Use of Cell Therapy and Biomedical Engineering in Vascular Access

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Disclosures

- Off Label use: Optiflow

- Consultant/Advisory Board: Bioconnect, Pervasis, WL Gore, NanoVasc, Proteon, Shire, Medtronic

- Grant/Research Support: NIH, VA, Bioconnect, WL Gore, Proteon, Shire

- Clinical Trial Support: NIH, Pervasis, Proteon, WL Gore
• Pathology and pathogenesis of dialysis vascular access dysfunction

• Interactions between hemodynamics and vascular biology (central to dialysis vascular access dysfunction)

• Novel therapies that target both hemodynamics and vascular biology

• Message for the future!!
A message for the present!!

• Current modalities and therapies for dialysis vascular access are not very effective

• Last real innovation in this field was the tunneled dialysis catheter (early 80’s)

• Huge unmet clinical need that needs to be addressed

Don’t worry, I’ll find a good site soon!!
Radiological presentation of dialysis vascular access dysfunction

- Perianastomotic stenosis
- AVF non maturation
- Stenosis at the graft-vein anastomosis
- Graft thrombosis
Histological presentation of dialysis vascular access dysfunction

- Migrated in from the media and perhaps the adventitia
- Response to endothelial and smooth muscle cell injury

Roy-Chaudhury et al. AJKD 2007
Dialysis access stenosis is a balance between vascular remodeling and neointimal hyperplasia.

Original lumen size

Significant Neointimal Hyperplasia + Expansive Remodeling

Final lumen size

200%
Mature AVF

Minimal Neointimal Hyperplasia + Negative Remodeling

100%

AVF maturation failure

25%

Adapted from Mike Conte
In an ideal world!!

Creation of dialysis access

Increased Flow

Increased endothelial production of NO

Increase in Flow

Vascular Response to Flow

Inhibits neointimal hyperplasia

Successful use of AV fistula/graft

Expansive or outward remodeling
Hemodynamic and vascular biology interactions

Upstream
Hemodynamics (Flow)

AVF/AVG Creation

Downstream
Vascular Biology (Response to Flow)

AVF/AVG Failure

AVF/AVG Success
Flow patterns and shear stress influence endothelial function

Hemodynamics 101

- Non laminar flow with oscillatory shear (LOW)
- Endothelial activation
- Increased Oxidative Stress
- Inflammatory gene profile (VCAM-1)

AVF/AVG
- Inward remodeling
- Neointimal hyperplasia

Laminar flow with laminar shear (HIGH)
- Endothelial quiescence
- Minimal Oxidative Stress
- Non-Inflammatory gene profile (Nitric oxide)

AVF/AVG
- Expansive remodeling
- No neointimal hyperplasia
Surgical configuration influences shear stress profiles

**Curved**

Uniform low velocity

**Straight**

High velocity

Blood flow is greater in the curved configuration.
Diameter is greater in the curved configuration

\( p < 0.05 \)
Anatomy, Shear and Stenosis!

Optimize surgical configuration for AVFs and PTFE grafts using surgical devices

Ideal flow patterns and shear stress profile in AVFs and PTFE grafts

Reduce AVF and PTFE graft stenosis
Intrinsic Endothelial (dys)function

• Hemodynamic forces can influence endothelial response = YES

• Intrinsic function or (dys)function the baseline endothelial cell and how this influences its response to shear stress alterations??
ESRD and CKD are states of massive endothelial dysfunction!!

- Uremia
- Oxidative stress
- Inflammation

Reduction in flow mediated dilation (*marker of endothelial function*)

*Kopel et al. F-PO1696, ASN 2009*
Uremic mice have increased AV fistula stenosis

Choi et al. JASN. 2008
Uremia and oxidative stress can result in neointimal hyperplasia independent of hemodynamics

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<table>
<thead>
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<tbody>
<tr>
<td>% Stenosis</td>
<td>46.6 ± 9.3</td>
</tr>
<tr>
<td>I/M Area Ratio</td>
<td>0.24 ± 0.07</td>
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<tr>
<td>Average IM Thickness</td>
<td>0.34 ± 0.12</td>
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<tr>
<td>Maximal IM Thickness</td>
<td>1.16 ± 0.30</td>
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Lee et al. NDT 2011
Hemodynamic and vascular biology interactions: *a challenge and an opportunity*

- **AVF and AVG Creation**
- **Optimize Upstream Hemodynamics (Flow)**
- **Optimize Downstream Biology (Response to Flow)**
- **Minimize Dialysis Access Dysfunction in 2010-2020**
Optimizing upstream hemodynamics and downstream biology using LOCAL therapy

**Upstream Hemodynamics**
- DEVICE 1: Optiflow
- DEVICE 2: Hybrid
- DEVICE 3: Spiral Flow

**Downstream Biology**
- CELL therapy (*Vascugel*)
- DRUG therapy (*Elastase*)
- VESSEL therapy
Why have we been so unsuccessful??

Hemodynamics and Vascular Biology

Vascular Injury → Neointimal Hyperplasia + Negative Vascular Remodeling → Stenosis → Thrombosis

ALMOST NOBODY

Green Zone for Efficacy

MOST

SOME
Excellent results as compared to historical controls

- 60 patient European study in Hungary and Greece
- Good data on an interim analysis (29 patients)

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>14d patency</th>
<th>42d patency</th>
<th>90d patency</th>
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<tbody>
<tr>
<td>Europe Study (on-going f/u)</td>
<td>100% (25/25)</td>
<td>92% (22/24)</td>
<td>83% (19/23)</td>
</tr>
<tr>
<td>Literature Control</td>
<td>n/a</td>
<td>80% (DAC)</td>
<td>68% (Falk, 2006)</td>
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Safety (n=41)

3 technical failures requiring device removal

Watch this SPACE!!!
Inducing Spiral Laminar Flow (Tayside Flow)

- Normal blood flow is spiral
- Turbulent blood flow at the outlet of a graft
- Spiral connector at the end of the graft converts turbulent flow into spiral flow
- Interesting concept but no clinical data at present
- SLOT technique (Shenoy)
Perivascular endothelial cell implants (Vascugel) improve patency in diabetics

Primary patency

Vascugel (n=25)

Placebo (n=11)

p = 0.0054

Roy-Chaudhury et al. ASN 2009, PO-1576
Perivascular elastase administration
(DRUG THERAPY)

- Recombinant elastase
- Applied to the adventitia
- Destroys the elastin in the vessel wall
- Results in a permanent increase in vessel calibre
Abluminal (perivascular) drug delivery

- Endovascular device such as the “Bullfrog” micro-infusion catheter (Mercator-Med)

Drug A initially followed by Drug B at 6 monthly intervals

Tailor therapies to the biological course of vascular stenosis
A Message for the Future!!

• Get away from the “one size fits all” paradigm
Individualize Vascular Access Care

• Stratify patients based on clinical and biological parameters

• Offer them the dialysis access that is best suited for them

• Individualize vascular access care through the use of novel technologies
Individualize Vascular Access Care using Novel Technologies

• 25 yr old with large veins and good endothelial function = AVF

• 50 yr old with average veins and moderate endothelial function = AVF “plus”

• 70 yr old with small veins and poor endothelial function = Graft “plus”

• 80 yr old with no veins, poor endothelial function and multiple co-morbidities = Catheter “plus”

“PLUS” = better anatomical configuration, local enhancement of vascular dilation, local anti-proliferative drug therapy, anti-infective and anti-thrombotic coatings
Technology can Change Existing Clinical Paradigms!!

- Catheter without infection, thrombosis or central stenosis

- *from* Fistula First to Catheter First and Last!!
We Live in Exciting Times for Dialysis Access Stenosis!!

It was the best of times…
- Advances in molecular pathogenesis
- Genomics and proteomics
- Advances in biomaterials and delivery technology

It was the worst of times…
- Huge clinical problem
- Growing population
- Elderly and clinically complex patients
- No effective therapies

SOLUTION