Implant Surface Technology: Material and Topography Influences Biochemical Responses
Reginald Davis, M.D., FAANS, FACS – Director of Clinical Research

“Biomimicry is an approach to innovation that seeks sustainable solutions to human challenges by emulating nature’s time-tested patterns and strategies.”

Solution
Biomimicry: Leveraging nature’s expertise to solve complex challenges
Solution
Biomimicry for bone growth: Mimic the structures that are integral to natural bone remodeling and production

Nature

nanoLOCK

Osteoclastic pits and nano-scaled textures within them

nanoLOCK Surface Technology

Osteoclastic Pits
	nanoLOCK Surface Features

Optical profilometer

Scanning Electron Microscope

Terms

• **Macro** is texture you can feel
  - Primary benefit is mechanical; resistance to migration
  - Concerns about a Macro Rough surface damaging endplates (subsidence)
  - Too much “Macro” impedes device insertion

• **Nano** is scale visible with Electron Microscope
  - Nano $10^{-9}$ (1 billionth of a meter)
  - Primary benefit is cellular response
  - Stimulate interactions with Host Stem cells/ Osteoblasts

• **Porous/ Porosity (pipes)**
  - Size/ Space for bone to grow
  - Just because there is space doesn’t mean bone will grow into it
  - Smooth surfaces when scanned (Electron Microscopy)
Hierarchy of Implant Surface Topography

- **Macro level (10^-3m)**: implant stability with endplate integrity
- **Micro level (10^-6m)**: cellular attachment/differentiation
- **Nano level (10^-9m)**: integrin interaction

Biomimicry:

“Nanotechnology exploits the unique advantage of direct interaction with cells on a molecular level.”

Nano-Structured Titanium

- Biologically Inspired implant surface which can be “sensed” by *Individual* Cells to drive Osteoblastic Differentiation
  ultimately leading to rapid bone formation and osseous integration
Early Bone Healing is Driven by Cells

- Cells participate in the healing process through cell signaling (Biological)
- The implant (material and surface) directly influences the biochemical response of host cells
- Remodeling of bone (Wolf’s Law) occurs later, after Primary healing
- Modulus of Elasticity is irrelevant

Peer-Reviewed Scientific Landscape

Net Bone Production Needs Three Things (Nano-structured implants CAN do this)

- **Up-regulate** osteoblasts
  - TGF-B1, BMP-2,4,7
- **Down-regulate** osteoclasts
  - OPG (Osteoprotegerin), TGF-B1
- **Up-regulate** angiogenesis
  - Angiopoietin-1, VEGF-A, FGF-2

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**Up-regulate Osteoblasts - TGF-B1, BMP-2,4,7**

Physiologic BMP production

![Graph showing physiologic BMP production](Graph.png)

TCPS = Tissue Culture Polystyrene
sTi = Smooth Titanium
rTi = Roughened Titanium (Micro scale)

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**Down-regulate Osteoclasts - TGF-B1, OPG** (Osteoprotegerin)

![Graph showing down-regulation of osteoclasts](Graph.png)

TCPS = Tissue Culture Polystyrene
sTi = Smooth Titanium
rTi = Roughened Titanium (Micro scale)
Up-regulate Angiogenesis – Angiopoietin-1, VEGF-A, FGF-2

<table>
<thead>
<tr>
<th>VEGF Levels</th>
<th>FGF2 Levels</th>
<th>ANG1 Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPS</td>
<td>MICE</td>
<td>JVM</td>
</tr>
<tr>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

TCPS = Tissue Culture Polystyrene
sTi = Smooth Titanium
rTi = Roughened Titanium (Micro-scale)

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Osteoblast Lineage Cells Can Discriminate Microscale Topographic Features on Titanium-Aluminum-Vanadium Surfaces

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Conclusions

- Small differences in topography will result in different cellular responses (#9).
- Best cellular response because
  - The micro topography mimics an osteoclastic resorption pit (10⁻²)
    • 10x 20x 8 microns
  - The Nano-structured specific surface (10⁻⁹) induced highest expression of integrins/mRNA driving osteoblastic differentiation
Cell Seeding was minimal

- Human mesenchymal stem cells (MSCs)
- 1,000 cells/cm² for early morphology and early migration experiments.
Discussion

- The results demonstrate that in all metrics, the two titanium surfaces outperformed the PEEK surface.
- EndoSkelton surface presented the most favorable overall results, demonstrating the random migration needed to efficiently cover a surface in addition to morphologies consistent with osteoblasts and preosteoblasts.
Biomimicry: Osteoclastic Pits

- Multiple surface characteristics were measured
- Only two parameters showed significant differences
  - Low Skewness (deep valleys)
  - High Kurtosis (sharp peaks)
Results – Cell Response - Osteoblasts

EndoSkeleton versus nanoLOCK

Clinical Significance?
Titan Spine Post-Operative Cost Analysis
Executive Summary
December 9, 2015

**Background: Phases 1 & 2**

- **Phase 1 Summary:**
  - Optum identified in its database 245 patients of 8 physicians utilizing Titan Spine devices during an 8-year period
  - This cohort was selected from a larger patient pool by meeting criteria for minimum post-index eligibility to permit analysis of post-operative outcomes

- **Phase 2 Objectives:**
  - Compare the post-operative outcomes and medical/drug utilization of patients implanted with Titan Spine devices ("treatment group") to those of patients undergoing similar surgeries involving non-Titan Spine devices ("control group"), identified via propensity score matching

**Phase 2 Results: Demographic Characteristics**

Titan Spine patients closely resemble competitor patients in terms of gender, ethnicity, and average age

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titan Spine</td>
<td>63%</td>
<td>37%</td>
</tr>
<tr>
<td>Competitor</td>
<td>62%</td>
<td>38%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>White</th>
<th>Black</th>
<th>Other</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titan Spine</td>
<td>50.4%</td>
<td>46%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Competitor</td>
<td>50%</td>
<td>48%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Average Age

- Titan Spine: 48.5 years
- Competitor: 48 years
Phase 2 Results: Demographic Characteristics

Both Titan Spine and competitor patients are most heavily concentrated in the Midwest; a greater percentage of competitor patients reside in the Northeast.

Phase 2 Results: Medical Characteristics

Titan Spine and competitor patients closely resemble each other in terms of spinal diagnosis, Charlson score, and other health indicators.

Phase 2 Results: Surgery Characteristics

Percentages of patients by surgery technique, number of treated levels, and surgery type are nearly identical between the two cohorts.
### Phase 2 Results: Post-Operative Outcomes by Percentages

92% of Titan Spine patients were able to attend post-operative physical therapy, versus 76% of competitor patients.

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>Titan Spine (%)</th>
<th>Competitor (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an infection</td>
<td>7.0%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Patients with an adjustment/revision</td>
<td>6.0%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Patients with physical therapy</td>
<td>91.5%</td>
<td>84.5%</td>
</tr>
<tr>
<td>Patients with an epidural or therapeutic injection</td>
<td>54.9%</td>
<td>54.3%</td>
</tr>
</tbody>
</table>

Arrows indicate statistical differences at a 95% confidence level or greater between Titan Spine and competitor patients.

### Phase 2 Results: Medical Utilization Outcomes by Patient Average

The average length of stay for index hospitalizations was 2.0 days per Titan Spine patients, versus 3.0 days for competitor patients. Titan Spine patients began physical therapy, on average, 51 days after surgery versus 118 days for competitor patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Titan Spine</th>
<th>Competitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay during index hospitalization</td>
<td>2.0 days</td>
<td>3.0 days</td>
</tr>
<tr>
<td>Number of patients</td>
<td>224</td>
<td>448</td>
</tr>
</tbody>
</table>

Arrows indicate statistical differences at a 95% confidence level or greater between Titan Spine and competitor patients.

### Phase 2 Results: Medical Cost Outcomes

Titan Spine Patients showed a lower total average standardized cost of medical treatment overall ($11,776), at post-op discharge ($6,618), and in costs post discharge tracked for 24 months ($5,158).

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<tr>
<th>Outcome</th>
<th>Titan Spine</th>
<th>Competitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total standardized cost of medical claims</td>
<td>$11,776</td>
<td>$139,841</td>
</tr>
<tr>
<td>Standardized cost of medical claims during index hospitalization</td>
<td>$6,618</td>
<td>$95,296</td>
</tr>
<tr>
<td>Standardized cost of medical claims after index hospitalization</td>
<td>$5,158</td>
<td>$44,545</td>
</tr>
</tbody>
</table>

Arrows indicate statistical differences at a 95% confidence level or greater between Titan Spine and competitor patients.
1 FDA Clearance for Spine Nano-technology

Device Description:
This traditional S/100 is intended to modify the surface treatment of Endoskeleton devices. The Endoskeleton system is an interbody and vertebral body system comprised of a variety of implant sizes and geometries to accommodate various patient anatomy and pathology. The modified surface technology provides a microscopic roughened surface with nano-scale features. All implantable components are manufactured from medical grade titanium alloy (Ti6Al4V- ELI).

Surface matters!

THANK YOU!