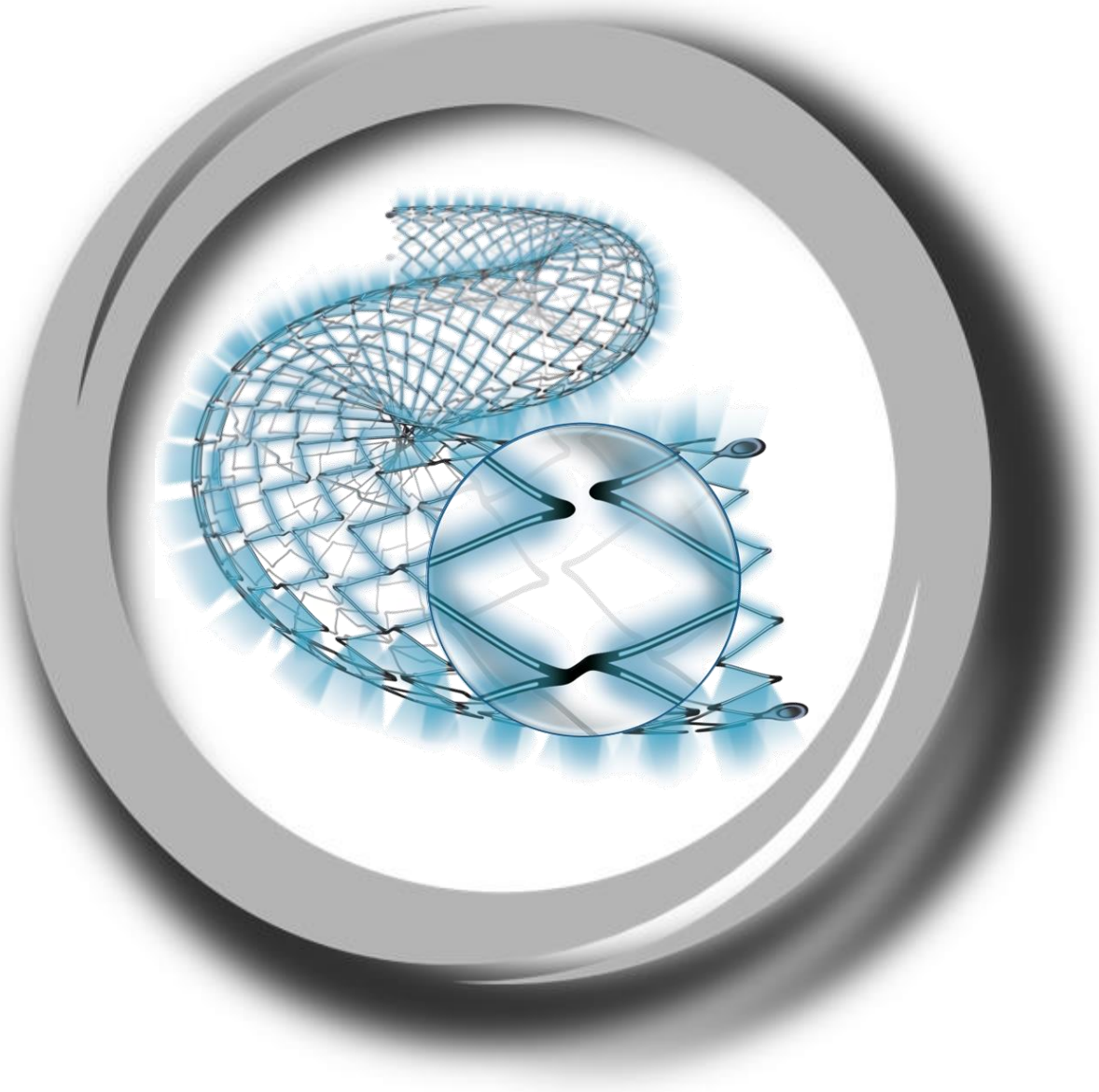
CIRSE 2018



Innovating SFA lesions treatment with NiTiDES

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Vascular Center Sankt Gertrauden - Berlin

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Alvimedica

The evolution of the SFA DES approach

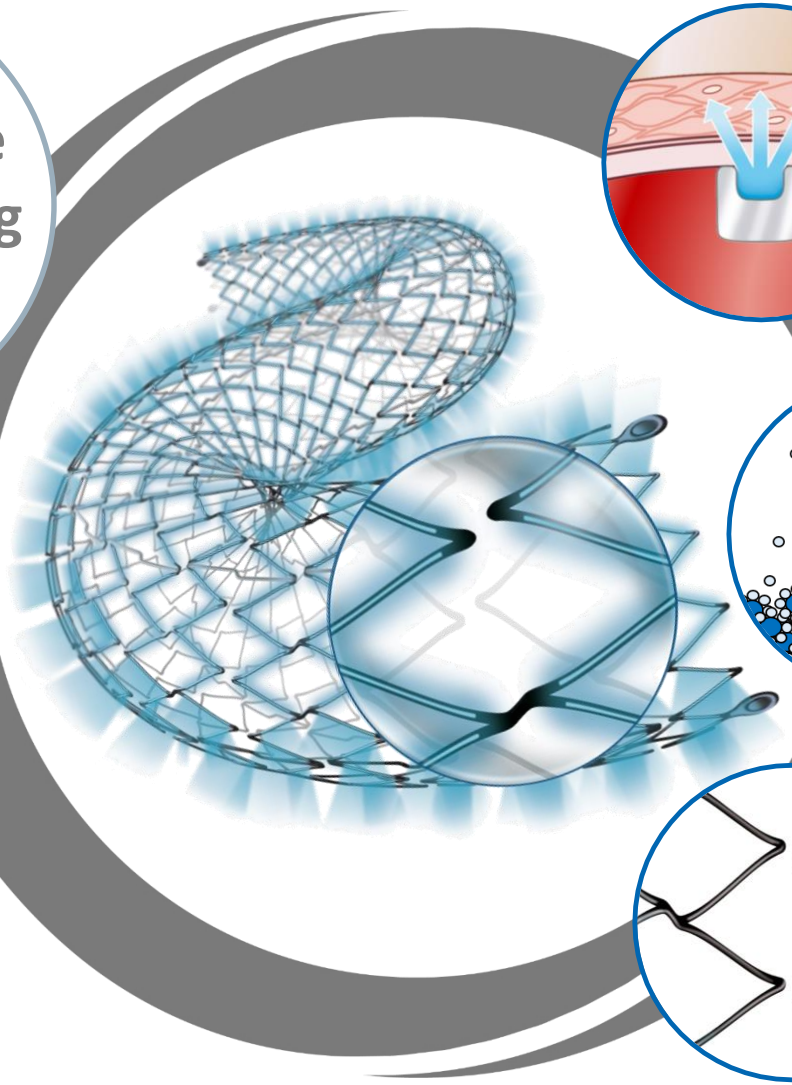
	Cordis	Cook	Boston
Drug	Sirolimus	Paclitaxel	Paclitaxel
Technology	Permanent Polymeric Matrix	Polymer Free	Permanent Polymeric Matrix
Elution Time	Sustained 1 / 2 months	Fast in some days	Sustained 1 year (too much?)
Pro	Drug	Polymer free approach	Sustain drug release
Cons	Polymeric Drawbacks	No sustained drug elution	Polymeric Drawbacks
	The idea to add a drug to a stent works, but the drawbacks of the polymer vanish the efficacy of the drug.	Eliminating the polymeric matrix the long term drawbacks are avoided, but the absence of the sustain release kinetic forced the choice of a more “aggressive” drug as the Paclitaxel.	The permanent polymeric matrix, able to sustain the drug elution up to 1 year, improved the medium term clinical results but it seems only delay the drawbacks, with an impact on the long term results.

Alvimedica patented polymer-free controlled drug elution technology

NiTiDES: Platform Characteristics

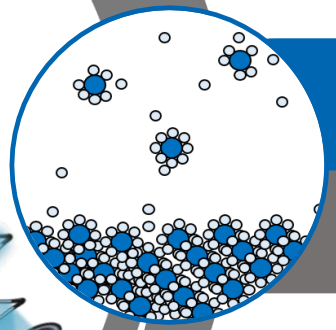
Polymer-Free self-expanding DES

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall



Abluminal Reservoir Technology

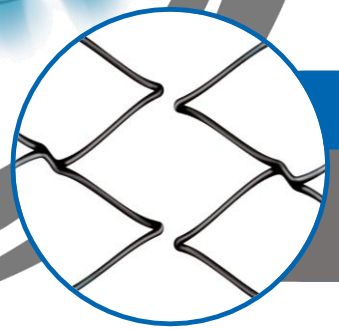
Controlled and directed elution to the vessel wall



Amphilimus™ Formulation

(Sirolimus + Fatty Acid)

Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy



Bio Inducer Surface (BIS)

2nd generation pure carbon coating

Optimal haemo-compatibility vs. lumen blood flow

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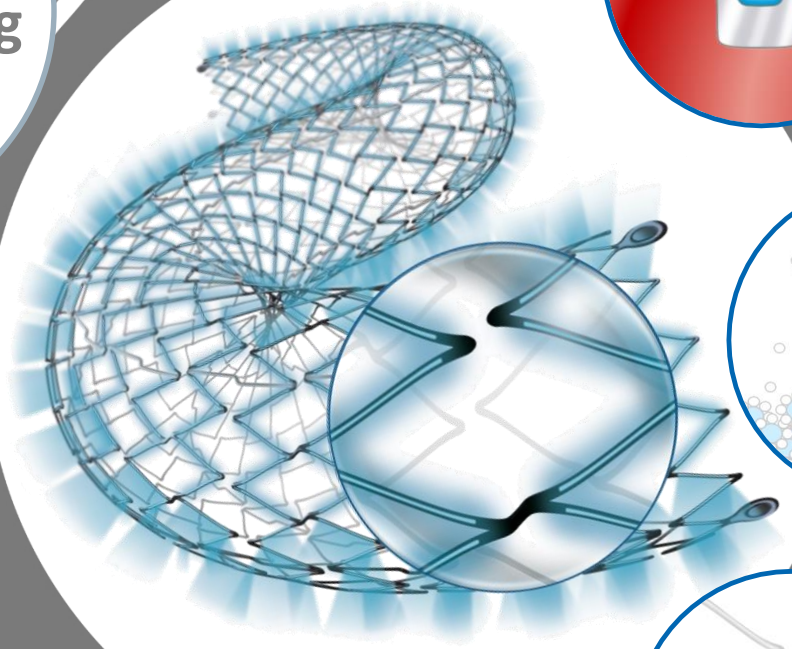

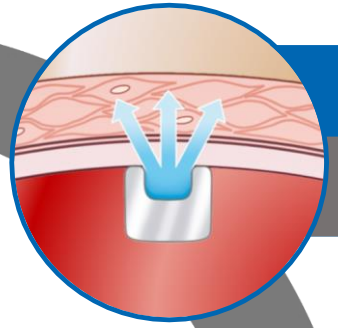

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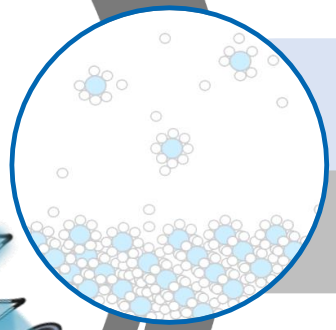

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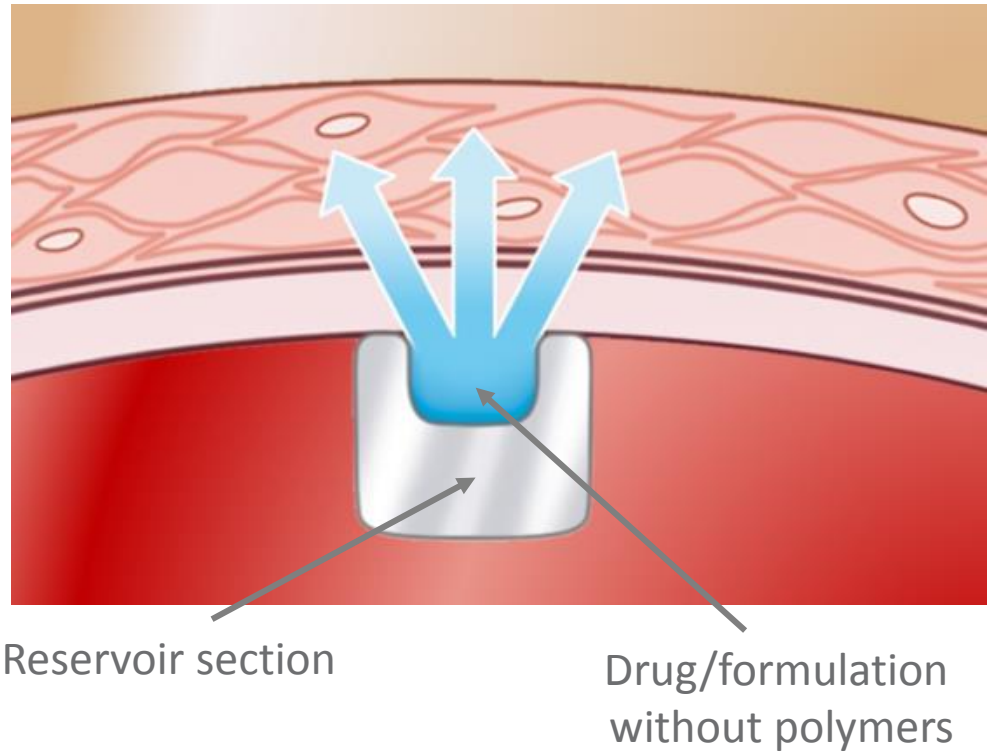
NiTiDES: Abluminal Reservoir Technology

In the **Abluminal Reservoir Technology** the drug is loaded in the reservoirs onto the stent platform without the need of any kind (durable or degradable) polymer.

The reservoirs are uniformly distributed on the stent struts



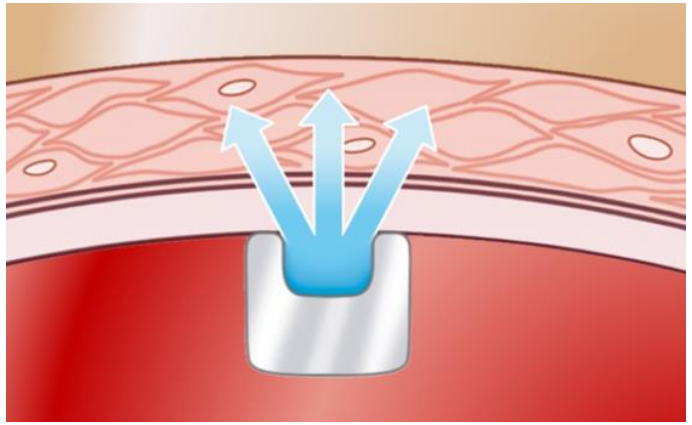
NiTiDES: Abluminal Reservoir Technology

The reservoir's design fixes the drug amount and elution kinetic to the vessel wall without the use of any polymer

THE FICK'S LAW:

$$\frac{\Delta m}{\Delta t} = -D \cdot A \cdot \frac{\Delta c}{\Delta x}$$

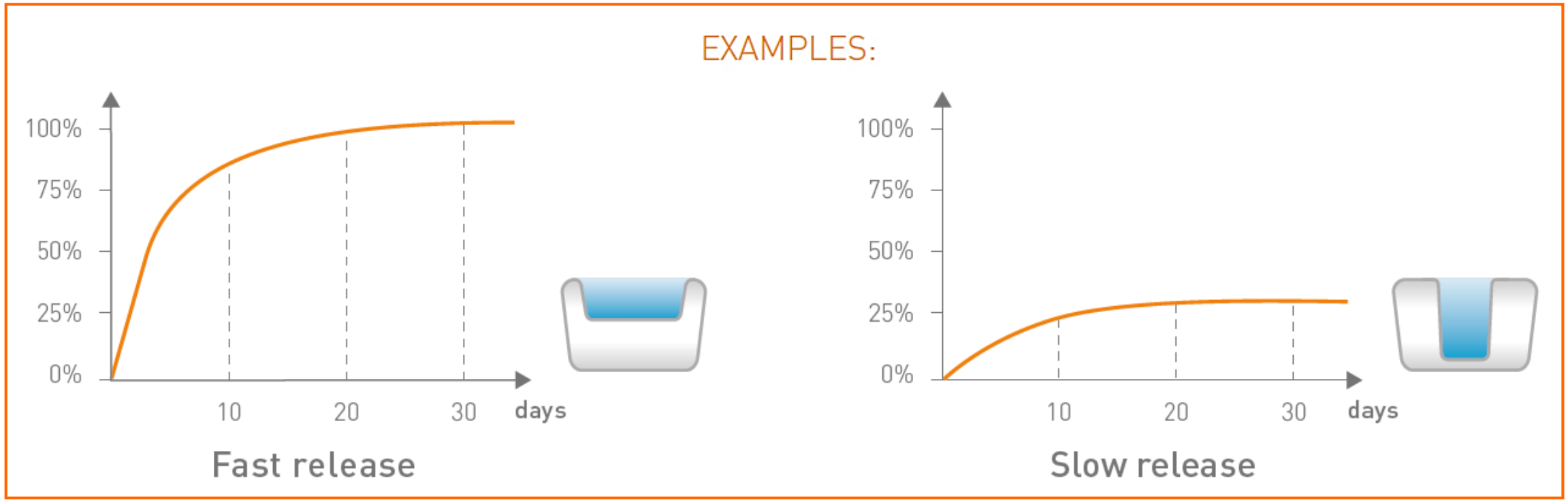
- $\frac{\Delta m}{\Delta t}$: Drug amount released over time
- D: Drug diffusion coefficient
- A: Area of the drug-vessel contact surface
- $\frac{\Delta c}{\Delta x}$: Drug concentration gradient



The amount of drug released overtime is proportional to the area of contact and to the drug concentration gradient.

NiTiDES: Abluminal Reservoir Technology

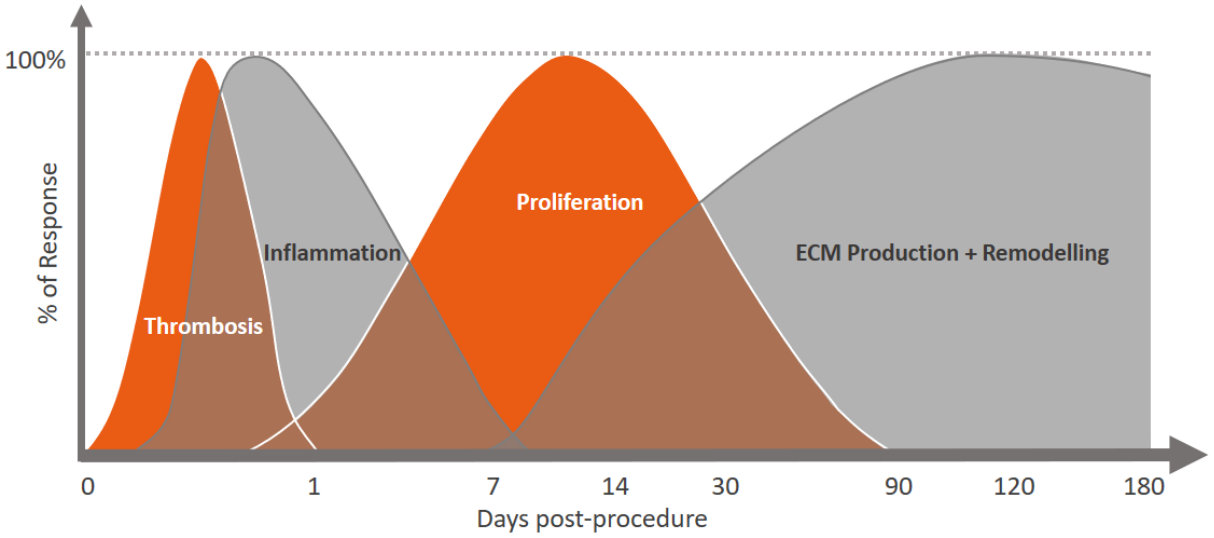
It’s possible to obtain a specific release kinetic curve working on the geometry (i.e. width and depth) of the reservoir without the use of any polymer:



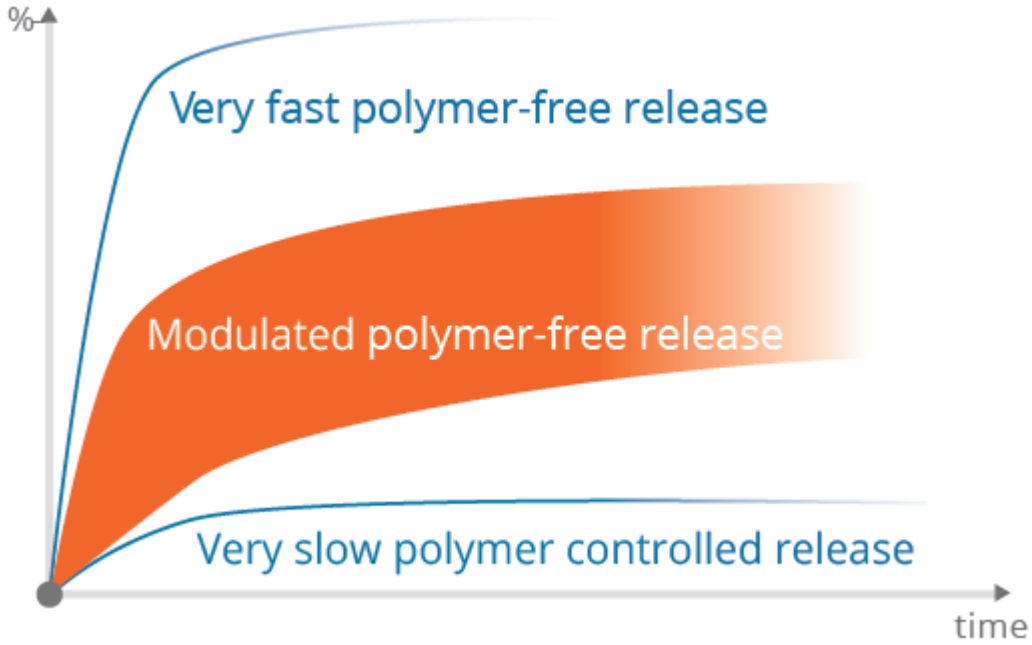
NiTiDES: Abluminal Reservoir Technology

To control the restenosis cascade, triggering factors and proliferation activities, we need to optimize and modulate the release kinetic of the drug, ideally without any inflammatory substances.

The restenosis cascade



The DES landscape



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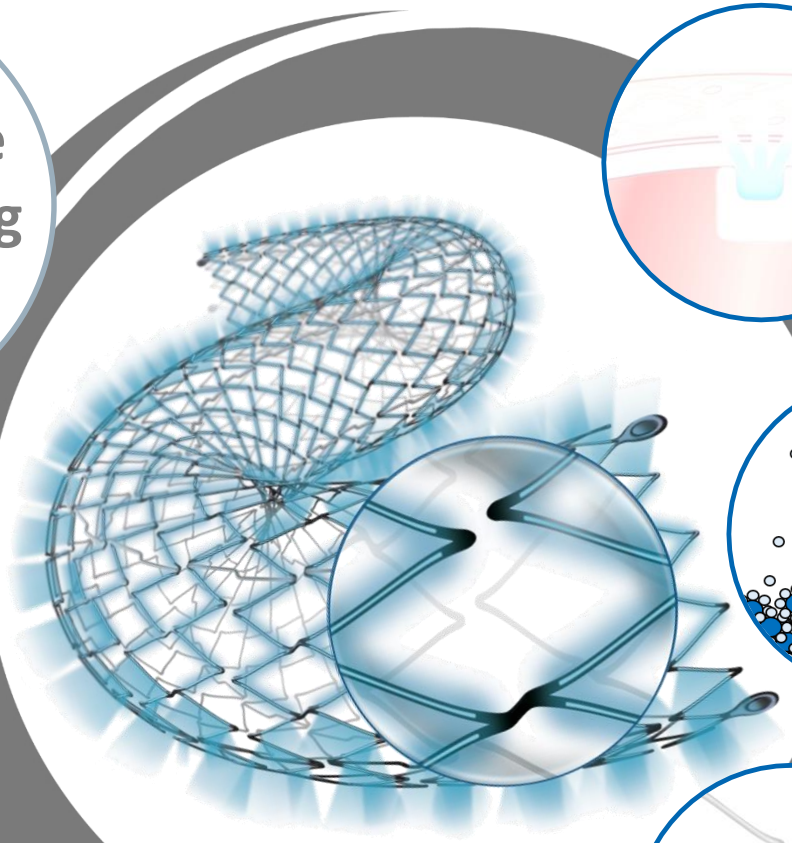

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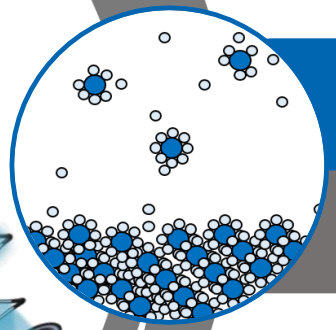
Controlled and directed elution to the vessel wall



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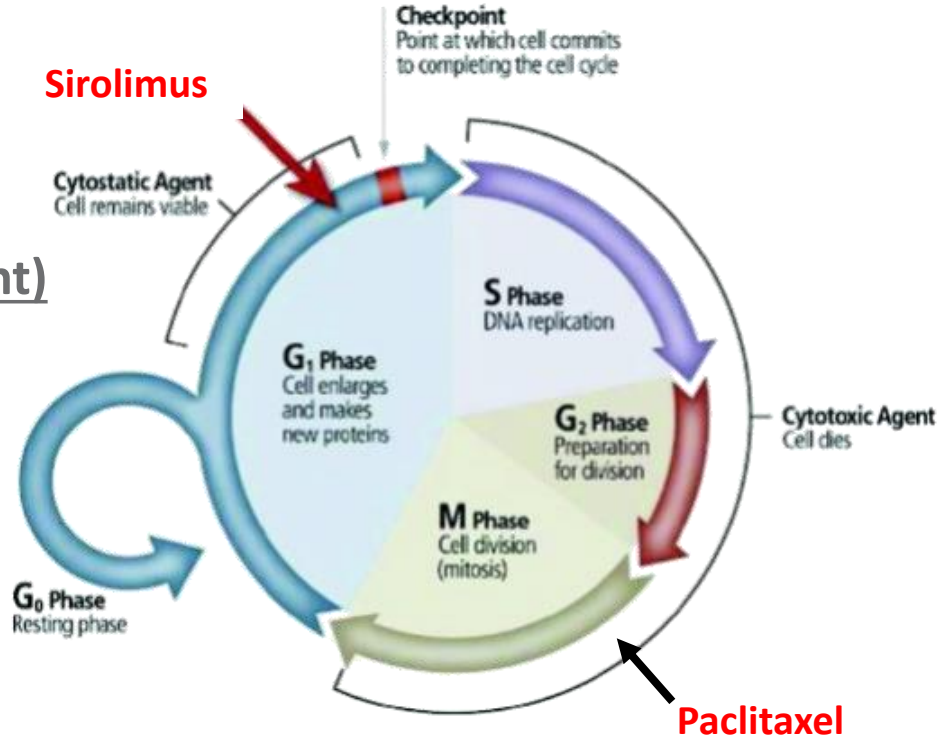
Which drug a SFA DES should release?

At today we can have different antiprolipherative drugs which act in different moments of the cell cycle:



Cytostatic Drug (immunosuppressant)

- Prevent proliferation of cells.
- Sirolimus and its analogue

Cytotoxic Drug (chemotherapyc)

- Induce the cellular apoptosis (death)
- Paclitaxel

It has been verified that coronary and femoropopliteal arteries have similar cell biology and they respond with a close antiproliferative mechanism after the delivery of the drug.

Which drug a SFA DES should release?

The ideal antiprolipheratives drug to release has to be:

- Effective
- With low toxicity
- With long tissue residence

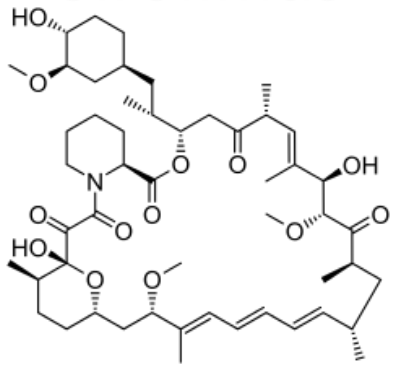
Drug characteristics	Paclitaxel	Sirolimus
Antiproliferative	very high	**very high**
Toxicity	very high	**limited**
Anti-inflammatory activity	low	**high**
Lipophilicity	high	**very high**
Uniformity of drug tissue distribution	high	**very high**
Tissue drug retention	high	**very high**

Sirolimus (or analogs) is the first choice in the coronary district and it fits all the SFA requirements.

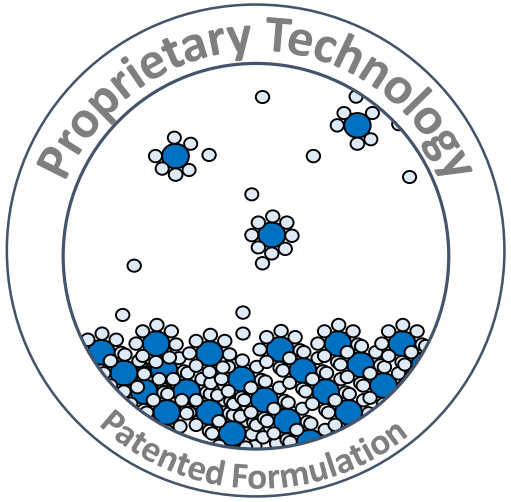
How we can empower the role of the drug?

NiTiDES: Amphilimus™ formulation

Sirolimus



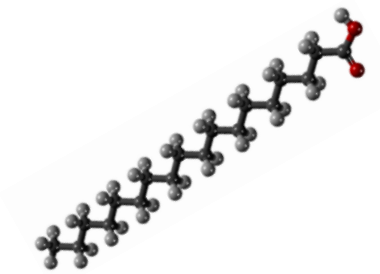
- Immunosuppressant
- Anti-proliferative action
- Anti-microbial
- Inhibitor of inflammatory cell activities
- High potency



Sirolimus and Fatty Acid are eluted together

Combined effect!!!

Fatty Acid

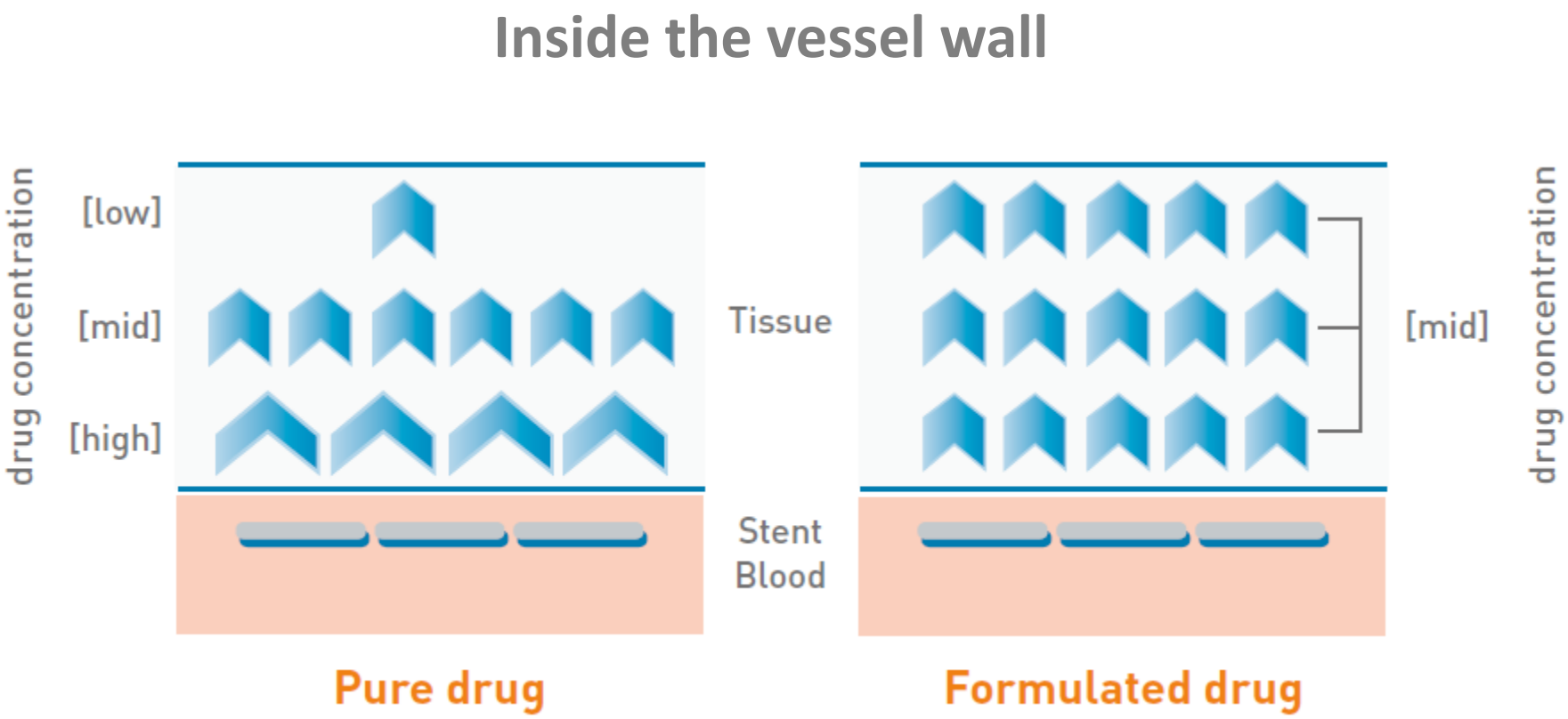


- Sustained drug elution timing
- Modulated drug bioavailability
- Raised homogeneous drug distribution
- Enhanced drug stability

Sirolimus molecule is 4 times bigger than the Fatty Acid molecule

NiTiDES: Amphilimus™ formulation

Fatty Acid (small molecules) are characterized by an excellent permeability through cell membrane that allows a homogeneous Sirolimus distribution and action on the whole vessel tissue

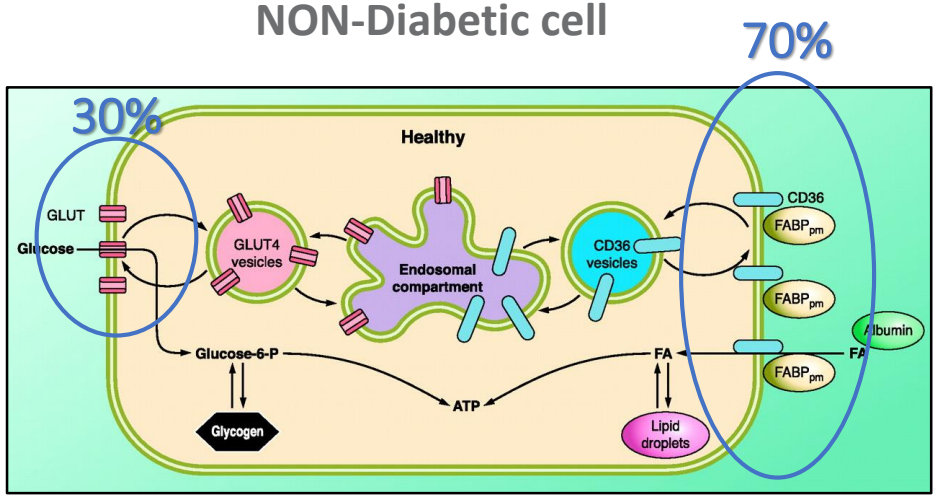


NiTiDES: Amphilimus™ formulation

Fatty Acids play a physiological role in standard metabolic process inside the cells.

In diabetes, as glucose uptake and oxidation are impaired, the fatty acids uptake is increased and fatty acids are used as source of energy:

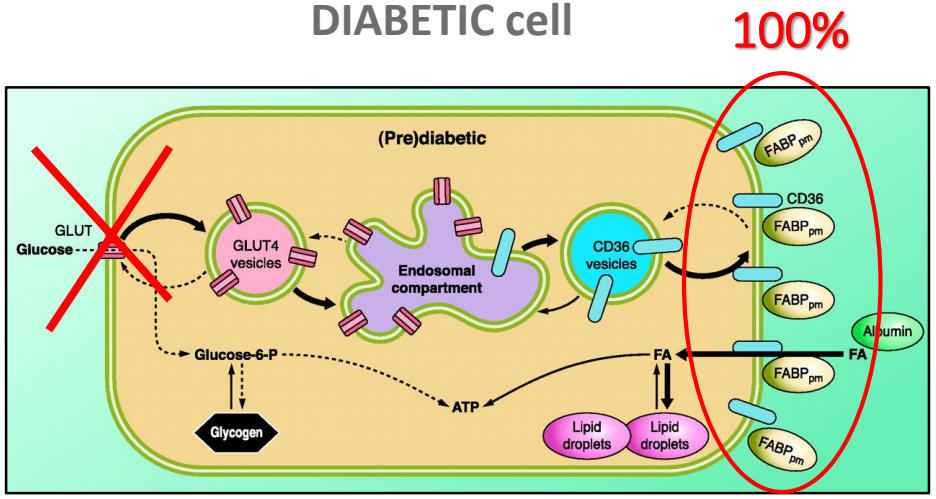
NON-Diabetic cell



Two pathways for ATP generation:

1. Glucose pathway (30%)
2. Fatty acid pathway (70%)

DIABETIC cell



Membrane protein overexpression leads to higher fatty acids bindings/ translocation. (Glucose pathway not active)

Membrane Fatty Acid Transporters as Regulators of Lipid Metabolism: Implications for Metabolic Disease – Glatz J; 2010 Physiol Rev 90: 367–417

NiTiDES: Amphilimus™ formulation

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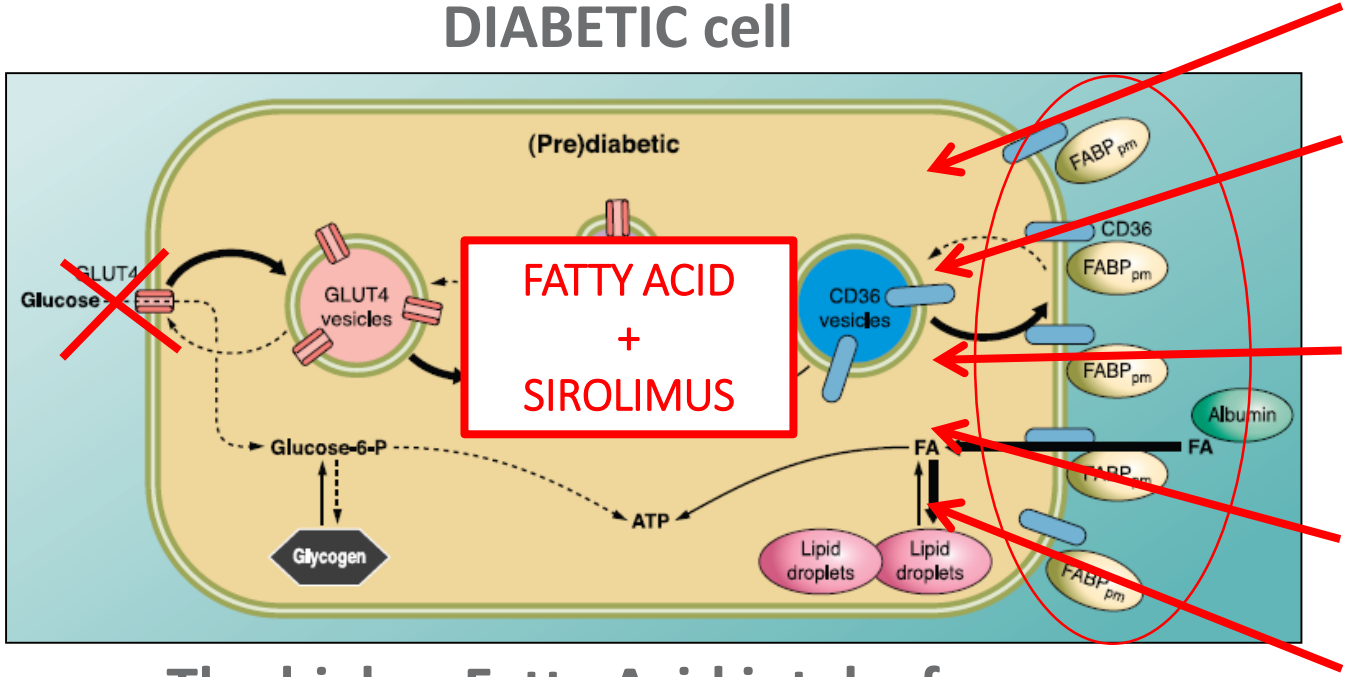

The higher Fatty Acid intake favors higher Sirolimus presence inside the diabetic cells (bioavailability).

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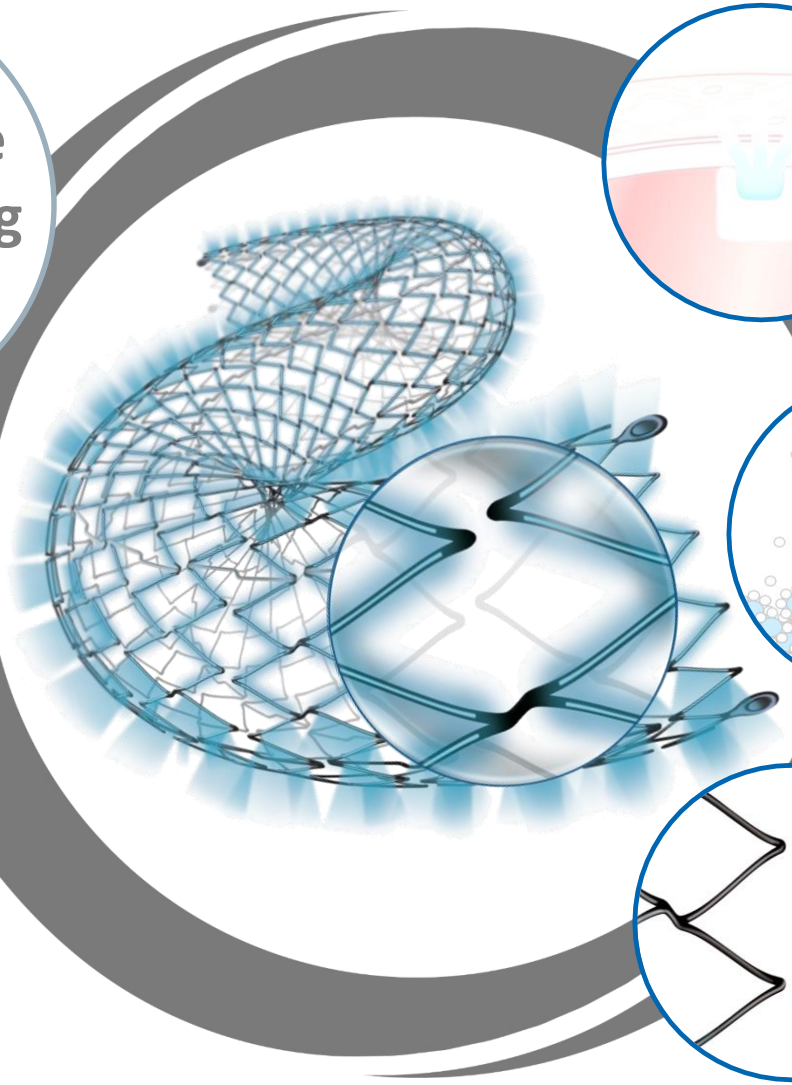

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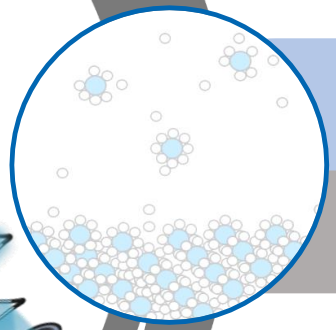

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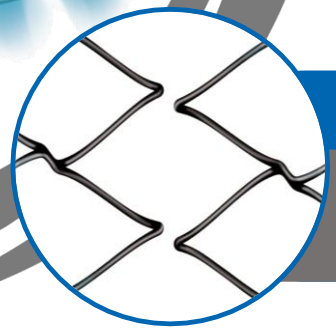

Bio Inducer Surface (BIS)

2nd generation pure carbon coating

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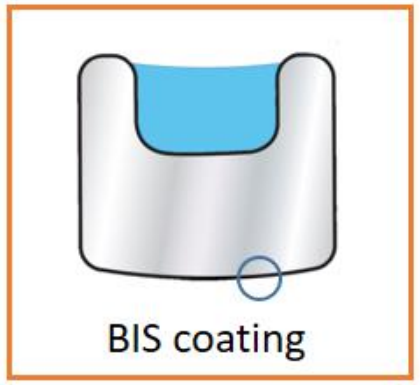
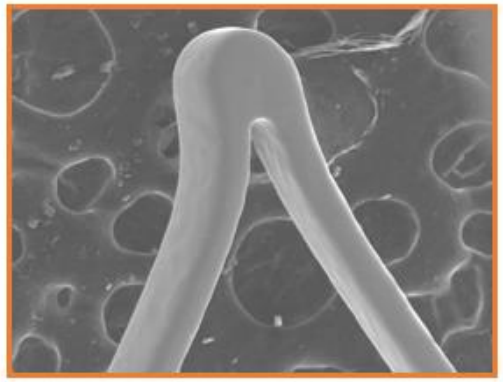
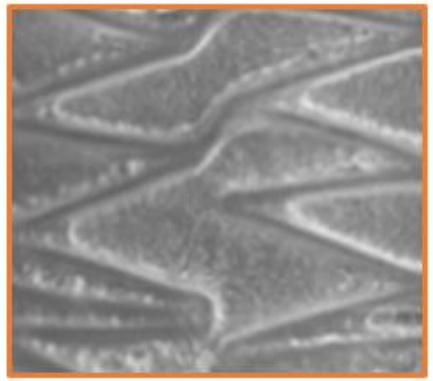
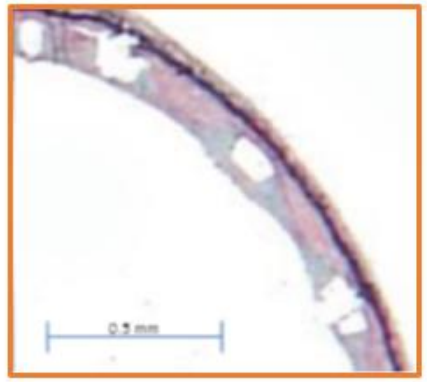
NiTiDES: Bio Inducer Surface

The Bio Inducer Surface (BIS), an ultra thin film (<0.3µm) of pure carbon coating, is INTEGRALLY applied to the Alvimedica stent platform.









The features of the Bio Inducer Surface are:

- **Surface able to accelerate endothelialization and to establish a functional layer**: Reduced thrombogenicity & reduced inflammatory trigger
- **Effective barrier versus heavy metal ions release**: Reduced inflammatory process
- **Inert physical/chemical surface:** Reduced foreign body reaction

NiTiDES: Conclusions

- The NiTiDES platform represents a breakthrough technology in the SFA DES landscape, able to overcome the intrinsic drug release kinetic limitations of the polymer free platforms thanks to the **Abluminal Reservoir Technology**.

- The **Amphilimus™ formulation** (Sirolimus + Fatty Acid) enhances an homogeneous drug distribution to the whole vessel tissue and an excellent permeation through cell membranes.

- Immediately after the NiTiDES implantation, the **Bio Inducer Surface (BIS)** improves its haemo compatibility and fasten endothelialization. Once the drug is completely eluted the BIS continues to maintain the enhanced biocompatibility properties.