New DES Drug Carrier Systems: Biostable, Bioabsorbalbe, and No Polymers, Elution Kinetics and Beyond

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Columbia University Medical Center
Cardiovascular Research Foundation
New York City

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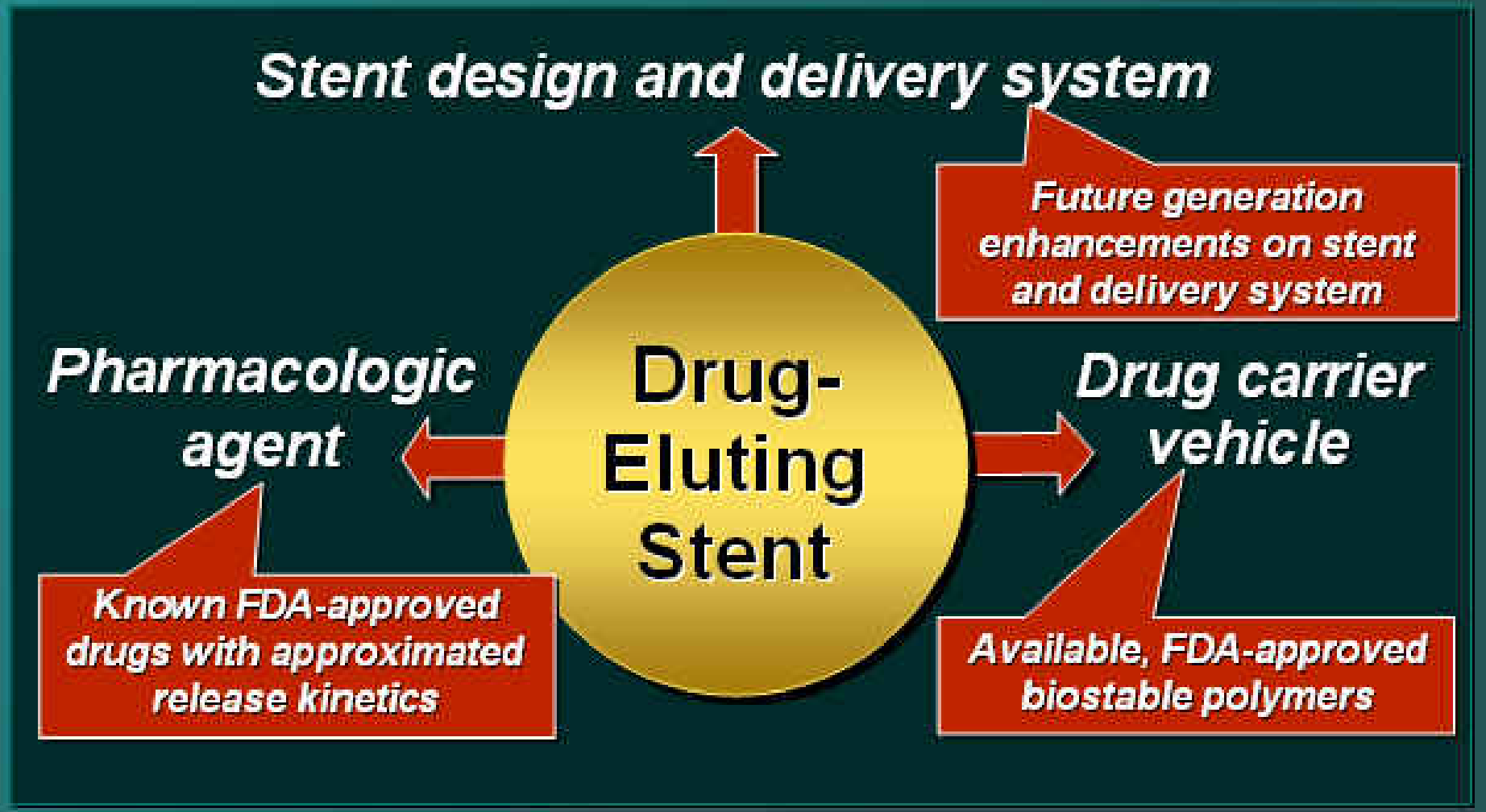
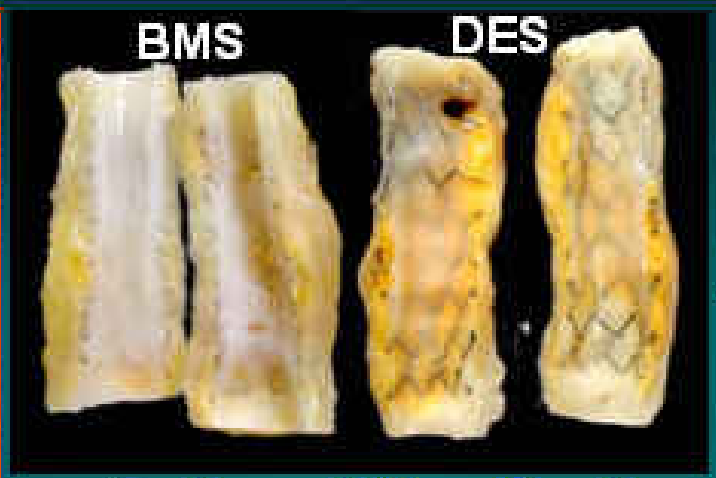
Drug-Eluting Stents

The First Generation



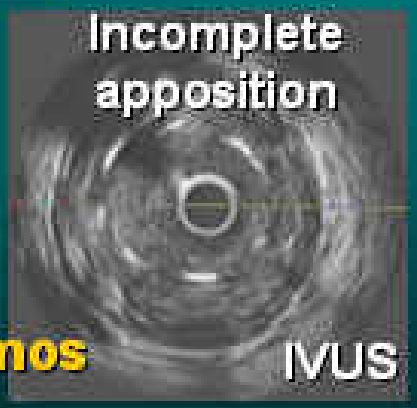
Drug-Eluting Stents….
the good, the bad, and the ugly!

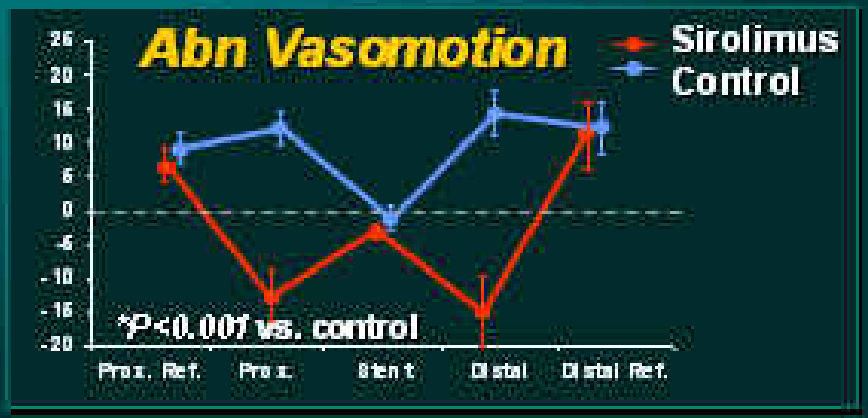


Delayed Healing!

Angioscopy

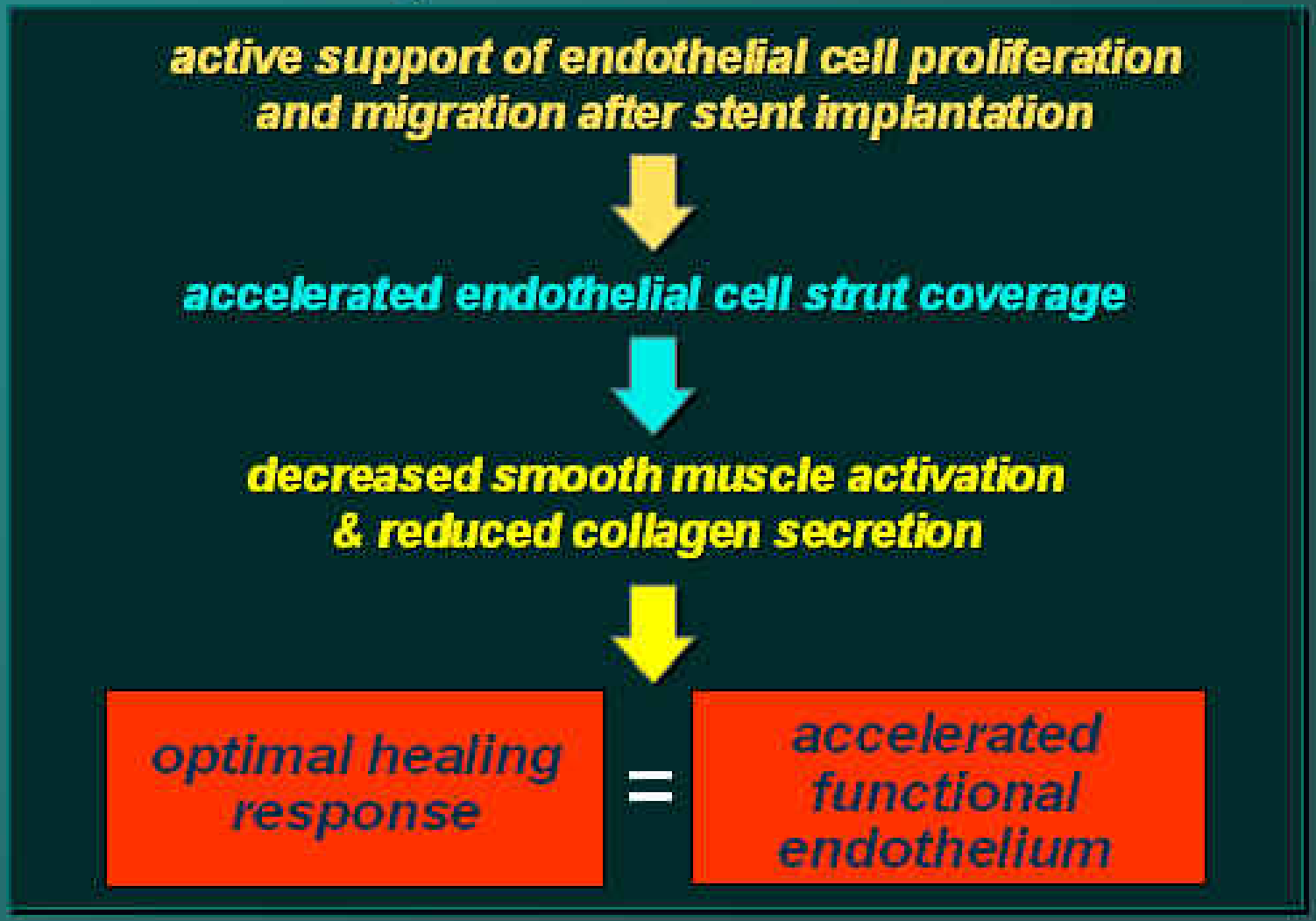
Inflammation





Future *Safe* DES Platforms

The Key is the Endothelium!



DES -2007

New DES Carrier Systems

- Biostable Polymers
- Bioaborbable Polymers
- No Polymers
- Elution Kinetics
- ...and Beyond

DES -2007

New DES Carrier Systems

- *Biostable Polymers*
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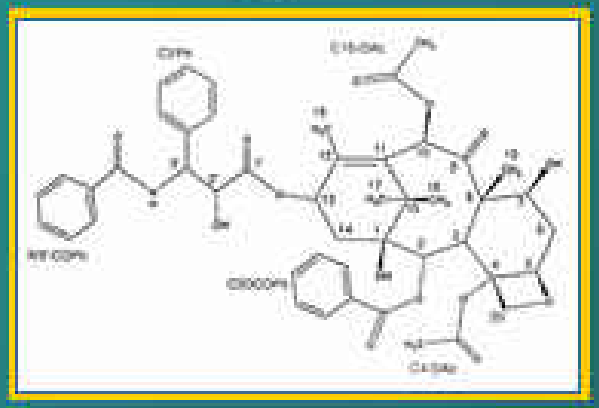
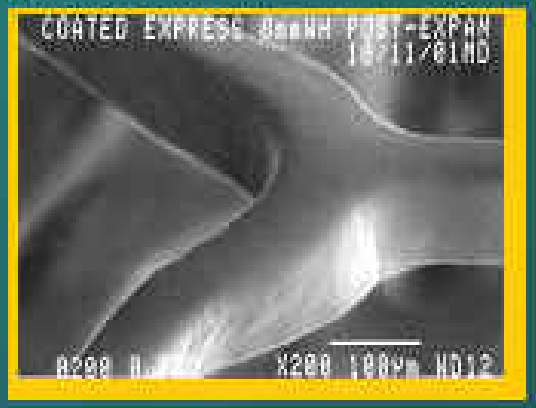
First Generation
Drug-eluting Stents in the U.S.

TAXUS



Paclitaxel

Drug



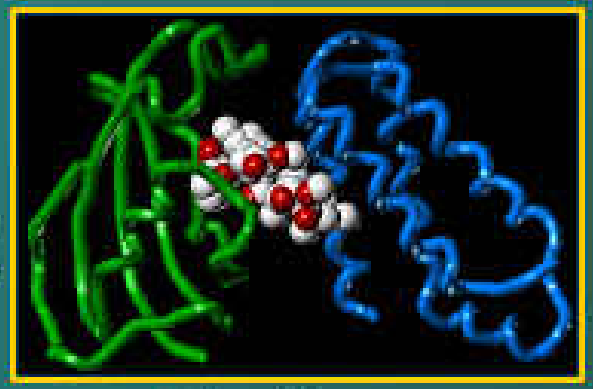
Polyolefin derivative

Polymer

Express^2

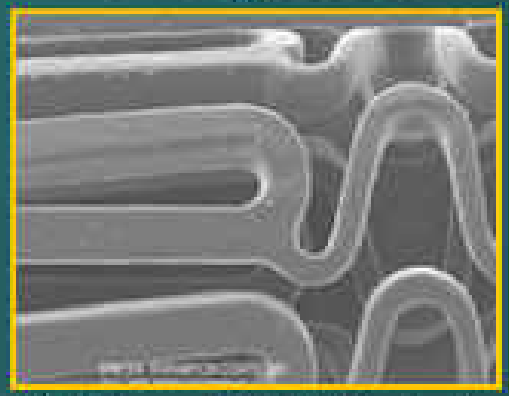
Stent

Cypher



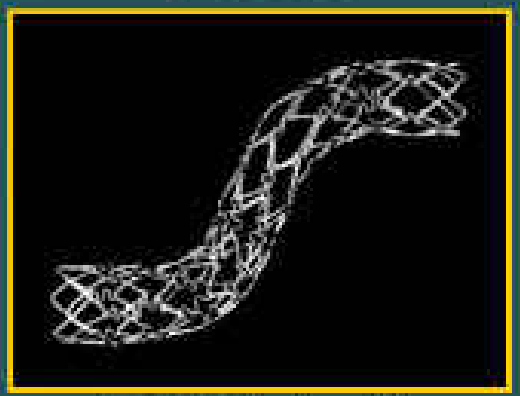
Sirolimus

Drug



PEVA + PBMA blend

Polymer



BX Velocity

Stent

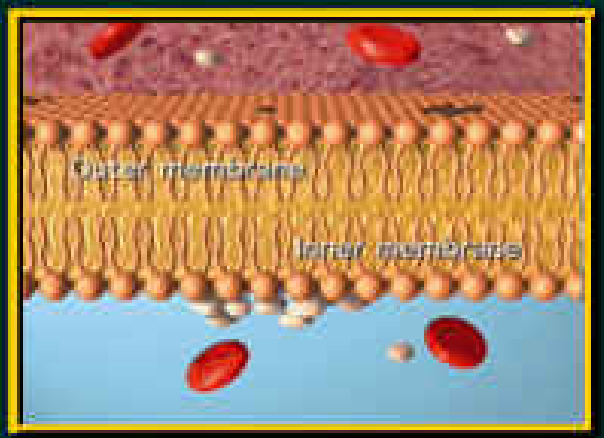
Endeavor DES System

Key Components

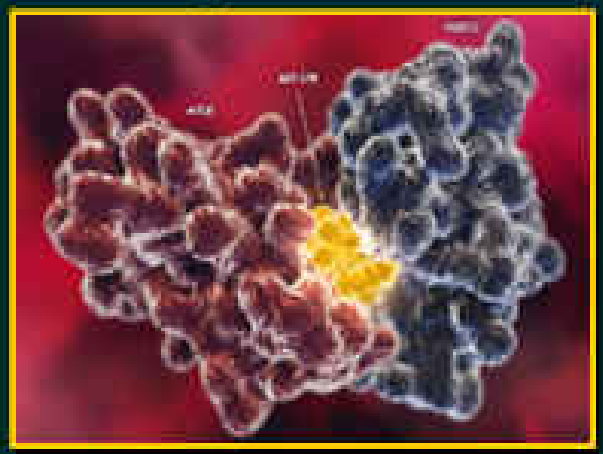
Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology

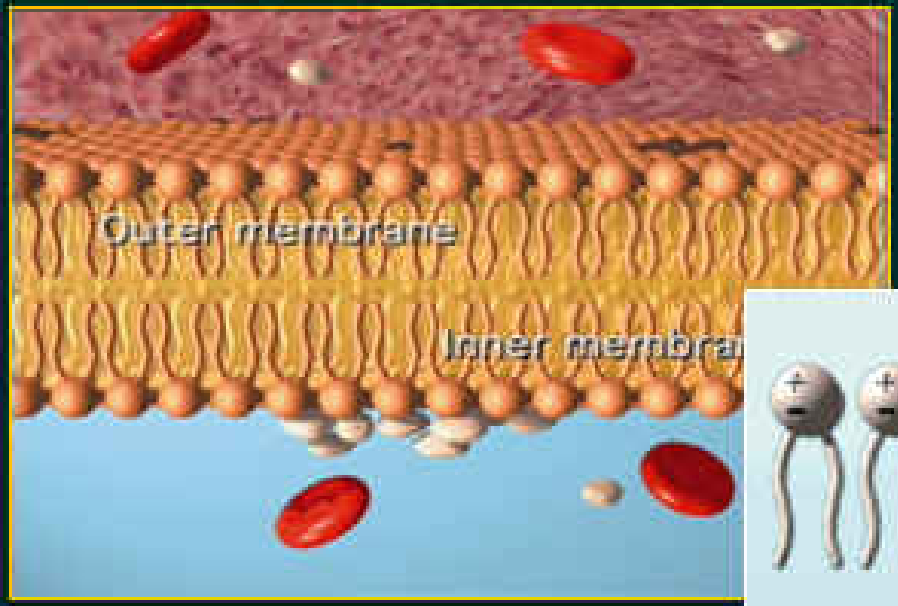


Drug: Zotarolimus



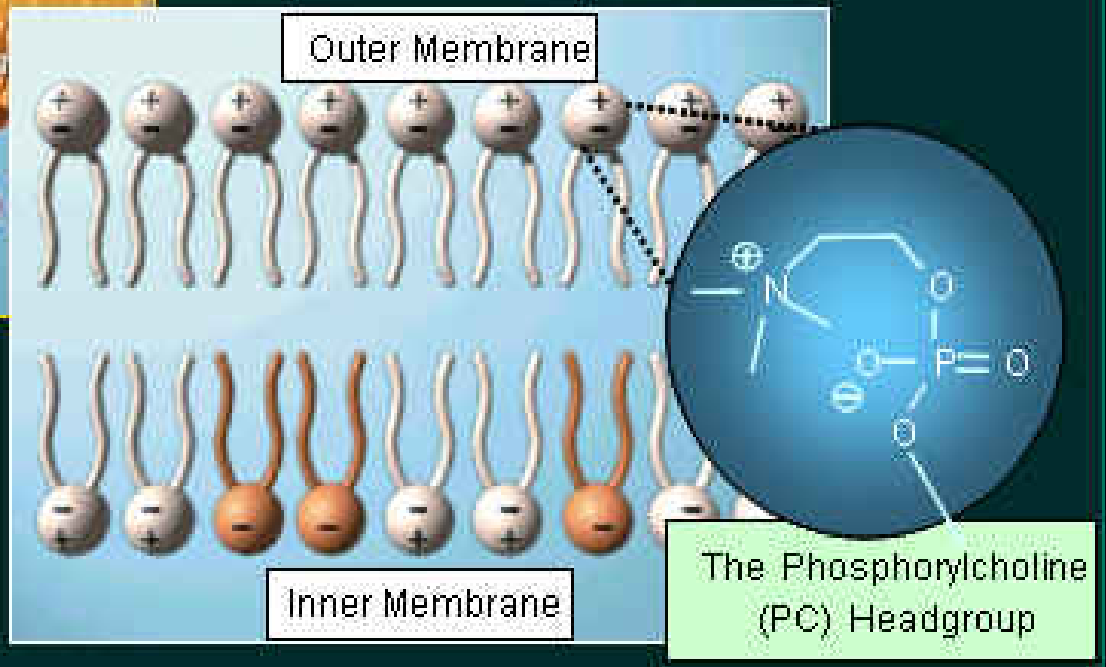
Endeavor DES System

PC Technology



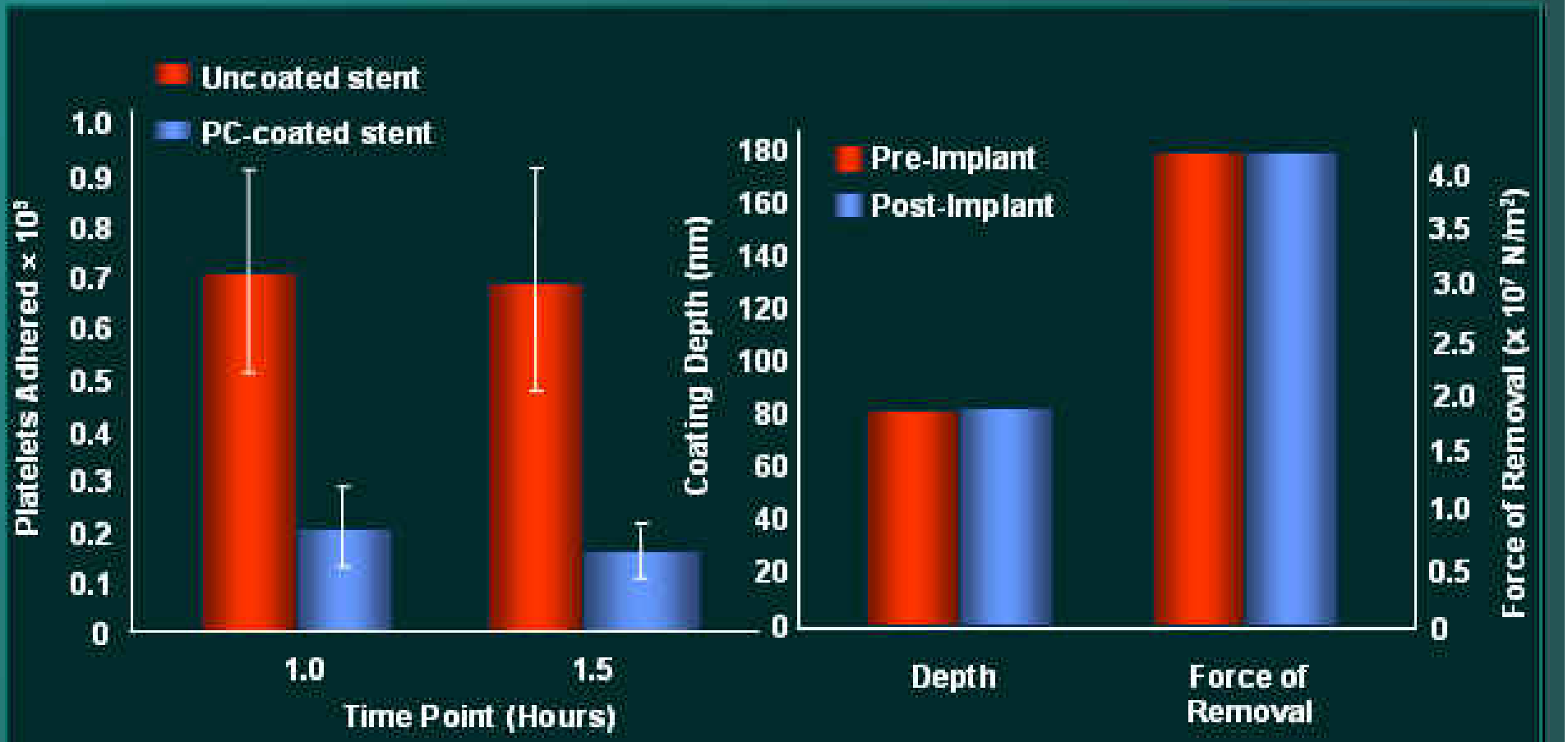
90% of phospholipids in the outer membrane of a red blood cell contain the PC (Phosphorylcholine) headgroup

PC[1] mimics the chemical structure of the phospholipid headgroup



Endeavor DES System

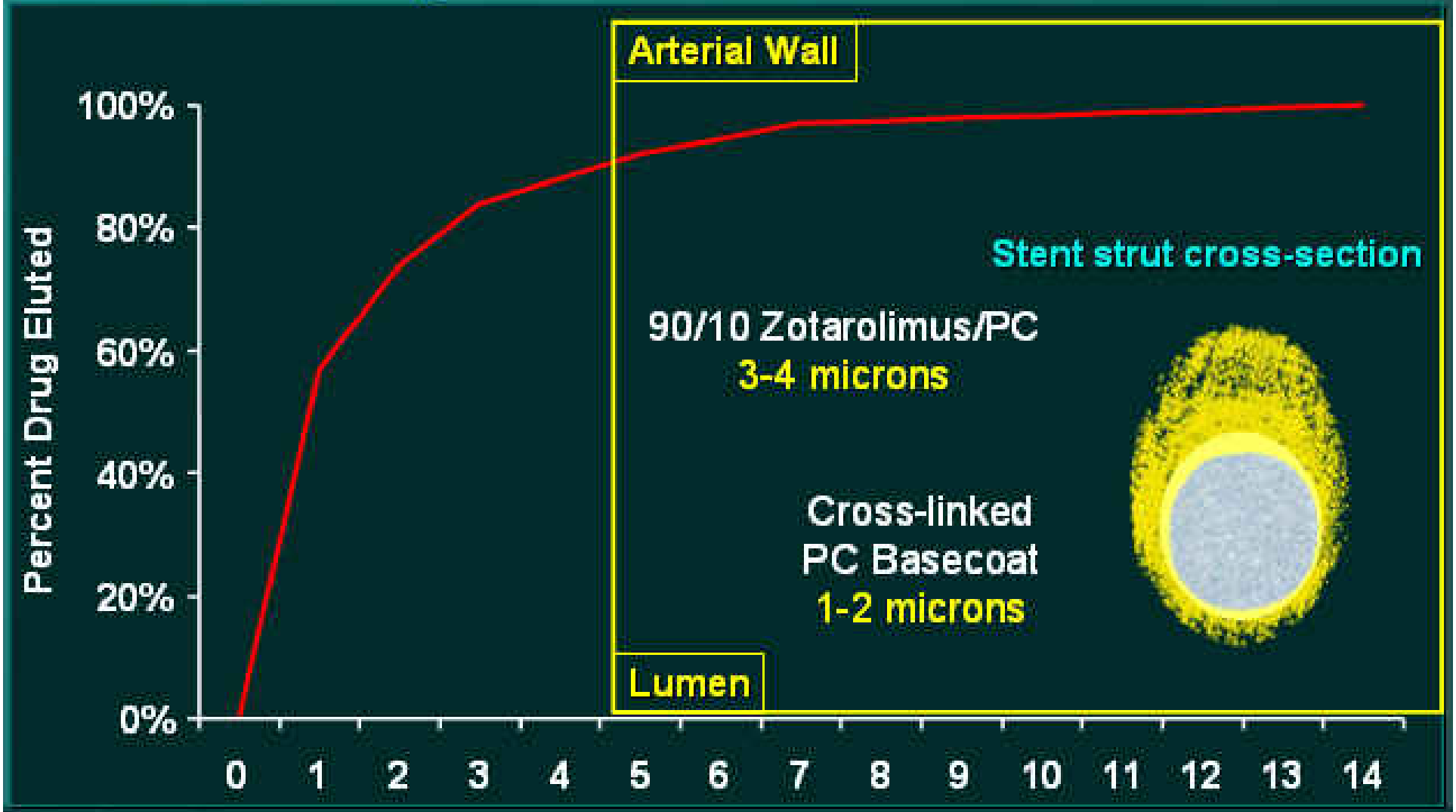
PC Technology



Non-thrombogenic ***Durable***

Endeavor Zotarolimus-PC Interaction

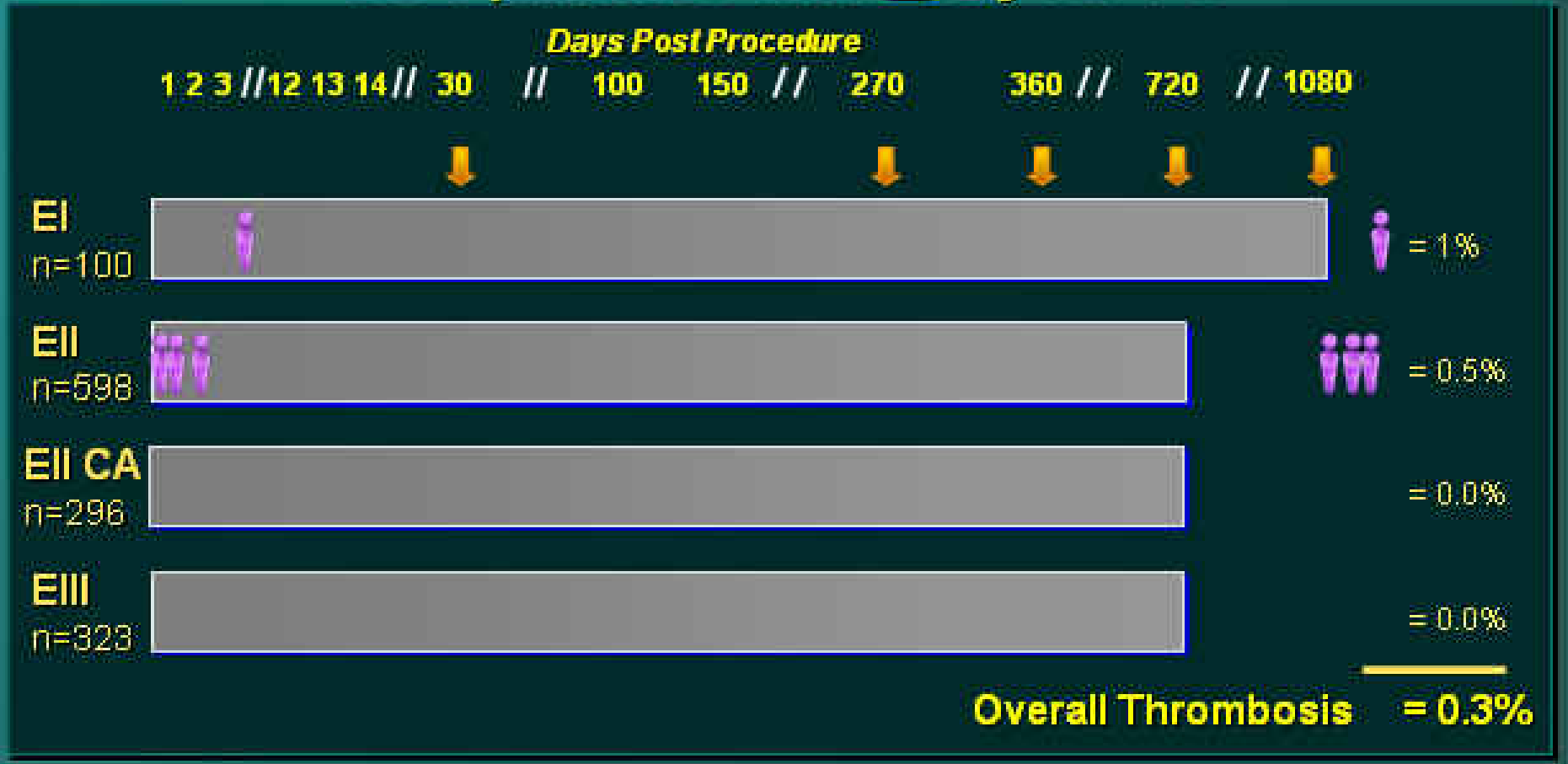
Drug Eluted by 14 days; Only PC Basecoat Left Behind



Endeavor Safety Analysis

Stent Thrombosis According to Prospective HCRI CEC Definitions

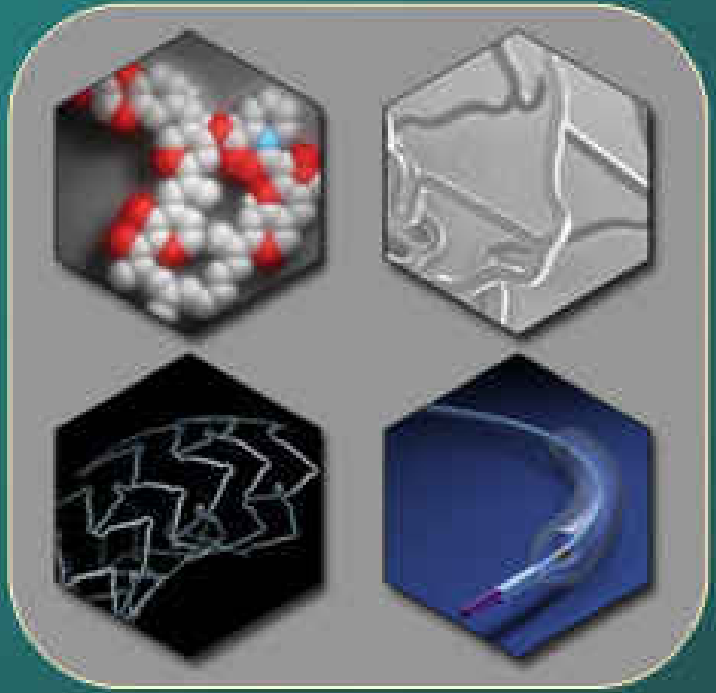
1317 patients with ≥ 2 year FU



Abbott XIENCE V
Everolimus-eluting Stent*

Everolimus

ML VISION®
Stent Platform



Durable
Fluoropolymer

ML VISION®
Stent Delivery
System

SPIRIT
Clinical Trials

Columbia University
Medical Center

*Identical to BSC Promus

Cardiovascular
Research Foundation

Xience Durable FluoroPolymer Characteristics

Physical Properties

Combination of acrylic and fluorinated polymers

- inert
- flexible, ductile
- thin, with high drug loading capacity

Rare comb of hardness and elongation

Mechanical Integrity

Strong adhesion to stent and balloon

Biocompatibility

Low thrombogenecity and inflammation

History of medical use

- bone cement (acrylic)
- sutures (fluorinated)

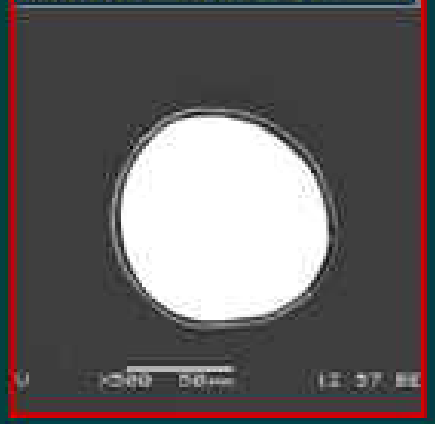
Manufacturability

High stability

Controlled Release

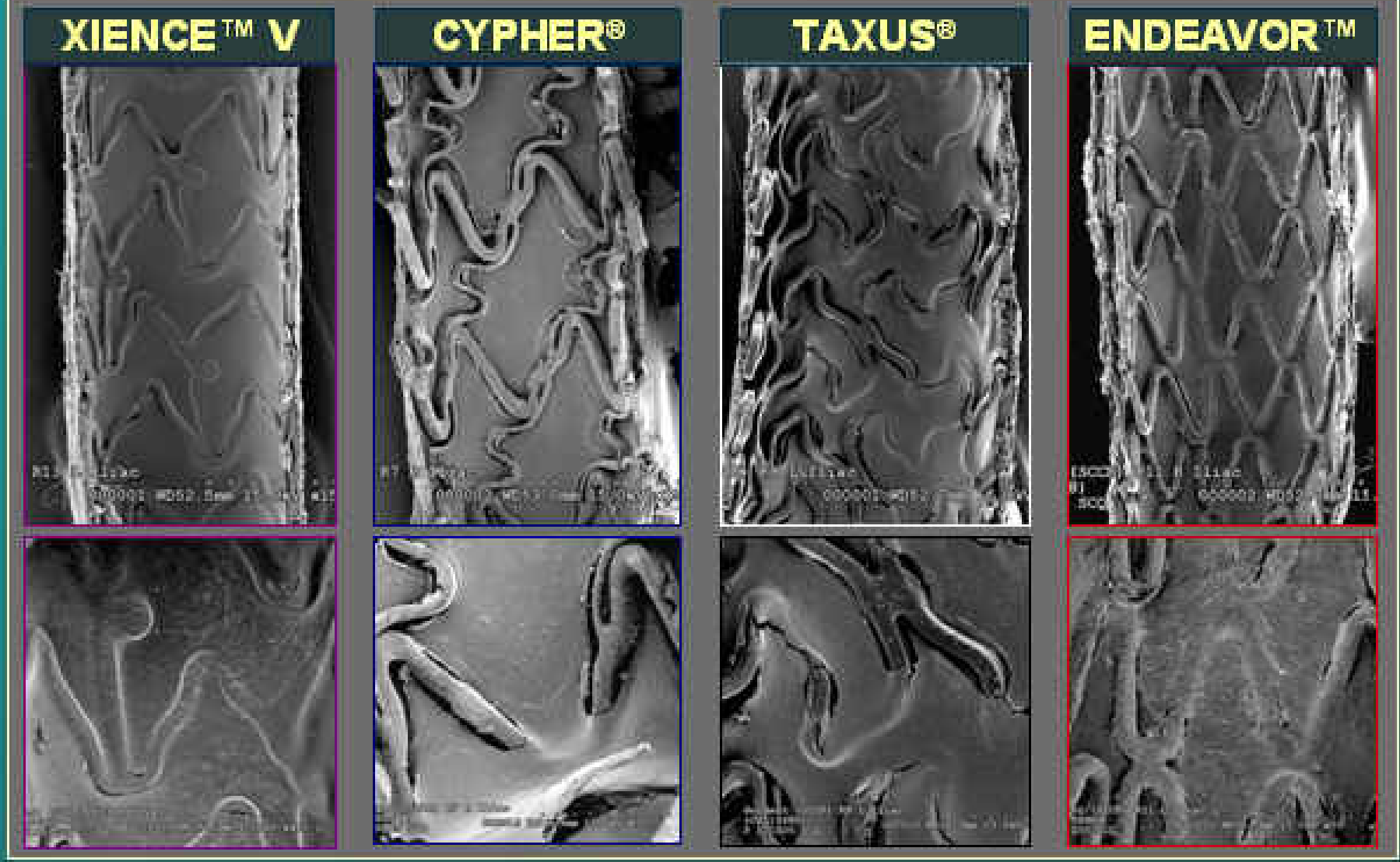
DES Strut and Polymer Thickness

3.0 mm diameter stents, 500x magnification

CYPHER®	TAXUS®	ENDEAVOR™	XIENCE™ V
			
Strut Thickness: **140 µm** Polymer Thickness: **12.6 µm** **Total: 152.6 µm**	Strut Thickness: **132 µm** Polymer Thickness: **16.0 µm** **Total: 148 µm**	Strut Thickness: **91 µm** Polymer Thickness: **5.3 µm** **Total: 96.3 µm**	Strut Thickness: **81 µm** Polymer Thickness: **7.6 µm** **Total: 88.6 µm**

Data on file at Abbott Vascular. Strut thickness per manufacturer's published specifications.

14 Day Endothelialization: Rabbit Iliac Model



Columbia University Medical Center

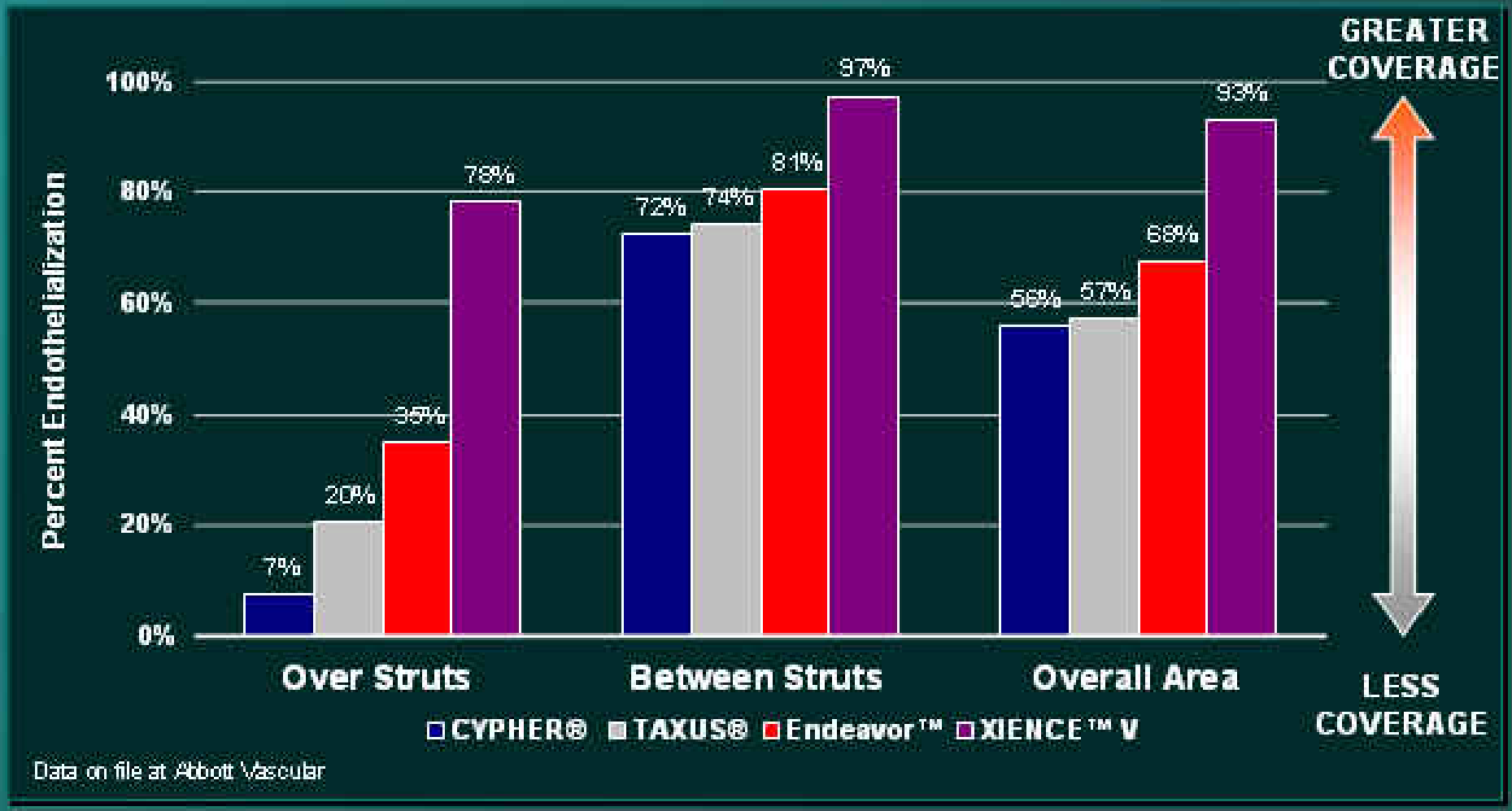
c/o R. Virmani, submitted

Cardiovascular Research Foundation

DES Re-endothelialization:

14-Day Rabbit Iliac Study

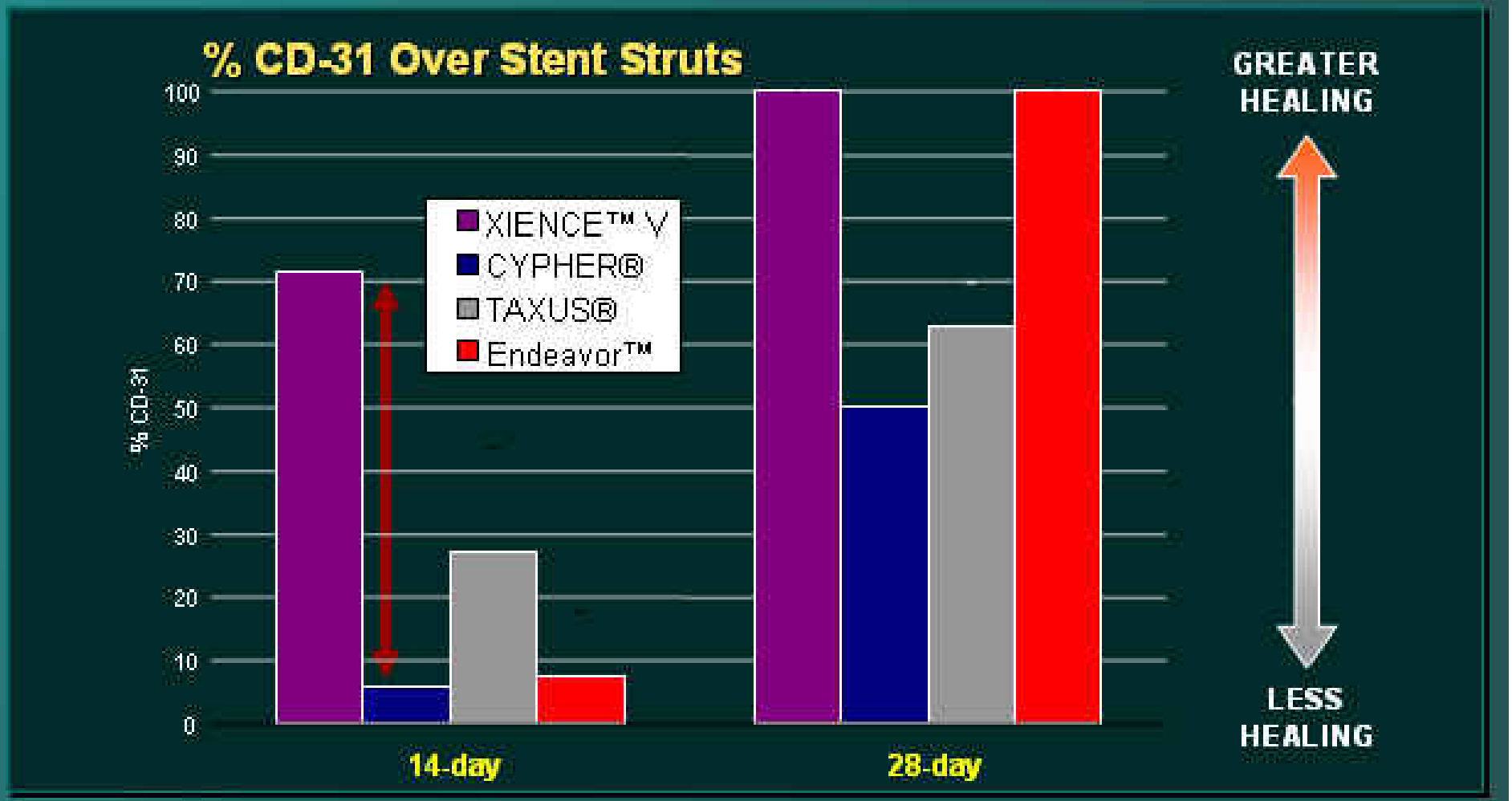
Xience thin fluoropolymer + everolimus



DES Functional Endothelium:

Rabbit Iliacs, CD-31 Staining @ 14-day

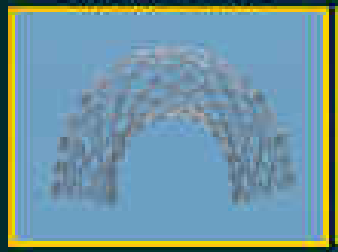
Xience thin fluoropolymer + everolimus



Endeavor Resolute

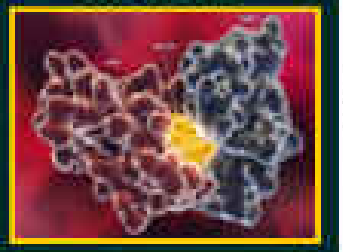
Retains three components of the Endeavor Coronary Stent System

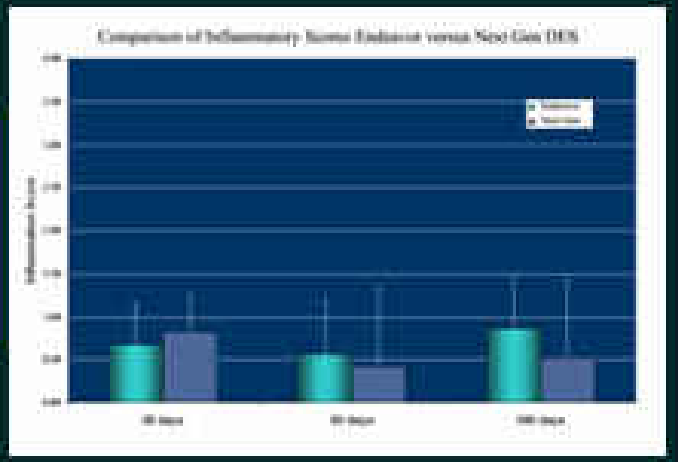
Driver Cobalt Alloy Stent



Stent Delivery System

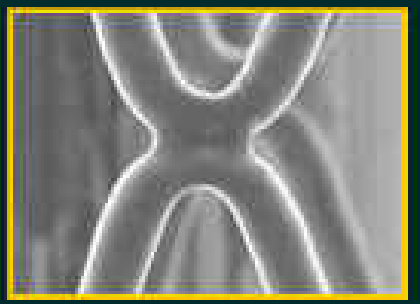
Drug: ABT-578





Novel Features:

- **Medtronic proprietary polymer design**
- **Extended release kinetics**
- **Biocompatibility equivalent to PC**
- **Ability to add multiple drugs with release kinetics**

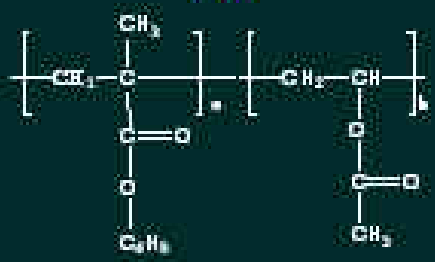


The BioLinx Polymer System

C10 Polymer

- Based primarily on hydrophobic butyl methacrylate to provide adequate hydrophobicity for zotarolimus

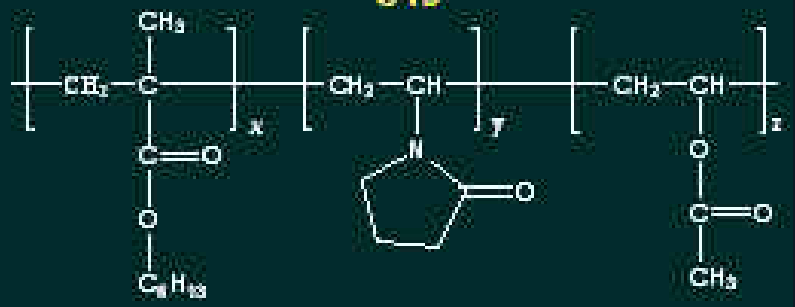
C10



C19 Polymer

- Manufactured from a mixture of hydrophobic hexyl methacrylate and hydrophilic vinyl pyrrolidinone and vinyl acetate to provide enhanced biocompatibility

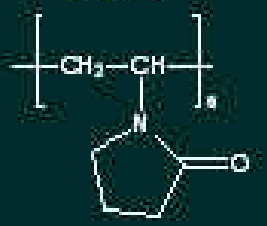
C19



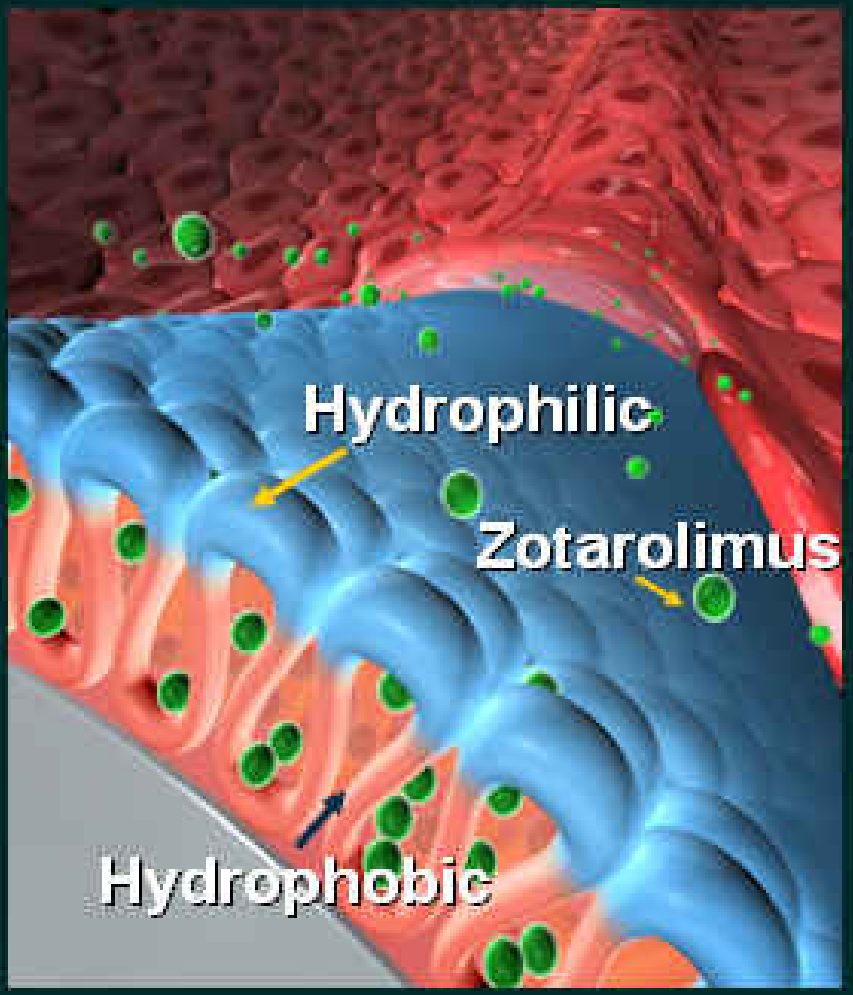
Polyvinyl Pyrrolidinone (PVP)

- Hydrophilic polymer increases initial drug burst and enhances biocompatibility

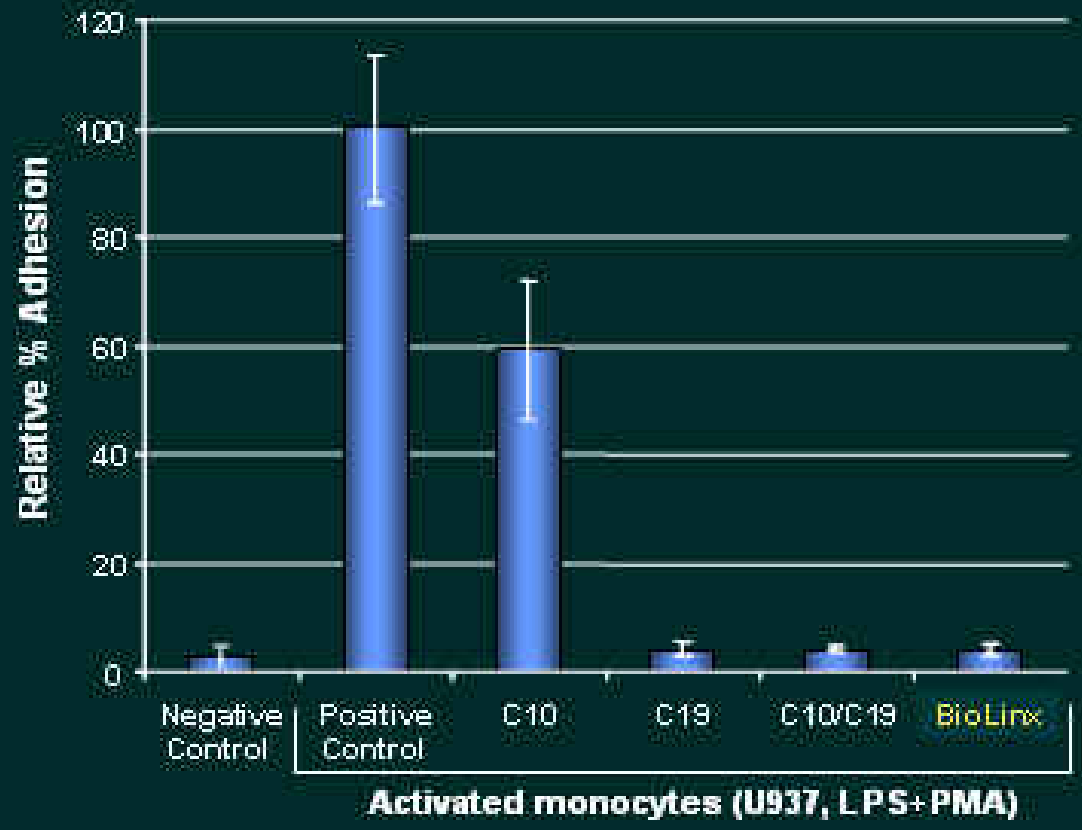
PVP



Endeavor Resolute
BioLinx Polymer System



Reduced Monocytic Adhesion to BioLinx Polymer System



Hydrophobic polymer (C10) induces the greatest inflammatory response

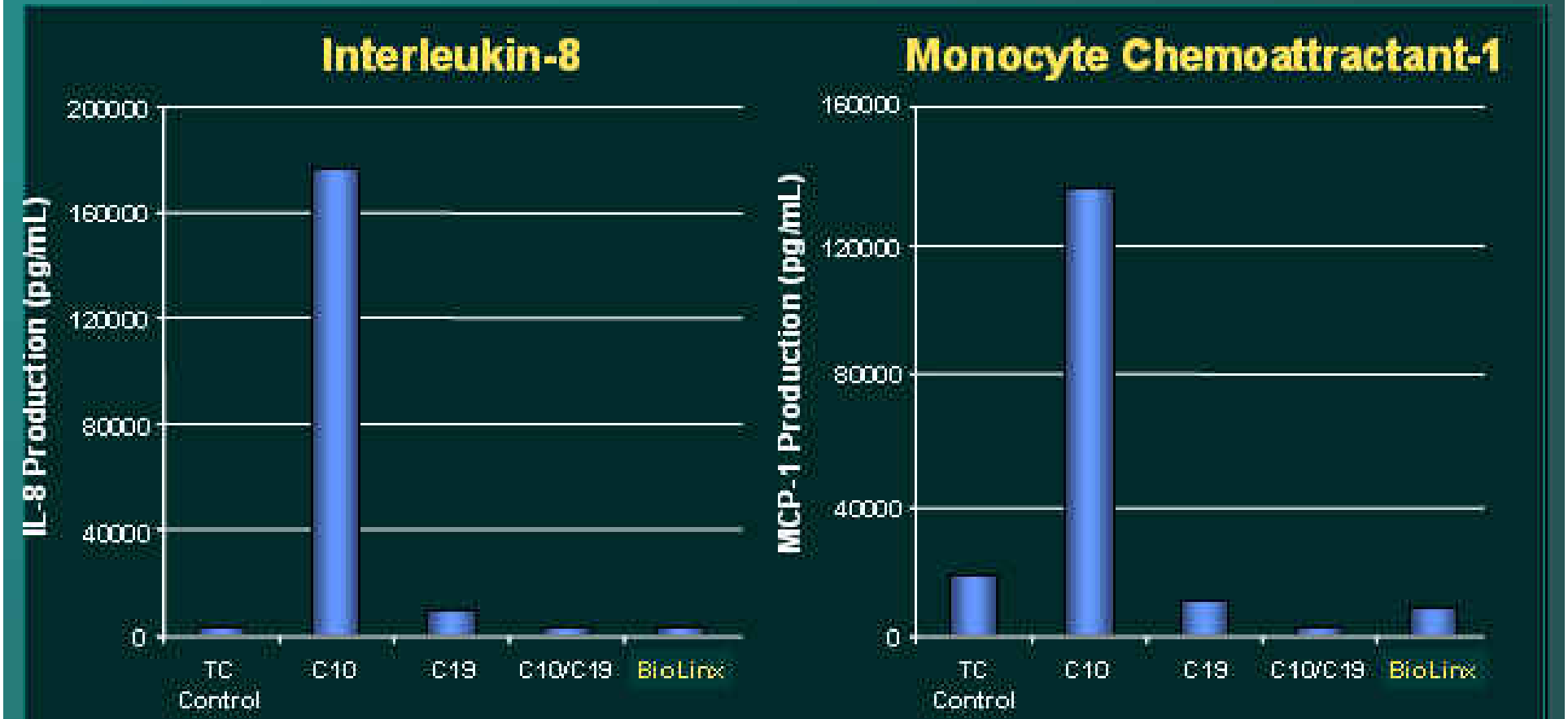
Hydrophilic polymer (C19) does not provoke an inflammatory response

The BioLinx polymer system (with a hydrophilic surface) maintains the favorable biocompatibilty feature of the hydrophilic C19 (see Table below)

Polymer	Contact Angle
C10	118°
C19	91°
C10 + C19 (30:70)	84°
BioLinx	94°

Activated monocytes do not bind to polymer blends containing C19

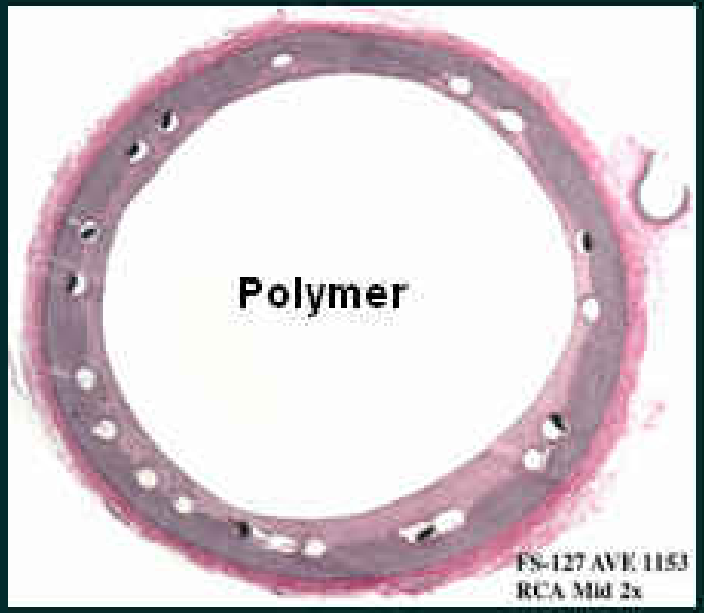
Cytokine Production by Monocytes



Monocytes cultured on polymer blends containing the hydrophilic C19 release low levels of inflammatory cytokines into the cell culture media

* TC= Tissue Culture Polystyrene

Biocompatibility of the BioLynx Polymer



Inflammation score
0.10 ± 0.21

Inflammation score
0.11 ± 0.38

Porcine coronary artery implants at 28 days

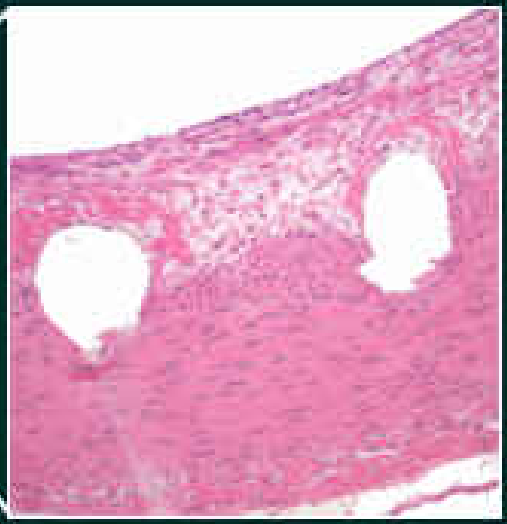
Endeavor Resolute

28 Day Results in Porcine Coronaries

Control

Endeavor Resolute

Endeavor Resolute



Reduced neointimal hyperplasia compared with control bare metal stents

New DES Carrier Systems

Biostable Polymers

- 1st generation DES biostable polymers have been suboptimal due to increased thickness (polymer burden), mechanical surface defects, increased inflammatory responses, and idiosyncratic hypersensitivity reactions.
- Newer (2nd) generation biostable polymers are thinner, have improved mechanical integrity, have more versatile kinetic release properties, and are more "biocompatible" with improved early healing and reduced inflammation.

DES -2007

New DES Carrier Systems

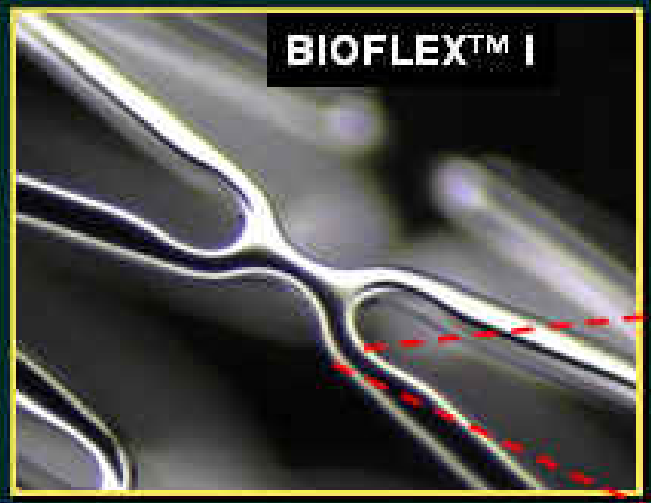
- Biostable Polymers
- *Bioaborbable Polymers*
- No Polymers
- Elution Kinetics
- …and Beyond

Biodegradable Polymers can be very *TRICKY!*

marked inflammatory responses

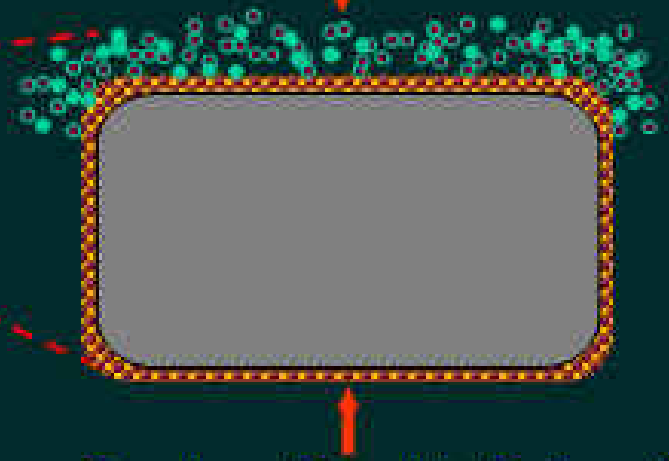
polymer swelling and physical degradation

BioMatrix® II Stent Platform Design



Biodegradable Drug/Carrier:

- Biolimus A9® / Poly (Lactic Acid) 50:50 mix
- abluminal surface only (contacts vessel wall)
- 15 µmeter coating thickness
- degrades in 9 months releasing CO_2 + water



Stent Platform:

- stainless steel (112 µm)
- corrugated ring, quadrature-link™ design
- radius link enhances axial fatigue life

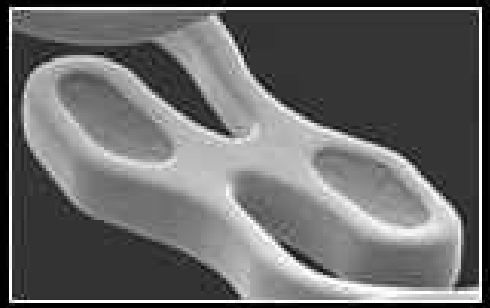
Parylene Durable Primer Coating:

- 5 µmeter thick, encapsulates stent
- prevents surface metal ion migration
- biostable + athrombogenic*

* Data per NHLBI sponsored study, available from BSI

CoStar® Paclitaxel-Eluting Coronary Stent System

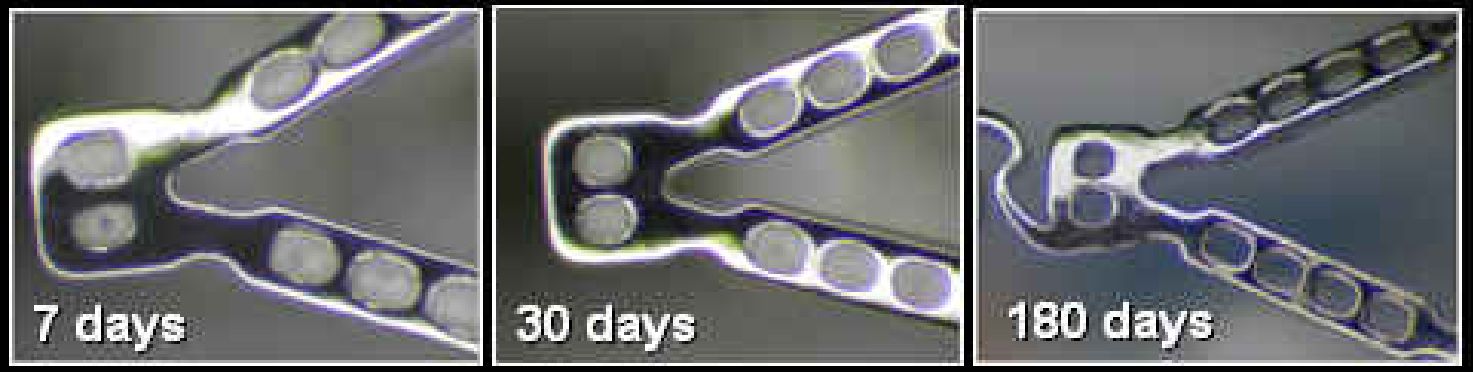
A Stent Specifically Designed for Controlled Drug Delivery from a Bioresorbable PLGA Polymer



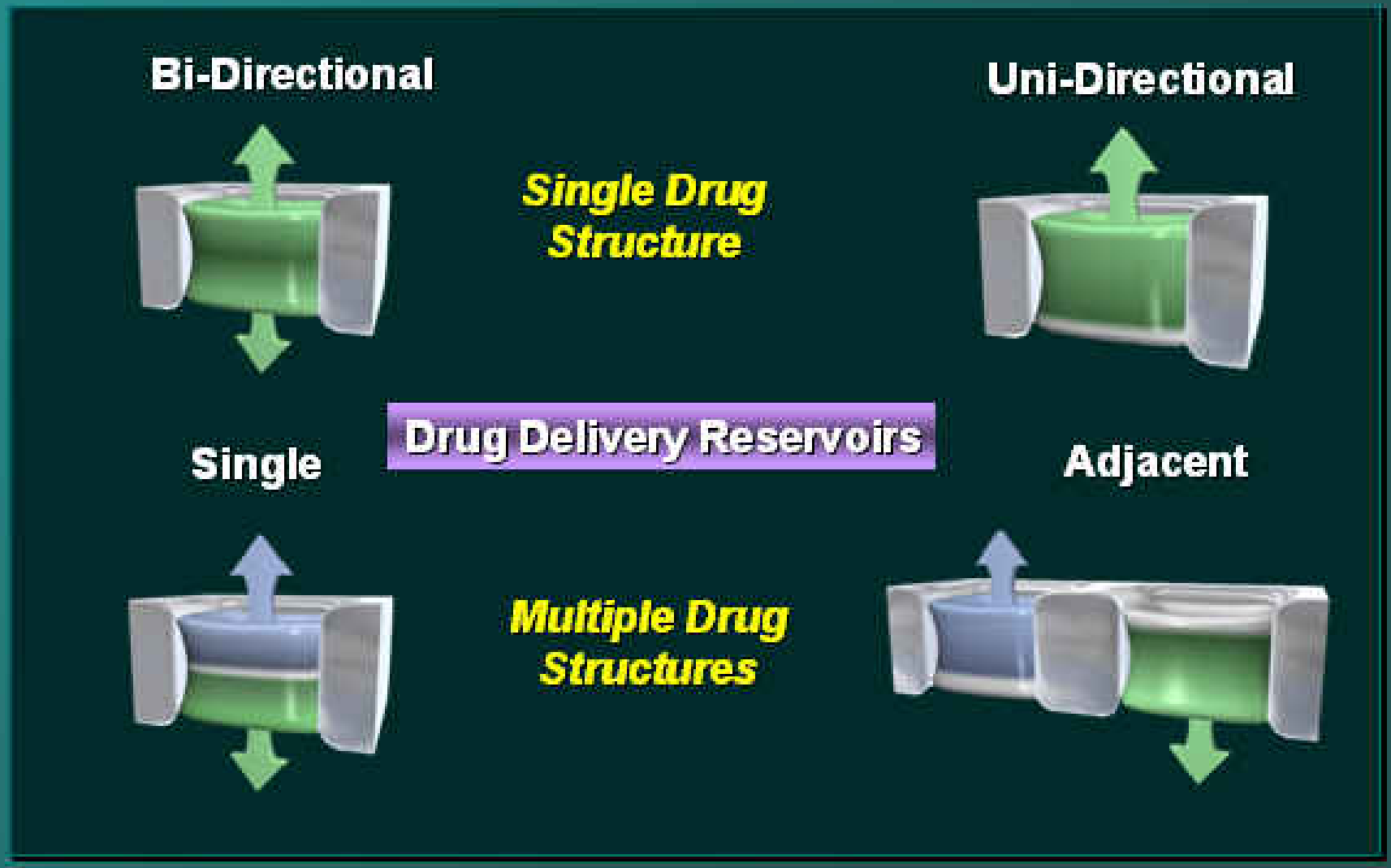
Reservoir inlays with PLGA bioresorbable polymers; reduced tissue-polymer contact area

CoStar Bioresorbable Polymer Reservoir System

- *PLGA bioresorbable polymer*
  - Fully resorbable in ~ 6 mos (current formulation)
  - Degrades into naturally occurring products; lactate and glycolate
  - Used in medical implants for several decades (e.g. sutures)
  - Different co-monomer ratios permit variable resorption times (few weeks to many months)



The Versatility of Reservoirs

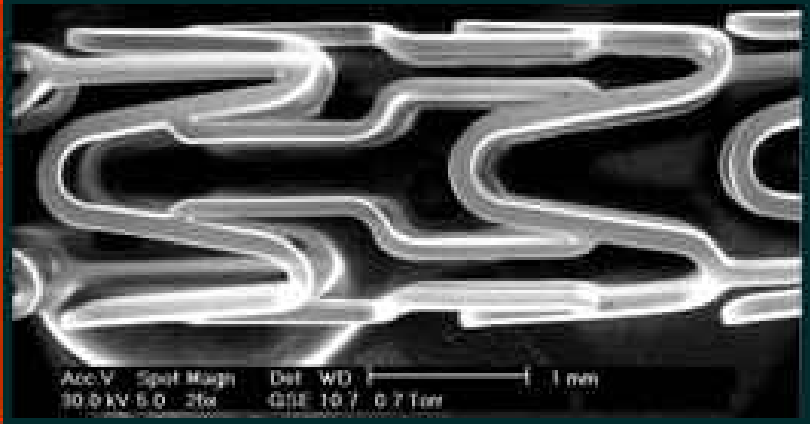


The Versatility of Reservoirs

- Reduced polymer-tissue contact
- Non-deformable (no surface damage)
- Increased polymer volume (3-10X current encapsulated polymers)
- Directional control (mural vs. bi-directional)
- Precise kinetic release patterns
- Ideal for dual drugs (increased capacity, independent release kinetics, hydrophilic drugs, directional specificity)

Supralimus-Eluting Stents

Supralimus™
Biodegradable Polymer Based Sirolimus Eluting Stent

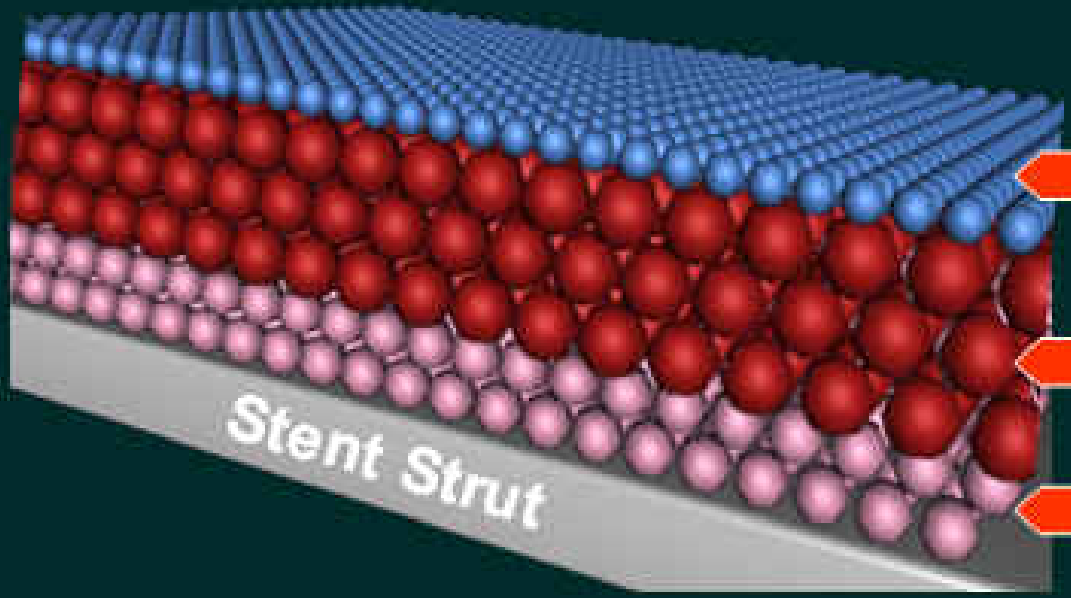


Platform

- Millennium Matrix
- 'Intermediate Cell Geometry', Slotted Tube Design
- 0.0032" strut thickness

- Drug: Sirolimus
- Drug Dosage: 102µg-16mm
- Unique Biodegradable Polymeric Blend
- Single layer of coating with drug free top coat
- 4-5 µm coating thickness

Synchronnium Sirolimus-Heparin Eluting Stent



0% Drug- Top layer
(Protective layer)

54% Drug-Middle layer
(Moderate Release)

46% Drug-Base layer
(Slow Release)

- Drug Dose: Sirolimus-1.19 µg/mm2, Heparin-0.28 µg/mm2
  (89 µg Sirolimus and 21 µg Heparin content on 16 mm stent)
- Unique Biodegradable Polymeric Blend includes-Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide and Polyvinyl pyrrolidone)

New DES Carrier Systems

Bioabsorbable Polymers

- Bioabsorbable polymers for DES systems have potential advantages, including diminished polymer burden and effects over time, which may improve long-term safety. *THE NEXT WAVE?*
- However, inflammatory responses due to polymer breakdown may be problematic and must be optimized.
- Several bioabsorbable polymer DES systems have been developed with acceptable characteristics and favorable early clinical outcomes.

DES -2007

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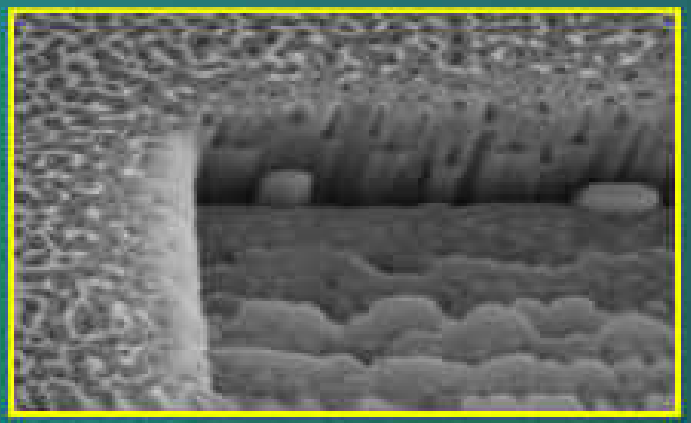
- …and Beyond

Nanoporous Ceramic Coating



Nanoporous Surface

- Nanoporous ceramic layer of aluminium oxide **(300nm thickness)** developed by AlCove Surfaces, Essen
- High mechanical stability
- No heavy metal ion dissolution
- Good tissue compatibility
- Anti-restenotic properties
- Suitable for drug release

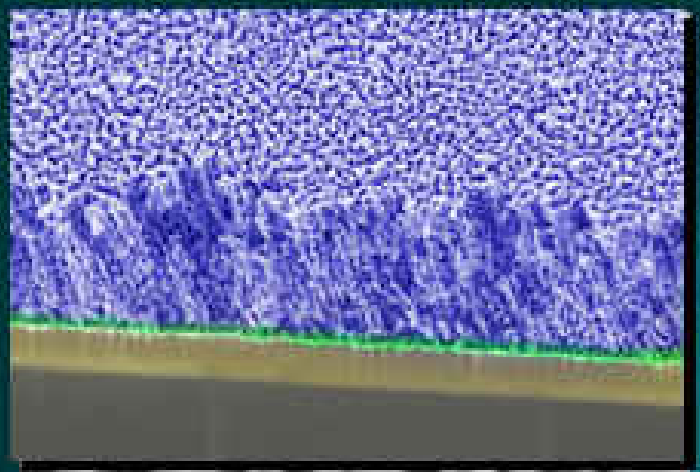
Jomed Tacrolimus DES

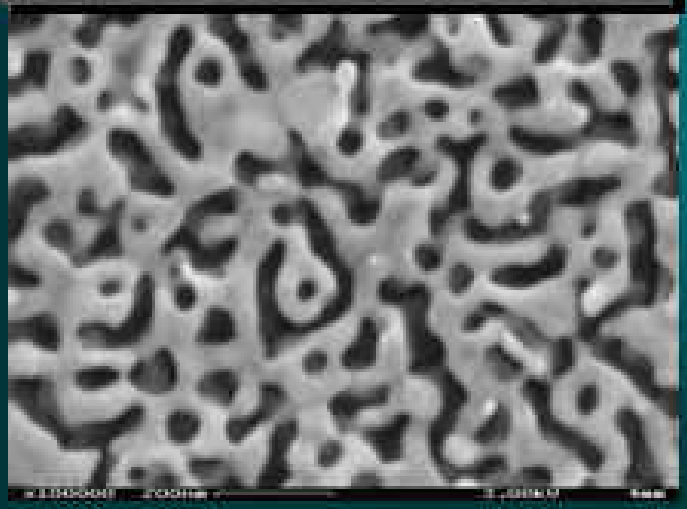
Comparison of Several Non-Polymeric Drug Delivery Stent Technologies

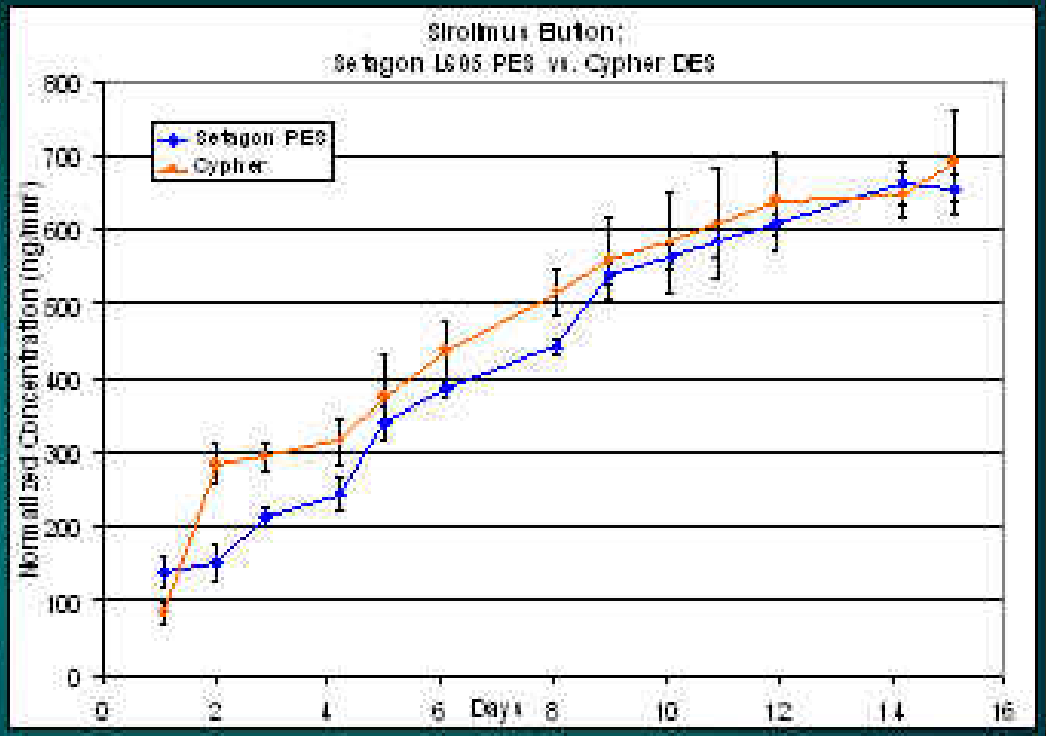
	Compatibility with Drugs	*Low-Residue Process*	*Surface Topography*	*Same Material as Stent*	*In vivo Drug Release Kinetics*	*Comments*
Setagon	High	Yes	Smooth	Yes	Days*	Nanoporous metal
Translumina	High	Yes	Rough	Yes	Hours+	Roughened surface, on site surface drug application
Blue Membranes	High	Yes	Rough	No	Days+	Micro- to macro-porous carbon/carbon composite
MIV Therapeutics	High	Yes	Smooth	No	Hours+	Thin hydroxy-apatite coating
Electroformed Stents Inc.	High	No	Rough	No	Days+	Electroplated coating
Medlogics/NTI	Low	No	Rough	No	Days+	Electrolysis co-deposition

* KDRs for can be extended to weeks/months with thin biodegradable top coats.
+ Predicted KDRs based on diffusion modeling analyses.

Setagon No Polymer System: Porosity & Elution Kinetics

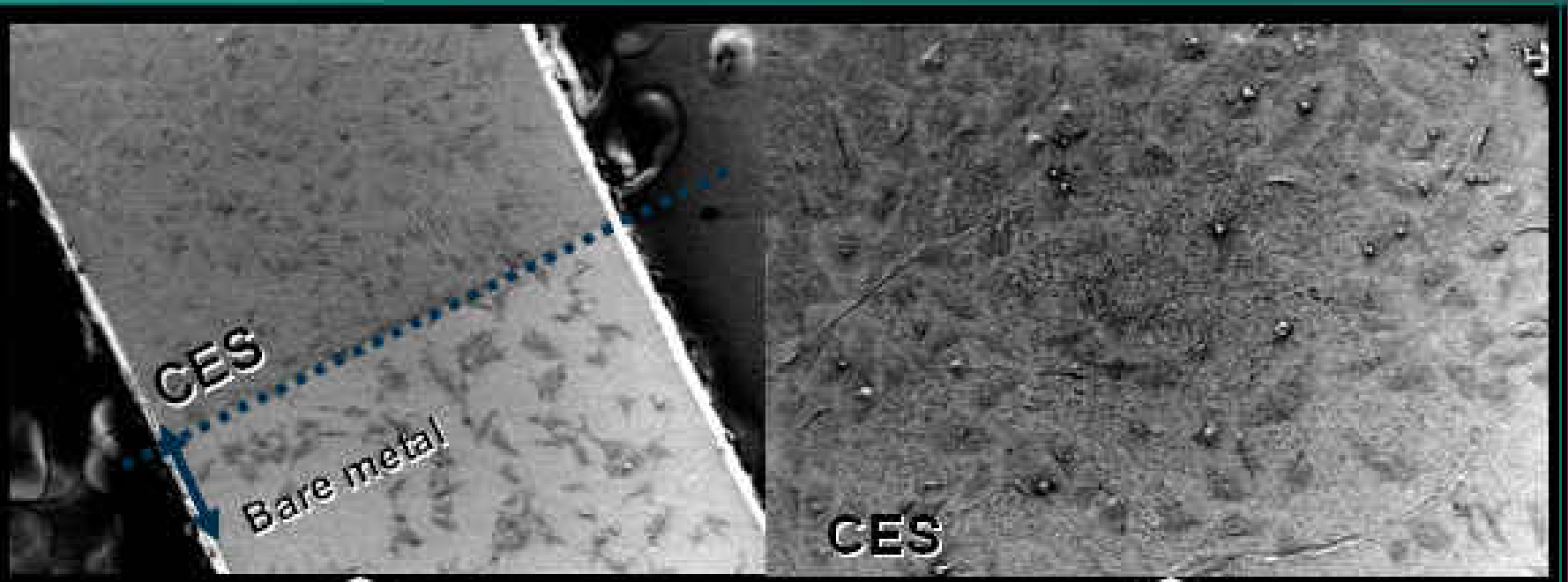






Nanoporous DES with thin bioabsorbable topcoat

Setagon Nanoporous Surface Enhances Adherence and Growth of Cultured Human Endothelial Cells Compared to Bare Metal (4-days)

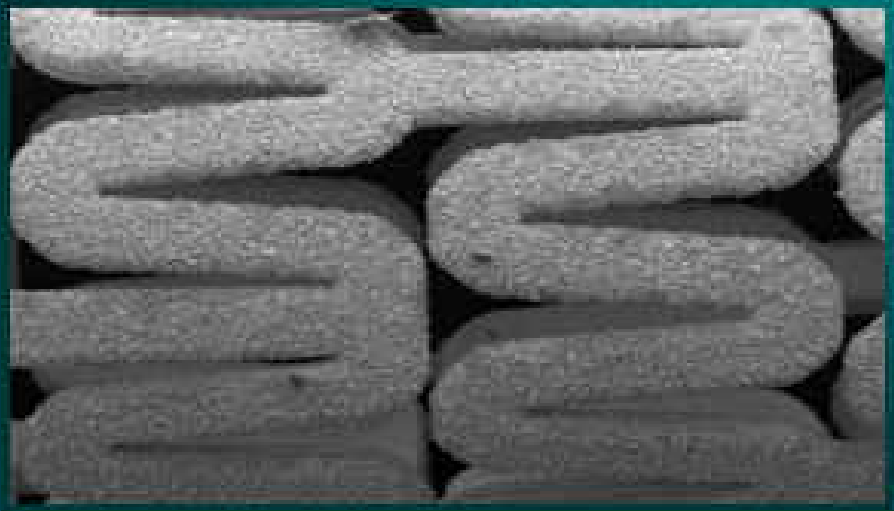


Poor Re-endothelialization on L605 bare metal.

Complete Re-Endothelialization on CES.

ESI DES System… Microporous

Gold ESI Stent with Microporous Coating

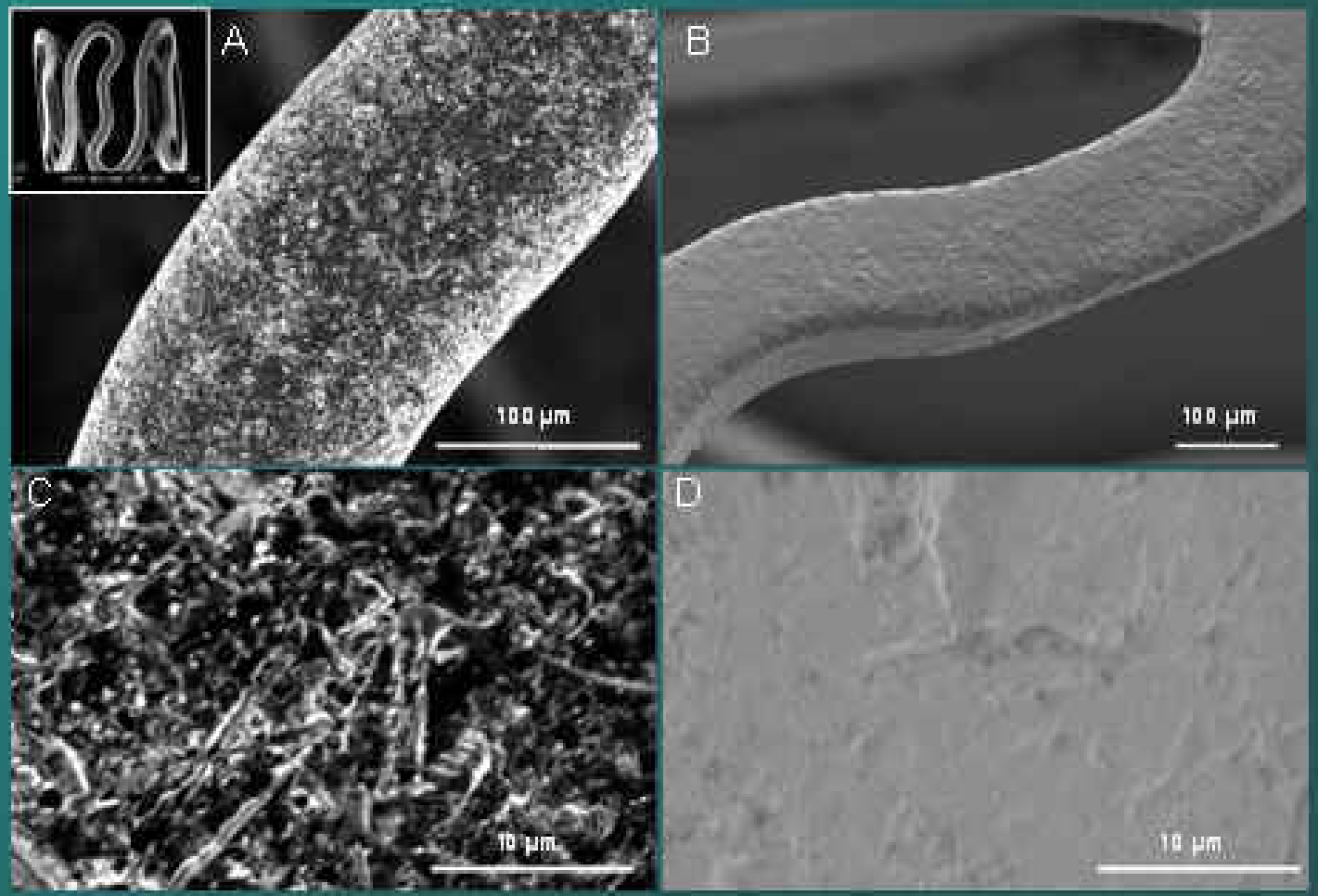


Translumina YUKON Stent (with sirolimus)

Stent Coating Machine & Stent Cartridge

Translumina YUK

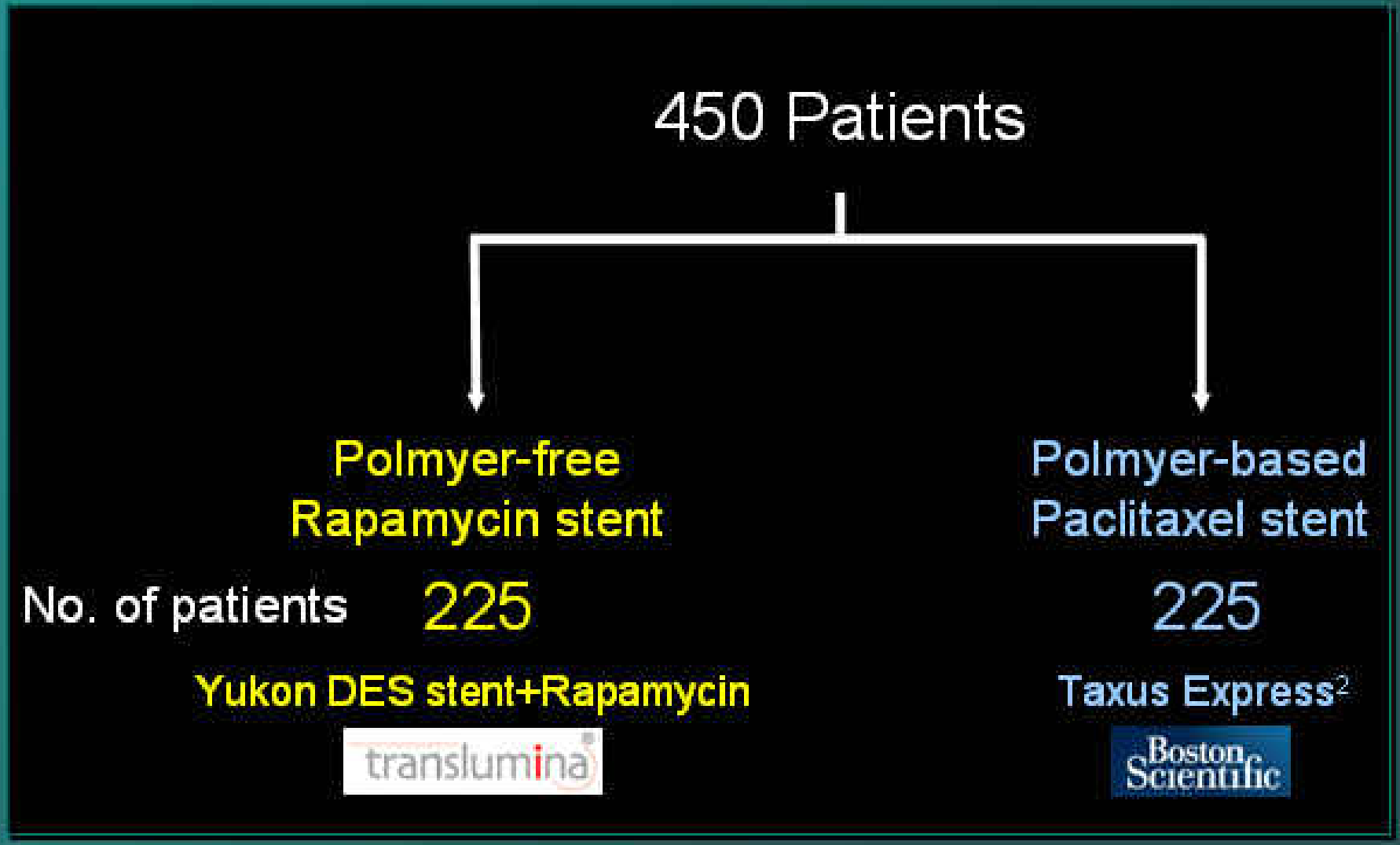
(microporous with



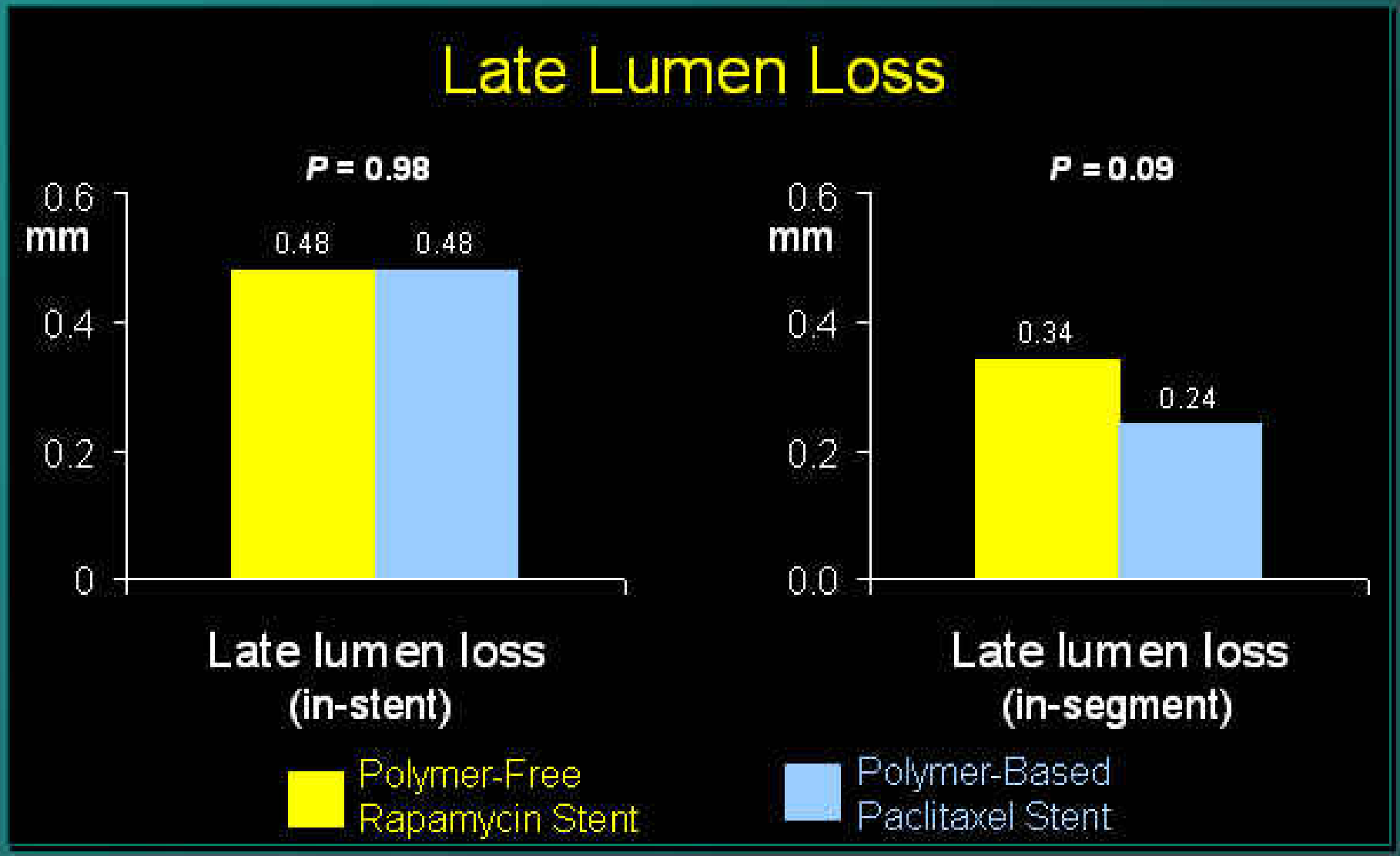
before

after

ISAR - TEST


450 Patients
Polmyer-free
Rapamycin stent
No. of patients
225
Yukon DES stent+Rapamycin
translumina
Polmyer-based
Paclitaxel stent
225
Taxus Express2
Boston Scientific

ISAR - TEST

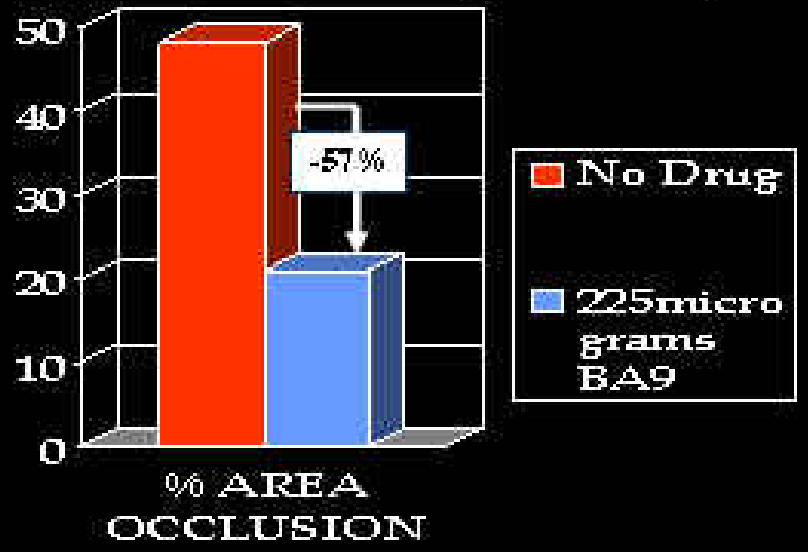

Late Lumen Loss
P = 0.98
0.6
mm
0.4
0.2
0
0.48
0.48
Late lumen loss
(in-stent)
P = 0.09
0.6
mm
0.4
0.2
0.0
0.34
0.24
Late lumen loss
(in-segment)
Polymer-Free
Rapamycin Stent
Polymer-Based
Paclitaxel Stent

BioMatrix Polymer-Free Freedom™ Stent

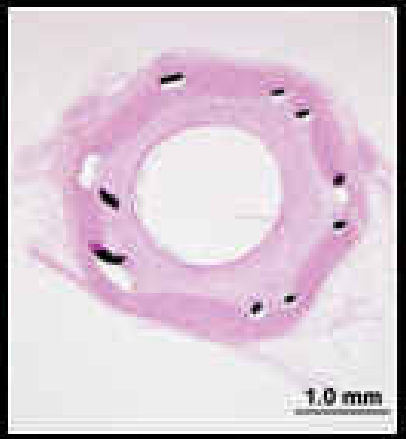
Selectively micro-structured surface holds drug in ablumenal pores or cavities; Pure Biolimus A9 impregnated within textured porous surface

BioMatrix Freedom DES vs. microstructured control in 28-day Porcine Overstretch Model

Histomorphometry Results	Arterial Area mm^2	Lumen/ Artery Ratio	Injury Score	Lumen Area mm^2 @28 day f/u
Bare Stent- Textured Abl. surface	7.76 mm^2	1.08	0.57	3.35 ±0.66
BioMatrix Freedom Textured surf. 225µg BA9	8.49 mm^2	1.08	0.50	5.68 ±0.68



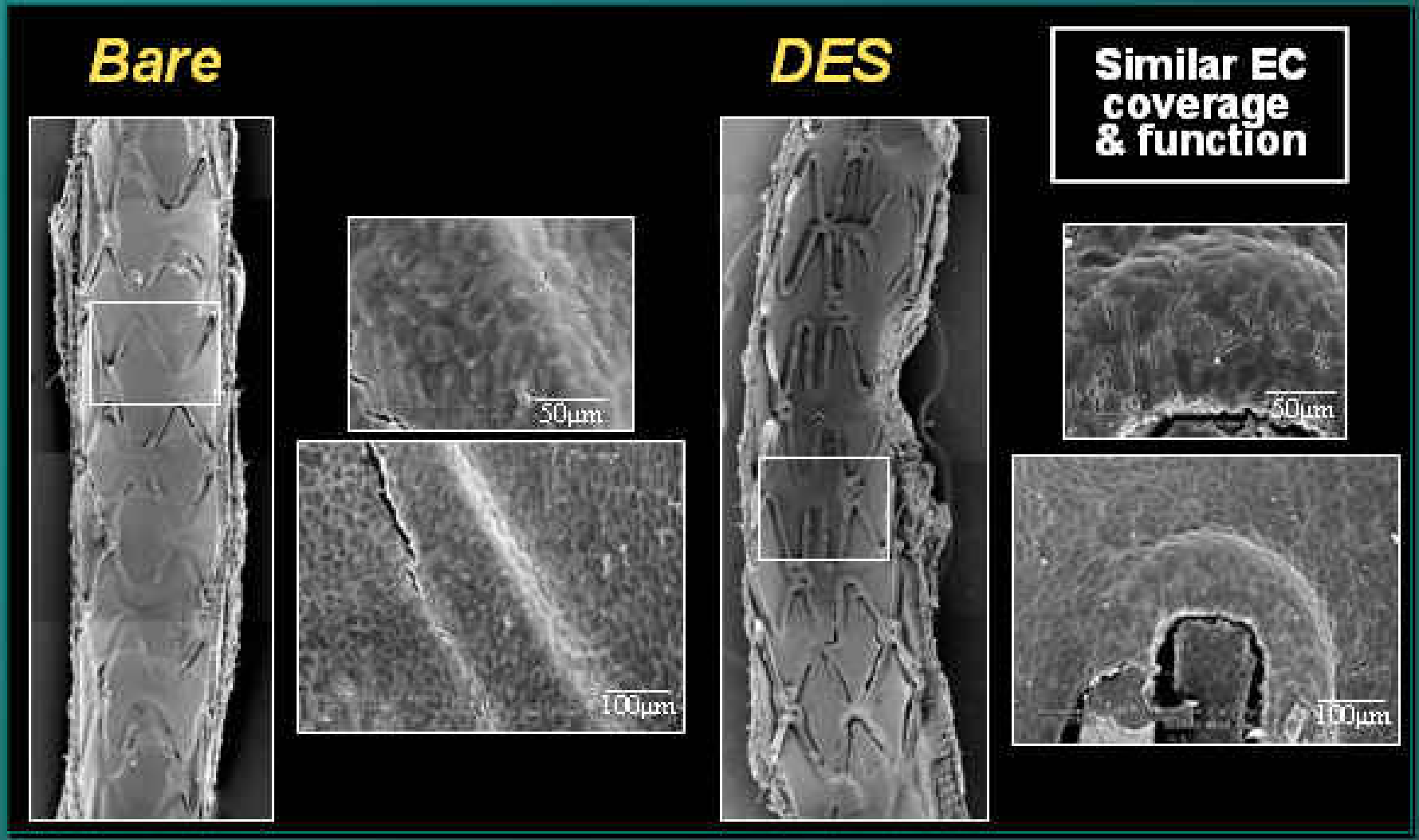
Biomatrix Freedom B9



Bare –Microstruct. Surf

BioMatrix Polymer-Free Freedom Stent

Rabbit iliac arteries @ 14 days



New DES Carrier Systems

No Polymer

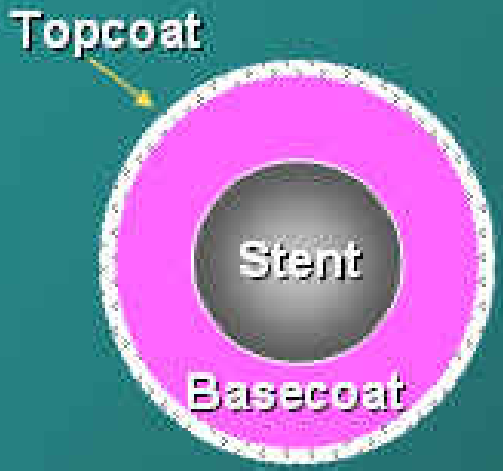
- Polymer-free DES systems are attractive as they eliminate all patho-biologic responses associated with artificial polymers and provide the possibility of short-term dual anti-platelet therapy.
- An added benefit may be improved endothelial cell adhesion and coverage due to the micro-structured surface; accelerated early healing.
- Problems abound including optimizing kinetic drug release patterns, inconsistent manufacturing and reduced drug loading capabilities.

DES -2007

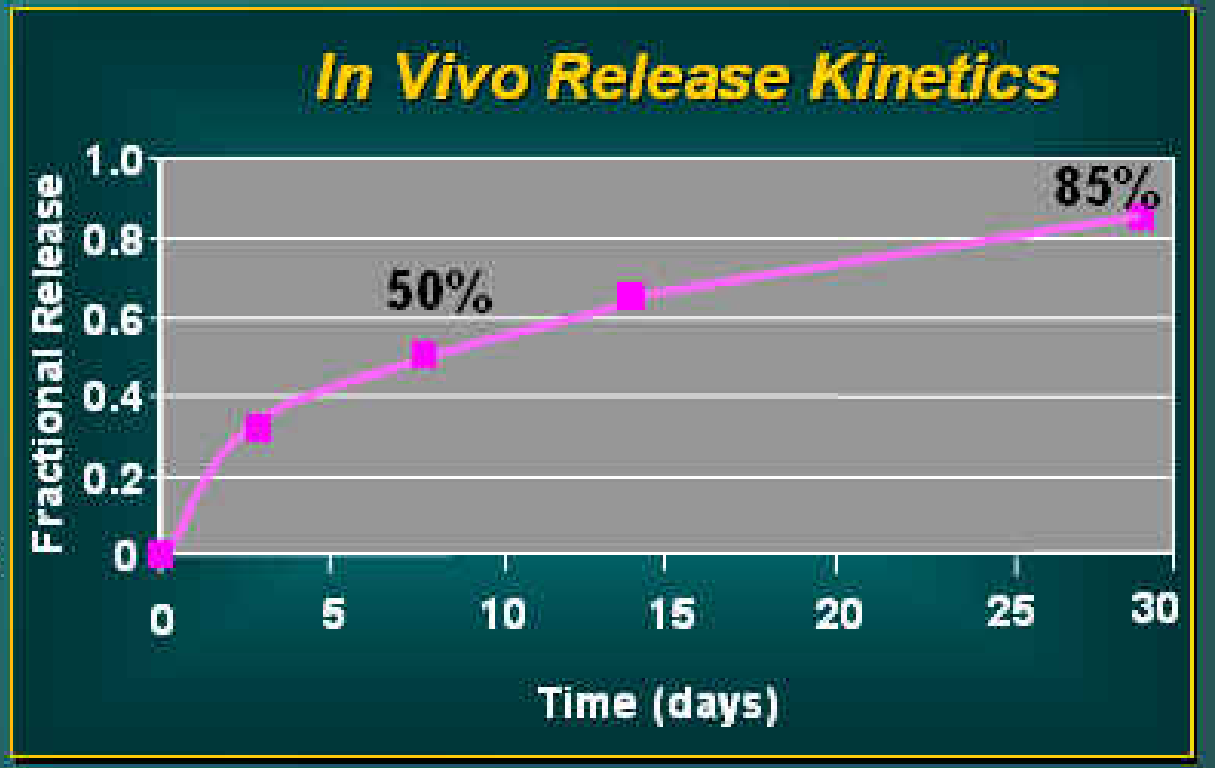
New DES Carrier Systems

- Biostable Polymers
- Bioaborbable Polymers
- No Polymers
- *Elution Kinetics*
- …and Beyond

Controlled Sirolimus Elution from Cypher™

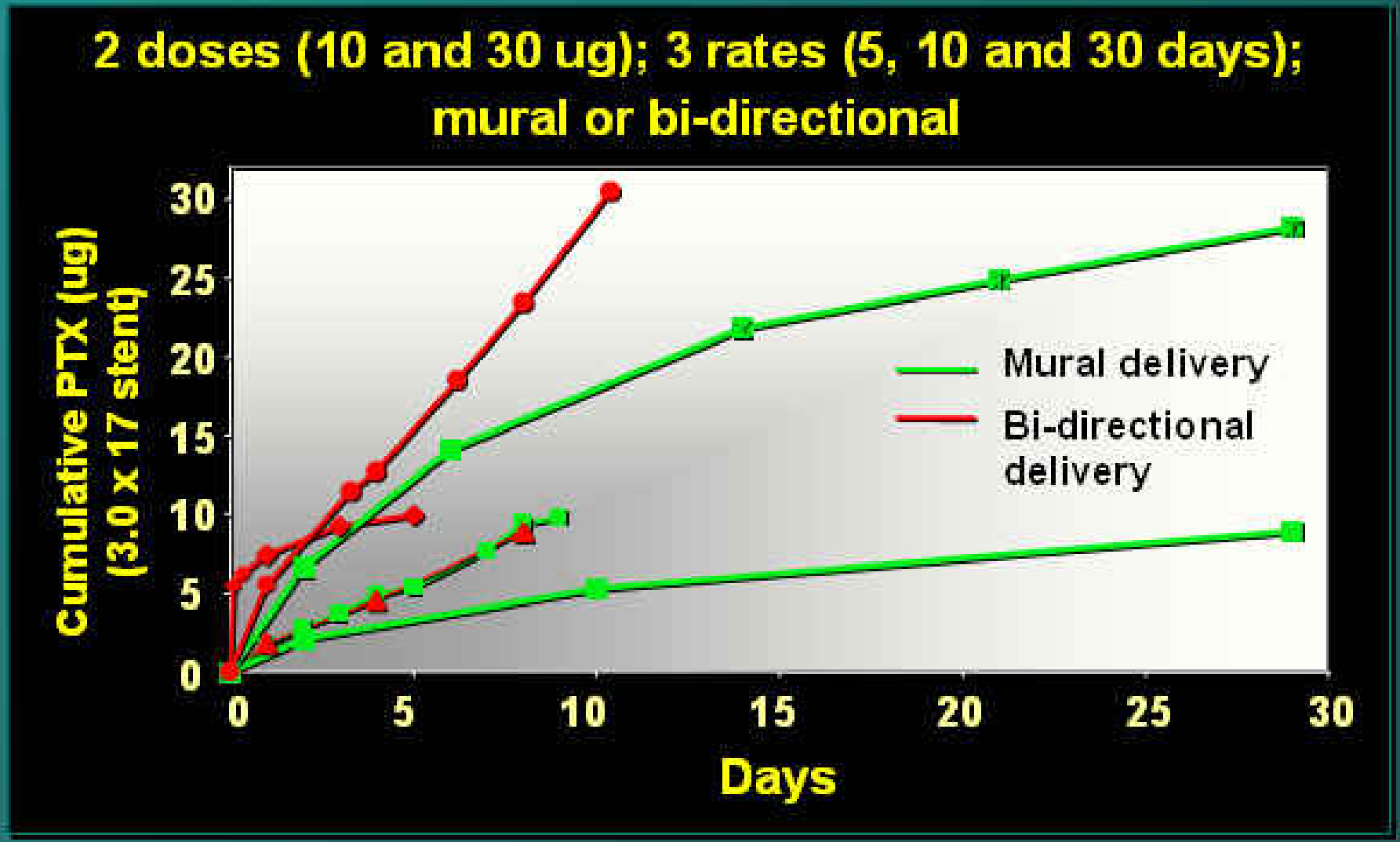


Basecoat = polymer/sirolimus
+
Topcoat = polymer only
(diffusion barrier)



Sirolimus is released in a controlled manner from a polymer matrix (PEVA + PBMA) bound to the stent; ALL of the drug is released within 3 months

PISCES Trial Release Profiles



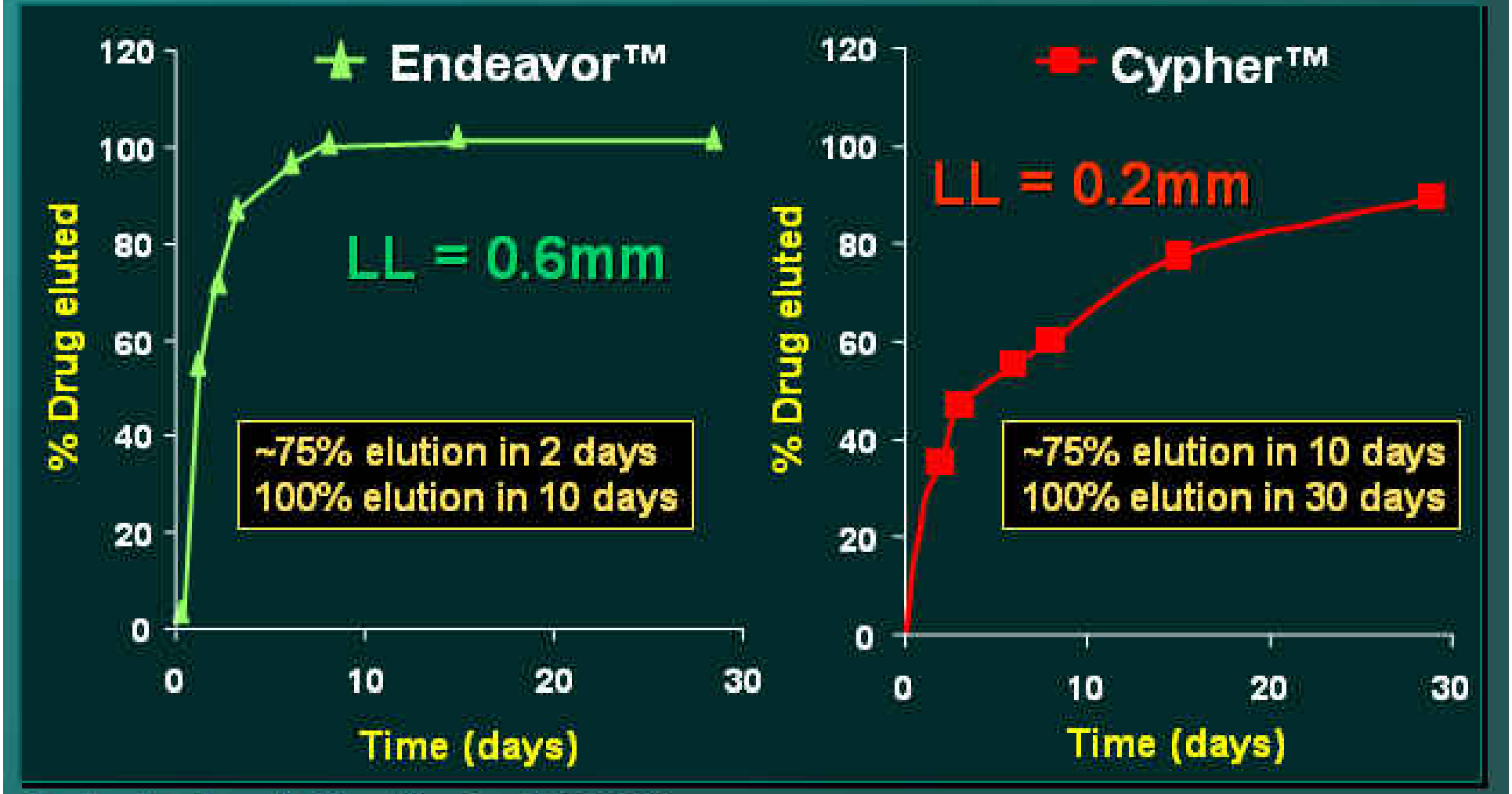
Release *in vitro* under infinite sink conditions

PISCES: In-Stent (Non-Paired) QCA

Late Loss (mm)

Comparison of *in vivo* Elution Rates

Rabbit iliac models

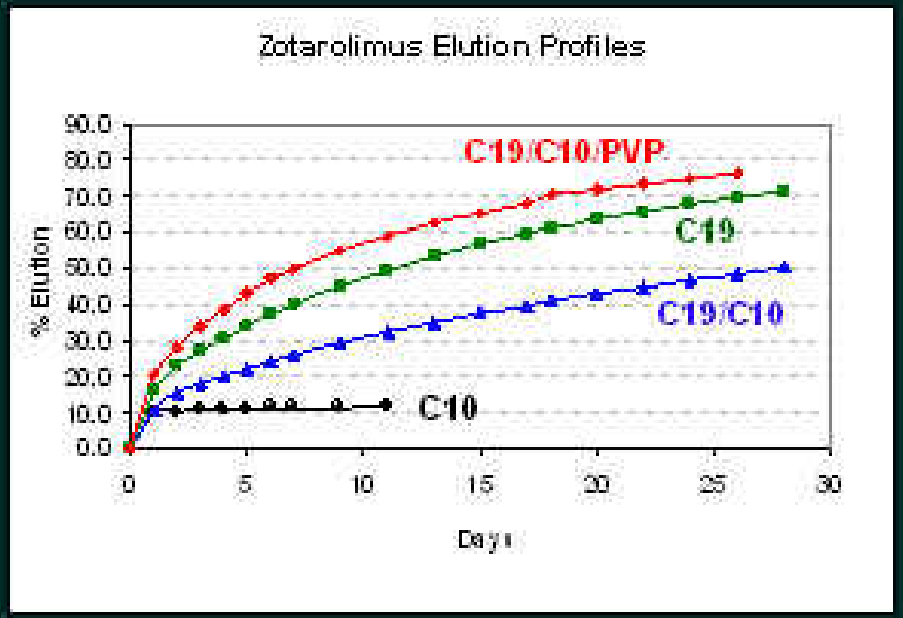


Cypher data from B. Chevalier, EuroPCR 2004
Endeavor data from G. Laarman, EuroPCR 2004

BioLinx Polymer System

Drug Elution Control

- **C10 polymer is lipophilic and aids in control of drug release. Alone it locks in the drug**
- **C19 polymer is primarily hydrophilic making it more biocompatibile and aids in drug elution**
- **PVP is hydrophilic, increases the initial drug burst and enhances the elution rate**

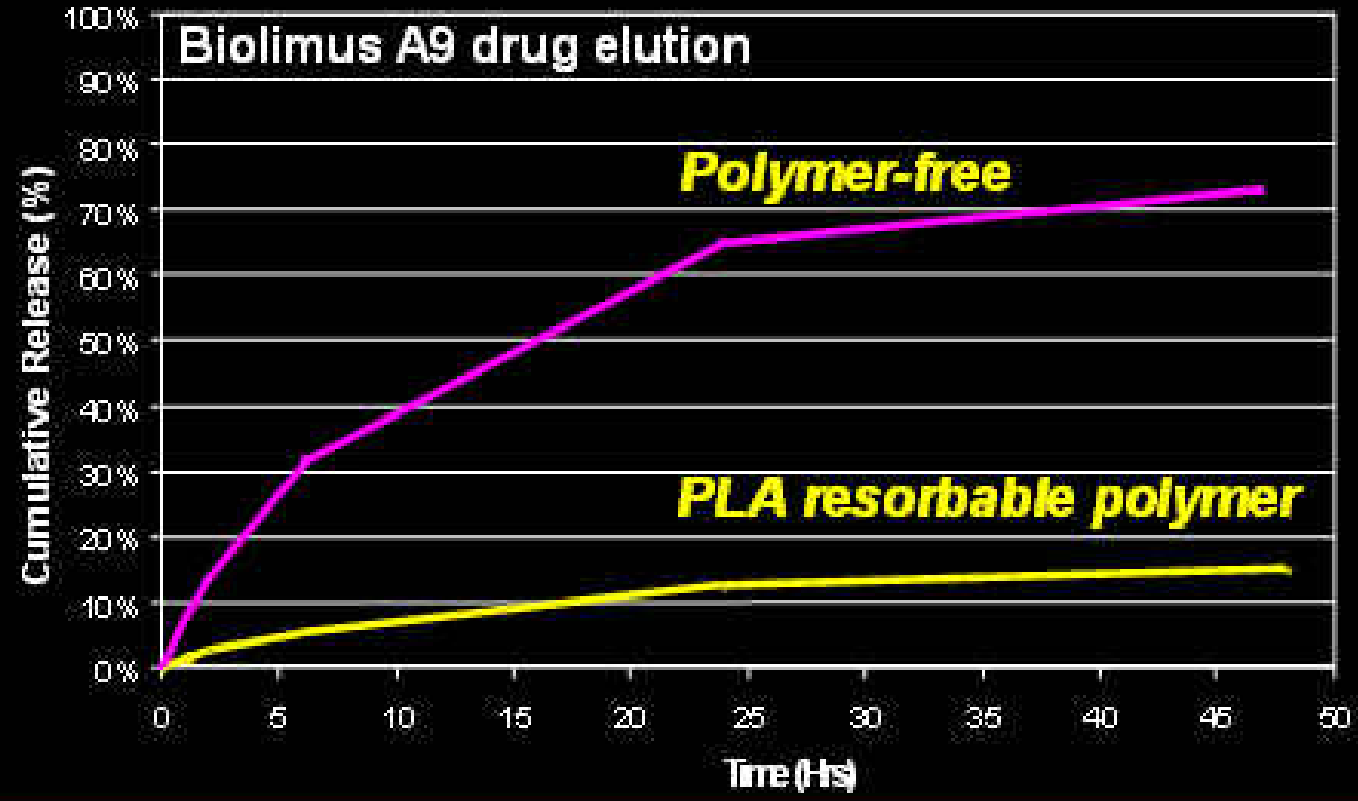


LL < 0.2mm

The BioLinx Polymer System blends C10, C19 and PVP for optimum elution

BioMatrix Polymer-Free Freedom™ Stent

Drug Elution is much faster from polymer-free vs. bioresorbable polymeric DES



New DES Carrier Systems

Elution Kinetics

- Kinetic drug release can be modulated from polymers and polymer-free DES by changing the thickness, composition, and internal architecture of the drug carrier system.
- Short-term drug release (< 2 weeks) of sirolimus (+ analogues) from carrier systems are associated with reduced neo-intimal hyperplasia suppression (higher late loss and restenosis).
- Polymer-free drug elution systems are challenged by rapid drug release which may limit effectiveness.

DES -2007

New DES Carrier Systems

- Biostable Polymers
- Bioaborbable Polymers
- No Polymers
- Elution Kinetics
- *…and Beyond*

DES -2007

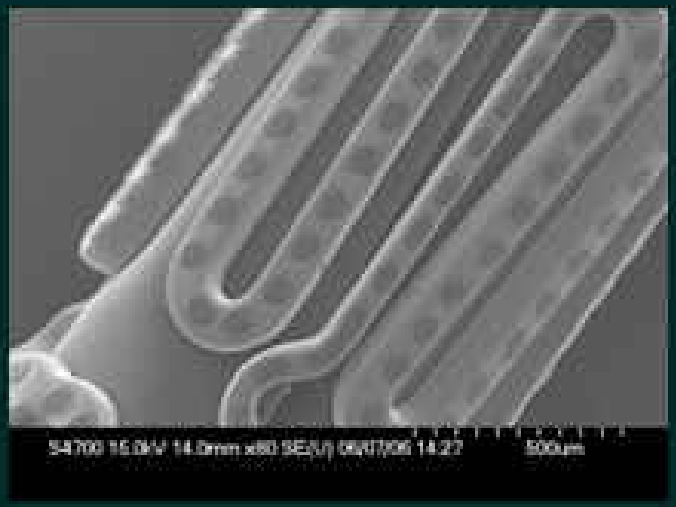
New DES Carrier Systems

- Abluminal polymer applications
- Nanoparticles
- Bioabsorbable stents
- Drug eluting balloons

Directional Drug Delivery
(ablumenal preference)

- ***Selective coating on the outside surface of the stent***
  - **Reduced drug/polymer**
  - **Lumenal surface BMS**
  - **Drug only where needed**

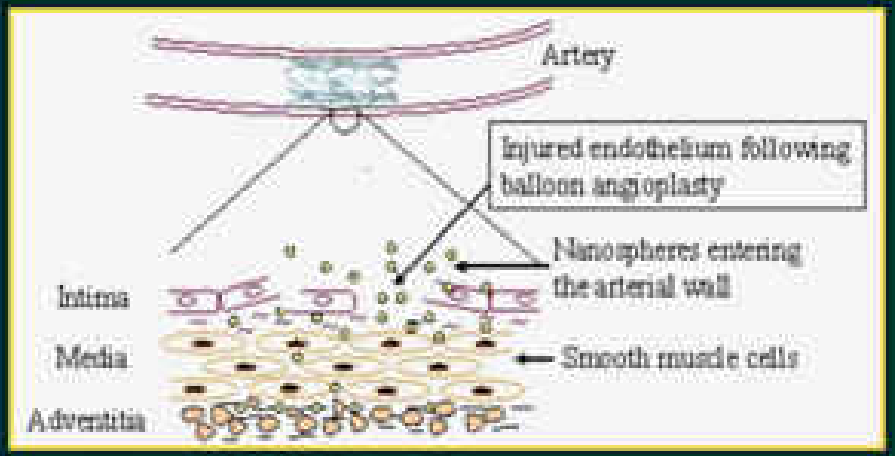
Labcoat JA™ Coating Technology



labcoat

Biodegradable Nano-particle Drug Elution

- particle size plays an important role in penetration and uptake of drug into arterial layer cells.
- There is a size-dependent NP penetration into the intact vessel wall.

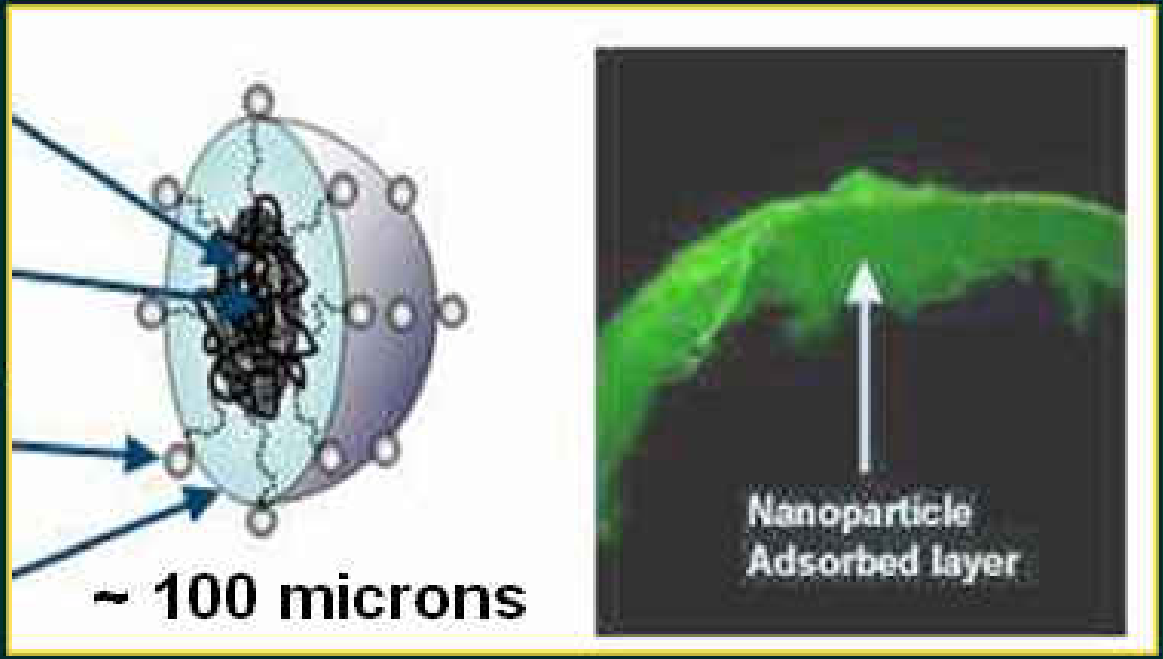


Biodegradable polymer:
Sustained release of drug

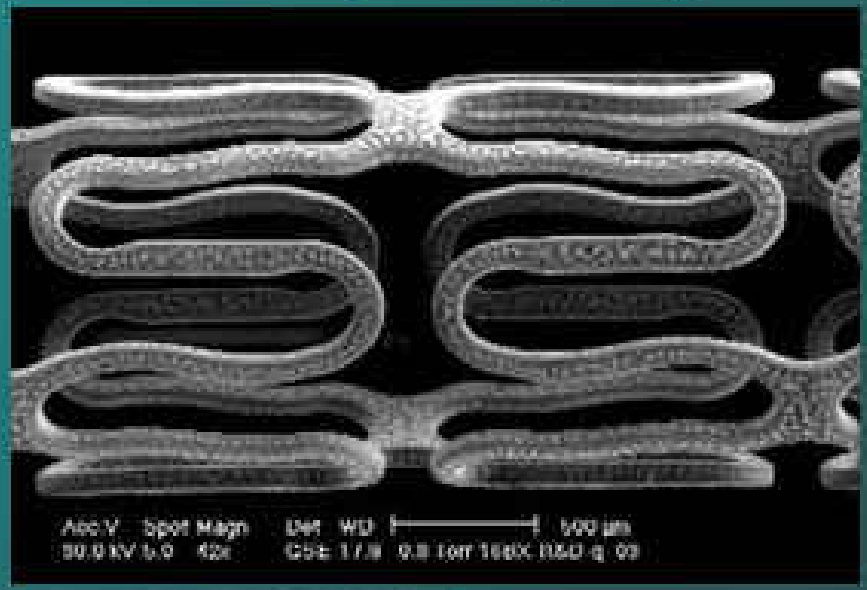
Hydrophobic core:
Containing drug

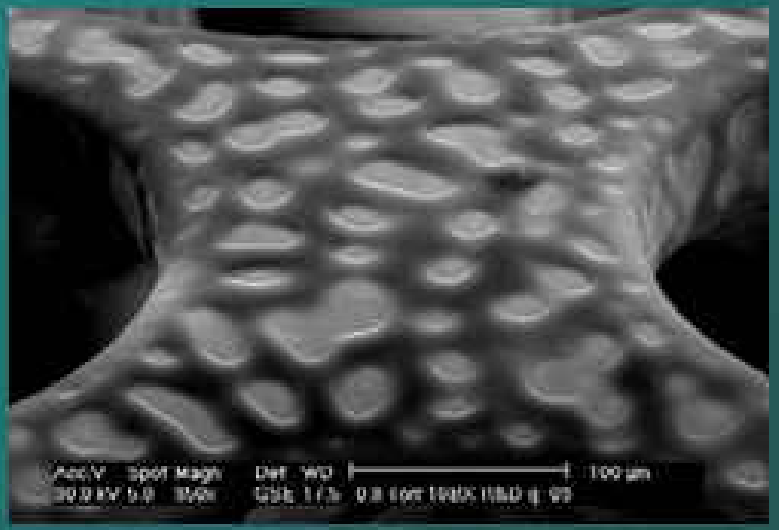
Targeting Functional Ligand:
Guided to target organ

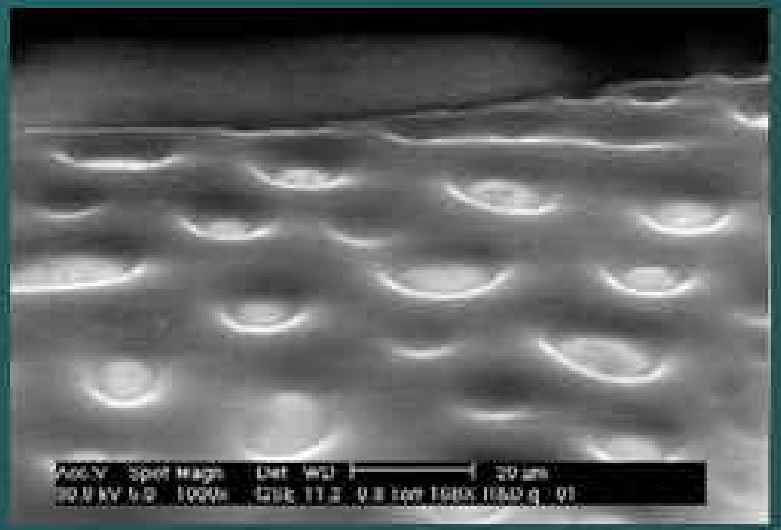
Hydrophilic surface:
Avoid to RES



Porous surface loaded with biodegradable nano-particles (thin polymer coat)







Bioresorbable: The Future of Stenting?

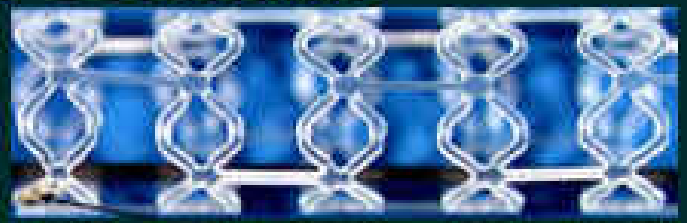
Past... Present... ...Future

Bare Metal Stent
More efficacious than POBA

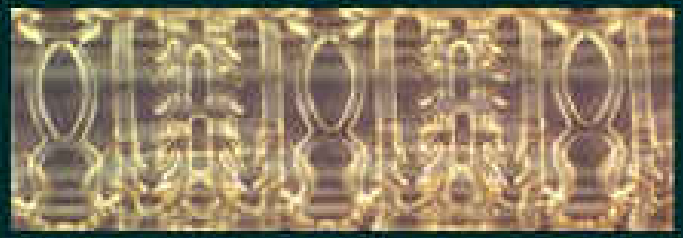
Metal DES
More efficacious than BMS

Boston Scientific

BVS



REVA



Cordis

Biotronik

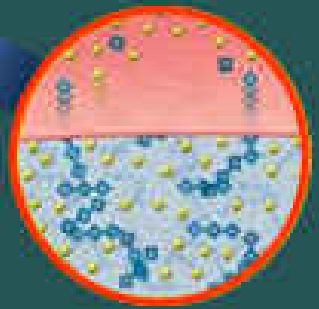
Abbott BVS Stent Components

ABSORB

BVS
Bioabsorbable
Stent Platform

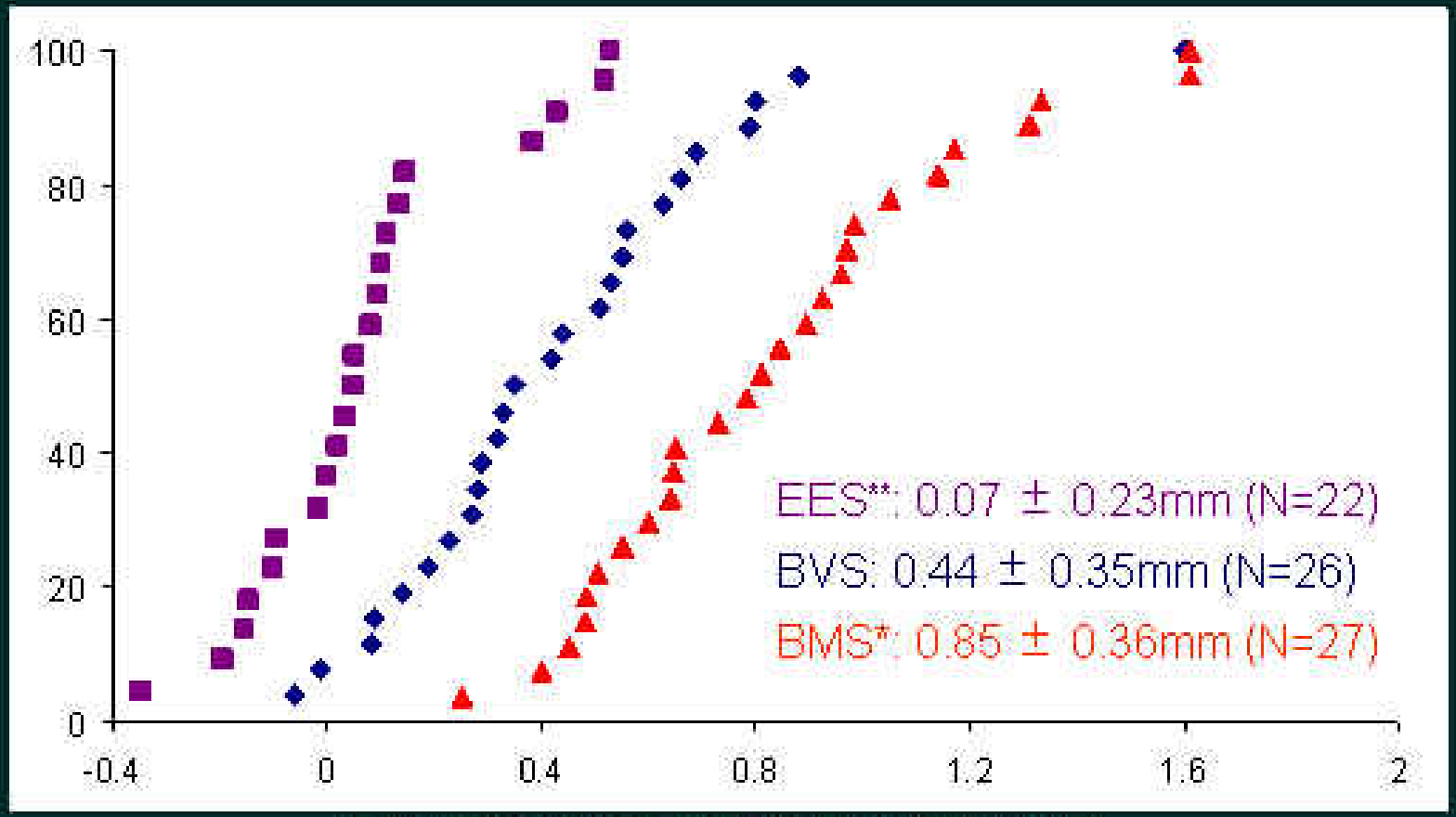
ML VISION®
Balloon SDS

Everolimus



Bioabsorbable
Polymer Coating

ABSORB
Angiographic Late Loss



* BMS loss from SPIRIT FIRST (n=27)

** EES loss of pts with 3.0 x 18mm for single lesion from SPIRIT FIRST and II (n=22)

ABSORB

IVUS Results (24 pts)

	Post-PCI	*Follow-up*	*% Difference*	*p-value*
Vessel area (mm2)	13.55	13.49	-0.4	NS
EEM-Stent Area (mm^2)	7.47	8.08	+8.2	0.003
Stent area (mm^2)	6.08	5.37	-11.7	<0.001
Neointimal hyperplasia area (mm^2)	0	0.30	NA	NA
Lumen area (mm^2)	6.08	5.07	-16.6	<0.001
Stent area obstruction (%)	0	5.55	NA	NA

New DES Carrier Systems

Final Thoughts-1

- There is a dramatic multi-facted effort to develop "safer" DES drug carrier systems, validating the concern that late stent thrombosis is partly related to current generation durable polymers.
- New biostable polymers are thinner, have improved mechanical stability, favor prolonged drug release, and are more biocompatible (less inflammation).
- A clear trend has emerged to reduce and eliminate the polymer carrier, either via bioabsorption (THE NEXT WAVE) or micro-textured polymer-free drug delivery surfaces (? the future).

New DES Carrier Systems

Final Thoughts-2

- Visionary concepts…including fully bioabsorbable stents and bioerodable nano-particles for drug delivery, are promising but will require extensive further experimental and clinical investigation.
- *It seems likely that this explosion of new technology directed towards improving DES safety will yield worthwhile clinical results in the near future!*