How To Innovate in CV Technology – TCT AP 2011, Seoul

Evolution of
Merilimus Eluting Coronary Stent System MITSU™
Novel Approaches to DES Creation

Ashok Seth

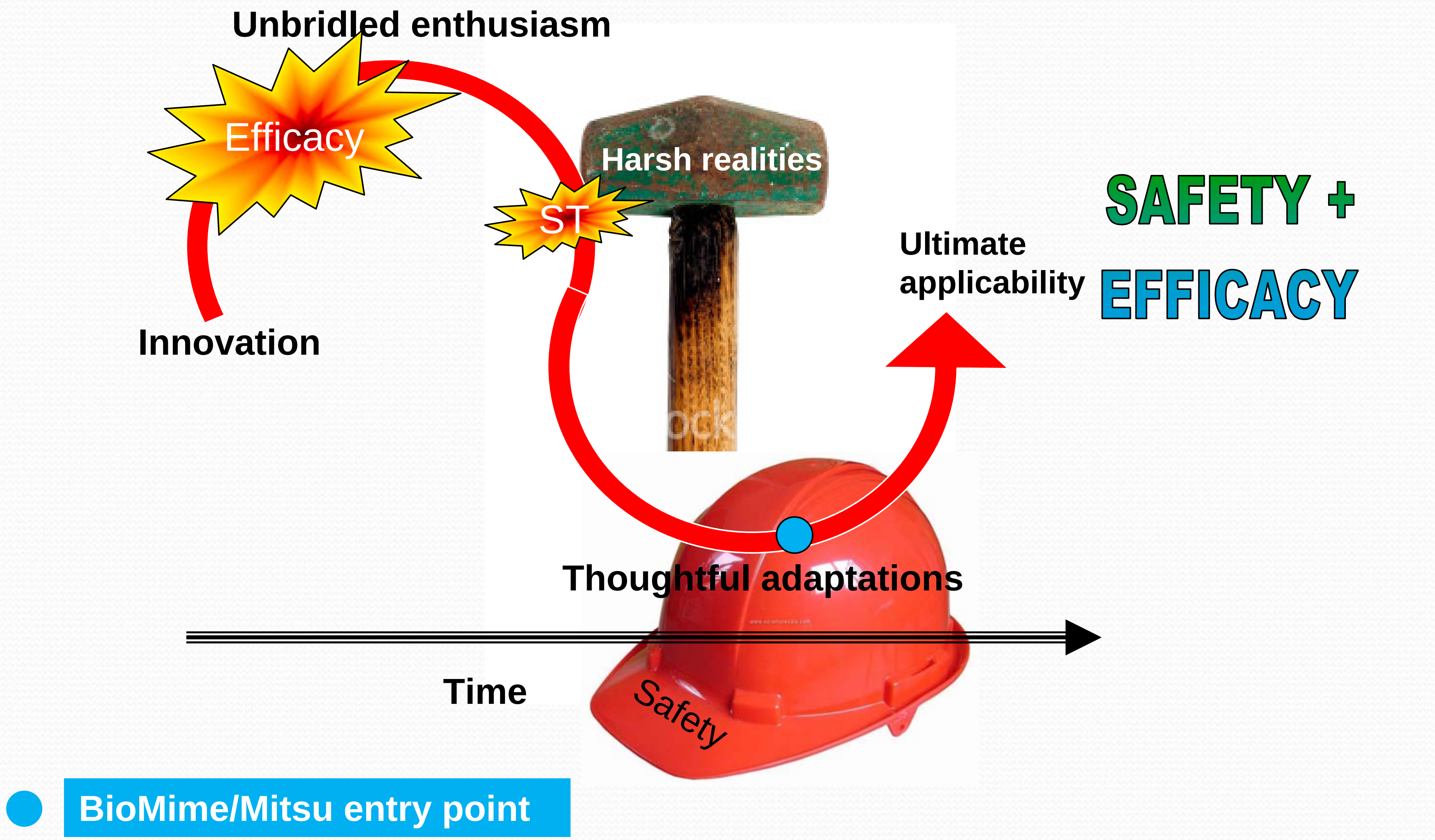
Chairman & Chief Cardiologist
Chairman Cardiology Council, Fortis Group of Hospitals

Fortis Escorts Heart Institute
New Delhi

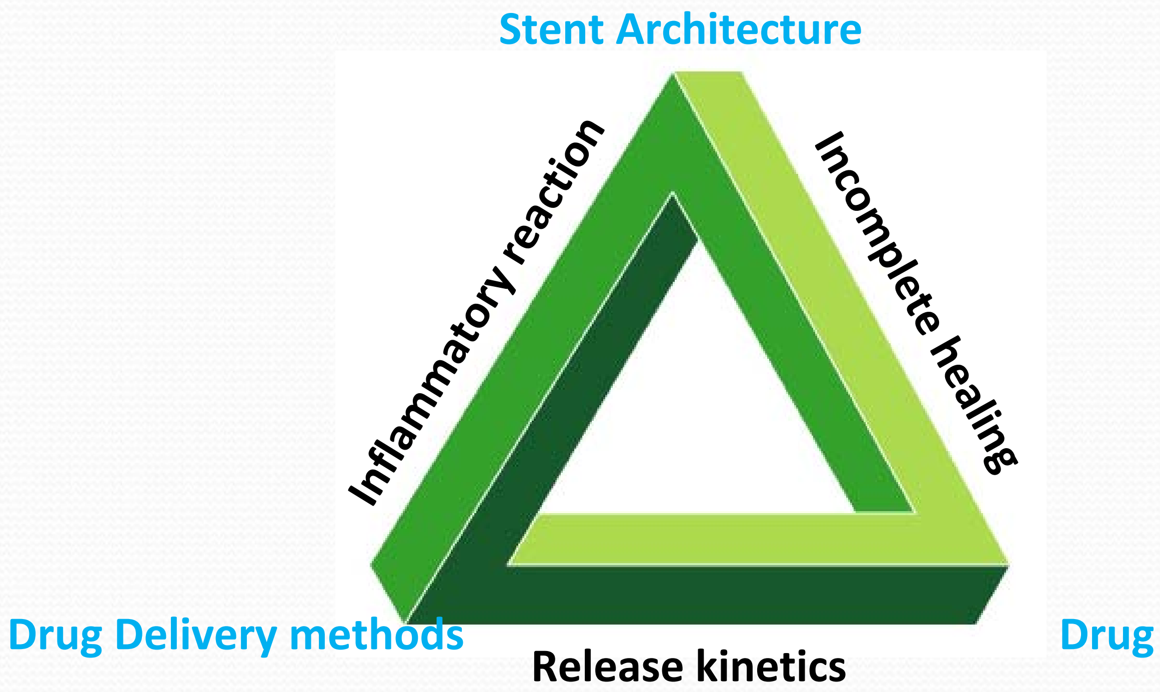
Disclosures

- Honorary Advisor to Merill LifeSciences

DES use – Paradigm Shift



Penrose's Problem in DES Creation



- Stent architecture, Polymer and Drug are the most **polarized** facets in DES construction

Penrose's impossible triangle

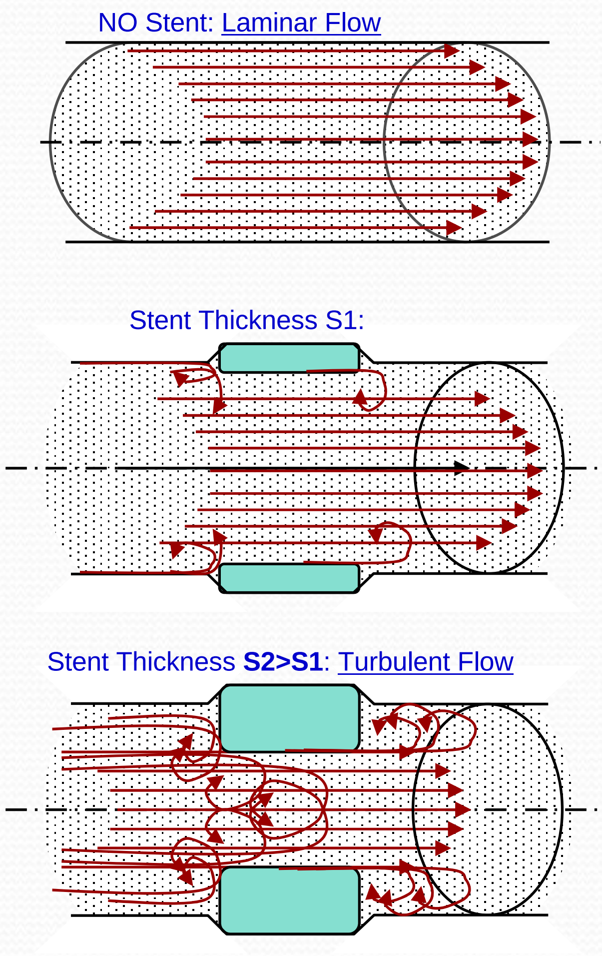
DES: A mechanical & pharmacological Approach to CAD. Paul Dobesh et al Pharmacotherapy, 2004

Drivers of DES Safety

- Acute drivers
  - Vessel injury
  - Complete apposition
  - Biodegradable polymers ***or no polymers!***
  - Premature cessation of antiplatelet Rx
- Long term drivers
  - Re-endothelialisation
  - Functional endothelium
  - No vessel wall inflammation

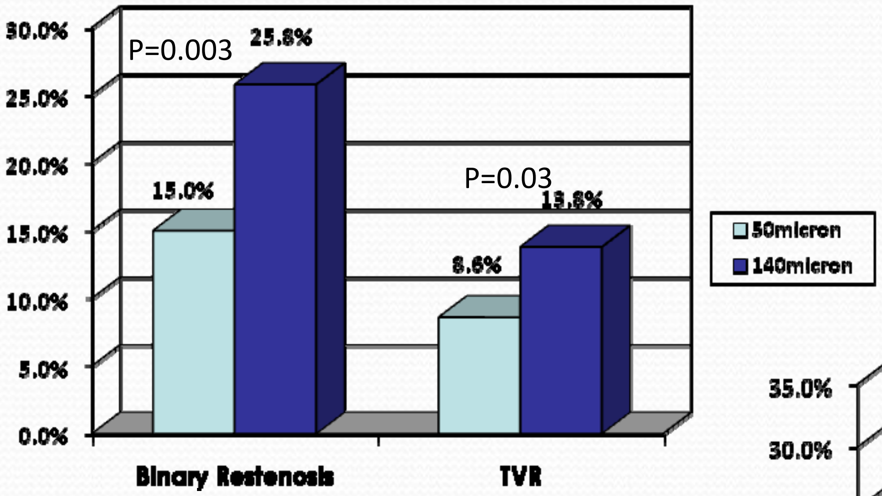
Thin Struts and Restenosis

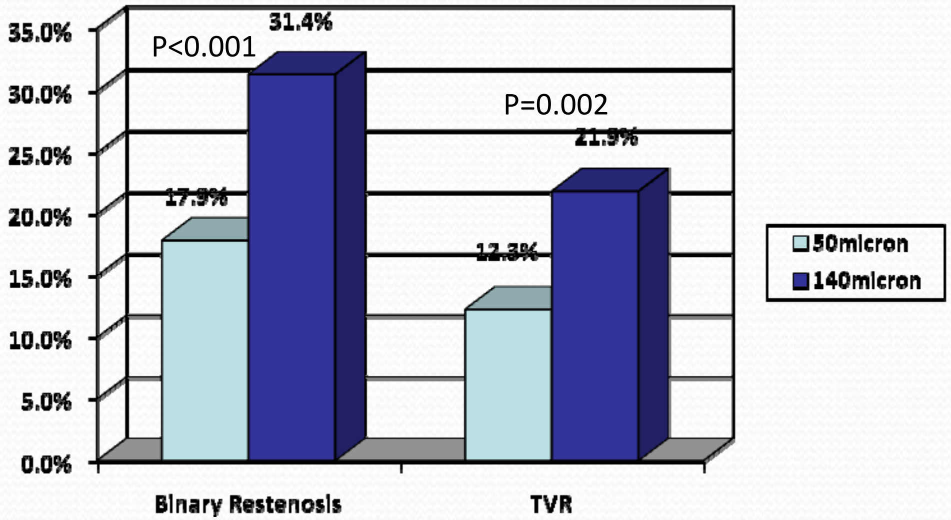
- Thin Struts allow for-
  - Low blood flow perturbance
  - Easy struts nesting to the vessel wall
  - Added flexibility and conformability
- **Improved clinical outcome***
- **Improved, faster endothelialization ****



- * 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

Thin is In!





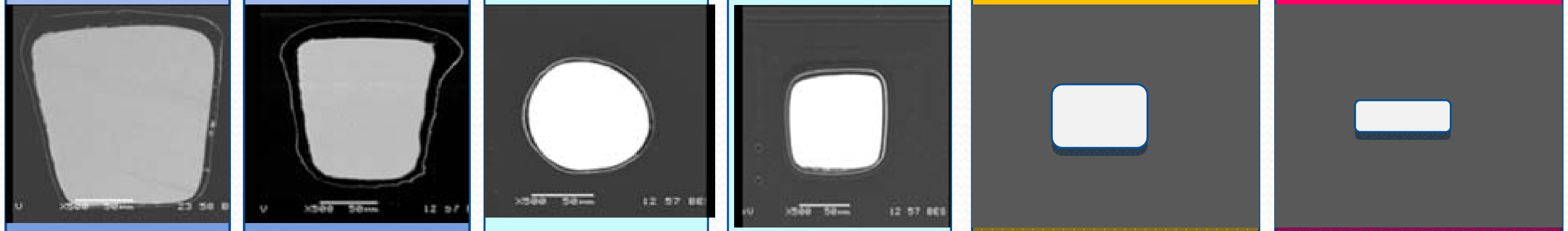
ISAR-STEREO Trial. Circulation 2001;103:2816-2821

ISAR-STEREO 2 Trial. JACC 2003;41:1283-8

Mitsu – Technology Approach

Features	Benefits
An “ultra-thin” stent.	Lowest possible vessel wall injury (↓ inflammation)
Hybrid stent design = optimal geometry.	Superior deliverability and conformability (“glove-like” fit and apposition)
	Improved healing = less stent thrombosis
New sirolimus analogue with preferred dosing and drug release kinetics.	Lowest possible restenosis
Polymer - free drug delivery.	Early discontinuation of DAPT

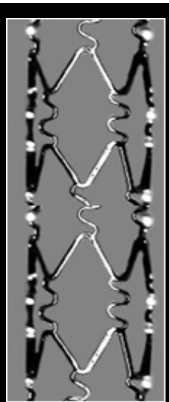
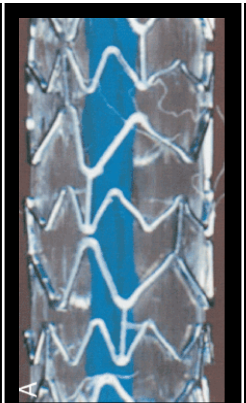
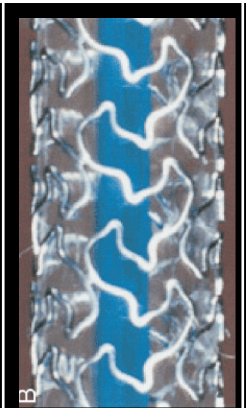
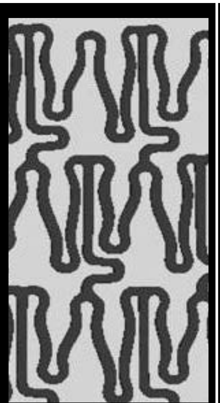
Moving towards biomimicry



	Cypher	Taxus	Endeavor	Xience V	BioMime	Mitsu
Strut thickness	140 µm	132 µm	91 µm	81 µm	65 µm	40 µm
Coating thickness	12.6 µm	16 µm	5.3 µm	7.6 µm	2 µm	< 2 µm
Polymer	PEVA-PBMA	SIBBS	PC	Fluoro	PLLA + PLGA	None
Drug	Sirolimus 1.4 µg/mm²	Paclitaxel 1.0 µg/mm²	Zotarolimus 10.0 µg/mm	Everolimus 1.0 µg/mm²	Sirolimus 1.25 µg/mm²	Merilimus 0.45 µg/mm²
	1st Gen	1st Gen	2nd Gen	2nd Gen	3rd Gen	4th Gen

3.0 mm diameter stents, 500X magnification

Stent design makes a difference!

Closed Cells 140µm	Open Cells 132µm	Open Cells 132µm	Open Cells 90µm	Open Cells 81µm	Hybrid Cells 65µm	Hybrid Cells 40µm
						
Bx Velocity	Express	Liberte	Driver	Multi-Link	BioMime	Mitsu

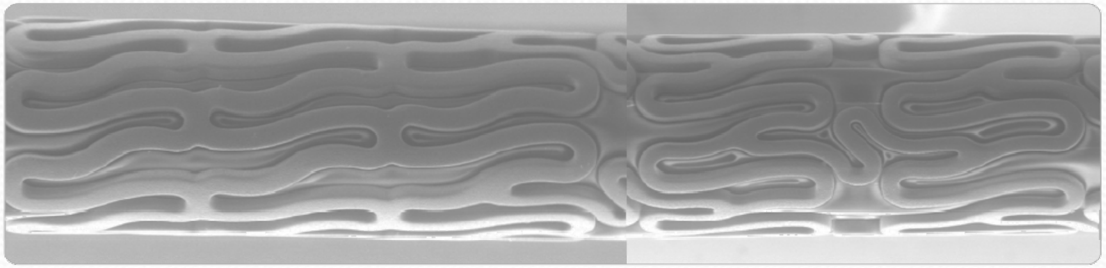
Closed cells Open cells

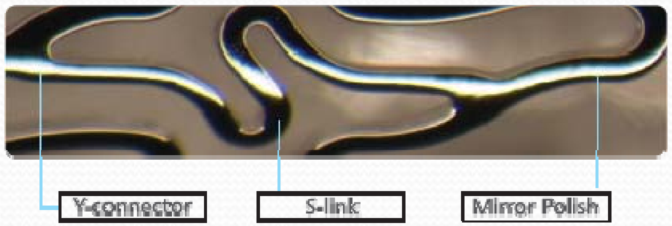
The “hybrid” design coupled with strut width variability eliminates the need for high strut thicknesses as required in earlier stent technologies

BioMime Stent Architecture

- Cobalt chromium (L605) platform with 65µm strut thickness.
- Hybrid cell design comprising of an intelligent mix of open and close cells resulting in excellent radial strength with a high flexibility.
- Unique strut width variability that ensure a <3% recoil and 0.29% foreshortening
- Special electro-polishing technique eliminates surface nickel oxides

SEM image of crimped BioMime SES at 50x

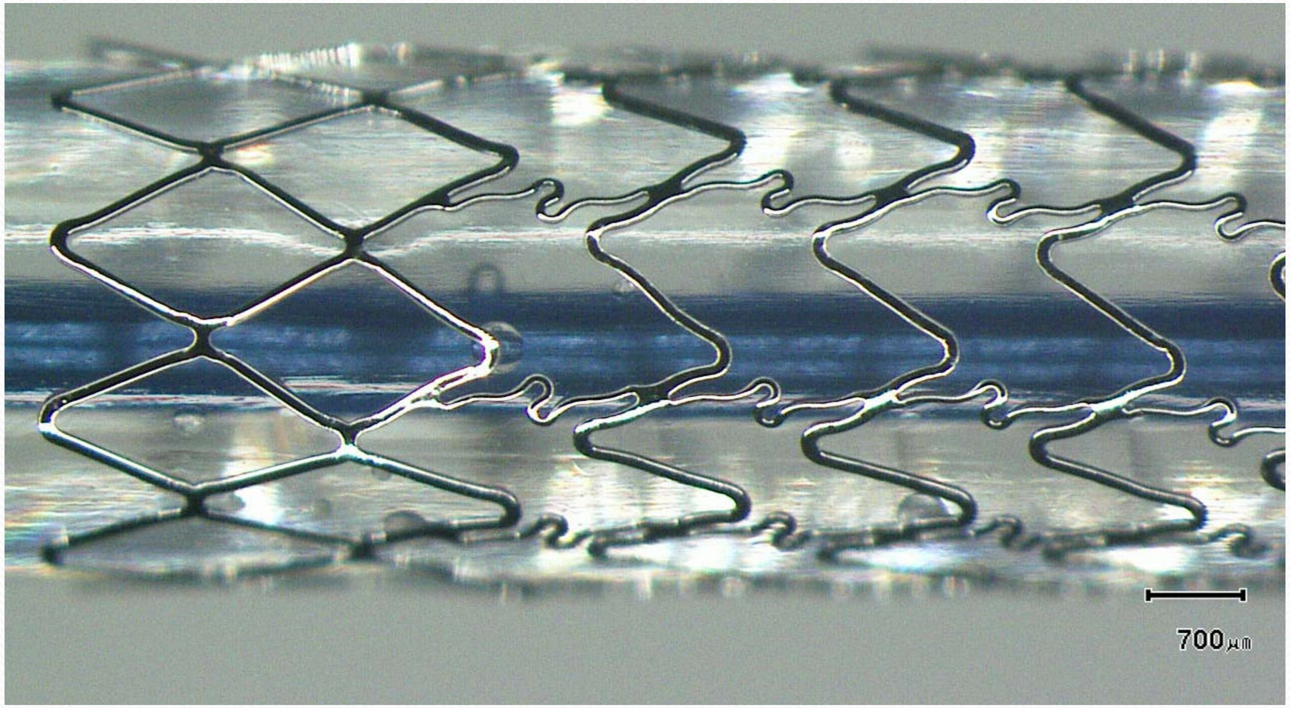




Closed cell at edges Open cell in mid - segment

Hybrid design

Mitsu – Cell Architecture



Strut thickness

Close cells at the edges

Open cells at the middle

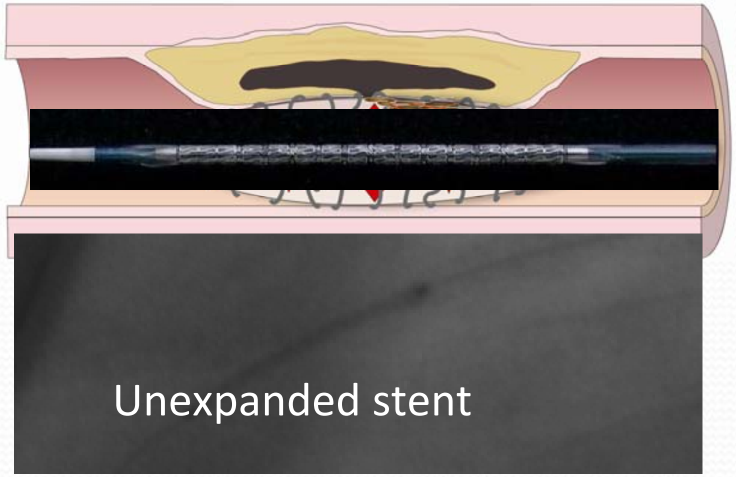
Mitsu – Stent Features

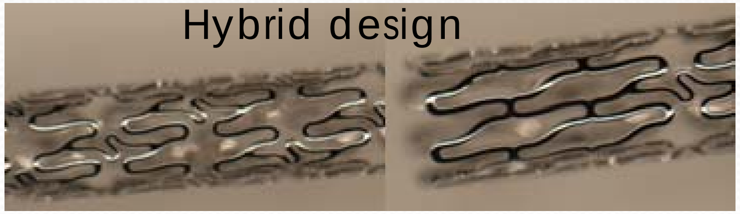
Material of construction	Cobalt Chromium L605
Strut thickness	40µm / 0.0016"
Strut width	Variable 50µm - 100µm
Dimensions	63 sizes - Ø 2.25 – 4.5mm / ℓ 8 – 40mm
Stent design	Hybrid – open cells in the middle and close at the edges
Radial strength	High 1.1 ± 0.10 ATM
Recoil	Low 3.26%
Foreshortening	Low 0.26%
Metal to artery ratio	16% - 18%
Pushability / Trackability	Excellent
Dog boning effect	Uniform expansion
Crossing profile crimped stent (3.0mm)	Low 0.96mm / 0.037"

Low injury design

- Conventional edge-flaring stent designs allow the stent to dog-bone during deployment.
- This dog-boning coupled with balloon overhang may cause edge injury.
- BioMime has struts with design variability which results in *morphology mediated expansion*™, having a propensity to minimize stent edge injury.

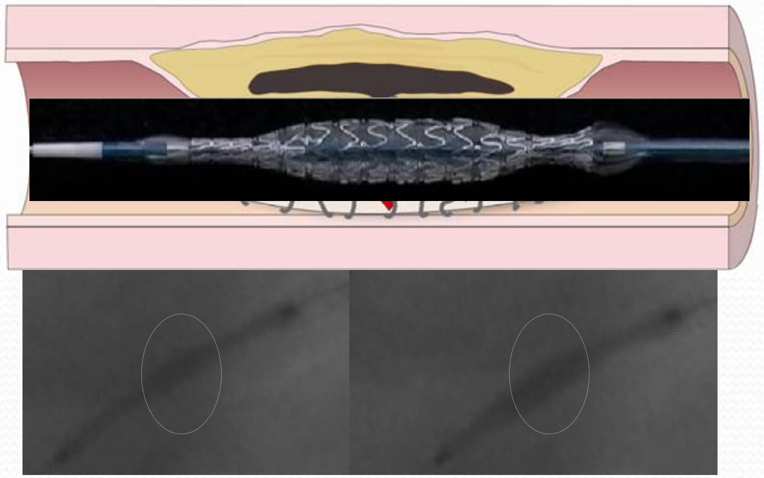
Morphology Mediated Expansion



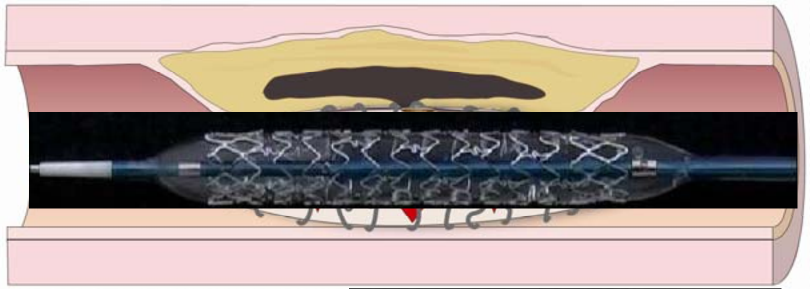


Open cells in mid segment   Close cells at edges

Propensity to minimize edge-injury

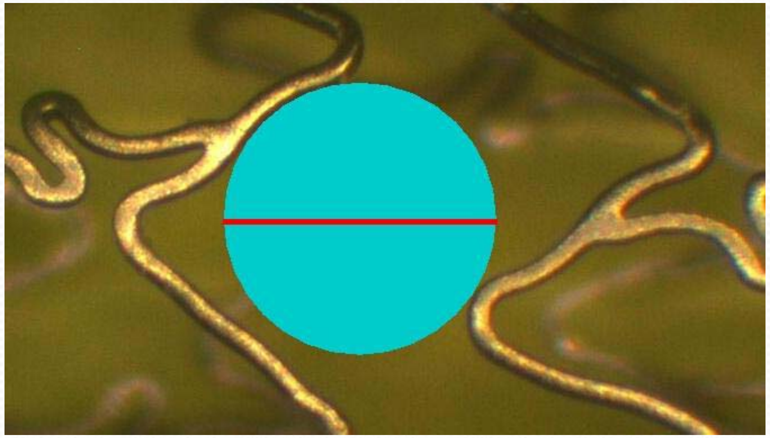


Morphology mediated expansion

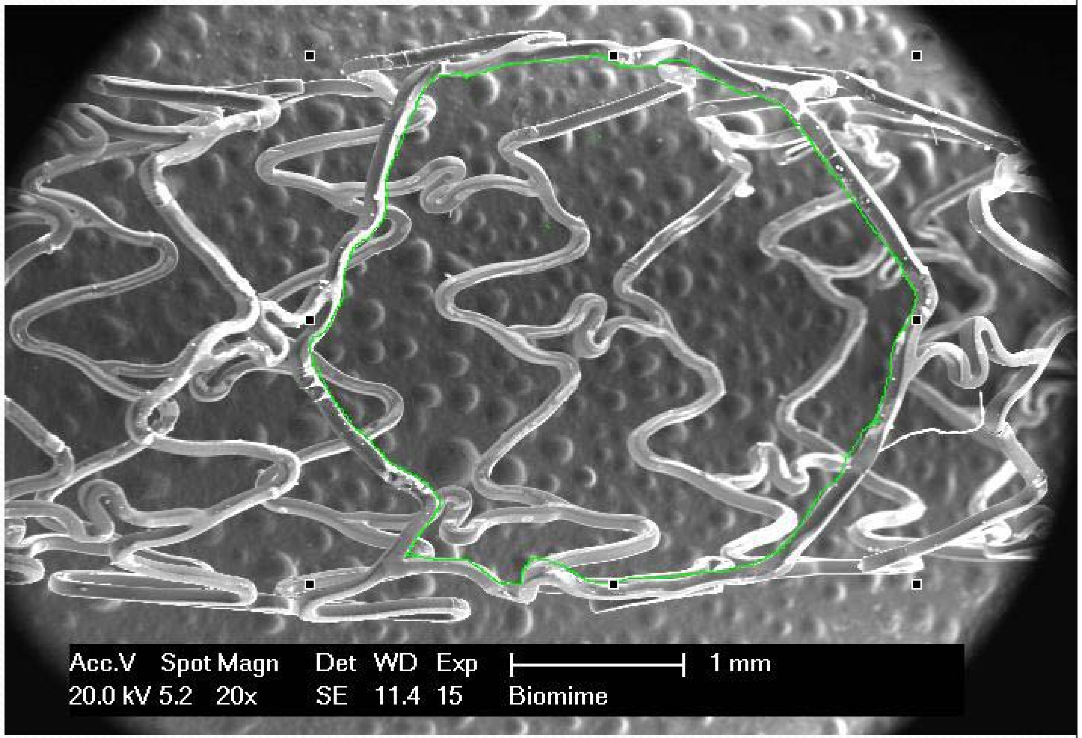


Note the narrow balloon shoulders which assist in minimizing balloon related vessel injury

Excellent Side Branch Access



The area of the largest circle circumscribable in the cell of the stent expanded to the nominal diameter:
$T_c = 0.71\ mm^2$



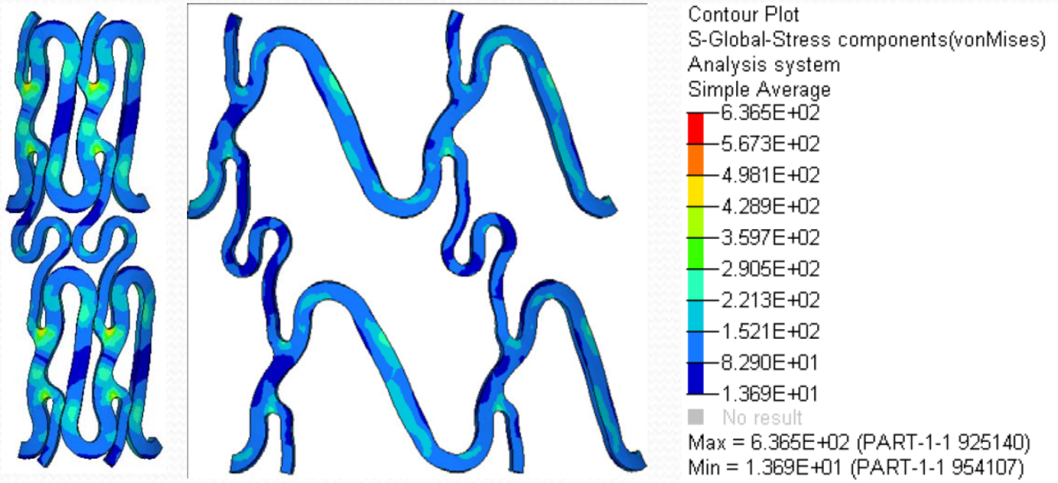
The expanded BIOMIME 3.0 x 16 mm stent after side branch expansion

Expanded cell perimeter that ensures side branch access: $K_{SBA} = 11.29$ mm

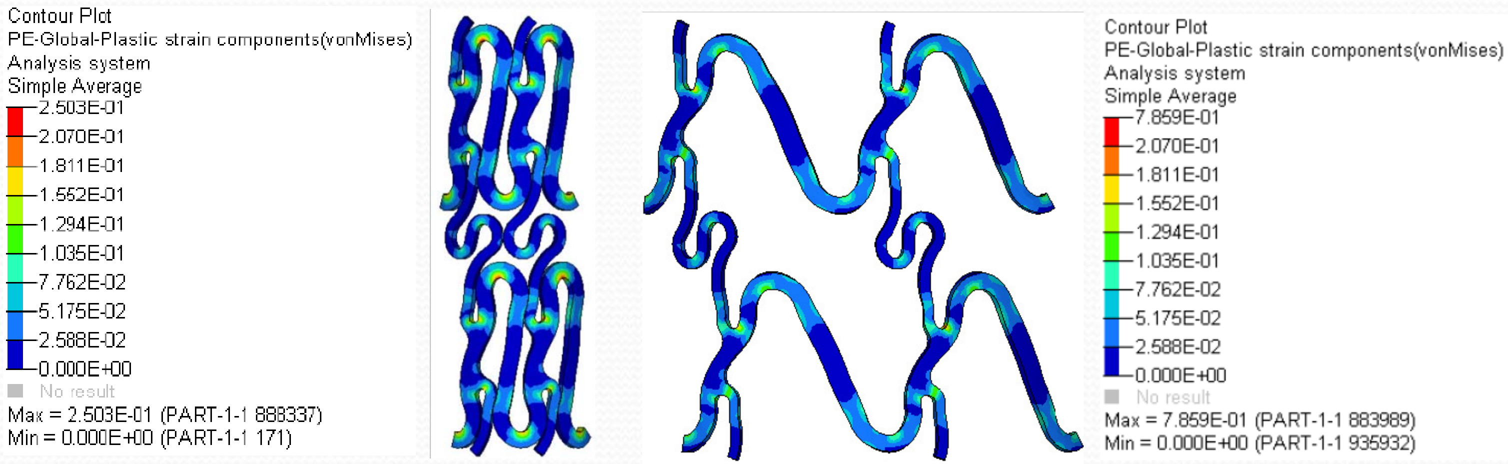
Expanded cell area that ensures side branch access: $T_{SBA} = 8.00\ mm^2$

Data on file with Meril Life Sciences.

FEA Analysis

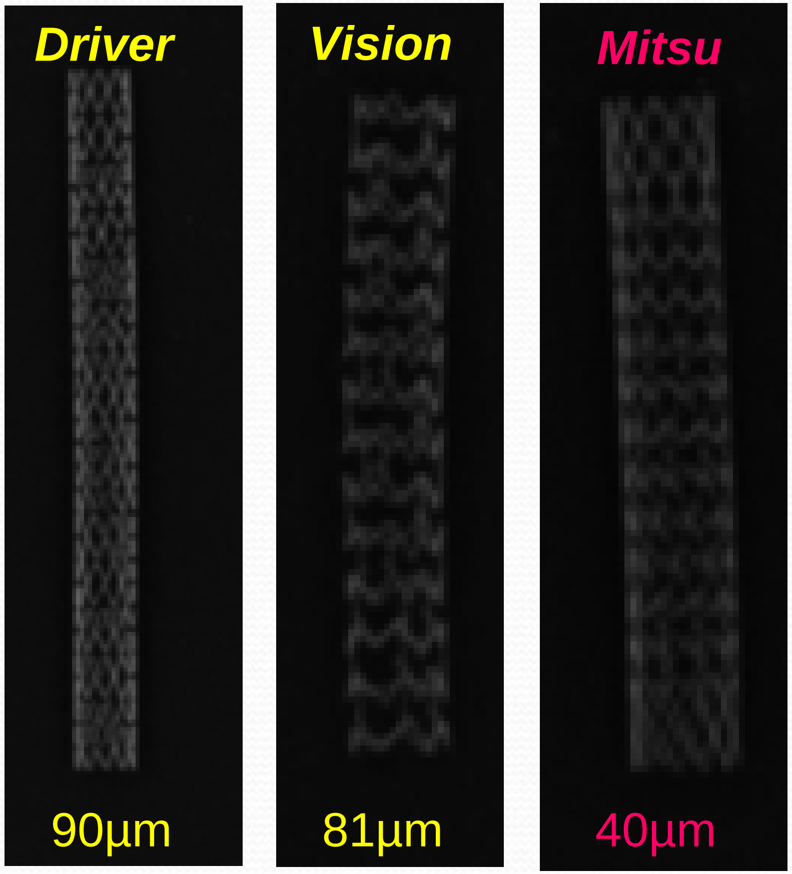


Following Crimping Following Expansion



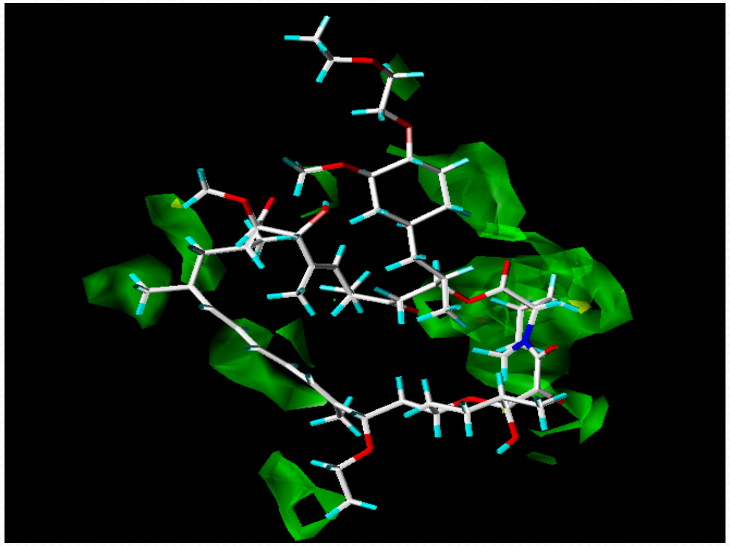
Following Crimping Following Expansion

Mitsu – Relative Radio-opacity



Equivalent radio-opacity due to stent design

Merilimus

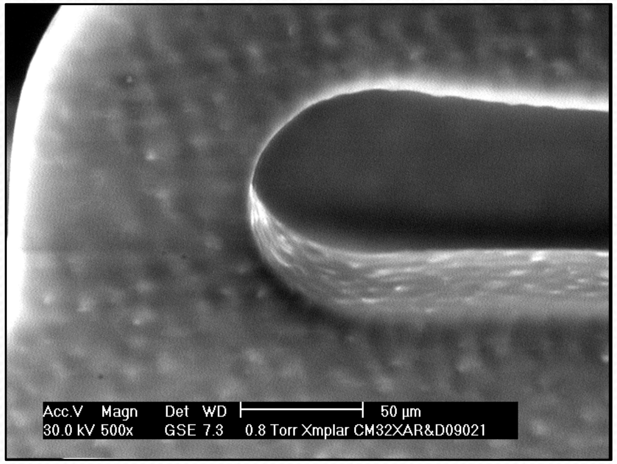


fkBP-12 receptor site adaptation by Merilimus molecule

- Merilimus is a Meril Life Sciences invention.
- Heterogeneous 5 member ring on the parent limus molecule.
- Better toxicological profile than Sirolimus and a wider therapeutic window (more lipophilic).
- Low drug dosing of 0.4µg/mm^2 possible to get optimal anti-proliferative effect.

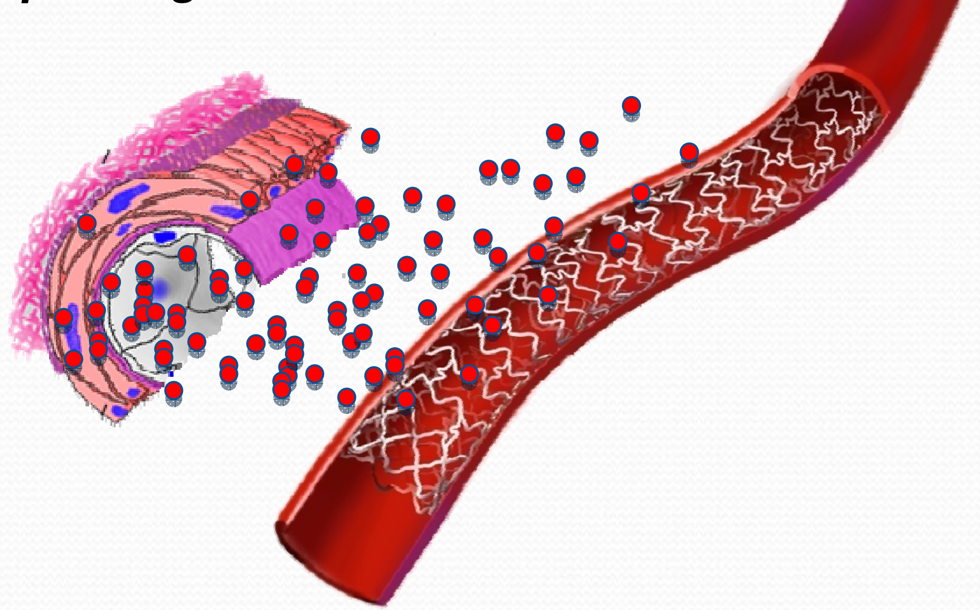
Nanotechnology

Unique Formulation - Solid lipid nano-spheres (SLN) consisting of Merilimus + Lipid (<500 nm)



SEM Image of Stent struts coated with nano-formulation

SLN rapidly leave stent and enter vessel wall with prolonged tissue residence time



Nanotech for Drug Delivery

Potential Benefits of Solid-Lipid Nanoparticles

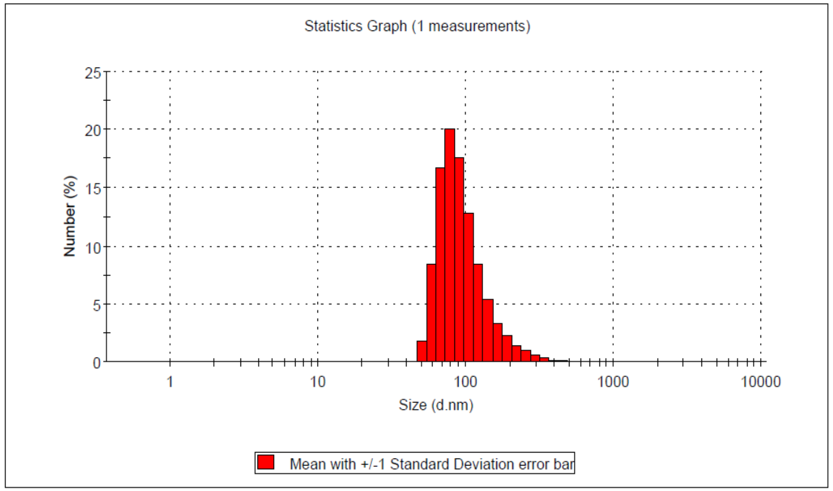
- Control and maintain in-tissue drug release
- Improved PK stability
- Enhanced cellular uptake
- Feasibility of carrying both lipophilic and hydrophilic drugs
- Lipids are biodegradable (excellent biocompatibility)
- Potential for lowering doses
- Potential to target different vascular layers by using differential NP size

Avg. Particle Size & Size Distribution

Z-Average (nm):	165.3763	Derived Count Rate (kcps):	520810.981471...
Standard Deviation:	0	Standard Deviation:	0
%Std Deviation:	0	%Std Deviation:	0
Variance:	0	Variance:	0

Size d.nm	Mean Number %	Std Dev Number %	Size d.nm	Mean Number %	Std Dev Number %	Size d.nm	Mean Number %	Std Dev Number %	Size d.nm	Mean Number %	Std Dev Number %
0.4000	0.0		5.615	0.0		78.82	20.0		1106	0.0	
0.4632	0.0		6.503	0.0		91.28	17.5		1281	0.0	
0.5365	0.0		7.531	0.0		105.7	12.8		1484	0.0	
0.6213	0.0		8.721	0.0		122.4	8.5		1718	0.0	
0.7195	0.0		10.10	0.0		141.8	5.3		1990	0.0	
0.8332	0.0		11.70	0.0		164.2	3.4		2305	0.0	
0.9649	0.0		13.54	0.0		190.1	2.2		2669	0.0	
1.117	0.0		15.69	0.0		220.2	1.4		3091	0.0	
1.294	0.0		18.17	0.0		255.0	0.9		3580	0.0	
1.499	0.0		21.04	0.0		295.3	0.5		4145	0.0	
1.736	0.0		24.36	0.0		342.0	0.3		4801	0.0	
2.010	0.0		28.21	0.0		396.1	0.2		5560	0.0	
2.328	0.0		32.67	0.0		458.7	0.1		6439	0.0	
2.696	0.0		37.84	0.0		531.2	0.0		7456	0.0	
3.122	0.0		43.82	0.0		615.1	0.0		8635	0.0	
3.615	0.0		50.75	1.8		712.4	0.0		1.000e4	0.0	
4.187	0.0		58.77	8.4		825.0	0.0				
4.849	0.0		68.06	16.7		955.4	0.0				

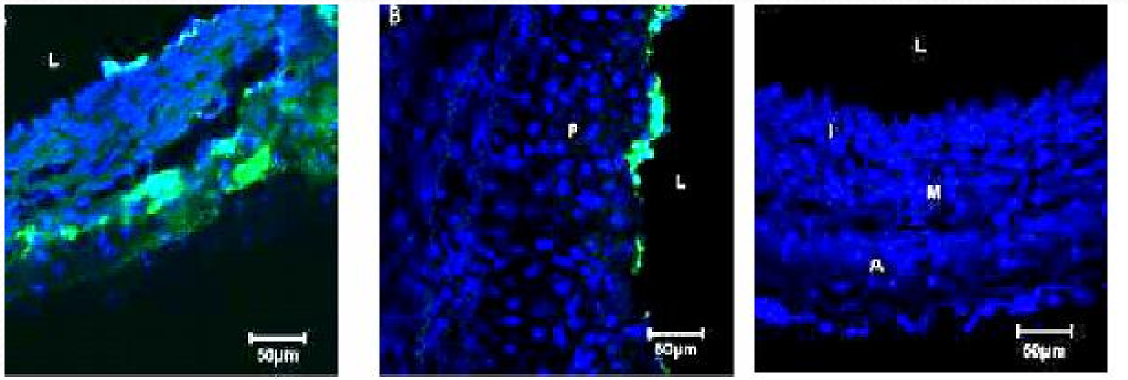
Average Particle Size (Z-Average) : 165.4 nm



Size distribution of Drug-Lipid Nanoparticles between 50nm and 500nm (80% ~127nm)

Nanotech for Drug Delivery

- Atherosclerotic plaque can be barrier to micro-particle vessel wall penetration; particle sizes < 300 nm are well suited for intra luminal drug delivery[1]
- < 110 nm Particles will reach up to adventitia layer in considerable amount[1]



Confocal images shows distribution of different size NP's in different arterial layers

1. Biodegradable paclitaxel loaded nanoparticles & stent coatings as local delivery systems for the prevention of restenosis. Dissertation. Dr. Thomas Kissel. Inst. for pharmaceutical technologie and biopharmacie, Marburg. 2004

Nanoparticle Stability – Zeta potential

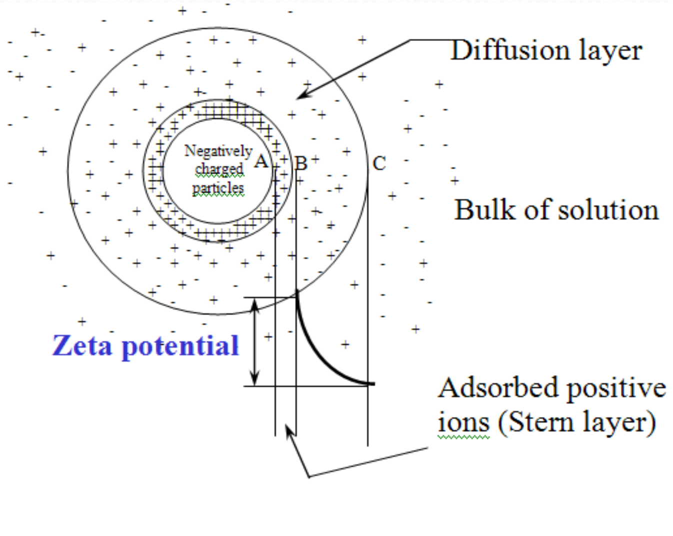


Fig. 1 Double Layer

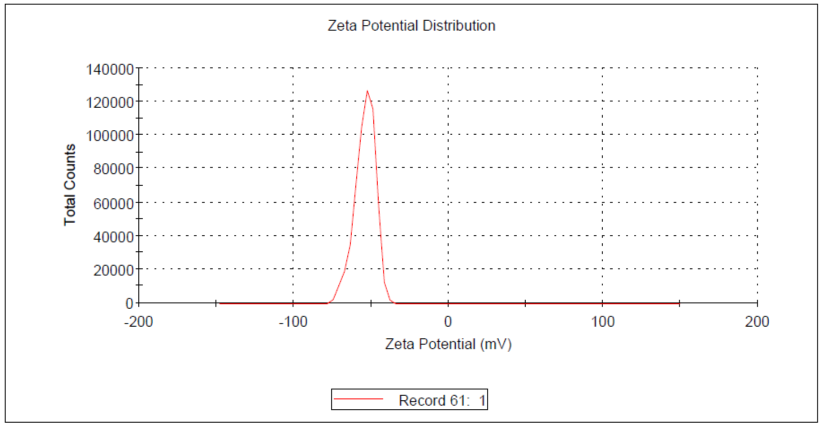
Table 1: Stability of suspensions with relation to Zeta Potential (Riddick, 1968)

Stability Characteristics	Avg. Zeta Potential in mV
Maximum agglomeration and precipitation	0 to +3
Range of strong agglomeration and precipitation	+5 to –5
Threshold of agglomeration	-10 to –15
Threshold of delicate dispersion	-16 to –30
Moderate stability	-31 to –40
Fairly good stability	-41 to –60
Very good stability	-61 to -80
Extremely good stability	-81 to -100

Results

			Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):	-53.9	Peak 1:	-53.9	100.0	6.55
Zeta Deviation (mV):	6.55	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	0.122	Peak 3:	0.00	0.0	0.00

Result quality : Good



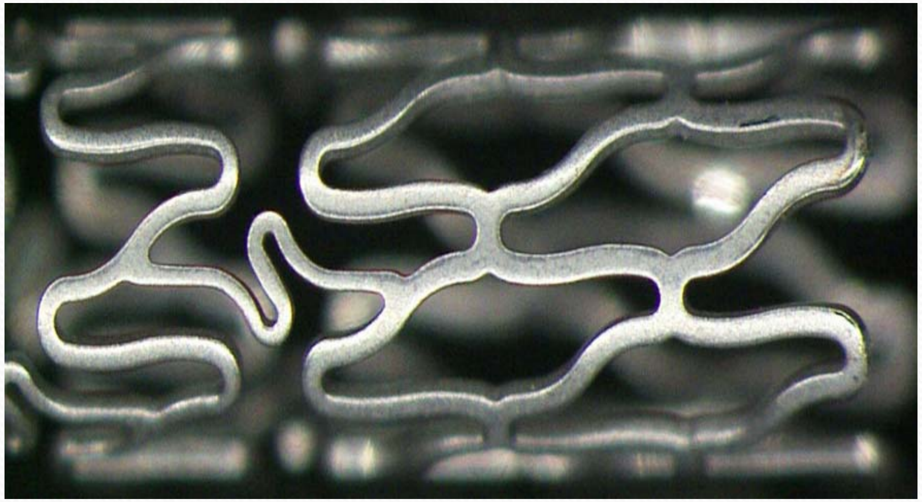
The Zeta potential value (-53.9 mV) indicates Good Stability of Drug-lipid nano particles in suspension.

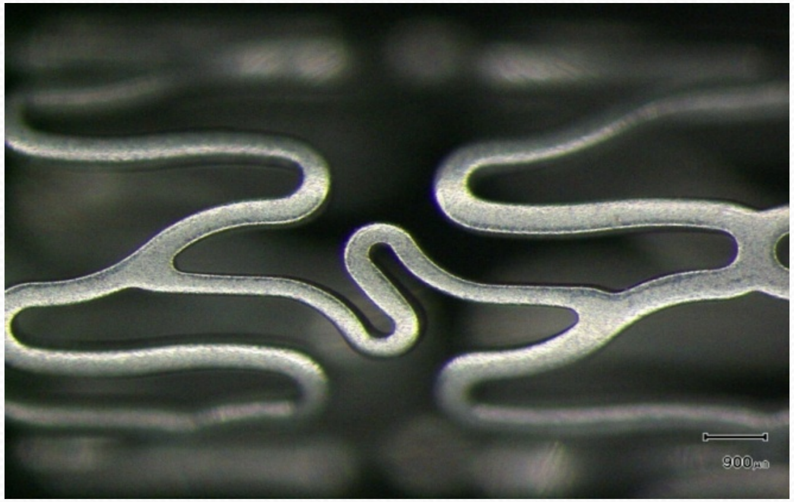
Zeta potential is the charge that develops at the interface between a solid Nanoparticles surface and aqueous medium. This potential, which is measured in MilliVolts, these are the dissociation of ionogenic groups in the particle surface and the differential adsorption of solution ions into the surface region.

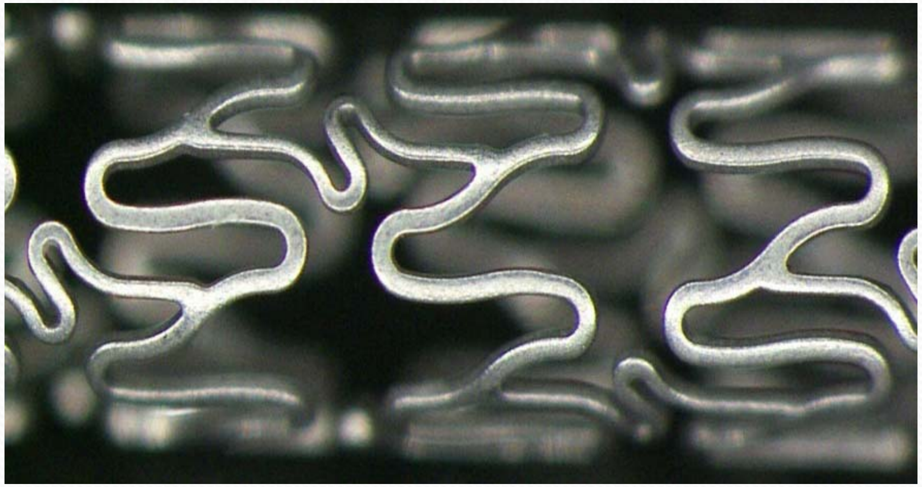
Mitsu – The formulation

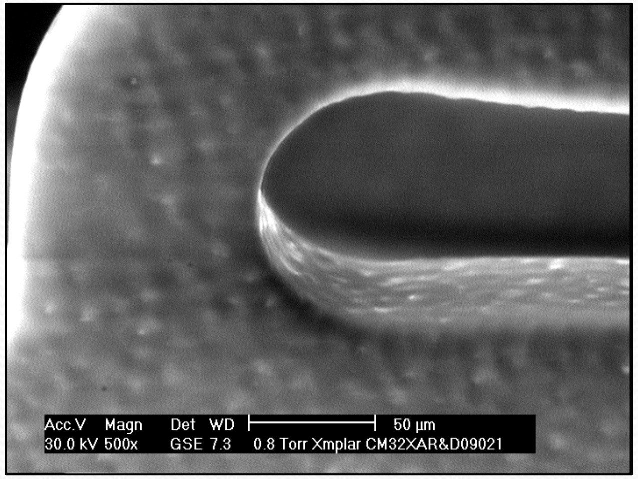
- Nanotechnology based coating.
- Designed for coating uniformity and lower drug dosage.
- Controlled and reproducible drug release kinetics.
- Rapid release of drug into tissue with "in-tissue" drug depot or reservoir effect.
- Renders the stent "coating-free" within a short time
  - Rapid tissue absorption (SLN has high tissue diffusion co-efficient)
  - Formulation ensures drug availability for 1 month

Optical Microscopic Images (Coating)





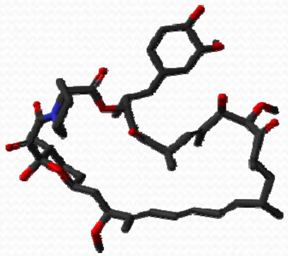




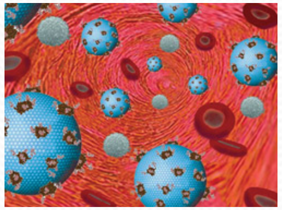
Mitsu - Summary

Stent System

Drug



Drug Delivery



- *40 µm thin stent*
- *Cobalt Chromium L605*
- *Hybrid stent design*
- *Variable strut width*
- *Tapered balloon shoulders*

- *Merilimus – new limus analogue*
- *Cytostatic, anti-inflammatory and lipophilic*
- *Wide therapeutic window*

- *Novel SLN polymer-free formulation*
- *Low drug for same effect*
- *Fast release kinetics*
- *Completely biocompatible and anti-inflammatory*

A unique differentiated new DES!