Bioengineered Vascular Access Grafts: Current Status

Michael S. Conte MD
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Disclosures

• Humacyte Inc- Scientific Advisory Board
• Discuss Investigational Products
  • Cytograft
  • Humacyte
  • Shire Regenerative Medicine

Hemodialysis Access: An Unmet Need

• 350,000 patients with end-stage renal disease receive hemodialysis each year
• Complications following AV access procedures are common (infection, blood clots (thrombosis), and stenosis)
• Vascular access failure rates are high
  - 50% - 75% of AV grafts fail at one year
  - 30% - 50% of AV fistulas fail to mature
• Re-interventions are invasive and expensive
  - 25% of all hemodialysis patient admissions result from vascular access complications
  - Annual costs > $1 billion per year

Sources:
• U.S. Renal Data System, USRDS 2009 Annual Data Report
• National Institutes of Health, 2009

Vascular Grafts for Vascular Access

- Standard of care for patients who are not fistula candidates: PTFE grafts

- Prone to infection
- Prone to intimal hyperplasia
- Poor compliance
- Inflammatory
- Prone to thrombosis

- Strong
- No vascular harvest required
- Affordable and off-the-shelf
- Used mostly ≥ 6 mm
- No branches
Biologic Grafts for AV Access: Desired Features

- Off the shelf and available in appropriate sizes
- Easy handling and suturability
- Mechanical strength and durability (punctures)
- Rapidly incorporates
- Resists thrombosis
- Resists infection
- Non-immunogenic
- Minimal hyperplastic/fibrotic response
- Maintains patency
- Low cost

Biologic Grafts for AV Access: Available Options

- Bovine carotid heterograft (Artegraft)
- Bovine mesenteric vein (ProCol)
- Bovine ureter graft (SynerGraft)
- Human umbilical vein (Dardik)
- Cryopreserved femoral vein
- Results to date
  - Appear more resistant to infection than ePTFE
  - Have not shown advantage in patency or stability

The Regenerative Medicine Mantra

To harness the body’s intrinsic capacity for self renewal and regeneration of cells, tissues, and organs.

Vascular Grafts for Low Pressure Systems

- Polymeric scaffold seeded with bone marrow mononuclear cells
- 25 patients in Japan, age 1-24, extracardiac total cavopulmonary connection
- Up to 7-yr followup (2010)
- Implanted first pediatric tissue engineered blood vessel in the US in 2011
- Not for dialysis, but it demonstrates the ability of a regenerative medicine product to function in the vasculature

Shinoka et al., J Thorac Cardiovasc Surg, 2005, 129:1330
**Cytograft Tissue Engineering, Inc.**

- Early clinical results show promise
- Skin (fibroblast) and vein (EC) biopsies for cells
- Autologous grafts require patients to wait 6-9 months for production
- They have developed a new allogeneic approach to shorten patient wait time: dehydrate and cryopreserve to devitalize (but not remove) cells
  - Allogeneic graft implanted into 3 patients
  - Will need to monitor immunologic response to cellular allogeneic grafts
  - Grafts require cryopreservation, which means that they cannot be stored onsite at hospitals long-term
- AV access trial in Europe and S.A.

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**Humacyte’s Vascular BioGraft Technology**

- No patient biopsy required
- Decellularization removes cells and allows tissues to resist immune response better than cellular tissues
- 1-Year shelf life in refrigeration
- Readily available “off-the-shelf”

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**Biomedical Platform Technology**

- Banked Cells from One Donor
- Many Grafts and Recipients

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**Cytograft Tissue Engineering, Inc.**

- Lifeline™ graft

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Humacyte Vascular BioGrafts: Mechanically Similar to Native Vasculature

<table>
<thead>
<tr>
<th></th>
<th>Suture Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human BioGrafts</td>
<td>178 ± 11 (37)</td>
</tr>
<tr>
<td>Human BioGrafts refrigerated 12 months</td>
<td>170 ± 22 (9)</td>
</tr>
<tr>
<td>Human saphenous vein</td>
<td>196 ± 29 (7)</td>
</tr>
<tr>
<td>Human internal mammary artery</td>
<td>138 ± 50 (6)</td>
</tr>
</tbody>
</table>

6mm diameter, 40cm length

Human BioGrafts for AV Access: Baboon Model

- Baboon AV access model: axillary artery to brachial vein, 1-6 months
- Accessible at 4 weeks with 16G needle
- Resistance to intimal hyperplasia and infection
- No dilatation or calcification
- Patency rate: 88%

Grafts Remodel with Host Cells, Become Living Tissue

For Connective Tissues - Matrix Directs Regeneration

Humacyte EU Dialysis Access Trial

- Clinical Phase I/II multi-center study in Poland
- Trial n=up to 30 evaluating safety and efficacy of graft as vascular prosthesis for dialysis access
  - Surgeons trained in US
- Safety review after 10 patients, up to 30
  - First implants Dec 2012
  - 8 implants to date
  - First dialysis use Feb 2013
- Safety review by independent Safety Monitoring Board April ‘13

**Endothelial Technology (Shire Regenerative Medicine)**

**Tissue Engineered Endothelium**

Quiescent endothelial cells embedded in a degradable matrix to create active bioregulatory factory

- **Matrix**
  - Local delivery, sustained release
  - Controlled growth and secretion
  - Immunologically tolerant

- **Allogeneic endothelial cells**
  - Fully qualified MCB and WCB
  - Lower COGS
  - 21 day RT shelf life (cryo possible)

**Vascugel Technology: Cells Embedded on a Matrix**

- Superior to Cells Alone
  - Anchorage-dependent cells require a substratum to obtain desired phenotype
  - Cells alone have poor survival and immunological profile
  - Cells & matrix provide platform for delivery of viable, functional cells

- Adult Differentiated Endothelial Cells Embedded on a Matrix
  - Endothelium
    - maintains and regulates homeostasis in multiple settings
    - secrete multiple endogenous factors for local delivery
  - Differentiated, functional cells
    - provide appropriate function and level of control
    - in a manner that can be quantified
  - Substratum allows for use of allogeneic cells
    - allows local, continuous delivery of multiple factors
    - with favorable survival and immunological profile
    - sustained, regulated delivery based on environmental signals
    - varying degrees of matrix degradation dependent upon desired application

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**Adventitial Regulation**

- EC do not need to reside at the luminal interface to regulate injury
- Blood vessels: tubular structure where the same cells make up the inner lining and the *vasa vasorum*
- Placing Vascugel in adventitia – supplementing EC pool to control and respond to injury

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**The Endothelium: A “Master Regulator” of a Broad Array of Critical Functions**

Proteins, Cytokines, Growth Factors regulated by the endothelium

- HSPG – Platelet Aggregation
- vWF – Inflammation
- PGI\(_2\) – Remodeling/Revascularization
- Angiotensin – Activation/Proliferation
- ACE – FGF-2
- BMPs – PDGF
- Prostaglandins – Endothelins
- E-selectin – IGFs

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Vascugel Regulation of Vascular Injury

1. Platelet aggregation & thrombosis
2. Inflammation
3. Activation/proliferation of other cells (SMC)
4. ECM remodeling & re-vascularization

by tissue-engineered endothelium

Vascugel (Vascular Injury “Master Regulator”)

1. Inhibit aggregation & thrombosis (HSPG, NO)
2. Decrease inflammation (TGF-β1)
3. Inhibit activation of problematic cells (NO, TIMP)
4. Promote positive remodeling and re-vascularization (NO)

Additional proteins, cytokines, growth factors, etc.

Endothelial Regulation (Inflammation, Thrombosis, Stenosis, Flow)

COX-2 PDGF MMPs E-Selectin IL-8 Tissue Factor VCAM-1 ICAM-1

Mechanism of Action

Vascugel Manufacturing Overview

Qualified Master and Working Cell Banks → Manufacturing Process → Marketed Product

Pharma grade COGs/Profit Margins

V-HEALTH Trial: Safety Study

- Phase I/II Safety Trial
  - Safety of Vascugel® Treatment after the creation of arterio-venous (AV) access for hemodialysis use
  - 65 patients (34 AVG/31 AVF)
  - Phase 1: 4 AVF/4AVG
  - Phase 2: 57 double blind, randomized 2:1 placebo controlled
- Endpoints
  - PRIMARY (2 and 4 weeks)
    - Incidence of local wound infection
    - Incidence of intervention to treat access complications
    - Incidence of acute thrombosis
  - SECONDARY (24 weeks)
    - Incidence and duration of patency
    - Measures of luminal diameter (angiography and US)
    - Immunological sensitization
- Patients consented into extension study at 24 week visit (~50%)

Conte MS et al J Vasc Surg 2009
AVG Vascugel Placement

Phase 1 (venous anastomosis)

Phase 2 (venous and arterial anastomosis)

AVF Vascugel Placement

Phase 1 & 2 (venous anastomosis)

Primary Endpoint – Safety AVF/AVG Population

<table>
<thead>
<tr>
<th>Time point Assessment</th>
<th>Vascugel n=46</th>
<th>Placebo n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local Wound Infection, Access Intervention or Thrombosis</td>
<td>3 (6.5%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>Local Wound Infection</td>
<td>2 (4.3%)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Access Intervention</td>
<td>0</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (2.2%)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>Local Wound Infection, Access Intervention or Thrombosis</td>
<td>5 (10.9%)</td>
<td>4 (10.5%)</td>
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<td>2 (4.3%)</td>
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Secondary Efficacy Trends: AVG Patency

- **Primary Patency** (blood flow through graft)
  - Begins at the time of access placement and ends at the time of any intervention
  - Patients in primary patency are counted in assisted primary

- **Assisted Primary Patency**
  - Begins at the time of access placement and ends at the time access blood flow is lost

<table>
<thead>
<tr>
<th>Patency</th>
<th>Primary (ITT)</th>
<th>Primary (mITT)</th>
<th>Assisted Primary (ITT)</th>
<th>Assisted Primary (mITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascugel</td>
<td>38%</td>
<td>49%</td>
<td>72%</td>
<td>78%</td>
</tr>
<tr>
<td>Placebo</td>
<td>23%</td>
<td>25%</td>
<td>58%</td>
<td>50%</td>
</tr>
</tbody>
</table>

| % Difference | 15%   | 24%   | 14%   | 28%   | 15%   | 16%   |

<table>
<thead>
<tr>
<th>24 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>30</td>
</tr>
<tr>
<td>Vascugel</td>
<td>38%</td>
</tr>
<tr>
<td>Placebo</td>
<td>23%</td>
</tr>
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</table>
Secondary Efficacy Trends: AVF Remodeling

- Statistical analyses on vein remodeling: multiple regression mixed models
  - age, gender, race, time post surgery, baseline diameter, vein location, diabetic status...
- Diabetes was a significant, negative predictor of venous remodeling
- Vascugel improved the rate of venous remodeling in diabetic patients compared to placebo

Vascugel™ Clinical Summary for AV Access Placement

- Excellent Safety Profile
  - No evidence of local or systemic safety concerns
- Early complication rates:
  - No difference in Safety Population
  - Trend of reduced early thrombosis in AVG Group
- Immunological response in small subset of patients
  - No clinical correlation to SAEs, patency etc
- Efficacy Trends (small # of patients)
  - Patency extended in AVG group
  - Lumen diameter increased in AVF DM group
- Positive End of Phase 2 Meeting
  - Data supports further clinical development– pending AVG and AVF trials
- Extension Study (up to 3 years)
  - Demonstrates long term safety and similar patency trends

Vein Remodeling (CDUS)
DM vs. Non-DM, p=0.03
Vein Remodeling (CDUS)
Vascugel vs. Placebo, p=0.05

Week 2
Week 4
Week 12
Week 24
Model-predicted change in vein diameter (mm)

Conte, MS et al, J Vasc Surg, 2011