Is Sirolimus Different from Analogues?

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Cordis Corporation

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Drug-Eluting Stents

- The successful integration of drug, device, and polymer technology
- Address vascular recoil, remodeling and hyperplasia in a single device
- Three component system:
  - Stent platform, coating matrix, and pharmaceutical agent

The Most Important Component of a Drug-Eluting Stent is the DRUG!
Drug-Eluting Stents That Have Failed

- Actinomycin D (Action – Guidant)
- Batimistat (Brilliant – Abbott)
- Dexamethasone (Stride – Biodyvisio)
- Angiopeptin (Biodyvisio)
- Estradiol (Easter – Biodyvisio)
- Tacrolimus (Jomed)
- C-myc antisense (Medtronic AVE, AVI Biopharm)
- Mycophenolic acid (Avantec)
- Paclitaxel stent sleeve (Score – Quanam)
- Paclitaxel nonpolymeric (Deliver - Cook/Guidant)
Sirolimus (Rapamycin)
“the Magic Bullet for Restenosis”

- Macrolide antibiotic
- Fermentation product
- Small stable molecule
- Highly lipid soluble
- Potent antiproliferative & immunosuppressive agent
- Marketed by Wyeth for renal transplantation (Rapamune®)
Why Did We Choose Sirolimus?

- Ultrapotent antiproliferative agent
- Cytostatic mechanism – won’t kill cells
- Chemically suitable for a device coating
- Wide margin of safety
- Excellent tissue pharmacokinetics (long $t_{1/2}$)
- Already developed for systemic use
- Effective in animal models
- Strong partnership with Wyeth
Sirolimus Inhibits TOR (Target of Rapamycin) the “Master Switch”

- A large cytosolic protein involved in growth factor and cytokine cell communication
- Controls entry into the cycle cycle ($G_1$ – $S$ phase)
- Important regulator of cell growth and proliferation
- Responsive to cell stress & injury
- Inhibited by sirolimus
Antirestenotic Mechanism of Sirolimus

Arterial Injury

Thrombosis

Inflammation

Growth Factors / Cytokines

Receptor activation

Smooth muscle cell

Signal transduction

TOR

+ FKBP

Sirolimus

Cell cycle

G0 → G1 → S → M → G2

SMC Proliferation

Migration

Matrix Secretion
Effect of Sirolimus on the Cell Cycle

- ↑p27 – natural cell cycle inhibitor
- Inhibits cell cycle proteins
- Blocks cell cycle in late G₁ phase
- Restores cell to resting state

Sirolimus Blocks Cell Cycle at the $G_1$ - S Checkpoint

- Cytostatic
  - Sirolimus

- Cytotoxic
  - Radiation
  - Actinomycin D
  - Taxanes

$G_0 \leftrightarrow G_1 \rightarrow S$-phase

DNA Synthesis

CDK2, cyclinE

↑P27

Return to resting state
Sirolimus Returns Smooth Muscle Cells to their Normal Resting State

- Induces shift from proliferative to contractile state
- Restores normal cellular morphology

Sirolimus Inhibits Proliferation and Inflammation in Stented Vessels

Canine 30day Iliac Artery Implant Study

**Neointimal Area**

- Metal (n=7)
- Polymer (n=7)
- Sirolimus (n=8)

**Inflammation Score**

- Metal (n=7)
- Polymer (n=7)
- Sirolimus (n=8)

(*p<0.05)*
Sirolimus Has a Broad Therapeutic Ratio

Evaluated at a dose density of 888 µg/cm²

Therapeutic Ratio of Cypher: >6X

Won’t overdose, safe in overlapped stents
Rapid Reendothelialization with Cypher

Animal 900 / 04-364 LCX – 30 days
Cypher Implantation in Porcine Coronary Artery -30 d

Complete Reendothelialization

Animal 900 / 04-364 LCX
Normal Reendothelialization with Cypher

3 days

14 days

30 days
Endothelialization of Overlapped Stents
30 Day Histopathology

Cypher 30 day

Factor VIII staining
Pt # 4 (Fast release)

SEM showed > 95% endothelized stent surface (F, G).
Uncovered stent strut (F, arrow).
## Competitive Landscape for DES

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Coating</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordis</td>
<td>Sirolimus</td>
<td>Nonabsorbable, Slow release</td>
<td>• CYPHER™</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Marketed WW</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Paclitaxel</td>
<td>Nonabsorbable, Slow release</td>
<td>• TAXUS™</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Marketed WW, except Japan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Express &amp; Liberte' stents</td>
</tr>
<tr>
<td>Medtronic</td>
<td>ABT - 578</td>
<td>Nonabsorbable - PC, Fast release</td>
<td>• Endeavor I, II (OUS), III (US)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Driver stent</td>
</tr>
<tr>
<td>Guidant</td>
<td>Everolimus</td>
<td>Bioabsorbable – PLA, Nonabsorbable (Champion, Vision)</td>
<td>• Champion - Future I, 2, 3, 4 (US)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Vision - SPIRIT I Trials, US '06</td>
</tr>
<tr>
<td>Abbott</td>
<td>ABT - 578</td>
<td>Nonabsorbable – PC, ZoMaxx</td>
<td>• ZoMaxx I (EU Pilot Trial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Trimax stent</td>
</tr>
<tr>
<td>Biosensors</td>
<td>Biolimus A9</td>
<td>Bioabsorbable - PLA</td>
<td>• Stealth I (EU Pilot Trial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Matrix stent</td>
</tr>
</tbody>
</table>
## Sirolimus & Paclitaxel: Fundamental Differences

<table>
<thead>
<tr>
<th>Class</th>
<th>Paclitaxel</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary utility</td>
<td>Chemotherapeutic</td>
<td>Immunosuppressant</td>
</tr>
<tr>
<td>Molecular target</td>
<td>Prevent tumor growth (Taxol®)</td>
<td>Prevents transplant rejection (Rapamune®)</td>
</tr>
<tr>
<td>Cellular effect</td>
<td>Inhibits microtubule function</td>
<td>TOR kinase</td>
</tr>
<tr>
<td>Cell-cycle block</td>
<td>G2-M</td>
<td>Inhibits growth factor signaling</td>
</tr>
<tr>
<td>Effect on SMC</td>
<td>Apoptosis</td>
<td>Late G1</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>Narrow</td>
<td>Cytostasis</td>
</tr>
<tr>
<td>Other effects</td>
<td>Anti-migratory</td>
<td>Anti-inflammatory</td>
</tr>
</tbody>
</table>

- **Paclitaxel**
  - Prevent tumor growth (Taxol®)
  - Inhibits microtubule function
  - G2-M
  - Apoptosis
  - Narrow
  - Anti-migratory

- **Sirolimus**
  - Immunosuppressant
  - Prevents transplant rejection (Rapamune®)
  - TOR kinase
  - Inhibits growth factor signaling
  - Late G1
  - Cytostasis
  - Broad
  - Anti-inflammatory
# Comparison of Polymer Coatings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CYPHER™</th>
<th>TAXUS ™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymers</td>
<td>EVA:BMA nonabsorbable</td>
<td>PIB:PS nonabsorbable</td>
</tr>
<tr>
<td>Thickness</td>
<td>~10µm</td>
<td>16 -18µm</td>
</tr>
<tr>
<td>Weight (drug + polymer)</td>
<td>~ 550 µg (3.0x18mm Bx)</td>
<td>1227 µg (16mm Express)</td>
</tr>
<tr>
<td>Drug dose</td>
<td>140µg drug/cm²</td>
<td>100µg drug/cm²</td>
</tr>
<tr>
<td>Design features</td>
<td>Diffusion control</td>
<td>Single layer</td>
</tr>
</tbody>
</table>
| Drug-elution profile       | 80% in 30 days  
  *Complete in 90 days* | 10% in 30 days  
  ~ 90% permanently entrapped |
| Other features             | Closed-cell  
  Multiple cell sizes | Open-cell  
  “One size fits all” |
The Cypher™ Coating

- Thin (10 µm), smooth, conformal coating tightly bonded to metal surface
- Blend of two non-absorbable polymers used in implantable medical devices
- Coating is elastomeric - expands without flaking or peeling
- Will not alter stent performance
- Tissue compatible
- Controls drug distribution and release

Less than 10% of a daily immunosuppressive dose of sirolimus is applied to a stent
TAXUS™ Polymer Coating

Translute™: 80:20 copolymer of Polyisobutylene:Polystyrene

- This material (Krayton rubber) is commonly found in tires, gaskets, hoses, gum, adhesives, etc.
- It is soft, elastic, and very sticky.
SEMs of Expanded TAXUS™ Stents

Adapted from Ormiston, et al. TCT2004
In Vivo Release of Sirolimus from the CYPHER™ Coating

In Vivo Release Kinetics in Porcine Coronary Arteries

Drug Elution profile:
- 80% in 30 days
- 90% in 60 days
- Complete in 90 days

\[ t_{1/2} = 8 \text{ days} \]
TAXUS – In Vivo Paclitaxel Elution

10% elution in 30 days

15% elution in 180 days

From M Russell, TCT 2002
Sirolimus Analog Structure Activity

 FKBP Binding Region

 Structural Diversity (C-42)

 mTOR Binding Region
Are All Sirolimus Analogs Alike?

In stent late loss (mm)

Bare metal stents

Sirolimus analogs

0.0    0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1.0    1.1    1.2

SIRIUS Control (8m)
Multi-Link VISION (6m)
DRIVER (6m)
ENDEAVOR 1 (12m)
ENDEAVOR 2 (8m)

STEALTH (6m)
FUTURE (6m)
REALITY (8m)
SIRIUS (8m)
E-SIRIUS (8m)
FIM (12m)
RAVEL (6m)
ABT-578
A9 Ever.
SUMMARY: Why Choose Cypher?

- Uses sirolimus!
  - Cytostatic – safely inhibits cell proliferation
  - Antiinflammatory & antiproliferative
  - Wide margin of safety
  - Controlled drug elution over 90 days
- Durable effect – over 5 years in patients
- Excellent safety (no increase in SAT) with two month antiplatelet medication.
- Lowest late loss of any DES
- Best outcome in complex clinical trials (SIRTAX, ISAR-DIABETES, Park Long Lesion Trial)