

Drug Eluting Stents





Drug Eluting Stents In PAOD

Assistant Clinical Professor of
Radiology and Surgery
University Of Illinois College of
Medicine at Peoria



Driving force in PAOD: Specifically where and why?

- One year patency rates:

- Carotids: 90-95%
- Iliacs: 80-85%
- Renals: 75-90%

- **SFA:** **22-65%**

Why is the FP segment problematic?



“Nature of the beast”

- **Small vessel**
- **More occlusions than stenoses**
- **Long segment involved**
- **Almost always calcified**
- **Mechanical deformation and stresses (Sirocco study)**

Strategies



- PTA
- Stent
- Radiation
- Cutting balloon
- Balloon delivered meds
- CryoTx PTA
- **DES**



What happens at the cellular level with endovascular treatment?

- **Vascular wall trauma**
 - Denudes intima and stretches media.
- **Incites a cascade of**
 - molecular and cellular events.
- **Leading to wound healing and**
RESTENSOSIS



Wound Healing- 3 Stages

1. Inflammatory Phase:
 - **PLT and GF activation**
2. Granulation Phase:
 - **Fibroblast and SMC migration to site of injury**
3. Remodeling Phase:
 - **Proteoglycan and Collagen synthesis in extra cellular matrix**

Restenosis

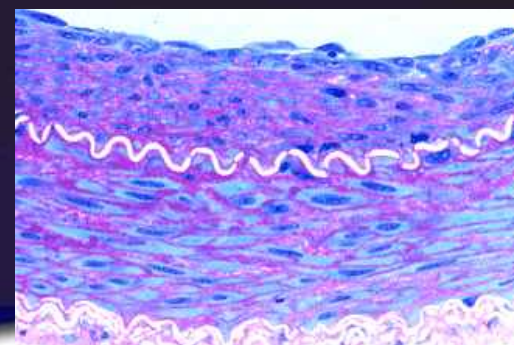
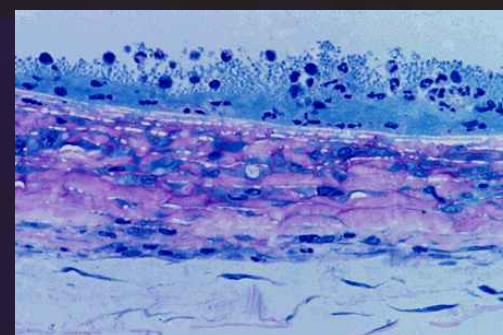
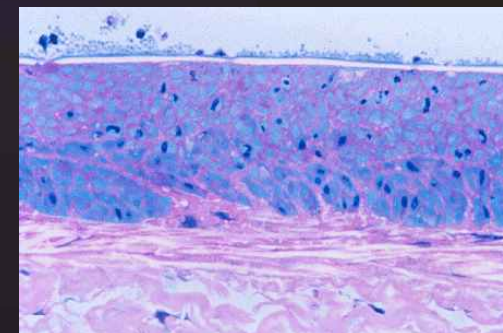
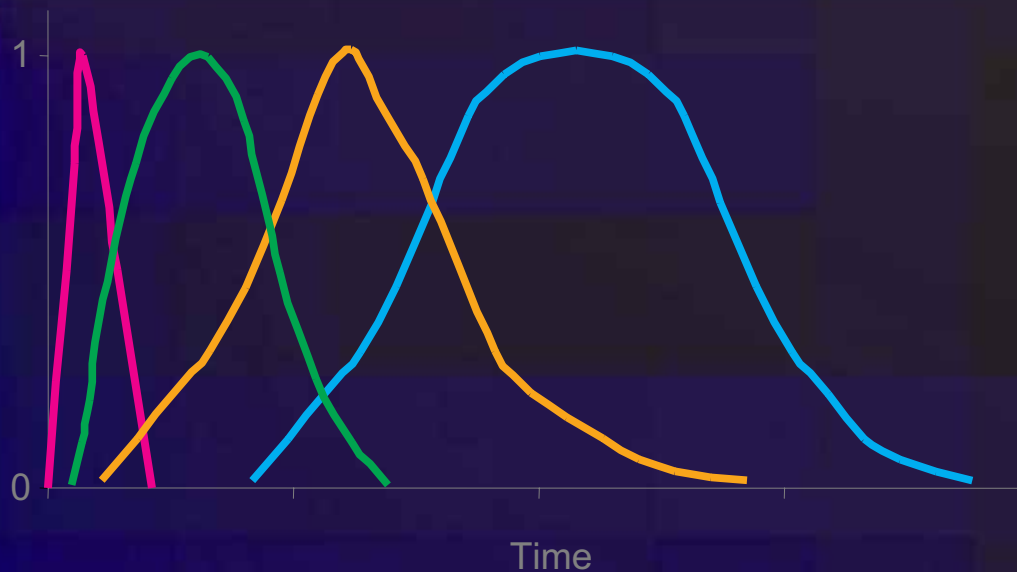


- **Incompletely understood**
- **Biologically complex**
- **The Achilles' heel of endovascular treatment**

Cascade of Events Leading to Wound Healing also leads to ISR

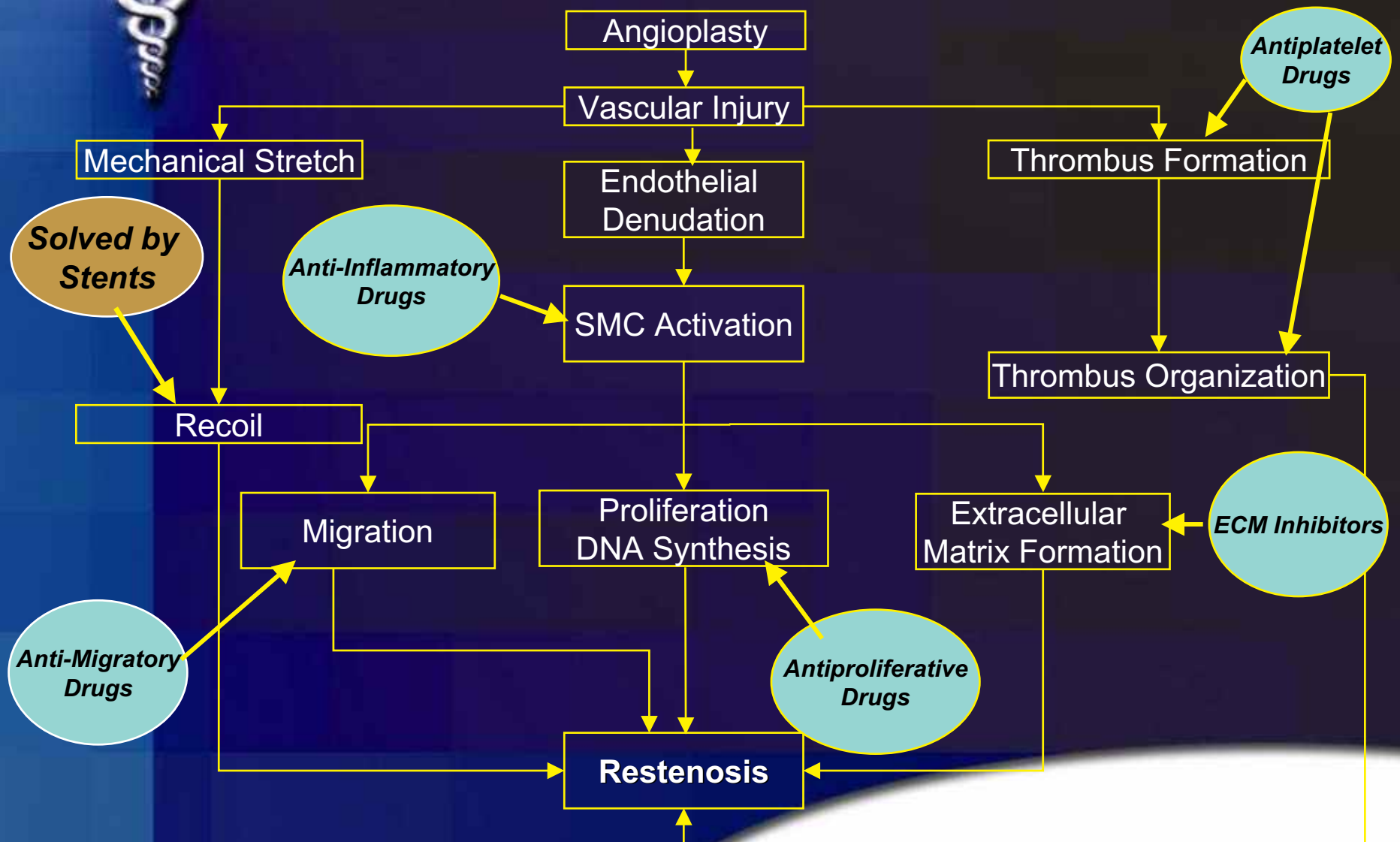


Fraction of Maximal Response

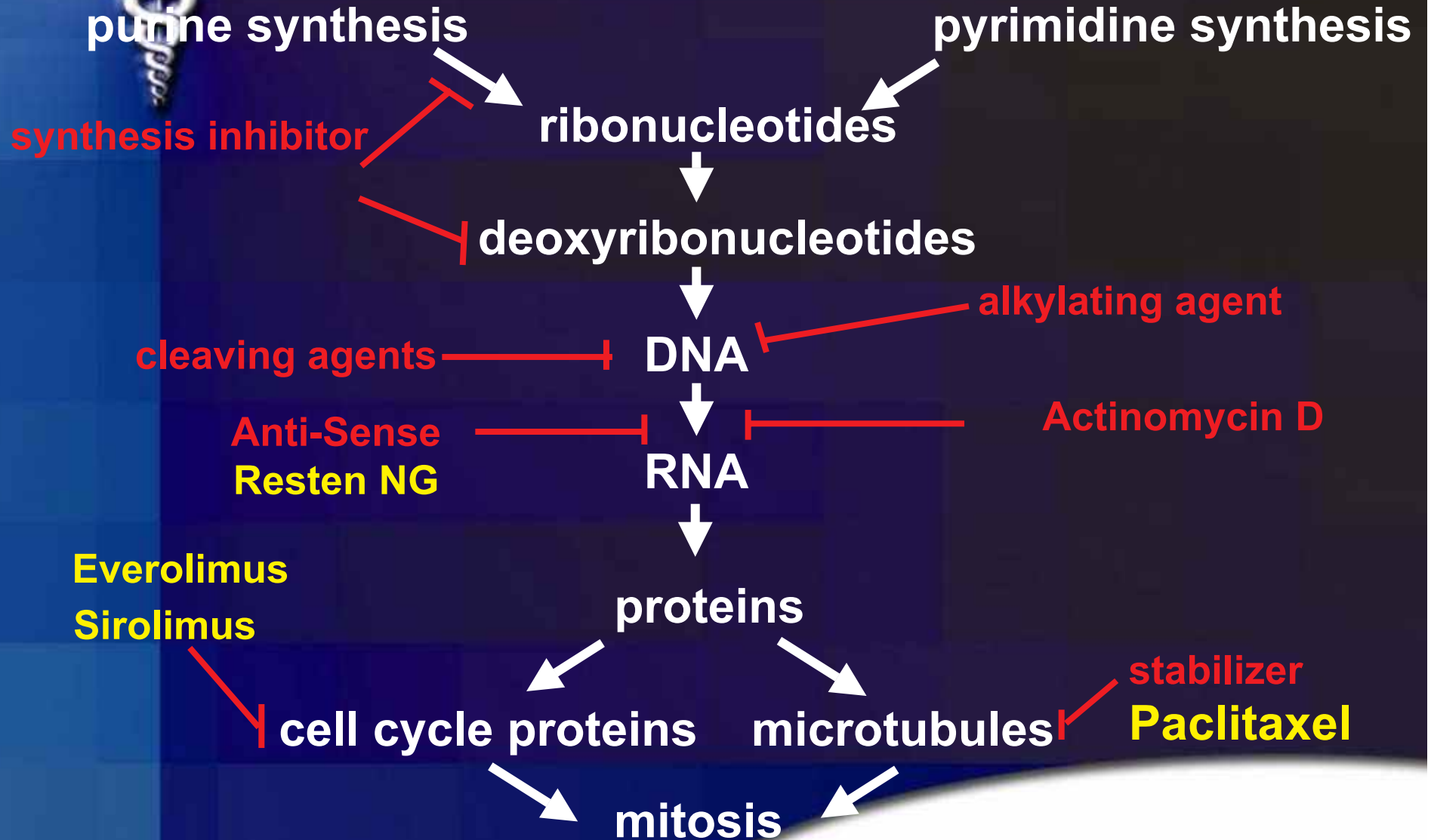


- Platelet Deposition
- Leukocyte recruitment
- VSMC migration / proliferation
- Matrix deposition

Restenosis Occurs by Complex Mechanisms



Drug selection: Antiproliferatives



Late Lumen Loss



- **Three distinct processes**
 - **Late vessel remodeling**
 - **Neointimal hyperplasia**
 - **Early elastic recoil**

Angioplasty vs. Stenting: Restenosis



- **Angioplasty:**
 - **Restenosis by a combination of all 3 mechanisms.**
- **Stenting:**
 - **Mechanical scaffolding**
 - resist elastic recoil and
 - constrictive vascular remodeling.
 - **Neo-intimal proliferation is main problem**

The “Magic Bullet”???



- **Pharmacologic agent**
 - Drug
- **Stent**
 - Open vs..
 - Closed cell design
- **Drug carrier**
 - Polymer
 - Bare

The Drugs





The Drugs

Immunosuppressive

- Sirolimus (TOR) Cordis
- Everolimus (TOR) Guidant
- Tacrolimus (FK506) Jomed
- Tranilast
- Mycophenolic acid
- Anti-neoplastic
 - Paclitaxel BSC, Guidant, Cook
 - Actinomycin-D
 - QP-2
 - ABT-578 Abbott
 - Vincristin
 - Methotrexate
 - Angiopeptin
- Anti-inflammatory
 - Dexamethasone (wet prep)
- Migration inhibitor
 - Batismastat
 - Halofuginone
- Enhanced healing
 - VEGF
 - 17-B-Estradiol
 - BCP 671
 - HMG-CoA-Reductase

Ensure Uniform Coating Integrity



Drug “Pools” or “Webs” are regions of uncontrolled drug release - AVOID

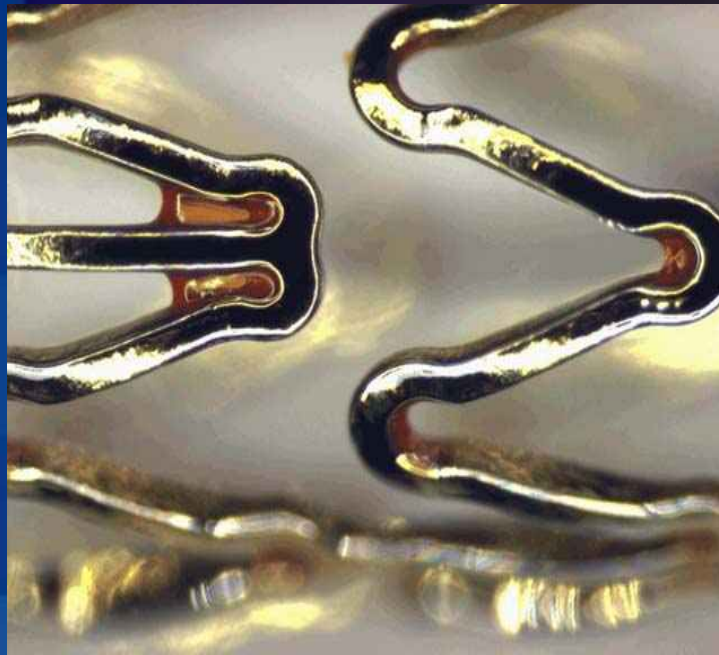


Fig. 1 – Pool Webs

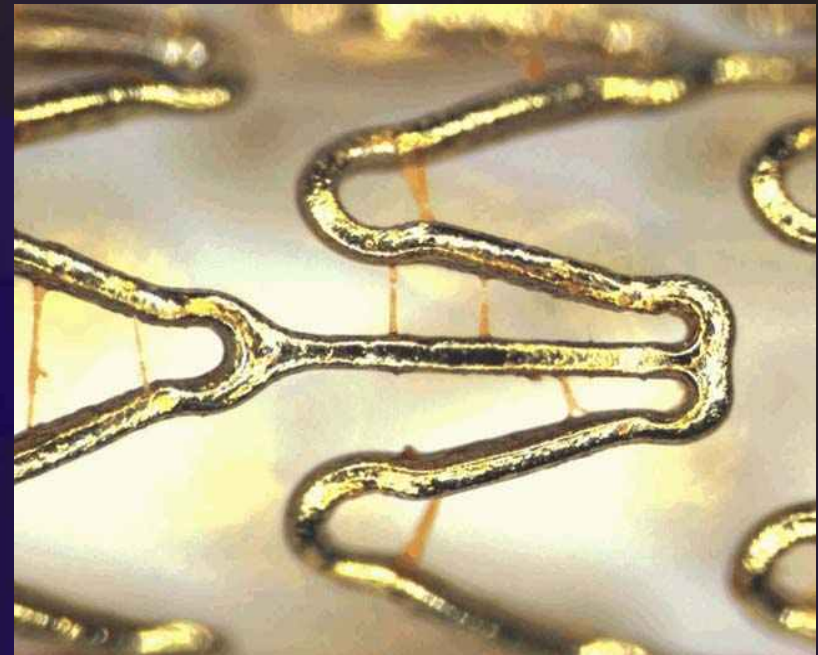
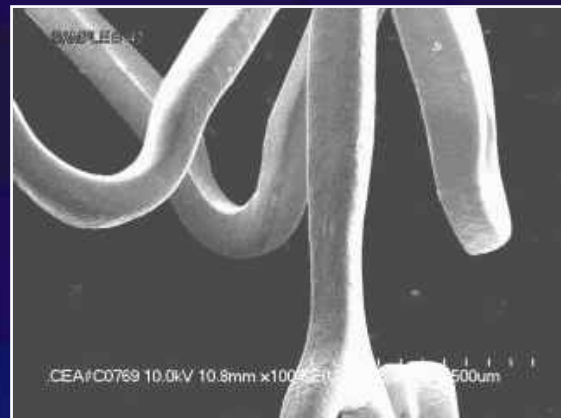


Fig. 2 – Cob Webs

Ensure Uniform Coating Integrity



No evidence of cracking or flaking



Sirolimus (Target of rapamycin)



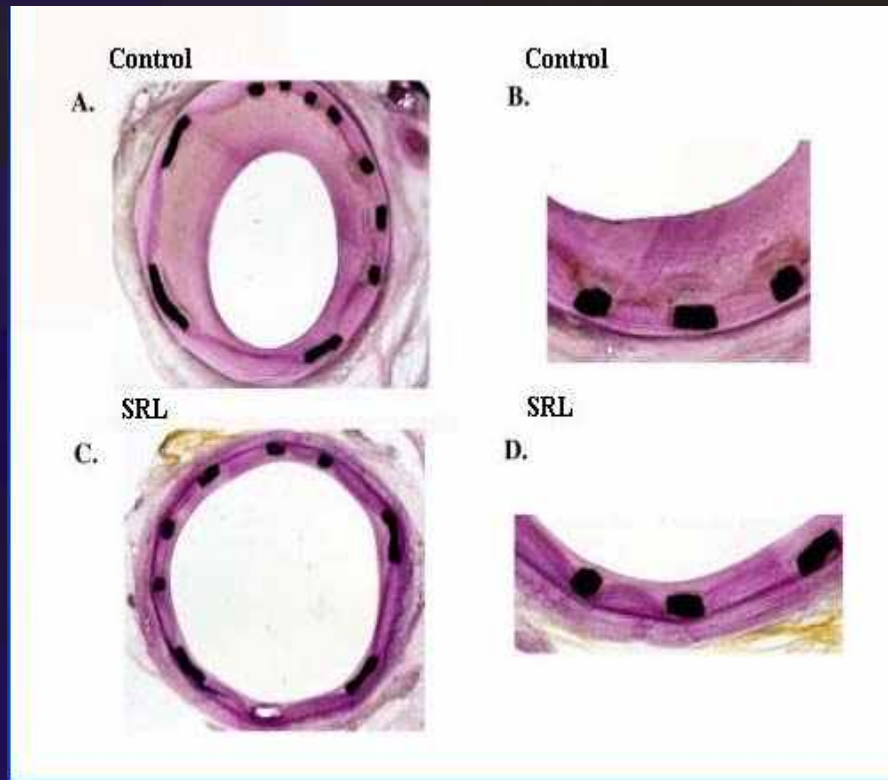
- Produced by fungus *Streptomyces hygroscopicus*
- Anti-fungal
- Immunosuppressive (anti-inflammatory, antiproliferative)
- Cytostatic inhibitor of cytokine and GF mediated cell proliferation
- Blocks G1/S transition of cell cycle
- FDA approved for tx of renal transplant rejection

Hiat BL. Catheter Cardiovasc Interv 2002 Mar;55(3):409-417

Oberhoff M. Catheter Cardiovasc Interv 2002 Mar;55(3):404-408



Drug-Coated Stents



Point of sirolimus action

Circulation 2001;104:1188-1193

Clinical trials

Sirolimus

FIM: 43 pts randomized to fast or slow rel. 18mm coated stent. 2yr: min NIH, late loss 0.09 slow, 0.32 fast

RAVEL (Sirolimus coated Bx Velocity stent, J&J)
Sirolimus/polymer coating 5 μ m thick

140 μ g/cm²

Slow release, 80% of drug released in 30 days

De novo lesions, single lesion 2.5-3.5 mm dia, 18 mm in length

238 patients; 120 w/ drug, 118 bare stent

Morice MC. N Eng J Med June 6, 2002; 346(23):1773-80

Drug-Coated Stents

Sirolimus

RAVEL cont

Angiographic restenosis at 6 mo. (> 50%)

drug coated stent- 0%

Bare stent- 27% (p<0.001)

Angiographic restenosis at 6 mo. in diabetic pt.s

drug coated stent- 0%

Bare stent- 42% (p=0.002)

MACE @ 1 yr: 6% DES, 29% bare-stent.

CABG, TVR, RS all 0%

Morice MC. N Eng J Med June 6, 2002; 346(23):1773-80

Clinical trials

RAVEL

Target lesion revascularization (TLR)

drug coated stent- 0%

Bare stent- 23% (p=0.001)

Event free survival (no MI or TVR)

drug coated stent- 6%

Bare stent- 29% (p<0.001)

Morice MC. N Eng J Med June 6, 2002; 346(23):1773-80

Drug-Coated Stents

RAVEL conclusions

- Elimination of instent neointimal hyperplasia
- Absence of restenosis or cardiac events in diabetics
- Antiproliferative, anti-migratory, and anti-inflammatory effects of sirolimus act in concert

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SIRIUS

1101 patients

Double blinded, 53 centers in US

Early report on first 400 patients*

In-segment 9 mo. angiographic restenosis

Sirolimus+stent- 9.2%

Bare stent- 32.3% ($p<0.001$)

9 mo. MACE(death, MI, or TVR)

Sirolimus+stent- 10.5 %

Bare stent- 19.5 % ($p=0.017$)

Final @ 8 months: 3% rate of restenosis in DES (91% reduction vs.. bare stent)

FREEDOM: PCI vs.. CABG in diabetics, 750 pts, MACE and mortality @ 5 yrs

ISR Registry: Cypher stent results consistent over 1 year; MACE 0%, no sign NIH (IVUS, angio)

Drug-Coated Stents in SFA

SIROCCO - SIROlimus Coated Cordis SMART nitinol self-expanding stent for the treatment of Obstructive superficial femoral artery disease

Europe and Canada

Blinded, randomized, prospective, feasibility study

36 pt.s, 18 in each group

6 mo.s in-stent restenosis (angiographic)

Sirolimus+stent	0.0%
Bare stent	17.6% ($p=0.23$)

6/33 stents w/ fractures

USA trial to follow

Everolimus (TOR)

Immunosuppressant

MOA: Suppression of GF-stimulated activation and proliferation of

Lymphocytes and

Mesenchymal cells

Blocks G1/S transition of cell cycle

FDA approved for tx of renal transplant rejection

SFA Trial to start enrolling 2004

FUTURE I (n=25 DES n=11 control) Sign reduction in ISR (IVUS and Angio)

FUTURE II to be present at TCT meeting

Drug-Coated Stents

Paclitaxel

Antineoplastic drug

Microtubule inhibitor, stabilizes dysfunctional microtubules

Prevents SMC migration and proliferation

FDA approved for the treatment of ovarian cancer

Blocks mitosis at the metaphase/anaphase transition

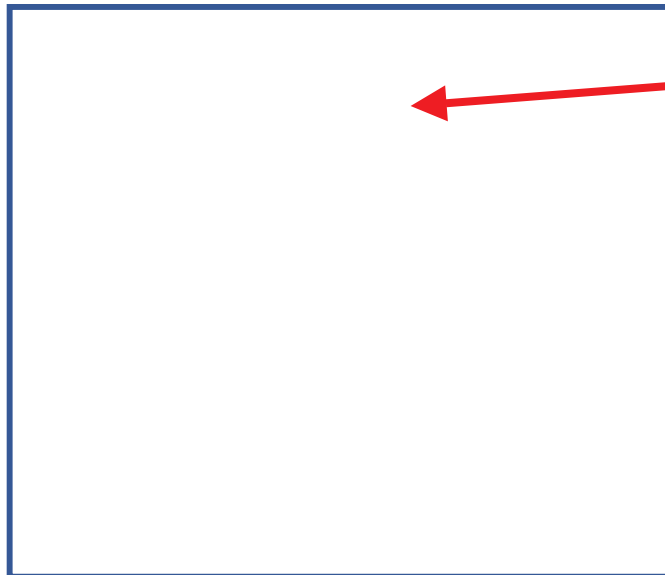
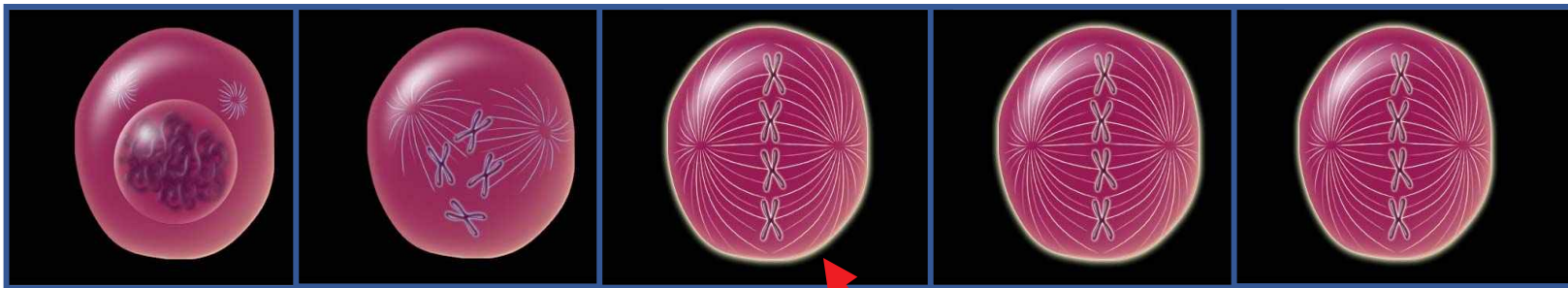
Delays healing- Need to give antiplatelet tx and ASA
X 90 days

Concentration in stents 28,000 x less than chemo

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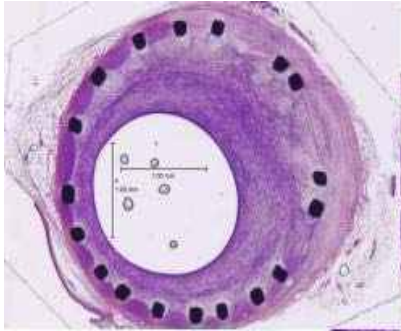
Drug-Coated Stents



**Point where paclitaxel
Stabilizes microtubules
In dysfunctional state**

Drug-Coated Stents

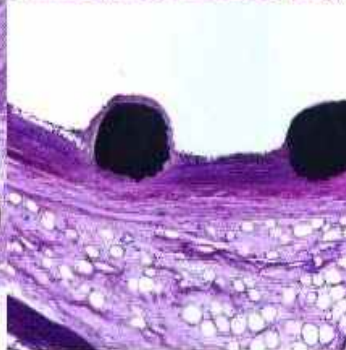
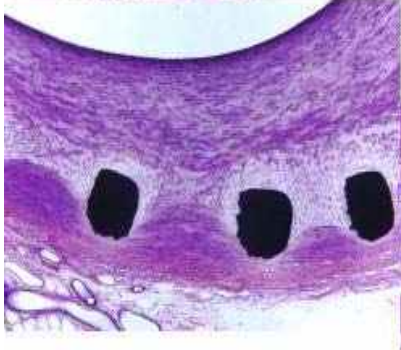
Control



Paclitaxel



Porcine model



Bare stent



Paclitaxel coated stent

Clinical trials-

Paclitaxel

ELUTES (European Evaluation of Taxol-Eluting Stents)

192 patients

Blinded RCT, Dose ranging and placebo

Found dose dependent reduction in angiographic stenosis (3% restenosis vs. 21% bare stents @ 6 mo)

No difference in clinical event-free survival

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Paclitaxel

SCORE (Study to COmpare REstenosis rate)

238 Patients

Multicenter RCT

Halted 2° excessive MI and subacute thrombosis rates in drug-coated stent group

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Paclitaxel

ASPECT; Asian Paclitaxel Eluting Stent Clinical Trial (n=177)

Demonstrated sign. dose dependant relationship in restenosis

High-does: 4%, Low-dose: 12%, Bare-stent: 27%

PATENCY, PAclitaxel-eluting sTENT for Cytostatic prevention of restenosis (n=50)

TAXUS I (n=61); Safety. 30d MACE 0% 6 mo ISR 0% vs. 10.3%

TAXUS II (n=536); Efficacy. slow vs. moderate release. MACE in slow rel 4.1%, in mod rel 1.4%

Paclitaxel

TAXUS III (n=30); single arm registry. No death, CABG, or TLR and 3.4% TVR

Taxus IV (n=2000) de novo and ISR, mod rel vs. placebo, ischemia TVR @ 9 mo

Taxus V: more complex lesions

TAXUS VI: European arm of TAXUS V.

TAXUS VII (n=528); pivotal study. ISR in mod rel DES vs. VBT

Tacrolimus

Immunosuppressive macrolide

Suppresses T cell activation

Inhibits rel of proinflammatory cytokines

Binds to FK binding protein 12 (Like Sirolimus and Everolimus) but MOA is different

Diminishes recruitment and activation of

Macrophages, IL-1, TNF and fibroblasts and platelet derived GFs. It may inhibit SMC prolifer and matrix production

Much less potent than TORs

EVIDENT and **PRESENT** trials ongoing

Actinomycin-D

Antineoplastic antibiotic

From *Streptomyces parvullus*

Binds to DNA inhibiting RNA synthesis

More cytotoxic than others

Increases cascade

Very narrow tx window- Difficult to control

The ACTION trial (ACTInomycin-eluting stent Improves Outcomes by reducing Neointimal hyperplasia), began June, 2001. ***Terminated prematurely d/t inc. stent thromboses.***

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Trials- Restenosis Rates

	DES	Control
<i>TAXUS</i>	0%	10%
<i>SIRIUS</i>	9%	31%
<i>SCORE</i>	7%	36%
<i>RAVEL</i>	0%	26%
<i>ELUTES</i>	3%	21%
<i>ASPECT</i>	4%	27%

Problems

Evidence of excessive early or late thrombosis

Hyper-proliferation responses

Aneurysms

Late restenosis- “Catch-up” phenomenon- especially in complex lesions

Results in complex lesion subsets not as good

Expect other **pathobiologic responses**

Trials and Problems

SCORE	Late thrombosis
RAVEL	Late Malapposition
ACTION	Restenosis/Aneurysm, stent thrombosis
TAXUS III miss	Edge effect- Geo
SIROLIMUS-ISR	Death, Restenosis
SIRIUS	Edge effect
SIROCO SFA	Stent fractures in

Other Intriguing Info

Oral Everolimus given to New Zealand white rabbits

Two doses – High (not tolerated well) and Low (no side effects)

Bare stent in iliac arteries

Both groups showed reduction in NIH

High: 46% Low: 42%

Low dose group also showed good healing over the stent without NIH

In Conclusion...

Everything looks great initially and it has been no different for DES

However data is still very favorable

Jury is out on complex lesion subsets but will probably be good

“You can’t fool Mother Nature”. Fine balance between vessel wall inhibition and injury

Bottom line: When DES are available we will use them! But probably in patient subsets.