Evolution of Novel BioMime™ Sirolimus Eluting Stent on a Biodegradable Polymer Platform

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Disclosure Statement of Financial Interest

I, Wojciech Wojakowski DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

DRUG ELUTING STENTS

Significant reduction of in-stent restenosis

and TLR vs. BMS, but:

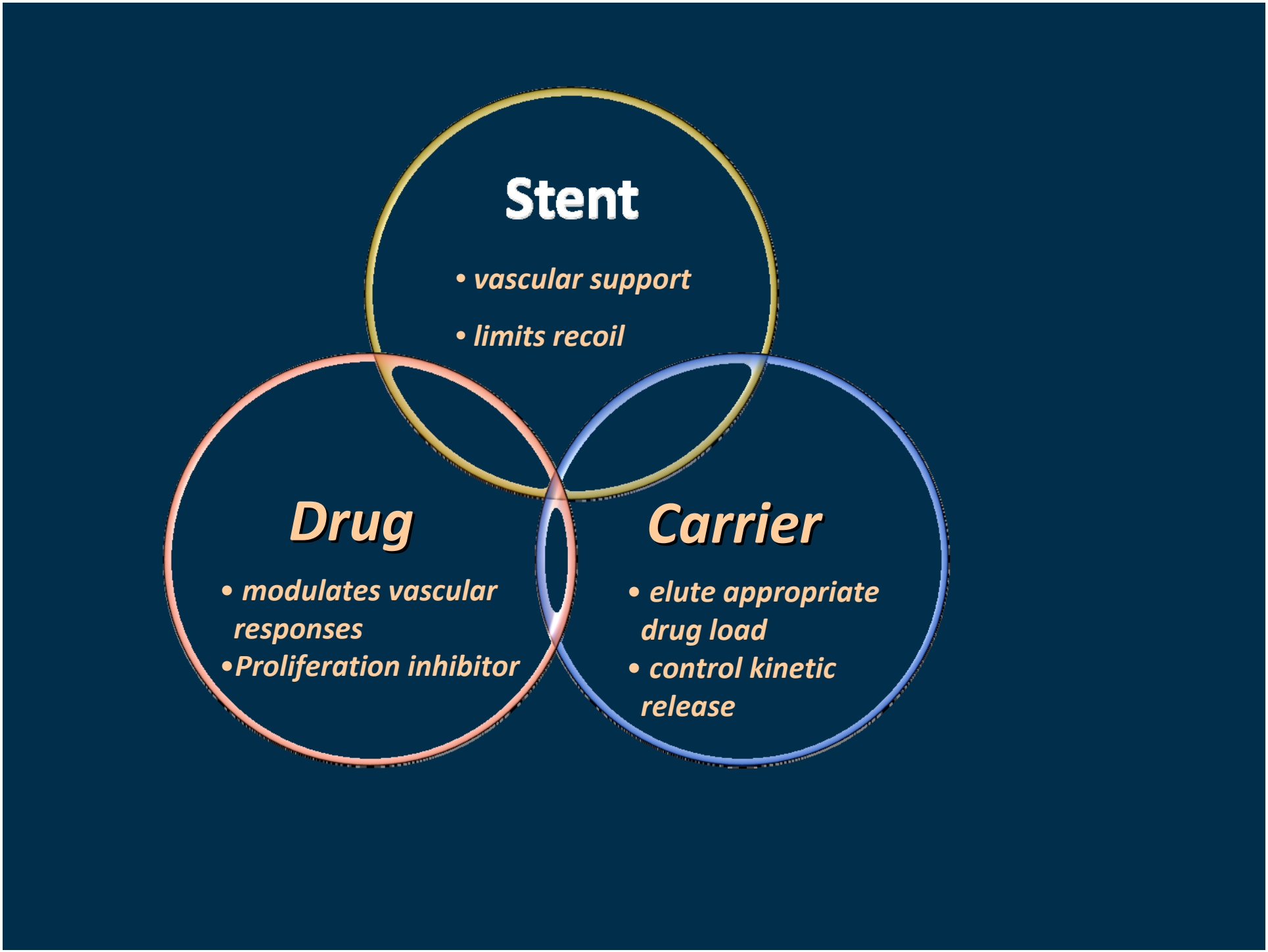
- ***ISR still present (7-15%)***
- ***Stent thrombosis is a valid safety concern***
- ***Procedure-, patient-, stent-related factors***

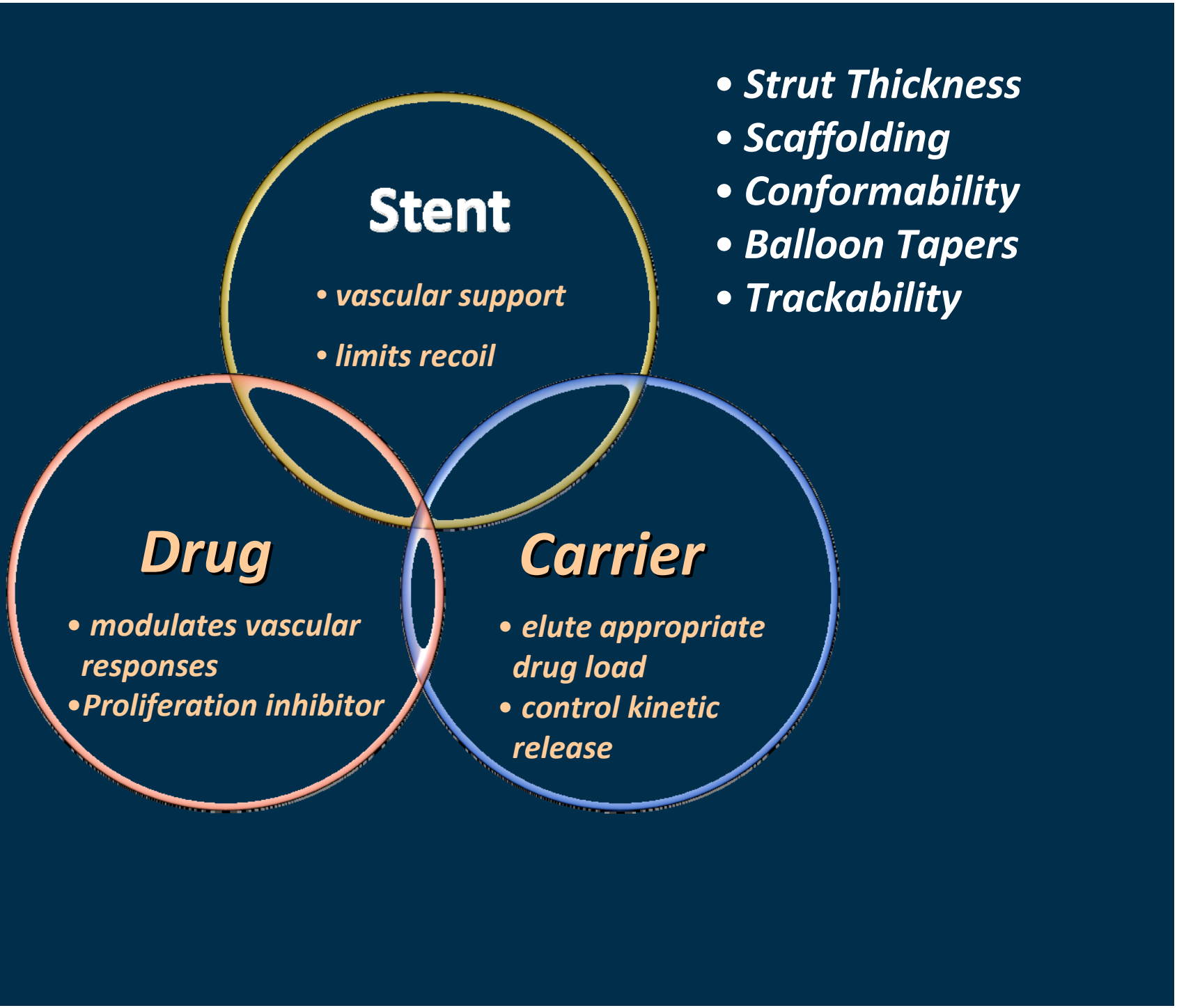
J Am Coll Cardiol 2010;56:1783–93
J Am Coll Cardiol, 2010; 56:1897-1907

STENT-RELATED FACTORS

- incomplete endothelialization/neointima coverage
- inflammatory reaction
- polymer/drug hypersensitivity reaction
- late incomplete apposition
- chronic drug toxicity
- endothelial dysfunction

J Am Coll Cardiol 2010;56:1783–93
Circulation. 2007;115:1051-1058.


Stent
• vascular support
• limits recoil
Drug
• modulates vascular responses
• Proliferation inhibitor
Carrier
• elute appropriate drug load
• control kinetic release


Stent
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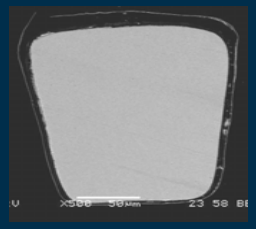
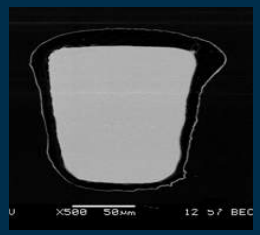
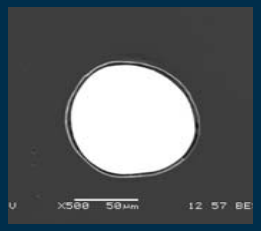
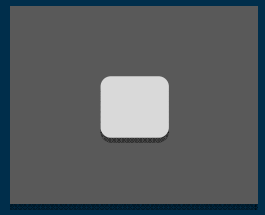
• control kinetic release
• Strut Thickness
• Scaffolding
• Conformability
• Balloon Tapers
• Trackability

STRUT THICKNESS – COMPARATOR BMS

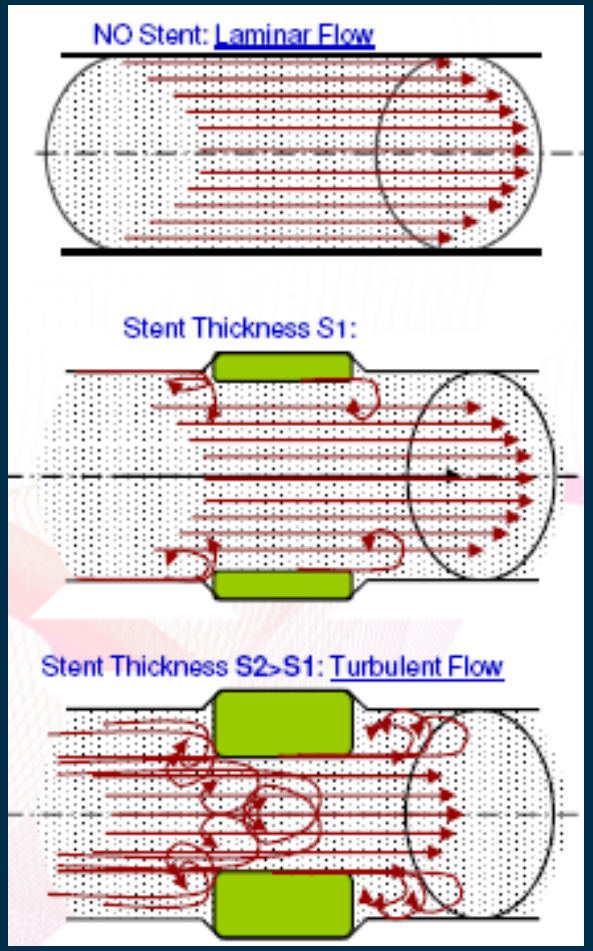
Minimizing Vessel Injury

BxVelocity	Liberte	Driver	Vision	NexGen
				
140 µm	132 µm	91 µm	81 µm	65 µm

3.0 mm diameter stents, 500X magnification

THIN STRUTS AND RESTENOSIS

- *Thin Struts as low as 65 μm (0.0026")*
  - *Low blood flow perturbance*
  - *Easy struts nesting to the vessel wall*
  - *Added flexibility and conformability*
- *Improved clinical outcome**
- *Improved, faster endothelialization ***



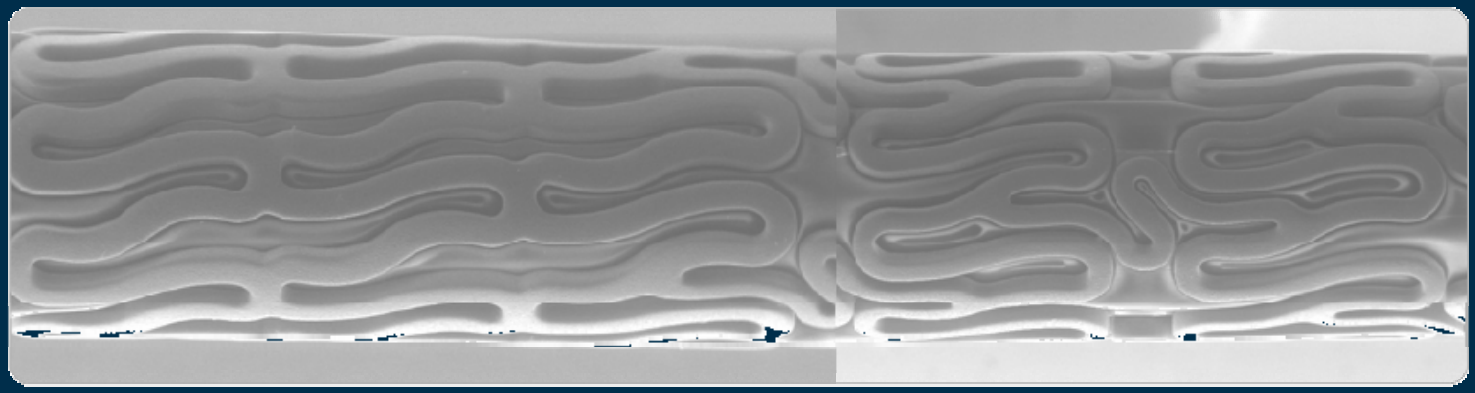
** Kastrati A, Schömig A, Dirschinger J, et al. Strut Thickness Effect on Restenosis Outcome (ISAR STEREO Trial). Circulation 2001; 103:2816-2821*

*** Simon C, Palmaz JC, Sprague EA. Influence of topography on endothelialization of stents: clues for new designes. J Lon Term Eff Med Implants. 2000;10:143-151*

OPTIMIZED STENT ARCHITECTURE

- BioMime™ stent is built on CE marked NexGen™ – cobalt chromium platform.
- Stent has a unique hybrid cell design comprising of an intelligent mix of open and close cell designs resulting in a structure which provides excellent radial strength with a high degree of flexibility
- Our special electro-polishing technique ensures an ultra-low strut thickness of 65µm.

SEM image of crimped BioMime SES at 50x

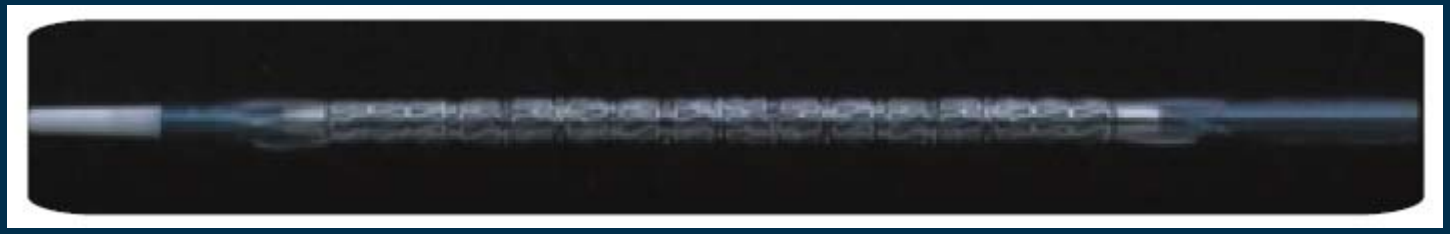


Closed cell at edges

Open cell in mid - segment

Hybrid design

MORPHOLOGY-MEDIATED EXPANSION



Crimped Stent

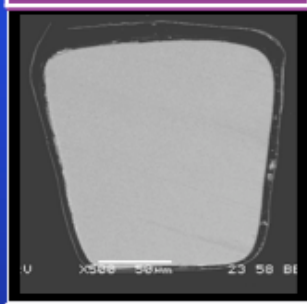
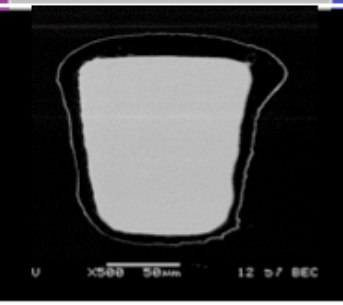
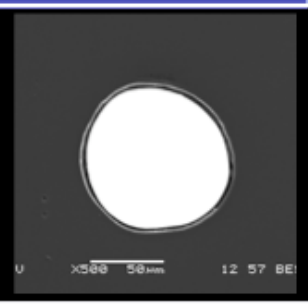
Morphology Mediated Expansion

Fully expanded stent

MINIMIZING STRUT AND POLYMER THICKNESS TO REDUCE INJURY AND IMPROVE HEALING

Momentum Towards Biomimicry

1st generation DES → *2nd generation DES*

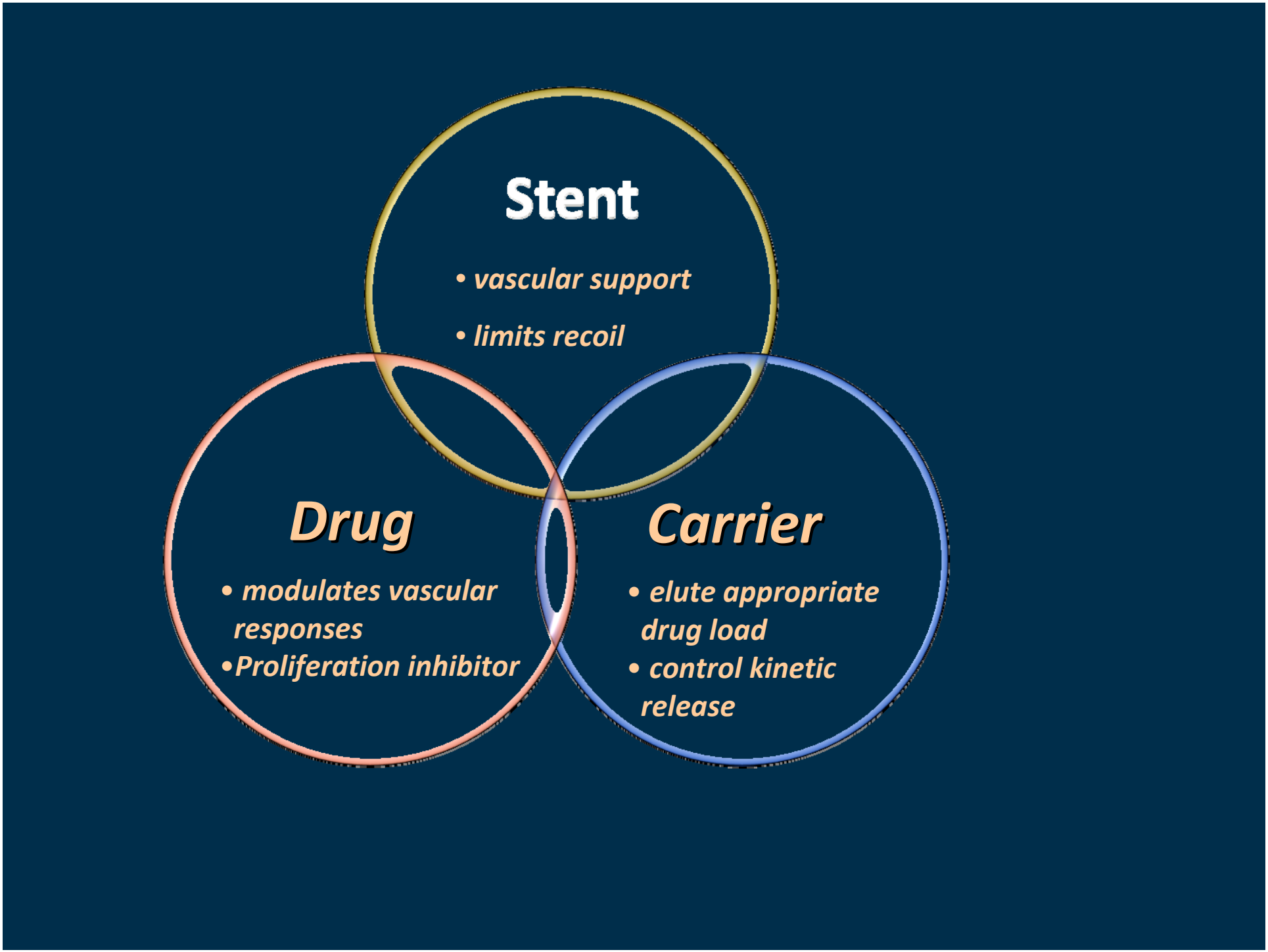
CYPHER®	TAXUS® EXPRESS	ENDEAVOR™	XIENCE™ V
			
Strut Thickness:	Strut Thickness:	Strut Thickness:	Strut Thickness:
140 um	132 um	91 um	81 um
Polymer Thickness:	Polymer Thickness:	Polymer Thickness:	Polymer Thickness:
12.6 um	16 um	5.3 um	7.6 um
PEVA+PBMA	SIBBS	PC	Fluoropolymer
Sirolimus	Paclitaxel	Zotarolimus	Everolimus

BioMime™

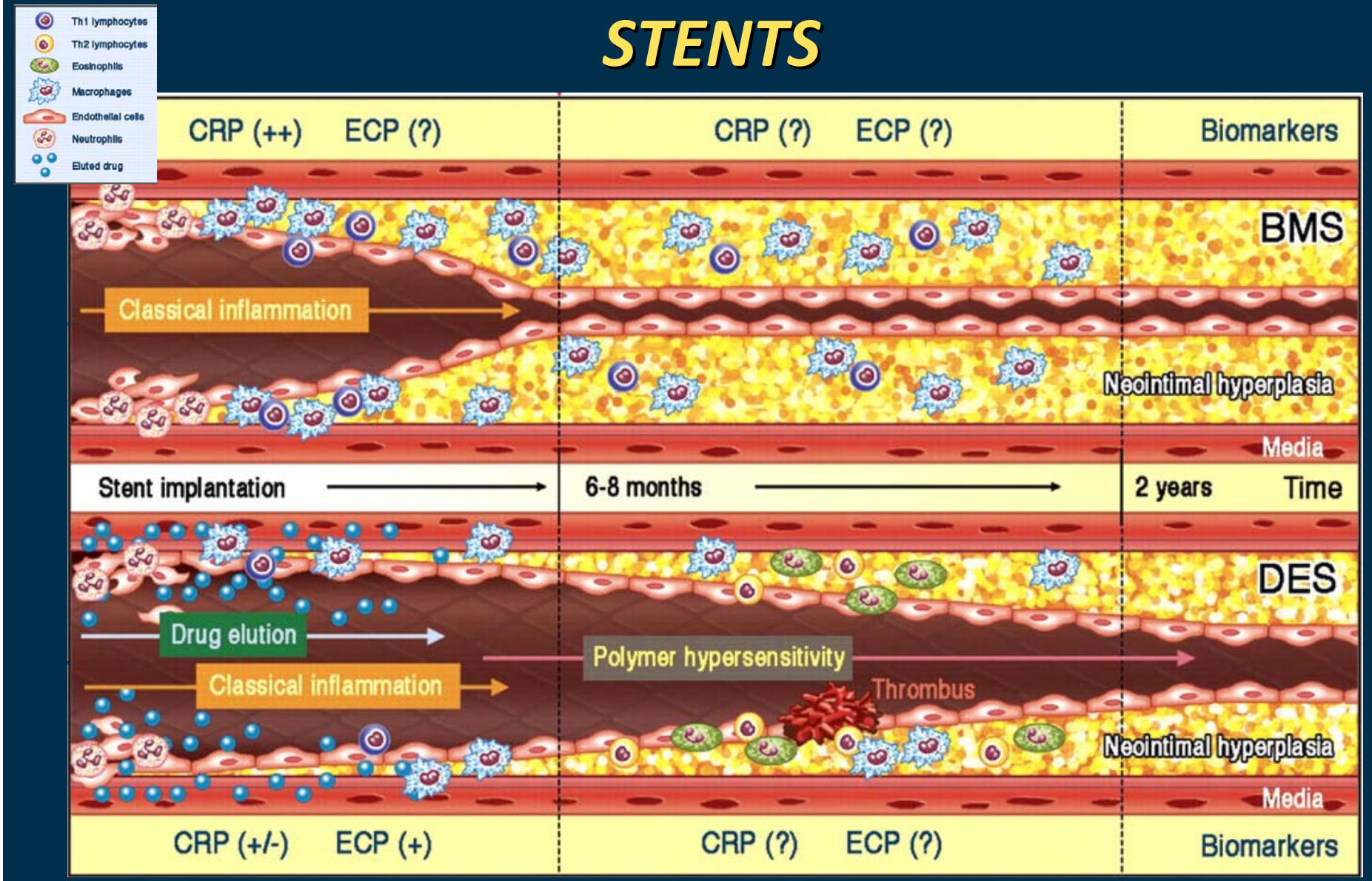
Strut Thickness:
65 µm
Polymer Thickness:
2 µm
PLLA & PLGA
Sirolimus

Total Drug Load (µg/mm²): ***per mm**

1.4 1.0 *10.0 1.0 1.25


Stent
• vascular support
• limits recoil
Drug
• modulates vascular responses
• Proliferation inhibitor
Carrier
• elute appropriate drug load
• control kinetic release

ADVERSE REACTION TO DRUG ELUTING STENTS



J Am Coll Cardiol 2010;56:1783–93

POLYMERS ON DES

- Stickiness
- Durability
- Hardness
- Elasticity

Coating integrity

Adhesive /cohesive

Drug release properties

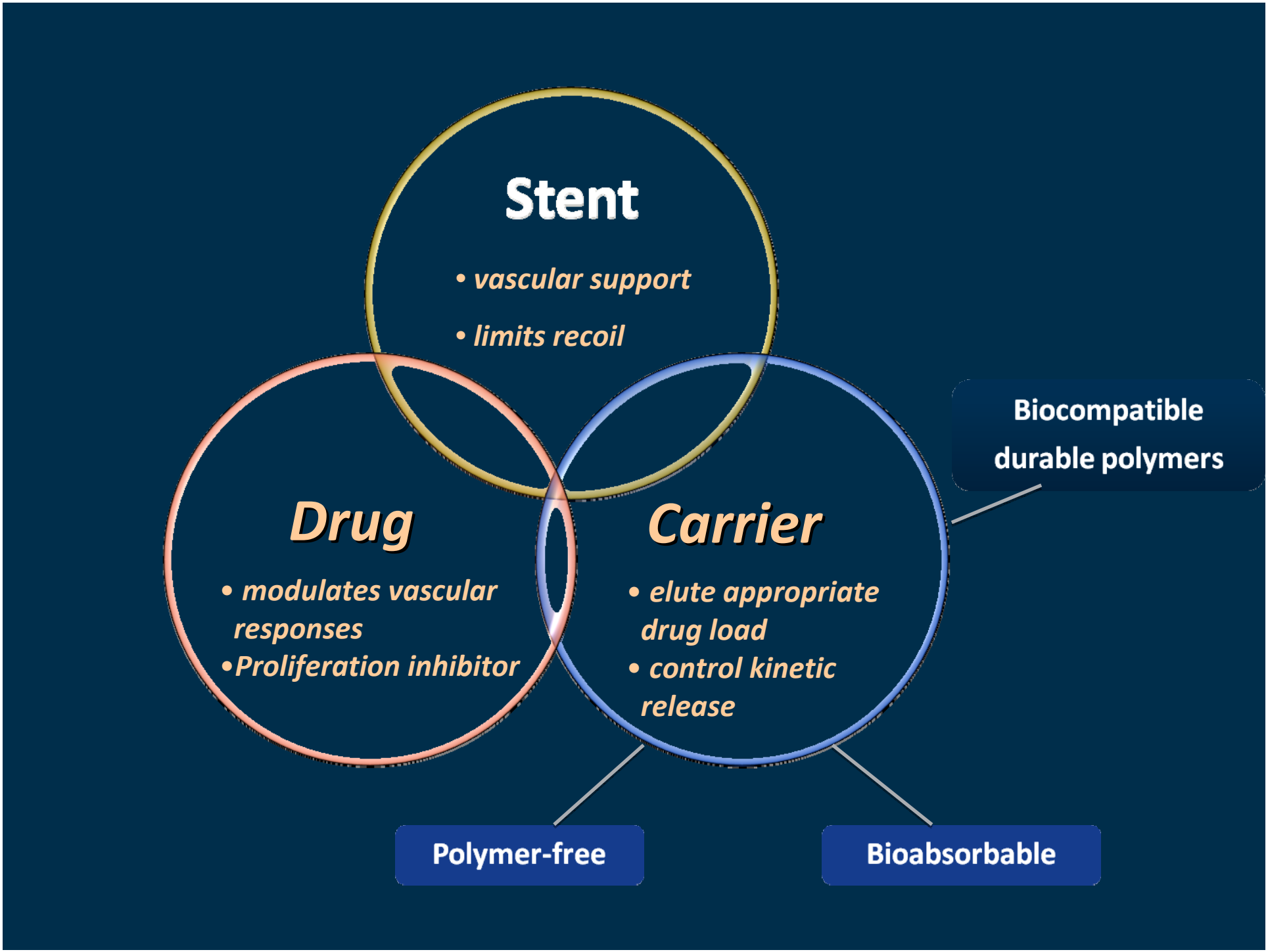
Non-thrombogenic in blood contact

Supports functional endothelium

Minimal chronic inflammation

Mechanical and drug release

Biocompatibility


Stent
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Drug
• modulates vascular responses
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Carrier
• elute appropriate drug load
• control kinetic release
Biocompatible durable polymers
Polymer-free
Bioabsorbable

BIOABSORBABLE POLYMERS

PROS

- *reduced chronic polymer toxicity*

CONS

- *release of proinflammatory polymer-derived compounds*

UNKNOWNS

- *Safety and efficacy of biodegradable polymer DES*

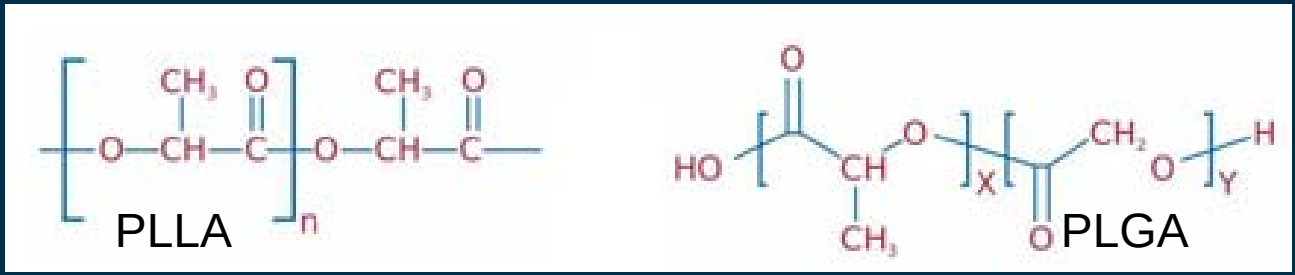
  is not inferior to first generation durable polymer based DES

- *Benefits need to be confirmed in larger populations*

  over longer FU to assess the risk of VLST

Windecker, TCT 2010

ABOUT BIOPOLY™



- BioPoly is Meril's propriety biodegradable co-polymer formulation
- Degradation by hydrolysis to carbon dioxide $CO_2$and water (H_2O)
- Degradation time of 40-50 days
- Offers uniformity in stent coating
- Is highly stable during EtO process without loss in polymer integrity
- Does not- web, crack, or lump on stent or balloon surface
- Exceptionally low coating thickness of <2 µm

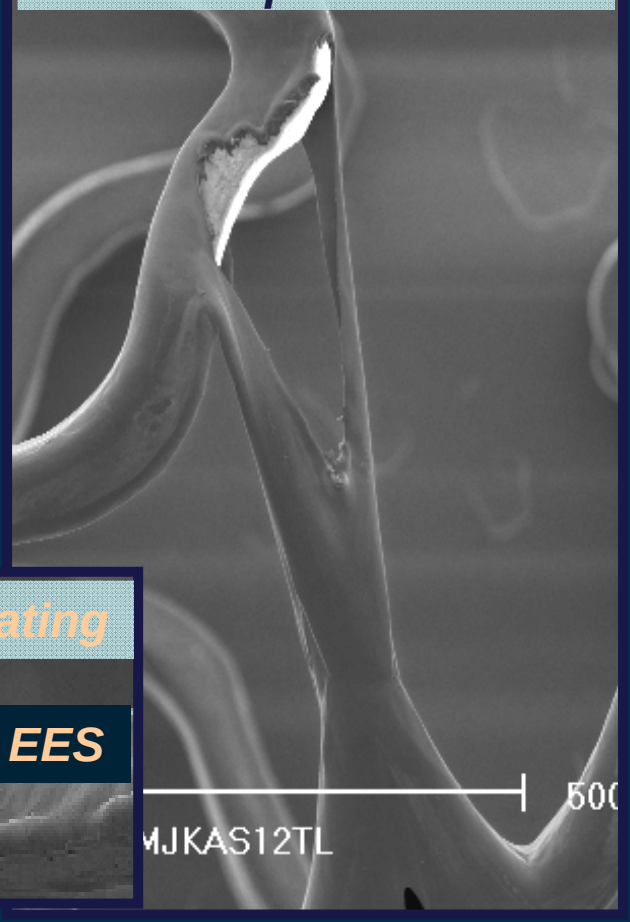
MECHANICAL INTEGRITY

Displacement of Coating

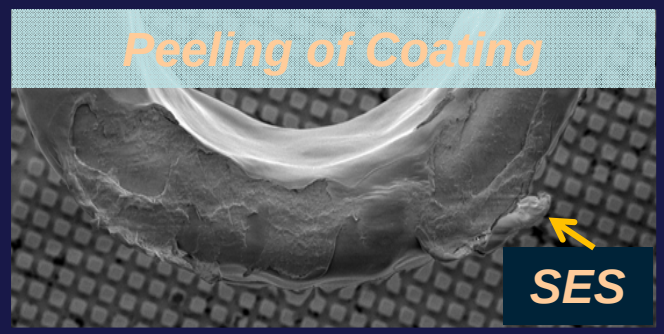
Webbing Without Metal Exposure

PES

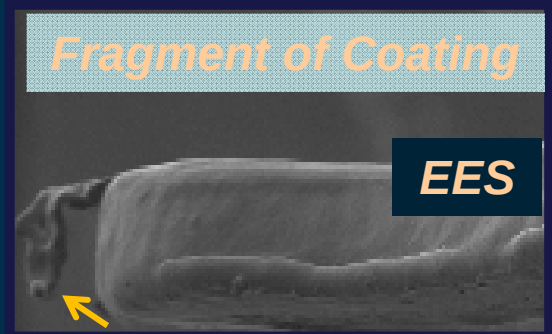
Webbing With Metal Exposure



Peeling of Coating



Fragment of Coating



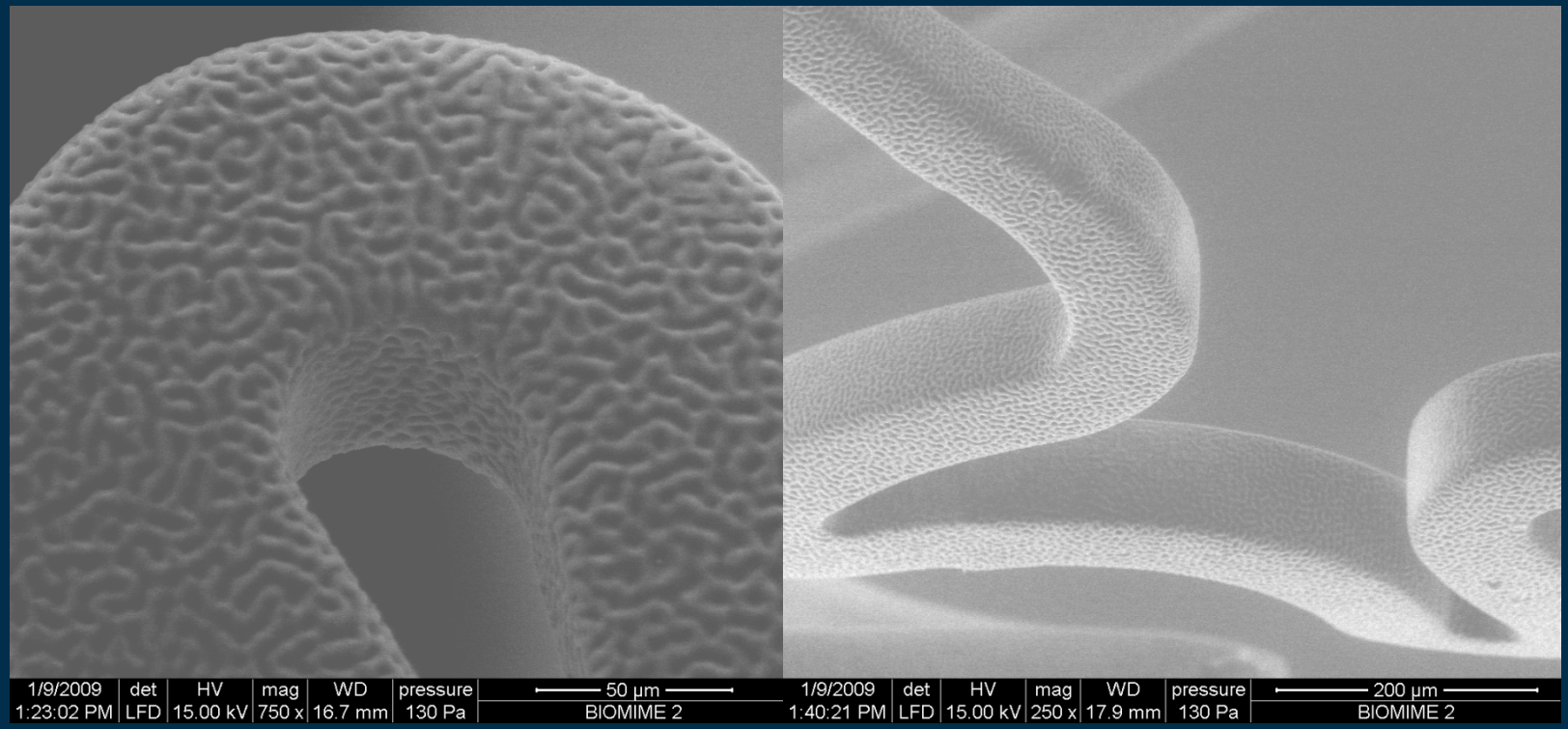
C. von Birgelen, TC Twente, Enschede, NL

COATING IRREGULARITIES OF DES

- *The total incidence of irregularities differed among DES*
- *Different DES types showed certain irregularities at constant locations, resulting in typical patterns*
- *All DES types showed some bare metal aspect, but incidence, shape, and size differ largely*
  - *SES & ZES showed some cracks*
  - *PES & EES showed wrinkles*
  - *SES showed "peeling of polymer" & coarse irregular excess of coating*
  - *PES had webbing with "large" bare-metal areas.*

Mod. from: Basalus et al., EuroIntervention 2009; 5:157-65 (free online access)

BIOMIME COATING INTEGRITY



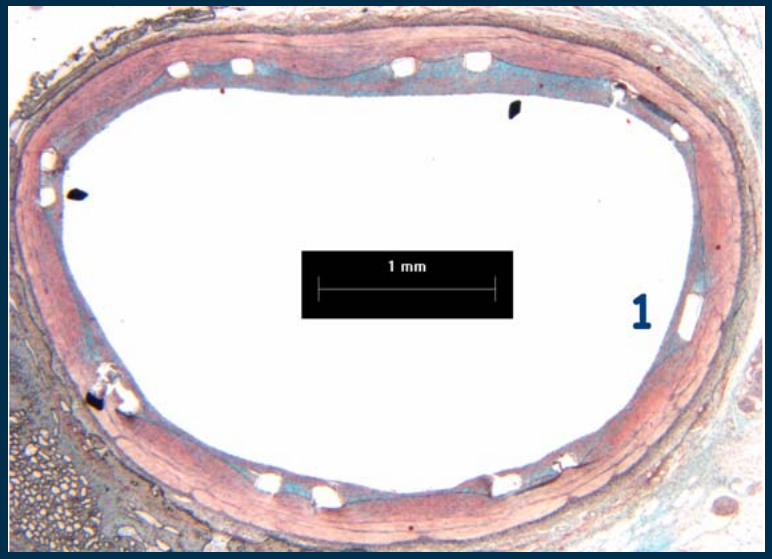
After inflation *After inflation*

It is important to know that post inflation. BioPoly™ adjusts to stresses generated at vulnerable areas – s-links & y-connectors due to its high elasticity

Data on file. SEM picutures BioMime Stent

28-DAY POLYMER RESULTS

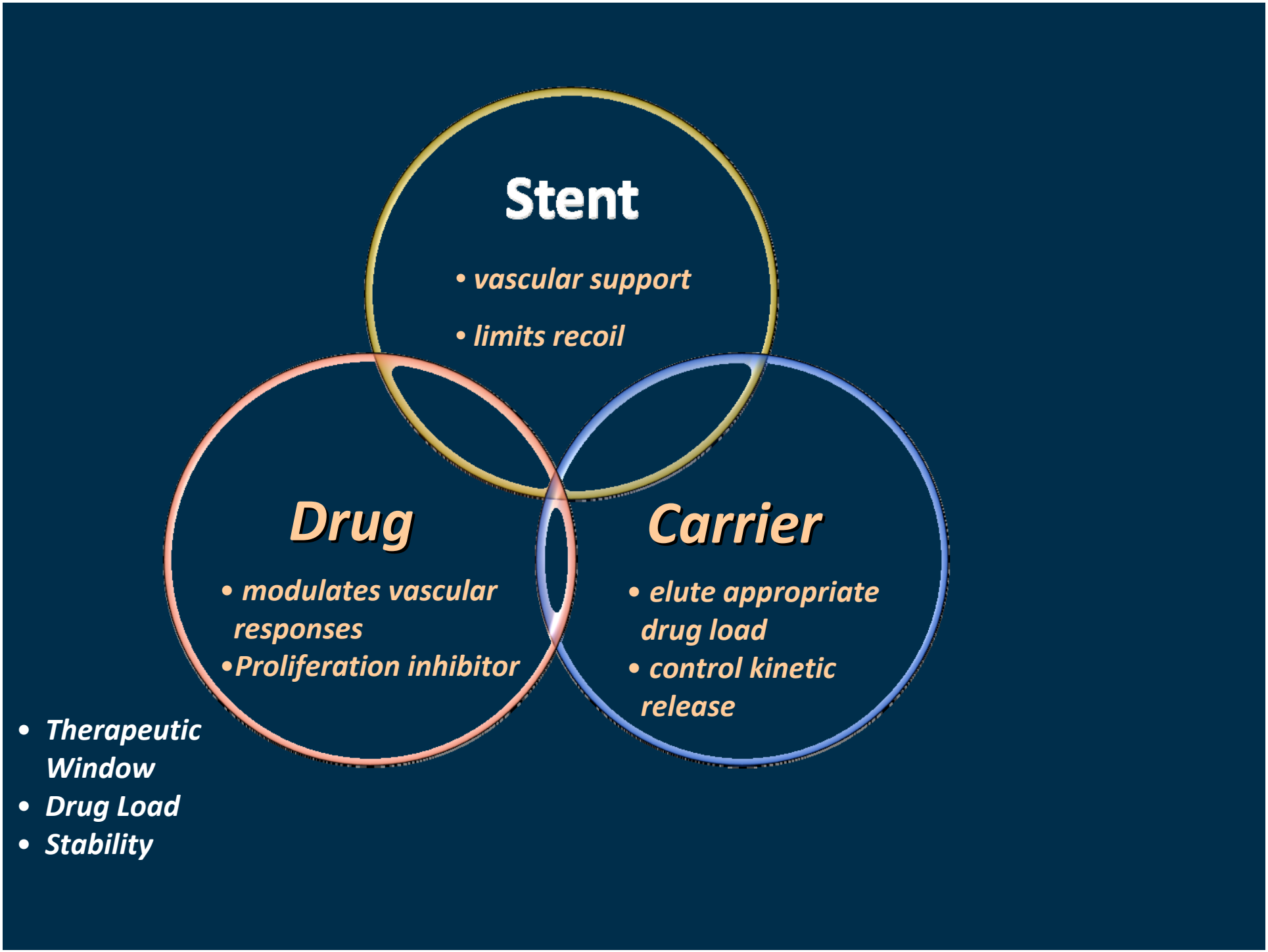
28-day results – Biodegradable Polymer coated 3.5 x13 in porcine LCx[1]



Absence of Fibrin, Hemorrhage Necrosis, Fibrinoid or Inflammation

No significant differences were found in terms of anatomopathologic features or morphometric measurements, including in-stent endothelialization or neointimal inflammation score versus BMS (all p>0.05)

1. Data on file


Stent
• vascular support
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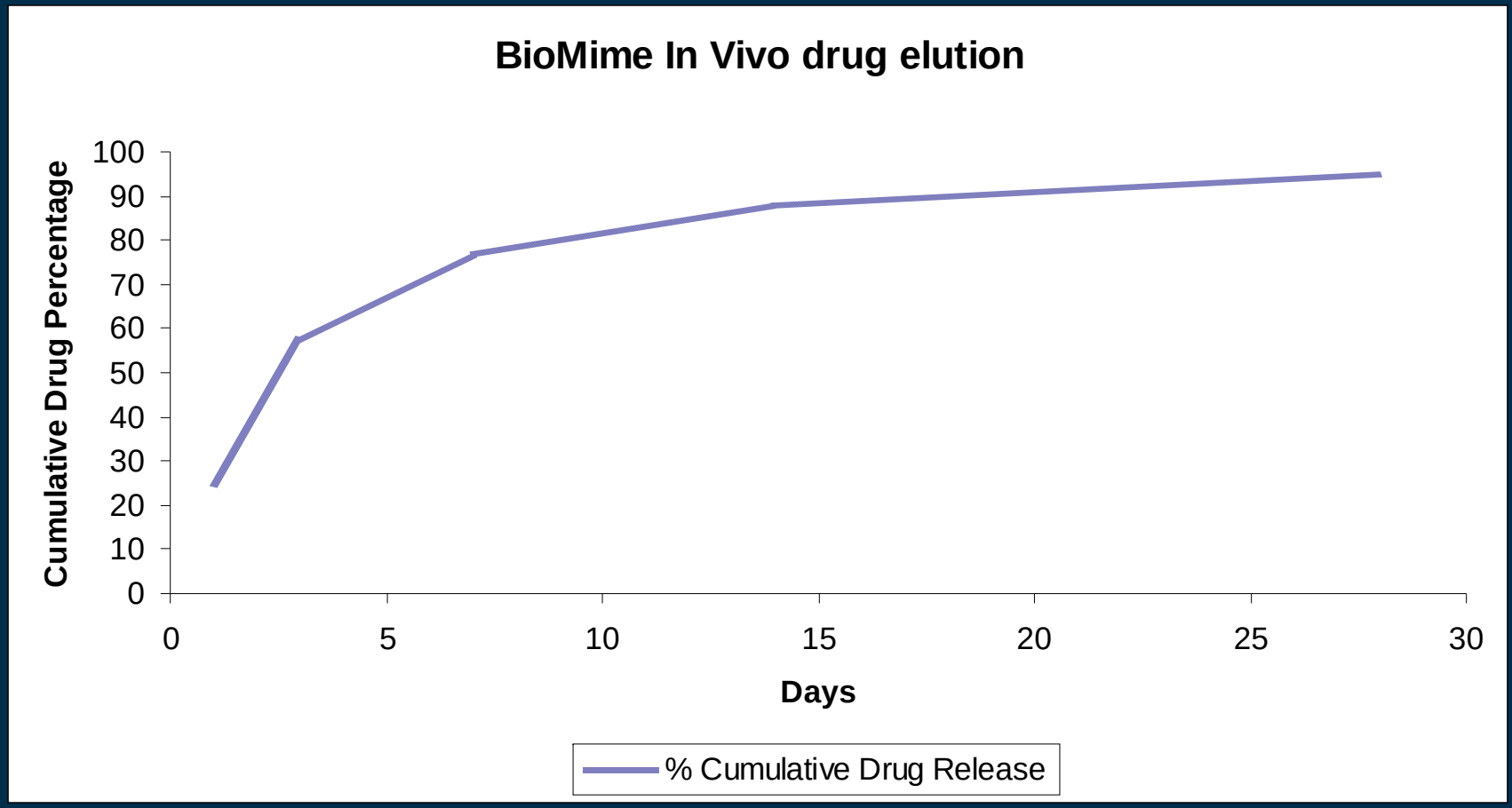
Drug
• modulates vascular responses
• Proliferation inhibitor
Carrier
• elute appropriate drug load
• control kinetic release
• Therapeutic Window
• Drug Load
• Stability

PHARMACOKINETICS (IN-VIVO)

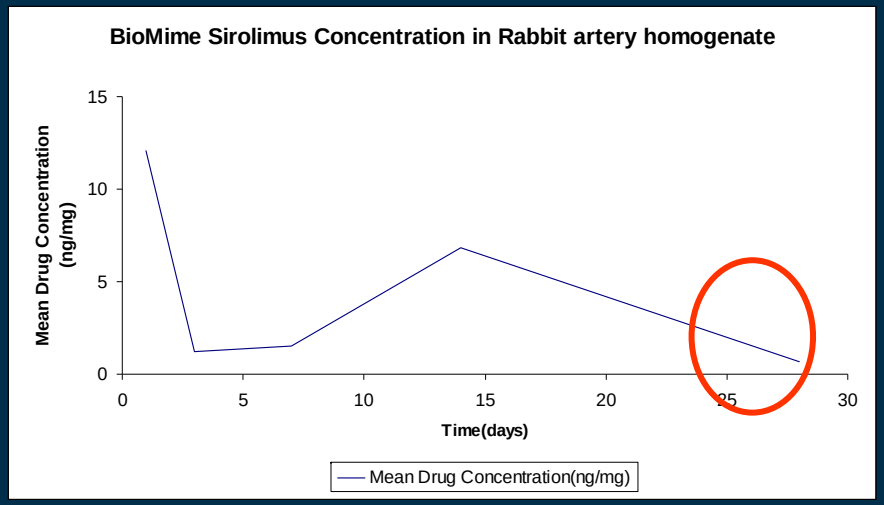
RABBIT ILIAC ARTERY MODEL



@100% of drug elutes in 30days

Data on file. Rabbit illiac model.

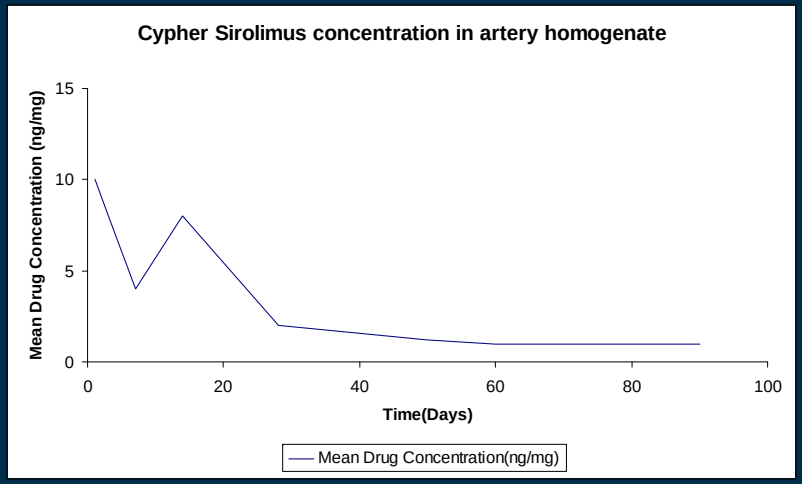
PHARMACOKINETICS (IN-VIVO)
RABBIT ILIAC ARTERY MODEL



BioMime™

Similar but slightly lower tissue concentrations than Cypher >25 days

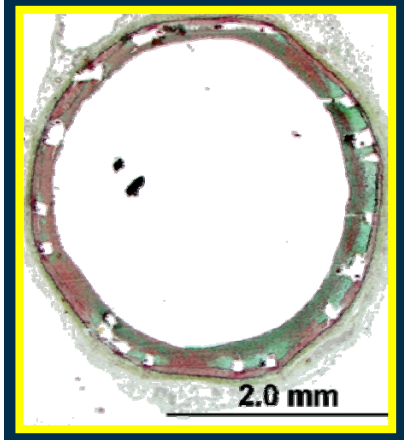
Cypher

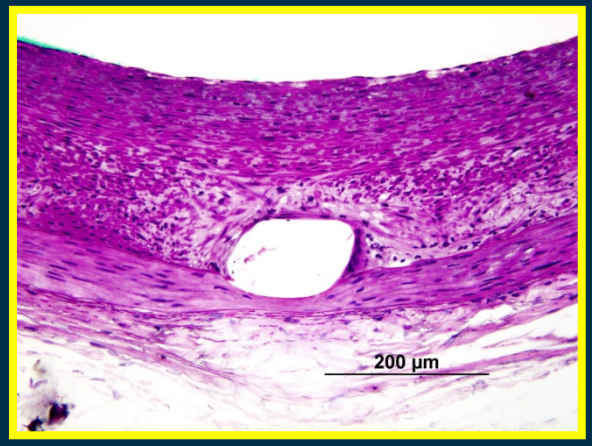


Data on file. Rabbit illiac model.

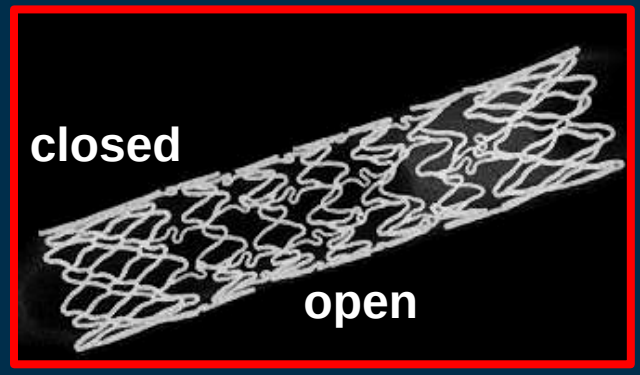
RABBIT ILIAC ARTERY IMPLANTS (28-DAYS)

Next generation BMS





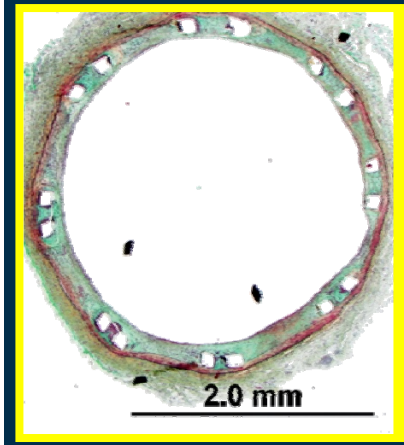
Absence of stent fractures

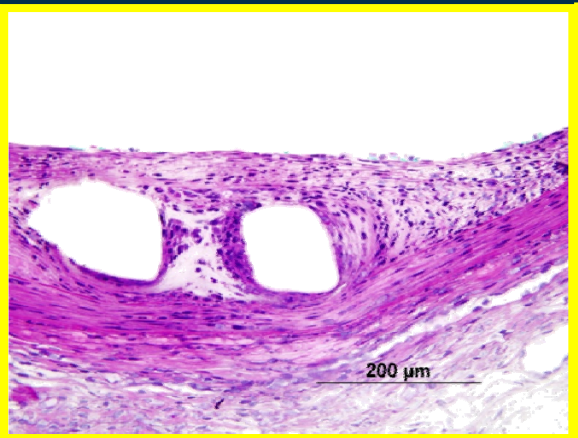


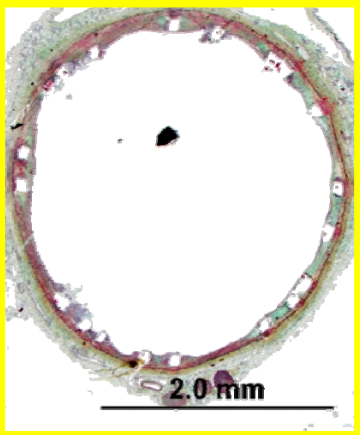
BioMime™ Drug Effects

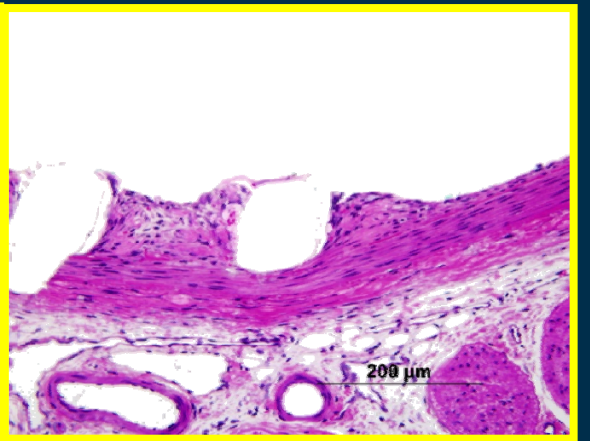
Decreased neointimal thickness

Delayed healing with evidence of uncovered struts



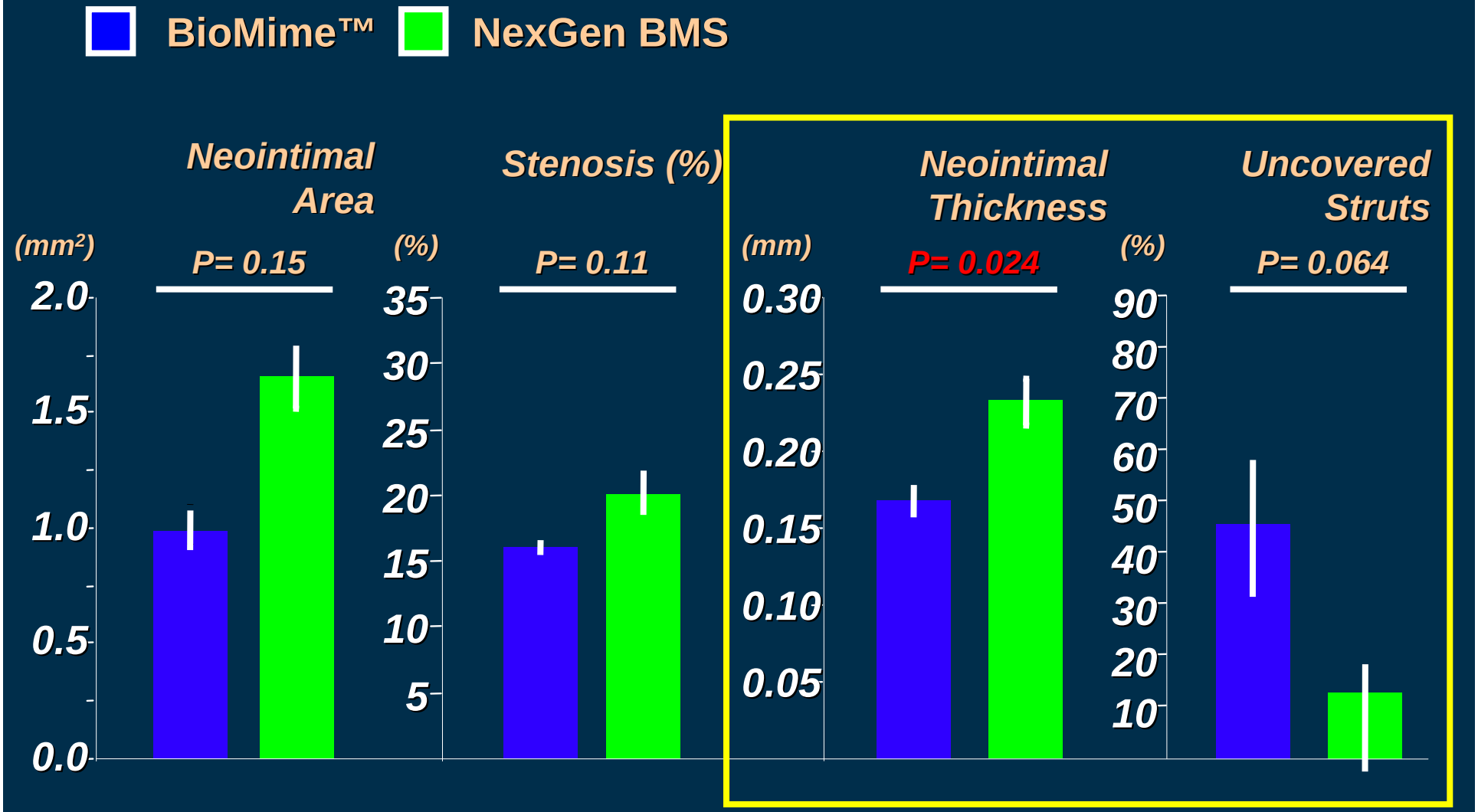






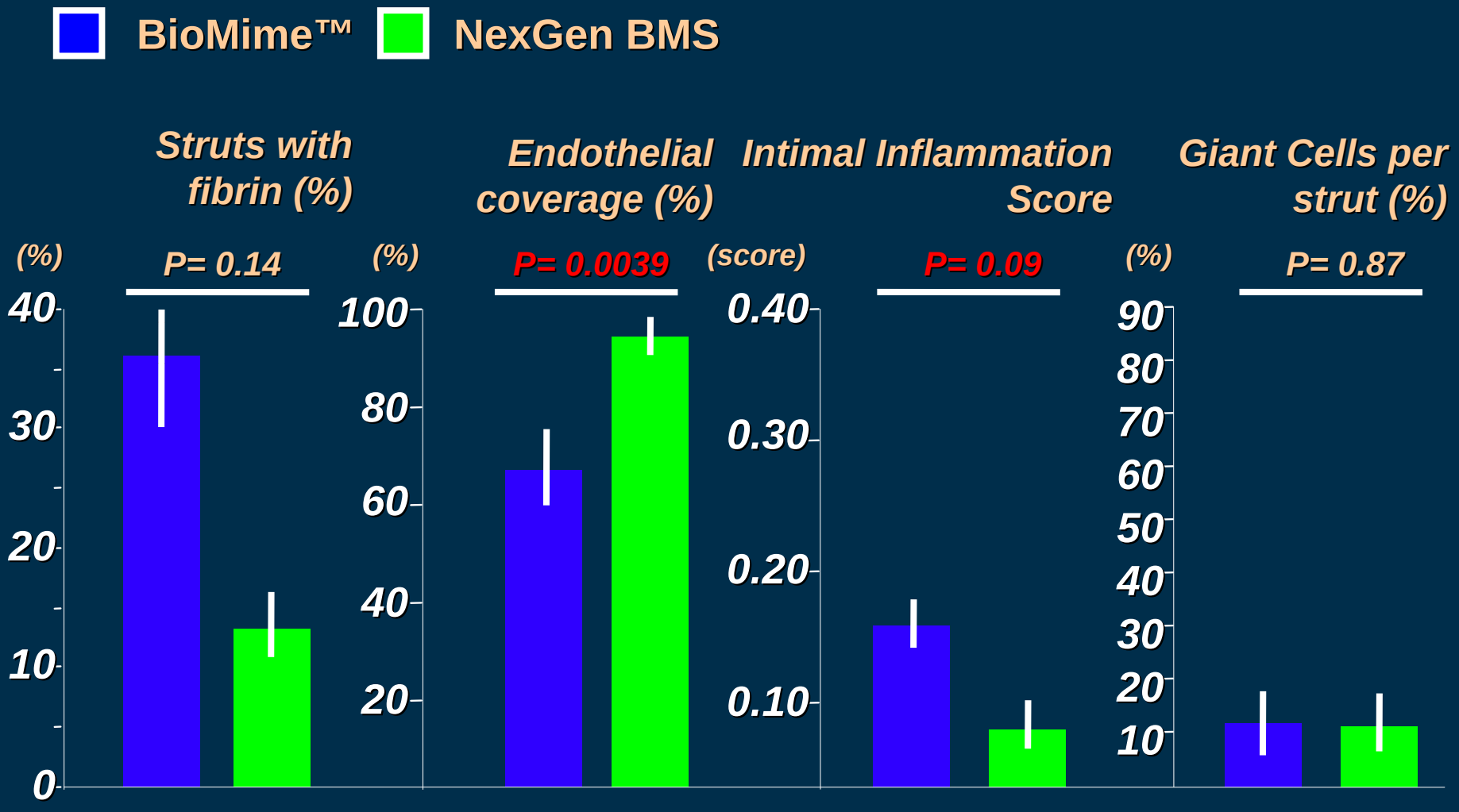
BIOMIME™ LIGHT MICROSCOPY ANALYSIS

28-DAY RABBIT ILIAC

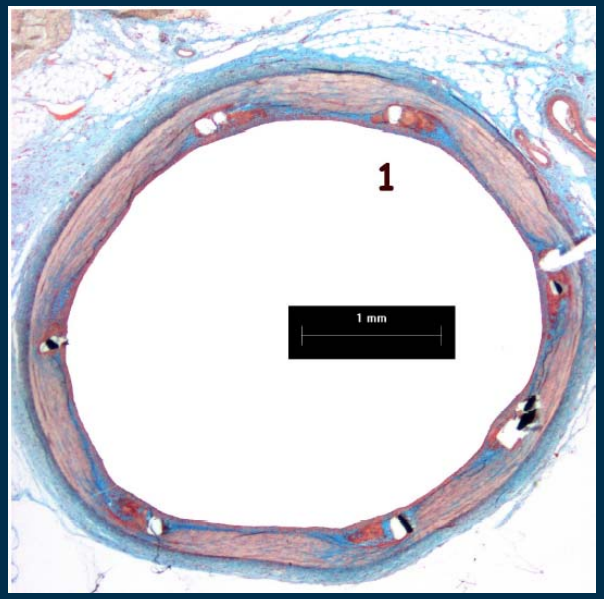


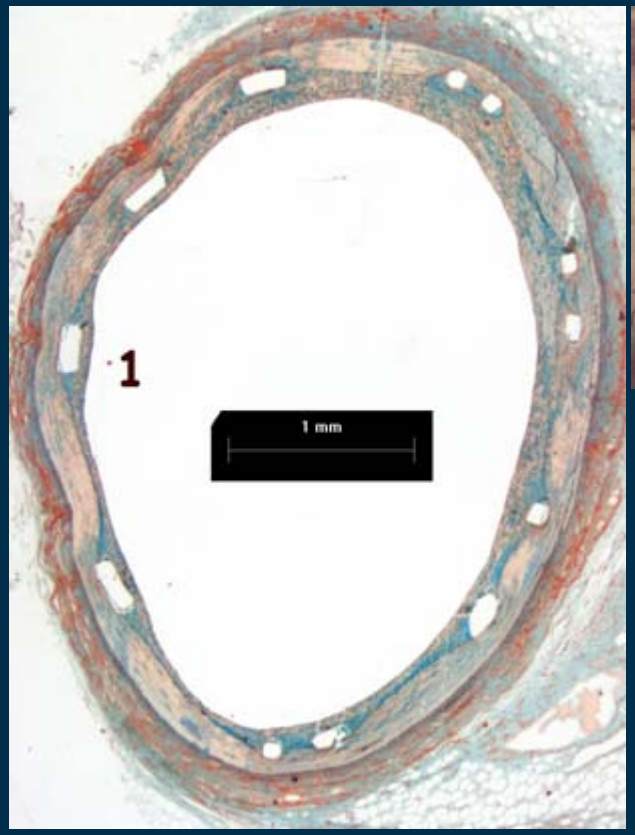
BIOMIME™ LIGHT MICROSCOPY ANALYSIS

28-DAY RABBIT ILIAC (CONT)



HISTOPATHOLOGY (SWINE STUDIES)





Note the RCA tortuosity

Cypher LCx

BioMime RCA

BioMime similar to Cypher @ 28 and 90 days

Data on file. Porcine model.

SUMMARY

- *Drug release and tissue concentration is similar to Cypher*
- *Due to its low injury score, BioMimeTM demonstrates equivalent neo-intimal scores to Cypher despite having low drug loading*
- *BioPolyTM has demonstrable non-inflammatory behavior in pre-clinicals*
- *Neointimal thickness with BioMimeTM is 34% less than its bare metal platform NexGenTM (p=0.024)*
- *Optimal scaffolding and wall apposition (hybrid closed and open cell format), highly flexible and deliverable stent system, low balloon overhang, low forshortening and recoil.*
- *Excellent polymer structural integrity*