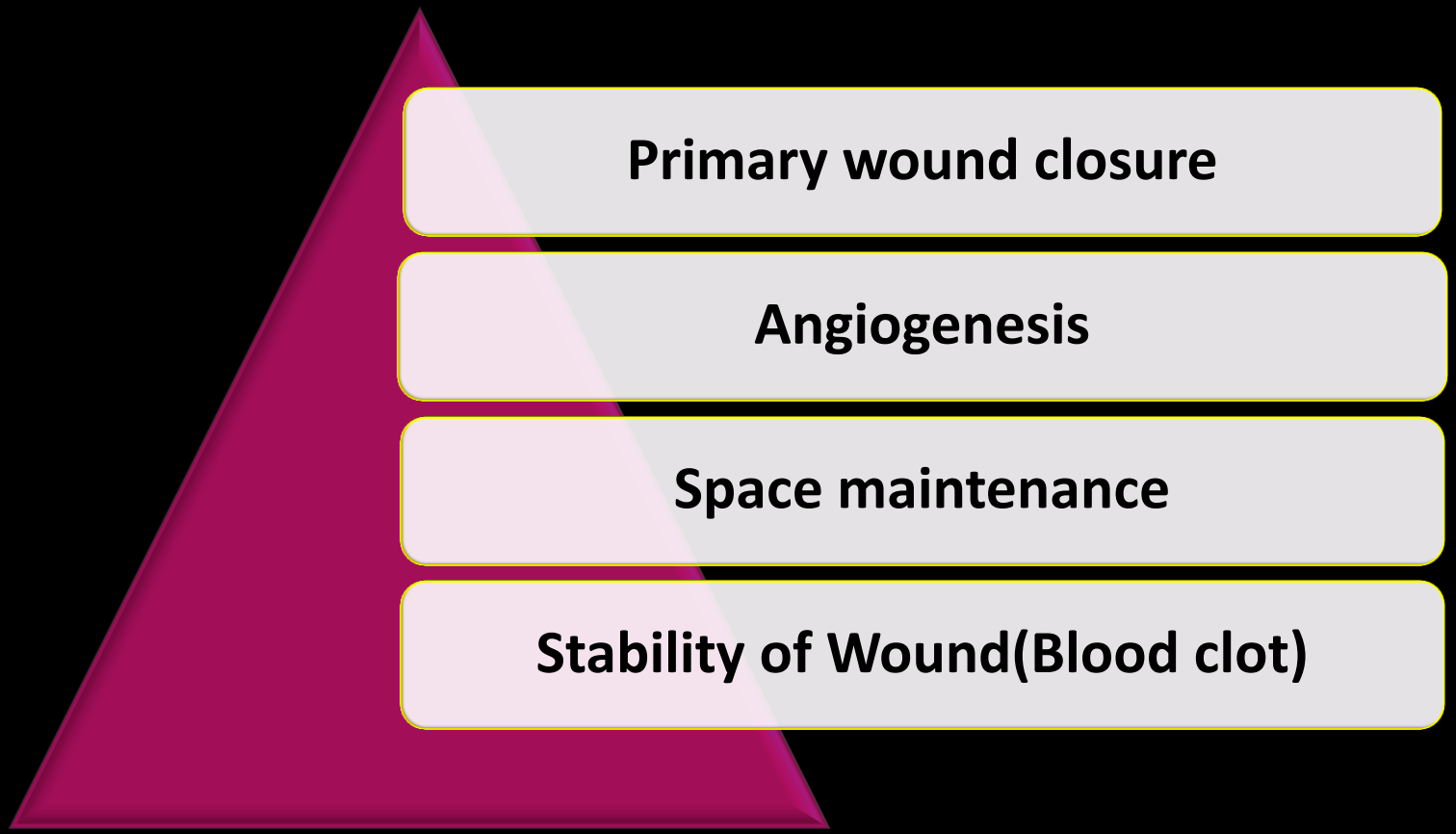
Cell mobilizing factors - Substance P

Cell homing facor- Stromal derived factor 1 alpha, stem cell factor

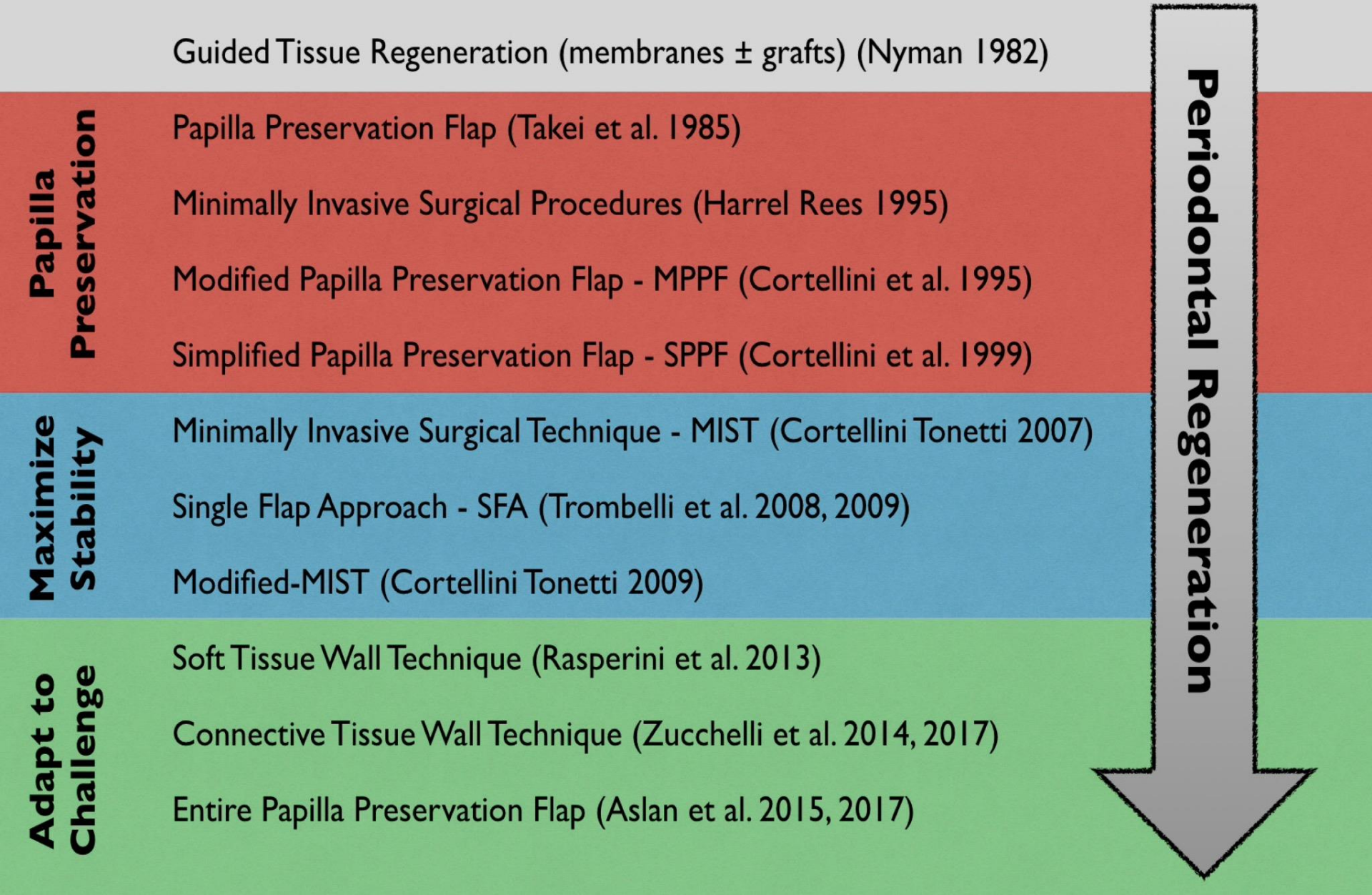
Growth factors- FGF, PDGF etc

# IMPORTANCE OF SURGICAL TECHNIQUES AND ROOT BIOMODIFICATION IN REGENERATION

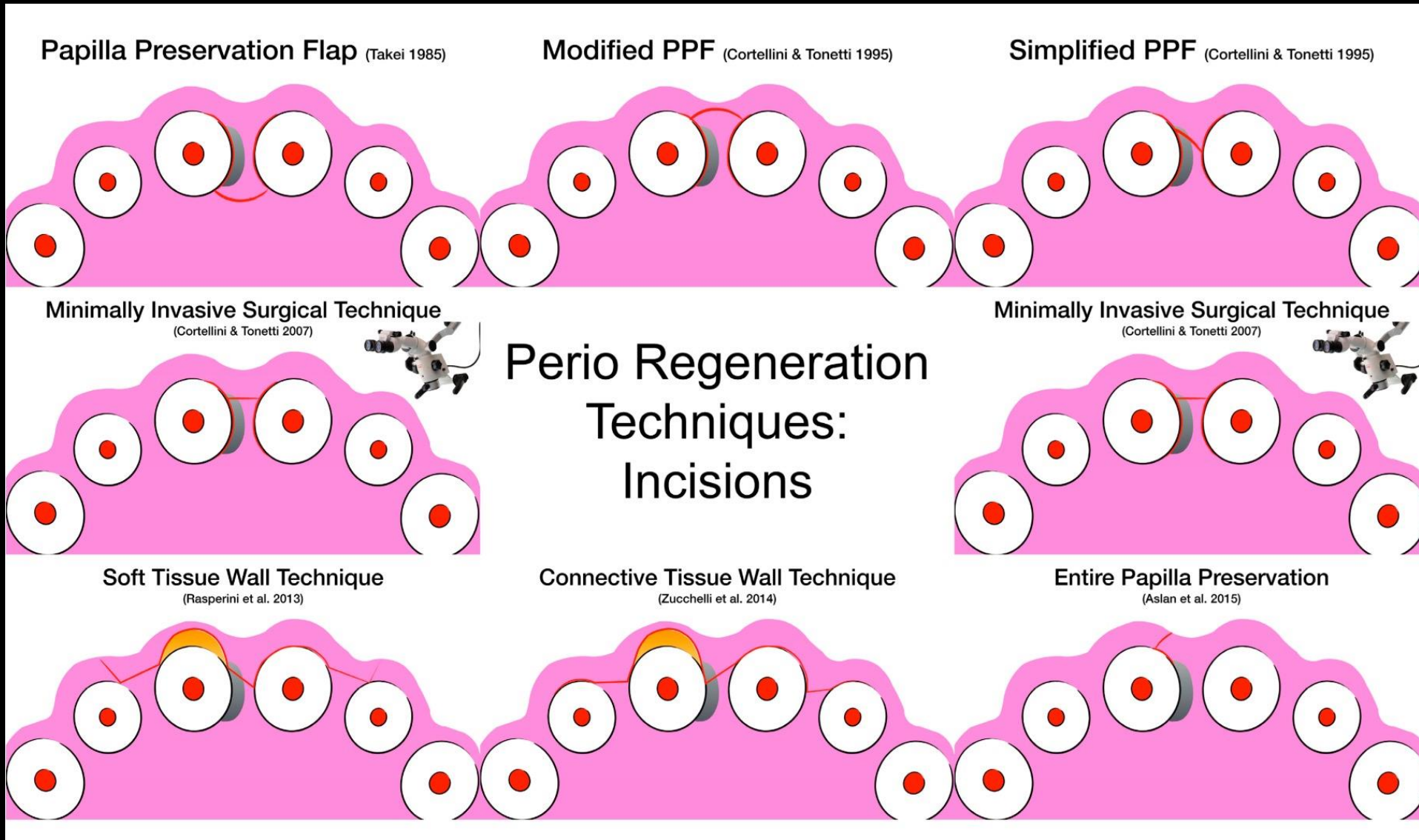
# “PASS” principle for regeneration



# Surgical Techniques for regeneration



# Schematic Representation



# Root Biomodification in regeneration

Rationale

Agents used

Advantages & Disadvantages

Current status

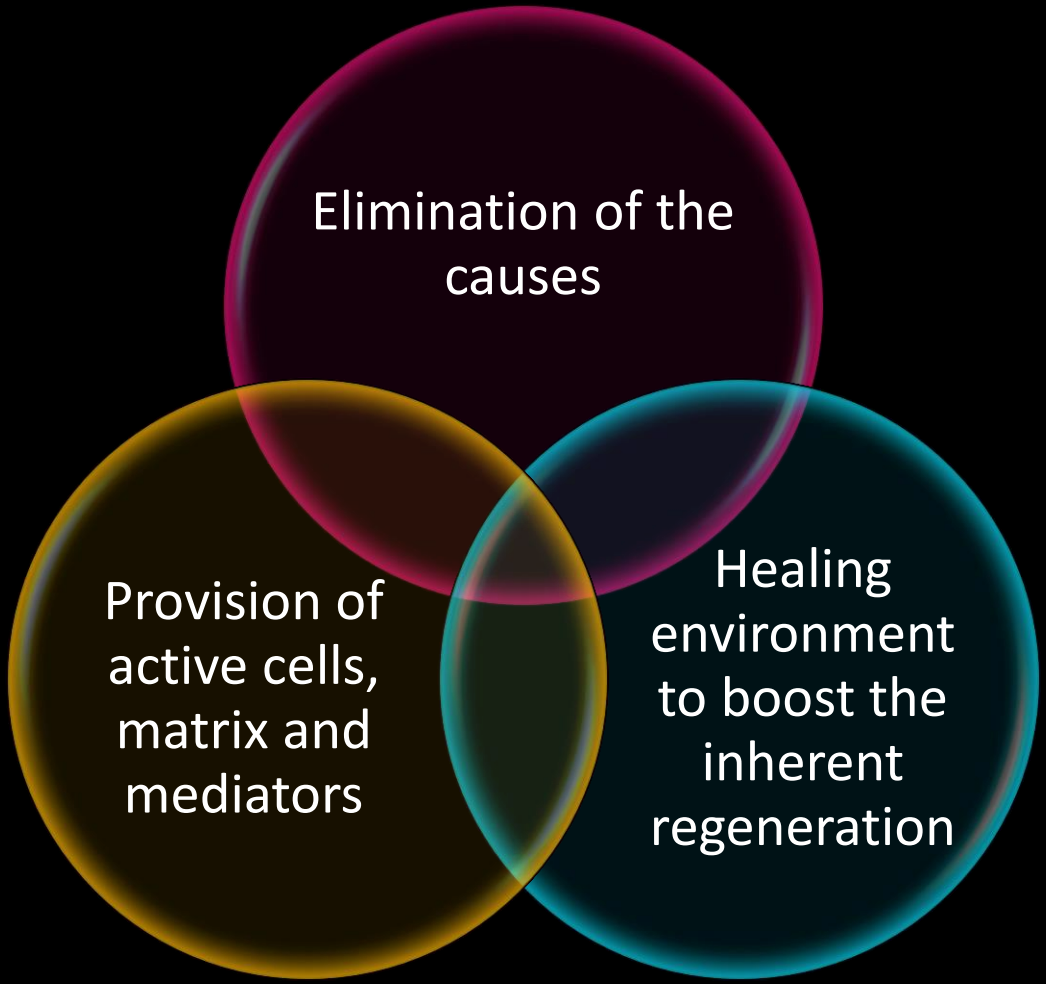
# Non surgical methods in Regeneration

Lasers-Evidence is still lacking
Host modulating Agents- SDD is effective, Statins are promising
Probiotics-Still inconclusive but promising
Ozone therapy-No evidence
Local drug delivery systems- Effective in gingival parameters and clinical signs

# Risk factor modification in Regeneration

Smoking- smoking cessation is effective
Diabetes- diabetes control is effective
TFO- Literature evidence is lacking
Genetics- Literature evidence is less

# To conclude


Elimination of the causes
Provision of active cells, matrix and mediators
Healing environment to boost the inherent regeneration

*Thank you*