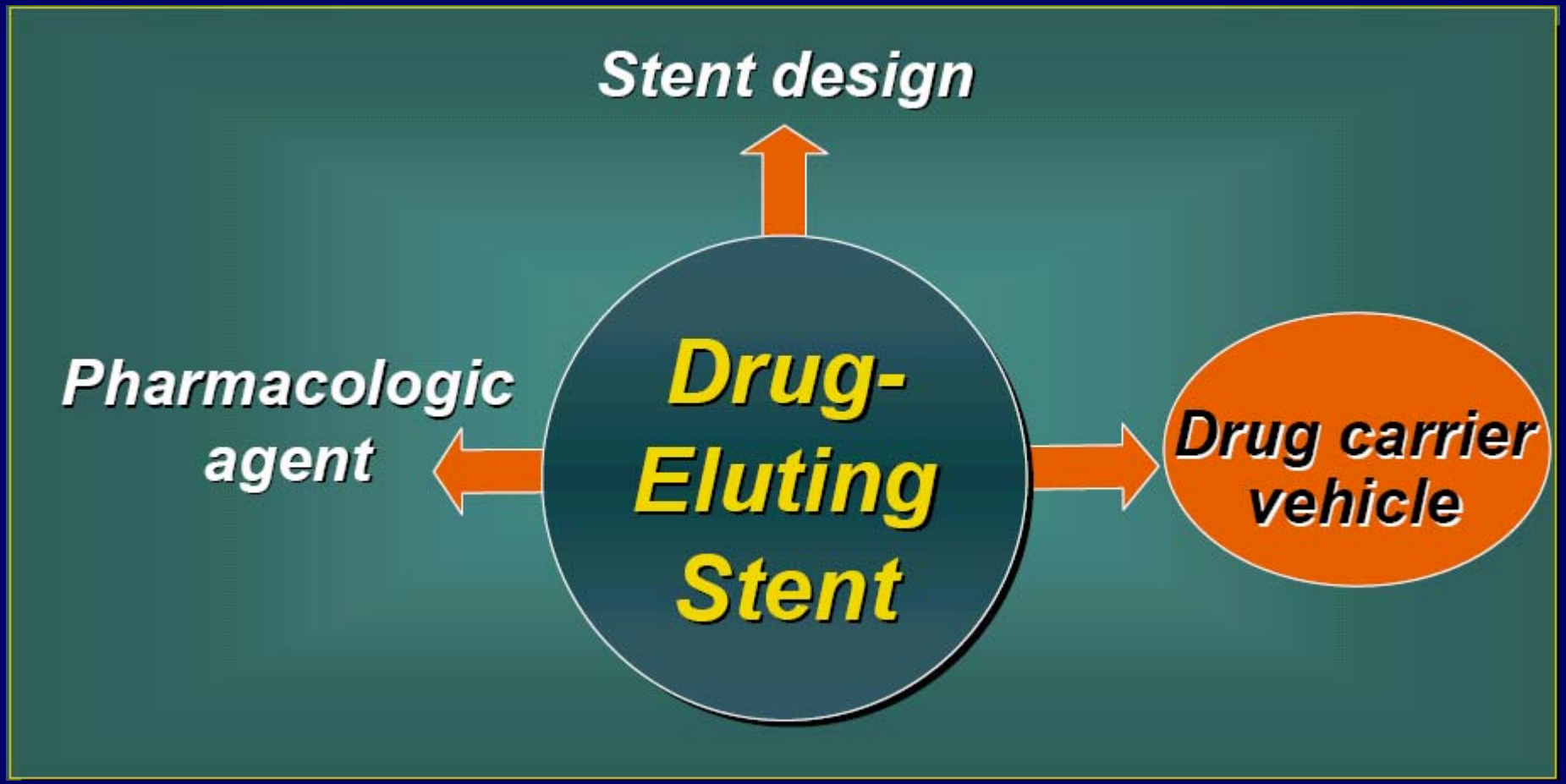
Polymers for DES

충북의대 순환기 내과
김 동운

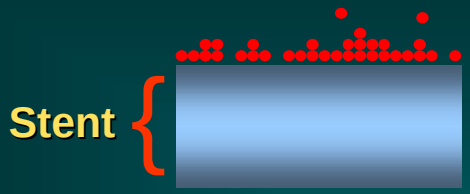
Drug-Eluting Stents



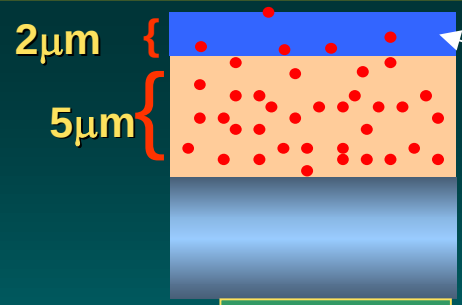
The Role of Polymer

- **Attachment of drug**
  - **since most compounds cannot be directly bound by chemical means**
- **Protection of drug**
  - **from mechanical or chemical loss during stent delivery**
- **Control rate of drug release**

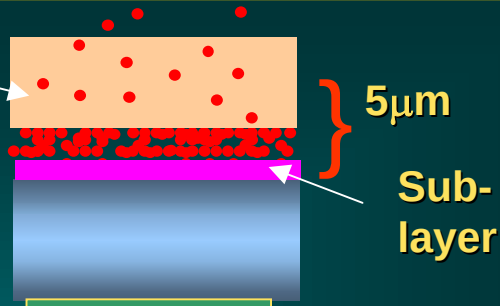
Methods of Stent-Mediated Drug Delivery



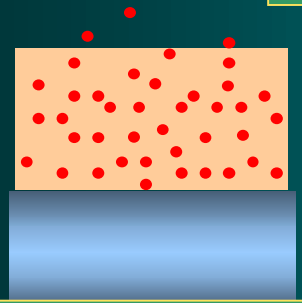
COOK



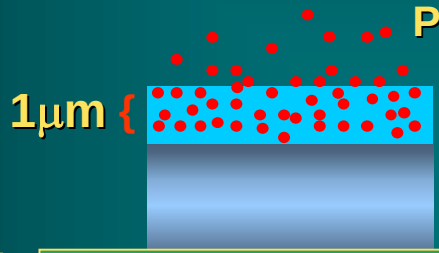
CORDIS



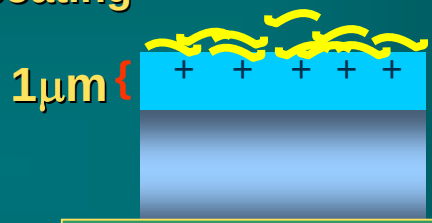
GUIDANT



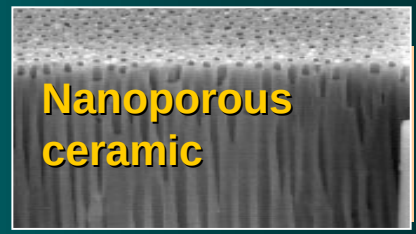
Boston Scientific



Bio*divYsio* Matrix LO



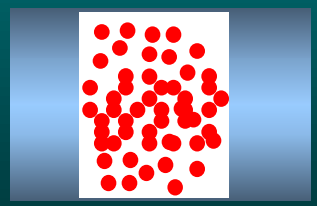
Bio*divYsio* Matrix HI



JOMED

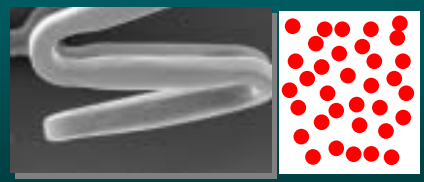
SORIN

Degradable inlays



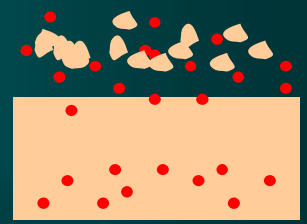
CONOR-Medsystems

Degradable polymer



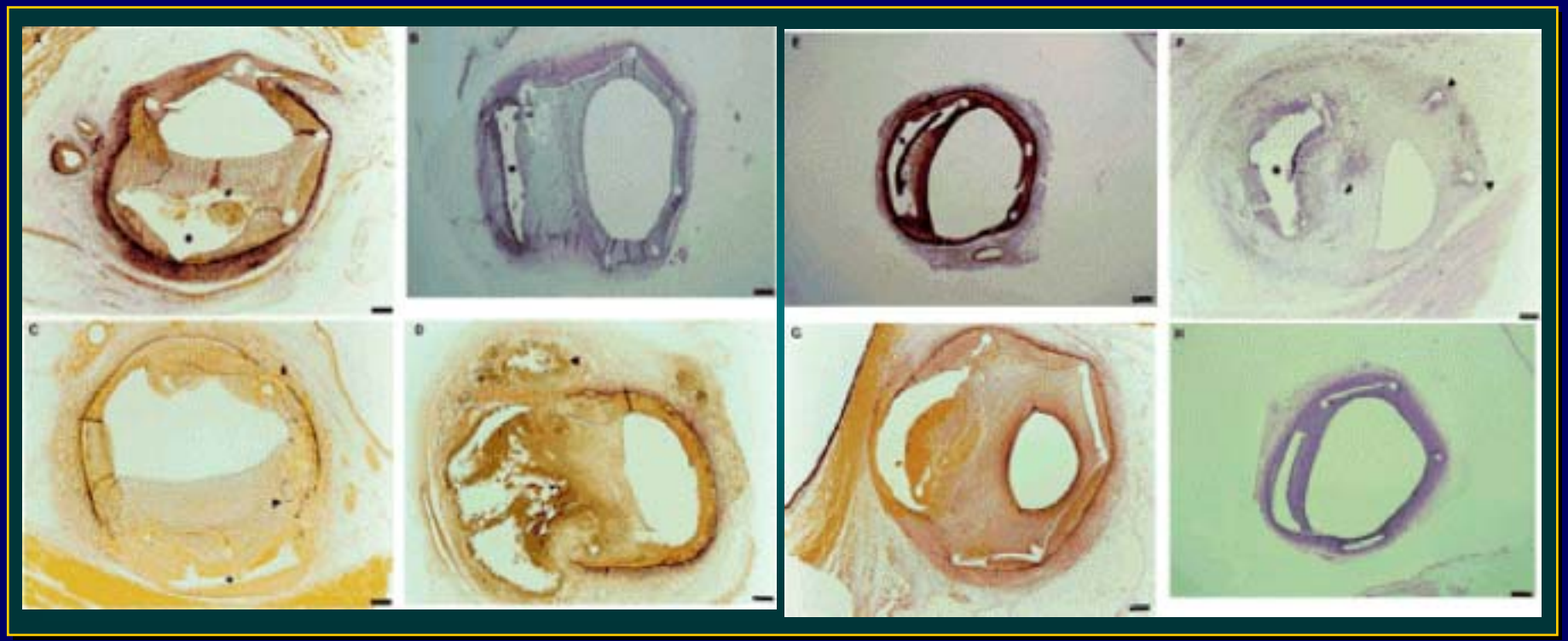
Biosensor

Degradable stent



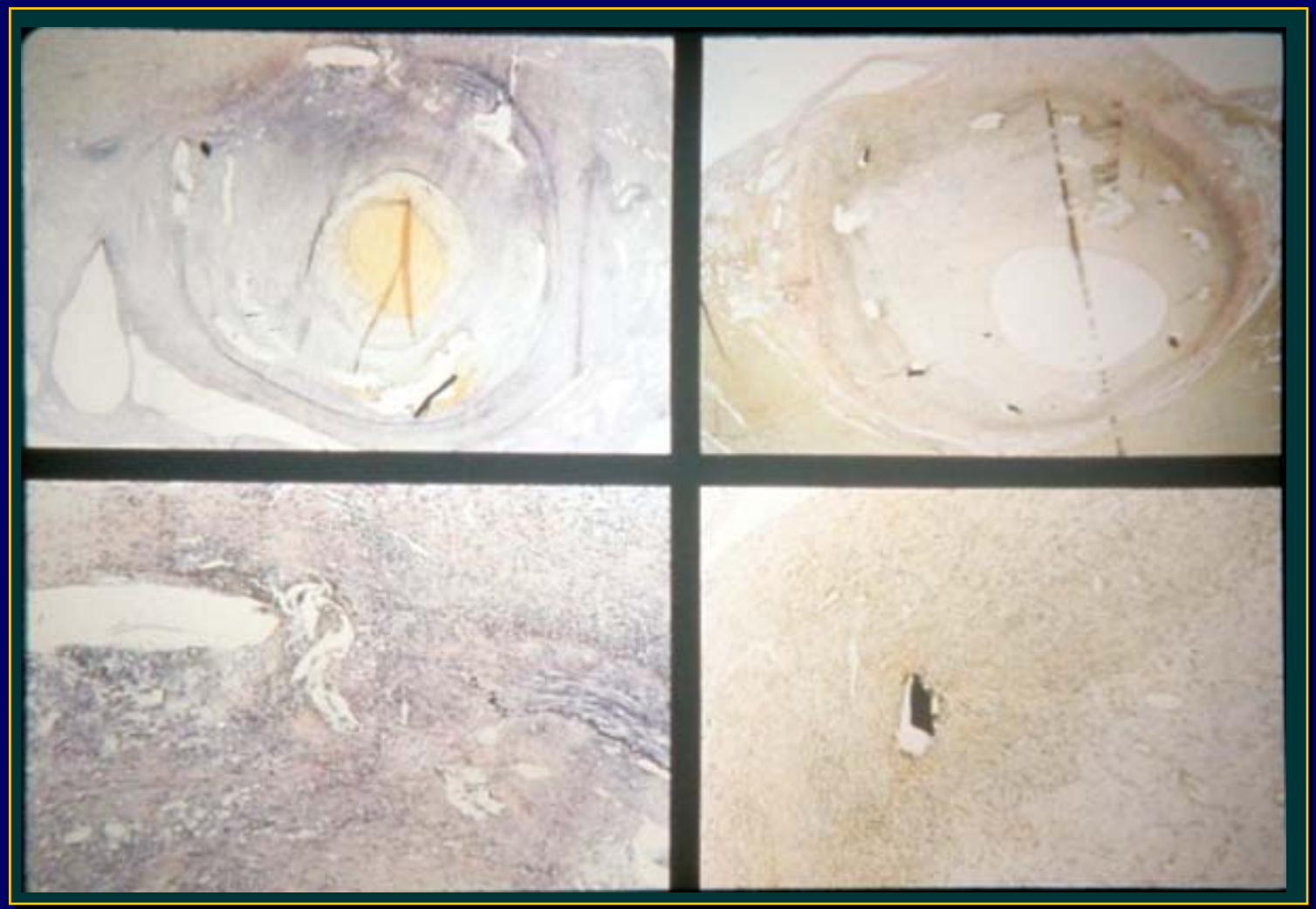
Igaki-Tamai

Biocompatibility



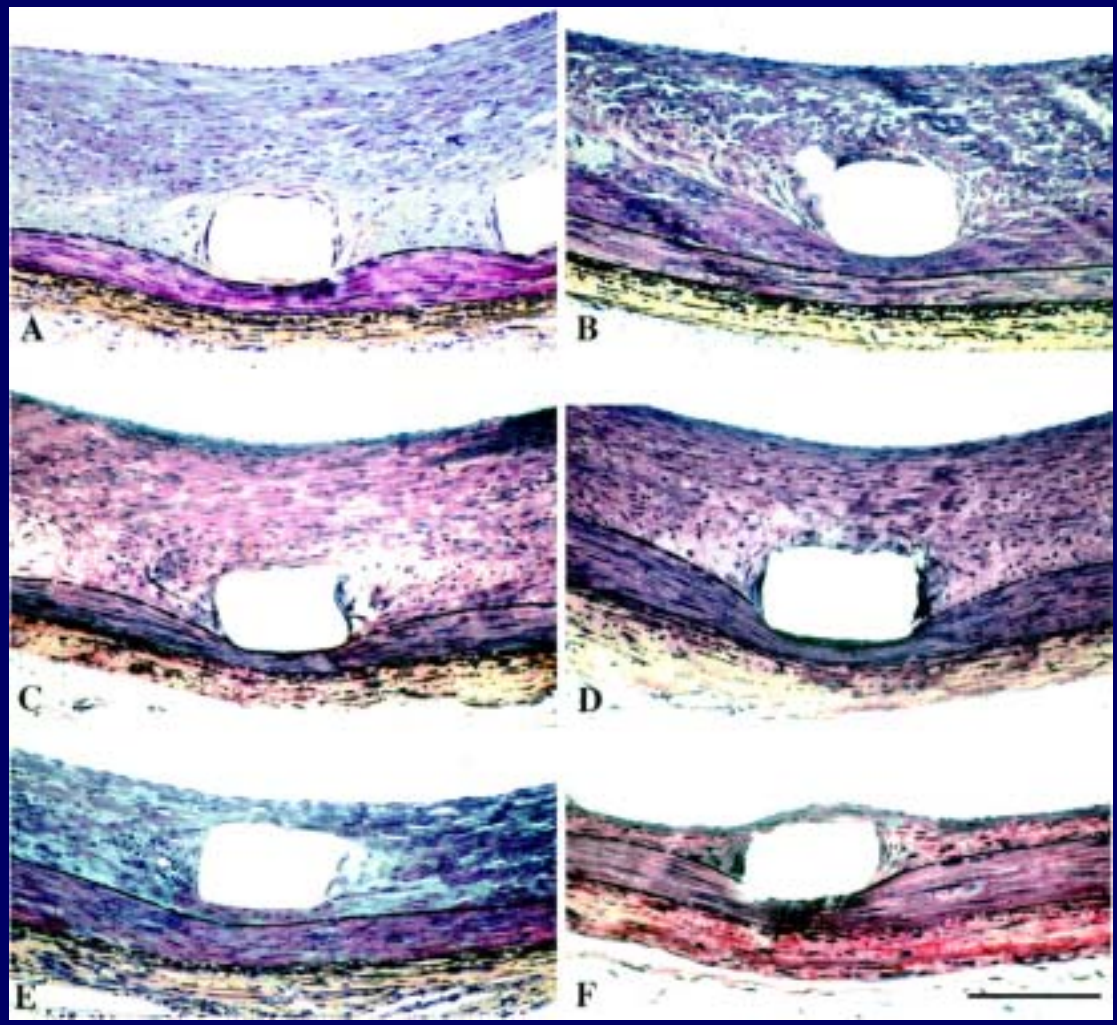
van der Giessen WJ, et al. *Circulation.* 1996

EVA (Ethylene Vinyl Acetate)-coated Paclitaxel Stent (Porcine Coronary Artery)



Unpublished Data, NIA

CSG(Chondroitin Sulfate and Gelatin)-coated Paclitaxel Stent (Rabbit Iliac Artery)

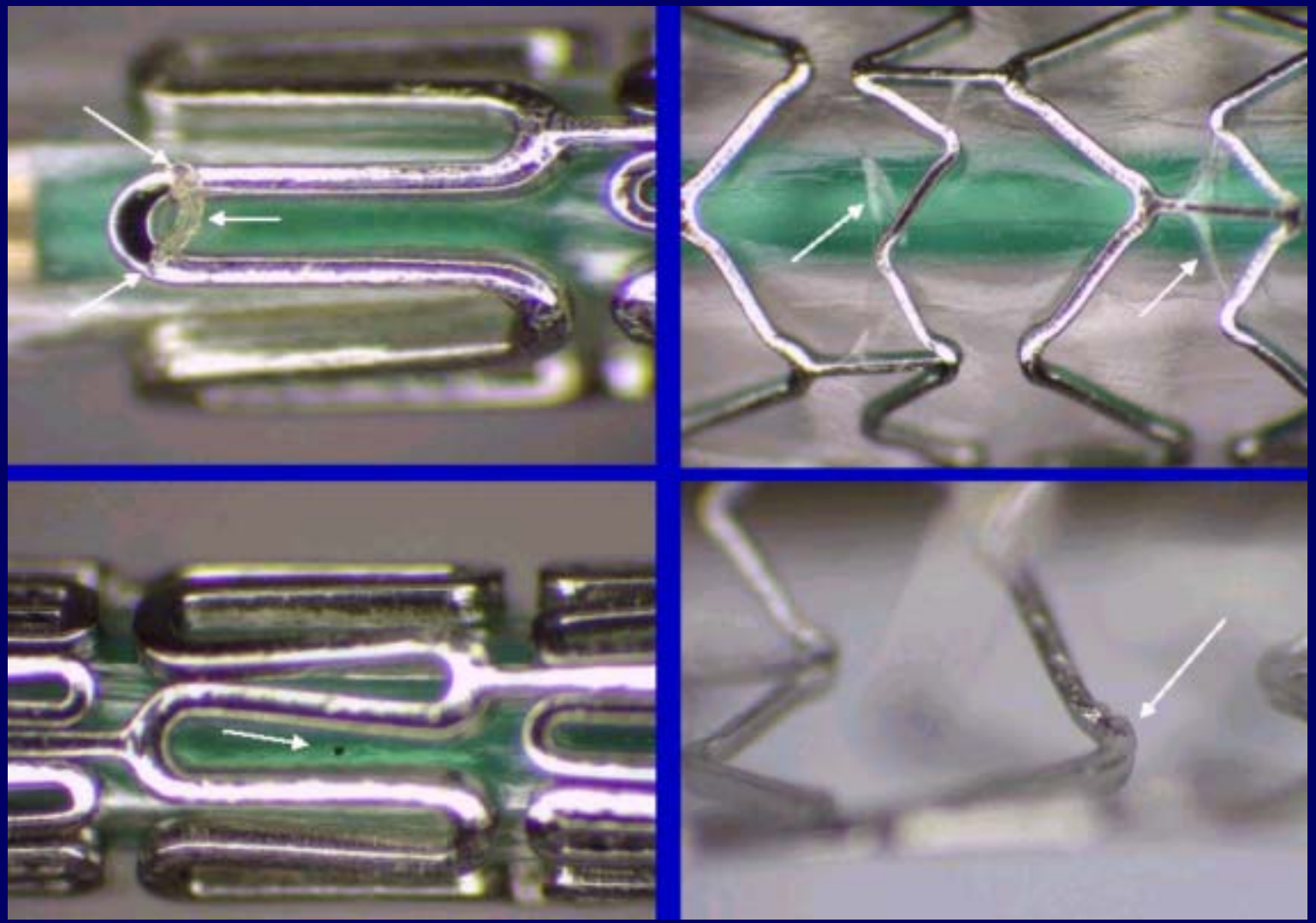


Farb A, et al. *Circulation.* 2001

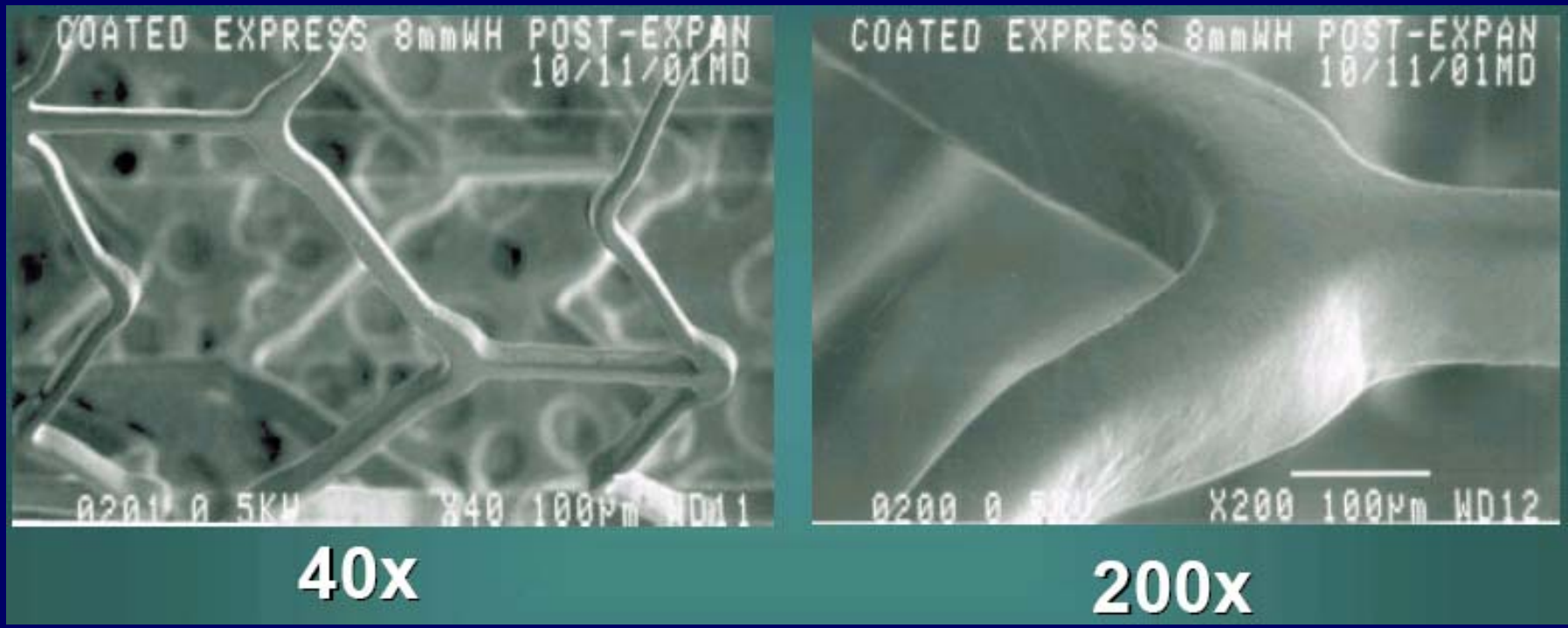
Biocompatibility

- Completely biocompatible
  - Non-inflammatory and Non-thrombogenic
  - Short and long term
    - Most biocompatible polymers may cause some foreign body reactions months or years later

Possible Deleterous Effects of Polymer-coated Stent



TAXUS: Polymer Integrity



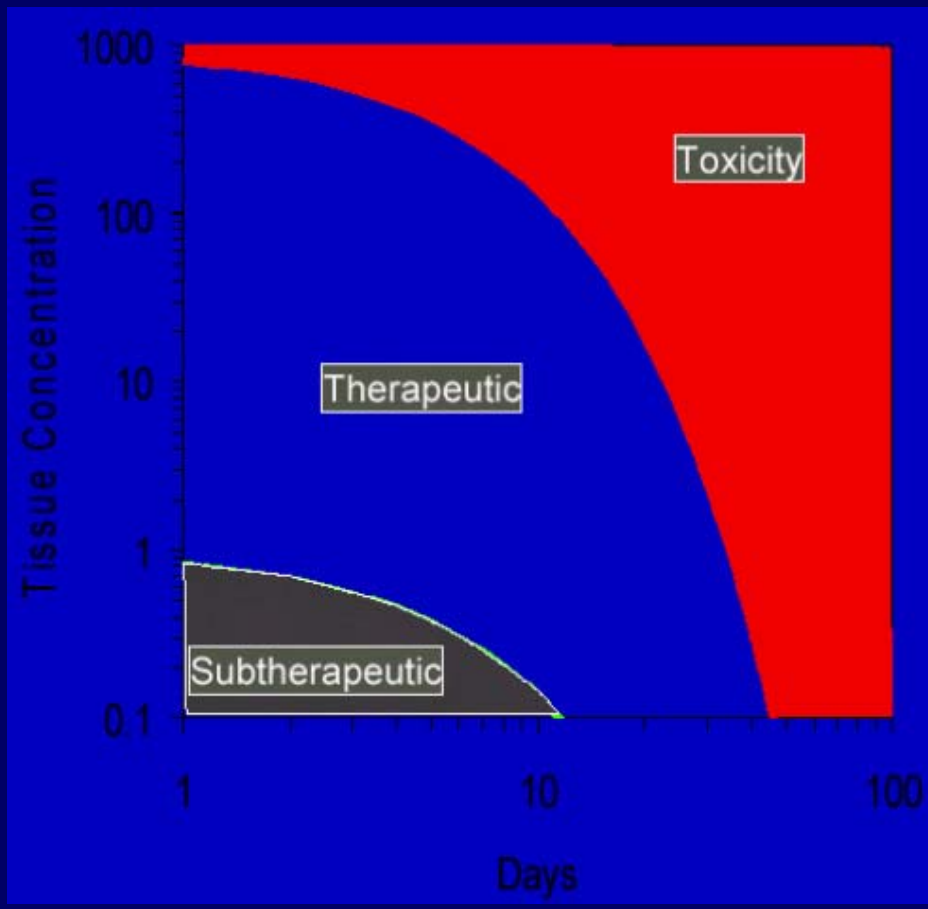
Coated, loaded, sterilized, expanded

Mechanical Integrity/Handling

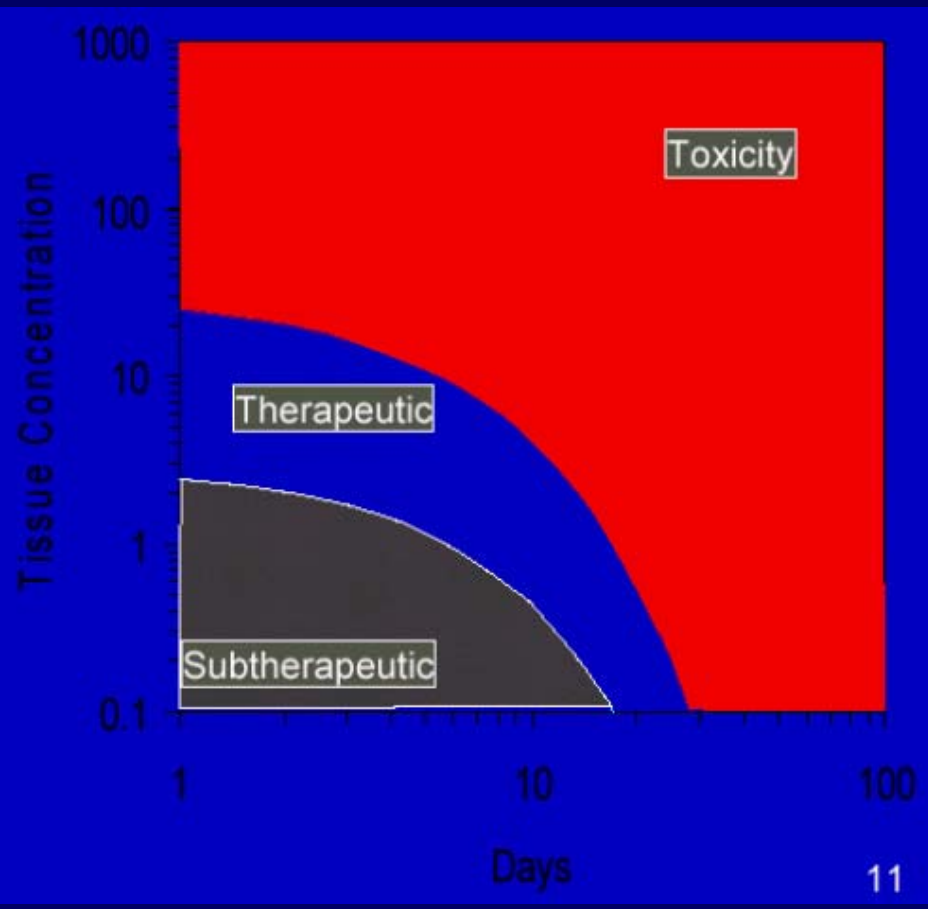
- Elastomeric
- No surface integrity changes
  - e.g. cracking, peeling
  - During rigorous clinical implantation procedures

Does it Matter? Tissue Pharmacodynamics Should Drive Stent Pharmacokinetics

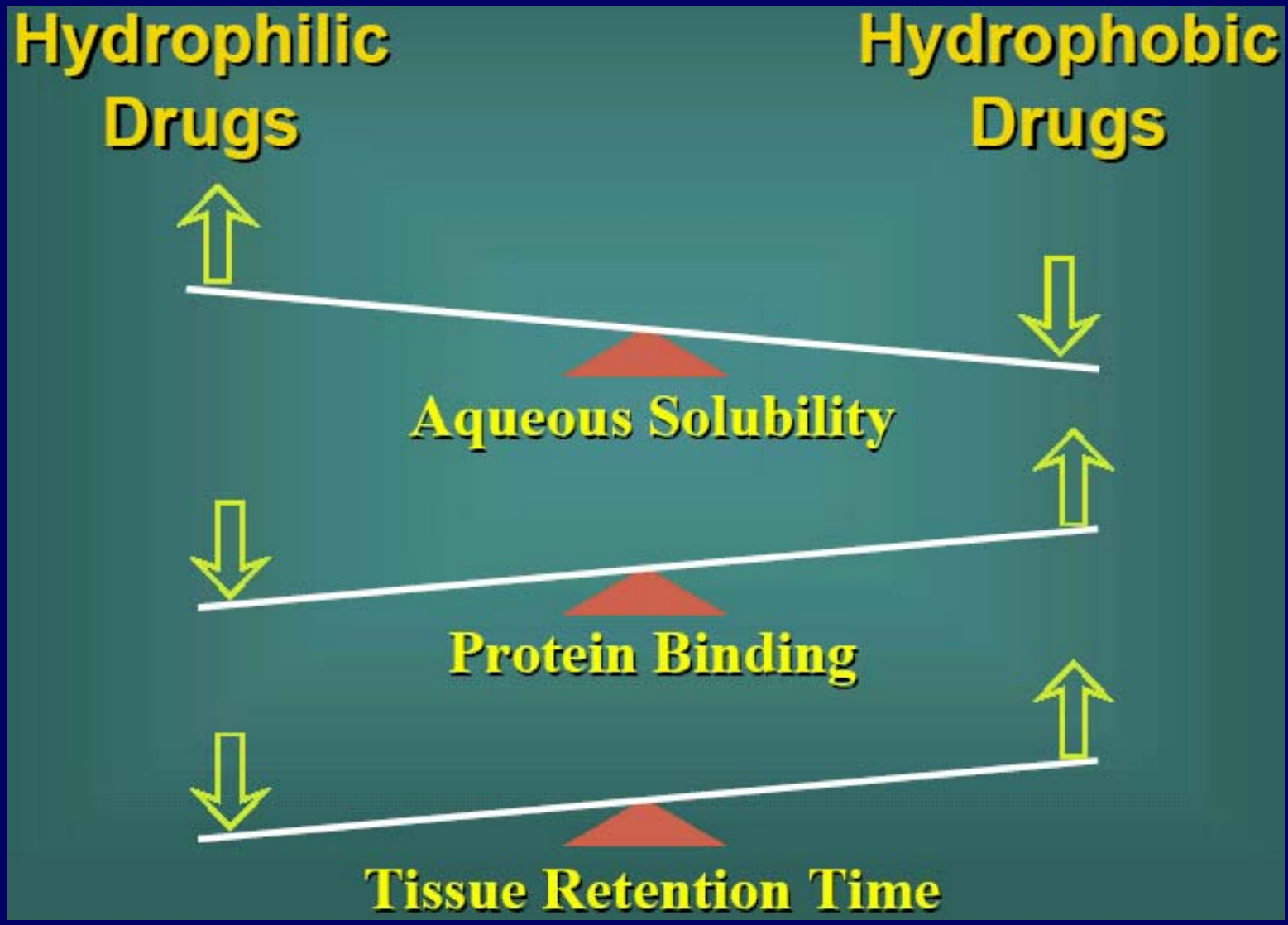
High therapeutic index, “3 logs”
Controlled release less important

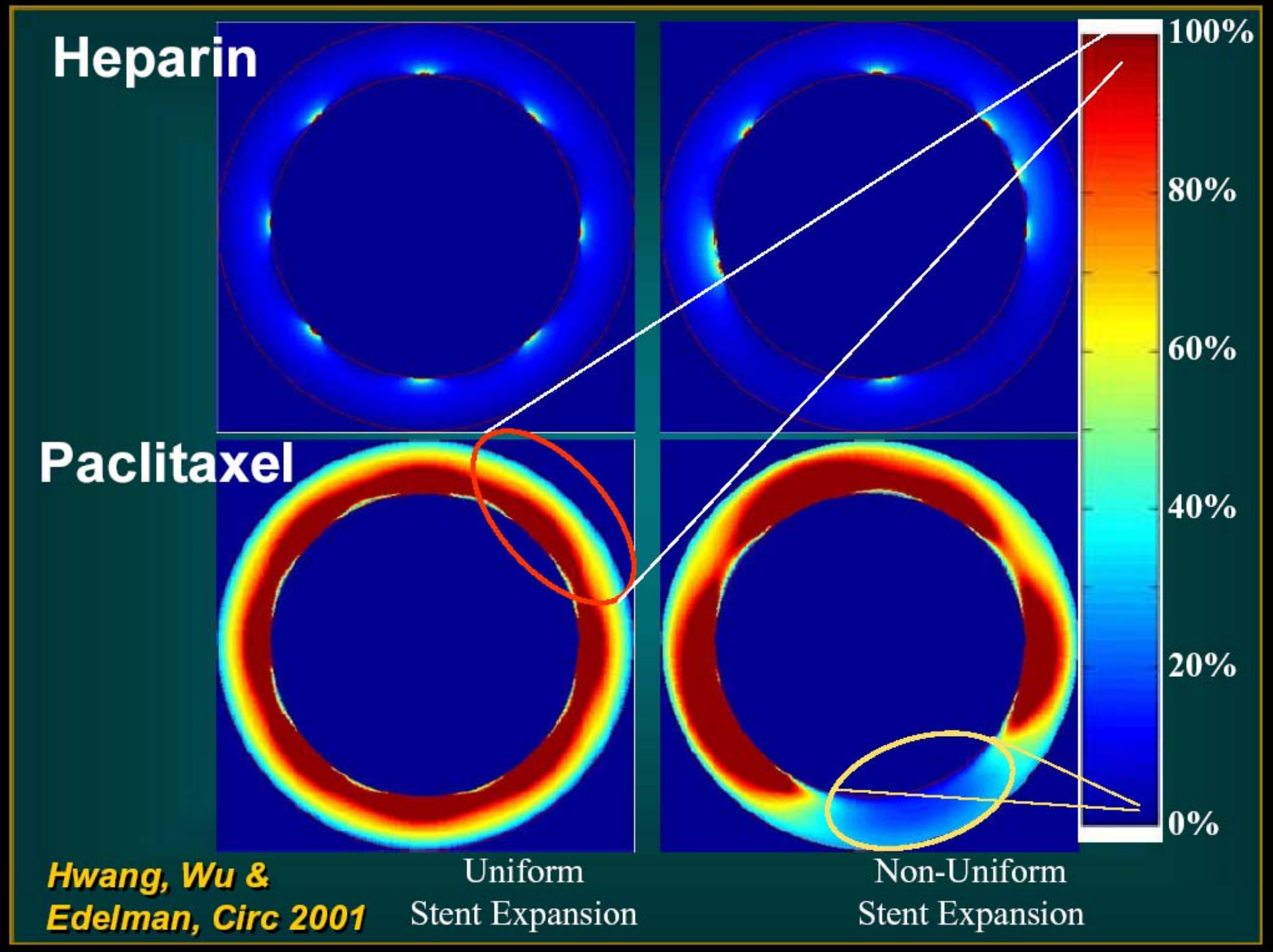


Low therapeutic index, “1 log”
Controlled release is critical



Arterial Transport Theory



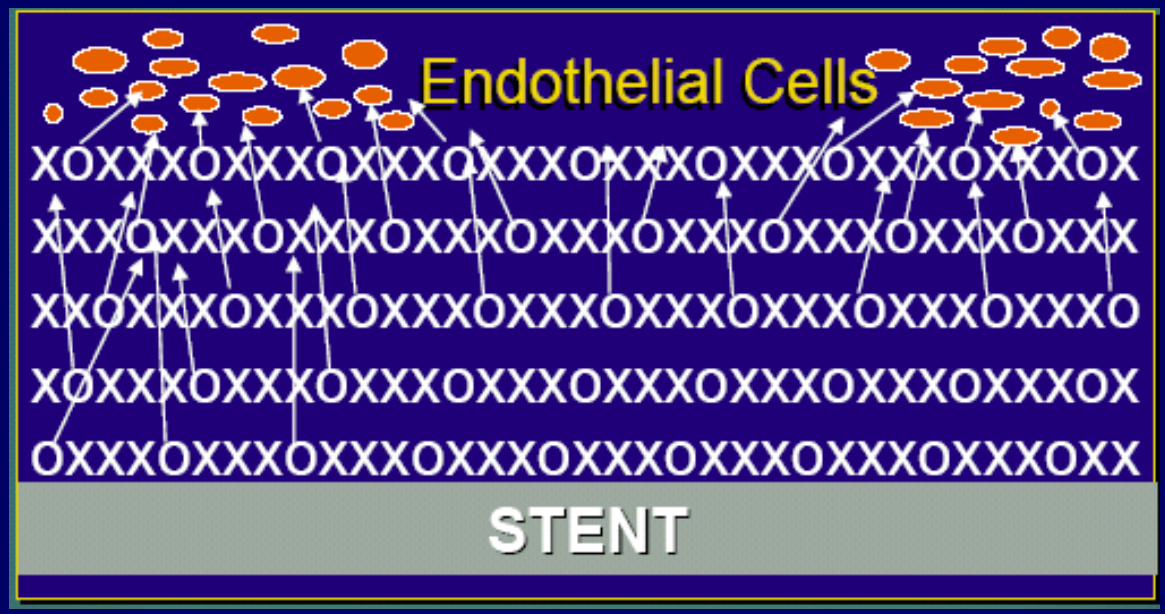

Heparin
Paclitaxel
100%
80%
60%
40%
20%
0%
Uniform
Stent Expansion
Non-Uniform
Stent Expansion
Hwang, Wu &
Edelman, Circ 2001

Drug Delivery Methods

- **Matrixing**
  - **Physical mixing of drug and polymer**
  - **Release of drug controlled by diffusion**
- **Conjugation**
  - **Covalent attachment of drug to polymer**
  - **Release of drug controlled by biodegradation of polymer through surface erosion**

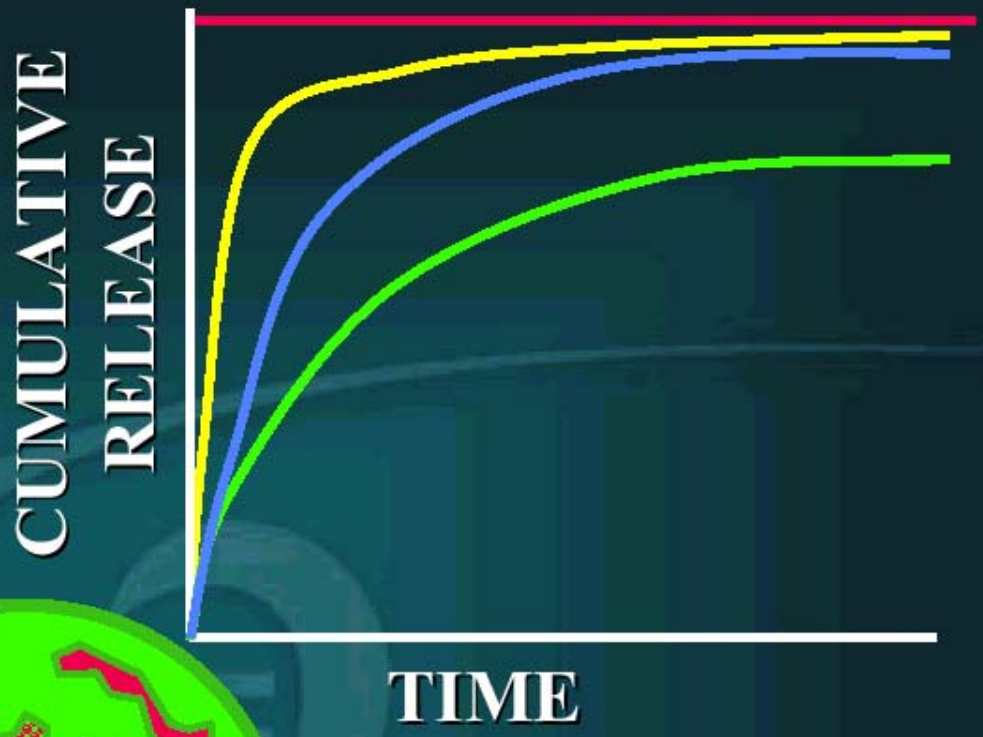
Conventional Polymer-based Drug Delivery

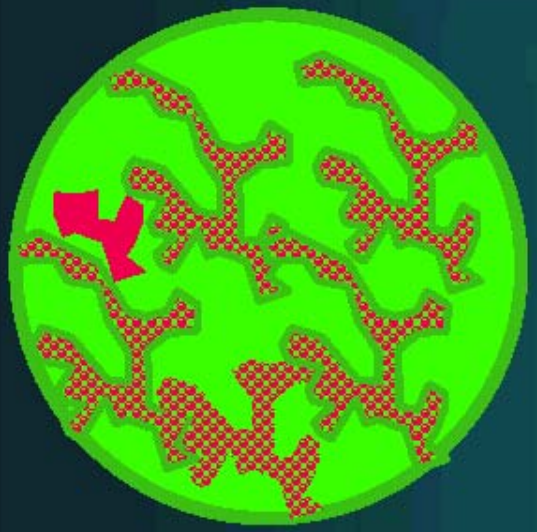
- Matrixed delivery
  - Diffusion

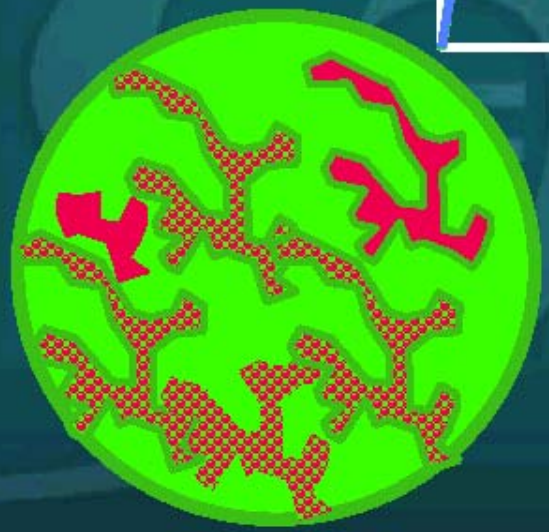


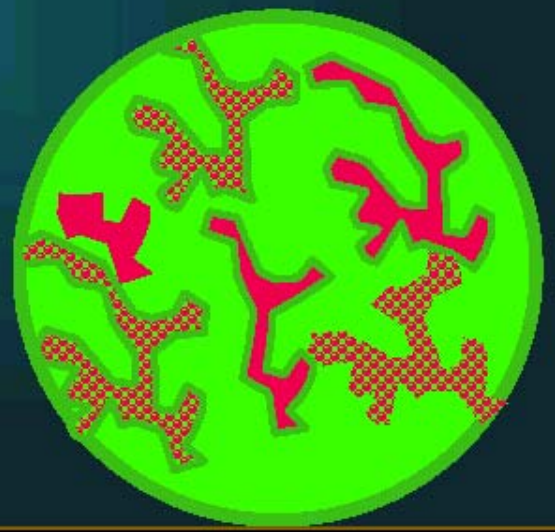
  - Peak concentrations may exceed therapeutic ceiling
  - Concentrations remain in therapeutic window for a short period of time

MATRIX SYSTEMS: Prolong Release







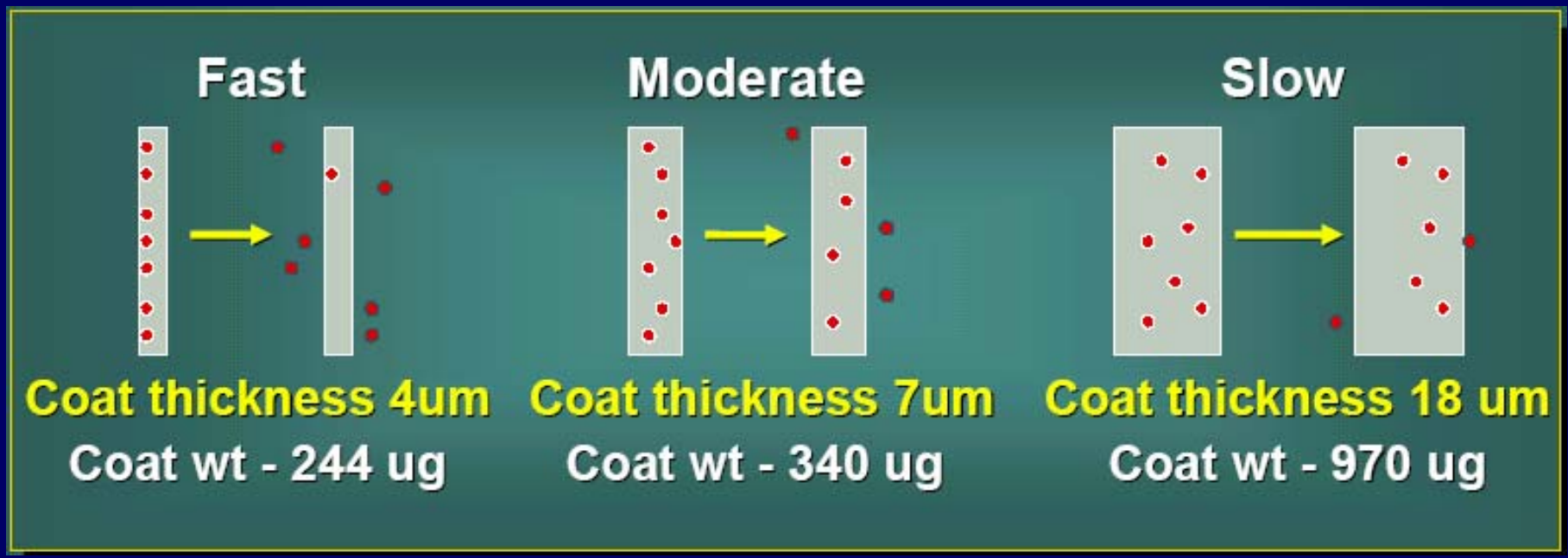


$$J = D\,\Delta C$$

$$J = (D'\,\rho/\tau)\,\Delta C$$

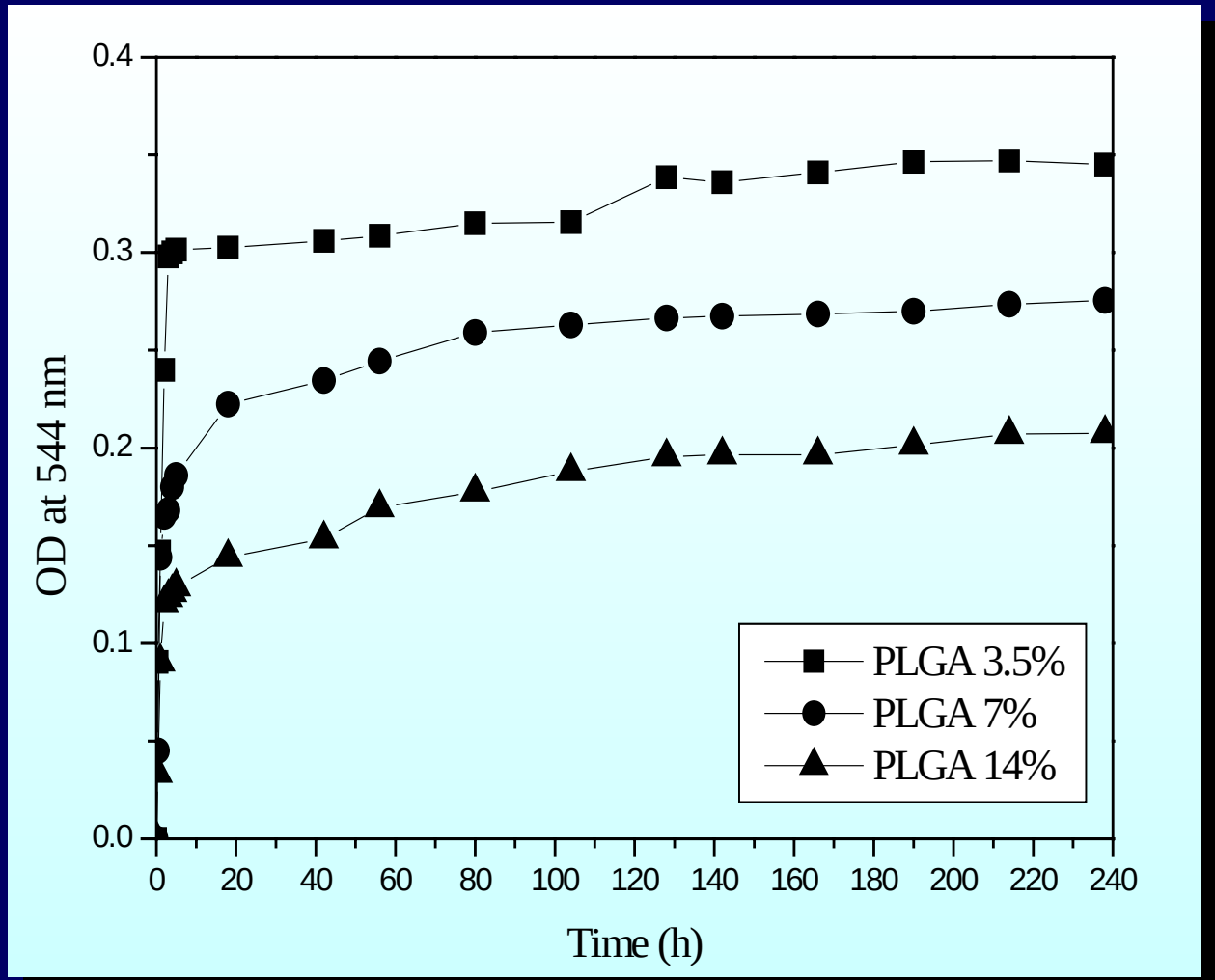
Polymer-based Drug Release Kinetics

For the same total loaded dose



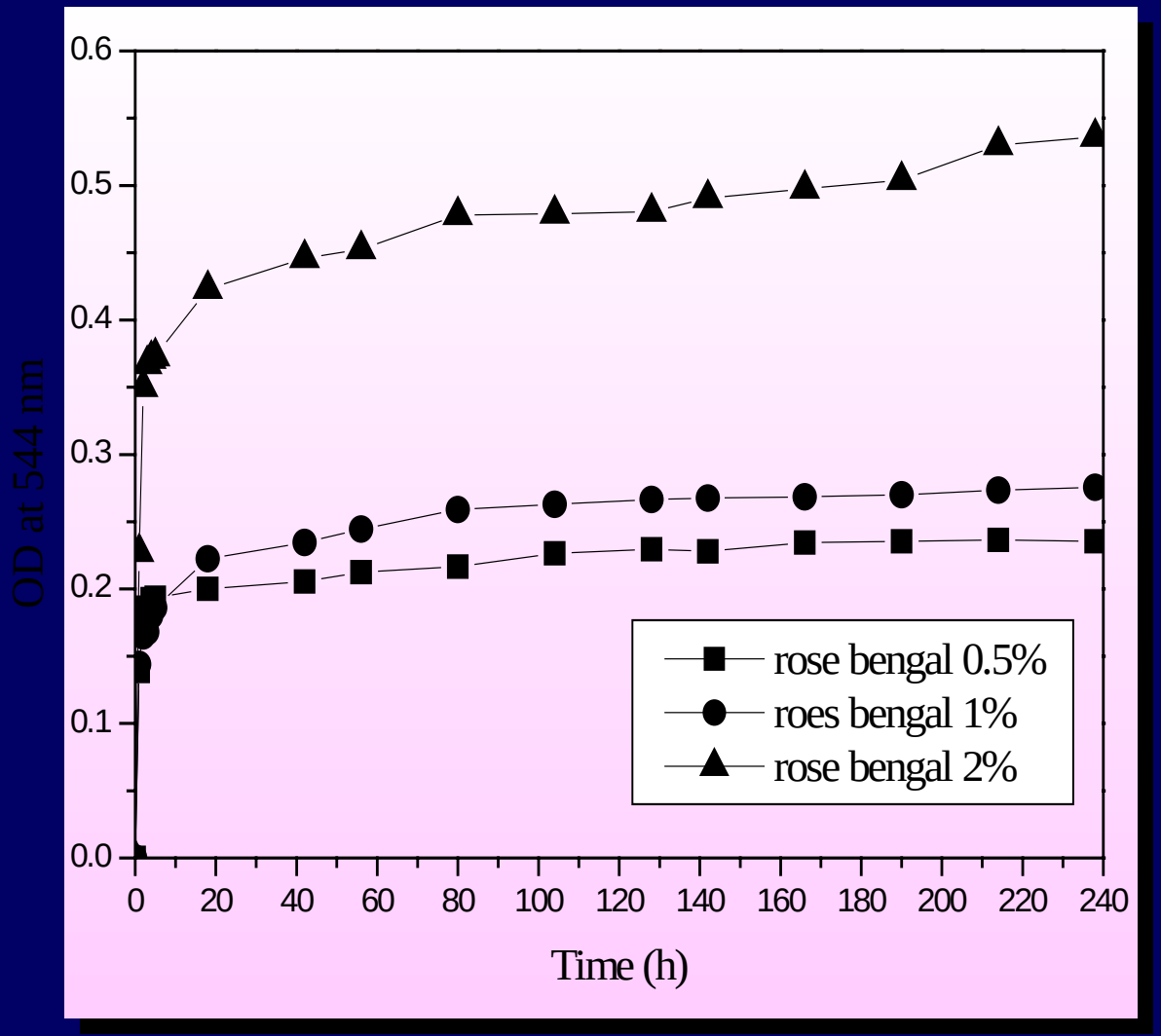
- Release kinetics altered via the drug/polymer ratio
- Total loaded dose altered via coating thickness/weight
- Increased coating thickness slows release of PTx

Effect of Polymer (PLGA) Concentration on *in vitro* Release



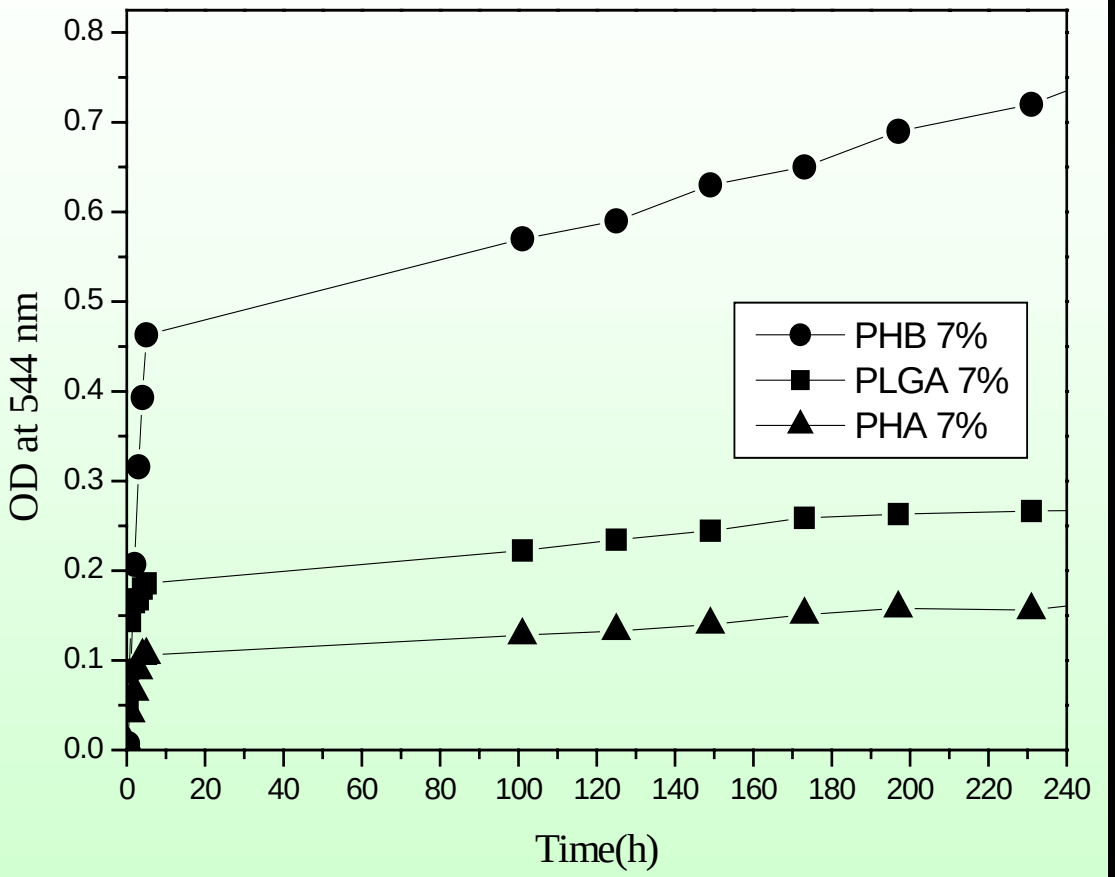
Poly(lactic-co-glycolic acid) (50/50 PLGA)
Rose bengal concentration 1%

Effect of Drug (Rose bengal) Concentration on *in vitro* release



PLGA concentration 7%

Effect of Polymer Types on *in vitro* Release



- **PLGA**

  Poly(lactic-co-glycolic acid) (50/50 PLGA)

- **MCL-PHA**

  Medium chain length polyhydroxyalkanoates

  Pseudomonas oleovorans

- **PHB**

  Poly(3-hydroxybutyrate)

  Ralstonia eutropa

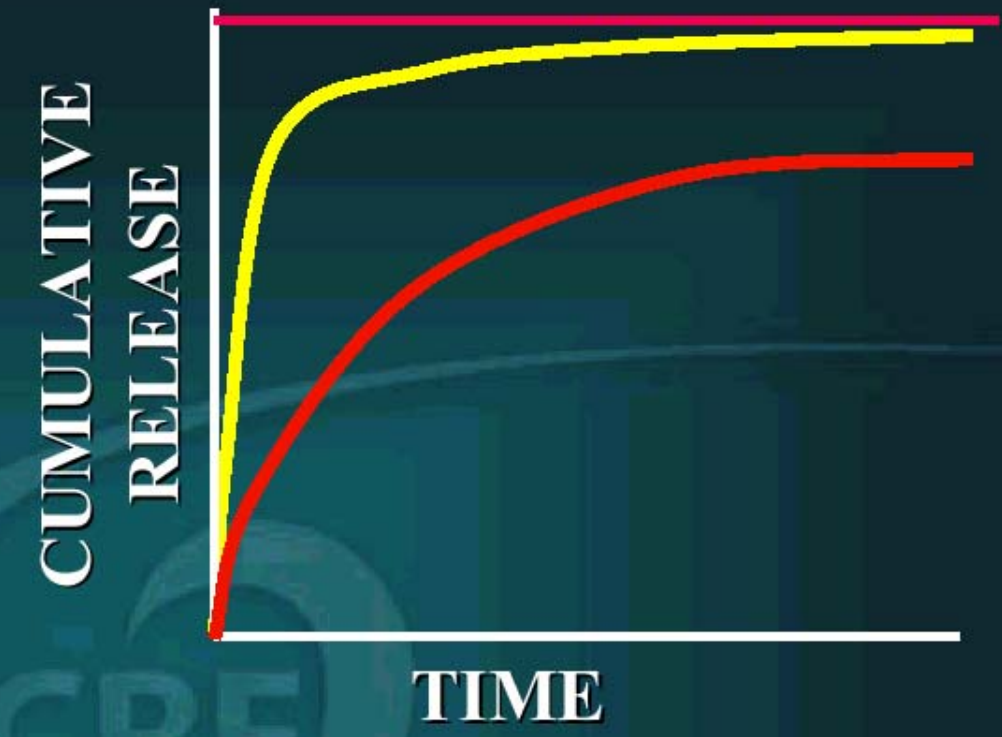
Rose bengal concentration 1%

OVERCOAT:
Prolongs release

$$J = D\,\Delta C$$

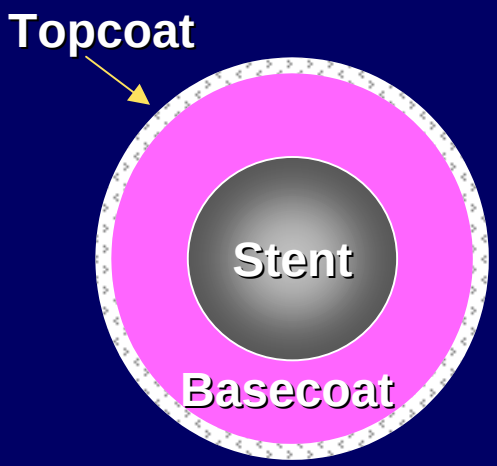
$$J = (D'\,\rho/\tau)\,\Delta C$$

$$J = (D'\,\rho/\tau)\,dC/dx$$

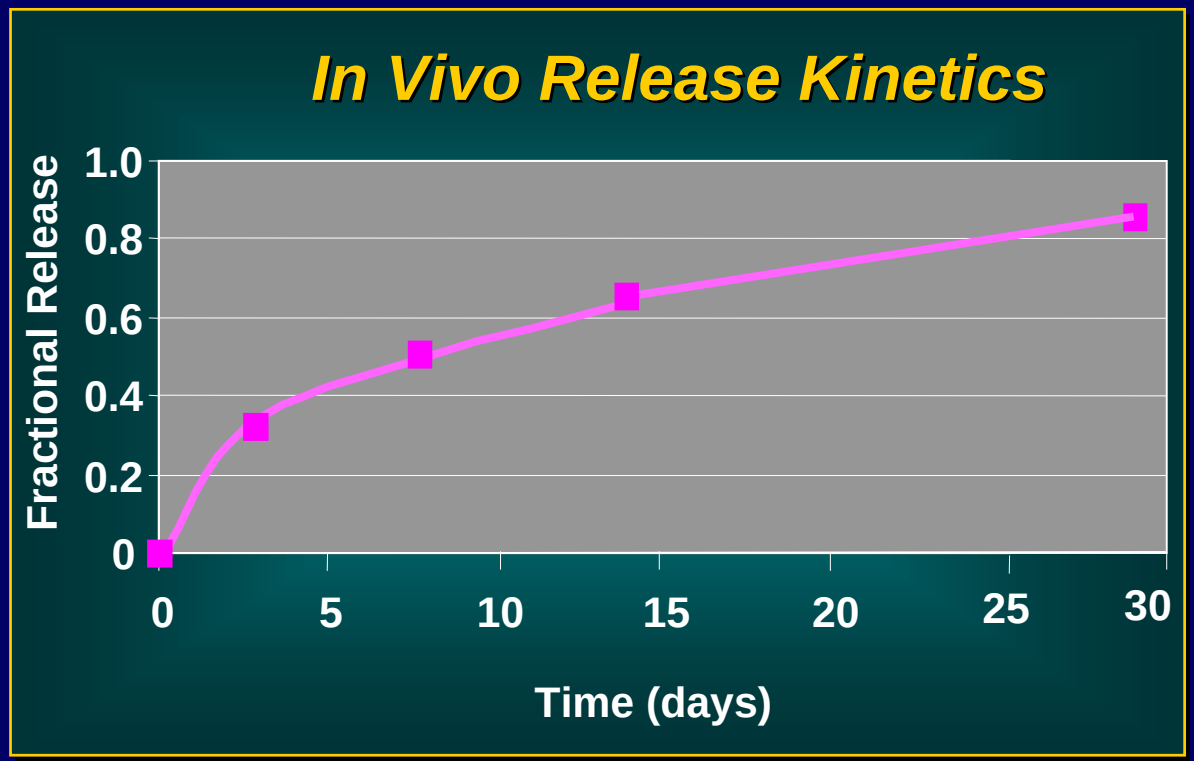


Controlled Sirolimus Elution from Cypher™

Sirolimus is released in a controlled manner from a polymer matrix bound to the stent

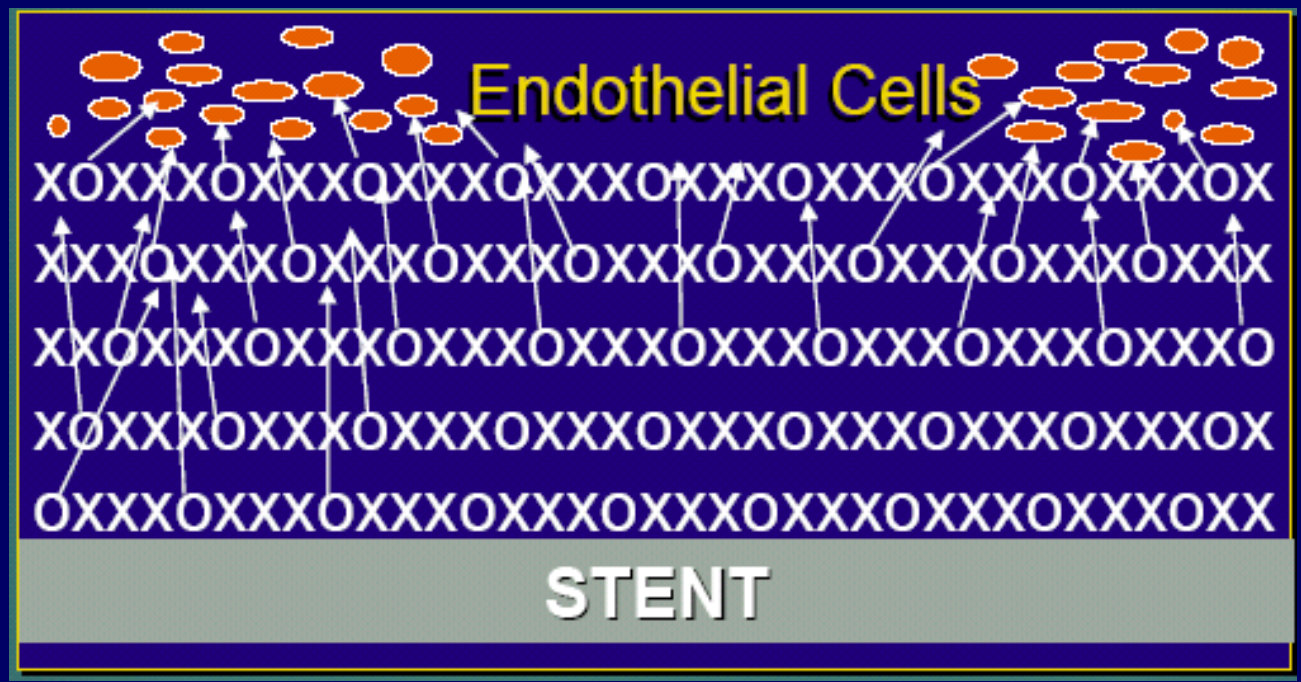


Basecoat = polymer/sirolimus
+
Topcoat = polymer only (diffusion barrier)



Resorbable Polymer-Drug Conjugates

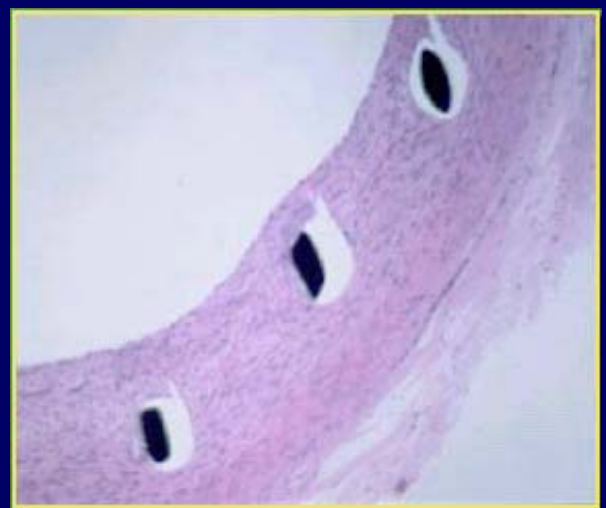
- Conjugated drug utilizing a resorbable polymer
- Controlled release as enzymatic surface erosion



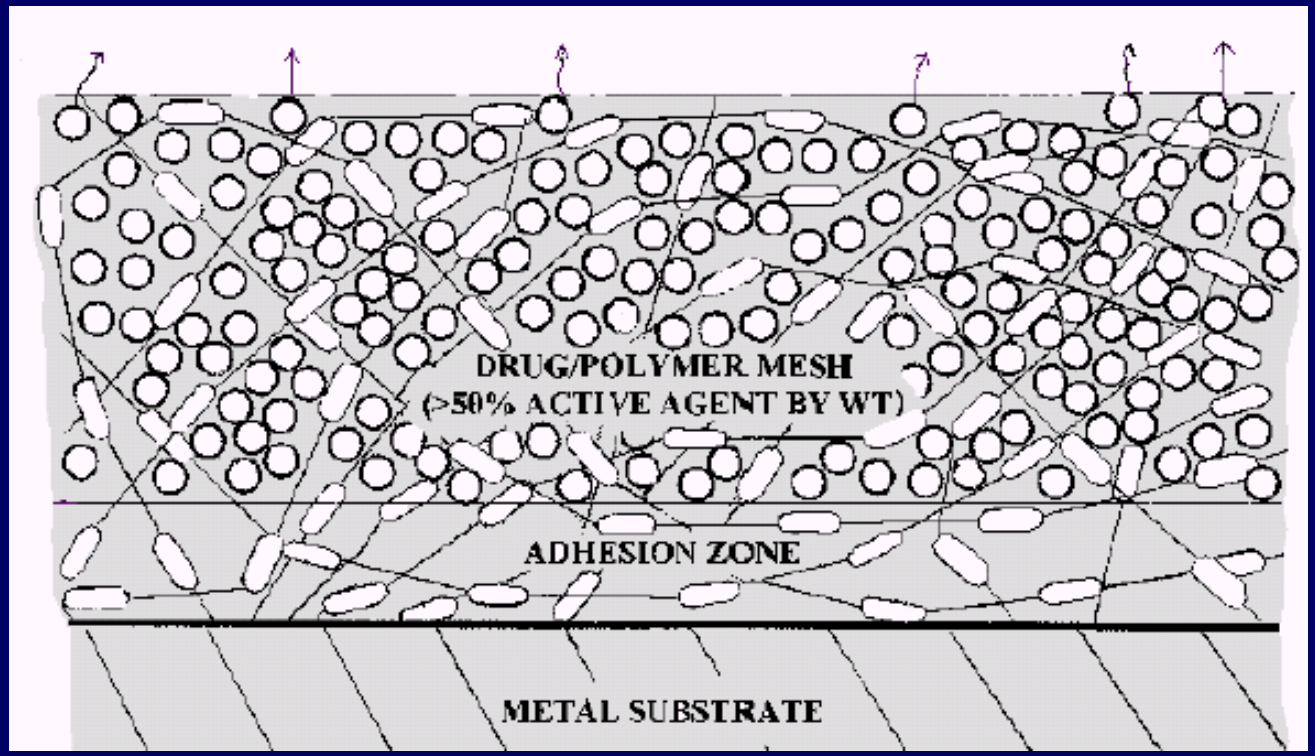
Poly (Ester Amide/Uretanes)

- Vascular compatible
- Bioabsorbable
- Highly elastic with good coating properties
- Amenable to covalent conjugation with biologically active drugs
- Can deliver drugs via matrixing, conjugation with surface erosion or a combination of both

•90 Days In Porcine Coronary Arteries



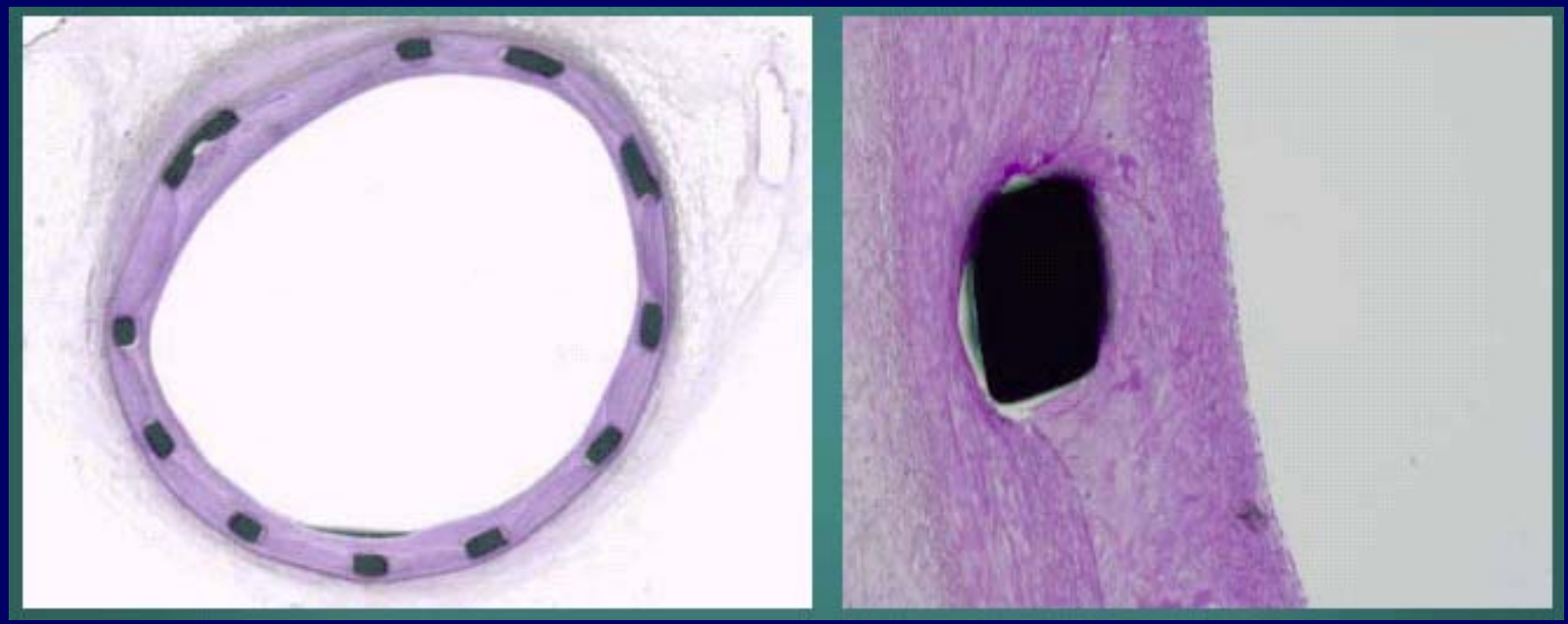
Drug-polymer Composite



- Drug molecules are entangled in a loose ‘net’ of long biodegradable polymer chains
- Dramatically reduced polymer load on tissue which reduced inflammatory responses

Drug-polymer Composite

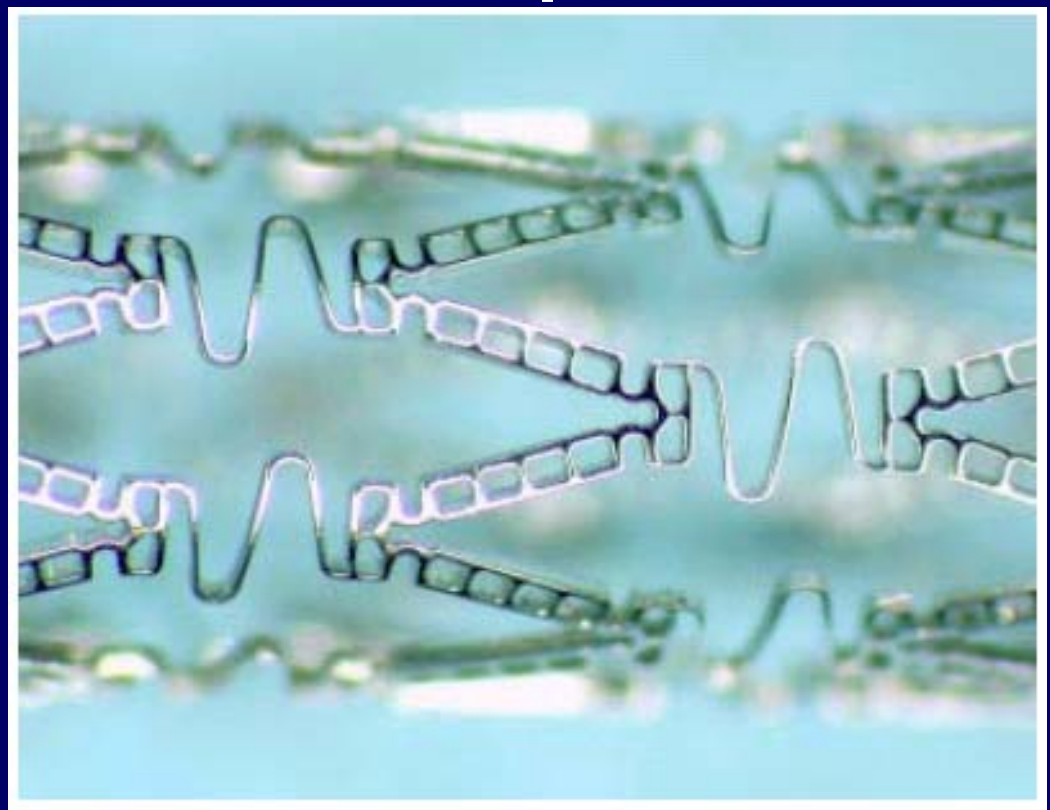
Resorbable PLA polymer
With Everolimus



Drug and polymer has been resorbed
Without inflammatory response
(30 and 90 days)

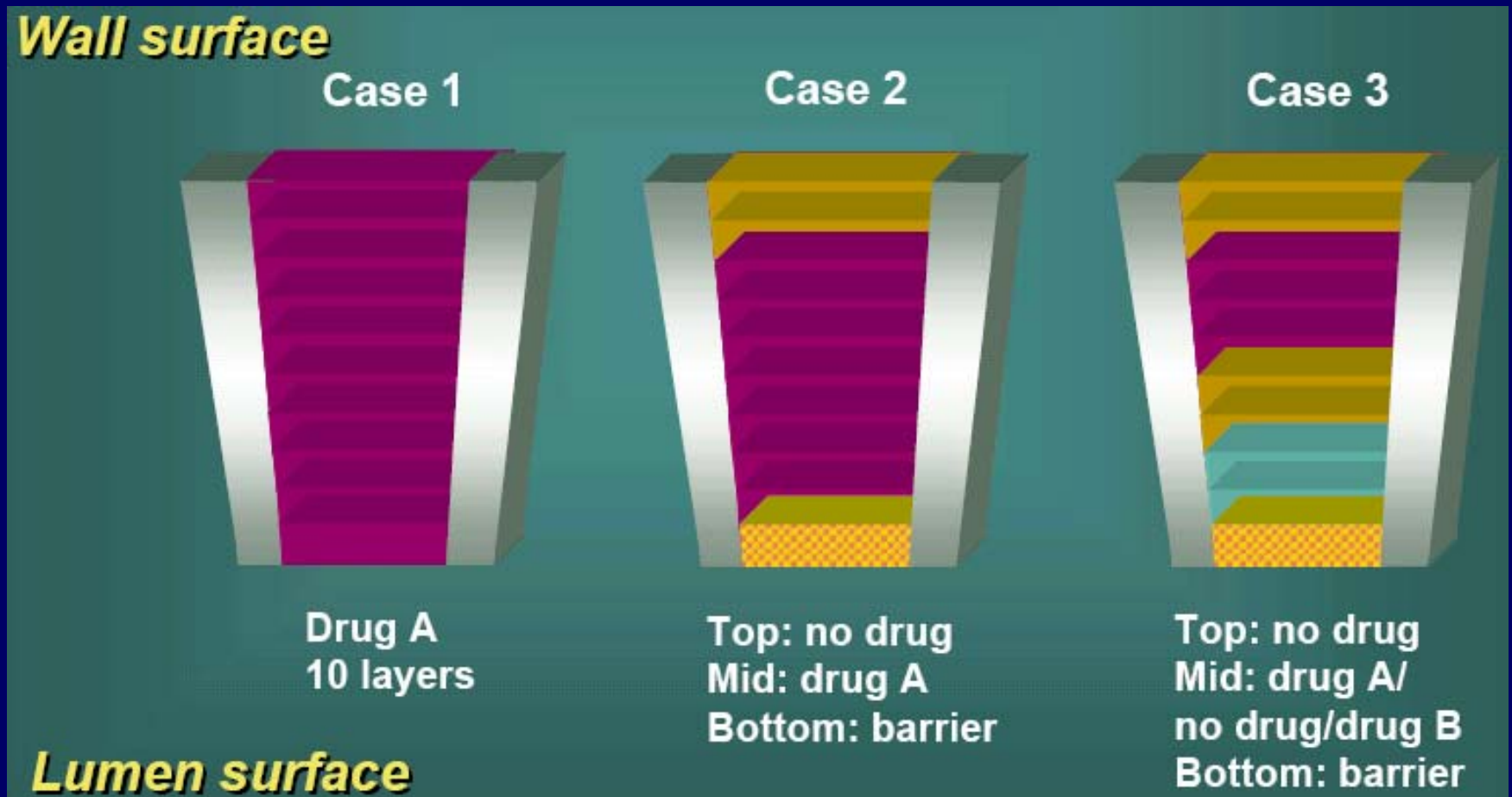
The Conor Drug Delivery Stent

- Multilayered erodable polymer with drug(s) in inlays
- 588 laser cut holes per stent



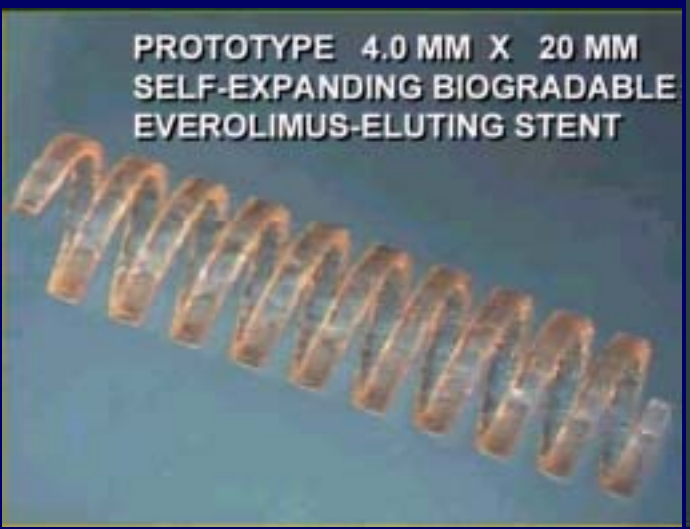
Multi-Layered Degradable Polymer Inlays

The " ultimate" in programmable Drug delivery systems



Drug Eluting Biogradable Stent

- **Drug delivery stents that provide temporary scaffolding, are compatible with cardiac MRI, and that Disappear after drug treatment of some or all of the vessel**



Advantages of a Polymer Carrier

- Mechanical integrity/handling
- Precise dose control
  - Uniform drug distribution
  - Uniform release
  - Ability to modify to achieve therapeutic release
  - Prevent overdosing
- Versability
  - Applicable to other drugs
  - Applicable to other implant platforms

Ideal Polymer

- Non-inflammatory and non-thrombogenic ("biocompatible") – short and long-term
- Predictable and "programmable" drug elution kinetics (bolus and extended release - timing and dose)
- Elastomeric without surface integrity changes (e.g. cracking, peeling) during rigorous clinical implantation procedures
- No alteration of incorporated drug activity
- No alteration of the structural and operational stent characteristics
- Logistic factors – sterilization, shelf-life, stability (in vivo), and expense