Thin Film Nitinol: A Unique Biomaterial for Next Generation Endovascular Devices

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Regulatory

CAUTION: We have not received approval from the FDA to market our Thin Film Nitinol Flow Diverting Stent. Our Thin Film Nitinol Flow Diverting Stent is classified as investigational devices and is limited by Federal (or United States) law to investigational use only.
Thin Film Nitinol (TFN) Technology Overview

TFN is a novel biomaterial produced on silicon wafers via sputter deposition. Sheets produced are ~5μm thick.
Deep Reactive Ion Etching (DRIE) is used to pattern the silicon wafer that TFN is sputter deposited on. Allows for patterning of TFN down to the sub-micrometer scale.
NeuroSigma has developed a high-throughput technique to produce micropatterned 3D TFN structures, low per unit costs.

1. DRIE used to produce a micropatterned silicon wafer (~1μm resolution)
2. First layer of TFN is sputter deposited
3. Sacrificial layer is sputter deposited to cover first TFN layer, long edges of rectangle exposed
4. Second layer of TFN sputter deposited on top of sacrificial layer
5. Multi-layer TFN construct annealed in cylindrical conformation. Up to 40 cylinders per wafer may be produced.
LEAD PRODUCT
THIN FILM NITINOL FLOW DIVERTER
The Pipeline Embolization Device is the only FDA approved flow diverting stent. Additional FDA approved devices expected in next 12 - 24 months. All known devices use the same “braided-wire” design.
3D TFN Cylinders are used to produce NSVascular’s proprietary flow diverting stent with a high pore density and a low % metal coverage.

CAUTION — The Thin Film Nitinol Flow Diverting Stent is an Investigational device, and is Limited by Federal (or United States) law to investigational use only.
The TFN flow diverter has a dramatically increased pore density as compared to braided wire devices.

**Pipeline Device**

- ~14 pores/mm²
- ~35% metal coverage

**TFN Flow Diverter**

- ~70 pores/mm²
- ~20% metal coverage
Why Does Flow Diverter Pore Density Matter?

50% Porosity

- Pore Density = 1 Pore/mm$^2$
- Total Edge Length = 2.84mm

50% Porosity

- Pore Density = 9 Pores/mm$^2$
- Edge Length = 8.64mm
In Vitro Testing of TFN Flow Diverter Laser Particle Image Velocimetry in Patient Based Aneurysm Models

Study performed by independent investigators at Arizona State University.
**In Vitro** Hemocompatibility of TFN

**Whole Blood Flow Loop**

Kealey et al. *Biomaterials* 2010
Whole blood flow loop shows that TFN acts as a scaffold for fibrin deposition.
Rabbit elastase aneurysm model. Testing performed at the Mayo Clinic.
Animals survived for 2 weeks (n=7), 4 weeks (n=8), and 12 weeks (n=4).

In Vivo Testing of TFN Flow Diverter Rabbit Elastase Aneurysm Model
### Summary of Angiographic Outcomes

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Number of Animals</th>
<th>Aneurysm Measurements (mm, avg.)</th>
<th>Angiographic Occlusion at Follow Up</th>
<th>Lumbar Artery Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Neck</td>
<td>Width</td>
<td>Dome</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>7</td>
<td>4.0</td>
<td>4.5</td>
<td>9.8</td>
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<td>4 Weeks</td>
<td>8</td>
<td>4.1</td>
<td>4.1</td>
<td>9.3</td>
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<tr>
<td>12 Weeks</td>
<td>4</td>
<td>4.0</td>
<td>4.5</td>
<td>9.3</td>
</tr>
</tbody>
</table>

In Vivo Testing of TFN Flow Diverter Rabbit Elastase Aneurysm Model
Histopathology confirms angiographic outcomes.
Good incorporation of TFN into vessel wall.
In Vivo Testing of TFN Flow Diverter
Endothelialization of Aneurysm Neck Region

CD31 Immunofluorescent staining for endothelial cells
4 week implant; Neck Area = 10.4mm²; Endothelialization = 89%

Cells exhibit confluent cobblestone morphology.

<table>
<thead>
<tr>
<th>Device</th>
<th>Implant Term (weeks)</th>
<th>Neck Orifice Area (mm²)</th>
<th>Neck Endothelial Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFN Flow Diverter</td>
<td>6.3</td>
<td>6.26</td>
<td>75 ± 16%</td>
</tr>
</tbody>
</table>
In Vivo Testing of Pipeline Flow Diverter Endothelialization of Aneurysm Neck Region

Kardirvel et al., Radiology; 2014.

8 week implantation of Pipeline flow diversion device in rabbit elastase aneurysm model
Human Studies of Braided Flow Show Problems with Healing and Endothelialization

A) Before Treatment
B) 1 Year Post Treatment

Patient died 1 month after follow-up angiogram from right MCA infarct secondary to flow diverter thrombosis

Szikora et al, AJNR, 2015

E) CD34 staining reveals no endothelial cells on the luminal surface – Arrows
F) Histologic section shows a thick aneurysm wall (*) and fresh thrombus (**)
**In Vivo Testing of TFN Flow Diverter Pore Density Optimization**

Device 1 – Low Pore Density TFN Micromesh: ~70 pores/mm²

Device 2 – High Pore Density TFN Micromesh: ~150 pores/mm²

Device 1 Mesh Schematic

Device 2 Mesh Schematic
Conclusions

Thin Film Nitinol is a novel biomaterial with advantages over currently available technologies
- Low profile (~5 micrometers thick)
- High fidelity DRIE micropatterning process allows for control of features down to single micron scale; facilitates rational design of medical device features on a biological (i.e. cellular) scale
- Excellent hemocompatibility and biocompatibility in preclinical testing to date

Thin Film Nitinol Flow Diverter for treating intracranial aneurysms is the first TFN-based medical device
- Dramatically higher pore density with less percent metal coverage than braided wire devices
- Laser cut nitinol support stent avoids problems with foreshortenting and delivery associated with braided wire devices
- In vitro testing shows improved flow diversion effect over braided-wire devices and a unique interaction with fibrin and the clotting cascade
- In vivo testing shows rapid aneurysm occlusion and better healing of the aneurysm neck than braided wire devices
- Preliminary optimization studies demonstrate that rational design of TFN can facilitate rapid vessel wall reconstruction

Additional medical devices based on Thin Film Nitinol are in development