# DES - What is Coming?

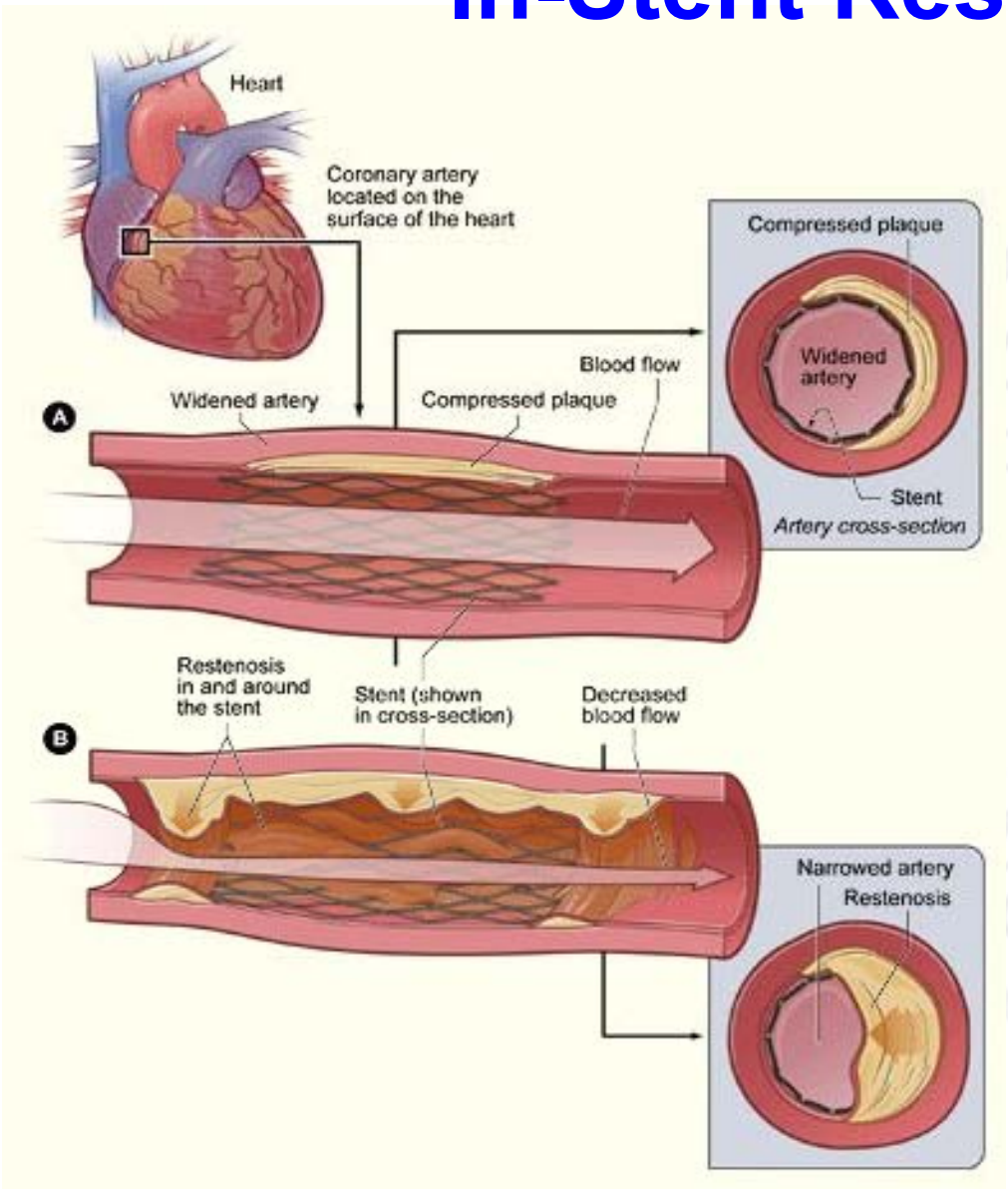
## Drug Delivery System:
## Coating / Polymer

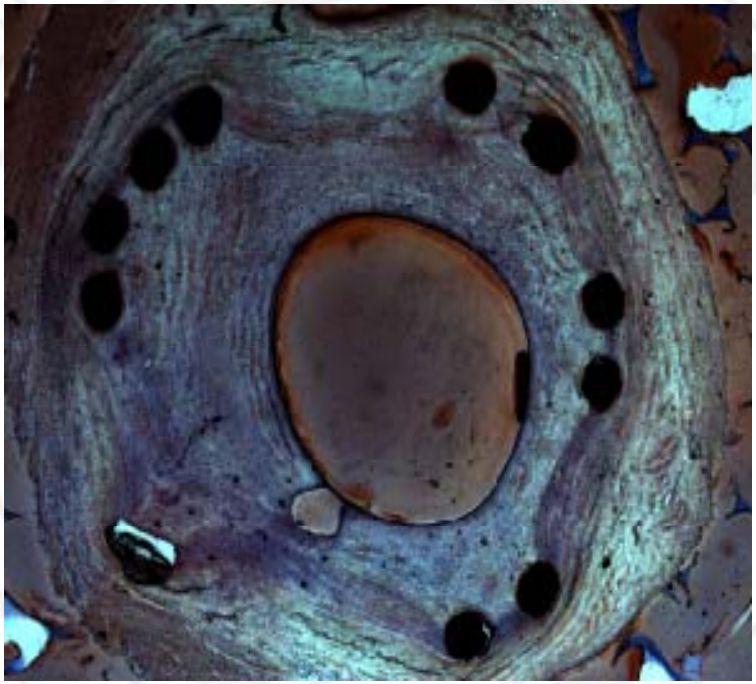
계명의대 심장내과

허 승 호

# Major Issue after BMS

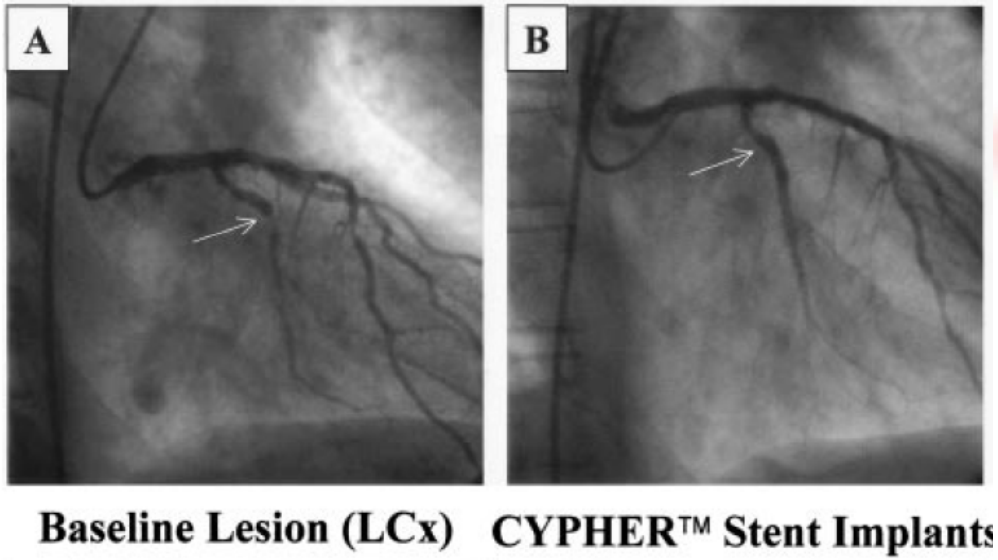
## ~ In-Stent Restenosis ~

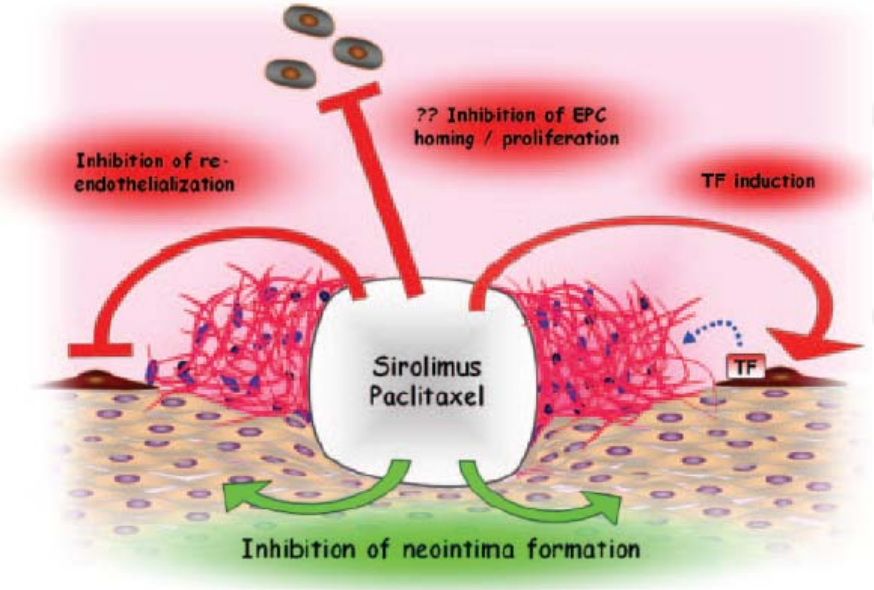


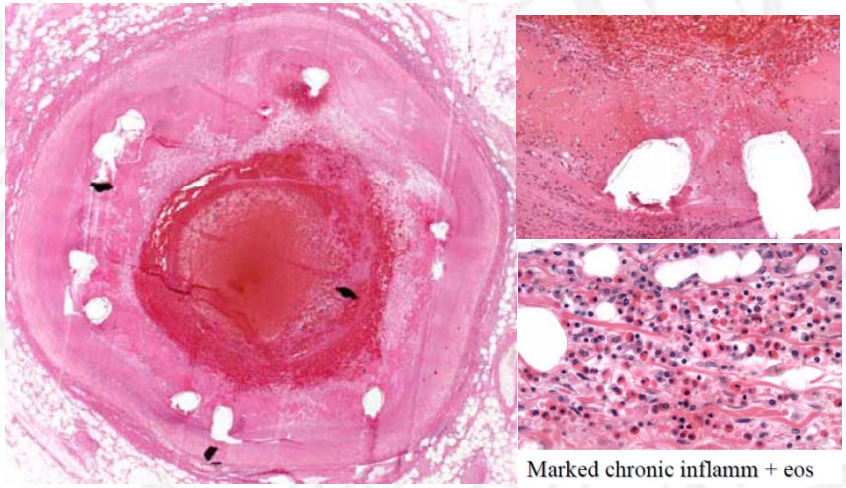



# Major Issue after DES

## ~ Stent Thrombosis ~

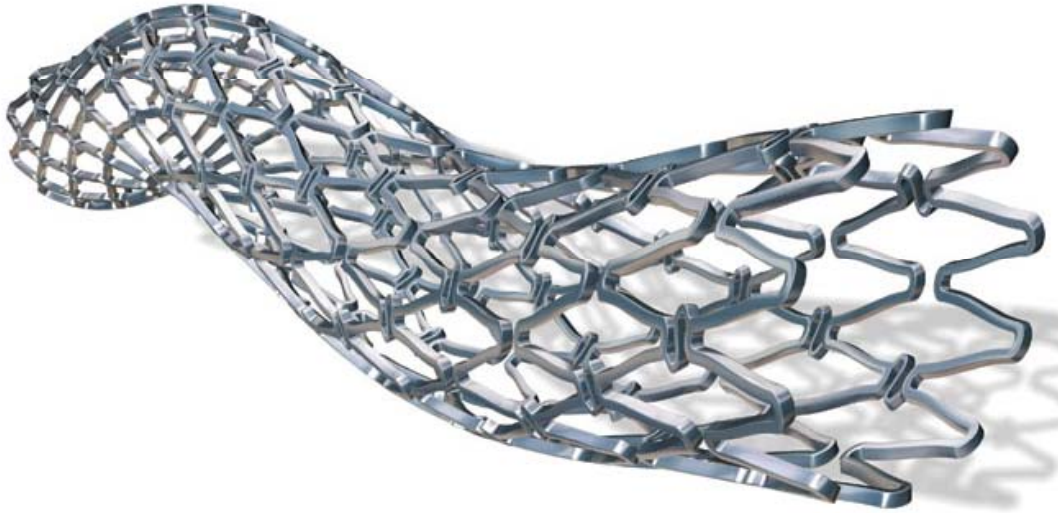



Virmani R. et al. Circ 2004;109:704

# DES Components



- Stent platform
- Drug
- Drug delivery system

  : coating

# The Way of Coating

- Inorganic materials

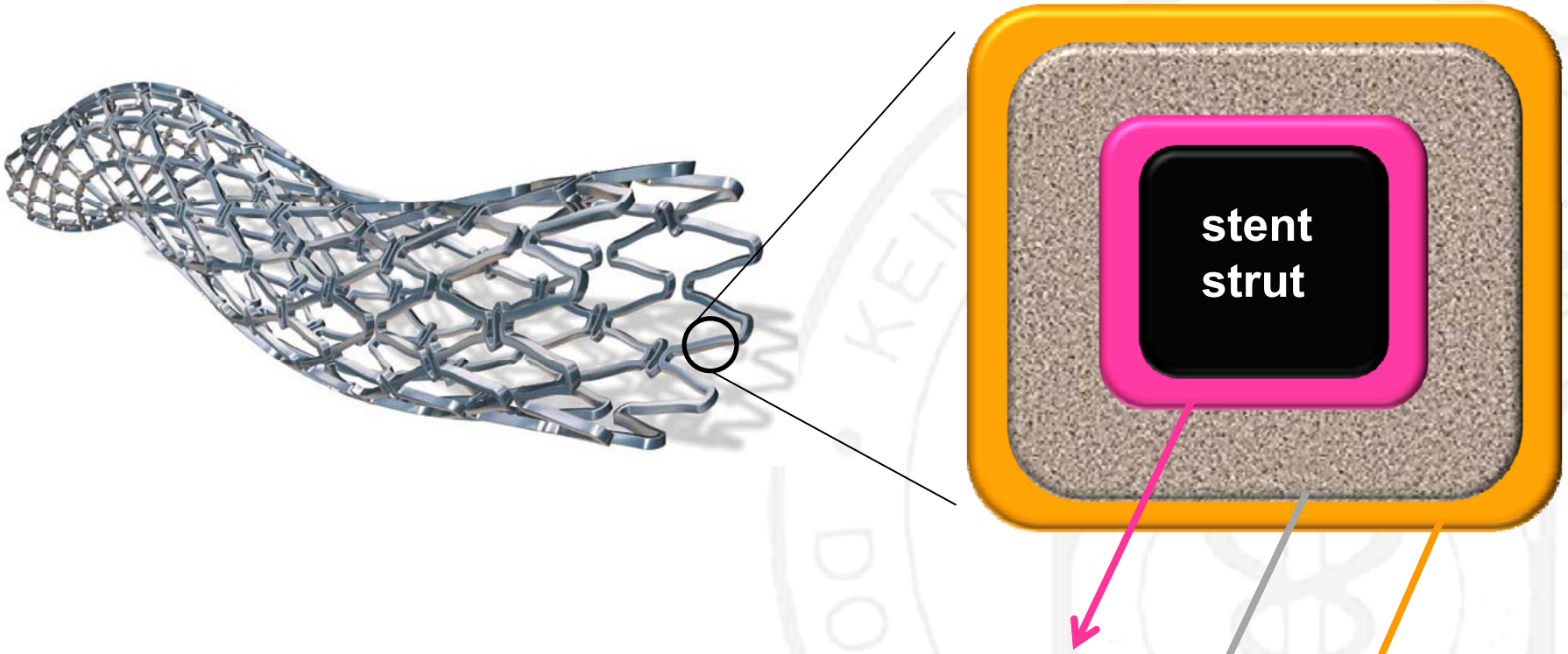
  : gold, iridium oxide, silicon-carbide, carbon

- Porous metals

- Endothelial cells

- Polymers

# Applications of Polymer to DES System




- Drug delivery system
  : coating / polymer
  - primer coat
  - base-coat w/ drug
  - top-coat (option)

# Classification of Polymers

- Biostable polymers

  PEVA (polyethylene-co-vinyl acetate), Parylene C
  PBMA (poly n-butyl methacrylate),
  SIBS (poly[styrene-b-isobutylene-b-styrene]),
  PET (polyethylene terepthalate)

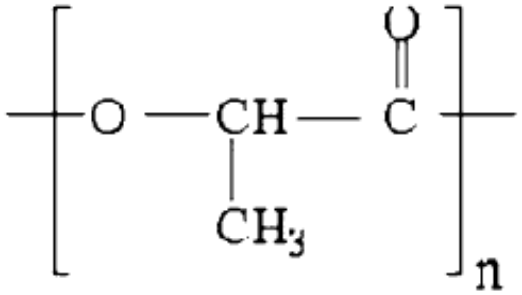
- Biodegradable polymers

  polyesters, polyurethane (PU), polyorthoesters,
  polyphosphazenes, polyanhydrides

- Biologic polymers

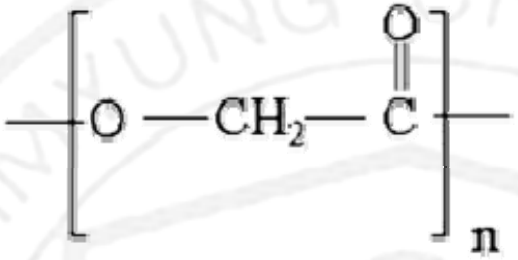
  phosphorycholine (PC), hyaluronic acid, fibrin

# Polyesters Familay in Biodegradable Polymer

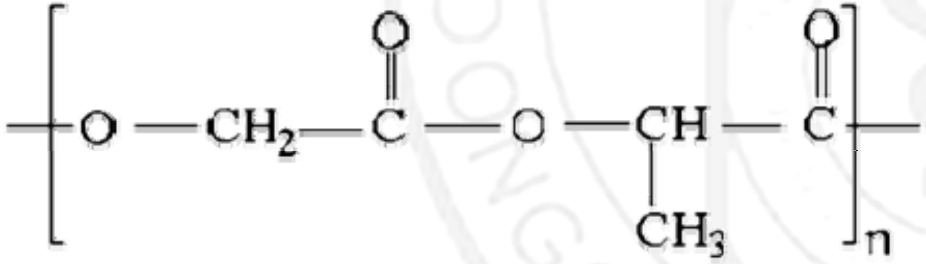


**polylactides (PLA)**

*Biomatrix™, Nobori™*



**polyglycolides (PGA)**



**poly(glycolic-co-lactic acid) (PLGA)**

*NEVO™*

# Hydrophilic vs. Hydrophobic

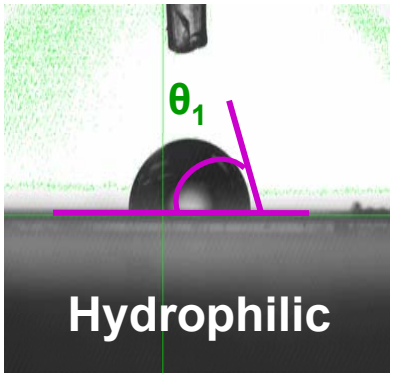
*Contact Angles determine if a polymer is hydrophilic or hydrophobic*

- Angle formed when **water drop** applied to **polymer surface**
- smaller angle = more hydrophilic

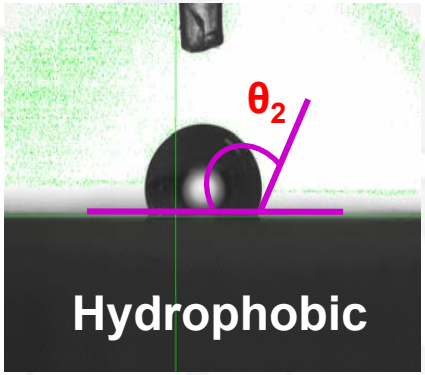
**Contact Angle**

**Hydrophilic Polymer**

*biocompatibility* ↑
*monocyte adhesion* ↓




$\theta_1 < \theta_2$




**Hydrophobic Polymer**

*extended drug release*

| | |
|---|---|
| **PC (Endeavor)** | **81°** |
| **BioLinx (Endeavor Resolute)** | **94°** |

| | |
|---|---|
| **PBMA (Cypher)** | **112°** |
| **SIBS (Taxus)** | **118°** |
| **Fluoropolymer (Xience V)** | **129°** |

**Water-loving** ——— **Water-hating**

# Polymers according to Individual DES

- 1st generation

  Cypher™, Taxus Liberte™

- 2nd generation

  Xience™, Endeavor™, Endeavor Resolute™

- New generation

  Biomatrix™, Nobori™

  Promus Element™, Nevo™

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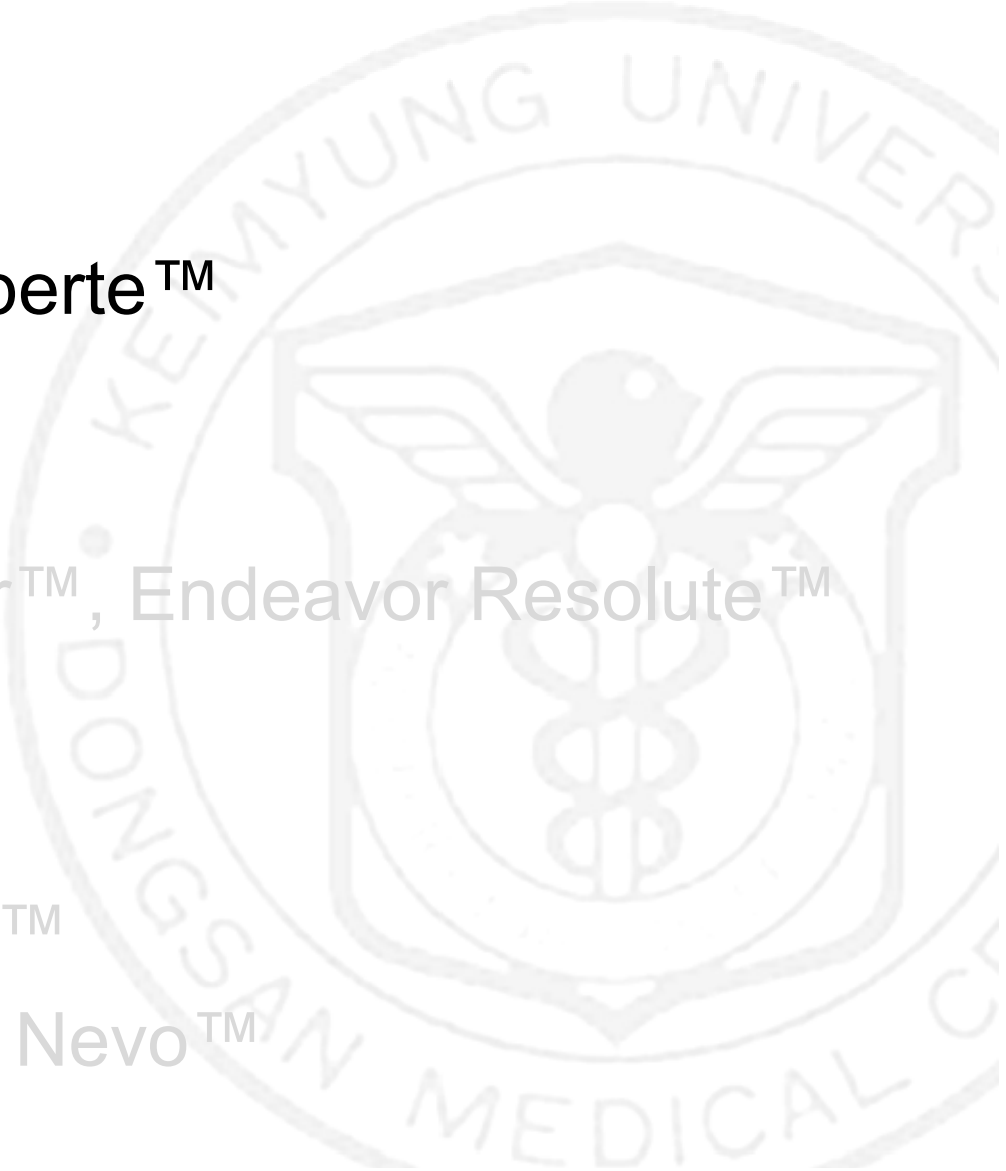
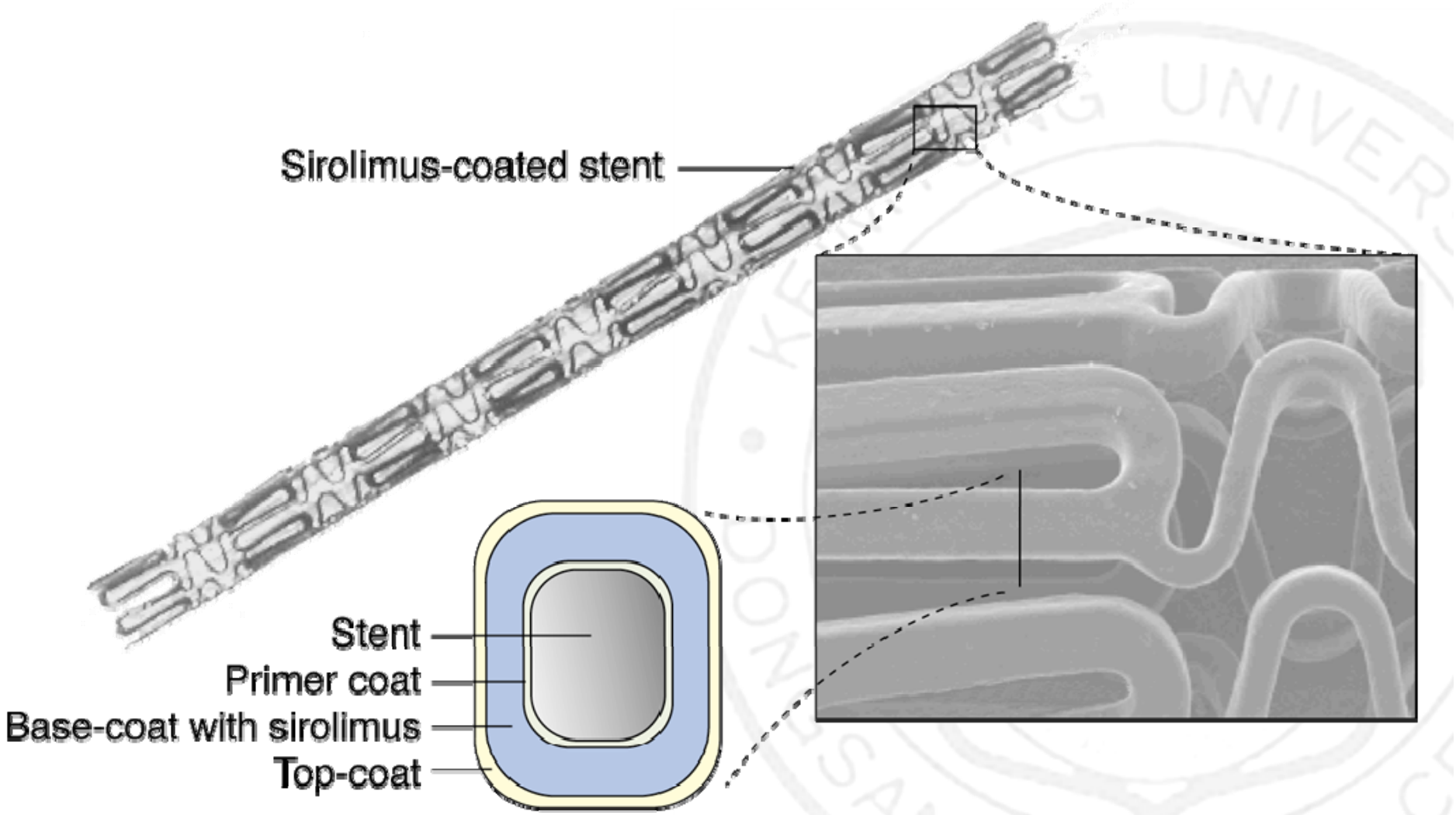
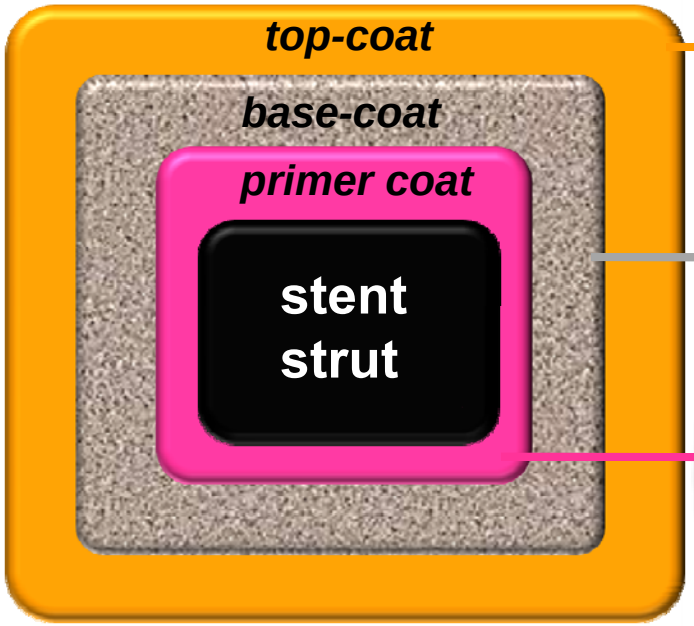


# Cypher™


Sirolimus-coated stent
Stent
Primer coat
Base-coat with sirolimus
Top-coat

# Cypher™

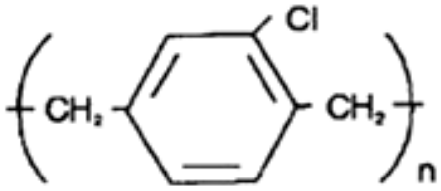
**3 layers:** biostable, hydrophobic



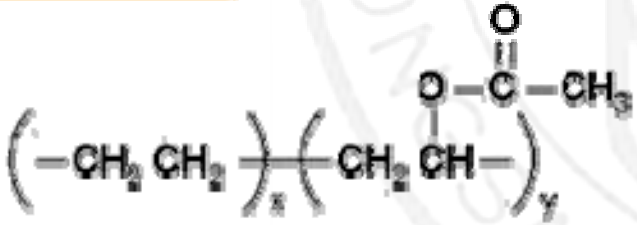

**PBMA**
(rate-limiting barrier, 0.6μm)

**PEVA+PBMA+Sirolimus**
(drug loaded matrix, 10μm)

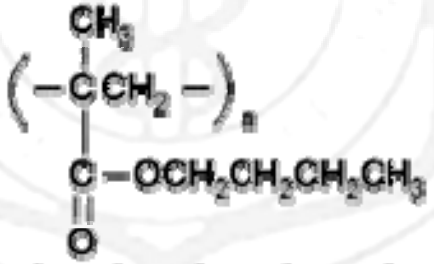
**Parylene C**
(2 μm)


Parylene C




polyethylene-co-vinyl acetate
(PEVA)



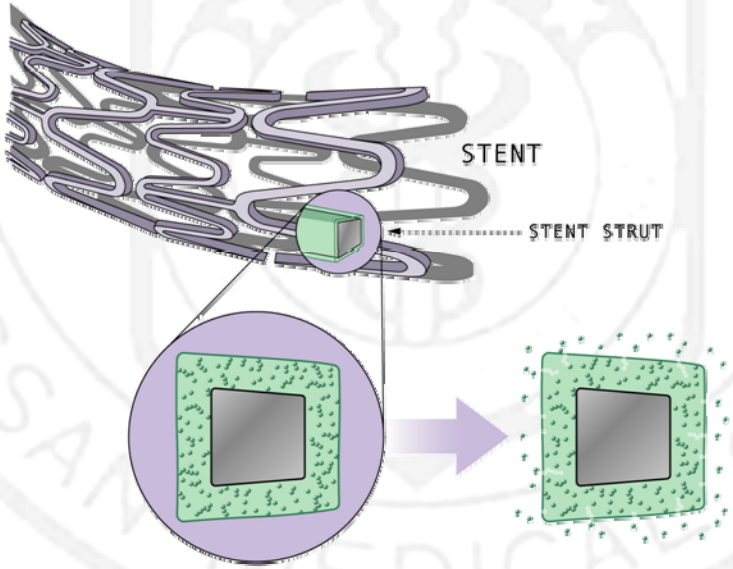

poly n-butyl methacrylate
(PBMA)

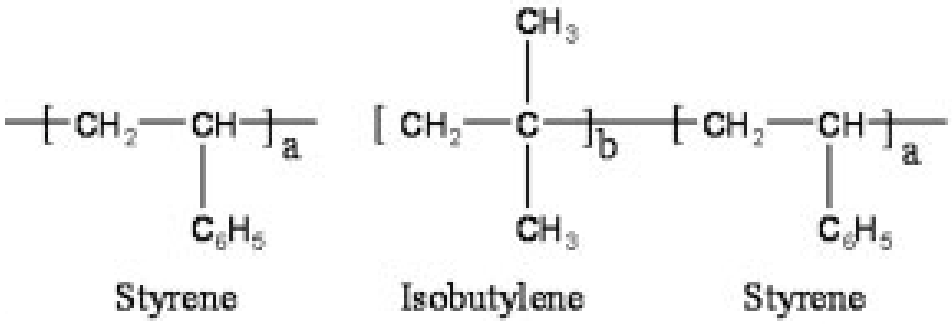
# Taxus™

**1 layer:** biostable, hydrophobic

No primer coat
No top-coat


**SIBS (Translute™)**
**+ Paclitaxel**

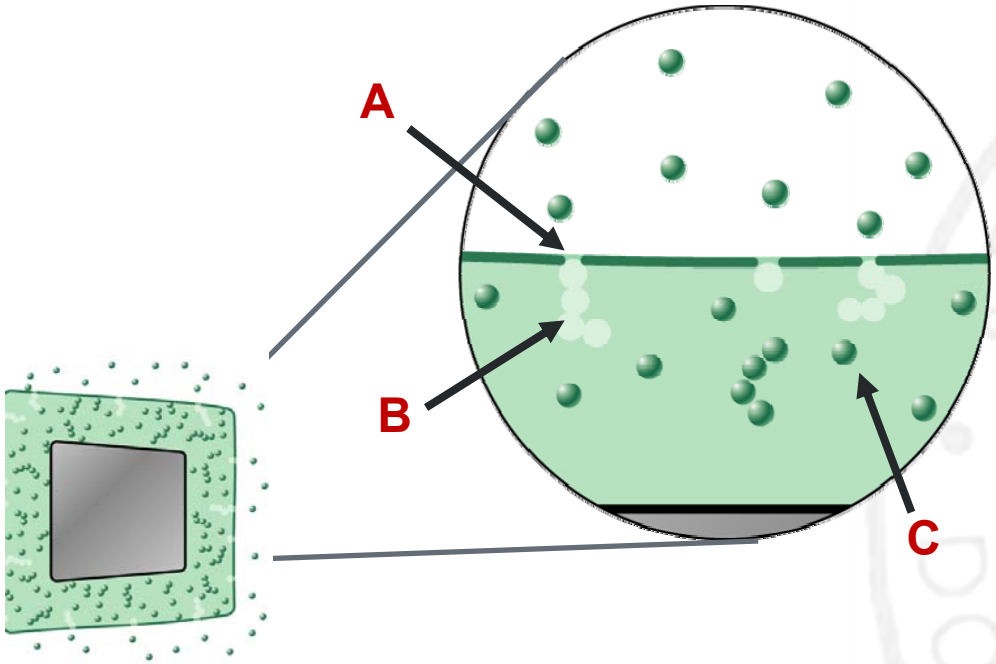



SIBS [poly(styrene-b-isobutylene-b-styrene)]

# Taxus™: Polymer Control Drug Release

The ratio of paclitaxel to polymer determines both the **amount** and the **timing** of drug release.




- Paclitaxel is **NOT SOLUBLE in Translute** and is **EMBEDDED** in a solid, particulate form
- **Burst release** in the first 48 hours,
  **Slow release** over the next 10 days, and
  **No further release** after 30 days
  (90% drug remains on polymer)

**A**. The paclitaxel on the surface is released first, comprising the **INITIAL BURST PHASE**

**B.** The subsurface particles that gain access to the external environment comprise the **PROLONGED RELEASE** of paclitaxel

**C**. Paclitaxel that is not exposed to the surface is **PERMANENTLY SEQUESTERED** in the polymer

# Polymers according to Individual DES

- 1st generation

  Cypher™, Taxus Liberte™

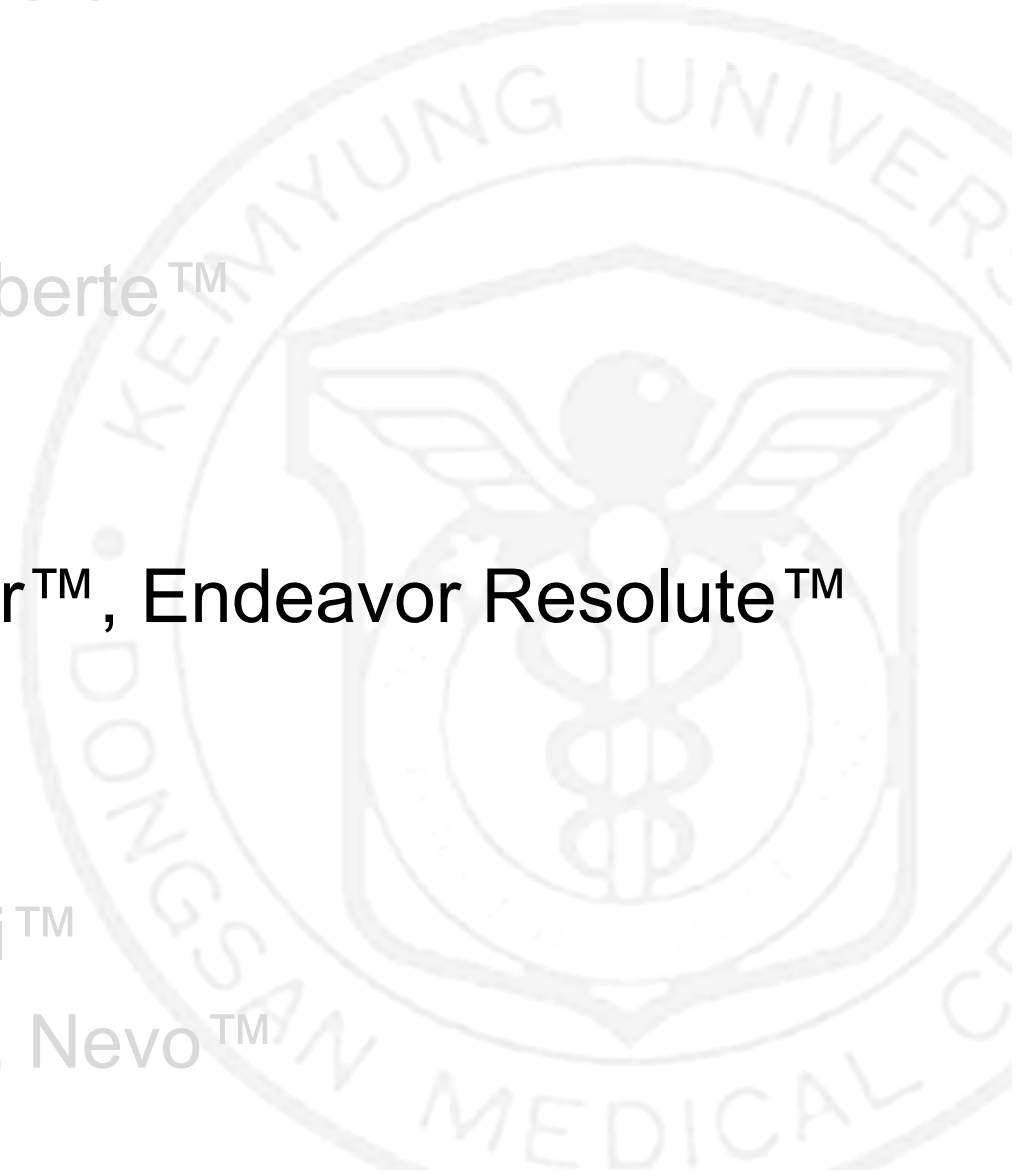
- 2nd generation

  Xience™, Endeavor™, Endeavor Resolute™

- New generation

  Biomatrix™, Nobori™

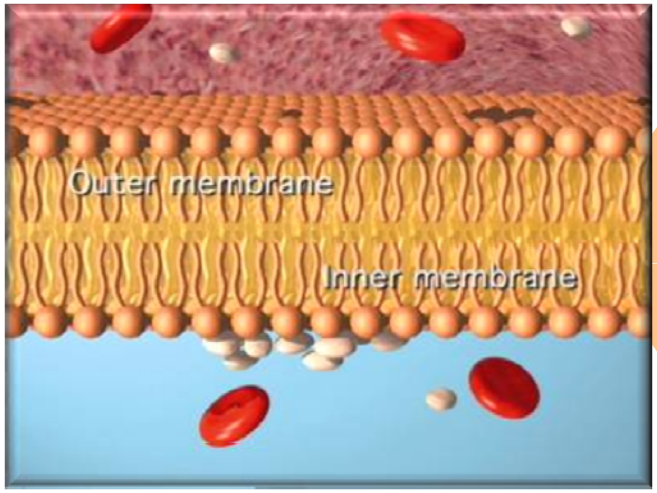
  Promus Element™, Nevo™

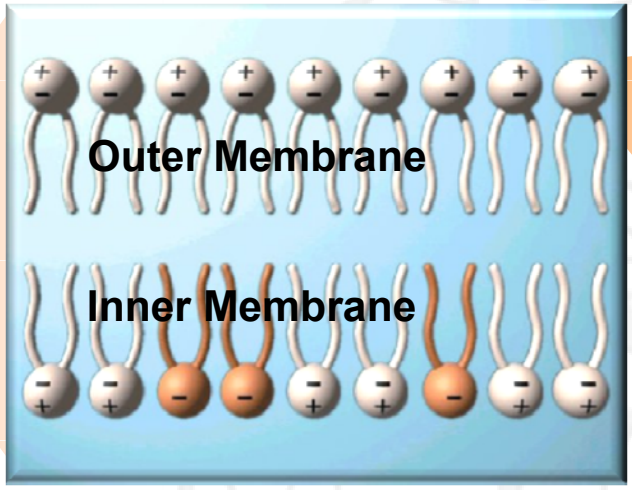


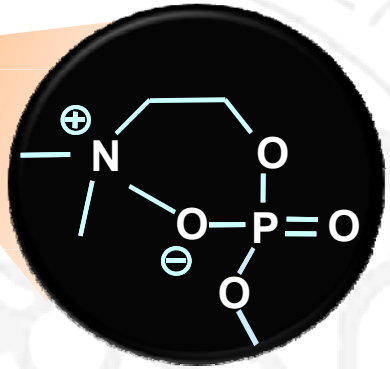
# Endeavor™

## ~ Phosphorylcholine (PC) Technology ~

- major component of the outer layer of cell (RBC) membrane
- PC mimics the chemical structure of the phospholipid head group




hydrophilic PC head group

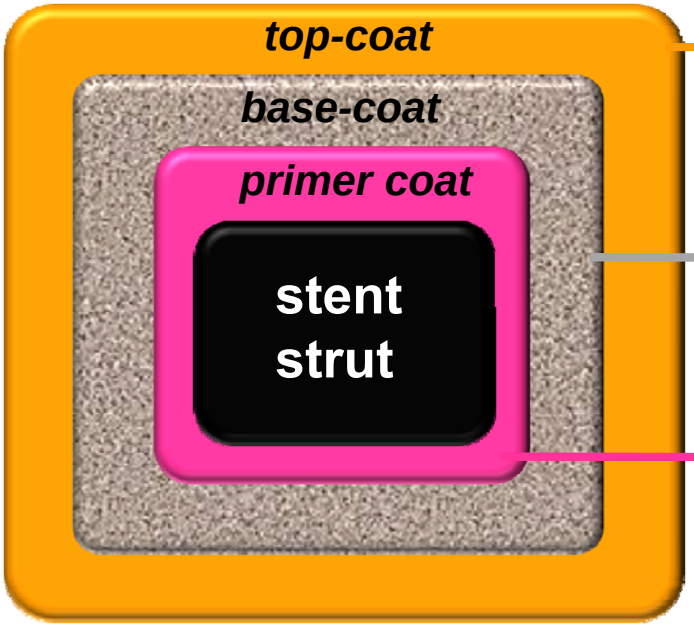
PC coating

- hydrophilic outer layer : high biocompatibility w/ reduced thrombogenic potential
- hydrophobic inner layer : drug carrier for slow elution
- biologically favorable effects on reduction of PLT activation , thrombus deposition, and rate of re-endothelialization

*Hayward JA . et al. Biomaterials 1984; 35:5*
*Pendyala L. et al. J Interven Cardiol 2009;22:37*

# Endeavor™

**3 layers:** biologic, hydrophilic & ~phobic




**PC**
(≈ 0.1 μm thick)

**PC**(10%) **+ Zotaro-limus**(90%)

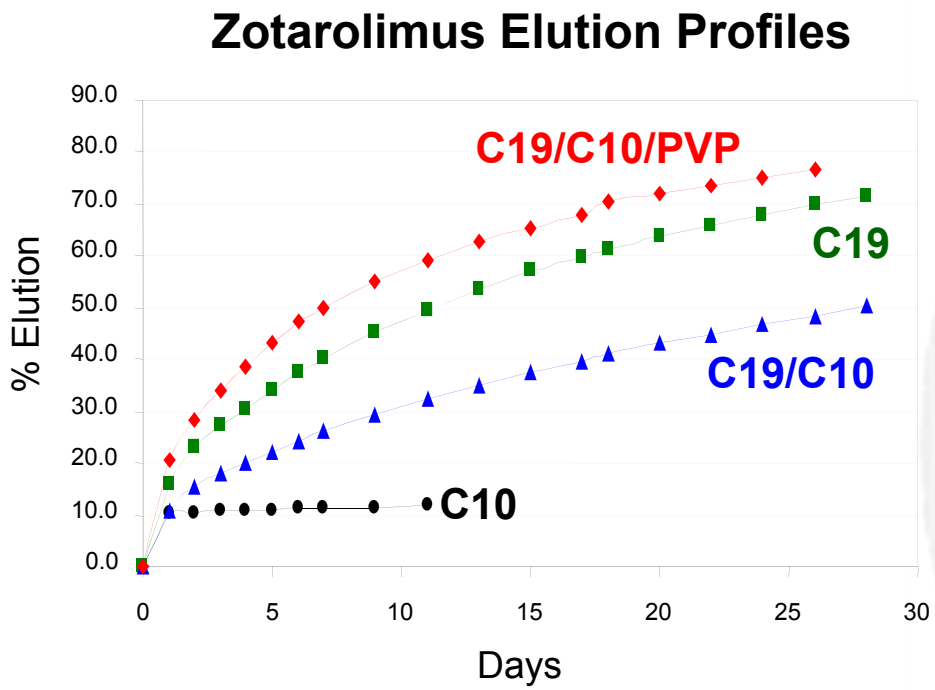
**PC**
(≈ 1 μm thick)

**Phosphorylcholine (PC)**

# Endeavor Resolute™

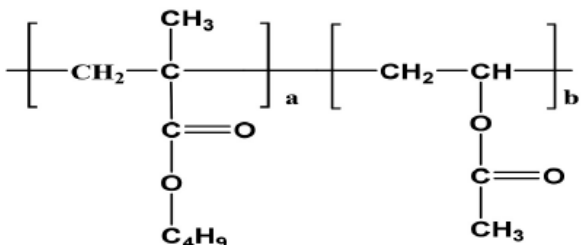
## ~ BioLinx Polymer System ~

- Blends **C10**, **C19** and **PVP** for extended elution

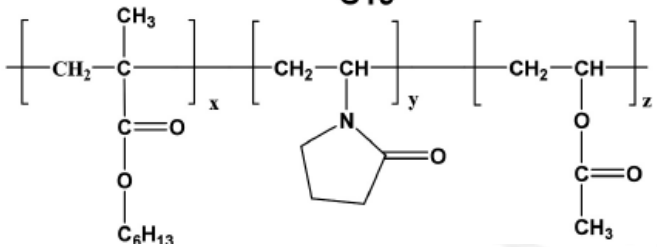



- **PVP**: hydrophilic, increases the initial drug burst and enhances the elution rate
- **C19 polymer**: primarily hydrophilic making it more biocompatible and aids in drug elution
- **C10 polymer**: hydrophobic and aids in extended drug release

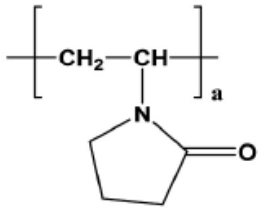
C10



C19



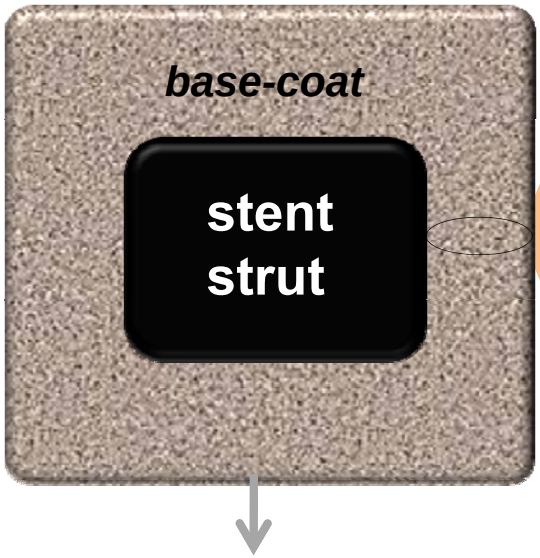
Polyvinyl pyrrolidinone (PVP)



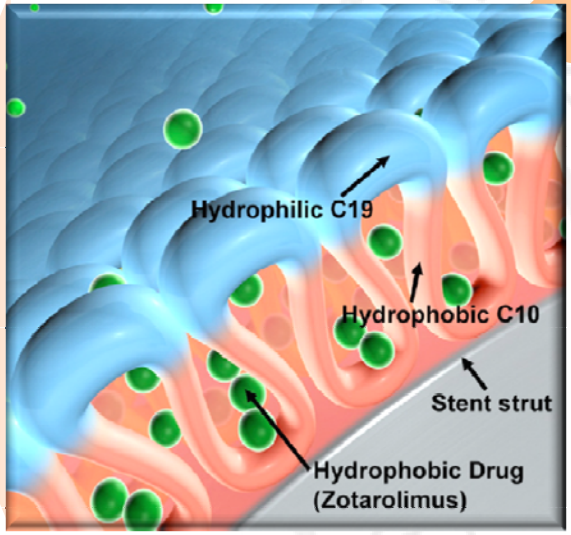
# Endeavor Resolute™

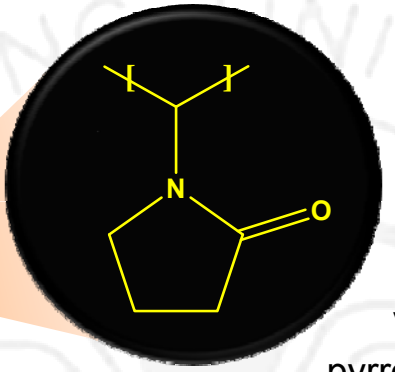
**2 layers:** biostable, hydrophilic & ~phobic

**No primer coat**
**No top-coat**




C19/C10/PVP
+
Zotarolimus



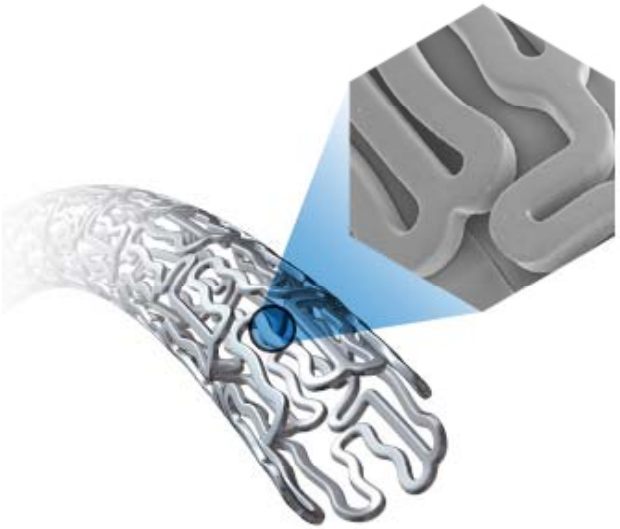




Vinyl pyrrolidinone groups

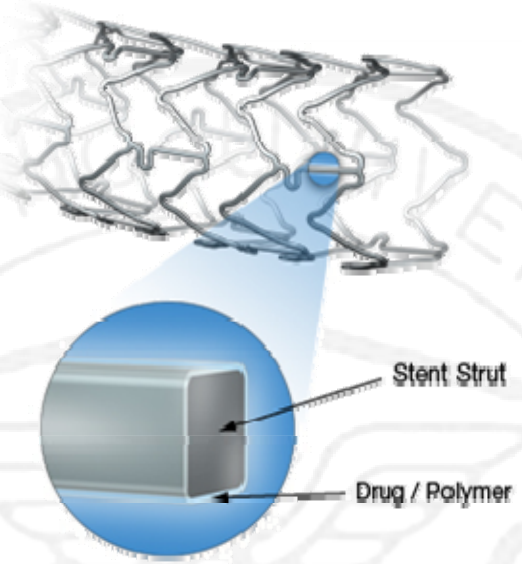
- **C19/PVP:**
  : hydrophilic outer layer
  - biocompatible
  - non-thrombotic
  - non-inflammatory

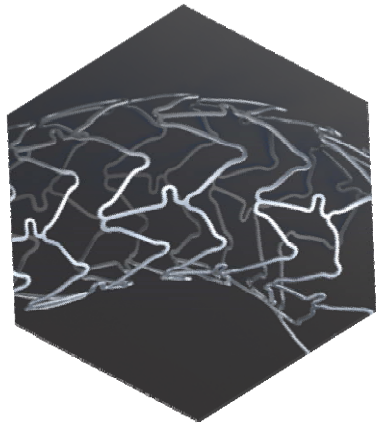
- **C10**
  : hydrophobic inner layer
  - high drug retention
  - uniform drug distribution

# Xience V™



**Fluoropolymer**



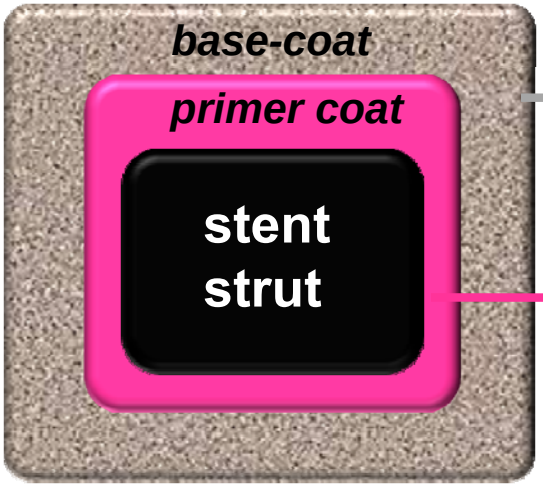



| | FLUOROPOLYMER USE |
|---|---|
| Drug Eluting Stent: | •XIENCE V Everolimus Eluting Coronary Stent System |
| Other Applications: | •arterial prostheses<br>•graft prostheses<br>•hemodialysis membrane<br>•vascular suture<br>•guiding catheter<br>•other blood contacting surfaces |

# Xience V™

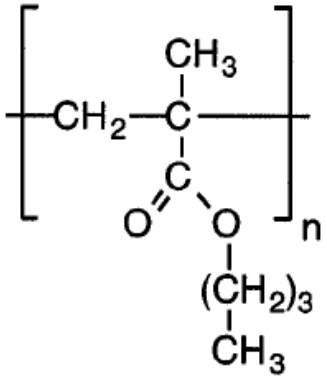
**2 layers:** biostable, hydrophobic

No top-coat



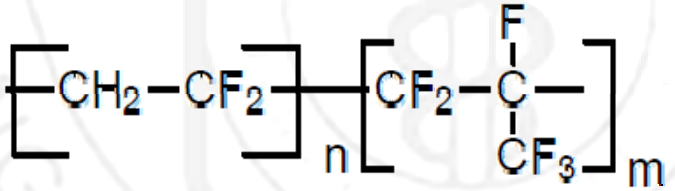

**PVDF-HFP+Everolimus**
(fluoropolymer)

**PBMA**
(acrylic polymer)



**PBMA**

poly n-butyl methacrylate

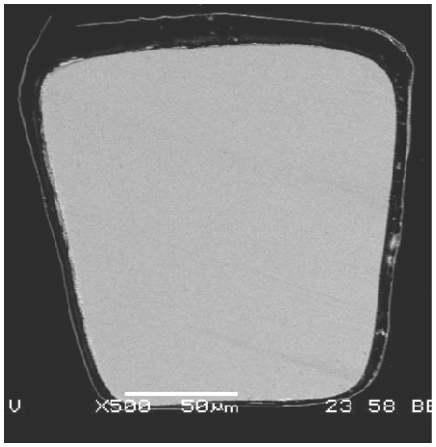
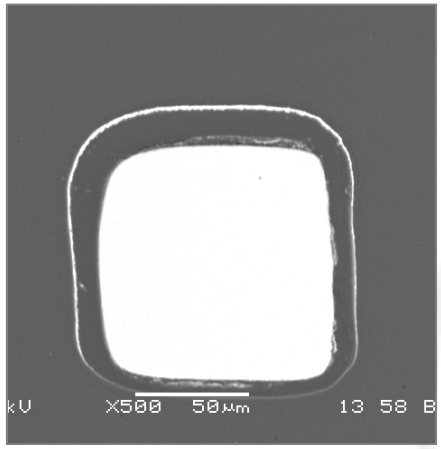
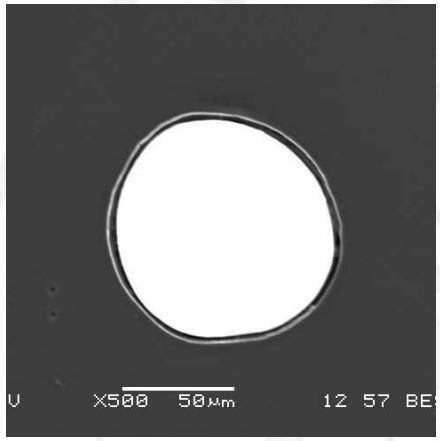
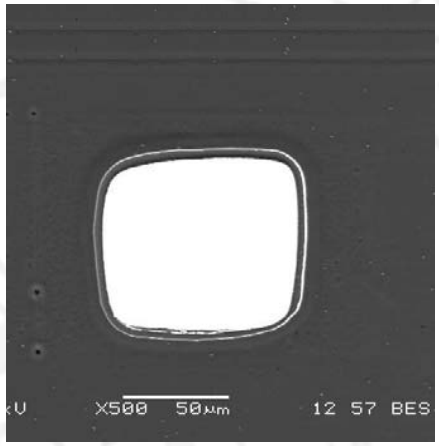


**PVDF-HFP**

poly (vinylidene fluoride-co-hexafluoropropylene)

# DES Strut and Polymer Thickness

3.0 mm diameter stents, 500x magnification

| CYPHER™ | TAXUS Liberté™ | ENDEAVOR™ | XIENCE V™ |
|---|---|---|---|
|  |  |  |  |
| **Strut Thickness:** | **Strut Thickness:** | **Strut Thickness:** | **Strut Thickness:** |
| 140 μm | 97 μm | 91 μm | 81 μm |
| **Polymer Thickness:** | **Polymer Thickness:** | **Polymer Thickness:** | **Polymer Thickness:** |
| 12.6 μm | 17.8 μm | **5.3 μm** | 7.6 μm |
| Total | Total | Total | Total |
| 152.6 μm | 114.8 μm | 96.3 μm | **88.6 μm** |

# Polymers according to Individual DES

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- 2nd generation

  Xience™, Endeavor™, Endeavor Resolute™

- New generation

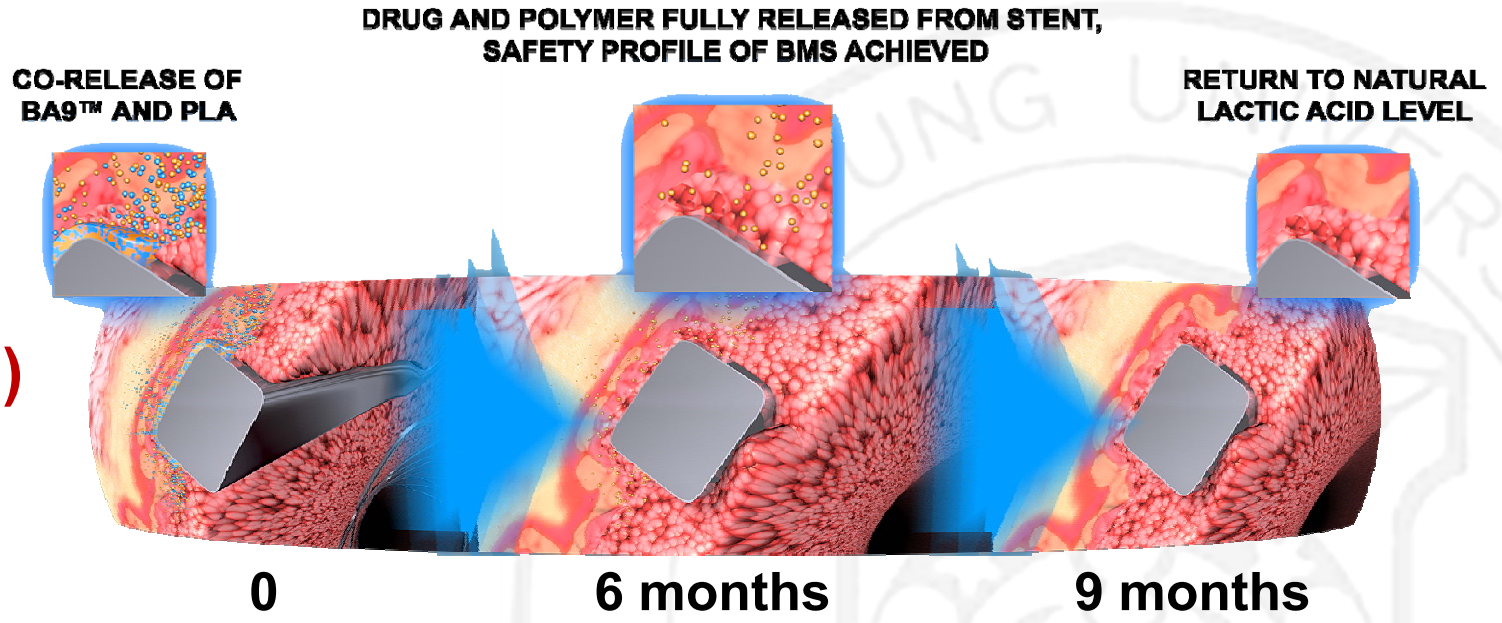
  Biomatrix™, Nobori™

  Promus Element™, Nevo™

# BioMatrix™ & Nobori™

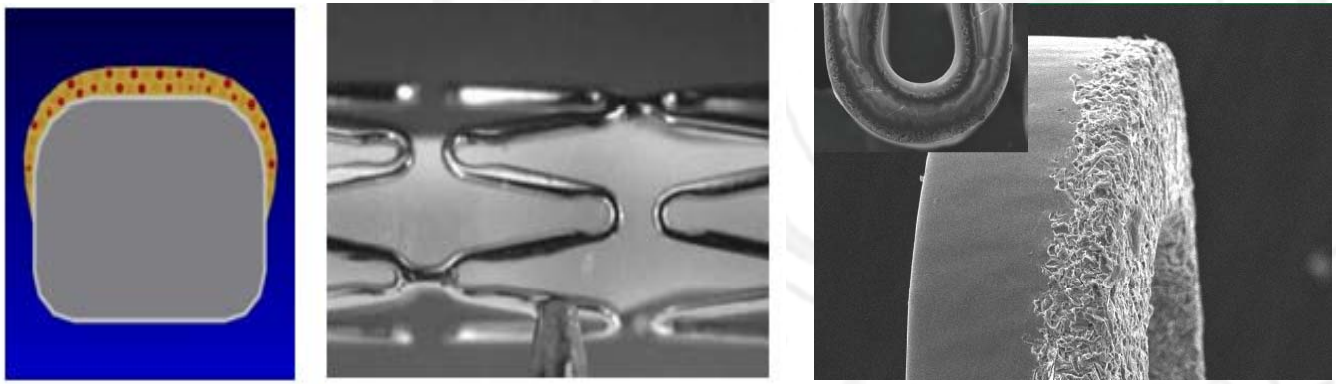
## Bio-degradable PLA (polylactides)

from DES to BMS
in 6 months




## Abluminal coating

- targets blood vessel walls
- small amounts are released into circulation

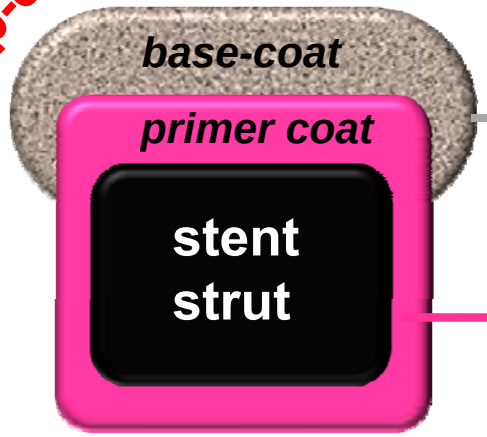


AutoPipette™ Coating Process

# BioMatrix™ & Nobori™

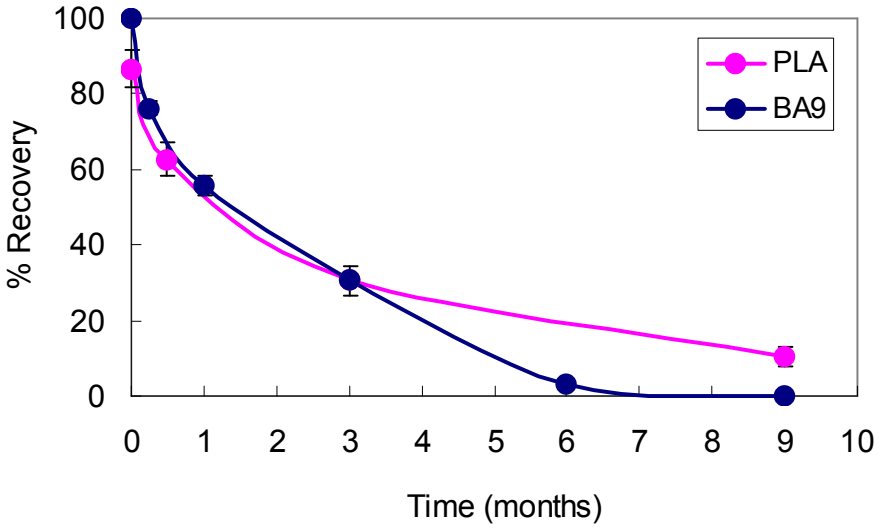
**2 layers:** biodegradable

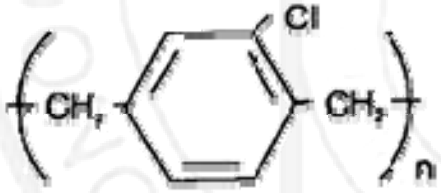
No top-coat



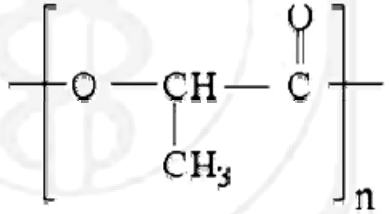

**PLA**+Biolimus A9™

**Parylene C**


**Parylene C**




**PLA**

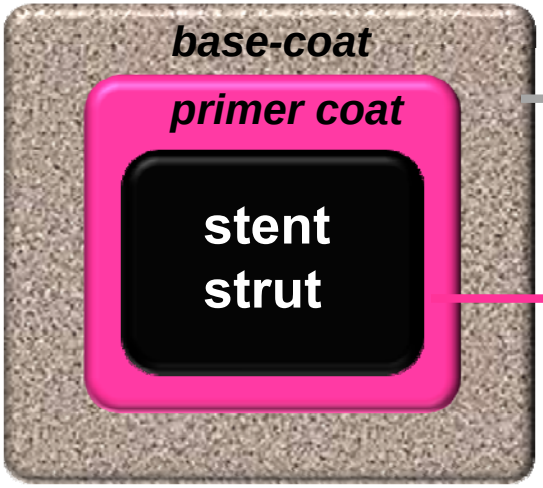
polylactides

# Promus Element™

**2 layers:** biostable, hydrophobic

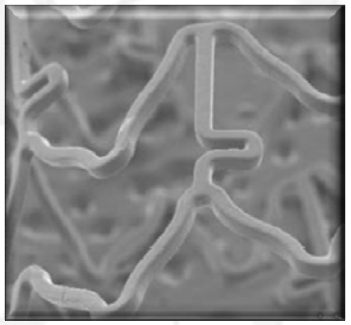
same as **Xience V**

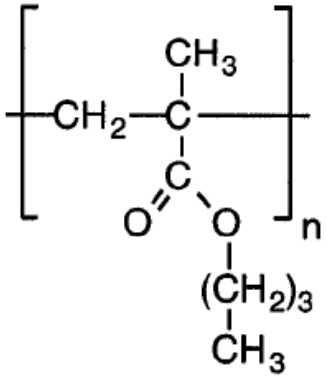
No top-coat




**PVDF-HFP+Everolimus**
(fluoropolymer)

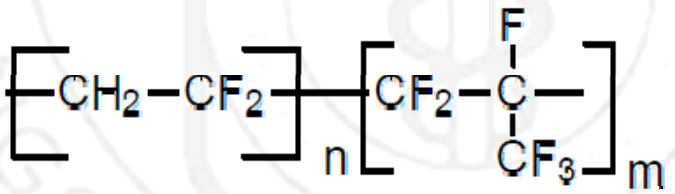
**PBMA**
(acrylic polymer)





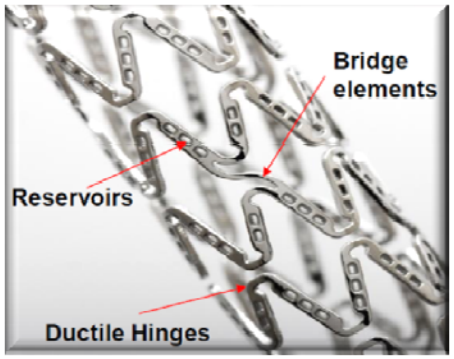

**PBMA**

poly n-butyl methacrylate




**PVDF-HFP**

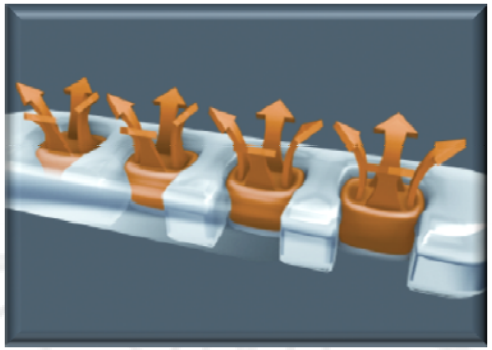
poly (vinylidene fluoride-co-hexafluoropropylene)



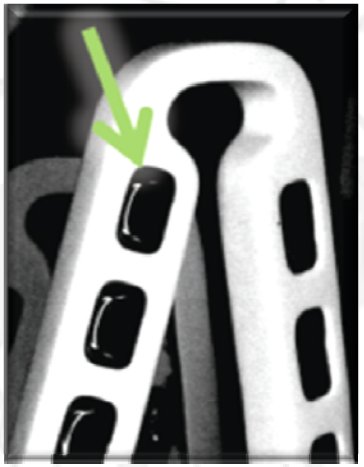

# NEVO™

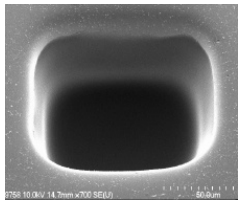
## ~ RES Technology™ ~

*(Reservoir Technology)*

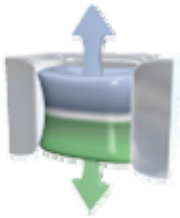


- concentrates the drug and a fully biodegradable polymer matrix
- eliminates the need for a surface polymer coating (tissue/polymer contact reduced by 75%)
- facilitates a controlled drug deliver (independent single or multiple-drug release)

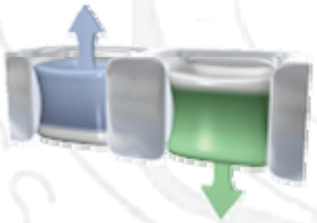




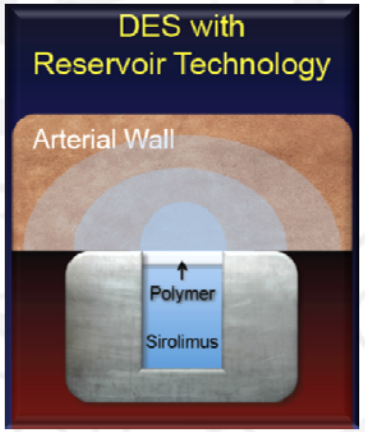
**Single Drug Single Release** (NEVO™)



**Dual Drug, Single Reservoir Bi-Directional Release** (future innovations)

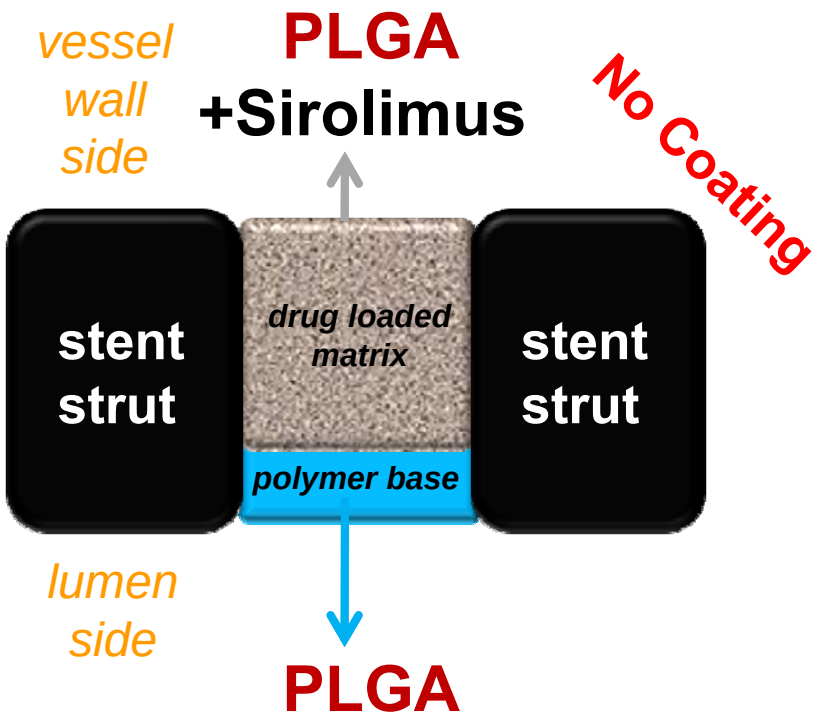


**Dual Drug, Bi-Directional Release** (future innovations)

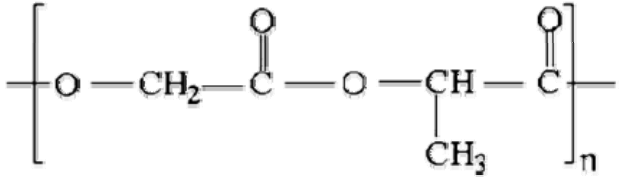


# NEVO™

**2 layers:** biodegradable

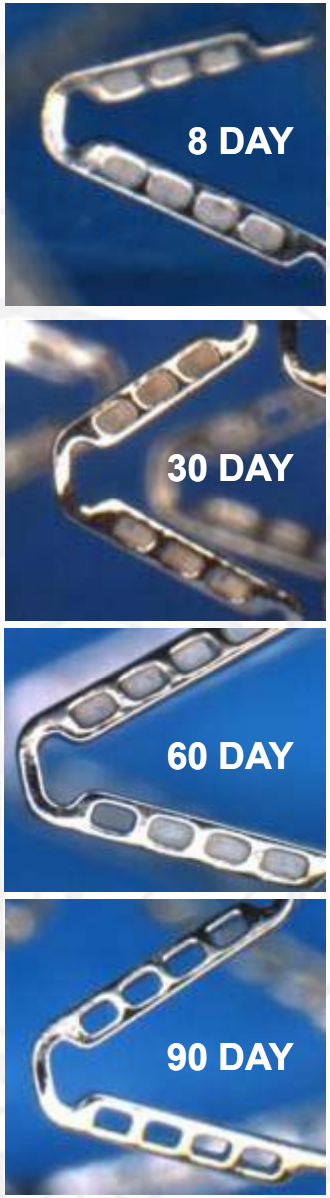



poly(glycolic-co-lactic acid)

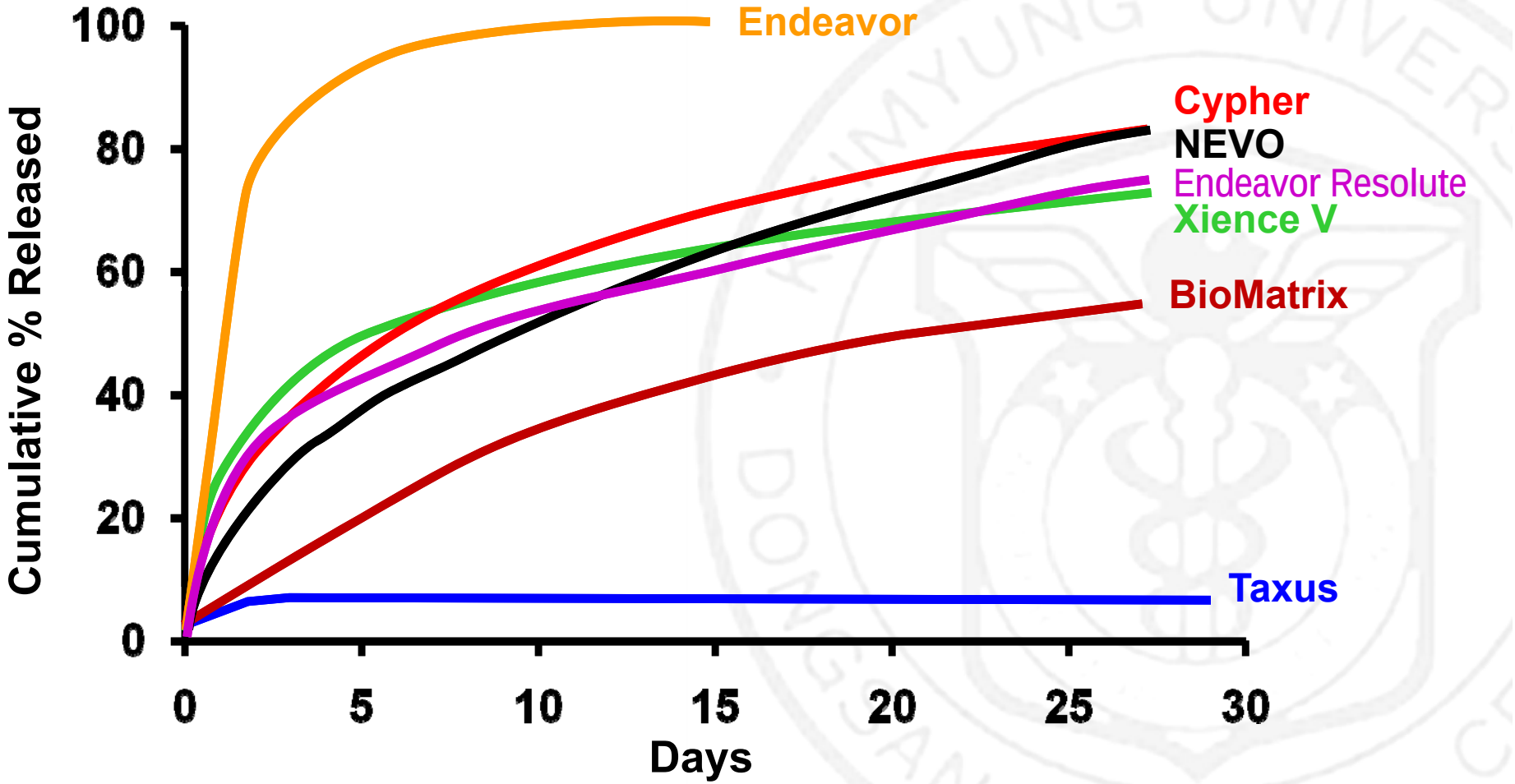


## PLGA polymer benefits

- complete resorption in 3-4 months
- fully metabolized
- highly biocompatible and hemocompatible
- controlled Sirolimus release without a surface coating

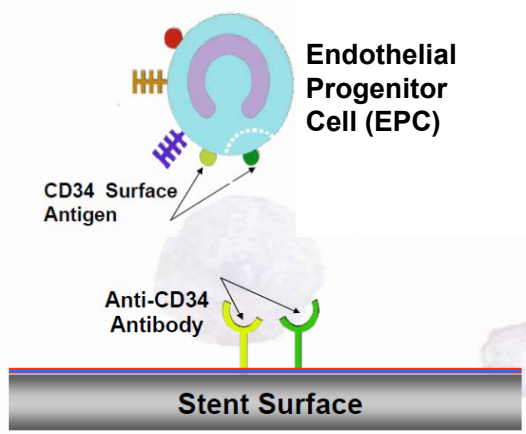


# DES: Drug Release Profile

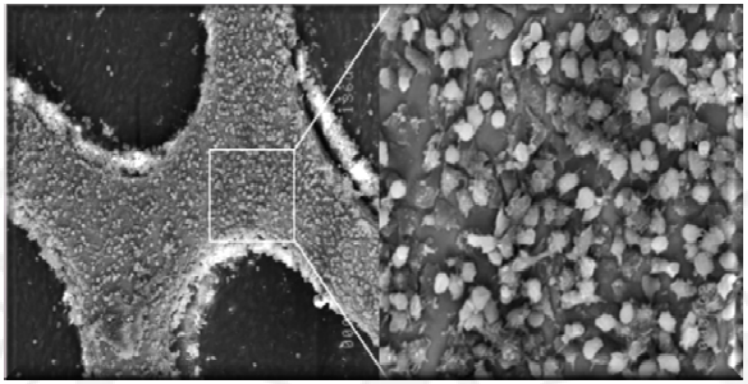


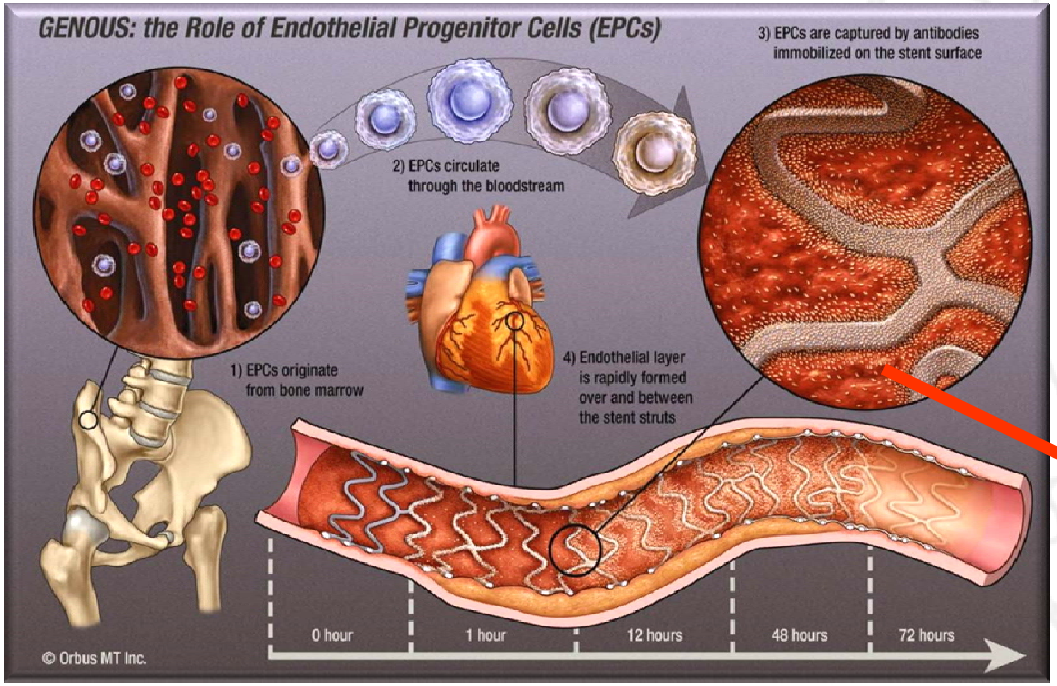
# Genous™ EPC-Capture Stent

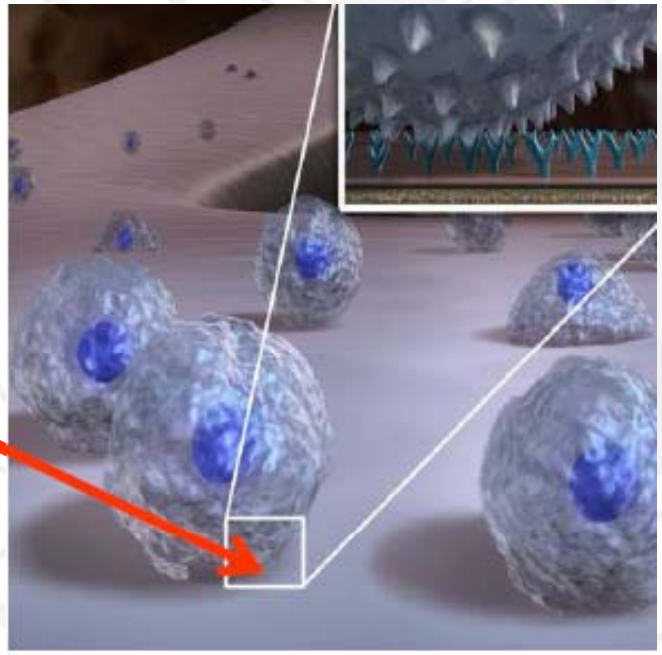
***No Polymer !***


***1 hr after Genous Stent implantation***



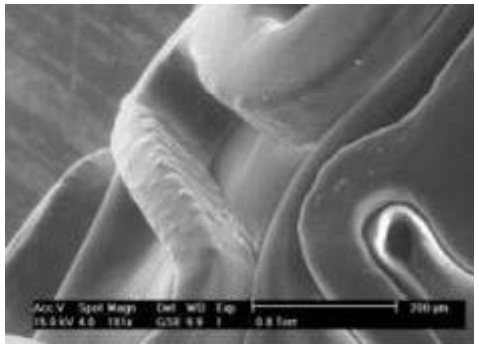


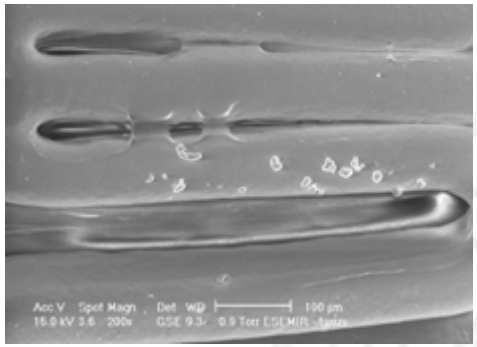
# Summary of Coating / Polymer

| DES | Drug | Coating layer | Polymer | Polymer type |
|---|---|---|---|---|
| Cypher | Sirolimus | 3 layers | Parylene C, PEVA, PBMA | biostable |
| Taxus Liberte | Paclitaxel | 1 layer | SIBS (Translute™) | biostable |
| Endeavor | Zotarolimus | 3 layers | Phosphorylcholine (PC) | biologic |
| Endeavor Resolute | Zotarolimus | 2 layers | BioLinx (C10/C19/PVP) | biostable |
| Xience V | Everolimus | 2 layers | PBMA, PVDF-HFP | biostable |
| Promus Element | Everolimus | 2 layers | PBMA, PVDF-HFP | biostable |
| BioMatrix | Biolimus A9 | 2 layers | Parylene, PLA | biodegradable |
| Nobori | Biolimus A9 | 2 layers | Parylene, PLA | biodegradable |
| NEVO | Sirolimus | 2 layers | PLGA | biodegradable |
| Genous | - | 1 layer | No polymer (Anti-CD 34 Ab coating) | - |

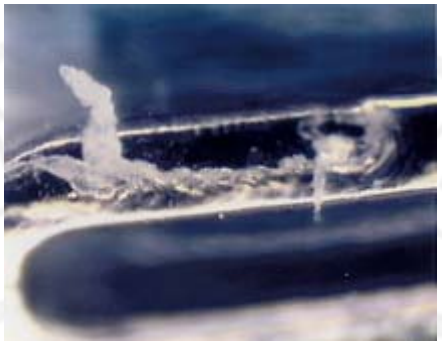
# Current Problems w/ Durable Polymers



**Non-uniform polymer coating**



**“Webbed” polymer surface leading to stent expansion issues”**

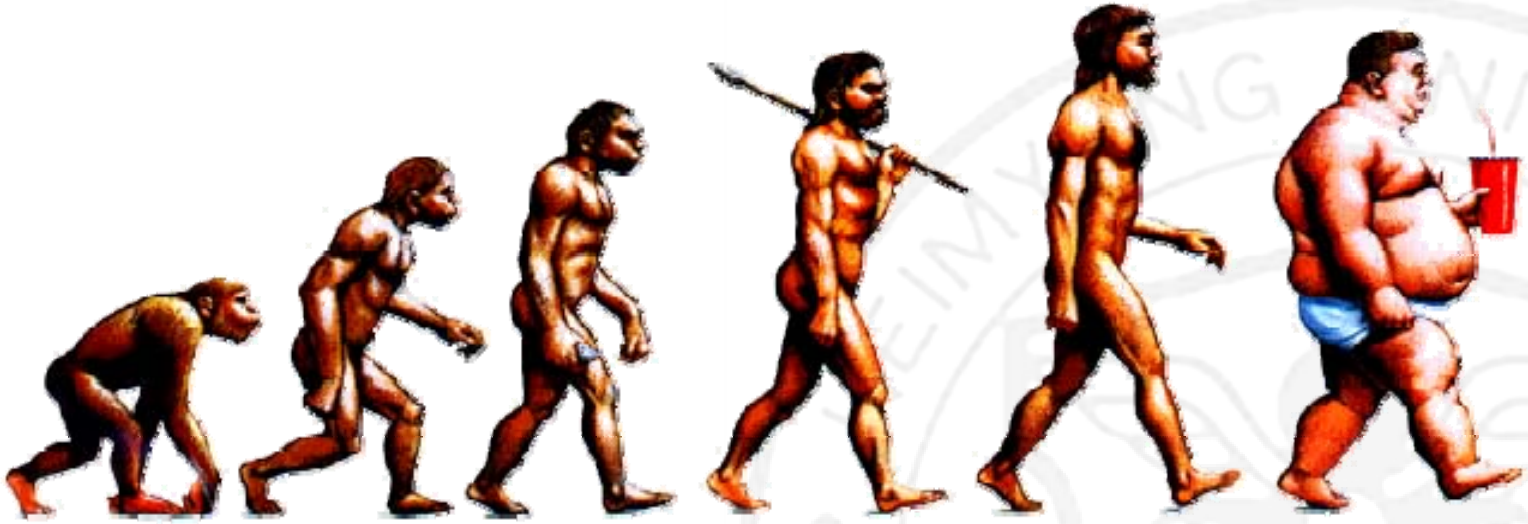


**Polymer delamination**

- **Durable Coatings-Potential for**
  - continuing source of inflammation
  - poor healing/thrombosis risk
  - inhomogeneous drug distribution and elution
  - poor adhesion and separation from stent
  - complex and costly manufacturing process

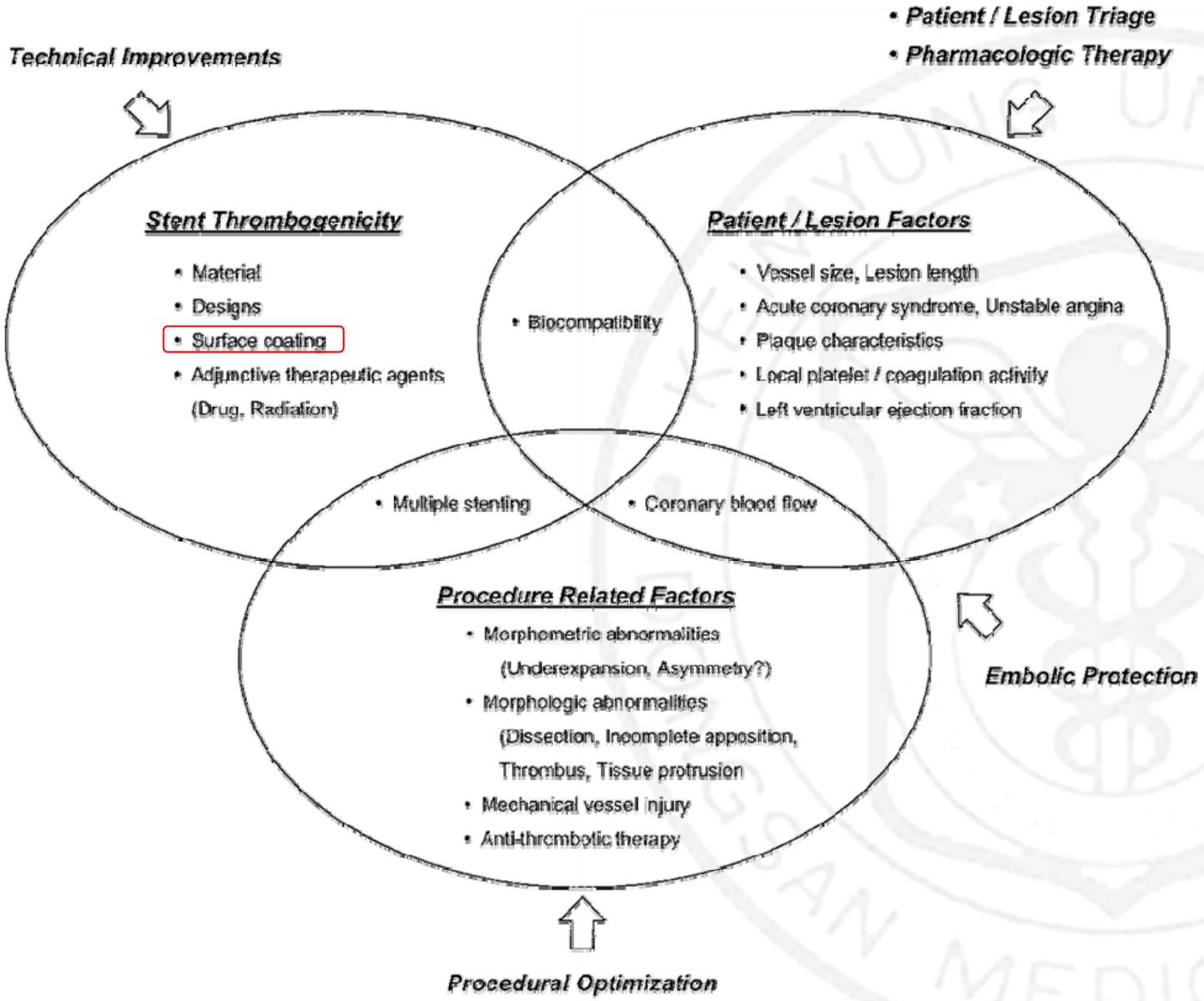
*Alexandre Abizaid. 2009 XV SOLACI Congress*

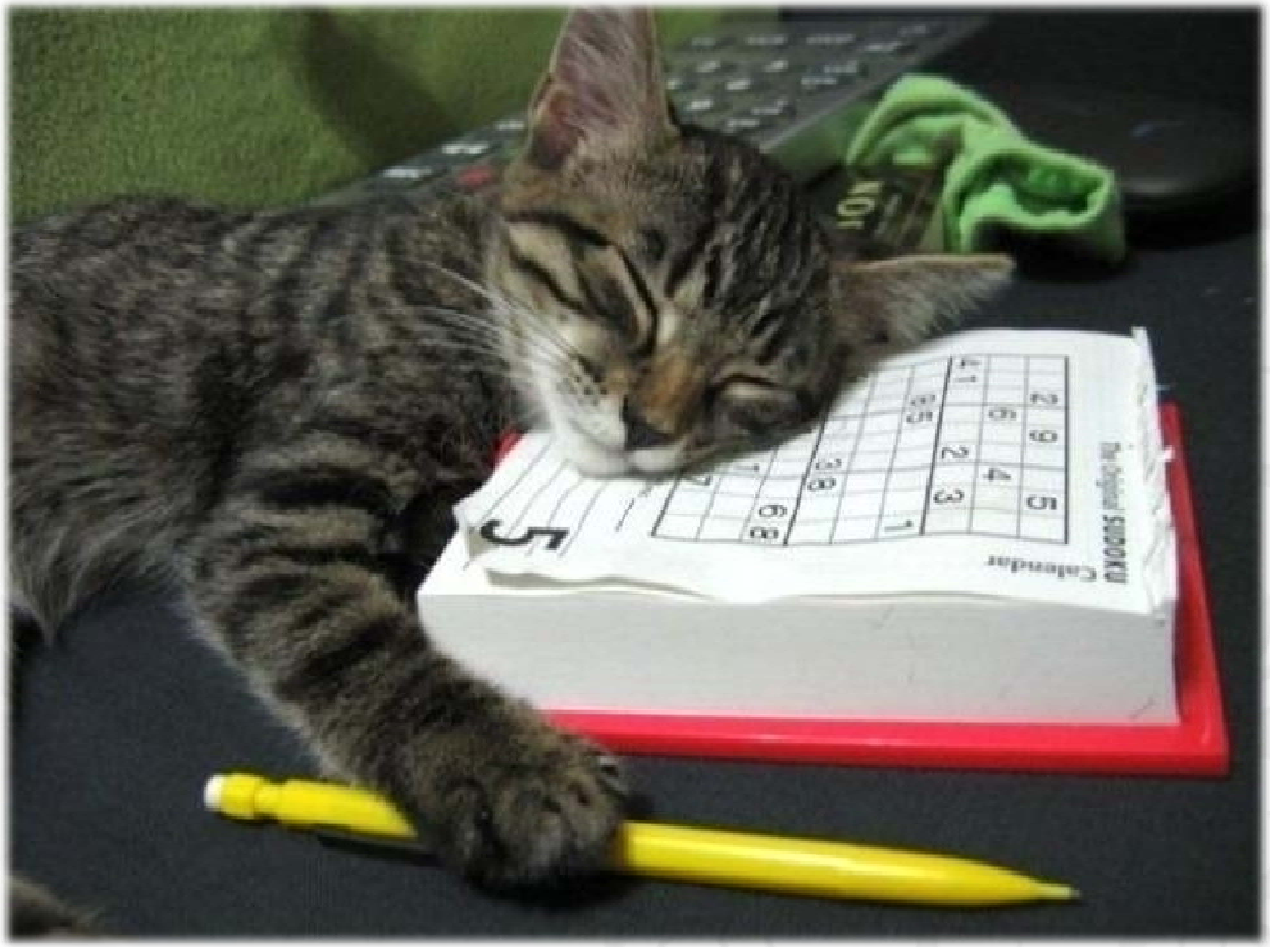
# Polymer Evolution



Durable (biostable) Polymer → Bio-degradable Polymer → The Best Polymer Is…… No Polymer

# Multiple Risk Factors Involved in the Development of Stent Thrombosis



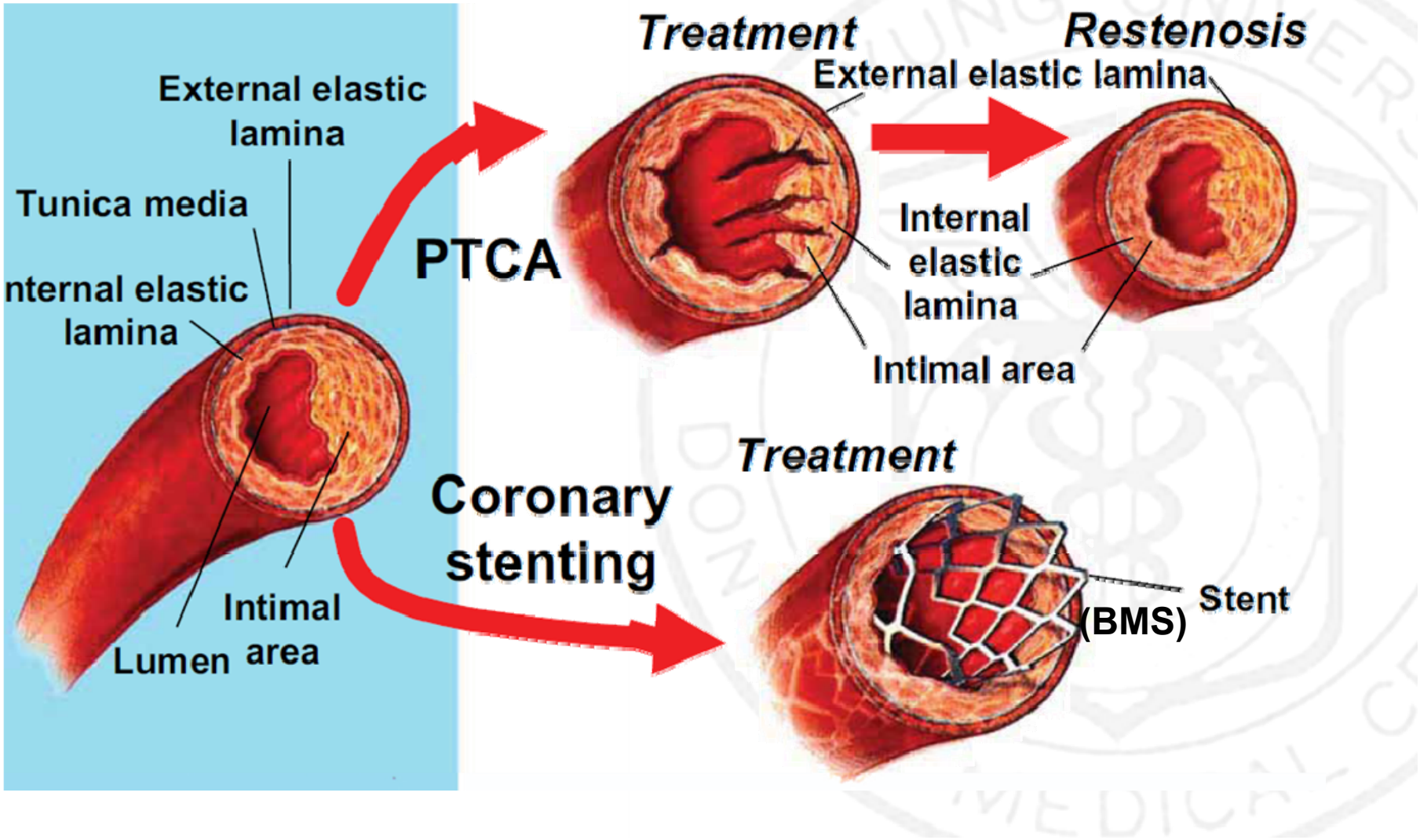



# THANK YOU

KEIMYUNG UNIVER
DONGSAN MEDICAL C

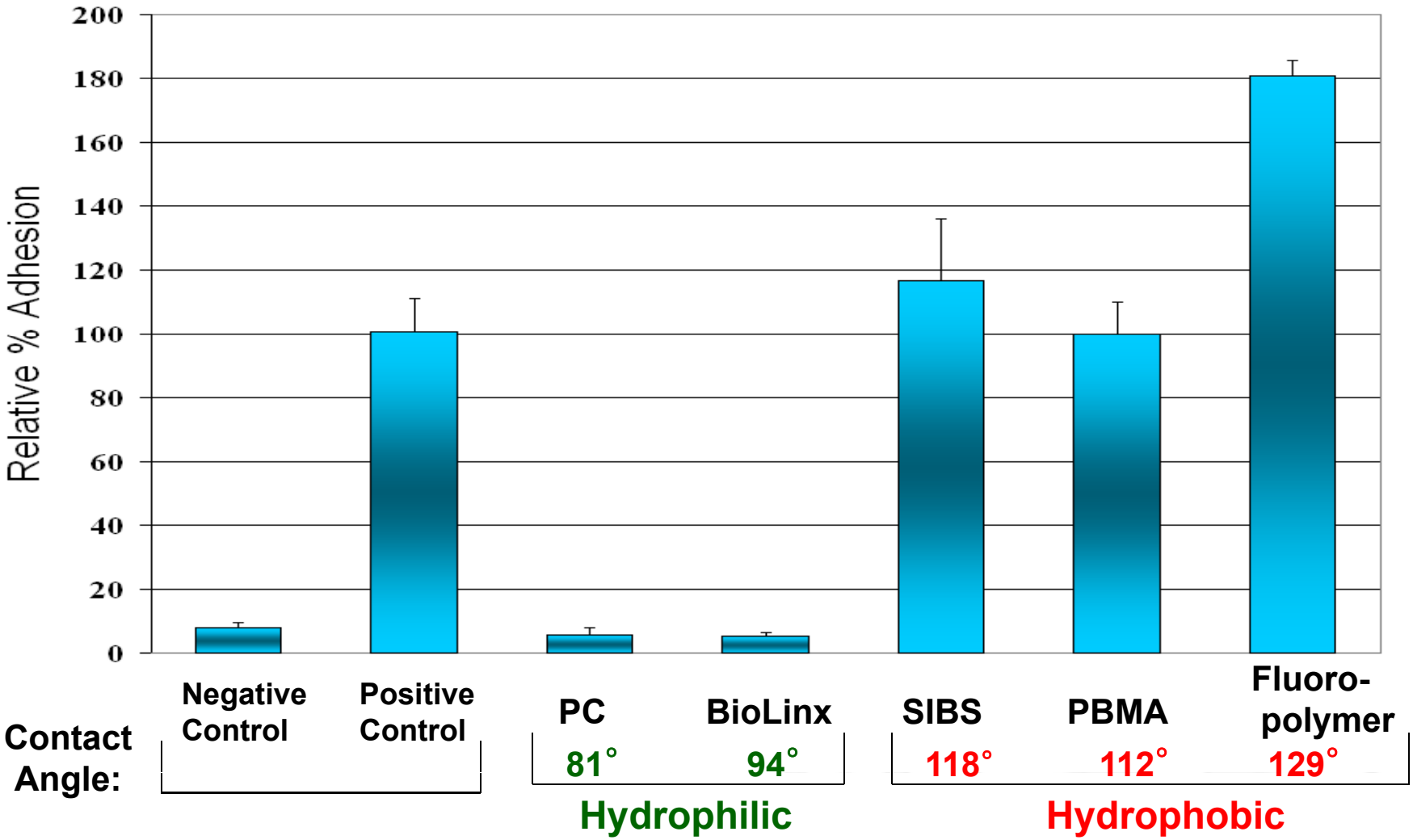
# Major Issue after POBA

## ~ Restenosis ~



# Monocyte Adhesion

***Correlates with Polymer Hydrophobicity***




*Combinatorial Chemistry & High Throughput Screening, 2009;12:1-13*

# Applications of Parylene

Pin-hole Free Conformal Coatings for:
- Medical
- Aerospace
- Telecommunications
- Military

- **Medical Applications**

- cardiac assisted implantable device
- catheter: improve lubricity
- pressure sensor
- guidewire
- needle
- epidural probe