Development of a Novel Sirolimus Eluting Pro-Healing Stent: Early Animal Data on Healing and Restenosis

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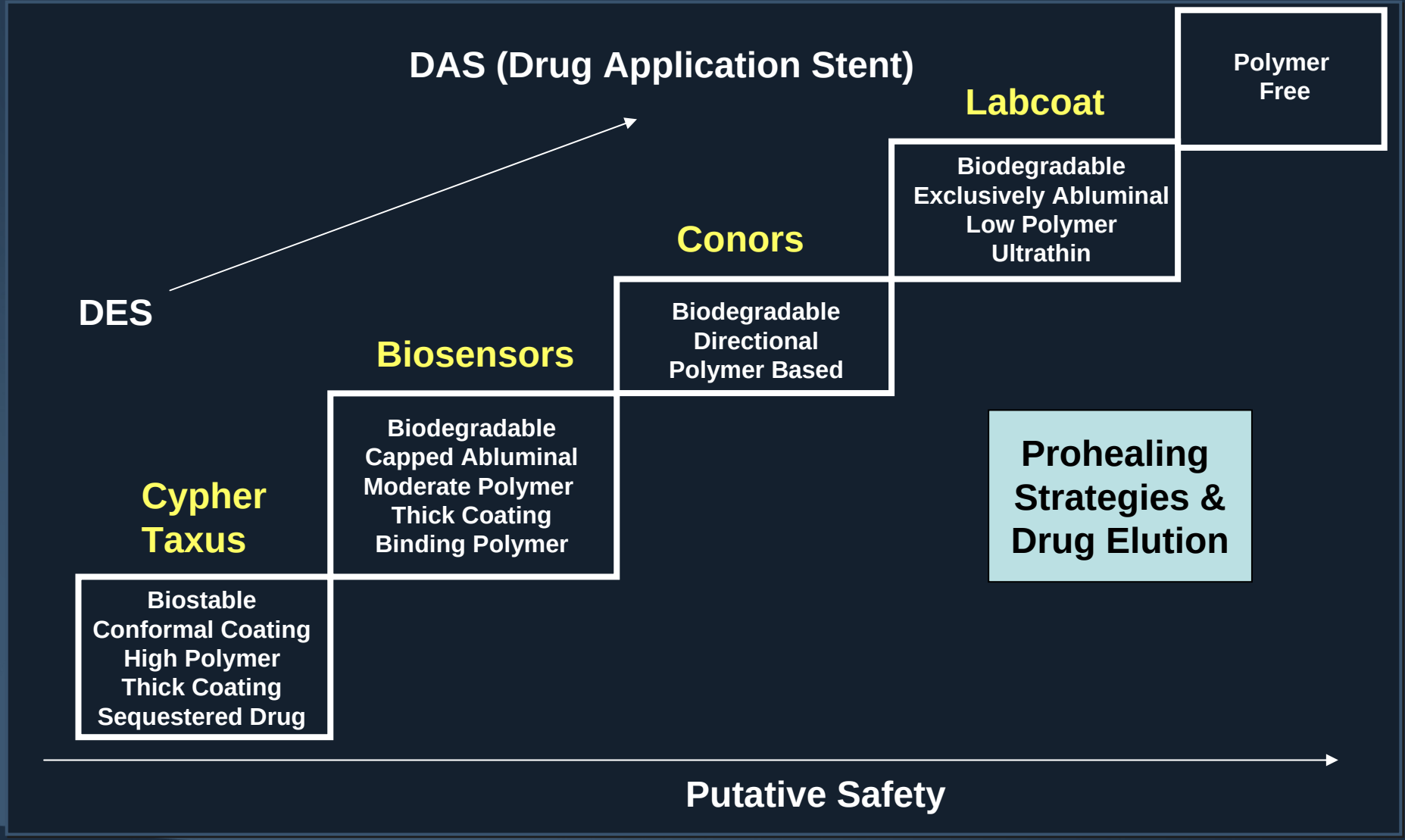
Evolution of DES Technology



Slide Modified and Courtesy of Art Rosenthal

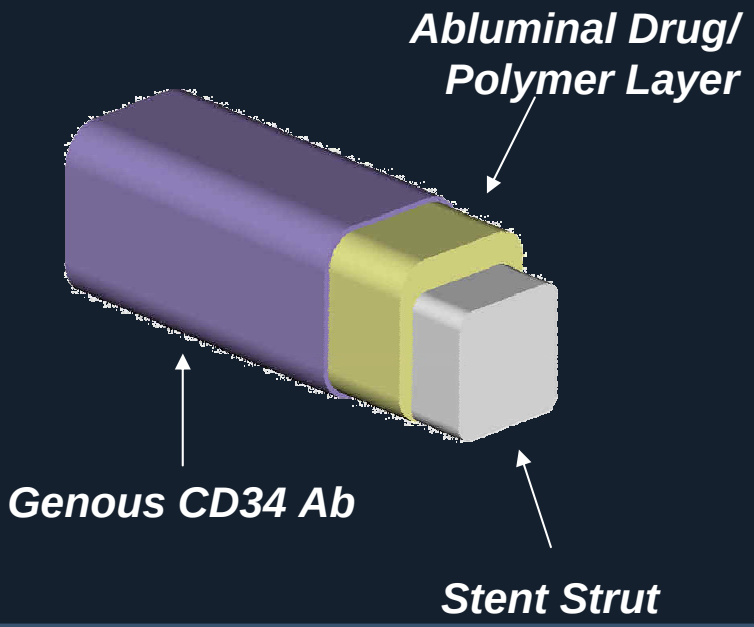
Directional Sirolimus Biodegradable Abluminal Coating and Anti-CD34 Surface Modification: Device Description

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.



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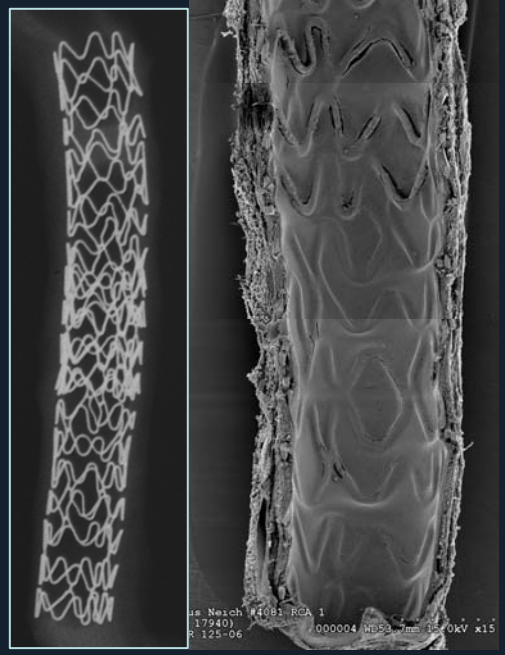
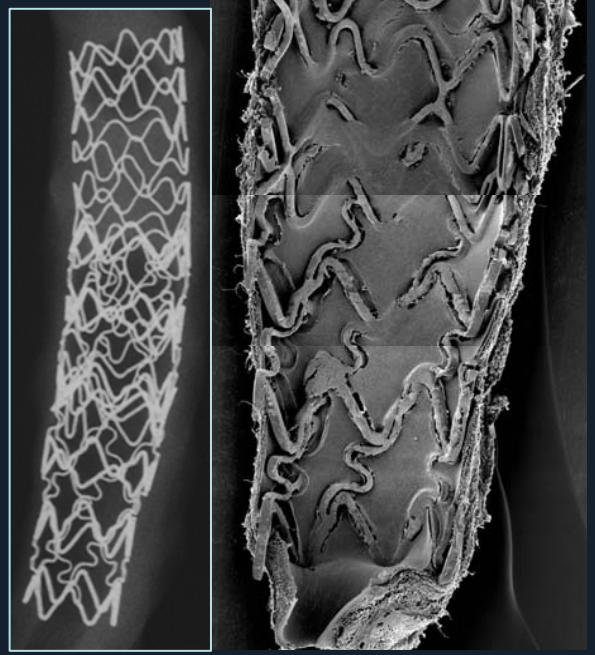
14-Day Porcine Coronary Artery SEM - Overlapping

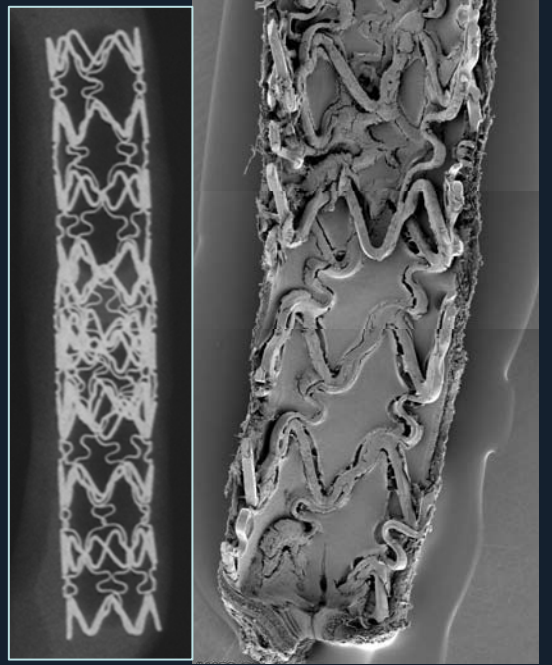
Genous + Genous



Cypher + Genous



Cypher + Cypher



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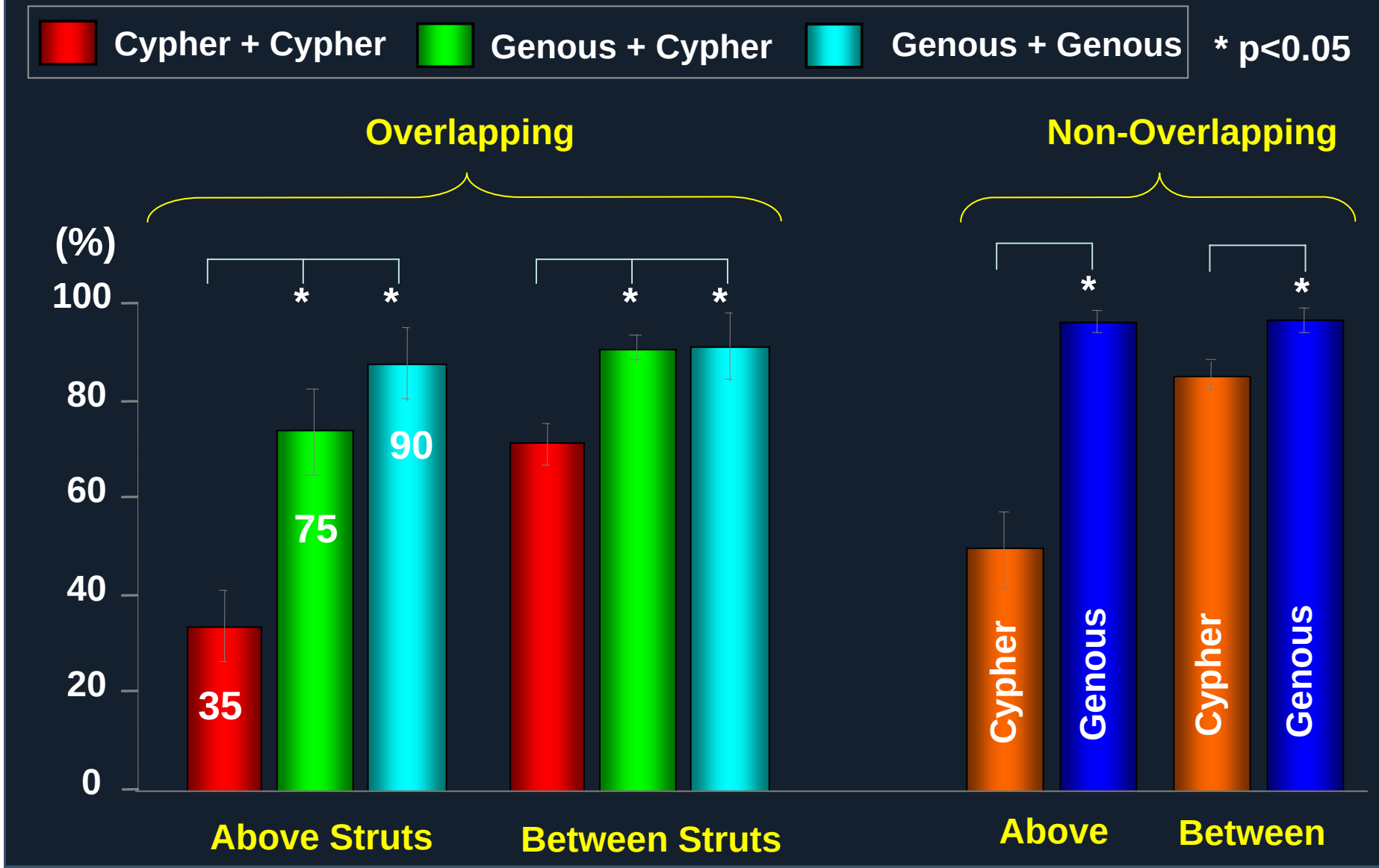
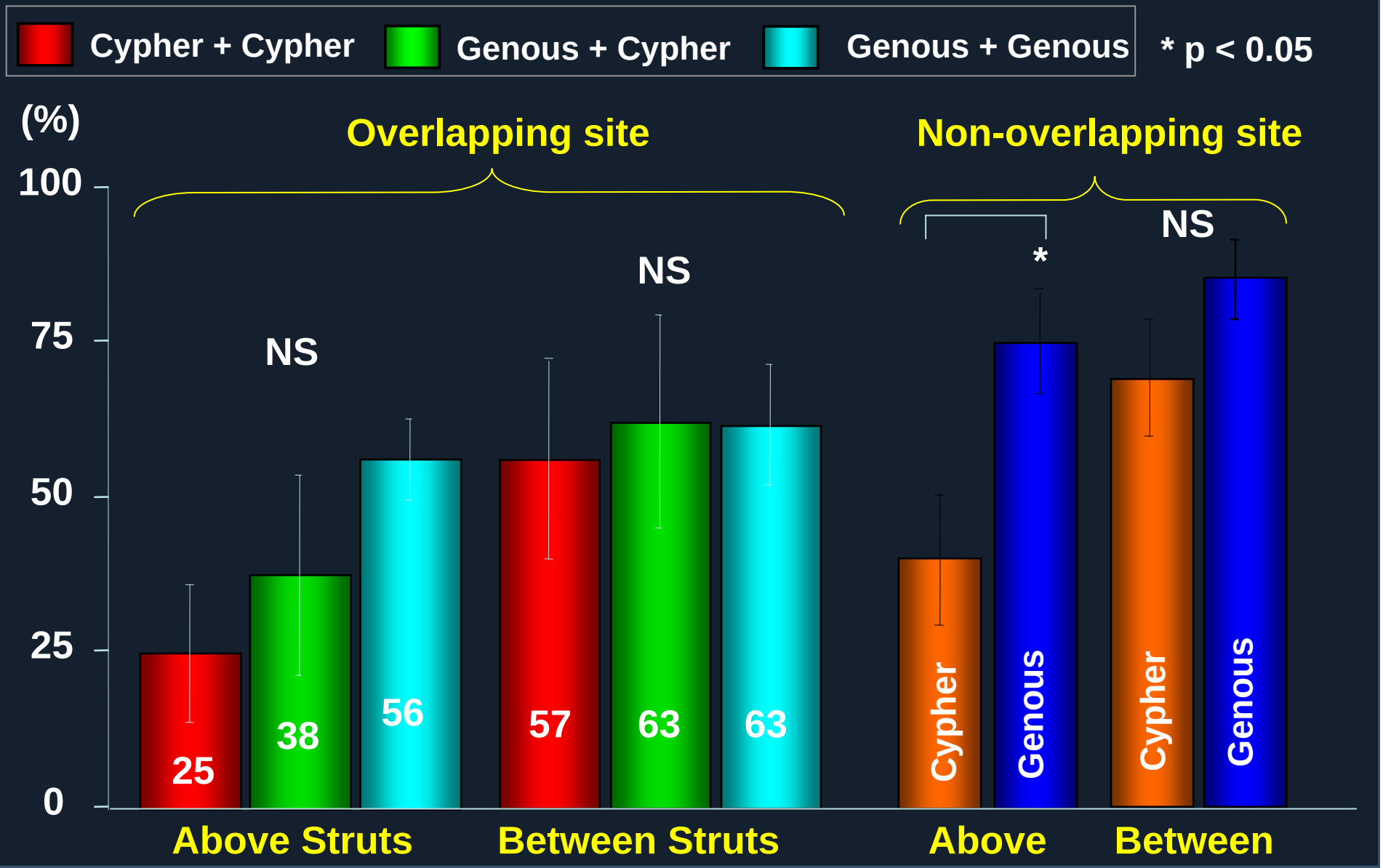
Endothelialization by SEM at 14 days



Endothelialization with CD31 (+) Cells at 14 Days



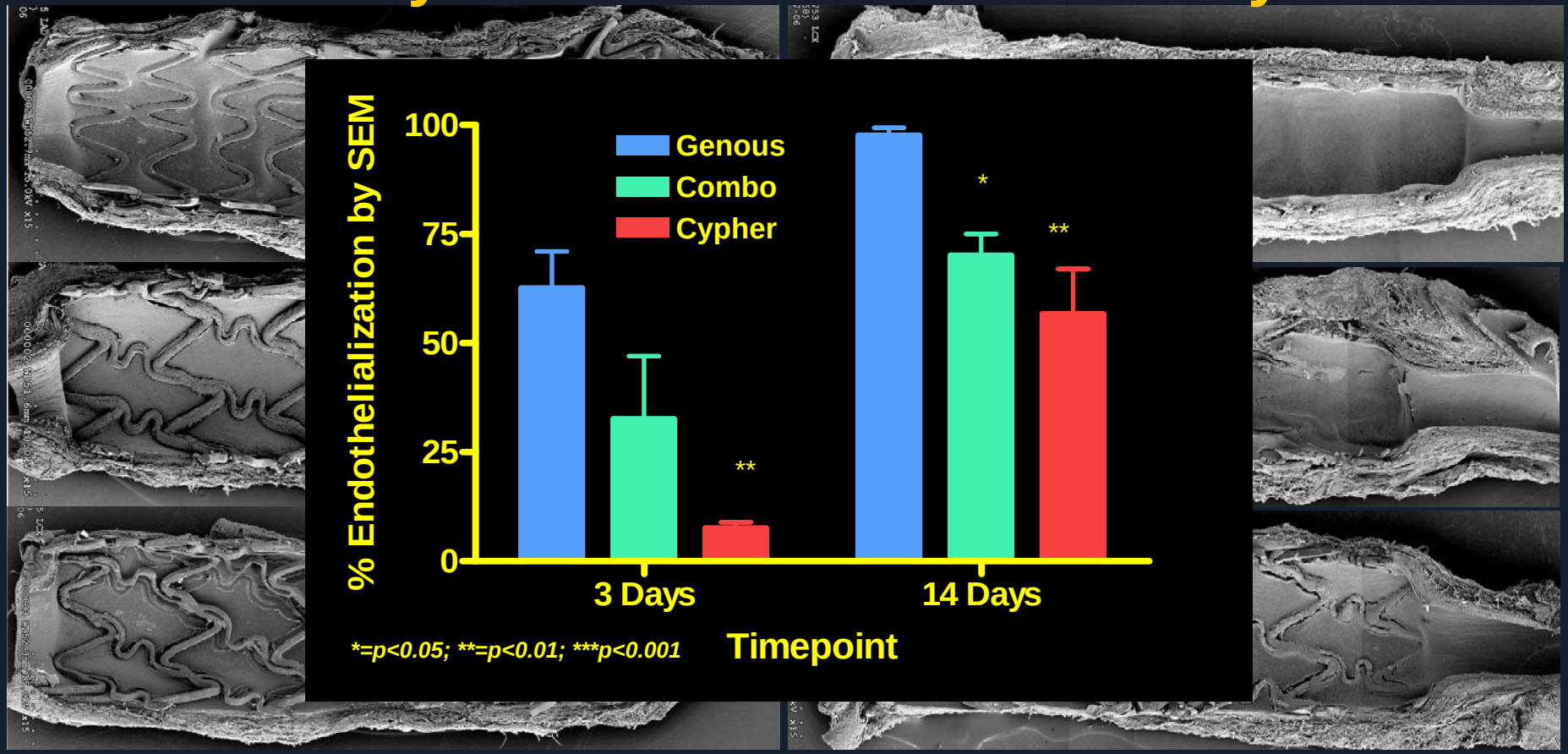
EPC Capturing and Drug Elution: Relevant Research Questions

1. **Could anti-CD34 coating increase the potential for healing in current DES platforms?**
2. **It is abluminal coating really superior than circumferential coating?**
3. **How drug partitioning affects elution kinetics?**
4. **Would partitioning drug elution have an effect on device's endothelialization?**
5. **Can we prove these hypothesis in current animal models?**

Could Anti-CD34 Coating Increase Stent Coverage in Current DES Platforms?

- **Objective:** To characterize EPC capture technology applied to commercially available Cypher stents.
- **Test Devices:**
  - AntiCD34/Cypher Combination (n=4 / timepoint).
  - Cypher (n= 4 / timepoint)
  - Genous (n=4 / timepoint)
- **Model:** Porcine Coronary Injury Model (1.1:1 BAR).
- **Time-Points:** 3 & 14 days.
- **Analysis:**
  - Endothelial Coverage by SEM
  - Endothelial Function by Confocal Microscopy.

Stent Surface Coverage by SEM in Stented Arteries at 3 and 14 Days



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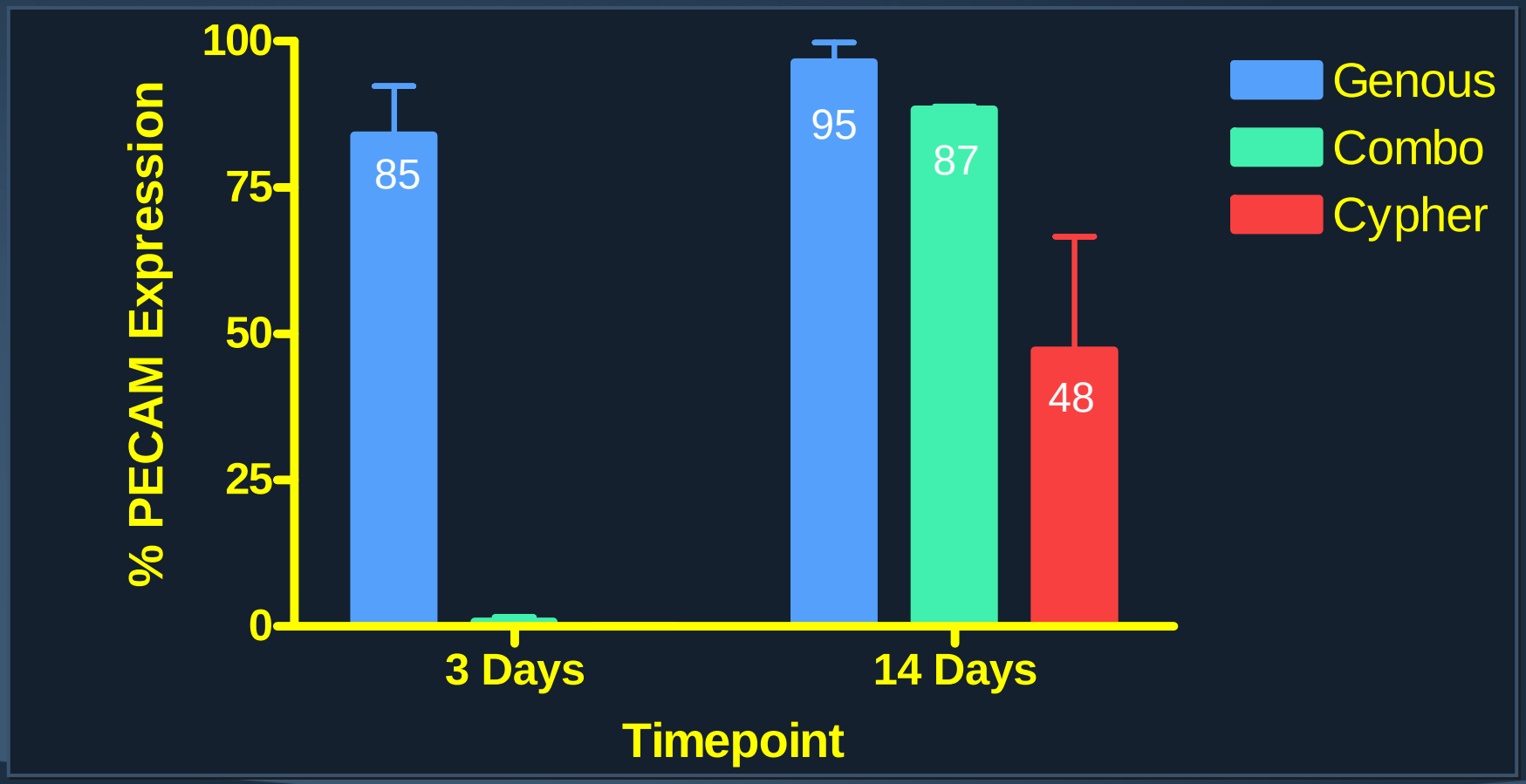
% Endothelialization by PECAM Expression in Confocal Microscopy in Stented Arteries: 3 and 14 Days



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It is Abluminal Coating Really Superior Than Circumferential Coating?

Background Data:

- Anti-CD34 coating on the Cypher stent enhanced endothelial cell coverage and functionality (PECAM expression) at 14 days.

Hypothesis:

- By separating EPC capture from drug delivery using the anti-CD34/DES Combo stents:
  - Minimize the amount of drug and polymer on the inner surface, therefore, one could improve endothelial cell function, while maintaining inhibition of neointimal growth.
  - Would partitioning of the drug increase the changes for device endothelialization?

Abluminal Porcine Study: Biodegradable Abluminal Coating

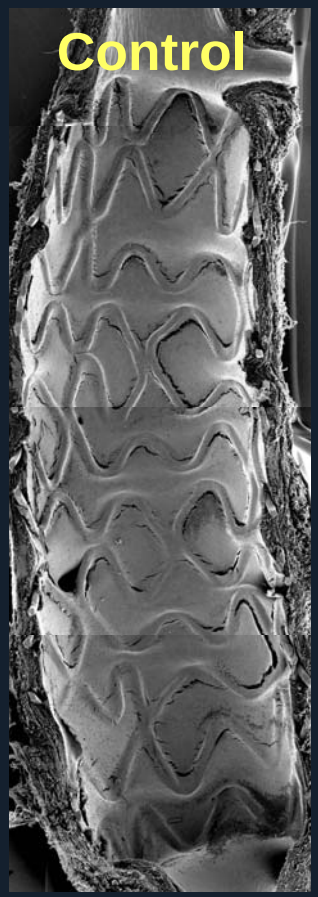
- **Objective:** To compare the differences on strut coverage and functionality of 2 different coating techniques using the core technology anti-CD34 coating in the porcine injury model.

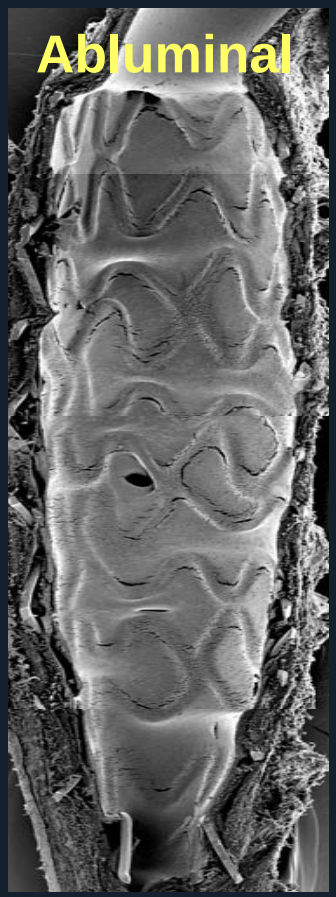
- **Test Devices:**
  - Anti-CD34 Stent + Sirolimus ***Abluminal Coating*** (n=18)
  - Anti-CD34 Stent + Sirolimus ***Uniform Coating*** (n=18)

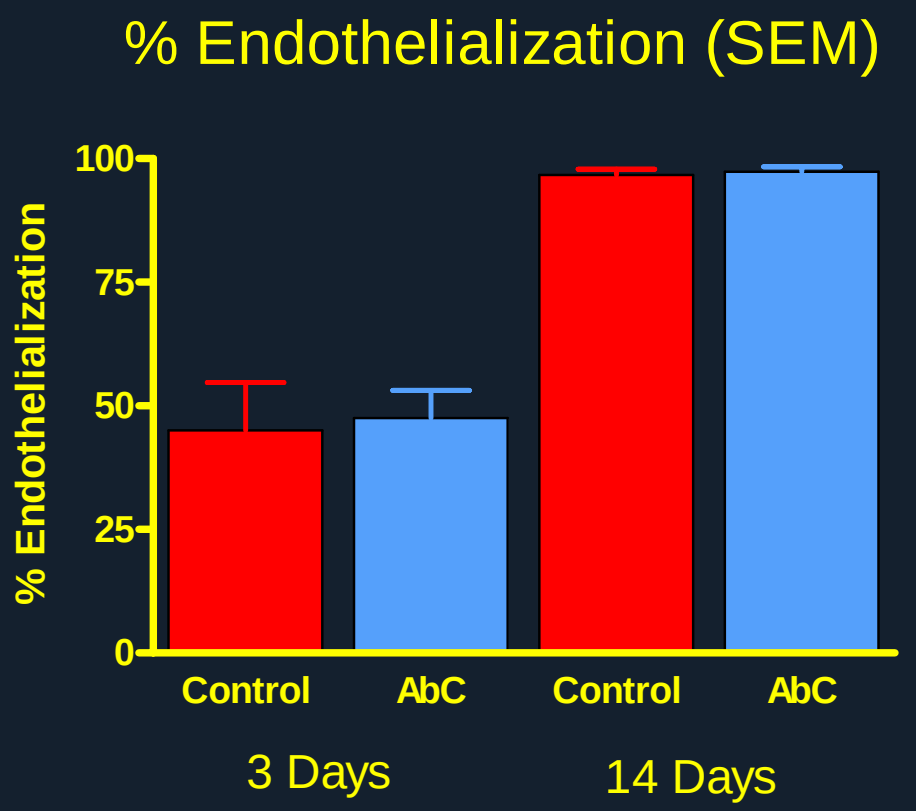
- **Analysis:**
  - 3 Days: SEM & IMH (n = 6 in each group = 12)
  - 14 Days: SEM & IMH (n = 6 in each group = 12)
  - 28 Days: Light Microscopy (n = 6 in each group = 12)

% Strut Endothelialization by SEM

3 & 14 Days is High but Equivalent in Both Groups







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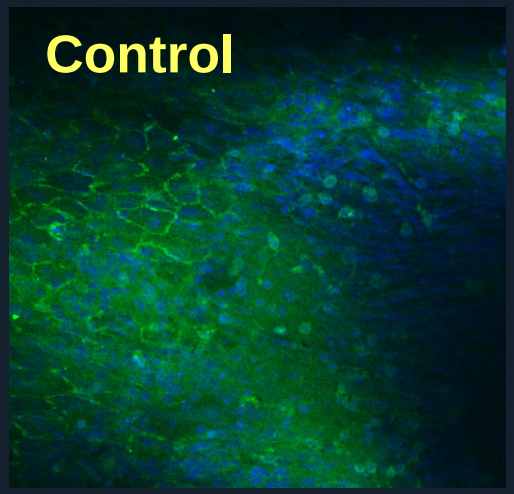
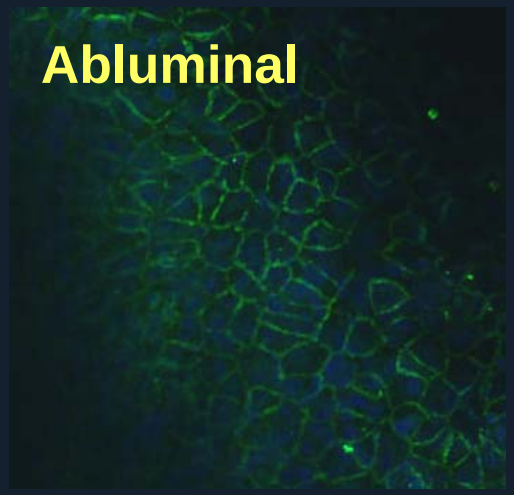
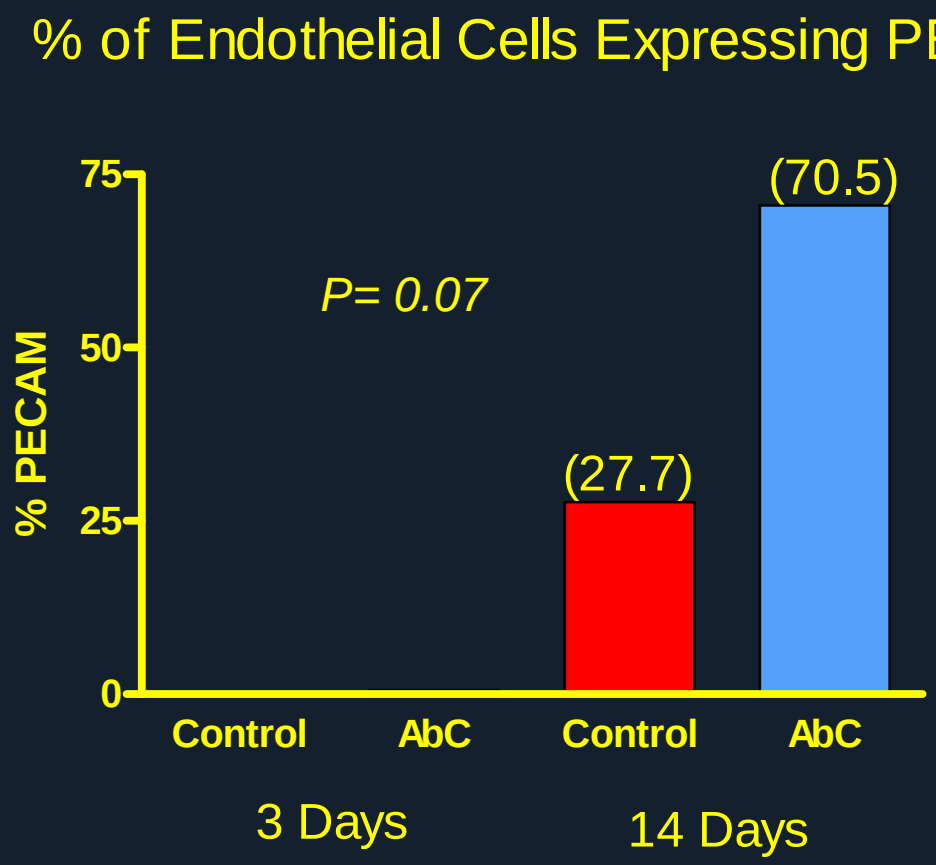
% PECAM Expression Above the Struts Higher Expression in Abluminal Combo







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28-Day Histology: Equivalent Reduction of Neointimal Thickness and Stenosis

	Combo Control	Abluminal Combo
NI Thickness (mm)	0.087 ±0.021	0.094 ±0.068
% Stenosis	17.19 ±4.35	18.57 ±6.43
Int. Inflammatory Score	0.94 ±1.14	0.56 ±0.62
Adv. Inflammatory Score	0.17 ±0.28	0.00 ±0.00
Fibrin Score	1.83 ±0.46	1.56 ±0.54

p=NS for all results

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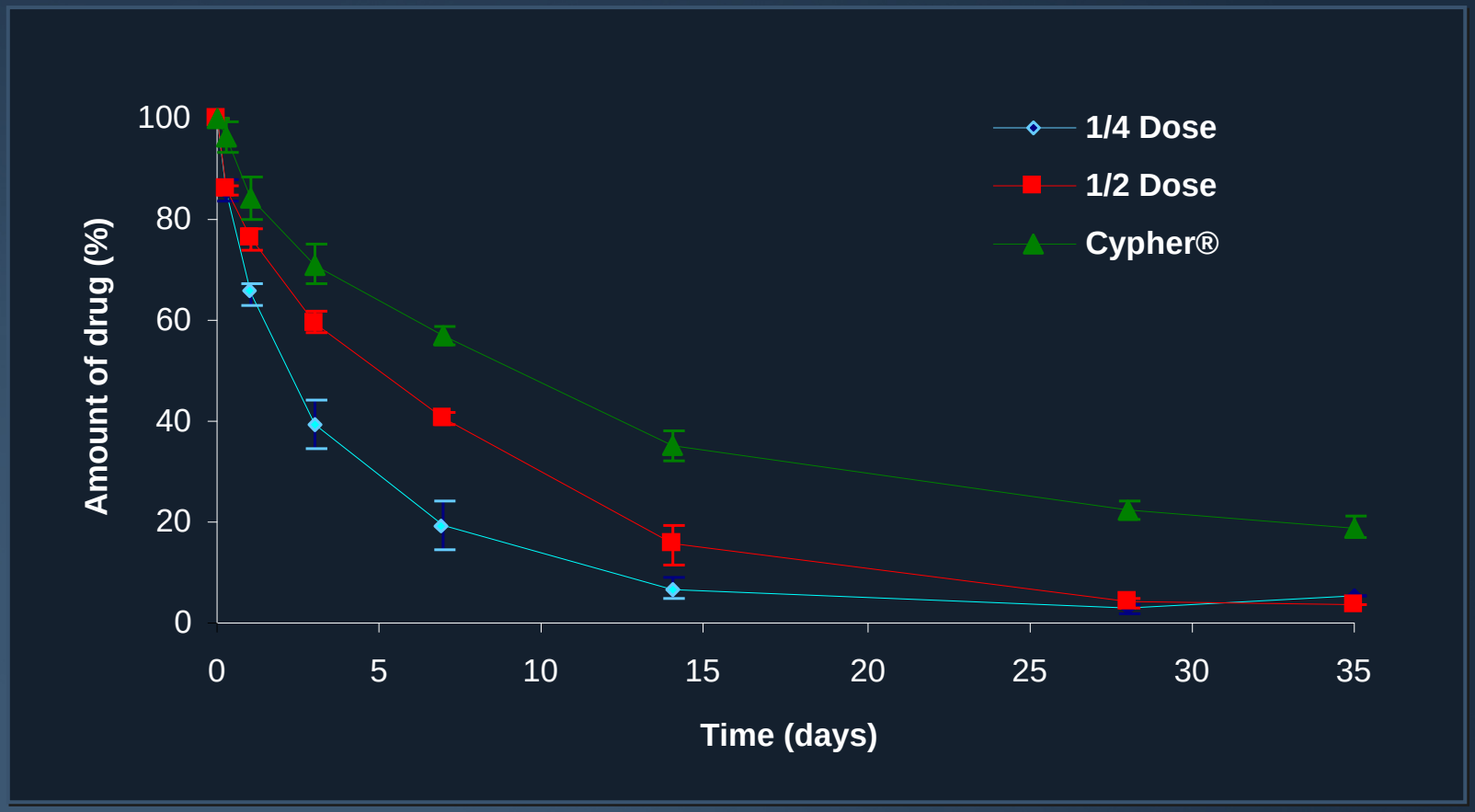
In Vivo Tissue Drug Kinetics of the Rapa Combo DES System in a Porcine Model

- **Objective:** To evaluate the local PK features of the Rapa Combo device up to 35 days in the porcine model.

- **Test Devices:**
  - Rapa Combo ¼ Dose (2.5 µg rapamycin/mm, n= 5).
  - Rapa Combo ½ Dose (5 µg rapamycin/mm, n= 5).
  - Cypher (10 µg rapamycin/mm, n= 4).

- **Analysis:**
  - Blood Collection: 15 minutes, 1, 3, 6 and 24 hours
  - PK analysis on stented arteries, myocardium, liver, kidney: 6 hours, 1, 3, 7, 14, 28 and 35 days

In vivo Elution of Rapamycin Remaining Drug on Stent by HPLC



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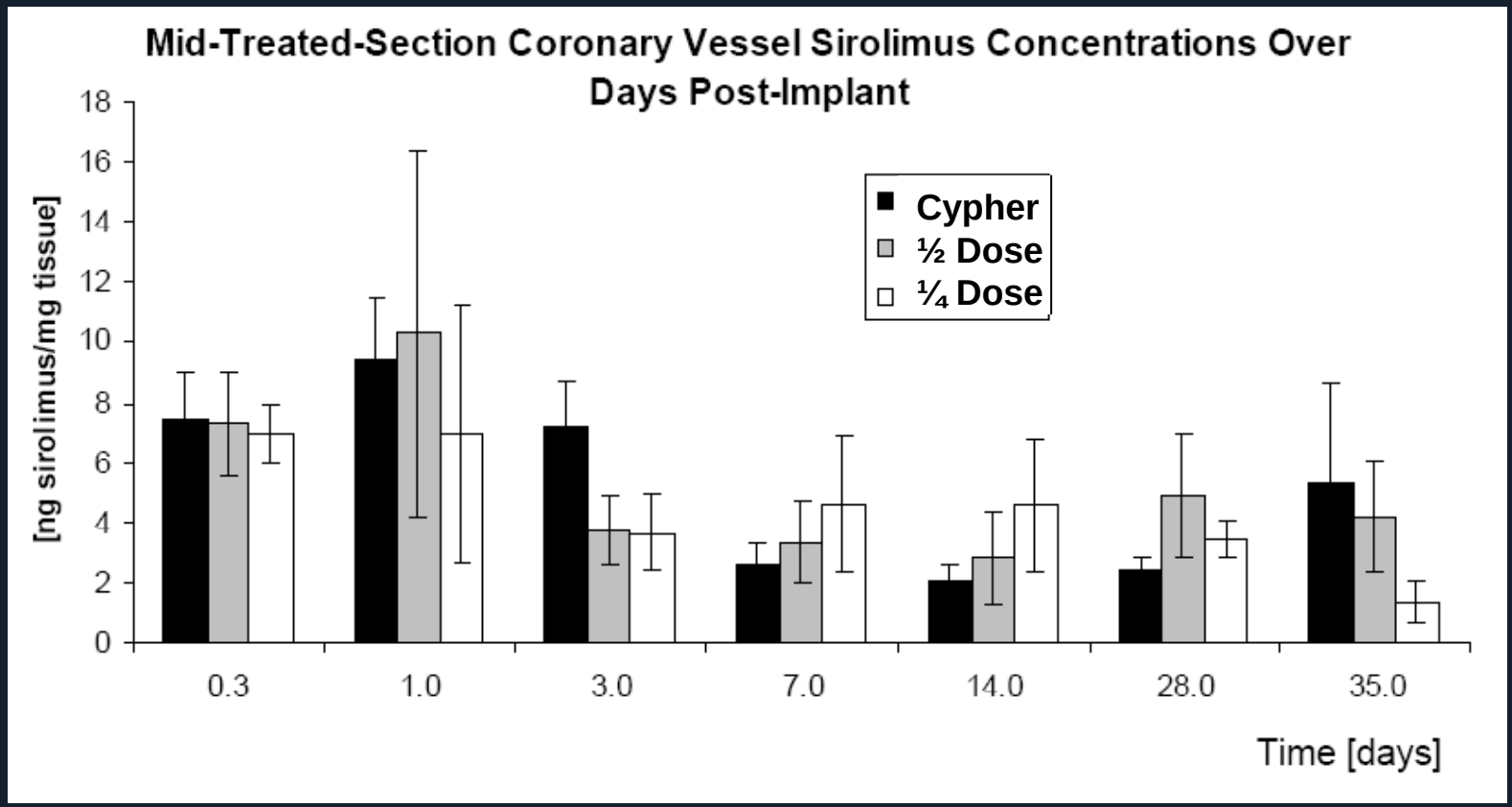
Mean Distribution of Sirolimus in Porcine Heart Tissues



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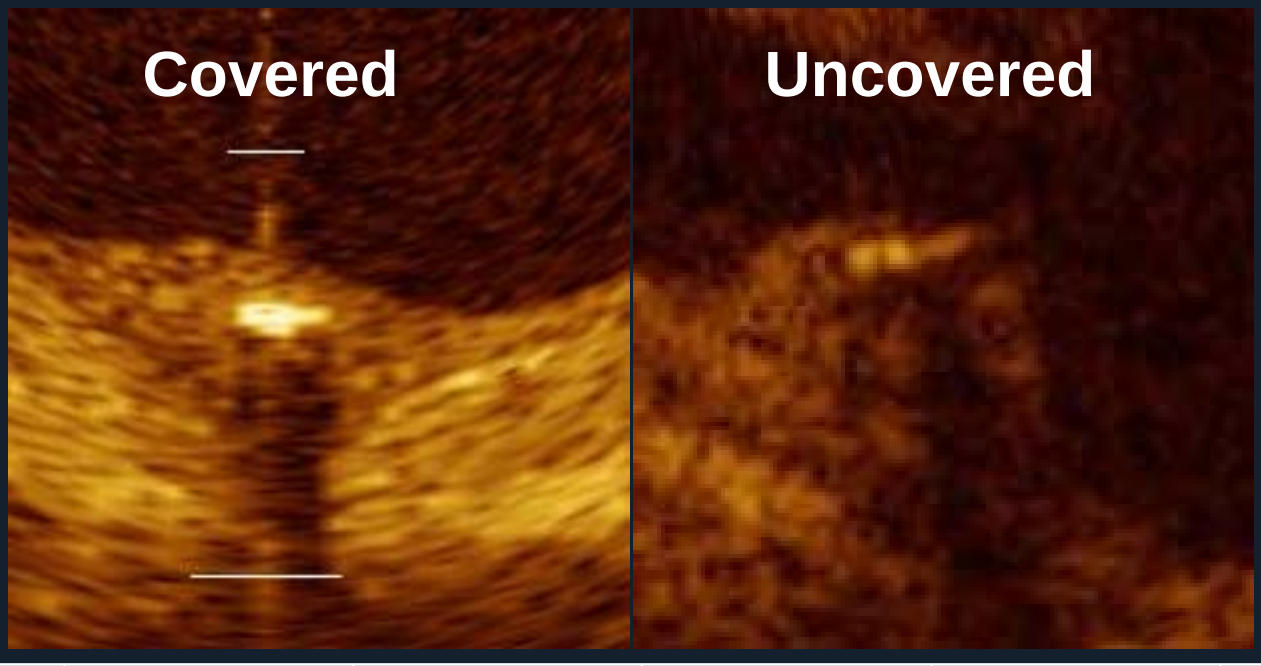
Effect of Rapamycin Dose on Healing and Neointimal Proliferation in a Porcine Coronary Model at 14 and 28 Days

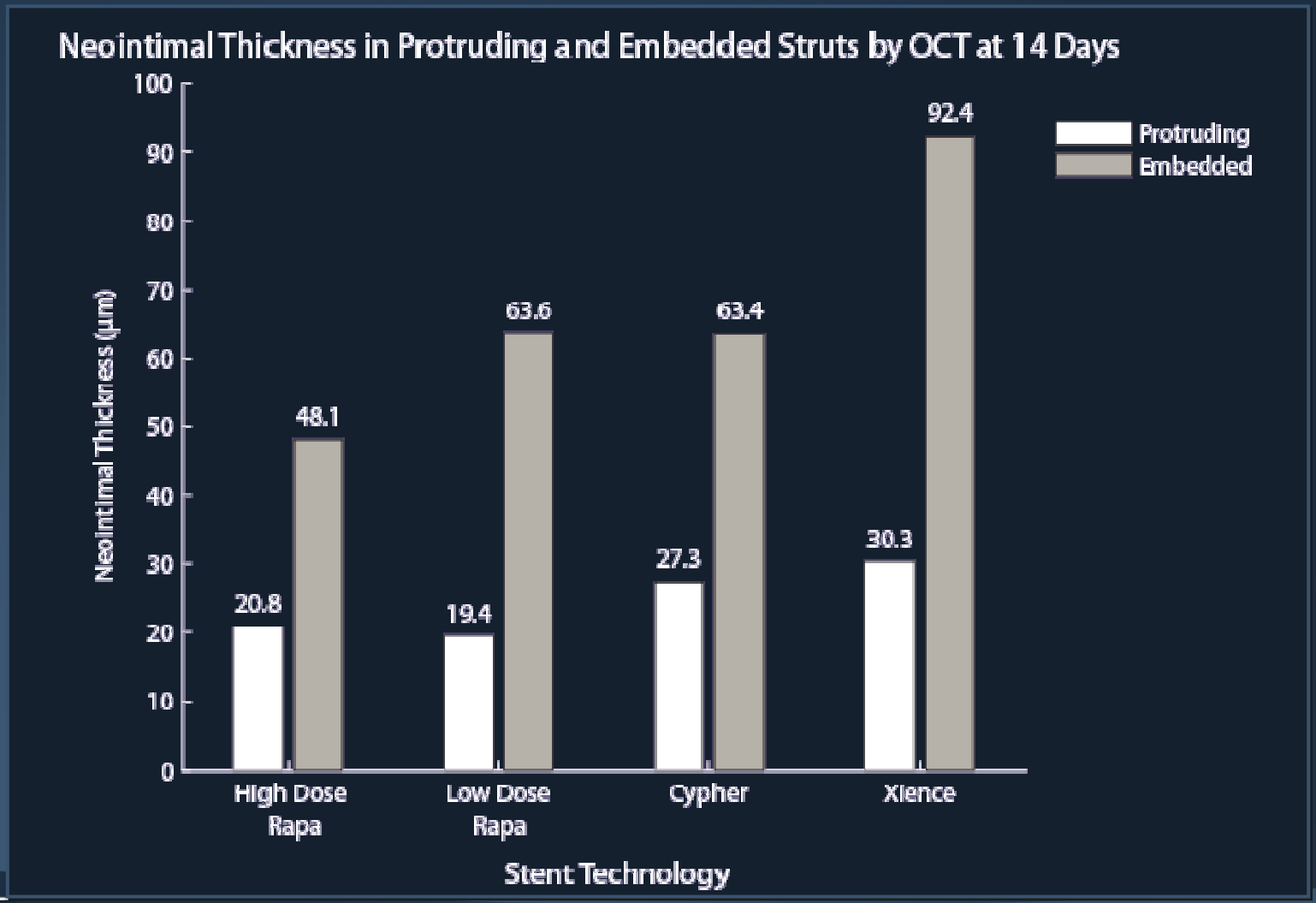
- **Objective:** To demonstrate the effect of dose on healing (anti-CD34 effect) and reduction of neointimal proliferation (rapamycin effect) utilizing imaging, and histology techniques.
- **Test Devices:**
  - Rapa Combo ¼ Dose (2.5 µg rapamycin/mm, n= 5)
  - Rapa Combo ½ Dose (5 µg rapamycin/mm, n= 5)
  - Cypher, Xience V, Genous.
- **Endpoints:**
  - 14 days:
    - SEM & IMH (4 stents in each HD and LD)
    - In vivo OCT evaluation: (4 in each group)
  - 28 days: OCT & LM (6 stents in Genous, HD and LD, 4 stents in DES controls).

In vivo 14 Days OCT Analysis: Strut by Strut Coverage Analysis



Total Number	½ Dose	¼ Dose	Cypher	Xience	Total
Covered strut	60 (16.62 %)	89 (24.79 %)	102 (30.63 %)	37 (9.89 %)	288 (20.18 %)
Uncovered strut	301 (83.38 %)	270 (75.21 %)	231 (69.37 %)	337 (90.11 %)	1139 (79.82 %)
Total Struts	361 (100 %)	359 (100 %)	333 (100 %)	374 (100 %)	1427 (100 %)

In vivo 14 Days OCT Analysis: Neointimal Thickness Covering the Strut



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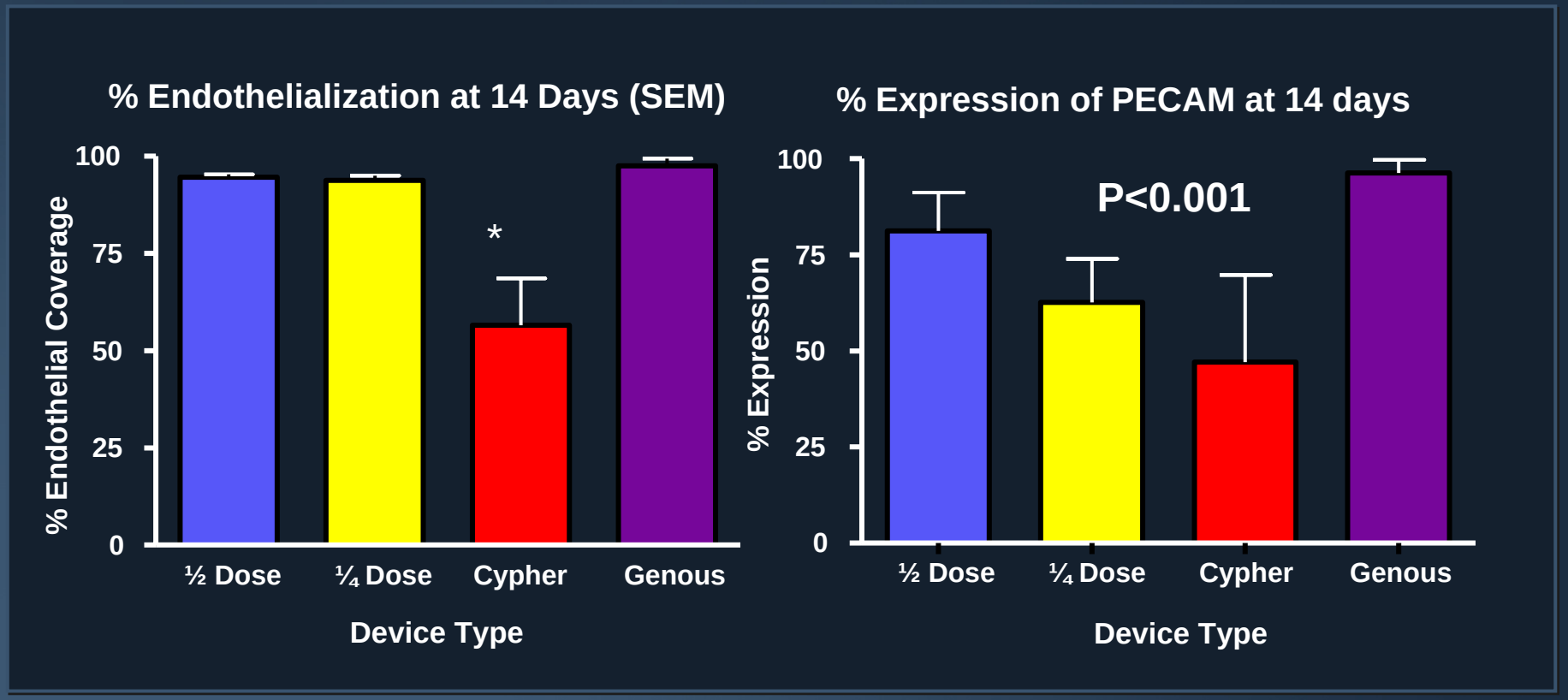
14-Day Endothelialization Rates by SEM and PECAM-1 Expression



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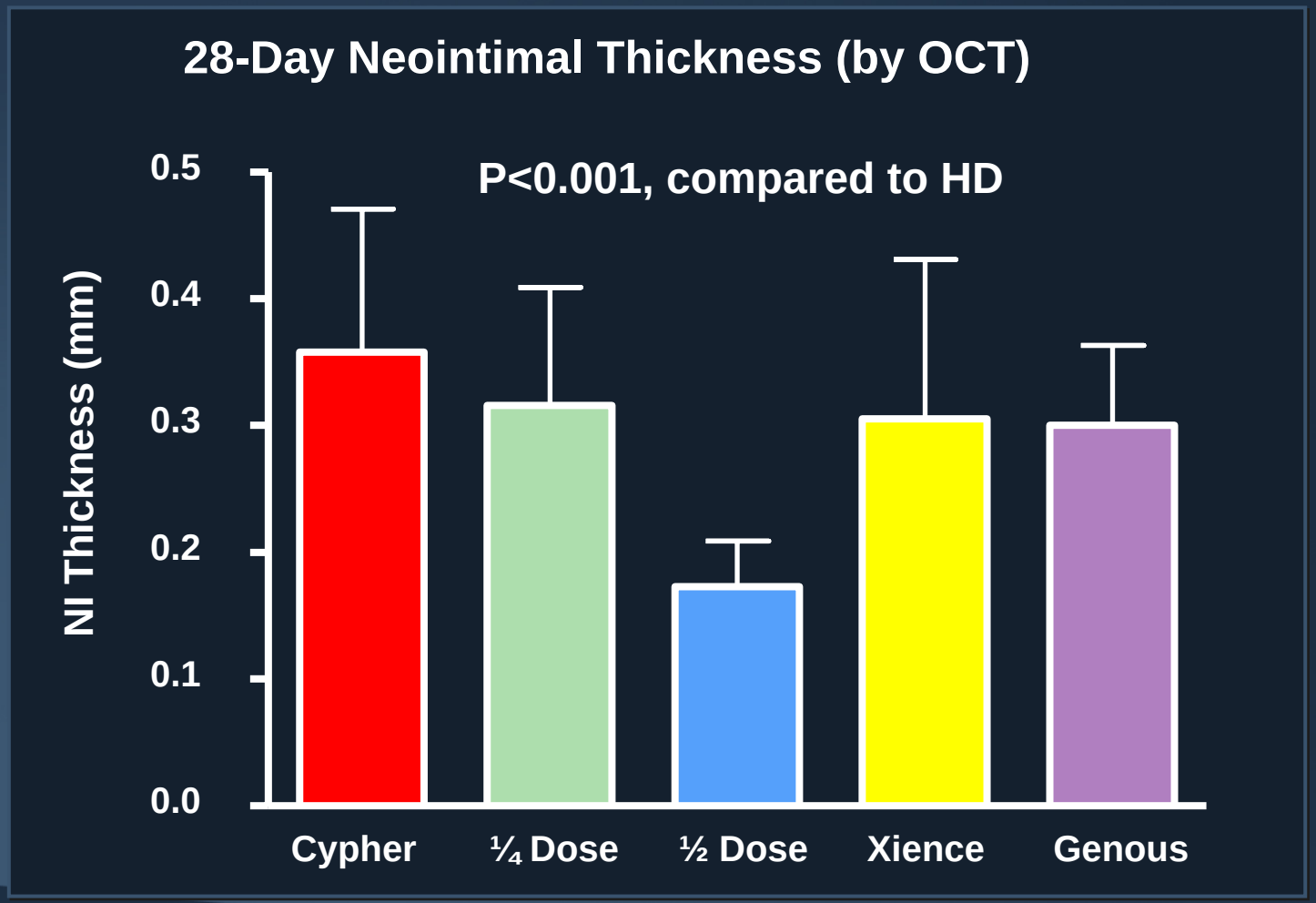
14-Day Histology Results

	Cypher	½ Dose	¼ Dose	Xience
Stenosis (%)	12.01±1.44	9.75±2.63	9.99±2.15	12.31±6.26
NI Thickness (mm)	**0.035±0.007**	**0.032±0.011**	**0.031±0.006**	**0.071±0.062**
Fibrin Score	2.04±0.64	**1.65±0.68**	**1.55±0.34**	**1.50±0.12**
Int. Inflammatory Score	1.05±0.19	**0.85±0.55**	**0.85±0.19**	1.95±1.41
Giant Cells (%)	50.51±17.02	**33.74±16.15**	**37.94±7.27**	47.01±17.22
Adv. Inflammatory Score	0.00±0.00	0.00±0.00	0.00±0.00	1.00±2.00
Granuloma (%)	0.00±0.00	0.00±0.00	0.00±0.00	**21.39±42.77**

N=4/stent type; no statistically significant differences

In vivo Evaluation of Neointimal Thickness by OCT at 28 Days



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28-Day Histology Results

	Genous n=6	Cypher n=3	½ Dose n=5	¼ Dose n=5	Xience n=3
Stenosis (%)	**36.55±10.88**	**33.48±5.41 ***	**19.92±5.60**	**26.04±8.74**	**22.22±6.27**
NI Thickness (mm)	0.29±0.12	0.21±0.019	0.12±0.050	0.18±0.073	0.15±0.049
Fibrin Score	0.067±0.16	2.00±0.72	**0.60±0.75**	1.32±0.50	**0.53±0.42**
Int. Inflam. Score	0.27±0.16	1.20±0.20	**0.28±0.23**	**0.24±0.33**	0.67±0.83
Giant Cells (%)	13.82±9.51	44.94±8.32	**10.06±7.13**	**6.04±7.55**	33.24±14.14**
Adv. Inflam. Score	0.13±0.24	0.20±0.20	0.24±0.54	0.52±0.59	0.13±0.12

*Cypher>Xience and HD; **Xience>Genous, HD and LD ($p<0.0001$)

Conclusions (I)

- In the present series of studies we demonstrated:
  - The safety profile of current DES technologies could be enhanced by having the additive effect of EPC recruitment.
  - Biological “compartmentalization” (abluminal coating) is possible and seems to be superior than circumferential coating.
  - Therapeutic levels of rapamycin can be maintained despite the fact that the total effective dose is reduced by 50% to 75%.
- OCT and histological analyses demonstrate that at 14 days:
  - There was a statistically significantly lower neointimal thickness by OCT in Rapa Combo ½ Dose compared to the other groups.
  - PECAM expression was higher in Rapa Combo ½ Dose (81.3±19.9%) compared to Rapa Combo LD stents (62.7±22.6%).

Conclusions (II)

- At 28 days:
  - Neointimal thickness and %AS were the lowest with Rapa Combo ½ Dose, and this correlated with statistically significantly lower neointimal thickness by OCT compared to the other groups.
- The nature of the animal model used in these studies (juvenile porcine) makes the evaluation of device endothelialization more challenging.
- These biological effects could potentially translate into a clinical advantage by improving vascular healing while maintaining effective control in neointimal proliferation.

The Skirball Center for Cardiovascular Research

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