Terrence Donnelly Heart Centre
St. Michael's Hospital
Toronto, Canada

Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

A Pro-healing Approach to Thrombo-Resistance and Restenosis Prevention: Endothelial Progenitor Cell Capture

Michael J.B. Kutryk, MD, PhD.

Angioplasty Summit 2004, Seoul Korea

ORBUS
MEDICAL TECHNOLOGIES

A New Paradigm Restenosis Prevention?

"As cardiologists, vascular biologists, and physicians, we must now consider an alternative to the "antitumor" approach to restenosis prevention and seek to restore the normal biology of the vessel wall rather than perpetuate its disruption."

DW Losordo, et al.
Circulation 2003:107;2635-7.

The Ideal Candidate?

- The ideal candidate for the reduction of restenosis must have the following characteristics:
  - Anti-proliferative effects on smooth muscle cells
  - Anti-migratory effects on smooth muscle cells
  - Anti-inflammatory properties
  - Anti-thrombotic properties
  - Vasodilatory properties

D. Taylor TCT 2003

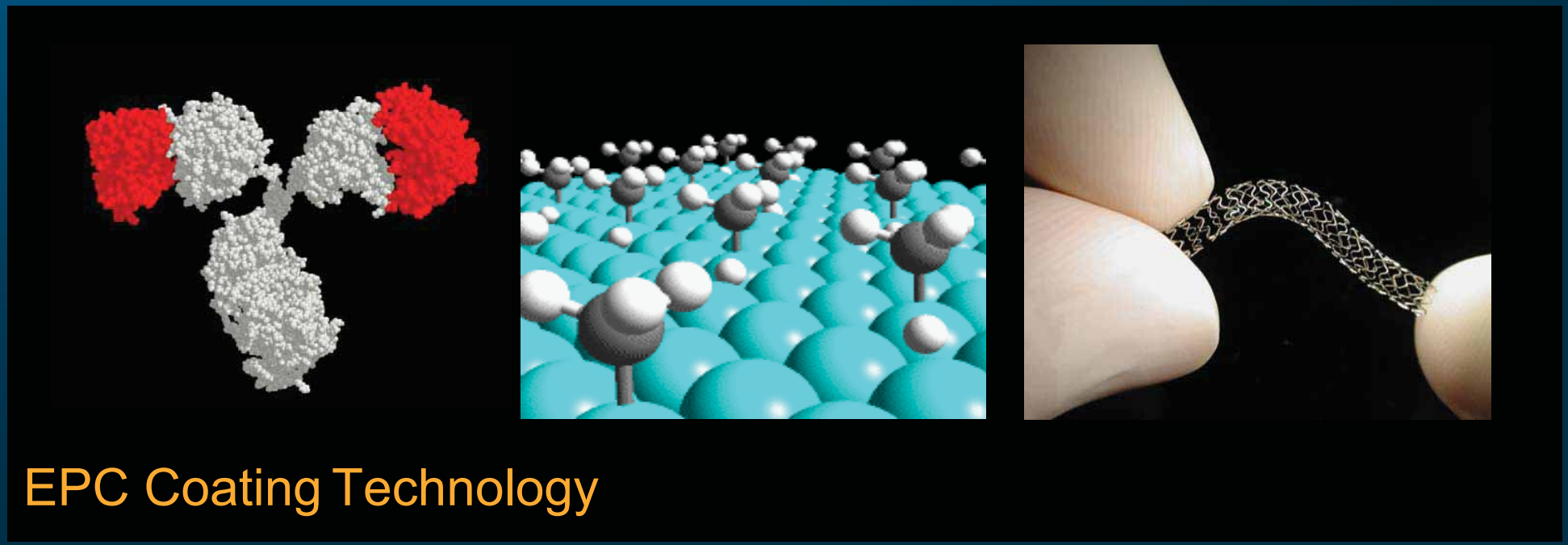
- the endothelial cell !

Introduction

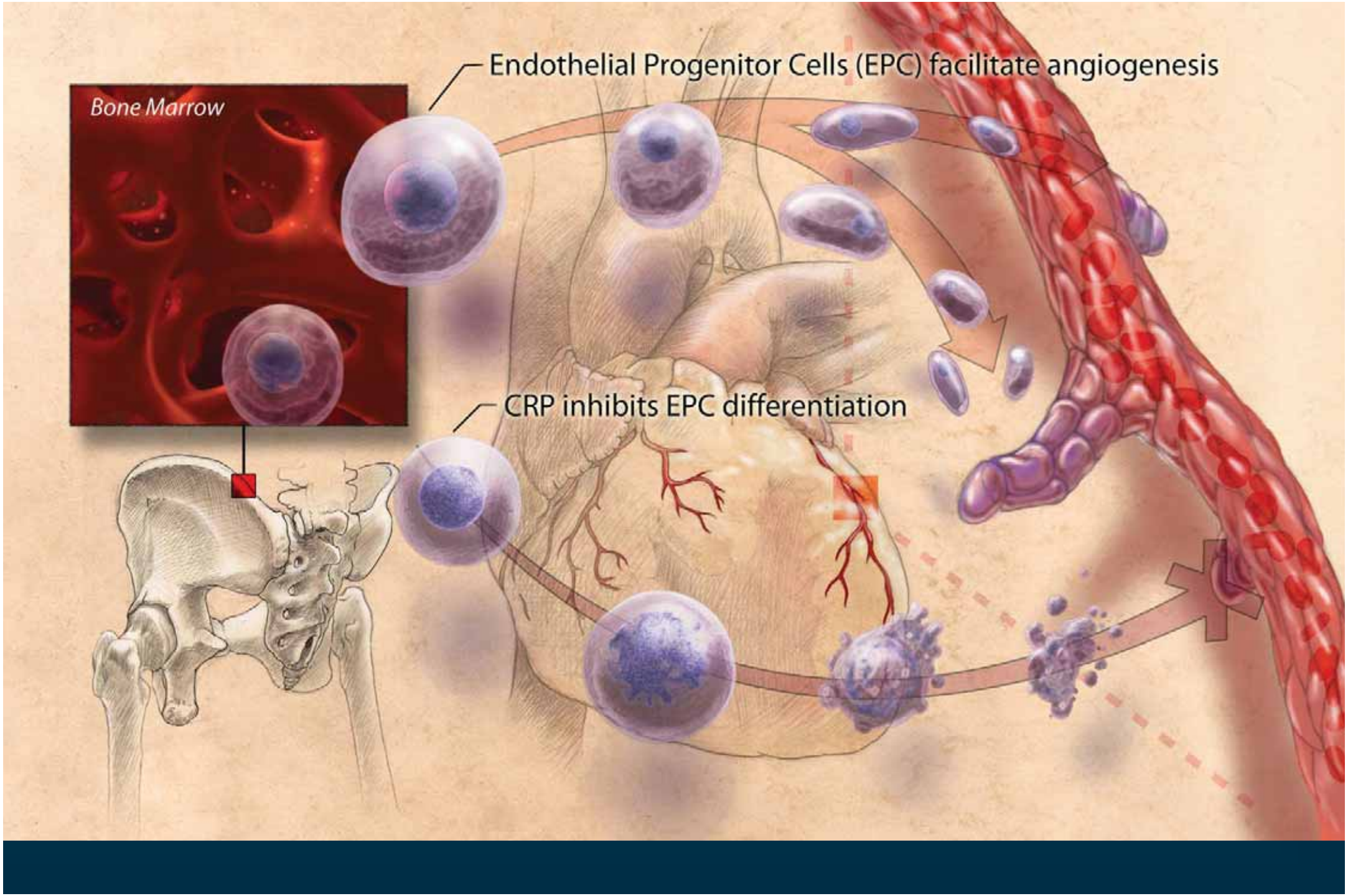
- Background
  - Despite considerable efforts over the last thirty years, attempts to develop ex vivo or in vivo techniques to seed or sod prosthetic vascular surfaces, stents and ePTFE vascular grafts, have failed because of:
    - a lack of an efficient means of transplanting endothelial cells and
    - the loss of normal endothelial function of ex vivo expanded cell cultures

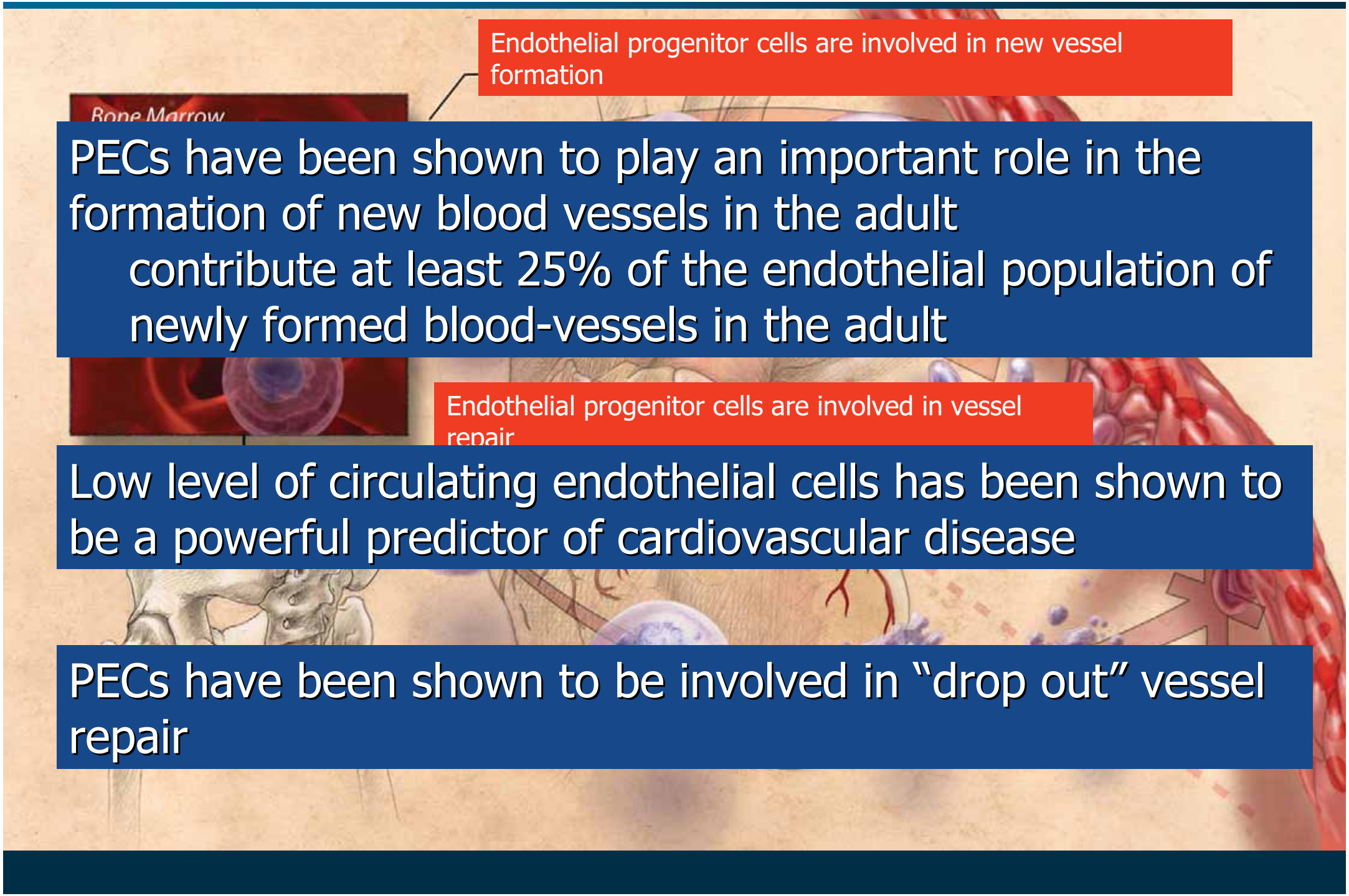
EPC Capture Coating

Aim: In vivo establishment of a confluent, functional, endothelial layer on the surface of prosthetic intravascular devices – "autoseeding"

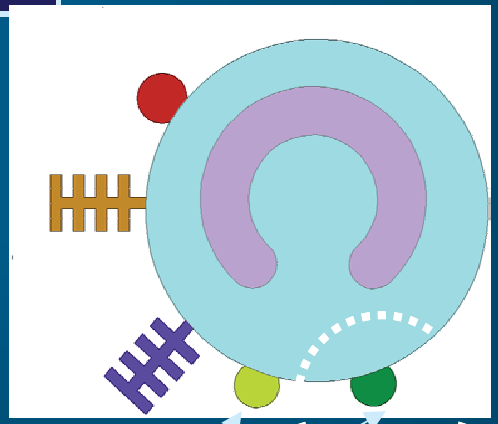


EPC Coating Technology


Endothelial Progenitor Cells (EPC) facilitate angiogenesis
Bone Marrow
CRP inhibits EPC differentiation


Endothelial progenitor cells are involved in new vessel formation
Bone Marrow
PECs have been shown to play an important role in the formation of new blood vessels in the adult
contribute at least 25% of the endothelial population of newly formed blood-vessels in the adult
Endothelial progenitor cells are involved in vessel repair
Low level of circulating endothelial cells has been shown to be a powerful predictor of cardiovascular disease
PECs have been shown to be involved in "drop out" vessel repair

EPC Capture Coating



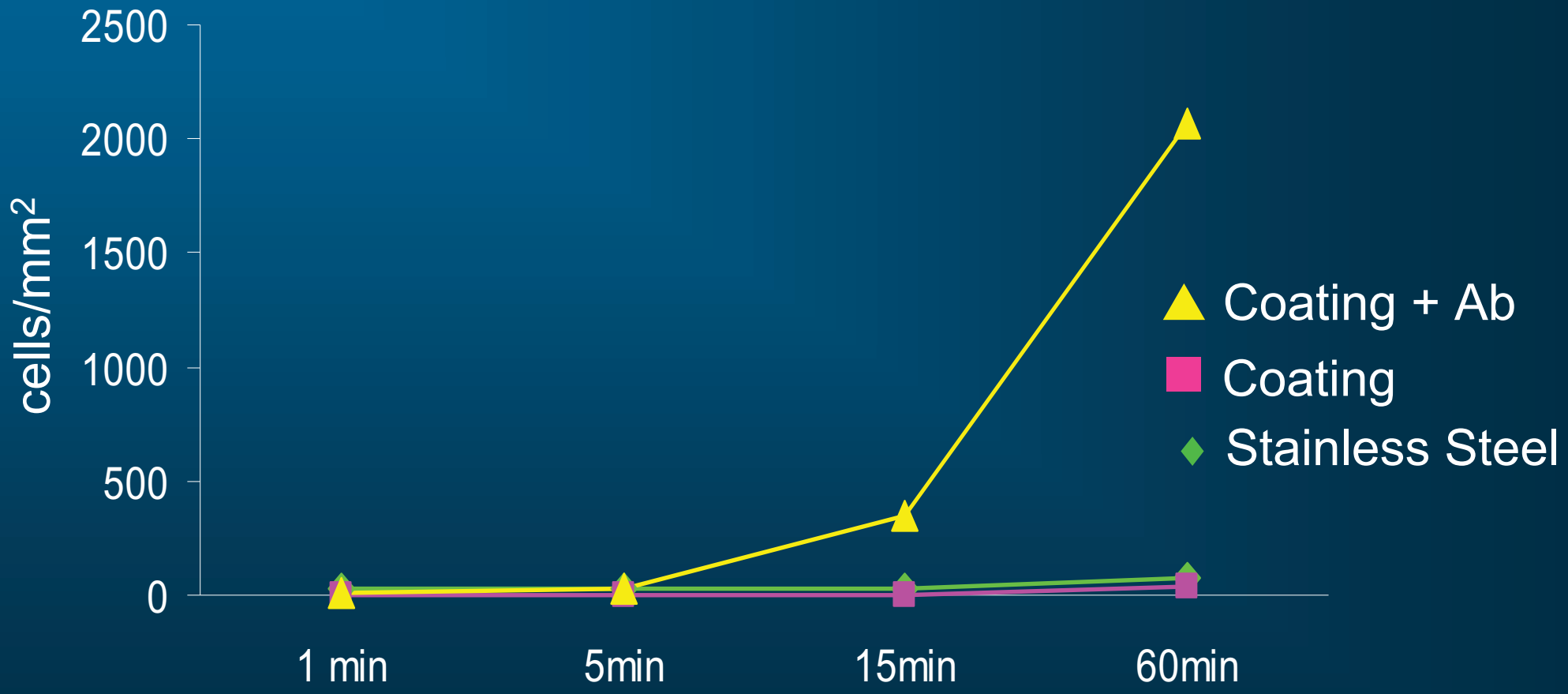
Endothelial Progenitor Cell (EPC)

CD34 Cell Surface Antigen

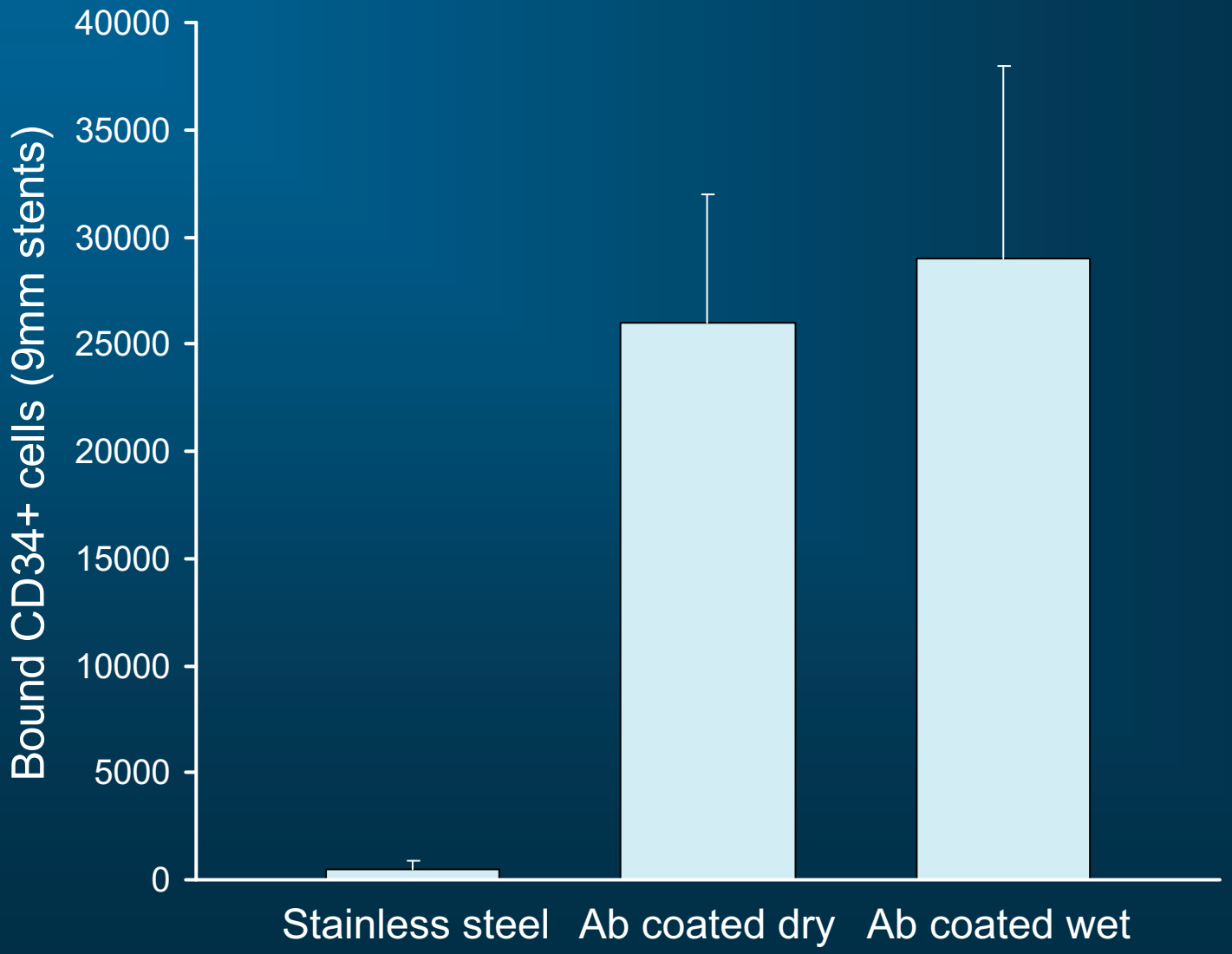
Anti-CD34 Antibody

Prosthetic Surface

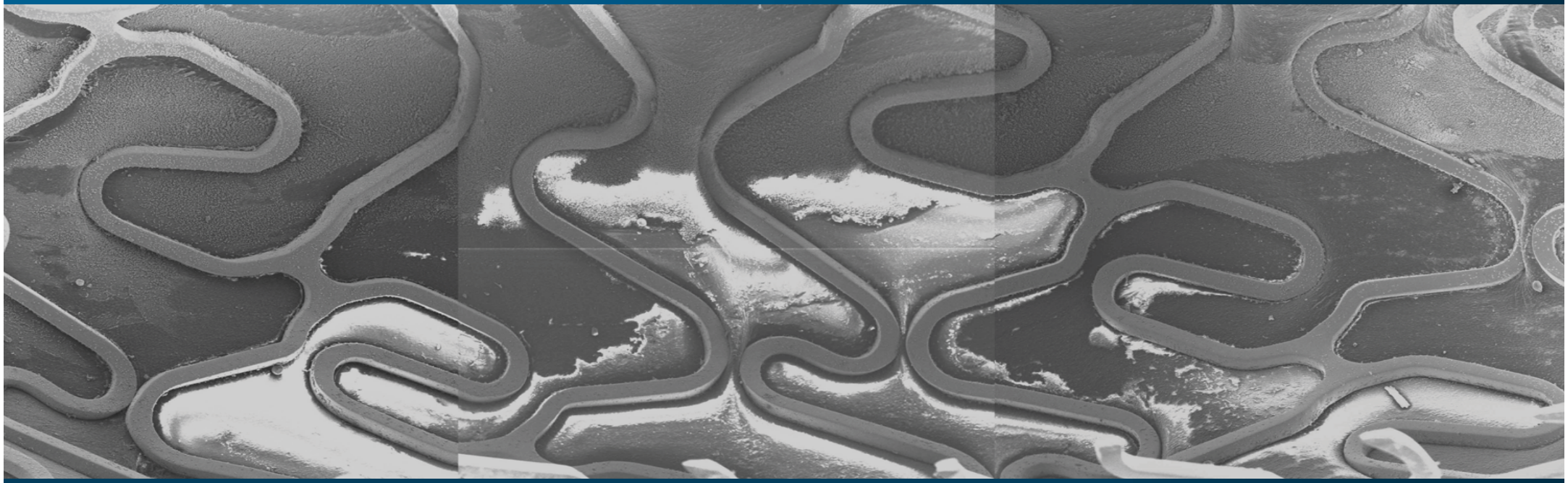
In vitro EPC capture



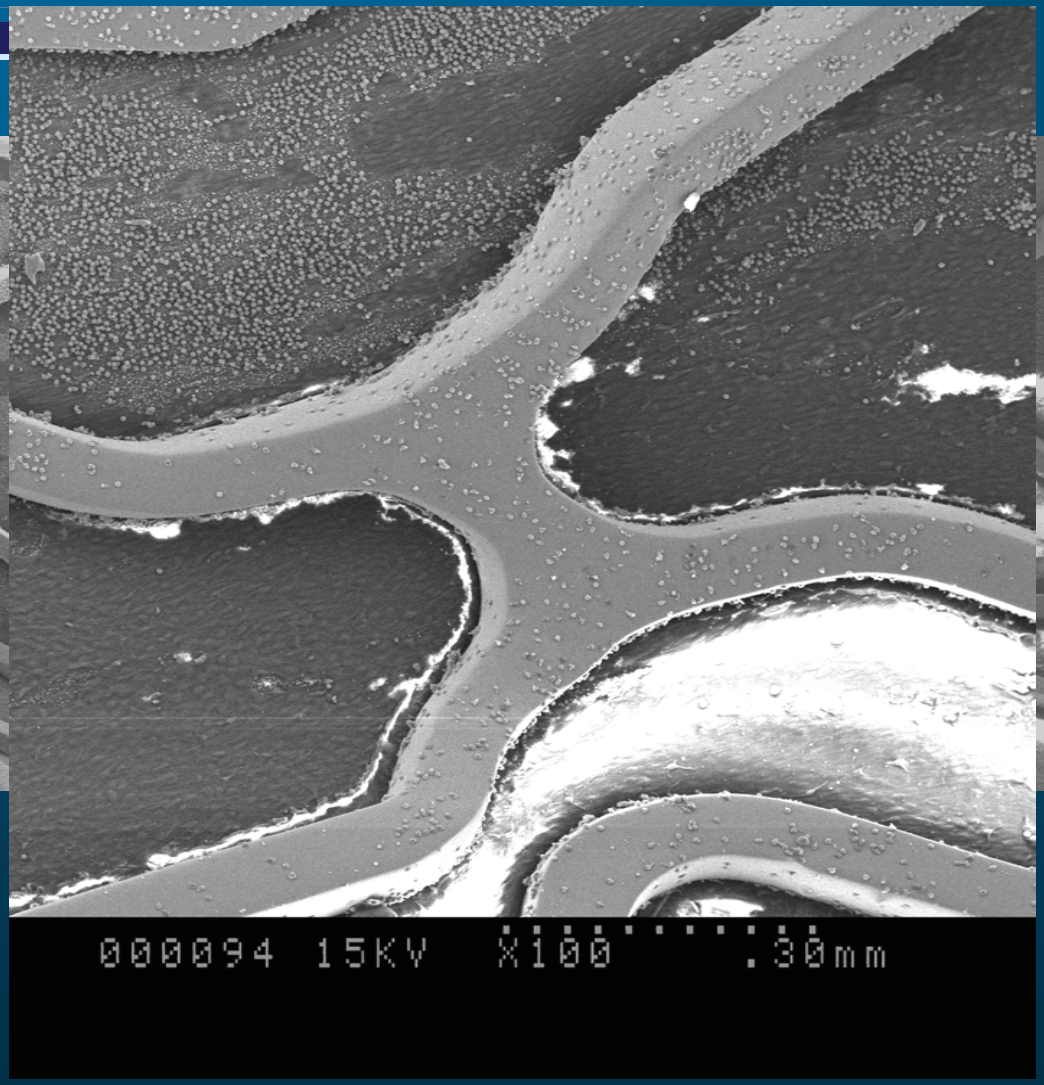
Immortalized CD34+ expressing cell binding assay

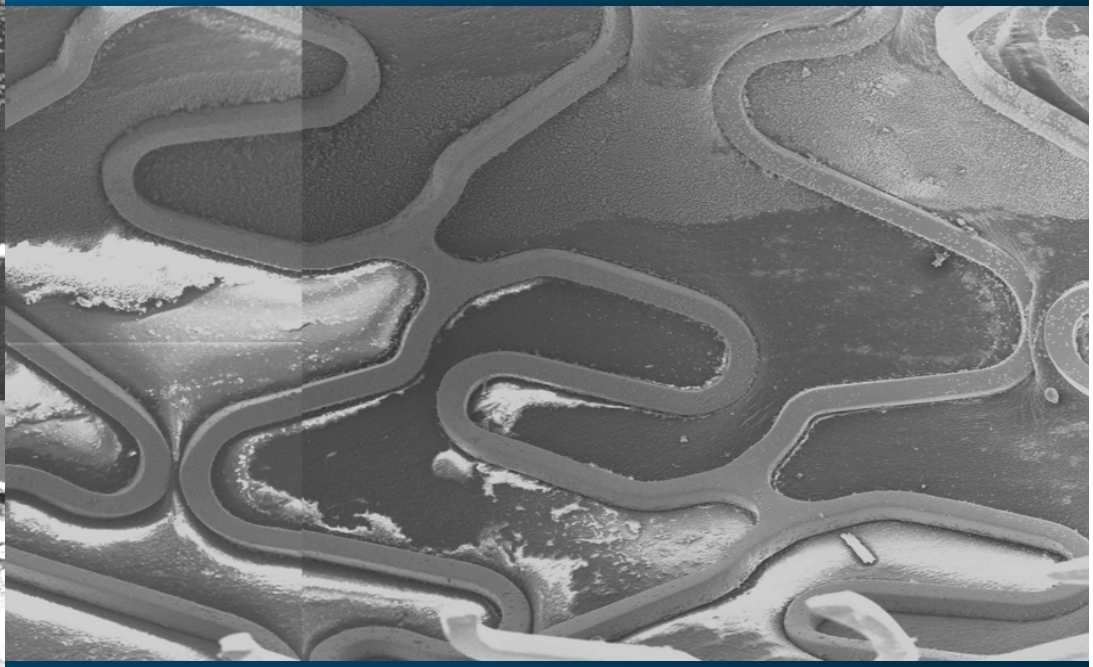


1h explant – Bare R-Stent

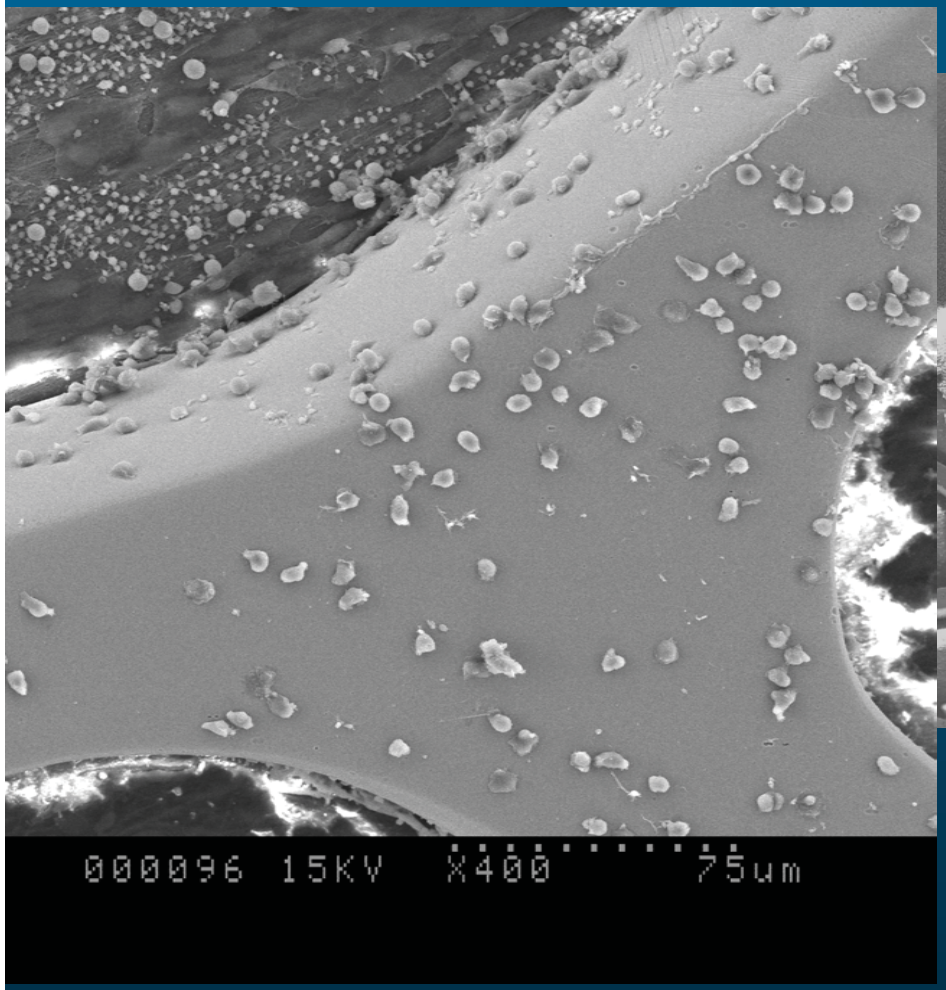


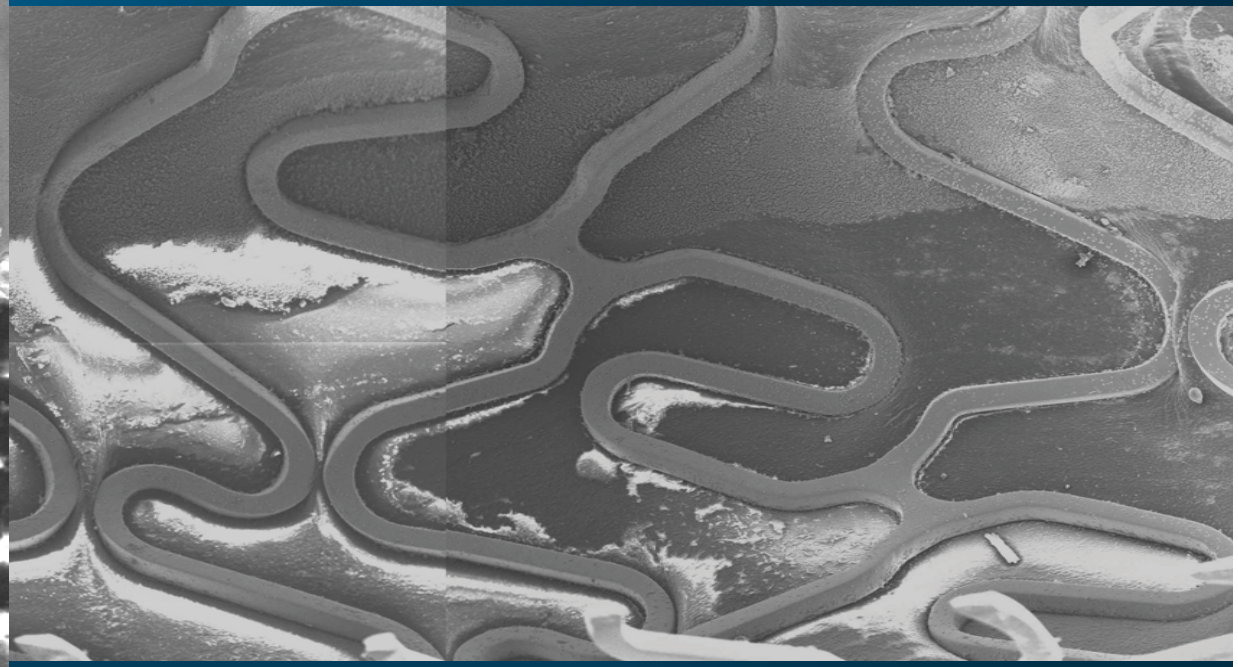
1h explant - Bare R-Stent





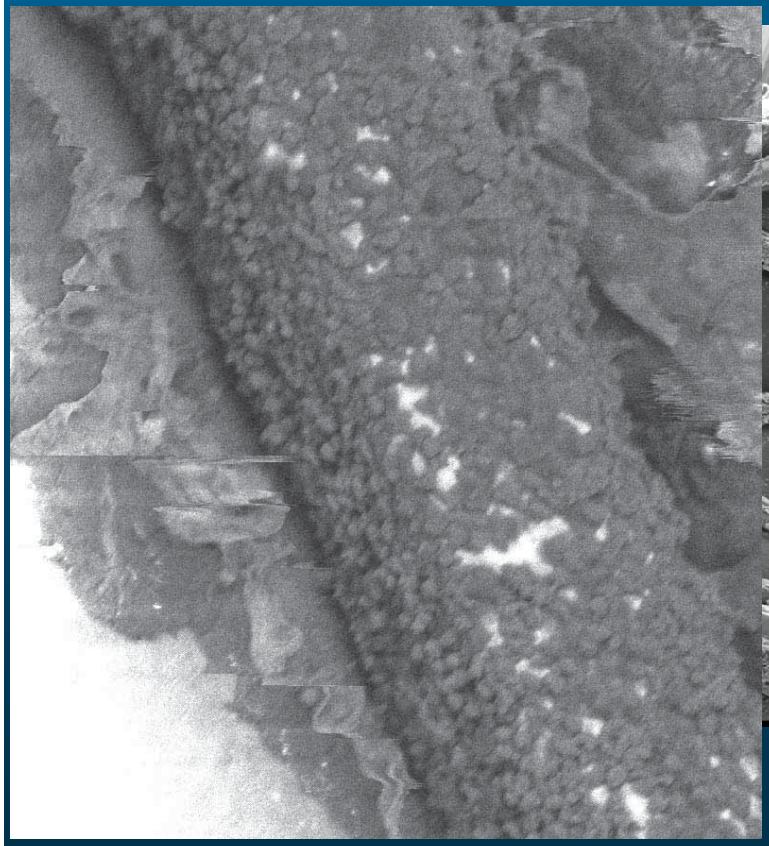
1h explant - Bare R-Stent

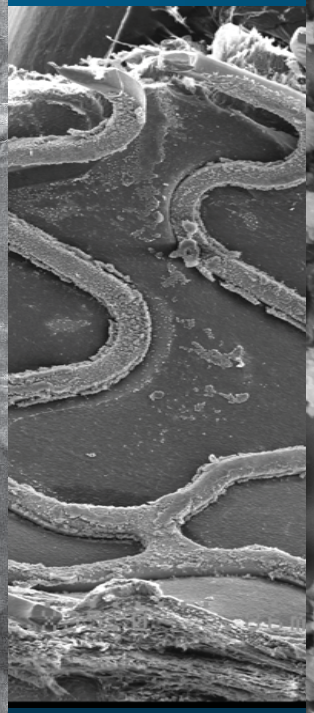


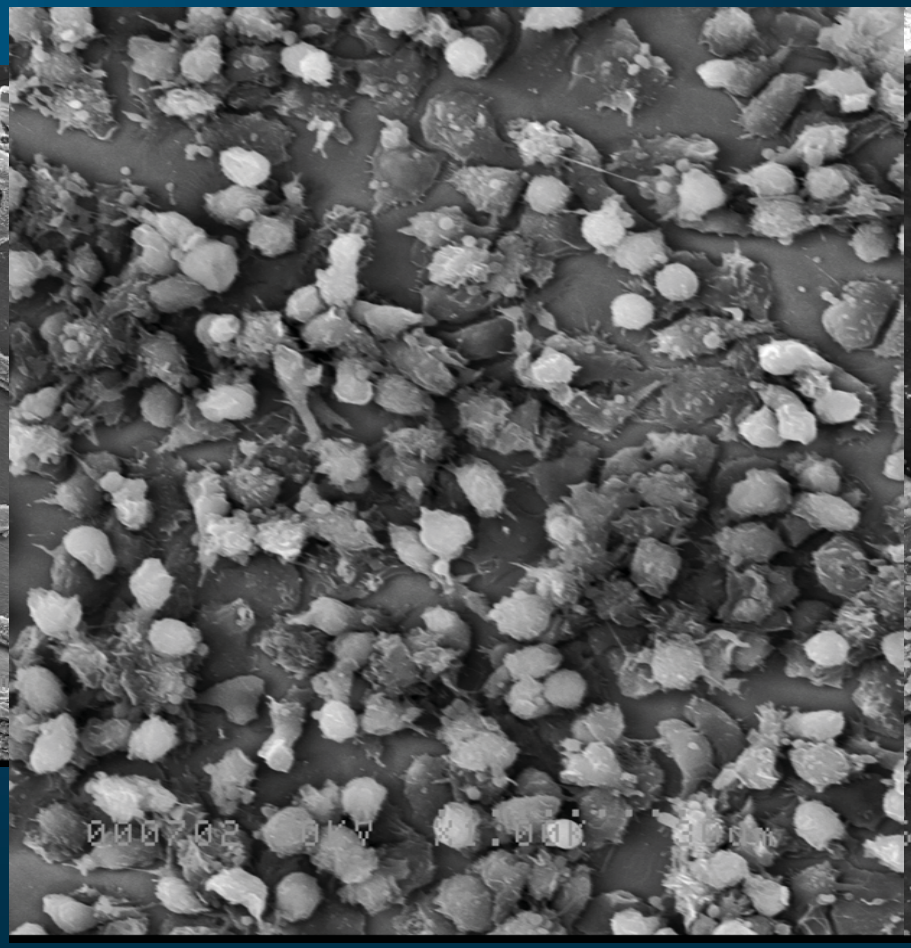


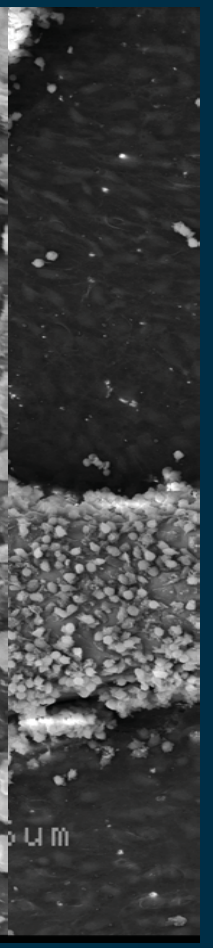
1h explant – Antibody Coated R-Stent

1h explant – Antibody Coated R-Stent

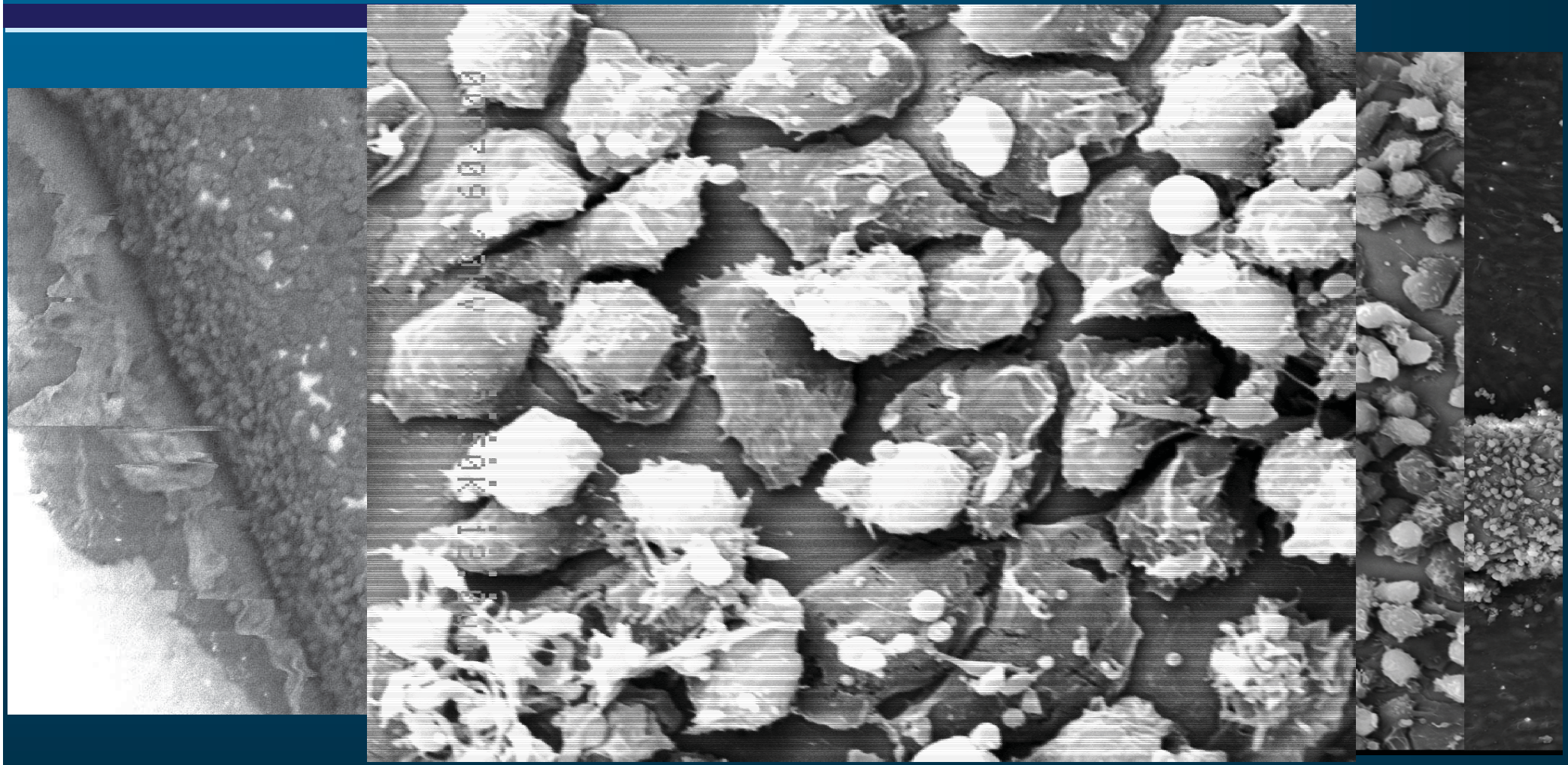






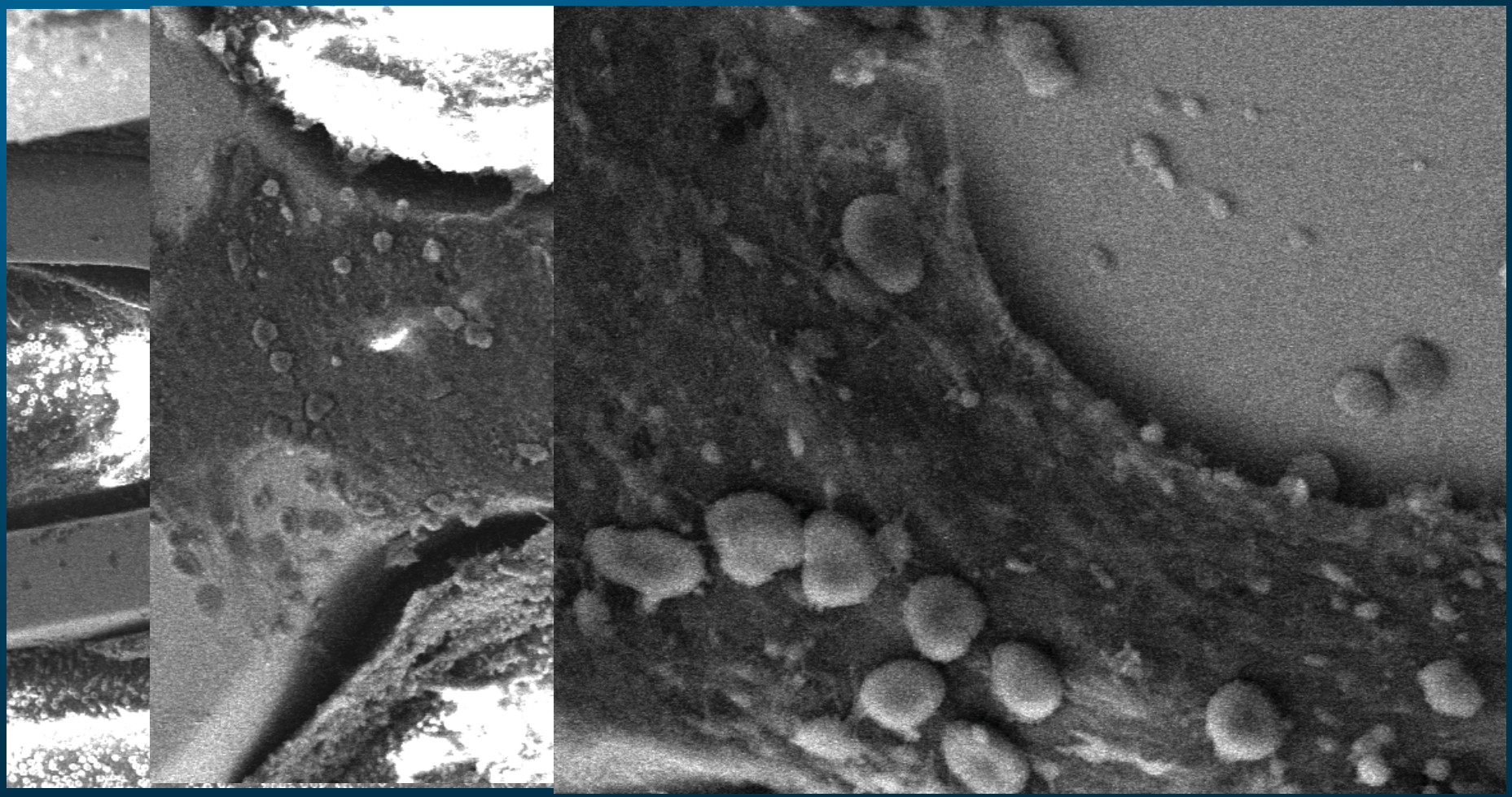


1h explant – Antibody Coated R-Stent

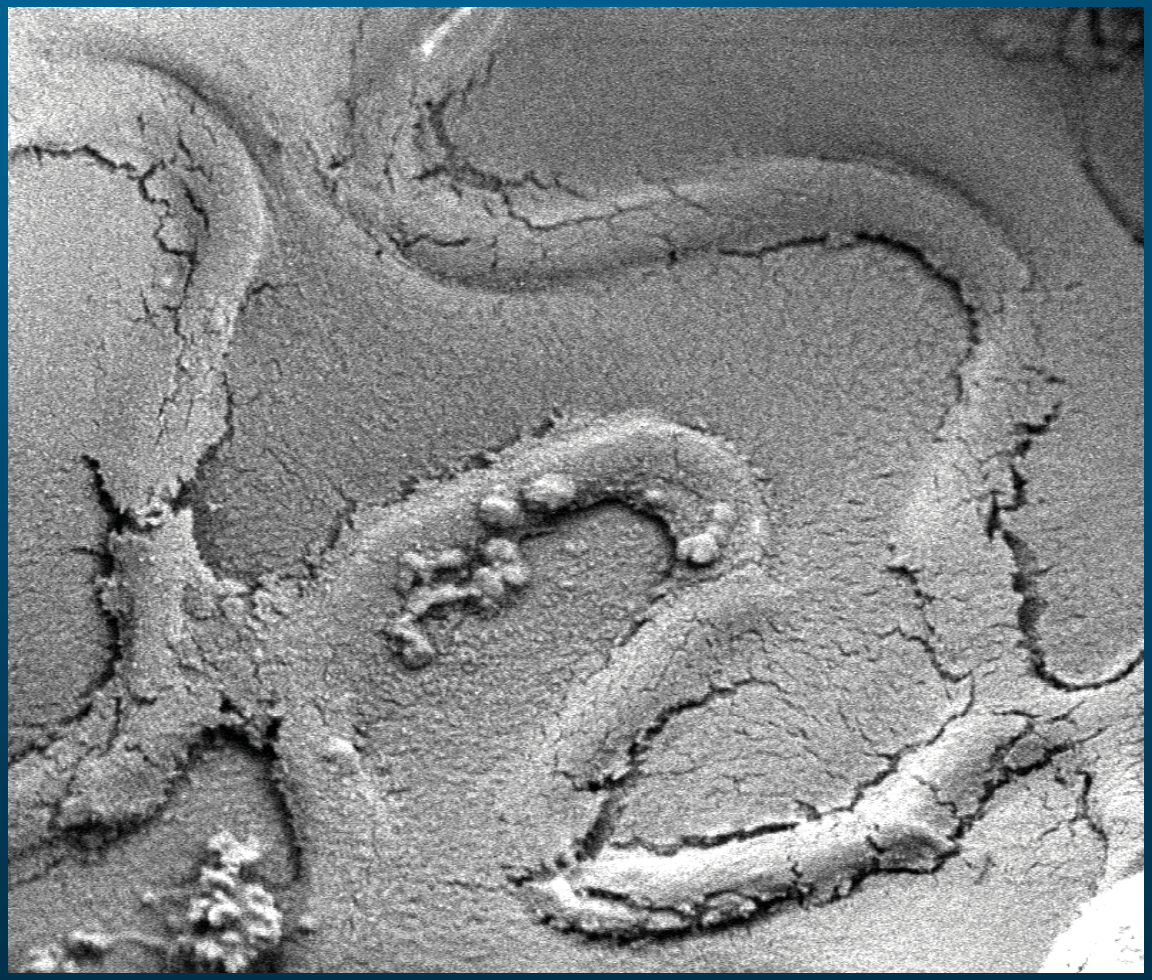


48h explant - Bare R-Stent

48h explant - Bare R-Stent

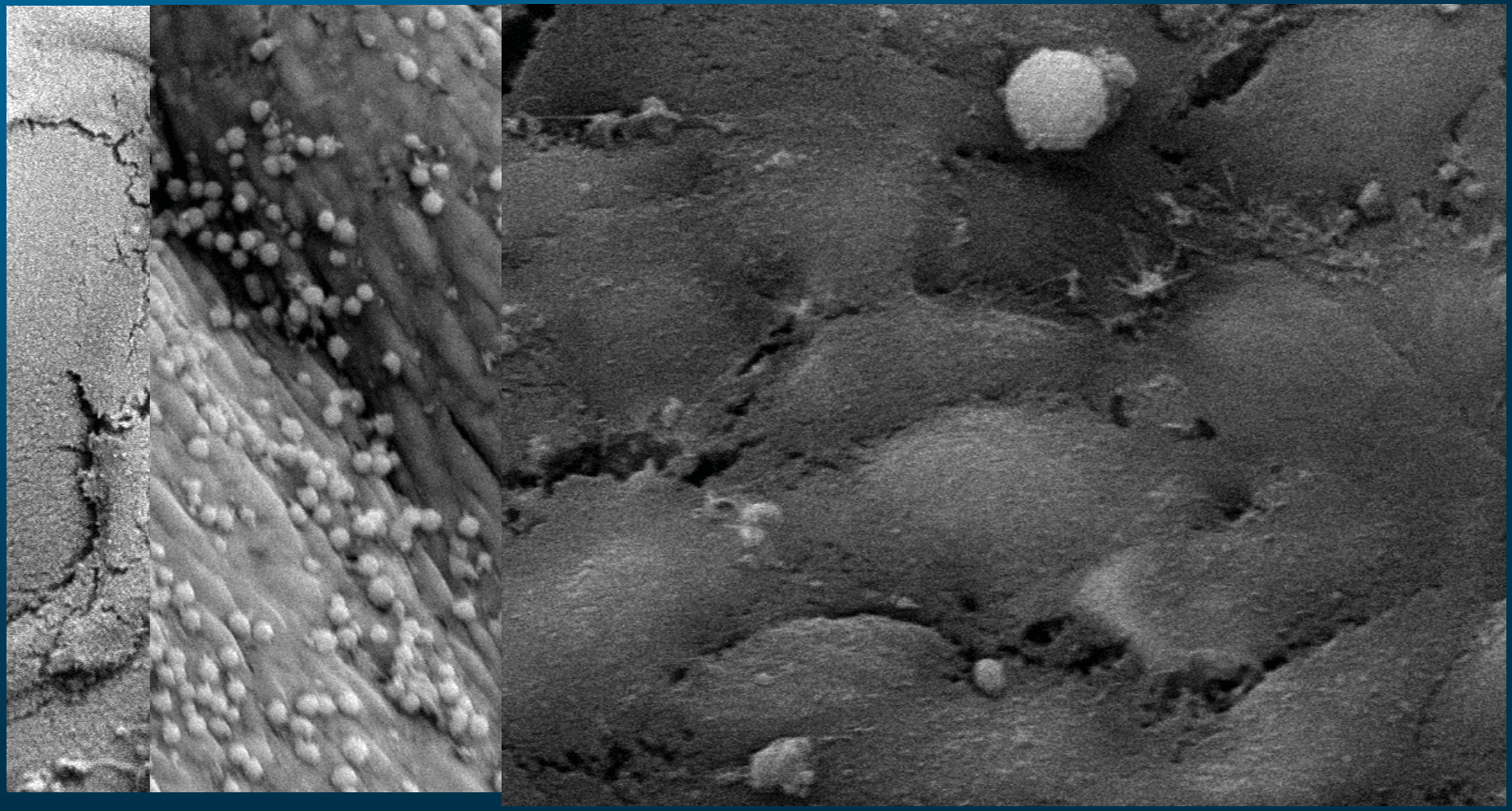


48h explant - Antibody Coated R-Stent



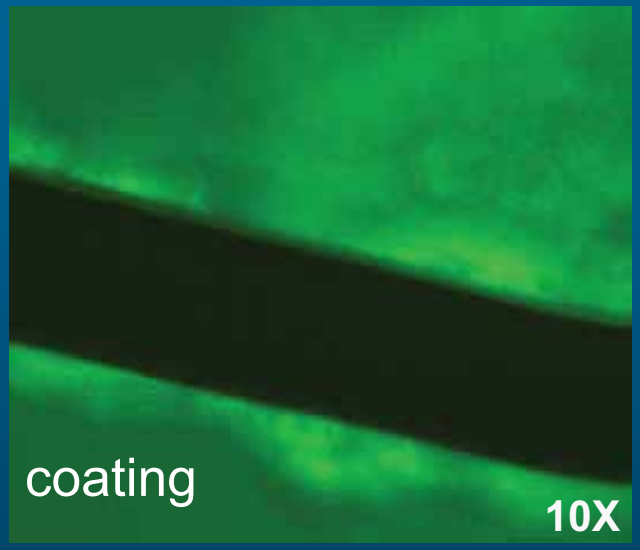
Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

48h explant - Antibody Coated R-Stent

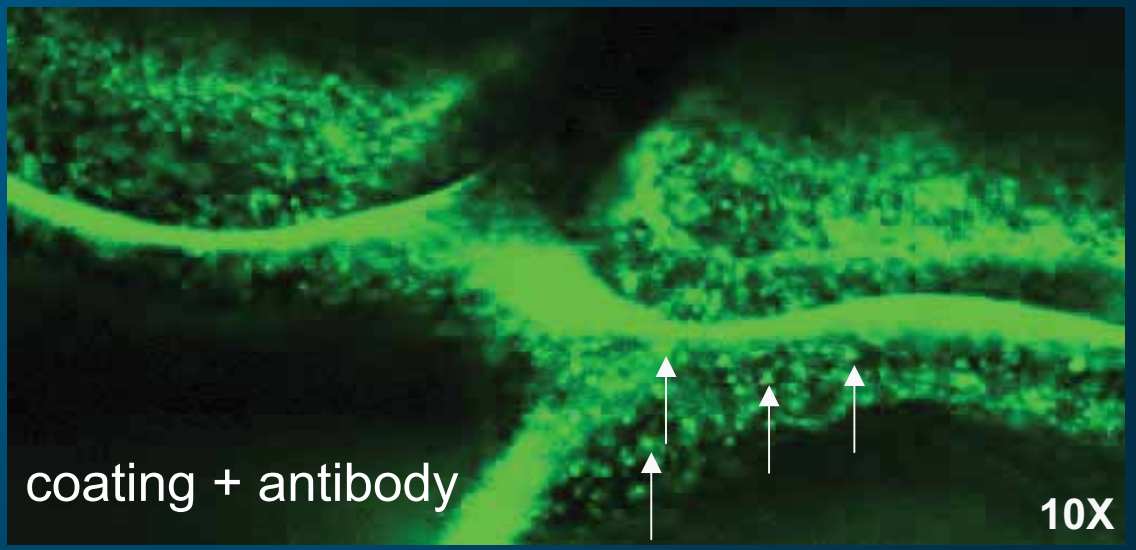


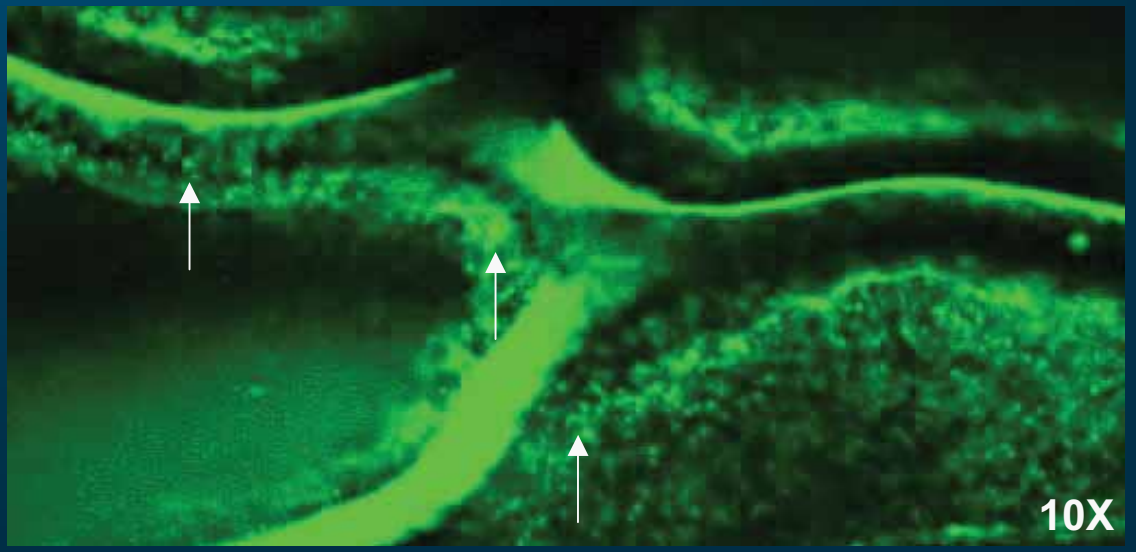
In Vivo EPC Capture – 48 hours

A



B





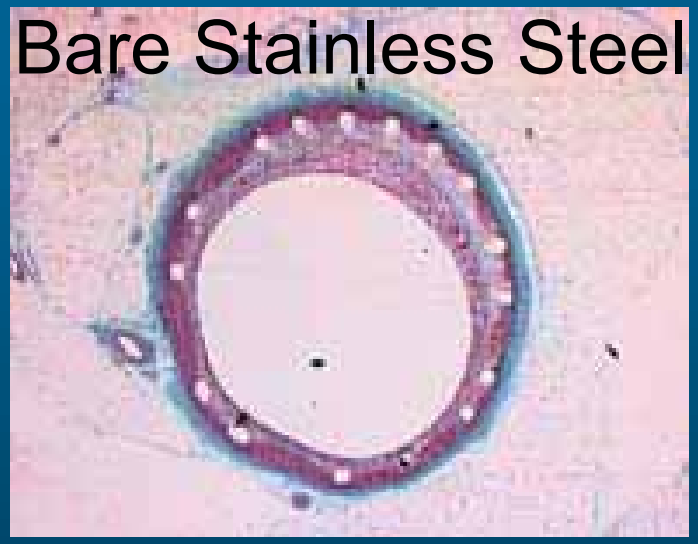
3.0 mm R stents with Antibody

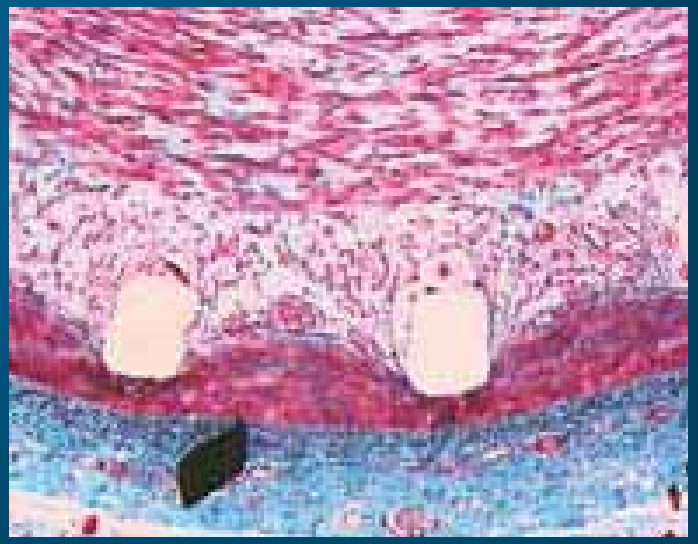
48 hours post implant

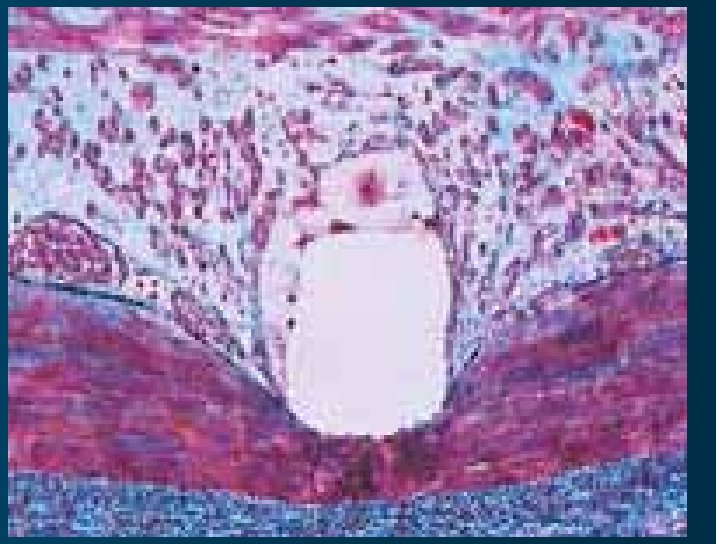
Stained with anti VEGFR-2

28 Day Histology

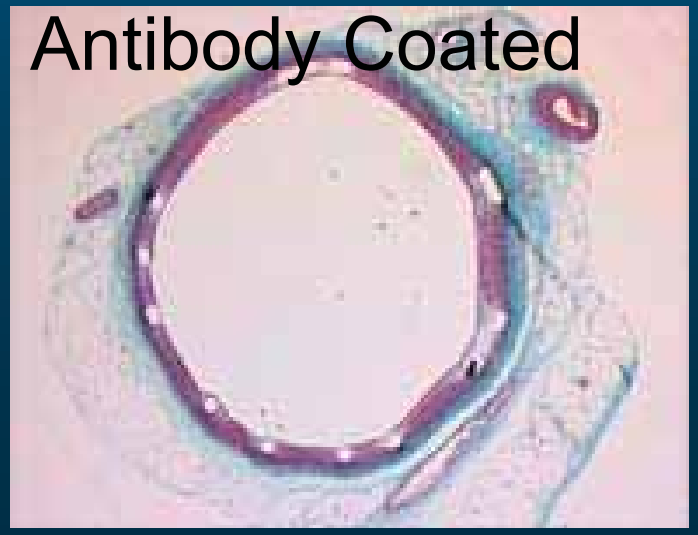
Bare Stainless Steel

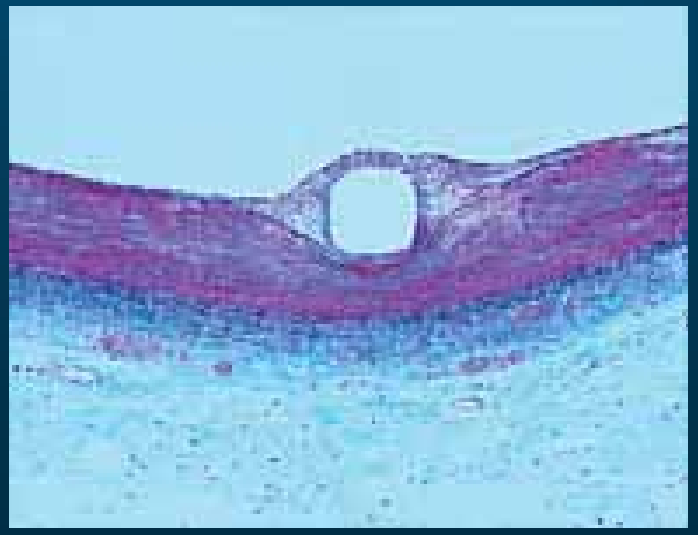


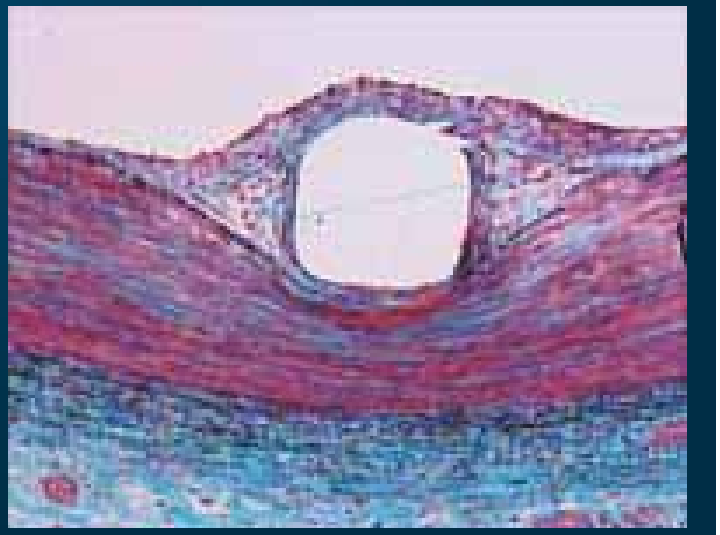




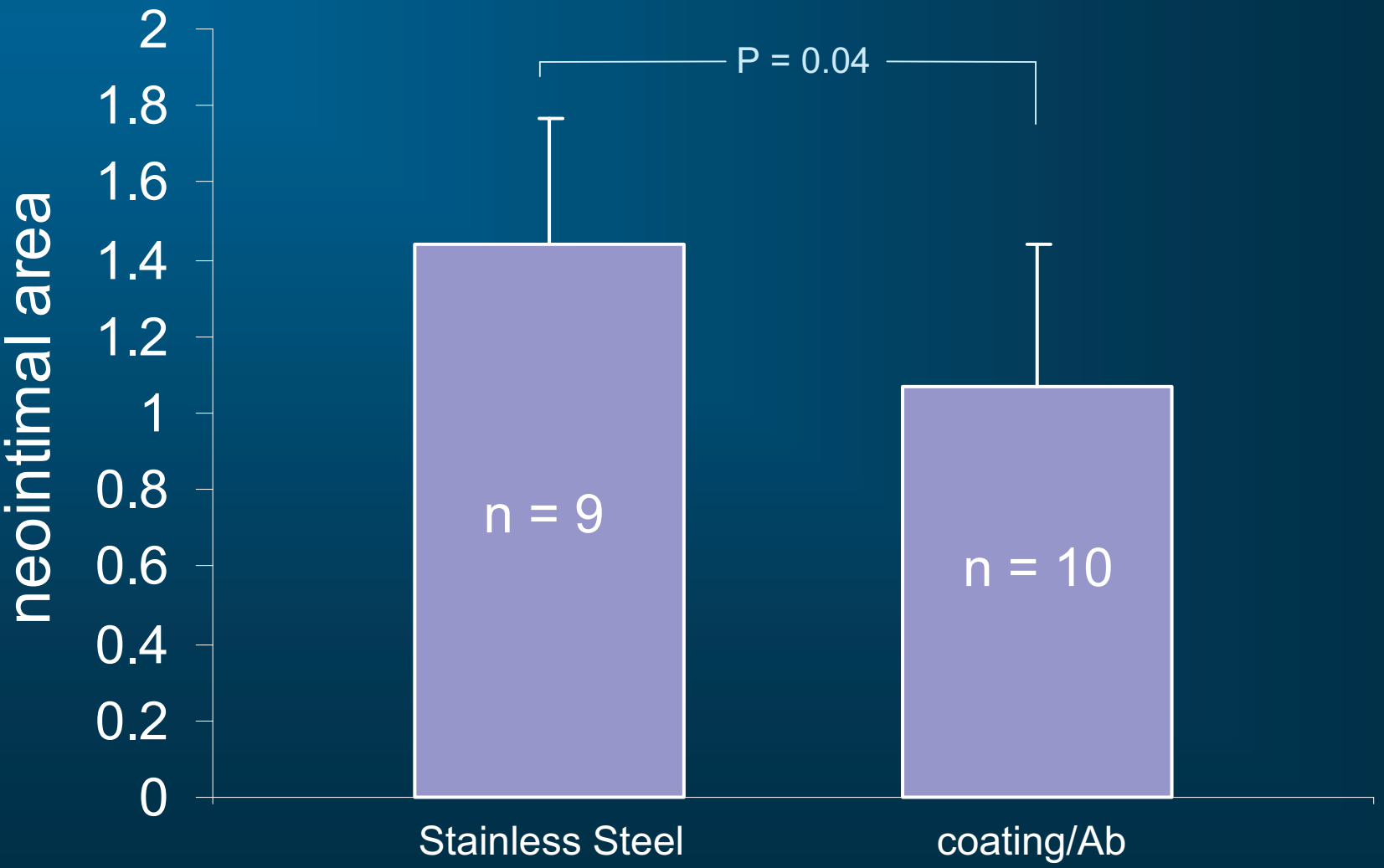
Antibody Coated







Neointimal area at 28 days



Pathology scores

	Inflammatory score	Injury score
Stainless Steel	0.75	0
Coating/Ab	0.76	0

Conclusions

This is the first demonstration of a successful technique for the endothelialization of an intravascular device by in vivo "autoseeding" with autologous endothelial cells.

Pre-clinical data show both the safety and the efficacy of EPC capture stents for the reduction (33%) of in-stent restenosis compared with bare stainless steel – supporting the initiation of the FIM-HEALING clinical trials.

HEALING I - FIM

Registry update

[Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (First In Man)]

HEALING I endpoints

Primary endpoint

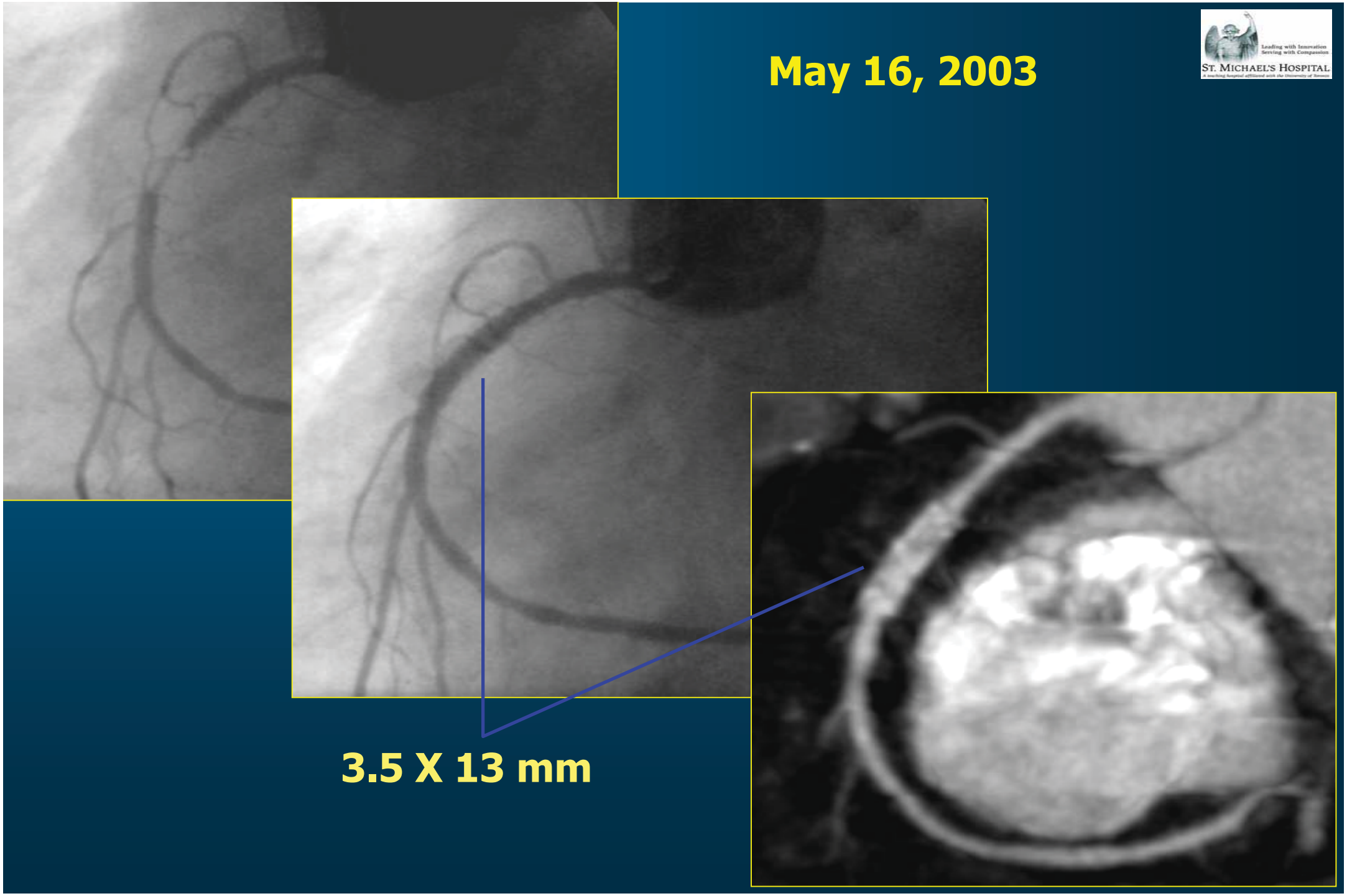
- Clinical safety: Absence of thrombosis, acute post-procedural, subacute at 30 days and late at 6 months

Secondary endpoints

- Clinical safety: MACCE within 30 days and at 6 Months
- Angiographic efficacy: Diameter stenosis at 6 months by QCA and IVUS

HEALING I

- 16 patients enrolled
  - Type A and B1 lesions
  - First patient in: 16 May 2003
  - Last patient in: 27 November 2003
  - Last patient out: 27 May 2004 (6 month follow-up)
- Study device: 13 mm and 18 mm "prototype" EPC Capture R Stent, wet formulated, hand-crimped
- Study results expected in late spring 2004


May 16, 2003
Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
3.5 X 13 mm

HEALING II
clinical registry

Healing II Objective

- Assess safety and efficacy of the EPC Capture R Stent™ in single *de novo* native coronary lesions

Healing II Endpoints

Primary endpoints

- Safety: MACE at 30 days
- Efficacy: % in-stent volume obstruction (IVUS)

Secondary endpoints

- QCA pre-, post-procedure and at 6-month f/up
- IVUS post-procedure and 6-month f/up
- TLR at 6 months
- MACE to 9 months
- Angiographic stent thrombosis

Trial design

- Multicenter, prospective registry study
- 60 Patients, 10 European centers
  - Single de novo lesion $\leq$ 12 mm in length
  - Reference diameter $\geq$ 2.5 mm and $\leq$ 3.5 mm
- Study device: 9 and 18 mm EPC Capture R Stent, dry, balloon mounted
- All patients to be followed clinically up to 9 months
- Repeat angiography and IVUS at 6 months

Trial design

- HAMA (human anti-murine antibody) testing will be performed pre-, post-procedure, at 30 days and at 6 months

Future Developments

- Antibody Targets
  - Epitope
  - Fragments
  - Chimeric or Humanized
- Intermediate Layers
  - Polysaccharide
  - C_{60} Fullerenes
- Device Designs
  - Stent Modifications
  - Grafts & Stent Grafts
  - Tissue Engineering