Requirements and specificities of a low dose DCB: The Stellarex case example

John Pedersen, Ph.D.
Sr. R&D Manager, Philips
Disclosure

Speaker name:

John Pedersen, Ph.D.

I have the following potential conflicts of interest to report:

☐ Consulting

☒ Employment in industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

☐ Other(s)

☐ I do not have any potential conflict of interest
DCB Requirements

• Primary mechanism of action is PTA – must have a suitable balloon catheter platform
• Adjunctive mechanism of action is via transfer of a drug to minimize restenosis
  • Drug must be absorbed in ~ 1 minute of inflation
  • Drug must remain at therapeutic levels for at least 28 days to have its desired effect
Why Paclitaxel?

- PTX is a lipophilic molecule → long residence time and short transfer time between the balloon and the tissue.
- PTX inhibits mitosis via irreversible stabilization of microtubules during cell division.

Cells get “stuck” here.
Anti-Restenosis Mechanism

Restenosis is believed to be a pathological wound healing reaction; a result of balloon injury, injury from atherectomy procedures, stent irritation, etc.

Paclitaxel interrupts smooth muscle cell (SMC) division by blocking microtubule disassembly, thus blocking restenosis.
Coating Design Principles

• Use lowest dose that will drive desired therapeutic response → minimize effect on non-target tissues
• Coating must be durable enough to survive passage through an introducer sheath, and passage through the vasculature to the treatment site
• Coating should transfer as much drug as possible to lesion during first inflation
• Coating needs to have attributes that make it manufacturable (suitable viscosity, solvents, etc).
DCBs are about Balance

Drug Morphology

Amorphous morphology \( \rightarrow \) shorter effect and higher durability

Crystalline morphology \( \rightarrow \) longer lasting effect and lower durability

Drug Dose

Transfer efficiency + low dose helps achieve this balance

Ineffective dose

Local or systemic toxicity

Ineffective dose

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Dose Matters

For DCBs in general, the dose that matters is the quantity of ptx finally transferred and resident in vessel.

U.Speck – Rationale and Likely Mechanism of Action of Paclitaxel-Coated Balloons – LINC 2016 oral presentation

Most ptx lost downstream:
Can we minimize loss? Maximize transfer?

- Lost downstream: 80%
- Transferred to tissue: 10%
- Residual on balloon: 10%

To increase dose delivered to tissue, can either increase total dose OR improve transfer efficiency.
Excipients and Molecular Weights

Higher Molecular Weight =
Slower dissolution + more durable mechanical properties

If other factors are held constant, polymer mechanical properties are driven by polymer size
Excipient + Hybrid PTX Structure

Use durable excipient to balance brittle crystalline paclitaxel for durability

Hybrid Paclitaxel (Amorphous + Crystalline Blend) balances durability with longer term tissue retention

PEG
- Hydrophilic
- Durable
- Easily metabolized and biocompatible

Polarized Image of Stellarex DCB at 50x magnification
Stellarex Coating Stability

Bench test shows coating stability under various handling conditions with minimal loss (<5%) and without insertion tool.

% of Label Claim

- Handled with dry gloves
- Handled with wet gauze
- Handled without touching the balloon surface
- Re-inserted with wet gauze

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Stellarex Coating Stability

Bench test show limited drug particulate loss, visible to eye and measurable under microscope

Microscopically Measured
Minimal Particulate loss of any size after tracking

- Small particulates (≥10µm/mm²)
- Large particulates (>100µm/mm²)

Macroscopically Evident
Particulate loss after bending (bend radius 20mm)


Bench test may not be indicative of clinical results.
DCB in Context: Pre-Clinical Evidence

Pre-clinical evidence confirms Stellarex limited distal embolization

- Independent, physician initiated DCB animal study
- Rabbit model / DCB deployed in Aorta
- 5 different DCB tested x 5 specimens: tot 25 rabbits
- blinded evaluation of ptx particles and dose by HPLC

ptx in Tibials

ptx muscles (global)

ptx remaining on balloon

R.Coscas, oral presentation – PERSPECTIVES, Dec 15th 2017
Clinical Results

Core-lab adjudicated* 1-year Primary Patency

Duplex derived Primary Patency based on PSVR ≤2.4 (●) or ≤2.5 (○). KM survival estimates at 360 (†) or 365 (‡) days.

* VascCore Core laboratory - Boston, MA, USA


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Final Thoughts

• Paclitaxel is well-suited to DCB delivery due to its rapid uptake and long residence time
• Excipients, solvents, and details of the coating process combine to form balance between durability, deliverability, and duration of effect of coating
• Successful balance of key DCB design attributes is shown in clinical results
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