

Creating Nanostructured Coatings to Improve Medical Device Performance while Obtaining Fast FDA Approval

Thomas J. Webster, Northeastern University, Boston, MA

There is an acute shortage of organs due to disease, trauma, congenital defects, and most importantly, age related maladies. The synthetic materials used in medical device applications today are typically composed of millimeter or micron sized particles and/or fiber dimensions. Although human cells are on the micron scale, their individual components, e.g. proteins, are composed of nanometer features. By modifying only the nanofeatures on material surfaces without changing surface chemistry, it is possible to increase tissue growth of any human tissue by controlling the endogenous adsorption of adhesive proteins onto the material surface. In addition, our group has shown that these same nanofeatures and nano-modifications can reduce bacterial growth without using antibiotics, which may further accelerate the growth of antibiotic resistant microbes. Inflammation can also be decreased through the use of nanomaterials. Finally, nanomedicine has been shown to stimulate the growth and differentiation of stem cells, which may someday be used to treat incurable disorders, such as neural damage. This strategy also accelerates FDA approval and commercialization efforts since new chemistries are not proposed, rather chemistries already approved by the FDA with altered nanoscale features. This invited talk will highlight some of the advancements and emphasize current nanomaterial coatings and processes used in medical device applications.

Creating Nanostructured Coatings to Improve Medical Performance While Obtaining Fast FDA Approval

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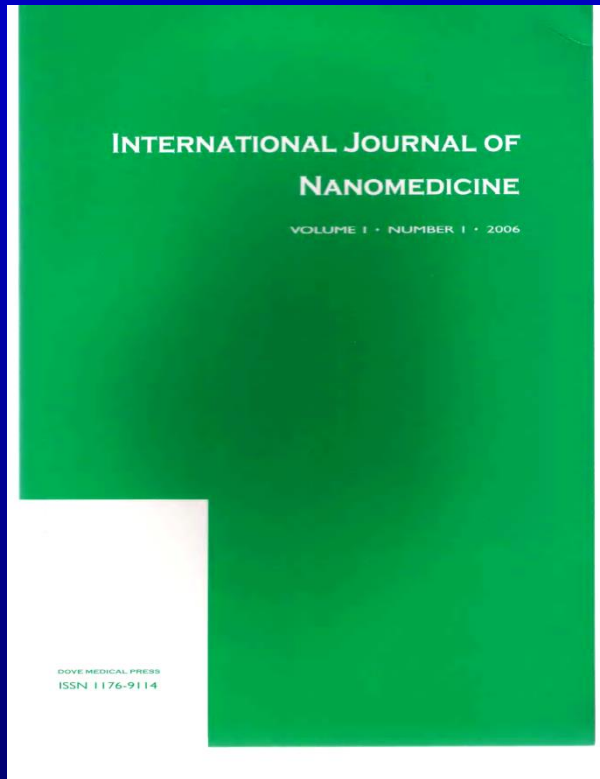
Th.webster@neu.edu

Disclosures

- I have a financial interest in some of the material to be presented via my involvement in:
 - Nanovis, LLC
 - Audax, Inc.
 - Perios, Inc.
 - NanoFe, Inc.
 - NanoSeleno, Inc.
 - NanoVault, Inc.
 - Ultratech, Inc.
 - Tyber Medical, Inc.
 - Stryker
 - Amedica
 - Vexti

It is all about taking “calculated” risks !

10 years ago, nobody was talking about
Open Access journals.
Now they are everywhere.



International Journal of Nanomedicine

5-year Impact Factor: 4.742

Average Time to First Review of Manuscript:
22 Days

We hosted 2 nano conferences at NEU: ITNano2013 and ITNano2014 and started the first ever Nanomedicine Academy

**These are risks worth taking,
but should we be
taking risks in healthcare ?**

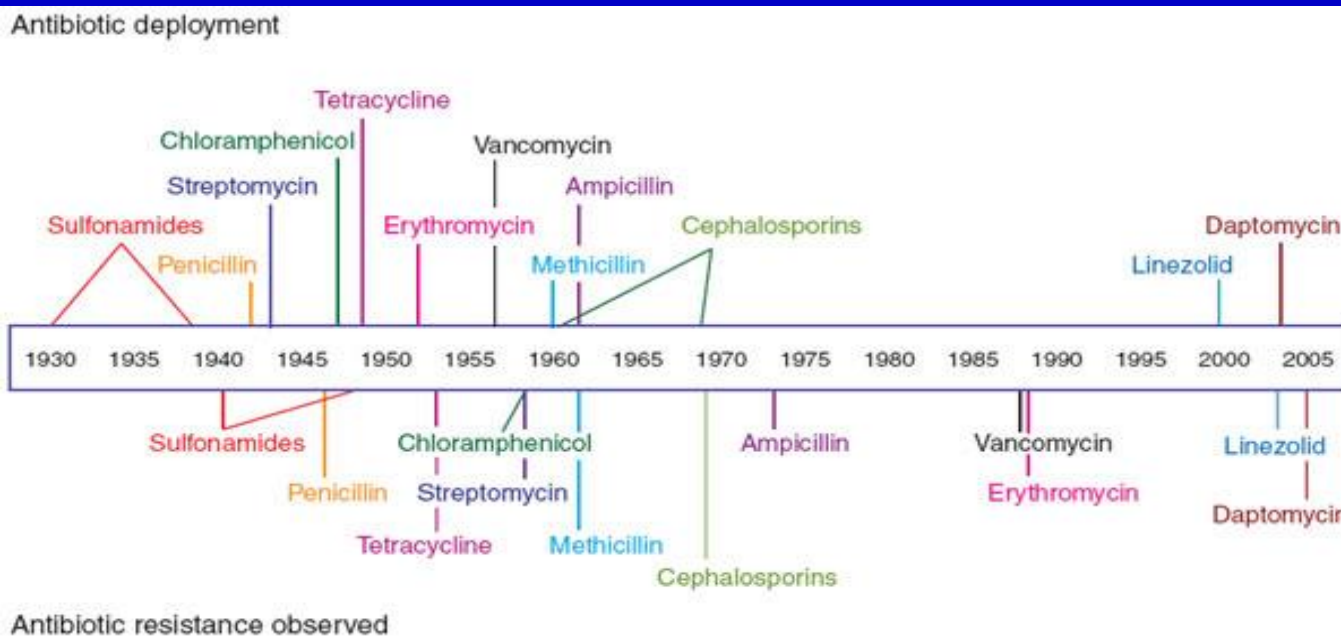
Current Problems in Healthcare



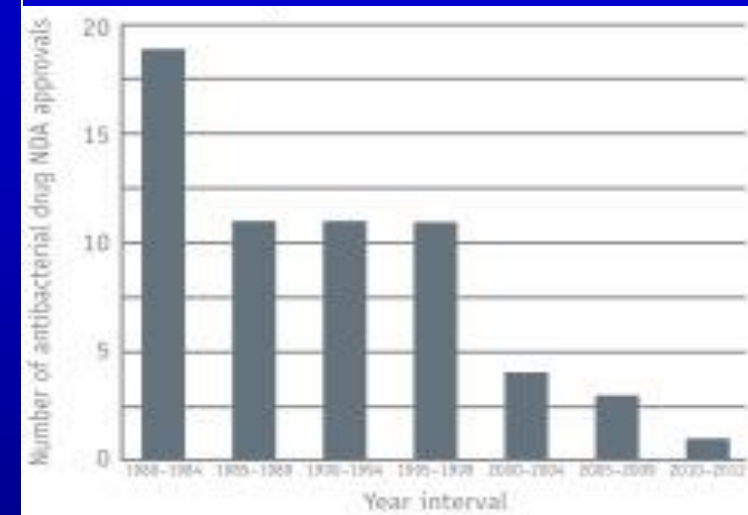
- Medical devices that fail
- Treating every patient the same
- Increasing costs
- Increasing patients
- Reactionary versus predictive
- And the list goes on...

What is the answer ?

What About Infection ?



Number of Antibacterial New Drug Application Approvals per Year



>2 million resistant infections/yr



Longer treatment durations



>23,000 deaths/yr



Undesirable side-effects



\$20 billion in excess direct healthcare costs



Immediate public health threat requiring **urgent** and **aggressive** action

20 Years Ago We Turned to Nanomedicine for Some Answers

Nanotechnology: The use of materials whose components exhibit significantly changed properties by gaining control of structures at the atomic, molecular, and supramolecular levels.

Nanomedicine: Applications of nanotechnology in medicine.

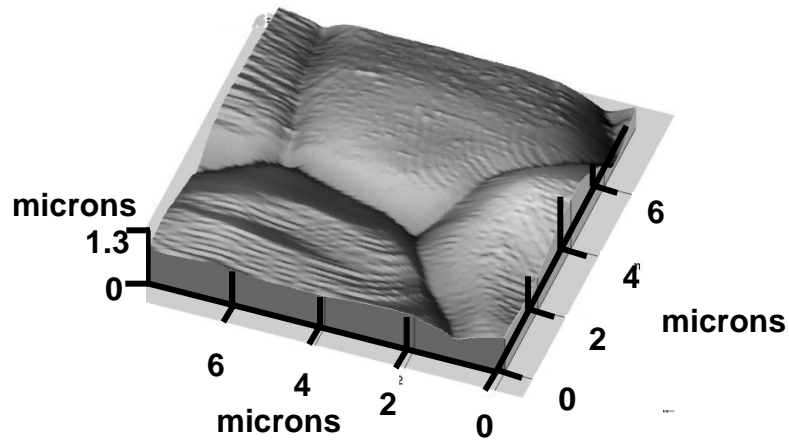
Why Use Nanotechnology In Medicine ?????

Nano-structured Medical Materials

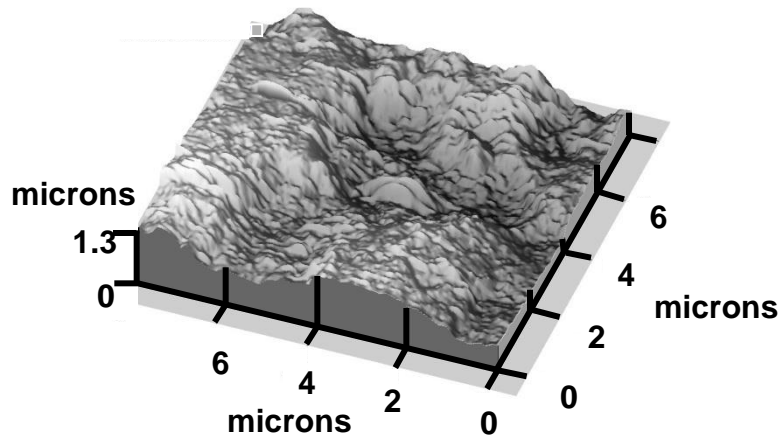
Compared to today's implant materials, nano-structured materials possess enhanced:

- surface area
- radio-opacity
- catalytic,
- optical,
- mechanical,
- electrical, and
- surface

properties that may improve existing biomedical implant applications.



Today's Implant

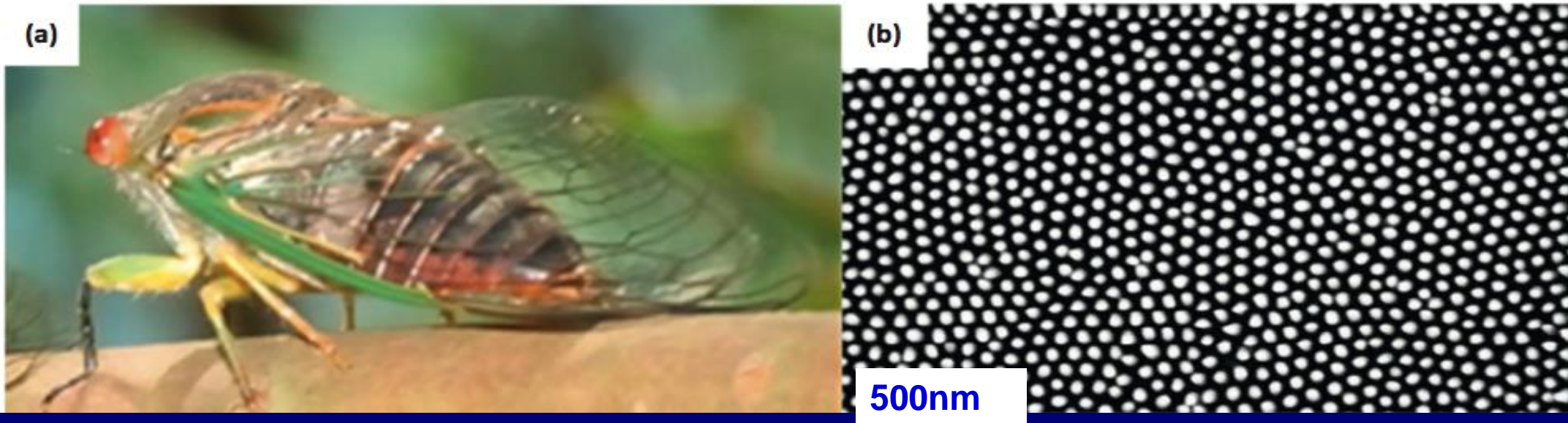


Nano-structured Implant

Nanostructures in Nature

It has been found that the nanopillars on cicada wings are inherently antibacterial, irrespective of surface chemistry (Ivanova et al., Small, 2012)

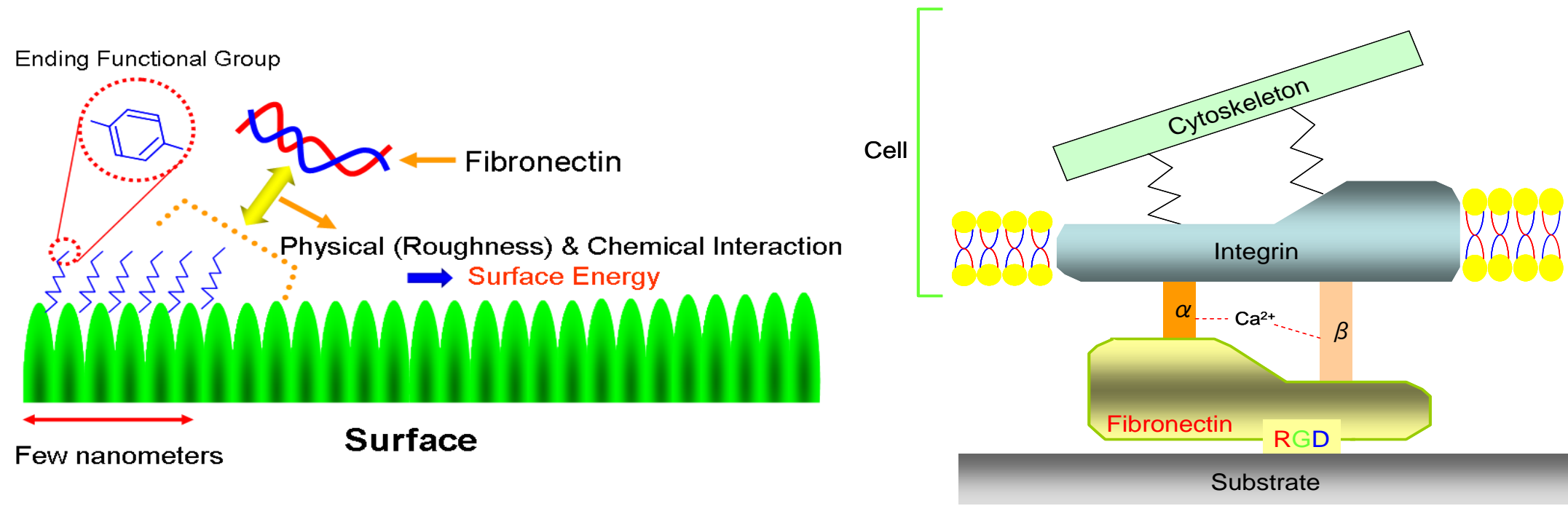
- Results show that the cicada wing surface appears to be bactericidal to *Pseudomonas aeruginosa*.



The nanopillar structures of the wing surfaces spaced 170nm apart from center to center. Each pillar was ~200nm tall, with a conical shape and a spherical cap 60nm in diameter.

The Cellular Micro and Nano-environment

Surface micro- and nano-scale topography, grain structure, chemistry, and substrate stiffness modulate cellular functions at the cell-substrate interface¹⁻⁶



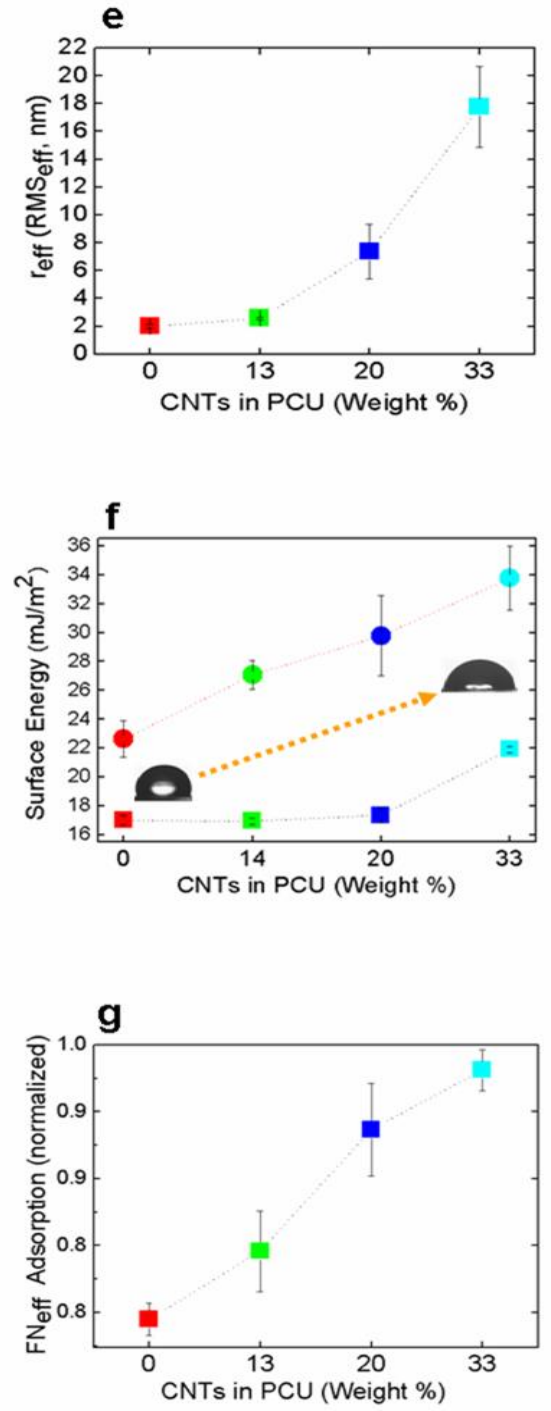
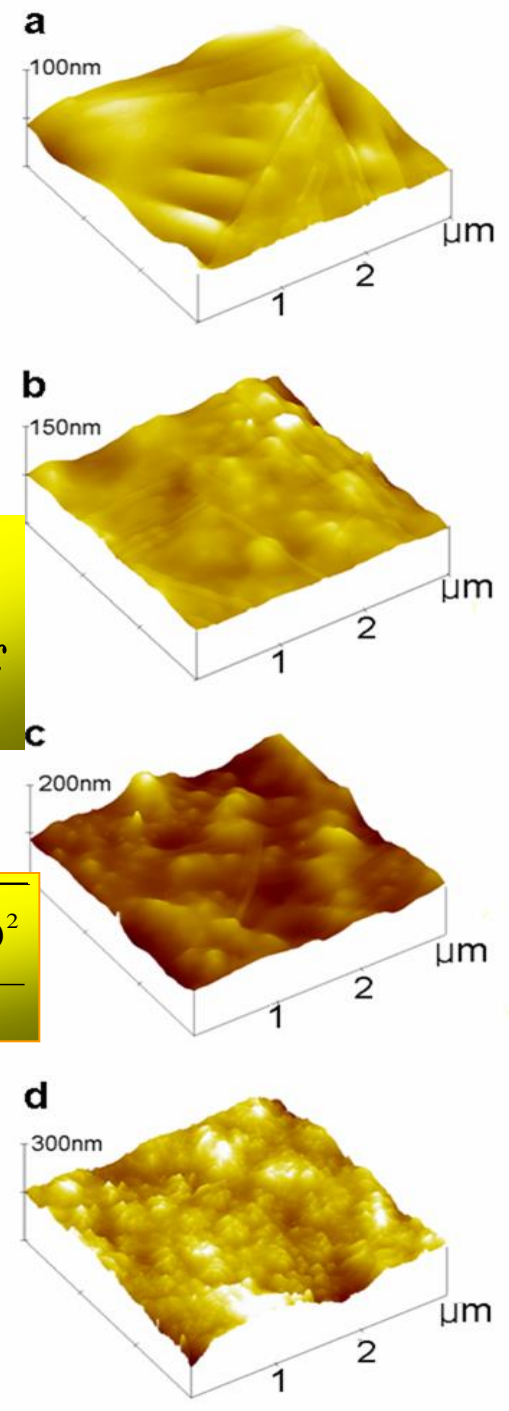
1. Webster, T. J. *et al.*, *Biomaterials* **21**, 1803–1810 (2000).
2. Nikkhah, M. *et al.*, *Biomaterials* **33**, 5230–5246 (2012).
3. Bagherifard, S. *et al.*, *ACS Appl Mater Interfaces* **6**, 7963–7985 (2014).
4. Guvendiren, M., Burdick, J. A., *Nat. Commun.* **3**, 792 (2012).
5. Dolatshahi-Pirouz, A. *et al.*, *ACS Nano* **4**, 2874–2882 (2010).
6. Dolatshahi-Pirouz, A. *et al.*, *J. Funct. Biomater.* **2**, 88–106 (2011).

Results

$$E_s(r_{eff}) = E_{0,s} + \rho r_{eff}$$



$$r_{eff} = \frac{S_{unit}}{S_{measured}} \cdot \sqrt{\frac{\sum_{i=1}^N (Z_{i,filtered} - Z_{ave,filtered})^2}{N}}$$



We can increase nanoscale roughness and not change chemistry to control protein adsorption

and the FDA likes this !

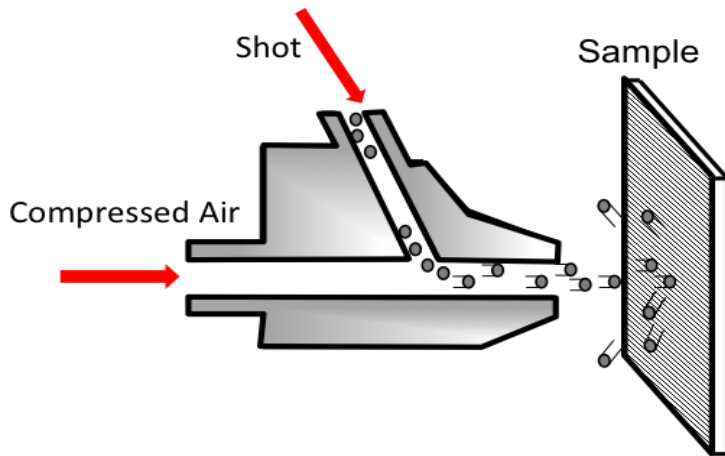
Challenge #1: We need to establish more quantitative models to predict material-protein interactions that control cell behavior.

**Challenge #2: Do not give up on
“old” materials, there are ways
to modify them to get “new” and
quick FDA approval**

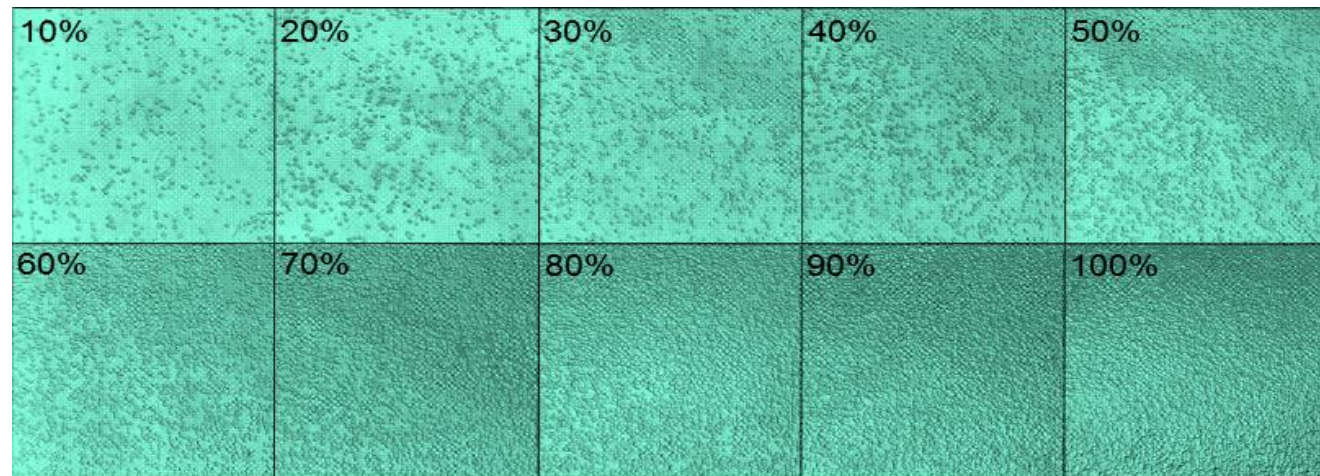
**The following are projects which
have all received FDA approval
with significant help from
start-up companies.....**

**(Starting with an approach that changes in both
surface roughness and grain size)**

Surface Modification Technique: Shot Peening

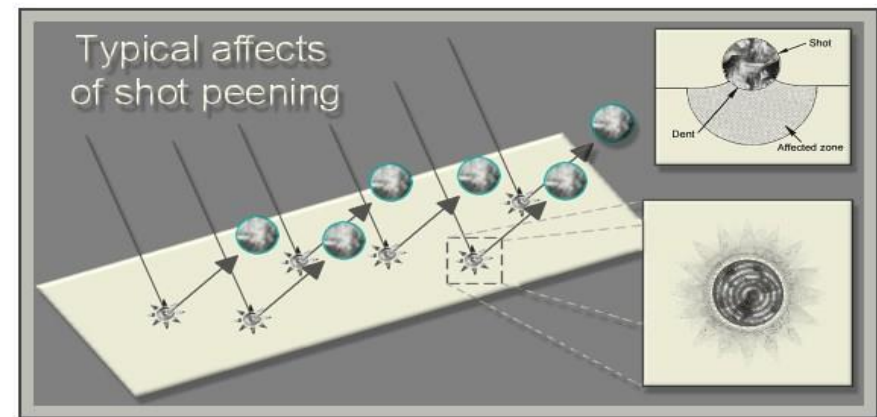


Surface coverage: is defined as the ratio of the area covered by plastic indentation to the whole treated surface area.



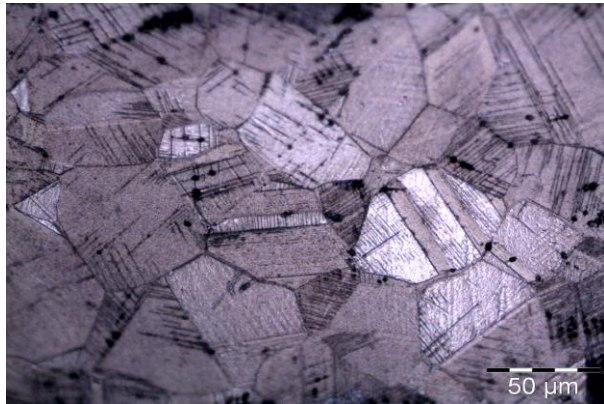
Shot peening effects:

- Residual stress
- Microstructural changes to the material
 - Dislocation density increase
 - Grain distortion
 - Phase change
- Surface roughness

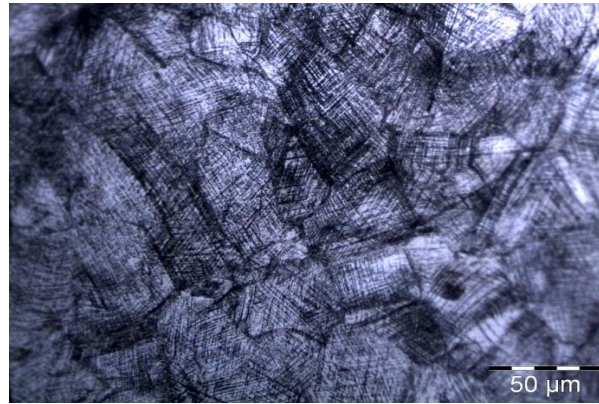


Grain Size Refinement

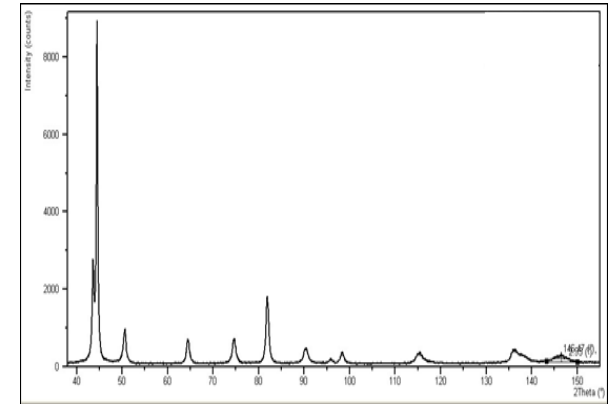
Grain sizes decreased with increasing shot peening treatment



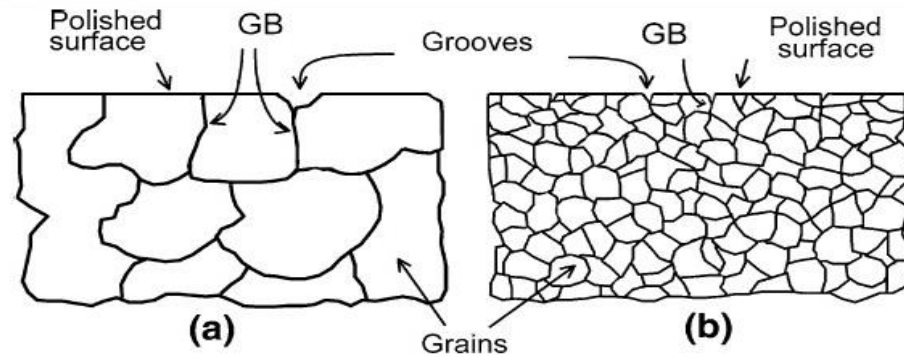
Average grain size 63 ± 5 (μm)



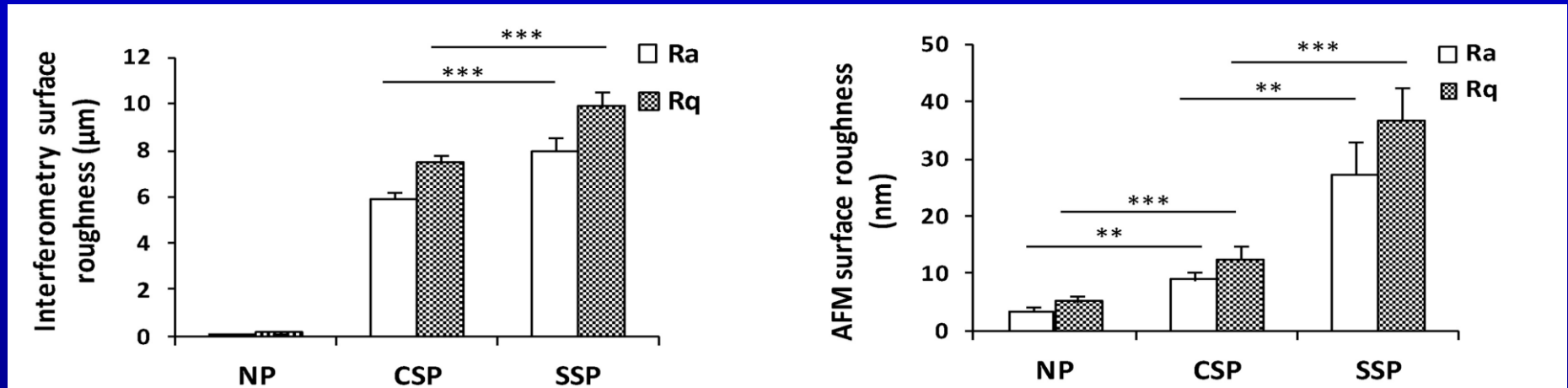
44 ± 4 (μm)



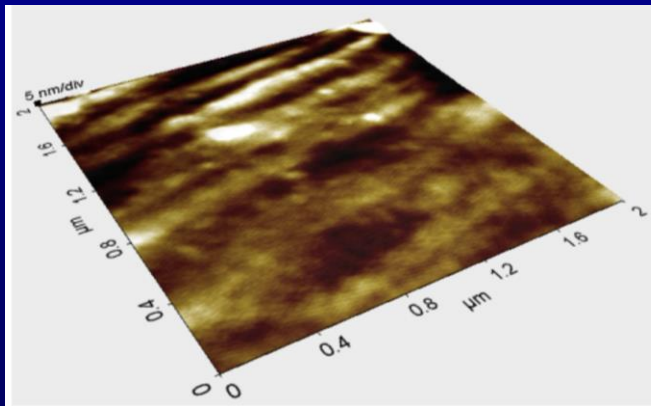
25 ± 5 (nm)



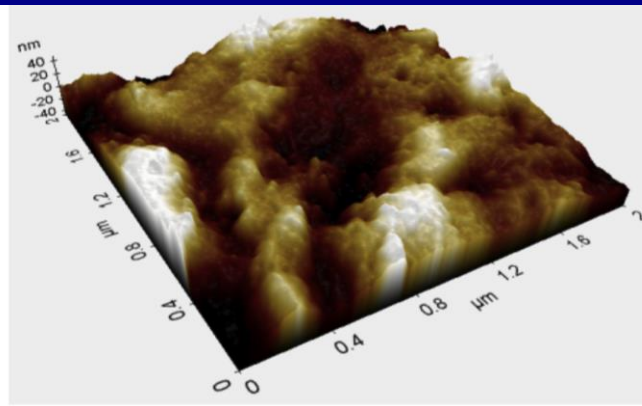
Stainless Steel: Increased Surface Roughness



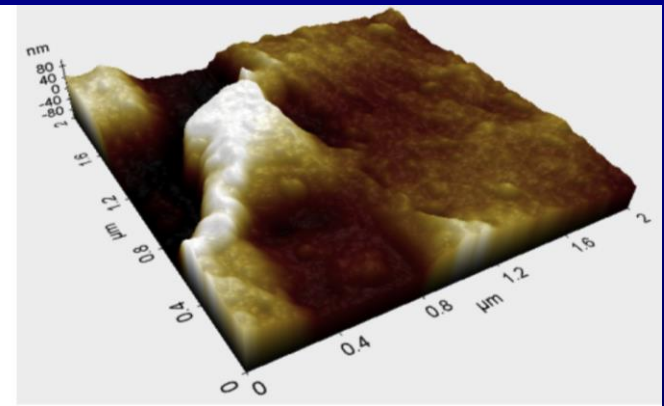
Ra = arithmetic mean, Rq = root mean square (rms) surface roughness
Data is mean ± St. Dev.; N=3, **p<0.05, ***p<0.005



NP



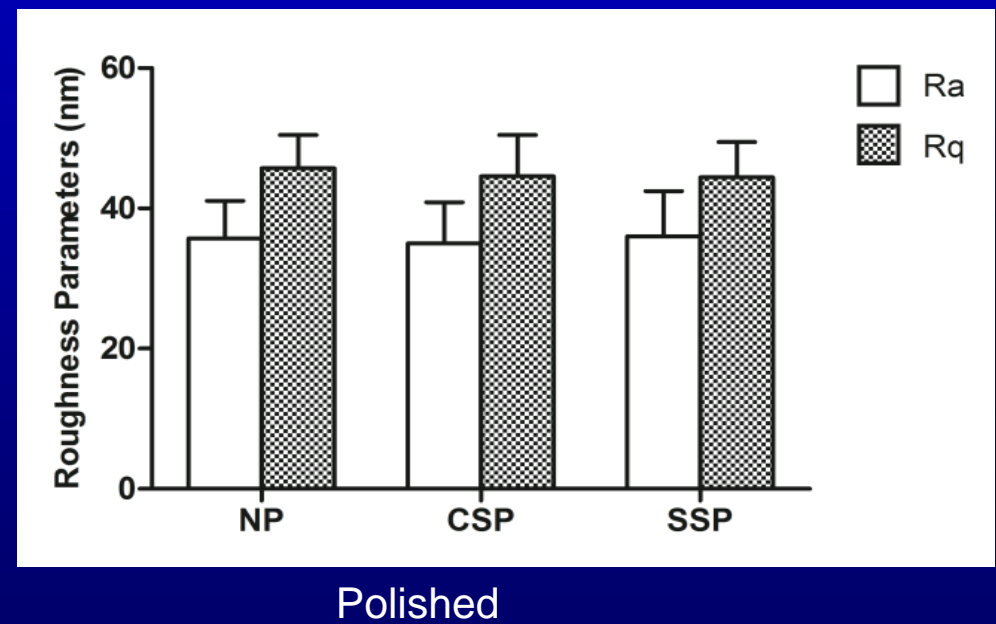
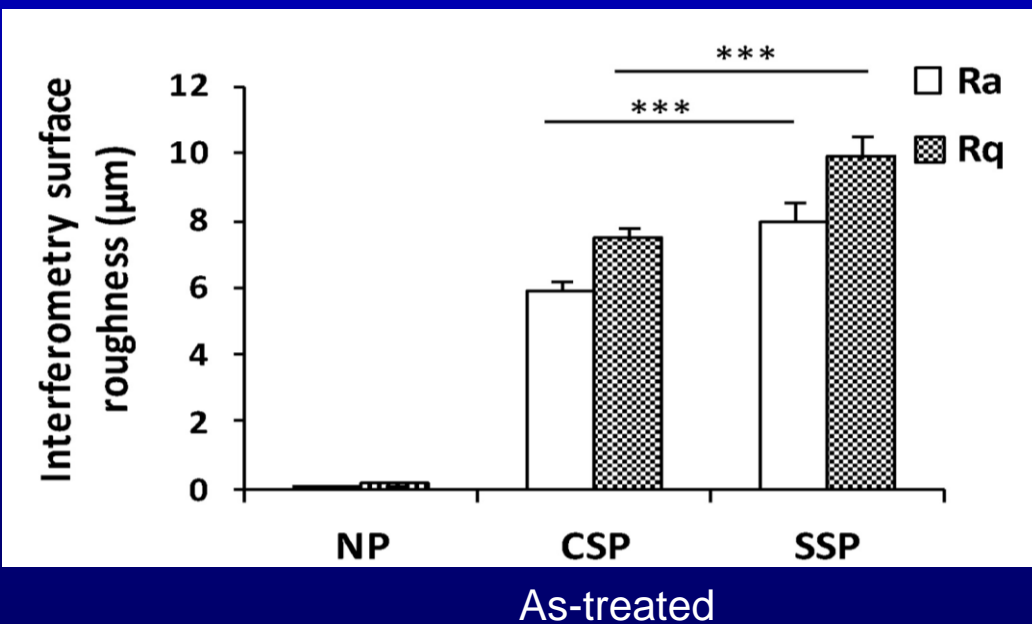
CSP



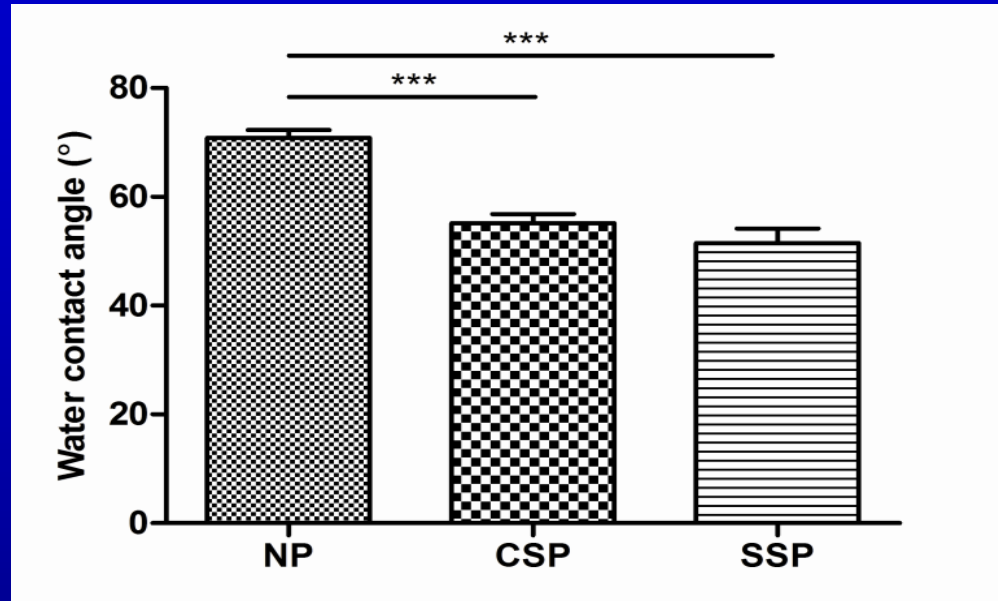
SSP

Stainless Steel: Separating Surface Roughness from Grain Size

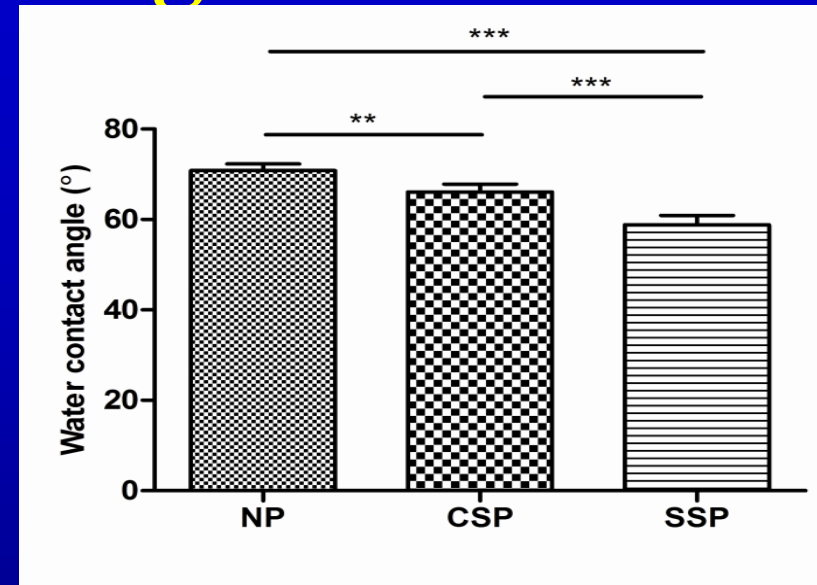
At this point, half of the samples (both treated and as-received) were ground and polished to obtain identical surface roughness for all samples.



Stainless Steel: Decreased Water Contact Angles

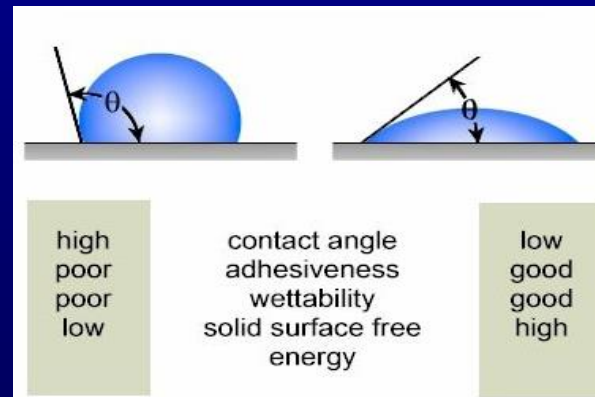


As-treated



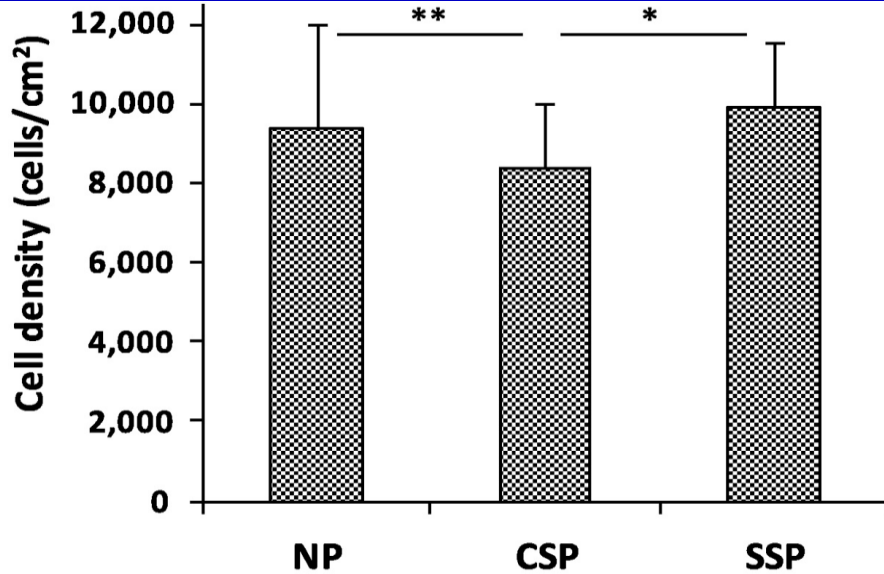
Polished

Data is mean \pm St. Dev.; N=3, **p<0.05, ***p<0.005

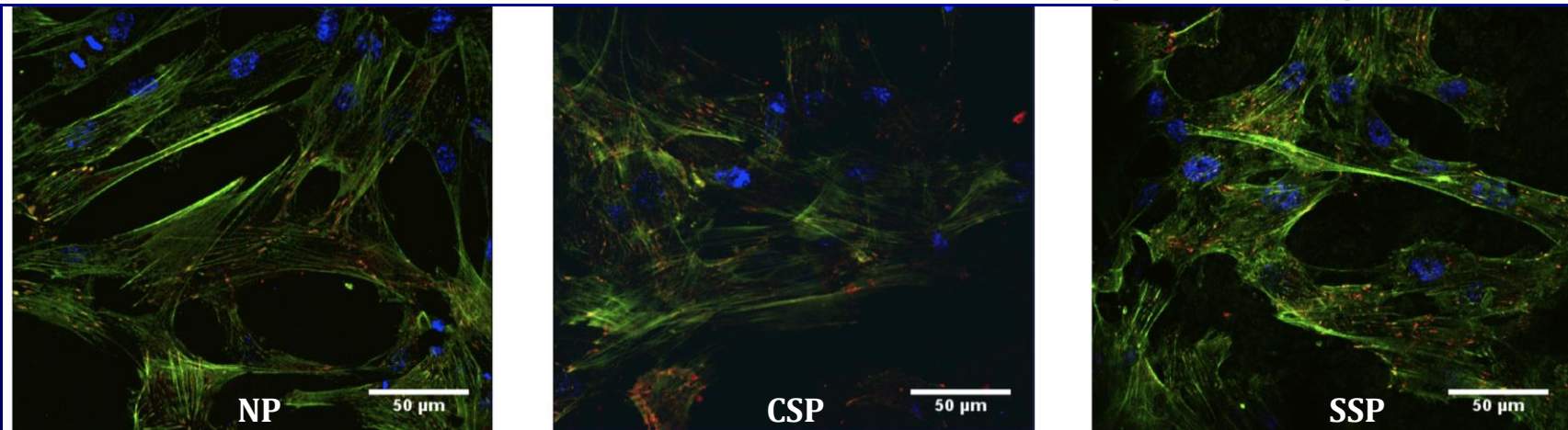
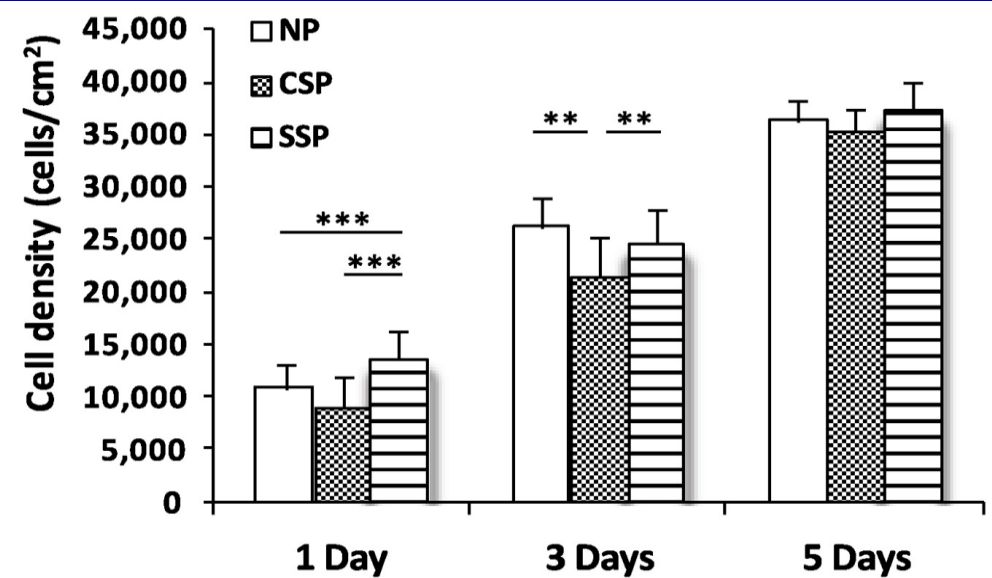


Adhesion and Proliferation of Osteoblasts on Non-Polished Samples

Osteoblast adhesion: 4 hours



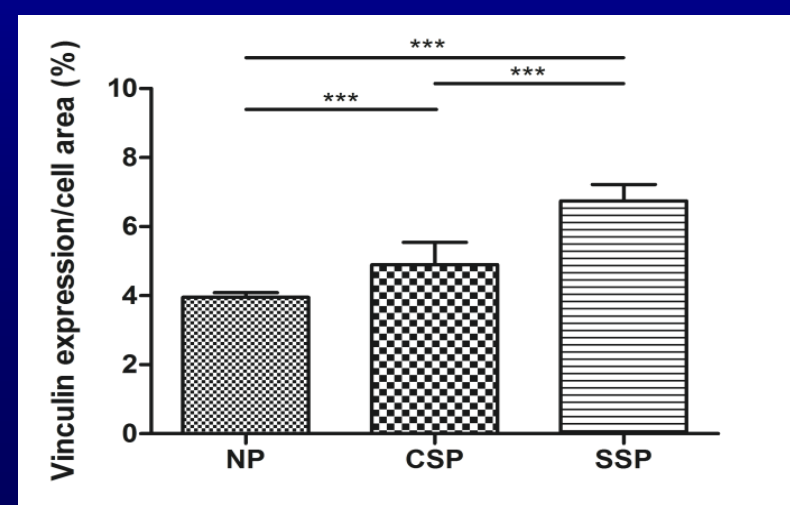
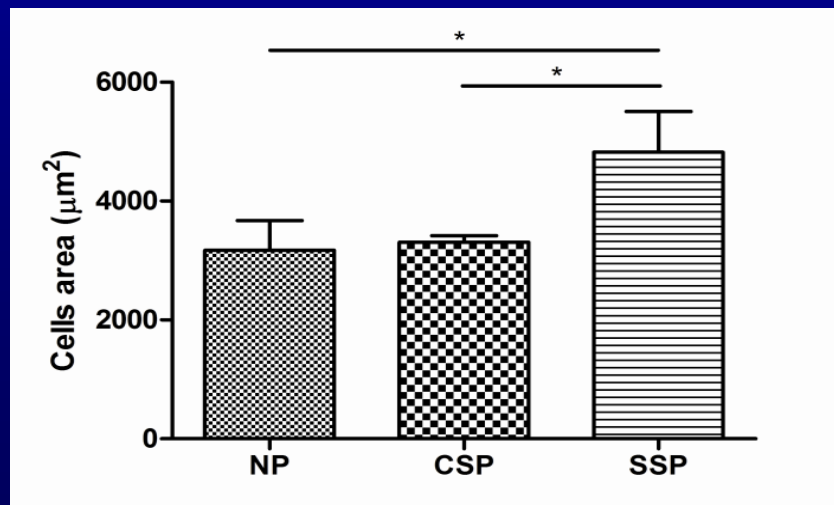
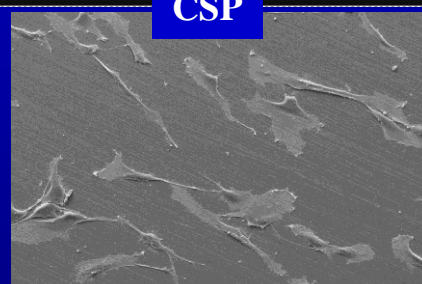
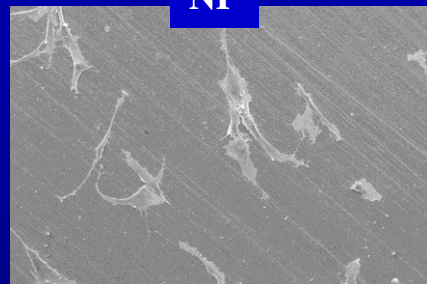
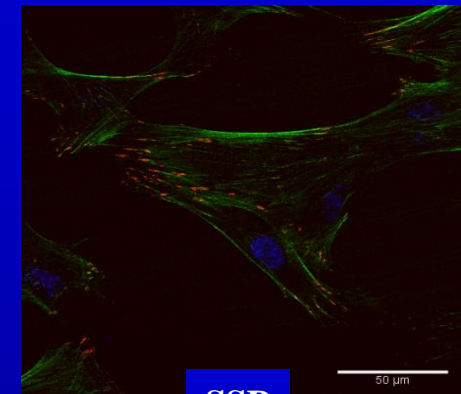
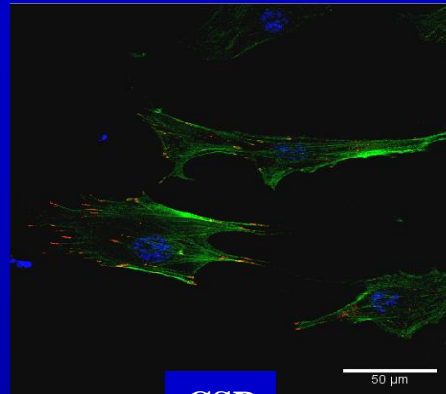
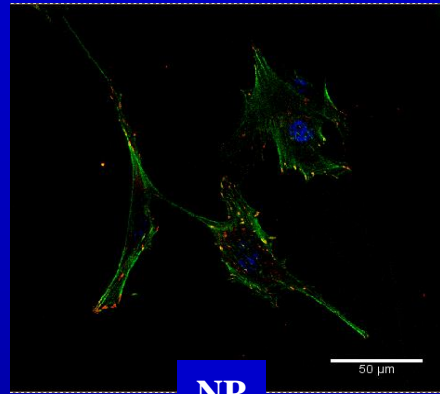
Osteoblast proliferation



Data is mean \pm St. Dev.; N=3, **p<0.05, ***p<0.005

Osteoblasts on as-treated samples after 3 days. Cytoskeleton, vinculin focal adhesions, nuclei

Osteoblast Morphology and Spreading on Polished Samples (1 Day)



Data is mean ± St. Dev.; N=3,
*p<0.05
***p<0.001

**So both nanoscale surface
features and nanoscale grain
sizes increase osteoblast
functions, but what about
bacteria ?**

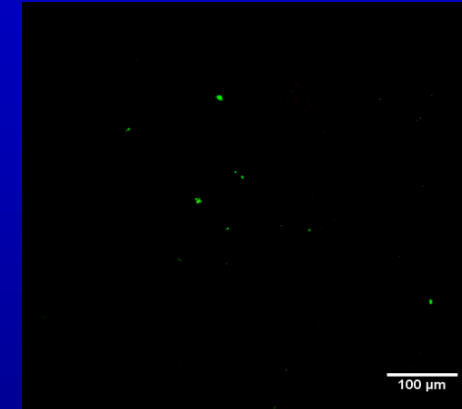
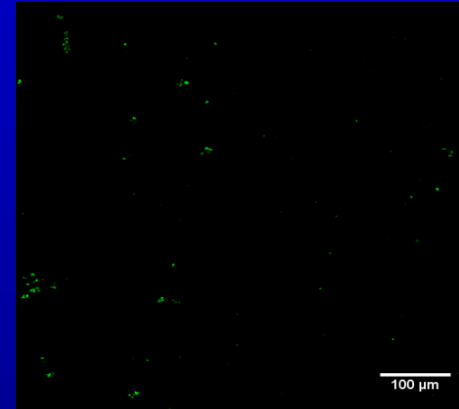
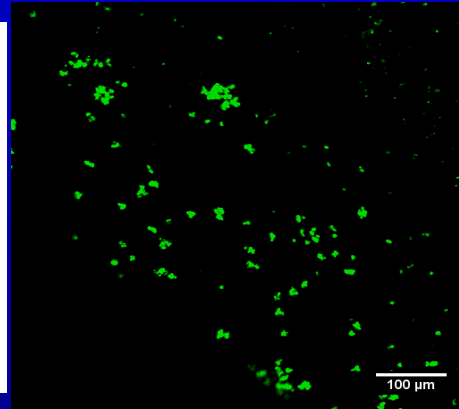
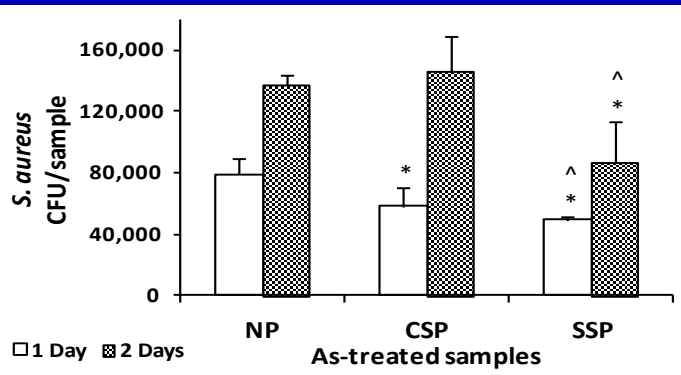
No, only nanoscale surface features. An example, *Staphylococcus aureus*

As-treated

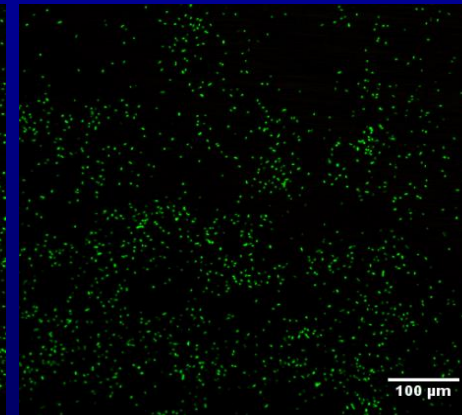
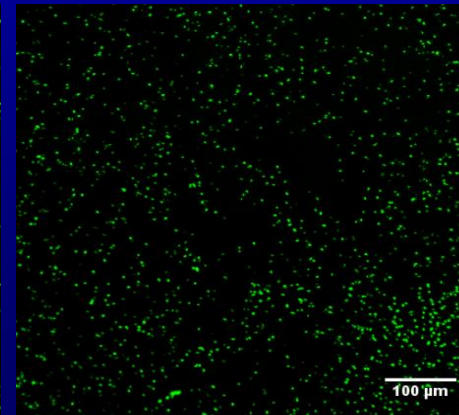
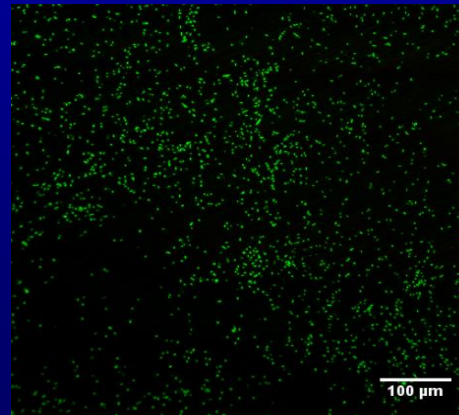
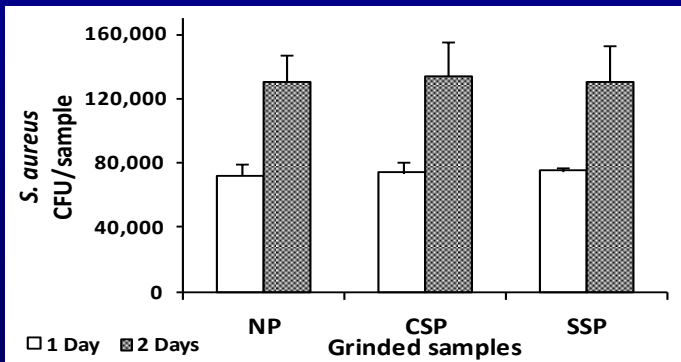
NP

CSP

SSP



Polished



N=3; Data is mean +/- St. Dev.;

*p<0.01 compared to NP at the same time point;

^p<0.01 compared to CSP at the same time point

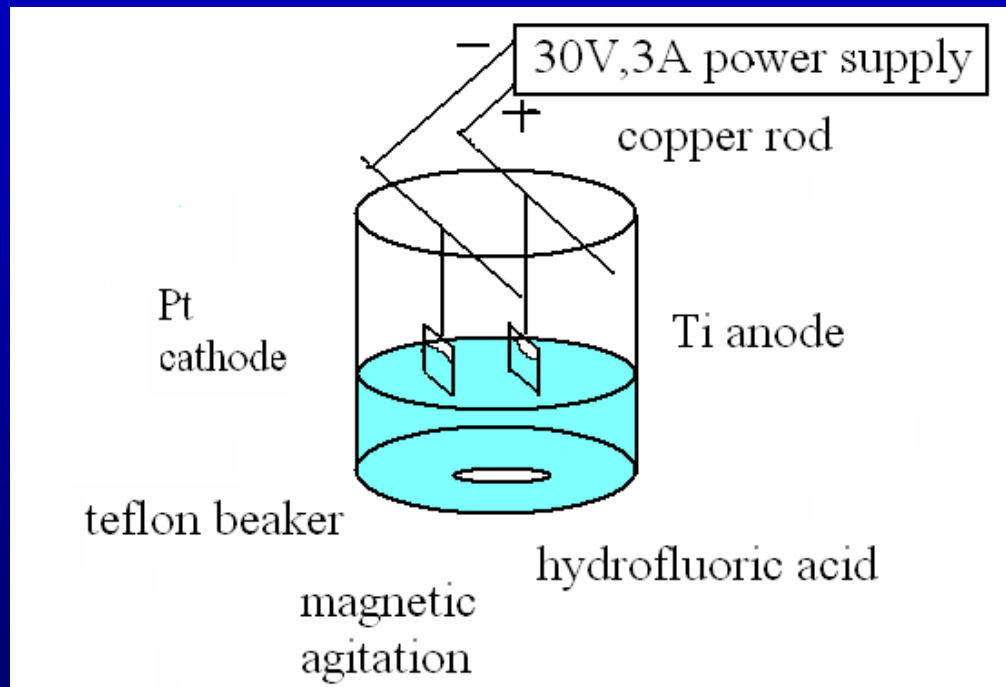
Challenge #3: We need a better understanding of how *individual material properties* influence mammalian and bacteria functions.

**The following are projects which
have all received FDA approval
with significant help from
start-up companies.....**

**(Now materials that change in only
surface roughness)**

Commercialized by Nanovis, LLC

Anodized Titanium



Sketch map of anodization system

PROCEDURES:

Pretreatment: chemical polishing using HF/HNO₃ mixture

Anodization: 0.5 or 1.5%HF

Voltage: 20V

Time: 20 min

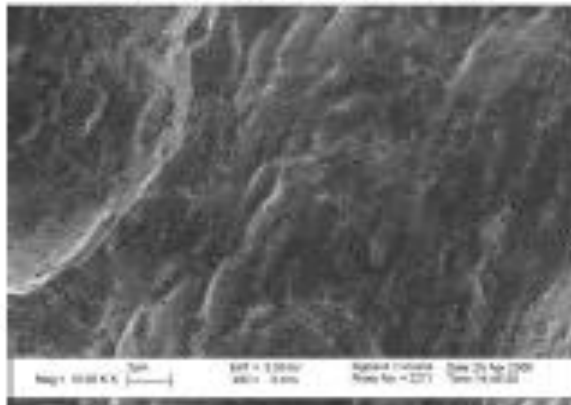
Rinse and dry

Clean: acetone and ethanol

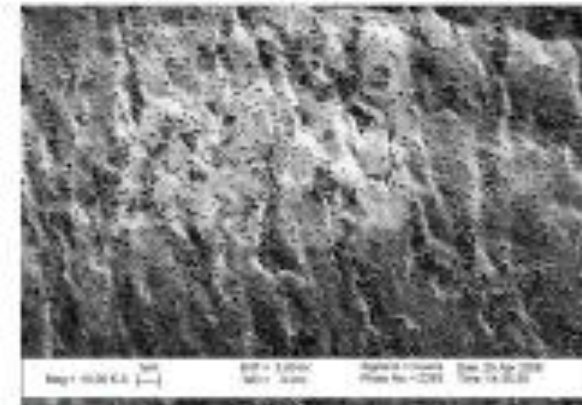
Sterilize

Anodized Ti Nanotubular Screws

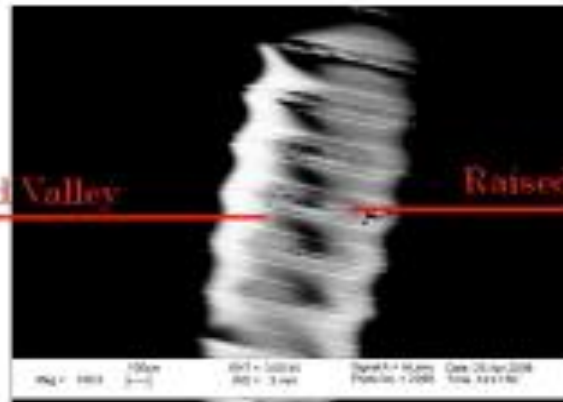
Low Magnification (10K)



Low Magnification (10K)

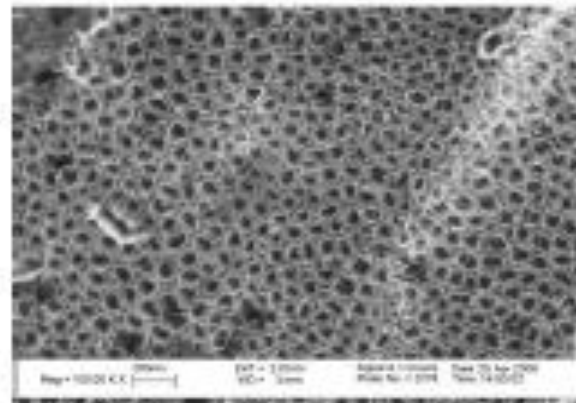


Nanotubular Pin

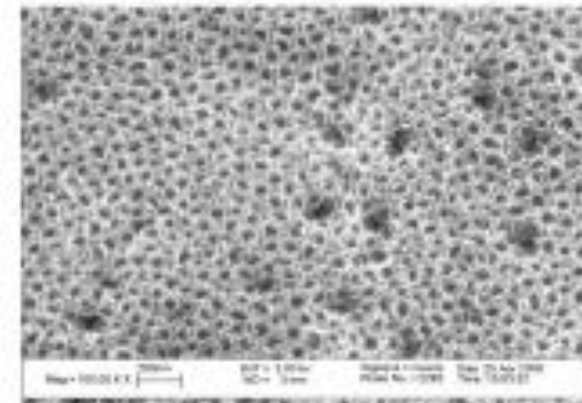


Grooved Valley ← → Raised Peak

Anodization



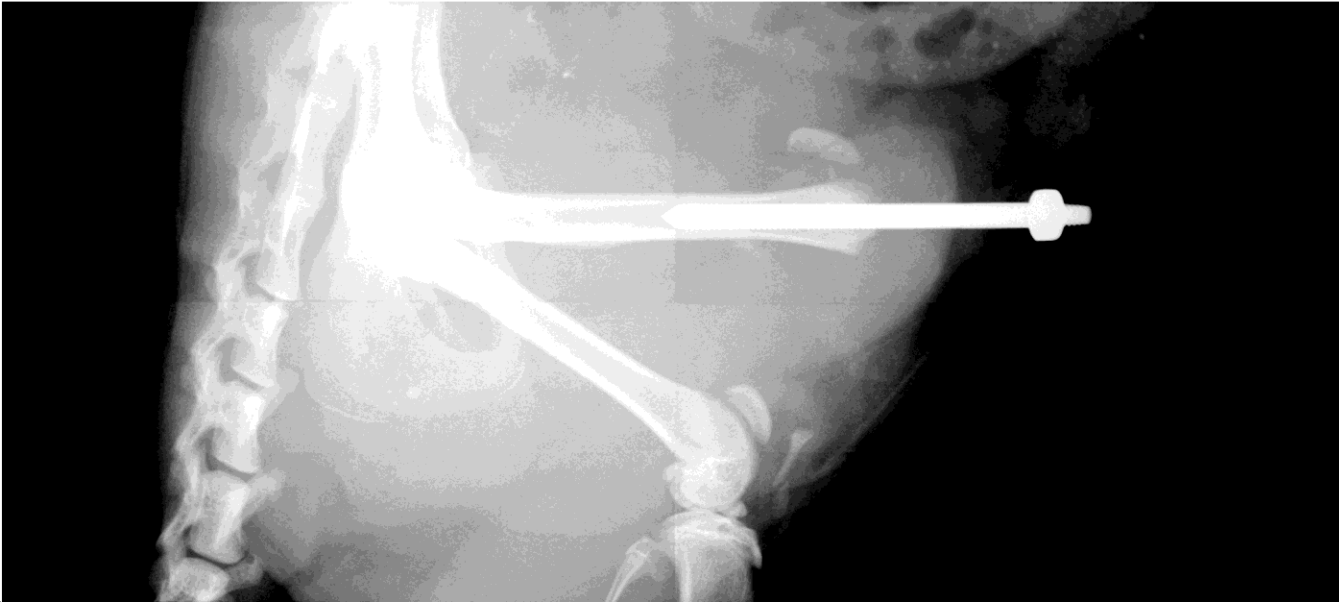
High Magnification (100K)



High Magnification (100K)

Anodized Titanium Amputee Rat Model

[PatientID]: J14, [Access#]: 052908_D7_4035, [Name]: PHASE_1, TCOID, [Gender]: , [Time]: 2008/05/29 12:27:07
[File]: I20080529122707, [StudyID]: , [Study]: , [Proc]: , [Position]:
[Physician]: , [TechID]: , [Tech]: , [Station]: FAXITRON, [Institution]:

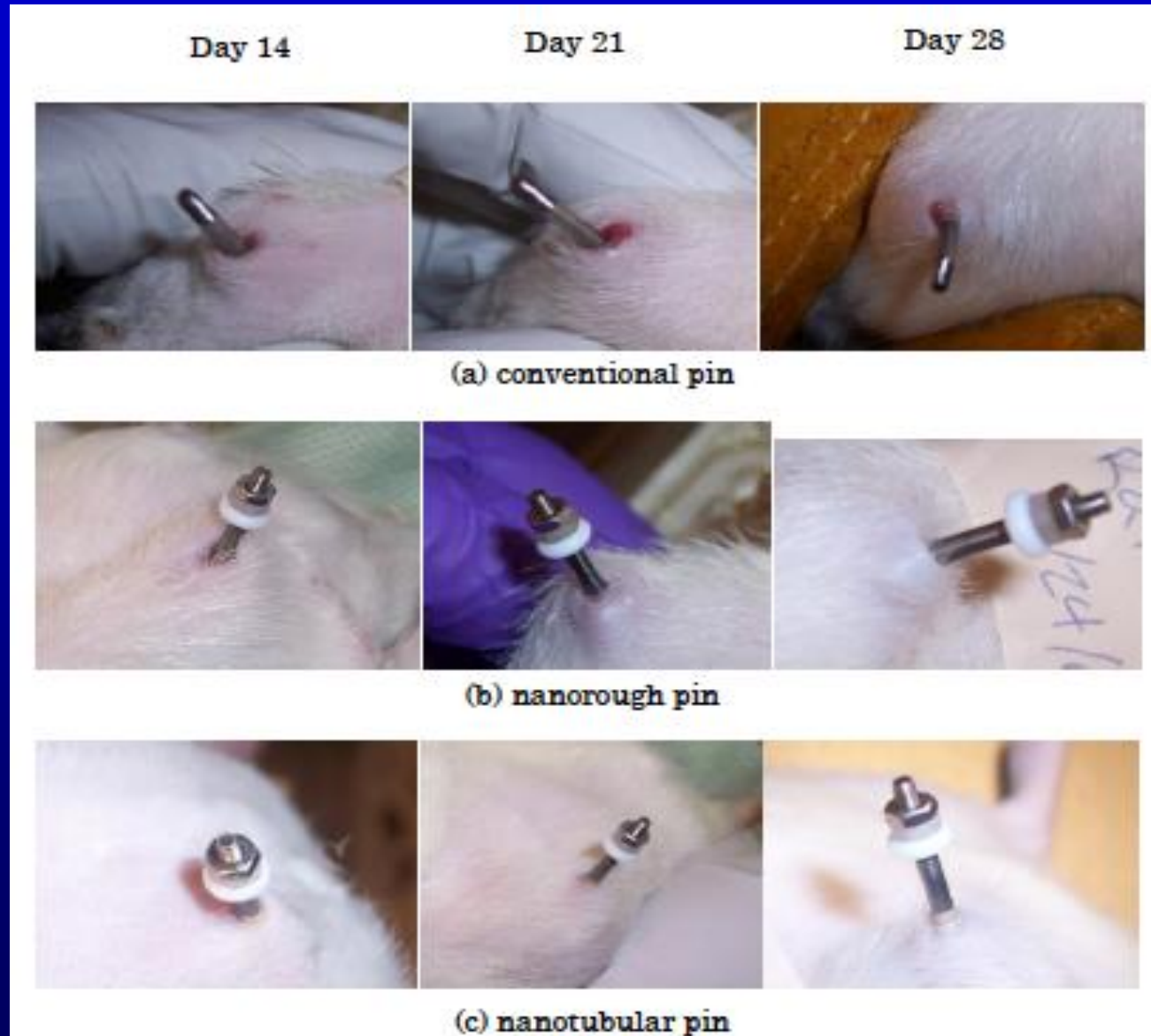


Ti Screw Insertion

Closed Wound with No Infection Surrounding Nanotextured Screws Only

Nanovis, LLC

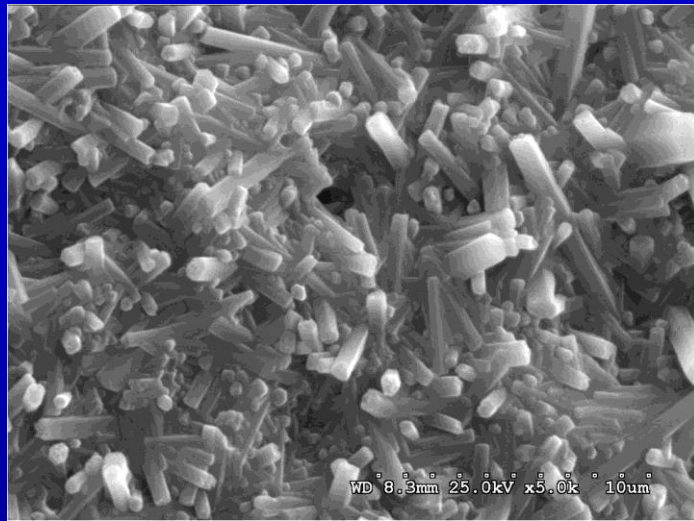
is now commercializing
this as a pedical screw



**Challenge #4: We have an
infection problem.**

**We need more biomaterial
approaches that (without
antibiotics) can inhibit bacteria
functions but not kill
mammalian cells.**

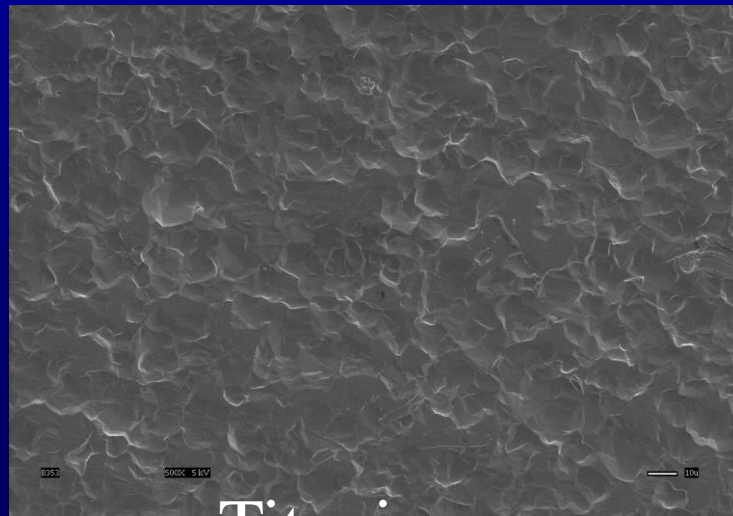
Commercialized by Amedica: Nanostructured Silicon Nitride



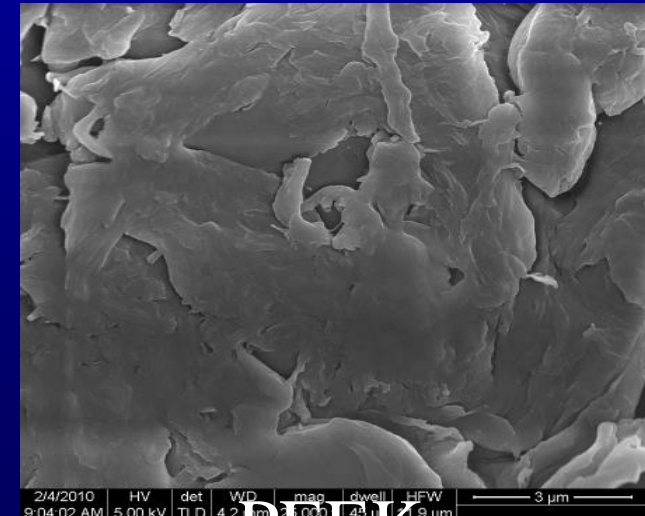
Nanorough Silicon Nitride



Smooth Silicon Nitride



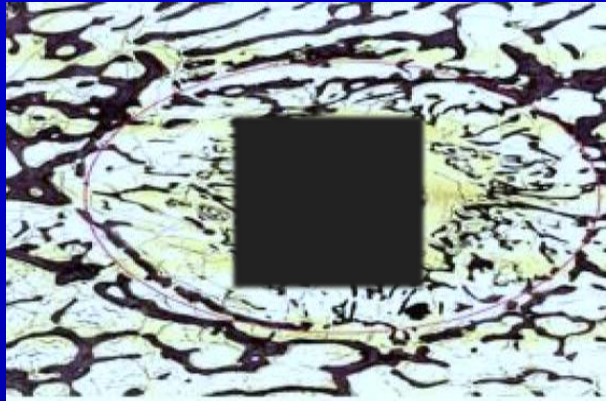
Titanium



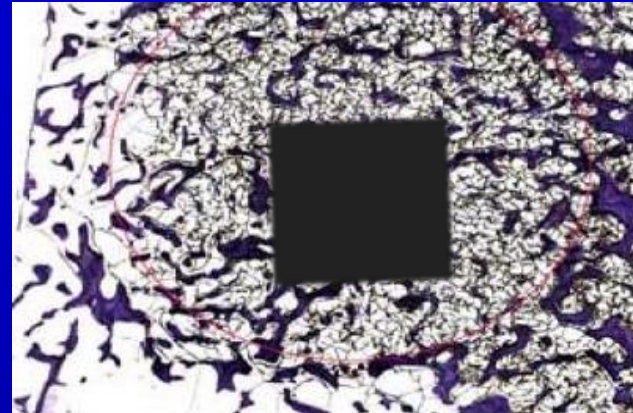
PEEK

Silicon Nitride: 3 Months (bacteria inoculation)

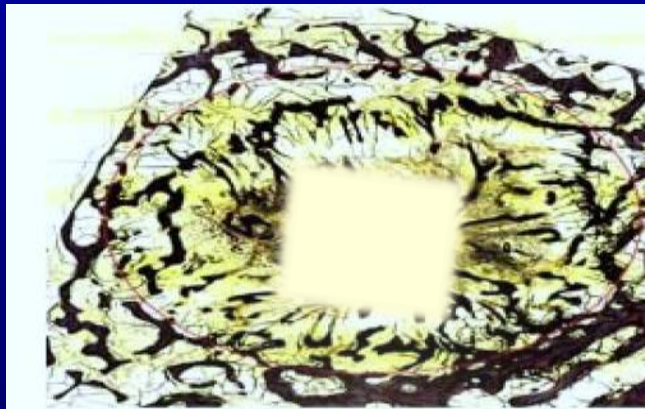
Rat calvaria
model



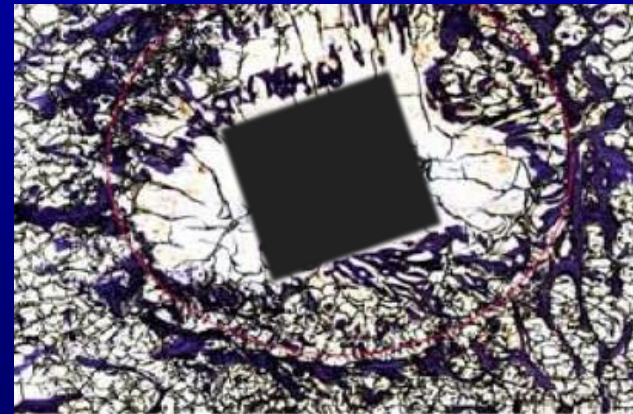
Titanium –
9% bone-implant interface
67% bacteria-implant interface
26% of new bone growth in surgical area
21% of bacteria growth in surgical area



Silicon Nitride (nano-rough) –
41% bone-implant interface
0% bacteria-implant interface
42% of new bone growth in surgical area
0% of bacteria growth in surgical area



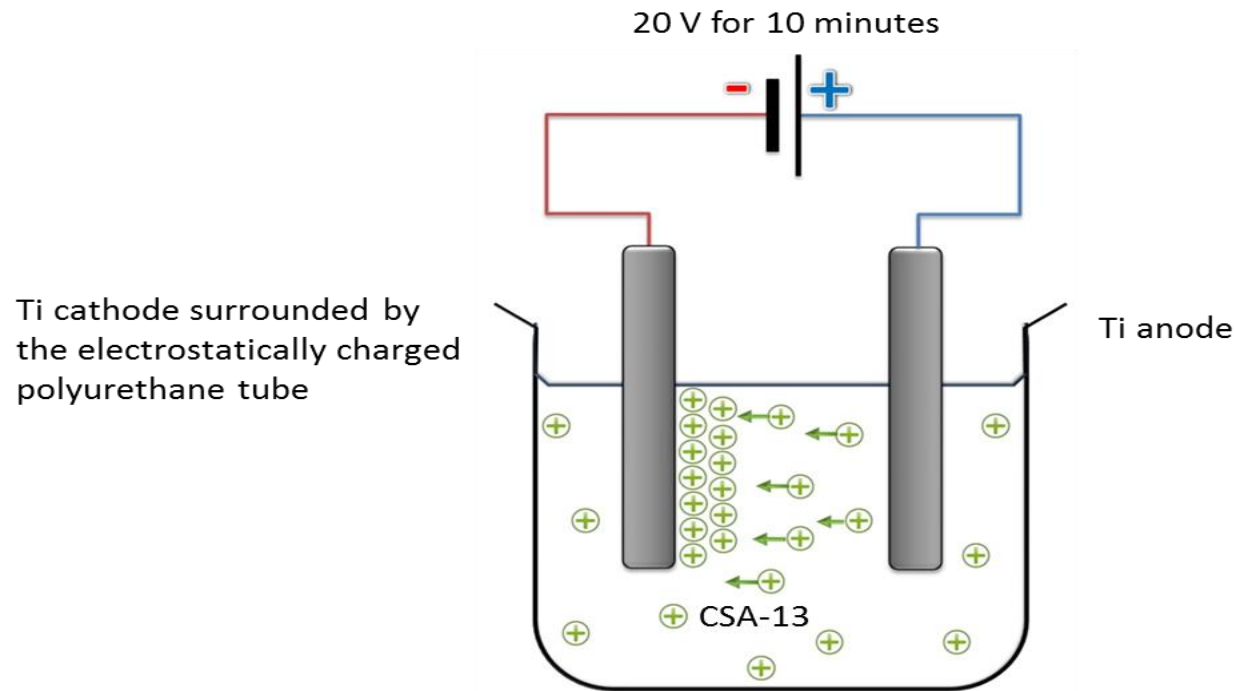
PEEK –
5% bone-implant interface
95% bacteria-implant interface
21% of new bone growth in surgical area
88% of bacteria growth in surgical area



Silicon Nitride (smooth) –
15% bone-implant interface
10% bacteria-implant interface
29% of new bone growth in surgical area
10% of bacteria growth in surgical area

Commercialized by Tyber Medical: Nanostructured Orthopedic Coatings

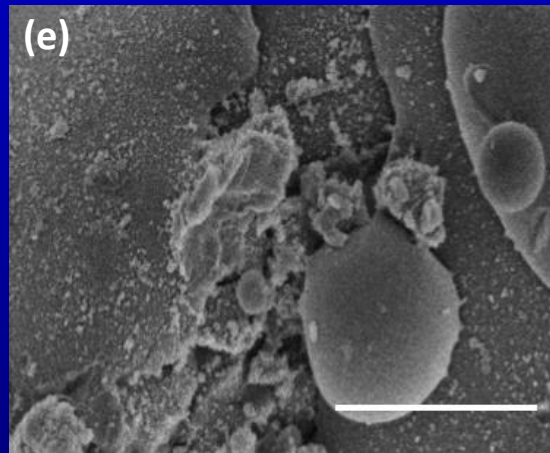
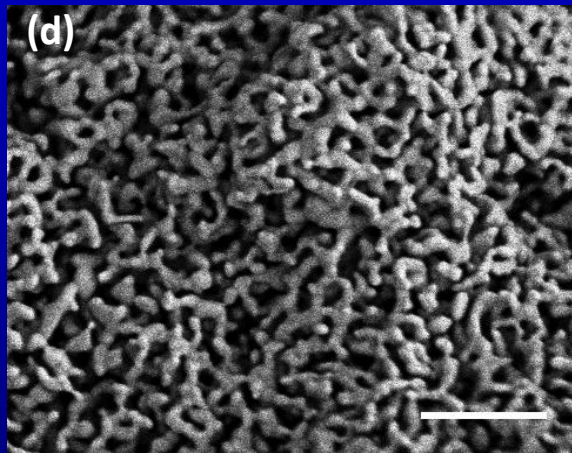
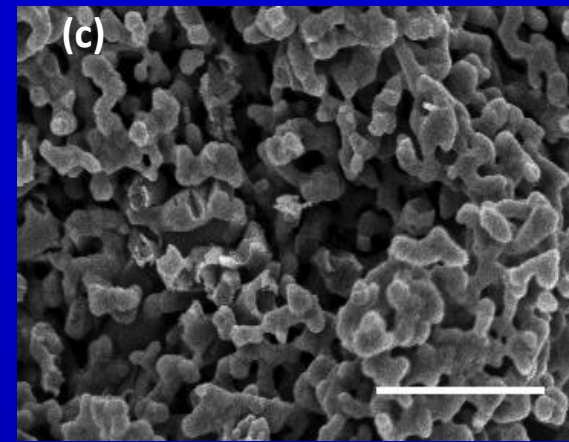
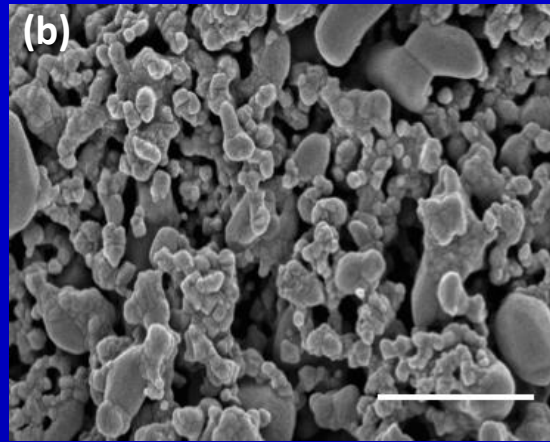
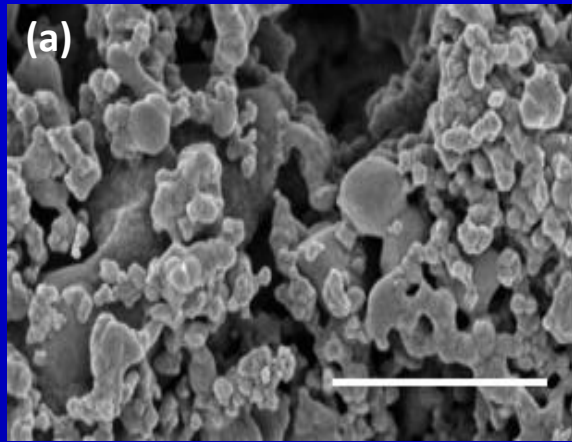
Electrophoretic deposition



Previous studies
have shown an
ability to
promote bone
growth

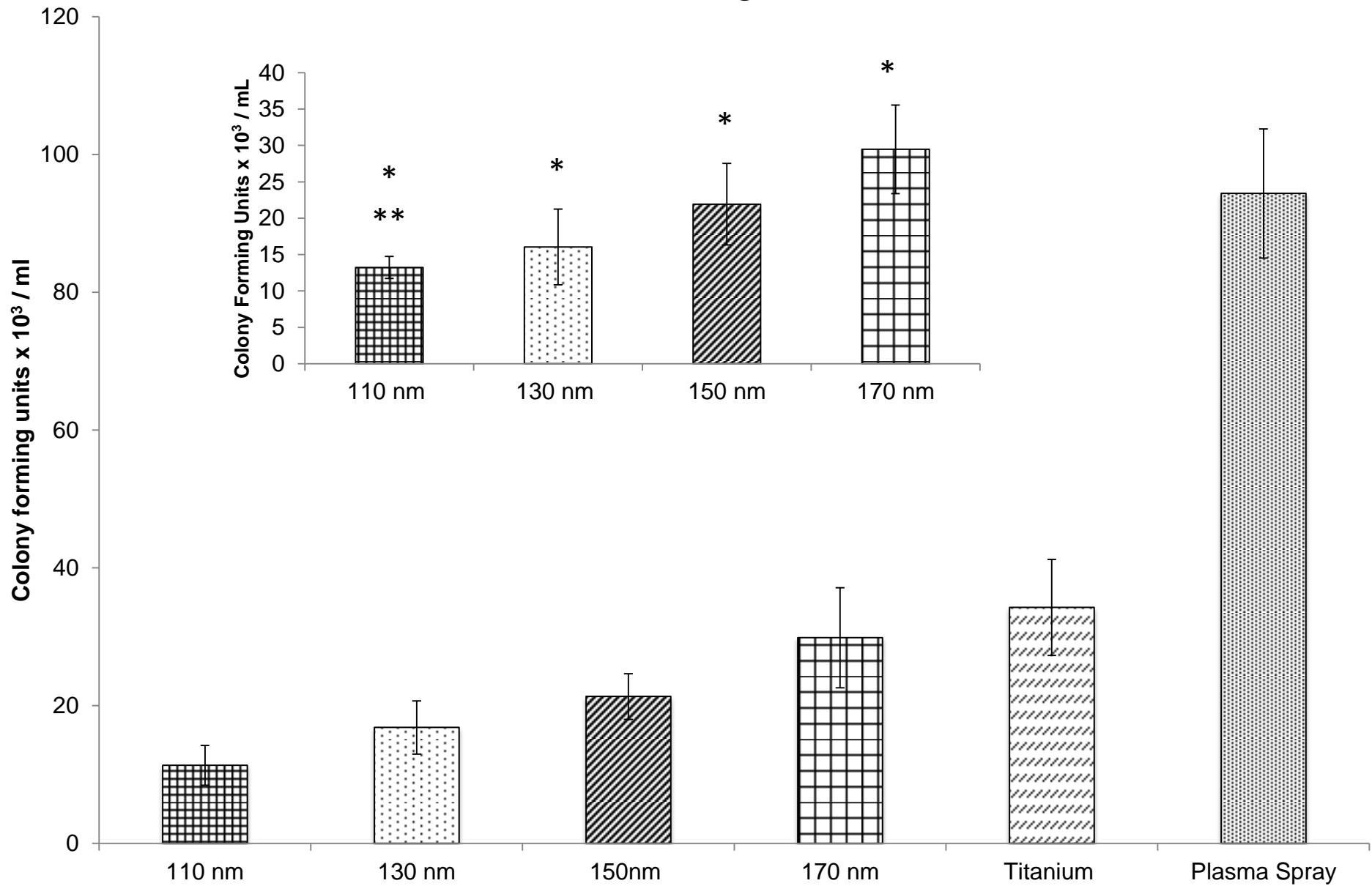
Advantages of the EPD process:

- Bioactivity of the protein is maintained.
- Uniform coating is achieved.
- Time and cost efficient.



SEM images of the Ti surfaces coated with (a) 170 nm, (b) 150 nm, (c) 130 nm, (d) 110 nm hydroxyapatite powders, (e) plasma sprayed micron sized hydroxyapatite onto Ti and (f) plain Ti. Scale bar: 1 micrometer

P. aeruginosa

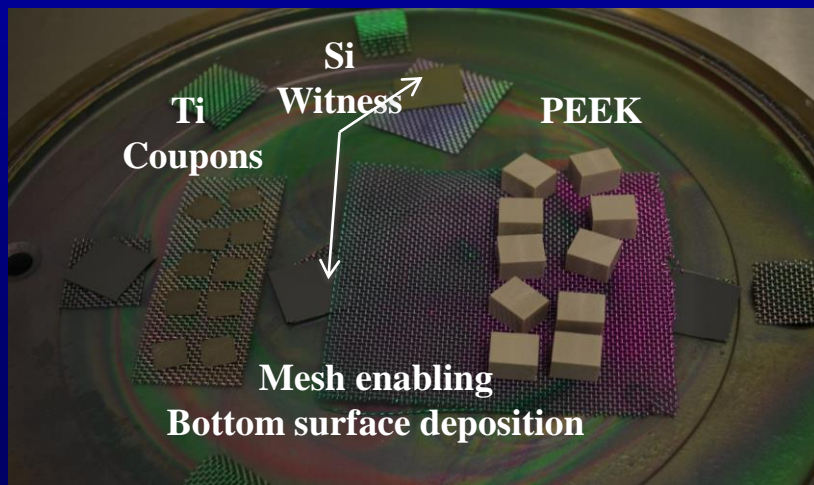


* P<0.01 compared with Ti (control); ** P<0.01 compared with plasma-sprayed-deposited hydroxyapatite on Ti

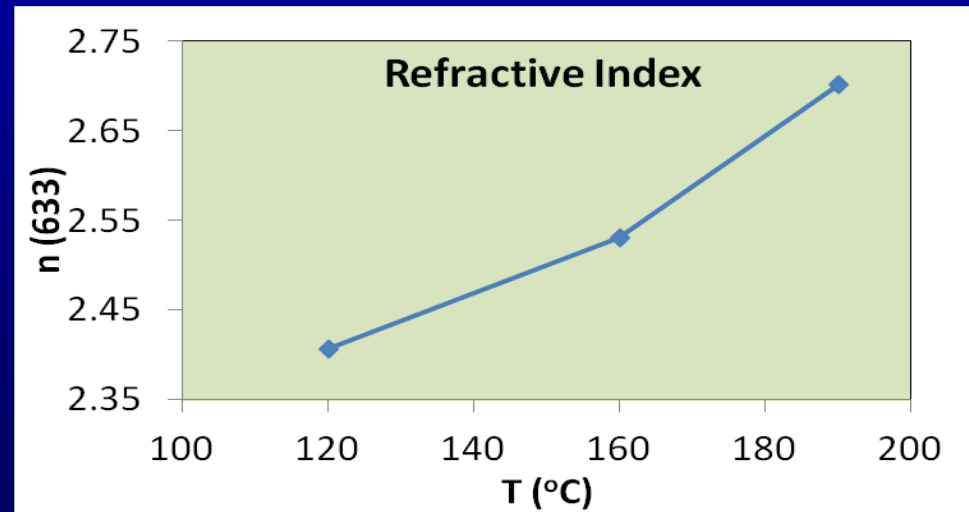
Applications in progress.....

Atomic Layer Deposition

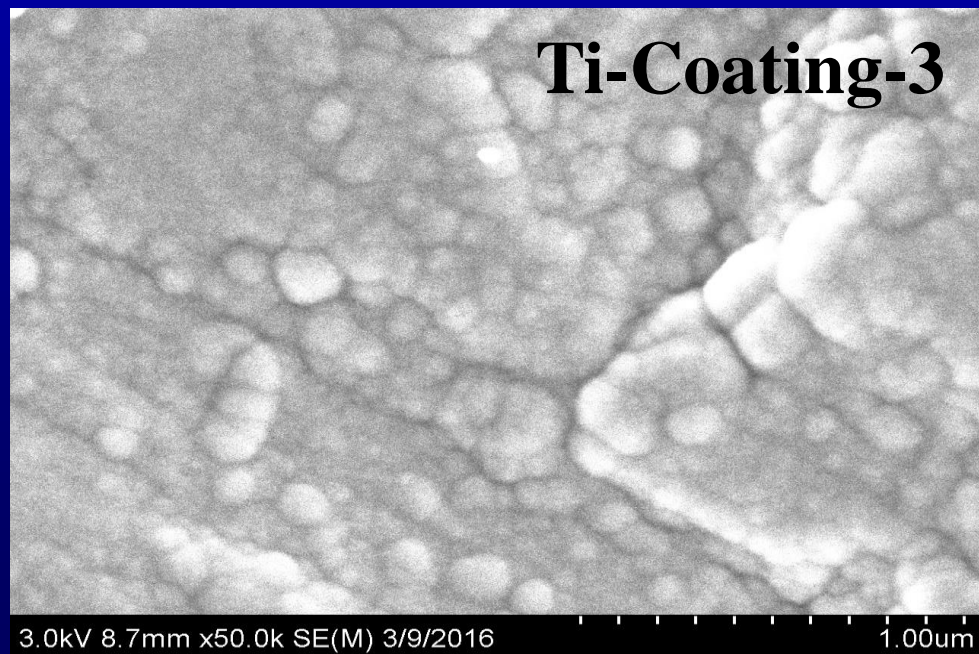
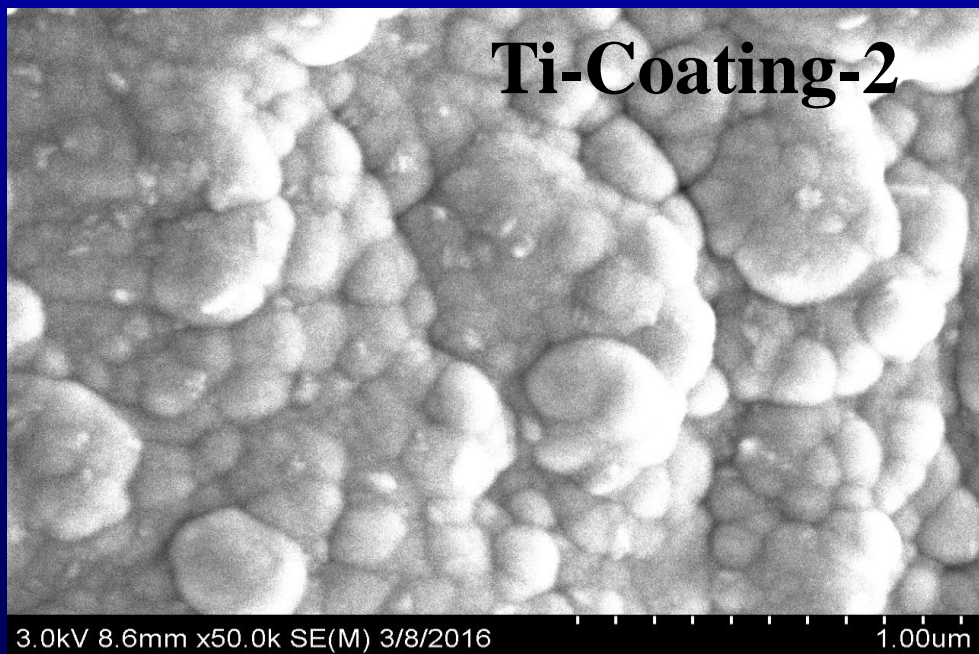
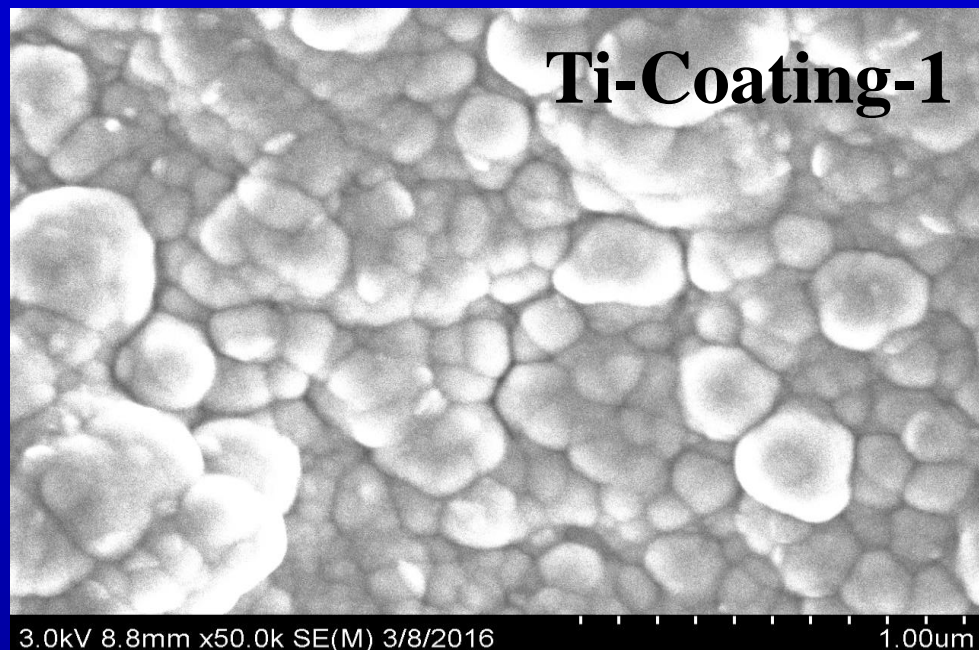
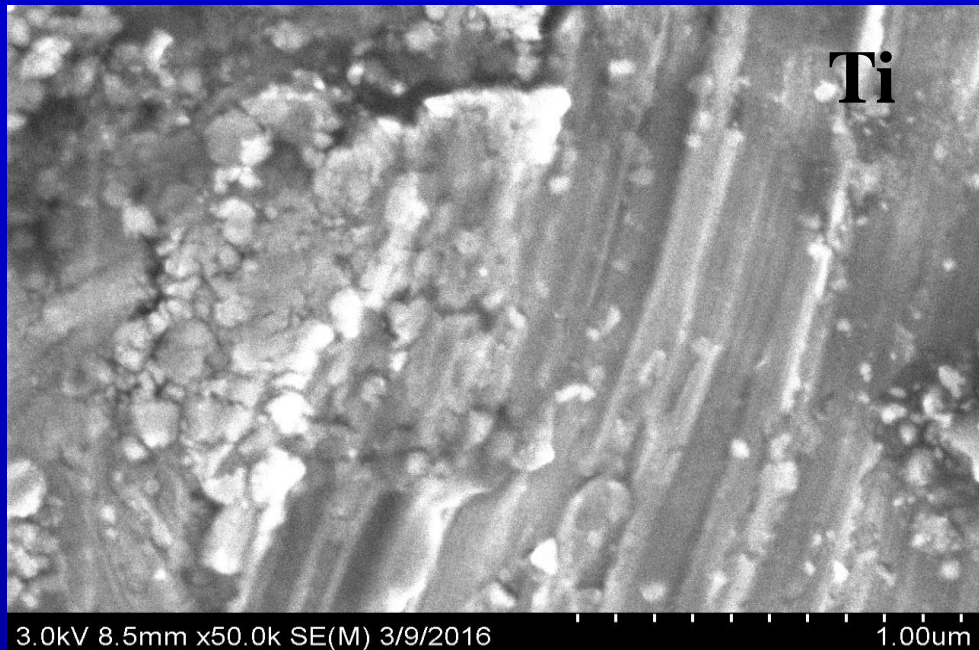
- ALD TiO_2 at 190°C, 160°C, 120°C, 100nm thick
 - Crystallinity is temperature dependent: Amorphous < 140°C, degree of crystallinity (anatase) increasing with temperature
 - Morphology is temperature dependent
 - T_g of PEEK is 143°C – adhesion of ALD film to PEEK is likely to be affected by temperature relative to T_g
 - Thick (~ 100nm) film allows development of crystal structure
 - Thicker film is also important for wear oriented applications



After Deposition

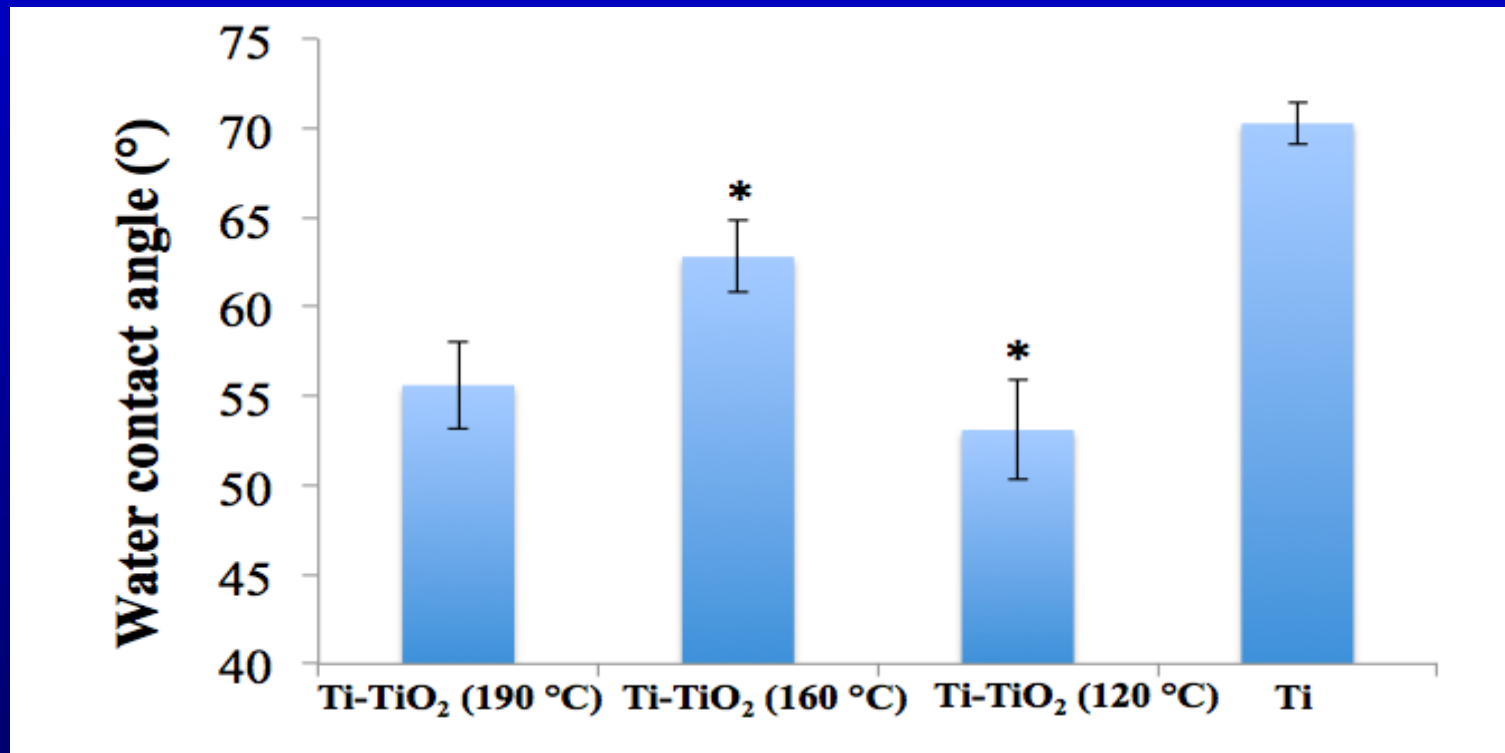


Strong dependence on temperature indicating densification/high crystallinity at higher temperature



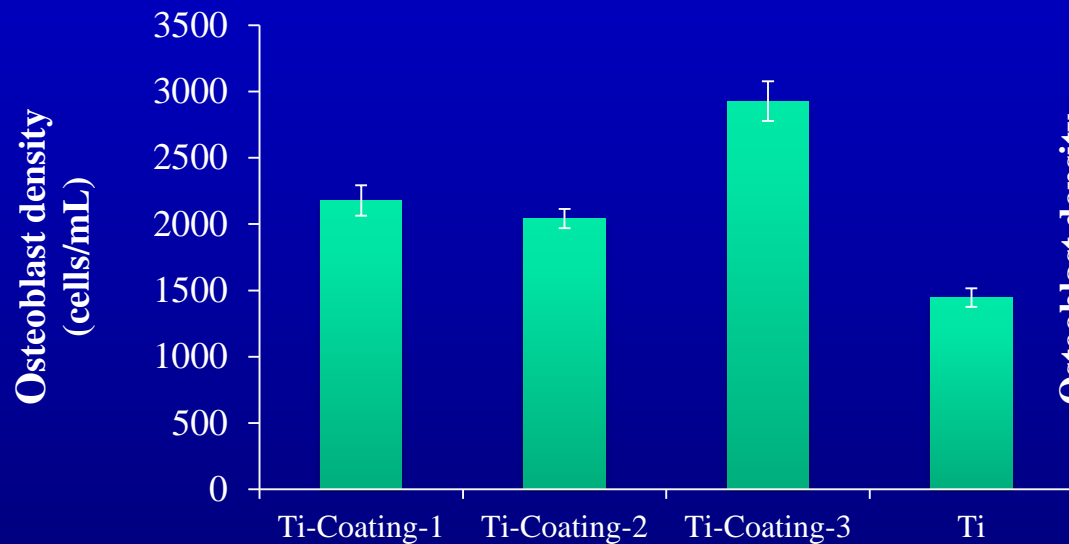
Water Contact Angle Analysis

→ More hydrophilic surface upon coating with TiO_2
This will change protein adsorption and cell responses

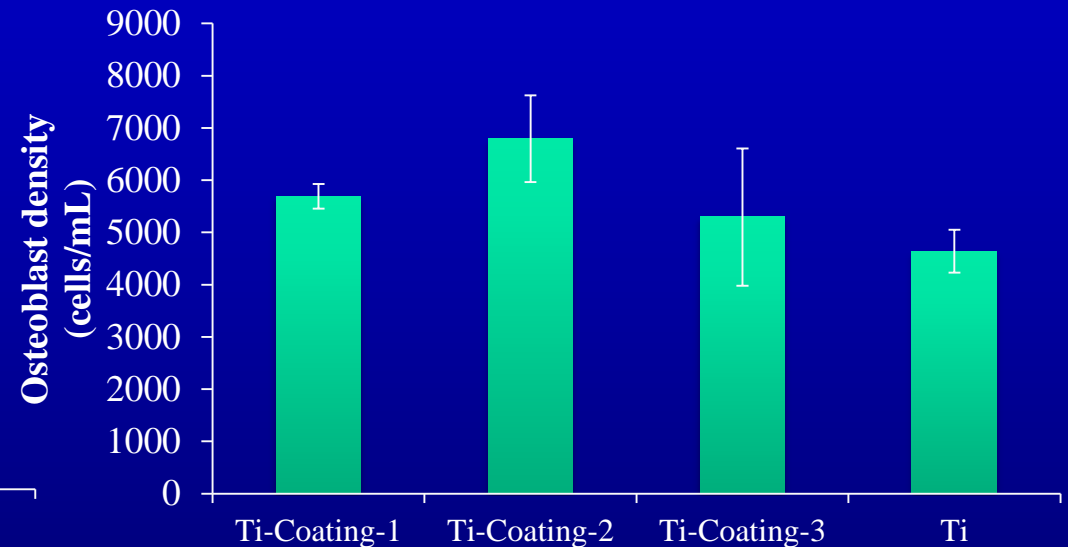


Water contact angle test for Ti samples with different TiO_2 coatings, N=3. Data represents mean \pm SD. * $p < 0.05$ compared with Ti control.

Osteoblast density increases on Ti samples coated with Ti using ALD

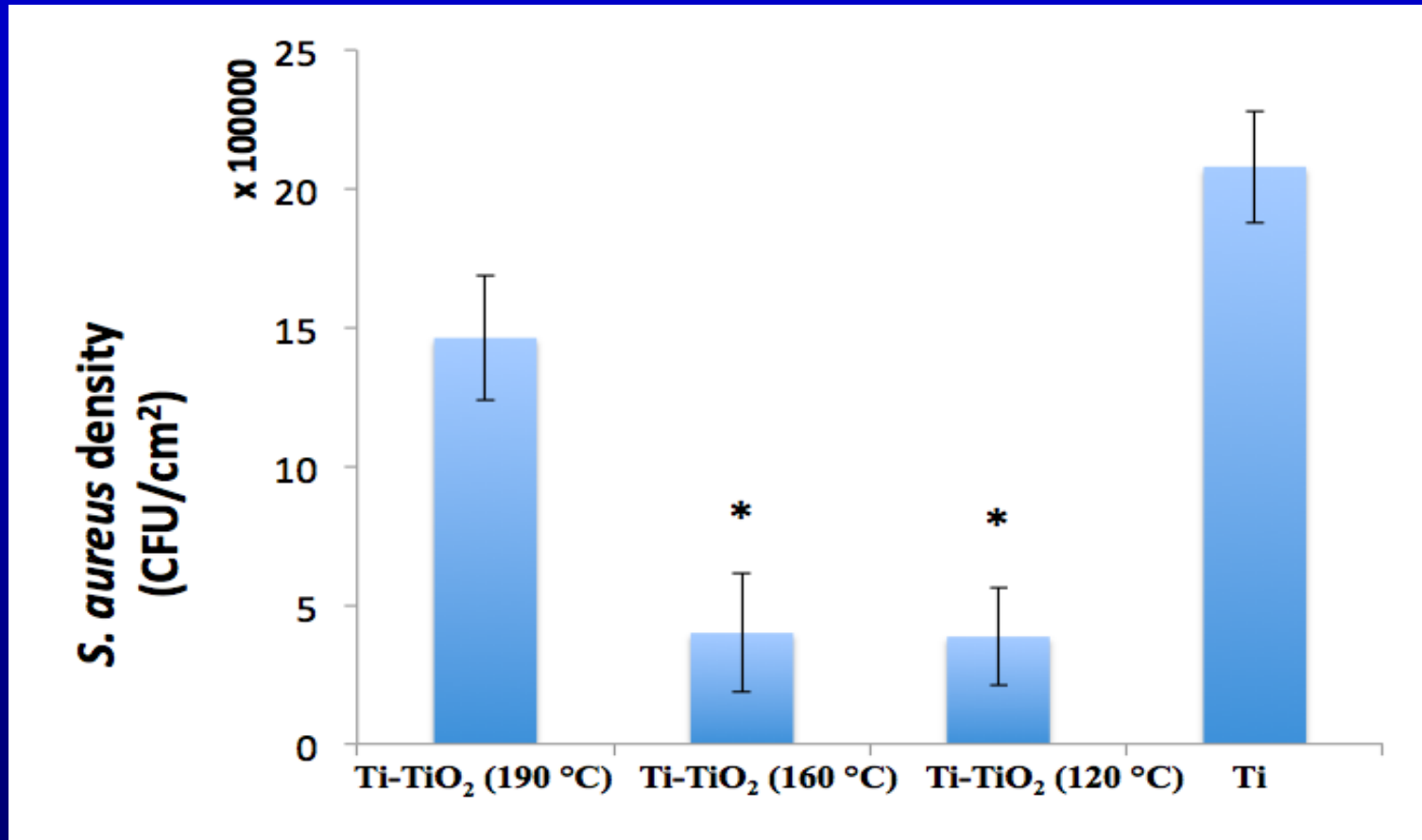


Osteoblast adhesion on Ti samples with different TiO₂ coatings.
Data represents mean \pm SD.



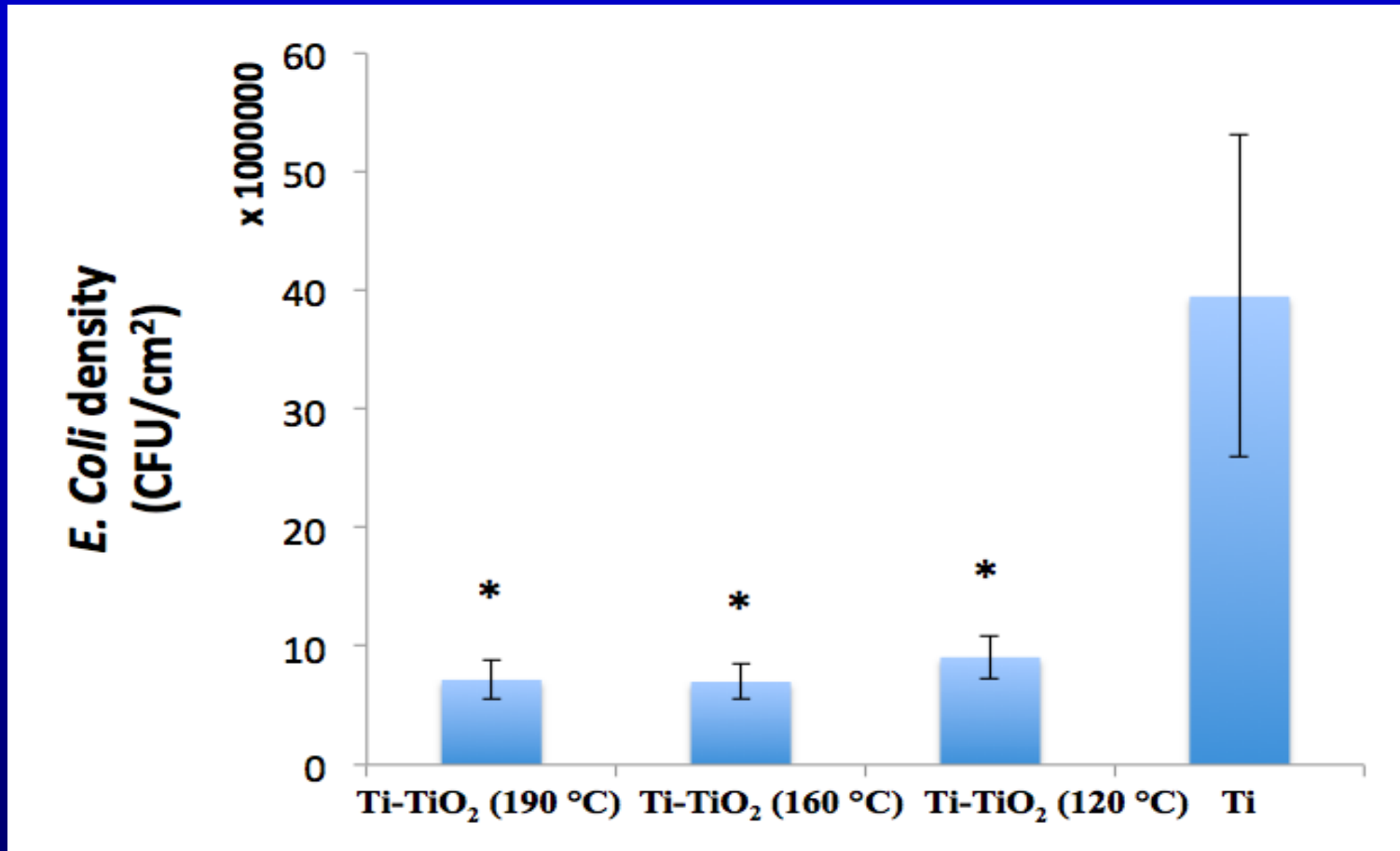
Osteoblast proliferation on Ti samples with different TiO₂ coatings after 7 days. n=3.
Data represents mean \pm SD.

→ Decreased *S. aureus* growth on Ti samples with TiO₂ coatings after 1 day

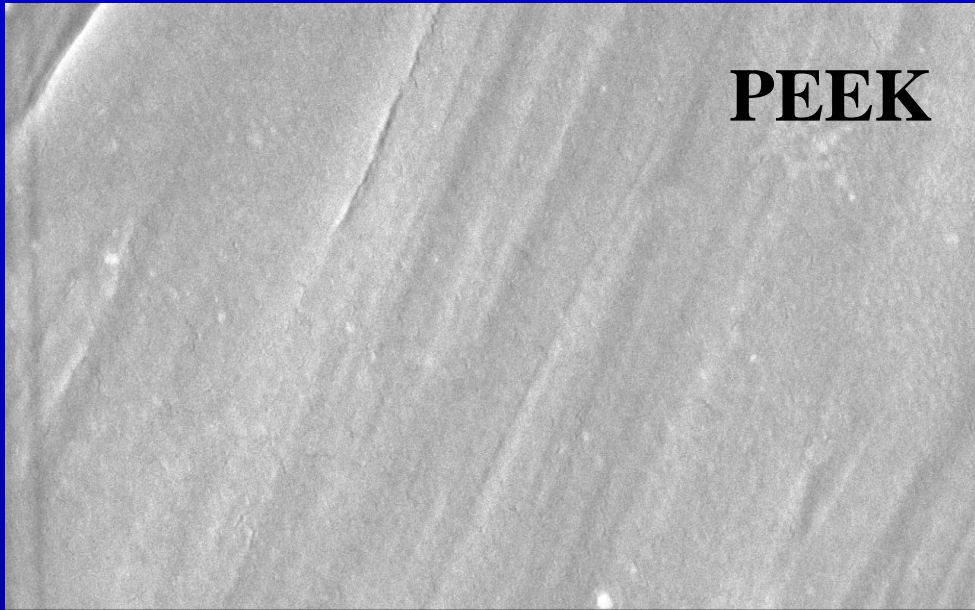


S. aureus growth on Ti samples with different TiO₂ coatings. Data represents mean \pm SD, N=3. *p < 0.05 compared with Ti control.

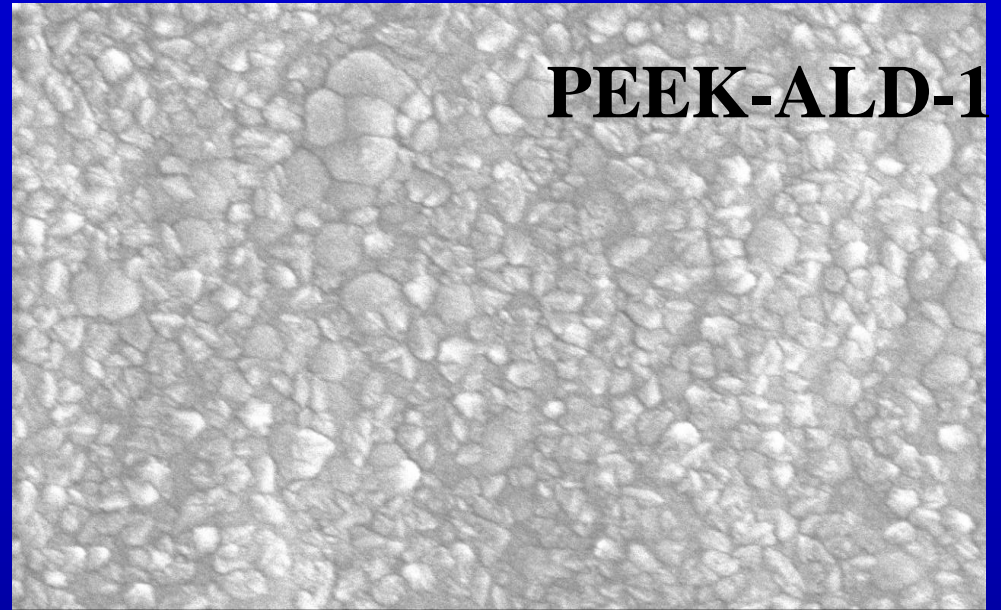
→ Decreased *E. coli* growth on Ti samples with TiO₂ coatings after 1 day



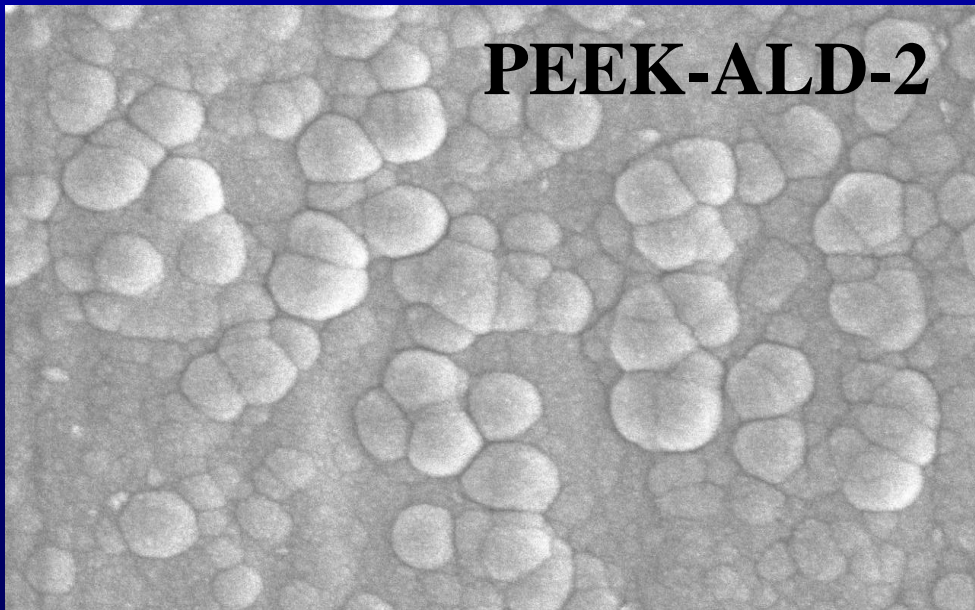
E. coli growth on Ti samples with different TiO₂ coatings. Data represents mean \pm SD, N=3. *p < 0.05 compared with Ti control.



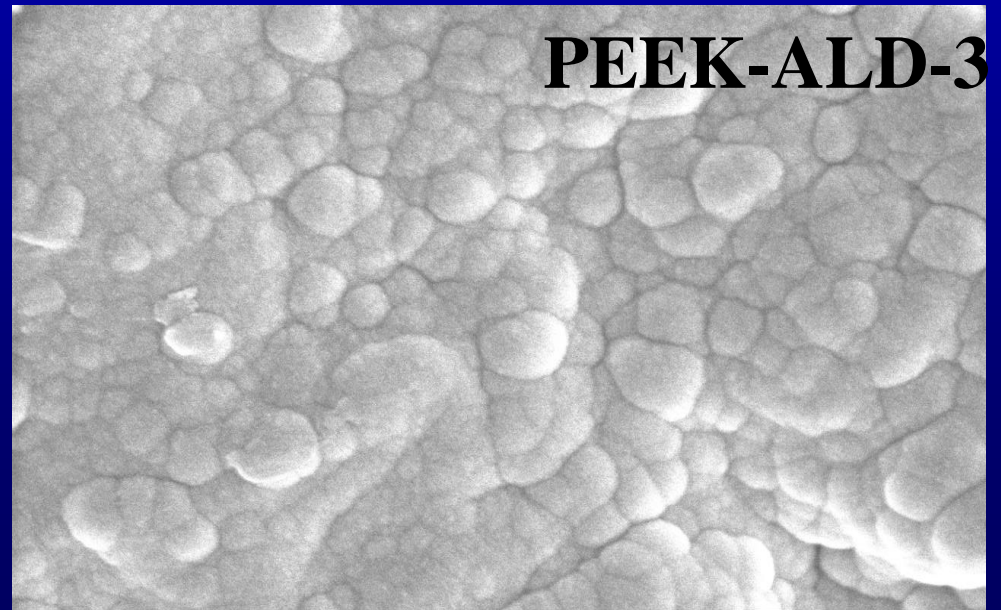
PEEK 3.0kV 7.7mm x50.0k SE(M) 3/10/2016 1.00um



PEEK 3.0kV 8.2mm x50.0k SE(M) 3/10/2016 1.00um

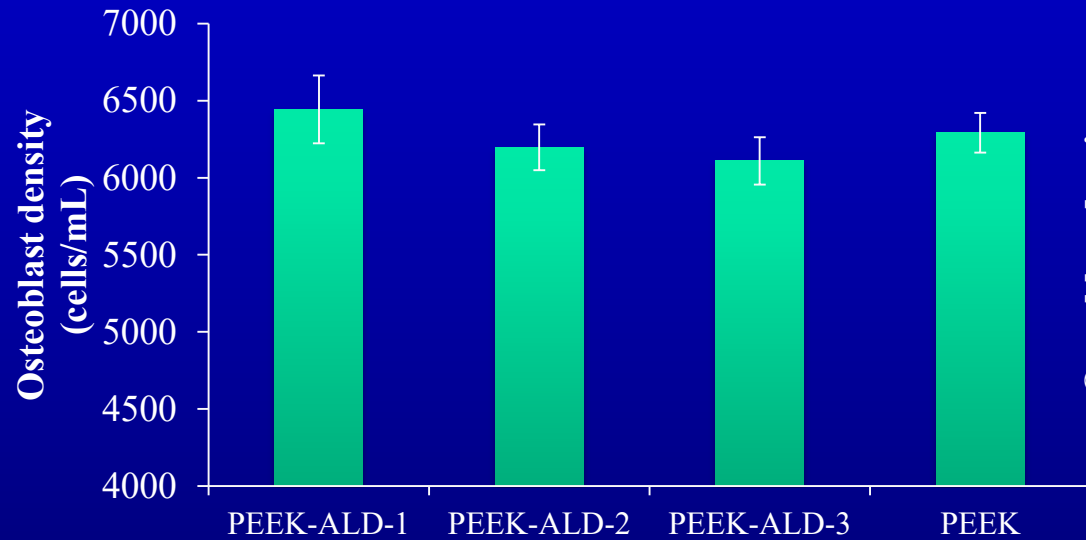


PEEK 3.0kV 8.1mm x50.0k SE(M) 3/10/2016 1.00um

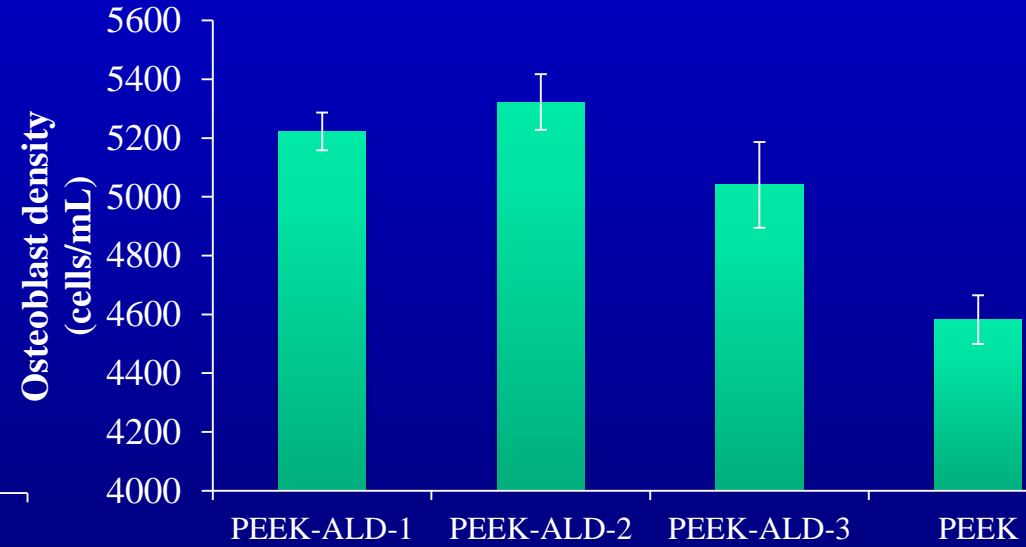


PEEK 3.0kV 7.7mm x50.0k SE(M) 3/10/2016 1.00um

Osteoblast density increases on PEEK samples coated with Ti using ALD



Osteoblast adhesion on PEEK samples with different TiO₂ coatings. n=3
Data represents mean \pm SD.

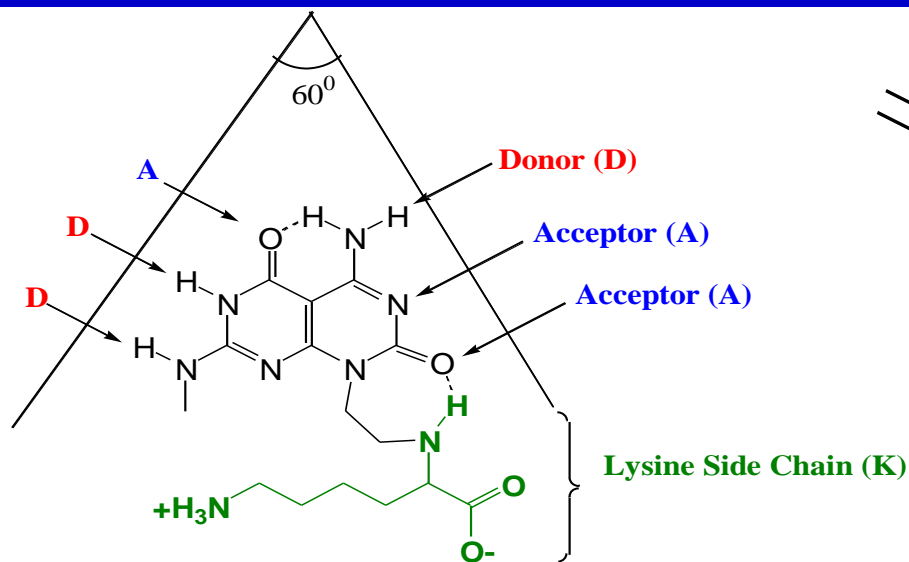


Osteoblast proliferation on PEEK samples with different TiO₂ coatings after 7 days. n=3
Data represents mean \pm SD.

**Self-assembled (*nano*)
chemistries that kill antibiotic
resistant bacteria**

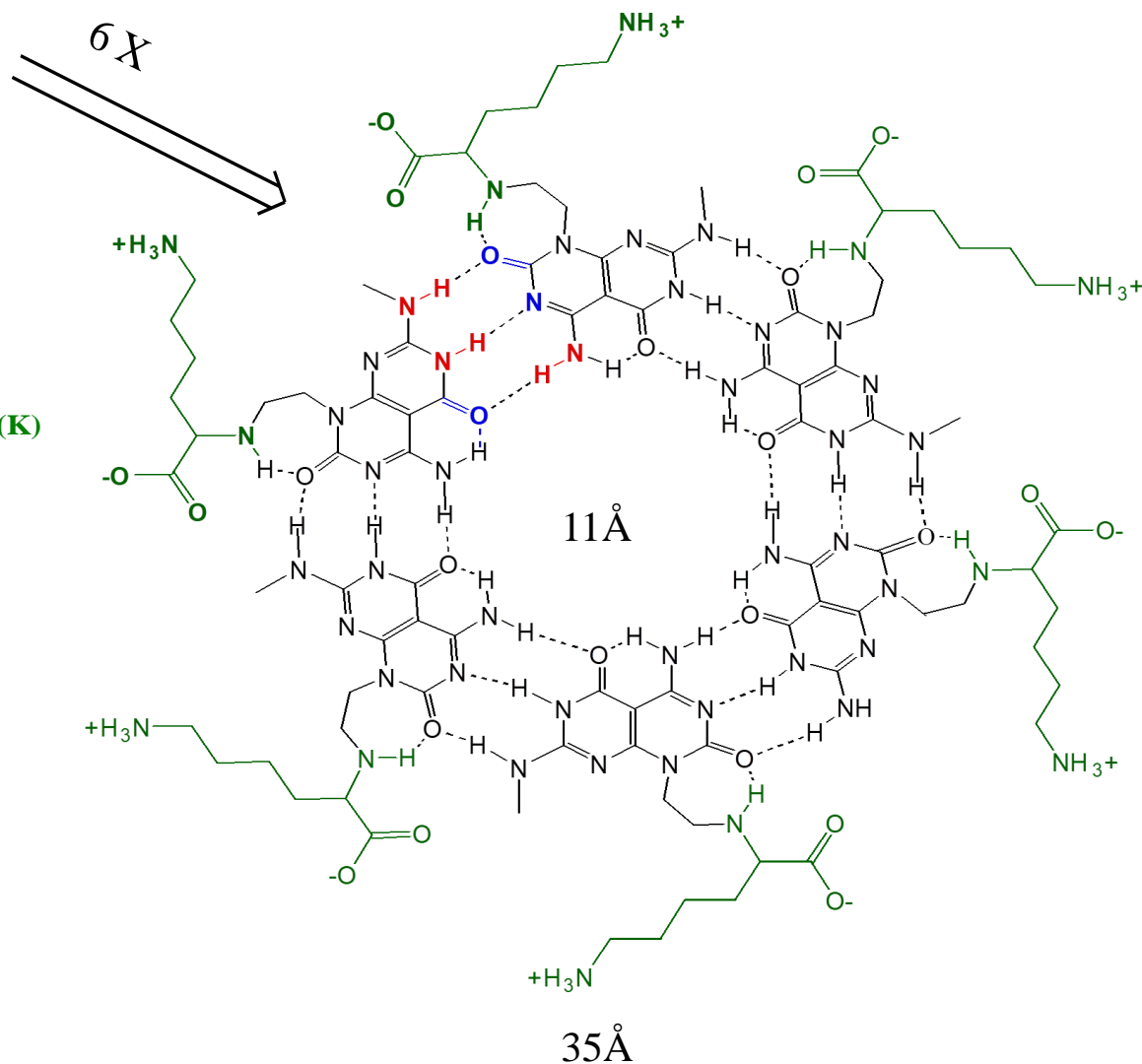
(not FDA approved)

Helical Rosette Nanotubes (HRN)



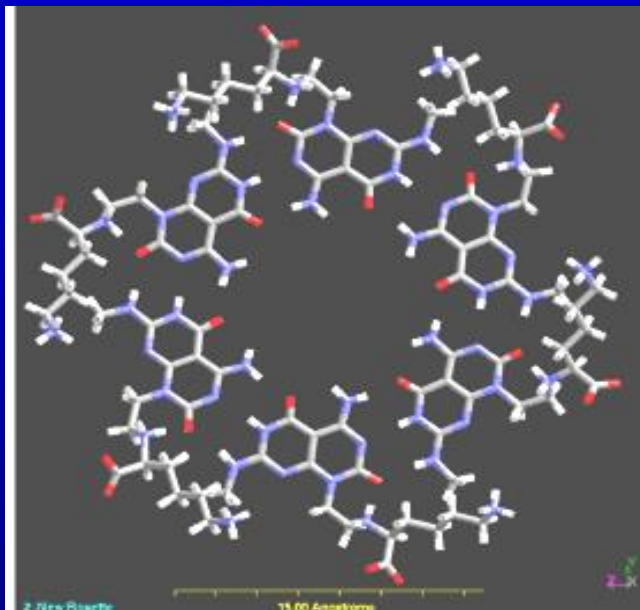
Features:

- Guanine DDA array
- Cytosine AAD array
- Side chain moiety dictates supramolecular chirality & surface chemistry
- Ethylene spacer unit linking base to chiral center allowing intramolecular H bond
- CH_3 group minimize peripheral access of water

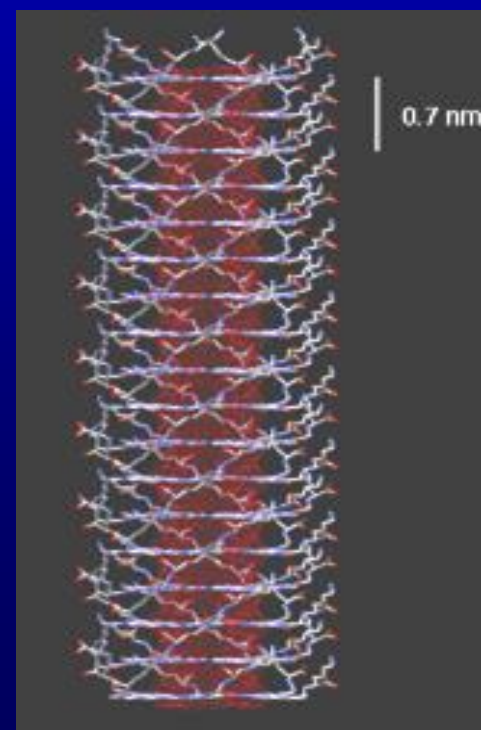


Six-membered supermacrocycle = "Rosette"

Commercialized by Audax: Helical Rosette Nanotubes (HRN)



Several rosettes stack up to form a nanotube with a hollow core 11Å across & up to several millimeters long.



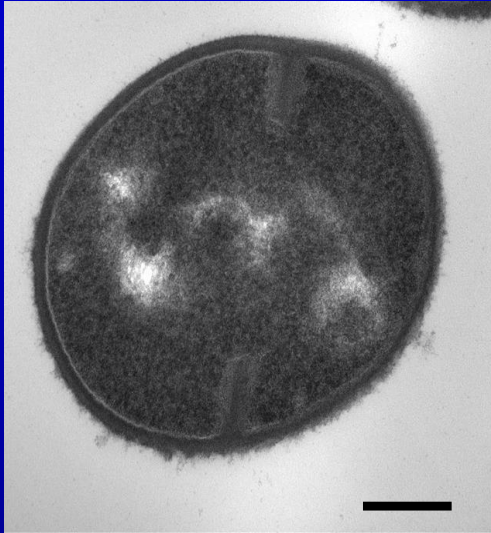
Self-Assembled Chemistries Killing Bacteria

Control

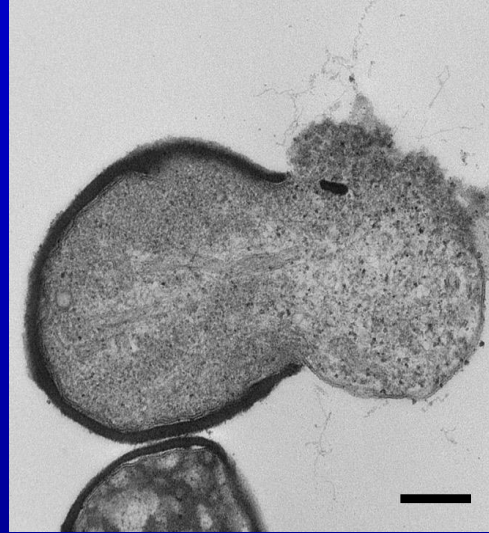
80 μ M ACA-nanorods treated

MRSA

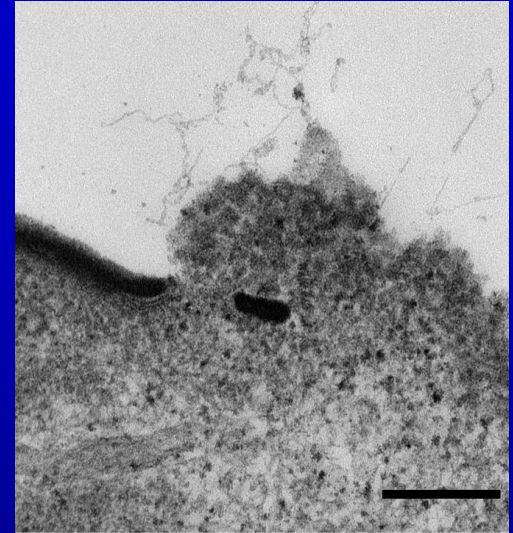
A



B



C

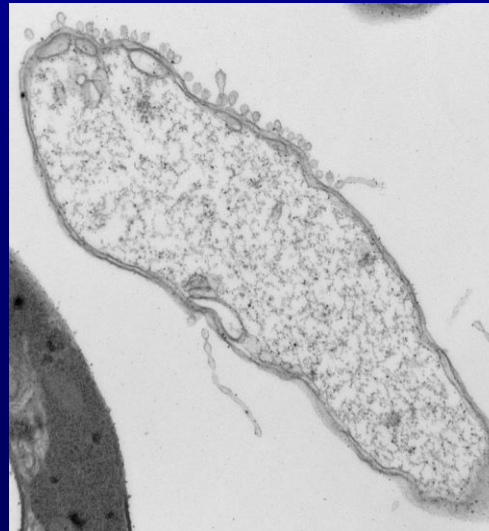


**MDR
*E.coli***

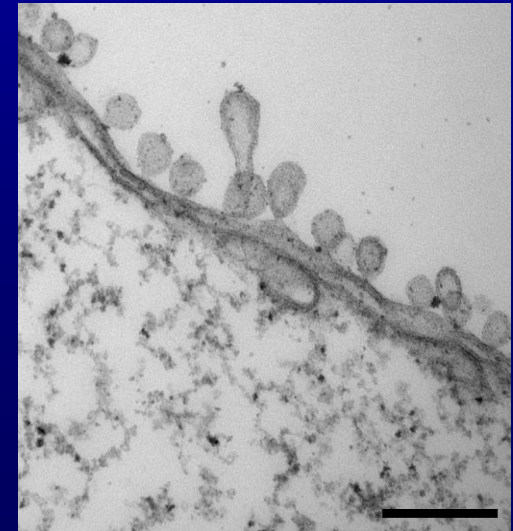
D



E



F

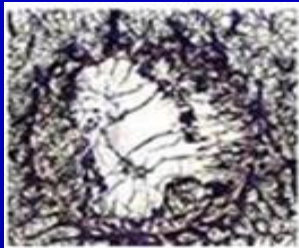


**Scale bar
= 200 nm**

Improved Bone Growth with HRNs

HRNs/pHEMA/nano-hydroxyapatite composites for repairing bone defects in the femur and tibia of pigs.

- Controls (Empty)



- Autografts



- RNT composites



- RNT composites with BMP peptide-c



Materials were implanted into the femur and tibia of pigs. After 8 weeks, X-ray intensities:

(Empty) 17.8

Self-assembled chemistries 68.8

Autograft 39.8

Thinking ahead

- Aren't these approaches still reactionary ?
- Won't the cost of healthcare continue to rise if we simply respond to health problems rather than predict them ?
- Won't this problem continue to get worse with greater patient numbers ?



**Challenge #5: We need
implantable sensors to create
more personalized medicine.**

Current Sensors Used in Medicine: Not at all Like our Immune System



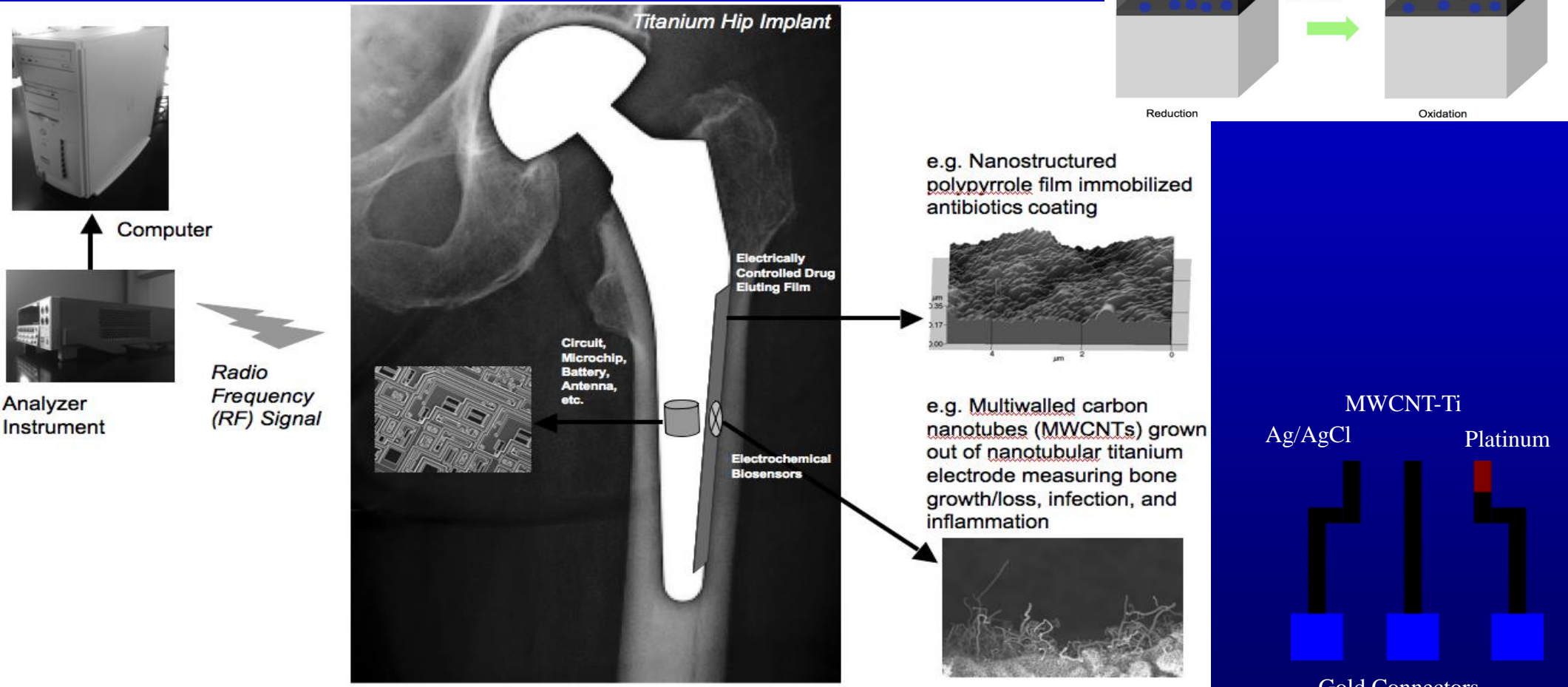
We have cells
that do this
in the body

But is this how our body senses events ?

**We need sensors that behave
more like our immune system.**

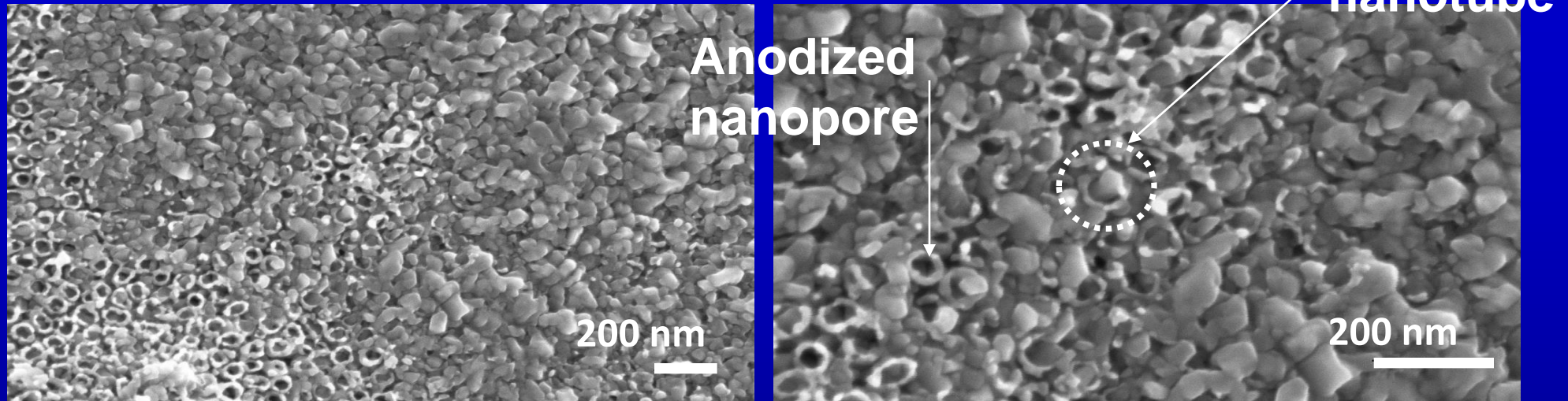
*(The next projects have not been approved by
the FDA)*

Basic Components of a Closed-Loop Sensing and Drug Administration

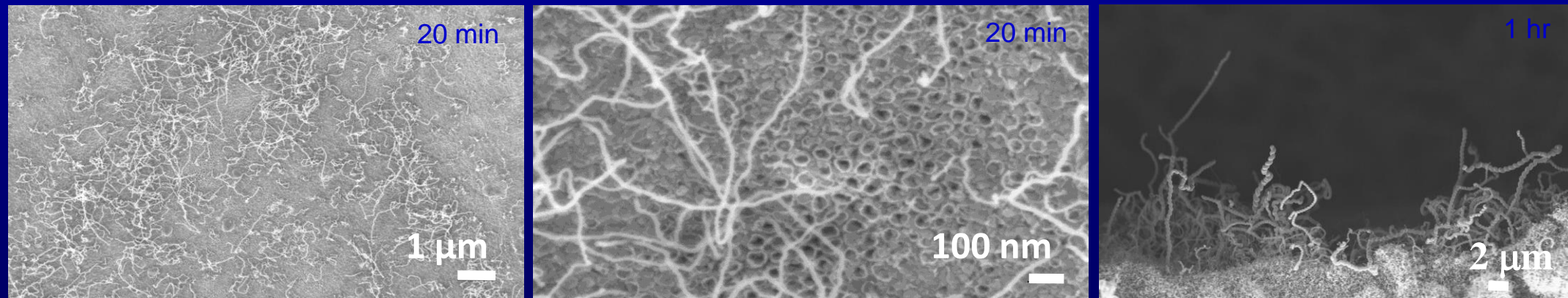


Real-time Detection of Proteins using Sensors and Releasing Drugs from a Polypyrrole Coating

Results: Our Sensor



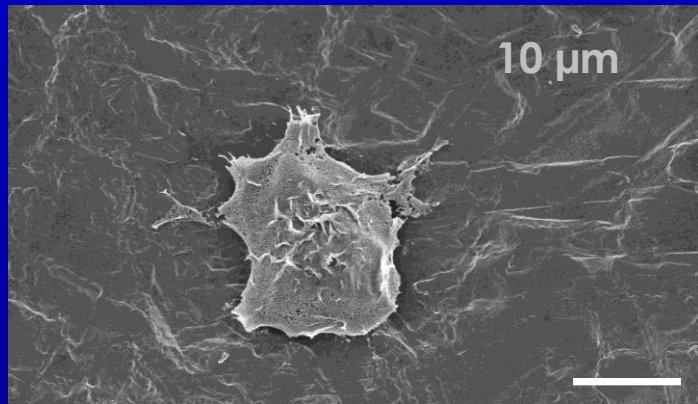
CNTs grown from the nanotubes of anodized Ti **without** a cobalt catalyst using CVD for 20 min.



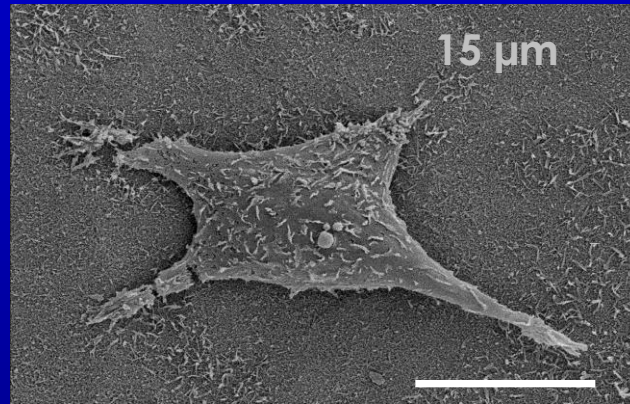
CNTs grown from the nanotubes of anodized Ti surface **with** a cobalt catalyst using CVD for 20 min and 1 hr.

Results: Our Sensor

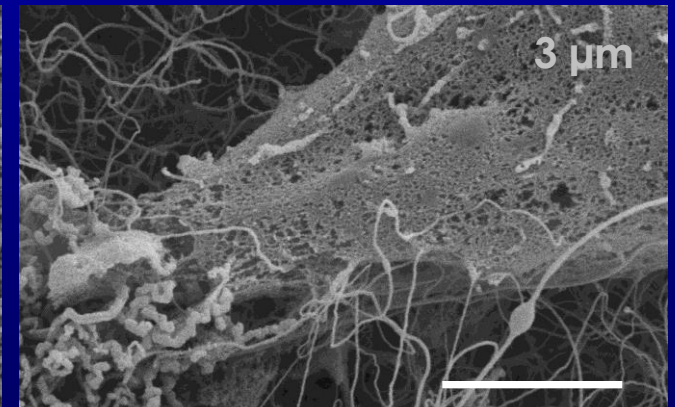
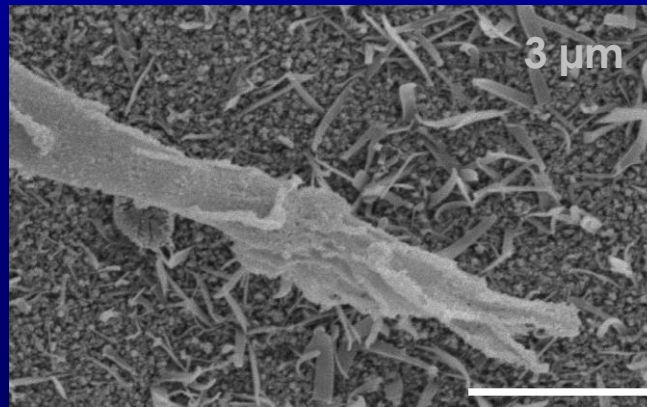
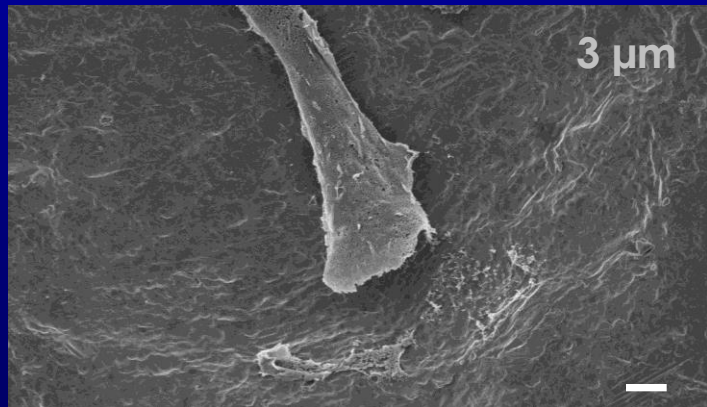
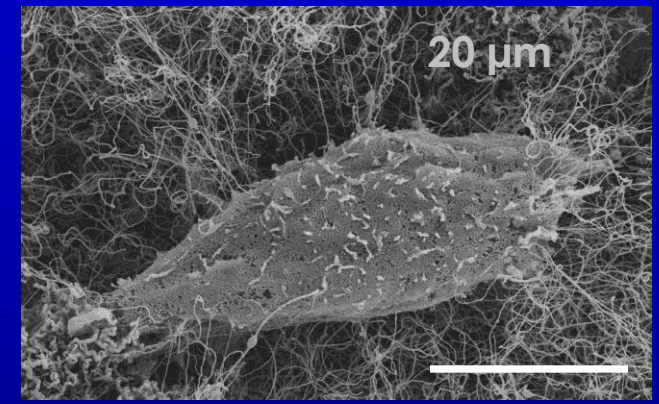
Titanium



Anodized titanium



Multiwalled carbon nanotubes grown out of anodized titanium (MWCNT-Ti)



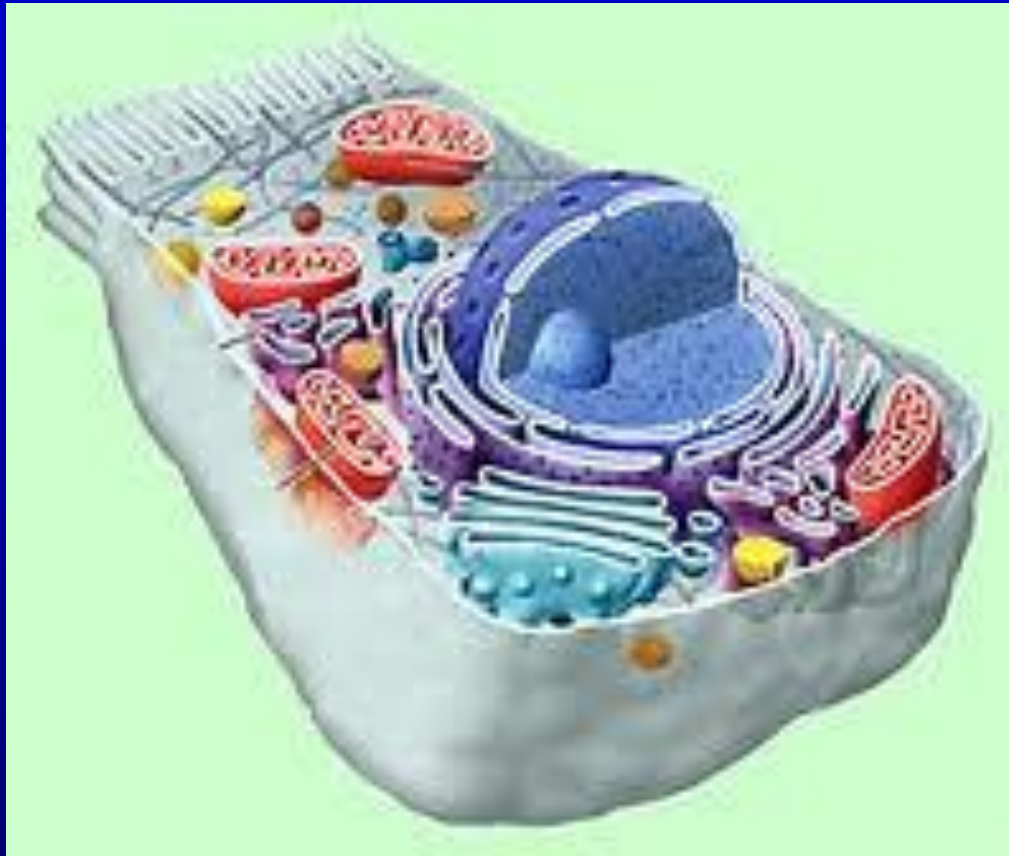
This sensor improves bone growth without even sensing

Next Generation of Sensors that Could be used in Medicine

Synthetic Cell Sensor:

Need energy
source

Need flexible
biocompatible
materials



Need processing
capability

Need responding
capability to aid
immune cells

Need adaptability

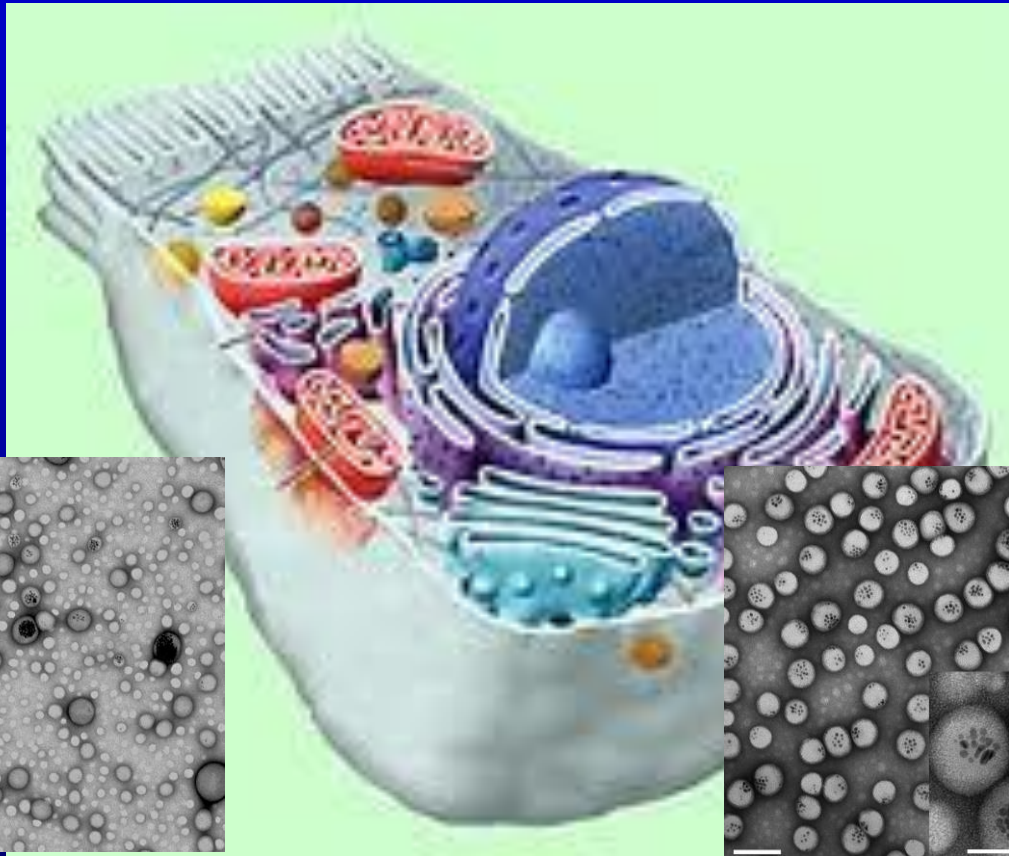
Same approach and sensors can be used on medical device surfaces and outside the body: Does not have to be a synthetic cell but nanotechnology needs to be involved.

Next Generation of Sensors that Could be used in Medicine

Synthetic Cell
Sensor:

Need energy
source

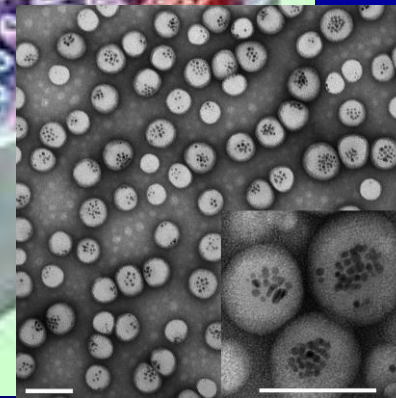
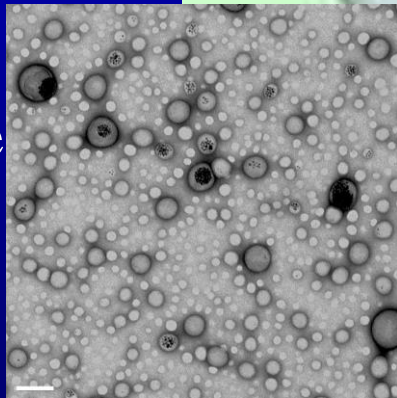
Need flexible
biocompatible
materials



Need processing
capability

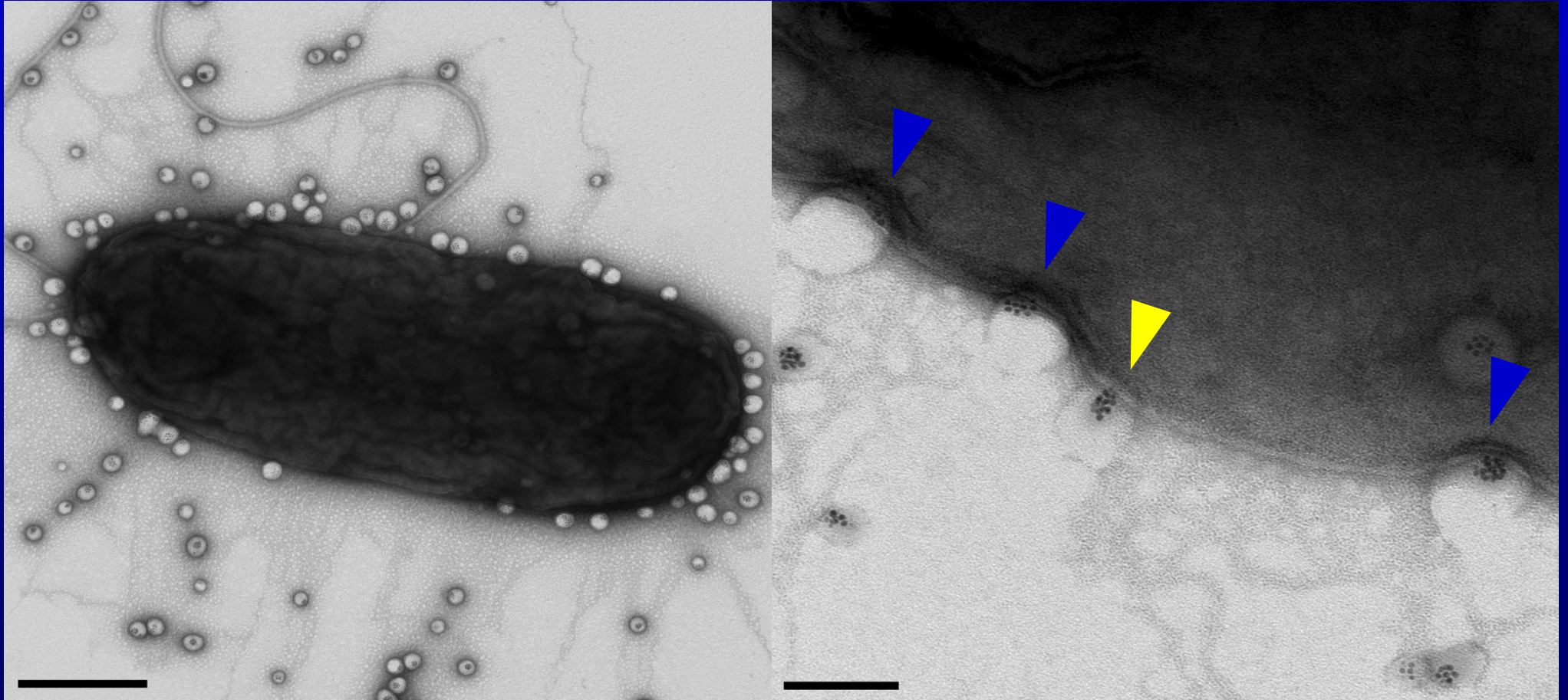
Need responding
capability to aid
immune cells

Need adaptability



Same approach and sensors can be used on medical device surfaces and outside the body: Does not have to be a synthetic cell but nanotechnology needs to be involved.

Synthetic Immune Nanoparticles



Scale Bars = 100nm

My Dream for the Future of Healthcare

- Our version of medicine must transition to predictive not reactionary.
- Our version of medicine must treat individuals not generalized for the whole population or age groups.
- Our version of medicine must be dynamic not static.
- Unless we change, our version of medicine today is *unlikely* to create treatments for all diseases for all people that last a lifetime.

Acknowledgements

Angstrom Medica and Spire Biomedical

Argonide Corp. and Applied Sciences, Inc.

Coulter Foundation- Early Career Award

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DePuy Orthopedics (Johnson and Johnson)

Indiana 21st Century Fund

Nanophase Technologies, Corp.

National Science Foundation

*Integrated Graduate Education and Research Training Fellowship (IGERT),
Nanoscale Exploratory Research, REU*

National Institute of Health

Nanobiotechnology Initiative

Showalter Foundation

Whitaker Foundation

Thank You!



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