Paclitaxel vs. limus agents: Mechanism of action, what are the challenges to move beyond paclitaxel?

Sahil A. Parikh, MD

Associate Professor of Medicine

Columbia University Irving Medical Center

New York, NY, USA

Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Employment in industry: No

Honorarium/Advisory Board:

Abbott Vascular, Boston Scientific, Medtronic, CSI, Philips, Janssen, Abiomed, Inari, Penumbra, Terumo Corporation.

Institutional grant/research support:

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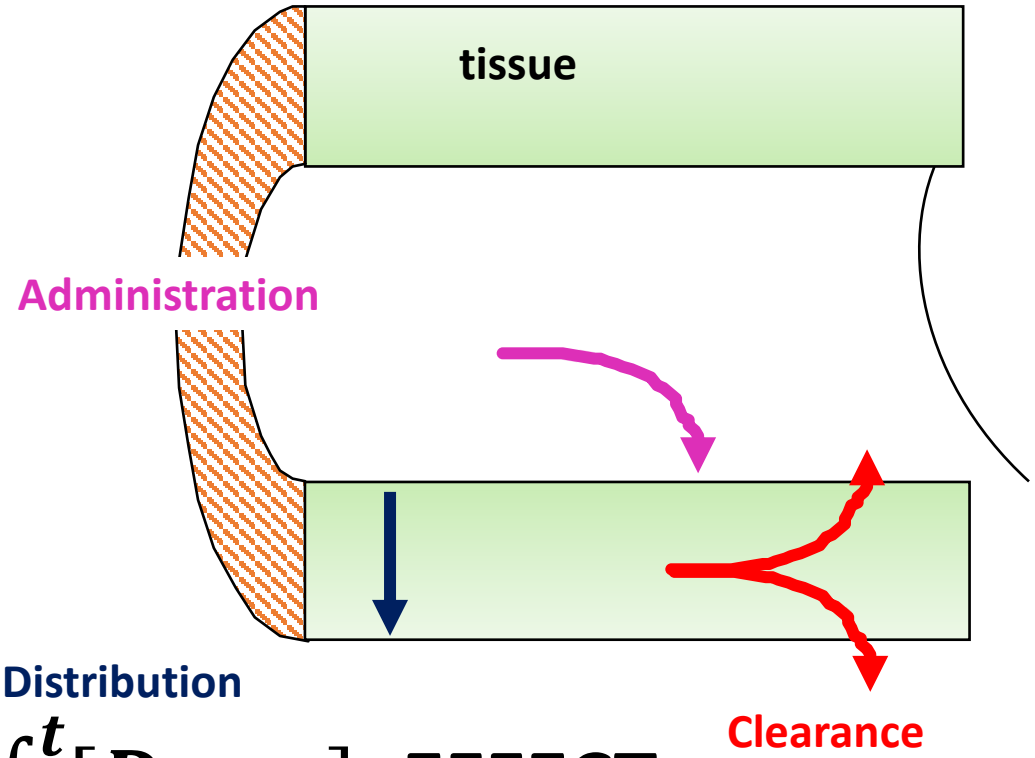
Owner of a healthcare company: No

Stockholder of a healthcare company: No

Modes of Local Endovascular Drug Delivery

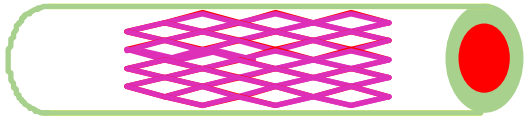
Target site



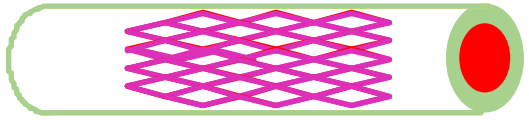
$$\int_0^t [Drug] \approx \text{EFFECT}$$

Endovascular modalities

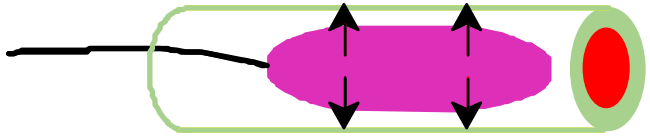
Drug release



Drug Coated Stent — FAST



Drug Eluting Stent — CONTROLLED/ SUSTAINED



Drug Eluting Balloon — FAST

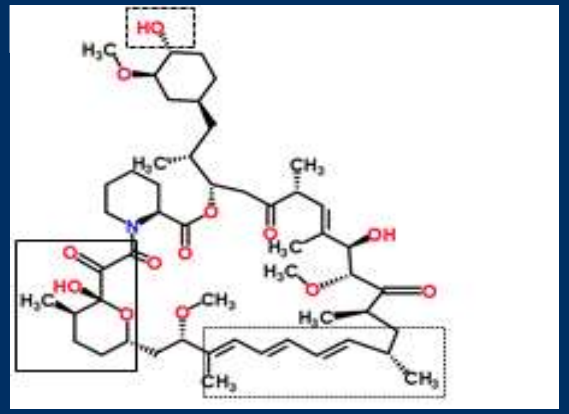
Drug “Coated” Balloon — FAST

Elements of an Effective DCB Formulation

- ✓ Must deliver large quantities of the drug within seconds
- ✓ Distribute within the media in the first few days
- ✓ Therapeutic drug levels must be maintained for more than 4 weeks
- ✓ Must allow rapid healing as compared to DES
- ✓ No need for long-term anti-platelet therapy
- ✓ Biologic effects must be observed by histology at 28-days
- ✓ Effective drug delivery to target tissue while avoiding non-target effect

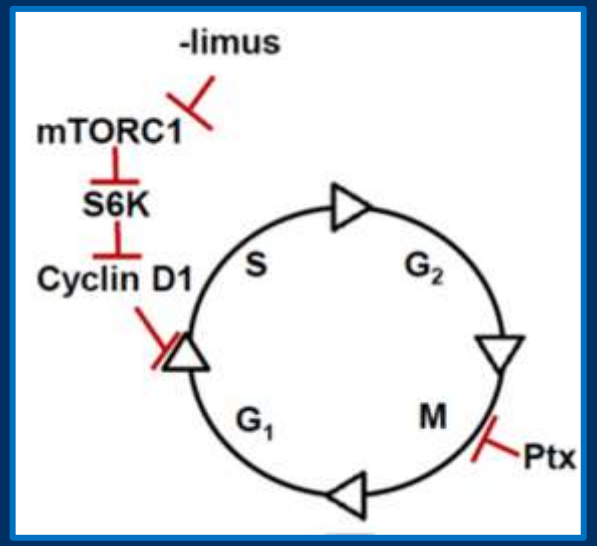
Sirolimus and Paclitaxel

Sirolimus



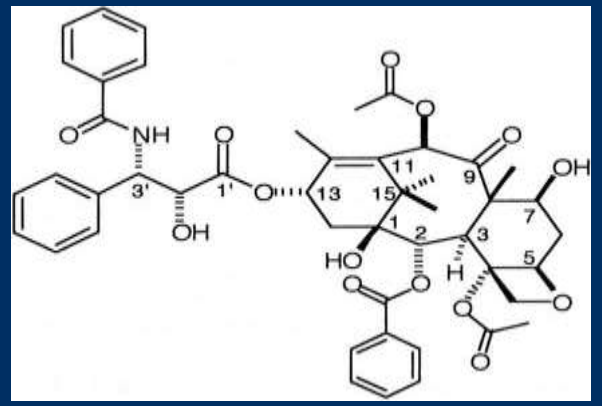
Solid line : FKBP12 binding site
Dotted line : mTOR binding site

Sirolimus inhibits mTOR and is part of the phosphatidylinositol kinase-related family of serine/threonine kinases.



Habib et al. Interventional Cardiology Clinics 2016;5:321-329

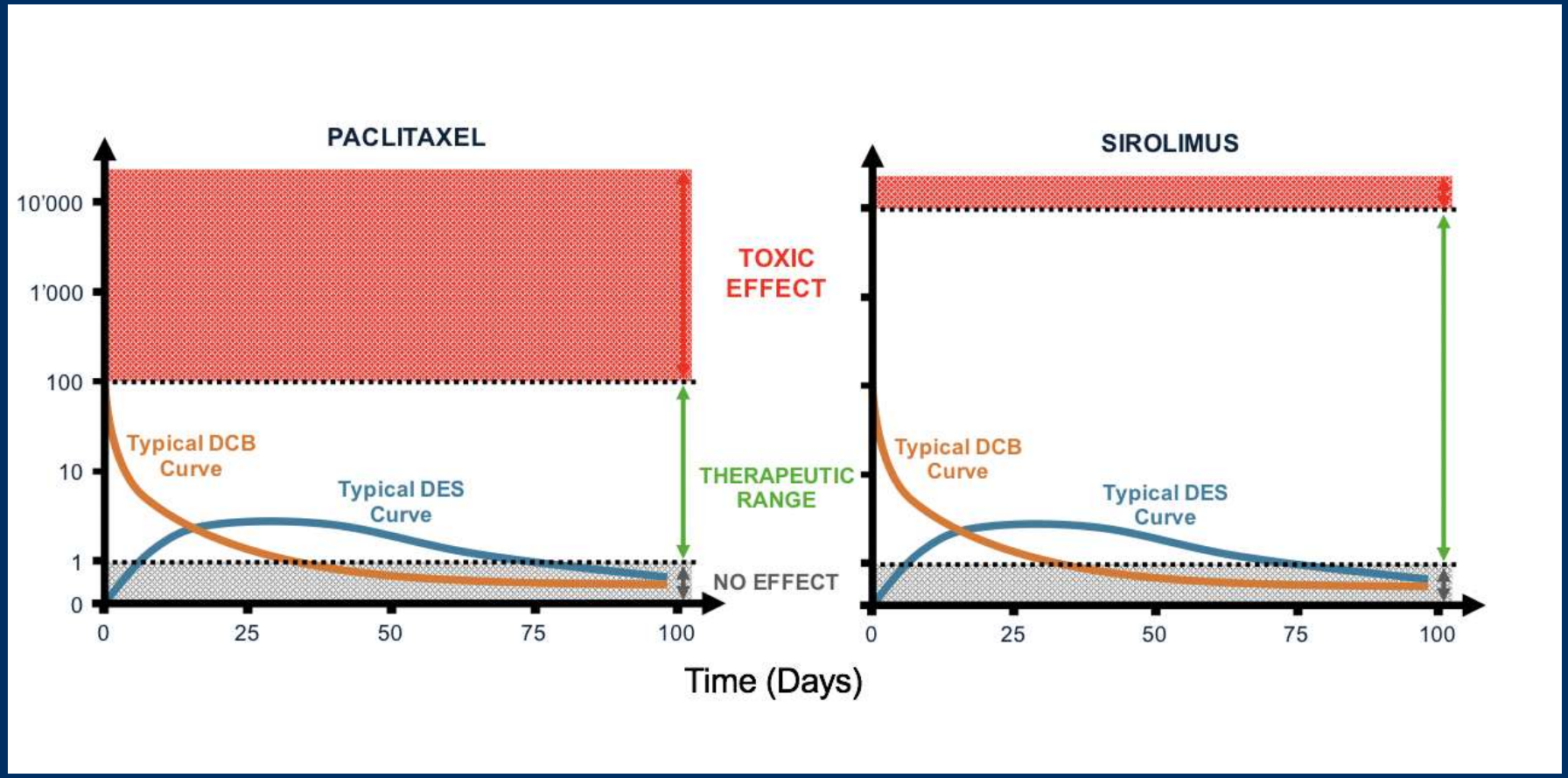
Paclitaxel



Paclitaxel binds to beta-tubulin and impairs microtubular disassembly and halts the cell cycle between G2 and M

Gupta ML et al. PNAS 2003;100:6394-6397

Paclitaxel has a Narrower Therapeutic Window Than Sirolimus



(Courtesy: Juan Granada at CRT 2014)

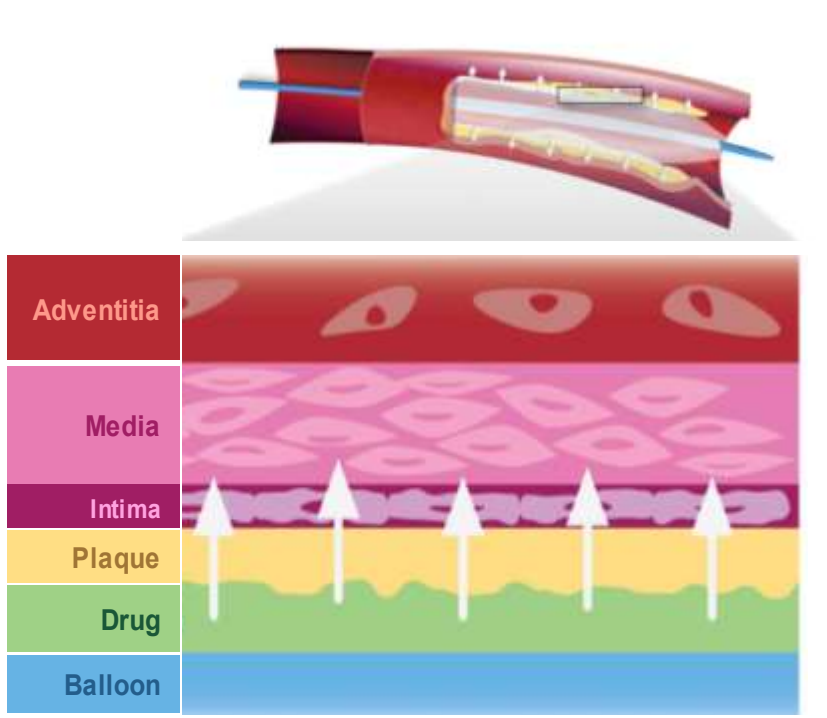
Differential Absorption and Retention of Paclitaxel and Sirolimus

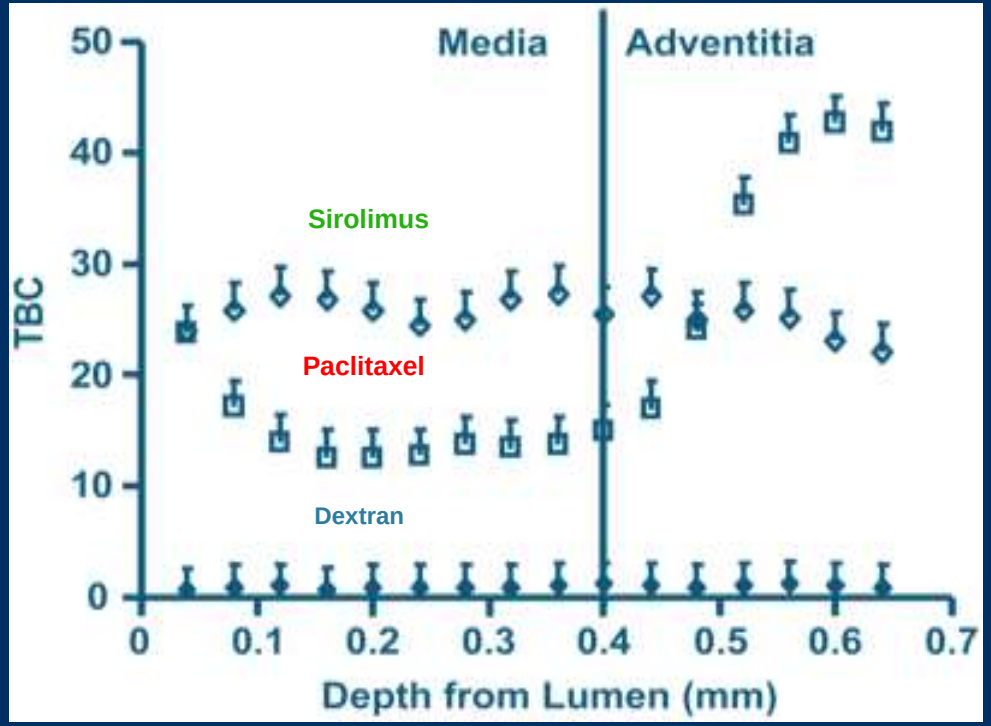
Paclitaxel

- Tends to localize in sub-intimal space and **partitions** significantly in adventitia.

Sirolimus

- Diffuses **slowly** and spreads throughout entire artery where it **dilutes down** to sub-therapeutic levels.

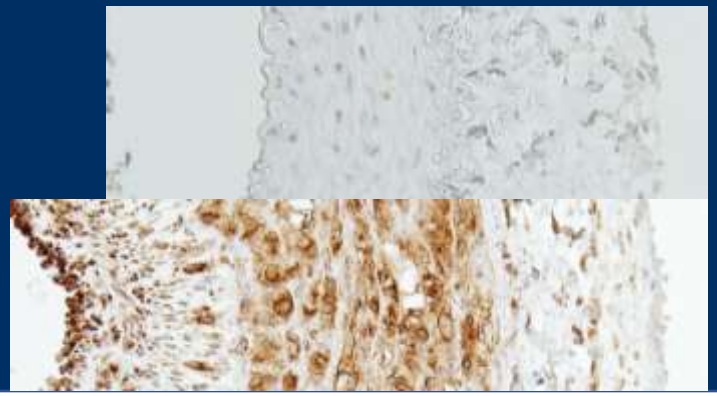




(Tissue Binding Capacity (TBC) of labeled Dextran, Paclitaxel and Sirolimus in 0.040-mm-thick bovine internal carotid tissue segments. Source: PNAS 2004)

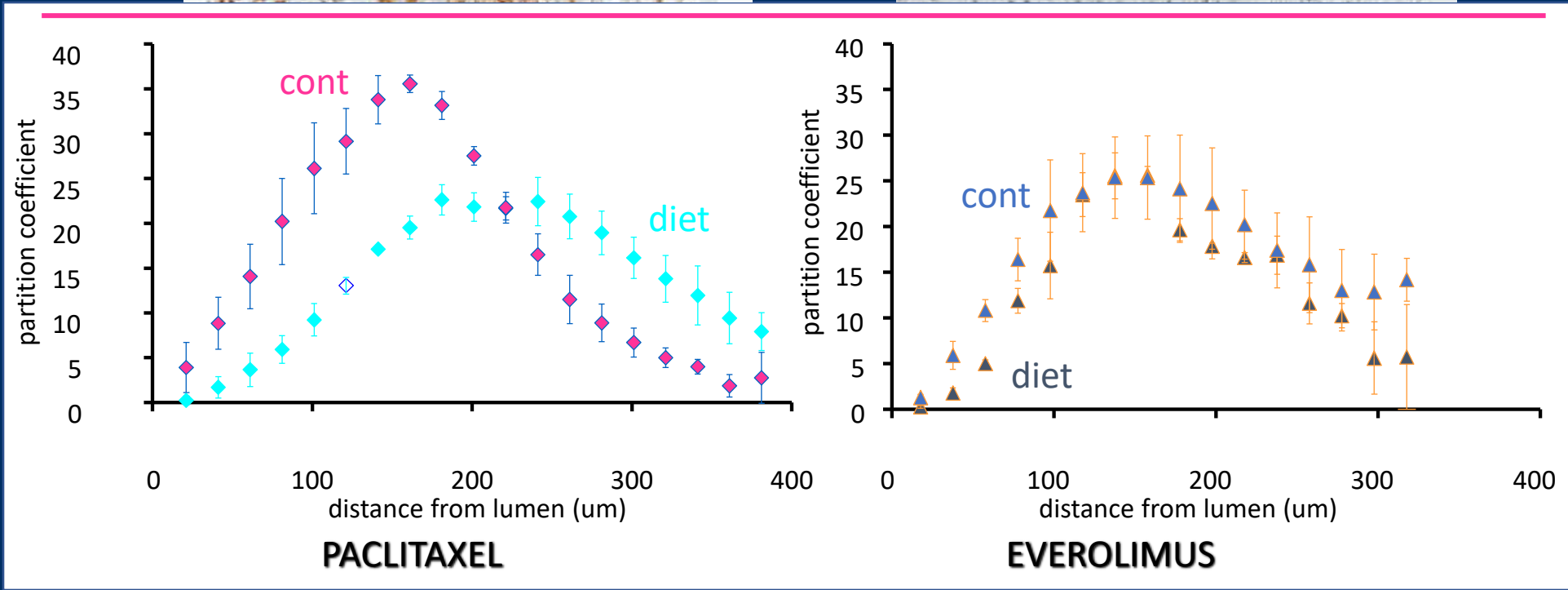
ARTERIAL STATE DIFFERENTIAL BINDING

TUBULIN



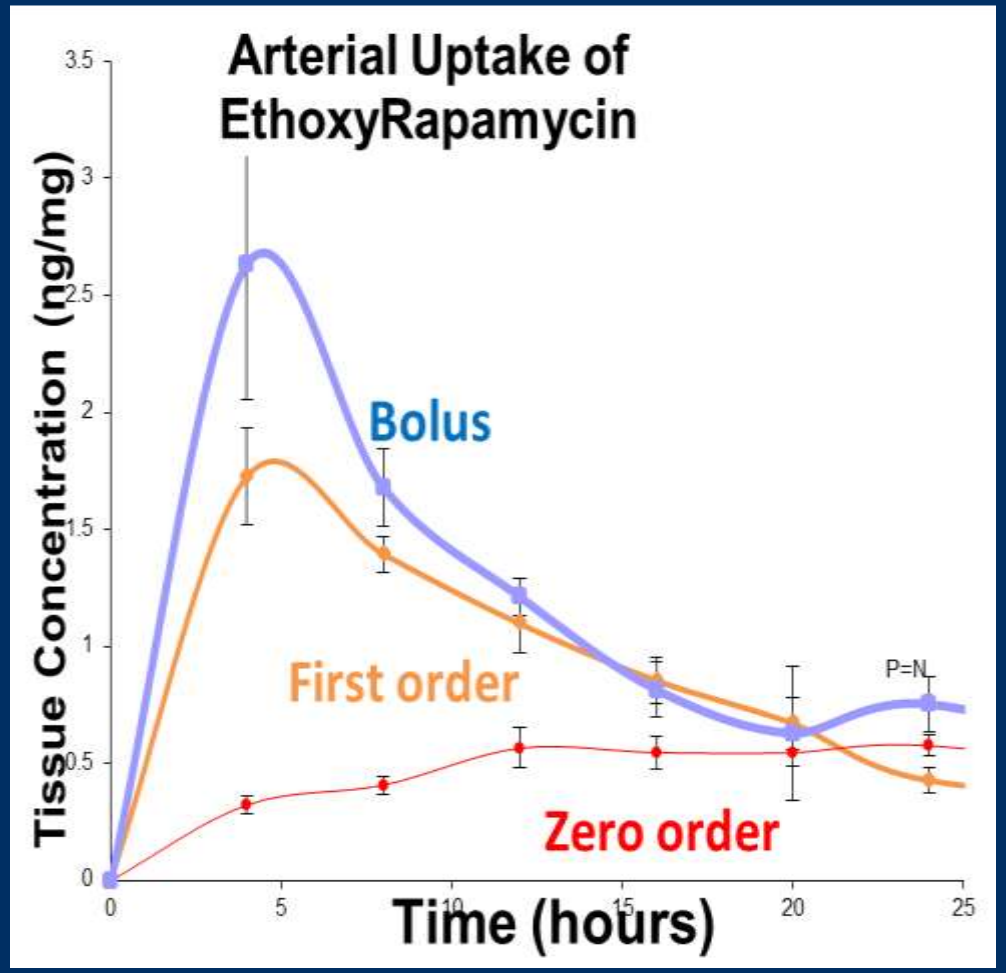
FK Binding Protein 12

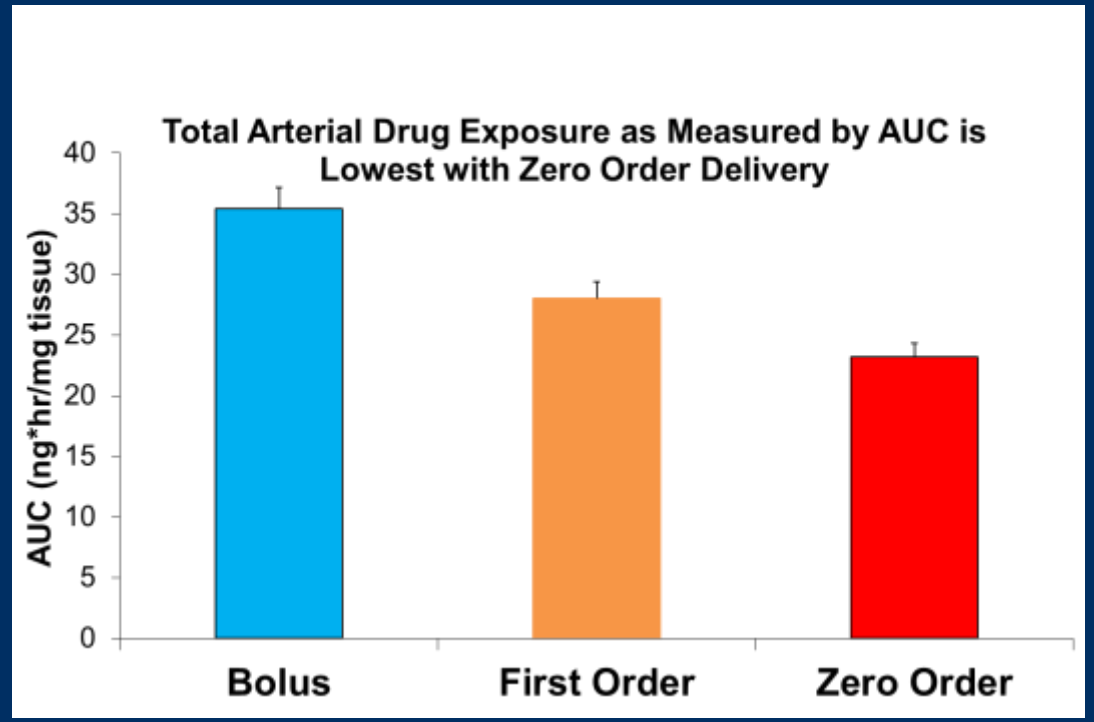
Tzafriri, et al JCR 2010



EX VIVO ARTERIAL UPTAKE ALSO DEMONSTRATES THAT PRESENTATION KINETICS IMPACT EARLY DRUG UPTAKE:

How much and how quickly you transfer drug to the artery matters





Courtesy: Sahil A. Parikh, MD

ARTERIAL DRUG UPTAKE FROM LOCAL DELIVERY VEHICLES CAN BE MODELED

Governing Equations, Boundary & Initial Conditions

Navier-Stokes Equations & Boundary Conditions

Eq 1 $$\frac{\partial v_z}{\partial z}+\frac{\partial v_r}{\partial r}=0$$

Eq 2 $$\mu\left(\frac{\partial^2 v_z}{\partial z^2}+\frac{\partial^2 v_z}{\partial r^2}\right)=\frac{\partial P}{\partial z}+\rho\left(v_z\frac{\partial v_z}{\partial z}+v_r\frac{\partial v_z}{\partial r}\right)$$

Eq 3 $$\mu\left(\frac{\partial^2 v_r}{\partial z^2}+\frac{\partial^2 v_r}{\partial r^2}\right)=\frac{\partial P}{\partial r}+\rho\left(v_z\frac{\partial v_r}{\partial z}+v_r\frac{\partial v_r}{\partial r}\right)$$

Eq 4 $$v_z(r,-L_{proximal})=V_c\left(1-\frac{(r-R)^2}{R^2}\right),\quad v_r(r,-L_{proximal})=0$$

Eq 5 $$v_z(\Omega_{coat}\cap\Omega_{blood}\ \&\ \Omega_{tissue}\cap\Omega_{blood})=v_z(2R,z)=0,$$
$$v_r(\Omega_{coat}\cap\Omega_{blood}\ \&\ \Omega_{tissue}\cap\Omega_{blood})=v_r(2R,z)=0$$

Eq 6 $$P(r,L_{distal})=0$$

Drug Transport Equations

Eq 7 $$\frac{\partial C_c}{\partial t}=D_c\left(\frac{\partial^2 C_c}{\partial z^2}+\frac{\partial^2 C_c}{\partial r^2}\right)$$

Eq 8 $$\frac{\partial C_b}{\partial t}+v_z\frac{\partial C_b}{\partial z}+v_r\frac{\partial C_b}{\partial r}=D_b\left(\frac{\partial^2 C_b}{\partial z^2}+\frac{\partial^2 C_b}{\partial r^2}\right)$$

Eq 9 $$\frac{\partial C_t}{\partial t}=D_t\left(\frac{\partial^2 C_t}{\partial z^2}+\frac{\partial^2 C_t}{\partial r^2}\right)$$

Drug Transport Boundary Conditions

Eq 10 $$C_b(r,-L_{proximal})=0$$

Eq 11 $$\left.\frac{\partial C_b}{\partial z}\right|_{r,z=L_{distal}}=0$$

Eq 12 $$\left.\frac{\partial C_b}{\partial r}\right|_{r=2R,z}=0$$

Eq 13 $$D_b\left.\frac{\partial C_b}{\partial r}\right|_{r=0^+,z}=D_t\left.\frac{\partial C_t}{\partial r}\right|_{r=0^-,z}$$

Eq 14 $$\left.\frac{\partial C_t}{\partial z}\right|_{r,z=-L_{proximal}\ ,L_{distal}}=0$$

Eq 15 $$\left.\frac{\partial C_t}{\partial r}\right|_{r=-W_{tissue},z}=0$$

Eq 16 $$D_c\left.\frac{\partial C_c}{\partial r}\right|_{r=0^+,z}=D_t\left.\frac{\partial C_t}{\partial r}\right|_{r=0^-,z}$$

Eq 17 $$D_c\left.\frac{\partial C_c}{\partial r}\right|_{\Omega_{coat}\cap\Omega_{blood}}=D_b\left.\frac{\partial C_b}{\partial r}\right|_{\Omega_{coat}\cap\Omega_{blood}},$$
$$D_c\left.\frac{\partial C_c}{\partial z}\right|_{\Omega_{coat}\cap\Omega_{blood}}=D_b\left.\frac{\partial C_b}{\partial z}\right|_{\Omega_{coat}\cap\Omega_{blood}}$$

Drug Transport Initial Conditions

Eq 18 $$C_c|_{\Omega_{coat}}=1\ @\,t=0$$

Eq 19 $$C_t|_{\Omega_{tissue}}=C_b|_{\Omega_{blood}}=0\ @\,t=0$$

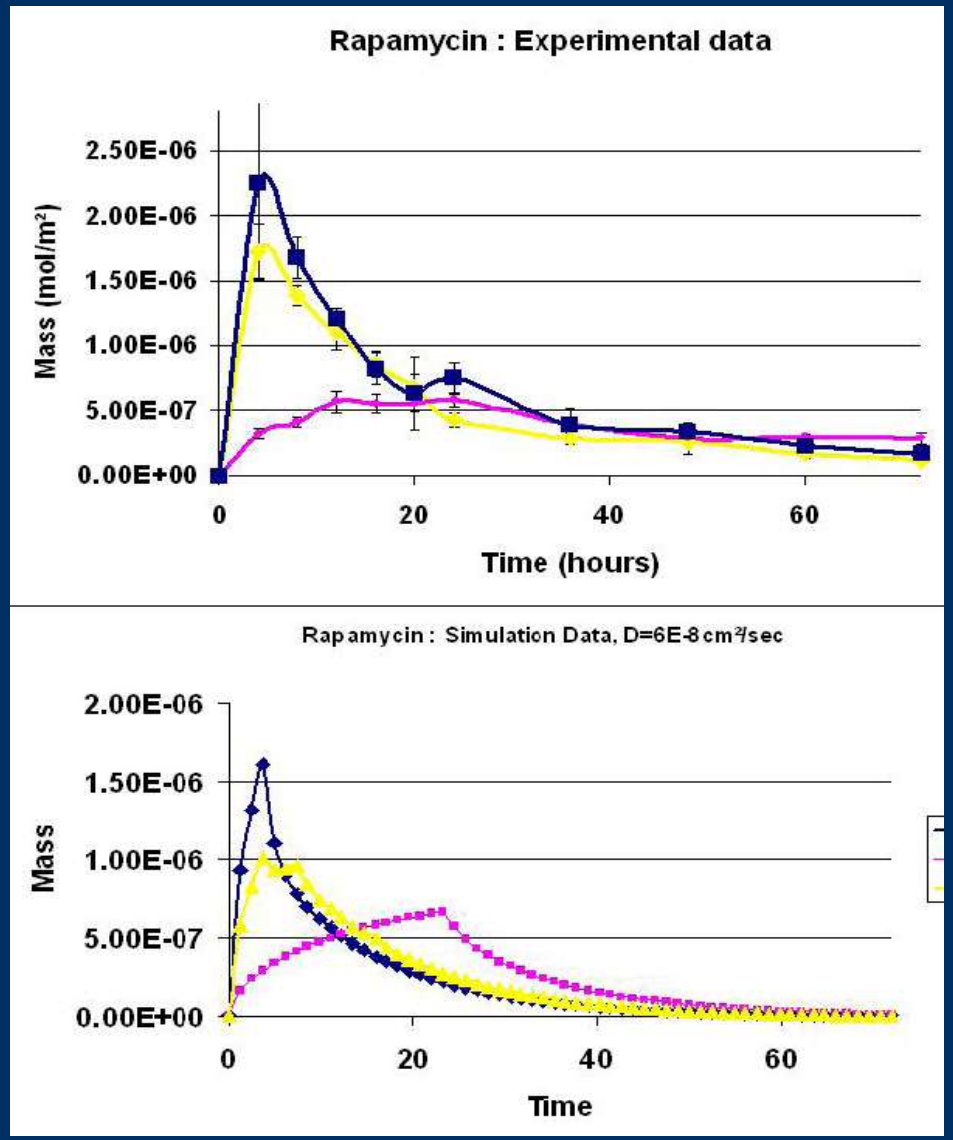
- Diffusion Mediated Transport
- Boundary Conditions Imply Minimal Convective Transport

Balakrishnan, et al. J. Control. Release, 2007

DIFFUSION MEDIATED FEM RECAPITULATE *EX VIVO* DATA

Empiric

Computed



Courtesy: Sahil A. Parikh, MD

Sirolimus offers potential benefits over Paclitaxel

Common anti-proliferative drug for DCB is currently **PACLITAXEL**, however, **SIROLIMUS** (rapamycin) offers potential benefits over Paclitaxel.

	SIROLIMUS (OR ANALOGS)	PACLITAXEL
Inhibition of SMC proliferation	+ +	+ +
Inhibition of SMC migration	+ +	+
Inhibition of EC proliferation	+ +	+ +
Pro-apoptotic effects	(+)	+ +
Therapeutic range	**WIDE**	**NARROW**
Safety margin	**10'000 fold**	**100 fold**
Anti-Restenotic impact	+ +	+
Anti-inflammatory properties	+ +	(+) / -
Tissue Absorption	**SLOW**	**FAST**
Tissue Retention	**SHORT**	**LONG**

Modified Wessely R, et al. JACC 2006:47(4);708–14.

Slide courtesy of Aloke Finn, MD

Sirolimus Coated Balloons – Technical challenges

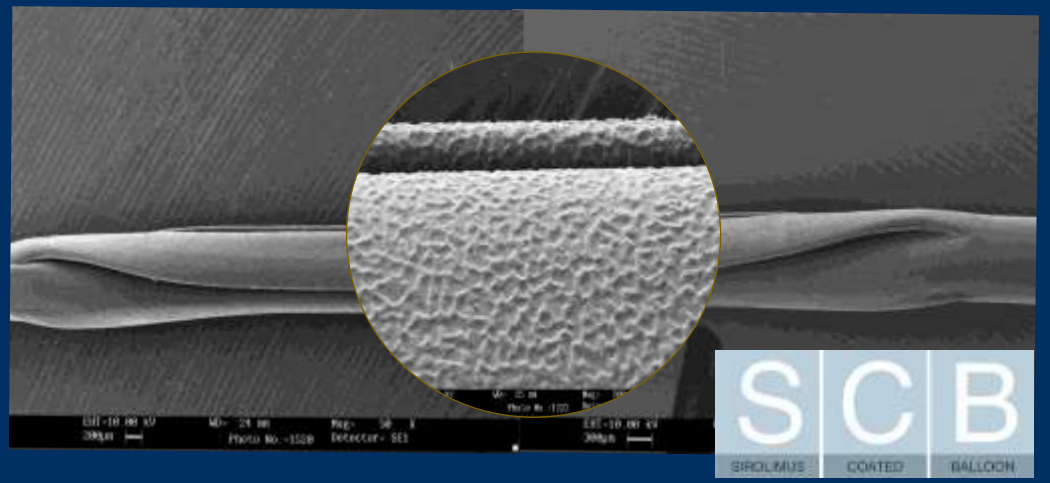
- **Enhance tissue absorption**
  - **Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of "instant glue" is required to transfer the drug from the balloon to the tissue efficiently**
  - **Potential solutions include alternate excipients or surface modification of balloons**
- **Extend tissue retention**
  - **Sirolimus must be continuously delivered over time, so some form of "time release mechanism" must be employed to maintain therapeutic levels**
  - **Potential solutions include nano-encapsulation, perivascular drug delivery, and crystalline formulations**

Slide adapted from Aloke Finn, MD

MAGIC TOUCH – Sirolimus Coated Balloon

- MAGICTOUCH® – SCB is Sirolimus Coated Balloon to treat coronary artery disease
- Delivers drug in 60 seconds
- Sub-micron particles
- Supersedes limitations of Paclitaxel

Nothing Leaves Behind



Slide adapted from Aloke Finn, MD

Summary

- ✓ Neointimal hyperplasia is the major cause of restenosis.
- ✓ Pharmacologic agents used on DES and DCB mainly inhibit SMC proliferation.
- ✓ The most commonly used anti-proliferative agent for DCB is currently Paclitaxel.
- ✓ Paclitaxel has a narrow therapeutic window compared with sirolimus and its analogues but is easier to deliver and has greater tissue residence time
- ✓ Delivery of sirolimus from a DCB that achieves sustained therapeutic concentrations of drug likely requires substrate modification of the drug
- ✓ Potential solutions are emerging and will be reviewed in the subsequent lectures