Lecture #13: Controlled Release Drug Delivery

Administration Routes

- Oral
  - released drug is absorbed in small intestine
  - phagocytosis of delivery vehicles (dia. < 10µm) in small intestine via M-cells (lymphatic tissue) of Peyer's patches
    - Advantages:
      - patient acceptance
      - convenient
    - Issues:
      - poor uptake
      - rapidly metabolized
      - chemical instability in GI tract

Administration Routes

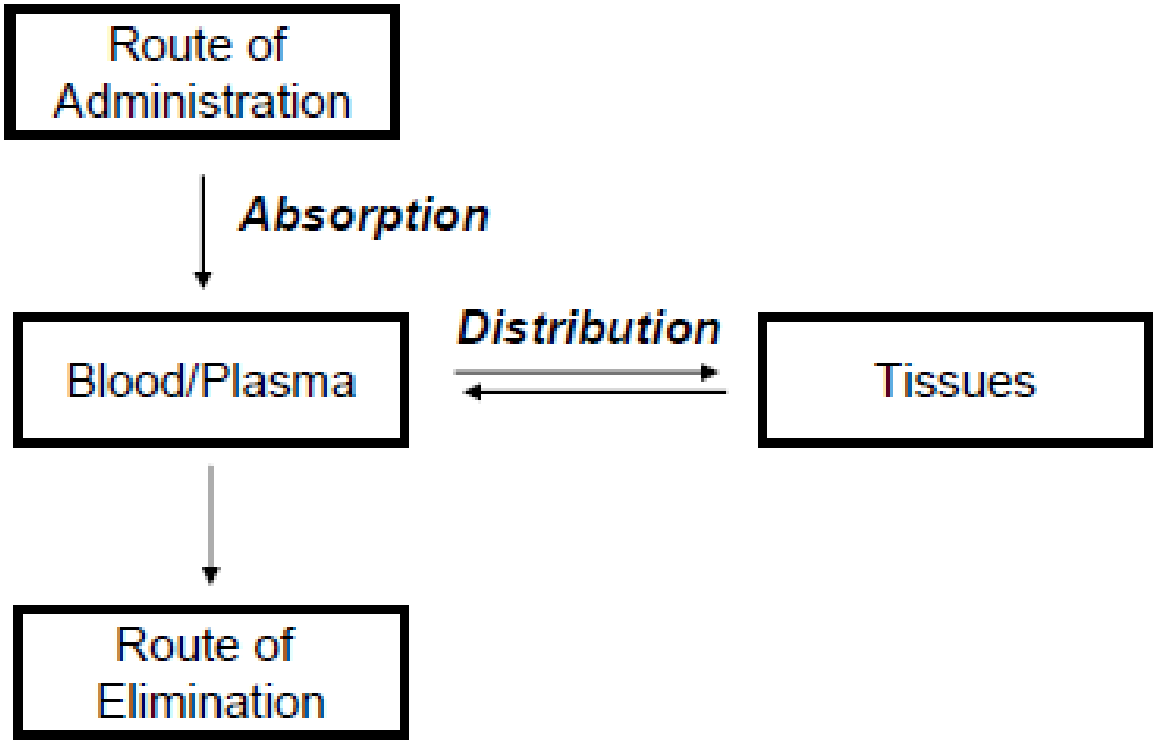
- Subcutaneous injection
  - phagocytosis, deposition in lymph nodes (dia. < 10µm)
  - particles collect at injection site (dia. > 30µm)
    - Advantages:
      - patient can administer
      - does not require digestion (nauseated patients)
    - Issues:
      - poor distribution to target
      - local tissue irritation/toxicity

Administration Routes

- Intravenous administration
  - systemic circulation for dia. < 4 μm (smallest capillary)
  - interaction with reticular endothelial system (RES)
    phagocytosis in liver, spleen, lungs, lymph nodes

    - Advantages:
      - effective systemic treatment
      - does not require digestion
    - Issues:
      - short circulation times
      - low penetration of endothelial lining of vasculature (requires dia. < 5nm)

Uptake and Distribution



Routes of administration

(1) Enteral -
- oral
- sublingual
- rectal

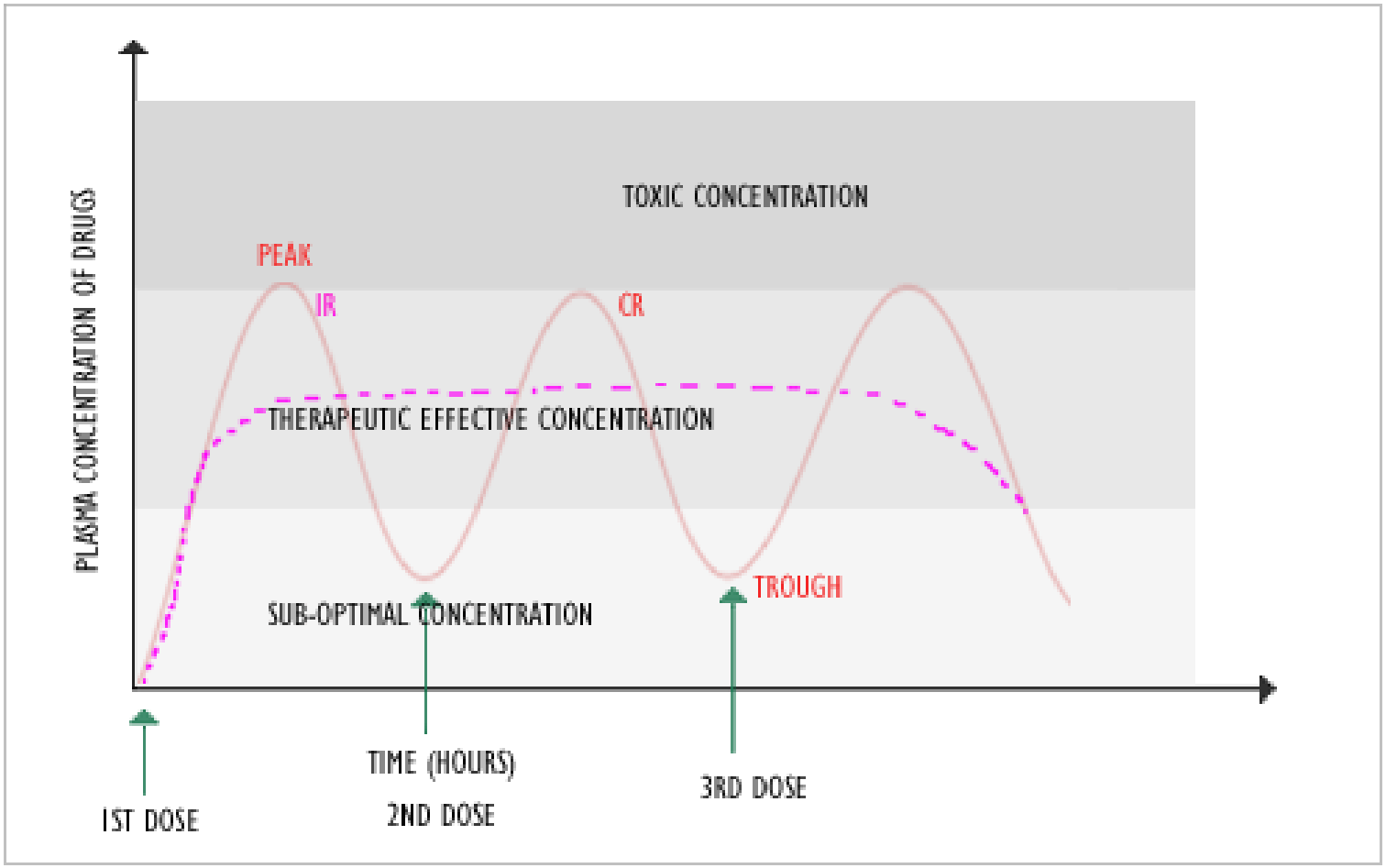
(2) Parenteral -
- intravenous (iv)
- intramuscular (im)
- subcutaneous (sc)

(3) Other -
- inhalation
- topical
- transdermal

Regranex

REGRANEX
GEL
0.01%
(becaplermin)
NET WT. 15g
Multi-dose tube
MILNER
PHARMACEUTICAL

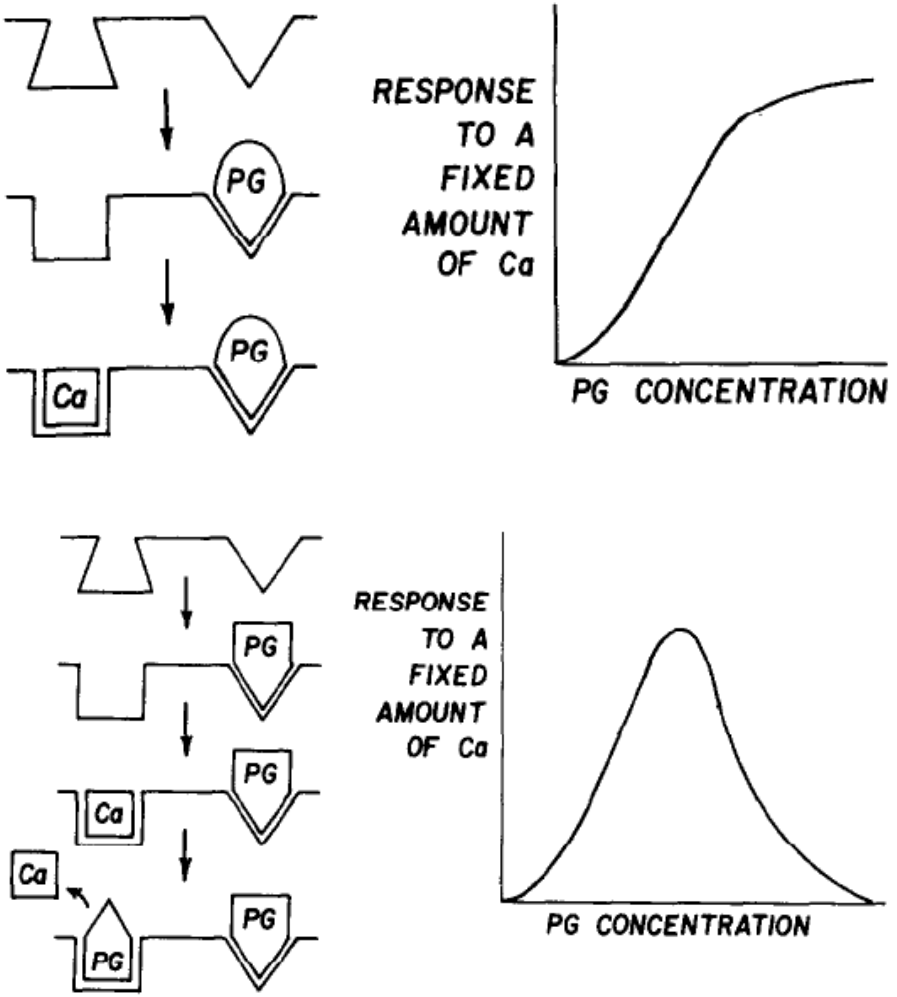
Controlled Release



Goal: Maintain effective concentration, prevent toxic doses

Dose Response

- Sigmoidal curve
- Degree of response to different doses of chemical can follow a normal distribution (Gaussian distribution)
  - Bell-shaped probability distribution:



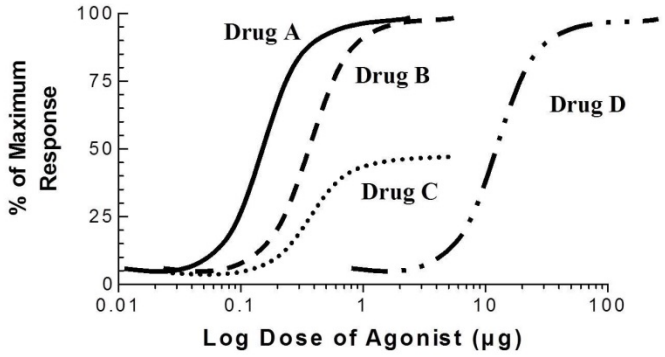
Horrobin

Dosing Metrics

- **Effective dose(ED)**
- **Toxic dose(TD)**
- **Lethal dose(LD)**
- **Therapeutic Index (TI)**

- **Relative safety of the drug:** Comparison of the effective dose and the toxic or lethal dose
  - Ratio of lethal or toxic dose to (therapeutically) effective dose
    - The larger the ratio, the greater the relative safety
  - Most commonly used index is the median dose,
    - ie the dose required to elicit response in 50% of a population
    - Note: the median does not give information about the slope of the dose-response curve
- **TI = LD_{50}/ ED_{50}**

- **Comparison of toxic effects: Potency and efficacy**
  - **Potency**
    - Range of doses over which a chemical produces increasing responses
  - **Efficacy**
    - Limit / plateau of dose-response curve on the response axis



Two Drugs

- **Drug 1 (e.g. digitoxin), TI= 2**
- **Drug 2 (e.g. diphenhydramine), TI=2,000**

- **For which drug does the release kinetics matter more?**

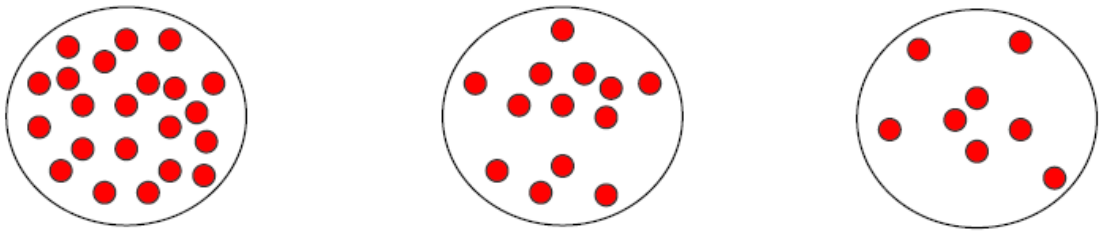
Diffusion Controlled Devices
Matrix Systems

Matrix Systems

- Drug can be dissolved or dispersed as solid particles
- Drug is released by diffusion out of a polymer matrix. Release rate depends on initial drug concentration (Rate control by choice of matrix: glassy matrix: D~10^{-10}-10^{-12} cm^2/s, rubbery matrix: D ~ 10^{-6}-10^{-7} cm^2/s)

$$M = S[D\ C_s(2A - C_s)t]^{1/2}$$

M=total amount of drug released, S=surface area available for drug delivery, D=diffusion coeff, C^s = solubility of the drug in polymer matrix, A= total drug concentration (dissolved drug + dispersed drug)



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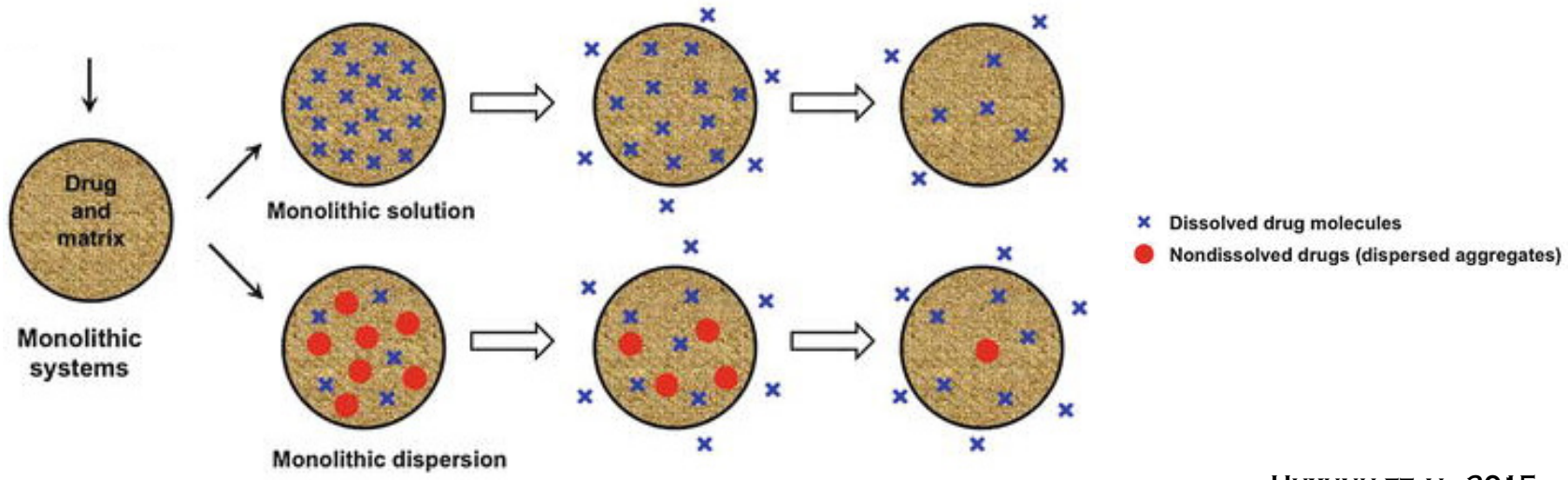


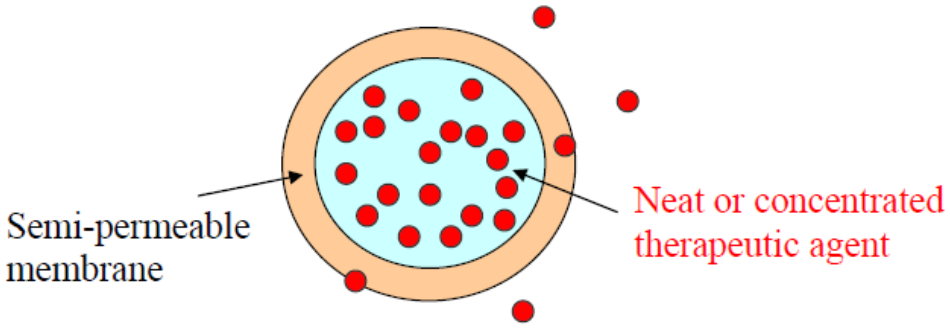
Huyunh et al. 2015.

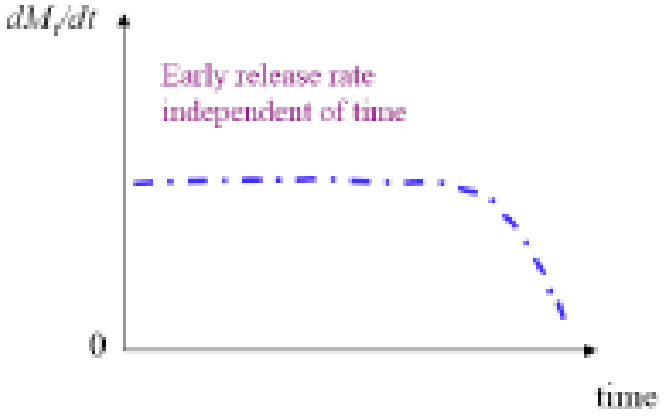
Reservoir Systems

- Drug release is controlled by a semi-permeable membrane
- Diffusion through membrane limits the release rate
  - advantage: *Constant release rate.*

$$M = SDK\frac{\Delta C}{h}\left(t + \frac{h^2}{3D}\right)$$

M=total amount of drug released, S=surface area available for drug delivery, D=diffusion coeff, K = membrane "partition" coefficient (unitless metric of drug solubility in membrane), h=thickness of membrane, ΔC=concentration difference





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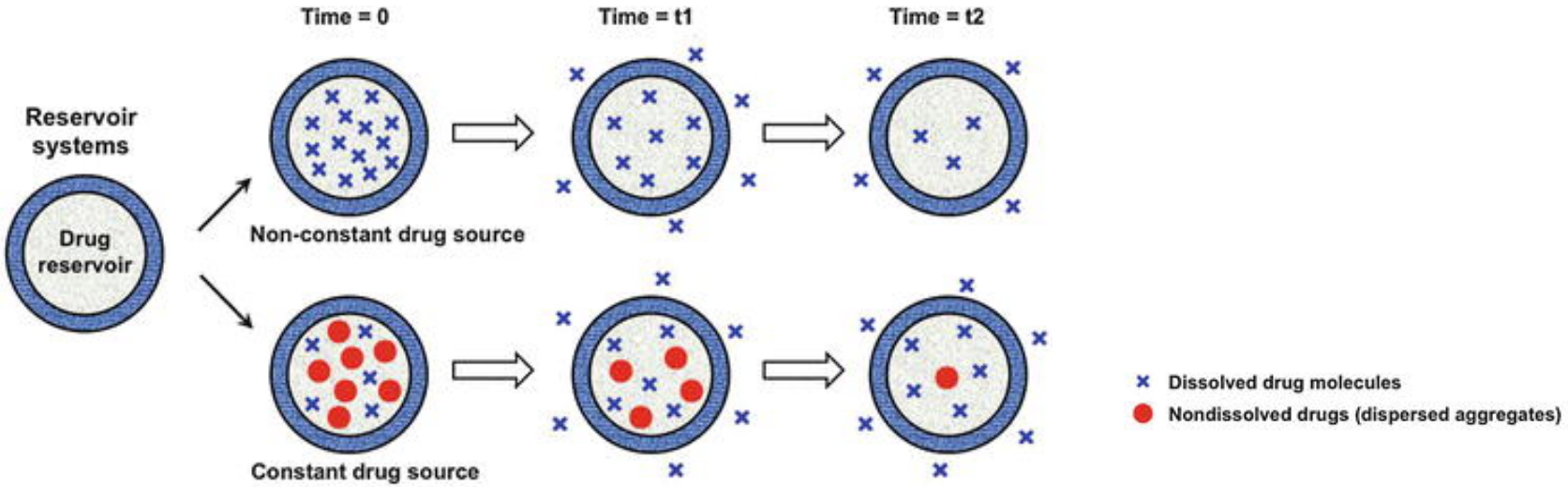


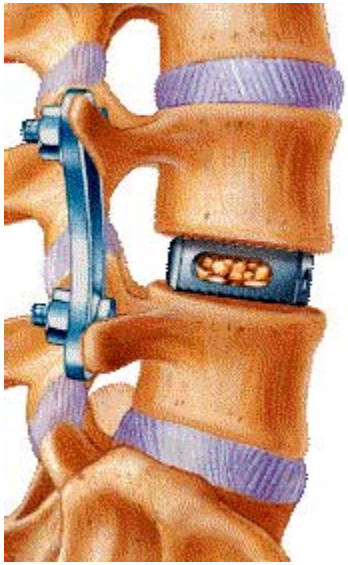
Huyunh et al. 2015.

Release Strategies in Tissue Engineering

Bioactive Proteins

- Hydrophilic and water soluble
- Large (molecular weight 5 to 2,000 kDa)
- Ex. BMP, TGF-β, VEGF, PDGF, FGF, fibronectin, laminin
- In contrast, traditional drugs are small molecules that can be hydrophobic

Application: Spinal Fusion Cage

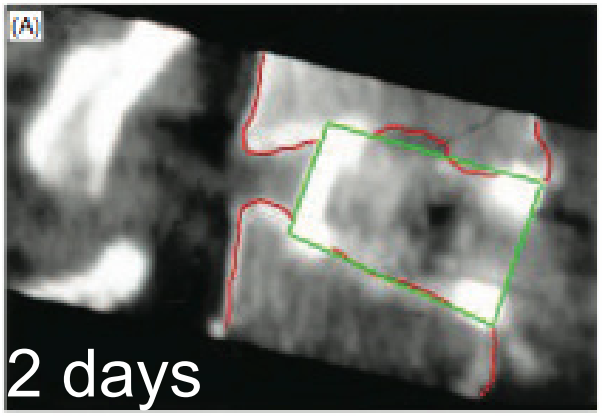


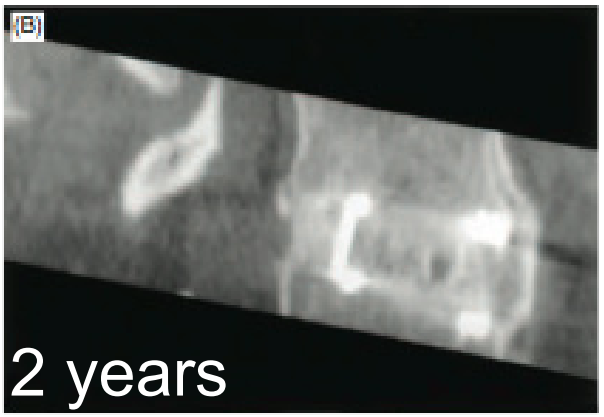
Disc degeneration

Post-operative X-Rays showing cage placement

BMP-2 in Collagen

- INFUSE (US) and InductOS (Europe)
- Delivered within spinal fusion cage (intervertebral disc removed and bone fusion is desired)
- BMP is present for at least 2 weeks



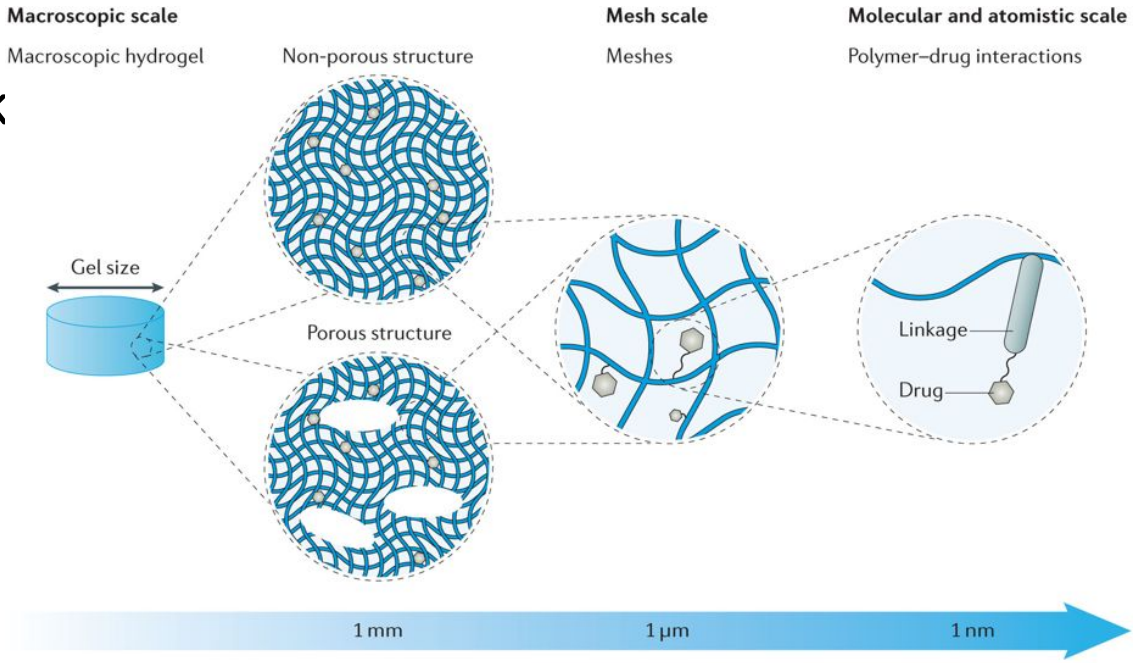


Physical Mixtures Without Entrapment

- Mix growth factors with collagen, gelatin, fibrin, etc.
- Hydrophilic hydrogel
- Pore size is too large to trap proteins, but weak affinity slows down release

Entrapment Within Hydrogel Matrices

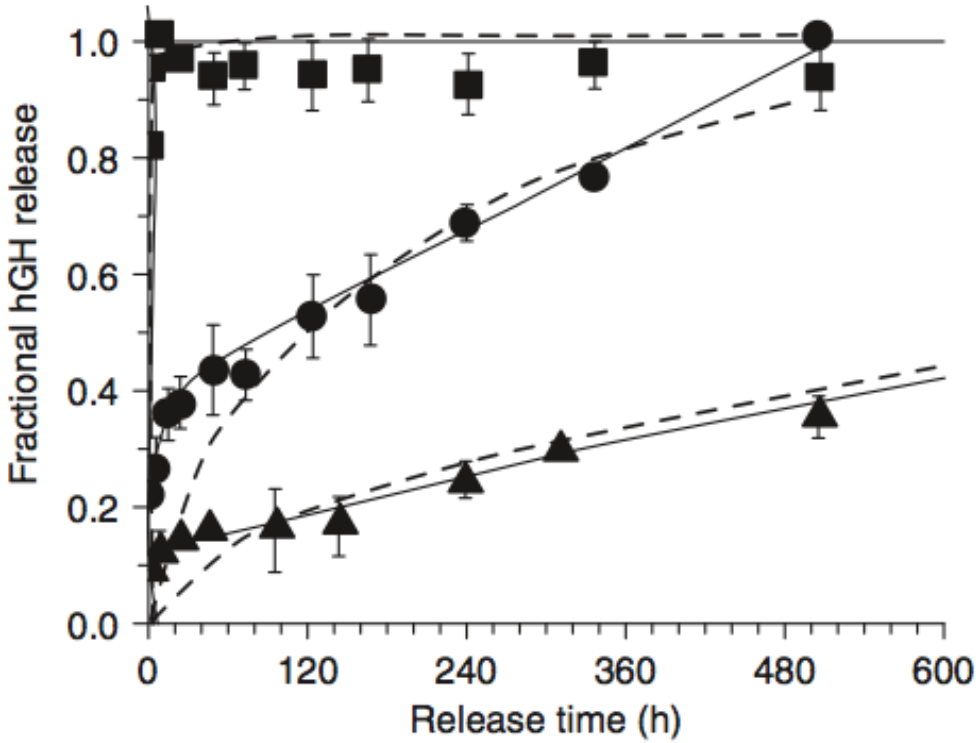
- Water-soluble molecules cross-linked for 3D network
- Proteins entrapped when distance between crosslinks is comparable to protein diameter



Nature Reviews | Materials

Li et al. 2016.

Chain Length Determines Release Characteristics



Release of HGH from 2-kDa PEG gel,10-kDa PEG gel, and 50/50 mixture of the two PEGs

Squares = 10kDa; Triangles = 2kDa, Circles = 50/50 mixture

Extending Delivery Time: Protein Solubility

- Non-glycosylated BMP-2 is less water-soluble
- Results in slower release profile
- Recombinant BMP-2 is non-glycosylated, in contrast to normal mammalian-cell BMP

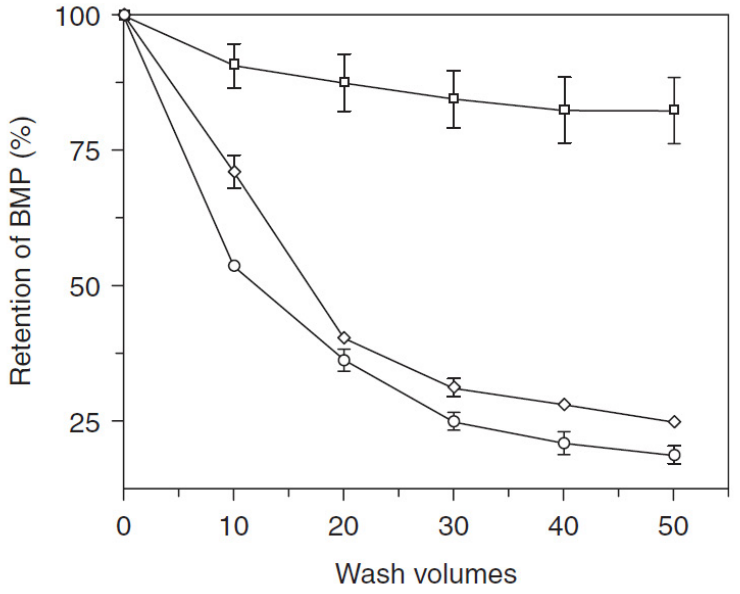


Figure 15.4 Nonglycosylated BMP-2 (produced in bacteria) demonstrates much less solubility than glycosylated BMP-2 (e.g. native or produced in mammalian cells). This limited solubility has been used to prolong release of protein from fibrin surgical matrices. Release *in vitro* is shown. Release of the nonglycosylated BMP-2 (squares) is very slow compared to release of the glycosylated protein (diamonds). When the nonglycosylated protein was complexed with heparin (circles), its release was accelerated and became as fast as the glycosylated protein.

Non-glycosylated BMP-2 in Fibrin

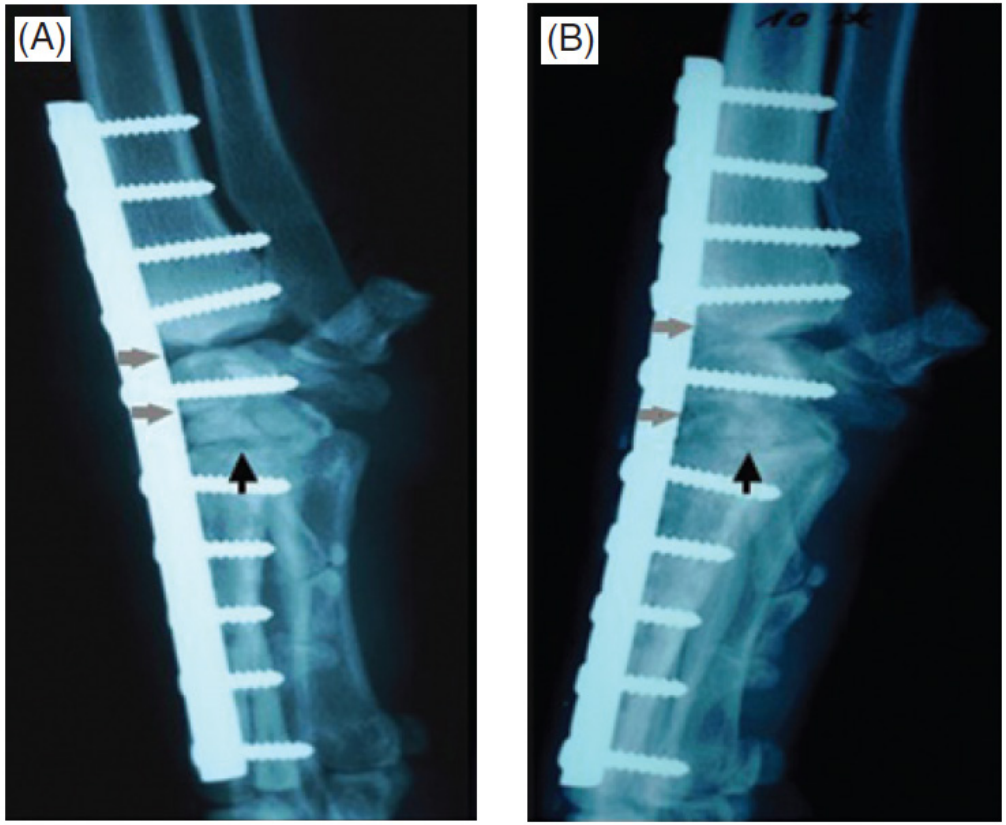
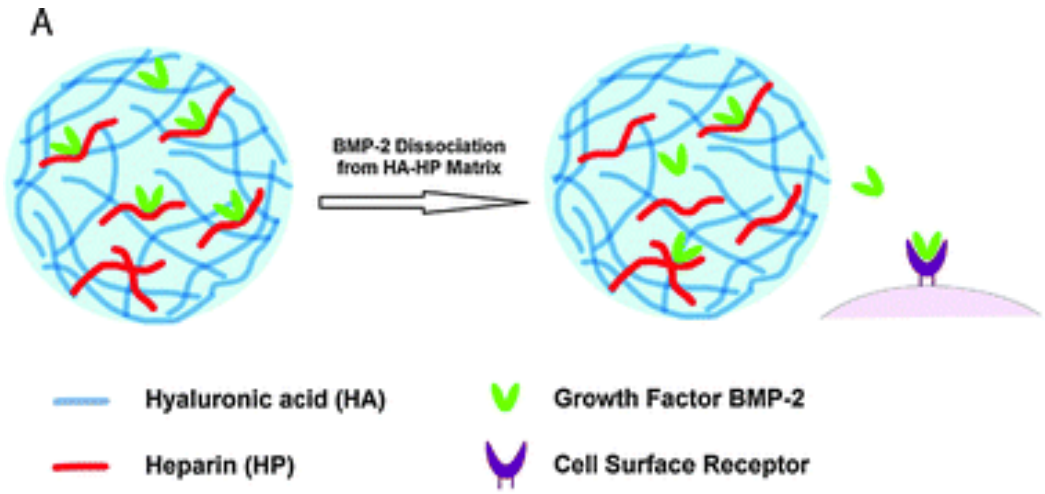
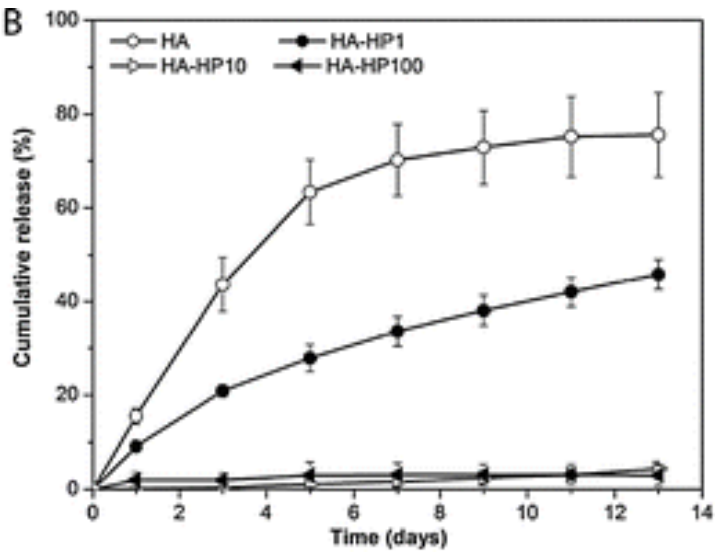


Figure 15.5 Nonglycosylated BMP-2 was used in fibrin surgical matrices to fuse the carpal joint complex in canine patients in pancarpal arthrodesis procedures.

Extending Delivery Time: Matrix Binding

- Most growth factors bind to heparin, a GAG protein
- Heparin can be linked to scaffold matrix to increase GF retention





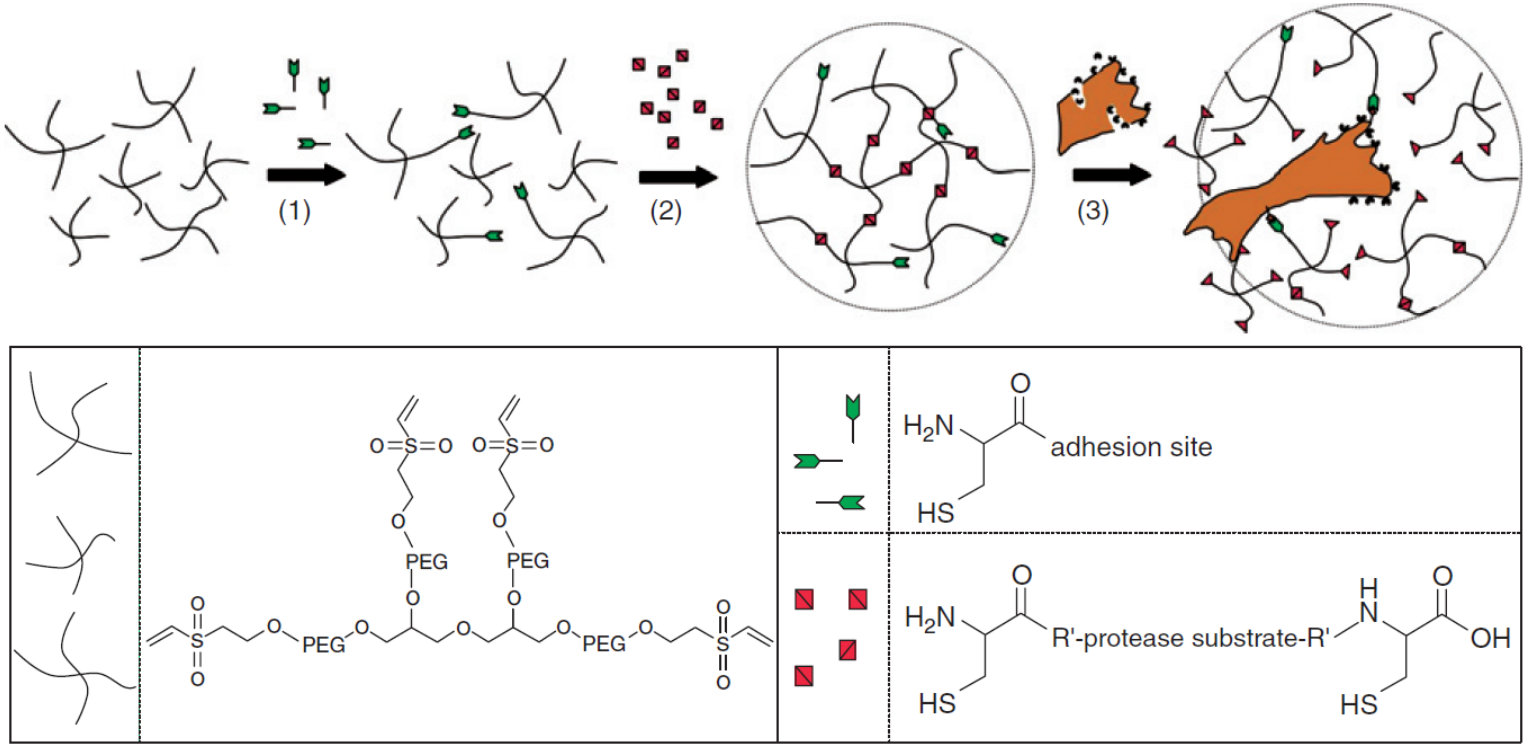
Xu et al. 2011.

Environmentally Responsive Hydrogels

- Hydrogels that exhibit swelling changes due to the external

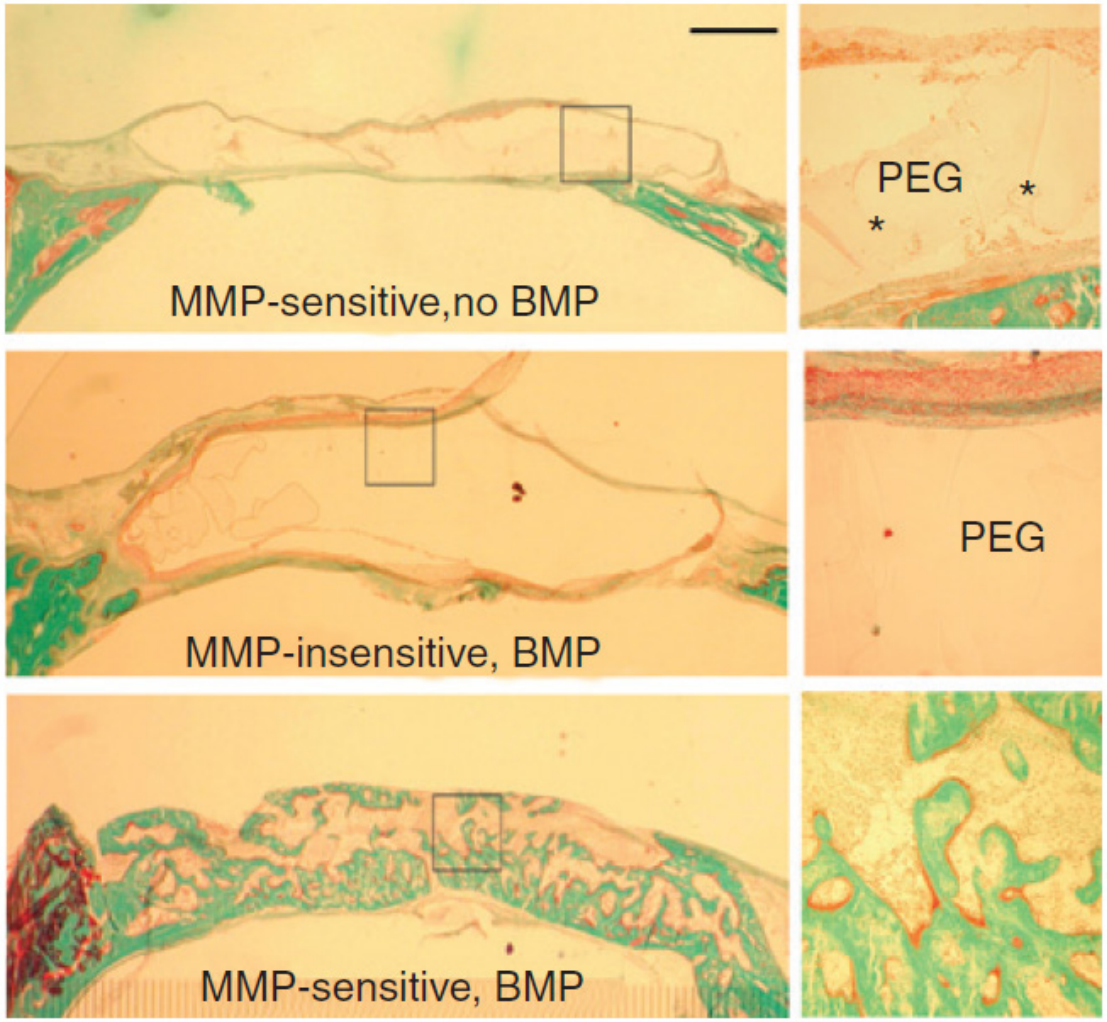
  - pH
  - Temperature
  - Ionic Concentration

Enzyme Responsive Hydrogels



Lutolf, 2003

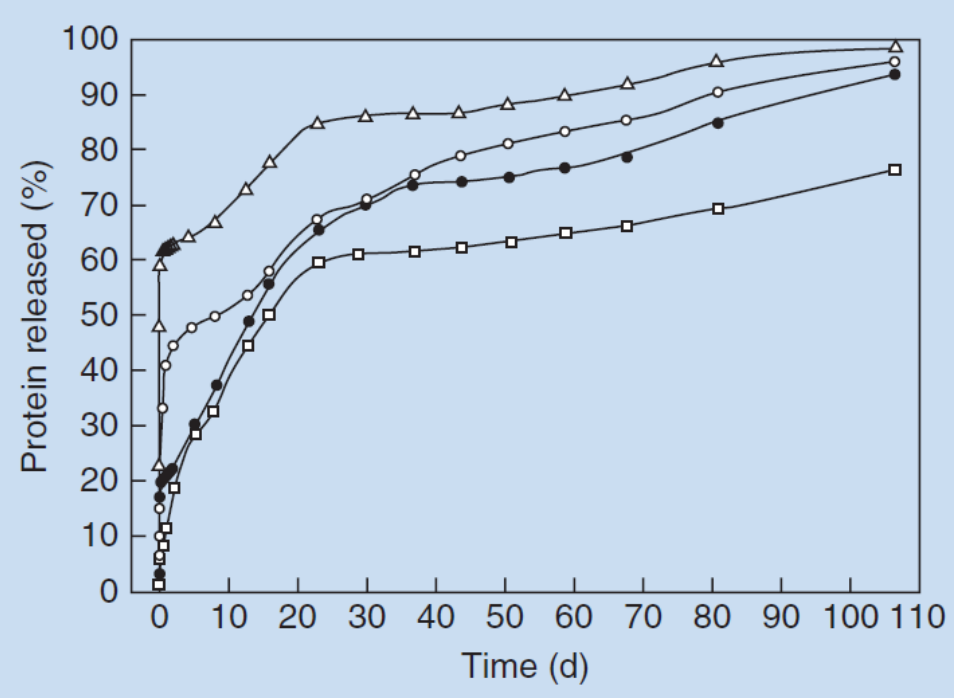
Enzyme Responsive Hydrogels



Lutolf, 2003

Protein Release From Hydrophobic Polymers

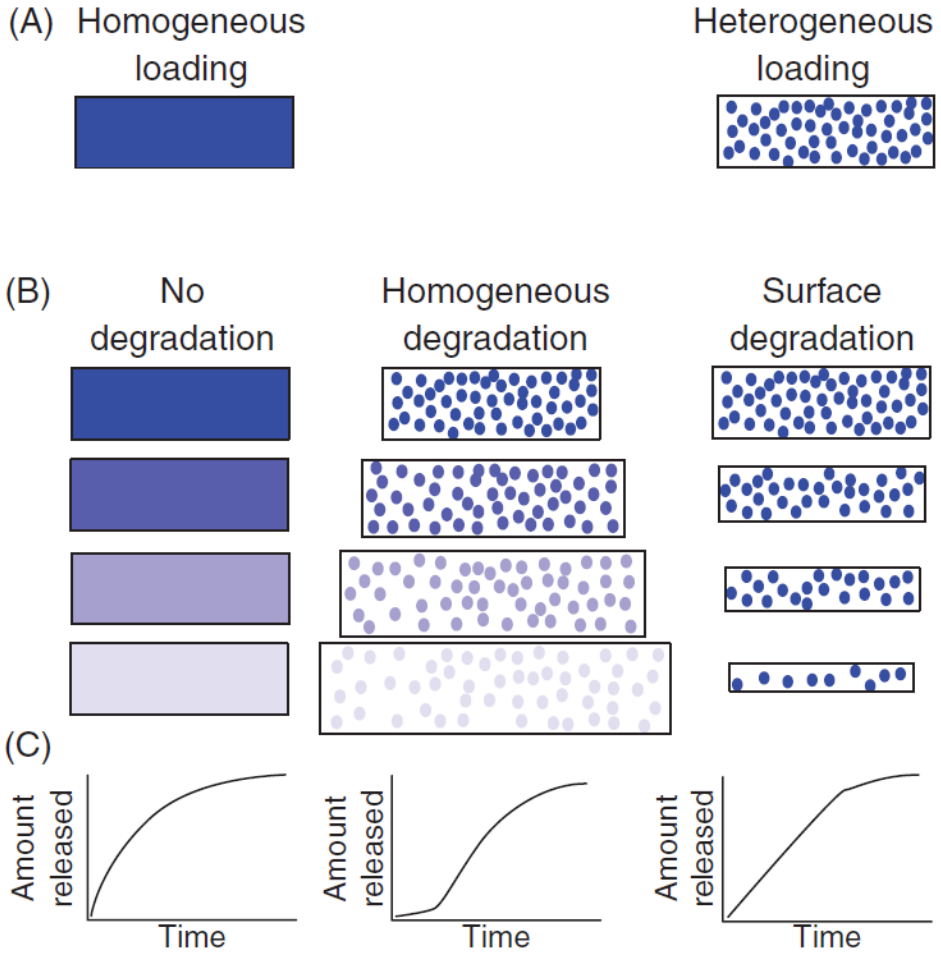
- Until 1976, most focused on release of hydrophobic drugs from hydrophobic polymers
- Dissolved protein in organic solvent will usually denature, BUT solid protein particles in organic solvent do not denature
- Mix protein particles into organic solution of hydrophobic polymer and evaporate solvent to form polymer
- Particle density should be great enough for interconnected pores



First release of protein from degradable hydrophobic polymer

Modes of Release From Degradable Polymer

- Proteins are insoluble in hydrophobic materials, giving heterogeneous loading
- Release can be controlled by diffusion, degradation, or a combination
- A linear release profile is often most desirable



Controlled Release: Degradable Hydrophobic Scaffolds or Particles

- Polyesters such as PLA, PGA, PCL, etc.
- Hydrolytic degradation
- Long duration of controlled released, with tunable release profile
- Hydrophilic drug distributes heterogeneously in hydrophobic scaffold

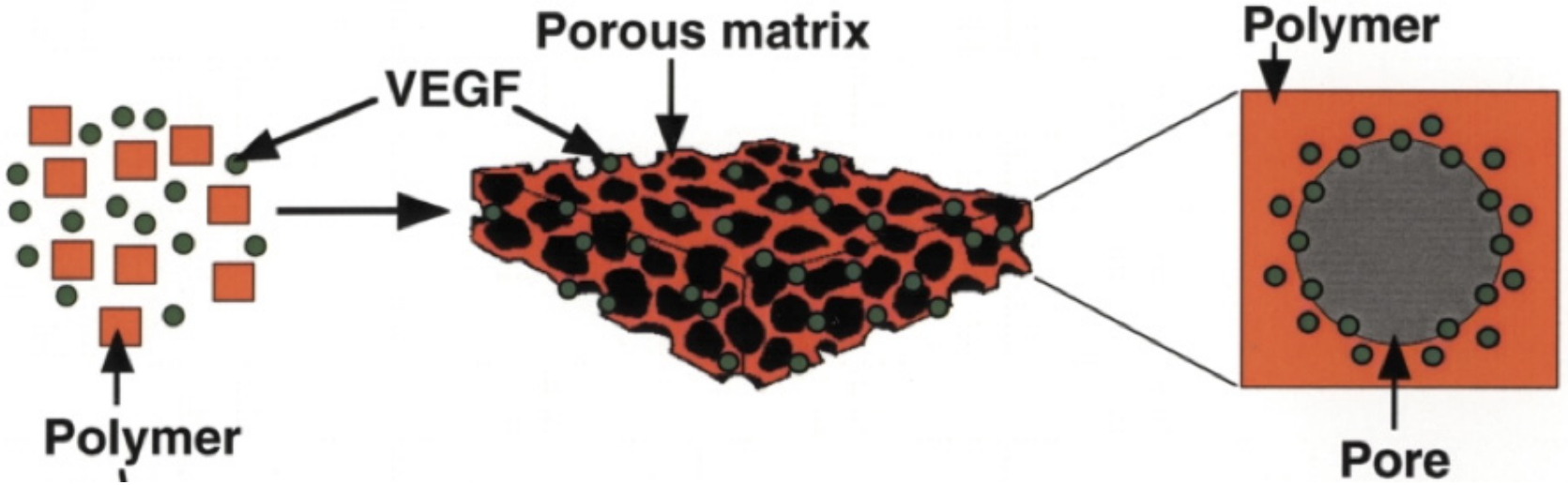
Creation of Protein-Polymer Constructs: Dry

1. Lyophilize protein into fine cake
2. Mill into small particles
3. Dissolve polyester in organic solvent
4. Suspend particles in solution
5. Evaporate solvent

Creation of Protein-Polymer Constructs: Wet

- Protein dissolved in aqueous buffer optimized for long-term storage stability
- Water-in-oil
  1. Mix aqueous protein solution with organic polymer solution
  2. Water immiscible in organic solvent and forms droplets (size depends on mixing energy)
  3. Evaporate solvent
- Water-in-oil-in-water

Load VEGF for Quicker Delivery



1. Grind up PLGA particles and mix thoroughly with VEGF solution
2. Freeze in liquid nitrogen and lyophilize
3. Mill to a powder and compression mold
4. Equilibrate with CO2 at high pressure
5. Rapidly reduce pressure to cause foaming (like opening soda bottle)
6. VEGF will be found at or near the surface of the PLG material

Richardson+, Polymeric system for dual growth factor delivery. *Nat Biotech* 2001

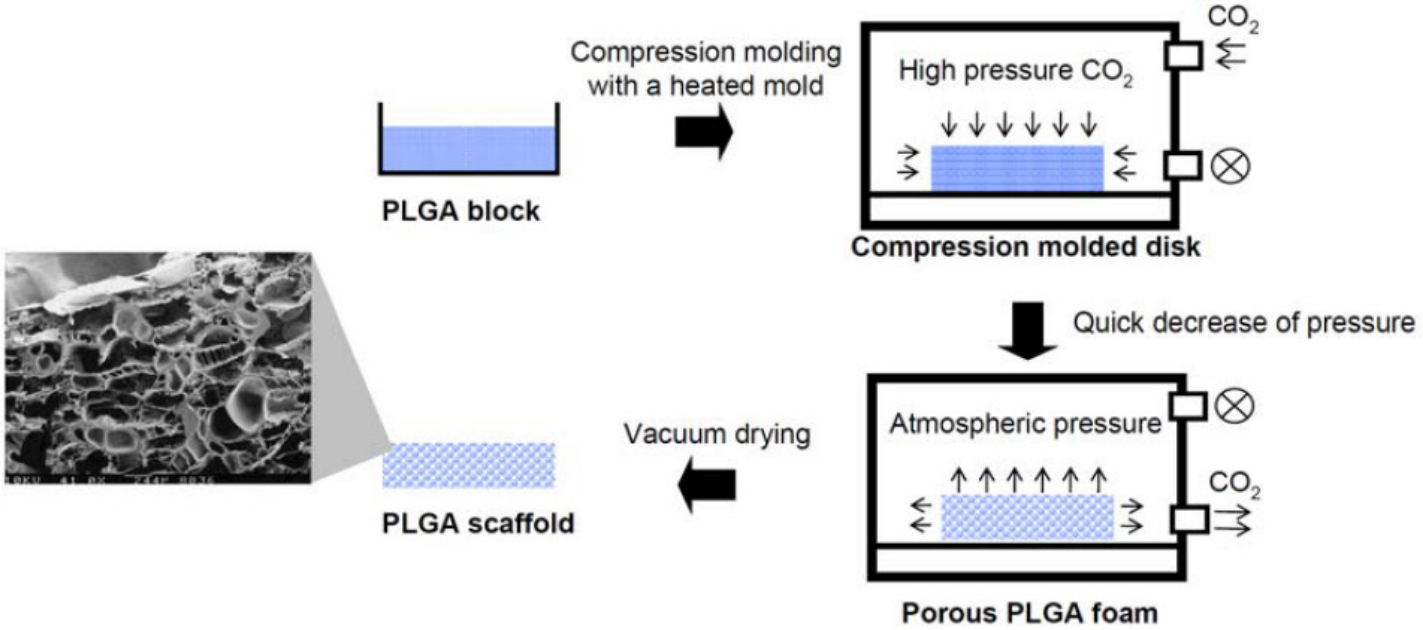
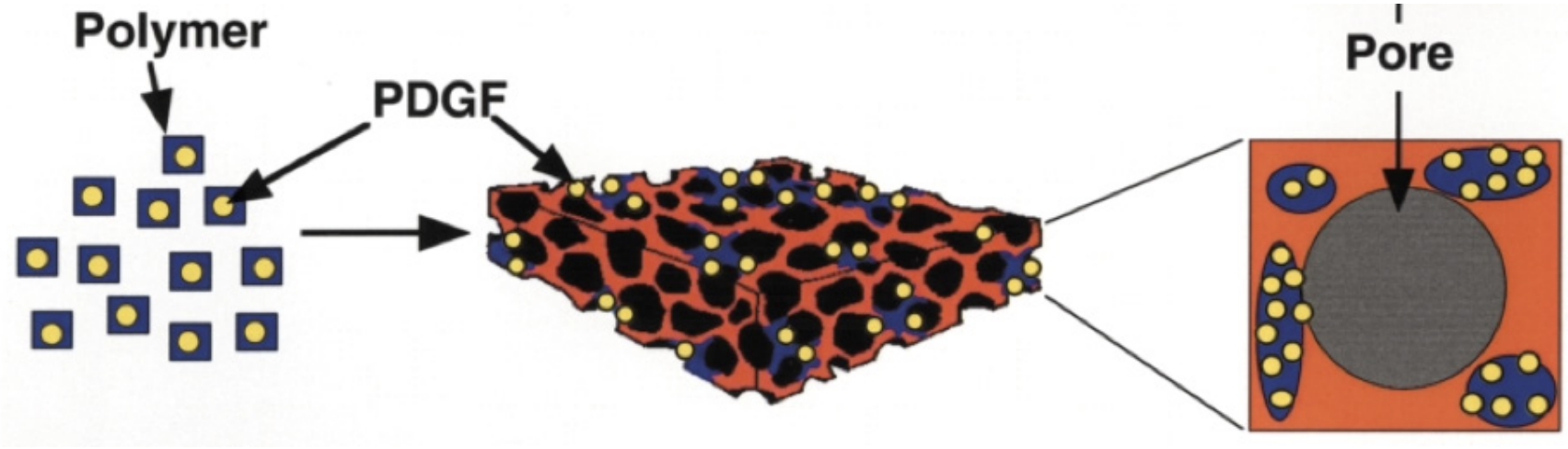


Figure 1.6 Schematic of gas foaming technique and the SEM image of a PLGA scaffold.

Ko, Young-Gwang
University of Tsukuba

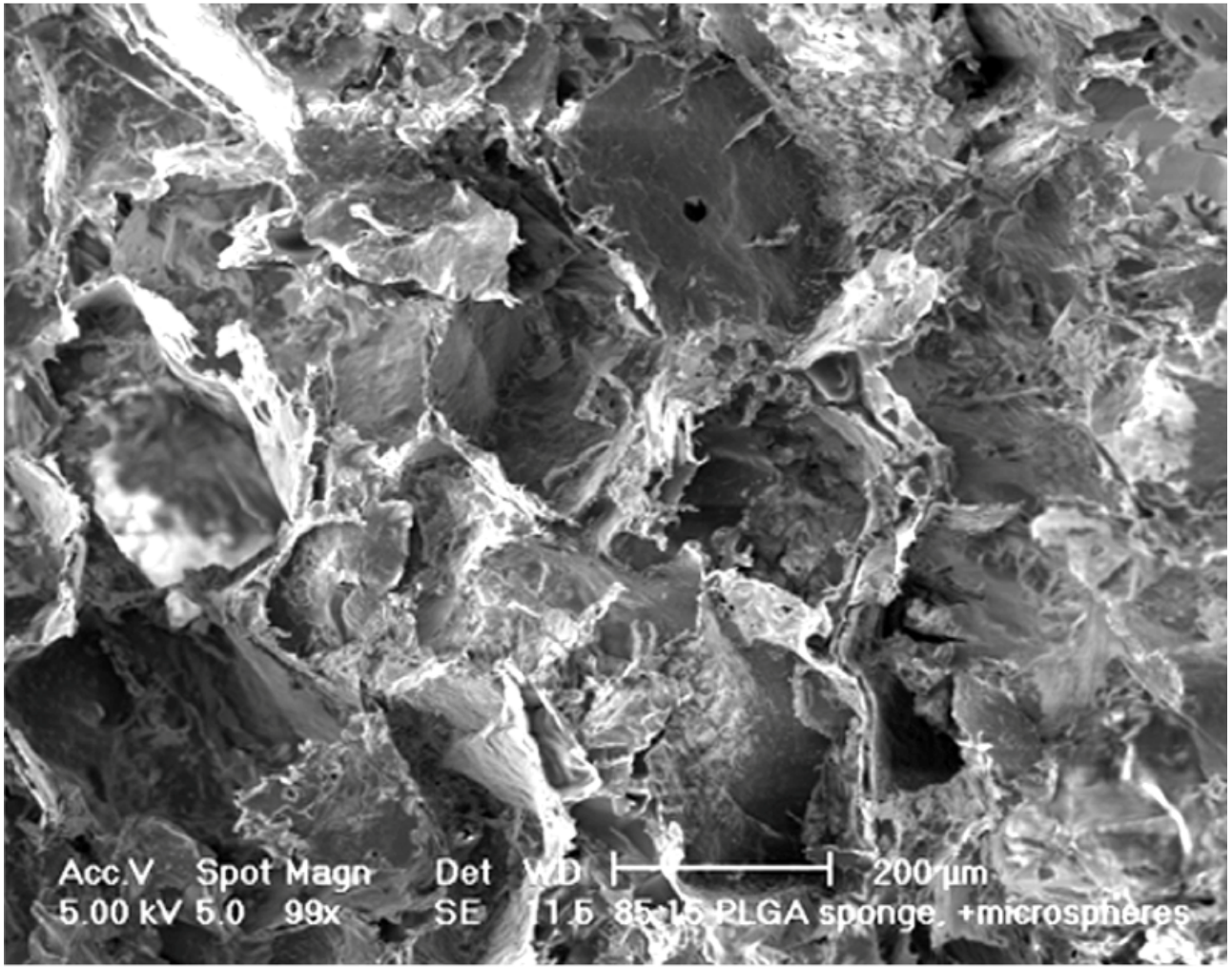
Load PDGF for Slower Delivery

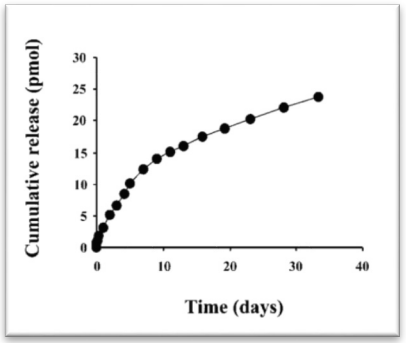


1. Entrap PDGF in PLGA polymer by water-in-oil-in-water method
2. Mix with PLGA-VEGF particles and follow previous gas foaming method
3. PDGF will be found encapsulated deep in the PLGA material

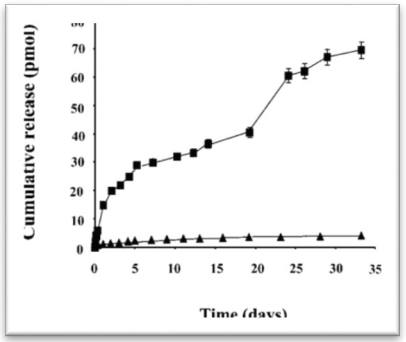
Richardson+, Polymeric system for dual growth factor delivery. *Nat Biotech* 2001

Fabricated Scaffold





VEGF release from scaffold

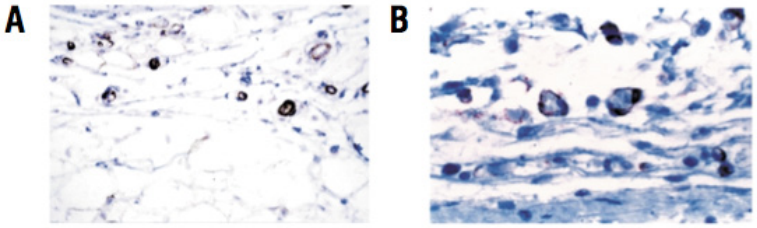


PDGF release from particles

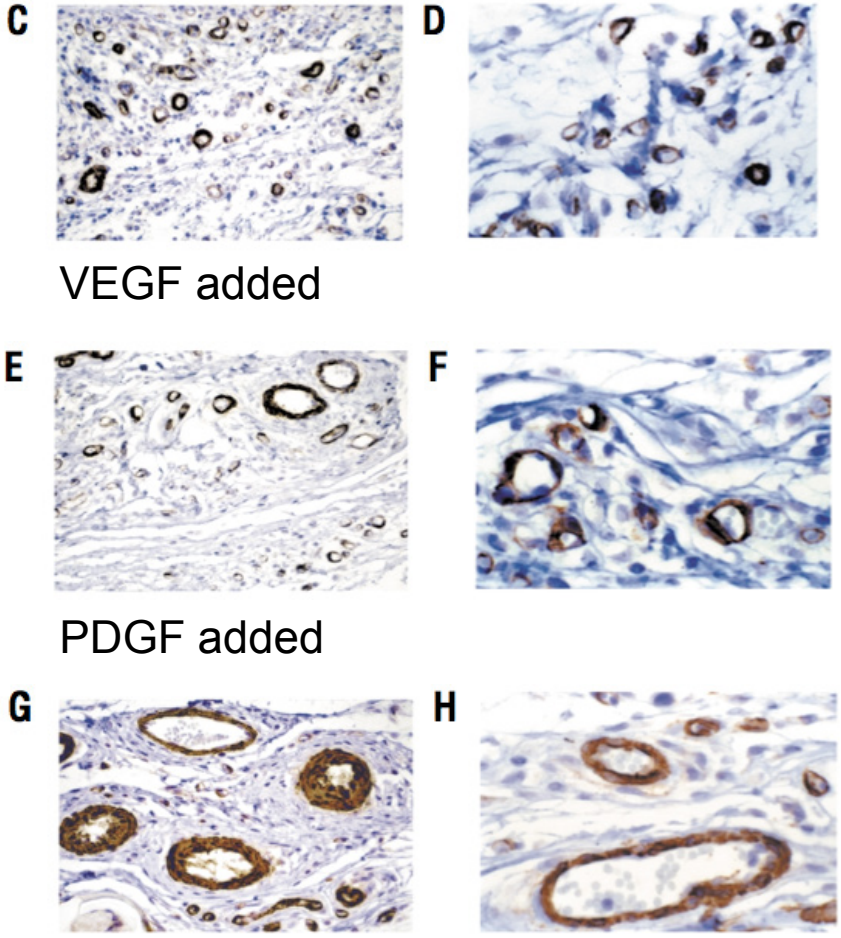
Richardson+, Polymeric system for dual growth factor delivery. *Nat Biotech* 2001

Dual Staggered Release

- Surface adsorption of VEGF
- PGDF internalized in microparticles



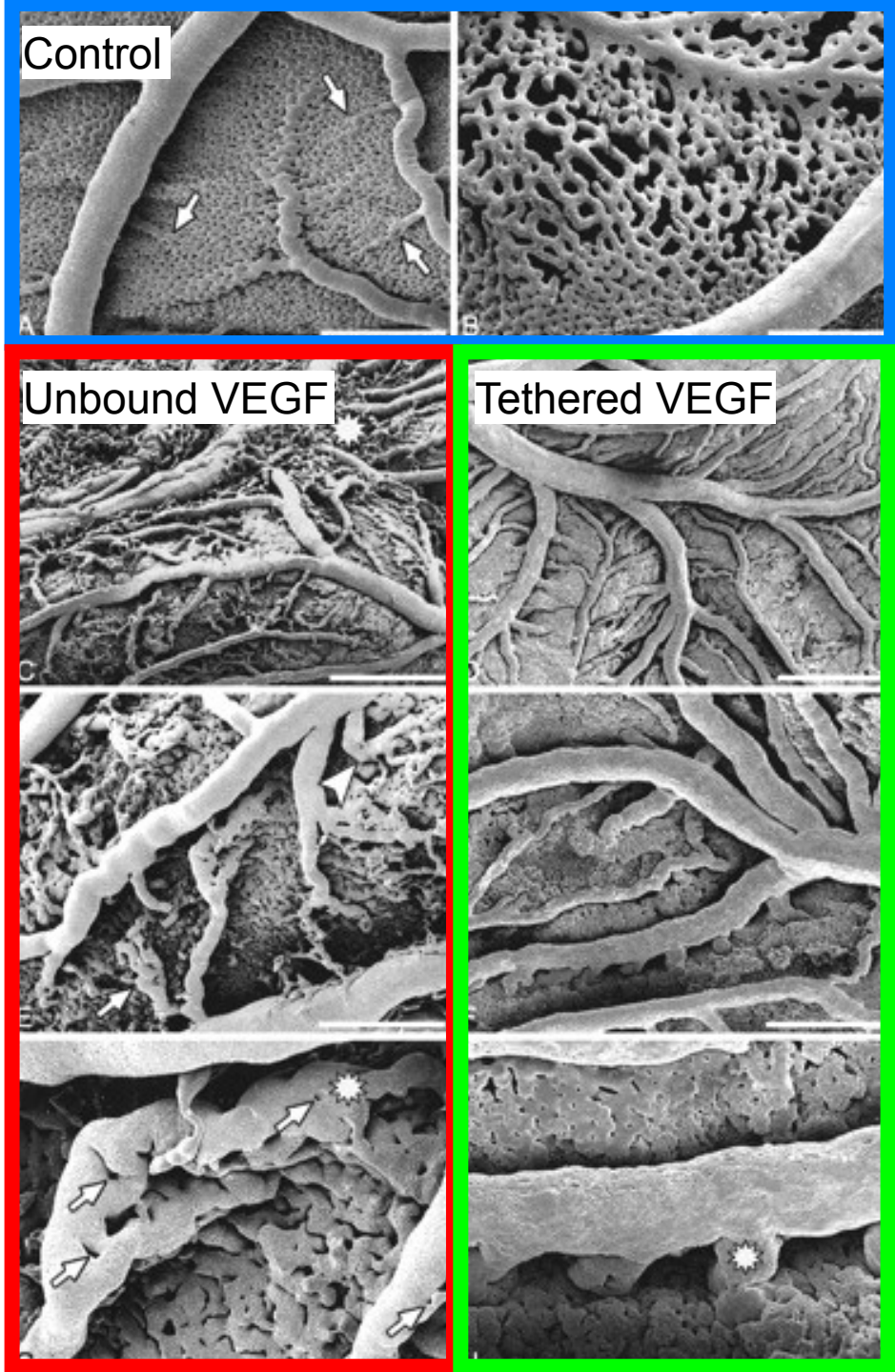
Scaffold alone. Minimal angiogenesis (staining of α-smooth-muscle actin)



Richardson+, Polymeric system for dual growth factor delivery. *Nat Biotech* 2001

Plasmin-activated release of VEGF-A

- Recombinant VEGF linked to Factor XIIIa substrate domain by intermediate plasmin substrate
- Slow on-demand release of VEGF to avoid wild angiogenic growth



Ehrbar+ *Circulation Research* 2004

Regranex

REGRANEX
GEL
0.01%
(becaplermin)
NET WT. 15g
Multi-dose tube
MILNER
PHARMACEUTICAL