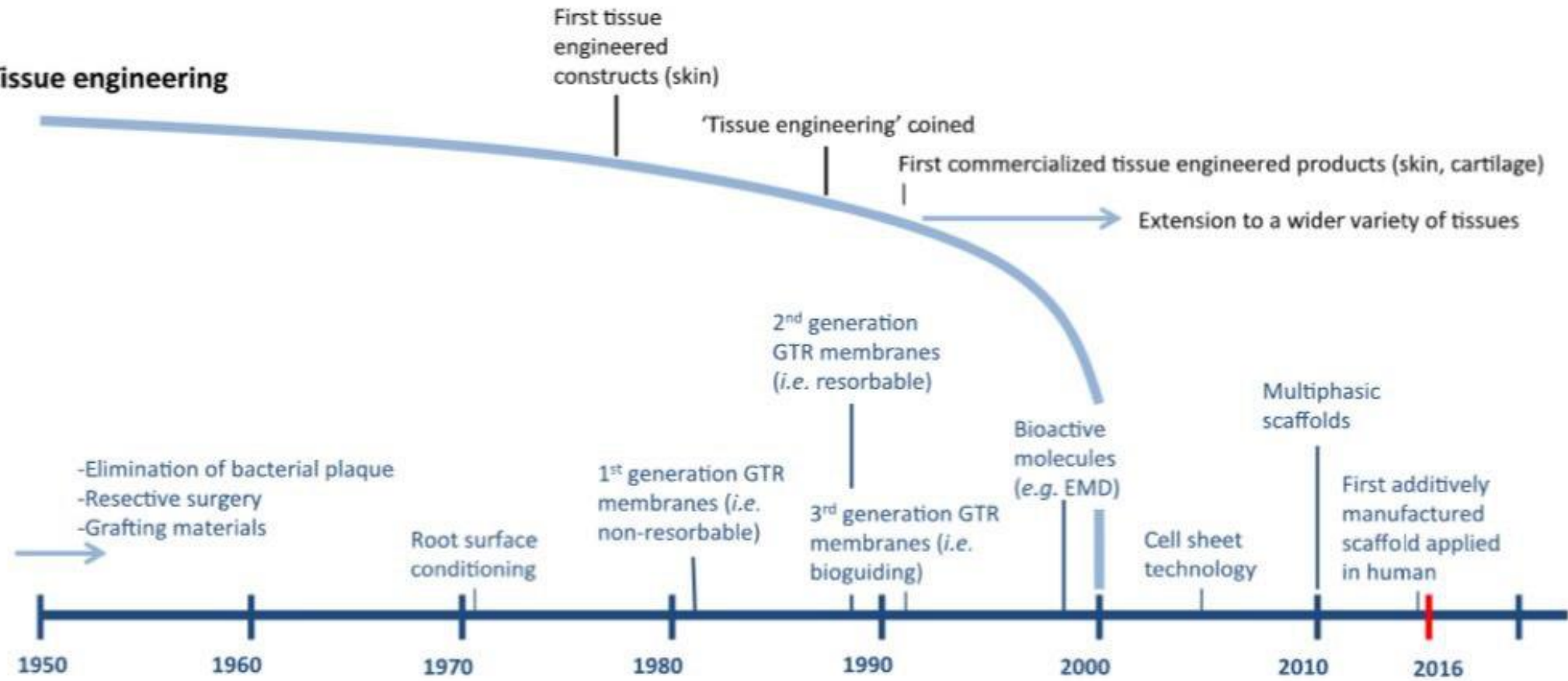# Introduction to 3D-printed Scaffolds in Periodontal Defects

3D-printed scaffolds are revolutionizing the treatment of periodontal defects, offering a tailored and precise approach to tissue regeneration.

Tissue engineering

First tissue engineered constructs (skin)

'Tissue engineering' coined

First commercialized tissue engineered products (skin, cartilage)

Extension to a wider variety of tissues

2nd generation GTR membranes (*i.e.* resorbable)

Multiphasic scaffolds

-Elimination of bacterial plaque
-Resective surgery
-Grafting materials

1st generation GTR membranes (*i.e.* non-resorbable)

Bioactive molecules (*e.g.* EMD)

First additively manufactured scaffold applied in human

Root surface conditioning

3rd generation GTR membranes (*i.e.* bioguiding)

Cell sheet technology

1950   1960   1970   1980   1990   2000   2010   2016

Periodontal therapy

-Combinations of techniques
-Vascularized constructs

Robotic dispensing of cell laden hydrogels

Biolaserprinting of cells
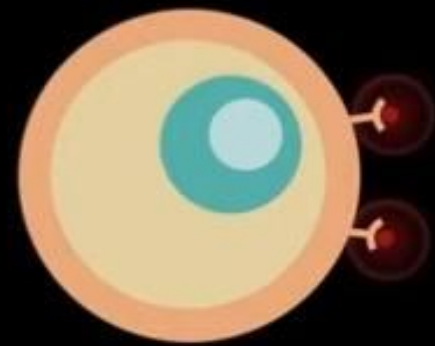
Additive manufacturing

Stereolithography

-'Organ printing' coined
-Inkjet printing of cells

Laser printing

Continuous inkjet printing

Drop on demand inkjet printing

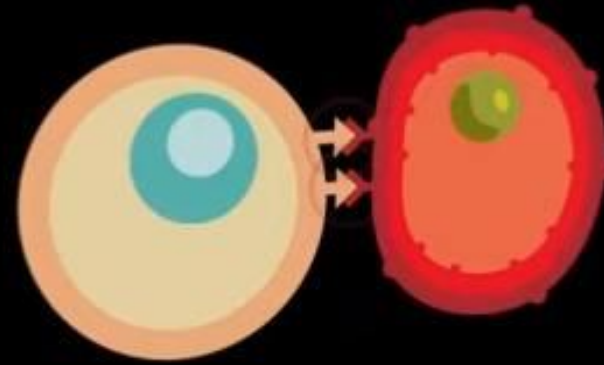-CAD/CAM introduced in the clinic
-Fused deposition modeling

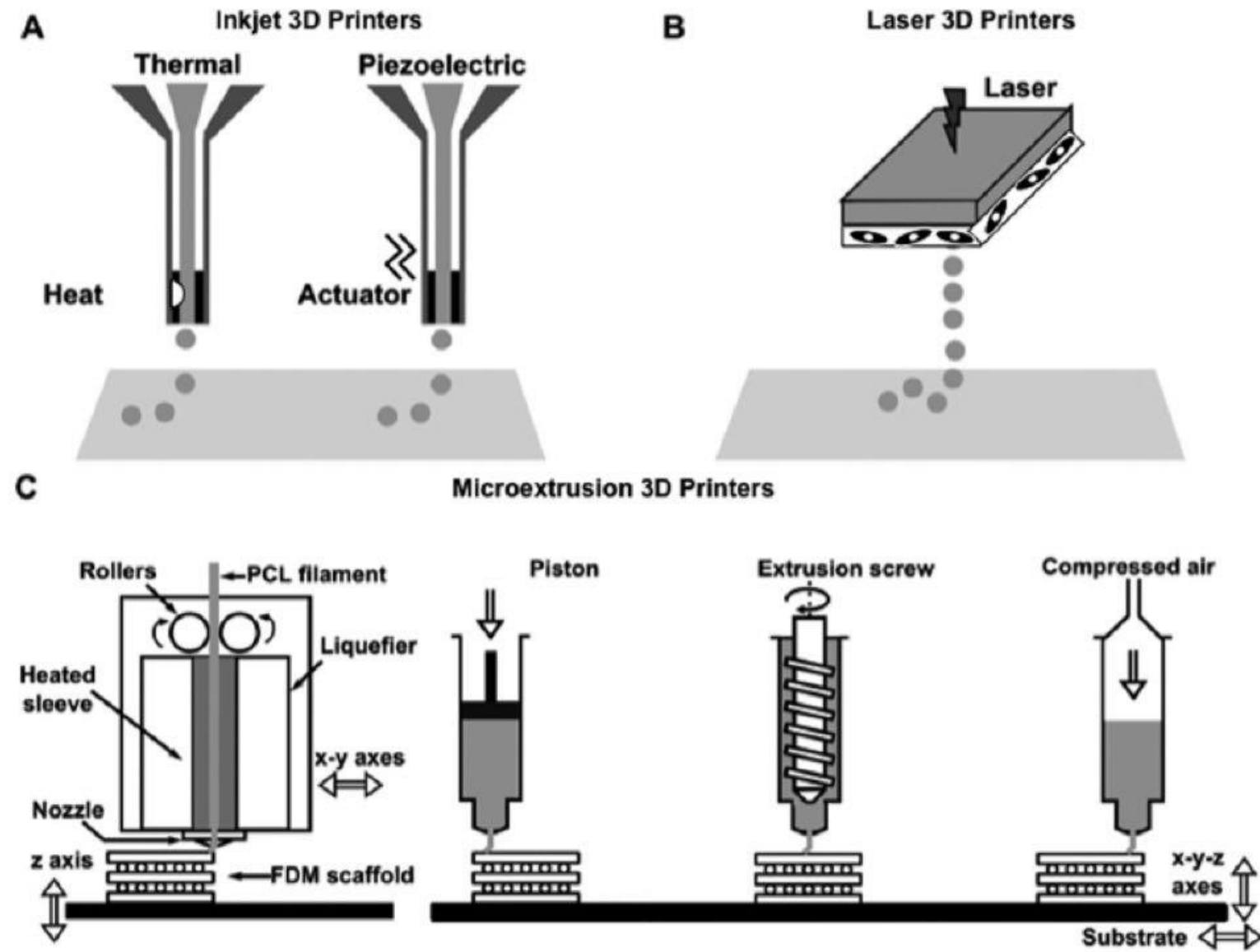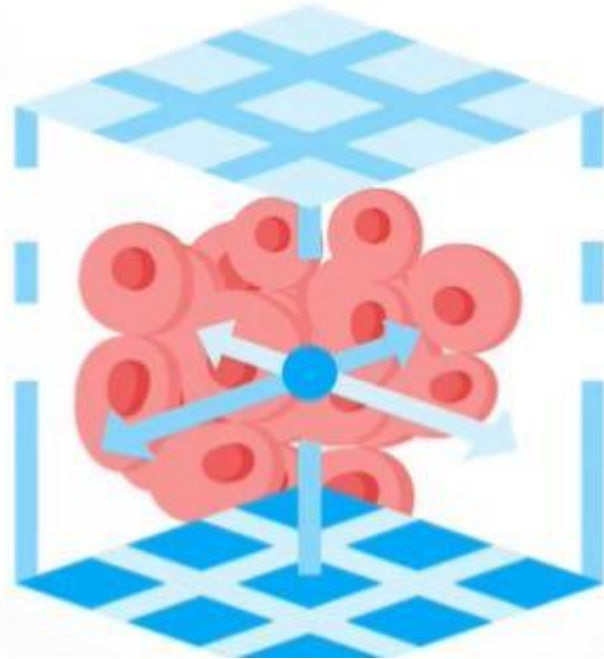Fused deposition modeled tissue engineering scaffolds

Three-dimensional printing technologies. (**A**) Inkjet printing. (**B**) Laser printing. (**C**) Extrusion printing.
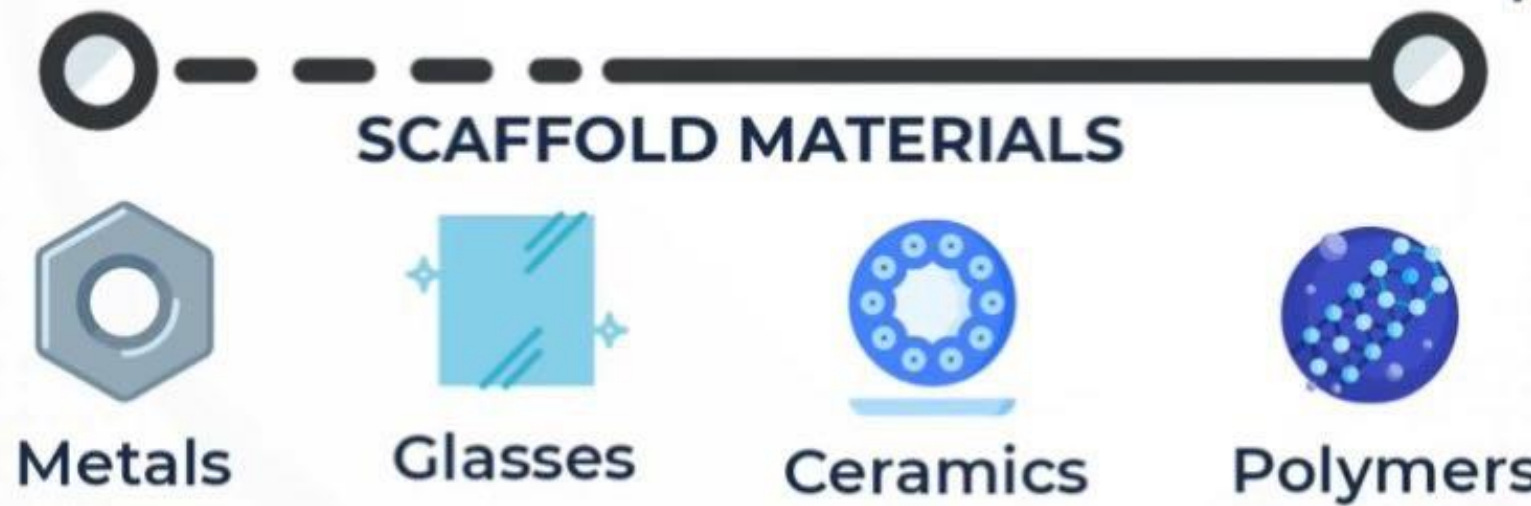
SCAFFOLD-BASED 3D CELL CULTURES

- Facilitate oxygen, nutrient, and waste transportation due to their porosity.

- Maturing cells interact with one another and eventually form structures that are similar to origin tissue.

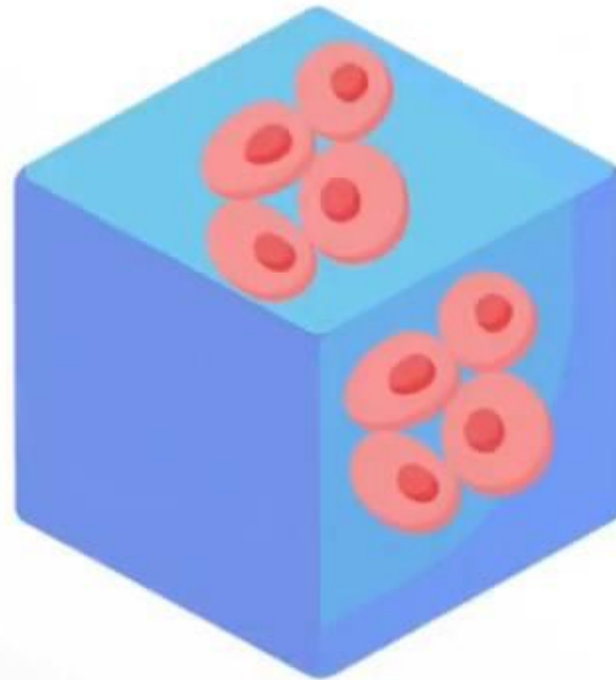- Aggregates are presented as heterogeneous-sized spheres

TYPES OF SCAFFOLDS

Membranes

Matrices

Hydrogels

SCAFFOLD MATERIALS

Metals

Glasses

Ceramics

Polymers

CF
www.clevaforce.com

HYDROGEL SCAFFOLDS

- Polymer networks extensively swollen with water
- Coated or embedded cells

HYDROGEL SCAFFOLDS

- Mimic ECM

- Contain water and natural biomolecules such as alginate, gelatin, hyaluronic acid, agarose, laminin, collagen, or fibrin

-Difficult gelling mechanism

Gel

POLYMERIC HARD MATERIAL-BASED SCAFFOLDS

- Cells are cultivated in presence of fibers or sponge-like structures

- Materials used for can be Polystyrene or Polycaprolactone
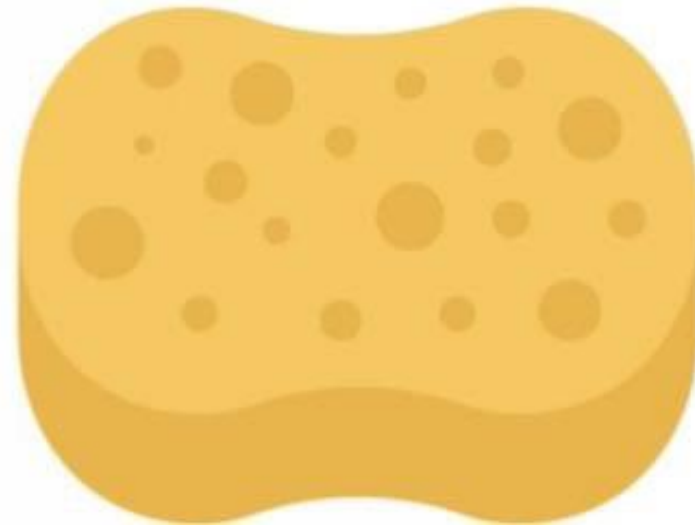
COMPOSITE SCAFFOLDS

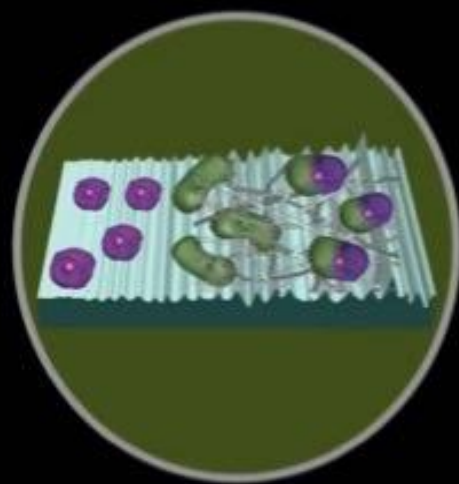- Made of two or more distinctly different materials

Ceramics + Polymers

Mechanical properties

Porosity

Hydrophilicity

Surface topography

Scaffold Properties

Biomaterial source
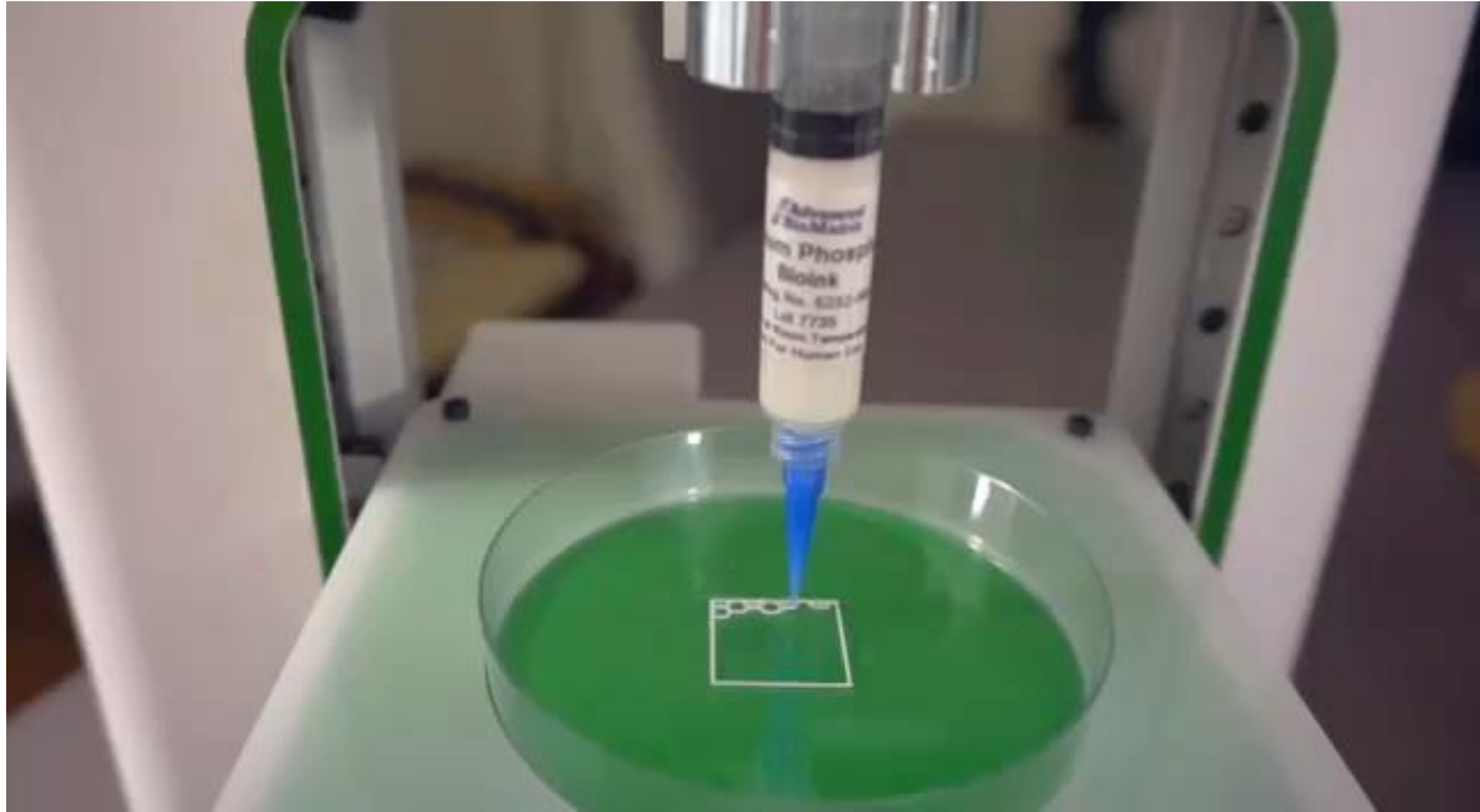
Current Evidence and Limitations

Advancements

New studies provide insights into the effectiveness of 3D-printed scaffolds in periodontal defect treatment.

Challenges

Limited long-term data poses challenges in fully assessing the outcomes and potential risks.

Animal Model Studies on Periodontal Defects

1 **Efficacy**

Animal model studies reveal promising outcomes in tissue regeneration and scaffold integration.

2 **Biocompatibility**

The biocompatibility of 3D-printed scaffolds is demonstrated through animal model research.

Table 1: Characteristics of the included studies

Study	3D scaffold manufacturing method/material/ characterization	Animal model/ number of animals/number of defects	Defect type/size/ location	Presence of biomolecules and/ or cells	Interventions	Length of follow-up (weeks)	Outcomes
Park *et al.*, 2012[20]	CAD-based wax molds printing PCL Ligament architecture: 0.225 mm diameter, 0.250 mm ligament interface and 0.175 mm interconnective space to the bone region Bone region: 0.500 mm diameter gel-loading inlet and 0.60-0.50 mm² window pores to contact residual bone tissue	48 athymic nude rats (48 defects)	Periodontal fenestration defects were surgically created on the buccal side of the mandible, exposing the distal root surface of the first molar (3 mm²× 2 mm²)	In random-porous scaffolds: 2.4×10⁵ hPDL cells/ scaffold or 2.4×10⁵ Ad-BMP-7-hPDL cells/scaffold In fiber-guiding scaffolds: 0.4×10⁵ hPDL in the PDL interface and 0.6×10⁵ hPDL in the bone region; or 0.4×10⁵ hPDLs and 0.6×10⁵ Ad-BMP-7-hPDLs both in the PDL interface and in the bone region	Group 1: Random-porous scaffolds + hPDL (*n*=6/time point) Group 2: Fiber-guiding scaffolds + hPDL (*n*=6/time point) Group 3: Random-porous scaffolds + Ad-BMP-7-hPDL (*n*=6/time point) Group 4: Fiber-guiding scaffolds + hPDL (ligament interface) + Ad-BMP-7-hPDL (bone region) (*n*=6/time point)	3 and 6	Mineralized tissue formation Defects treated with fiber-guiding scaffolds (Groups 2 and 4) had greater amounts of total mineralized tissue than defects treated with random-porous scaffolds (Groups 1 and 3) Only defects treated with fiber-guiding scaffolds had cementum-like tissue deposited over the dentin Functional PDL formation Only fiber-guiding scaffolds guided PDL formation with an orientation oblique to the mineralized tissue
Park *et al.*, 2014[21]	CAD-based wax molds printing PCL Ligament architecture: 0.225 mm diameter, 0.250 mm ligament interface, and 0.175 mm interconnective space to the bone region Bone region: 0.500 mm diameter gel-loading inlet and 0.60-0.50 mm² window pores to contact residual bone tissue	48 athymic nude rats (48 defects)	Periodontal fenestration defects were surgically created on the buccal side of the mandible, exposing the distal root surface of the first molar (3 mm²×2 mm²)	2.4×10⁵ hPDL cells/ scaffold	Control: Amorphous PCL scaffolds without hPDL (*n*=12/ time point) Test: Fiber-guiding scaffolds seeded with hPDL (*n*=12/time point)	3 and 6	Micro-CT Defects treated with fiber-guiding scaffolds containing hPDL formed more mineralized tissues at 3-and 6-week Histology In the amorphous scaffold group, newly formed fibrous tissue had a parallel orientation and failed to attach to the root surface. In the fiber-guiding scaffold group, the construct guided PDL fiber alignment. Newly formed PDL fibers connected obliquely/perpendicularly to the root surface
Pilipchuk *et al.*, 2018[22]	CAD based PDMS molds printing PCL (bone region)/ PLGA + PCL (PDL region)	Athymic male rats (83 defects) number of animals not reported	Periodontal fenestration defects were surgically created unilaterally on the buccal side of the mandible, exposing the distal root surface of the first molar (wide×height=3 mm×2 mm)	AdPDGF-BB on the PDL compartment and AdBMP-7 on the bone compartment	Negative control: Amorphous PDL area and bone area (*n*=10/3 weeks; *n*=6/6 weeks; *n*=5/9 weeks) Pattern + empty: Patterned PDL area and bone area (*n*=6/3 weeks; *n*=6/6 weeks)	3, 6, and 9	Mineralized tissue formation At 3 weeks, greater bone volume was observed for all groups with gene delivery relative to the control group, without differences between the gene delivery groups. The percentage of bone defect fill was greater in pattern + single and amorphous + dual groups than in control group

Study	3D scaffold manufacturing method/material/ characterization	Animal model/ number of animals/number of defects	Defect type/size/ location	Presence of biomolecules and/ or cells	Interventions	Length of follow-up (weeks)	Outcomes
	PDL region: Micropatterned pillars with height of 100 μm and interpillar distance of 150 μm (pillar lengthwide=150 μm × 150 μm and grooves wide × deep=15 μm × 30 μm), connected to a 150 um base Bone region: A porous, amorphous and 250 μm thick scaffold Total scaffold thickness=0.5 mm			On the PDL region: 5×10^5 hPDLs (except the single-gene delivery group, in which hGFs were seeded onto patterned AdPDGF-BB-coated PDL region) On the bone region: 5×10^5 hGFs	Pattern + single: AdBMP-7 immobilized patterned PDL area and AdBMP-7 immobilized bone area (with hGF cells in both regions) (n=6/3 weeks; n=6/6 weeks) Amorphous + dual: AdPDGF-BB immobilized, amorphous PDL area and AdBMP-7 immobilized bone area (n=6/3 weeks; n=6/6 weeks; n=5/9 weeks) Pattern + dual: AdPDGF-BB immobilized, patterned PDL area and AdBMP-7 immobilized bone area (n=10/3 weeks; n=6/6 weeks; n=5/9 weeks)		At 6 weeks, all groups except for the control group demonstrated nearly complete bone fill. Greater percentage of bone fill was found in the amor + dual and pattern + dual groups compared to the negative control group PDL formation Only soft tissues of patterned groups aligned obliquely to the root surface and were more likely to organize like native PDL Nanoindentation The stiffness of the regenerated tissues from the pattern + dual group were indistinguishable from that of native tissues both at 3 and 9 weeks. In contrast, the tissues formed in the control group were less stiff than native bone
Lian et al., 2020[23]	CAD electrospinning writing Bilayered: PLGA and gelatin gel composite with or wihout Cu-loaded MSNs Average fiber diameter of 10.2±0.5 μm, fiber spacings of 400 μm and lay-down patterns of 0°-90° Scaffold dimensions not mentioned	24 sprague dawley rats (24 defects)	Periodontal vertical defects were surgically created on the palatal aspect of the maxillary first molars (length × wide × deep= 3 mm × 1 mm × 2 mm)	Cu ions	Control: No treatment (n=6) PLGA/gelatin composite scaffolds (n=6) PLGA/gelatin composite-MSNs scaffolds (n=6) PLGA/gelatin composite-Cu@ MSNs scaffolds (n=6)	12	Micro-CT Cu@MSNs-PLGA/gelatin scaffold treated sites presented reduced CEJ-ABC distance, increased new bone volume and bone mineral Histological examination While control group defects were mainly filled with fibrous connective tissue, Cu@ MSNs- PLGA/gelatin scaffolds promoted complete periodontal regeneration
Daghrery et al., 2021[24]	CAD electrospinning writing PCL with or without F/CaP-coating 8 mm² × 8 mm², 0.45 mm thick and 500 μm strand spacing	12 Fischer 344 rats (24 defects)	Periodontal fenestration defects (3 mm × 2 mm × 1 mm) were surgically created bilaterally on the mandible exposing the distal root of the first molar and the mesial root of the second molar	F/CaP ions	Control: No treatment (n=4/time point) PCL scaffolds (n=4/time point) F/CaP-coated PCL scaffolds (n=4/time point)	3 and 6	Micro-CT At 3 and 6 weeks, bone volume, bone fill, and tissue mineral density were significantly higher in F/CaP-coated scaffolds compared to the other groups. At 6 weeks, near complete bone coverage was found in F/CaP-coated scaffold treated sites Histology

Study	3D scaffold manufacturing method/material/ characterization	Animal model/ number of animals/number of defects	Defect type/size/ location	Presence of biomolecules and/ or cells	Interventions	Length of follow-up (weeks)	Outcomes
He *et al.*, 2022[25]	CAD based printing BCG	Female beagle dogs Total number of animals and defects not reported	One-wall intrabony defects (wide × length=5 cm × 4 cm) were surgically created at the distal site of the mandibular second premolar and the mesial site of the mandibular fourth premolar	Mo ions	Control: No treatment (*n*=5) BCG scaffolds (*n*=5) Mo-BCG scaffolds (*n*=5)	8	F/CaP-coated scaffolds led to the regeneration of new alveolar bone, cementum, and PDL as early as 3 weeks postimplantation. At 6 weeks postimplantation, F/CaP-coated scaffold treated sites had a more robust and organized periodontium compared to sites treated with noncoated scaffolds Micro-CT Larger amounts of new bone were found in defects treated with Mo-BGC scaffolds, with newly formed PDL in the radiolucent zone Histology The newly formed alveolar bone, functional PDL and newly formed cementum were found only in defects treated Mo-BGC scaffolds

Cu – Copper; Mo – Molybdenum; ABC – Alveolar bone crest; BMP – Bone morphogenetic protein; AdBMP-7 – Adenovirus-encoding BMP-7; AdPDGF-BB – Adenovirus-encoding platelet-derived growth factor subunit B; BGC – Bioactive glass ceramic; CAD – Computer-aided design; CEJ – Distance between cement enamel junction; F/CaP – Fluorinated calcium phosphate; hGF – Primary human gingival fibroblasts; hPDL – Primary human PDL cells; MSN – Mesoporous silica nanoparticle; PCL – Poly-ε-caprolactone; PDL – Periodontal ligament; PDMS – Polydimethylsiloxane; PLGA – Poly (lactic-co-glycolic acid); hPDLs – Human PDL cells; CT – Computed tomography; BCG: Bacillus Calmette–Guérin; *n* – Sample size

Results

- At 3 weeks, all groups showed greater bone volume compared to the control group, with no differences between the groups.

- The pattern + single and amorphous + dual groups exhibited a higher percentage of bone defect fill than the control group.

- By 6 weeks, all groups except the control group demonstrated nearly complete bone fill, with the pattern + dual and amorphous + dual groups showing a greater percentage of bone fill compared to the negative control group.

Clinical Implications and Potential Applications

Medical Use

3D-printed scaffolds have potential applications in various periodontal treatments and surgeries.

Dentistry

These scaffolds may revolutionize dental implant procedures and periodontal surgeries.

Future Research Directions

1

Material Development

Further research aims to enhance scaffold materials for improved biocompatibility and degradation properties.

2

Clinical Trials

Future studies seek to conduct large-scale clinical trials to assess the scaffolds' effectiveness in humans.

3

Regulatory Approval

Research will focus on obtaining regulatory approvals and standardization for clinical use.

Conclusion and Key Findings

1

Significant Progress

The research demonstrates significant progress in 3D-printed scaffold technology for periodontal defects.

2

Challenges Addressed

Key findings address the challenges and limitations identified in the current evidence.

3

Promising Prospects

The study offers promising prospects for the future of periodontal defect treatments.