Advances in Surface Engineering of Spine Implants to Stimulate Biologic Responses

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Disclosures

- Titan Spine, LLC: Consulting fees, royalties
Implant Surface Osseous Integration
Emerging area of interest in spine
Surface Matters

“Surface technology is a complete blind spot to most spine surgeons. It’s because spine surgeons have been brainwashed to think the implant doesn’t matter, or else we wouldn’t be putting plastic in between two bones and hoping it will fuse.”

— Paul Slosar, MD
Surface Matters

• “Our research shows that a small change in implant surface structure at the sub-micron level has a large impact on the bone formation response that is created. The osteogenic environment created by a nano-scale titanium surface may enhance implant stability and fusion.”
  — Barbara Boyan, Ph.D.
WHY TITANIUM?

Bone has a natural affinity for titanium

“Nature allows bone cells to attach to the titanium surface and the result is a firm and permanent anchorage for a prosthetic reconstruction.”

-Branemark (father of dental osseointegration)
Bone Physiology
Cells interact at micron/ nano scale

Macro: $10^{-3}$ m

Micro: $10^{-6}$ m

Sub-Micron/ Nano: $10^{-9}$ m

Cells

Integrins
Surface chemistry and topography affect:
• Surface energy
• Protein adsorption
Drive a favorable cellular response (fusion)
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
• **Micro** is scale visible with Electron Microscope
  – *Micron* $10^{-6}$ / *Nano* $10^{-9}$
  – Primary benefit is cellular response
  – Stimulate interactions with Host bone
• **Porous/ Porosity**
  – Size/ Space for bone to grow
  – Just because there is space doesn’t mean bone will grow into it
  – Smooth Ti (Electron Microscopy)
Surface Hierarchy

- **Macro** level ($10^{-3}$m): anti-expulsion surface (not important to cells)
- **Micron** level ($10^{-6}$m): Osteoclastic-like pits that allow osteoblast insertion and circumvent the resorptive phase of bone remodeling
- **Nano** level ($10^{-9}$m): nano-scale features bind with stem cell membrane through proteins
  - up-regulation of osteoblasts, down-regulation of osteoclasts, and up-regulation of angiogenesis
PEEK vs. Titanium

• PEEK is a polymer
  – Spine market (almost exclusively)...no other significant use for other bone applications
  – New offerings: PEEK coated with Ti
  – Radiolucent
  – Modulus of Elasticity (Irrelevant)
  – Fibrous tissue at contact surface between PEEK and host bone
PEEK vs. Titanium

• Titanium
  – Widely used across all many Bone applications
  – Bio-compatible
  – Compatible with MRI and CT
  – Bone ingrowth directly onto surface of some Implants (surface dependent)
  – (Re-) Emerging as the material of choice for interbody fusion implants
Ti Plasma Spray Coatings (TPS)
(plasma spray abandoned years ago in Dental industry)

- PEEK + Ti (plasma spray)
- Bone-implant interface
  - smooth Ti (micron-scale)
  - Rough > smooth > PEEK
- Plasma spray Ti
  - Delamination risk
  - Particulate debris
- MOE
  - Not clinically relevant
  - All spine implants have substantially higher MOE than host bone
- Radiolucent
COATINGS ON TITANIUM

- Ti particulate debris/shedding has been observed following implantation in animal models
Osteoblasts exhibit a more differentiated phenotype and increased bone morphogenetic protein production on titanium alloy substrates than on poly-ether-ether-ketone.

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Micron-rough Ti Surface Promotes Osteoblast Differentiation

Biomarker for bone formation

“Turn off” osteoclast activity

TCPS = Tissue Culture Polystyrene
sTi = Smooth Titanium
rTi = Roughened Titanium (Micron scale)
Micron-scale Roughness > Smooth Ti > PEEK

Physiologic BMP production

BMP2 Levels

BMP4 Levels

BMP7 Levels
Angiogenesis

Basic Science

Rough titanium alloys regulate osteoblast production of angiogenic factors

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![Graphs showing VEGF, FGF2, and ANG1 levels for different conditions: TCPS, PEEK, sTiAlV, rTiAlV.](image-url)
Implant Materials Generate Different Peri-implant Inflammatory Factors: PEEK Promotes Fibrosis Micro-textured Titanium Promotes Osteogenic Factors*

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*Whitecloud Award Winner; Best Basic Science Paper; SRS/IMAST 2014
Introduction

• Osteoblastic differentiation of human mesenchymal stem cells (MSCs) is influenced by implant surface properties.

• PEEK
  – cells fail to exhibit increased alkaline phosphatase activity or osteocalcin production

• Titanium rough-textured (micron/ nano scale)
  – exhibit increased markers of osteoblastic differentiation
Clinical

• In-vitro studies are supported by in-vivo results examining peri-implant bone formation in sheep spine ¹

• Histologically, implants fabricated from PEEK
  – have a fibrous connective tissue surface interface

• Ti-alloy implants
  – demonstrate a close approximation with surrounding bone ¹,²

Methods

• Human MSCs cultured on
  – TCPS (tissue culture polystyrene) control
  – PEEK
  – smooth Ti-alloy (smooth Ti)
  – Micron / nano rough Ti-alloy (MMN) disks

• Cell morphology and osteoblastic differentiation were assessed

• mRNAs for pro-inflammatory cytokines were measured and fold changes compared to control
  – 2x fold change considered significant
Osteoblastic Phenotype

Alkaline Phosphatase Specific Activity

- Early marker

Osteocalcin

- Later marker

* vs TCPS
# vs PEEK
$ vs Smooth
Inflammation

Fold Change/TCPS

CCL2  CD40LG  IL1A  IL1B  IL6  IL8  TLR4  TNF

PEEK  Smooth  MMN
Apoptosis

Fold Change/TCPS

CASP1  FAS  MCL1  TNFRSF10A  TNFRSF10B  TNFRSF1A

PEEK  Smooth  MMN
Necrosis

Fold Change/TCPS

FAS, GRB2, PARP1, PVR, RIPK1, TNFRI, TNFRII, TXNLD

PEEK, Smooth, MMN
**Pro-inflammatory Interleukins**

* vs TCPS
# vs PEEK
$ vs Smooth
Discussion

• We previously reported that cells on micro-textured Ti produce pro-angiogenic and pro-osteogenic factors whereas those on PEEK do not \(^1,^3,^4\).
  – BMP 2, 4; VEGF

• Human MSC’s respond to the surface characteristics of implants
  – Cytokine mediators drive osteoblastic vs. fibroblastic cell transformation
  – Micron/ Nano (10 \(^{-9}\)) scale topography is what a MSC cell “sees”

Conclusion

• PEEK promotes Fibrosis Environment
  – Hypo-vascular
  – High Inflammatory cytokine micro-environment
  – Poor Cell Viability (spindle/ ↑apoptosis/ hypocellular)

• Micron Nano Ti promotes Osteogenic Environment
  – Angiogenesis / BMP
  – Low inflammation
  – Good Cellular viability (robust/ low apoptosis/ no necrosis)
A Prospective Study of a Unique Lumbar Interbody Fusion Implant; Clinical and Radiographic Outcomes at 1 and 2 year follow up

Paul J. Slosar, Adam Cabalo, James B. Reynolds

SpineCare Medical Group/ San Francisco Spine Institute
Clinical Outcomes

VAS Leg Pain 24 month

VAS Back Pain 24 month
Clinical Outcomes

ODI

55.0

36.0

32.2

30.5
Clinical Results

• Meaningful Clinical Improvements
  – ODI >15 and VNS >3
  – Achieved in the majority of cases

• The clinical outcomes at 12 and 24 months were not significantly different than the results at 6 months.
Interobserver Agreement Using Computed Tomography to Assess Radiographic Fusion Criteria With a Unique Titanium Interbody Device

Paul J. Slosar, MD, Jay Kaiser, MD, Luis Marrero, MD, and Damon Sacco, MD

Abstract
The accuracy of using computed tomography (CT) to assess interbody fusion in patients with titanium implants has been questioned in the past. Radiologists have reported difficulty assessing fusion bone quality because of metal artifact and small graft windows. A new titanium interbody implant with a large footprint and a wide graft aperture has been developed.

We conducted a study to determine the interobserver reliability of using CT to assess radiographic fusion variables with the new titanium interbody device. Patients underwent anterior lumbar interbody fusion with the same titanium interbody implant. Reconstructed CT images were obtained randomly at 6, 9, or 12 months. Two independent radiologists reviewed the scans. Interobserver reliability was calculated using the \( \kappa \) statistic.

Fifty-six spinal fusion levels (33 patients) were analyzed. The radiologists agreed on 345 of the 392 fusion data points reviewed (\( \kappa = .88 \)). Agreement for solid fusion formation was 0.77.

This interbody device demonstrated minimal artifact and minimal subsidence, and trabecular bone was easily identified throughout the implant in the vast majority of cases reviewed. High interobserver agreement was noted across all radiographic variables assessed.
Results

• 33 patients

• 56 spinal fusion segments
  – 17 males / 16 females
  – Average age 46 years (range 23-66 yrs)
  – 6 patients (18%) were nicotine users.
Results
Artifact/ Subsidence

<table>
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<tr>
<th>Reviewer</th>
<th>Artifact</th>
<th>Subsidence</th>
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<tbody>
<tr>
<td></td>
<td>Grade 0</td>
<td>Grade 1</td>
</tr>
<tr>
<td>A</td>
<td>43 (77%)</td>
<td>12 (21%)</td>
</tr>
<tr>
<td>B</td>
<td>54 (96%)</td>
<td>2 (4%)</td>
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Agreement 0.80 0.95

Artifact : Grade 0: Mild; Grade 1: Moderate; Grade 2: Non-diagnostic

Subsidence: >3 mm
# Results

## Overall Fusion Grade

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Grade 5</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 2</th>
<th>Grade 1</th>
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<td>45 (80%)</td>
<td>8 (14%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B</td>
<td>51 (91%)</td>
<td>5 (9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Agreement**

<p>| | |</p>
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<tbody>
<tr>
<td>Same Grade</td>
<td>0.77</td>
</tr>
<tr>
<td>Within 1 Grade</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Grade 5: Definitely Fused;  
Grade 4: Probably Fused;  
Grade 3: Indeterminate;  
Grade 2: Probably Not Fused;  
Grade 1: Definitely Not Fused
Old Titanium Technology
Minimal Artifact

Edge of implant
Surface integration

Linear lucency/no subsidence
Radiographic Conclusions

• The titanium implant studied demonstrated minimal artifact, minimal subsidence, and trabecular bone was easily visualized.

• Radiographic fusion criteria can be reliably assessed using CT scans with a high degree of interobserver agreement.
Biological Conclusions

• PEEK
  – promotes Fibrosis Environment

• Smooth Ti
  – Better than PEEK
  – Not as effective as Micron/ Nano scale Ti

• Micron Nano Ti
  – promotes Osteogenic Environment

• PEEK with External Coatings
  – Concerning mechanical issues
Summary

• Welcome focus on the science of spine implant materials and their impact on bone physiology
  – Neutral/ Negative/ Positive
  – Implant is NOT simply a carrier for your biologic

• Evolution of the science of spine implant materials
  – Goal: Improved outcomes for patients
Thank you