Sirolimus Coated Balloons in the Coronary Artery

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Disclosures

Grant/Research/Clinical Trial Support

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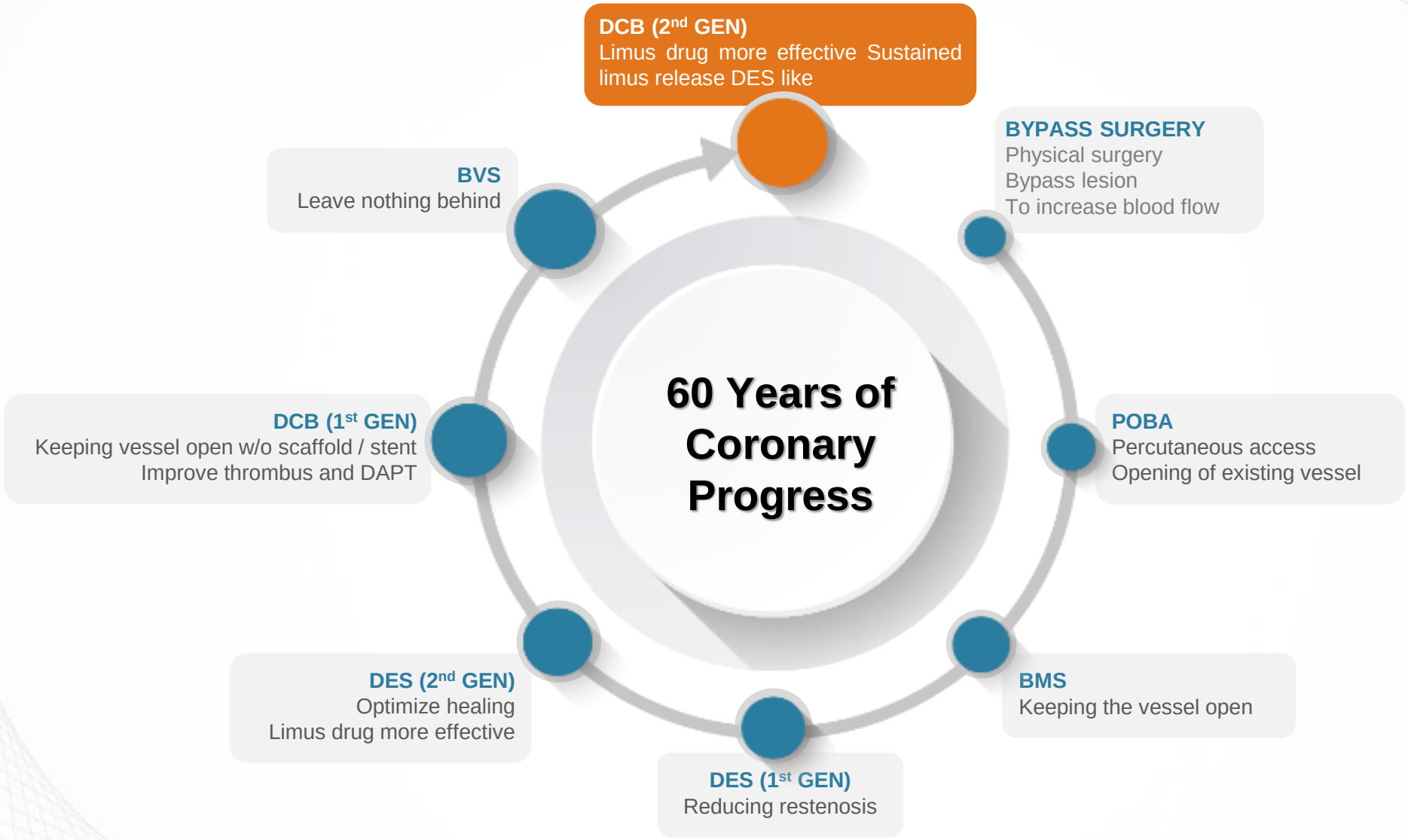
Speaker's Bureau

Abbott Vascular; Boston Scientific; Cook Medical;

Consultant/Advisory Boards

Boston Scientific; Medtronic; Cook Medical;

60 years Coronary Progress…



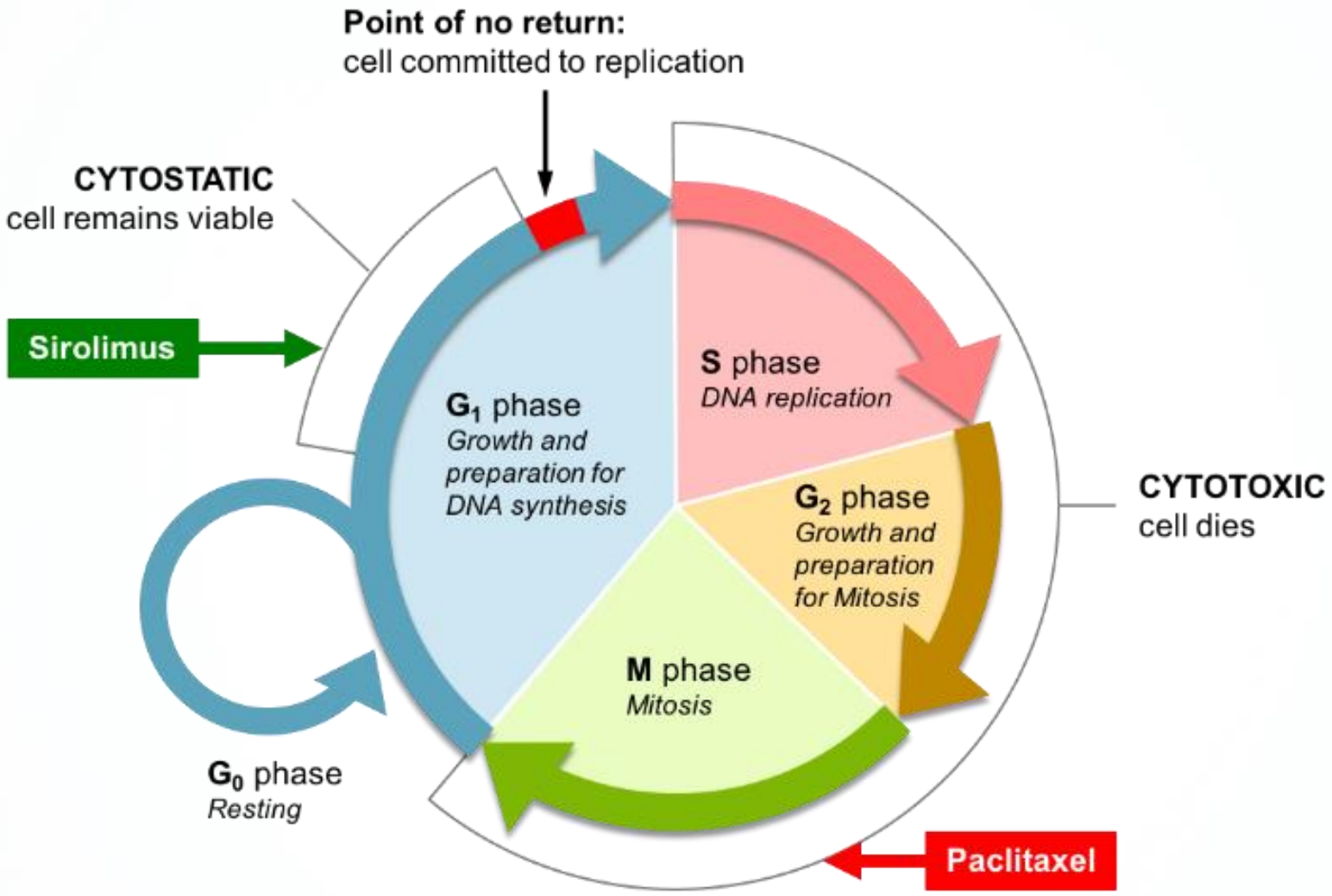
CE Mark and FDA Approved Drug coated Balloon Devices (Coronary Artery)

Common anti-restenotic drug for DCB is **Paclitaxel**

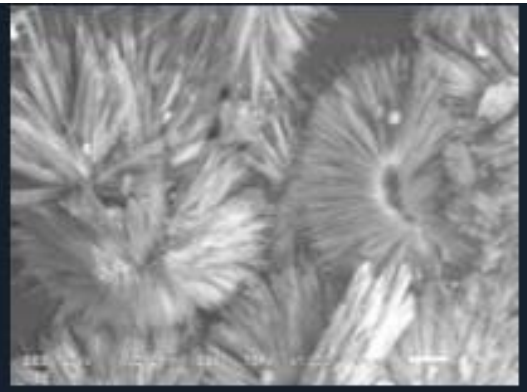
Product	Company	Drug	Drug dose ($\mu g/mm^2$)	Excipient
Elutax SV	Aachen Resonance, Luxembourg,	Paclitaxel	2.0	None
SeQuent Please	B. Braun, Melsungen, Germany	Paclitaxel	3.0	Iopromide
Biostream	Biosensors, Jalan Tukang, Singapore	Paclitaxel	3.0	Shellac
Pantera Lux	Biotronik, Buelach, Switzerland	Paclitaxel	3.0	Butyryl-tri-hexyl Citrate
Agent*	Boston Scientific, Marlborough, MA, USA	Paclitaxel	2.0	Acetyl-tri-butyl Citrate
Restore / Primus	Cardionovum GmbH, Bonn, Germany	Paclitaxel	3.0	Shellac
Support C	Eucatech, Weil am Rhein, Germany	Paclitaxel	3.0	Butyryl-tri-hexyl citrate
DIOR / BioStream	Eurocor / Biosensors	Paclitaxel	3.0	Shellac
Essential	iVascular, Barcelona, Spain	Paclitaxel	3.0	Organic ester
IN.PACT Falcon	Medtronic vascular, Santa Clara, CA, USA	Paclitaxel	3.5	Urea
Danubio	Minvasys, Genn evillers, France	Paclitaxel	2.5	Butyryl-tri-hexyl Citrate
SELUTION*	**Med Alliance, Irvine, CA, USA**	**Sirolimus**	**1.0**	**Cell adherent technology**
Magic Touch*	**Concept Medical, Surat, India**	**Sirolimus**	**1.27**	**Nanolute technology**

* US IDE Studies approved for ISR (enrolling) and De Novo (planning)

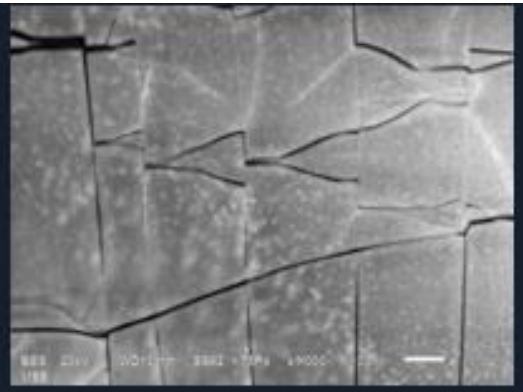
Mode of Action in Sirolimus and Paclitaxel



Paclitaxel Formulation Types
Impact on Biological Performance



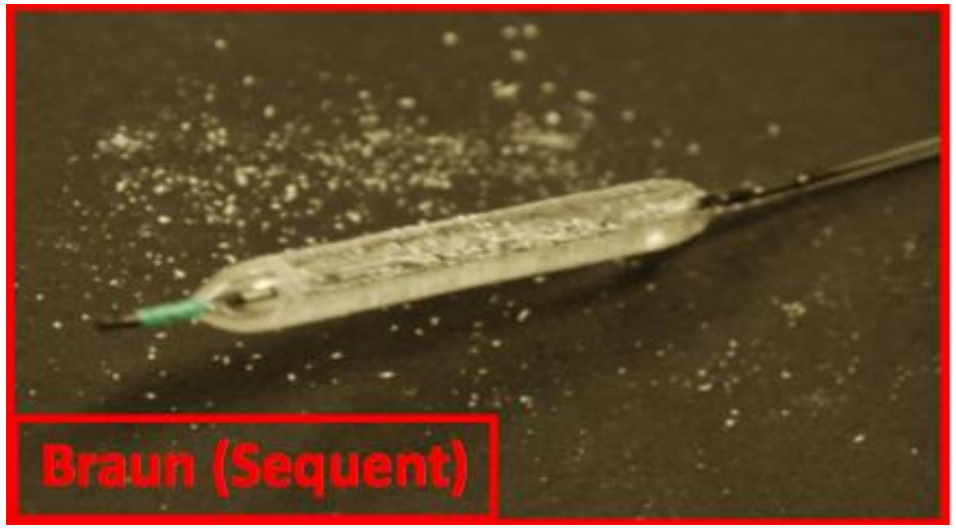
Crystalline Coating



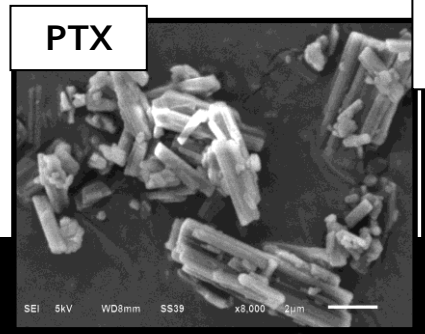
Amorphous Coating

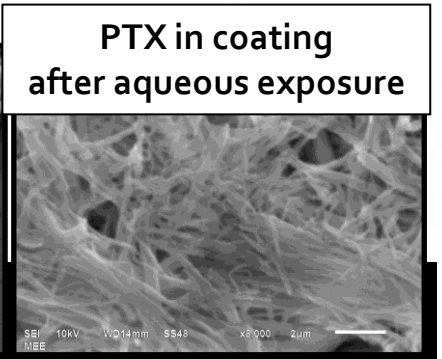
	Crystalline	Amorphous
Particles Released	+++	++
Uniform Coating	++	+++
Drug Transfer to Vessel	+++	+++
Drug Retention vs. Time	+++	+
Biological Effectiveness	+++	++
Vascular Toxicity	+++	++

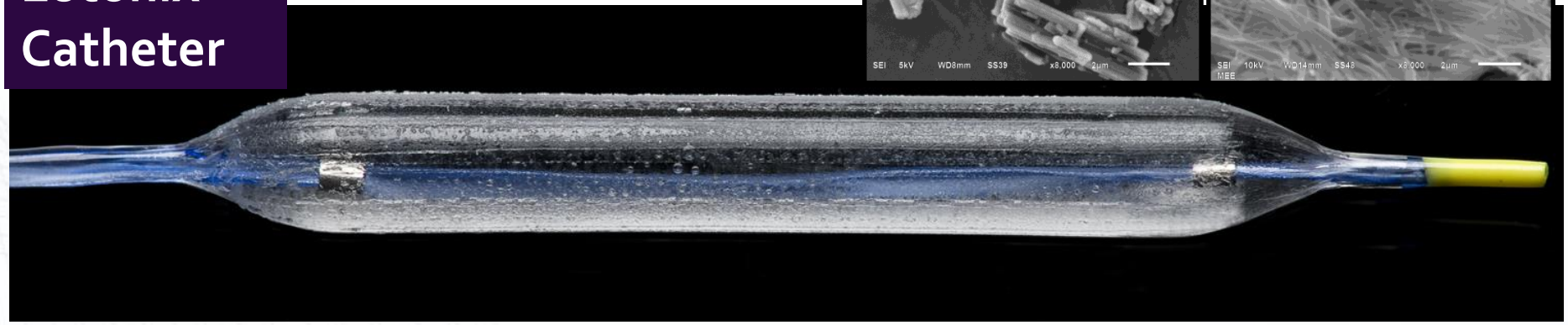
Coating Integrity is Variable



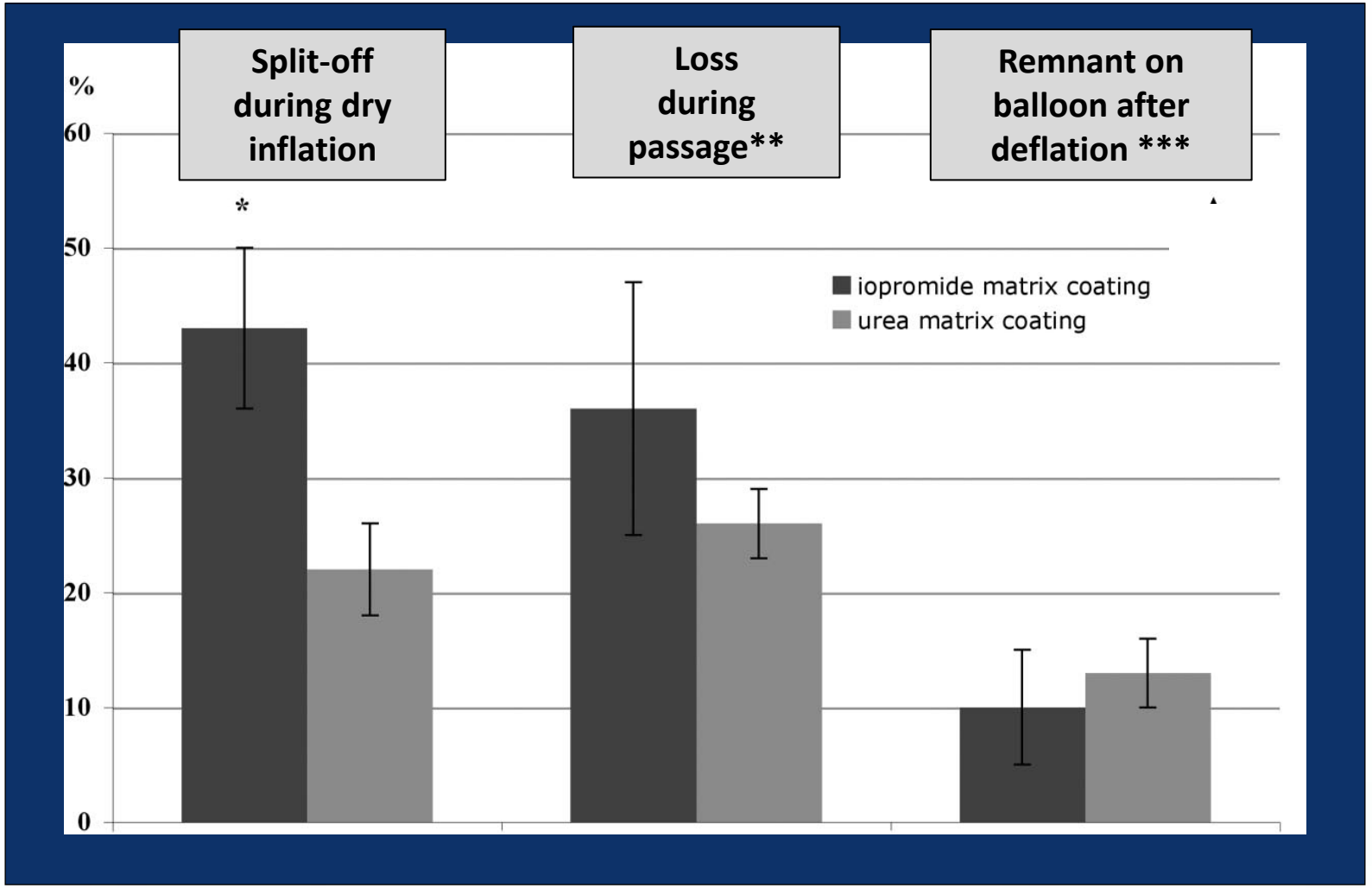
Lutonix Catheter





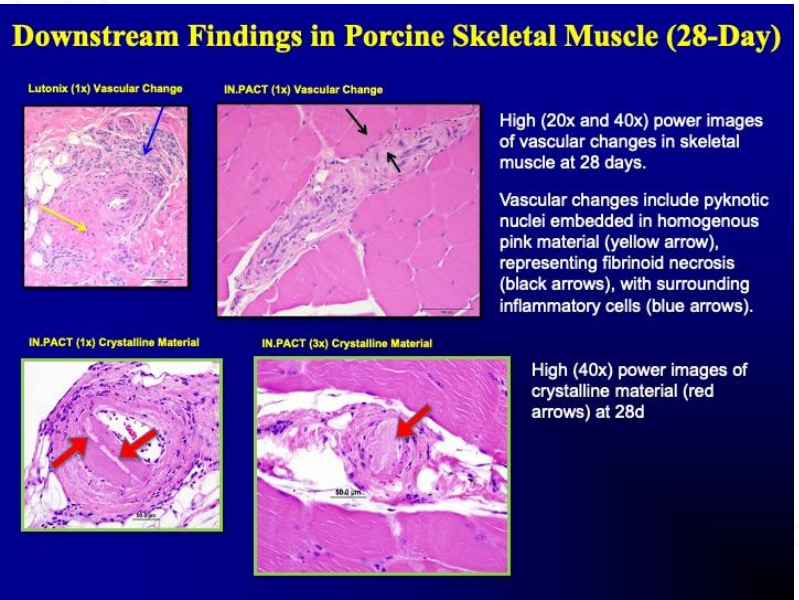


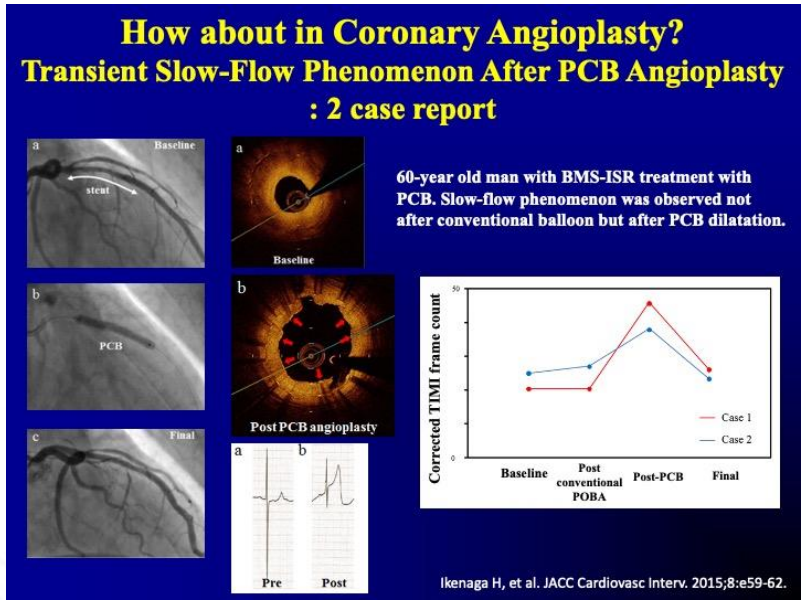
PTX Adherence to Balloon: iopromide versus urea coating

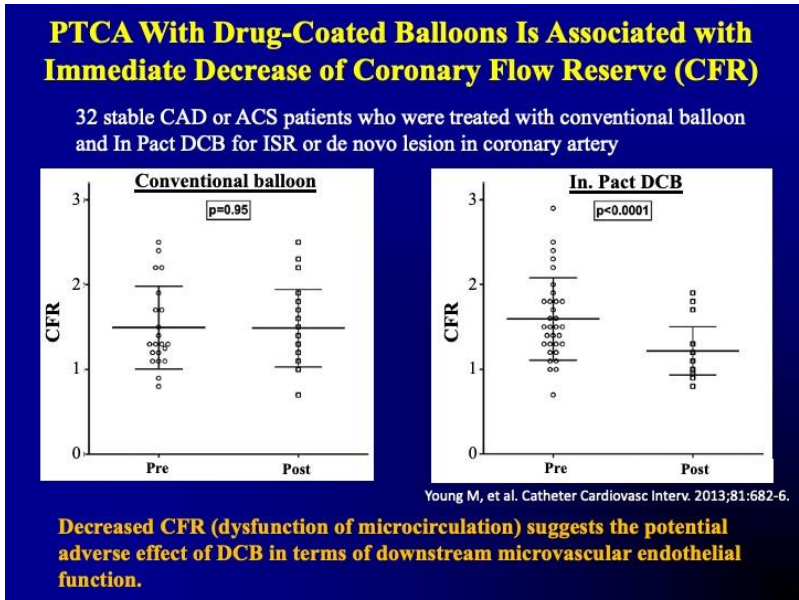


Kelsch et al. Invest Radiol. 2011;46:255-

- Sirolimus is the standard for coronary artery disease treatment via DES and proven to be safe and effective
- Ptx modifications (crystalline form) means coating integrity and transfer are variable with substantial portion lost downstream into blood and tissues
- Loss of Ptx into body remains a significant safety concern which was further exacerbated by Katsanos analysis in published in JAHA







Sirolimus DCB

- **What are the differences between sirolimus and paclitaxel?**
- **Which is the better drug of choice, sirolimus or paclitaxel?**

Differences between Sirolimus and Paclitaxel

Sirolimus offers potential benefits over Paclitaxel

Attribute	Sirolimus (or Analogs)	Paclitaxel
Mode of action	Cytostatic	Cytotoxic
Margin of safety	10’000 fold	100 fold
Therapeutic range	Wide	Narrow
Anti-restenotic	Yes – lower late lumen loss	Yes
Anti-inflammatory	Yes	No
Tissue absorption	***Slow***	***Fast***
Tissue retention	***Short***	***Long***

Sirolimus is *drug of choice* for coronary DES supported by solid clinical based evidence.

(*Wessely R, et al. J Am Coll Cardiol. 2006)*

Sirolimus Coated Balloons – Technical challenges

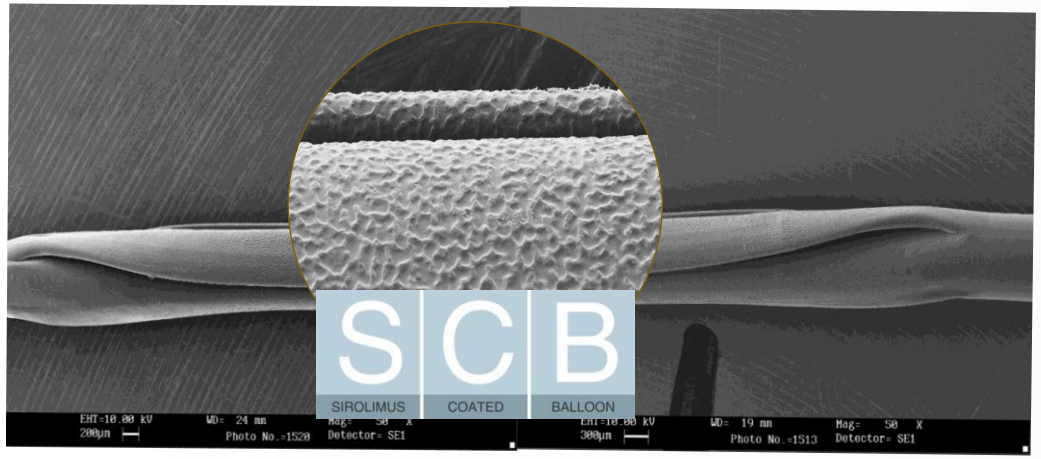
In order to Demonstrate efficient transfer and sustained tissue drug levels mechanisms of delivery may be even more complex than required for Ptx

The effect of excipients and carriers need to be closely examined

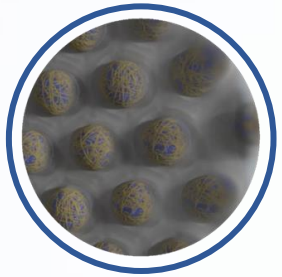
- Enhance tissue absorption
  - Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently
- Extend tissue retention
  - Sirolimus must be continuously delivered over time, so some form of “time release mechanism” must be employed to maintain therapeutic levels

MAGIC TOUCH – Sirolimus Coated Balloon

- MAGICTOUCH® – SCB is Sirolimus Coated Balloon to treat coronary artery disease
- Delivers drug in 60 seconds
- Sub-micron phospholipid particles which encapsulate sirolimus

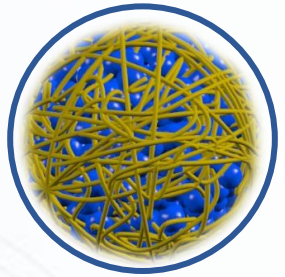


The device: SELUTION SLR™ designed to embrace Sirolimus & overcome the technological challenges



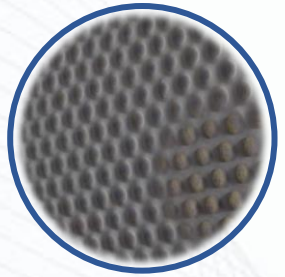
Proprietary MicroReservoir Technology

- Creation of MicroReservoirs combining sirolimus & biodegradable polymer
- Sirolimus - a proven safe & effective cytostatic drug
- Offering a wider therapeutic range



MicroReservoirs: Miniature Drug-Delivery

- Optimal size MicroReservoirs to achieve pharmaco- kinetic release profile comparable to best in class DES
- Consistent and predictable drug release
- Sustained therapeutic effect for up to 90 days[1]



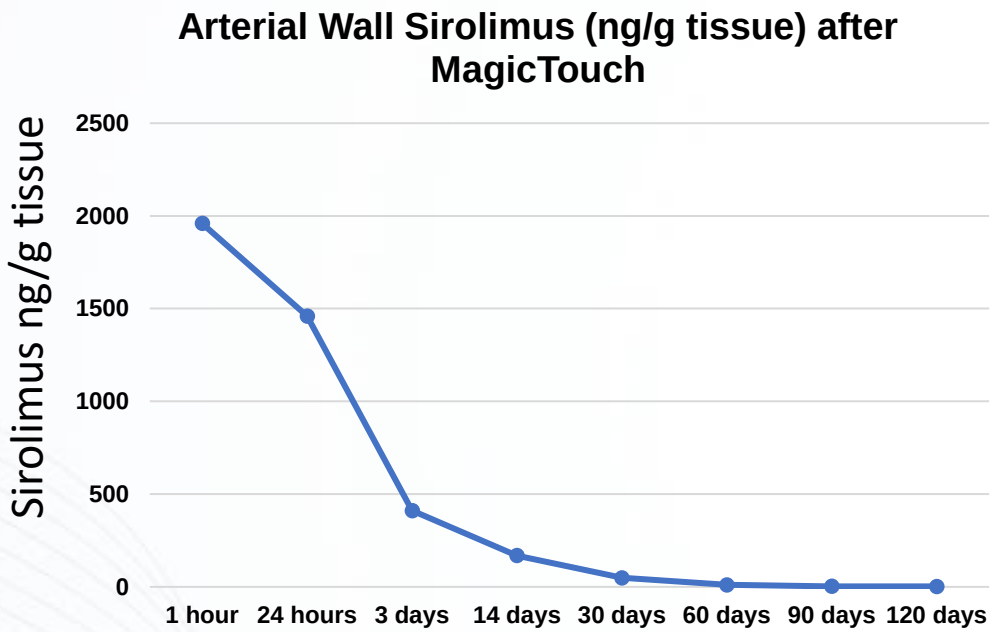
Cell Adherent Technology (CAT™)

Proprietary amphipathic lipid technology which binds MicroReservoirs to the balloon surface

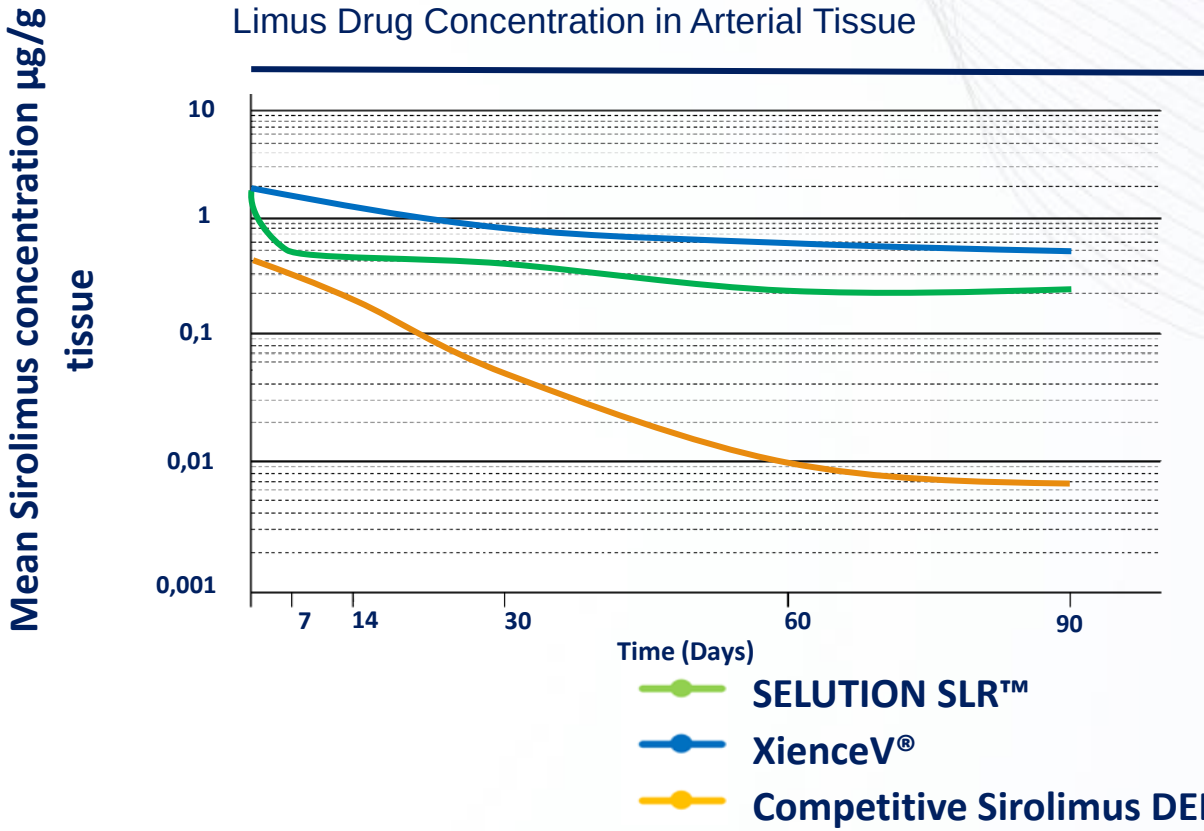
- Contains and protects micro-reservoirs during insertion and inflation
- Enhances drug retention and bioavailability, allowing for a lower drug dose concentration on the balloon surface (1 µg/mm²)
- Optimizes transfer of MicroReservoirs to the tissue and maximizes the cellular uptake of sirolimus

1.Drug concentration evident in MicroReservoirs and tissue - Data on file at M.A. Med Alliance SA

MagicTouch Coronary PK



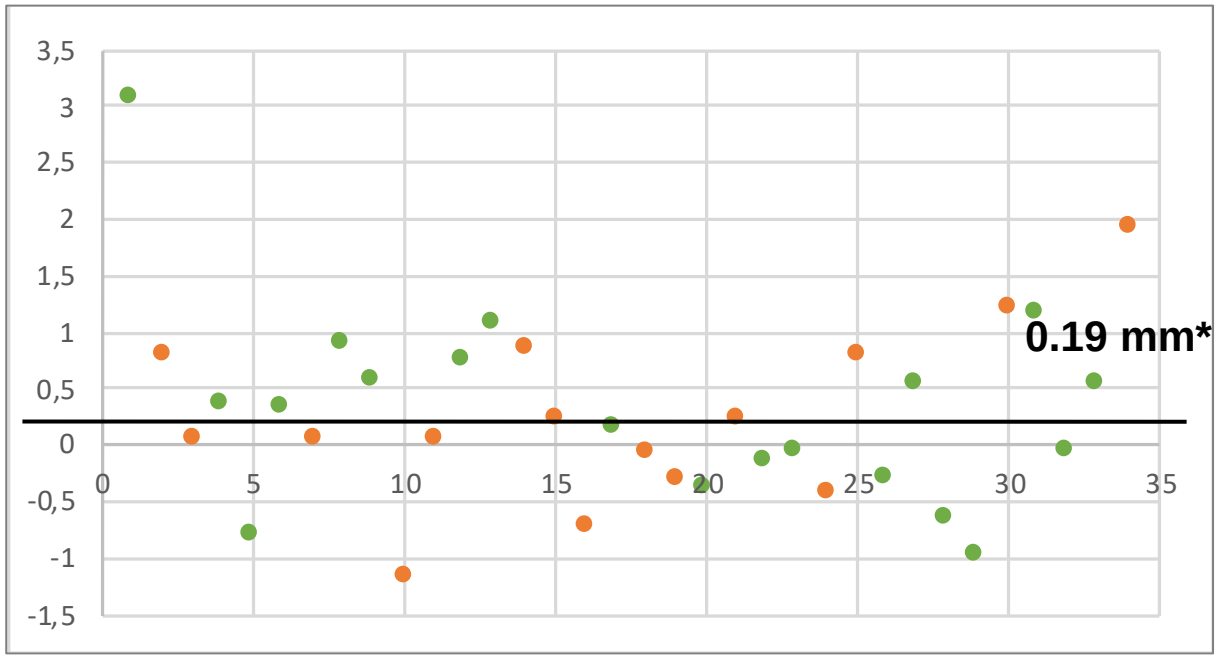
SELUTION PK



Efficacy confirmed in different vascular beds

FIM SELUTION SFA

Late Lumen Loss @ 6 mo
(n = 34)

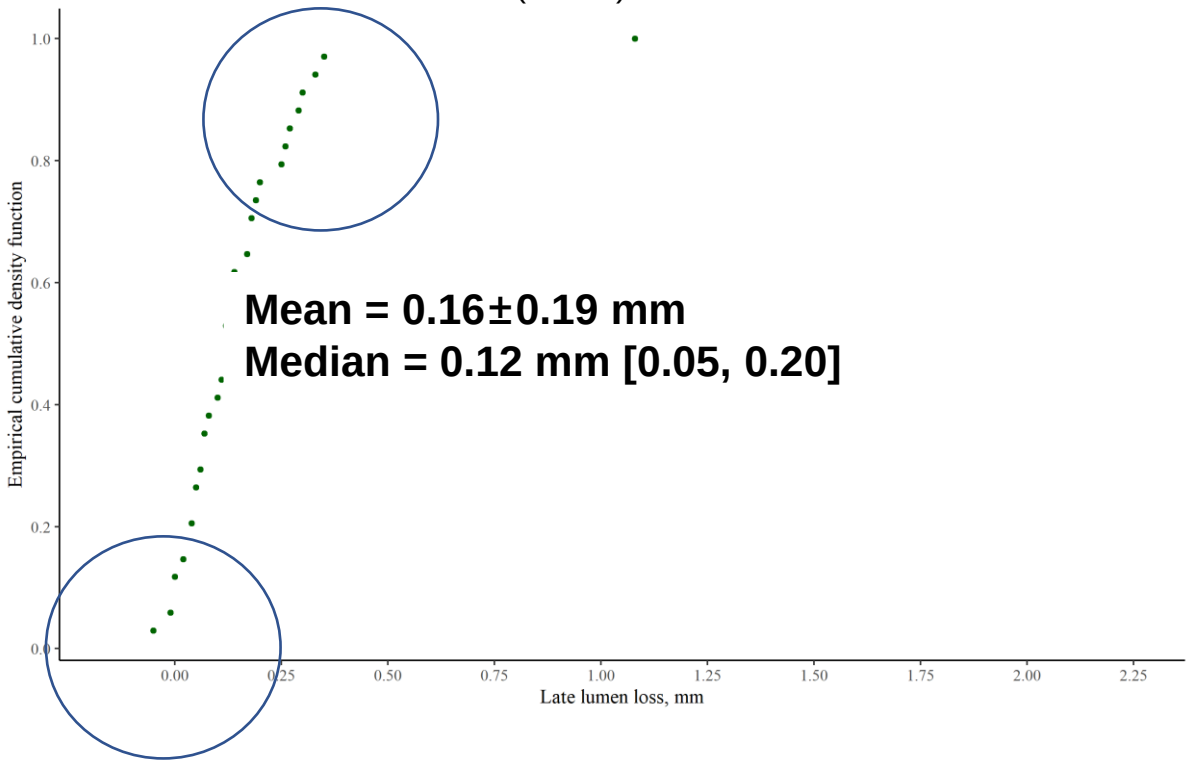


- Calcified Target Lesion (CoreLab assessed by 360 score)

*Late Lumen Loss presented as median value

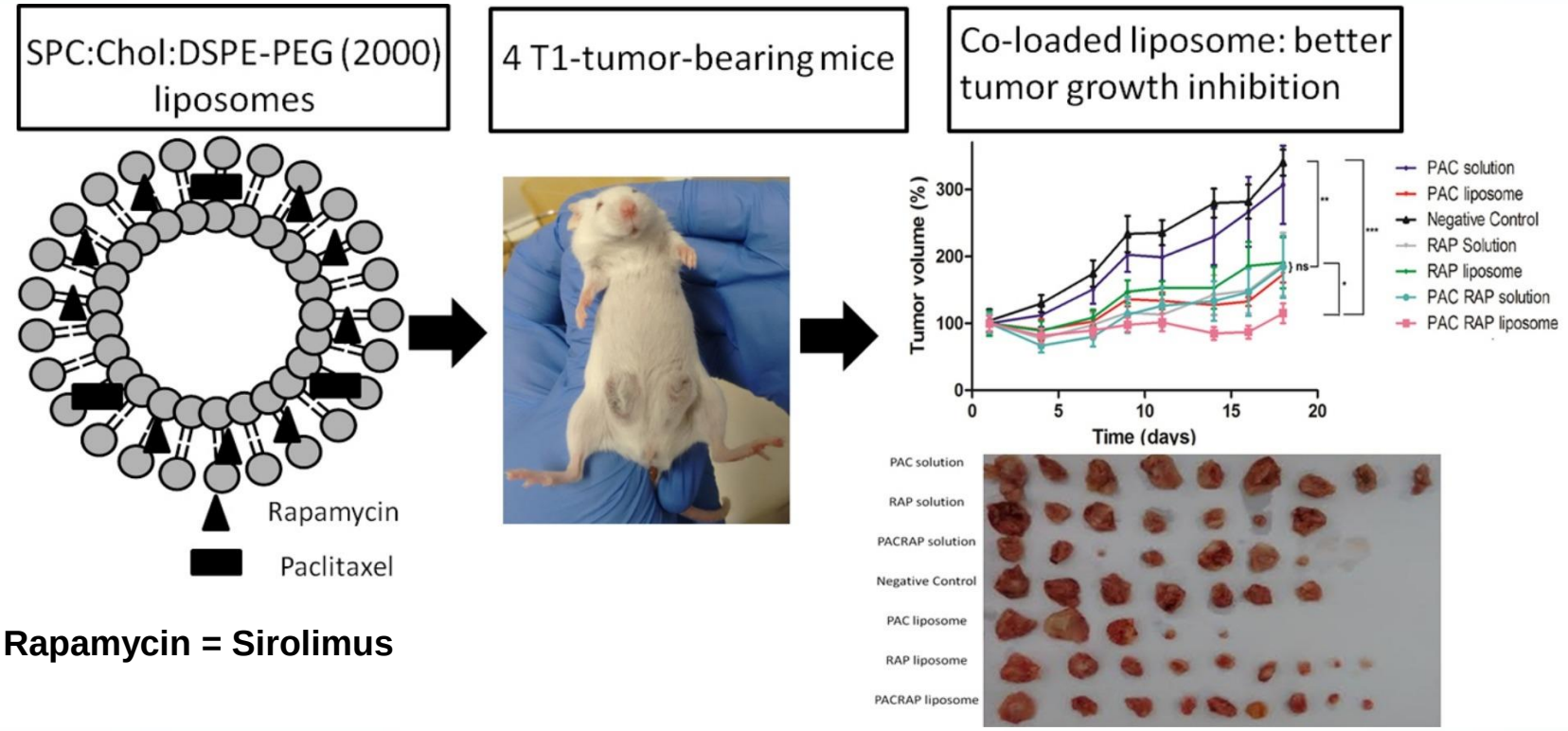
FIM SELUTION De Novo Coronary

Late Lumen Loss @ 6 mo
(n = 34)



Combination Use of Paclitaxel and Sirolimus

- Conventional drug coated balloons are composed of mainly a single drug, such as Paclitaxel or Sirolimus.
- The combinational use of Sirolimus and Paclitaxel has been shown to have a synergistic effect in clinical trials for cancer treatment.



Rapamycin = Sirolimus

Josimar O, et al. Colloids Surf B Biointerfaces. 2016

Sirplux™ (Dual-API DCB)

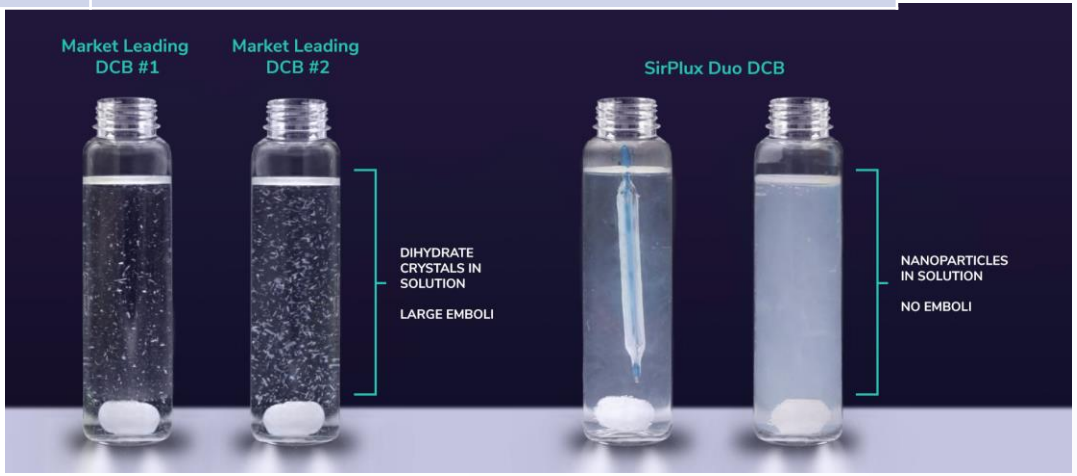
Sirolimus and Paclitaxel Dual Active Pharmaceutical Ingredients

	Dual-API	Conventional DCB
Type of drug	Combination of Paclitaxel and Sirolimus	Single drug (Paclitaxel or Sirolimus)
Drug dose (ug/mm^2)	1.5	2.0-3.5
Excipient	biodegradable functionalized nanoparticles (f-NP)	Urea Polysorbate/sorbitol Polyethylene glycol
Flaking on bench test	Less	Large
Indication	-	Peripheral and coronary artery

- **Sirolimus** Sirolimus IC_{50} = 29,066 ng/mL
- **Paclitaxel** Paclitaxel IC_{50} = 1,156 ng/mL
- **SRL:PTX** SRL:PTX IC_{50} = 132 ng/mL

ACHIEVED SAME CELL VIABILITY, WITH 10X LESS PTX IN SOLUTION

Combination Index =0.14898
Strong Synergism



Combination Dual Drug Treatment Demonstrates Powerful Results

SirPlux Duo™ has over 20x Less Paclitaxel Than the Competition and More Sirolimus

Advanced NanoTherapies

SirPlux Duo™ 3.00x20

1.5 µg/mm² Total Drug Dose:

PTX = 28 µg

SRL = 254 µg

PTX

Medtronic

Prevail™ 3.00x20
3.5 µg/mm² - Total Drug Dose:
PTX = 660 µg

Boston Scientific

Agent™ 3.00x20
2.0 µg/mm² - Total Drug Dose:
PTX = 377 µg

SRL

MedAlliance
SWISS • MEDICAL • TECHNOLOGY

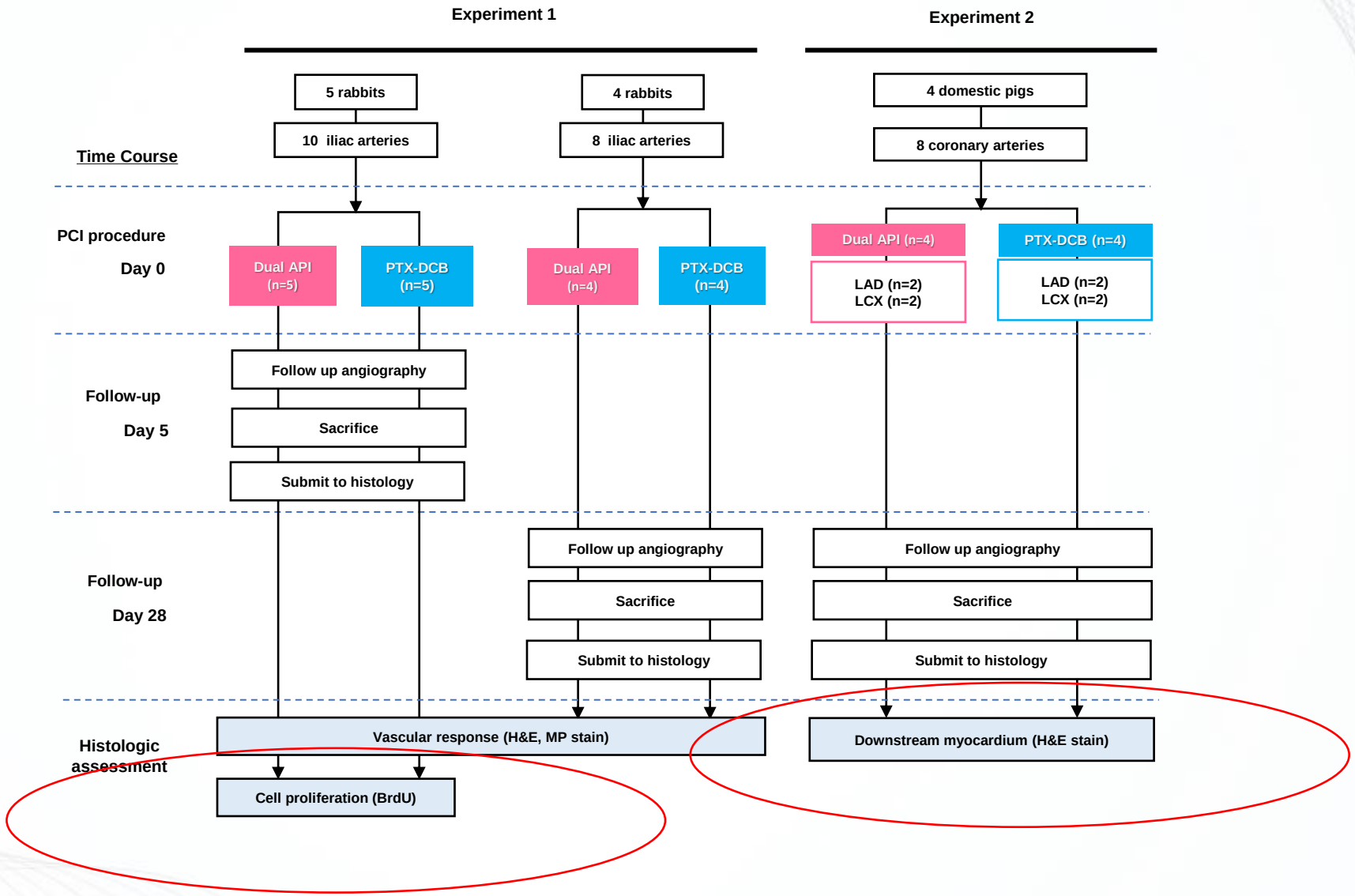
Selution™ 3.00x20
1.0 µg/mm² - Total Drug Dose:
SRL = 189 µg

Concept Medical™

Magic Touch™ 3.00x20
1.27 µg/mm² - Total Drug Dose:
SRL = 239 µg

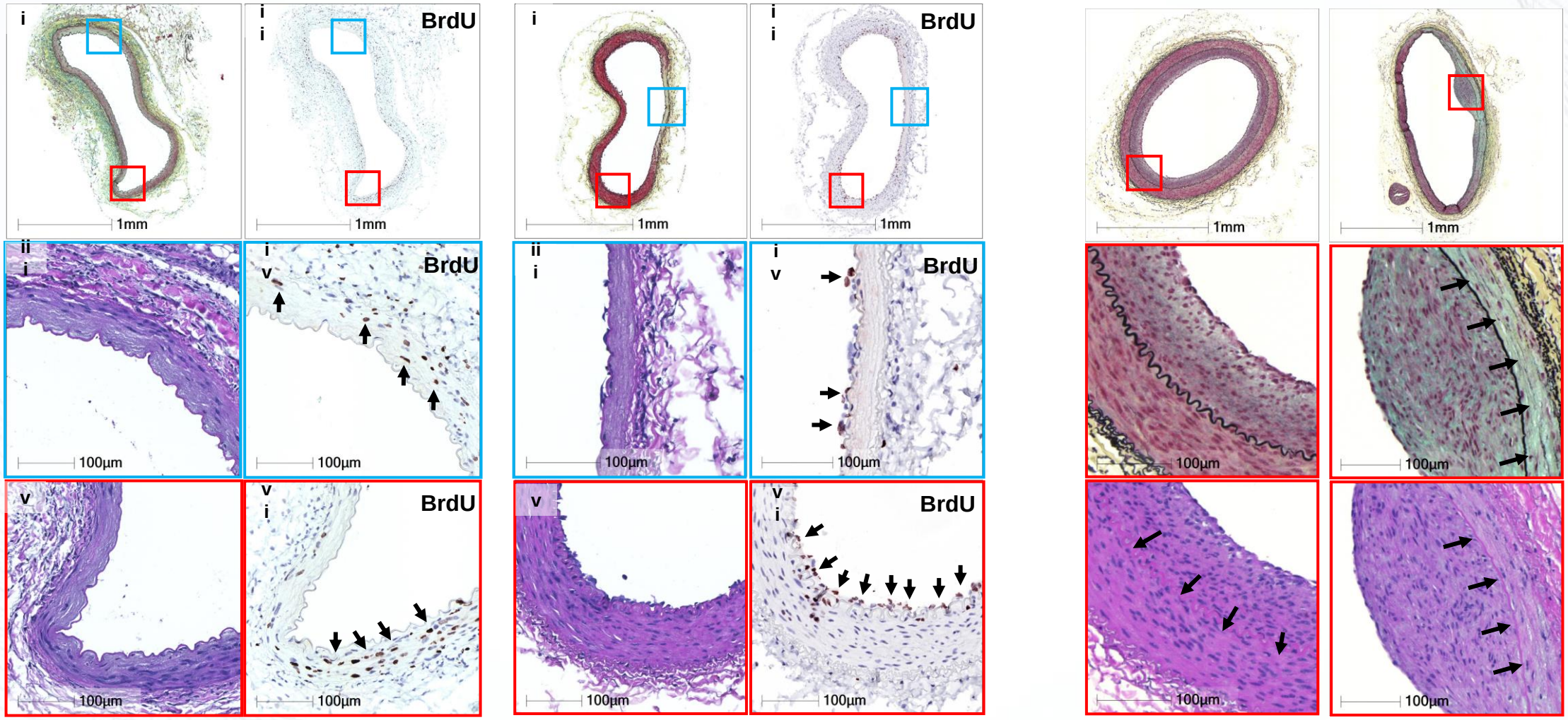
**Total drug doses calculated by multiplying target drug loading (µg/mm²) by surface area (mm²)*

SirPlux versus Conventional PTX-DCB



Representative histology 5 and 28 days after the treatment with Dual-API DCB and PTX-DCB

5 day (Rabbit iliac artery) 28 day



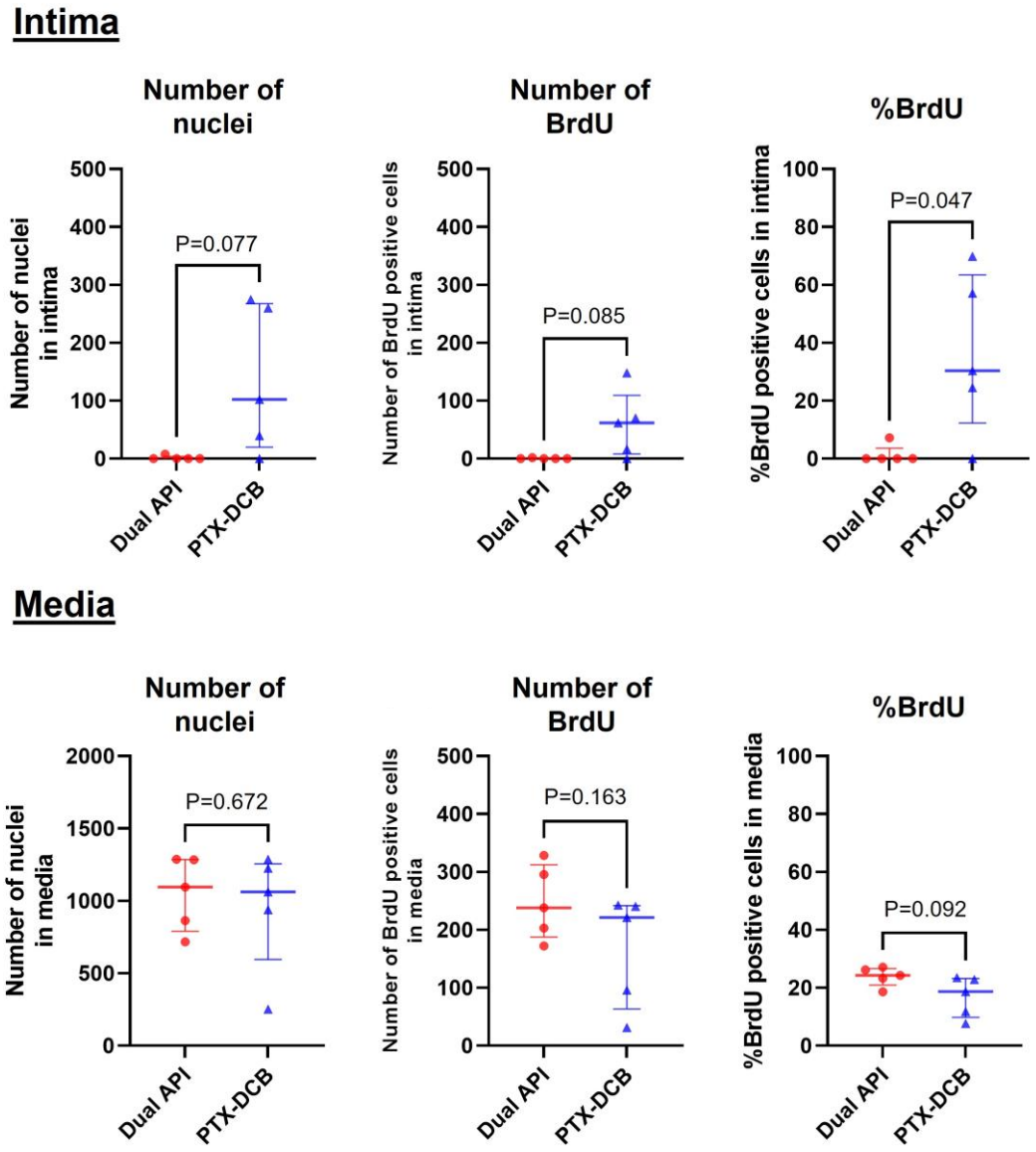
Majority of BrdU+ cells are in media

Majority of BrdU+ cells are in intima

Healed SMC loss

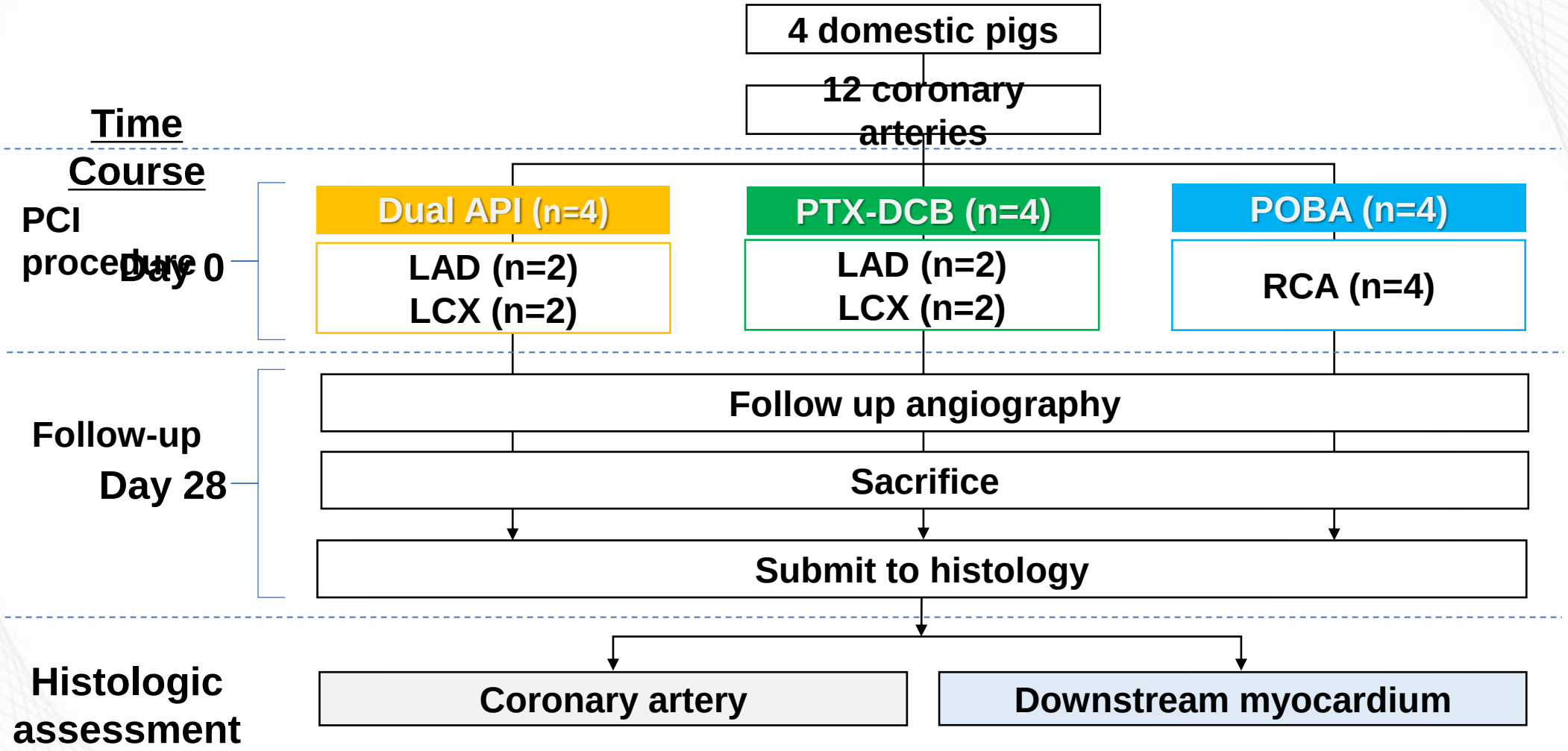
Residual SMC loss

Intimal cell proliferation at 5-day timepoint (Rabbit iliac model)



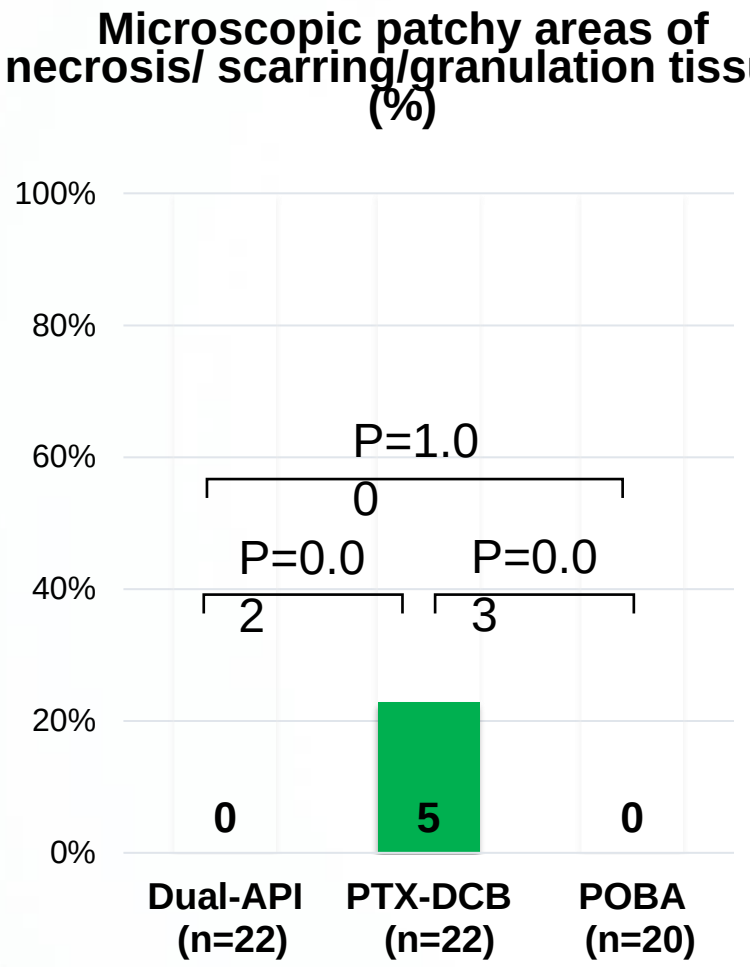
- Presence of BrdU positive cells reflects the presence of cell proliferation in the tissue.
- Percent BrdU positive cells showed less in Dual-API compared to PTX-DCB for both intima

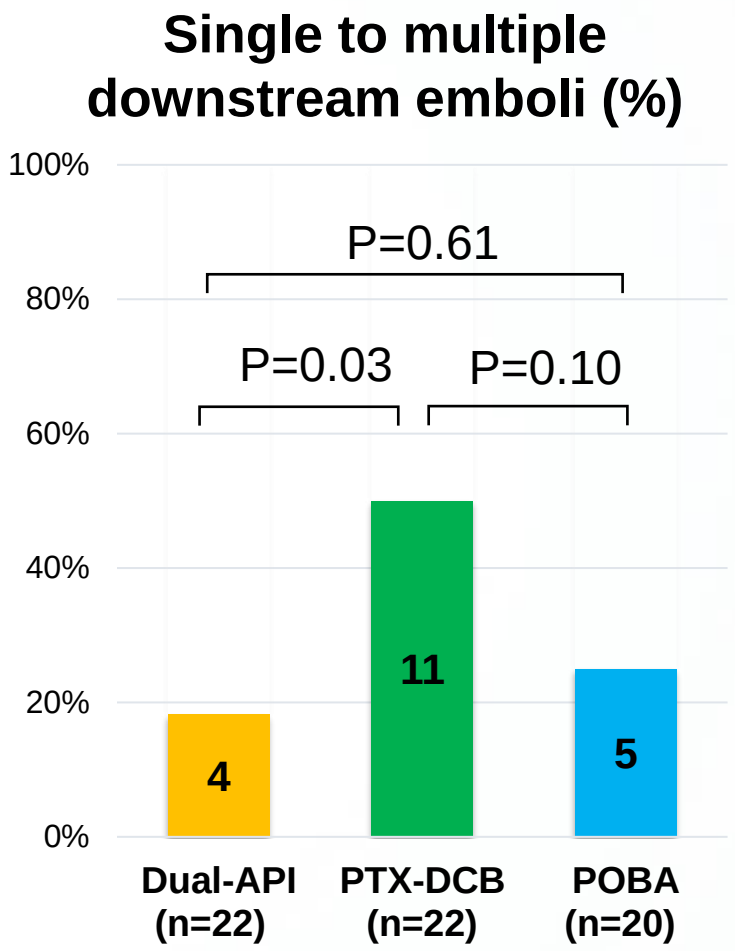
Study Flow


4 domestic pigs
12 coronary arteries
Time Course
PCI procedure
Day 0
Dual API (n=4)
LAD (n=2)
LCX (n=2)
PTX-DCB (n=4)
LAD (n=2)
LCX (n=2)
POBA (n=4)
RCA (n=4)
Follow-up
Day 28
Follow up angiography
Sacrifice
Submit to histology
Histologic assessment
Coronary artery
Downstream myocardium

Histology Results for Downstream Myocardium

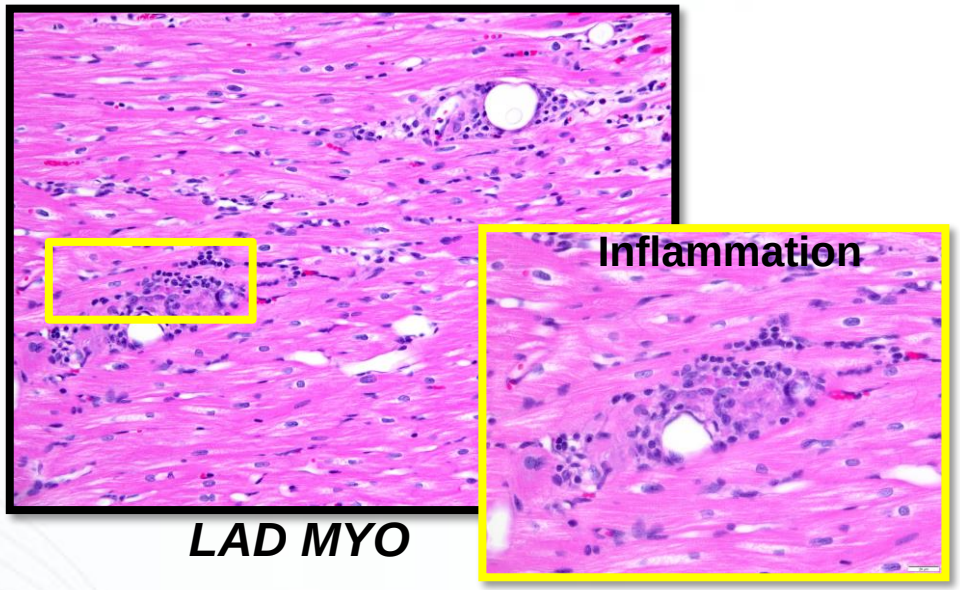
A total of 64 histology sections were analyzed for downstream myocardium.

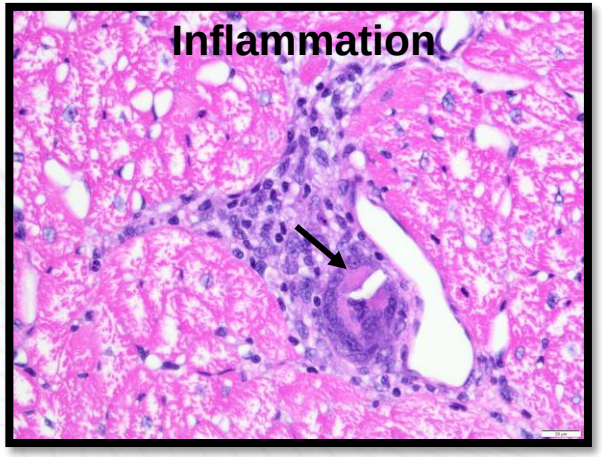




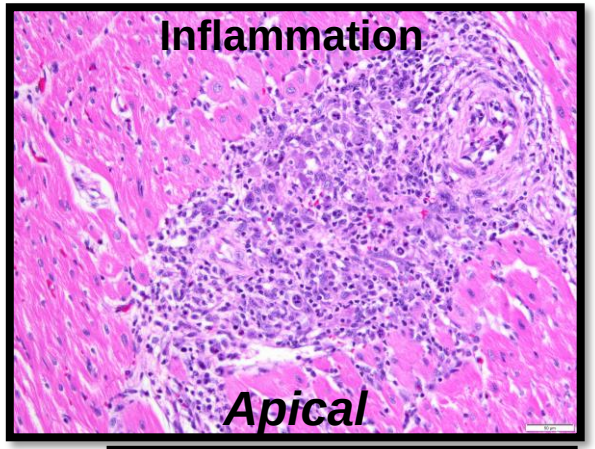
Representative Histology of Downstream Myocardium After the Treatment with Dual API and Agent DCB

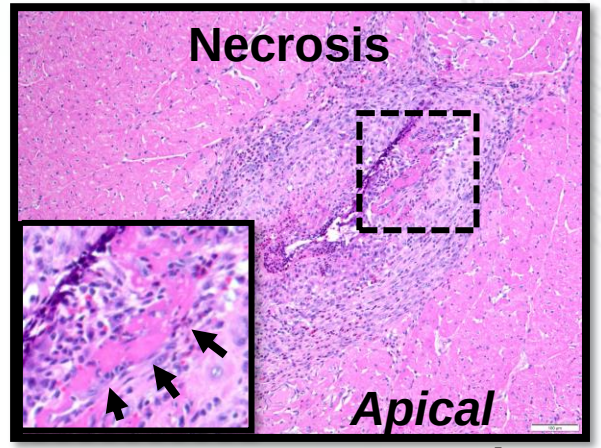
Dual-API

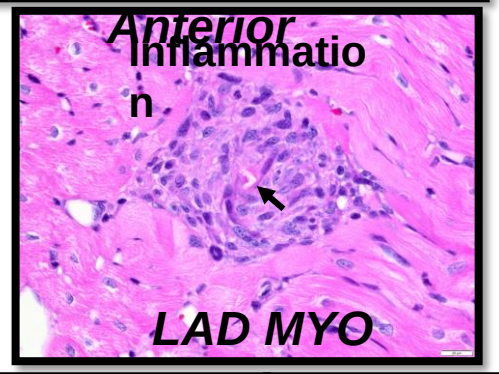


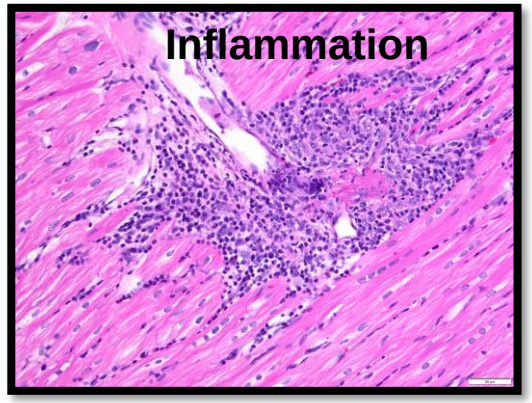


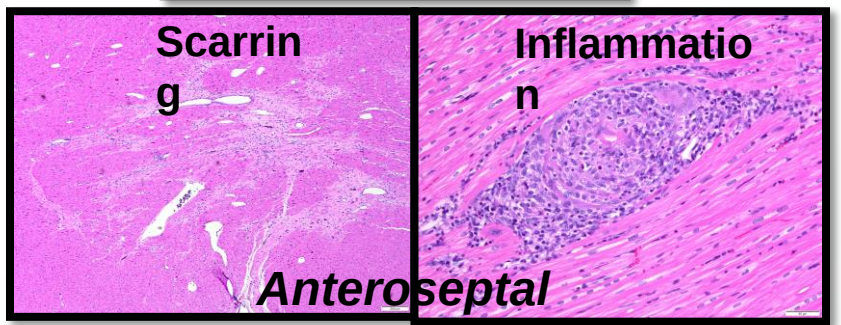
PTX-DCB











Conclusion

- DCB technology continues to evolve as it matures for peripheral applications but is relatively nascent for coronary applications
- PTX-DCB are effective but come with risks of inefficient PTX transfer with loss into body and into non target downstream beds of crystalline PTX
- Sirolimus coated balloons have yet to be approved but FDA but represent an important development in DCB technology but their effectiveness remains to be proven
  - Sustained release of limus remains an important challenge with most SCB employing polymer or nanoparticle carriers
- The Dual-API DCB (Sirplux™) device offers the advantage of using a combination of sirolimus and PTX (10:1) ratio encapsulated within nanoparticles.
  - Offers synergy between both anti-proliferative drugs each with its own MOA
- Animals experiments suggest superior anti-proliferative capacity of Dual-API DCB compared to commercially available PTX DCB
- Nanoparticle formula of the Dual-API DCB resulted in fewer emboli and decreased tissue injury compared to the PTX-DCB in the downstream myocardium.
- The future of DCB technology is bright with many new devices coming into the market in the coming year