Neues Coating-Konzept beim Drug Eluting Balloon

S.H. Duda

Gefäßzentrum
am Jüdischen Krankenhaus

Proven effectiveness of Paclitaxel to prevent restenosis

Paclitaxel blocks transition between metaphase and anaphase and induces cell death

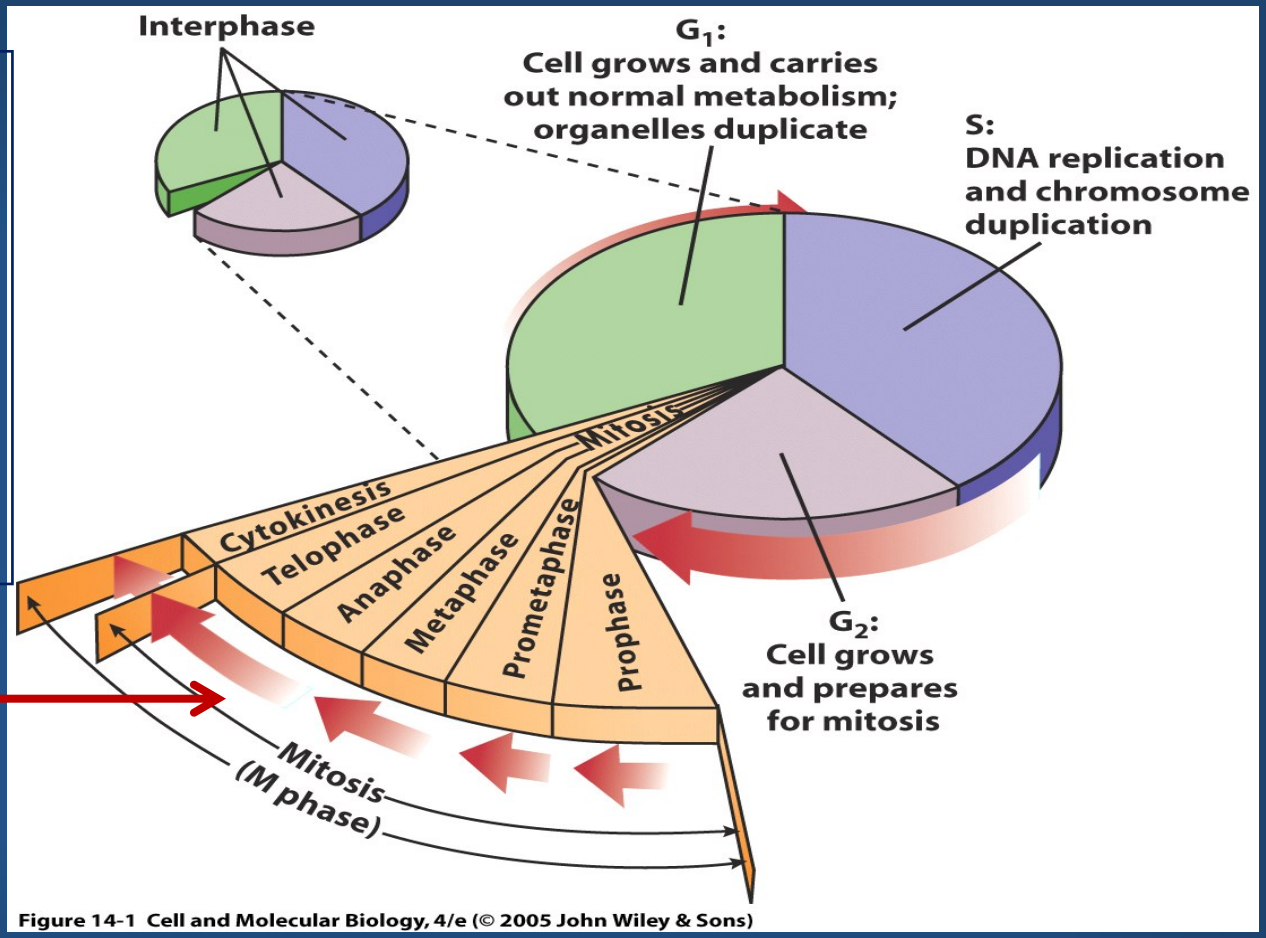
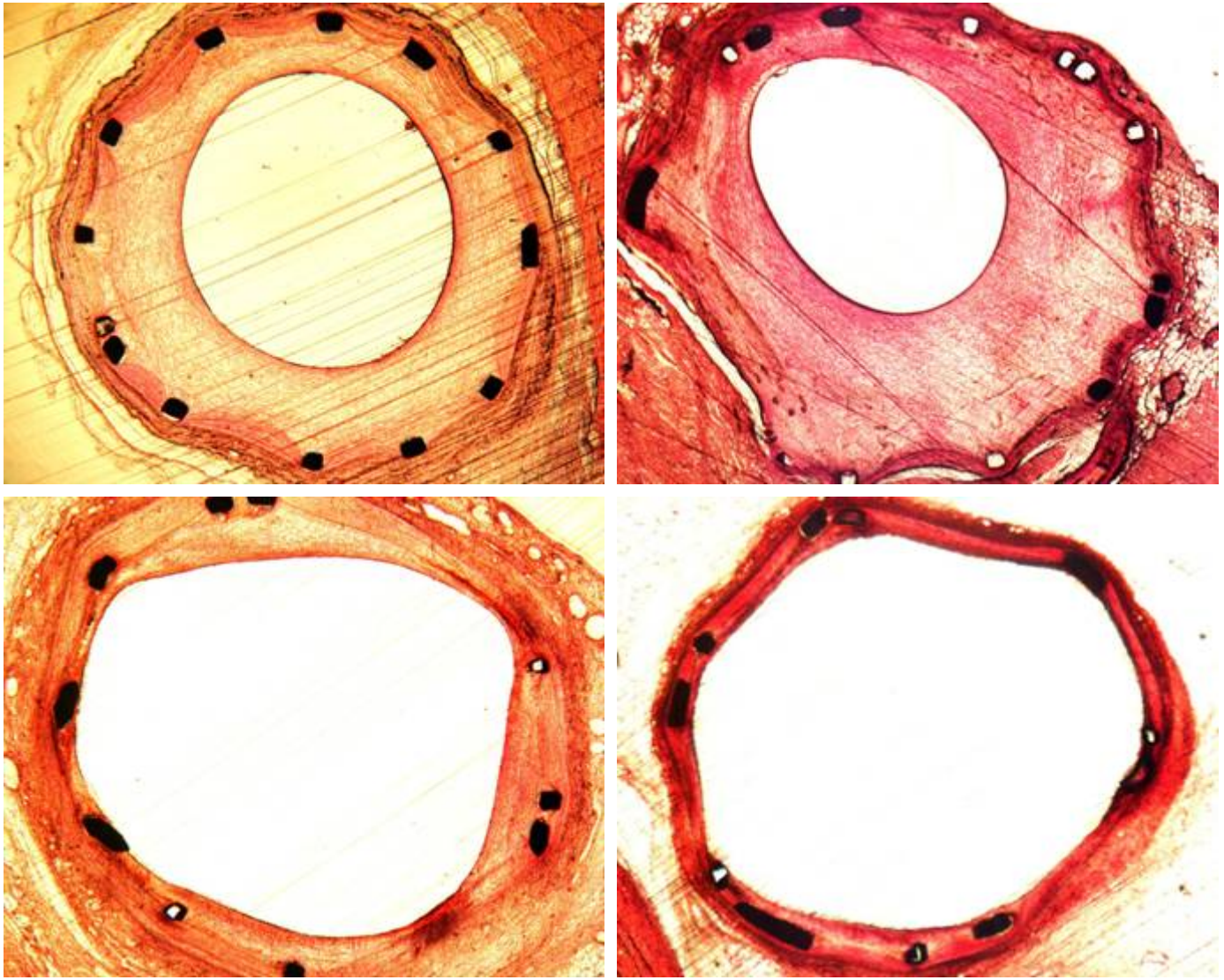


Figure 14-1 Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

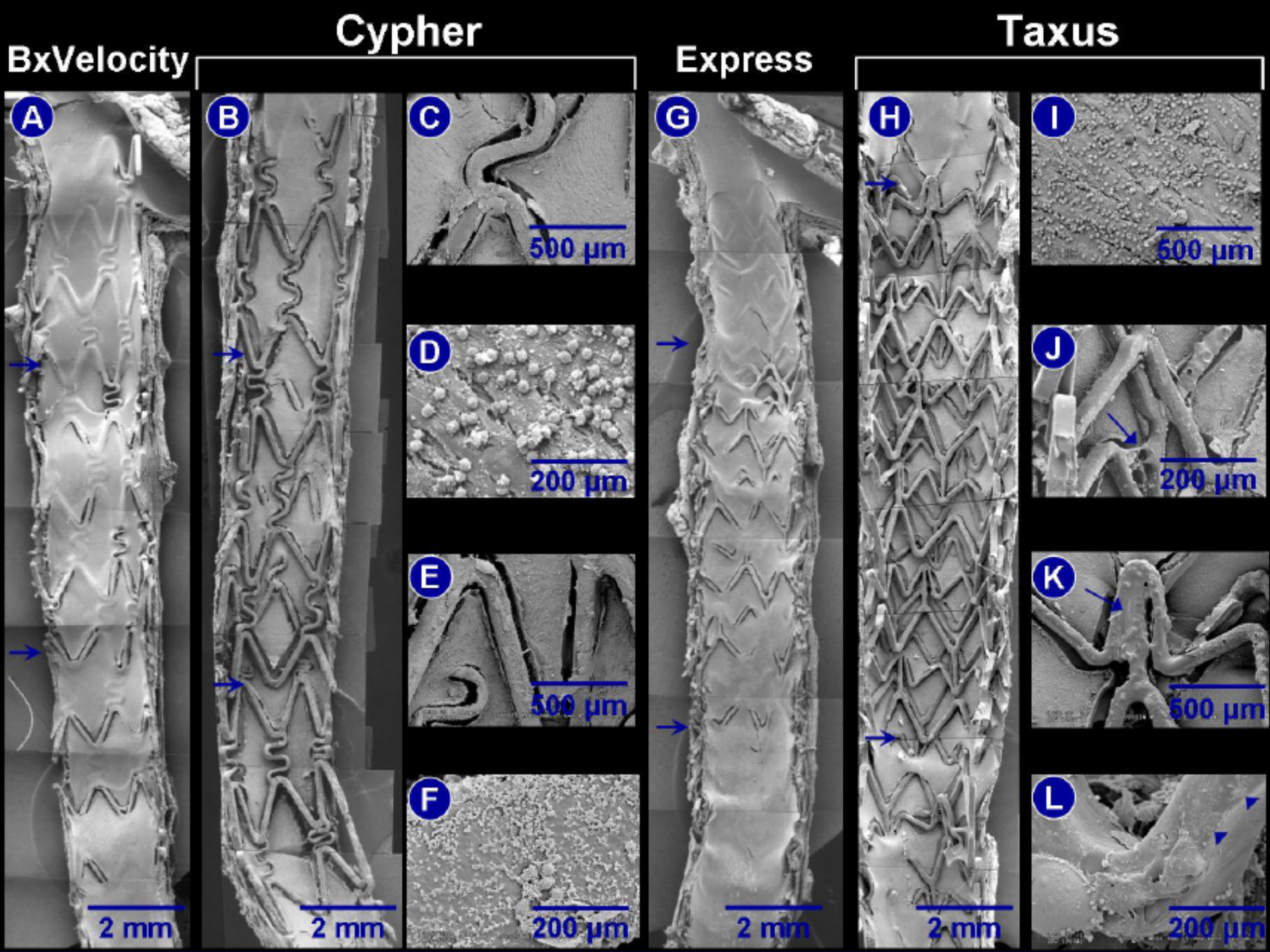
Paclitaxel targets microtubules

Approach: Paccocath



Coronary arteries of pigs

Scheller and Speck et al. Circulation 2004; 110: 810 - 4

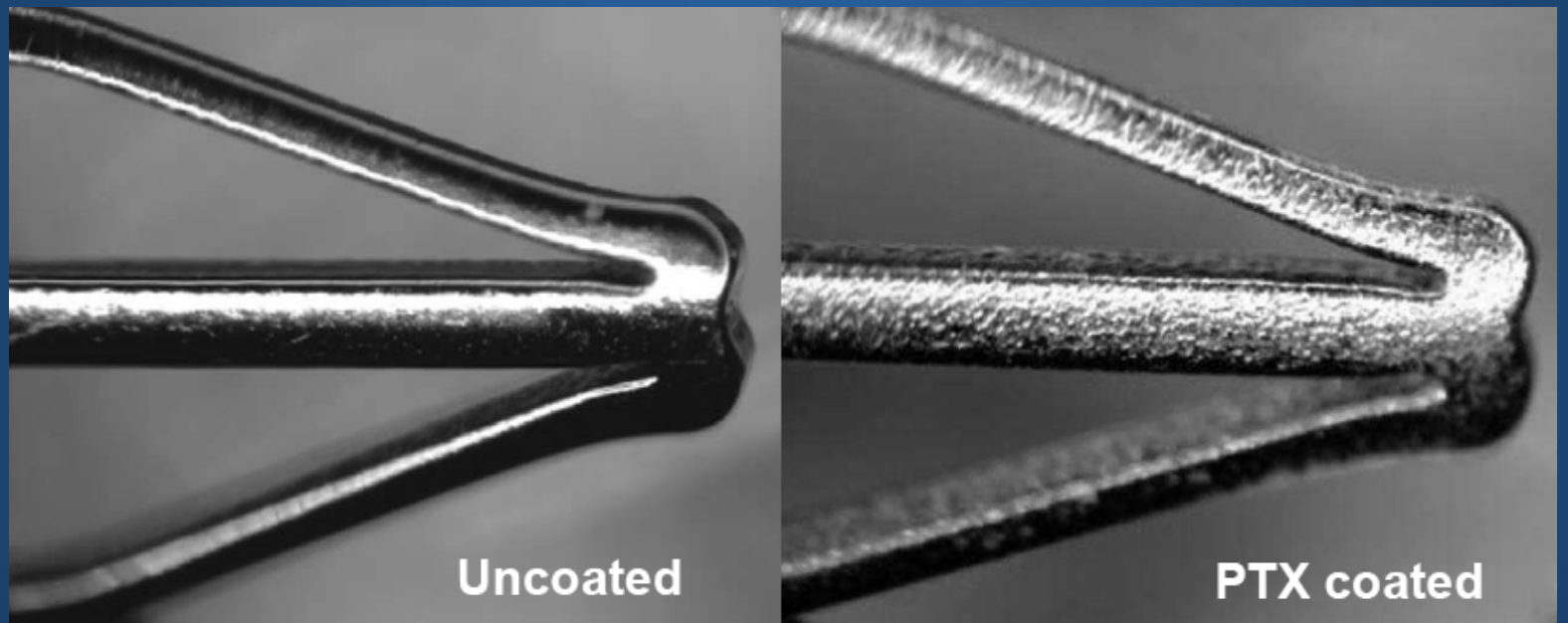

BxVelocity
Cypher
Express
Taxus
A
B
C
D
E
F
G
H
I
J
K
L
2 mm
2 mm
500 µm
200 µm
500 µm
200 µm
2 mm
2 mm
500 µm
200 µm
500 µm
200 µm

DES Issues

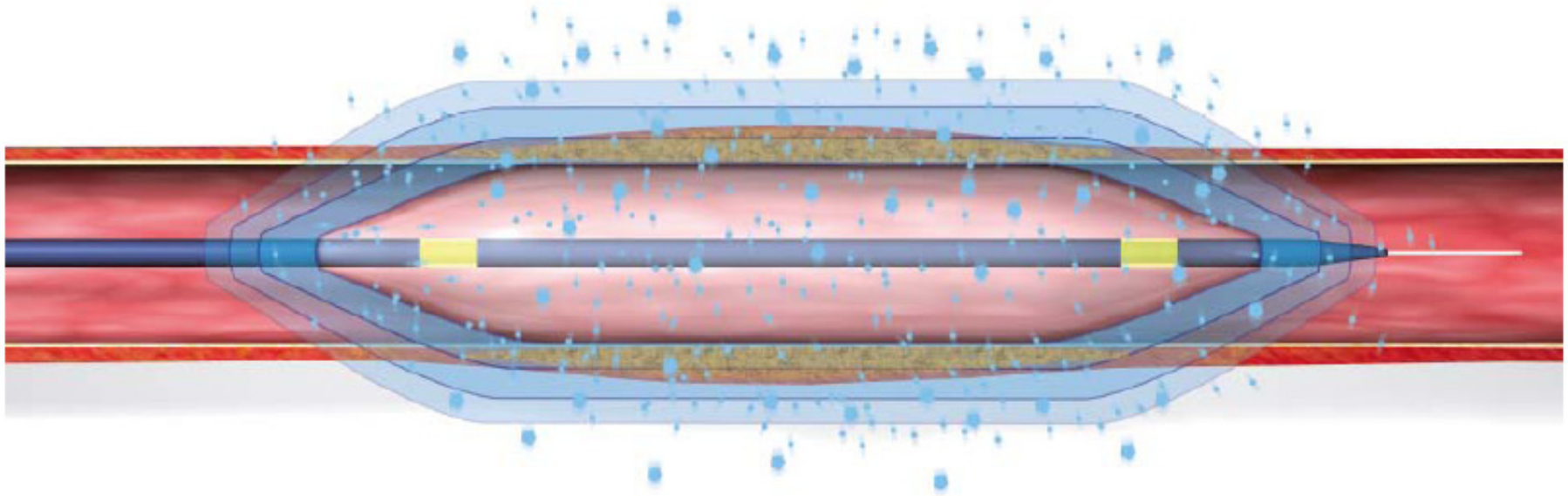
1) Stent Fractures in the SFA
2) Polymer: Adverse Effects
3) Delayed Healing

Zilver® PTX™

- **Paclitaxel only**
  - **No polymer or binder**
  - **3 µg/mm^2 dose density**
- **Zilver®, self-expanding nitinol stent**



DEB Concept



Some DCBs Work, others Do NOT

Success:

TLR at 2 years					
Indication	Study	Formulation	DCB	POBA	TAXUS
Coronary ISR	Paccocath ISR I & II[1,2]	Paclitaxel + Iopromide	4%	37%	
	PEPCAD II[3*]		6%		15%
SFA	THUNDER[4]		15%	52%	
	FemPac[5]		13%	50%	

[1]Scheller 2006 *NEJM* 355(20):2113-24. [2]Scheller 2008 *Clin Res Cardiol 97(10):773-81*. [3]Unverdorben 2009 *CIRC 119(23):2986-94*; *TLR at 1 years for PEPCAD II; follow-up ongoing but only 12 month data reported. [4]Tepe 2008 *NEJM* 358(7):689-99. [5]Werk 2008 *CIRC* 118:1358-65.

Failure:

TLR at 9 months					
Indication	Study	Study Flaw	DCB	TAXUS	CYPHER
Small Vessel CAD	Piccoleto[6*]	Paclitaxel Alone	32%	10%	
DeNovo CAD	PEPCAD III[7]	DCB w/Pre-crimped stent vs DES	11%		5%

[6]Cortese 2009 PCR Presentation: Paclitaxel-eluting balloon versus paclitaxel-eluting stent in small coronary vessel disease; *TLR at 6 months for Piccoleto. [7]Hamm 2009 AHA resentation: Paclitaxel-eluting PTCA-Balloon in Combination with the Coroflex Blue Stent vs the Sirolimus Coated Cypher Stent in the Treatment of Advanced Coronary Artery Disease

Cambridge Consultants

Market strategy report

Table 1: Key players active in developing DEB technologies

Company	DCB Name	Drug formulation
Aachen Resonance GmbH (distributed by Biotronik AG in UK, Switzerland, Benelux, Italy and Ireland).	ELUTAX®	Formulated with a matrix of pure Paclitaxel
B. Braun Melsungen AG	SeQuent® Please	Paclitaxel with ioporimde formulation (Paccocath® technology)
Bayer AG (MEDRAD, Inc.)	CotavanceTM with Paccocath® coating technology	Paclitaxel with ioporimde formulation (Paccocath® technology)
Caliber Therapeutics, Inc.	TADD (Targeted Angioplasty Drug Delivery)	Rapalog-based with unknown formulation
Cook Group, Inc.	Advance® 18PTX®	Paclitaxel with unknown additive-based formulation
Eurocor AG	DIOR®	***Paclitaxel + Shellac***
Invatec s.r.l.	IN.PACT™ Amphirion	Paclitaxel with FreePac™ hydrophilic formulation
Lutonix, Inc.	Unknown	Paclitaxel with unknown formulation

Competition: patents

INVATEC TECHNOLOGY CENTER GMBH [CH/CH]; Hungerbüelstrasse 12 A 8500 Frauenfeld (CH) *(All Except US)*.
SCHELLER, Bruno [DE/DE]; (DE) *(US Only)*.
SPECK, Ulrich [DE/DE]; (DE) *(US Only)*.

SCHELLER, Bruno; (DE).
SPECK, Ulrich; (DE).

(EN) The present invention relates to novel combinations of balloon catheters and active ingredient preparations adhering to the surface of the balloon membrane. The present invention further relates to coating methods for producing said balloon catheters, and to the use thereof for the treatment and prophylaxis of vascular diseases.

(DE) Die vorliegende Erfindung betrifft neue Kombinationen von Ballonkathetern und an der Oberfläche der Ballonmembran haftenden Wirkstoffzubereitungen. Des weiteren betrifft die vorliegende Erfindung Beschichtungsverfahren zur Herstellung dieser Ballonkatheter sowie deren Verwendung zur Behandlung und Prophylaxe von Gefäßerkrankungen.

Competition: patents

(WO/2004/028582) MEDICAL DEVICE FOR DISPENSING MEDICAMENTS

Biblio. Data | Description | Claims | National Phase | Notices | Documents

Latest bibliographic data on file with the International Bureau

Pub. No.: WO/2004/028582
Publication Date: 08.04.2004
Chapter 2 Demand Filed: 19.04.2004

International Application No.: PCT/DE2003/002871
International Filing Date: 26.08.2003

IPC: ***A61L 29/16*** (2006.01), ***A61L 31/16*** (2006.01)

Applicants: **SPECK, Ulrich** [DE/DE]; (DE).
SCHELLER, Bruno [DE/DE]; (DE) *(US Only)*.

Inventors: **SPECK, Ulrich**; (DE).
SCHELLER, Bruno; (DE).

Agent: **WABLAT, Wolfgang**; Potsdamer Chaussee 48, 14129 Berlin (DE) .

Priority Data: 102 44 847.7 20.09.2002 DE

Title: (EN) MEDICAL DEVICE FOR DISPENSING MEDICAMENTS
(DE) MEDIZINISCHE VORRICHTUNG ZUR ARZNEIMITTELABGABE

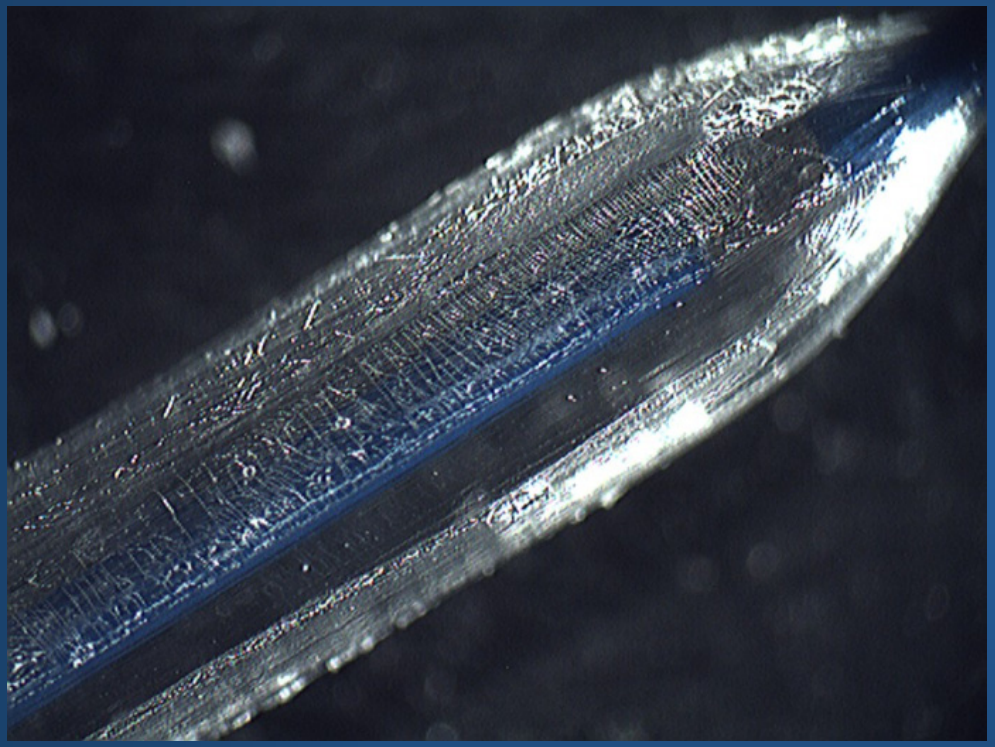
Competition: patents

Abstract: (EN) For selective treatment of diseased tissue sections or organ parts, the surface of medical devices entering into contact with areas thereof under pressure is coated with lipophilic substantially water-insoluble medicaments binding to various tissue components with good adherence thereto, said medicaments having an effect thereupon a short time after entering into contact therewith without exerting a harmful influence upon adjacent healthy tissue.

(DE) Zur selektiven Therapie erkrankter Gewebeabschnitte oder Organteile ist die Oberfläche von diese Bereiche unter Druck kontaktierenden medizinischen Vorrichtungen mit lipophilen, weitgehend wasserunlöslichen und an beliebige Gewebebestandteile bindenden Arzneistoffen guthaftend beschichtet, die an der betreffenden Stelle sofort nach Gewebekontakt in nur kurzer Kontaktzeit und ohne schädigenden Einfluss auf benachbartes gesundes Gewebe ihre Wirkung entfalten.

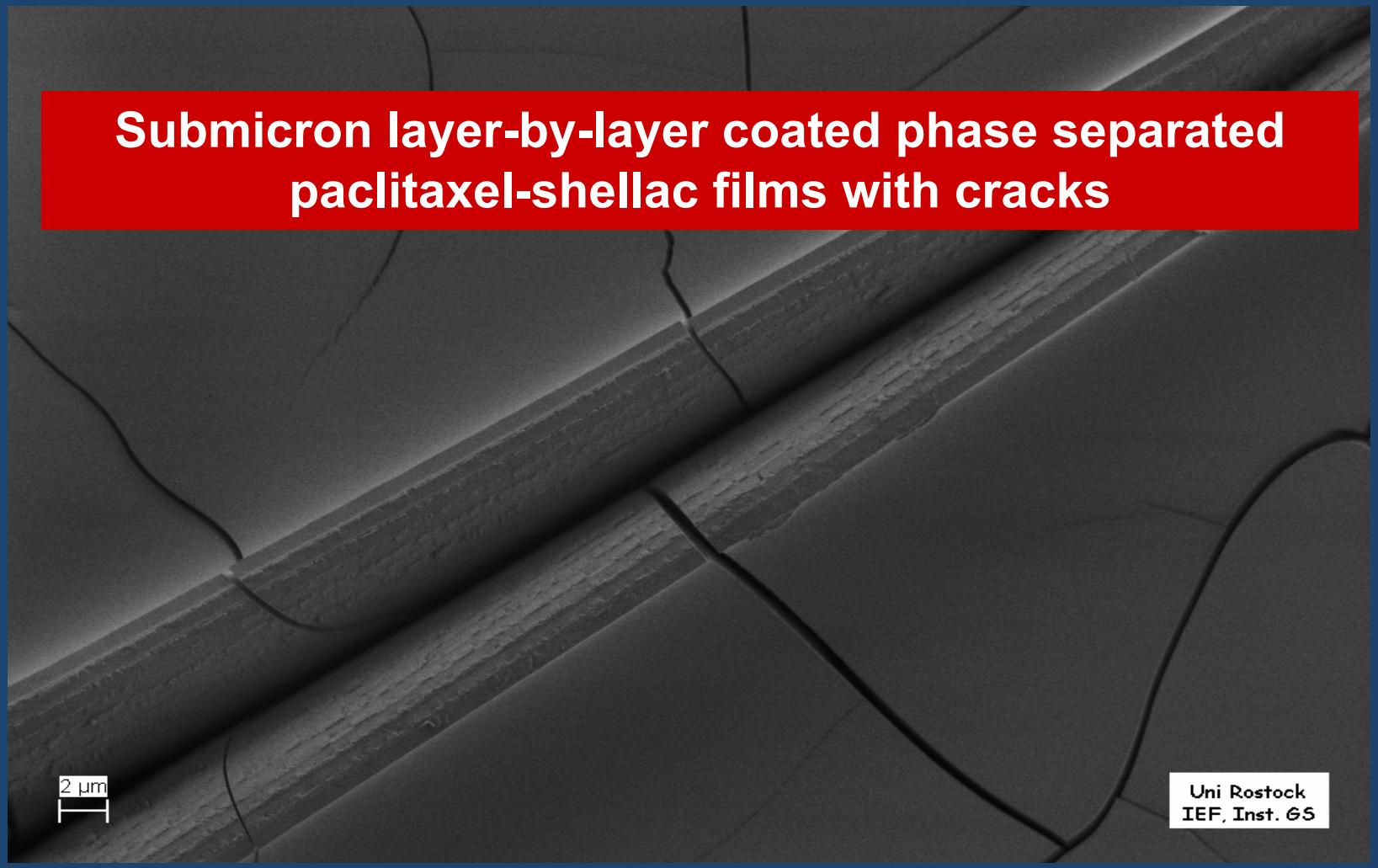
DEB appearance

Shellac: non-milky appearance

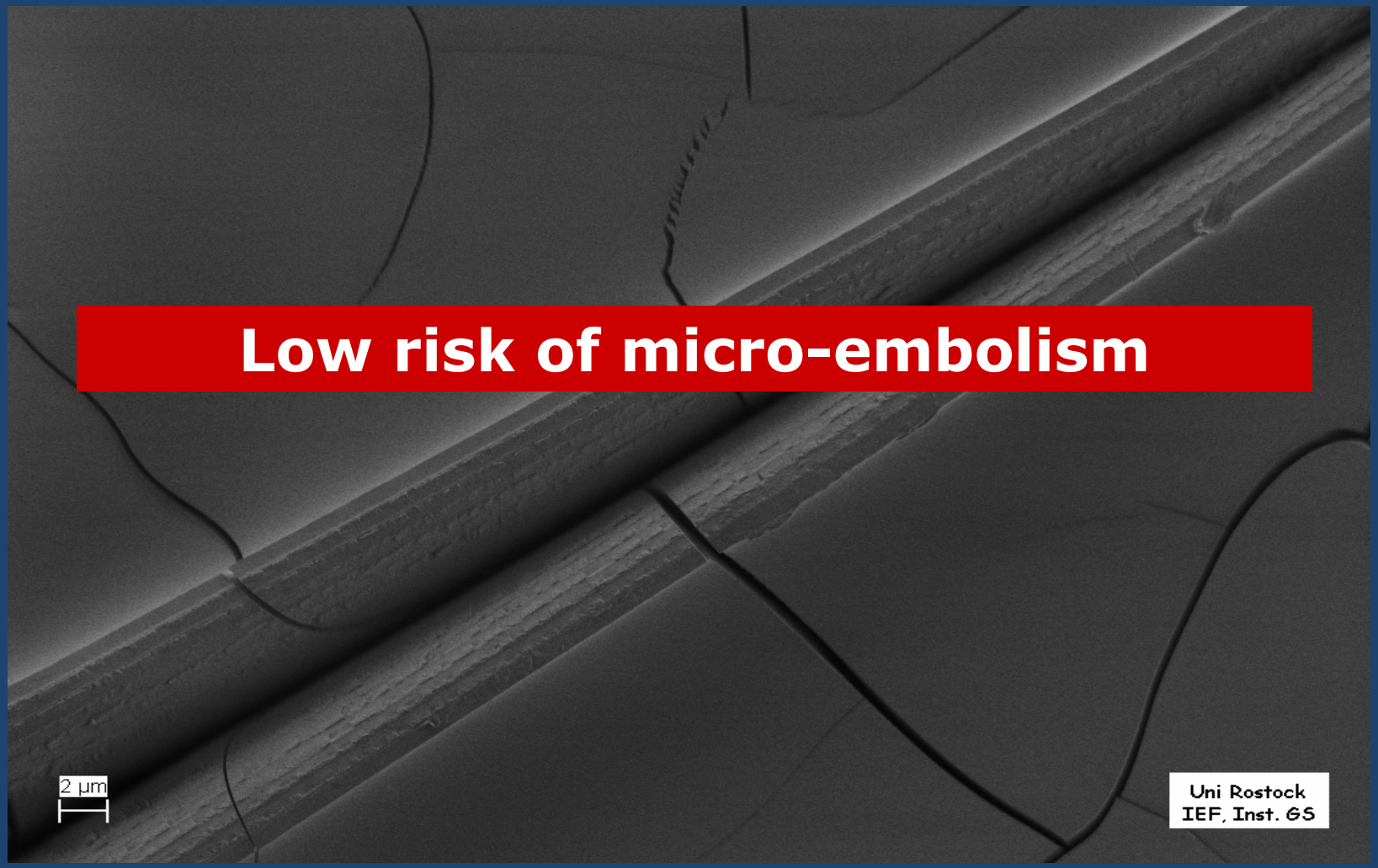


Compared to competitive products Shellac gives balloon a shiny appearance

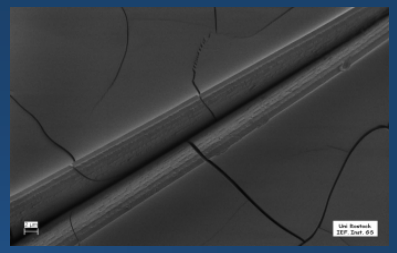
Coating surface: non-crystallin



Coating surface: non-crystallin



Production technology



- **Micropipetting technology**
  - Micropipetting ensures homogeneous and controllable method of coating
- **Coating layer by layer**
- **No-thickening by layer coating**
  - Only 6 µm layer thickness

Production technology

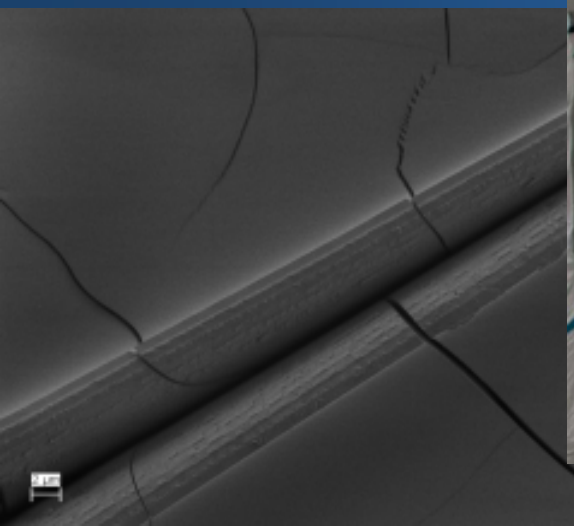
Advantages of the micropipetting technology

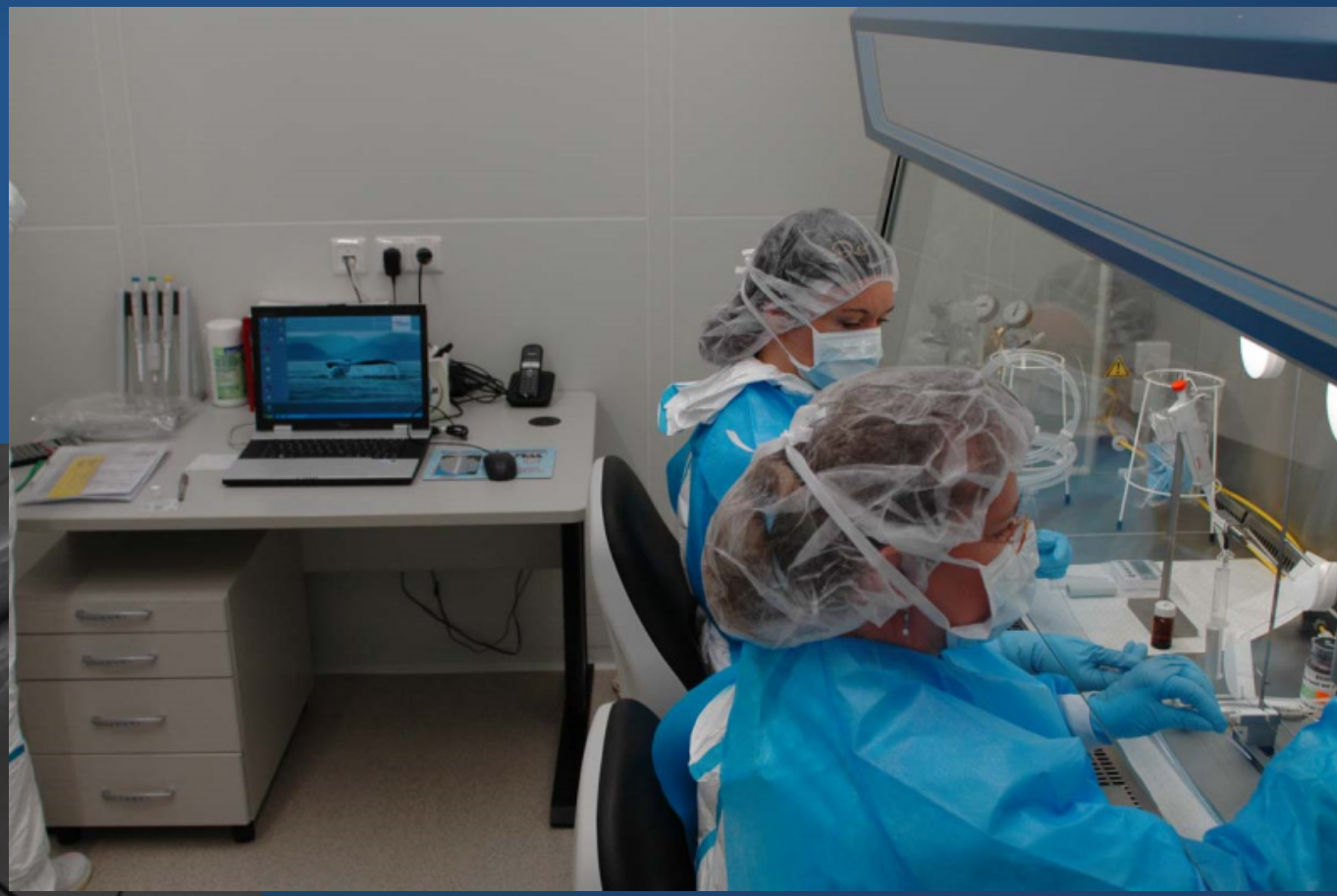
- **dose control**
- **Homogeneous coating over length and diameter**
- **Reproducibility of appearance, dosage, homogeneity**
- **Balanced adherence and drug transport properties**

Requirement	Dose control	Reproducibility	Homogeneity	Effect
Spray coating	Poor	Good	**Very good**	Mid
Dip coating	Very poor	Poor	Poor	Very low
Micropipetting	**Very good**	**Very good**	**Very good**	**High**

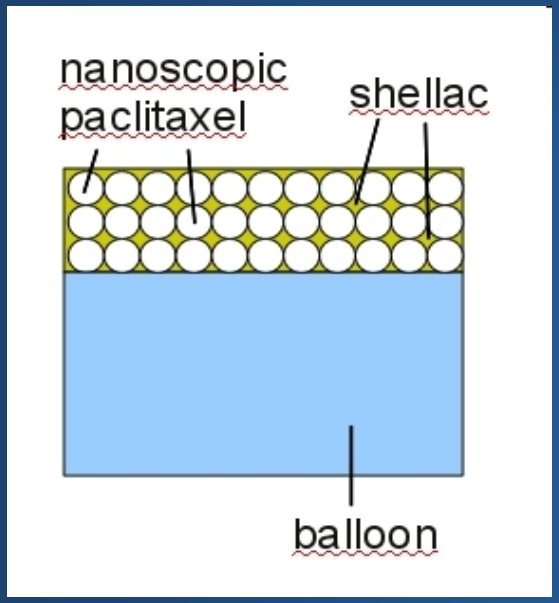
Production technology

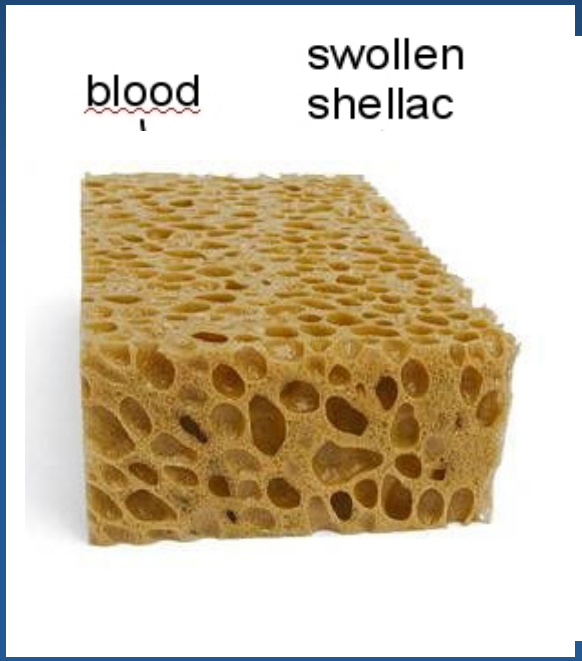
- **Micropipetting allows coating solution to go into pockets under folds**

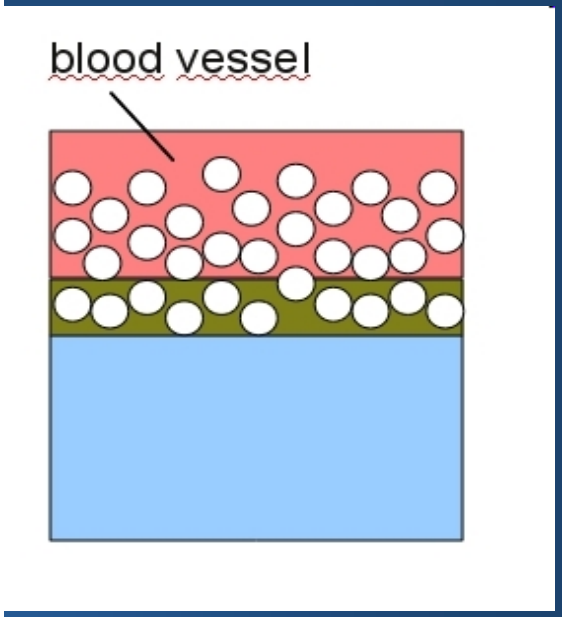




Shellac is not a polymer





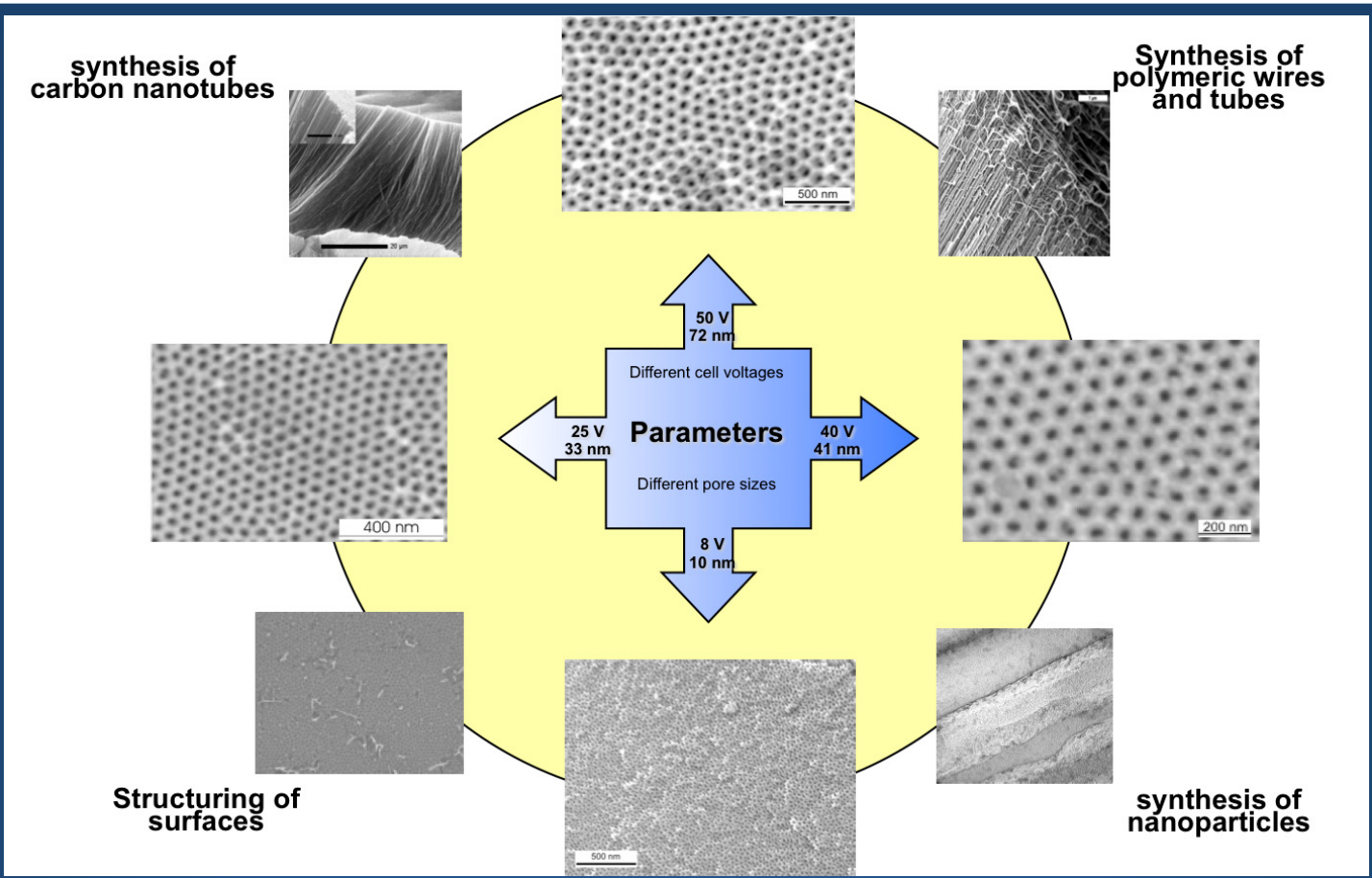


coated balloon

in contact with blood

inflation

Nanoscopic Paclitaxel

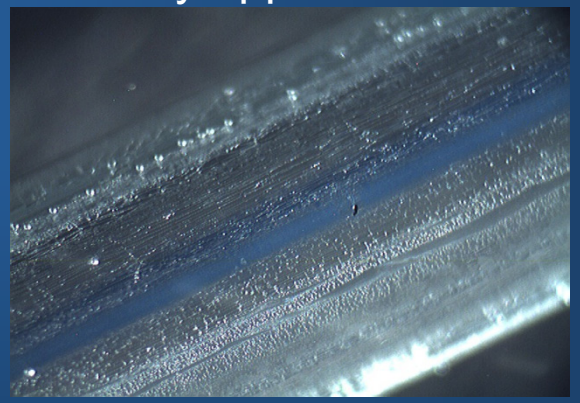


Nanoscopically structured materials show self-organization of single shape persistent molecules into well-defined supramolecular structures

Shellac

- Paclitaxel balloon surface: 3 µg/mm²
- Coating method is a 1:1 mixture of Paclitaxel (Ph.Eur. 5.0) and Shellac (Ph.Eur. 4.8)
- The Coating is CE marked
- Shellac is well established in Cosmetics, as food coating and Tablet coating.
- Shellac is recognized as safe (GRAS) by the FDA
- Balloon inflation time recommended: 30 – 45 sec. @ nominal balloon pressure

The optical refraction of Shellac gives balloon a shiny appearance



Shellac

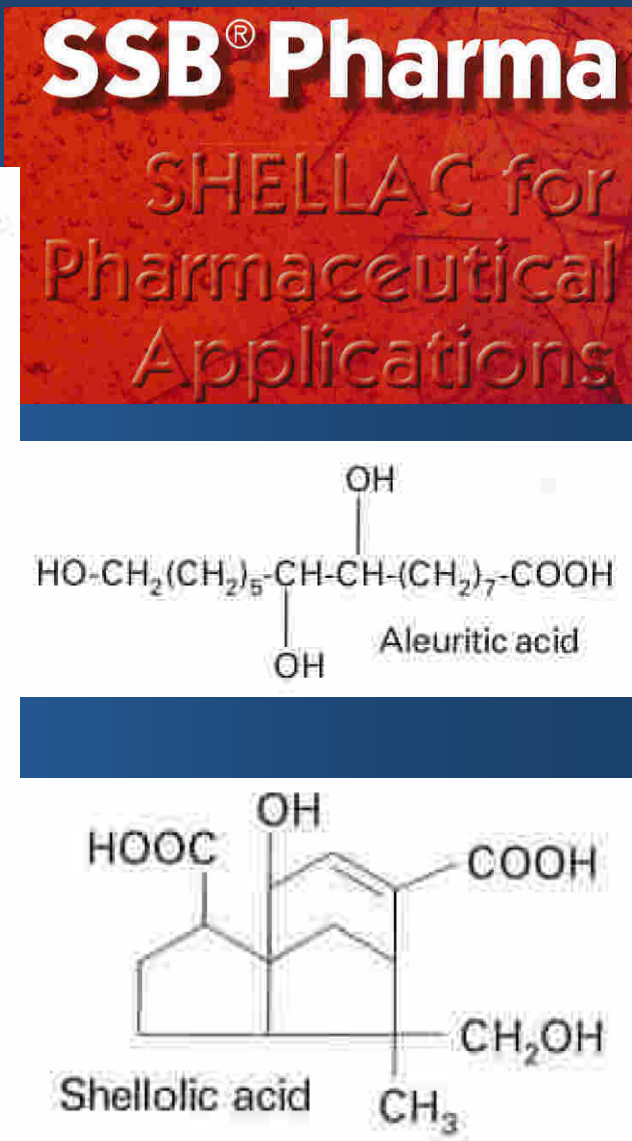
- Shellac: secretion product of K*erria lacca*
- “natural plastic”

Shellac

SSB® Pharma is a natural, edible and biodegradable polymer that is produced by refining the resinous secretion (more commonly known as "lac") of an insect (Kerria lacca). This polymer is described in the USP and Ph. Eur. as "shellac".

It is an anionic polymer based on polyesters, and consists of a mixture of polyhydroxy polycarboxylic esters, lactones and anhydrides. Principle components include aleuritic acid, shellolic acid, jalaric acid and other aliphatic acids.

SSB® Pharma is thermoplastic, and has a fairly low melting point (75°C-80°C). It is tasteless and odorless.



Shellac

- food addition (E904)
- tablet coating (resistant to gastric acid)

JUNIOR research group

Evaluation of Shellac in case of coating for intravascular intruments –

Test of *in vitro*-compatibility

Kirsten Peters[1]*

[1]Arbeitsbereich Zellbiologie (*Nachwuchsgruppe), Universität Rostock

Experimental design

- **The absence of endothelialization can lead to thrombosis [Van Belle et al., 2007]**
- **Polymers could be a trigger for an inflammatoric reaction**
- **An inflammatoric reaction is responsible for a delayed reendothelialization and could cause destruction of neointima**

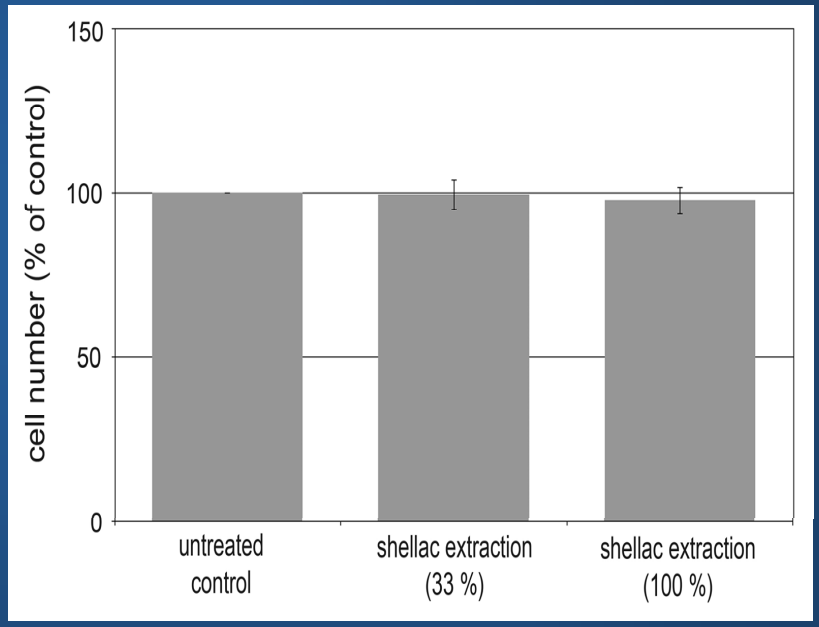
Experimental design

- **Shellac coating was performed by spraying a commercially available shellac suspension on glass and polished titanium alloy discs**
- **Investigated cell types: Human dermal EC (HDMEC) and humane smooth muscle cell (HSMC)**
- **Exposition with extraction product and direct contact**
- **Investigation of metabolic activity**
- **Investigation of pro-inflammatoric response**

Evaluation of metabolic activity

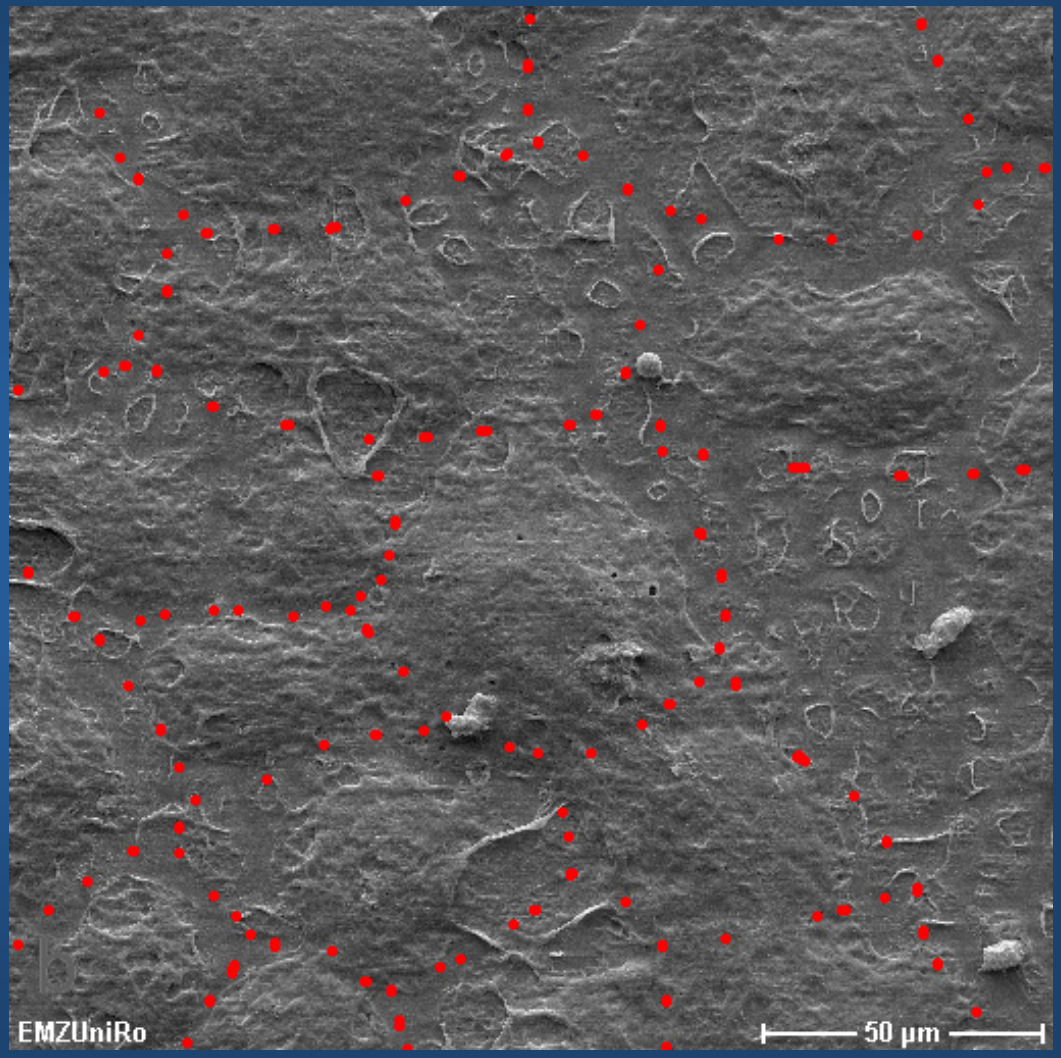
- **Shellac extraction products did not show any impairment of EC and SMC viability, proliferation as well as metabolic activity.**

Metabolic cell activity

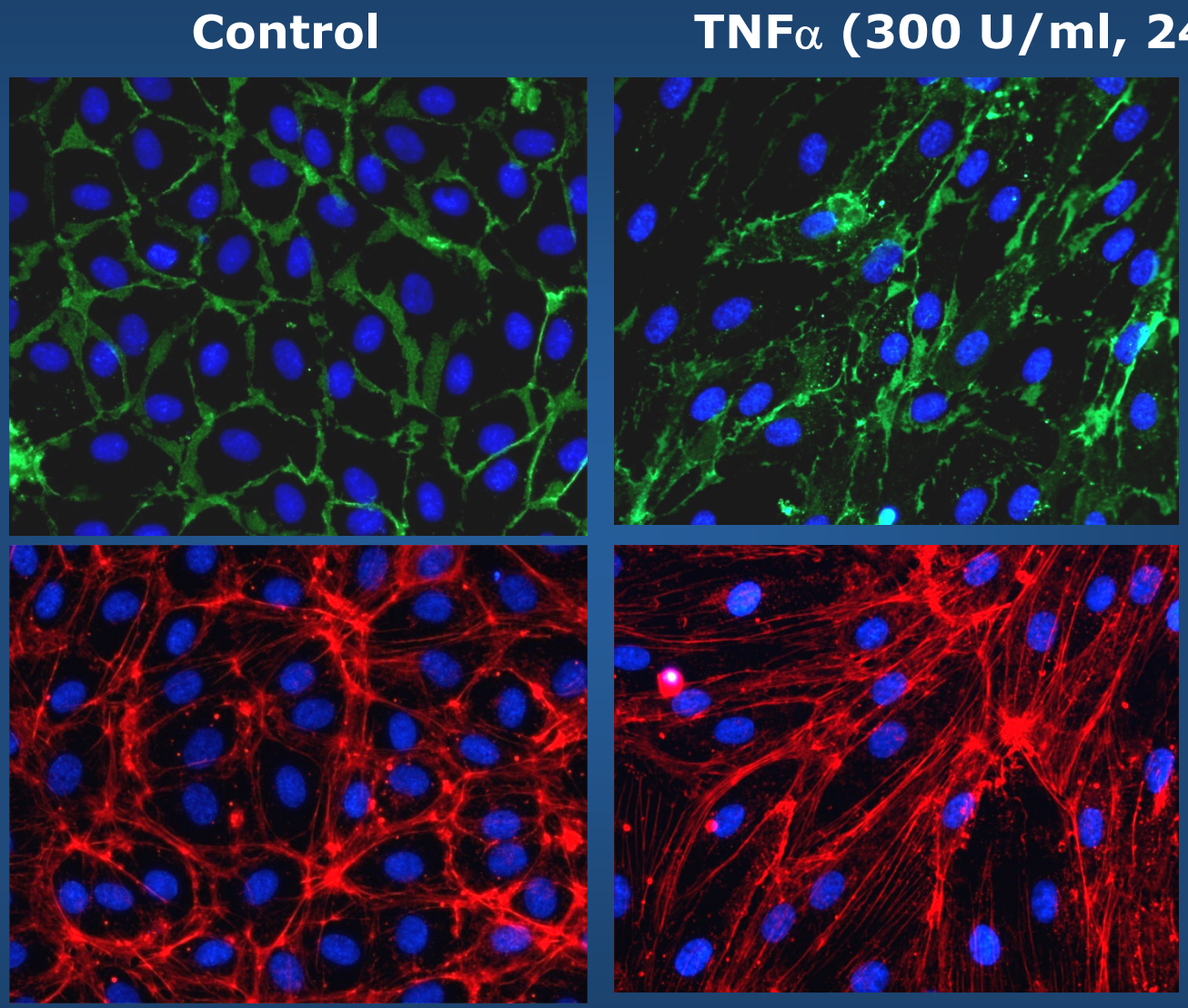


Endothelial cell phenotype in contact to shellac

- **Human dermal EC (HDMEC) in vitro in direct contact to shellac coating (scanning electron microscopy)**



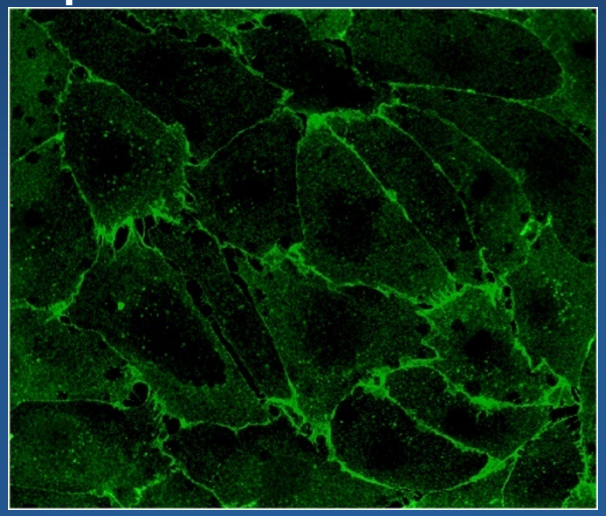
Interendothelial contacts *in vitro*



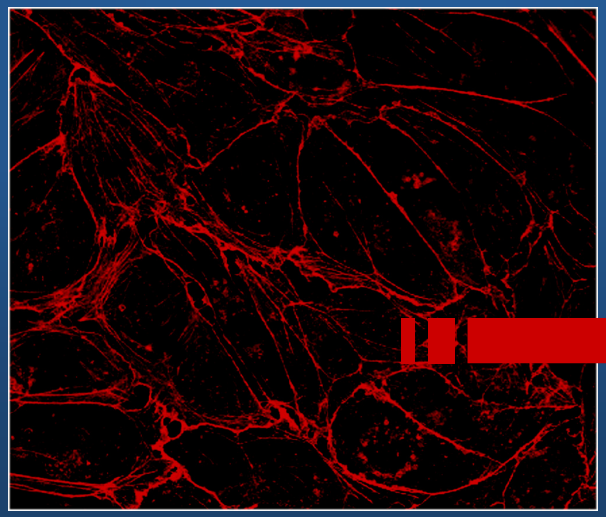
Interendothelial contacts *in vitro*

Human dermal EC (HDMEC) *in vitro* after 24 h cell culture supernatants with Shellac extraction products

CD31



F-Aktin

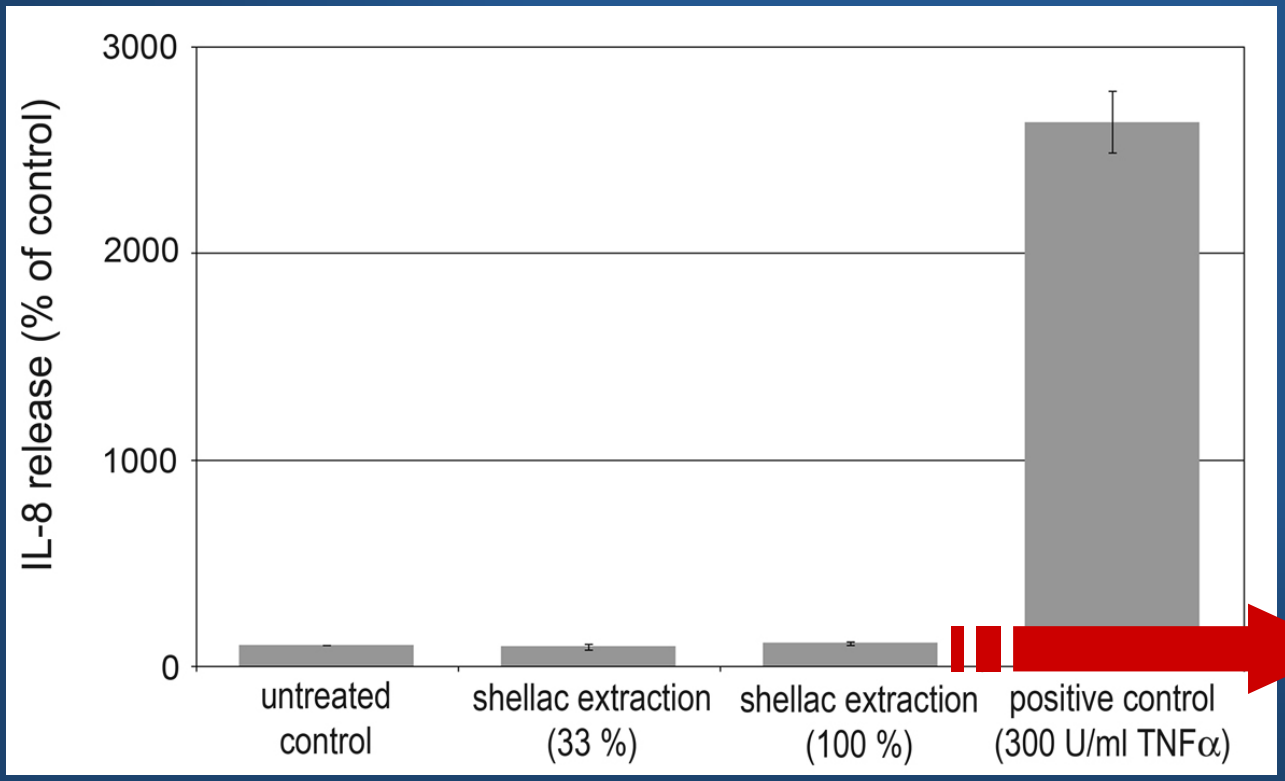


<u>No</u> sign of activation

Pro-inflammatory activation?

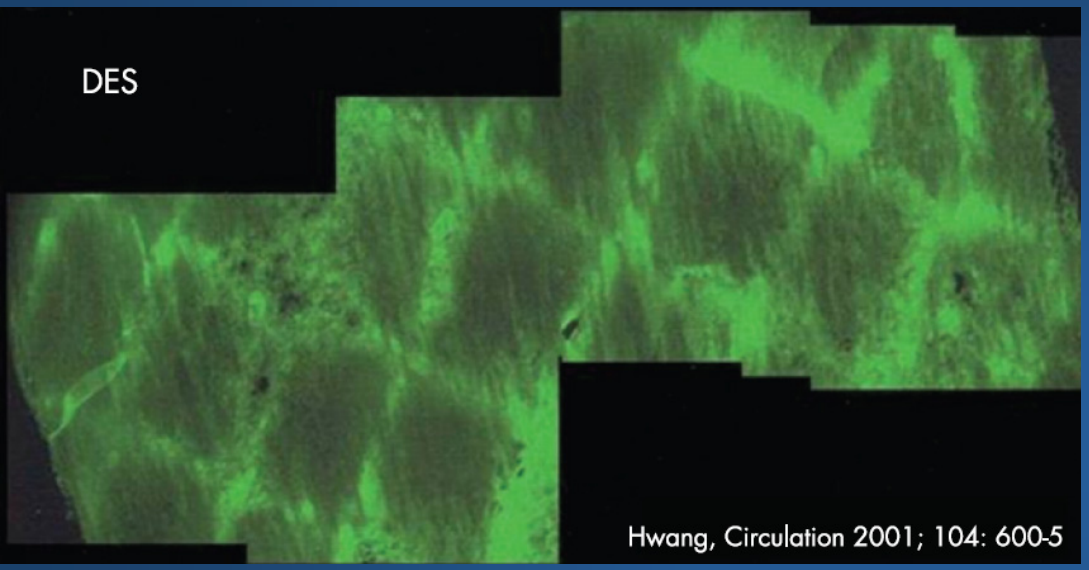
IL-8-release

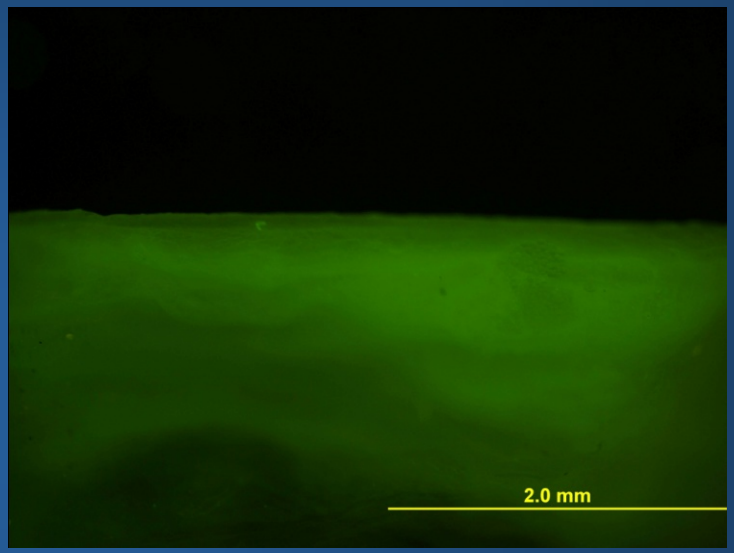
- **Shellac extraction product (24 h extraction)**
- **Exposure of confluent Human dermal EC (HDMEC) with extraction product (24 h extraction)**
- **TNFα as positive control group**



No increase in pro-inflammatory activation (shown by IL-8 release) observed

Endothelial surface of porcine coronary arteries after Dior balloon dilation

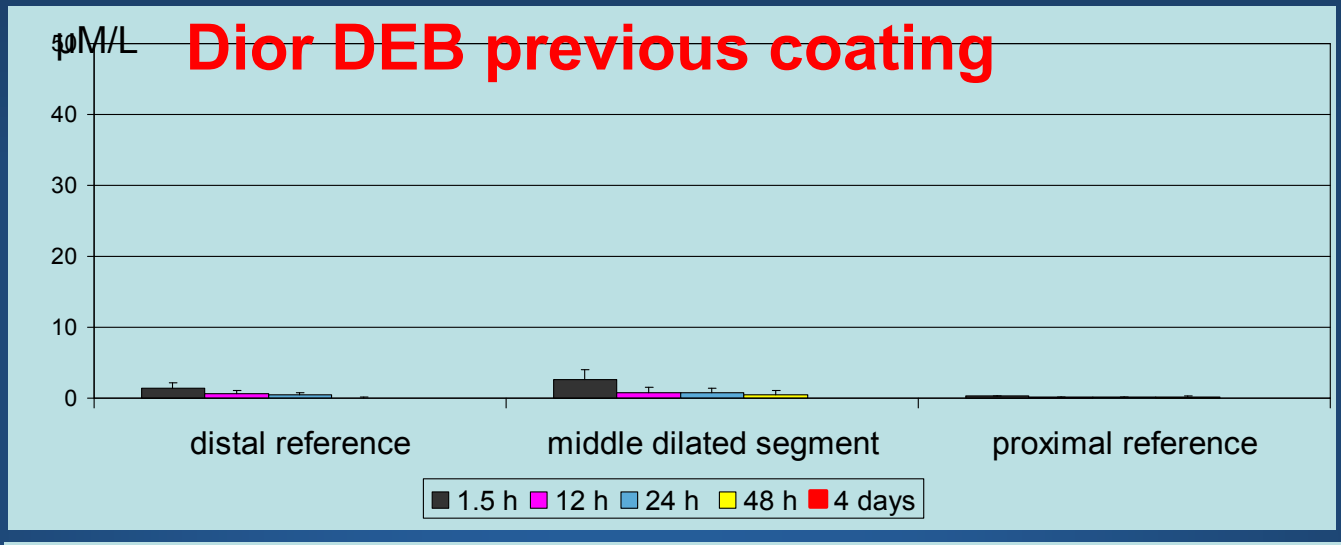


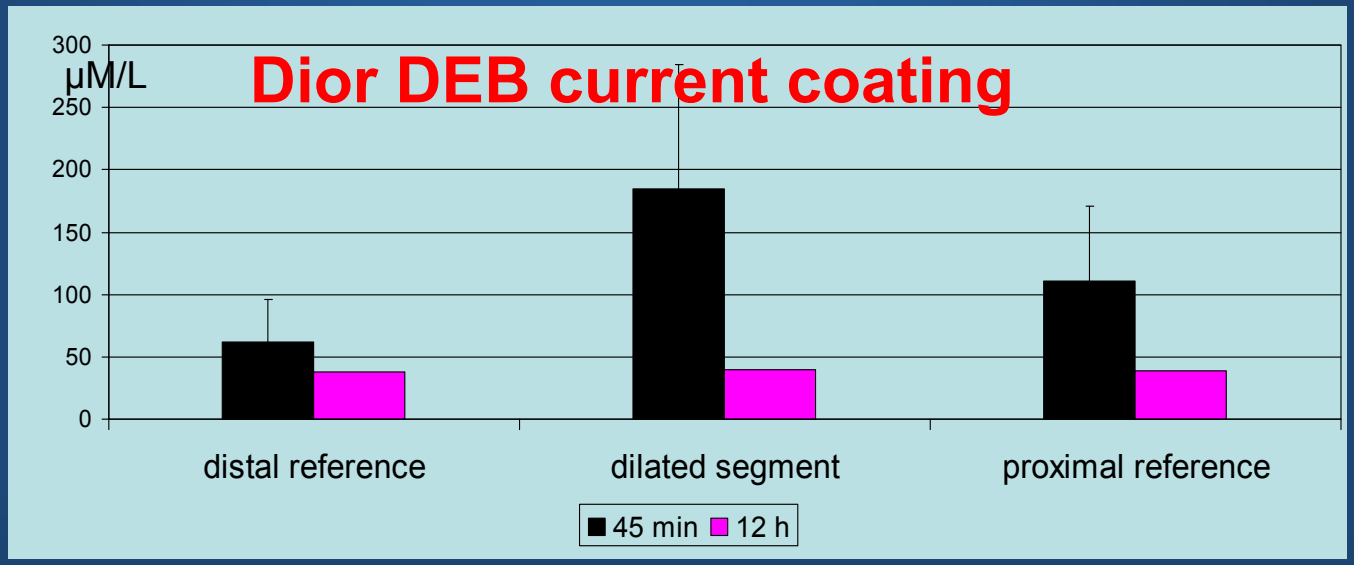


Artery post-paclitaxel-eluting stent: small amount of drug penetrated into the arterial wall, uneven drug distribution

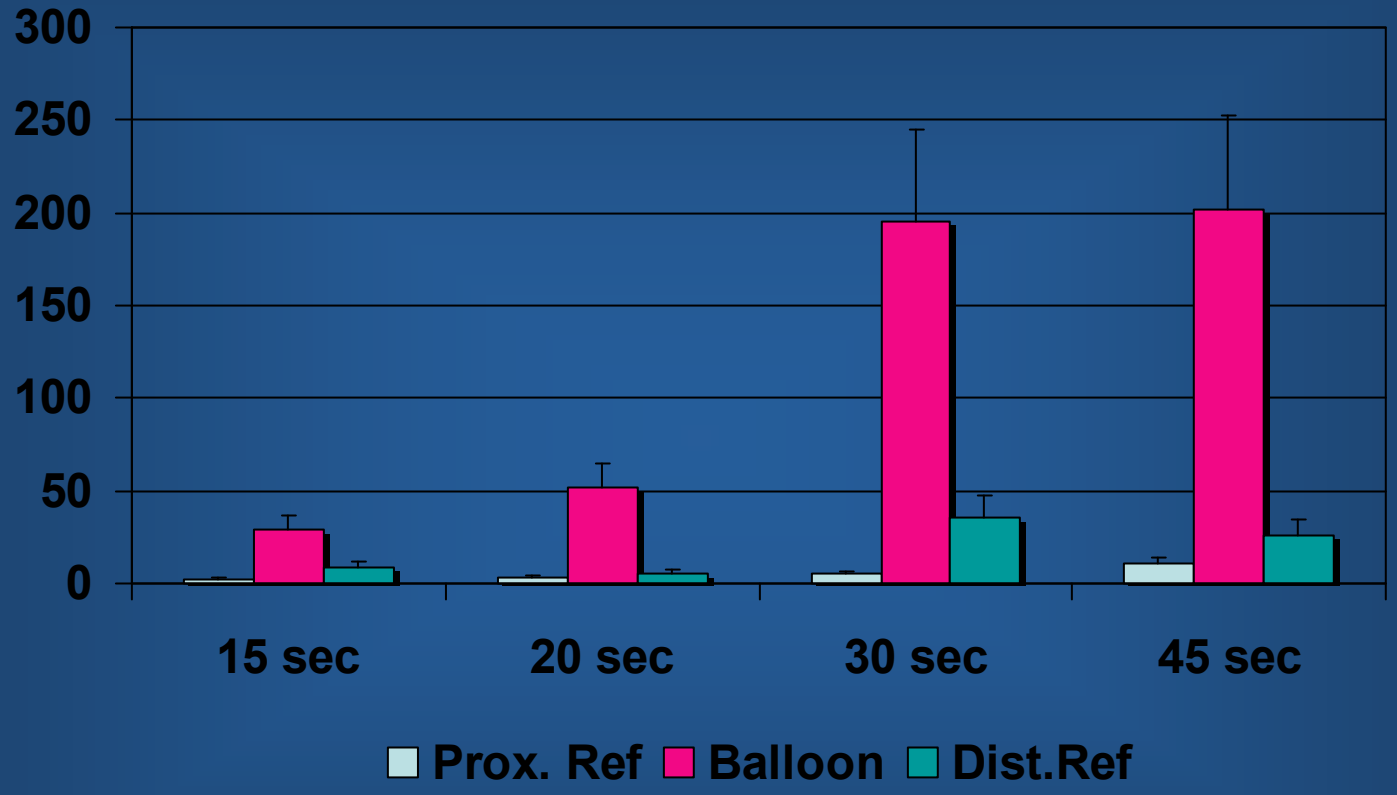
Artery post-paclitaxel-eluting Dior balloon:
large amount of drug within the arterial wall, uniform drug distribution

Artery tissue paclitaxel concentration



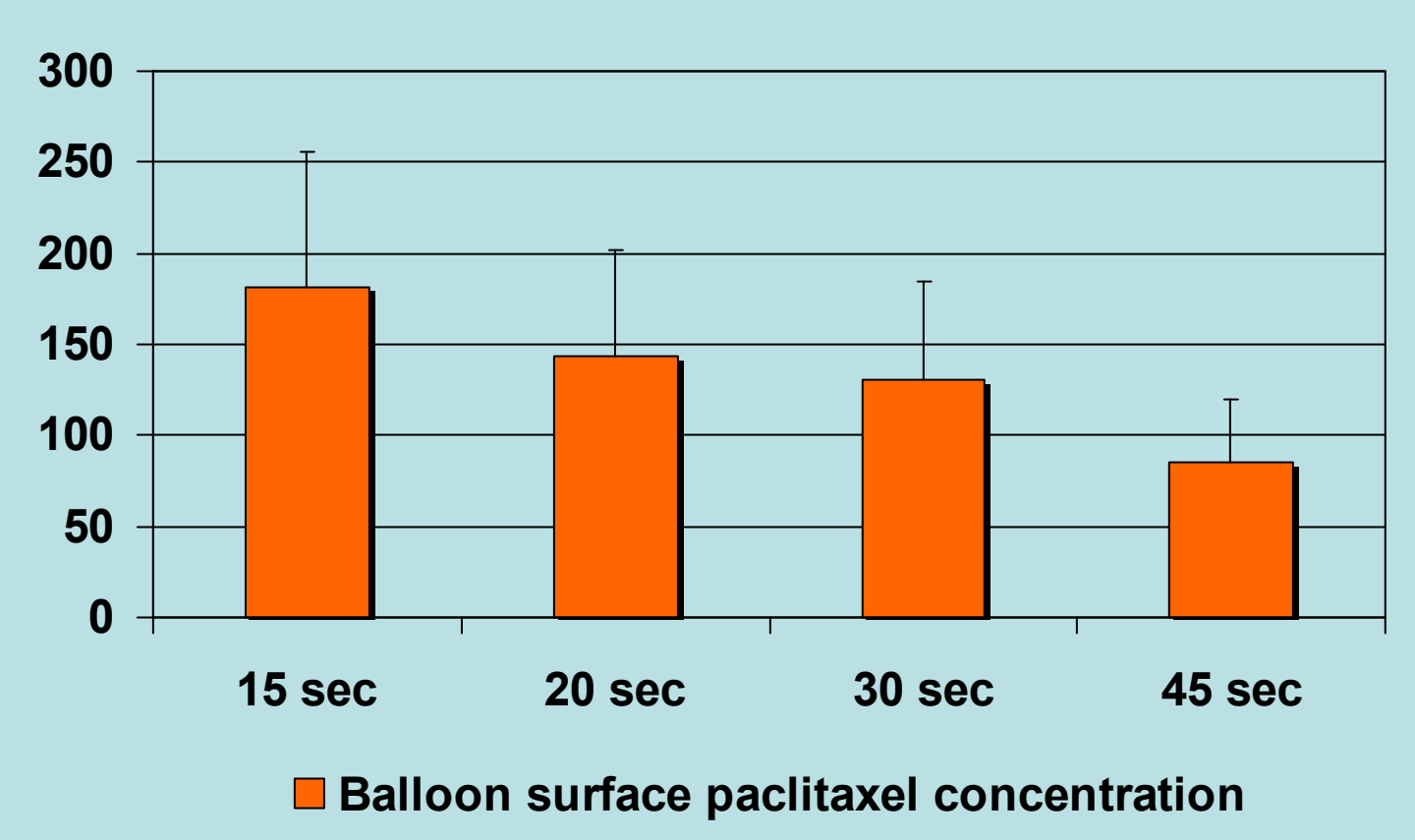


Time-dependent tissue concentrations of paclitaxel from the Dior balloon N=29**

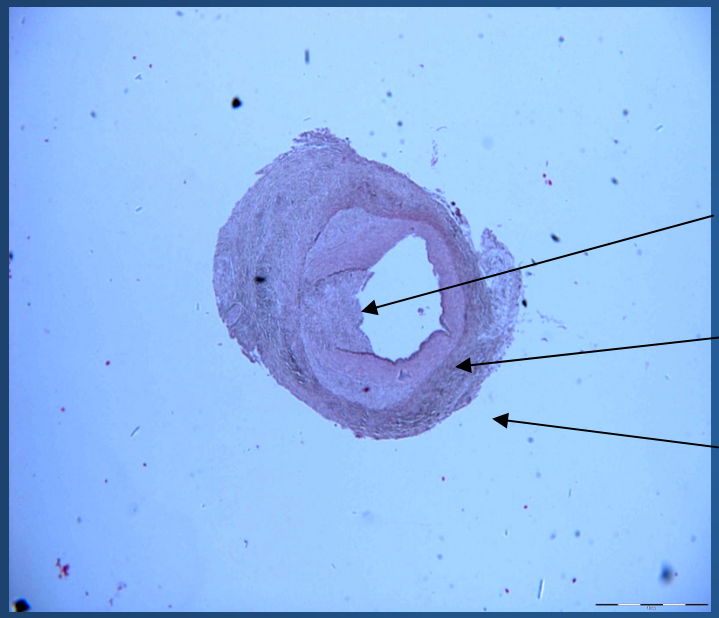


** Gyöngyösi et al

Inflation time-dependent tissue paclitaxel concentration



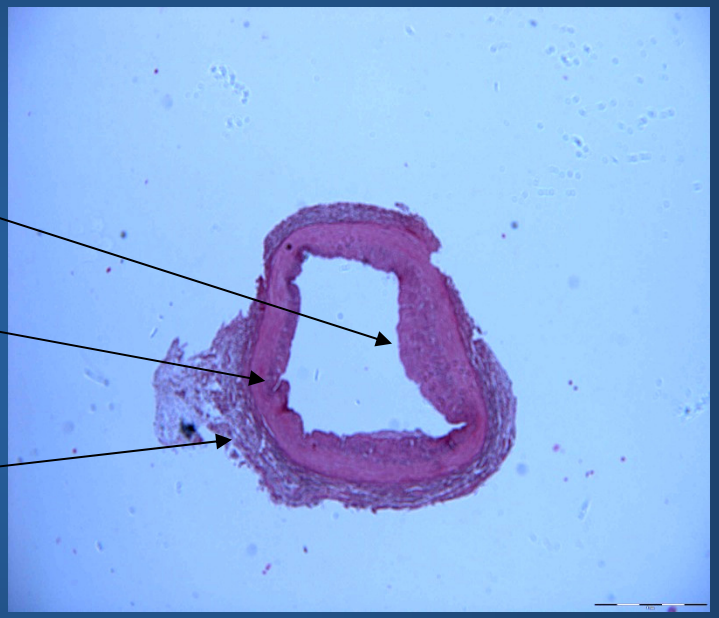
Histological results 14 days post-Balloon overstretch injury



neointima

media

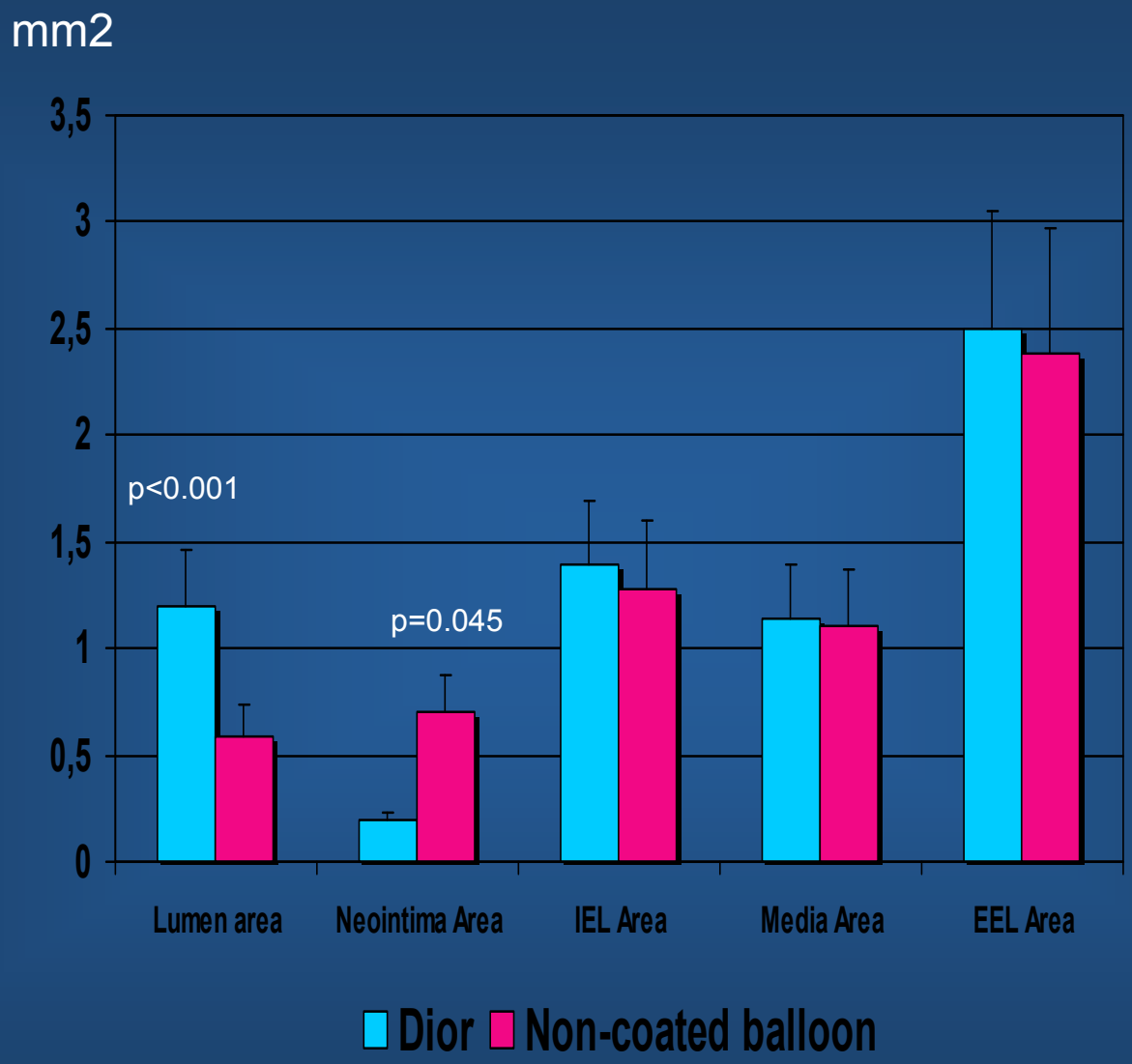
adventitia



Uncoated balloon

Dior balloon

Quantitative histological results N=12 *



**Gyöngyösi et al

Biomaterials 30 (2009) 632–637

Contents lists available at ScienceDirect

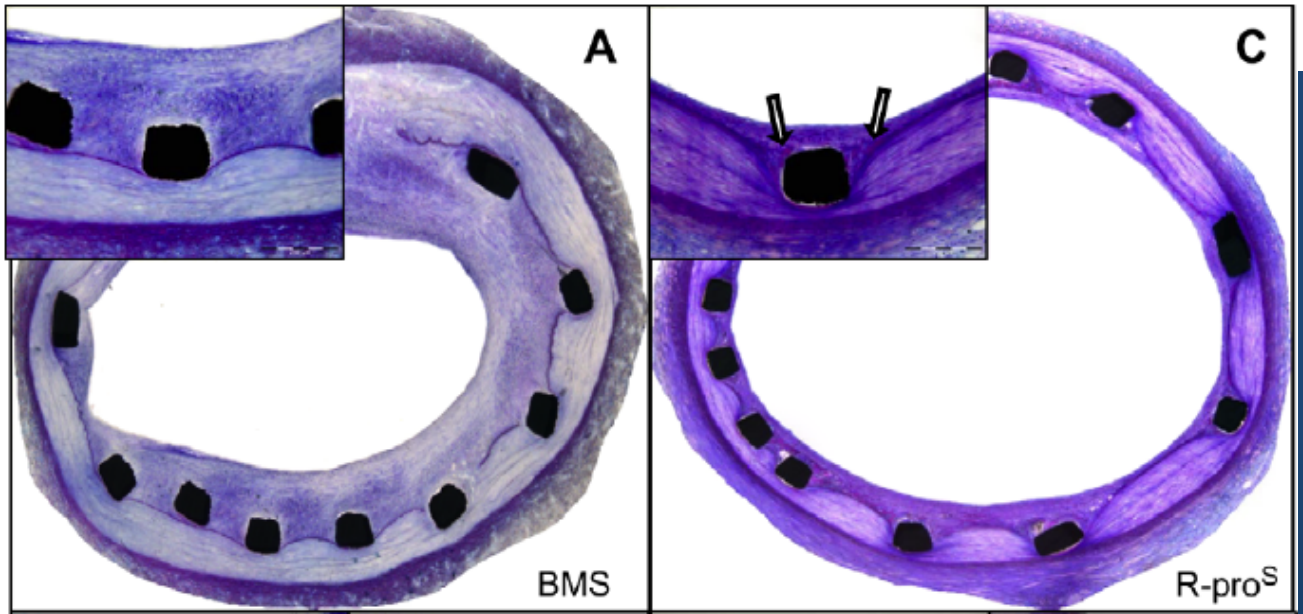
Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

The pre-clinical assessment of rapamycin-eluting, durable polymer-free stent coating concepts

Kristin Steigerwald [a,1], Sabine Merl [a,1], Adnan Kastrati [a], Anna Wieczorek [a], Marc Vorpahl [a], Raimund Mannhold [b], Michael Vogeser [c], Jörg Hausleiter [a], Michael Joner [a], Albert Schömig [a], Rainer Wessely [a,*]

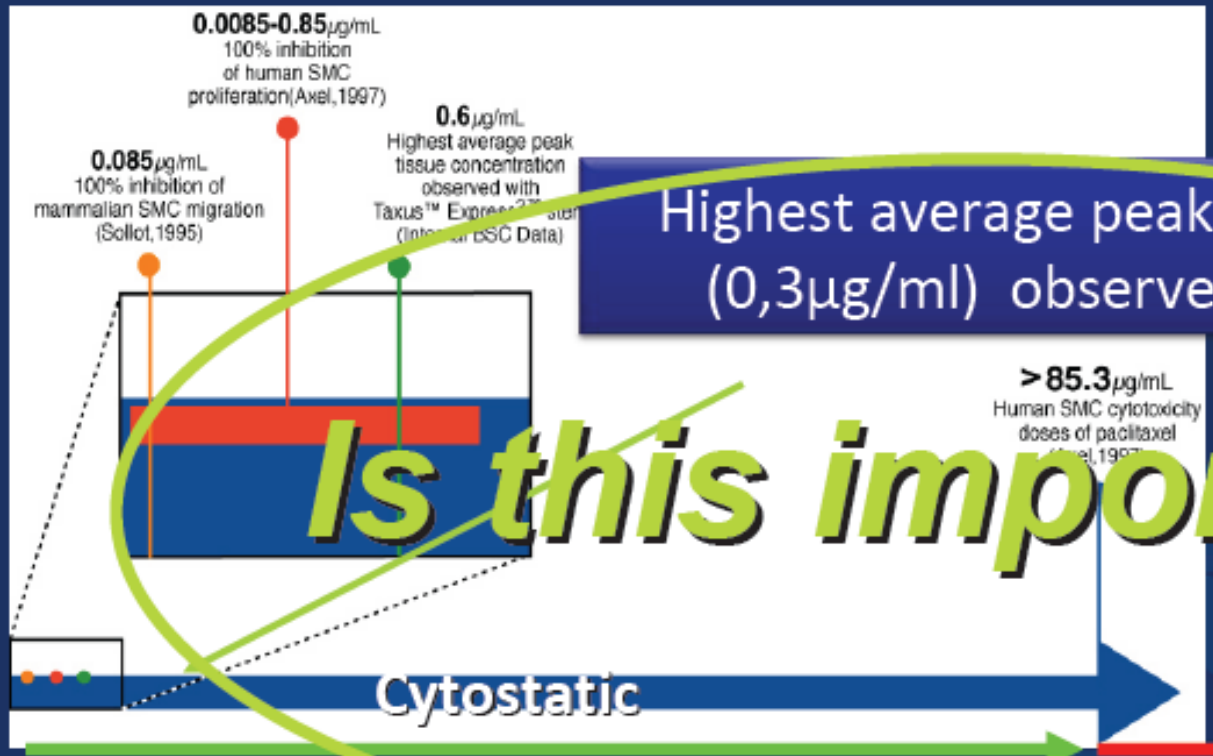
[a] Deutsches Herzzentrum and 1 Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich, Germany
[b] Molecular Drug Research Gro
[c] Institut für Klinische Chemie,



Therapeutic Window *

1. The ideal drug needs to inhibit cell proliferation without killing the cells.

2. Paclitaxel has a dose dependant effect associated with a large therapeutic window.



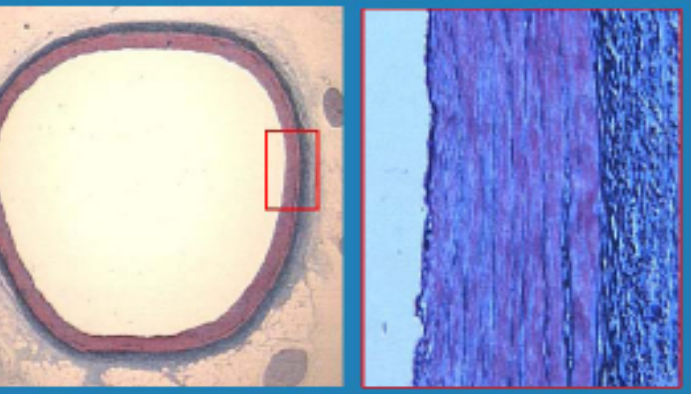
Highest average peak tissue concentration (0,3µg/ml) observed with DIOR™ PEB

Is this important ??

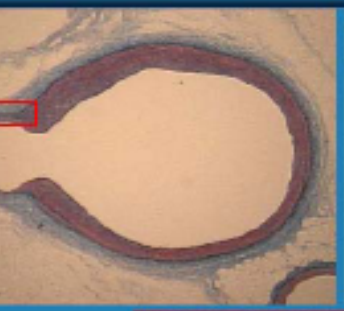
* Axel et al: Circulation. 1997; 96:636-645; Sollot et al; J. Clin.Invest. 1995; 95: 1869-1876;

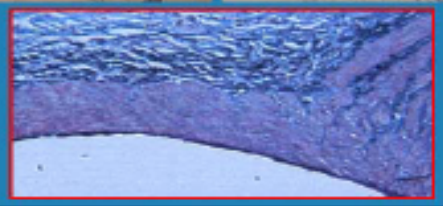
Restenosis Inhibition - Therapeutic Window

Normal Coronary Artery in Pigs



Coronary Aneurisms After
Paclitaxel – Coated Balloon in Pigs
4 wks.





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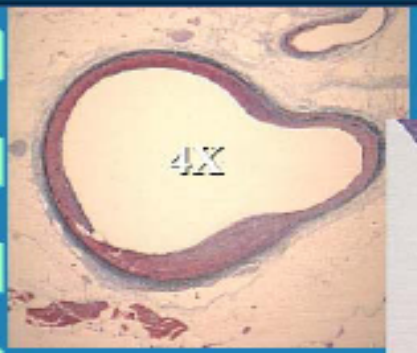
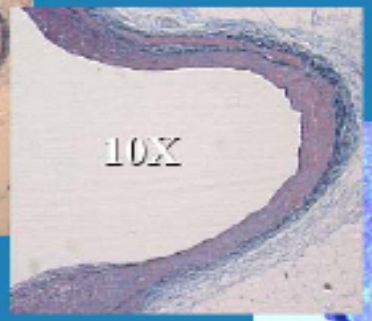
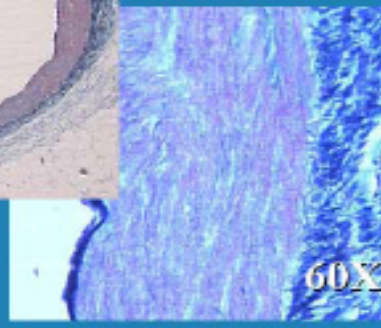






Coronary Aneurisms After
Paclitaxel – Coated Balloon in Pigs
Aneurisms in High Dose PEB Group

By Dr. Echevarri –Solaci 2008 Cancun

DEB – Randomized Clinical Trials

- **Peripheral artery disease**
  - THUNDER (SFA) / uncoated balloon
  - FemPac (SFA) / uncoated balloon
  - Piccolo (ongoing) (BTK) / uncoated balloon
  - CopaCobana (SFA in-Stent) /uncoated balloon
  - River (SFA-US) / uncoated balloon
  - Euro-Canal and US-Canal

'Non-PACCOCATH' – randomized clinical trials for PVD

- Advance 18 (POBA vs. DCB): Cook, 100/100 patients randomized
- Levant I (POBA vs. DCB): Lutonix, 100/100 patients randomized (Levant II planned)
- In.pact SFA: Invatec – Euro/US Study start QIII/2010
- In.pact Deep: Invatec BTK vs. POBA
- EuroCor: 2 studies in SFA
- further studies with other DCB and other drugs in the near future

FREEWAY STENT STUDY

Stent angioplasty with Paclitaxel-coated balloons versus plain stent angioplasty for prevention of restenosis due to intimal hyperplasia in peripheral arterial occlusive disease

Principal Investigator:
Prof. Dr. med. Josef Tacke
Institut für diagnostische und interventionelle Radiologie und Neuroradiologie
Klinikum Passau
Innstr. 76
94032 Passau
Germany
josef.tacke@klinikum-passau.de

Objective and study design

Comparison of Paclitaxel-Coated Balloon (FREEWAY) with POBA in case of postdilation of Nitinol stents in the treatment of superficial femoral (SFA) or popliteal arteries (P I segment).

Prospective, randomized, multi-center, two-armed phase-III study conducted in Austria and Germany.

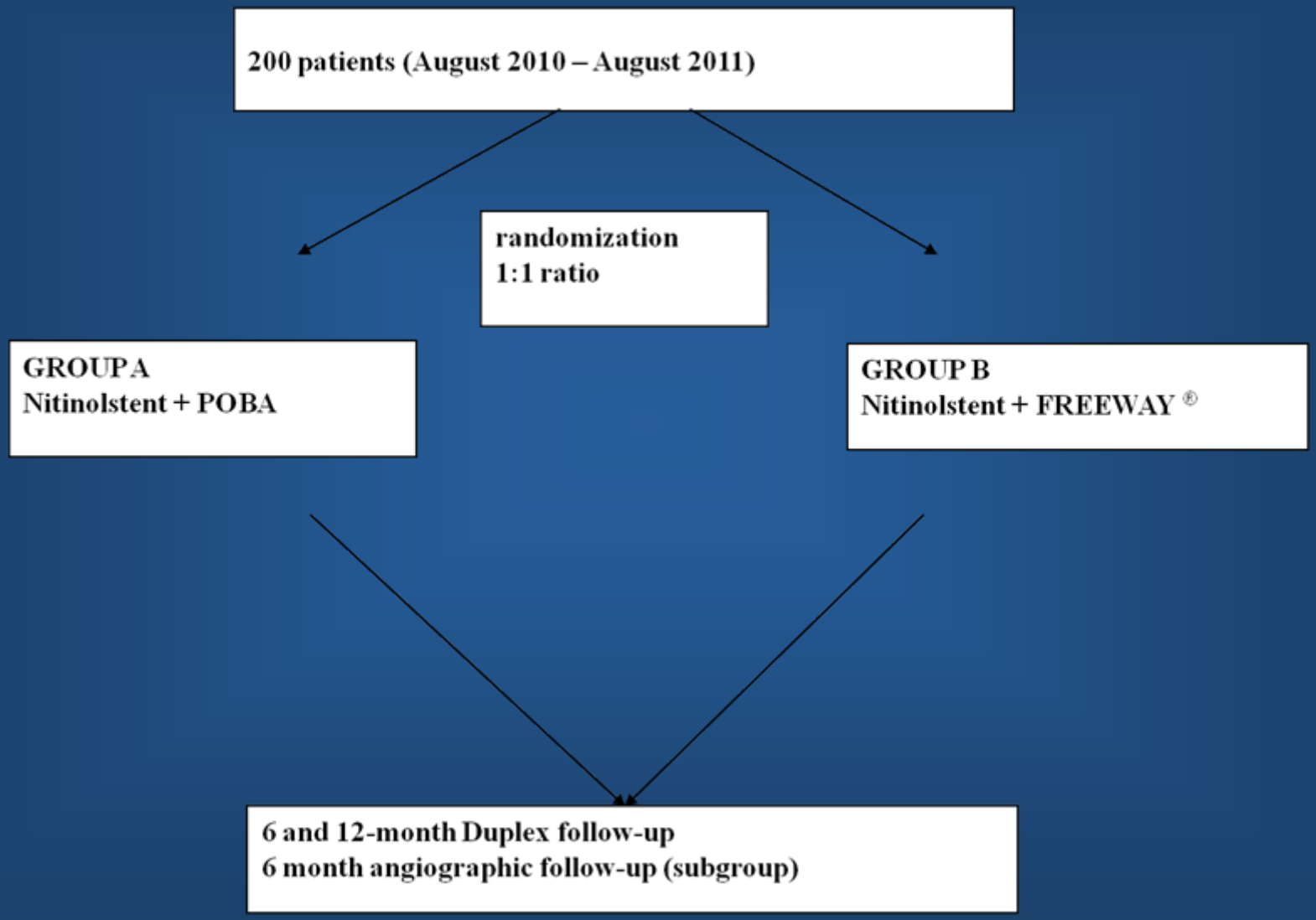
200 patients

Design: POBA versus FREEWAY®

Primary endpoint:

- **Rate of clinically driven target lesion revascularization at 6 months ***

Flowchart


200 patients (August 2010 – August 2011)
randomization
1:1 ratio
GROUP A
Nitinolstent + POBA
GROUP B
Nitinolstent + FREEWAY ®
6 and 12-month Duplex follow-up
6 month angiographic follow-up (subgroup)

FREERIDE STUDY

Prospective, Randomized, Controlled, Multicentre, Open Study
Release of Paclitaxel during PTA versus PTA alone for the treatment of de-novo occluded, stenotic or, reoccluded, restenotic superficial femoral (SFA) or popliteal arteries

Principal Investigator:

Prof. Dr. med. Karl-Ludwig Schulte
Vascular Center Berlin /Dept. Internal Medicine
Ev. Hospital Königin Elisabeth Herzberge
Academic. Teaching Hospital of the Charité Herzbergstraße 79, 10365 Berlin, Germany

Objective and study design

Comparison of Paclitaxel-Coated Balloon (FREEWAY) with POBA in the treatment of de-novo occluded, stenotic or, reoccluded, restenotic superficial femoral (SFA) or popliteal arteries.

Prospective, randomized, multi-center, two-armed phase-III study conducted mainly in Europe.

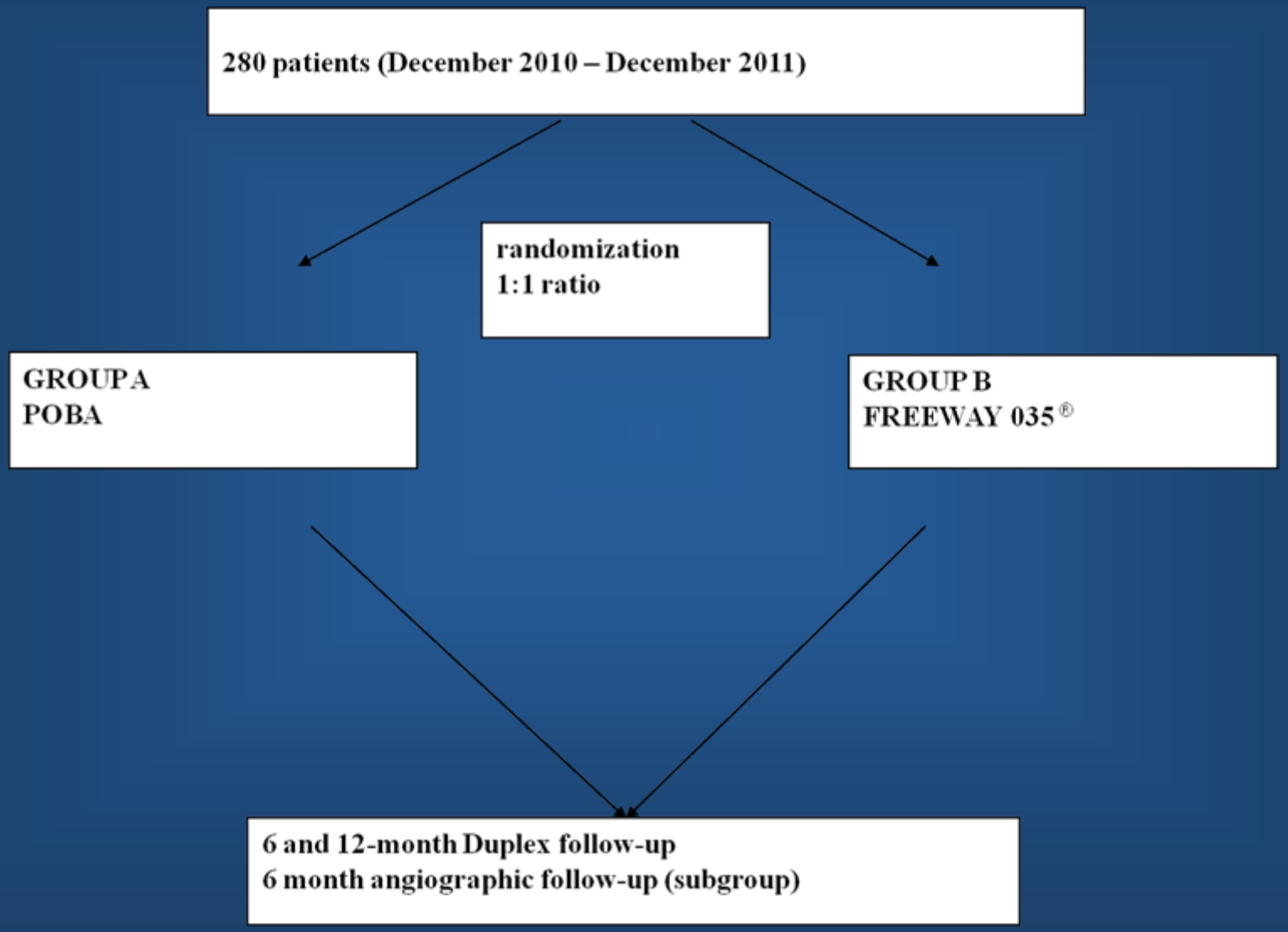
280 patients

Design: POBA versus FREEWAY 035®

Primary endpoint:

- **Rate of clinically driven target lesion revascularization (TLR) at 6 months ***

Flowchart


280 patients (December 2010 – December 2011)
randomization
1:1 ratio
GROUP A
POBA
GROUP B
FREEWAY 035®
6 and 12-month Duplex follow-up
6 month angiographic follow-up (subgroup)

Conclusion on DEB Technology for PVD

Two independent trials showed efficacy of paclitaxel balloons

BUT

- Enthusiasm based on 100 patients (Thunder, FemPac)
- We have to learn about limitations (e.g. with stents, dose effect, calcification)
- Europe: more than 5 different DEBs under development + available:
  despite the same drug: some will work other will not!