Bioengineered AV Grafts: They Are Finally Happening!

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None of the data presented in this lecture is intended to be perceived as “claims” for the potential clinical use of the bioengineered vascular graft discussed today.

Vascular Grafts and Failure

- 40% of CABG vein grafts are occluded at 1 year.¹
- Primary patency of lower leg vein bypass is 70% at 5 years in the best hands.²
- Significant wound issues related to vein harvest sites (nearly 15%).³


Synthetic Vascular Dialysis Grafts

- Poor long-term patency
  - Neointimal hyperplasia
  - Stenosis
  - Thrombosis
  - Graft infections
  - Graft wall deterioration/abuse
- DAC study indicated loss of patency in 75% of AVGs at one year¹

Histology of Implanted ePTFE Grafts

Blood likes to move through tubes lined by cells
Blood likes to move through tubes that wiggle
Even the best veins don’t like being arteries

Bioengineered Blood Vessels

- Bioengineered blood vessels represent a potentially unlimited source of bypass grafts
- However, in vivo implantation studies have been marked by acute graft rupture, thrombosis and failure

Bioengineered Blood Vessels: Created from Human Vascular Smooth Muscle Cells

1. Human Cells Isolated and Banked
2. Cells are Used to Culture Bioengineered Vessels in Bioreactors
3. Decellularization Removes Cells
4. Bioengineered Vessel Without Branches

Bioengineered Blood Vessels: Mechanically Similar to Native Vasculature

<table>
<thead>
<tr>
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<th>Suture Strength (g)</th>
<th>Burst Pressure (mmHg)</th>
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<tbody>
<tr>
<td>HAVG</td>
<td>181 ± 18 (16)</td>
<td>3337 ± 343 (10)</td>
</tr>
<tr>
<td>Human saphenous vein</td>
<td>196 ± 29 (7)</td>
<td>1599 ± 877 (7)</td>
</tr>
<tr>
<td>Human internal mammary artery</td>
<td>138 ± 50 (6)</td>
<td>3196 ± 1264 (16)</td>
</tr>
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SEM shows fluid tight surface, with porous interior for cell infiltration.

No weeping at physiologic pressures (N=31)

Bioengineered Blood Vessels: Matrix of Acellular Vascular Grafts

Bioengineered Blood Vessels for AV Access: Baboon with Graft Cannulation

- Arteriovenous model, 1-6 months
- Accessible at 4 weeks, 16G needle
- Overall patency of 80% (11/14 animals), including 5 animals patent at 6 months
- No immunosuppression
- No increase in PRA
- No delayed hypersensitivity
- No graft calcification

Bioengineered Blood Vessels: Human Prototype Implanted into Primates (Baboon)
Observations in Preclinical Studies (Baboon Model): Post-Implant Gross Observations of Bioengineered Blood Vessels

Investigational Bioengineered Vessels Repopulate with Host Vascular Cells and Remodel: Baboon

In preclinical studies, investigational bioengineered vessels:
• repopulate with vascular cells

Little Intimal Hyperplasia in Investigational Bioengineered Vessels in Preclinical Studies

Venous anastomosis in a baboon

Bioengineered Vessel
ePTFE

Intimal to Medial Ratio (3 months)

<table>
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<tr>
<th>Arteriovenous access creation method</th>
<th>Ratio of intimal area to medial area at venous anastomoses</th>
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<tbody>
<tr>
<td>TEVGs in a baboon model</td>
<td>0.37±0.10</td>
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<tr>
<td>ePTFE grafts in a baboon model</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>ePTFE grafts in a porcine model</td>
<td>0.87</td>
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• Little foreign body reaction
• Less mTOR activated smooth muscle proliferation than autologous vein

First Experience in Man

Study Design
- Open label, single arm study, 3 sites in Poland, initiated in Dec. 2012
- Upper arm arteriovenous (AV) access for hemodialysis
- End stage renal disease (ESRD) patients who are not candidates for fistula creation
- Use for dialysis from 8 weeks
- Monthly clinical and ultrasound monitoring for first 6 months
- Patients followed for up to 2 years
- 28/30 patients enrolled

Objectives
- Evaluation of safety and tolerability in dialysis patients
- Evaluation of patency and intervention rates
- Assess changes in Panel Reactive Antibody (PRA)
- 6 Month primary endpoint

Study Patient Population and First Human Implant
- 28 Caucasians [17 Male, 11 Female]
- Mean Age: 60 years (Range: 30 – 73)
- Mean BMI 28 (Range: 16 – 38)
- Concomitant diseases
  - Hypertension in 82%
  - Diabetes in 46%
  - Vascular disease in 39%
- 4.1 ± 1.7 prior access procedures/patient

Initial Data on Investigational Bioengineered Vessels

100% Overall Patency
- All 28 vessels patent
- 20/28 without intervention
- No infections, no aneurysm

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Summary

- Off-the-shelf bioengineered vascular grafts are possible
- Non immunogenic
- Integrate with native tissue, repopulate and remodel
- Post implant with increased strength and little intimal hyperplasia
- First-in-man pilot clinical trial underway in Poland and the US for hemodialysis access and PAD

Thank You
8 of 28 patients lost primary patency since December 2012

- 10 patency interventions in these 8 patients
  - 8 thrombectomies (1 with revision of anastomosis, 1 with angioplasty)
  - 2 venous anastomosis angioplasties without thrombosis
- 71% Primary unassisted patency

1 steal syndrome: cuff placed