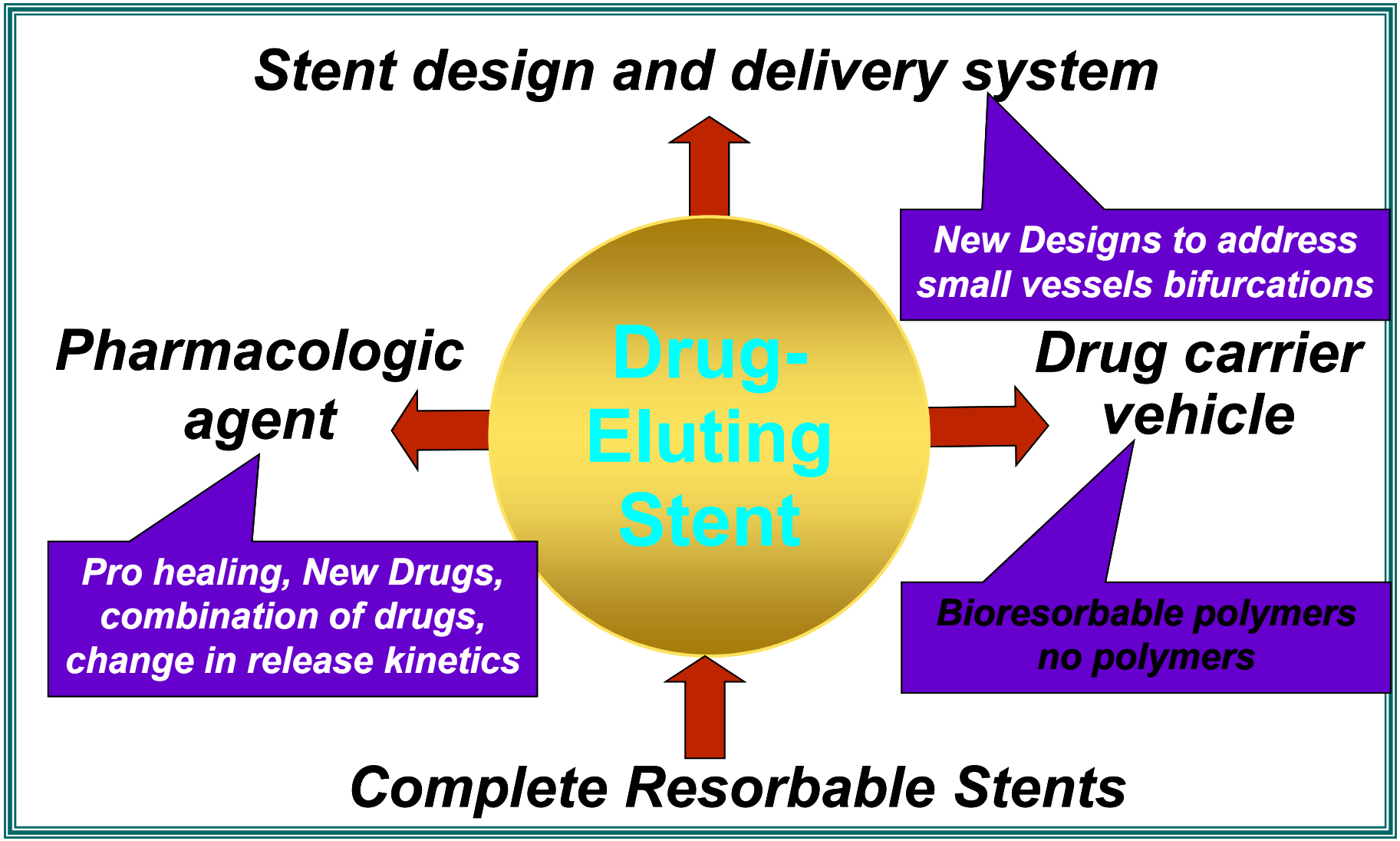
Nanoparticle or Nanomatrix Technologies for Drug Eluting Stents

Ron Waksman, MD, FACC, FSCAI
Professor of Medicine, Georgetown University,
Associate Chief of Cardiology,
Washington Hospital Center, Washington DC

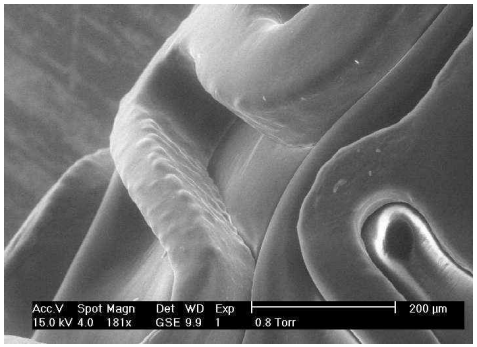
Drug-Eluting Stents

Next Generation

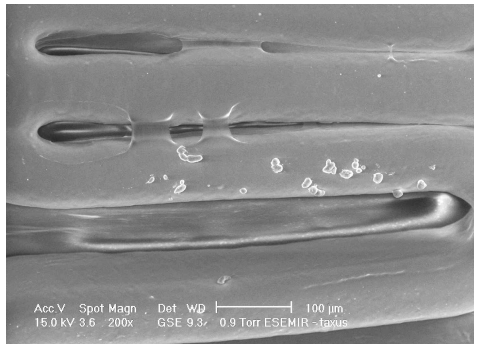


Current Problems with Polymers

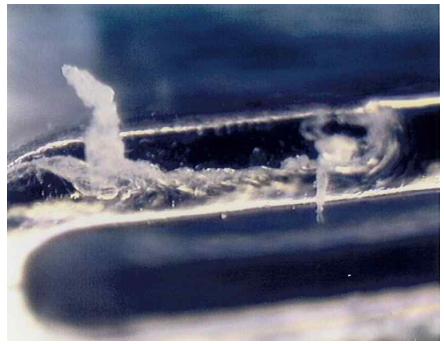
Shortcomings often associated with polymers during stent delivery



Non uniform polymer coating



Webbed" polymer surface leading to stent expansion issues"



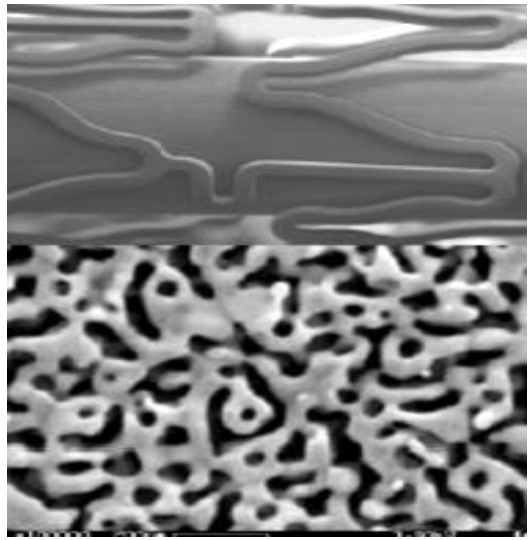
Polymer delamination

Durable Coatings-Potential for:

- -Continuing source of inflammation
- -Poor healing/thrombosis risk

New Polymers and Coating

- **Bioabsrobable Polymers**
  - **PLLA**
  - **PLA**
  - **PLG**
  - **PLGA**
- **No Polymers**
  - **Textured Surface**
  - **Depot Technology**
  - **Setagon Nano Technology**
  - **Surface Modifications**
  - **Nano membranous Filters**
  - **Photolithographic Etching**
  - **Hydroxyappetite HA**



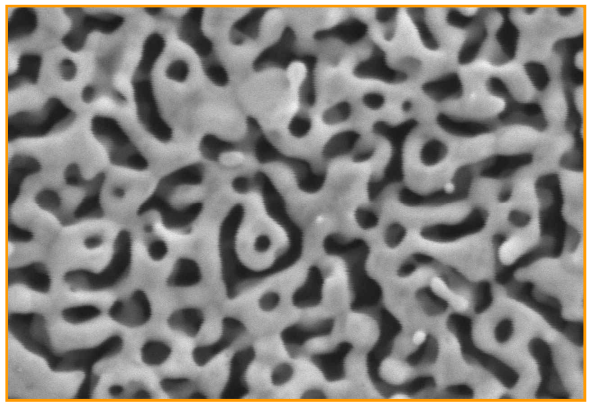
Future Generation DES

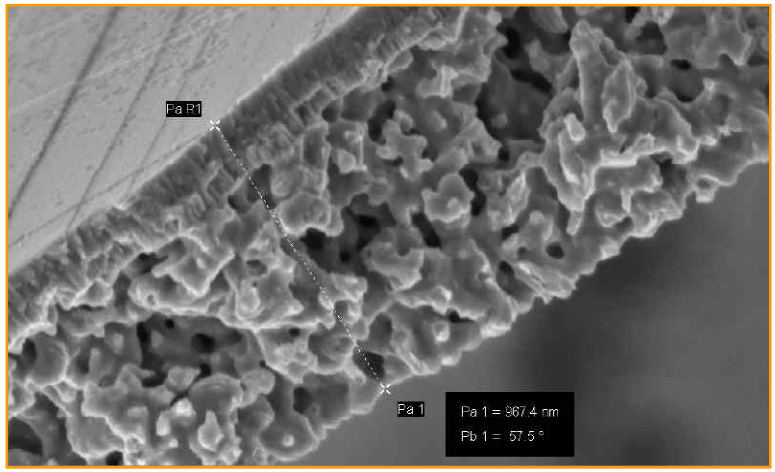
DES Nanotechnology

Goal: Further enhance combination of low TLR, long-term safety, and reduced DAPT requirements

Technology

Porous, non-polymeric stent surface with the ability to deliver a therapeutic agent





Development Targets

- Ability to provide for rapid, healthy endothelialization
- Ability to inhibit restenosis and cell proliferation
- Dependency of Plavix

Nanoporous Concept

Drug Eluting Stent without Polymer

- Polymer Coating replaced by Metal Coating
- Metal Coating is porous to hold the drug
- Metal Coating composition is the same as the bulk stent

Expectations

- Achieve a BMS surface at time of implant
- Expect similar safety as BMS due to same composition
- Expect control of elution due to pores
- Easily scaled manufacturing that is cost effective

NANO TECHNOLOGY
Advantages of new technology

ADVANTAGES OF NANO CARRIERS BASED DRUG DELIVERY SYSTEMS

- **SUBSTANTIAL INCREASE IN THE INTRA-CELLULAR UPTAKE**
- **INCREASING DRUG CONCENTRATION AND PRESENCE**
- **INCREASED BIO-AVAILABILITY**
- **MORE PERMEABILITY IN THE SUB-MUCOSAL LAYERS**
- **PROLONGED RESIDENCE TIME AT SITE**

NANO TECHNOLOGY
Advantages of new technology

ADVANTAGES OF NANO CARRIERS BASED DRUG DELIVERY SYSTEMS

- NANO COVERSION CREATES OPPORTUNITY TO ALTER PHARMACO-KINETICS OF DRUG AS PER NEED UTILIZING VARIOUS LINKAGES TO BUILD HIERARCHIAL STRUCTURES. THE EFFECTIVENESS HELPS IN REDUCING THE HIGH INITIAL DOSES OF DRUG.

- WITH TARGET BASED DRUG DELIVERY UTILIZING NANO CARRIERS REDUCE NON-SPECIFIC DRUG DOSE TO NON- TARGET TISSUE, AND DECREASES IRRITATION CAUSED IN TISSUE

- IMPROVES STABILITY OF DRUG IN-VIVO BECAUSE OF ENCAPSULATION PROCESS

New DES Coating Options

- Current DES polymer-coating technology uses dip- and/or spray coating methodology. These methods are useful for coating stents with strongly lipophilic drugs such as sirolimus but not for
- water-soluble drugs.

- Nanoparticle-mediated drug delivery systems (DDS) are poised to transform the development of innovative therapeutic devices.

- Bioabsorbable polymeric NP-eluting stent may provide an efficient and prolonged delivery compared with dip-coating stent.

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MINI-FOCUS: STENT TECHNOLOGY

Formulation of Nanoparticle-Eluting Stents by a Cationic Electrodeposition Coating Technology

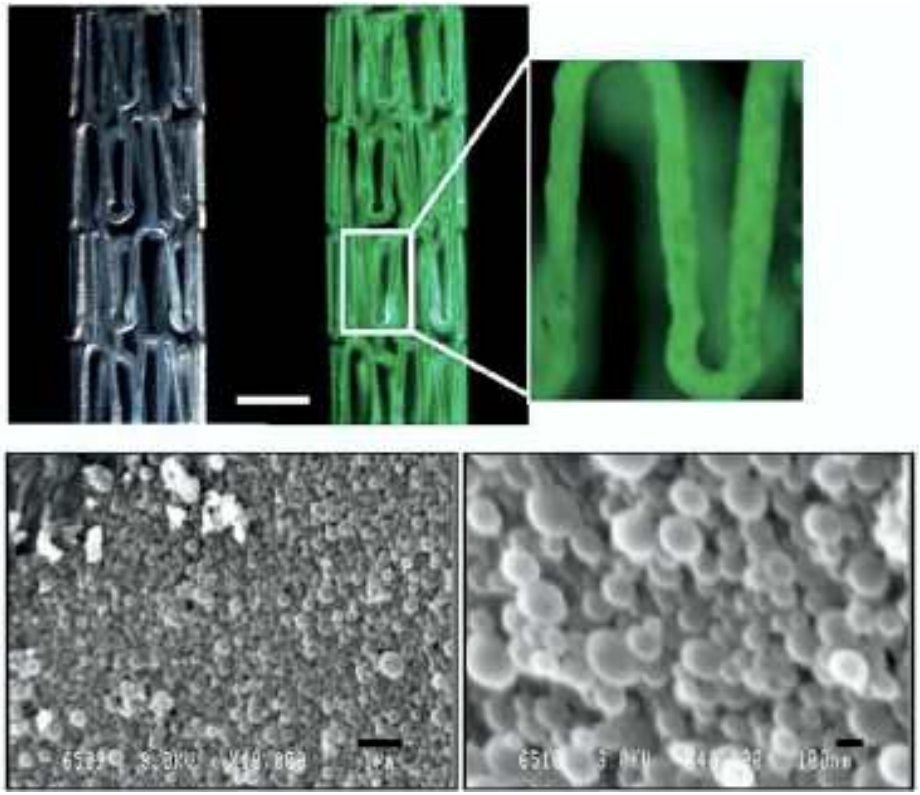
Efficient Nano-Drug Delivery via Bioabsorbable Polymeric Nanoparticle-Eluting Stents in Porcine Coronary Arteries

Kaku Nakano, PHD,* Kensuke Egashira, MD, PHD,* Seigo Masuda, MD,* Kouta Funakoshi, MD,* Gang Zhao, MD, PHD,§ Satoshi Kimura, MD,† Tetsuya Matoba, MD, PHD,* Katsuo Sueishi, MD, PHD,‡ Yasuhisa Endo, PHD,¶ Yoshiaki Kawashima, PHD,‖ Kaori Hara, PHD,# Hiroyuki Tsujimoto, PHD,# Ryuji Tominaga, MD, PHD,† Kenji Sunagawa, MD, PHD*

Fukuoka, Aichi, Kyoto, and Osaka, Japan; and Shanghai, China

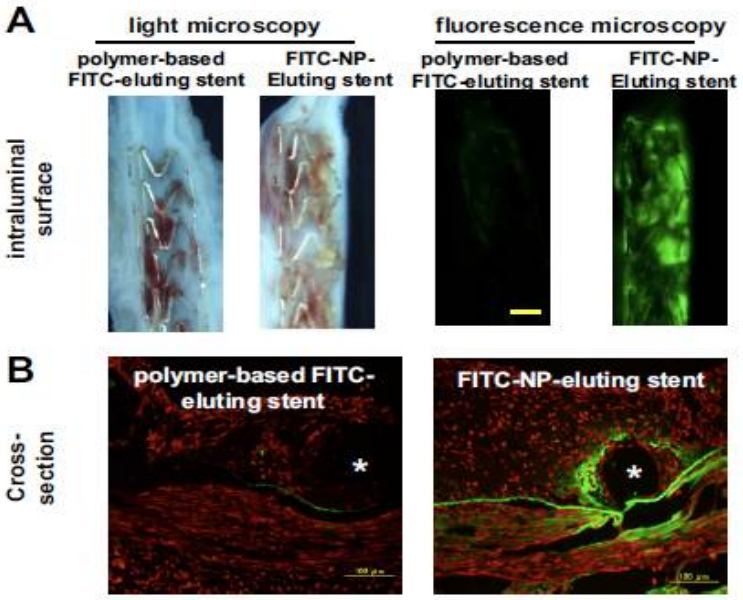
METHODS

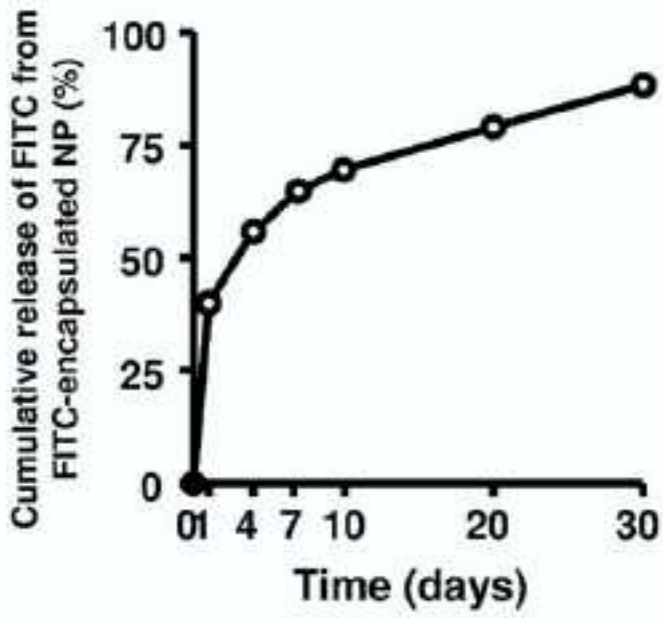
Cationic NP encapsulated prepared with a fluorescence marker (FITC) by emulsion solvent diffusion method to formulate an NP-eluting stent with a novel cation electrodeposition coating technology, and compared the in vitro and in vivo characteristics of the FITC-loaded NP-eluting stent with dip-coated FITC-eluting stent and bare metal stent.

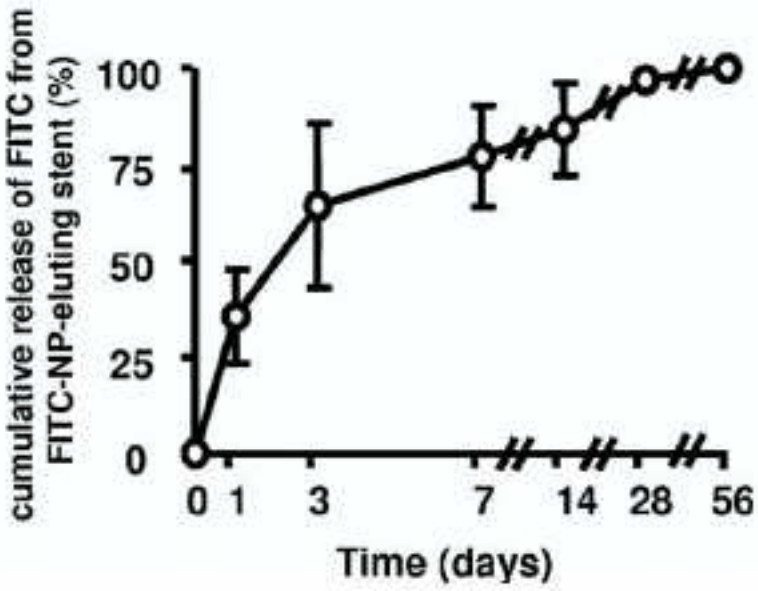


Kaku Nakano et al (J Am Coll Cardiol Intv 2009

The NP was taken up stably and efficiently by cultured vascular smooth muscle cells in vitro. In a porcine coronary artery model in vivo, substantial FITC fluorescence was observed in neointimal and medial layers of the stented segments that had received the FITC-NP-eluting stent until 4 weeks. In contrast, no substantial FITC fluorescence was observed in the segments from the polymer-based FITC-eluting stent or from BMS.







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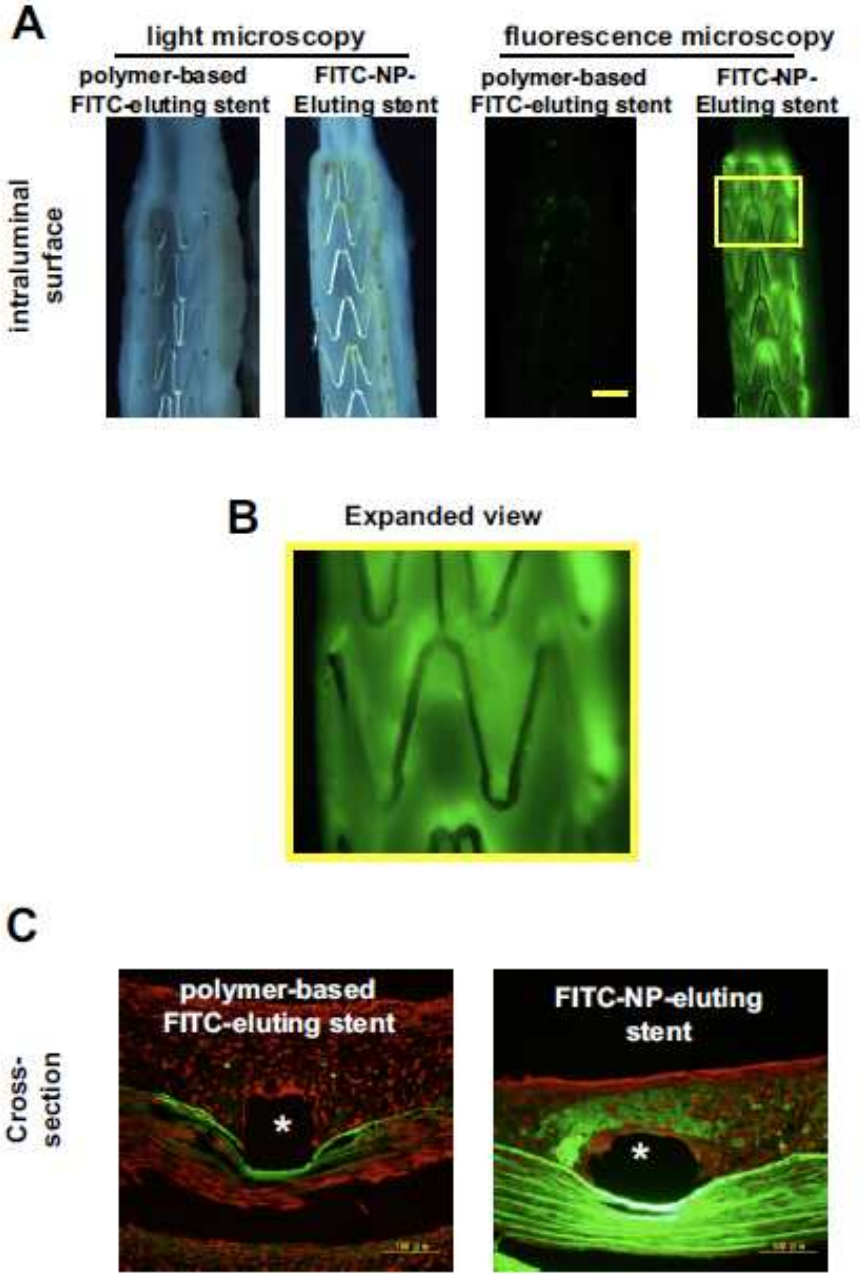
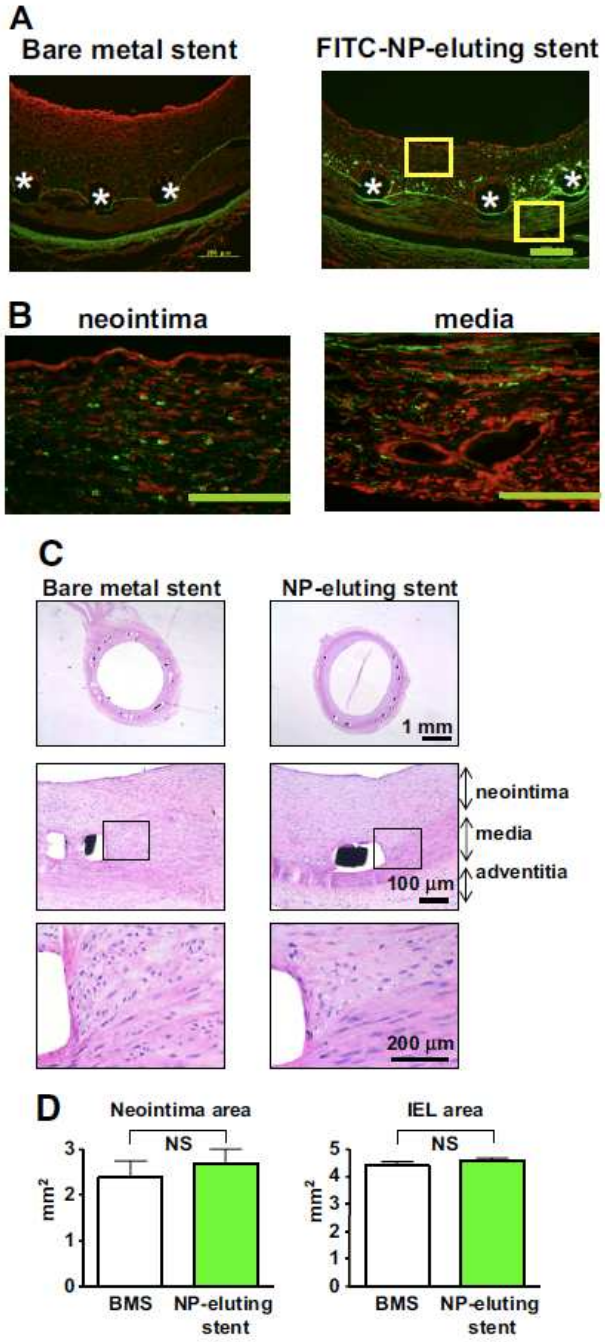




Kaku Nakano et al (J Am Coll Cardiol Intv 2009

FOCUS *np* – npDES System

Envision Scientific Pvt. Ltd. INDIA

STENT PLATFORM **COBALT CHROMIUM**

Good Stent design reduces arterial wall injury. Optimal amount of Metal in Artery has been found to reduce Restenosis rates. – THIN STRUTS : 73µ

STENT DELIVERY SYSTEM **LOW ENTRY PROFILE**

Highly deliverable system with low step-less tip and flexibility is desirable.
Good track ability in tortuous vessels increases success rates. – 0.016" TIP ENTRY PROFILE

COATING DESIGN **PRE CRIMPED STENT WITH NANO PARTICLES**

Restenosis in existing Drug eluting stents found is mostly Focal or Edge Re-stenosis, and may be because of drug insufficiency in areas.

DRUG SELECTION **SIROLIMUS DRUG**

Sirolimus have been found to have good immunosuppressive and anti-proliferative properties.

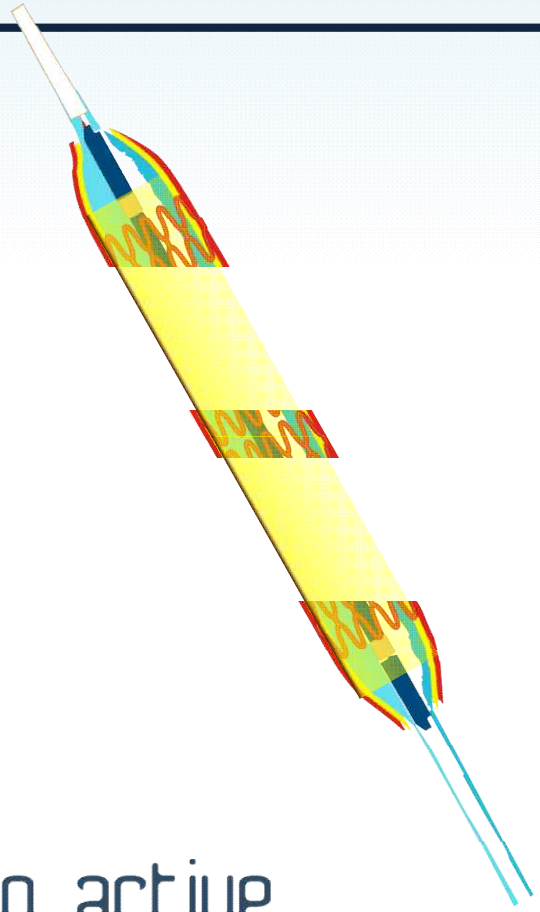
NANO PARTICLES **POLYMER FREE DESIGN**

Size does matter and so does absorption efficiency is dependent on the size of drug/drug carrier. Variable size nano carriers are created.

FOCUS *np* – npDES System

DESIGN DETAILS

Pre-crimped Stent Coating Design | **Coating Stent & Balloon**



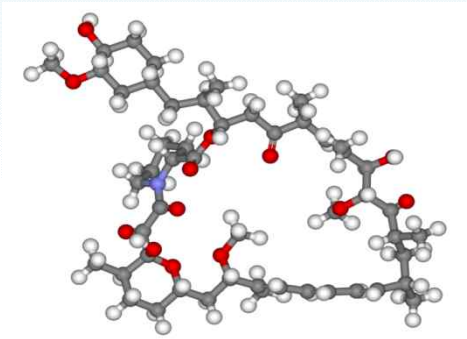
- **Coating on Pre-crimped Stent – Active coating on Stent and Balloon**
- **Eliminate Inner layer coating on Stent (Abluminal Coating Only)**
- **Enhance *np* Drug delivery to tissue by increasing Drug delivery area – Delivery both from Stent and Balloon**
- **Current system only delivers drug up to 14~18% (which is Metal to Artery Ratio) of Lesion and hence "UNTREATED AREAS" are created.**
- **Special Coating Equipment and Method Designed (PATENT ON MACHINE FOR COATING)**

nano active
COATING TECHNOLOGY

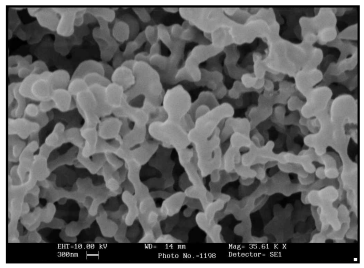
FOCUS *np* – npDES System

DESIGN DETAILS

Drug Selection & *np* Conversion	Sirolimus Drug



Sirolimus Drug

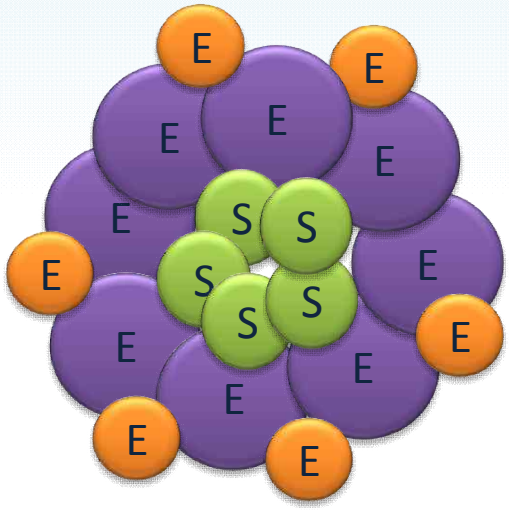


- SIROLIMUS Drug – High Safety & Efficacy proved
- Limus Molecule with its variants is drug of choice for many Cardiologist –Clinical Results
- Sirolimus nano particle (*np*) created in variable size range: 20 ~ 1000 nano meters
- Stabilization of *np* of Drug done

FOCUS *np* – npDES System

DESIGN DETAILS

np **Drug Delivery Design W/o Polymer** | **Excipient Selection**



Encapsulated Structure

- **Polymer Free Approach was Key design objective**
- **Two Excipient selected for creating a Programmed Drug Release kinetics**
- **Encapsulated Drug nano particle created**
- **Drug Carrier properties enhances Drug Delivery**
- **Sirolimus (S), Excipient 1 (EX1) and Excipient 2 (EX2)**

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COATING TECHNOLOGY

FOCUS *np* – npDES System

DESIGN DETAILS

Programmed Drug Delivery fm Device	Drug *np* preparation Sequence

1	Nano Crystal of Drug created
2	Nano Particles of Excipient created
3	Stabilization of Drug Nano Crystal using of Excipient
4	Encapsulation process of Drug into Excipient (Two different range created
5	Encapsulated Nano Sphere formulation created (Top and Bottom Layer)

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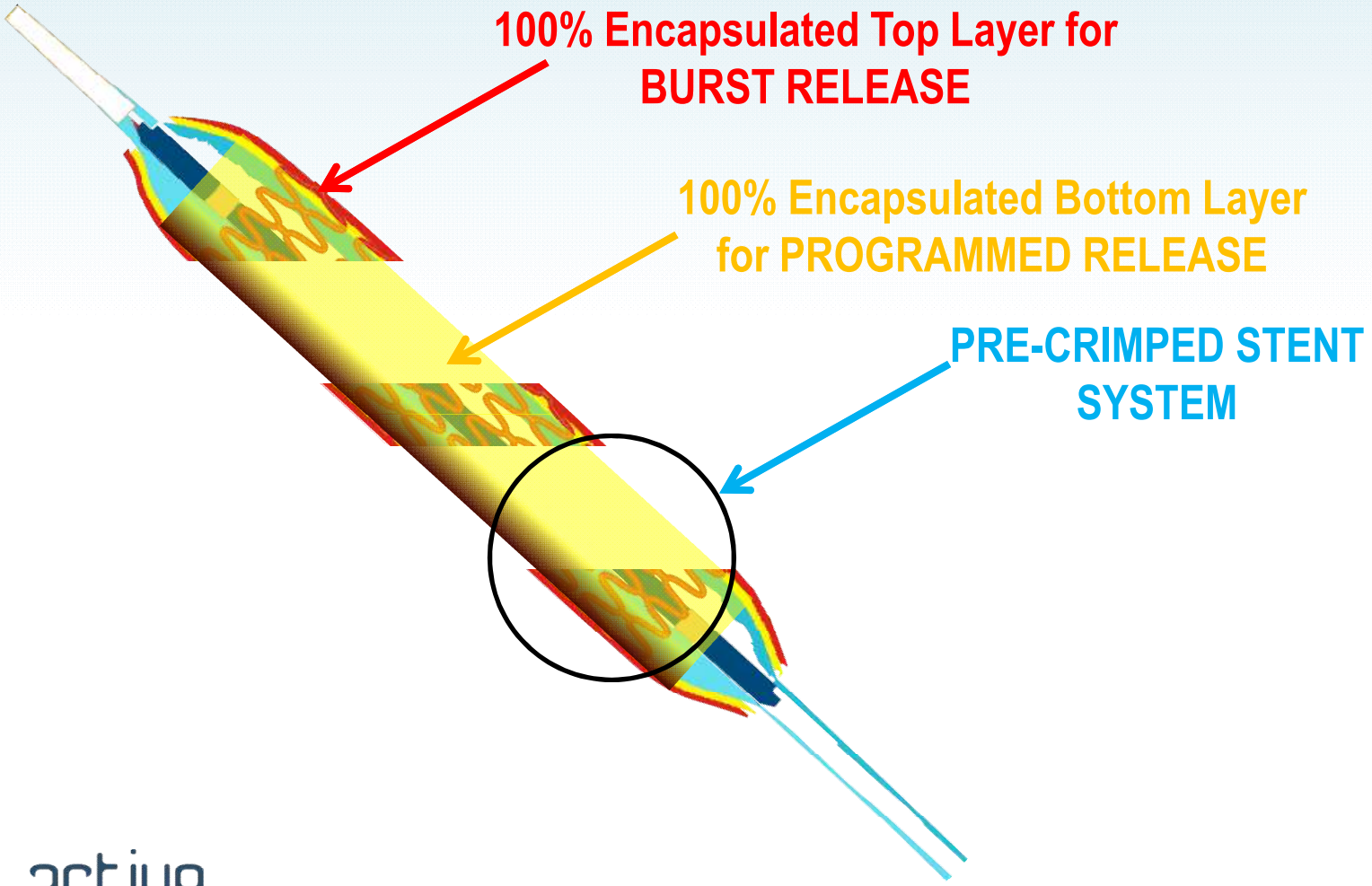
COATING TECHNOLOGY

FOCUS *np* – npDES System

COATING DESIGN



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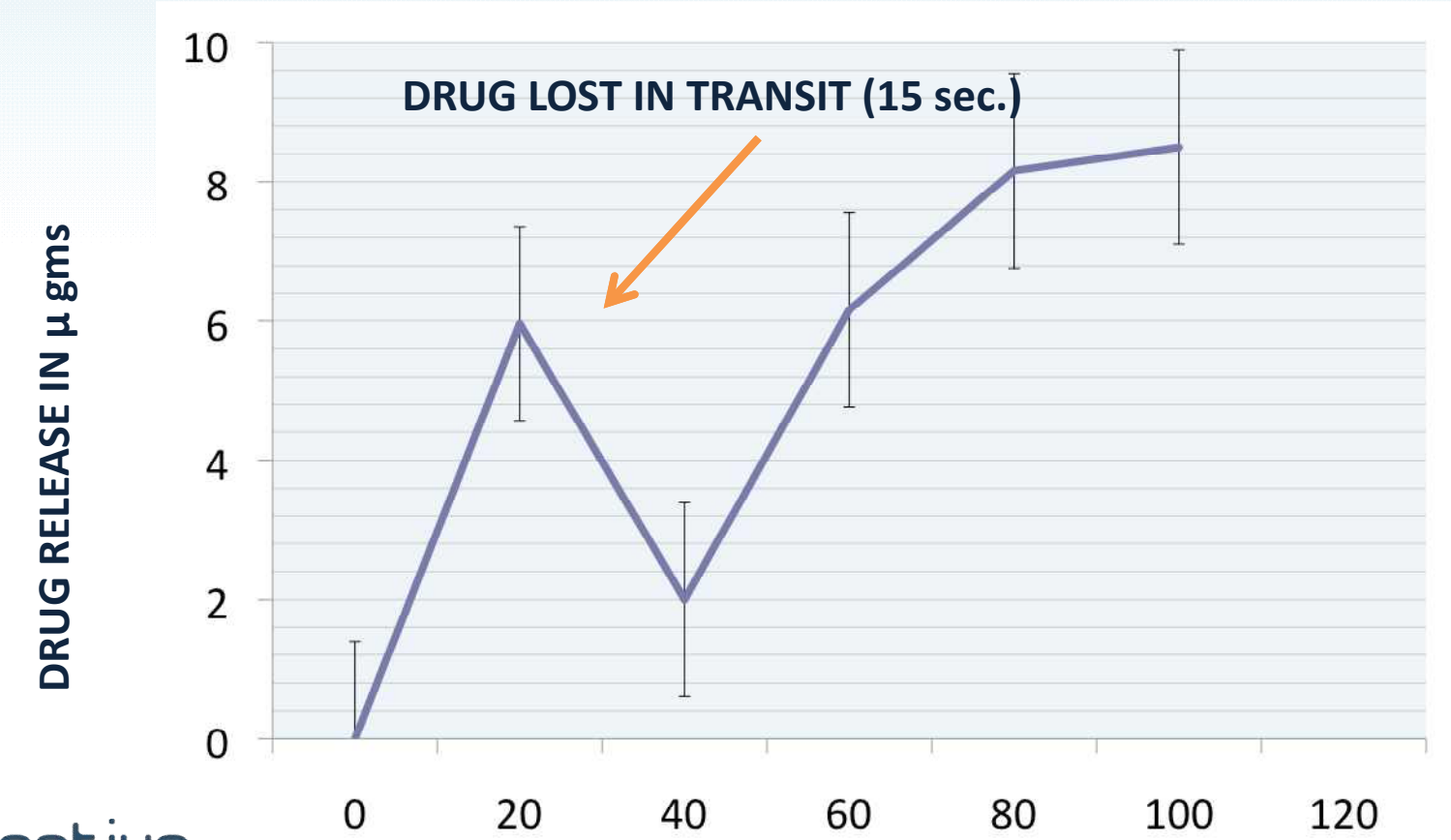
COATING TECHNOLOGY

FOCUS *np* – npDES System

Programmed Drug Delivery fm Device **Drug Release I – Burst Release**



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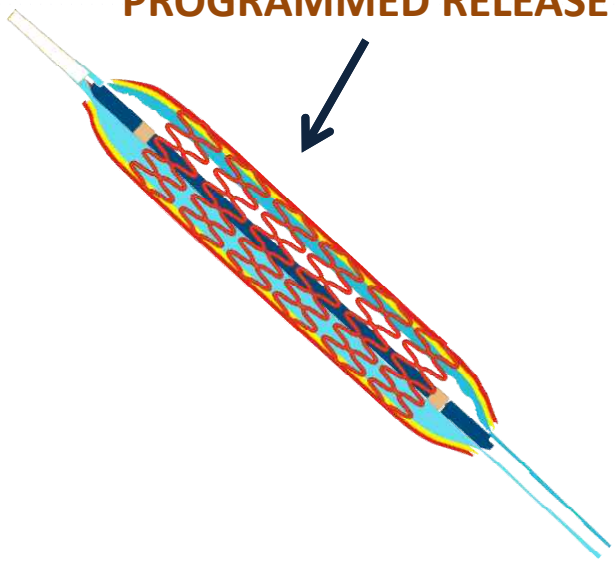
COATING TECHNOLOGY

FOCUS *np* – npDES System

Programmed Drug Delivery fm Device	Drug Release II – Programmed Release

100% Encapsulated Bottom Layer for PROGRAMMED RELEASE

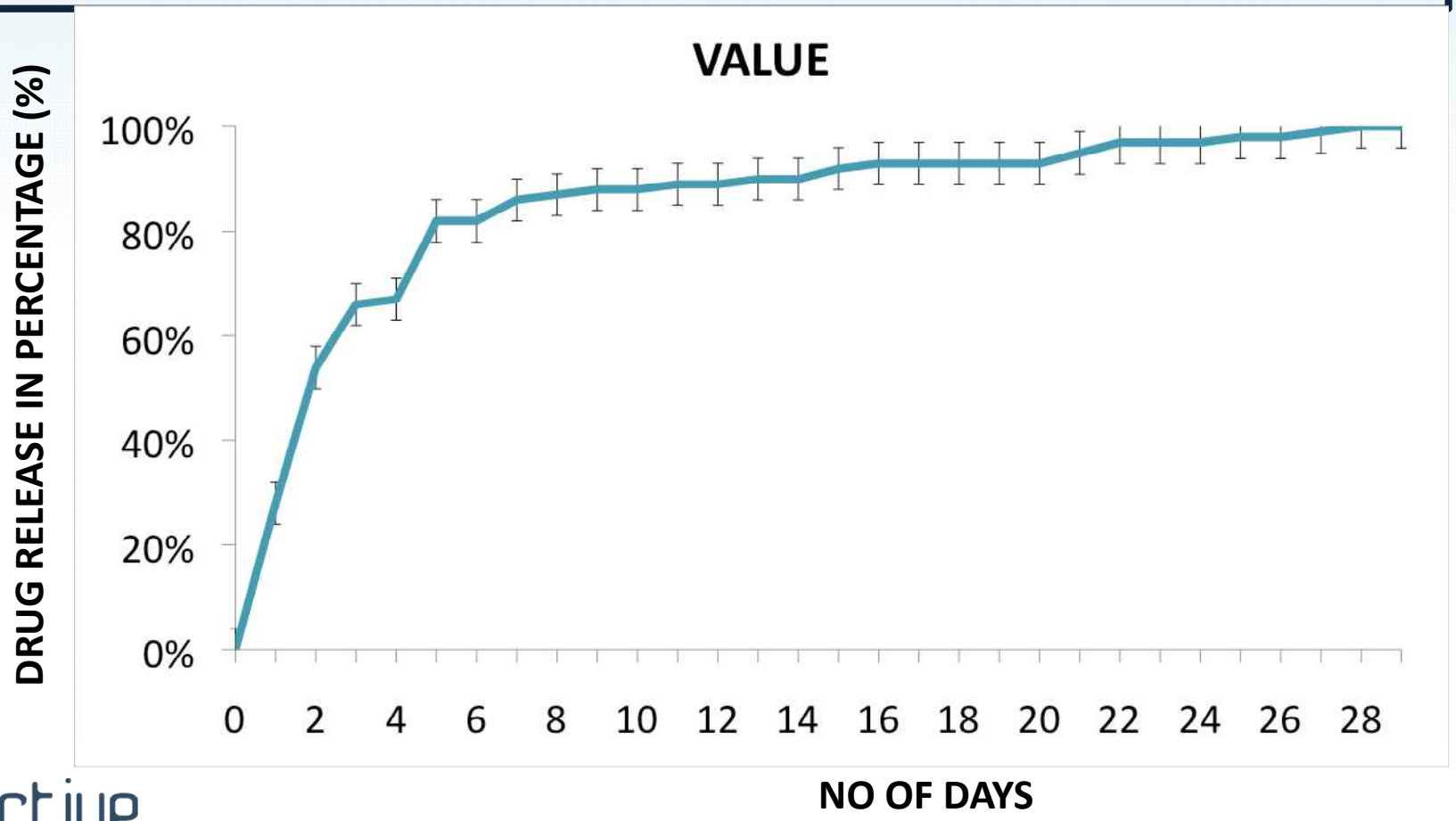


- **Bottom Layer is programmed to release complete np Spheres in arterial tissue**
- **Complete Release in 28 Days**
- **Easily absorbed in tissue because of particle size**
- **Programmed release kinetics from Stent**
- ***np* Drug has a longer in-tissue release because of encapsulation in excipient**

nano active COATING TECHNOLOGY

FOCUS *np* – npDES System

Programmed Drug Delivery fm Device **Drug Release II – Programmed Release**



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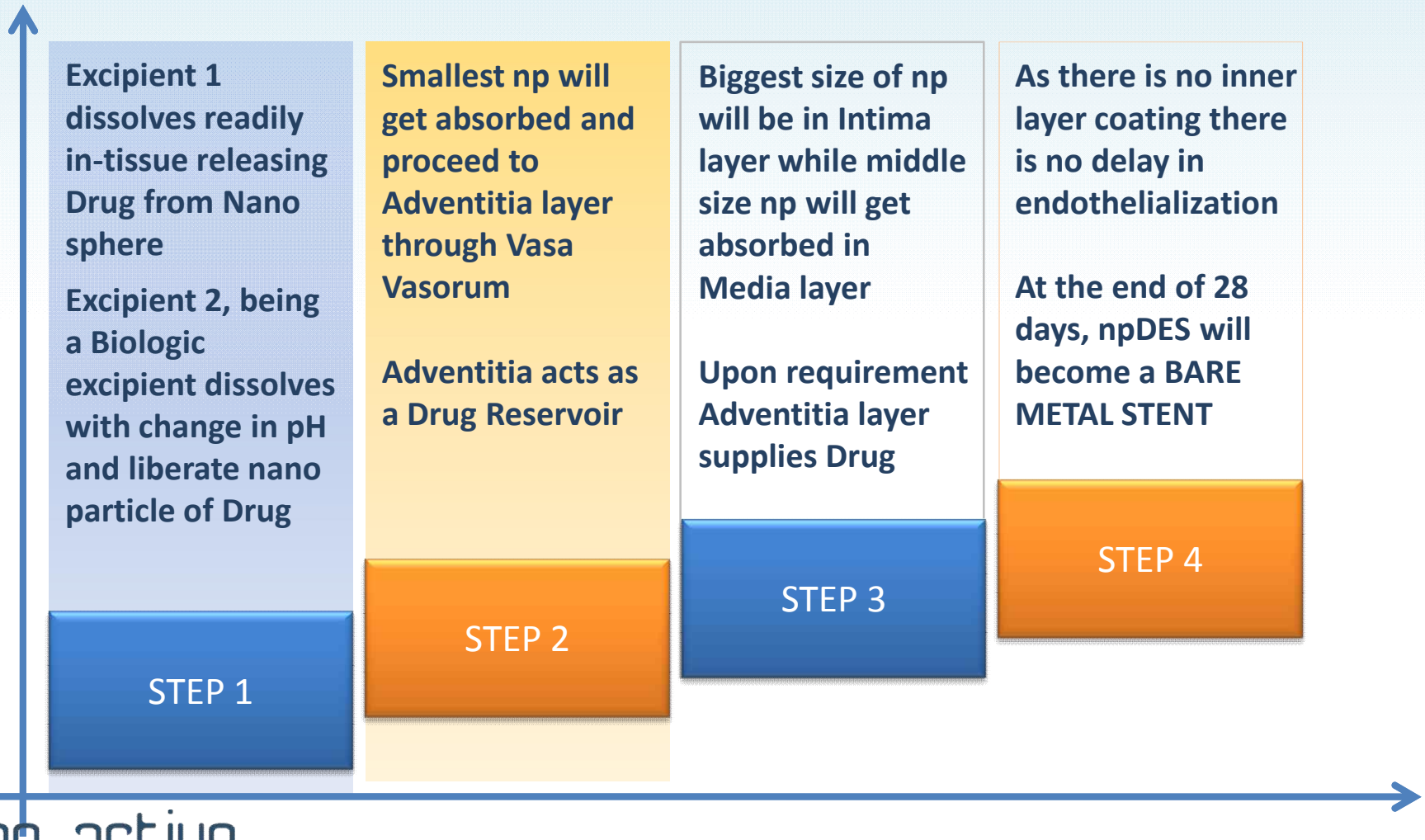
COATING TECHNOLOGY

FOCUS *np* – npDES System

MECHANISM OF ACTION



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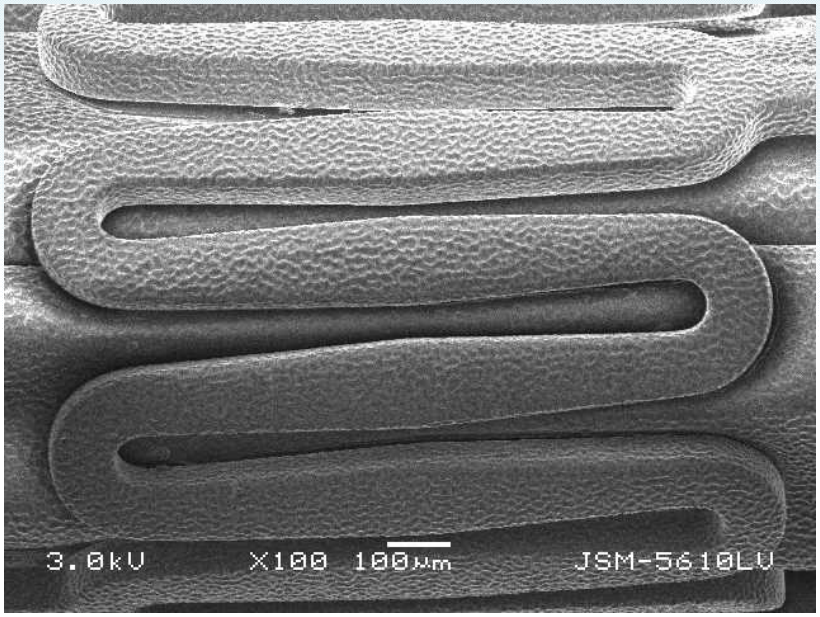
COATING TECHNOLOGY

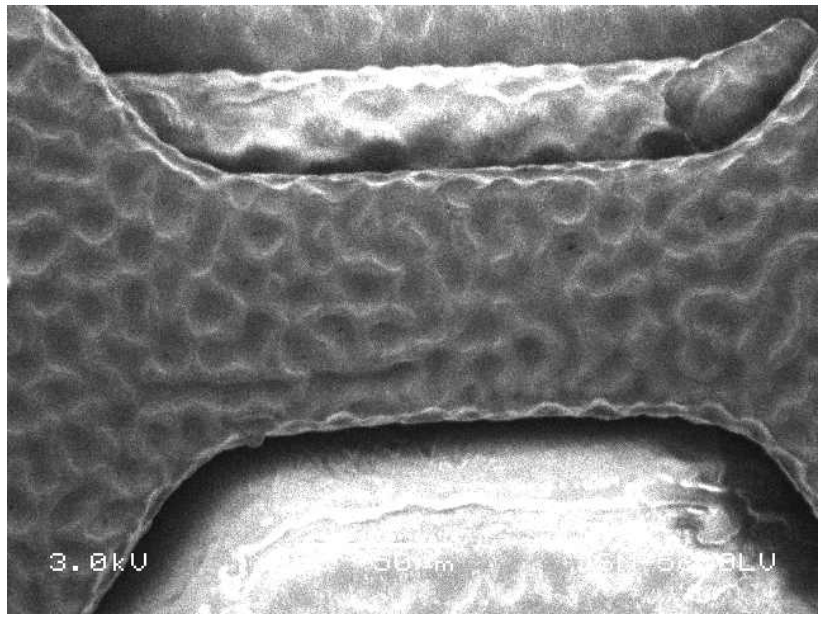
FOCUS *np* – npDES System

HI RESOLUTION SEM IMAGES



Coated balloon – Crimped Stent

High Resolution Images



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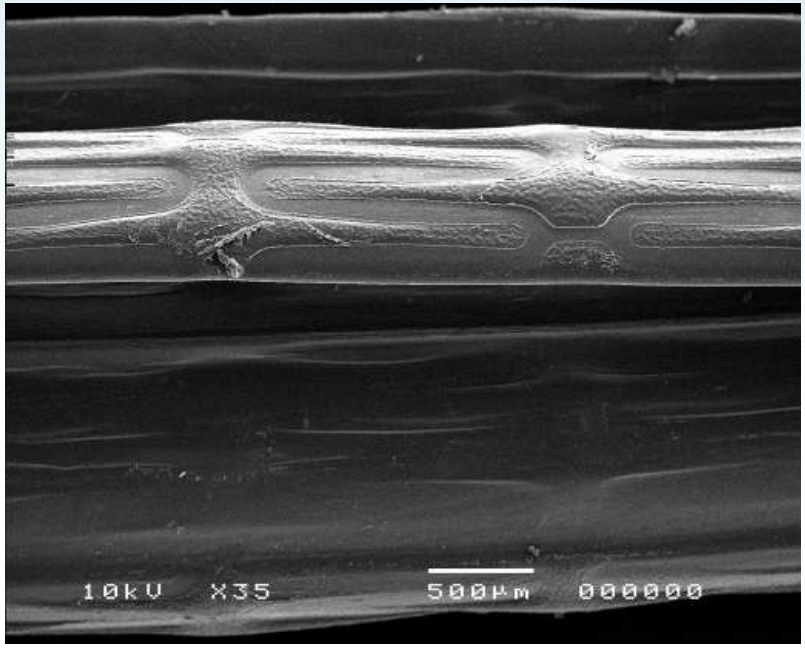
COATING TECHNOLOGY

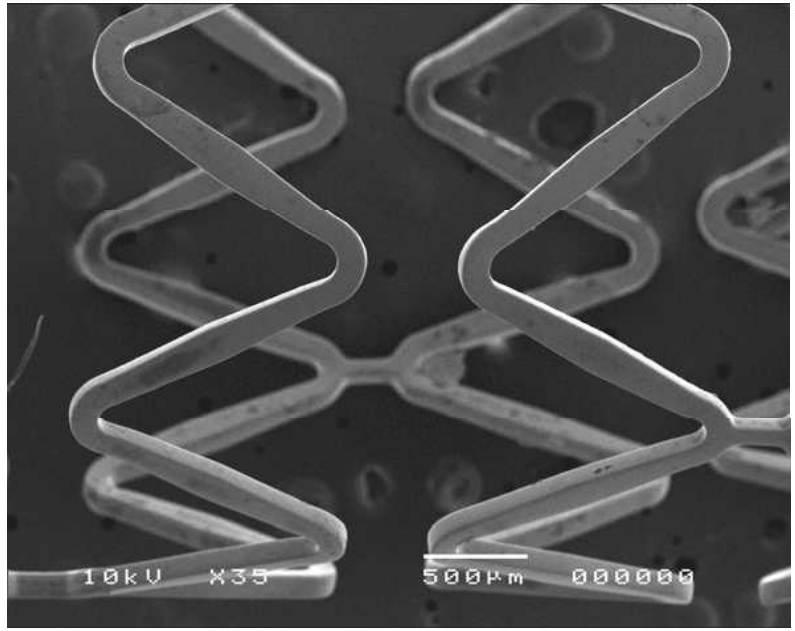
FOCUS *np* – npDES System

HI RESOLUTION SEM IMAGES



Coated balloon (stent is removed)

Coated stent in expansion state



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COATING TECHNOLOGY

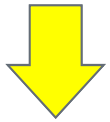
Future *Safe* DES Platforms

The Key is the Endothelium!

active support of endothelial cell proliferation and migration after stent implantation

accelerated endothelial cell strut coverage

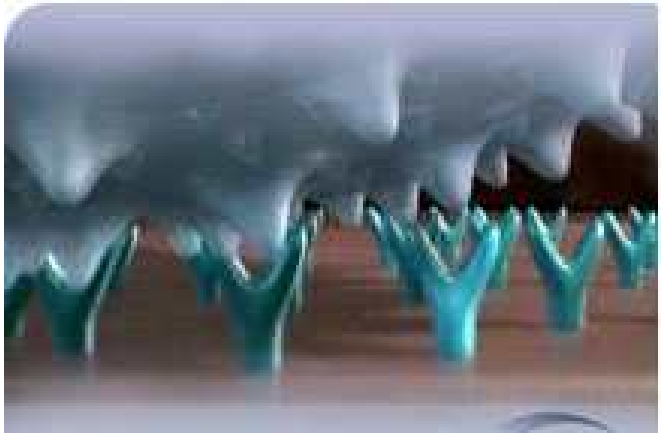
decreased smooth muscle activation & reduced collagen secretion



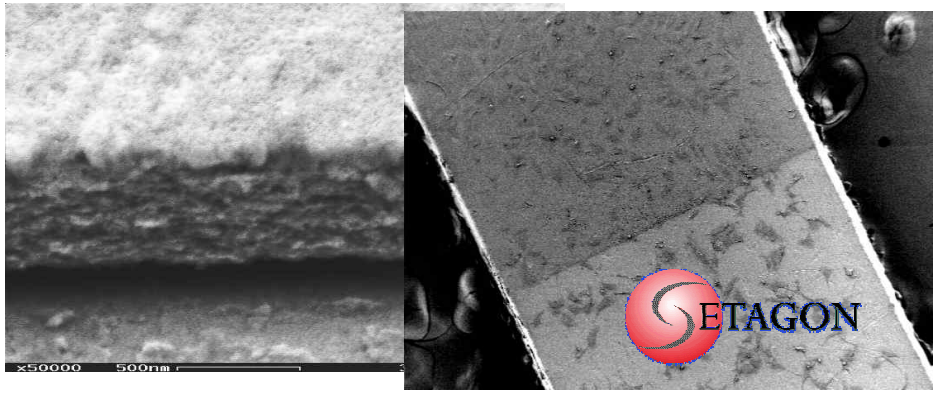
optimal healing response = ***accelerated functional endothelium***

Surfaces to Encourage Cell Growth

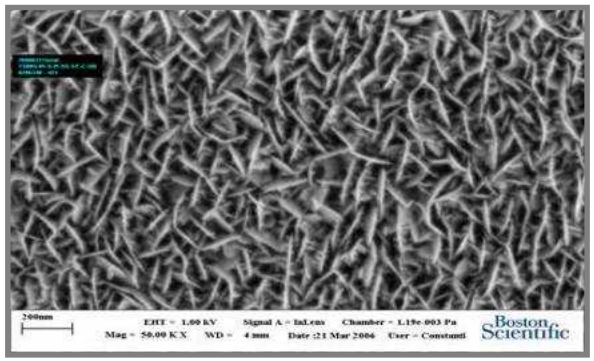
Bioactive surfaces to accelerate functional endothelialization



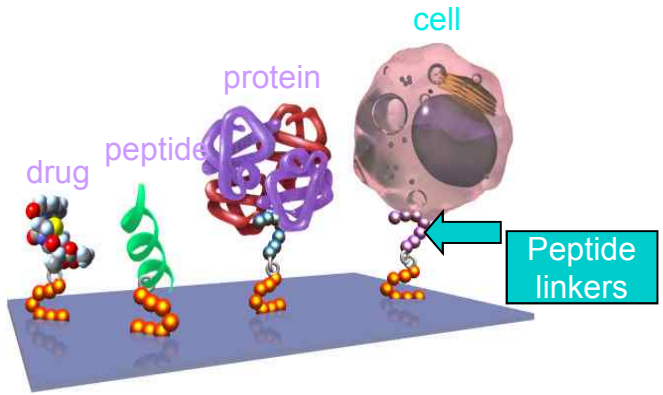
Orbus – EPC Capture



Nanotextured Surfaces



Example of IrOx



Cell specific peptide linkers (Affinergy)

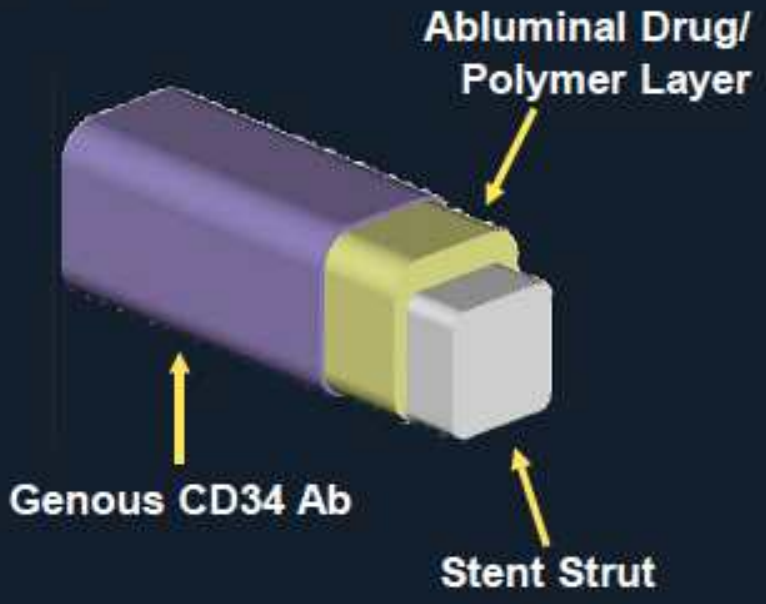
Directional Sirolimus Biodegradable Abluminal Coating and Anti-CD34 Surface Modification

Genous Technology:

- Anti-CD34 surface to promote healing through rapid stent endothelialization

Genous-DES Technology:

- Rapamycin (5 µg/mm) applied in biodegradable SynBiosys polymer on the abluminal side



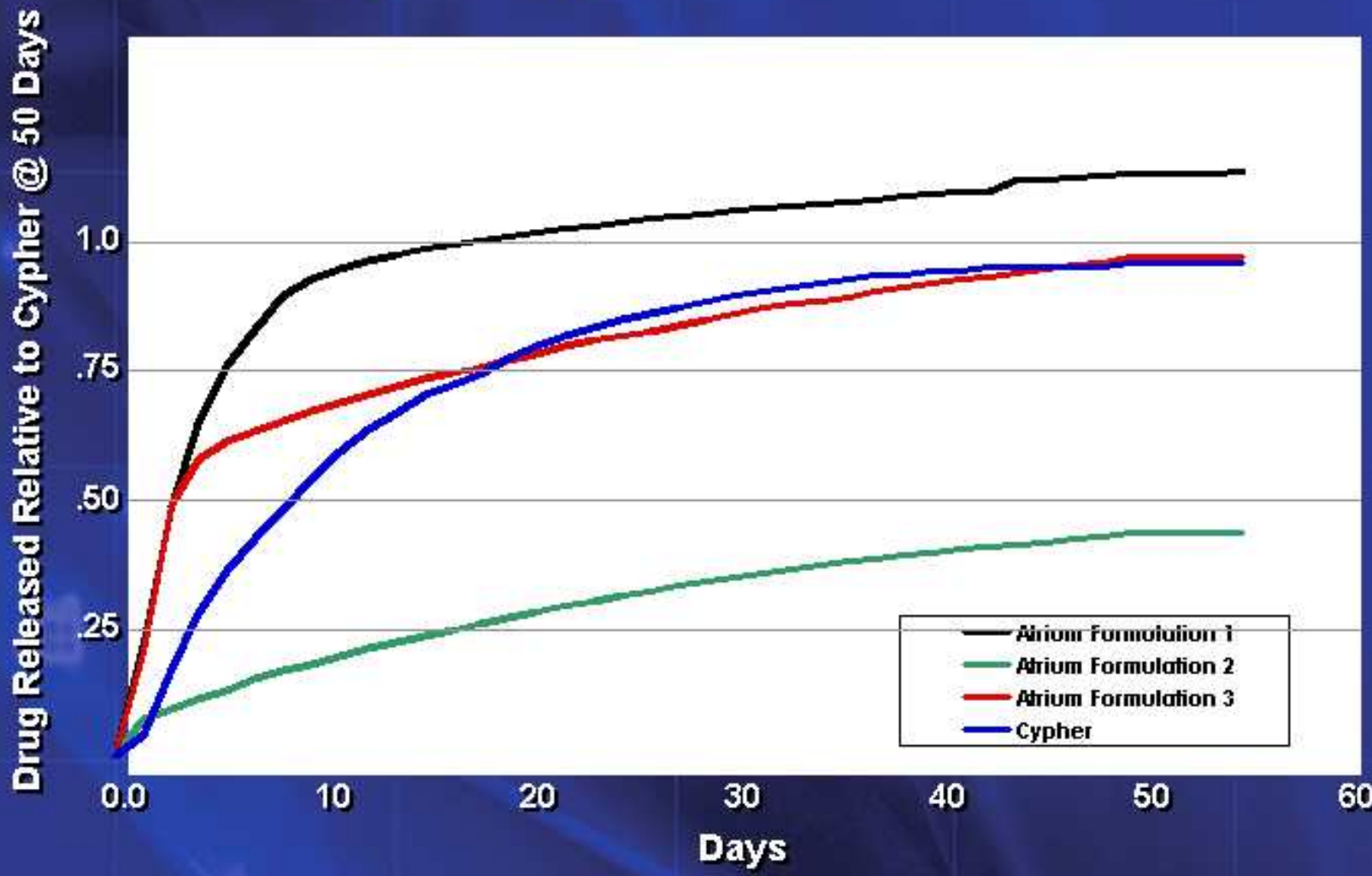
Atrium Bioabsorbable Oil Coating

Novel BAO Coating Process

- Proprietary Omega-3 fatty acid blend
- Non-polymeric oil based coating

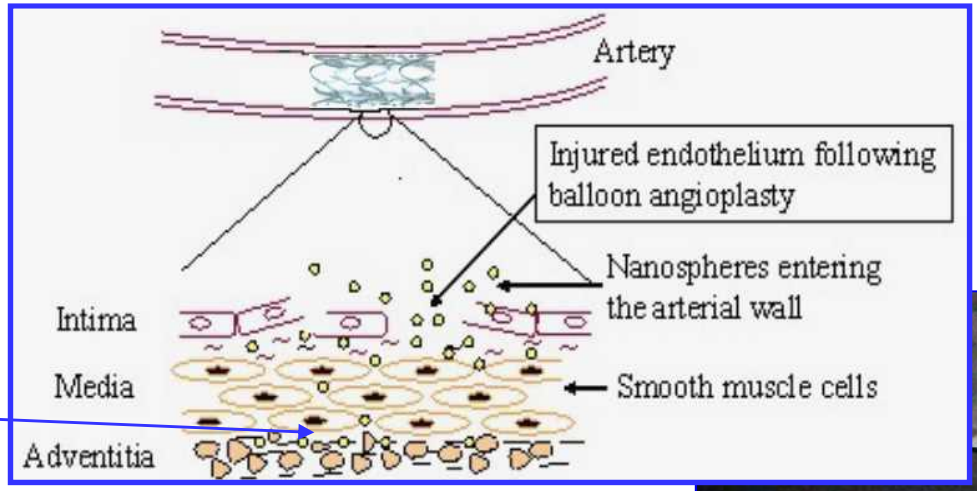
- Coating applied after stent is crimped
- Both balloon and stent are coated for treatment of entire lesion segment

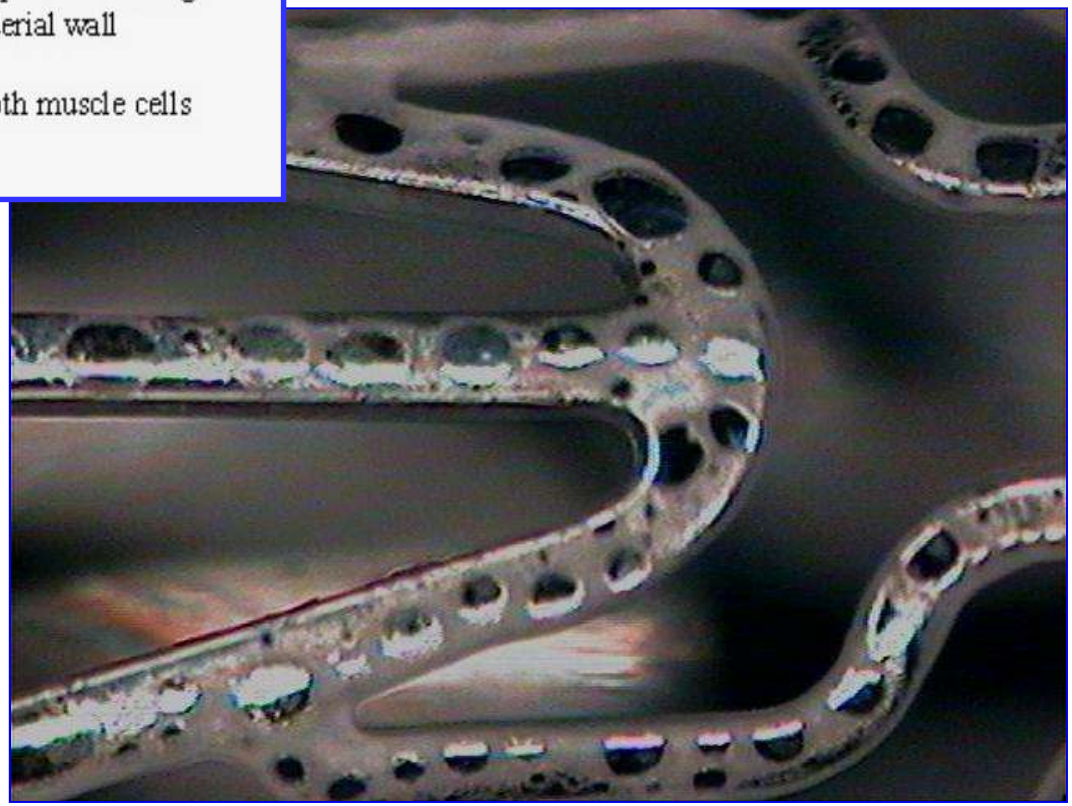
BAO Rapamycin Release Curve*



*Phosphate Buffered Saline Solution

Drug elution mechanism from biodegradable Nanoparticles (Sahajanand Medical)

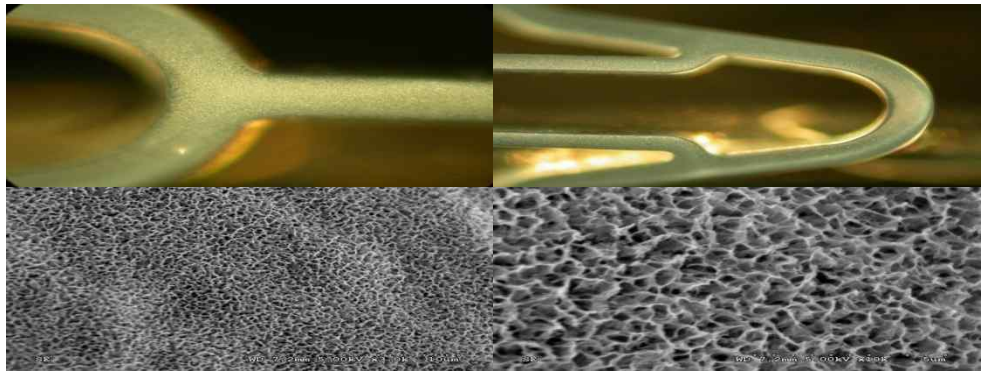


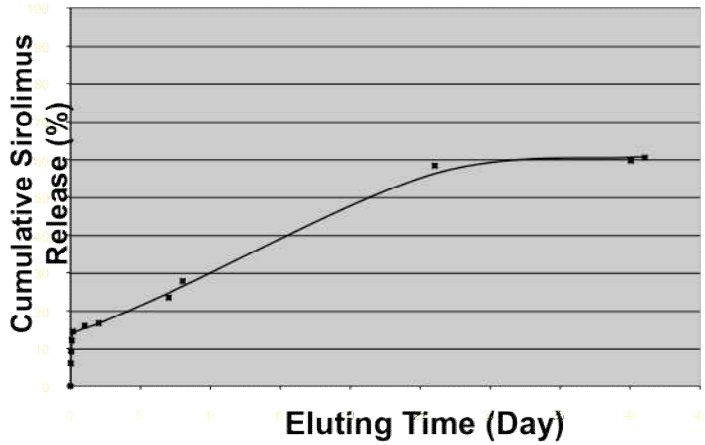


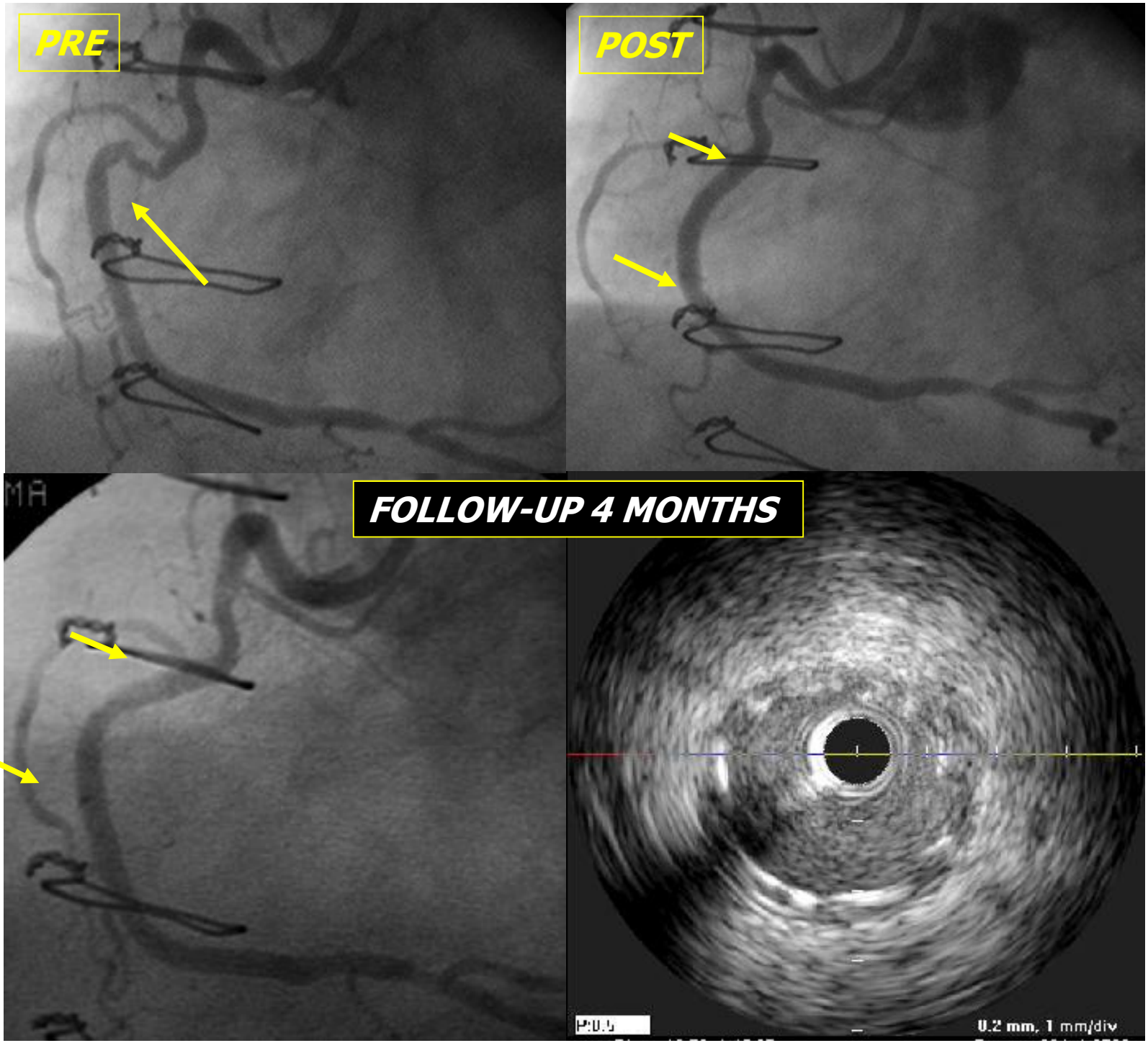
Porous biodegradable polymeric base layer

VESTASYNC MIV
Core Technologies

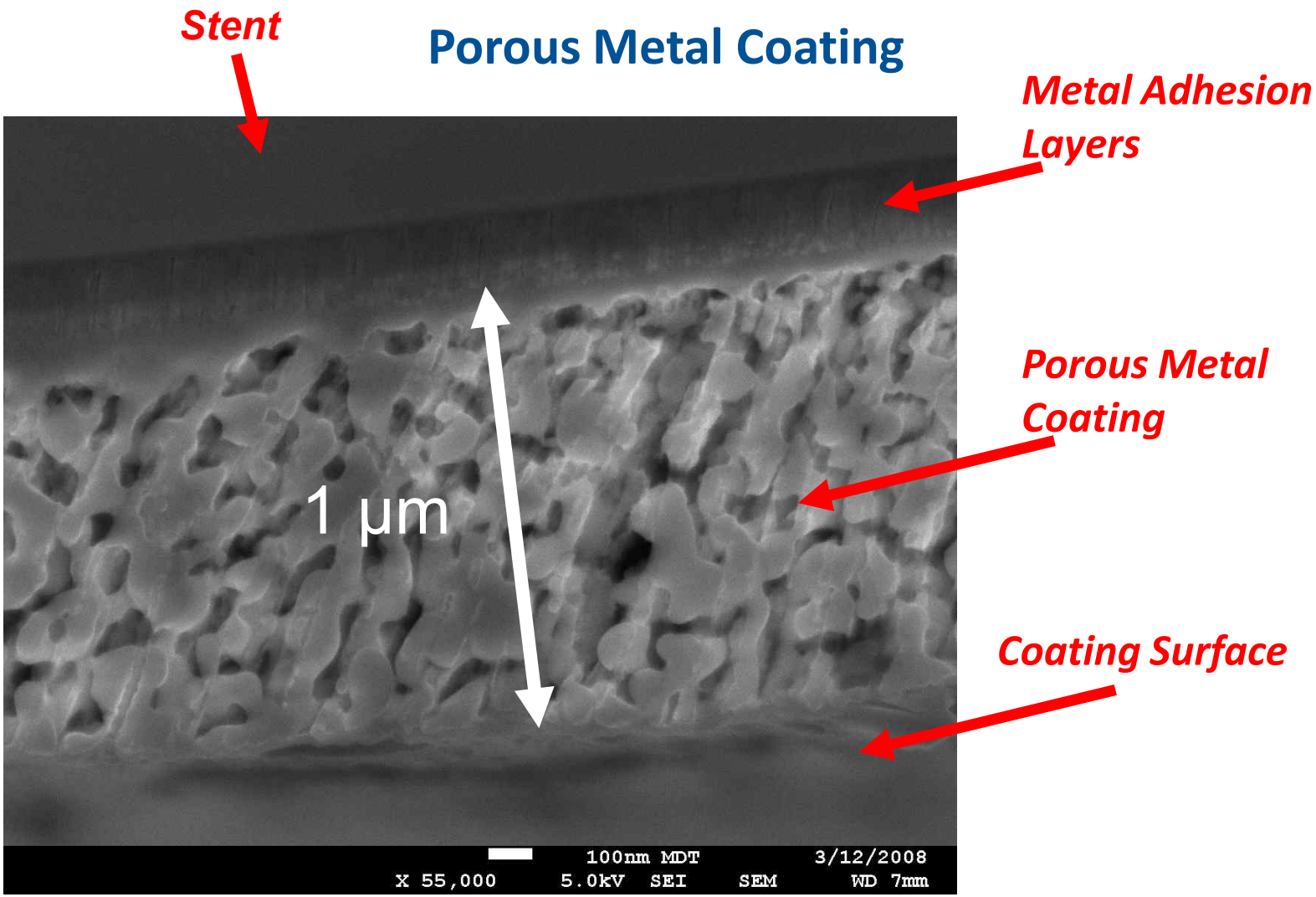
- **Thin Strut Stent Platform**
- **HAp Surface Modification**
- **Polymer Free Drug Formulation**





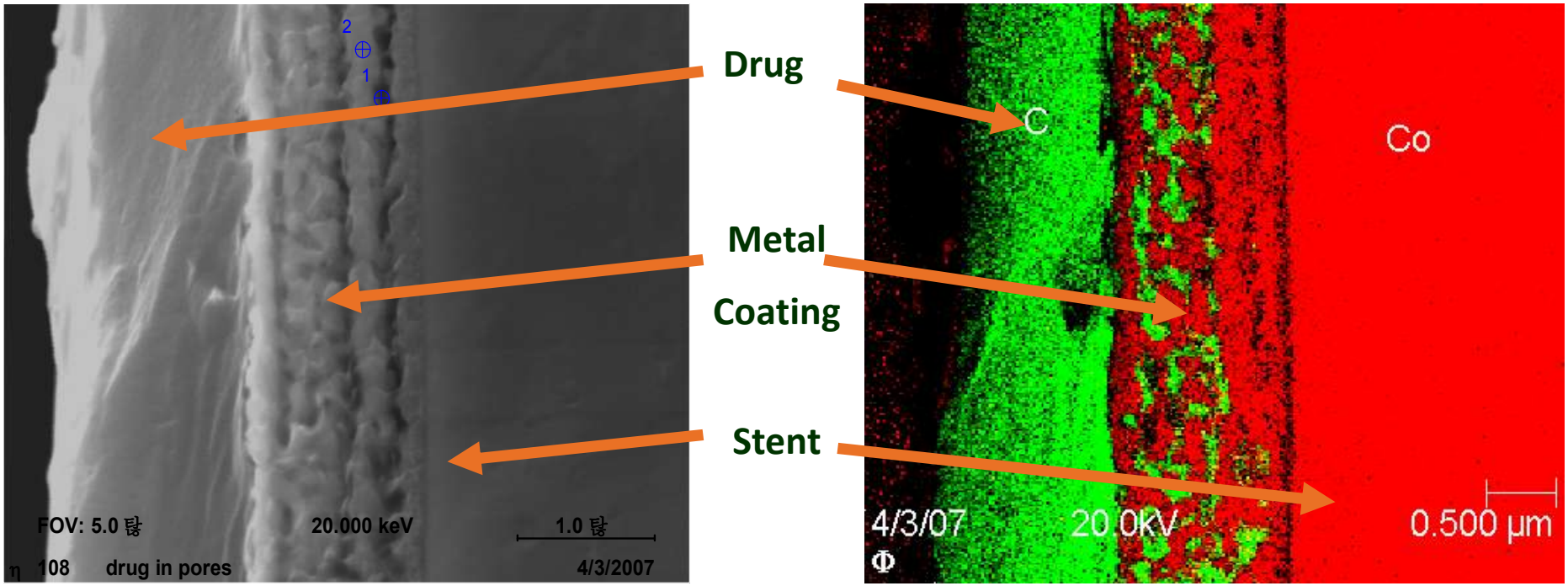

PRE
POST
FOLLOW-UP 4 MONTHS
0.2 mm, 1 mm/div

Nanopores - What do they look like?



Nanopores – Drug Load Capacity

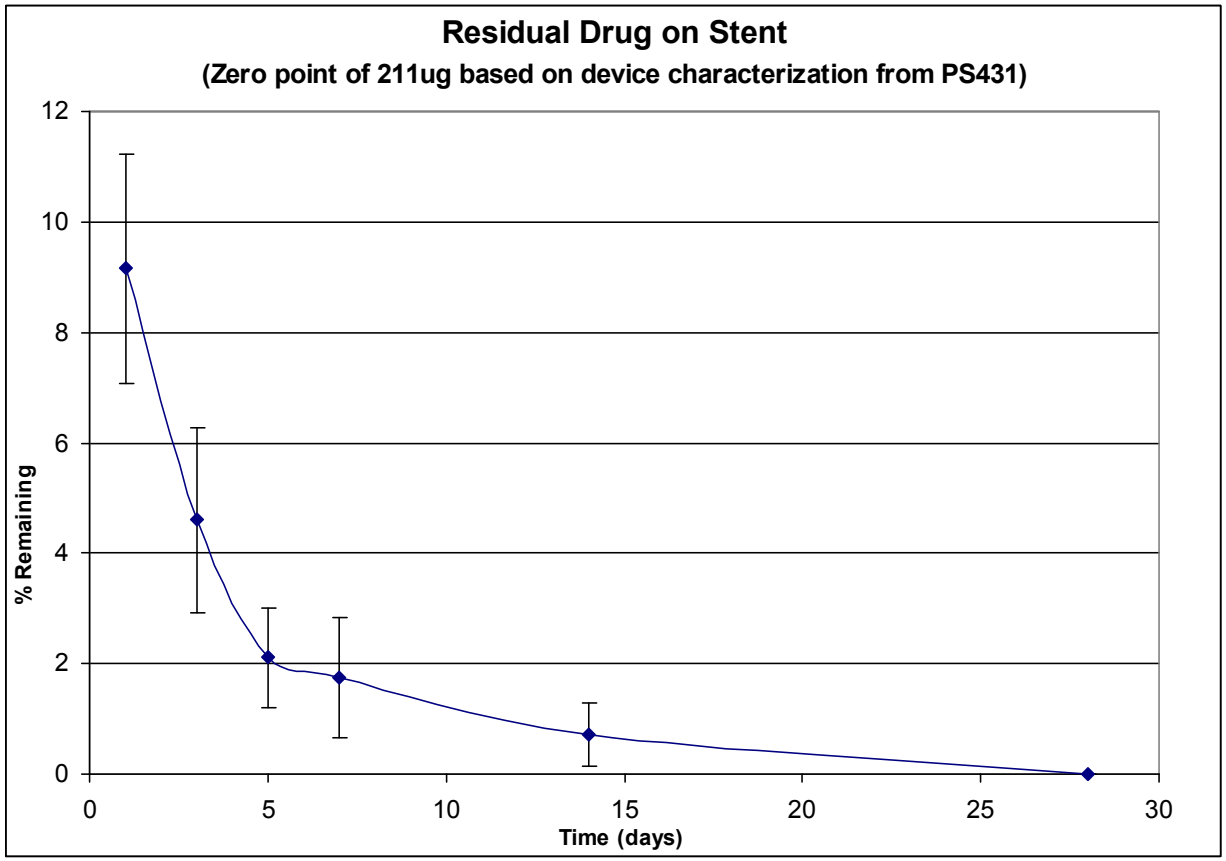
Elemental Analysis of a Drug Loaded Cross Section



Majority of the drug is on top of the metal coating

Nanoporous

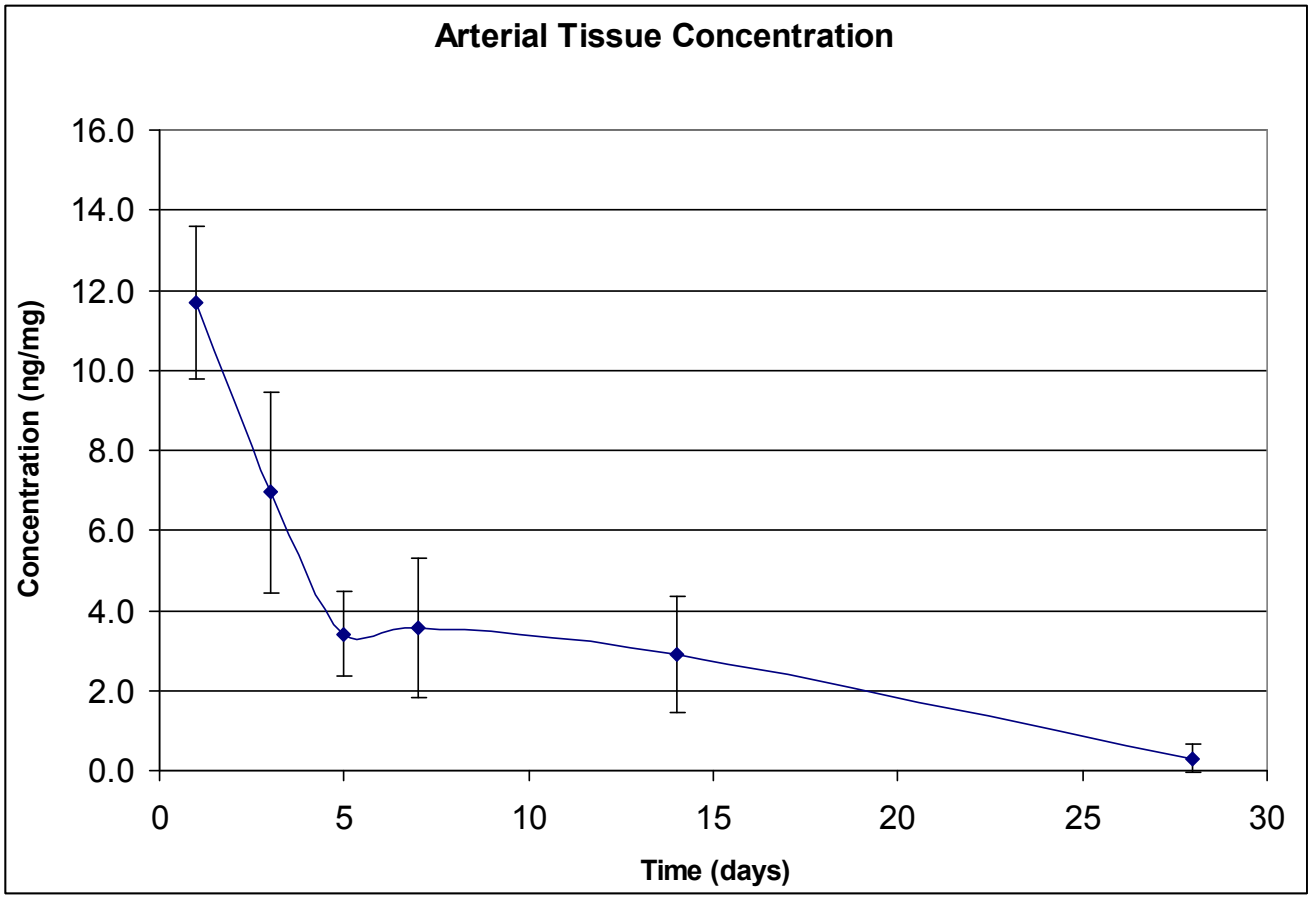
Drug Elution in porcine coronary artery model



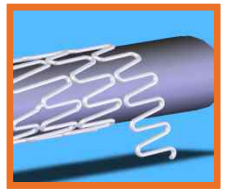
Current prototypes result in burst release—may make efficacy challenging

Nanoporous

Drug Elution in porcine coronary artery model



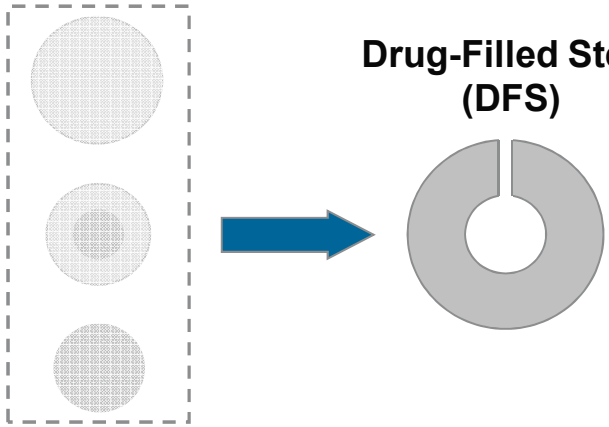
Current prototypes result in burst release—may make efficacy challenging

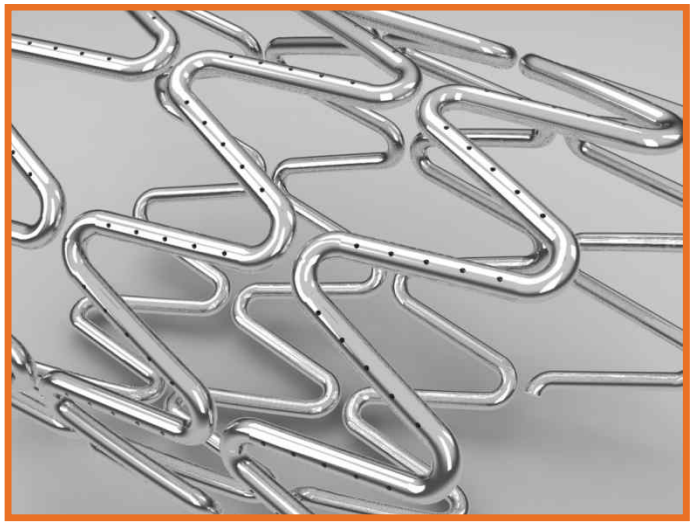


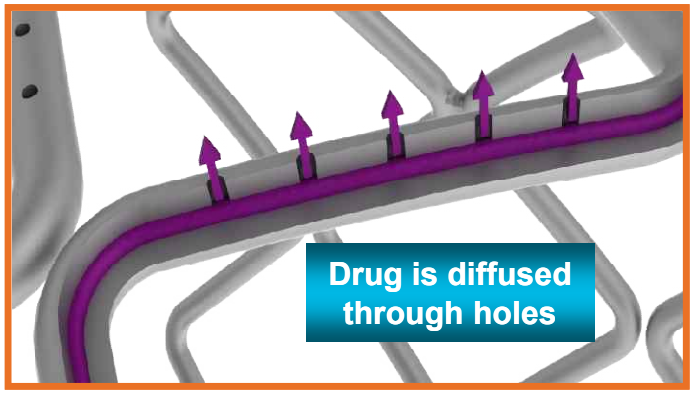
Drug Filled Stent

Continuous Innovation

Drug-Eluting Stents



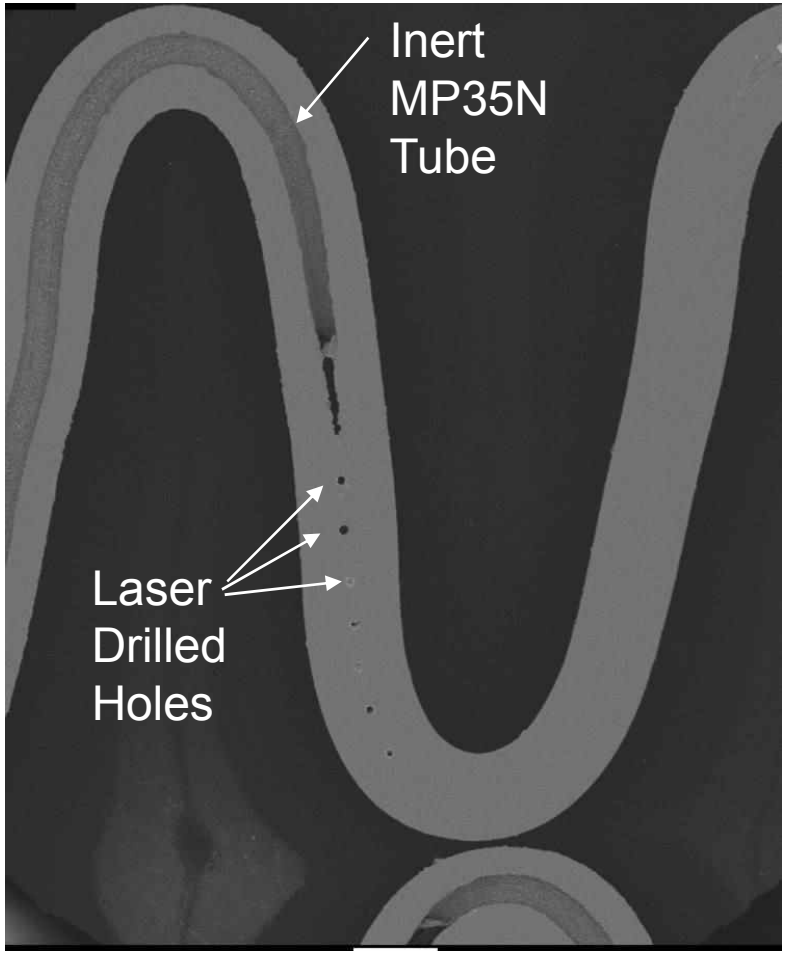




- Hollow core stent filled with drug
- Drug released through diffusion physics
- The size and number of holes allows for controlled and tailored drug elution profiles
- BMS surface is left behind (no Polymer)

Caution: New technologies and product concepts discussed in this presentation are not approved for sale or commercial use.

Medtronic Drug Filled Stent (DFS)

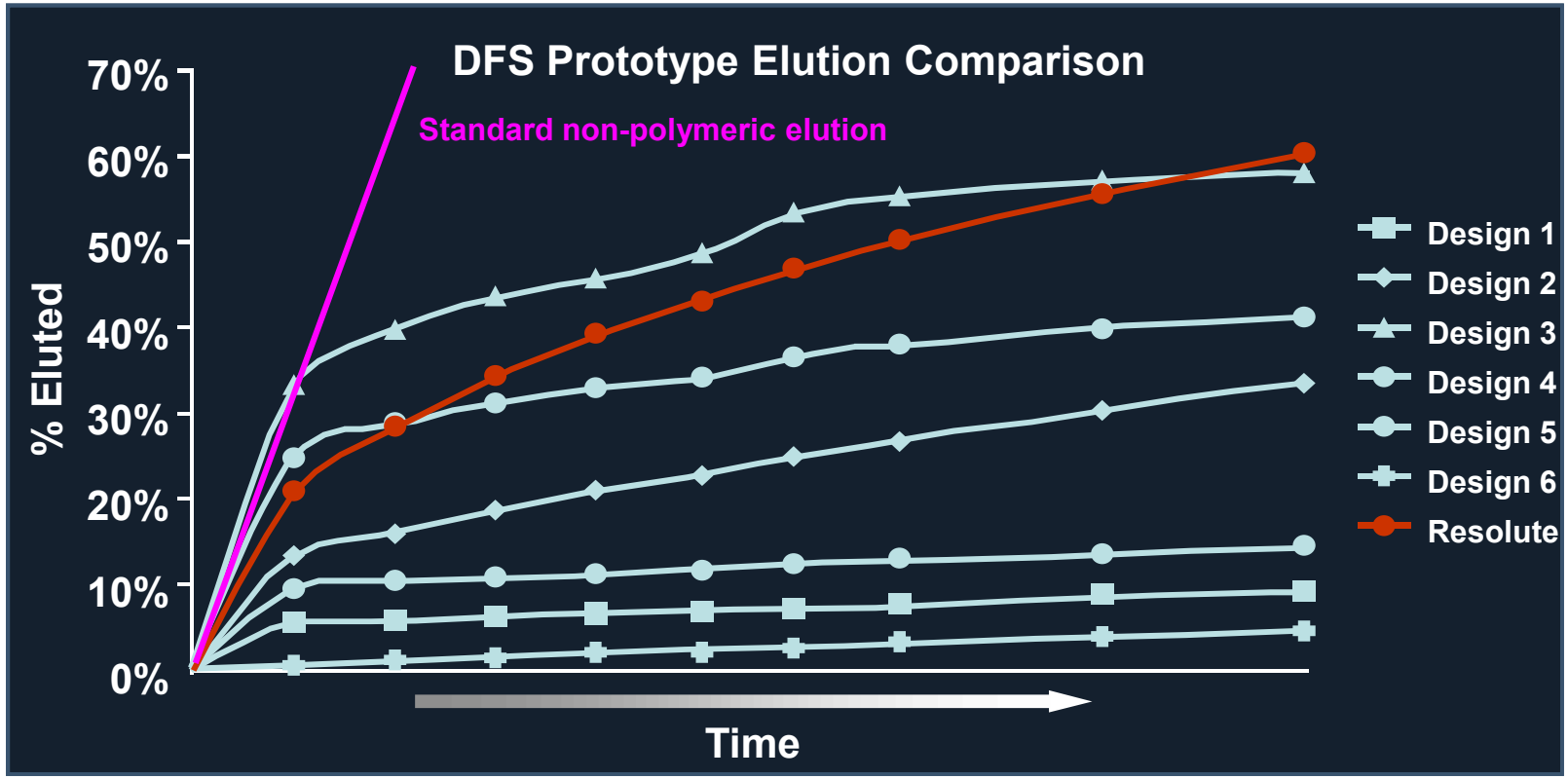


Designed to Address All Issues That Have Challenged Various DES Approaches

- Essentially a BMS surface
- Targeting previous drug carrier concerns:
  - Polymer biocompatibility ***(no polymer)***
  - Inflammation upon polymer degradation ***(no polymer)***
  - Surface coating durability ***(no surface coating)***
- Allows for controlled, prolonged, and tailored elution profiles
  - Has not been possible with other non-polymeric approaches

Medtronic Drug Filled Stent (DFS)

Controlled Elution



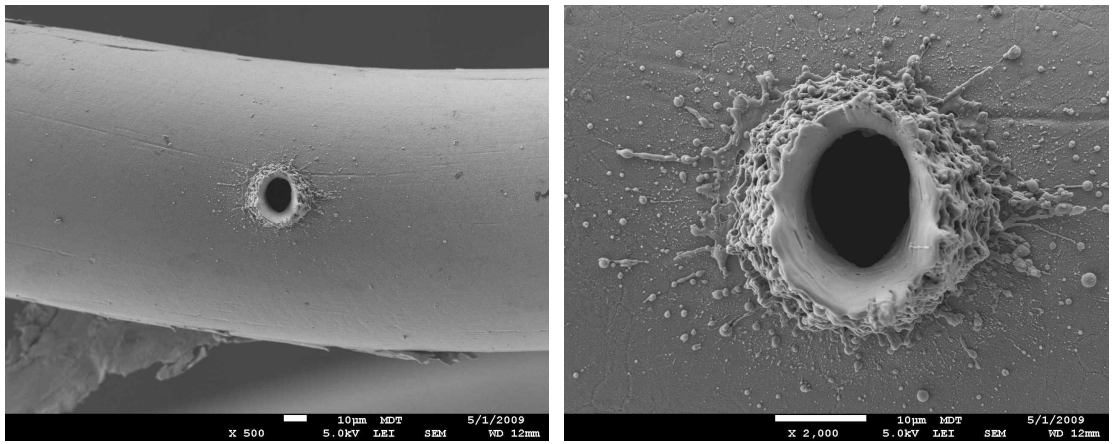
Preliminary testing suggests a variety of elution profiles possible

Development Progress

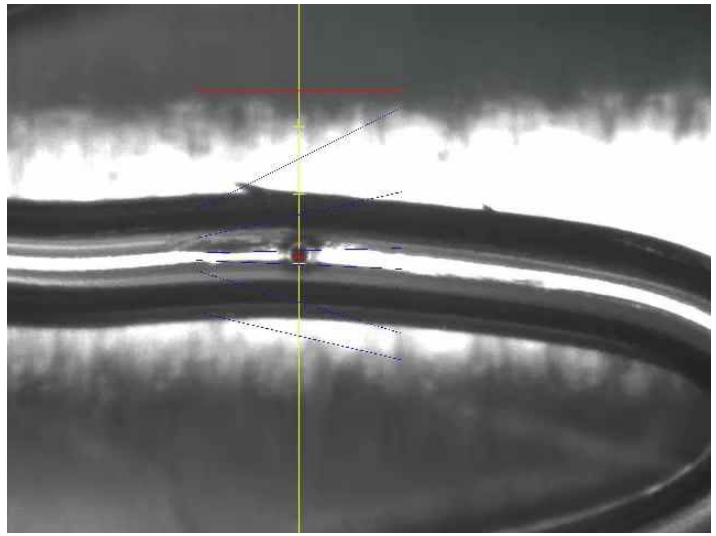
Major advancements in key milestones

- **Stent Forming**
- **Drilling**
- **Filling**
- **Eluting**
- **Testing**

Initial Prototypes



January 2010 Prototypes



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NANOPARTICLES AND NANOMATRIX
Future of the Nano technology for DES

- The motivation for nanoparticles and nanomatrix technology for DES is to continue improve safety and if possible efficacy.
- Nanoparticles can penetrate deeper to the vessel wall and improve efficacy
- Nanomatrix may offer a substitute to a polymer and enable the freepolymer concept
- There are challenges in terms of the capacity of the surface to carry suficient drug and the pharmacokinetics of the technology
- While preclinical trials support the efficacy
- The future of the technology will depend on clinical performance and prove that enhance endothelialization will be associated with freedom form prolonged DAPT

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