Biomaterial Solutions to Clinical Concerns
Silicon Nitride Ceramic

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Current Interbody Materials are a Compromise

- Biomaterials:
  - Bone autograft, allograft
  - Polymers, i.e., PEEK
  - Porous metals (titanium, tantalum)
- Solutions-
  Materials, Micro-, Nano-, 3-D, Scaffolds, Additives, Putties, Bone void fillers, Stem Cells, Amniotic therapies, HA, Coatings Surface treatments, Design Variations

History

- Bones were healing long before surgery or surgeons
- *The Edwin Smith Papyrus* (copied circa 1600 BC)
- Fusion works
  - Cloward 1908, 1958 ACDF
  - *Faldini 2010* 100% success
- What are we improving on?
- The donor site

Ideal Spine Interbody Device

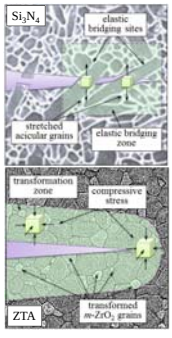
- Biocompatible, strong, stable, non-toxic
- Easier Imaging, Reasonable Cost
- Osteoconductive: Porous, roughness
- Osteoinductive
  - Stem Cell Stimulation
  - Into osteoblasts and HA
- Antimicrobial Surface
- Bone ingrowth into device
- Avoid added components and expense
- Custom implants -3D manufacture

Si_3N_4 Industrial History

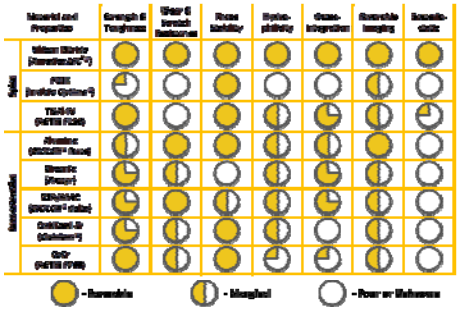
- High strength and fracture toughness
- High pressure, high temperatures
  - Automotive engines, gas turbines, aerospace, electronics
- Low coefficient of thermal expansion, extreme thermal shock resistance
- Dimensional precision by machining
- Impervious to chemical attack (HF, H_2SO_4)
- Resistant to corrosion (sea-water tidal valves)
- Extreme: The Biomedical Environment

Material Technology

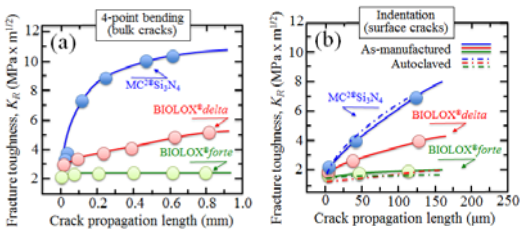
- Non-oxide ceramic (zirconia, alumina, ZTA)
- Powders → Additives → Slurry → Shape → HIP → Polish Grind
- Lumbar fusion (Sorrell *et al.* 2004, World Biomat. Cong.)
  - Reaction-bonded Si_3N_4 (Heat Si in N_2, 1200°C; 150-200 hours)
  - 15-year follow-up of n=30
- Si_3N_4 + ~ Yttria, Alumina ceramic powders
- ~30,000 implants (cervical, lumbar) with 8-year follow-up
- Material resists internal crack propagation



Comparisons of Orthopedic Materials



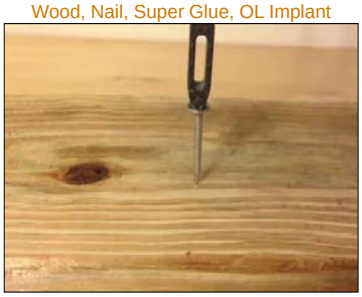
Fracture Toughness of Medical Ceramics



B. J. McEntire, *et al.* "Surface toughness of silicon nitride bioceramics: II, Comparison with commercial oxide materials." *Journal of the Mechanical Behavior of Biomedical Materials*, **54**, (2016): 346-359.

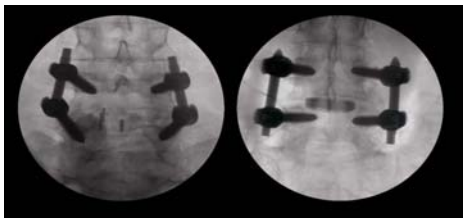
An Example of Si_3N_4's Strength and Toughness

Wood, Nail, Super Glue, OL Implant



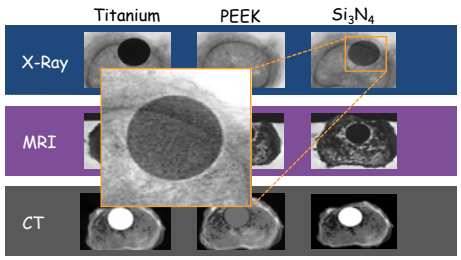
It's Definitely Easier to See…

PEEK Silicon Nitride



Si_3N_4 radiolucency provides **greater visibility** allowing for accurate device placement and post-op fusion detection

Comparisons Using Different Imaging Modalities



J. Bernero, et al., "Medical Imaging Characteristics of Silicon Nitride," *SAS Conference*, Miami, (2008)

11

Wetting Behavior of Biomaterials

Polyetheretherketone | Medical grade Ti Metal | "As-Fired" Si_3N_4

SiYAlON-Glazed Si_3N_4 | N_2-Treated Si_3N_4 | Oxidized Si_3N_4

R. M. Bock, *et al.*,"Bacteriostatic Behavior of Surface Modulated Silicon Nitride in Comparison to Polyetheretherketone and Titanium." *J. of Biomed. Mater. Res., Part A* (2016).

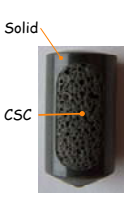
12

Effect of Surface Treatment on Hydrophilicity

13

Osteoconductivity of Si_3N_4

Ovine condylar implant – 12 and 24 week evaluation



Ø11mm x 20mm

CSC: Cancellous structured ceramic ~72% porous, 450 μm average pore size

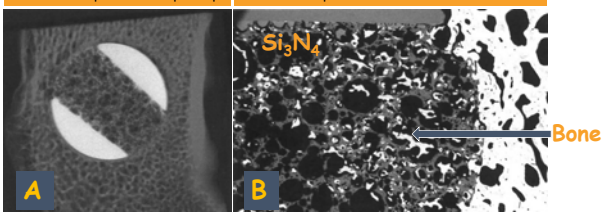
M. C. Anderson, et al., "Bone In-Growth into Porous Silicon Nitride," *J. Biomed. Mat.*, **92A**, [4], 1598-1605, (2010).

14

Osteoconductivity of Si_3N_4

In-vivo Ovine Medial Femoral Condyle Study

Retrieved implant 12 wks post-op | Bone penetrated >3mm into C^{5}C®



15

Si_3N_4 – Naturally Nanostructured

- As-fired: Nanostructured –cell adhesion
- FDA: "at least one dimension in the size range of approximately 1 nanometers (nm) to 100 nm"
- I micrometer = 1,000 nanometer
- Sub-micron topography is common in ceramics
- No need for expensive re-engineering of the surface

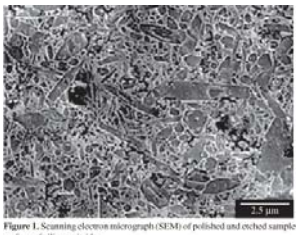
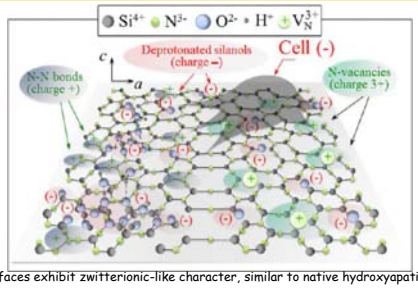


Figure 1. Scanning electron micrograph (SEM) of polished and etched sample surface of silicon nitride.

Surface: Osteoblast Cell Proliferation Mechanism



- Si_3N_4 surfaces exhibit zwitterionic-like character, similar to native hydroxyapatite.

Silicon Nitride and Non-Stoichiometric Chemistry

Non-stoichiometric compounds (almost always solid inorganic compounds) having elemental composition in proportions that cannot be represented by integers. In such materials, some small % of atoms are missing, or an excess of atoms are packed into an otherwise perfect lattice work.

Tools: Raman Spectroscopy, Energy-dispersive X-ray spectroscopy (XDS), SEM, X-ray photoelectron spectroscopy (XPS), Fourier transform infrared spectroscopy (FTIR)…all molecular and sub-molecular probes.

Surface Modulation of Silicon Nitride

Oxygen-rich — Balance of Surface Functional Groups — Nitrogen-rich

Si-OH ⟷ Si-NH$_2$

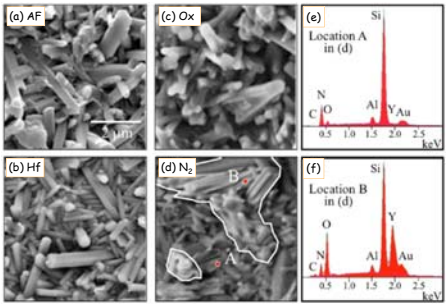
$$Si-OH_{(s)} \leftrightarrow Si-O^-_{(s)} + H^+_{(aq)}$$

$$Si-NH^+_{3\,(s)} \leftrightarrow Si-NH_{2\,(s)} + H^+_{(aq)}$$

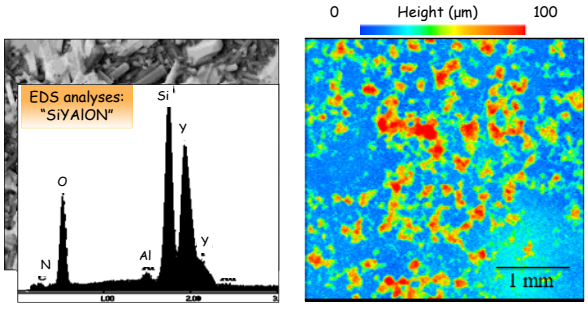
- Silicon Nitride Surface Treatments
  - As-Fired.
  - HF Etch.
  - Thermal Annealed in Nitrogen (1400°C, 30 min).
  - Thermal Oxidized in Air (1070°C, 7 h).
  - Polished.

R.M. Bock, *et al.*, "Surface Modulation of Silicon Nitride Ceramics for Orthopaedic Applications," *Acta Biomater.*, 26 318-330 (2015).

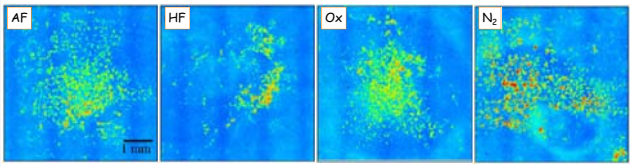
Surface Modulated Microstructures



Preferred Adhesion Sites by SaOS-2 Cells



Hydroxyapatite Growth on Surface Modulated Silicon Nitride



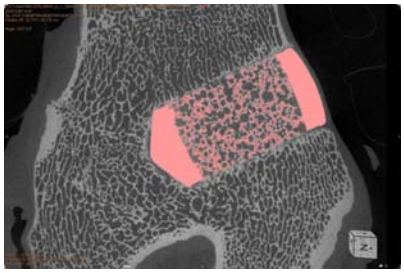
(μm)
100 0

- Significantly greater HAp growth occurred on N_2-annealed Si_3N_4 samples.

G. Pezzotti, *et al.*, "In Situ Spectroscopic Screening of Osteosarcoma Living Cells on Stoichiometry-Modulated Silicon Nitride Bioceramic Surfaces," *ACS Biomater. Sci. Eng.*, 2 [7] 1121–1134 (2016).

Faster healing: Porous Si_3N_4 at 4 Weeks

- Micro-CT Scan of ovine femoral condyle implant
- Excellent bone apposition at 4 weeks post-implantation

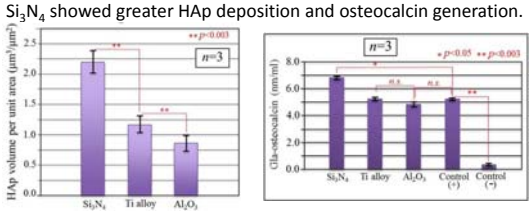


Schwartz Lab- University of Rochester

- In vivo model of bone healing
- Nanostructure vs "Nano-flat"
- Dip implants in a MRSA broth
- Day-by-day cell-level analysis
  - Day 5 MSC flat on implant
  - Day 10 osteoblastic differentiation
- "Nano-flat" implants:
  - No bone formation
  - Still resisted bacterial adhesion

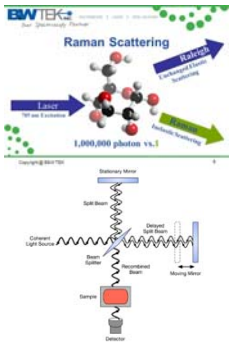
Osteoinductivity: Stem-Cells → HA Deposition

- *In vitro* study using murine bone marrow stromal cells.
- Three different biomaterials (Si_3N_4, Al_2O_3, and Ti).
- Monitored differentiation into osteoblasts and native bone formation.
- Si_3N_4 showed greater HAp deposition and osteocalcin generation.

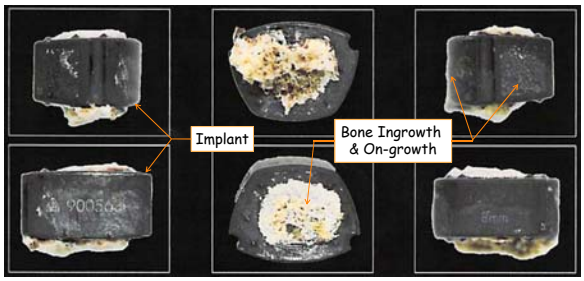


Raman Spectroscopy, EM, FTIR

- Molecular fingerprinting – 2 key findings
- Si-substituted HA (Si-HAps)
  - Accelerate bone formation
  - Silicon is critical element
- SiYAlON glass-like phase on surface
  - Variations in Silicon Nitride structure
  - Range: $Si_{3-3(m+n)/4}Al_nY_mO_xN_{4-2x/3}$.
  - Replace Si, N with Al, Y, O
  - Bioactive glasses promote bone healing

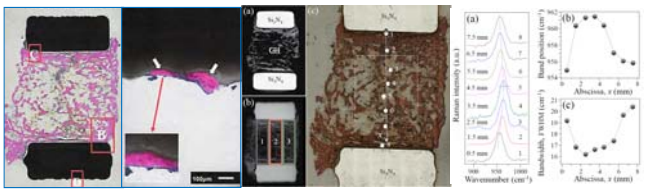


Spinal Fusion Explant – 10 Months *in vivo*



27

Raman Spectroscopy Examination of Explant

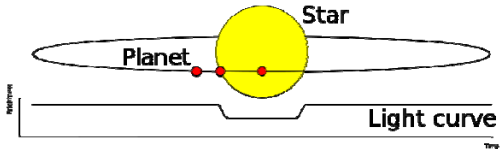


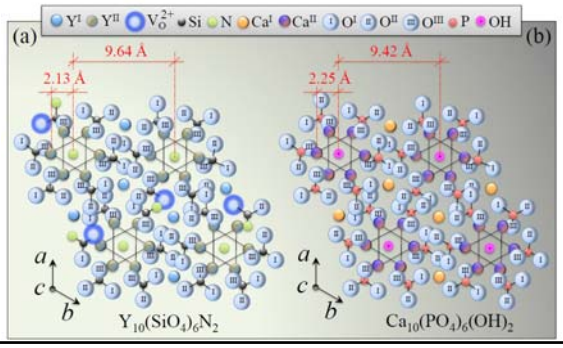
- Band shifts near Si_3N_4 surfaces indicate incorporation of Si and N into native hydroxyapatite.

28

Light bending, wavelength alterations

Doppler Spectroscopy



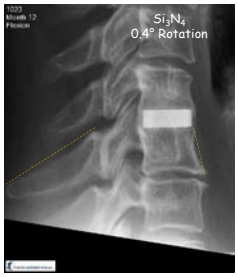


What Does the Science Mean?

- First time a material has induced living cells
  - To make Si- and Ni- substituted HA
  - Kick-starting new bone formation
  - So far we have added similar things
- Bagel v Bagel with Cream Cheese

- Faster fusion till 36 months (Ball 2017)
- C-spine fusion (Arts et al 2017)
  - Randomized clinical trial
  - Autograft PEEK vs Porous Silicon Nitride
  - Similar outcomes at 24 months

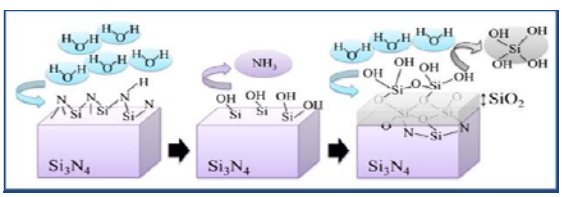
Clinical Assessment – Fusion at 12 Months



M. P. Arts, *et al.*, "Outcomes of Anterior Cervical Fusion with PEEK versus Ceramic," (in press) (2017).

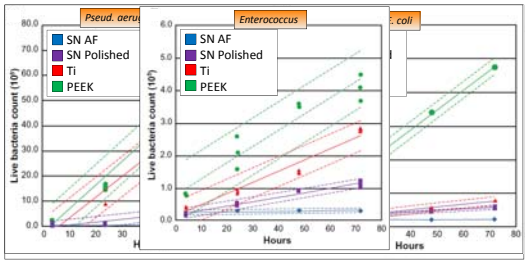
32

Why is silicon nitride antimicrobial?



- Surface chemistry consists of silicon diimide $Si(NH)_2$ groups which release ammonia (NH_3) and silicic acid (H_4SiO_4) into biological fluids.
- NH_3 is converted to peroxynitride anion $O{=}NOO^-$ which is toxic to bacteria.
- Bioavailable silicic acid aids rapid bone formation limiting implant exposure to planktonic microbes.
- Acicular grained nano- and micro-rough surface resists bacteria adhesion.

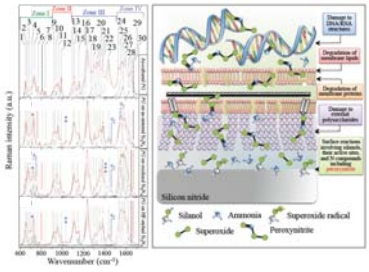
In vitro Bacteriostatic Behavior of Biomaterials



34

Resistance to Dental Bacteria

In vitro study using Raman spectroscopy to characterize metabolic processes of *P gingivalis* when exposed to silicon nitride

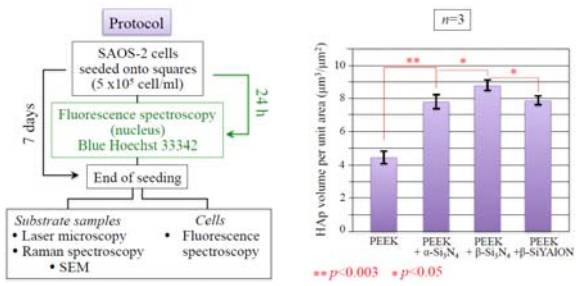


- Raman spectrum of living cell culture provides a wealth of information
- Exposure to treated silicon nitride surfaces showed varying degrees of:
  - Disintegration of DNA nucleotides (6-8)
  - Increase in membranous lipids (4,5)
  - Inhibition of metabolic activity via reduction in phenylalanine (12)
  - Formation of peroxynitrite (**)
  - Suppression of polysaccharide peaks indicates substantial breakdown of cell walls (13)
  - Among many other observations
- Hints at interaction mechanisms between cell and surface leading to slowed metabolism, oxidative damage, and lysis

AMEDICA Confidential

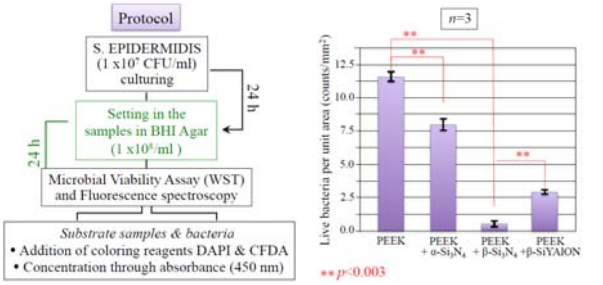
35

Osteoconductivity of a 15% Si_3N_4/PEEK Composite



36

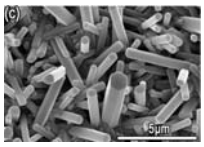
Bacteriostatic Behavior of a 15% Si_3N_4/PEEK Composite

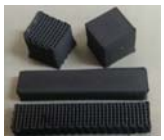


37

3-D Printing

- Cost of Si_3N_4 implants is comparable to PEEK
- Further efficiency with 3-D printing
- Existing manufacturing already consistent
- First time 3-D printed Si_3N_4 implants
  - Rahaman et al 2016





SUMMARY & CONCLUSIONS

Bone healing occurs on its own

Daily change in biochemical, molecular, ionic events from 1-30 days

Will help identify truly bioactive materials (Bone ↔ Implant)

That can impact clinical outcomes in a meaningful way

And improve the lives of surgeons, and patients