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15 years of commercializing nanomedicine into real medical products

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15 Years of Commercializing Medical Devices Using Nanotechnology

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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.
  - SensoNano, Inc.
  - Tyber Medical, Inc.
  - Stryker
  - Amedica
  - Vexti

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 ?

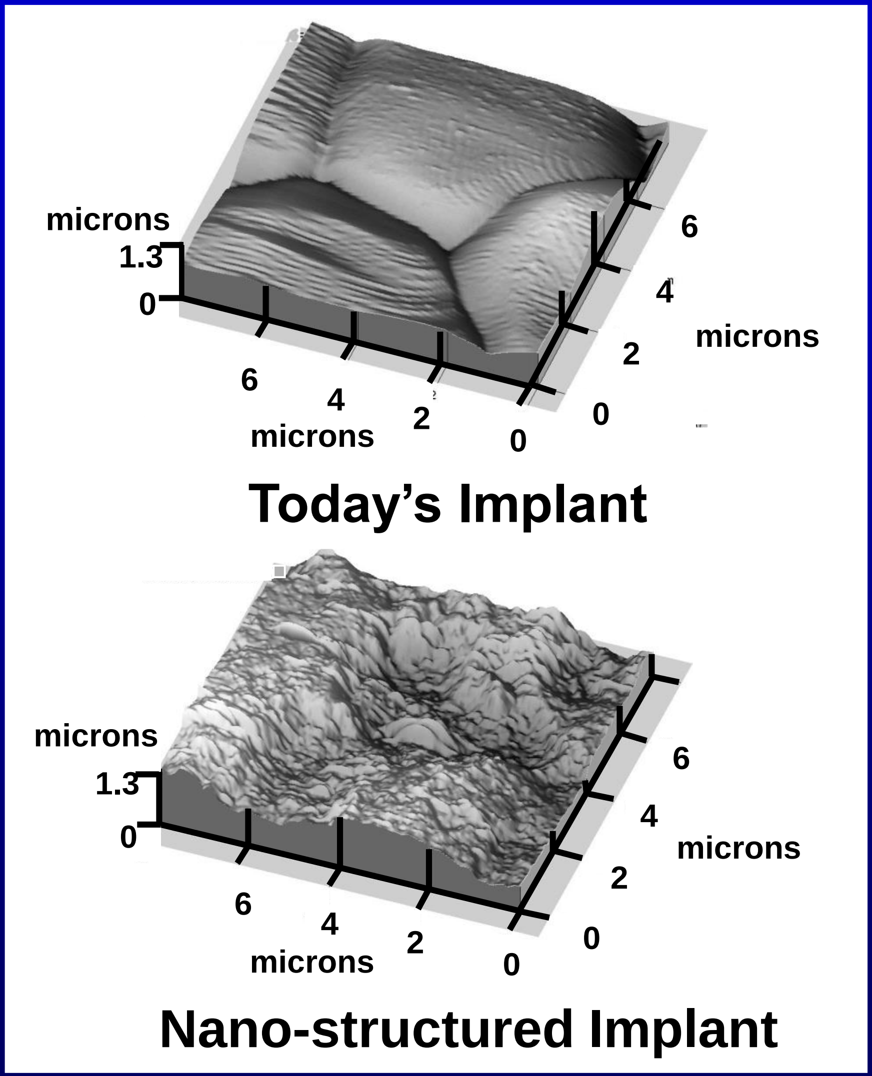
15 Years Ago We Turned to Nanomedicine for Some Answers

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



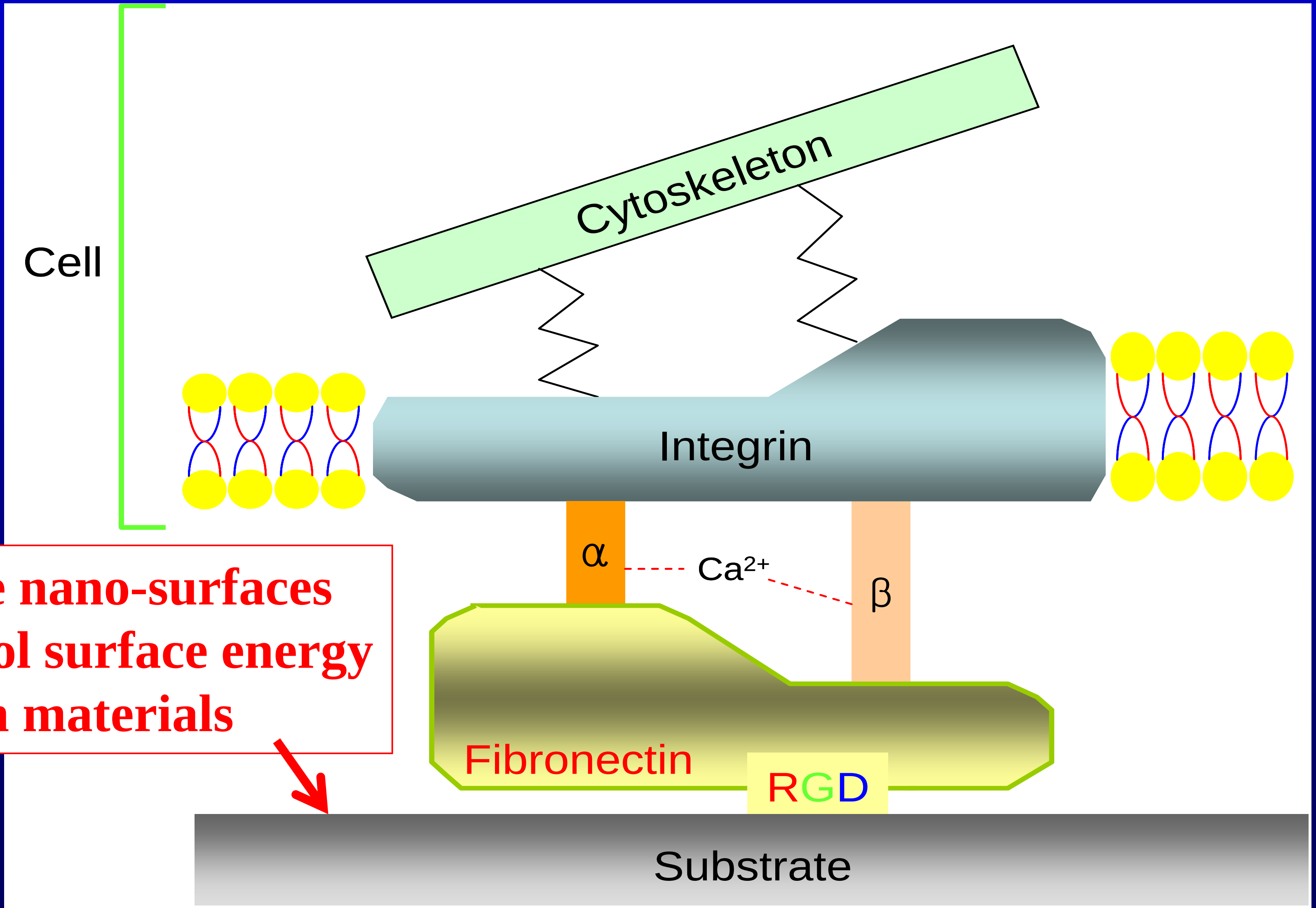
Compared to today's implant materials, nano-structured materials possess enhanced:

- surface area
- radio-opacity
- catalytic,
- optical,
- mechanical,
- electrical, and
- <u>surface</u>

properties that may improve existing biomedical implant applications.

T. J. Webster, in <u>Advances in Chemical Engineering Vol. 27</u>, Academic Press, NY, pgs. 125-166, 2001.

Initial Protein Coatings on Biomaterials Control Everything



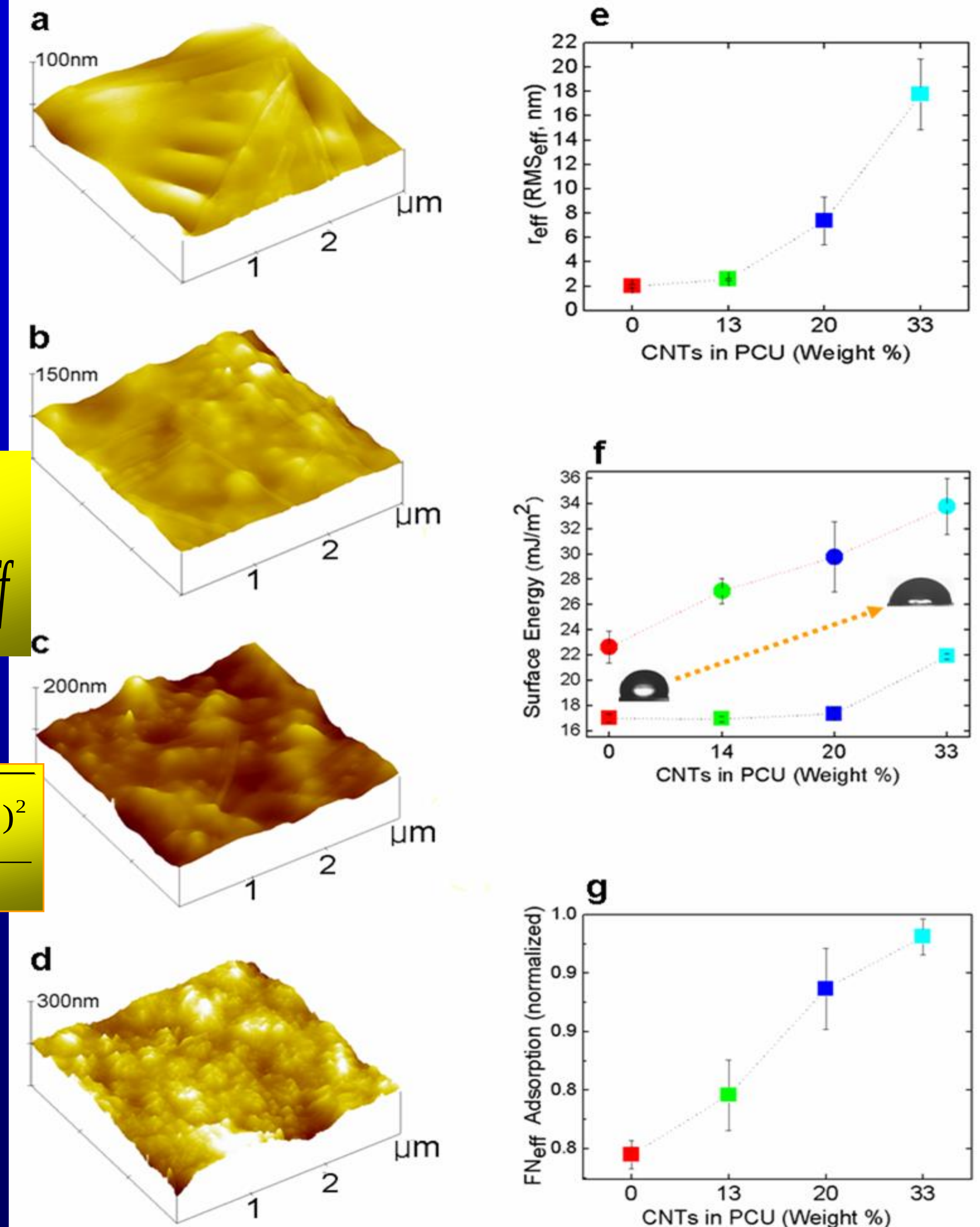
Create nano-surfaces to control surface energy on materials

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

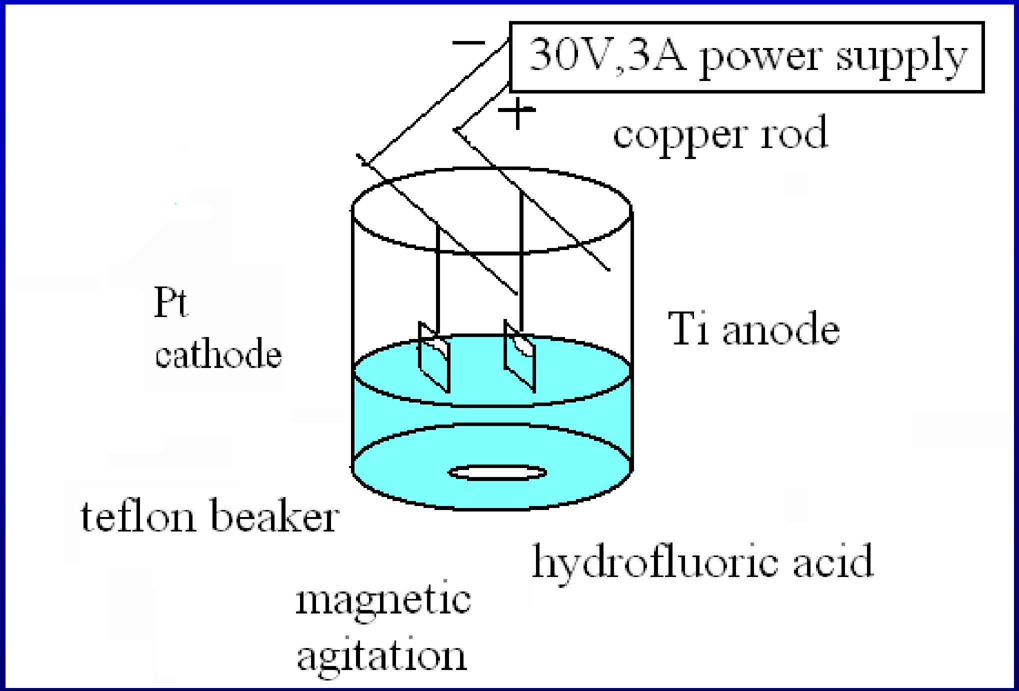
and the FDA likes this !

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 make them "new" and obtain quick FDA approval

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

<u>Commercialized by Nanovis, LLC</u>
Anodized Titanium



Sketch map of anodization system

<u>PROCEDURES:</u>

<u>Pretreatment</u>: chemical polishing using HF/HNO_3 mixture

<u>Anodization</u>: 0.5 or 1.5%HF

<u>Voltage</u>: 20V

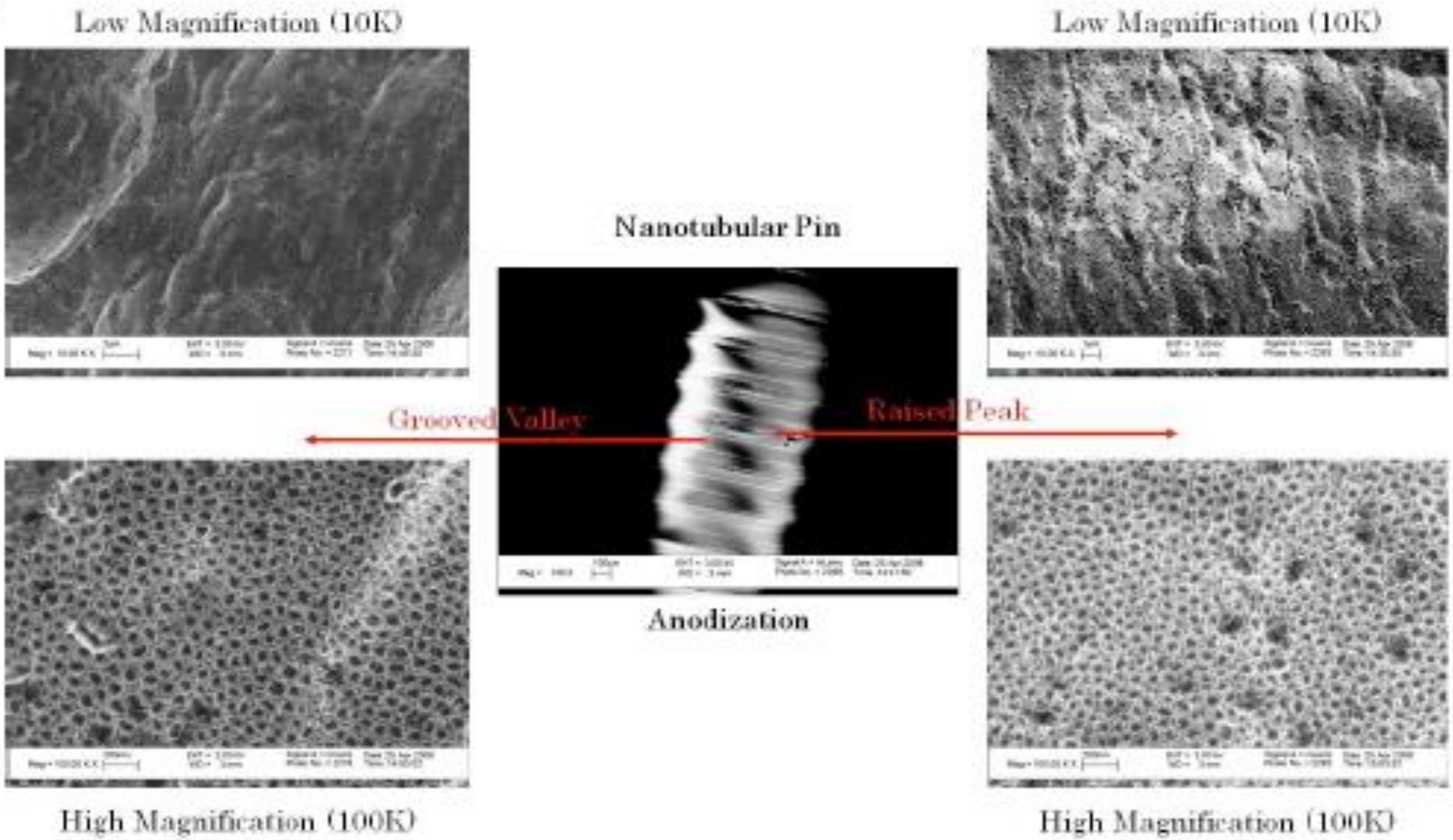
<u>Time</u>: 20 min

<u>Rinse and dry</u>

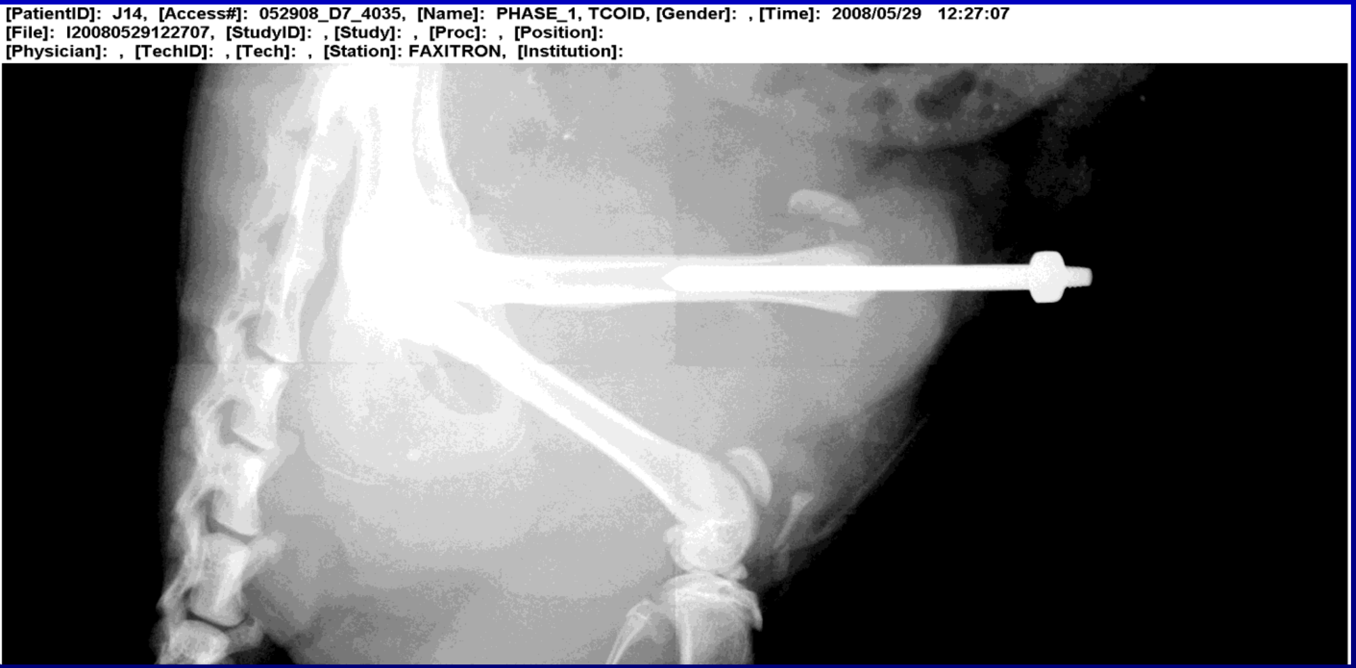
<u>Clean</u>: acetone and ethanol

<u>Sterilize</u>

Anodized Ti Nanotubular Screws



Anodized Titanium Amputee Rat Model



Ti Screw Insertion

Rat Walking on Anodized Titanium Implant as Soon as 3 Days After Surgery

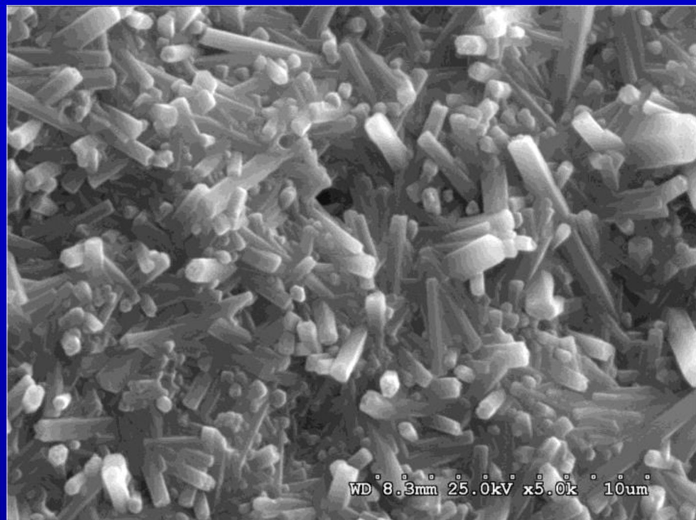
Closed Wound with No Infection Surrounding Nanotextured Screws Only

Nanovis, LLC
is now commercializing
this as a pedical screw

Challenge #3: We have an infection problem.

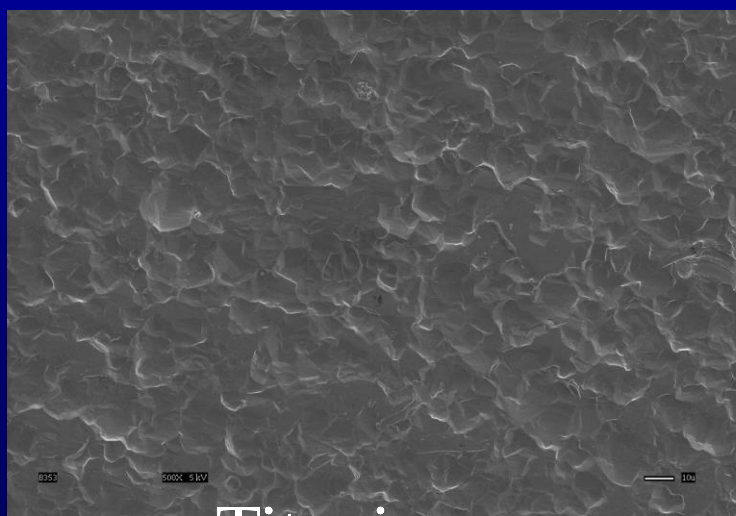
We need more biomaterial approaches that (without antibiotics) can inhibit bacteria functions but not kill mammalian cells.

Commercialized by Amedica:
Nanostructured Silicon Nitride

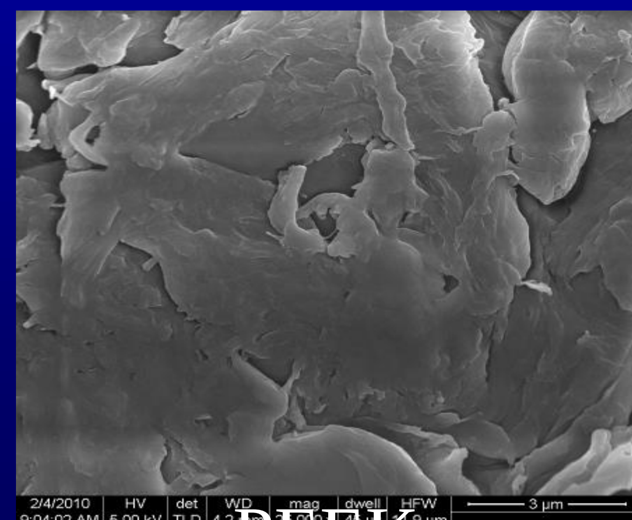


Nanorough Silicon Nitride

Smooth Silicon Nitride



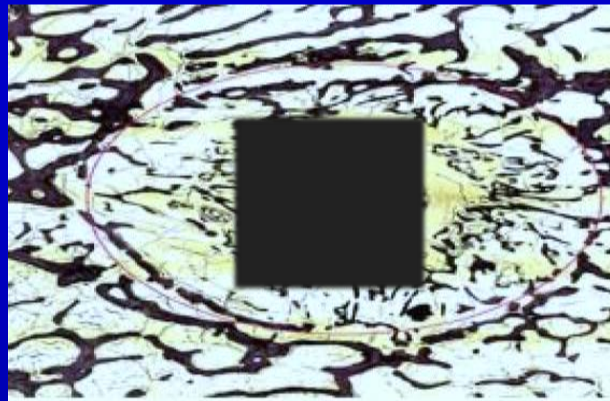
Titanium



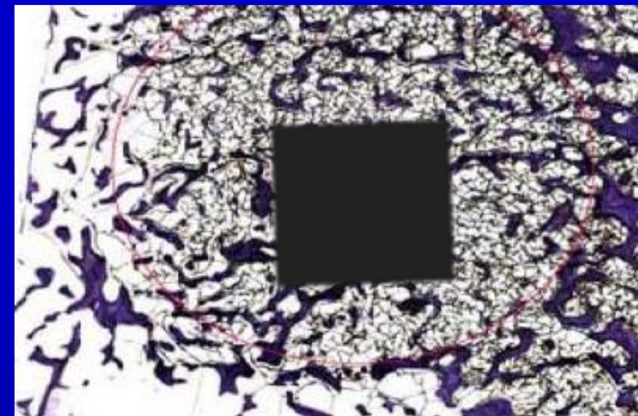
PEEK

Silicon Nitride: 3 Months (bacteria innoculation)

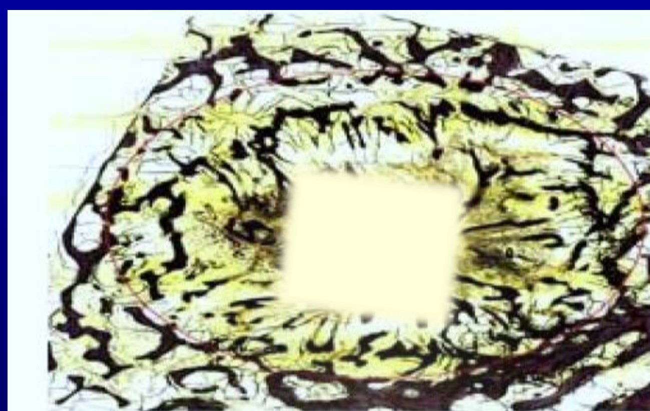
Rat calvaria model



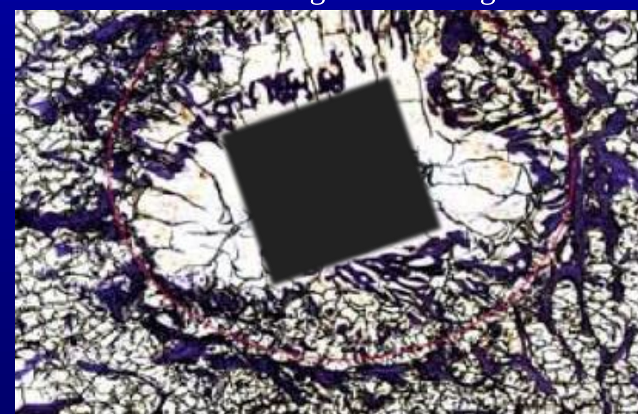
Titanium –
9% bone-implant interface
67% bacteria-implant interface
26% of new bone growth in surgical area
21% of bacteria growth in surgical area



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



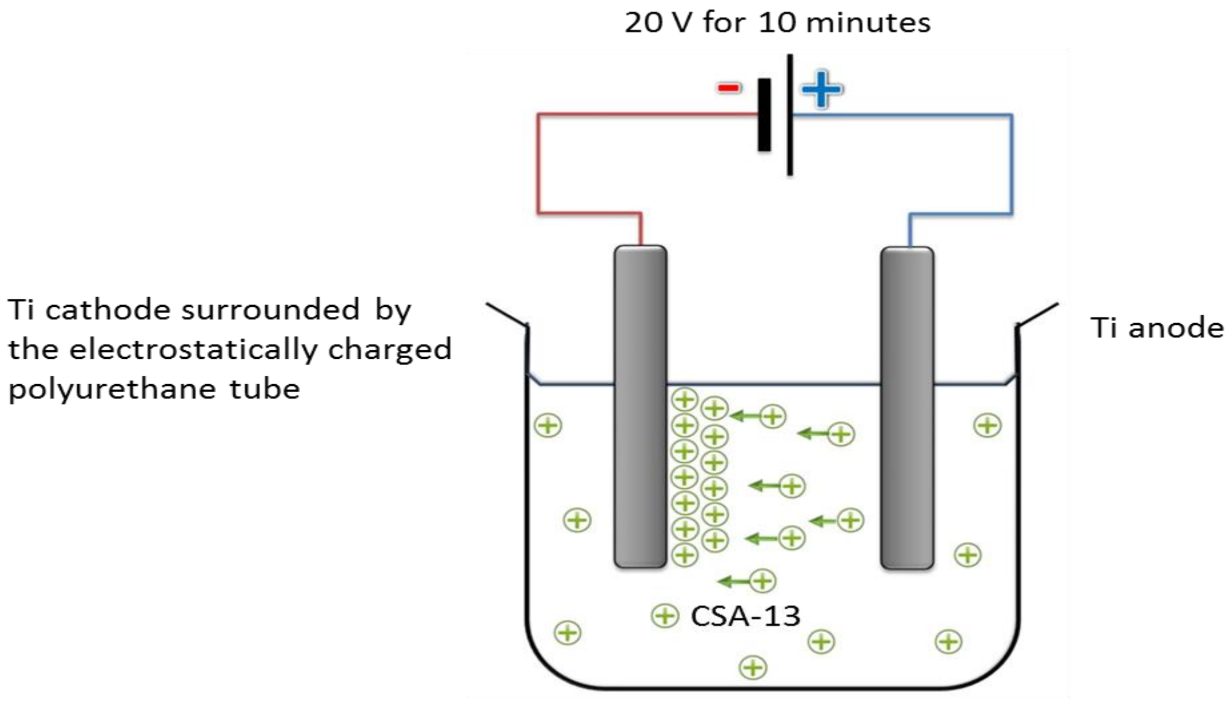
PEEK –
5% bone-implant interface
95% bacteria-implant interface
21% of new bone growth in surgical area
88% of bacteria growth in surgical area



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

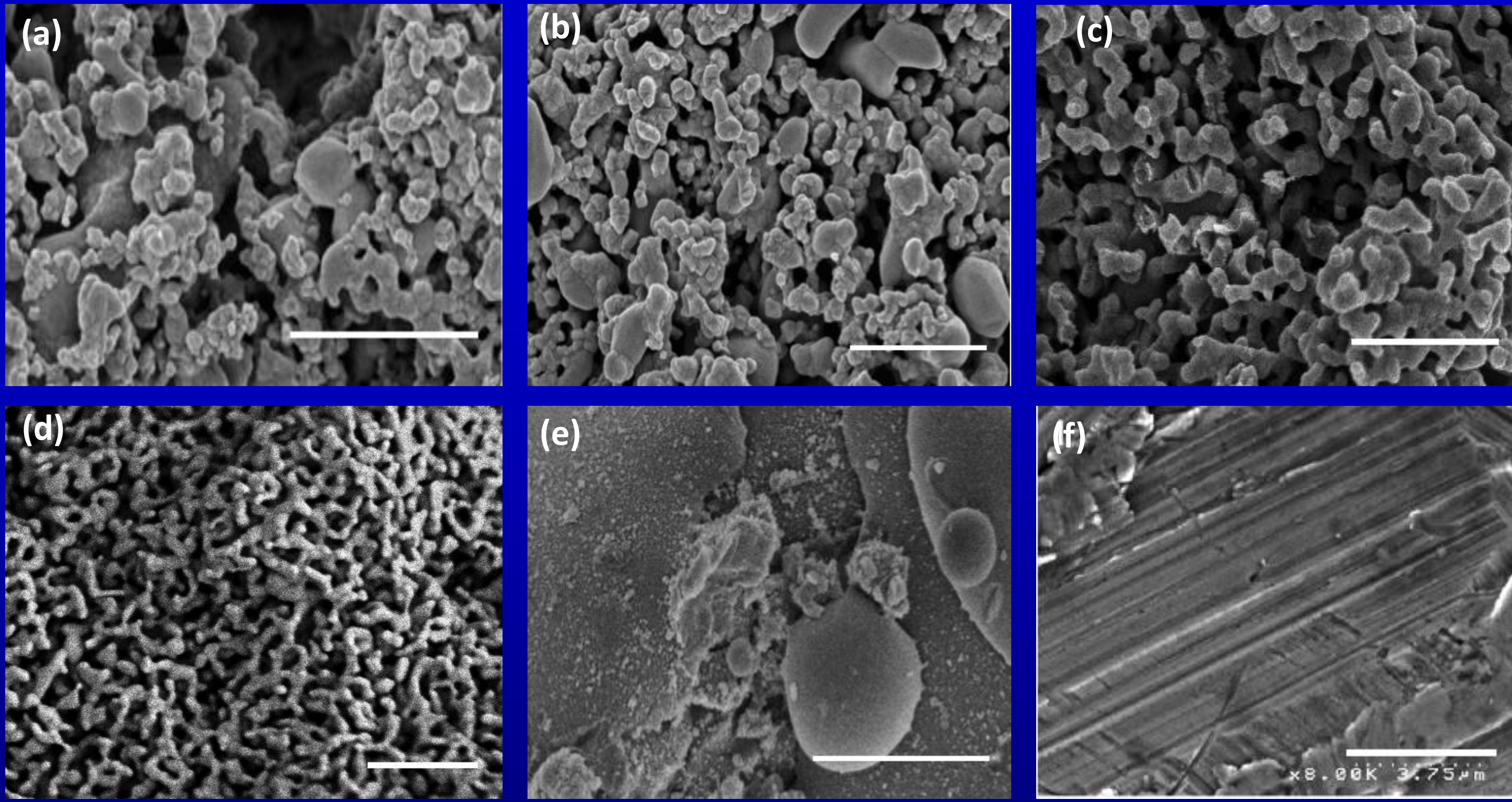
Electrophoretic deposition



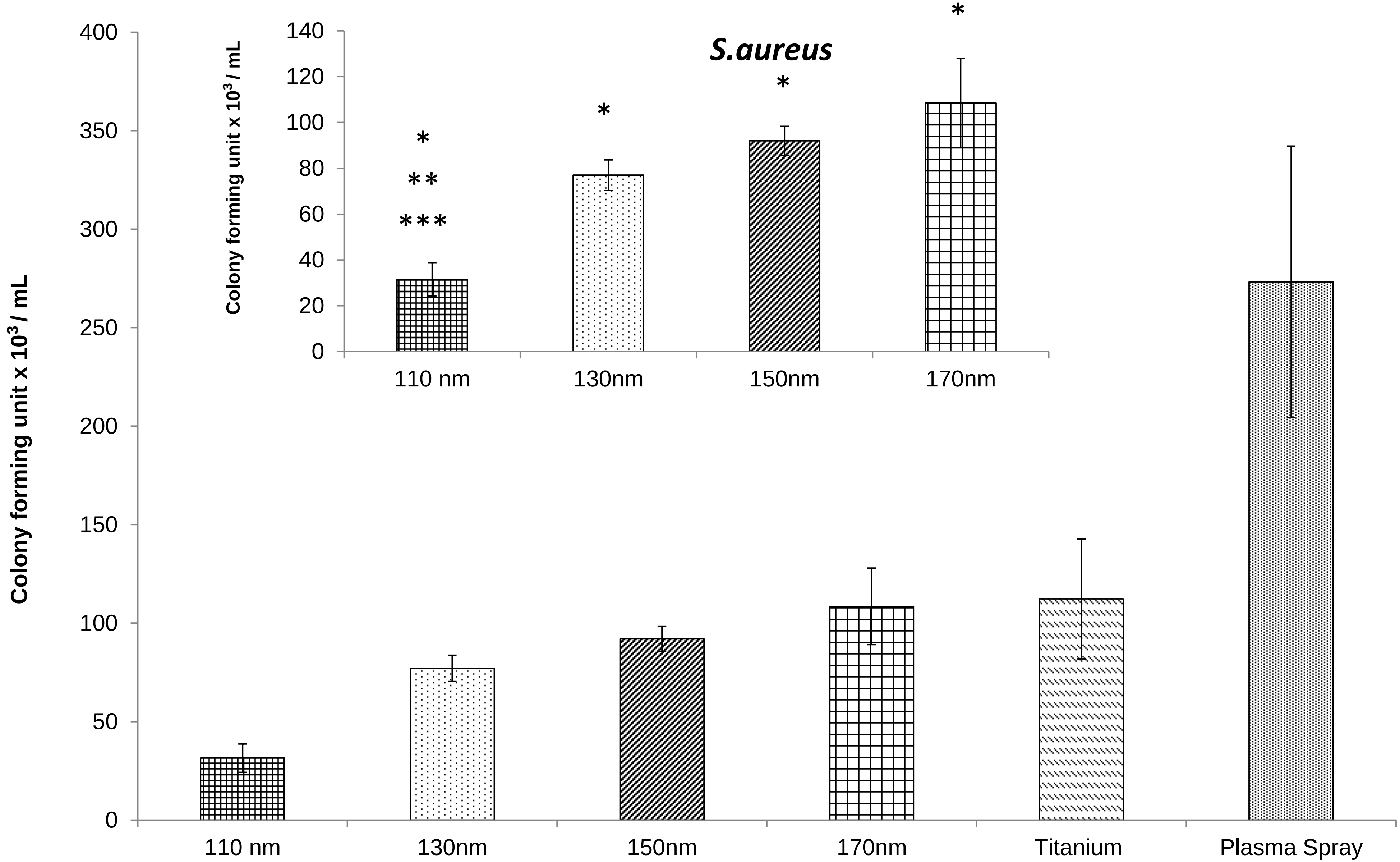
Previous studies have shown an ability to promote bone growth

Advantages of the EPD process:

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

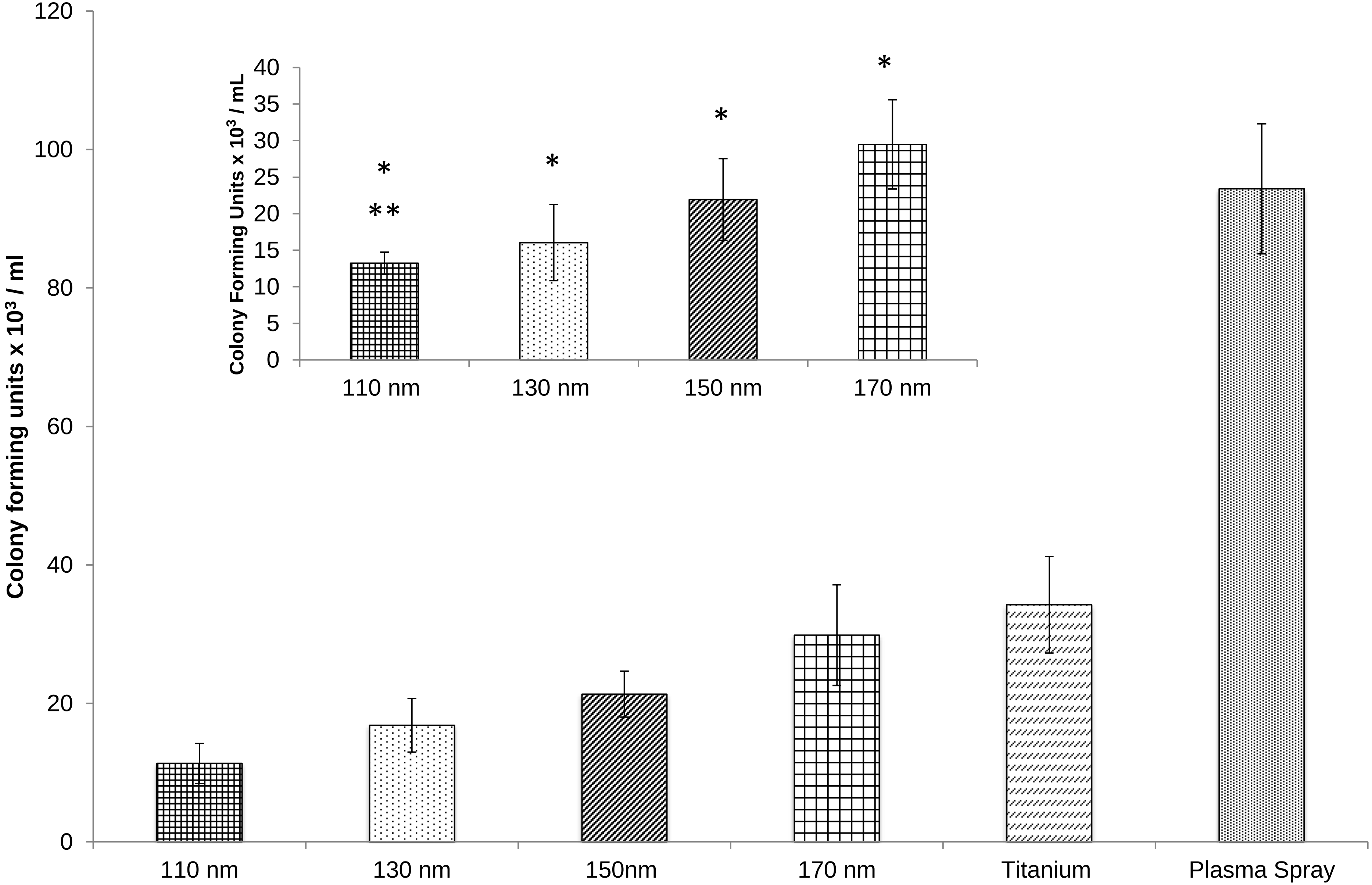


SEM images of the Ti surfaces coated with (a)170 nm, (b) 150 nm, (c) 130 nm, (d)110 nm hydroxyapatite powders, (e) plasma sprayed micron sized hydroxyapatite onto Ti and (f) plain Ti. Scale bar: 1 micrometer

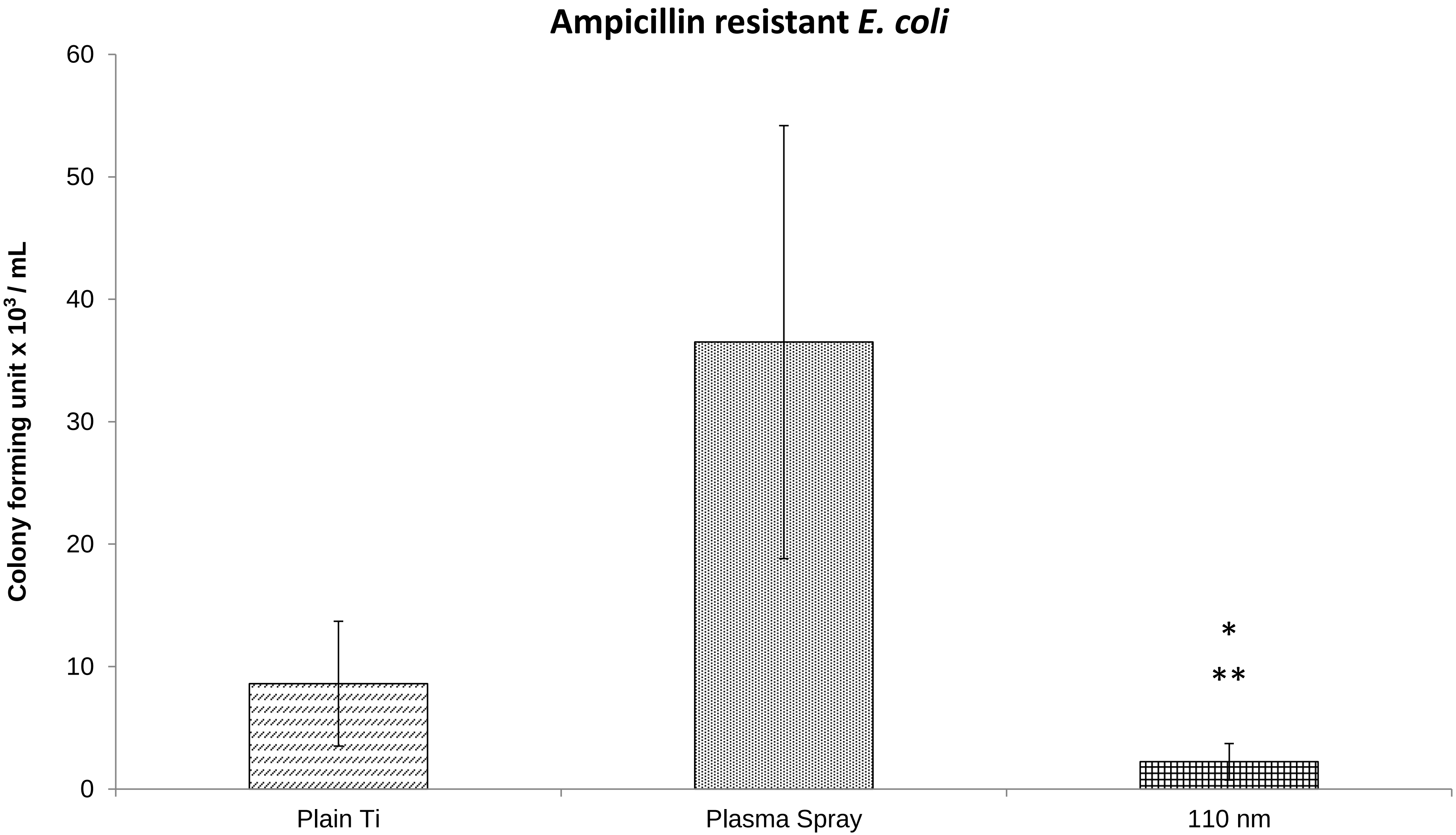


* P<0.01 compared with plasma-sprayed-deposited hydroxyapatite on Ti; ** P<0.01 compared with Ti (control); ***P <0.01 compared with samples coated with 170 nm hydroxyapatite by EPD.

P. aureginosa



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

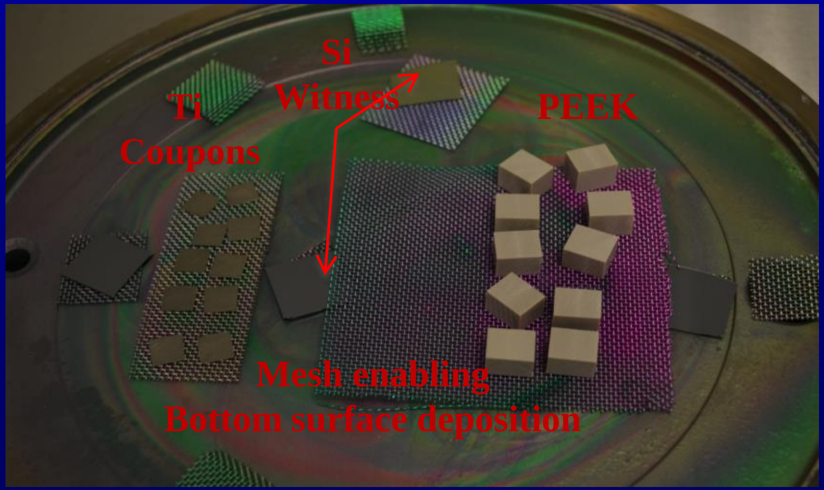


* P<0.01 compared with Ti (control); ** P<0.01 compared with plasma-sprayed-deposited hydroxyapatite on Ti

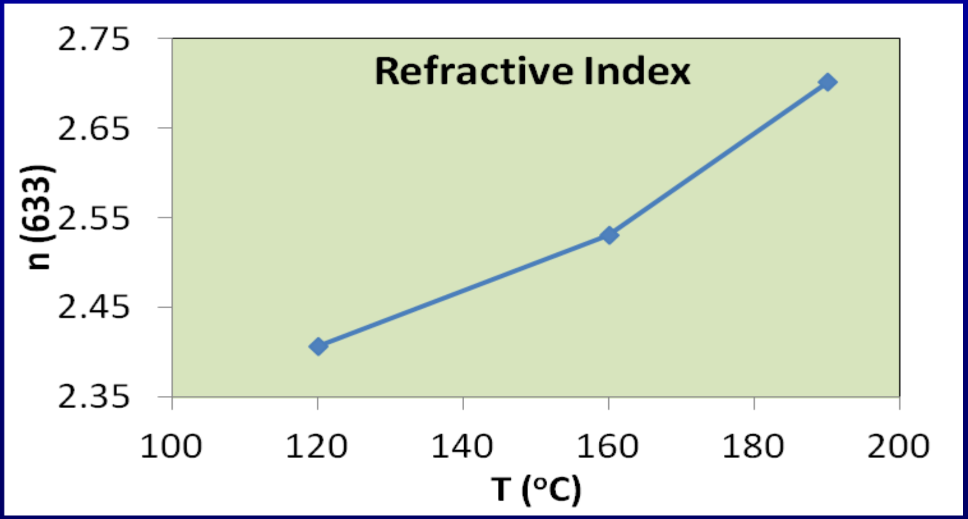
Another FDA approved nanotechnology process…..

Atomic Layer Depositions

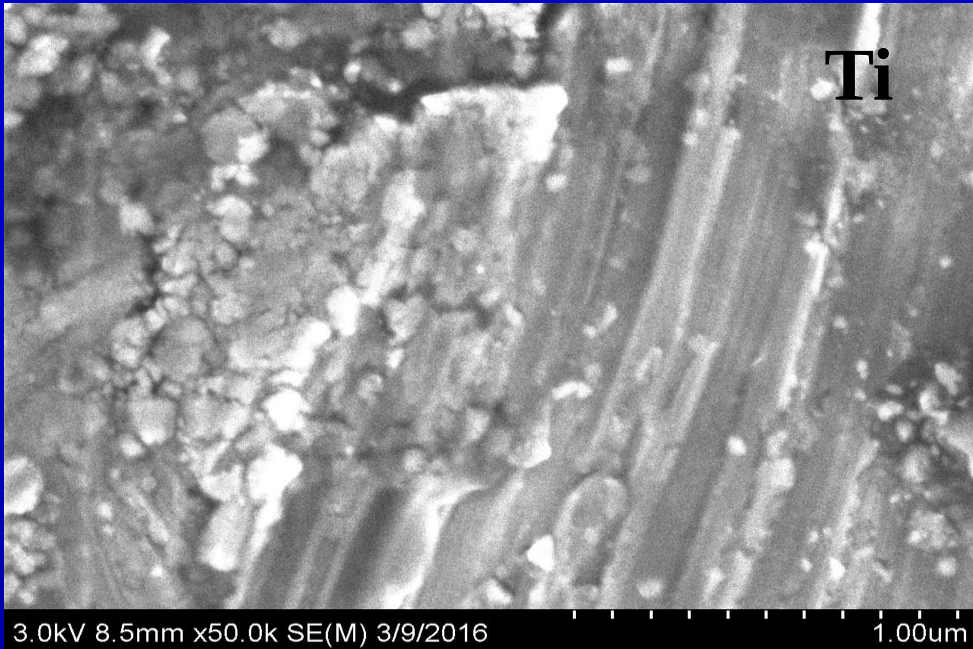
- ALD TiO_2 at 190ºC, 160ºC, 120ºC, 100nm thick
  - Crystallinity is temperature dependent: Amorphous < 140ºC, degree of crystallinity (anatase) increasing with temperature
  - Morphology is temperature dependent
  - T_g of PEEK is 143ºC – adhesion of ALD film to PEEK is likely to be affected by temperature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

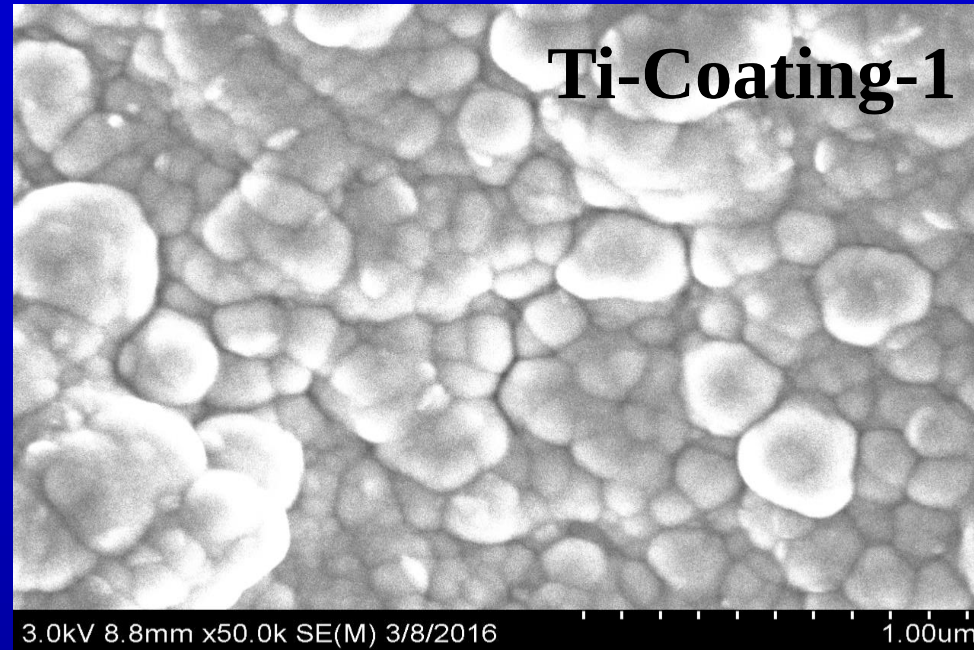


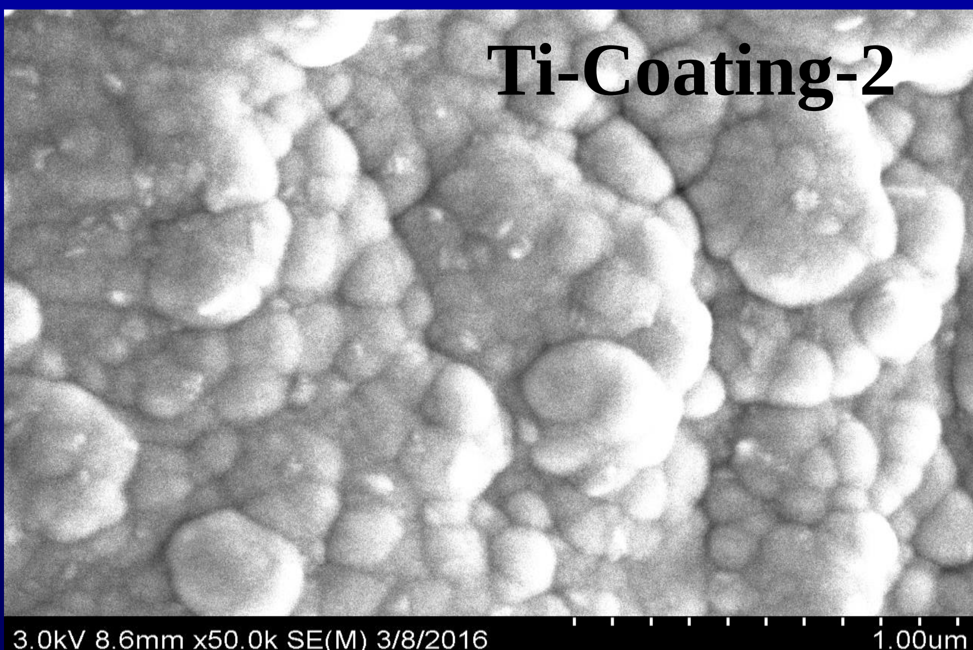
After Deposition

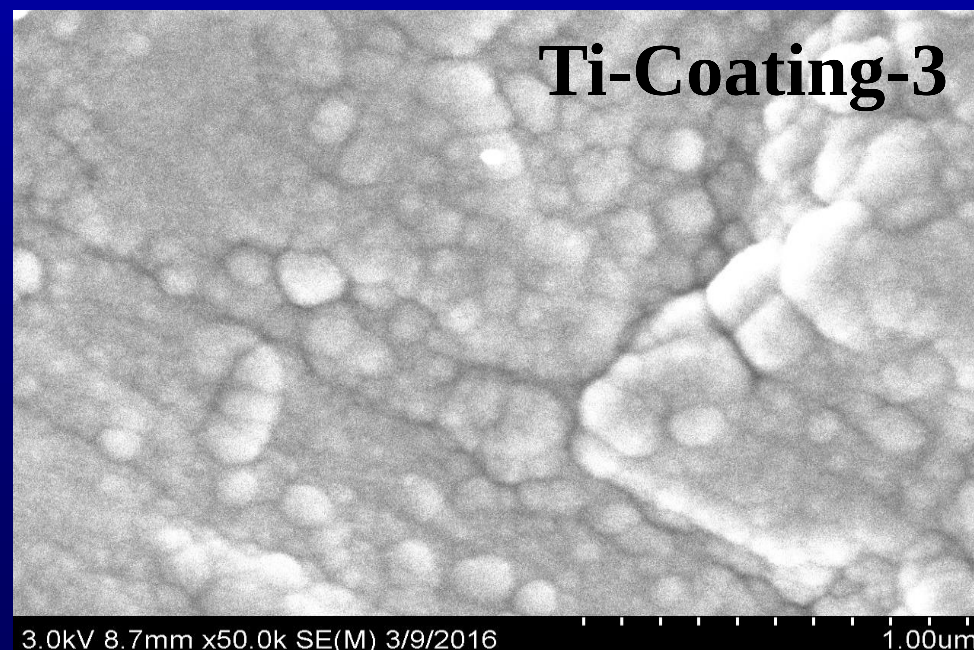


Strong dependence on temperature indicating densification/high crystallinity at higher temperature

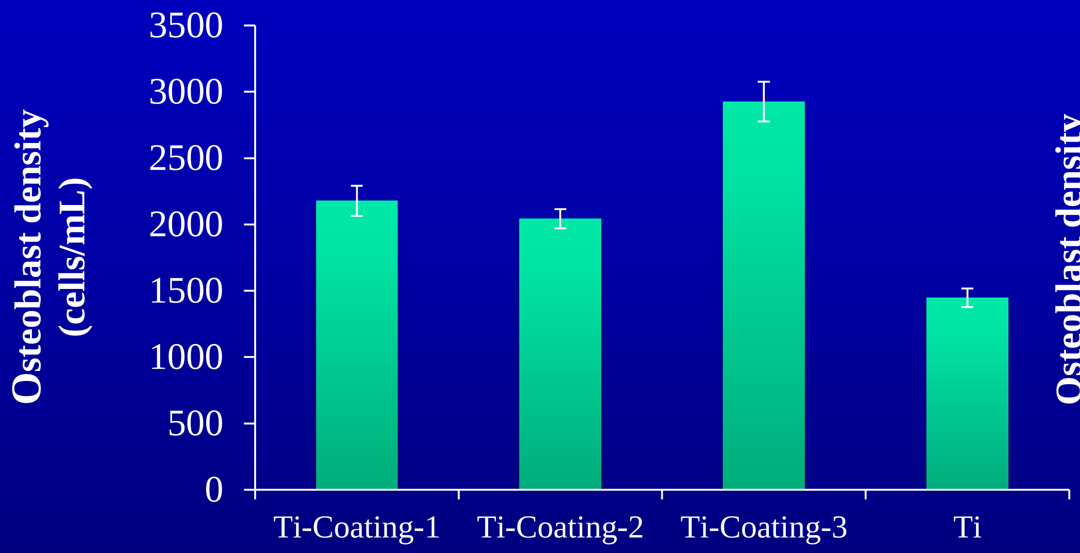

Ti
3.0kV 8.5mm x50.0k SE(M) 3/9/2016
1.00um


Ti-Coating-1
3.0kV 8.8mm x50.0k SE(M) 3/8/2016
1.00um

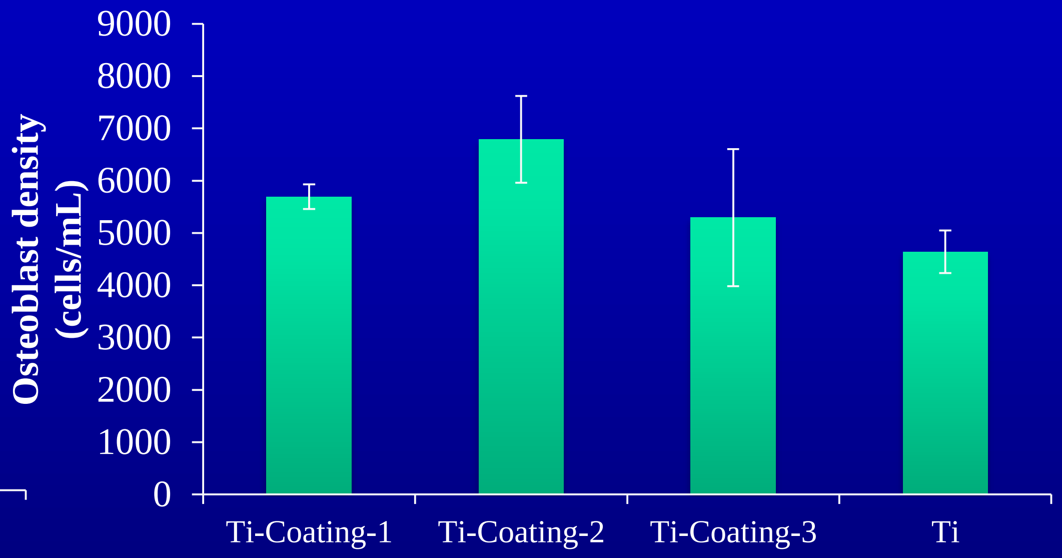

Ti-Coating-2
3.0kV 8.6mm x50.0k SE(M) 3/8/2016
1.00um


Ti-Coating-3
3.0kV 8.7mm x50.0k SE(M) 3/9/2016
1.00um

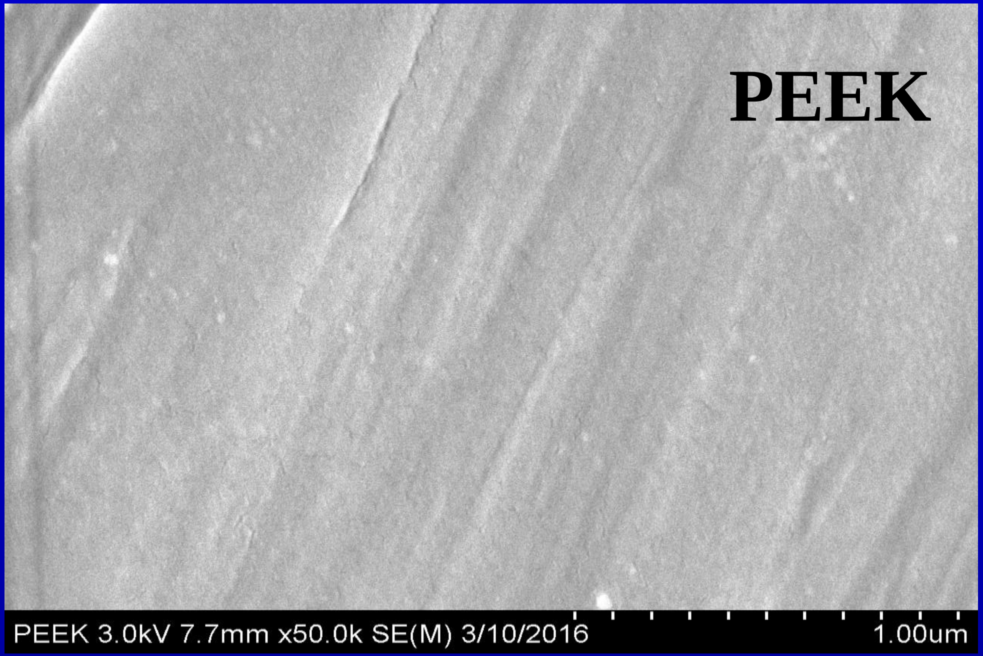
Osteoblast density increases on Ti samples coated with Ti using ALD

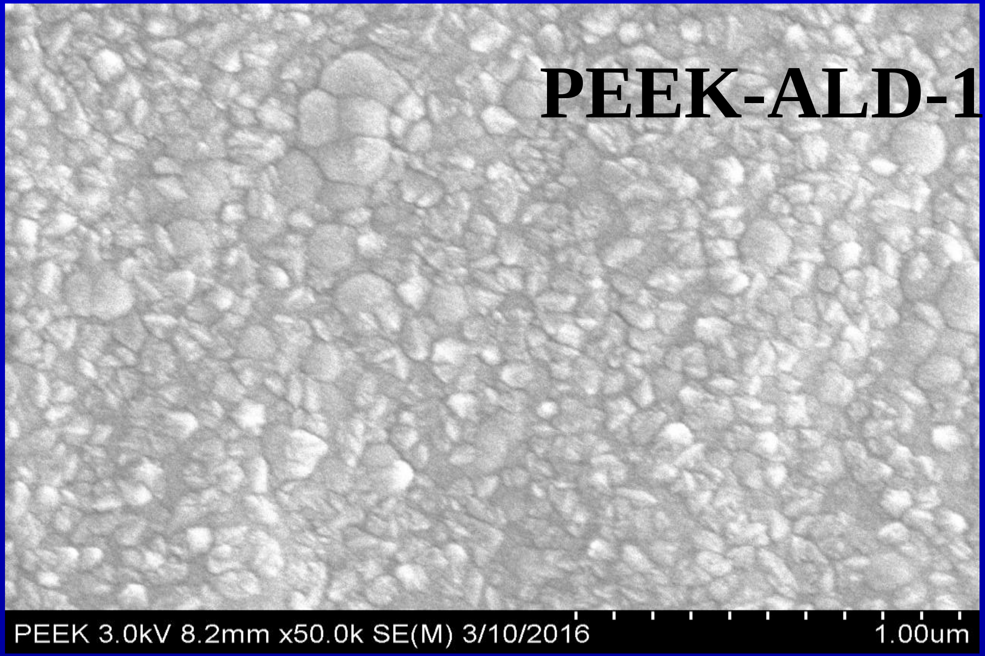


Osteoblast adhesion on Ti samples with different TiO_2 coatings.
Data represents mean ± SD.

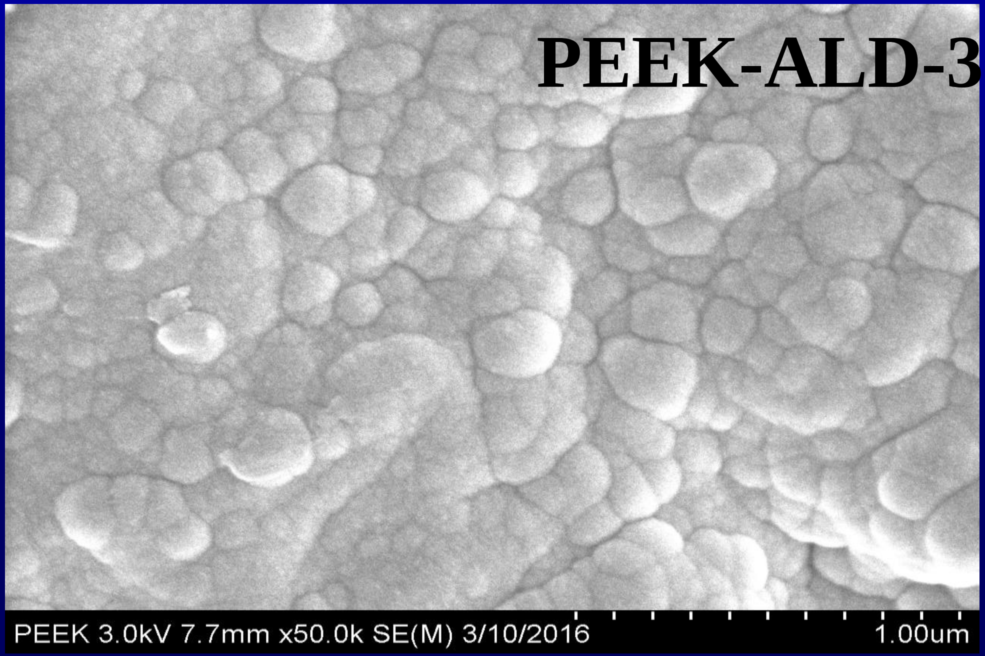


Osteoblast proliferation on Ti samples with different TiO_2 coatings after 7 days. n=3.
Data represents mean ± SD.

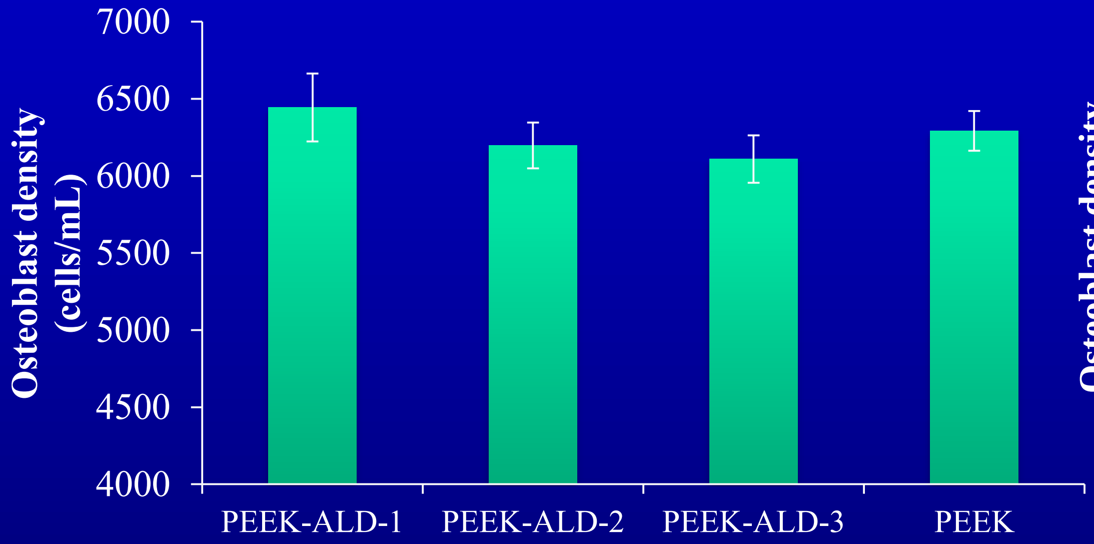

PEEK
PEEK 3.0kV 7.7mm x50.0k SE(M) 3/10/2016
1.00um

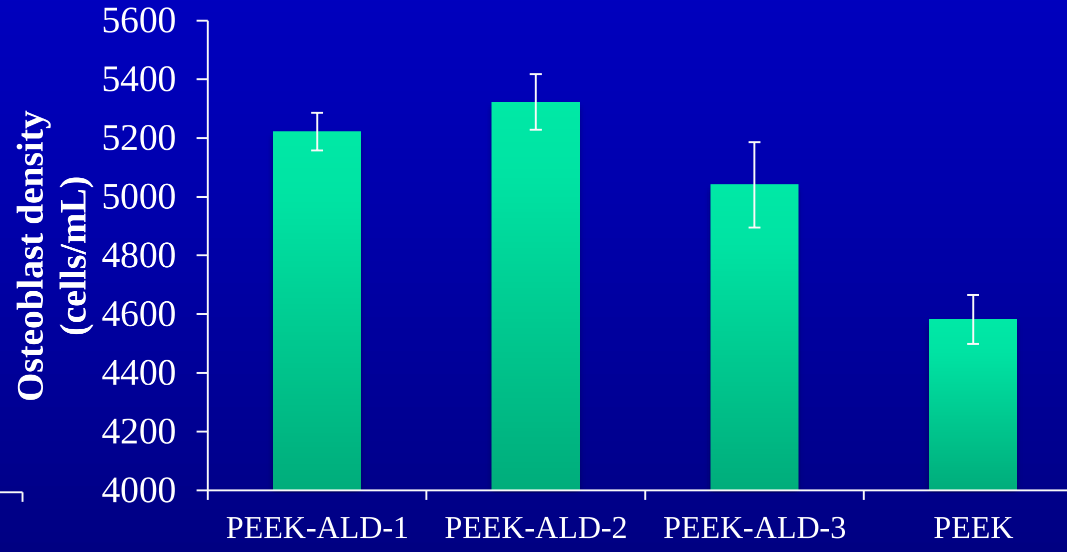

PEEK-ALD-1
PEEK 3.0kV 8.2mm x50.0k SE(M) 3/10/2016
1.00um


PEEK-ALD-2
PEEK 3.0kV 8.1mm x50.0k SE(M) 3/10/2016
1.00um


PEEK-ALD-3
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 TiO_2 coatings. n=3
Data represents mean ± SD.

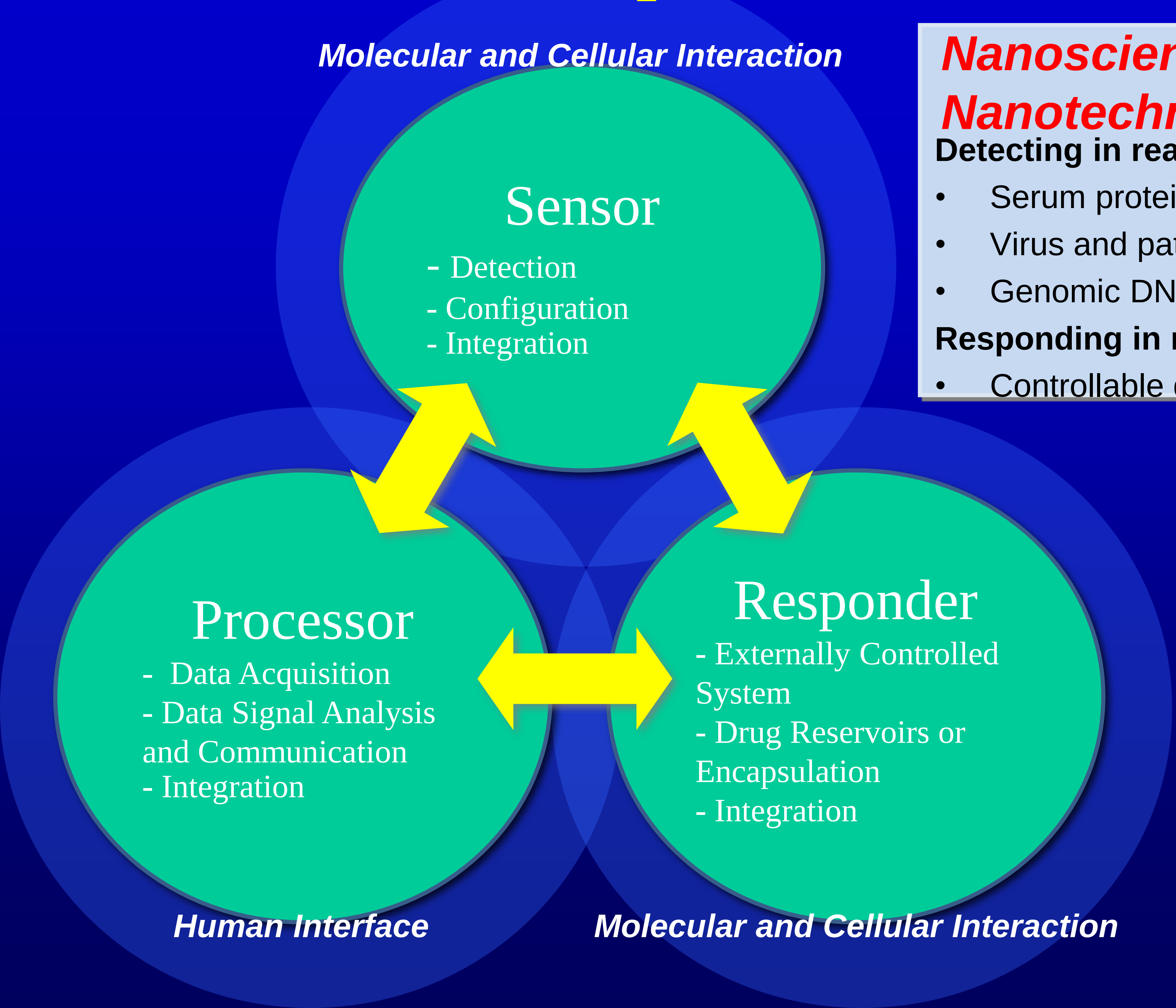
Osteoblast proliferation on PEEK samples with different TiO_2 coatings after 7 days. n=3
Data represents mean ± SD.

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 #4: We need implantable sensors to create more personalized medicine.

Need Development of In Situ Sensors



Nanoscience and Nanotechnology

Detecting in real time:

- Serum proteins and disease marker proteins.
- Virus and pathogens
- Genomic DNA

Responding in real time:

- Controllable drug delivery system

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

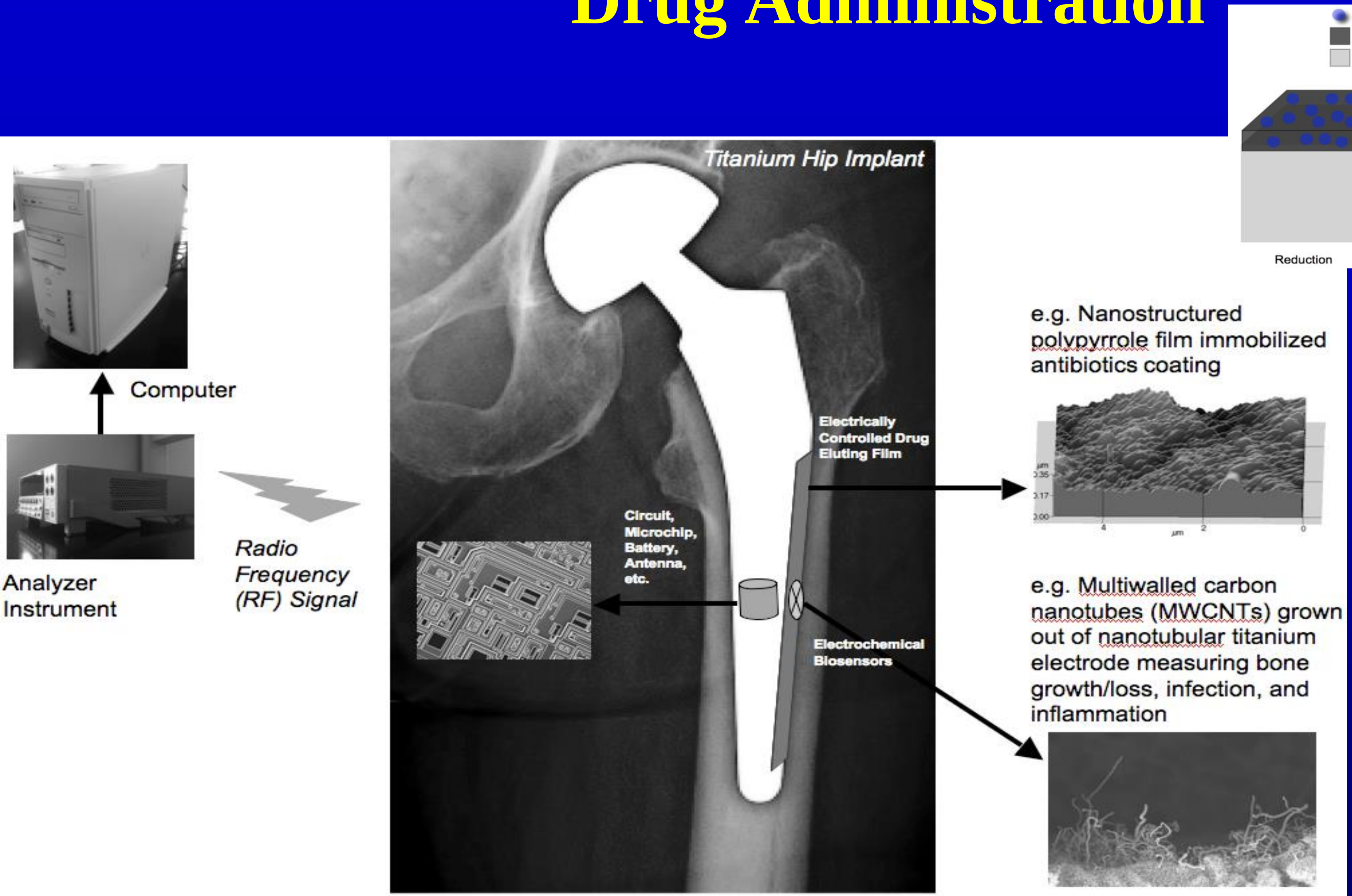
We have cells that do this in the body

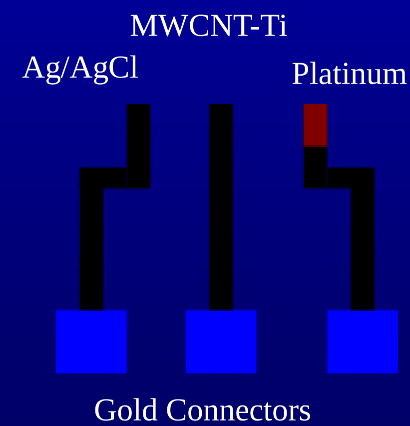
But is this how our body senses events ?

We need sensors that behave more like our immune system.

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

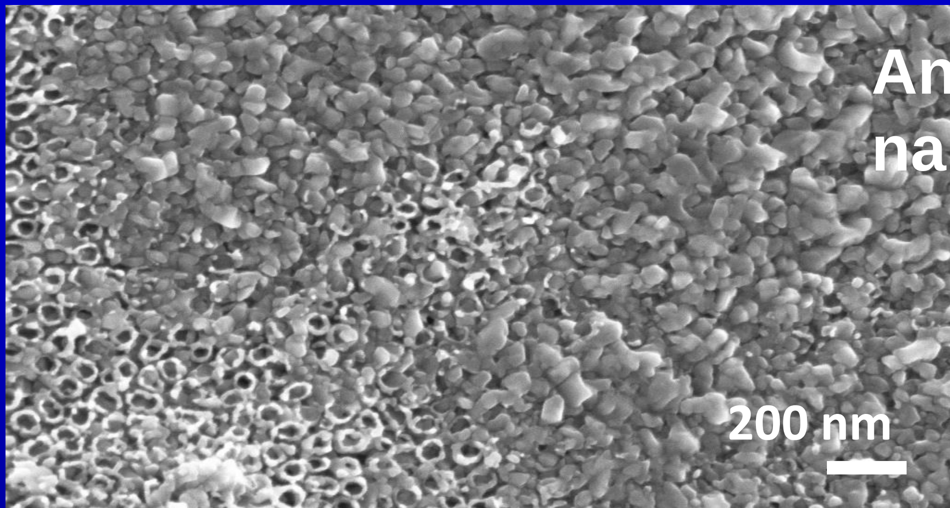
Basic Components of a Closed-Loop Sensing and Drug Administration

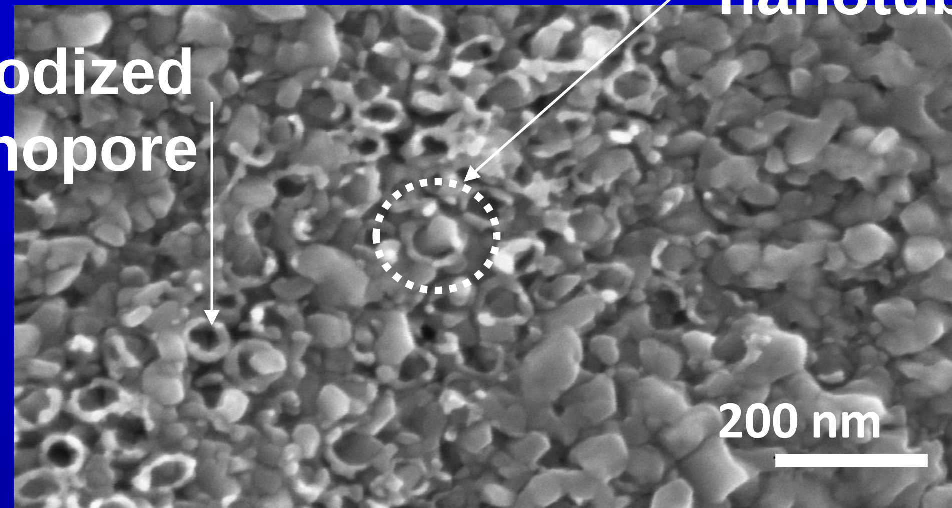




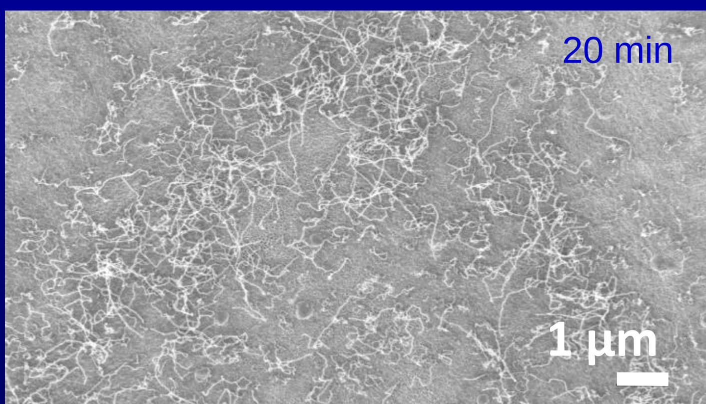
Real-time Detection of Proteins using Sensors and Releasing Drugs from a Polypyrrole Coating

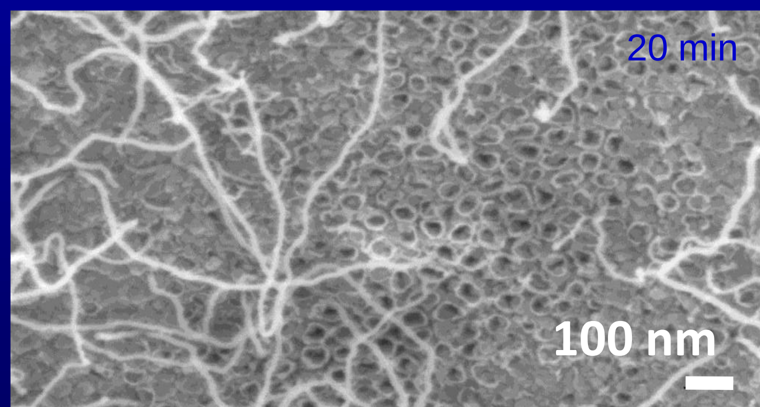
Results: Our Sensor

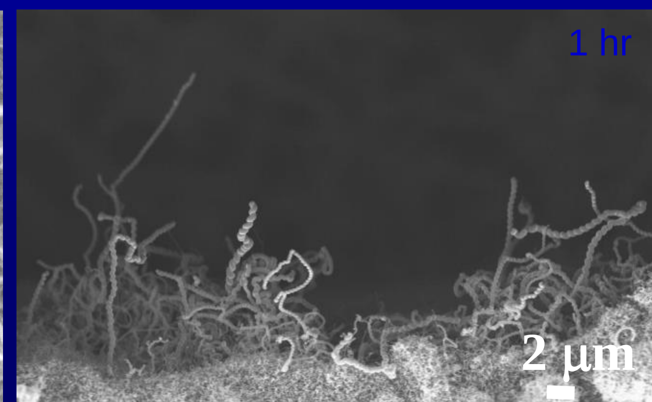




CNTs grown from the nanotubes of anodized Ti **without** a cobalt catalyst using CVD for 20 min.



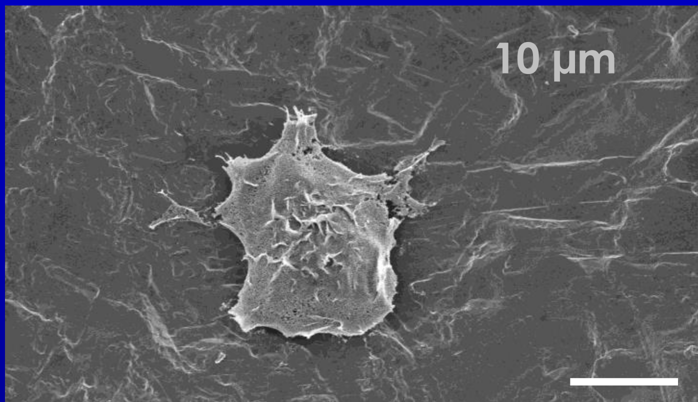


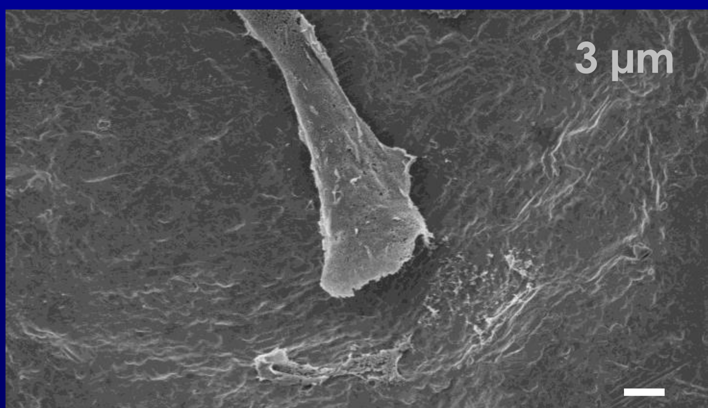


CNTs grown from the nanotubes of anodized Ti surface **with** a cobalt catalyst using CVD for 20 min and 1 hr.

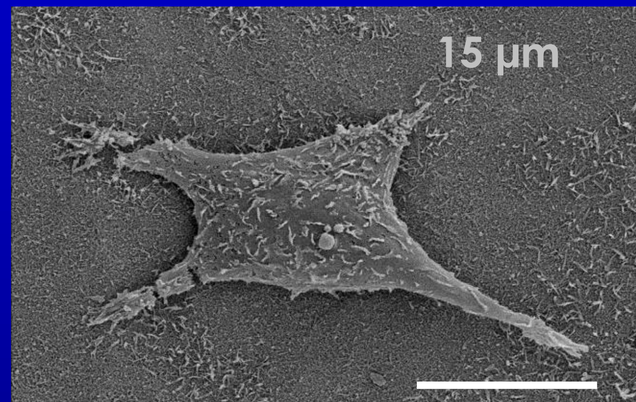
Results: Our Sensor

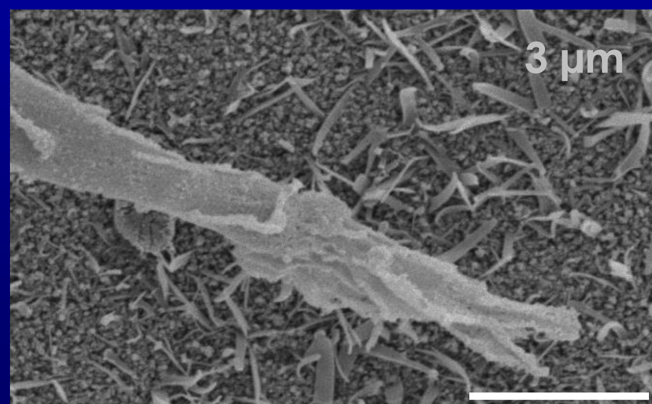
Titanium





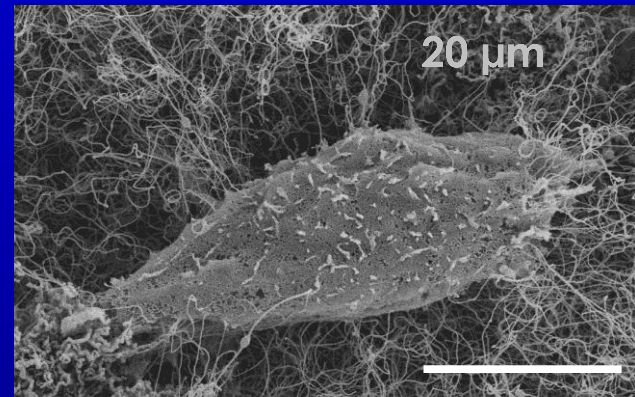
Anodized titanium

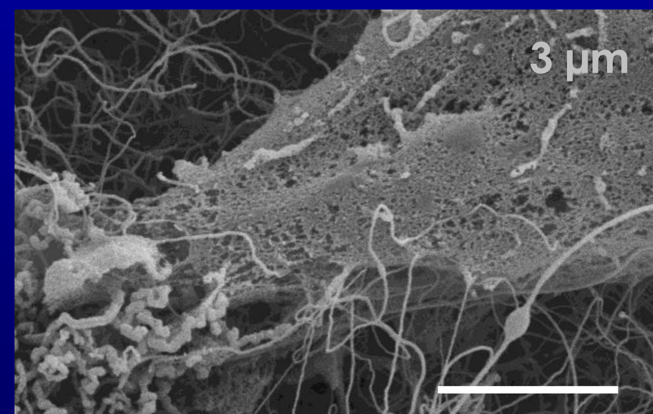




Multiwalled carbon nanotubes grown out of anodized titanium

(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

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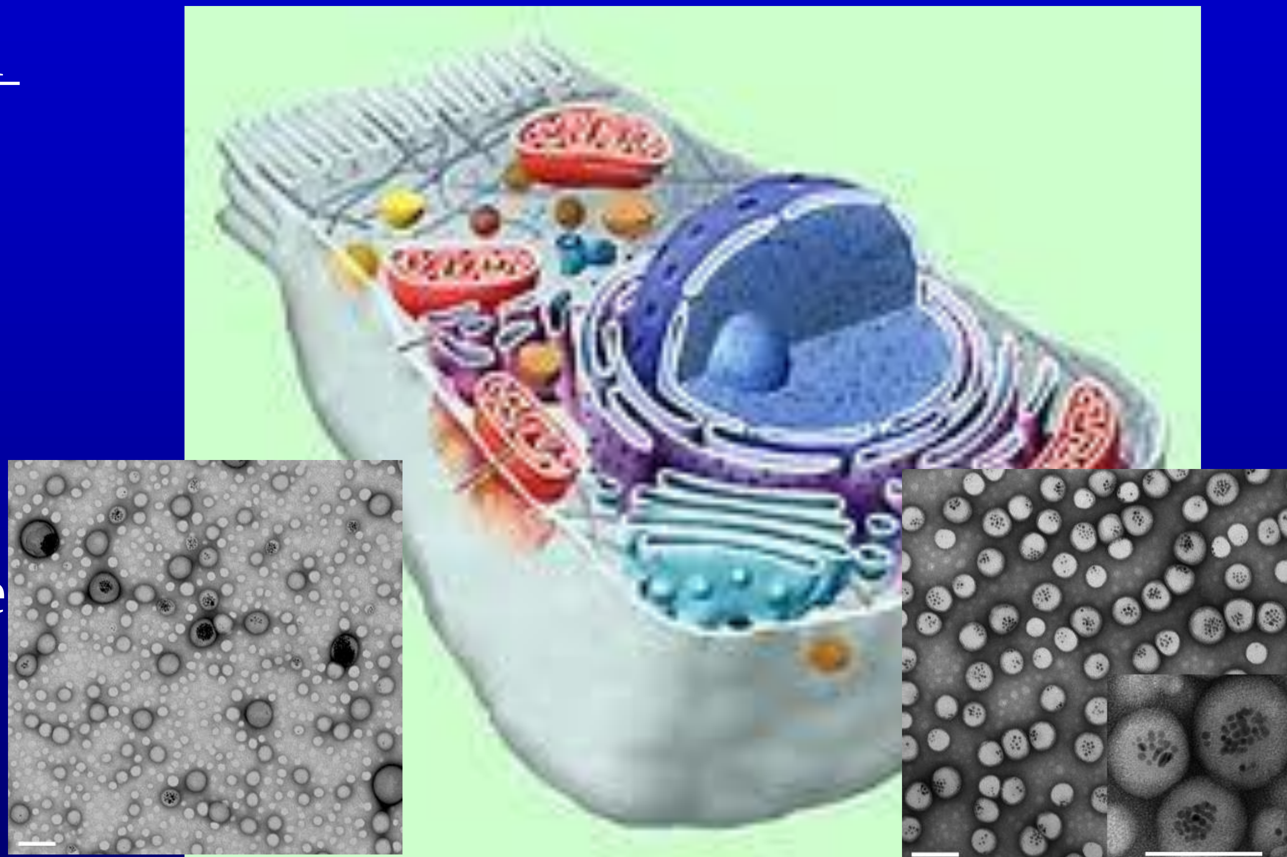

Need processing capability

Need responding capability to aid immune cells

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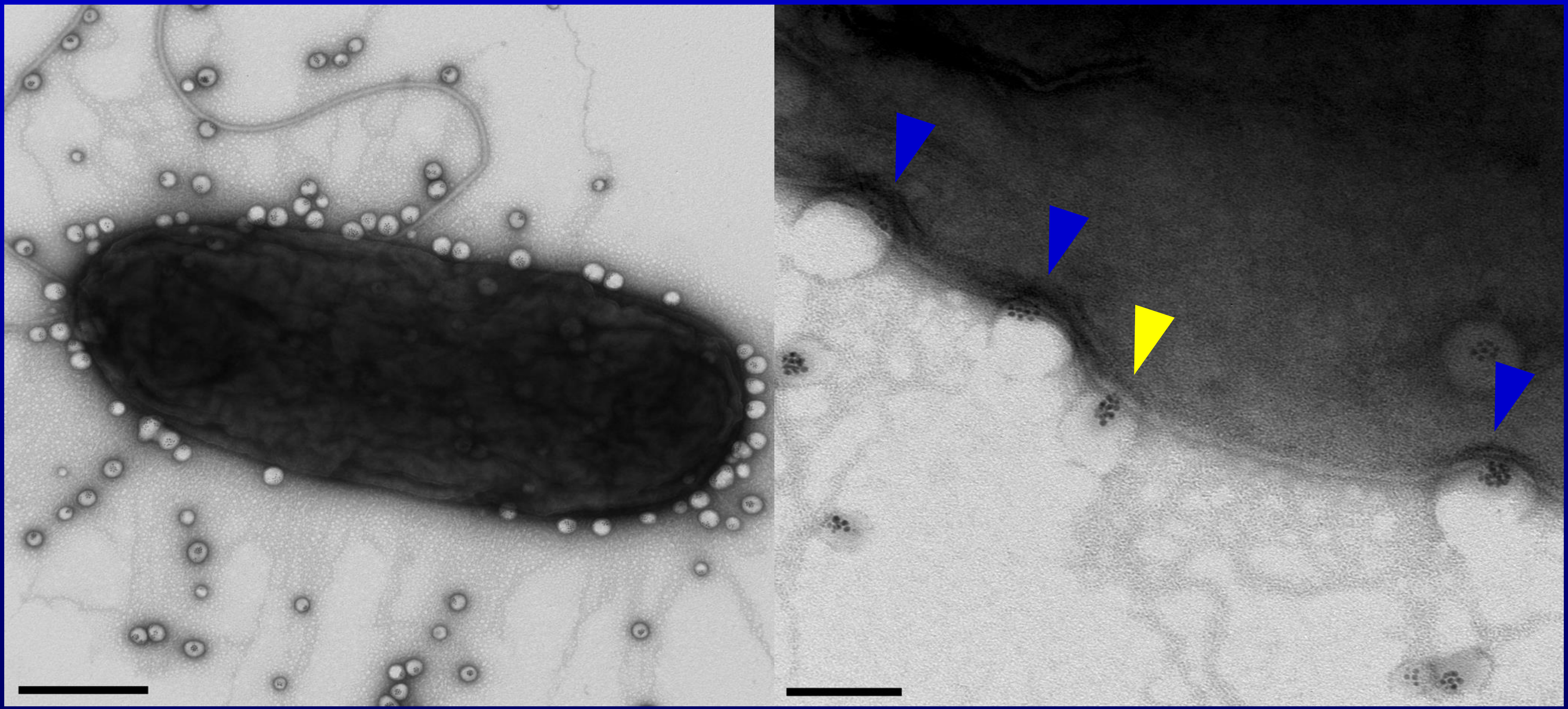
Same approach and sensors can be used on medical device surfaces and outside the body: Does not have to be a synthetic cell but nanotechnology needs to be involved.

Synthetic Immune Nanoparticles



Scale Bars = 100nm

Geilich BM, et. al. *Nanoscale.* 7 (2015) 3511-3519

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 generalize for 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.

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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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