The International Implantable and Interventional Medical Device Emerging Technology Conference
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面向生物活性骨科植入材料的表面改性技术

Surface modification toward bioactive orthopaedic implants

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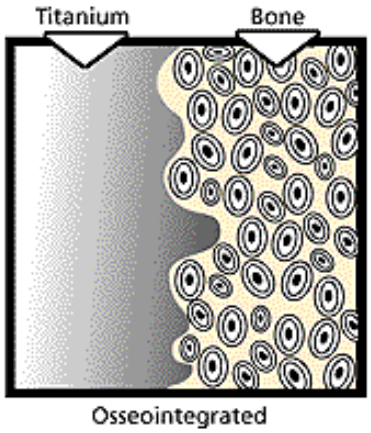
http://web.suda.edu.cn/binli

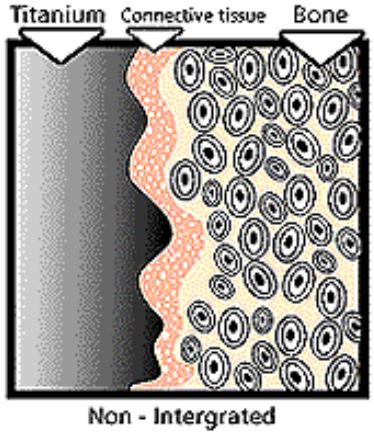
Integration between orthopaedic implant and bone tissue

Type of integration	Characteristics	Material type	Requirement
Morphological integration	Mechanical embedding/locking	Bioinert materials	Morphological matching
Biological integration	Ingrowth of new bone tissue into the porous implant	Porous materials	Absence of large shear stress
Bioactive integration	Formation of chemical bonding between implant and host bone tissue	Bioactive materials	Hydroxyapatite surface
Osseointegration	Non-fibrotic, direct contact between implant and newly formed bone tissue	Bioactive materials	Bioactively functionalized surface

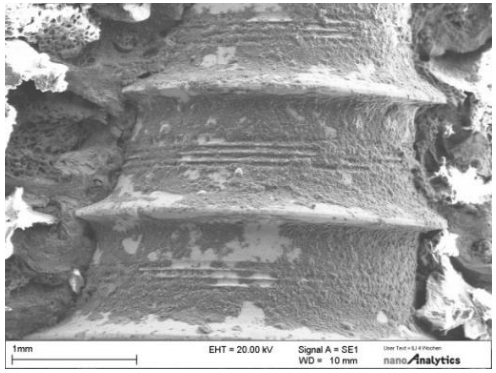
Osseointegration of implants

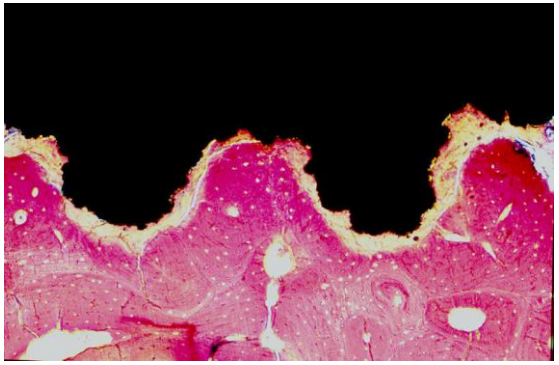


Osseointegrated



Non - Intergrated

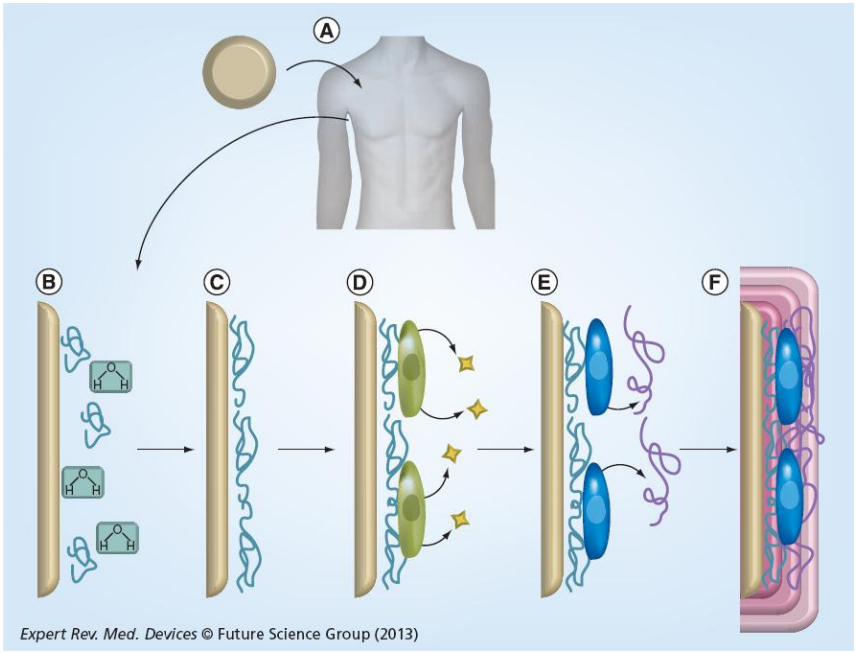


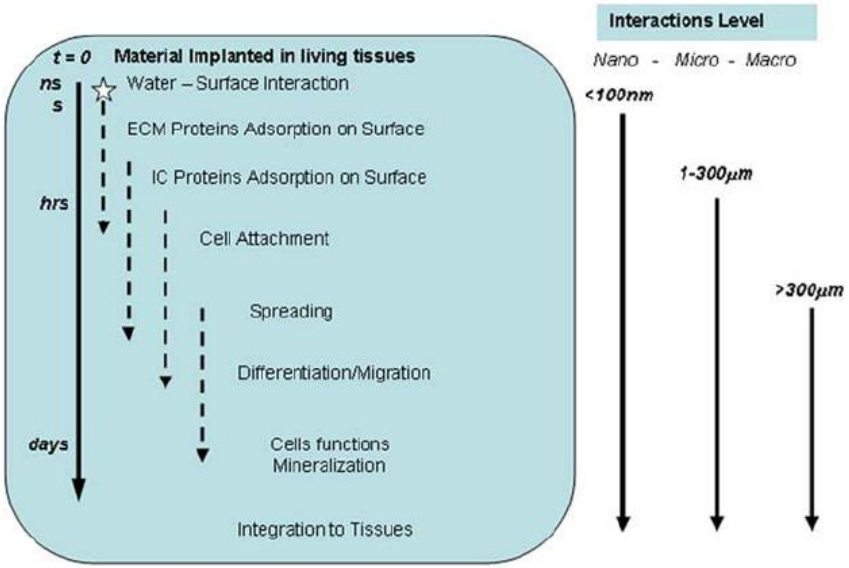


An implant is bio-mechanically osseointegrated if there is no progressive relative motion of living bone and implant under functional levels and types of loading for the entire life of the patient.

Brånemark et al., J Rehab Res Dev 2001; openi.nlm.nih.gov

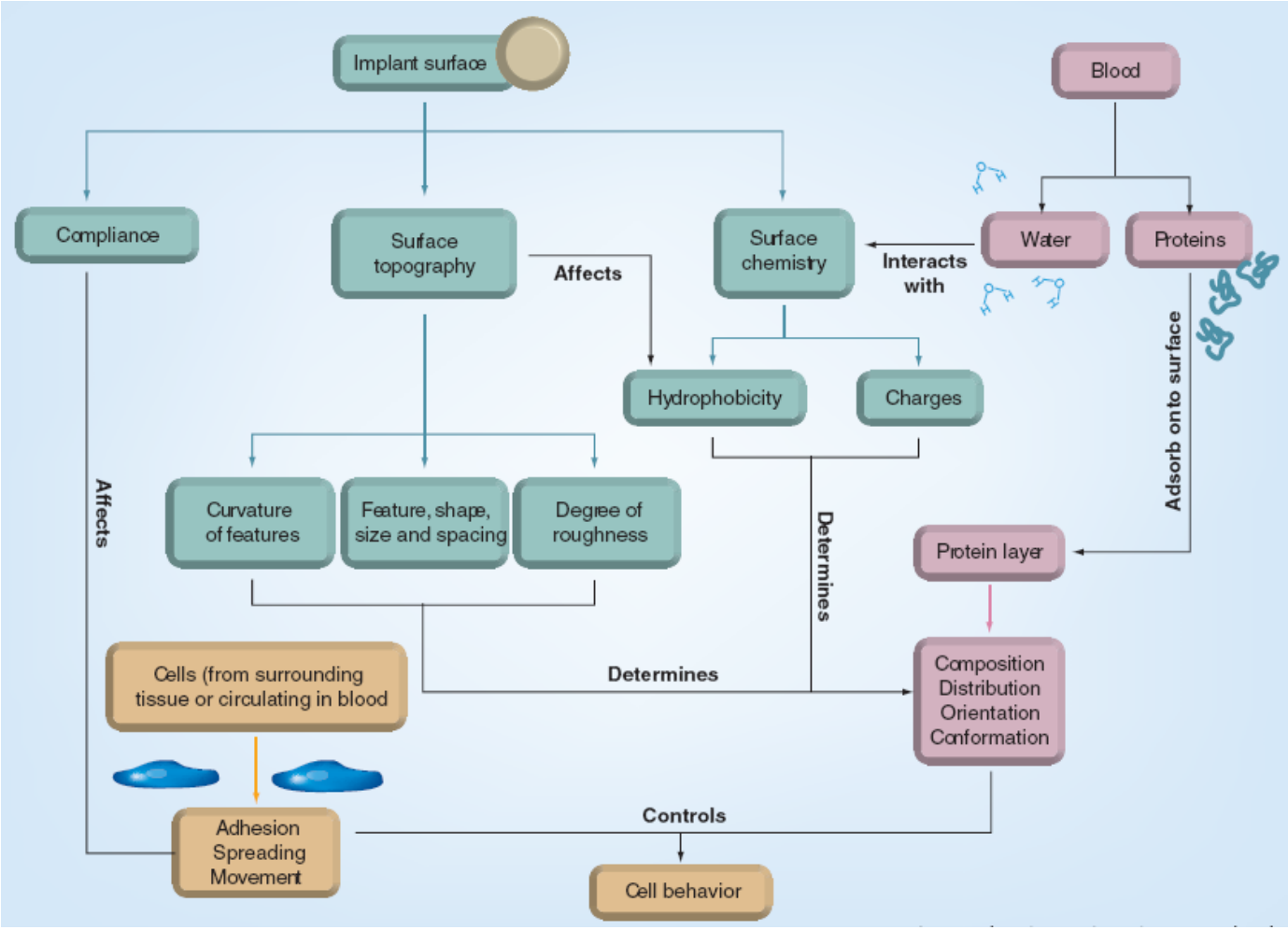
Cell-surface interactions





Harvey et al., Expert Rev. Med. Devices, 2013; Roach et al., J Mater Sci- Mater Med, 2007

Surface features that affect cell behavior



Harvey et al., Expert Rev. Med. Devices, 2013

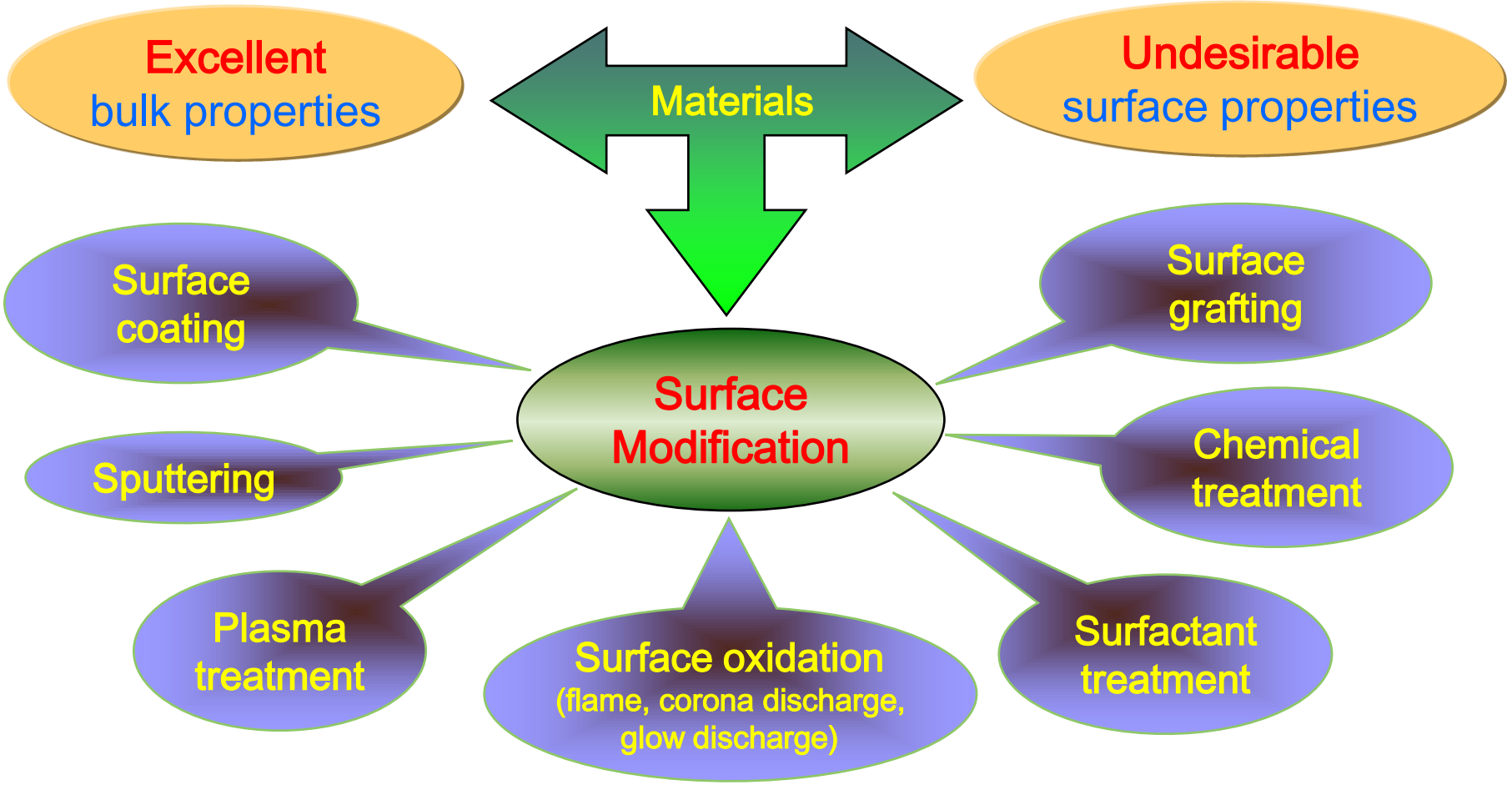
Effects of surface features

Table 1. A comparison of the effect of surface features on protein adsorption and cell response.

Surface property	Hydrophobicity and protein adhesion	Cell response (and tissue response)
Surface roughness	Increased roughness gives increased hydrophobicity [23–25]. Affects protein distribution [32]. Proteins fill valleys (depending on other properties [30,31,33])	Increased roughness led to increased cell migration (due to uneven distribution of proteins [31]). Roughness improves tissue integration and reduces fibrous capsule formation [23–25]
Grooves and ridges	Proteins may unfold/change conformation at groove/ridge boundaries making receptor ligands more accessible [43]	Cytoskeleton and cell body align to narrow grooves and ridges. Cell proliferation rates are lowered and RNA expression is altered [40–46]
Pits and pillars	Proteins may accumulate in pits creating uneven distribution – strongly affected by pit size [51,52]	Cells crawl into pits >25-μm diameter. Nanopits increase cell motility [27,48–53]. Pillars create a stronger effect and affect genomic response [54–58]
Curvature	Protein orientation and activity are greatly affected by curvature – dependant on protein [63]. Sharpness of feature edges affects protein unfolding and receptor-ligand accessibility [60]	Concave pits: 3D environment to the cell. Curved surfaces require distortion of cell cytoskeleton [22,59]. Fibers: cells elongate along flat surface direction rather than around curved one [62]
Compliance	Compliance has a direct effect on cell response rather than through controlling protein adhesion	Increased actin organization, cell spreading and cell density on stiffer or harder substrates [64,65]. Protein production and cell differentiation are also affected [67]. Cells migrate to stiffer/more strained areas [66]
Chemistry	Surface hydrophobicity can be controlled by the chemistry and in turn affect protein adsorption and orientation/conformation [74,75]. Or surface can be modified with functional peptides (e.g., RGD) for direct cell attachment [76–81]	Can control cell response by controlling protein adsorption or arrangment of functional peptides. Can switch on/off cell attachment/behaviors [82,83]

Harvey et al., Expert Rev. Med. Devices, 2013

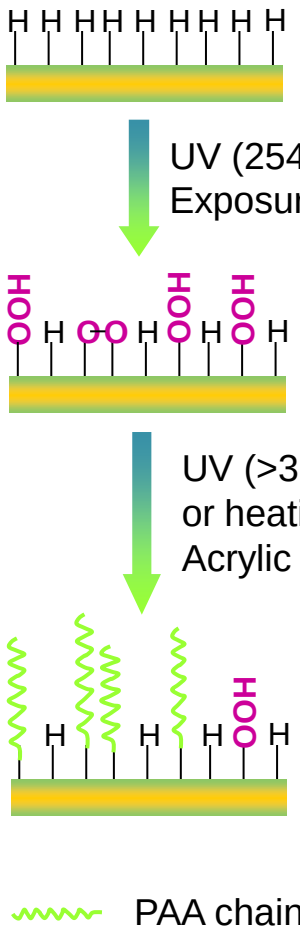
Surface modification of materials



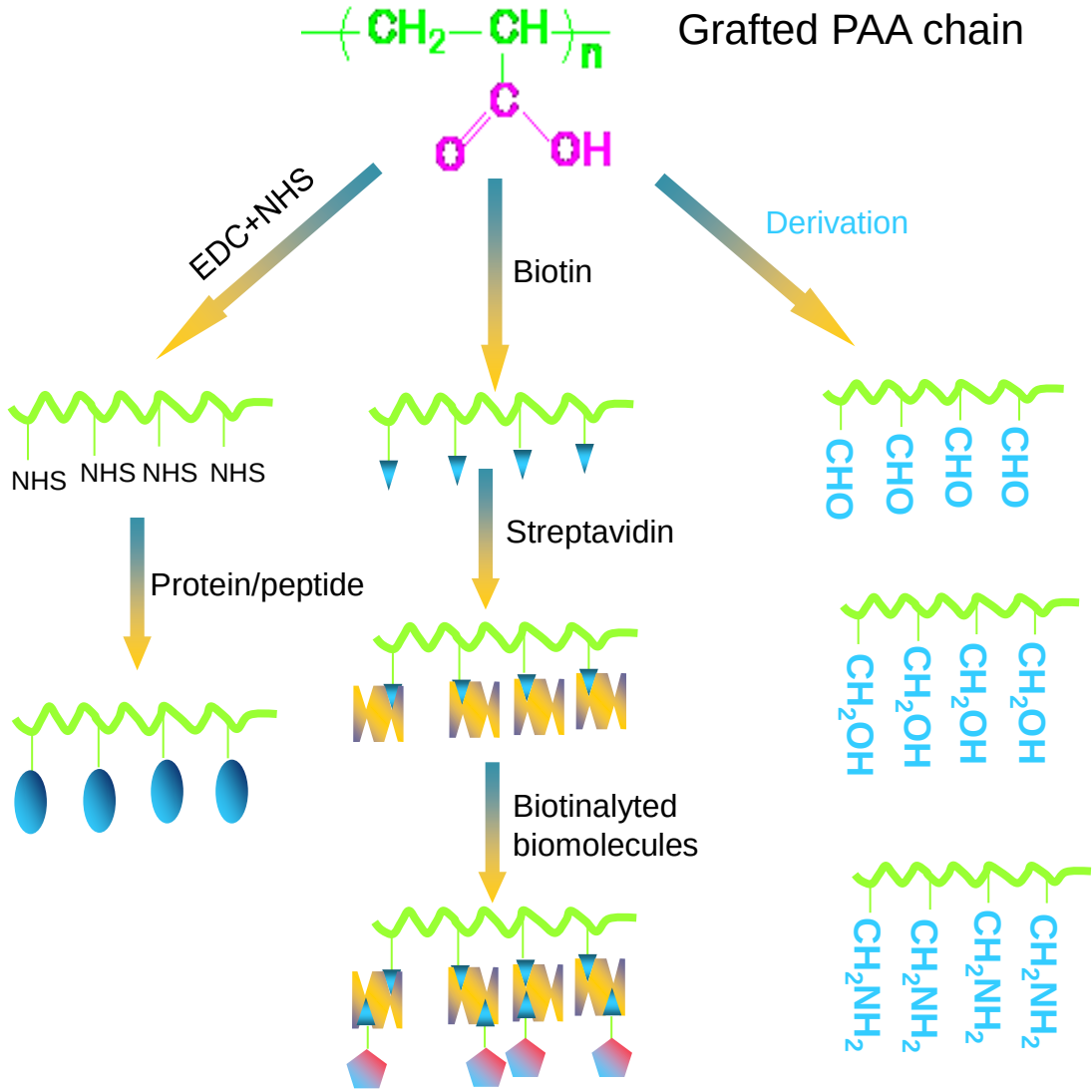
Strategies for surface modification of orthopaedic implants

- **Topographical changes**
  - Surface roughness, grooves/ridges, pits/dots/pillars, curvature…
- **Physical coating**
  - Protein coating, hydroxyapatite coating, sputtering, plasma assisted ion implantation, laser melting…
- **Chemical conjugation**
  - Strong and stable covalent bonding of bioactive molecules (e.g., adhesive peptides & proteins, growth factors, transcription factors) to surface
- **Molecular recognition**
  - Active capture and enrichment of bioactive molecules (in vivo)
  - Antibody, molecular imprinting, aptamer
- **Cell sheet wrapping**

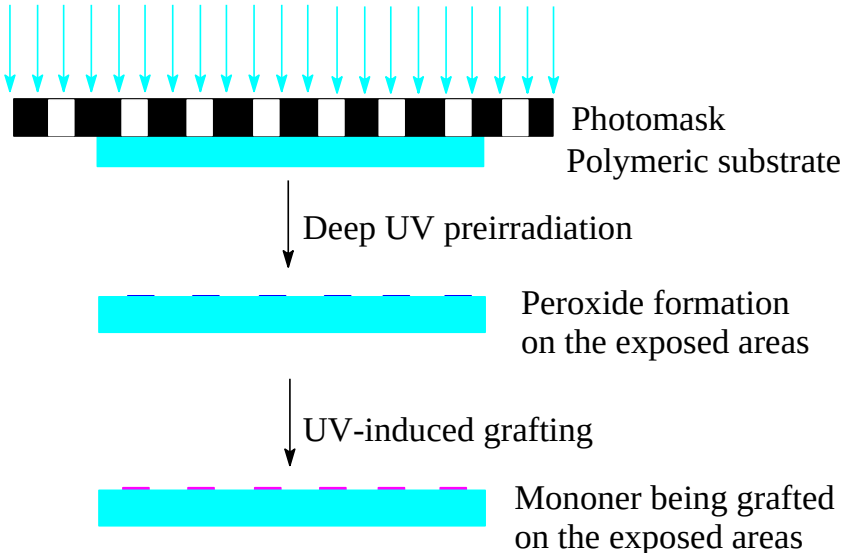
Surface grafting of poly(acrylic acid) — a platform technique

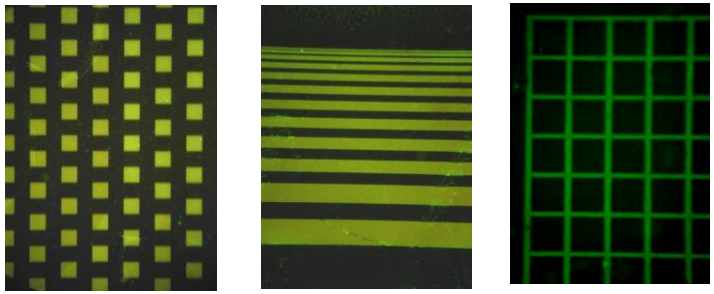


Two-step photografting of PAA on polymer surface

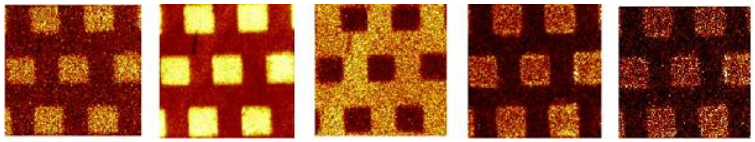


Conjugating protein via PAA Grafting

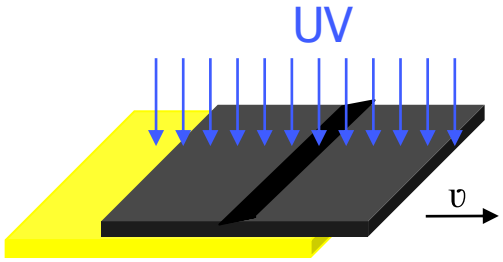


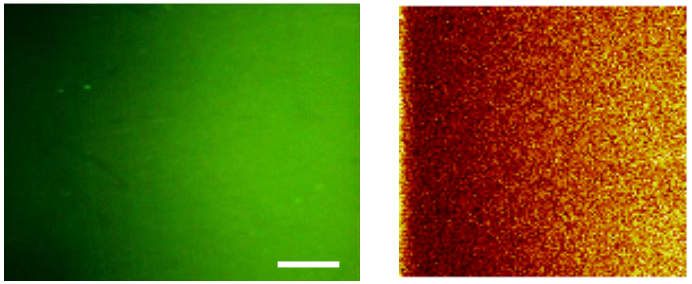


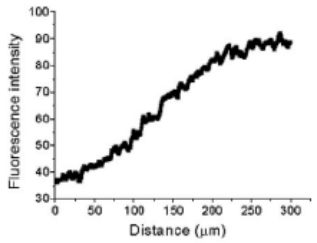
Fluorescence microscopy



ToF-SIMS

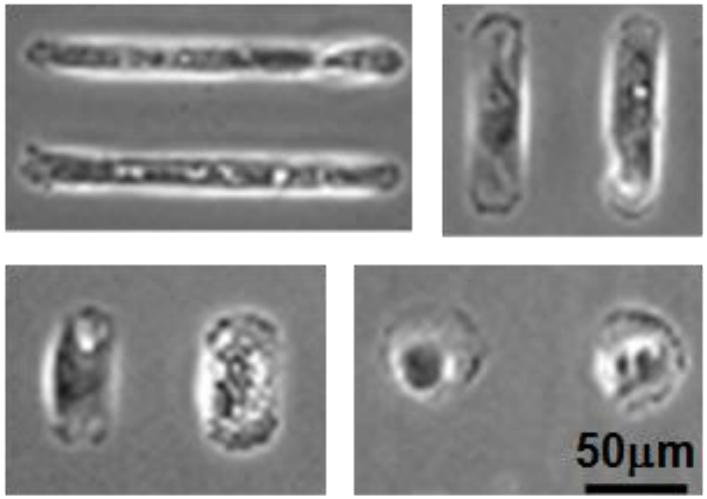


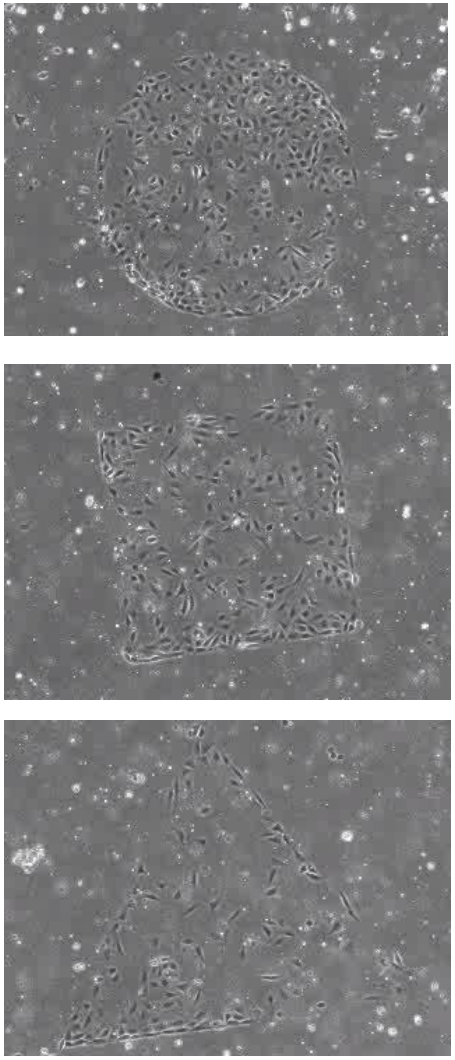




Li et al., Biomaterials, 2005; Li et al., J Biomed Mater Res A, 2006

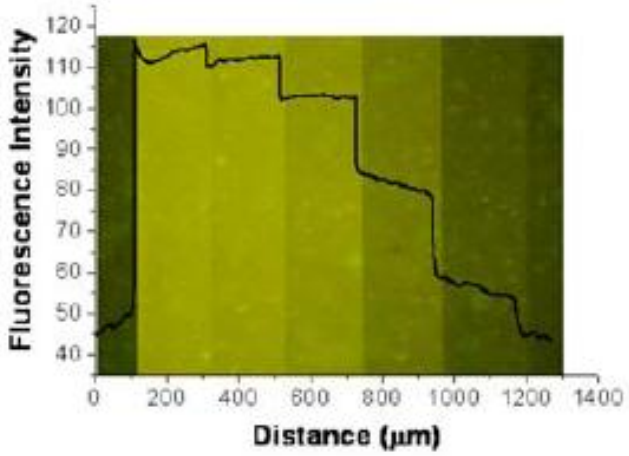
Patterned single cells and cell islands



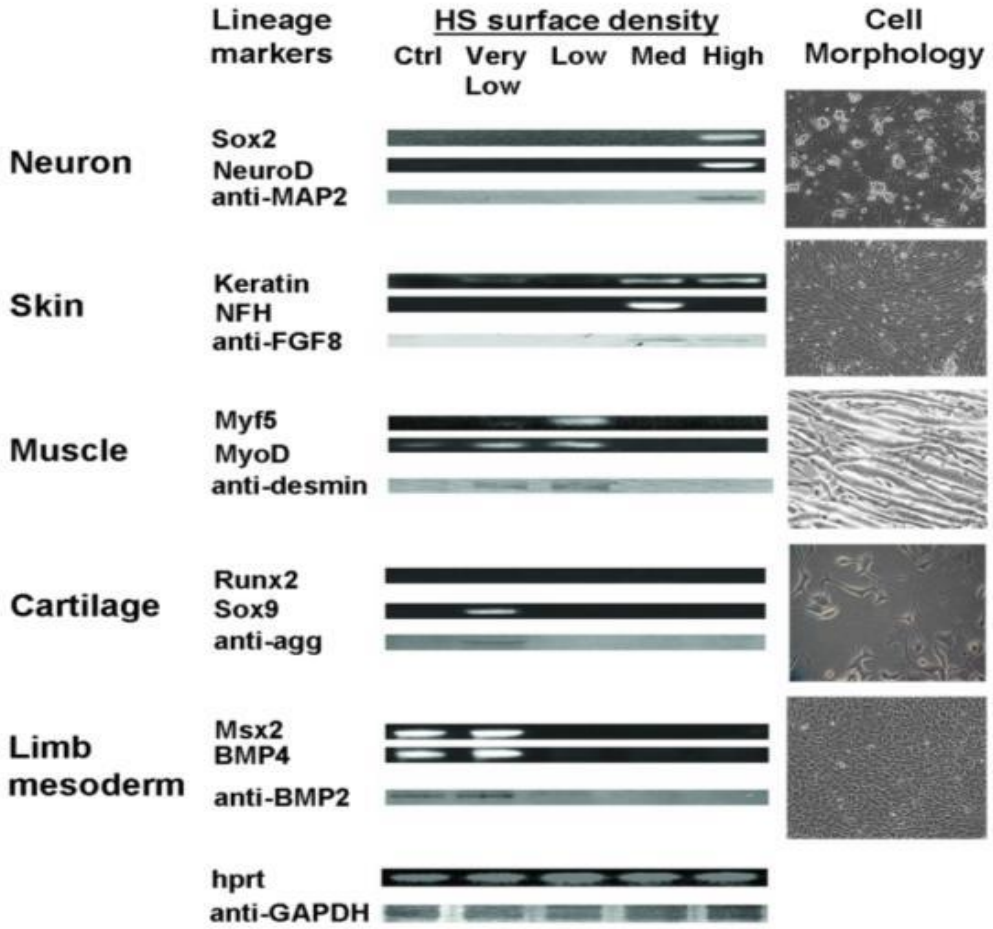


Li et al., Cell Motil Cytoskel, 2007; Li et al., J Biomech, 2009

Micro-gradient directed lineage commitment of progenitor cells

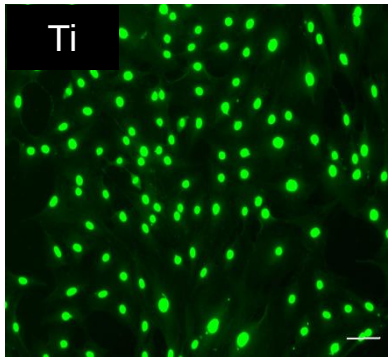


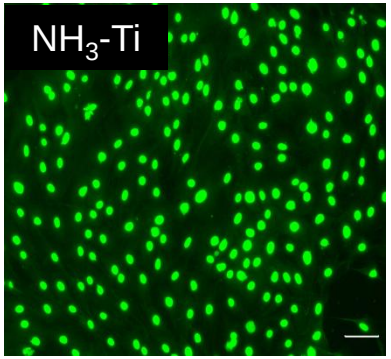
Sonic Hedgehog (Shh)

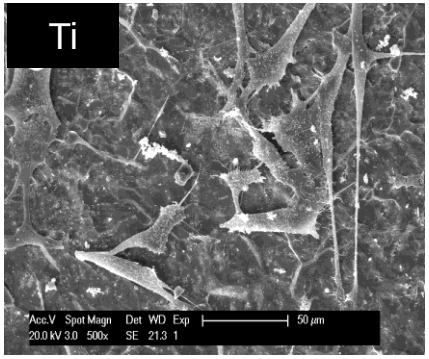


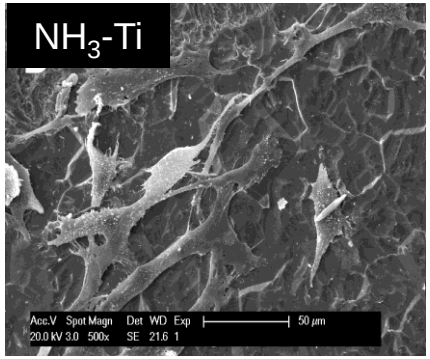
Li et al., J Contr Release, 2013

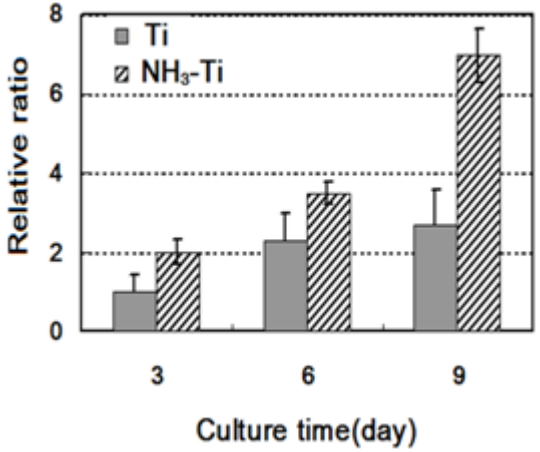
Enhanced osteogenic differentiation on chemically treated surfaces



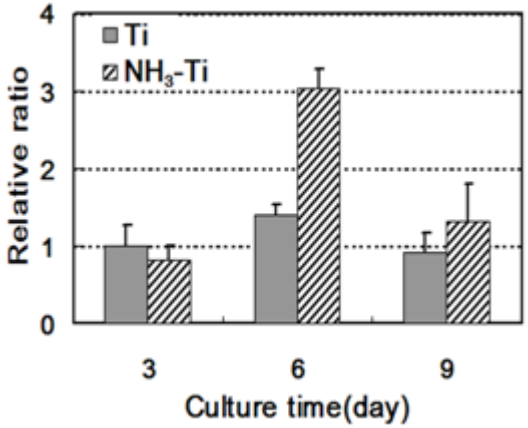




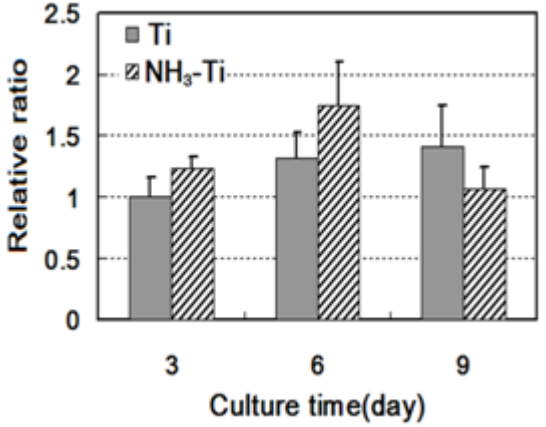




COL-I



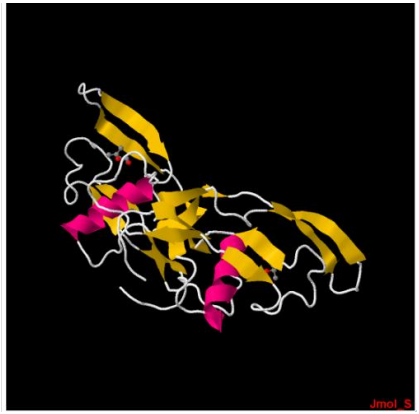
osteocalcin (OC)

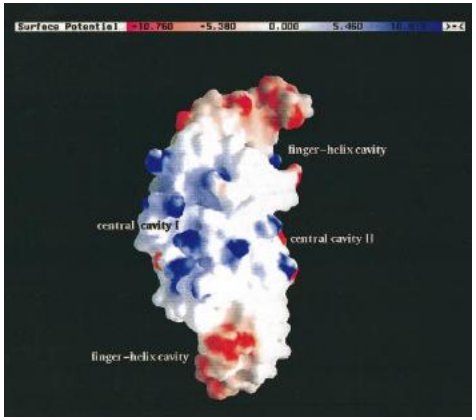


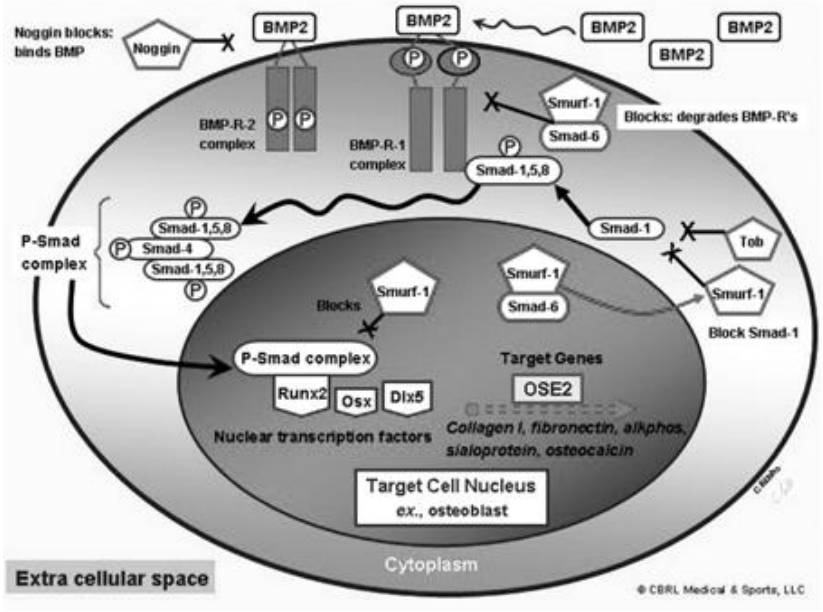
bonesialoprotein (BSP)

Liu et al., Appl Sur Sci, 2012

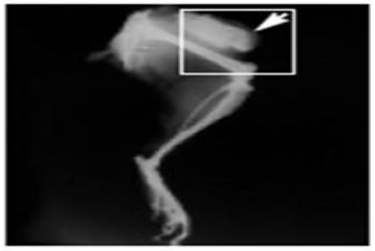
Bone morphogenetic protein 2 (BMP-2)





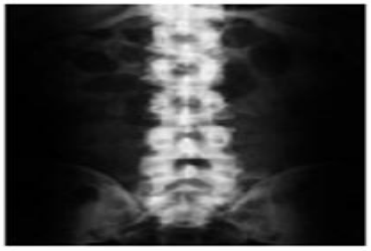


1965



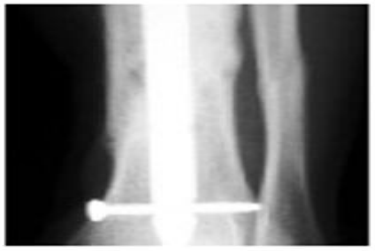
Osteoinductive effect of BMP being discovered

2002



rhBMP being approved by FDA for lumbar spine fusion

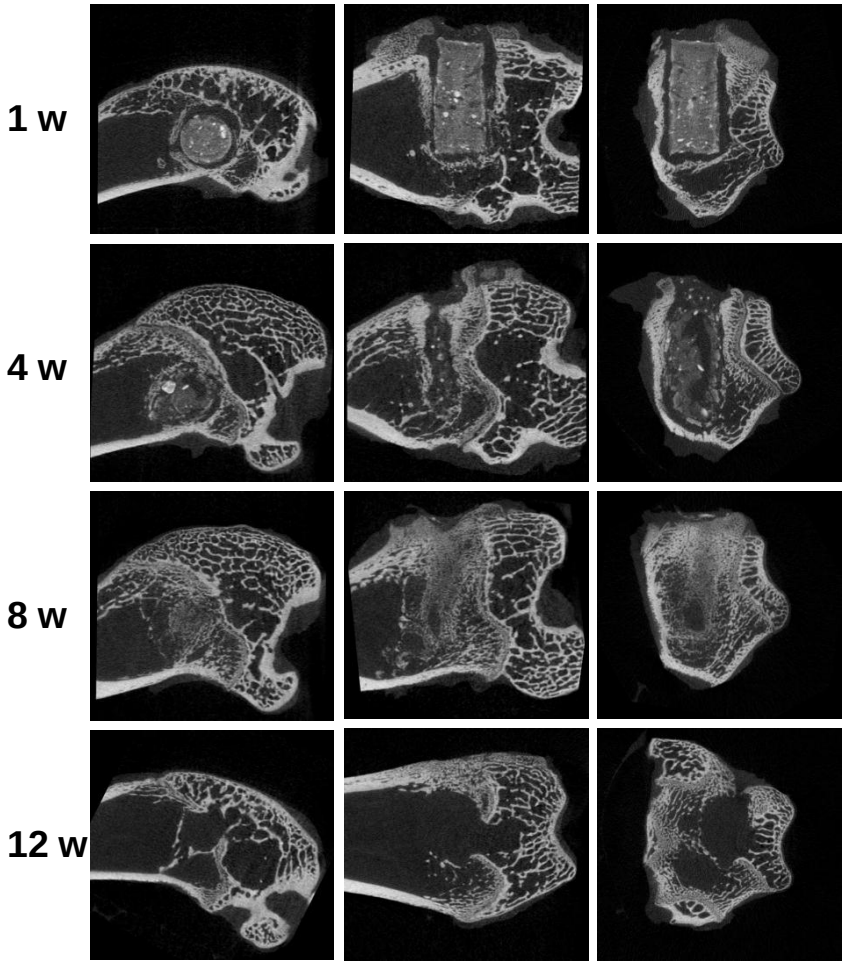
2004

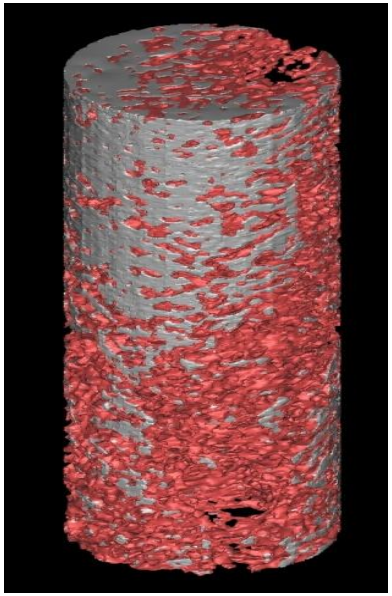


rhBMP being approved by FDA for open tibial fractures

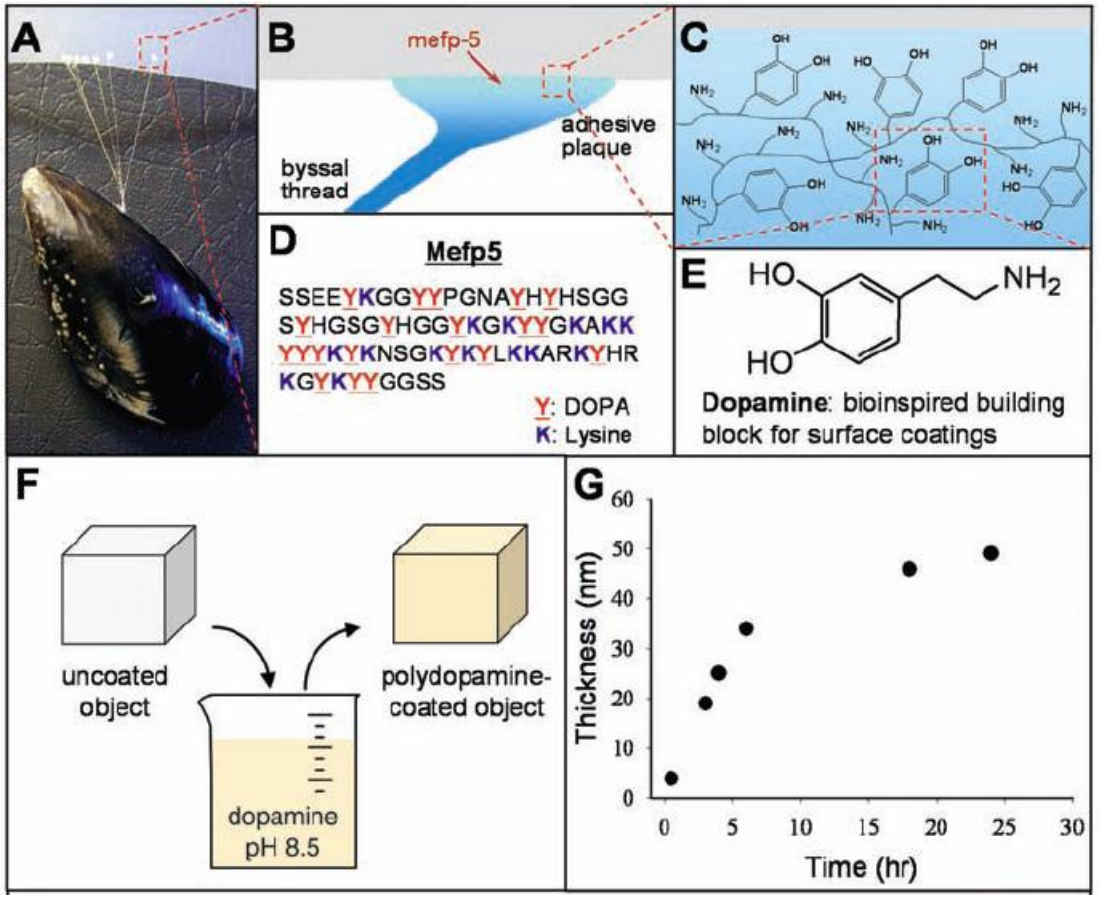
Repair of femoral condyle defects

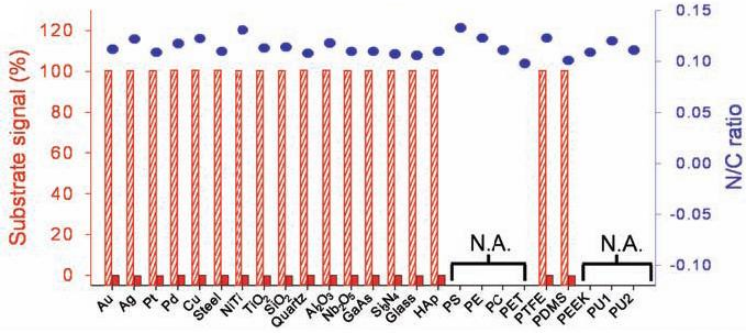
rhBMP-bound HAp

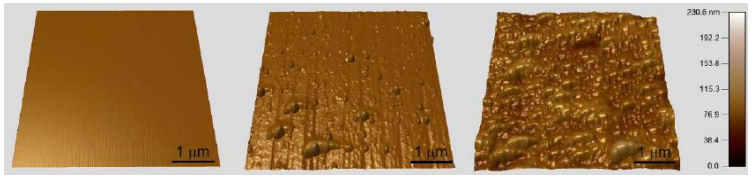


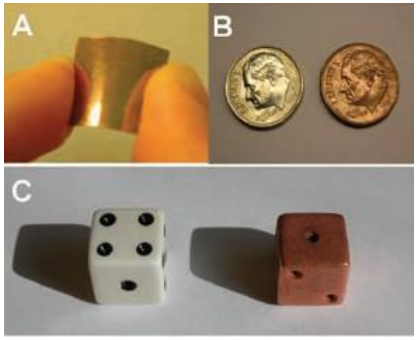


Mussel-inspired surface coatings via polydopamine chemistry





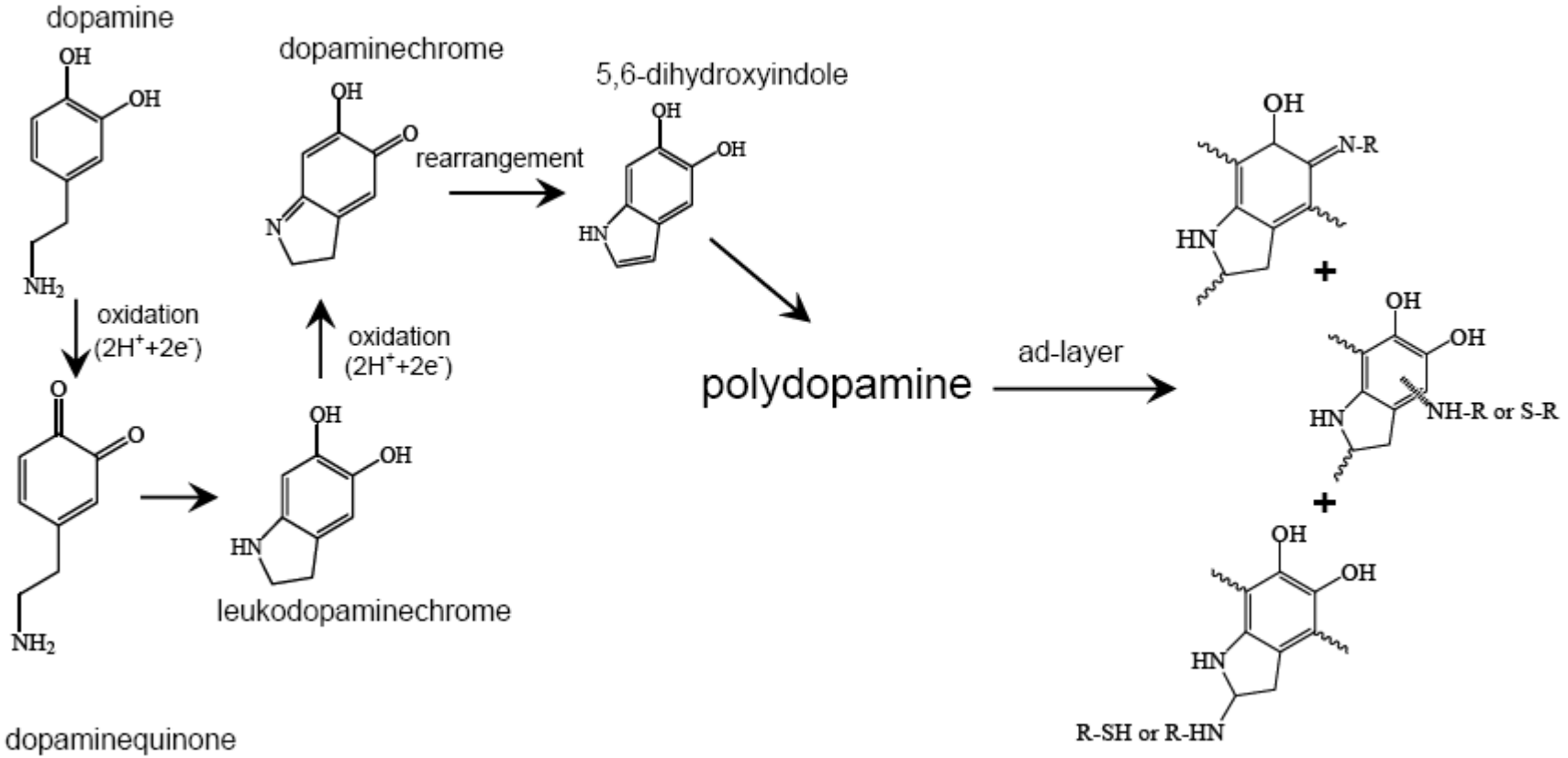




polydopamine (pDA)

Lee et al., Science, 2007

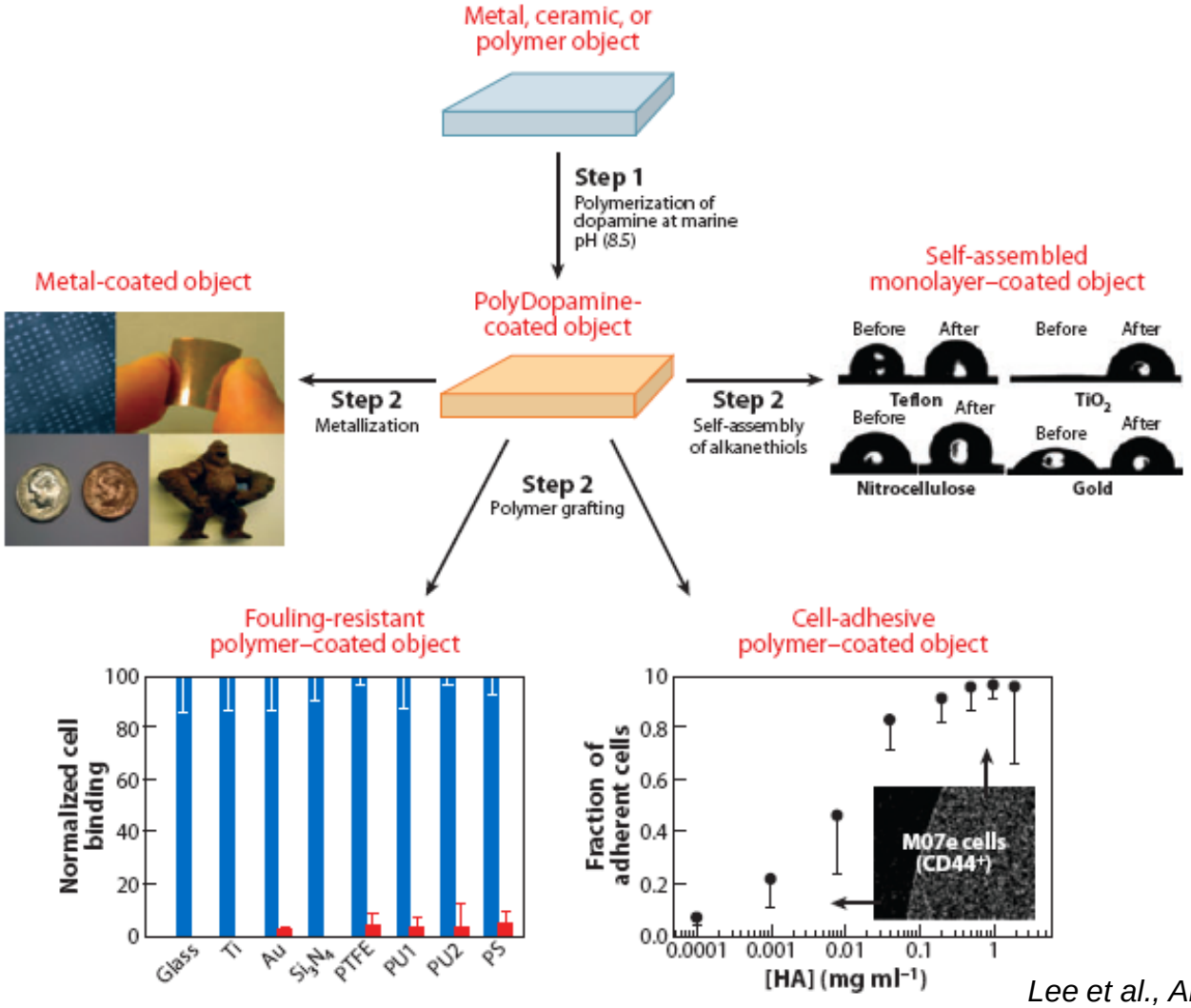
Polymerization mechanism of dopamine



Simple dip-coating, yet strong chemical bonding

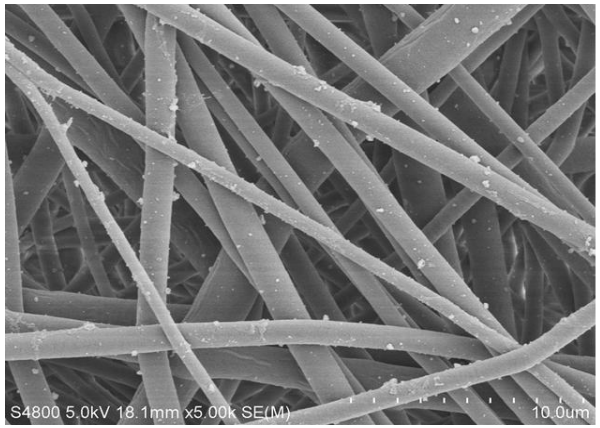
Lee et al., Science, 2007

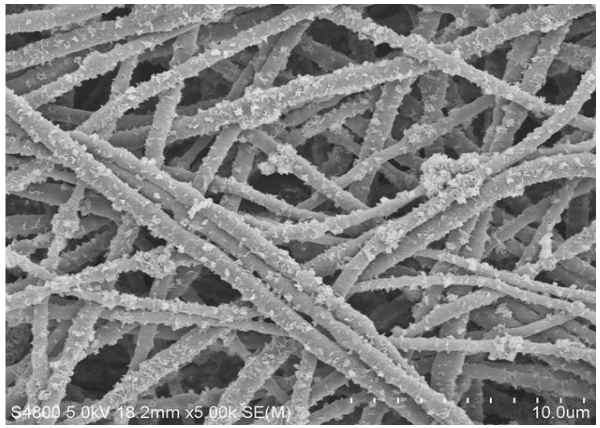
pDA coating as a platform for surface modification



Lee et al., Annu Rev Mater Res, 2011

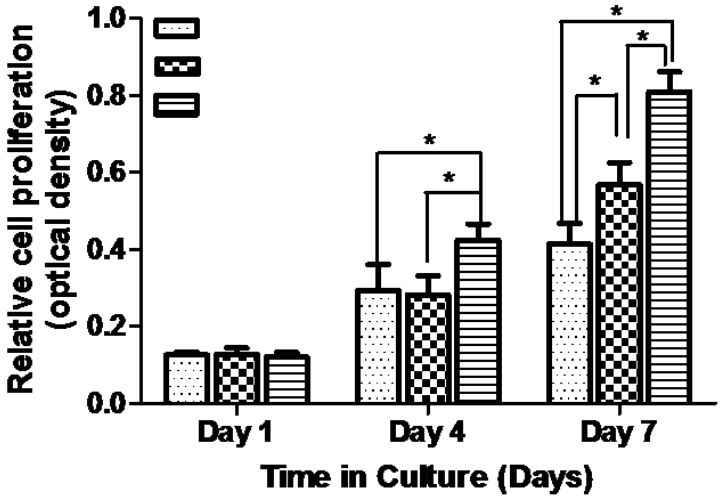
pDA coating facilitates mineralization

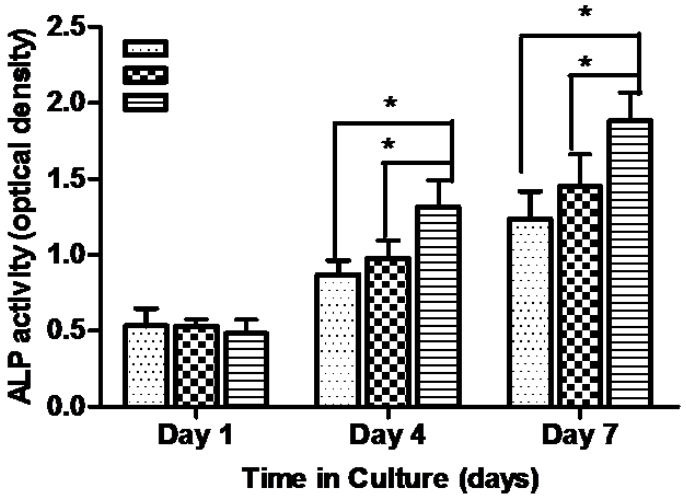




w/o coating

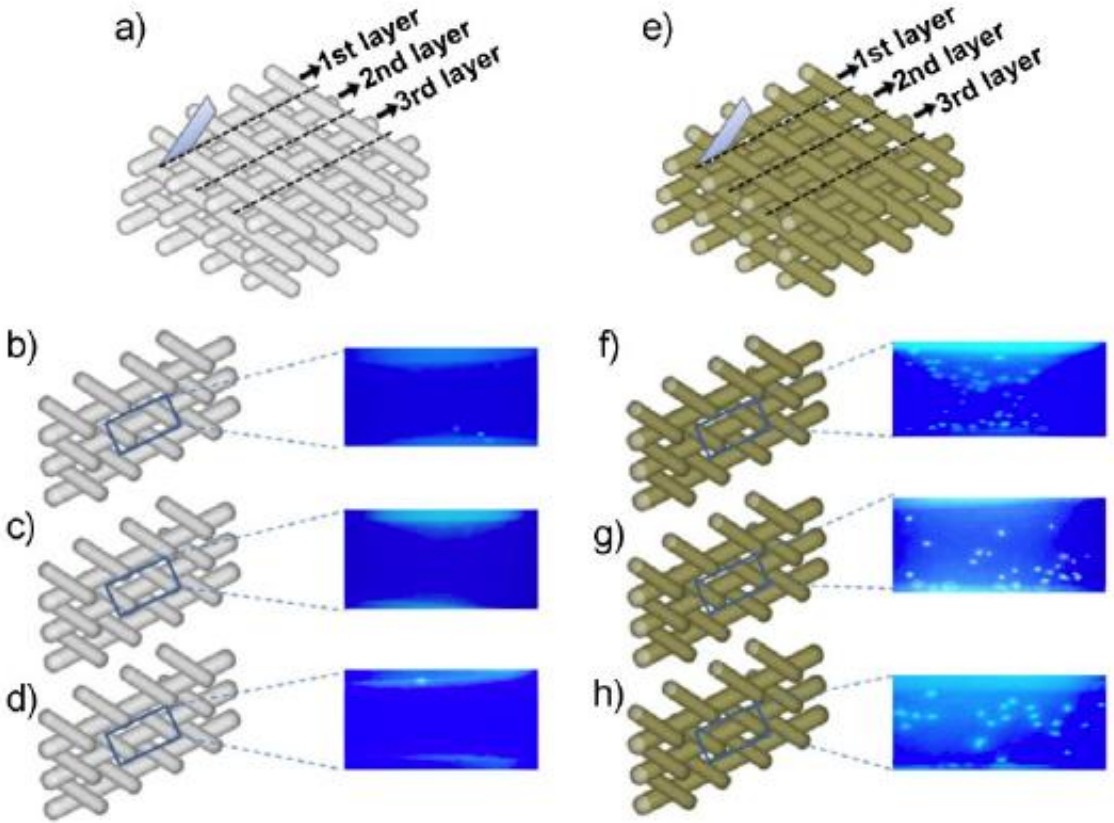
pDA-coated

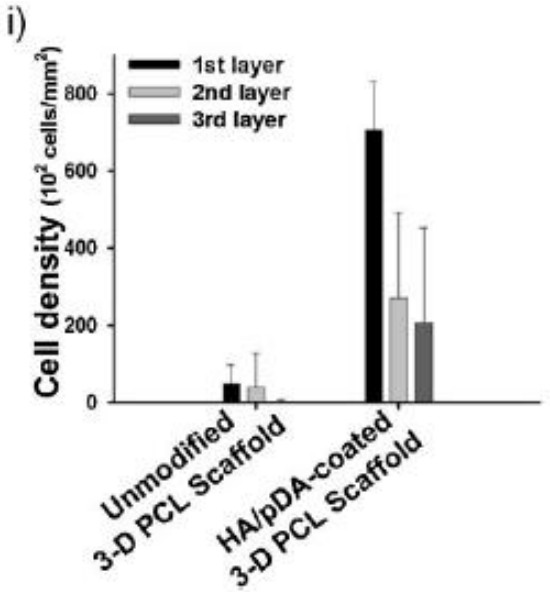




Dong et al., Mater Sci Eng C, 2014

pDA coated surface facilitates cell infiltration in 3D scaffolds

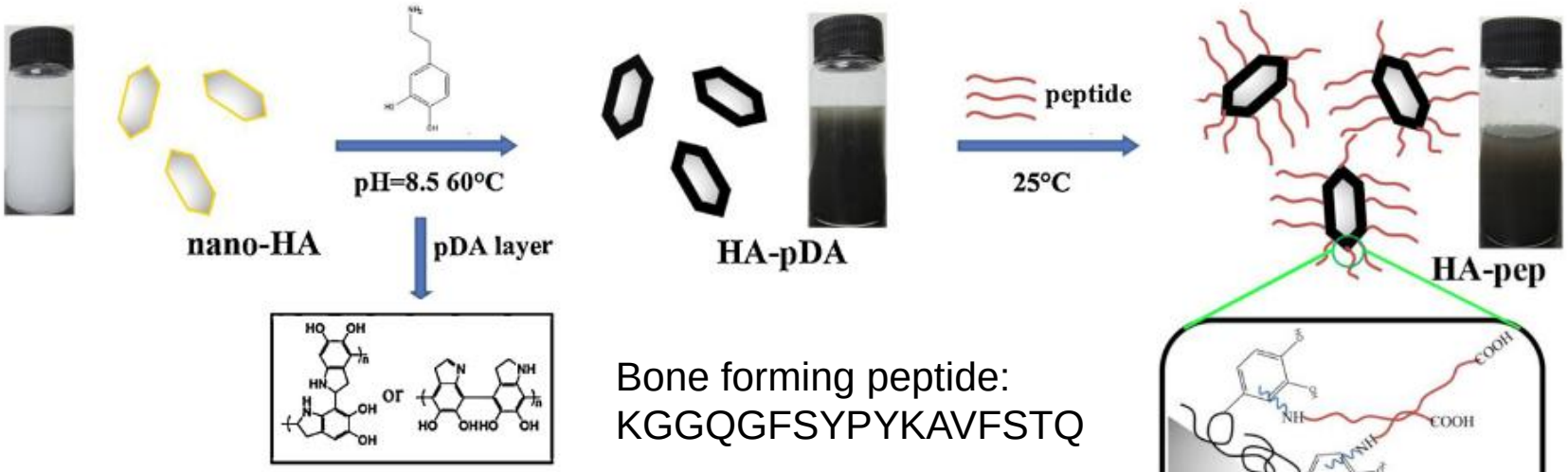




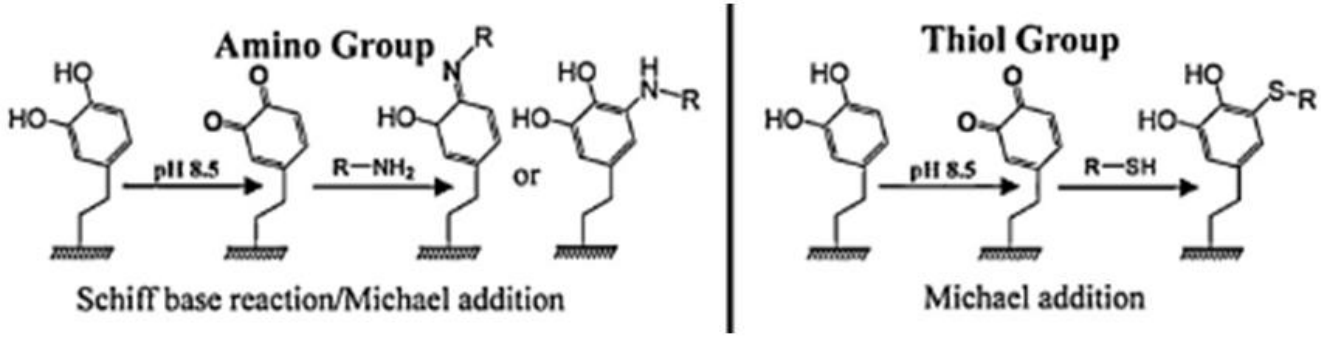
w/o coating **pDA-coated**

Jo et al., Macromol Biosci, 2013

Peptide decorated HA with enhanced bioactivity via pDA coating

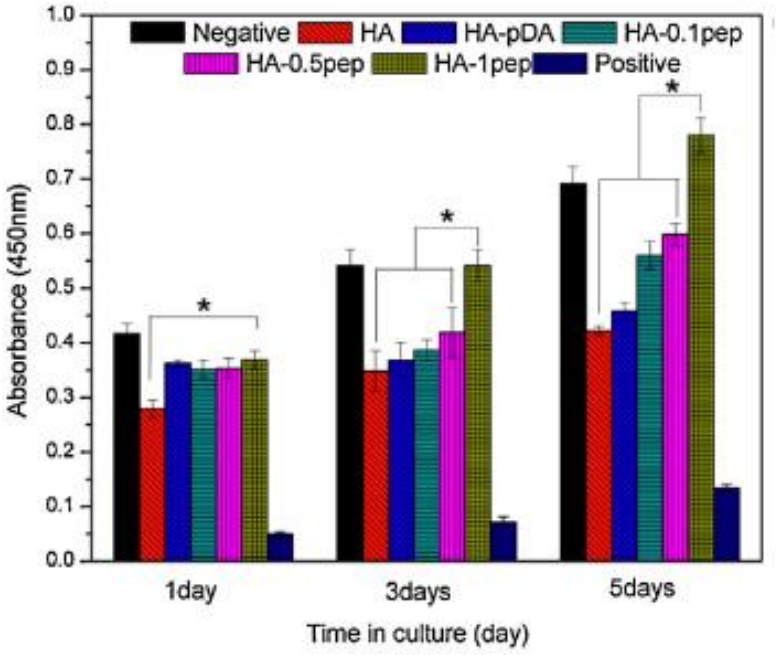


Bone forming peptide:
KGGQGFSYPYKAVFSTQ

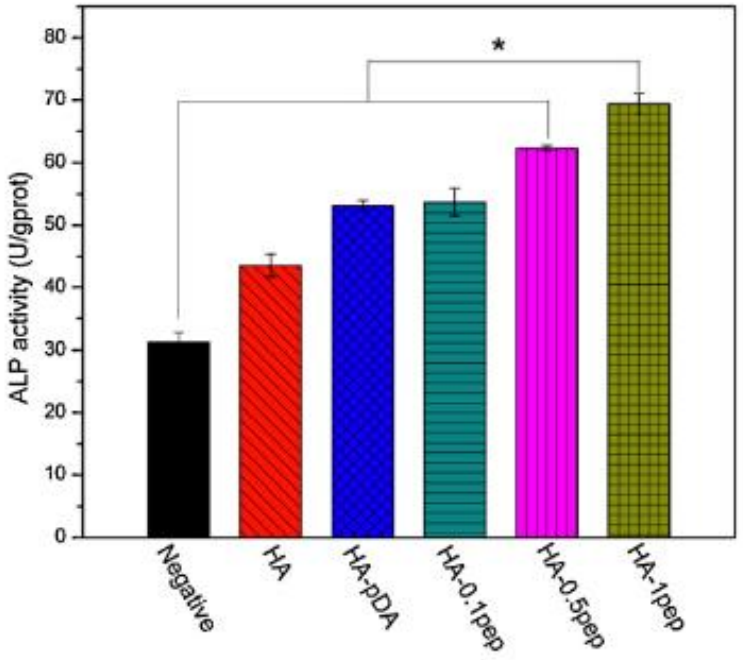


Sun et al., Colloids Surf B- Biointerfaces, 2013

Proliferation and differentiation of osteoblastic cells



Cell proliferation



ALP activity

Sun et al., Colloids Surf B- Biointerfaces, 2013

Strategies for surface modification of orthopaedic implants

- **Topographical changes**
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  - Active capture and enrichment of bioactive molecules (in vivo)
  - Antibody, molecular imprinting, aptamer
- Cell sheet wrapping

Disadvantages of rhBMP usage

High cost
€2970 per grade III A and B open tibia fracture (Germany)

Short half life

High dosage of use
More than 100-folds higher dose of rhBMP (up to milligram) compared to its physiological level is required to induce new bone formation in animals

Complications associated with high-dosage rhBMP

- **Exaggerated bone resorption**
- **Excessive bone formation**
- **Nerve cell reactions in unintended areas**

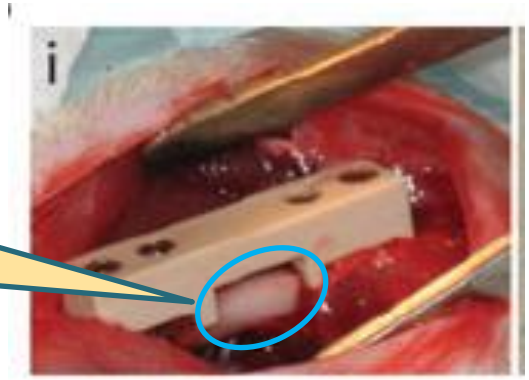
Endogenous bioactive molecules?

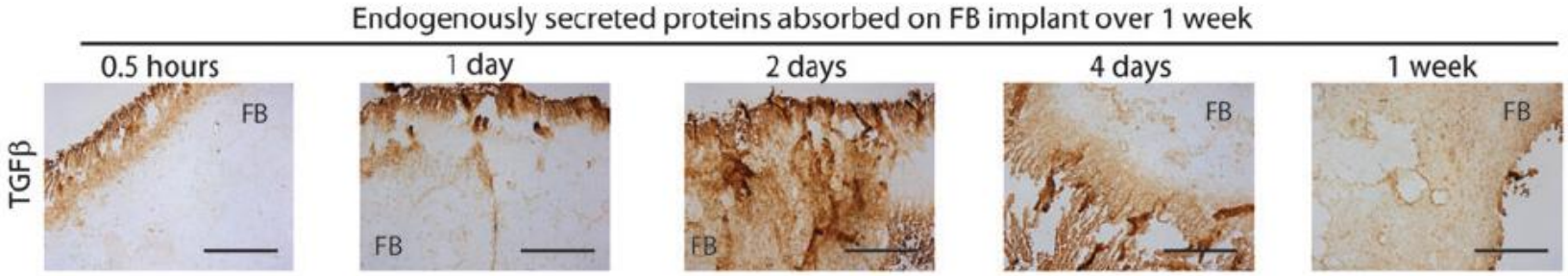
Acquiring endogenously secreted proteins

FlexBone:

nanocrystalline hydroxyapatite (50 wt%)

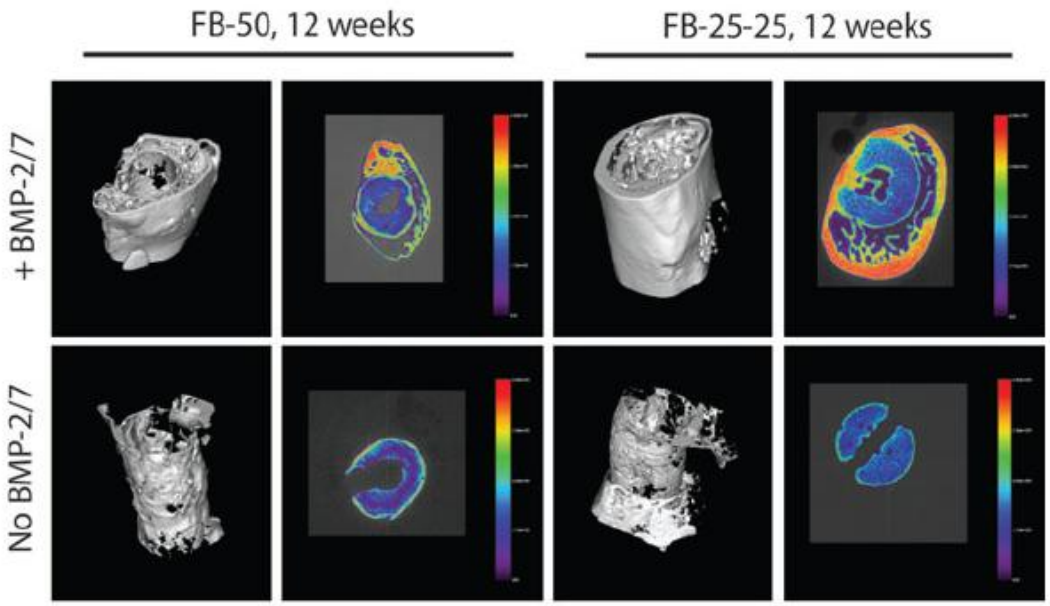
poly(hydroxyethyl methacrylate) hydrogel

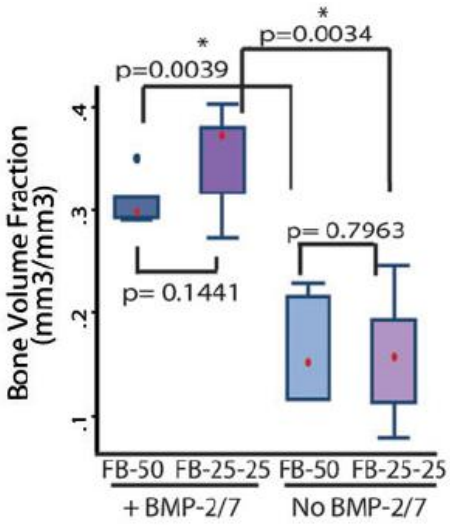


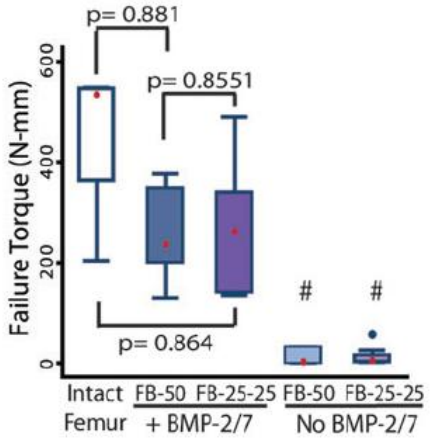


Filion et al., Tissue Eng A, 2011

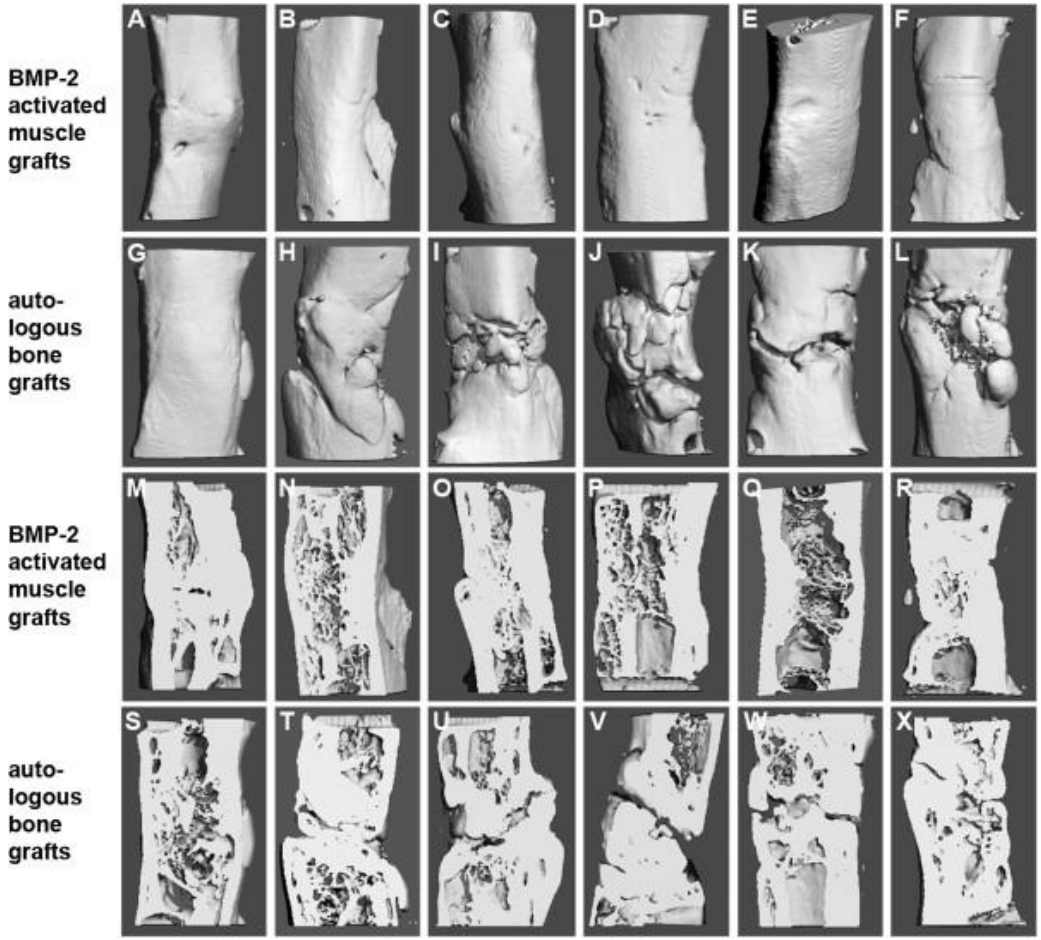
FlexBone-filled defects healed better when supplemented with rhBMP

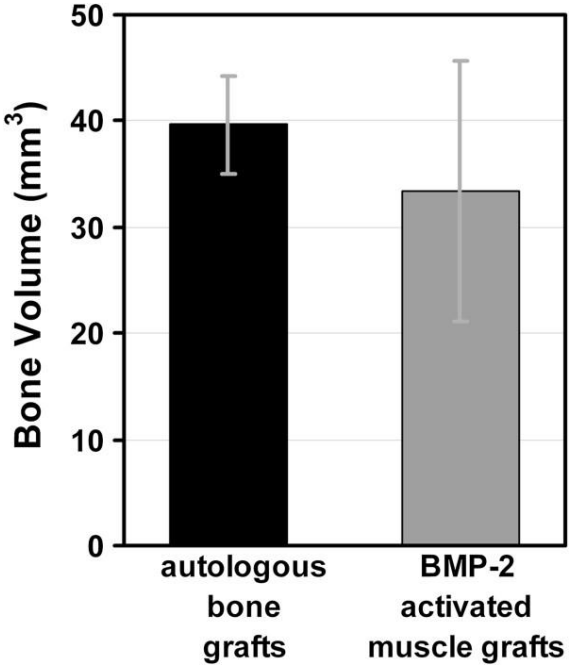






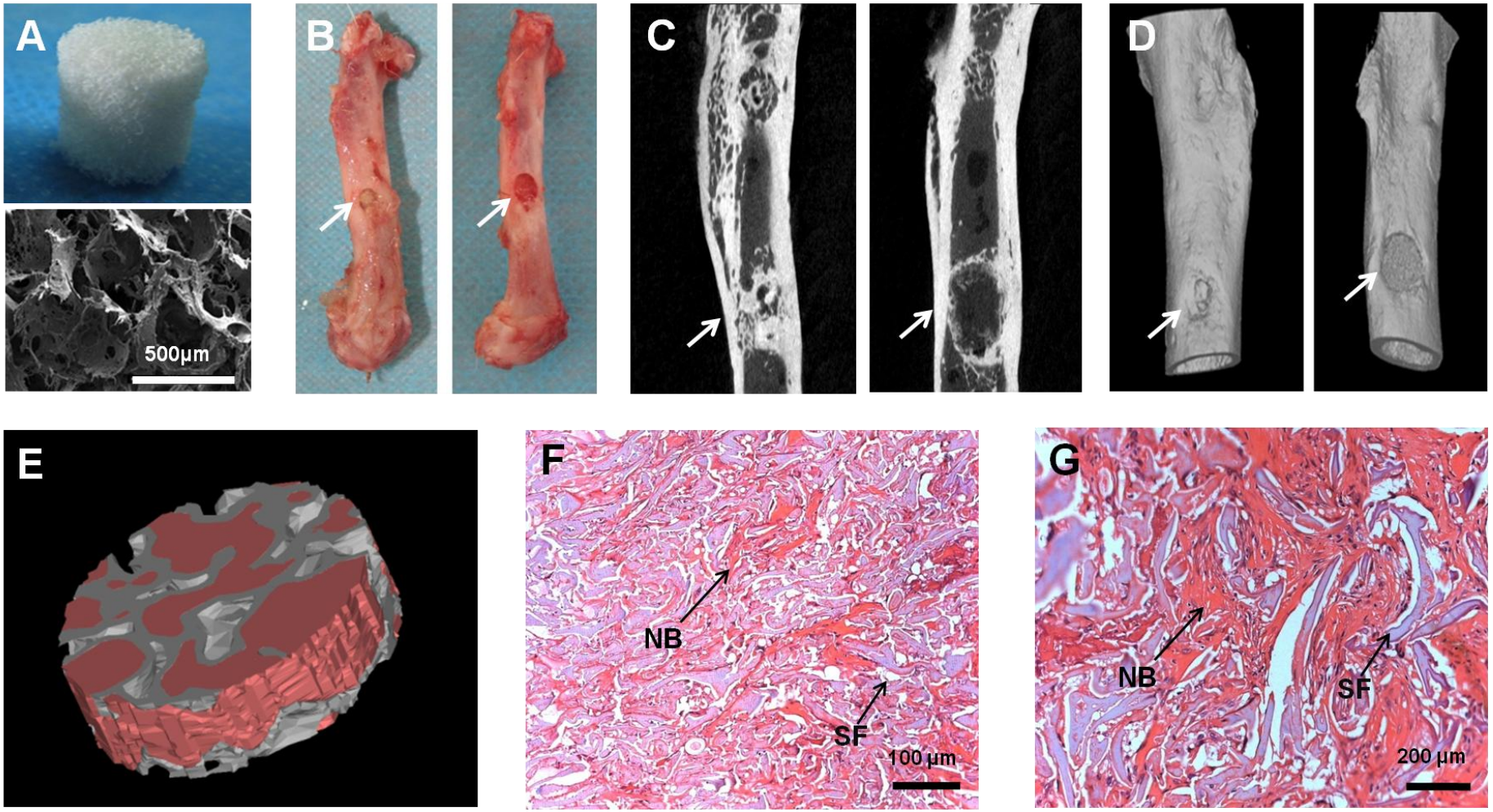
Making use of the autologous BMP



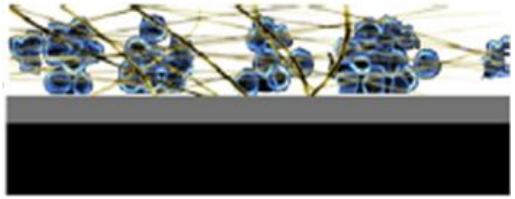


Betz et al. BMC Biotechnology, 2013

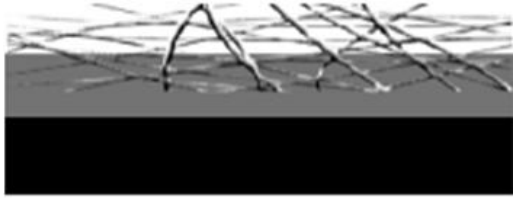
Harvesting BMP-2 using its antibody



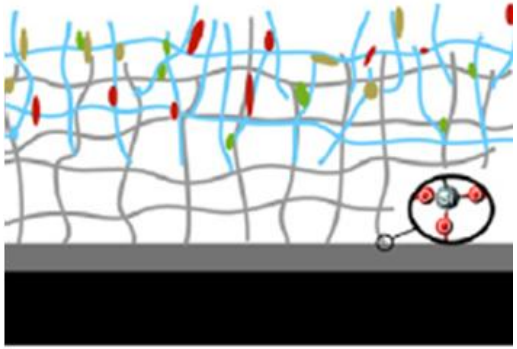
Physical entrapment of bioactive molecules at implant surface



Establishment of natural interactions with the fibrils



Anodic oxide growth

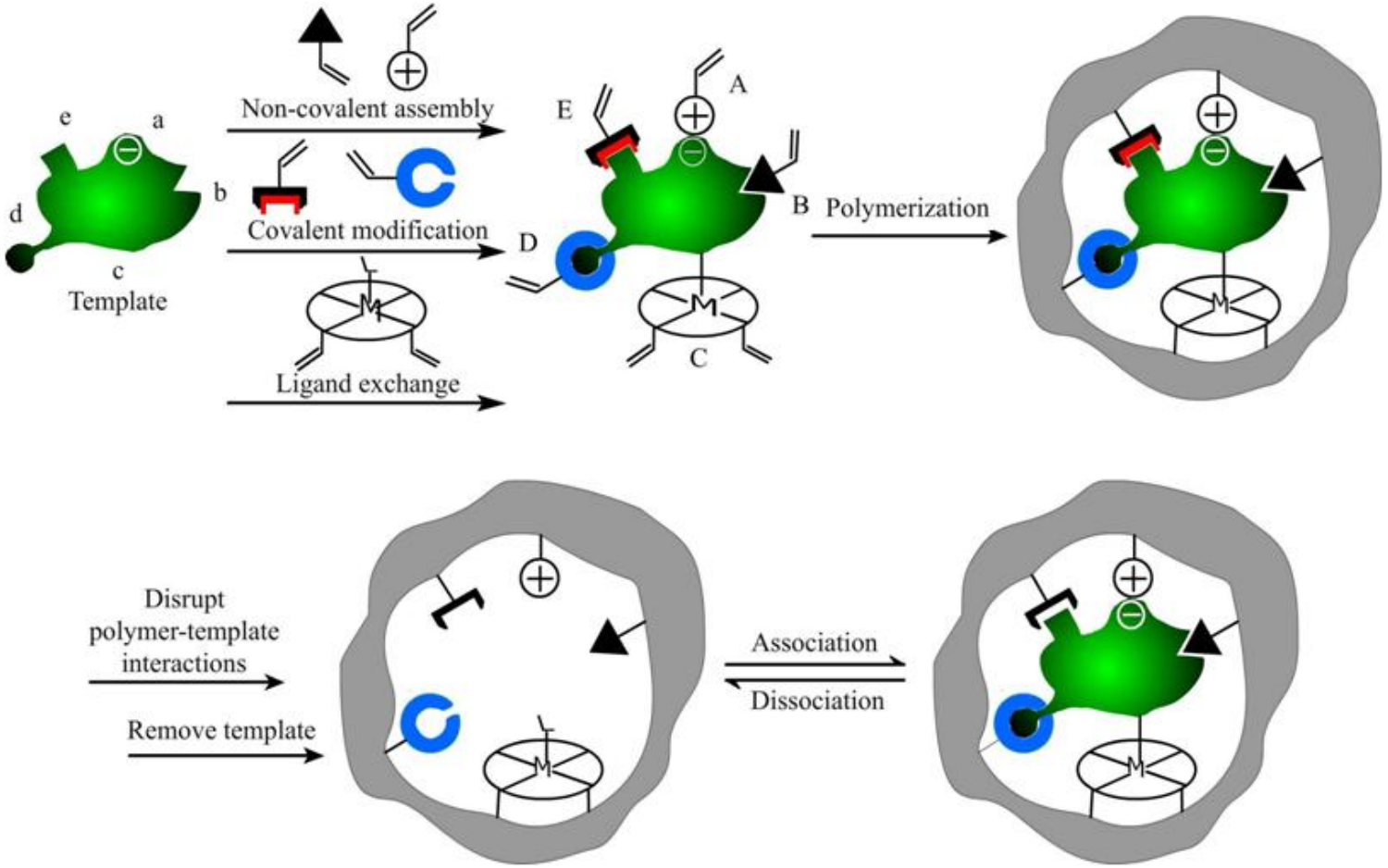


Physical entrapment in the polymer brush

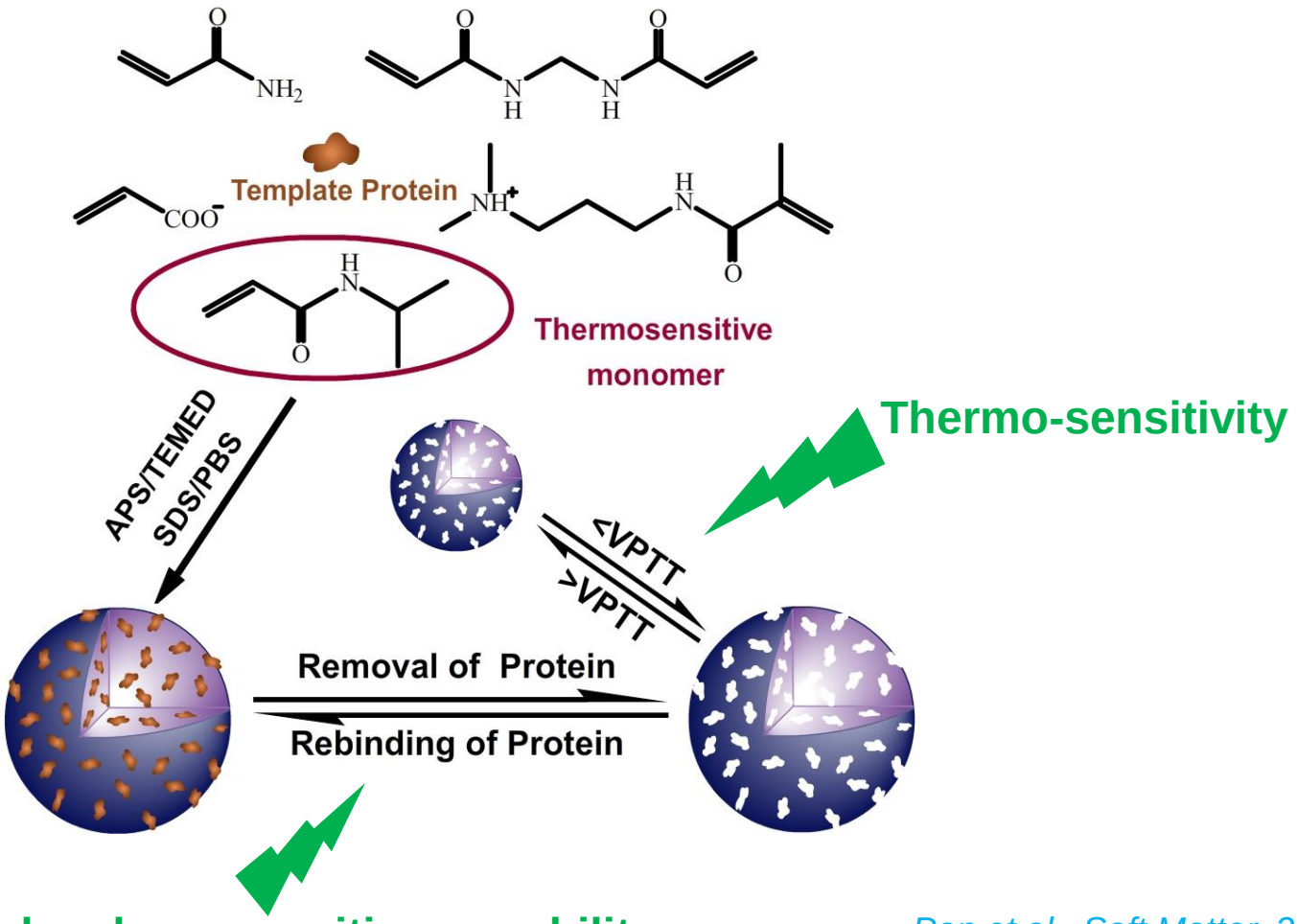
Incorporation into porous coating

Tejero et al., Prog Polym Sci 2014

Molecular imprinting



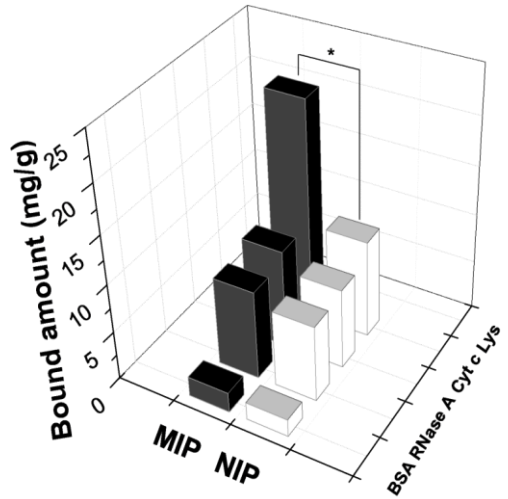
Imprinted nanogels for specific binding and controlled release of proteins

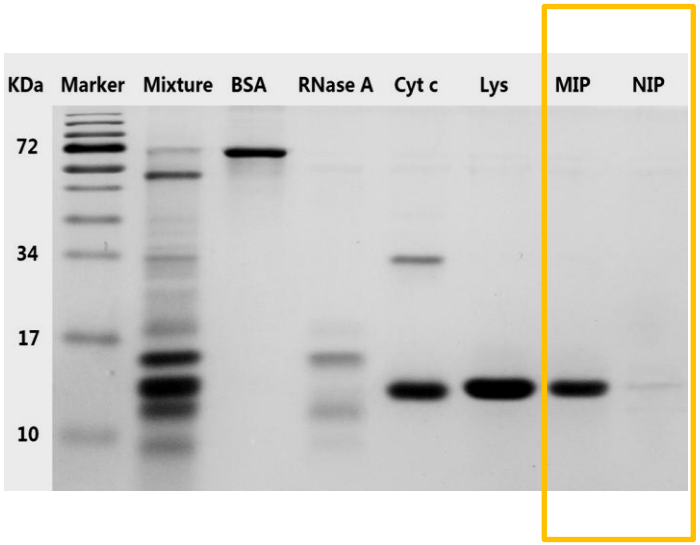


Pan et al., Soft Matter, 2013

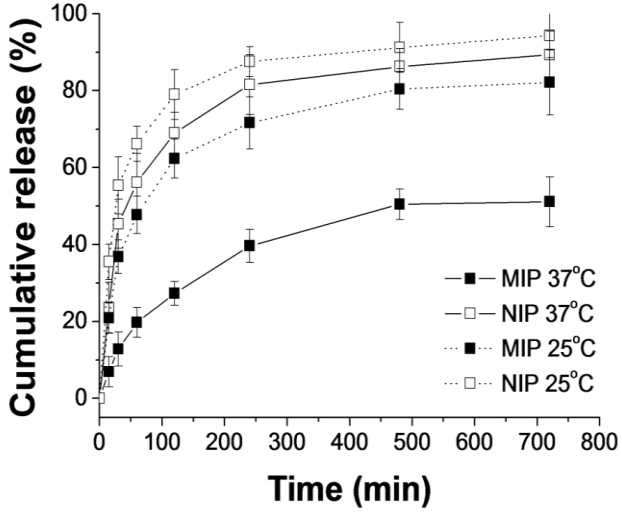
Specific binding and controlled release

Binding



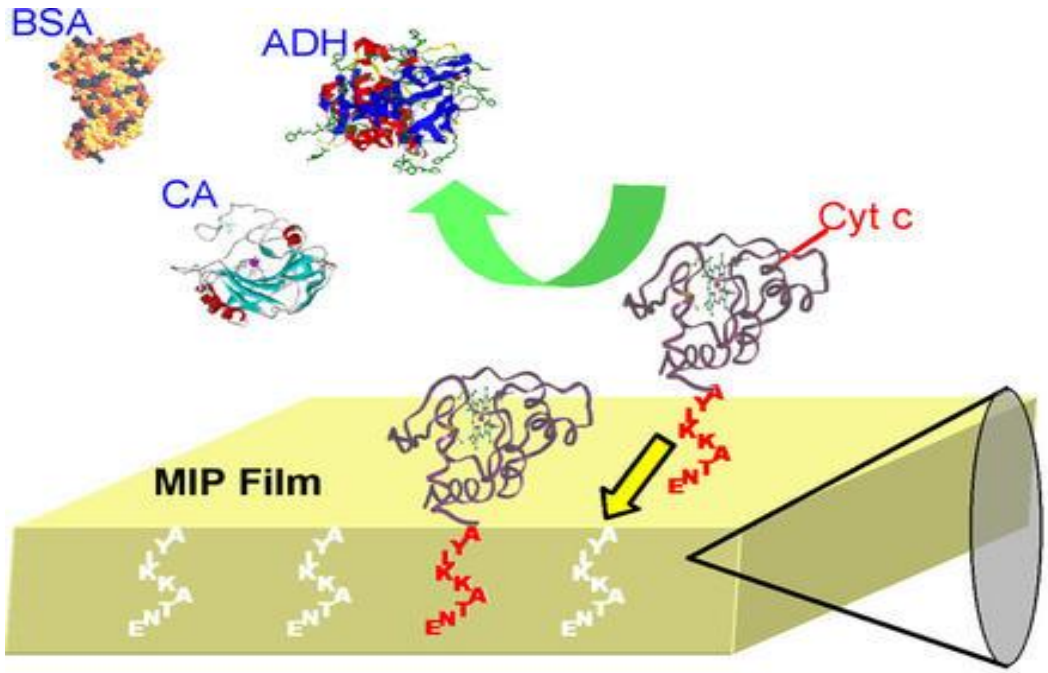


Release

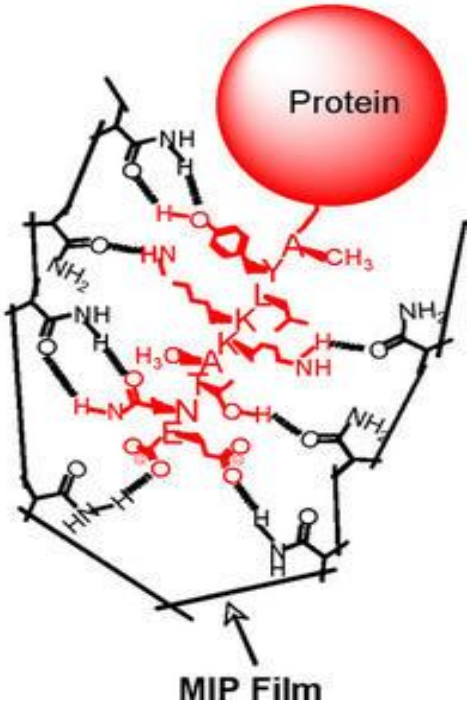


Template protein: lysozyme

Epitope imprinting

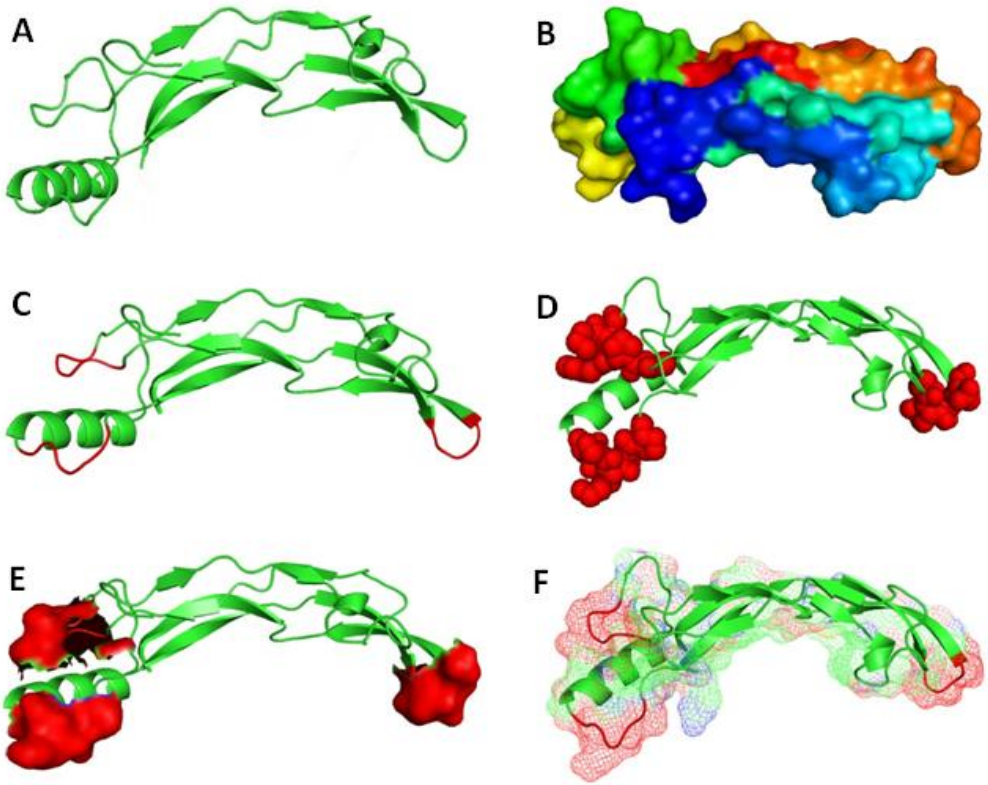


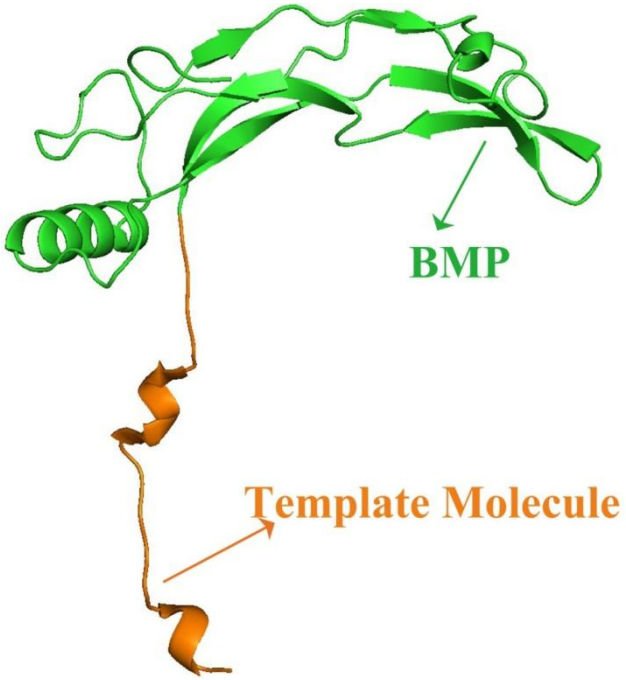
MIP film imprinted with the c-terminus peptide sequence of cytochrome *c* (Cyt *c*) selectively captures Cyt *c* from a solution of 5 proteins.



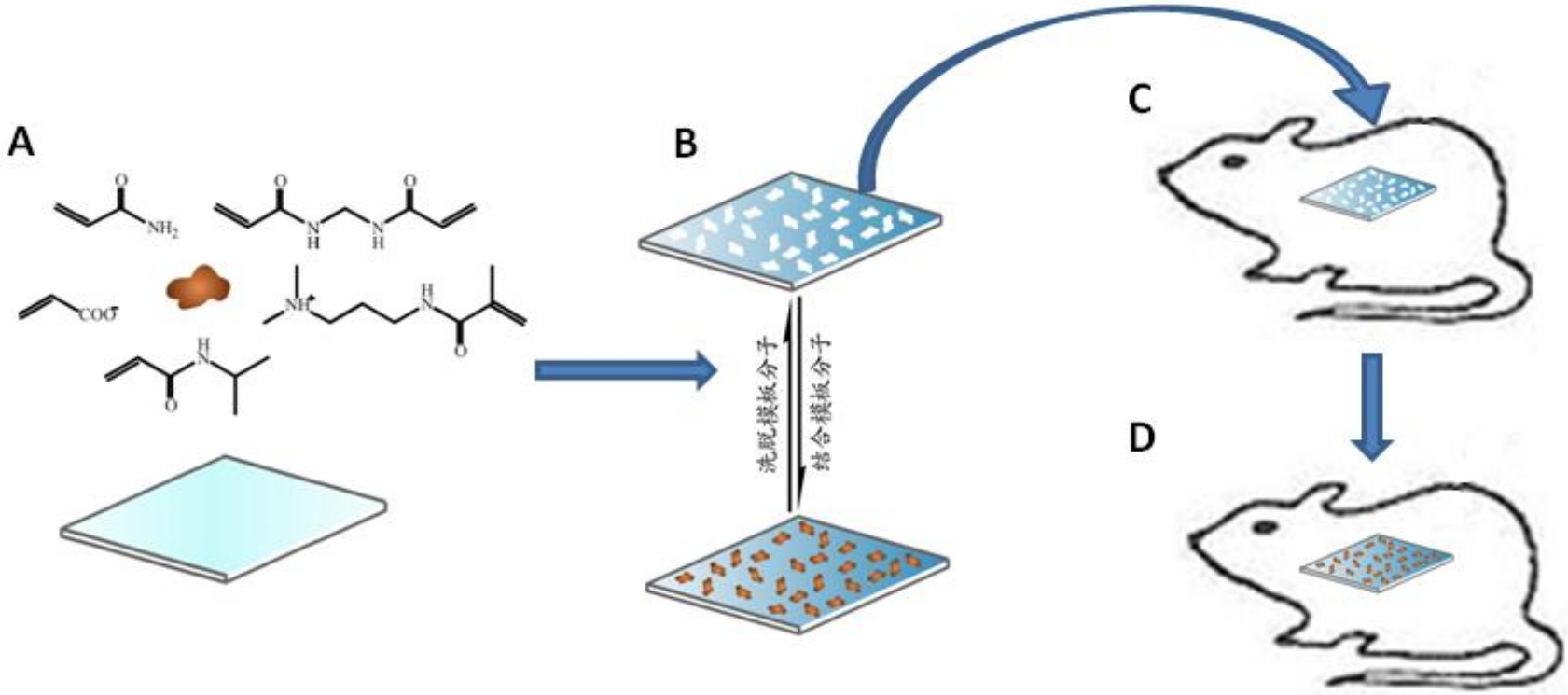
Nishino et al., Angew Chem Int Ed 2006

Epitope imprinting of BMP-2 ?





BMP-2 imprinting for in-situ bone regeneration



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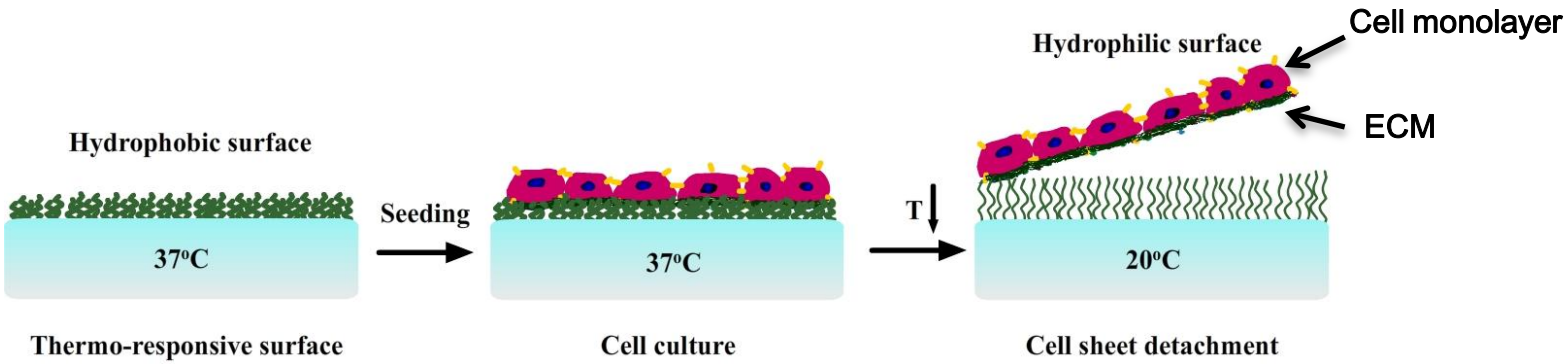
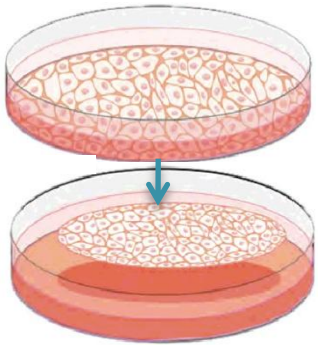
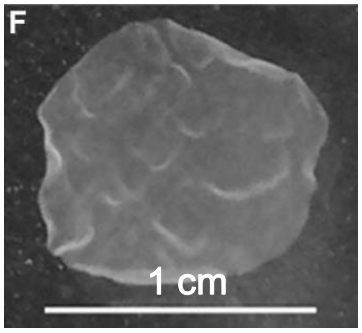
Cell sheet technology



Non-invasive cell sheet detachment

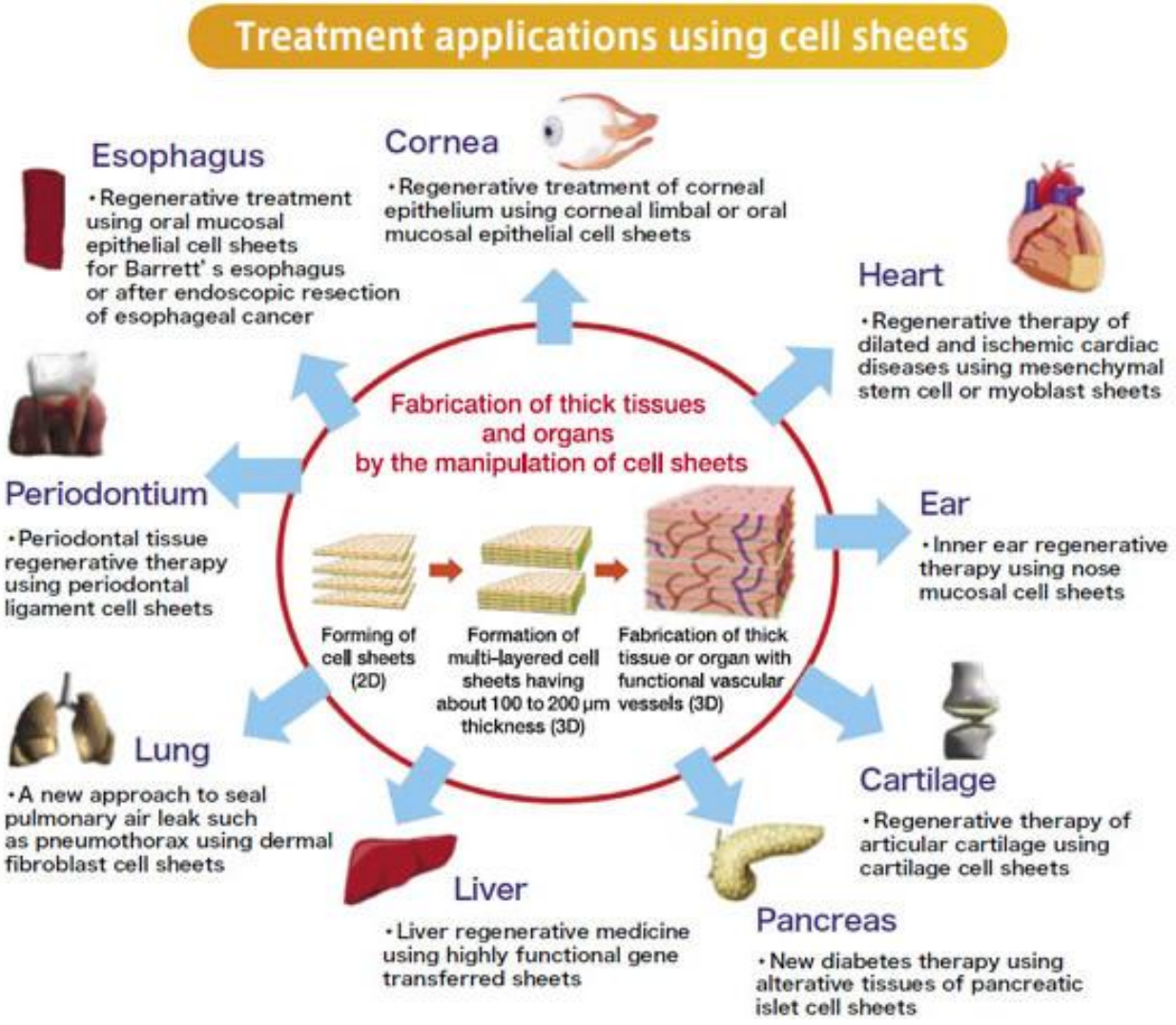




Detached cell sheet

Miyahara et al., Nat. Med. ***2006****; Nakamura et al., Bone* ***2010****; Haraguchi et al., Nat. Protoc.* ***2012***

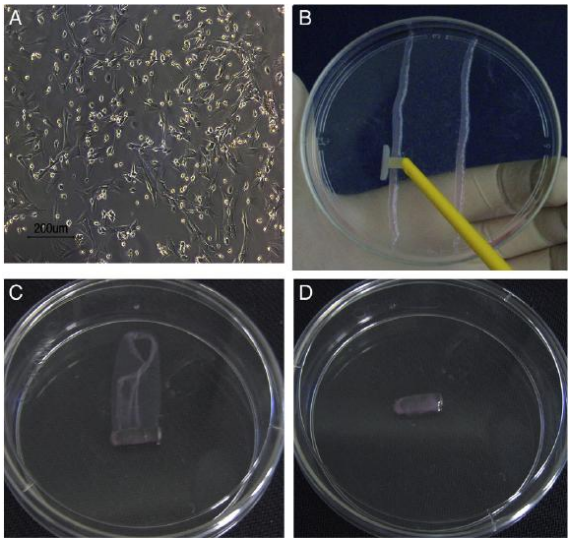
Potential cell sheet therapies

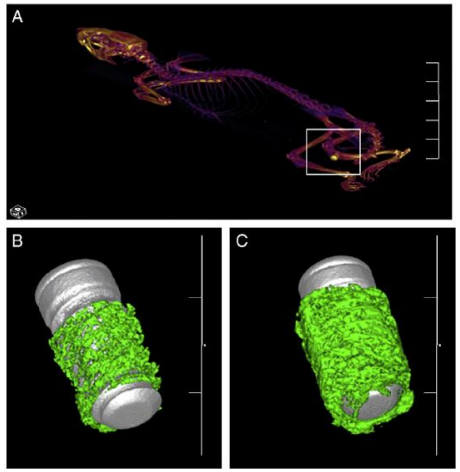


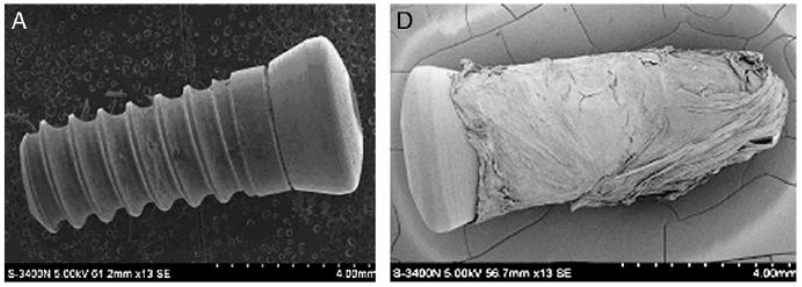
Prof. Teruo Okano

twmu.ac.jp

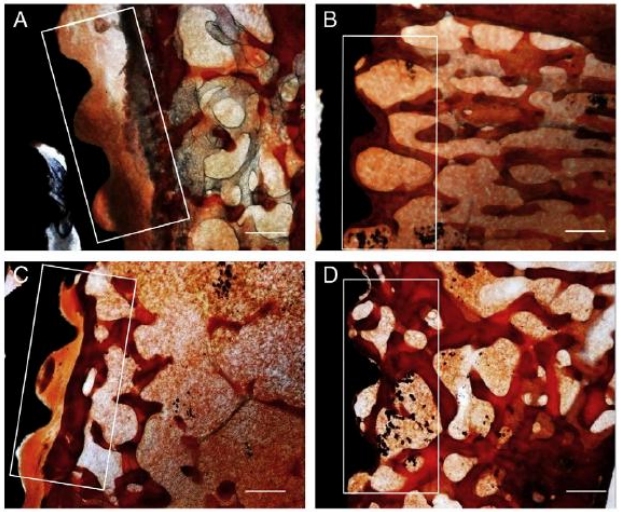
Stem cell sheet wrapping enhanced osseointegration





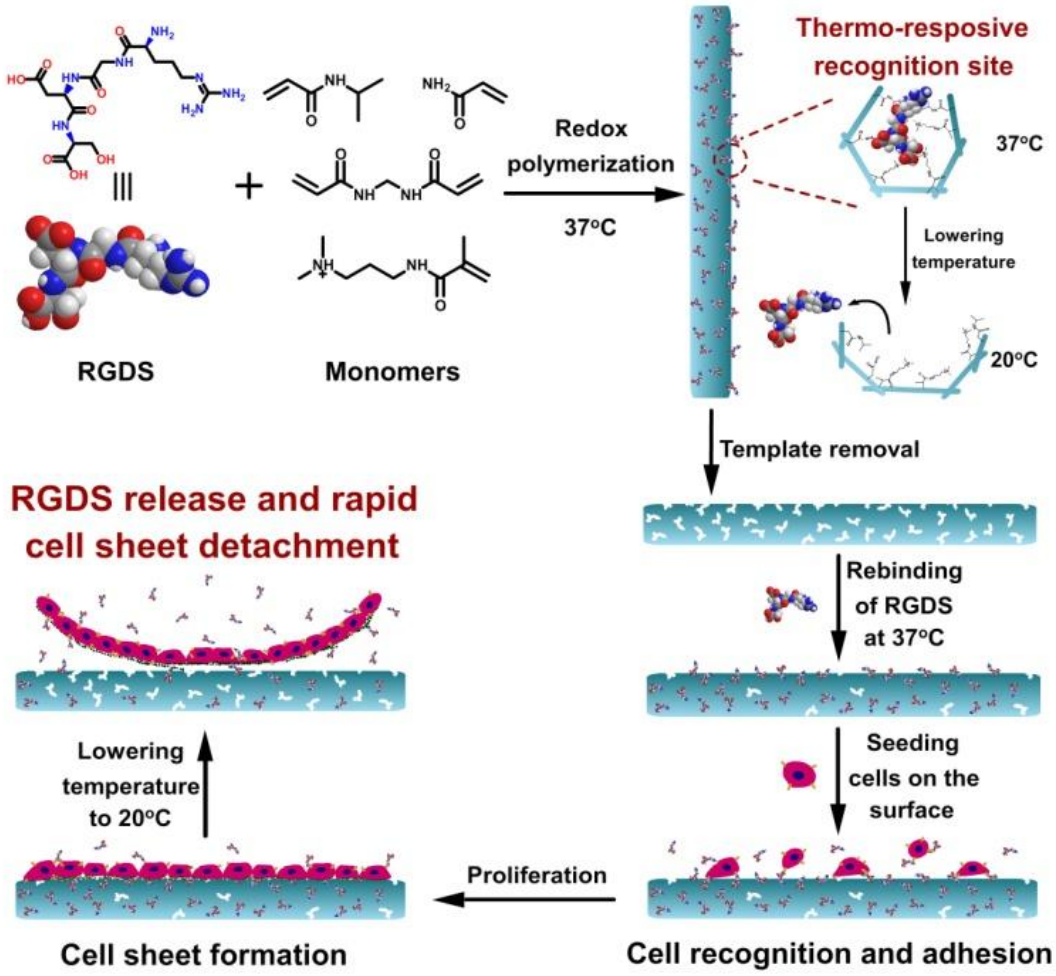


w/o cell sheet with cell sheet



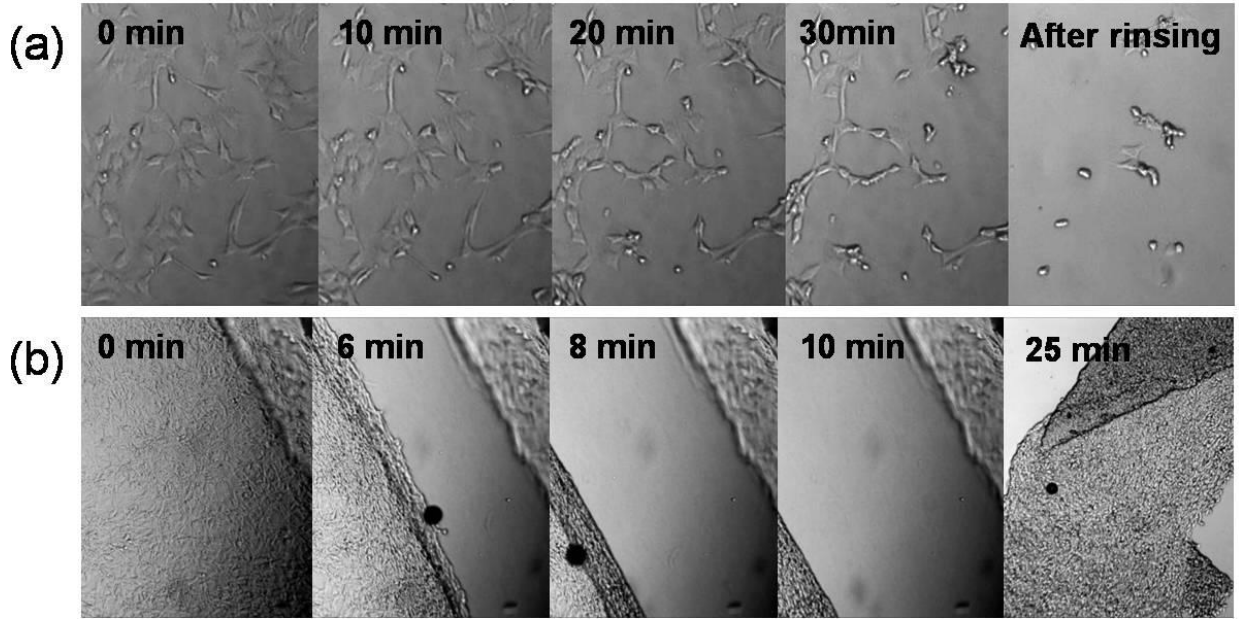
Yu et al., Bone, 2011

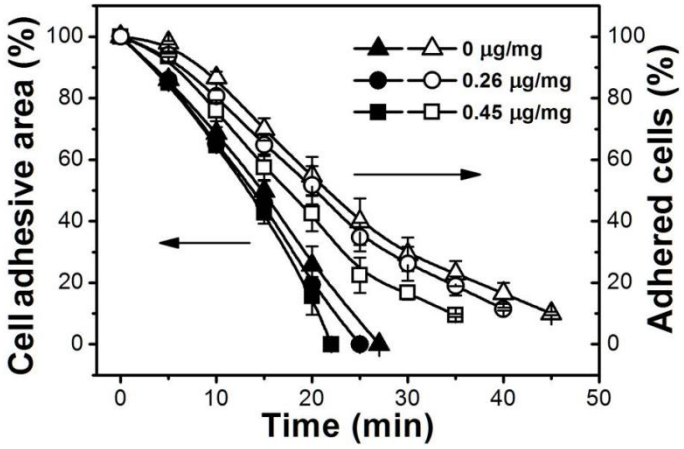
RGDS imprinted thermo-responsive hydrogel for cell sheet harvest

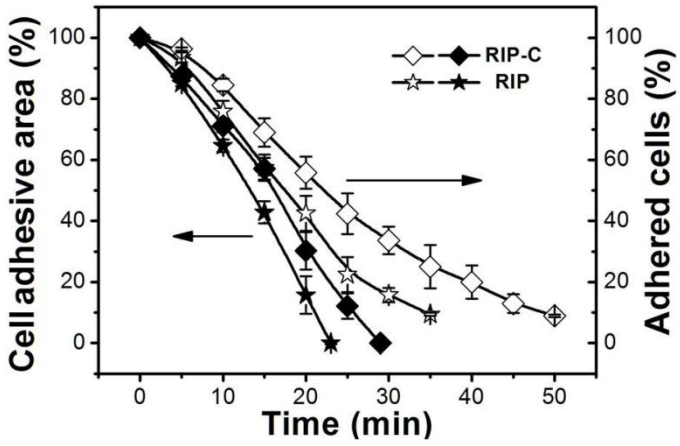


Pan G, et al. ***Angew Chem Int Ed*** 2013

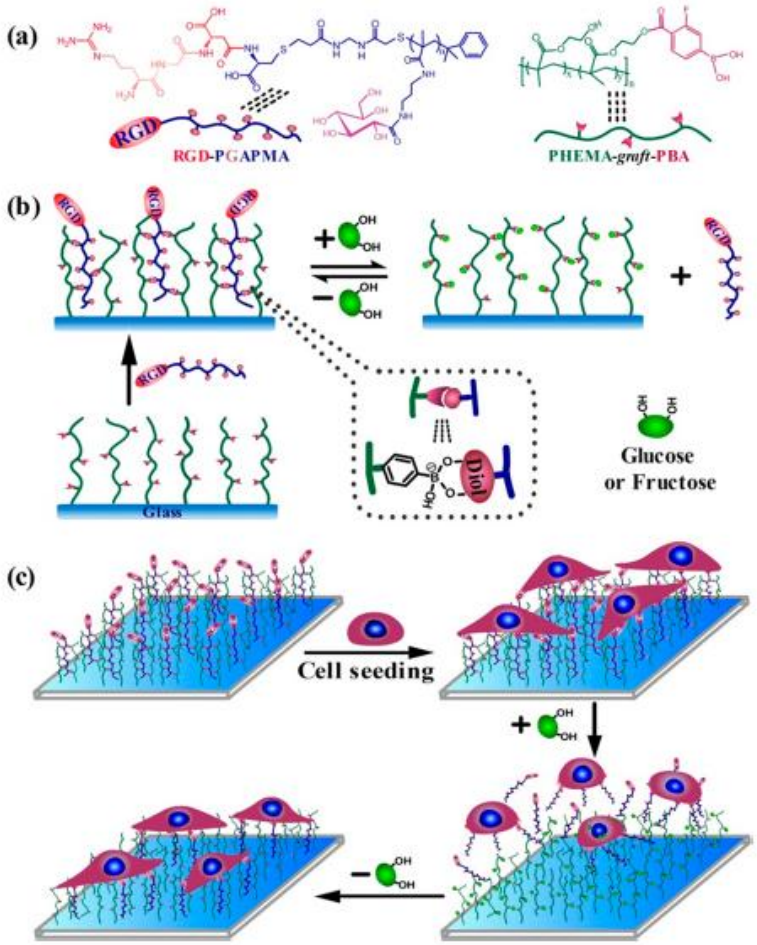
Cell detachment from RGDS-imprinted hydrogels

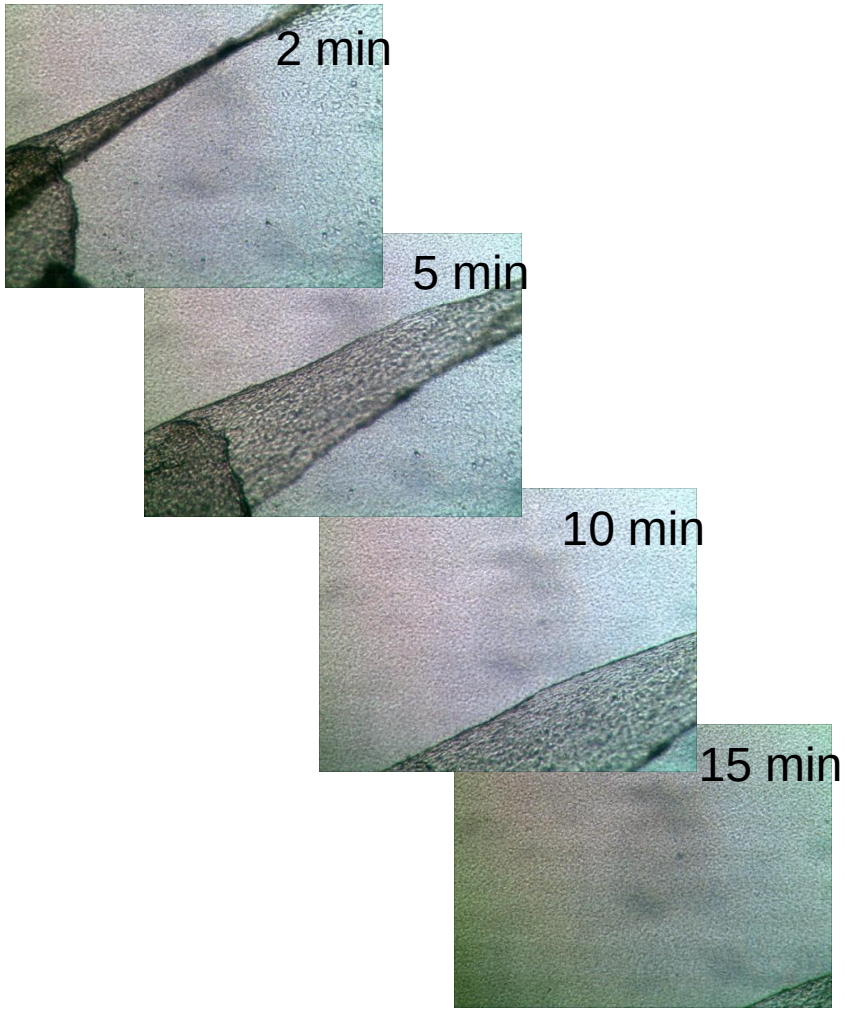






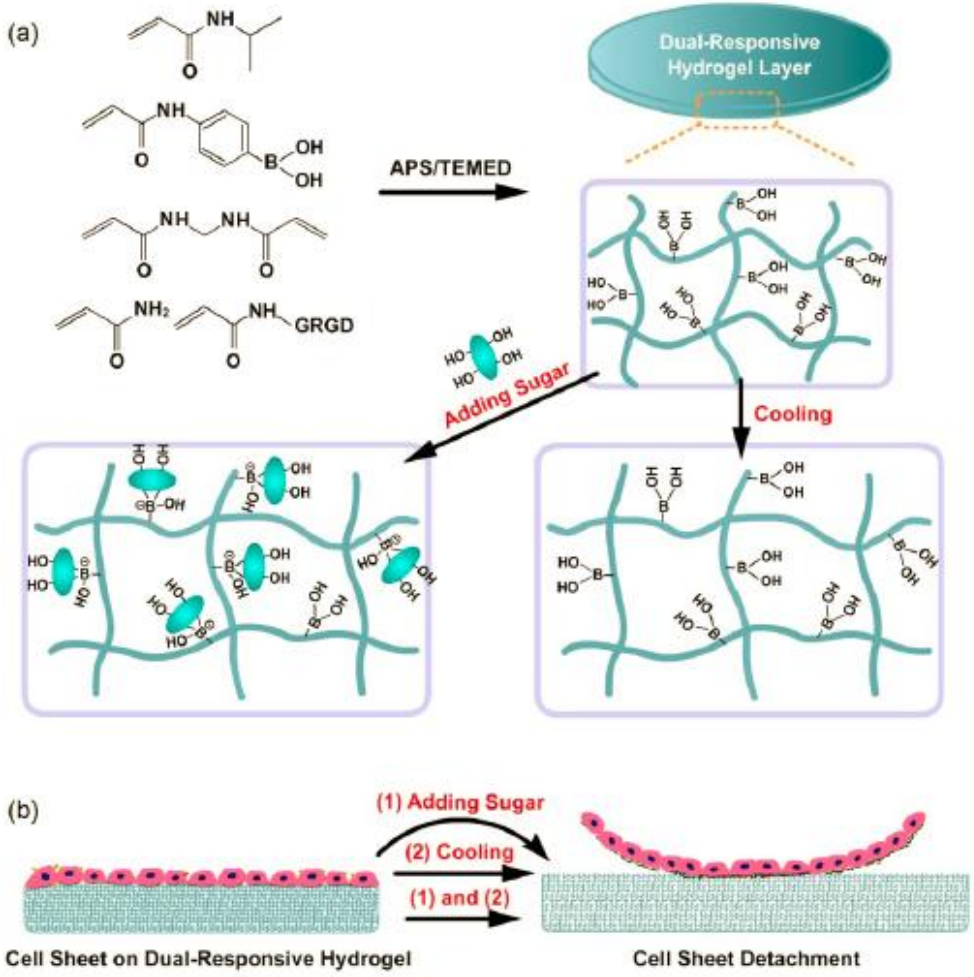
Glucose-sensitive cell adhesive hydrogels for cell sheet harvest

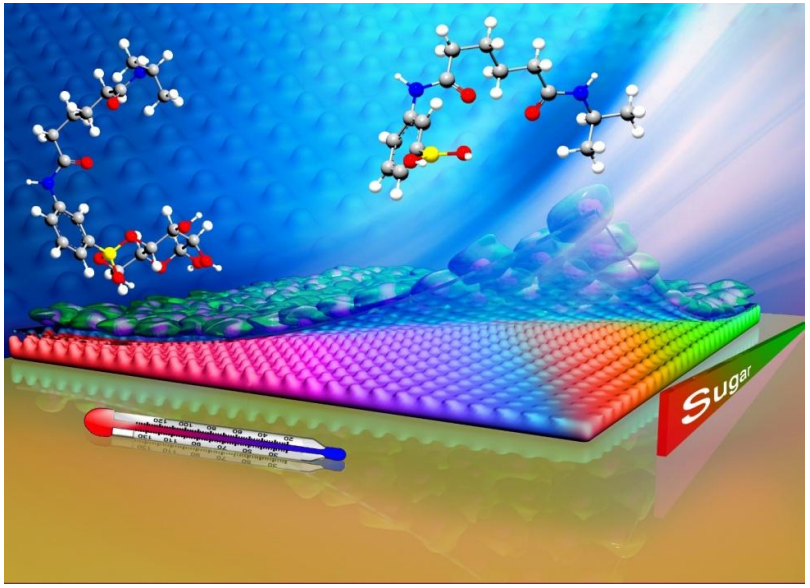




Pan G, et al. ***J Am Chem Soc*** *2014*

Saccharide and temperature dual-responsive hydrogels





Back cover

Guo B, et al. ***Chem Comm*** *2015*

Summary

- Bioactive surface modification of implant materials through chemical binding of bone-stimulating substances promotes bone formation and remodeling.
- Endogenously secreted signaling molecules or growth factors may be locally captured and enriched to promote bone defect repair and osseointegration.
- Harnessing the surface features of implants enables effective manipulation of their biological functions and should be given full consideration in implant design.

Acknowledgment

- National Natural Science Foundation of China (81171479, 81471790)
- NSF of Jiangsu Province (BK2011291)
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- Soochow University-Ideal R&D Center for Medical Devices

Thank you!