
Laser Spine Institute
Implant Surface Technology:
Material and Topography Influences Biochemical Responses
Reginald Davis, M.D., FAANS, FACS – Director of Clinical Research
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BIOMIMICRY
INSTITUTE
"Biomimicry is an approach to innovation that seeks sustainable solutions to human challenges by emulating nature's time-tested patterns and strategies."
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Solution
Biomimicry: Leveraging nature's expertise to solve complex challenges
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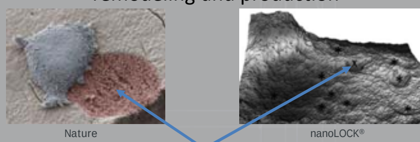
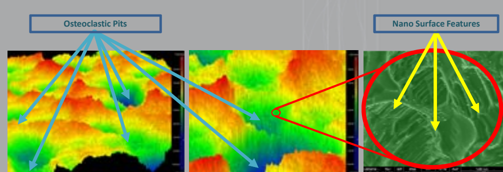
Solution

Biomimicry for bone growth: Mimic the structures that are integral to natural bone remodeling and production



Osteoclastic pits and nano-scaled textures within them

nanoLOCK Surface Technology



Optical profilometer

Scanning Electron Microscope.

Terms

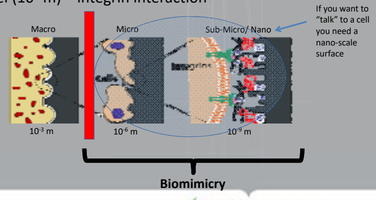
- **Macro** is texture you can **feel**
  - Primary benefit is mechanical; resistance to migration
  - Concerns about a Macro Rough surface damaging endplates (subsidence)
  - Too much “Macro” impedes device insertion
- **Nano** is scale visible with Electron Microscope
  - **Nano 10^{-9} (1 billionth of a meter)**
  - Primary benefit is <u>cellular</u> 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^{-3}m) – implant stability with endplate integrity

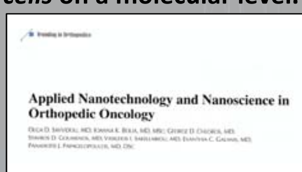
Biochemical Influence Barrier

- **Micro** level (10^{-6}m) – cellular attachment/differentiation
- **Nano** level (10^{-9}m) – integrin interaction



Biomimicry:

"Nanotechnology exploits the unique advantage of *direct interaction with cells* on a molecular level."



Applied Nanotechnology and Nanoscience in Orthopedic Oncology

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

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Peer–Reviewed Scientific Landscape

1. Olivares-Navarrete, R., Gittens, R.A., Schneider, J.M., Hyzy S.L., Haithcock, D., Ullrich, P., Schwartz, Z., Boyan, B.D. **Osteoblasts exhibit a more differentiated phenotype and increased BMP production on titanium alloy substrates than PEEK**. **Spine J. 2012** Mar; 12(3):265-72.
2. Olivares-Navarrete, R., Hyzy S.L., Gittens, R.A., Schneider, J.M., Haithcock, D., Ullrich, P., Schwartz, Z., Boyan, B.D**. Rough titanium alloys regulate osteoblast production of angiogenic factors. Spine J. 2013** Nov; 13(11):1563-70.
3. Girasole, G., Muro, G., Mintz, A., Chertoff, J., **Transforaminal lumbar interbody fusion rates in patients using a novel titanium implant and demineralized cancellous allograft bone sponge. Int J Spine Surg. 2013** Dec; 7(1): 95-100.
4. Slosar, P.J. Technological advancements in spinal fusion implants**: A summary of the current scientific and clinical research on titanium engineered surfaces. J. Spinal Research Foundation. 2014**; 9(1): 35-41.
5. Gittens, R.A., Olivares-Navarrete, R., Schwartz, Z., Boyan, B.D**. Implant osseointegration and the role of microroughness and nanostructures: Lessons for spine implants. Acta Biomater 2014** Aug; 10(8): 3363-3371.
6. Olivares-Navarrete, R., Hyzy S.L., Gittens, R.A., Berg, M.E., Schneider, J.M., Hotchkiss, K., Schwartz, Z., Boyan, B. D. **Osteoblast lineage cells can discriminate microscale topographic features on titanium-aluminum-vanadium surfaces. Ann Biomed Eng. 2014** Dec; 42(12): 2551-61.

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Peer-Reviewed Scientific Landscape

7. Slosar, P. J., Kaiser, J., Marrero, L., Sacco, D**. Interobserver agreement using CT scans to assess radiographic fusion criteria with a unique titanium interbody device. Am J Orthopedics**. 2015 Feb; 44(2): 86-9.
8. Olivares-Navarrete, R., Hyzy S.L., Slosar, P.J., Schneider, J.M., Schwartz, Z., Boyan, B.D**. Implant materials generate different peri-implant inflammatory factors: PEEK promotes fibrosis and micro-textured titanium promotes osteogenic factors. Spine. 2015** Mar; 40(6): 399-404.
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10. Matteson, J.L., Greenspan, D.C., Tighe, T.B., Gilfoy, N., Stapleton, J.J. **Assessing the hierarchical structure of titanium implant surfaces. J Biomed Mater Res B.** [In Press] EPub 29 May 2015.
11. Kienle, A., Graf, N., Wilke, H.J. **Does impaction of titanium-coated interbody fusion cages into the disc space cause wear debris and/or delamination? Spine J. 2016 Jan;** 16(2): 235-242.
12. Banik, B., Riley, T., Platt, C., Brown, J. **Human mesenchymal stem cell morphology and migration on microtextured titanium. Front Bioeng Biotechnol. 2016 May**; 4(41) doi: 10.3389/fbioe.2016.00041.

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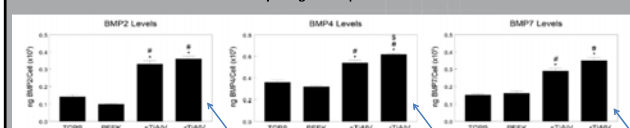
Up-regulate Osteoblasts - TGF-B1, BMP-2,4,7

Physiologic BMP production



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

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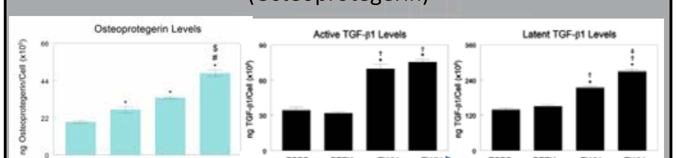
Down-regulate Osteoclasts – TGF-B1, OPG (Osteoprotegerin)



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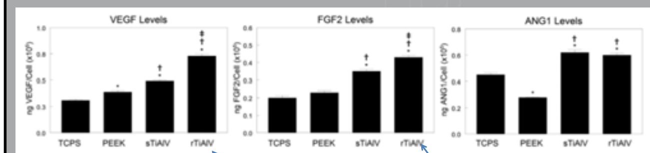
Up-regulate Angiogenesis – Angiopoietin-1, VEGF-A, FGF-2



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

Rene Olivares-Navarrete,[1] Sharon L. Hyzy,[1] Mark E. Berg,[2] Jennifer M. Schneider,[2] Kelly Hotchkiss,[1] Zvi Schwartz,[1,4] and Barbara D. Boyan[1,3,4,5]

[1]Department of Biomedical Engineering, Virginia Commonwealth University, Richmond, VA, USA; [2]Titan Spine LLC, Mequon, WI, USA; [3]Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA; [4]Department of Periodontics, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; and [5]School of Engineering Virginia Commonwealth University, 601 West Main Street, Suite 331a, Richmond, VA 23284, USA

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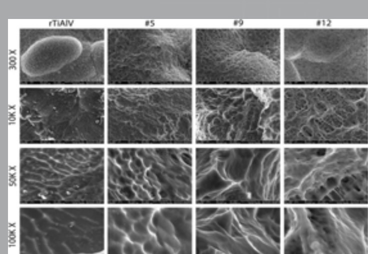

Scanning electron microscopy images of rough titanium alloy (rTiAlV) or substrates with modified topography (#5, #9, and #12). Images were taken at 300× (10 μm scale bar), 10 k× (1 μm scale bar), 50 k× (100 nm scale bar), and 100 k× (100 nm scale bar)

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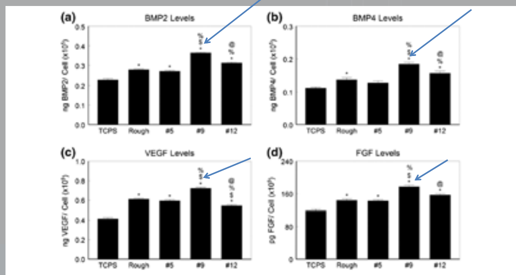
#9 = nanoLOCK

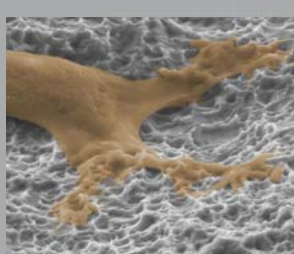
Local factor production by osteoblasts (#9)



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^{-6})
    - 10x 20x 8 microns
  - The Nano-structured <u>*specific surface*</u> (10^{-9}) induced highest expression of integrins/ mRNA driving osteoblastic differentiation

Osteoblastic interaction with Nano-scale Ti



frontiers
in Bioengineering and Biotechnology
ORIGINAL RESEARCH

Human Mesenchymal Stem Cell Morphology and Migration on Microtextured Titanium

*Brittany L. Banik[1], Thomas R. Riley[2], Christina J. Platt[3] and Justin L. Brown[1]**

Cell Seeding was minimal

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

Human Stem Cell Study

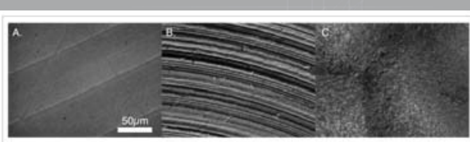


FIGURE 1 | Surface morphology of PEEK and titanium samples. (A) PEEK, **(B)** smooth titanium, and **(C)** rough, acid-etched endoskeleton surface.

Human Stem Cell Study – 24 hours

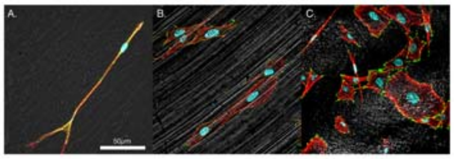


FIGURE 3 | Representative morphologies of MSCs. (A) PEEK, **(B)** smooth titanium, and **(C)** rough, acid etched endoskeleton surface, at 24 h. Immunofluorescence was carried out to examine the focal adhesion protein vinculin (green), the actin cytoskeleton (red), and the cell nuclei (blue). Additionally, a gray scale depiction of the surface was obtained with reflected DIC. The results demonstrated the trends observed in **Figure 2** with cells on the smooth surfaces moving toward an elongated spindle-shaped morphology, whereas the cells on the rough surface demonstrated a range of morphologies from spindle-shaped cells to cuboidal and stellate-shaped cells. In particular, the cuboidal and stellate cells in C. are representative of morphologies expected of osteoblastic differentiation. Scale bar indicating 50 μm applies to **(A–C)**.

Human Stem Cell Study – 7 days

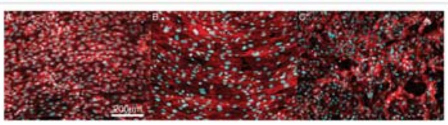
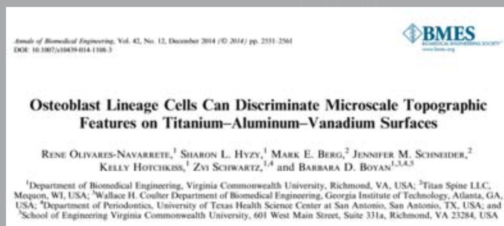


FIGURE 7 | Representative images of confluent cells stained for actin (red) and the cell nuclei (blue). (A) PEEK, **(B)** smooth titanium, and **(C)** rough, acid-etched endoskeleton surface, after 7-day culture. The cells on PEEK and smooth titanium demonstrate an elongated morphology in a uniform direction, whereas cells on the acid-etched endoskeleton surface demonstrate a branched random morphology. Scale bar indicating 200 μm applies to **(A–C)**.

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.



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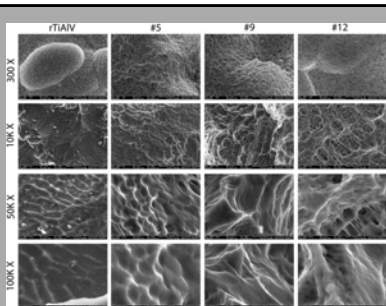

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Biomimicry: Osteoclastic Pits

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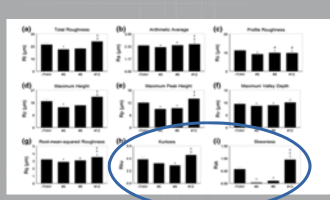
- Multiple surface characteristics were measured
- Only two parameters showed significant differences
  - Low Skewness (deep valleys)
  - High Kurtosis (sharp peaks)



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Results – Cell Response - Osteoblasts

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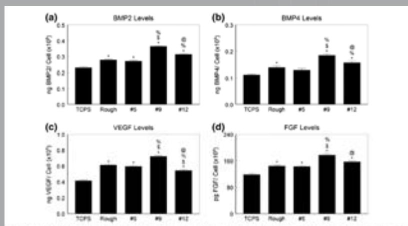

FIGURE 4. Local factor production by normal human osteoblasts on microstructured Ti6Al4V. Osteoblasts were cultured on TCPS, rTiAlV, #5, #9, or #12 surfaces and secretion of BMP2 (a), BMP4 (b), VEGFA (c), and FGF (d) measured in the conditioned media. * $p < 0.05$ vs. TCPS; $ $p < 0.05$ vs. rTiAlV; ^ $p < 0.05$ vs. #5; @ $p < 0.05$ vs. #9.

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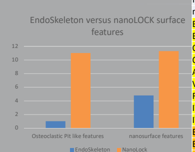
EndoSkeleton versus nanoLOCK



	EndoSkeleton	NanoLock	% increase	
Osteoclastic Pit like features	1	11	1000%	
nanosurface features	4.8	11.3	135%	
BMP 2	0.23	0.38	65%	Human Osteoblast
BMP 4	0.13	0.19	46%	Human Osteoblast
Osteocalcin	16	20	25%	Human Osteoblast
Osteoprotegerin	7	8	14%	Human Osteoblast
Alkaline Phosphatase	6	9	50%	Human Osteoblast
VEGF	0.28	0.36	29%	Human Osteoblast
FGF	150	190	27%	Human Osteoblast
ITGA2	1.3	1.8	38%	Human Osteoblast
ITGB1	1.4	1.7	21%	Human Osteoblast
BMP 2	1.8	2.4	33%	Human Stem Cell
BMP 4	0.32	0.43	34%	Human Stem Cell
Osteocalcin	55	74	35%	Human Stem Cell
Osteoprotegerin	14.4	20.1	40%	Human Stem Cell
Alkaline Phosphatase	13.5	18	33%	Human Stem Cell
VEGF	0.95	1.2	26%	Human Stem Cell
FGF	120	190	58%	Human Stem Cell
ITGA2	2	3	50%	Human Stem Cell
ITGB1	1.8	2	11%	Human Stem Cell

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Clinical Significance?

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Titan Spine Post-Operative Cost Analysis

Executive Summary

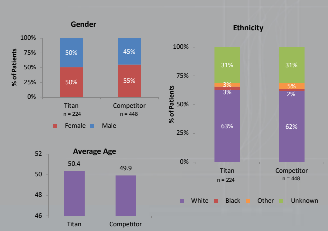
December 9, 2015

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

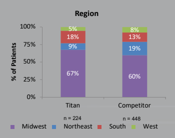
Phase 2 Results: Demographic Characteristics

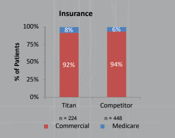
Titan Spine patients closely resemble competitor patients in terms of gender, ethnicity, and average age



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





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

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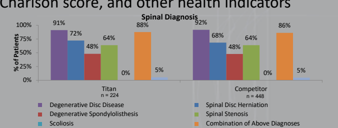
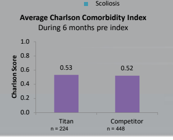
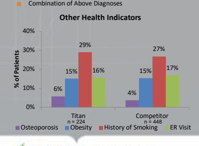
Phase 2 Results: Medical Characteristics

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







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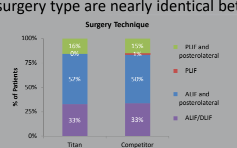
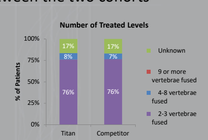
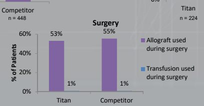
Phase 2 Results: Surgery Characteristics

Percentages of patients by surgery technique, number of treated levels, and surgery type are nearly identical between the two cohorts







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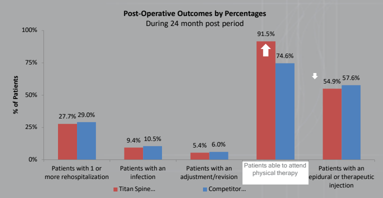
Phase 2 Results: Post-Operative Outcomes by Percentages

92% of Titan Spine patients were able to attend post-operative physical therapy, versus 75% of competitor patients



Titan Spine Patients	224
Competitor Patients	448

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

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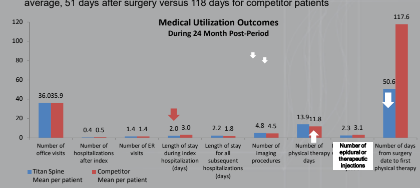
Phase 2 Results: Medical Utilization Outcomes by Patient Average

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



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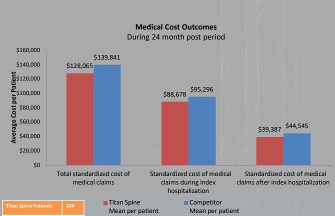
Phase 2 Results: Medical Cost Outcomes

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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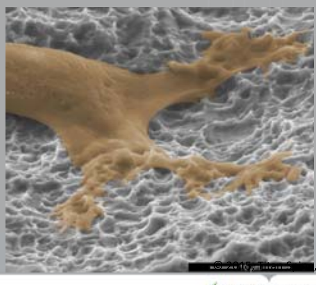
1 FDA Clearance for Spine Nano-technology

Device Description:
This traditional 510(k) 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!



[redacted], LLC