Bringing the Hospital to the Patient: Advances in Implantable Nano Sensors

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2020-03-05

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Life Expectancy in the U.S.

The Economist

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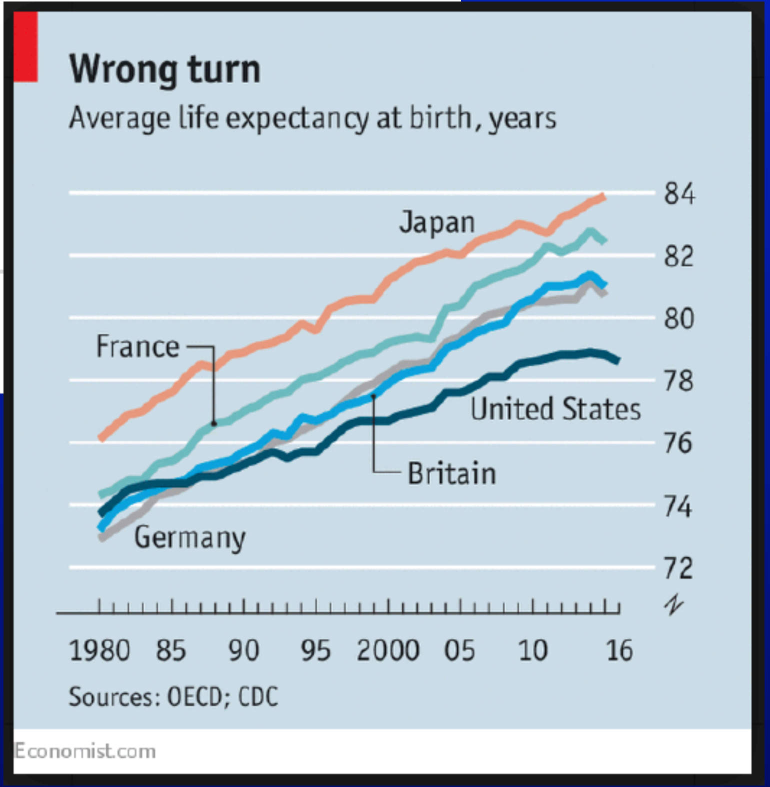
Not great, again

Life expectancy in America has declined for two years in a row

That's not really meant to happen in developed countries

Print edition | United States ›

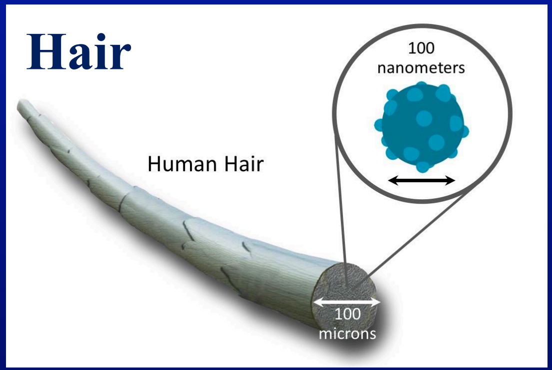
Jan 4th 2018



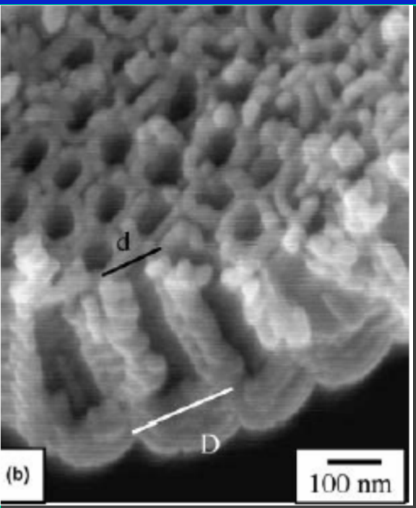
25 Years Ago We Turned to Nanomedicine for Some Answers

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

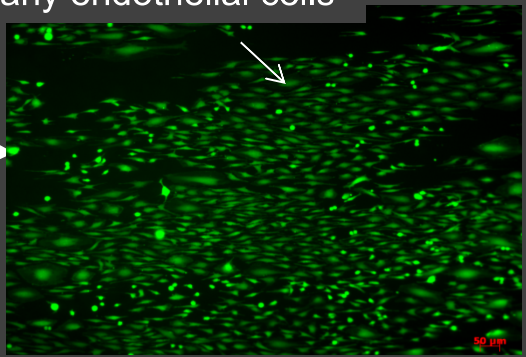
Nanomedicine: Applications of nanotechnology in medicine.

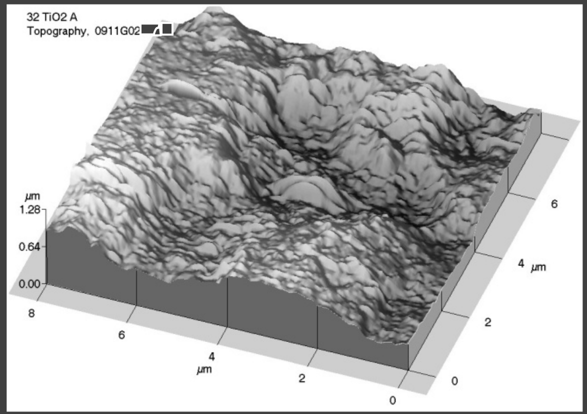


Nanostructured Surfaces Improving Health *Now*

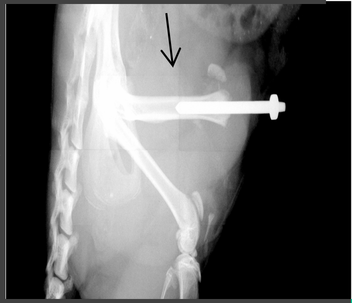


Many endothelial cells



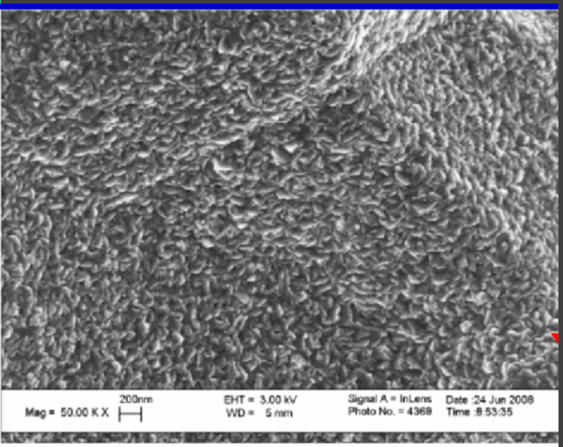


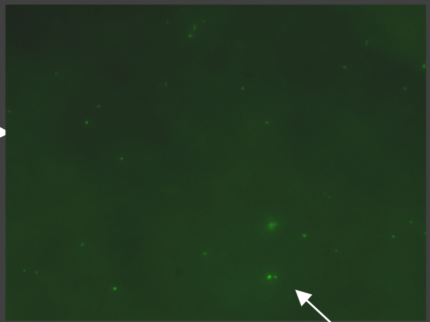
Increased bone growth



Bone Growth

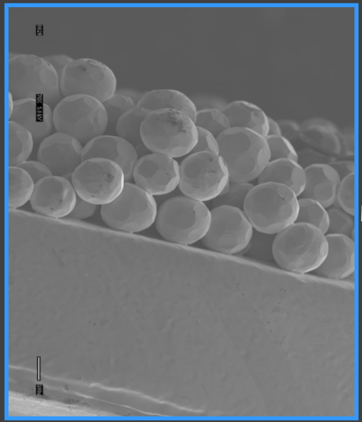
Vascular Endothelialization



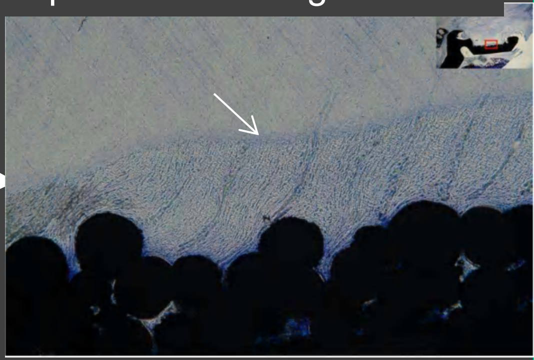


Few *Staph Epi*

Antibacterial

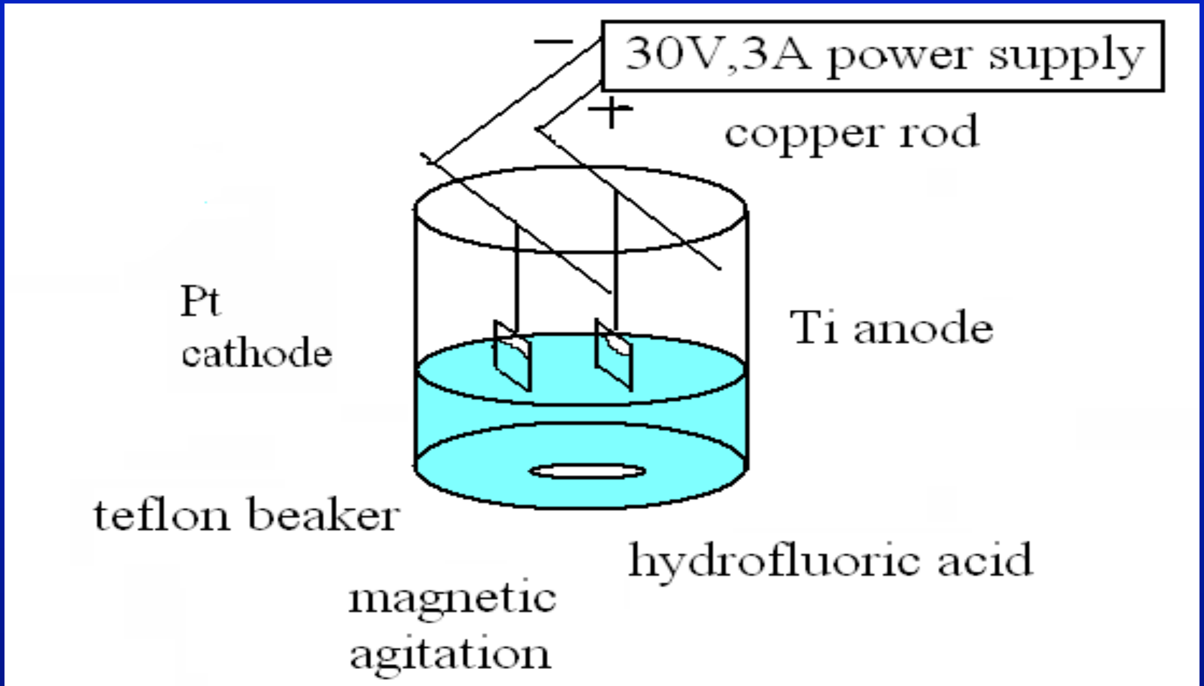


Perpendicular collagen fibers



Orthopedic Soft Tissue

Helping Amputees



Sketch map of anodization system

PROCEDURES:

Pretreatment: chemical polishing using HF/HNO_3 mixture

Anodization: 0.5 or 1.5%HF

Voltage: 20V

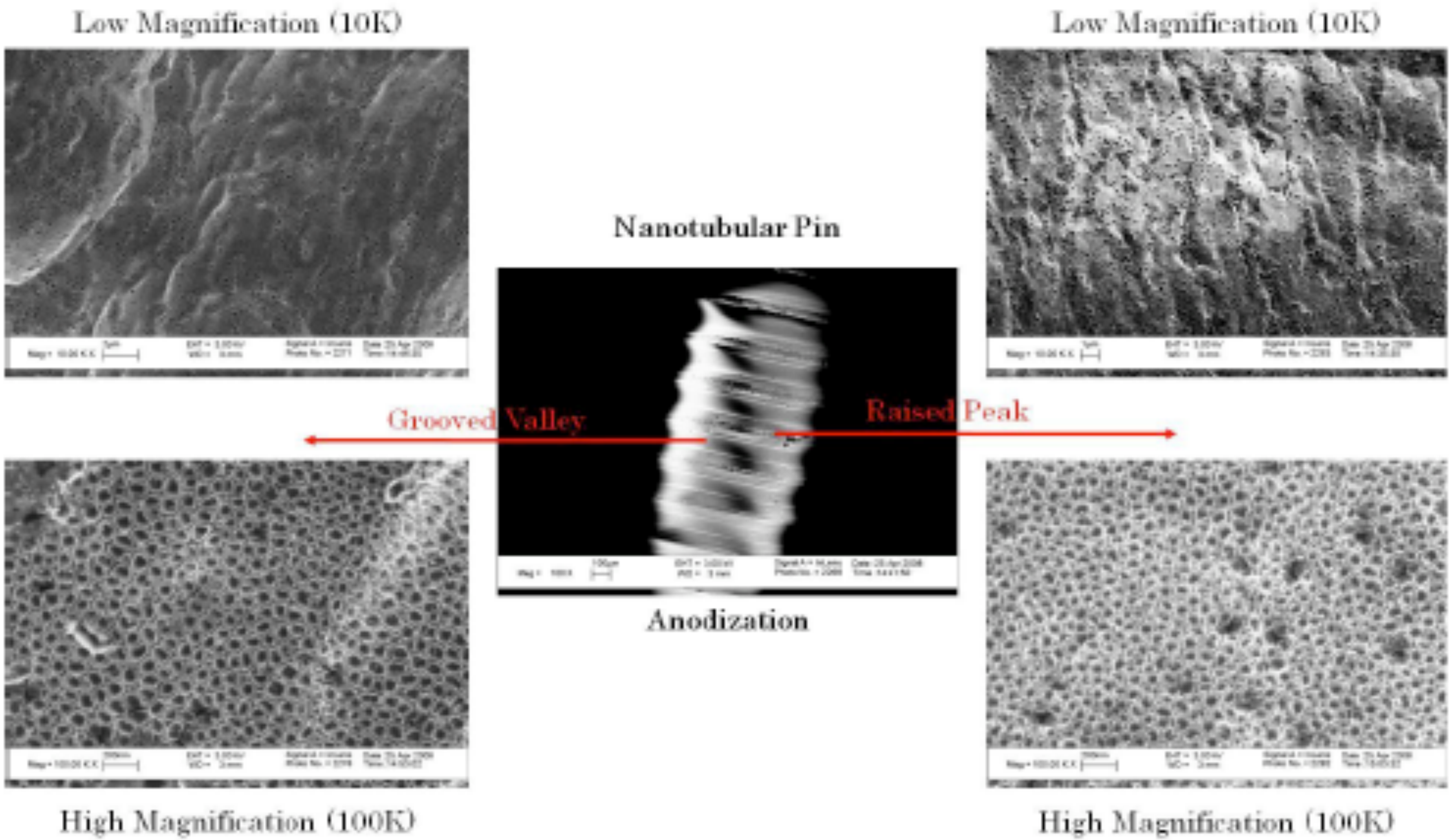
Time: 20 min

Rinse and dry

Clean: acetone and ethanol

Sterilize

Anodized Ti Nanotubular Screws for Osseointegrated Amputee Devices

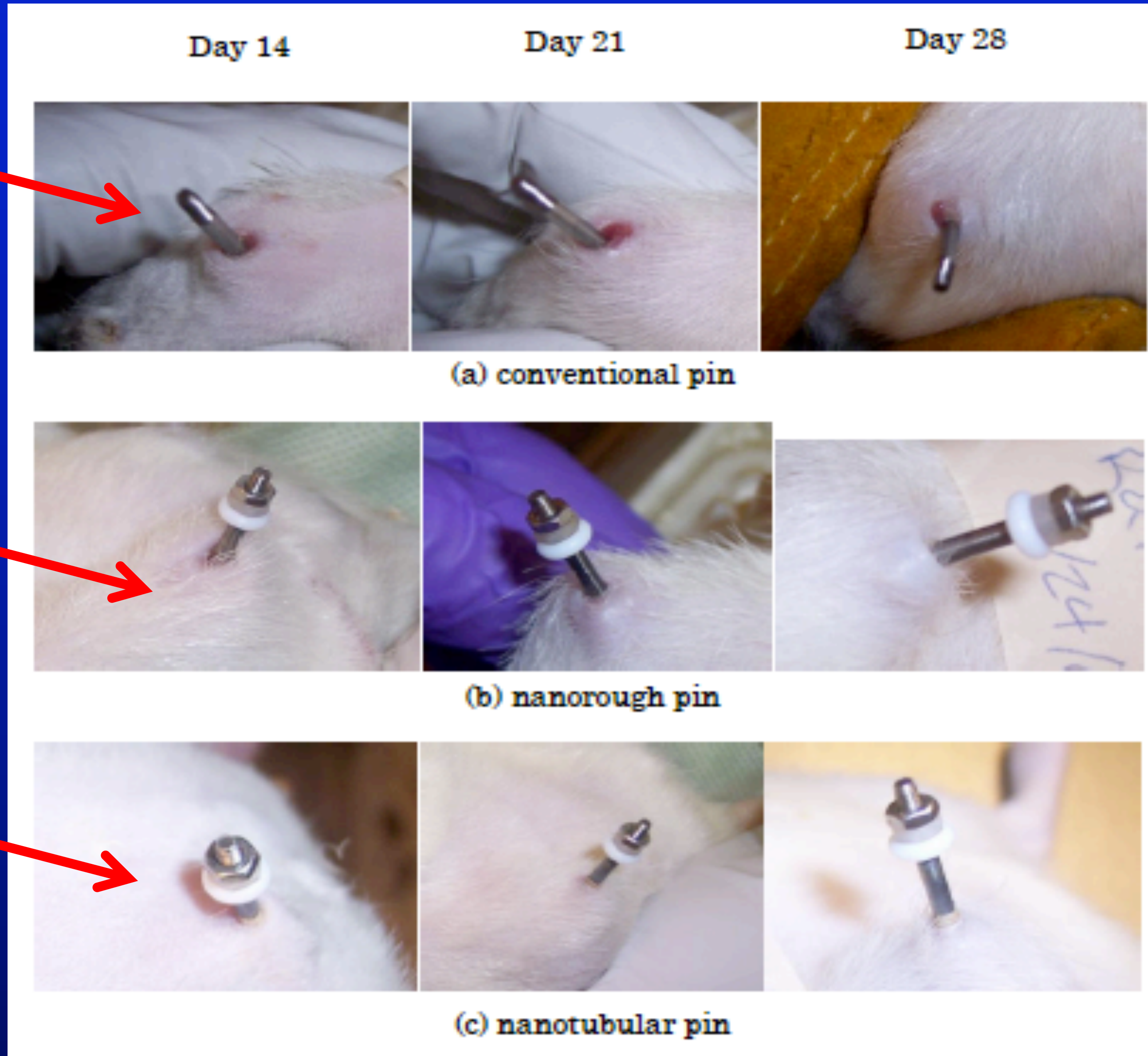


DISTRIBUTION STATEMENT A. Approved for public release; distribution is unlimited

Closed Wound with No Infection Surrounding Nanotextured Screws Only

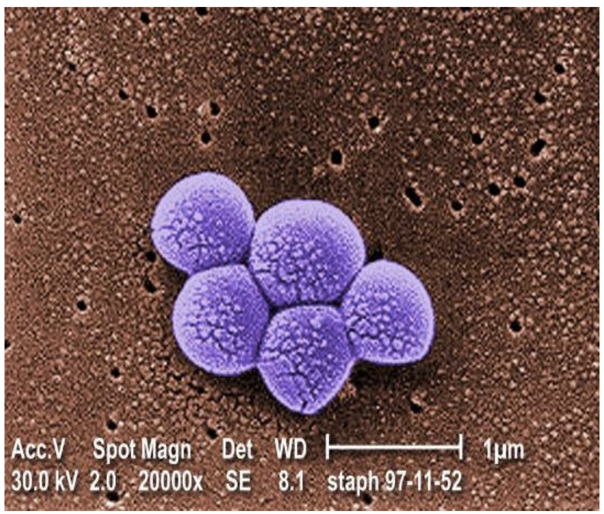
Open wound

Anodized nanostructured screws decrease infection, promote skin closure, and increase bone growth



The Emergence of Antibiotic Resistant Bacteria

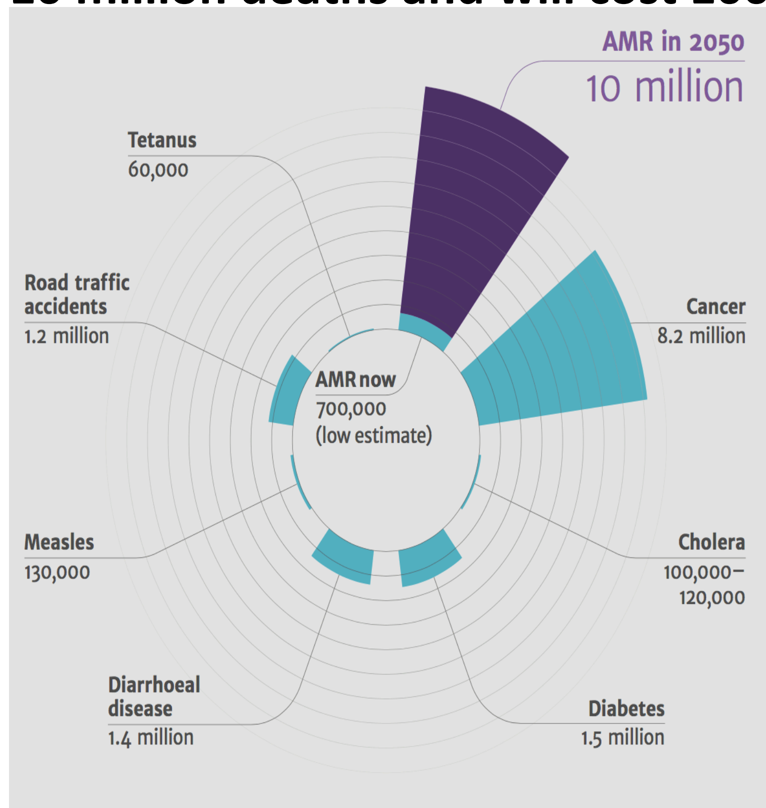
Colistin-resistant *Escherichia coil* (*E.coil*)



Methicillin-resistant *Staphylococcus aureus* (MRSA)

Bacterial antibiotic resistance causes

- **More than 2 million cases of illness and 23 thousand deaths annually (in the U.S. only)**
- **In 2050, about 10 million deaths and will cost 100 trillion USD annually**



https://www.cdc.gov/drugresistance/;
https://amr-review.org/Publications.html

THE PROBLEM. ANTIMICROBIAL RESISTANCE TO ANTIBIOTICS (AMR)

What does the future looks like?

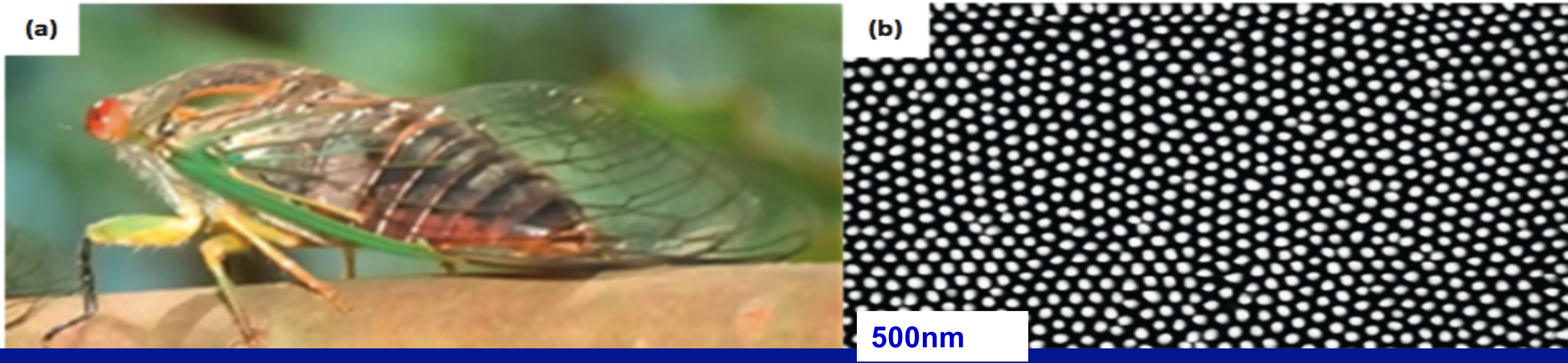
BY 2050, ONE PERSON WILL DIE EVERY 3 SECONDS

So why do nanostructured surfaces *reduce* infection and *increase* tissue growth without drugs ???

Nanostructures in Nature

It has been found that the nanopillars on cicada wings are inherently antibacterial, irrespective of surface chemistry.

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

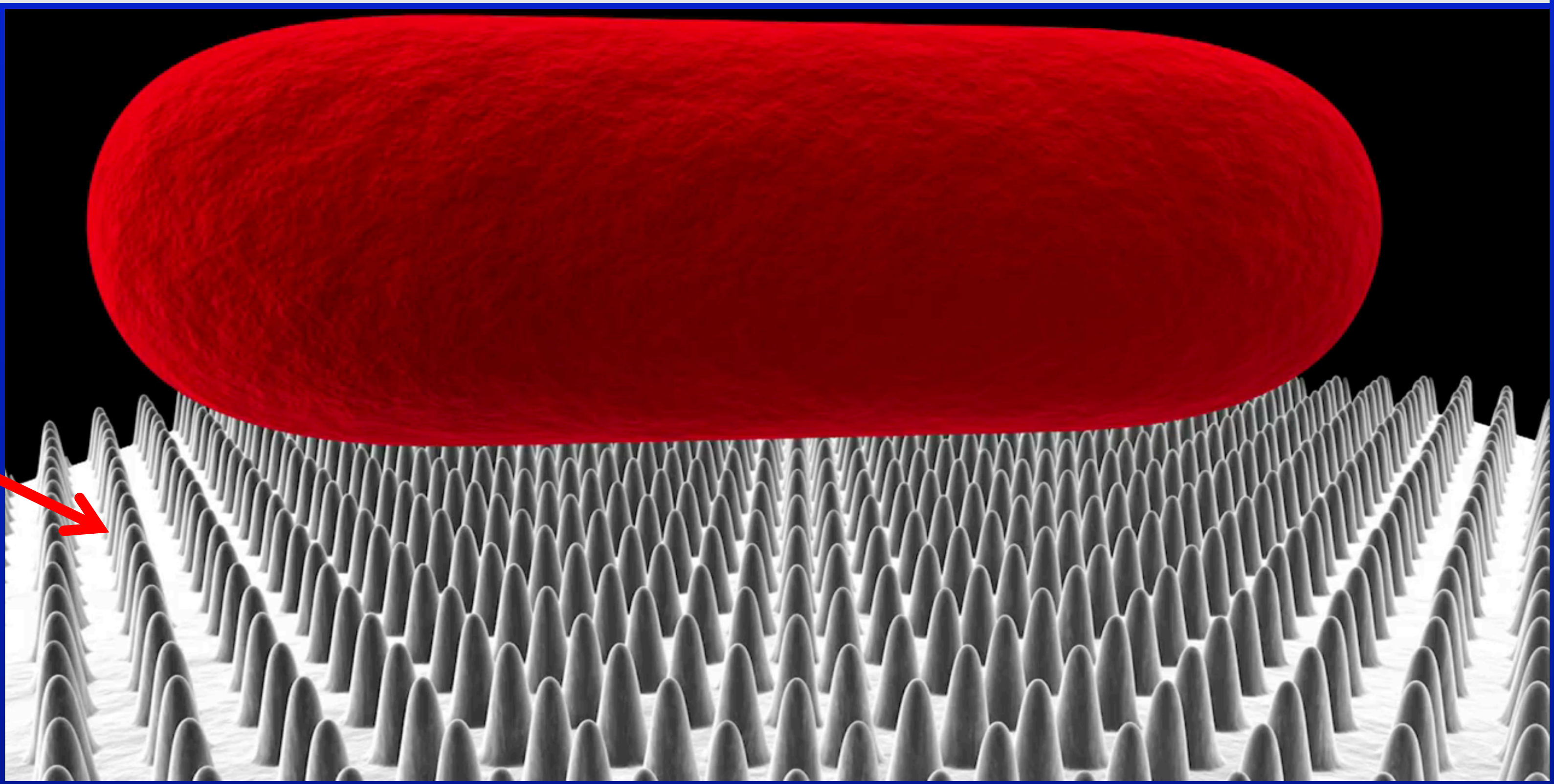


The nanopillar structures of the wing surface are spaced 170nm apart from center to center. Each pillar is ~200nm tall, with a conical shape and a spherical cap 60nm in diameter.

Pogodin et al. Biophysical model of bacterial cell interactions with nanopatterned cicada wing surfaces. *Biophys. J.* 2013, 104, 835-840.

Possible Reason: Biophysical model

These surfaces can decrease infection and promote tissue growth

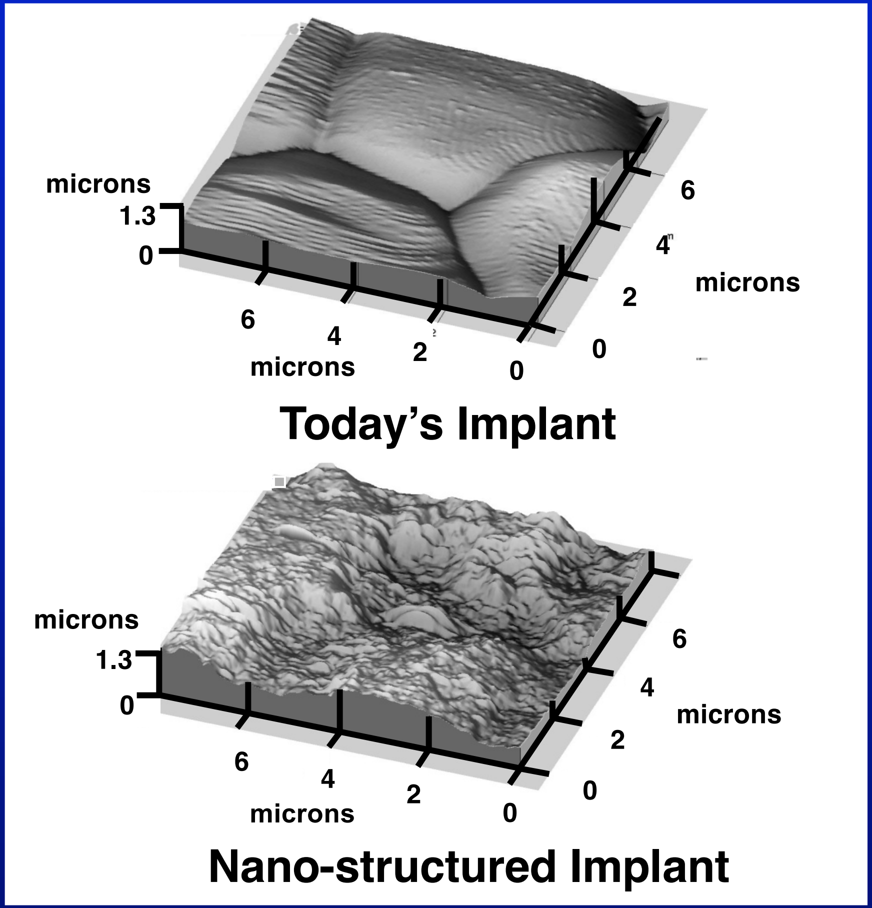


Biophysical model of bacterial cell interactions with nanopillars

Mechanism: As the bacteria try to attach onto the nanopillar structures, the cell membrane stretches in the regions suspended between the pillars. If the degree of stretching is sufficient, this may lead to no attachment or cell rupture.

Pogodin at al. *Biophysical model of bacterial cell interactions with nanopatterned cicada wing surfaces*. Biophysical Journal, Volume 104, pp. 835-840, 2013.

Possible Reason: Unique Properties of Nano-structured Medical Devices



T. J. Webster, Advances in Chemical Engineering Vol. 27, 125-166, 2001.

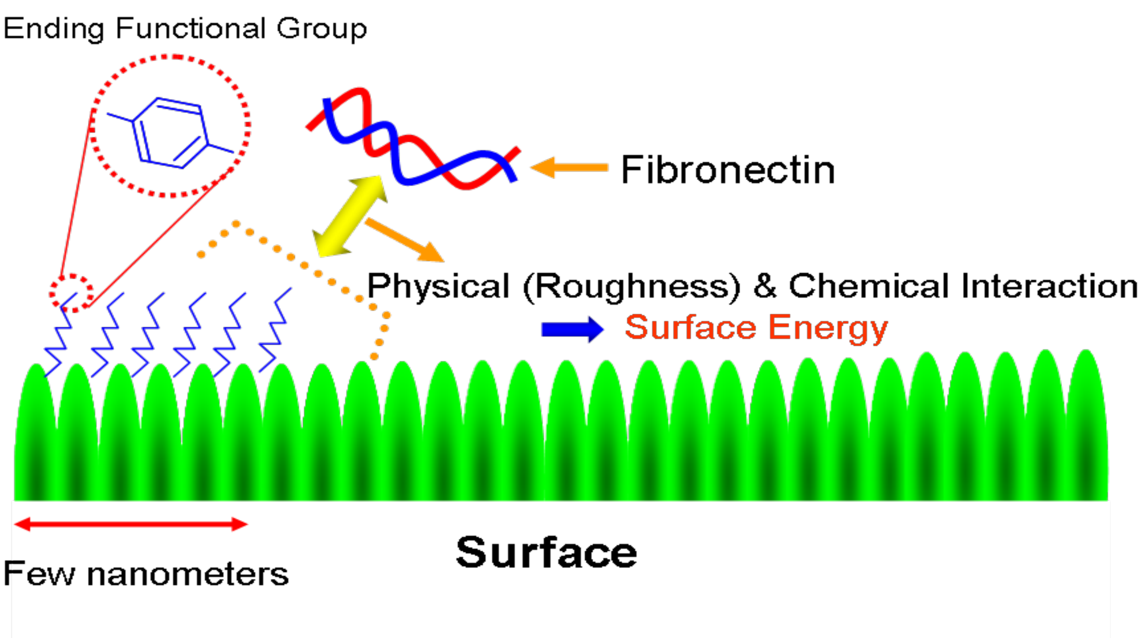
Compared to today's implant materials, nano-structured materials possess enhanced:

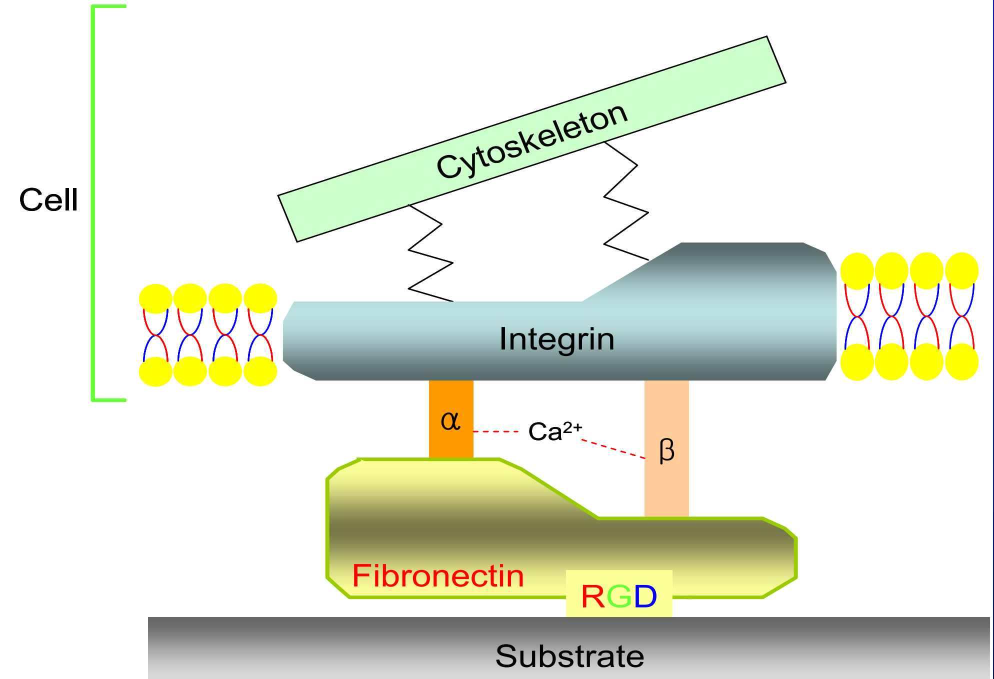
- surface area,
- radio-opacity,
- catalytic,
- optical,
- mechanical,
- electrical, and
- surface

properties that may improve existing biomedical implant applications.

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 interface[1-6]





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).

Predicting Optimal Surface Roughness

Step 1: Obtain data for the surface tension of at least three liquids.

Solvents	Surface Tension (mN/m)		
	γ	γ_p	γ_d
DI Water	72.8	46.4	26.4
Ethylene Glycol	47.7	21.3	26.4
Glycerol	63.4	26.4	37

Step 2: Obtain contact angle measurements.

Contact Angle (θ)		Square Lattice	Hive™ Lattice
S(1)	DI Water	91.0°	72.6°
S(2)	Ethylene Glycol	46.0°	48.9°
S(3)	Glycerol	94.4°	80.5°
Wenzel-Corrected Contact Angle (θ_w)		**Square Lattice**	**Hive™ Lattice**
S(1)	DI Water	91.0°	69.7°
S(2)	Ethylene Glycol	45.1°	40.4°
S(3)	Glycerol	94.5°	79.0°

Step 3: Apply Owens/Wendt theory for surface energy values.

$$\frac{\sigma_L(\cos\theta + 1)}{2(\sigma_L^D)^{1/2}} = (\sigma_S^P)^{1/2}\frac{{\sigma_L^P}^{1/2}}{{\sigma_L^D}^{1/2}} + (\sigma_S^D)^{1/2}$$

σ_L^D = dispersive component of the surface tension of the wetting liquid

σ_L^P = polar component of the surface tension of the wetting liquid

σ_S^D = dispersive component of the surface energy of the solid

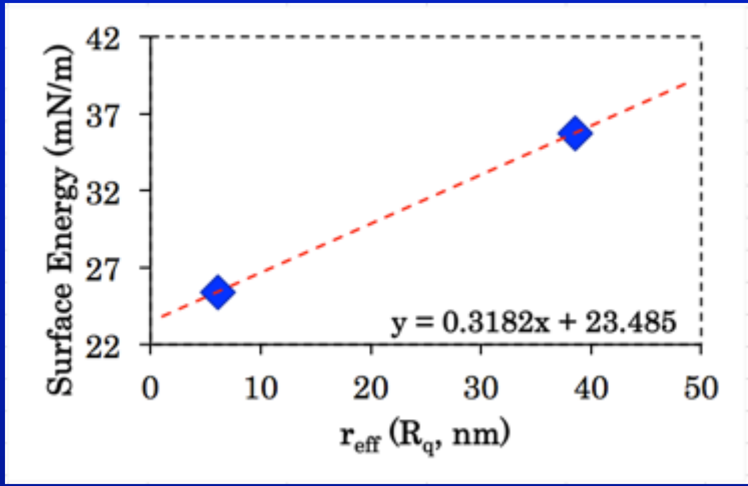
σ_S^P = polar component of the surface energy of the solid

https://www.kruss-scientific.com/fileadmin/user_upload/website/literature/kruss-ar213-en.pdf

Predicting Optimal Surface Roughness

Step 4: Apply Khang Equation

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



Substrates (Ti6-Al4-V)	Surface Energy (mN/m)			Root-Mean-Square Roughness, R_q (nm)
	γ	γ^p	γ^d	
Square Lattice	25.4	3.4	22.0	6.08
Hive™ Lattice	35.7	30.2	5.5	38.5

Khang D, Kim SY, Liu-Snyder P, Palmore GTR, Durbin SM, Webster TJ. Enhanced fibronectin adsorption on carbon nanotube/poly(carbonate) urethane: Independent role of surface nano-roughness and associated surface energy. Biomaterials. 2007;28:4756–68.

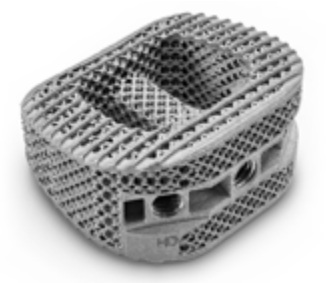
Step 5: Estimate optimal surface roughness

The optimal Ti surface energy for restricting bacterial biofilm attachment to an implant is **42.5 mN/m**.

When ρ = 0.3182 and $E_{0,s}$ = 23.485

$r_{optimal}$ = 60.5 nm

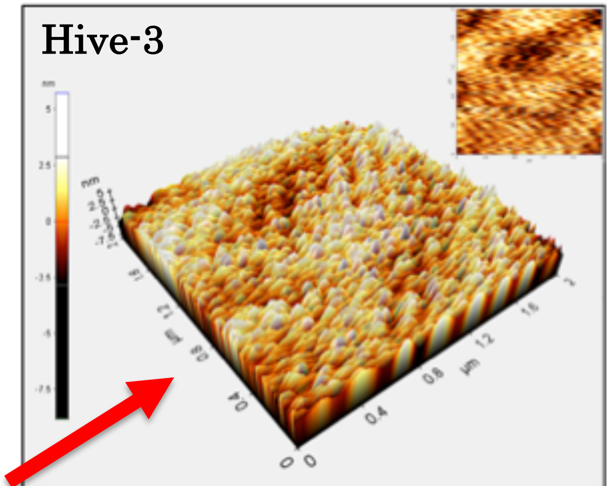
Nanoroughness on 3D Printed Spinal Implants (Hive-3)



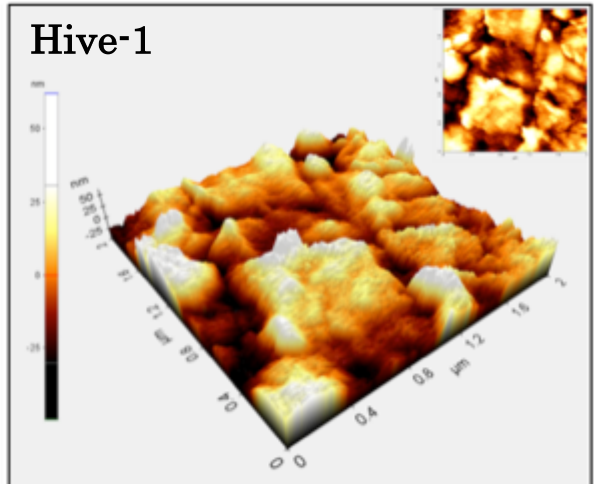
This surface matches our predicted roughness to decrease infection and promote bone growth

Analyses performed on Hive™-1 & Hive™-3 samples, square lattice face.

AFM



Rpv (nm)	Rq (nm)	Ra (nm)	Rz (nm)	Rsk	Rku
14.6	1.46	1.151	13.1	0.151	3.520



Rpv (nm)	Rq (nm)	Ra (nm)	Rz (nm)	Rsk	Rku
110.5	15.6	12.5	107.5	-0.208	2.988

Instrument: Parks Scientific XE-7 AFM
XEI Software

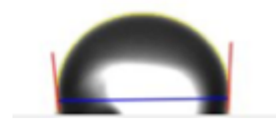
CONTACT ANGLE

DI H_2O

$\theta = 91.0°$

$C_2H_6O_2$

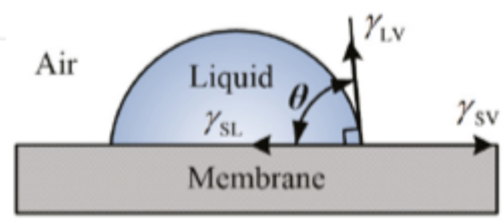
$\theta = 46.0°$



$C_3H_8O_3$

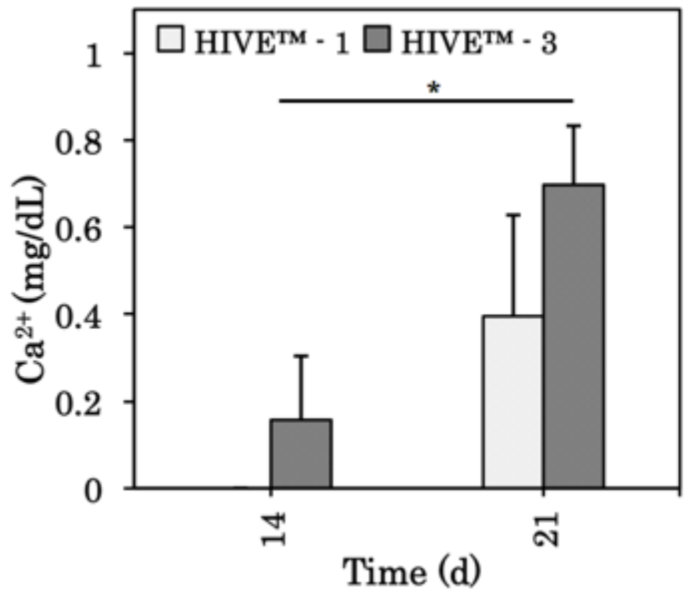
$\theta = 94.4°$

Instrument: Phoenix 150 Contact Angle Analyzer
ImageJ Software



Improved Calcium Deposition on 3D Printed Nano Surface

Calcium Deposition Data – Abcam Calcium Assay Kit



Our prediction works to develop implants that can decrease infection and improve bone growth *without* drugs

*Mineralization assay results are shown, which indicate the capacity for Hive-3™ implants to promote calcium deposition, and, consequently, osteointegration and growth over 14 and 21 days. Data represents the mean ± SD: N=9; *p≤0.05.*

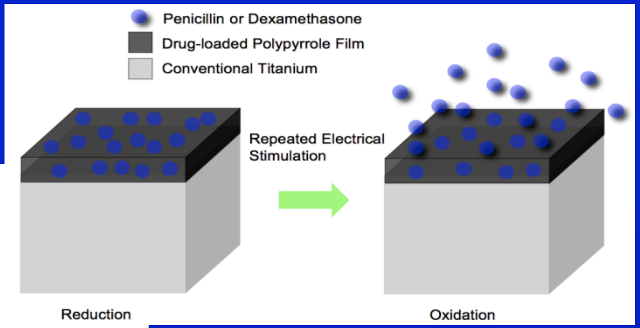
Implantable Nanosensors

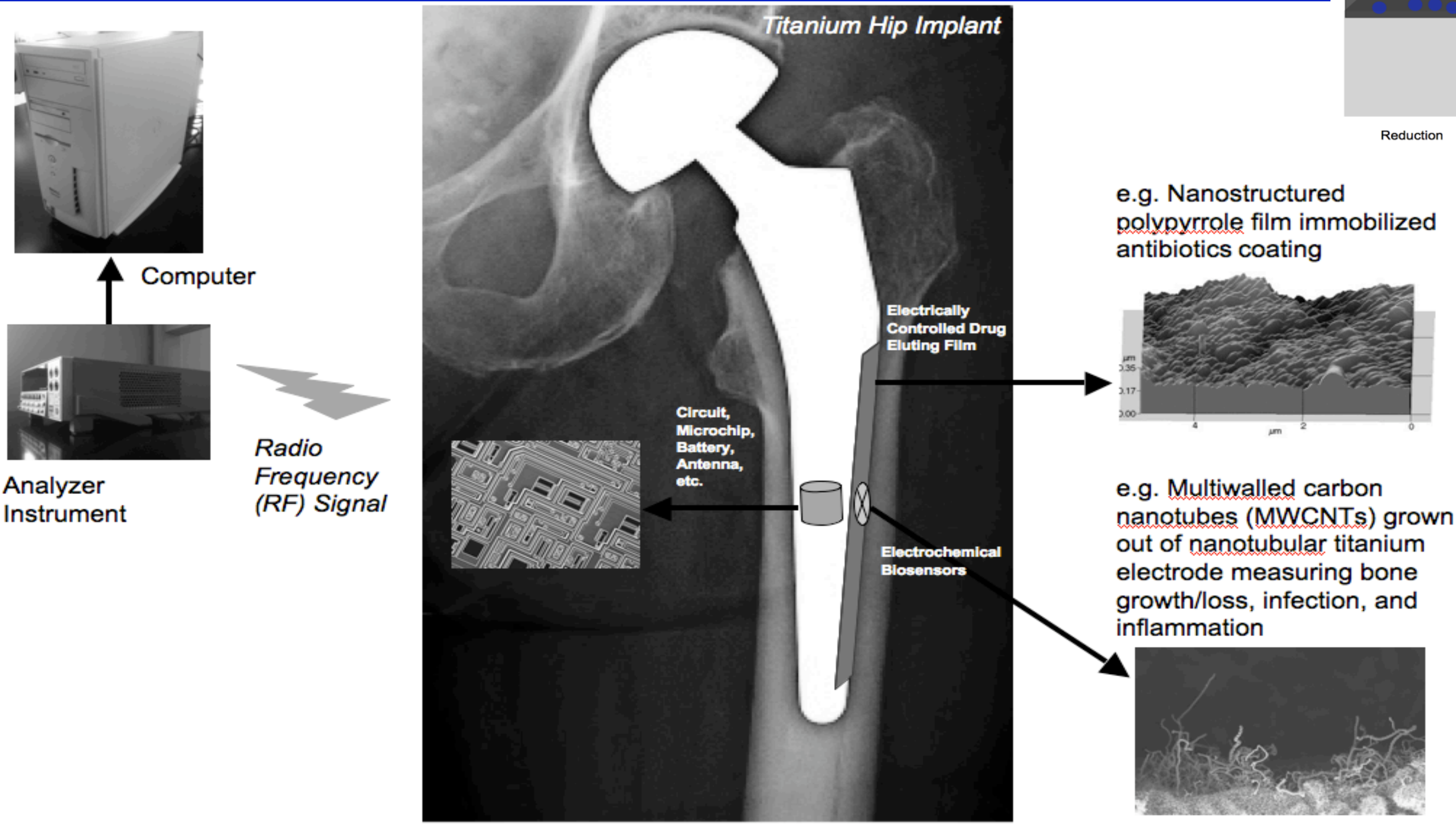
Current Sensors Used in Medicine: Not at all Like our Immune System

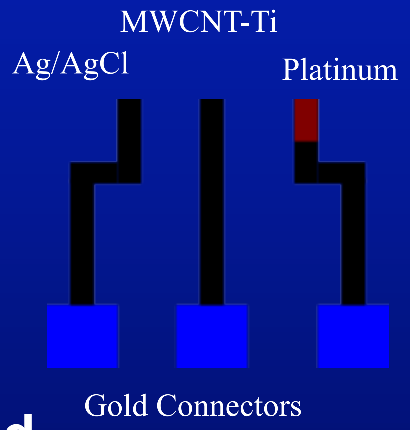
But is this how our body senses events ?

Our body senses "cellular functions"

Implantable Nanosensors: Hip





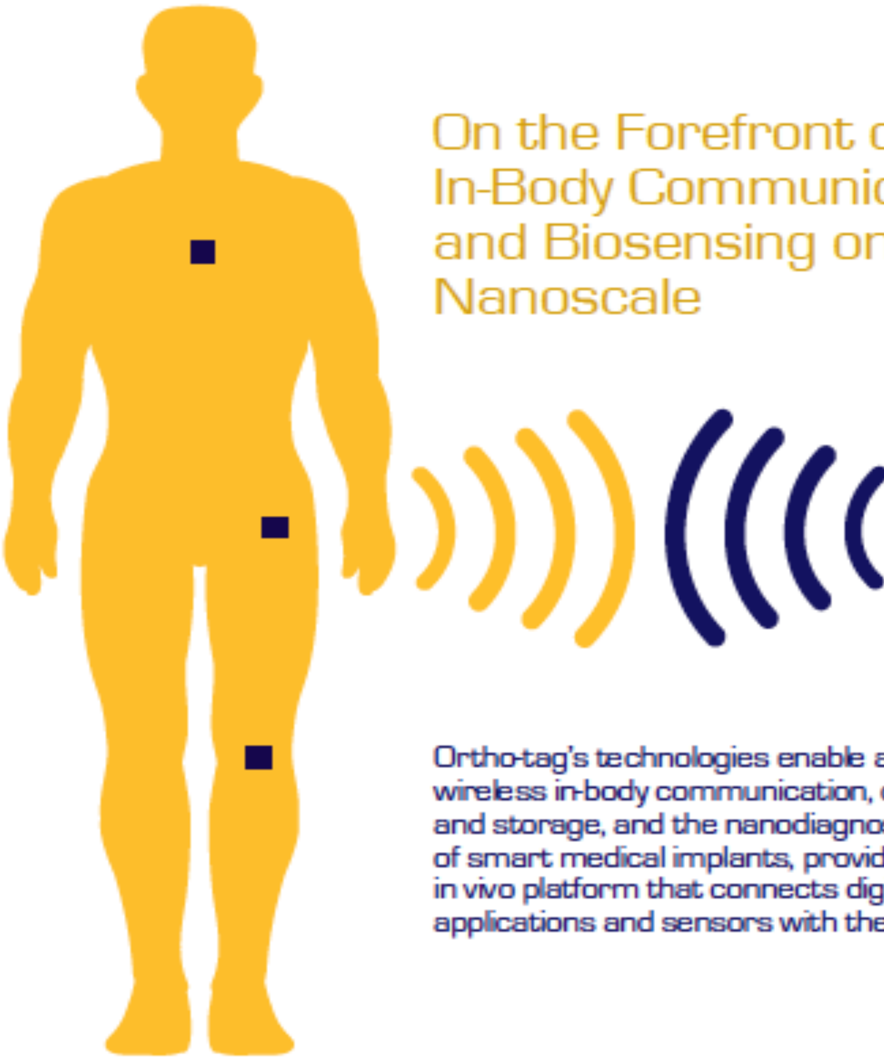


Real-time Detection of Proteins/Cells/Tissue using Sensors and Releasing Drugs from a PLGA/Polypyrrole Coating

Implantable Nano Sensors

On-going issues with implantable sensors:

- **Validation**
- **Data storage**
- **Data security**



On the Forefront of
In-Body Communication
and Biosensing on the
Nanoscale

Ortho-tag's technologies enable and enhance wireless in-body communication, data exchange and storage, and the nanodiagnostic functionality of smart medical implants, providing a versatile, in vivo platform that connects digital health applications and sensors with the human body.

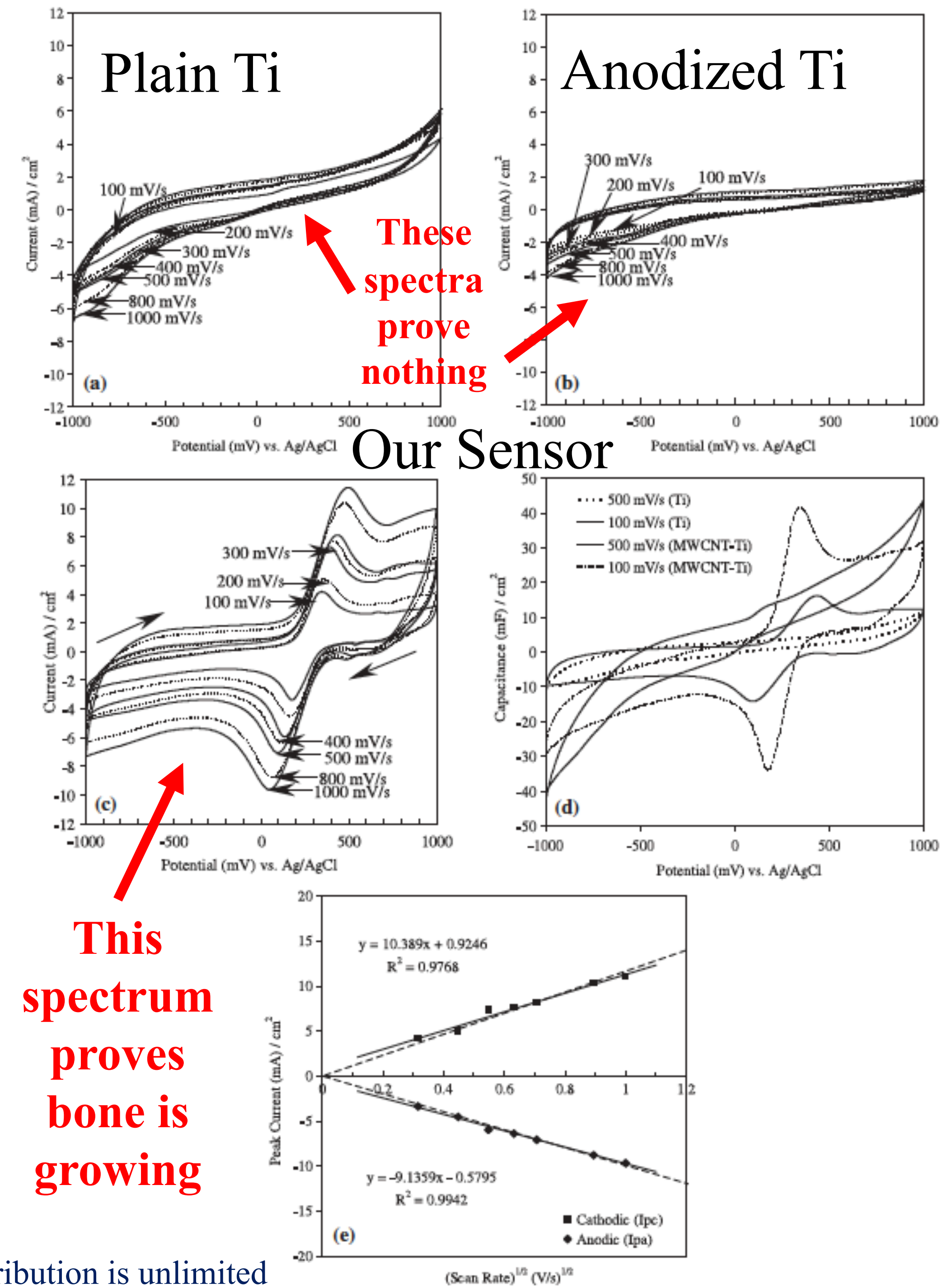
Wand to collect information and stimulate implant

But does this translate in vivo ??

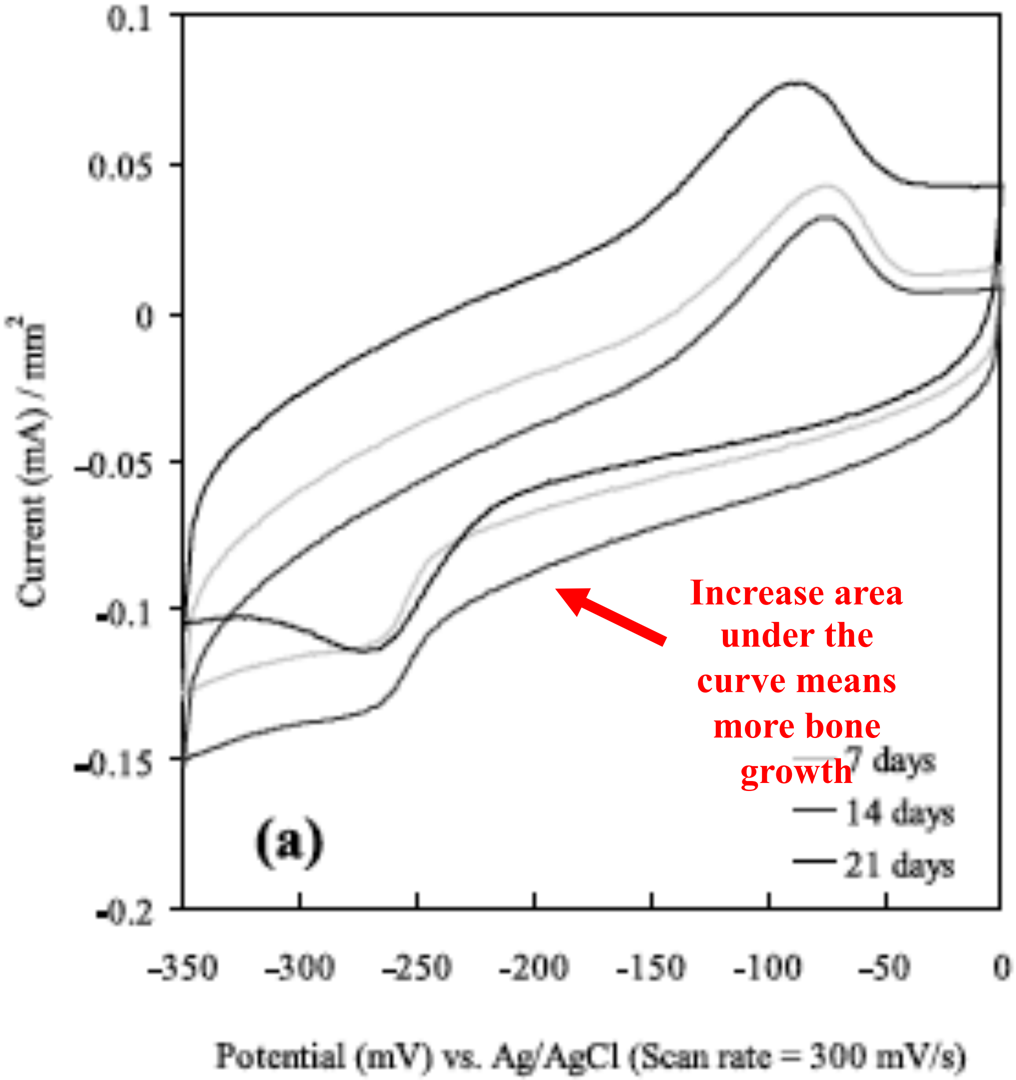
- Implanted square titanium-based sensors into rat calvaria
- Some samples, forced an infection via pre-seeding 10^5 *Staph. epi* (and other bacteria in separate experiments) CFU per implant
- Determine bacteria presence, macrophage presence, and bone growth via characteristic cyclic voltammograms
- Assessed tissue growth up to 3 months

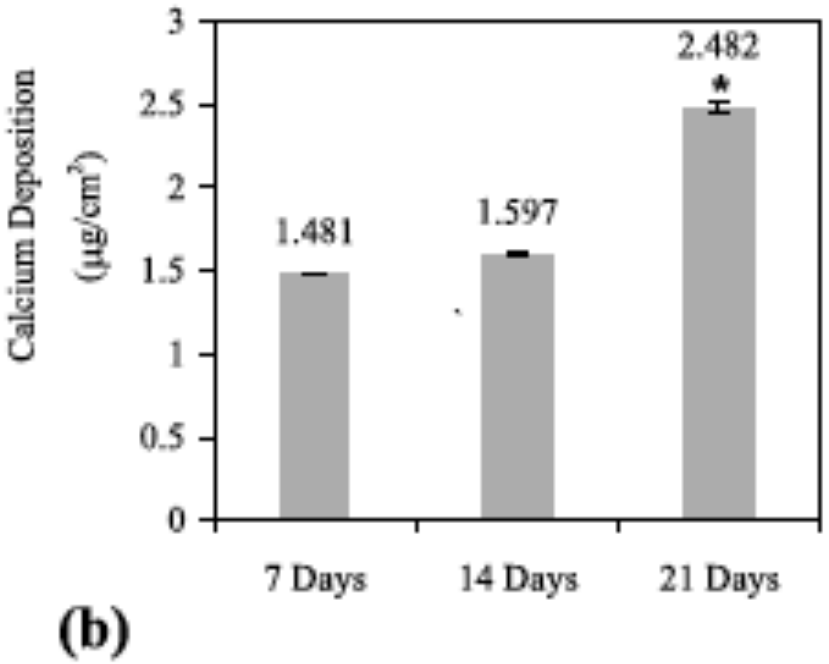
Characteristic CVs:

Proving We Transitioned a Hip Implant into a Sensor



Characteristic CVs: Showing Increased Bone Growth With Time





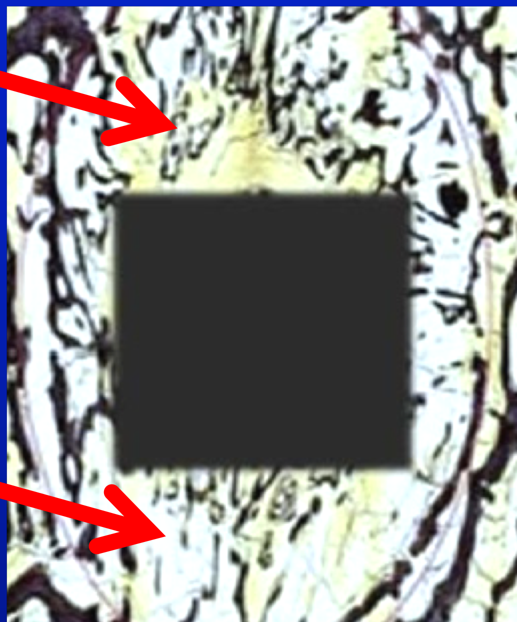
Reversal of Infection to Increased Bone Growth: 7 Days Post Implantation

Similar results for bone cancer and inflammation

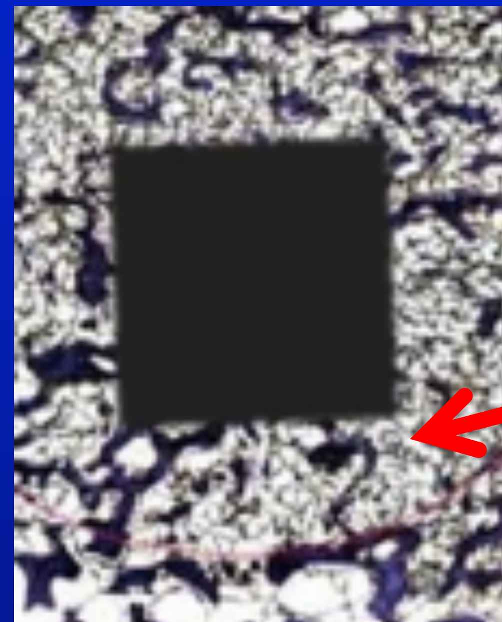
Push-Out Strength: 0.11MPa

0.71 MPa

Yellow: Stain for bacteria



Pre-seeded with *Staph epi*
Plain Ti



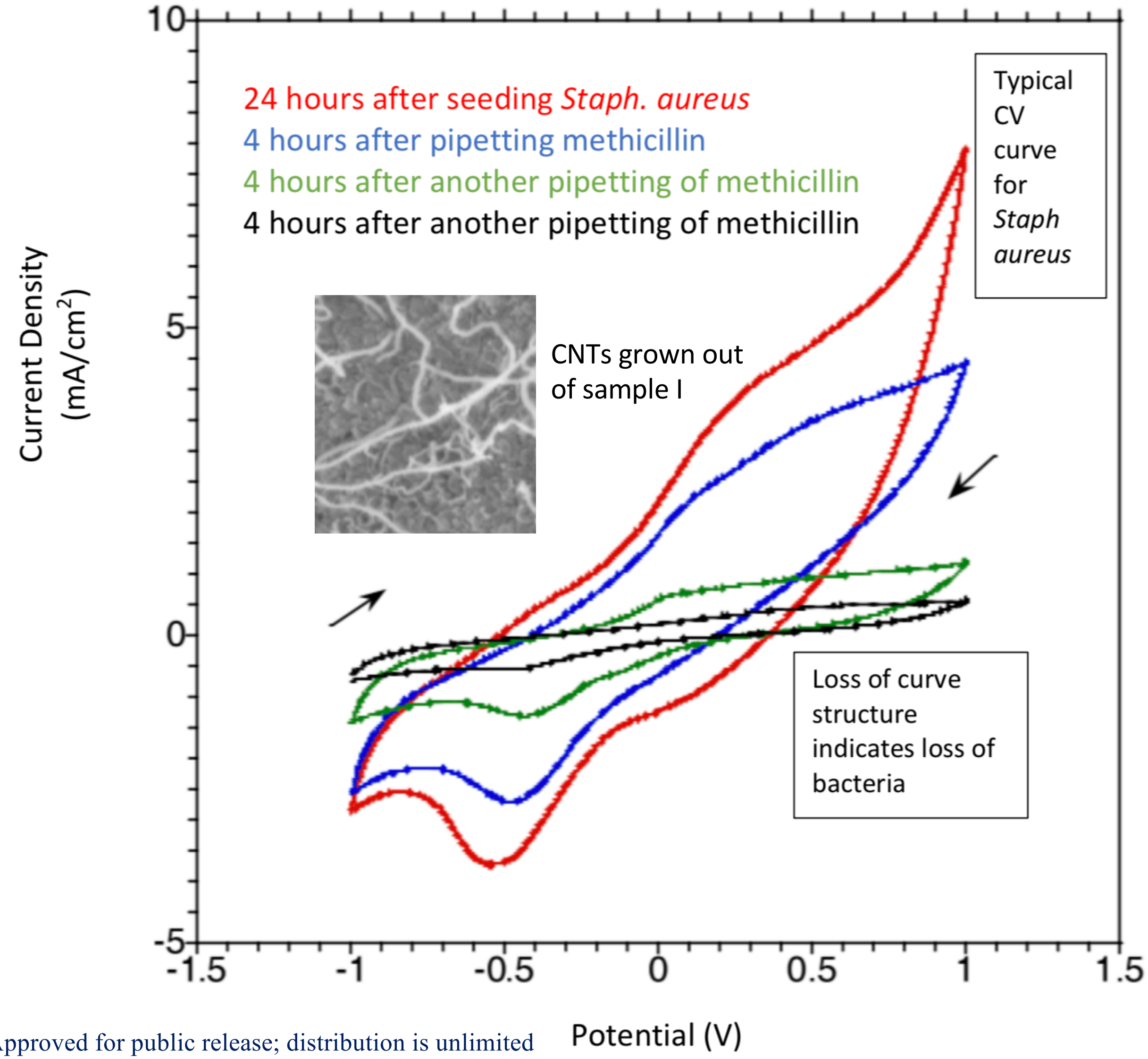
Purple: Stain for bone growth

Pre-seeded with *Staph epi*
Release of gentimicin and BMP-7 after 1 day
Our sensor

Similar for *Pseudomonas*, MRSA, and *E. coli*

CV of Bacteria Before/After Application of Antibiotic

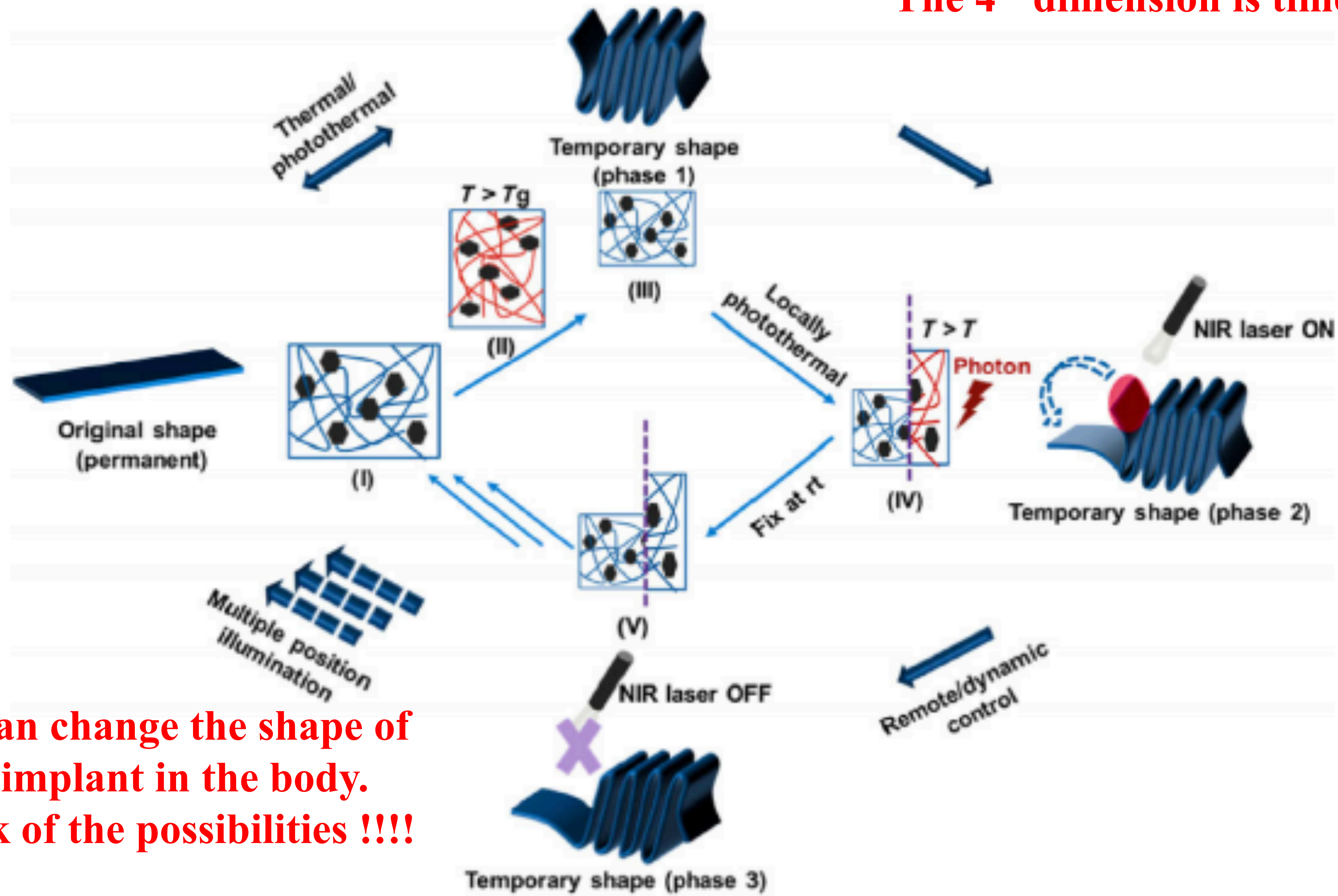
We can also provide information to surgeons if a specific antibiotic is working !



Another Example……

Ever Heard of 4D Printing ????

The 4th dimension is time.

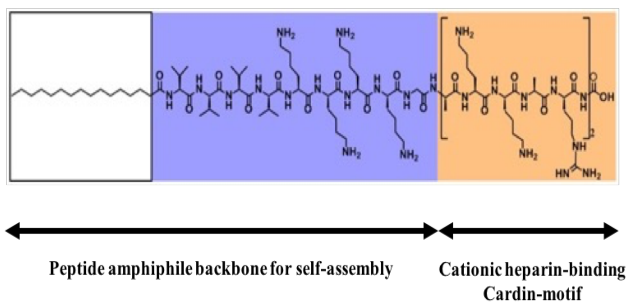


We can change the shape of
an implant in the body.
Think of the possibilities !!!!

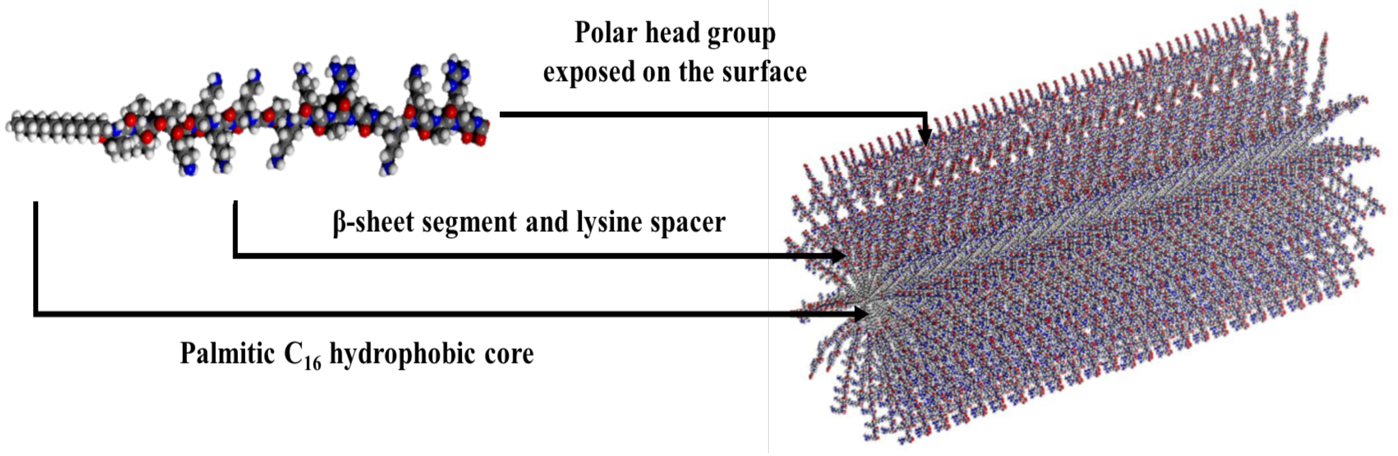
Matrix Which Can Change Shape On-Demand

Self-assembling antibacterial cationic amphiphilic peptide (ACA-PA)

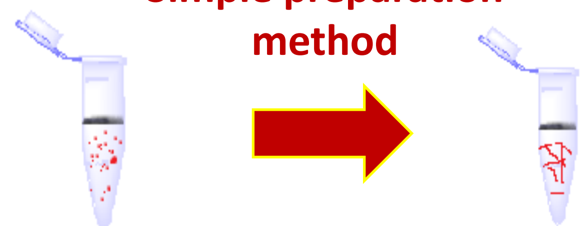
A



B



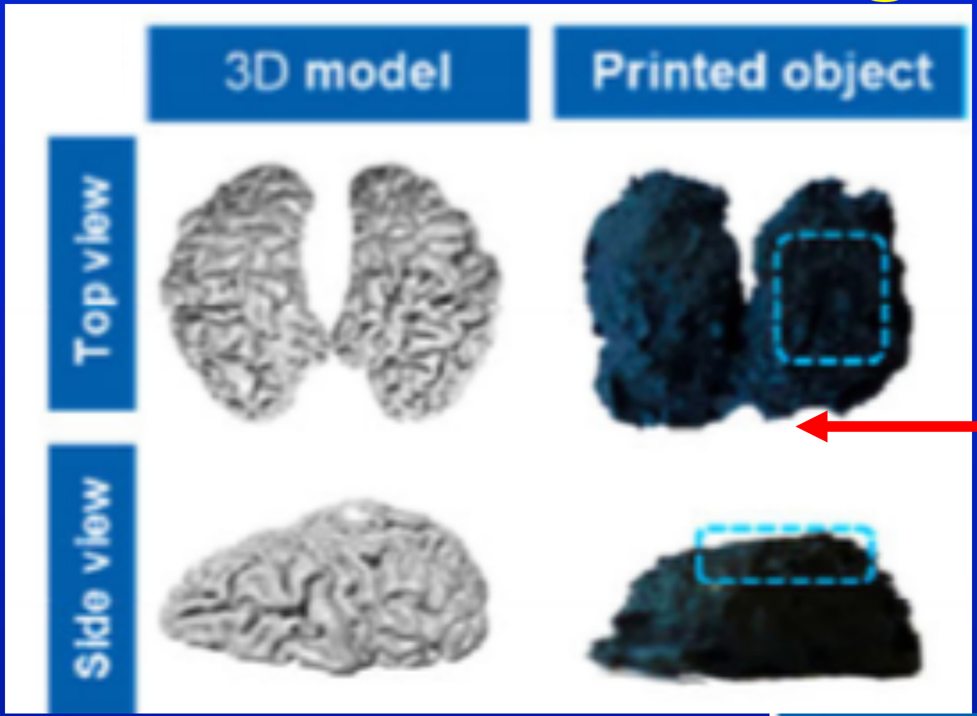
Simple preparation method



Dissolve peptide in water

Nanoparticles self-assemble

4D Printing Implantable Sensors



We can 3D print any shape

On-demand change of shape upon application of infrared wavelengths

<u>We can change any shape to release</u>:

- Pain killers
- Anti-inflammatory agents
- Increase pressure to promote tissue growth

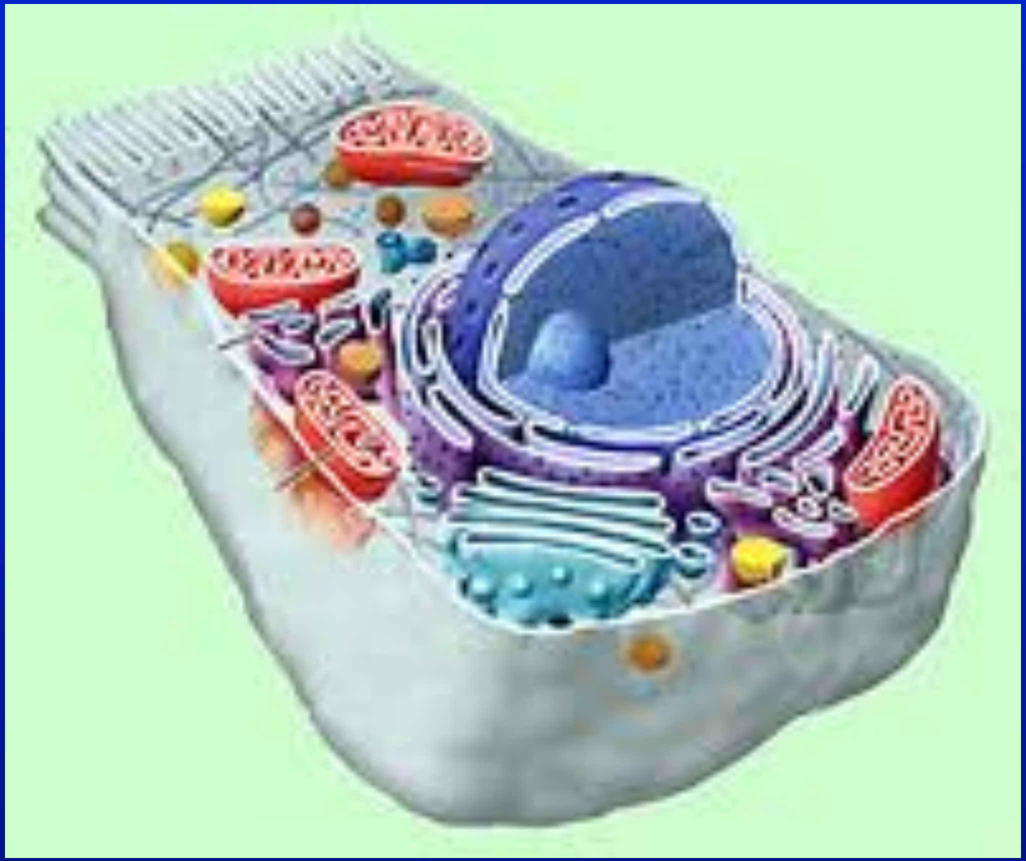
Another Example……

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

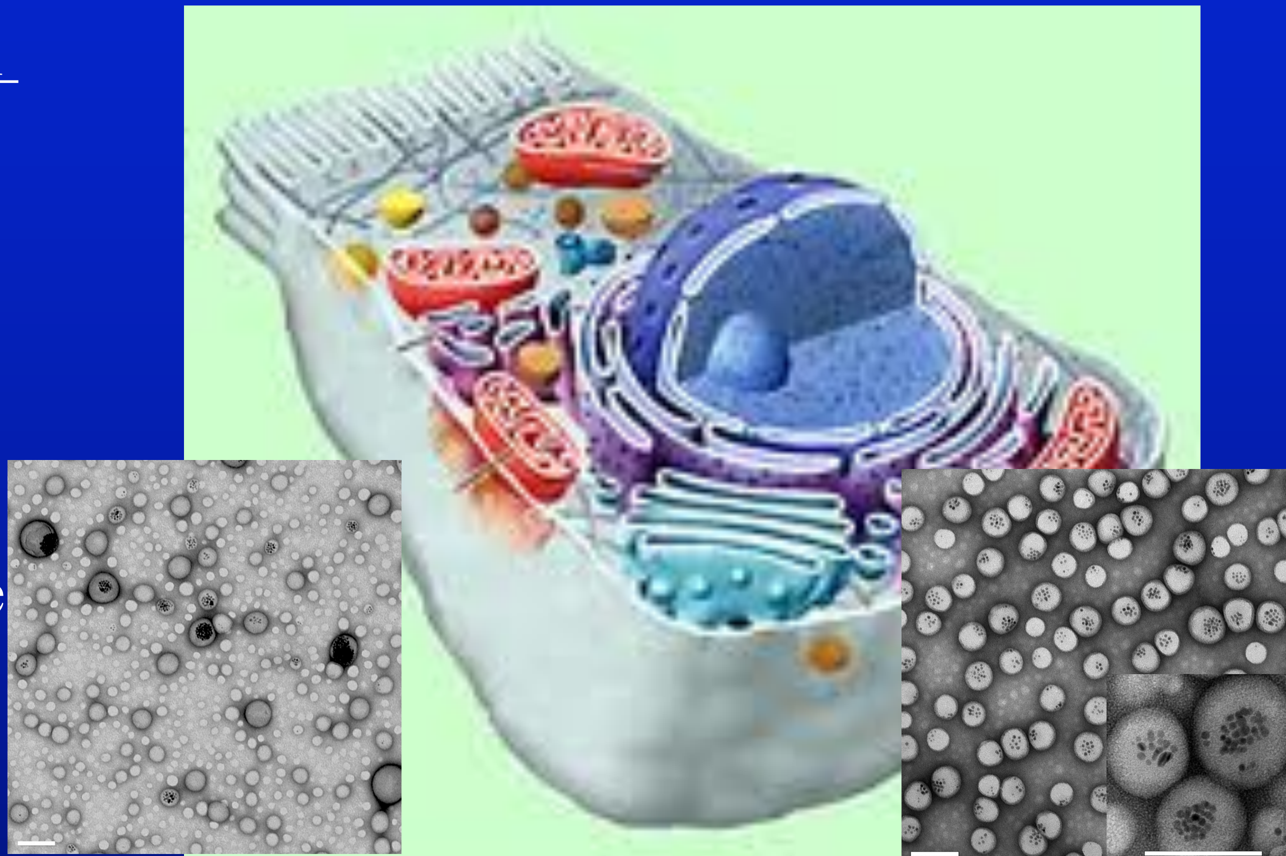
Synthetic nano cells can survey the body for disease, cell mutations, altered immune system, and more to treat such problems immediately.

Next Generation of Sensors that Could be used in Medicine

Synthetic Cell Sensor:

Need energy source

Need flexible biocompatible materials



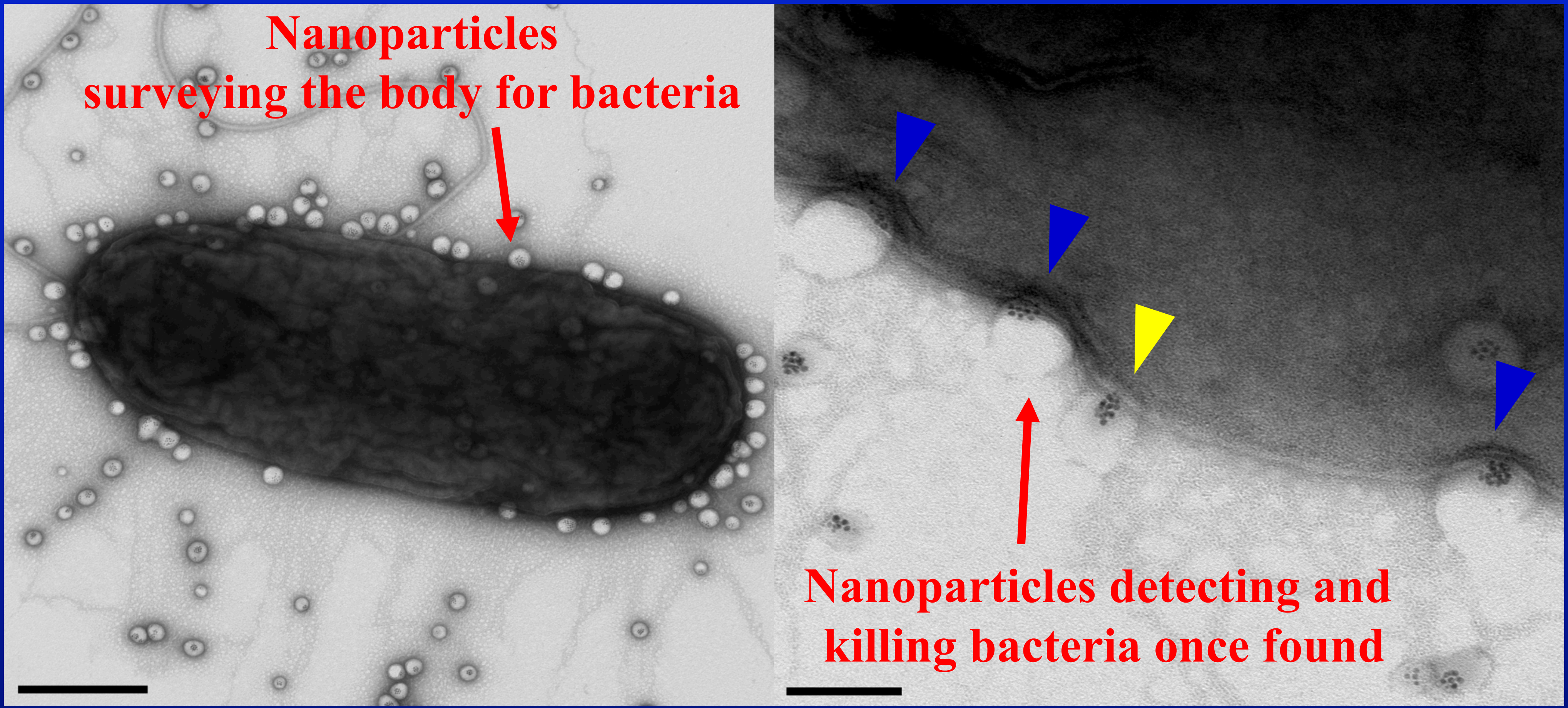
Need processing capability

Need responding capability to aid immune cells

Need adaptability

Synthetic nano cells can survey the body for disease, cell mutations, altered immune system, and more to treat such problems immediately.

Synthetic Immune Nanoparticles



Scale Bars = 100nm

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

And remember…

vs.

How many sensors do we have in both ?

Thank You Again !

<u>E-mail for any questions/collaborations/comments</u>:

th.webster@neu.edu