Biomedicine Applications of Nanotechnology towards Sustainable Public Health

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Associate Editor ACS Nano

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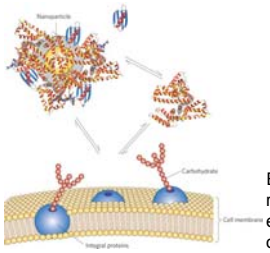
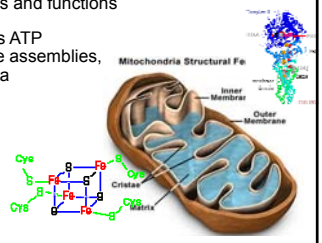
Much of Biology is carried out at the Nanoscale dimension

1. Proteins, lipids, nucleic acids and carbohydrates exhibit nanoscale size, shape, surface recognition features and functions
2. Many biological processes such as ATP production take place in nanoscale assemblies, e.g. energy producing mitochondria

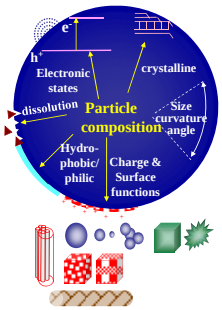


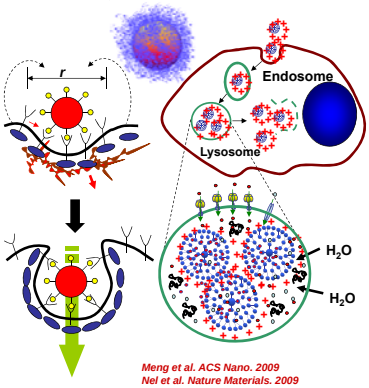


Engineered nanostructures can readily interact with bio-molecules, e.g. the protein corona of nanoparticle on its way to the cell surface

The Cellular Nano/bio Interface

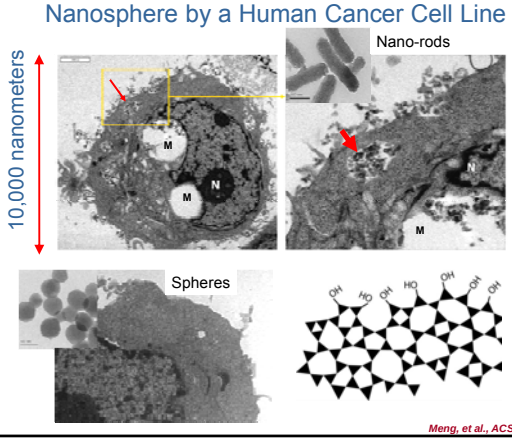
Large number of novel physicochemical properties





Meng et al. ACS Nano. 2009
Nel et al. Nature Materials. 2009
Nel et al. Accounts Chem Res, 2012

Dynamic Sensing of a Silica Nanorod vs a Nanosphere by a Human Cancer Cell Line



Meng, et al., ACS NANO, 2011

Top Ten Nanotechnology Applications most likely to benefit Developing Countries

1.	Energy storage, production, and conversion	Novel hydrogen storage systems based on carbon nanotubes and other lightweight nanomaterials Photovoltaic cells and organic light-emitting devices based on quantum dots Carbon nanotubes in composite film coatings for solar cells Nanocatalysts for hydrogen generation Hybrid protein-polymer biomimetic membranes
2.	Agricultural productivity enhancement	Nanoporous zeolites for slow-release and efficient dosage of water and fertilizers for plants, and of nutrients and drugs for livestock Nanocapsules for herbicide delivery Nanosensors for soil quality and for plant health monitoring Nanomagnets for removal of soil contaminants
3.	Water treatment and remediation	Nanomembranes for water purification, desalination, and detoxification Nanosensors for the detection of contaminants and pathogens Nanoporous zeolites, nanoporous polymers, and attapulgite clays for water purification Magnetic nanoparticles for water treatment and remediation TiO_2 nanoparticles for the catalytic degradation of water pollutants

Salamanca-Buentello et al PLoS Medicine. 2005. 2, 97

Top Ten Nanotechnology Applications most likely to benefit Developing Countries

4.	Disease diagnosis and screening	Nanoliter systems (Lab-on-a-chip) Nanosensor arrays based on carbon nanotubes Quantum dots for disease diagnosis Magnetic nanoparticles as nanosensors Antibody-dendrimer conjugates for diagnosis of HIV-1 and cancer Nanowire and nanobelt nanosensors for disease diagnosis Nanoparticles as medical image enhancers
5.	Drug delivery systems	Nanocapsules, liposomes, dendrimers, buckyballs, nanobiomagnets, and attapulgite clays for slow and sustained drug release systems
6.	Food processing and storage	Nanocomposites for plastic film coatings used in food packaging Antimicrobial nanoemulsions for applications in decontamination of food equipment, packaging, or food Nanotechnology-based antigen detecting biosensors for identification of pathogen contamination
7.	Air pollution and remediation	TiO_2 nanoparticle-based photocatalytic degradation of air pollutants in self-cleaning systems Nanocatalysts for more efficient, cheaper, and better-controlled catalytic converters Nanosensors for detection of toxic materials and leaks Gas separation nanodevices

Salamanca-Buentello et al PLoS Medicine. 2005. 2, 97

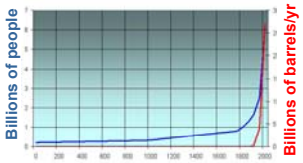
Top Ten Nanotechnology Applications most likely to benefit Developing Countries

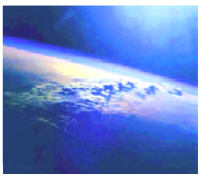
8.	Construction	Nanomolecular structures to make asphalt and concrete more robust to water seepage Heat-resistant nanomaterials to block ultraviolet and infrared radiation Nanomaterials for cheaper and durable housing, surfaces, coatings, glues, concrete, and heat and light exclusion Self-cleaning surfaces (e.g., windows, mirrors, toilets) with bioactive coatings
9.	Health monitoring	Nanotubes and nanoparticles for glucose, CO_2, and cholesterol sensors and for in-situ monitoring of homeostasis
10.	Vector and pest detection and control	Nanosensors for pest detection Nanoparticles for new pesticides, insecticides, and insect repellents

Salamanca-Buentello et al PLoS Medicine. 2005. 2, 97

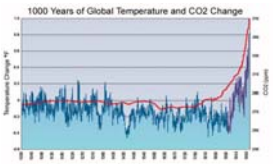
The Quest for Energy and the introduction of the Anthropocene

Billions of People and Oil production





Introduction of the Anthropocene in a thin atmospheric sliver



Google Images

Climate Change and Human Health

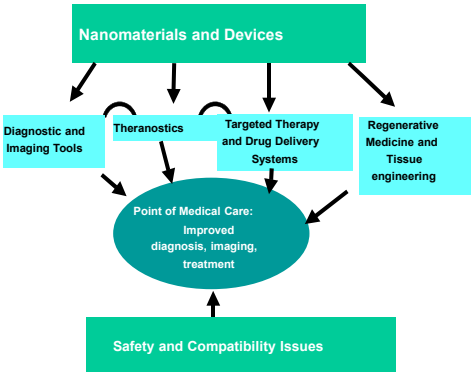
http://ete.cet.edu/gcc/?/healtheffects_teacherpage/
http://www.climatecommunication.org/affects/human-health/

Why is Nano key to Energy and Global warming?

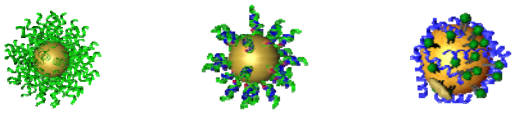
The dimensional scale of the physical phenomena that are required for saving, capture, conversion, storage, transmission, and dissipation of energy is inherently NANO

- Exciton (electron hole pair) dimension - Photovoltaics
- Bandgap engineering by quantum confinement – energy absorption, multi-exciton
- Photocatalytic reaction center – photosynthesis, water splitting
- Specific Surface Area – energy storage, catalytic activity
- ↓Friction/ ↑Lubrication/ ↑Adhesion
- Diffusion and Convection – thermal, electrical, chemical transport
- Saving of energy

Pillars of NanoMedicine



What is Nanomedicine?

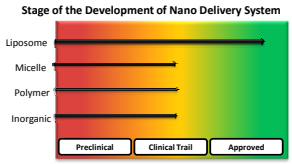


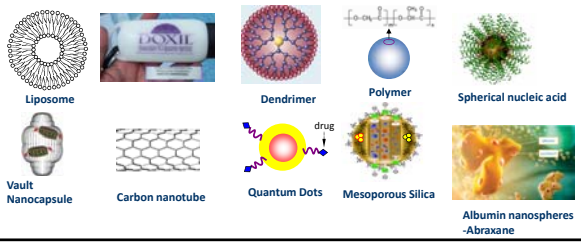
The design and synthesis of biologically interactive nanoscale systems that enable medicinal technology advances in:

- **Prevention, diagnostics, treatment of diseases, including personalized, point of care modalities**
- **Preservation and improvement of human health**
- **Chronic and acute pain relief** by leveraging significant advantages nanosystems hold over traditional methods for sensing, imaging, reconstruction, delivery and interactivity of biological systems.

Examples of Nanocarriers for Drug Delivery

- Drug encapsulation:
  ↑ circulation half-life, protection
- ↓ Drug toxicity
- Synergistic drug combinations
- Systemic siRNA delivery and co-delivery with drugs
- Theranostics and multifunctional design
- Off-patent drugs

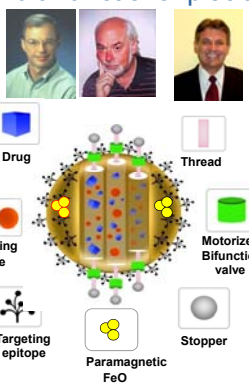


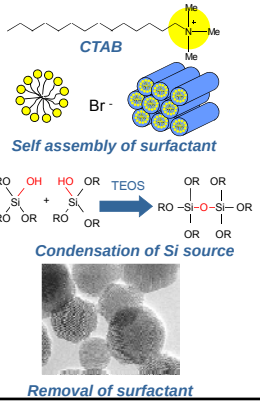


Nanoparticle Drug Delivery in Cancer

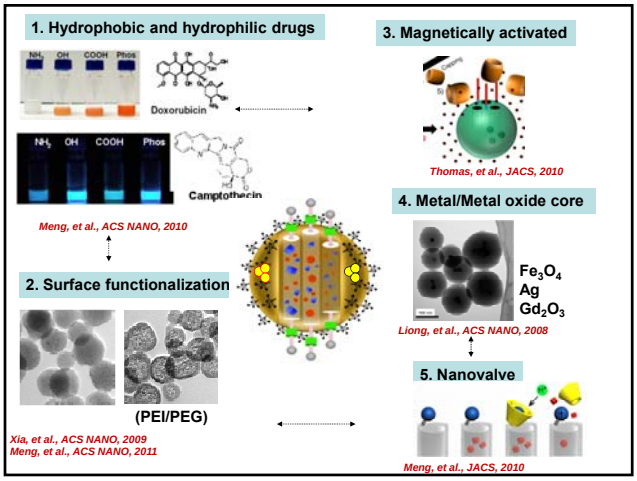
- Encapsulation, increased circulation time, retention at the tumor site (passive targeting)
- Active targeting
- Reduced drug toxicity (including hydrophobic drugs)
- Systemic siRNA delivery, which can be combined with drugs
- Combination therapy to overcome tumor drug resistance
- Nanoparticles designed as multi-functional systems with tumor targeting ability, therapeutic and theranostic capabilities
- Waves of therapy as an engineered approach to treatment

The Mesoporous Silica Nanoparticle as a multi-functional platform for controlled delivery

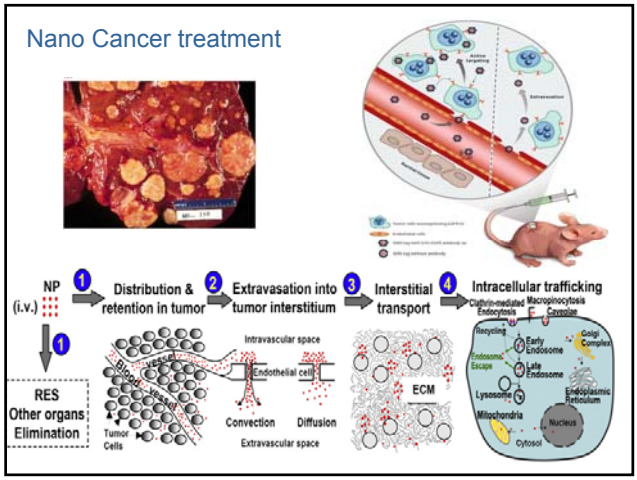




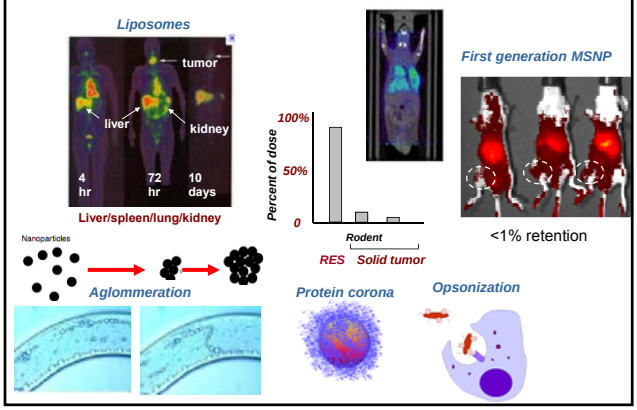
Liong, Lu, Tamanoi, Zink, et al. ACS Nano , 2, 889-896 (2008)



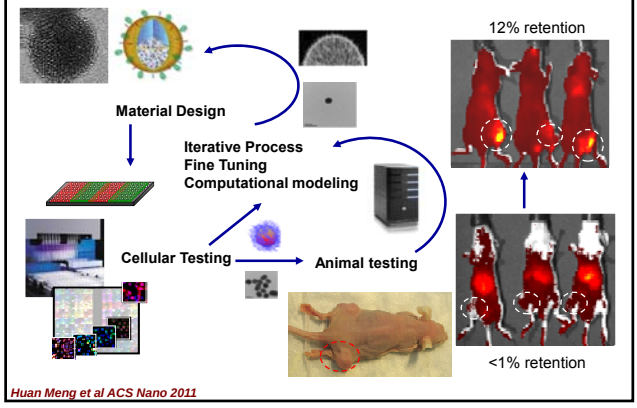
Nano Cancer treatment



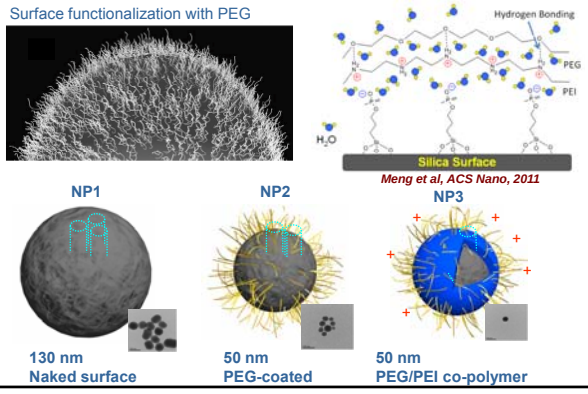
Systemic Drug Delivery Challenges and the need to adapt the Nano carrier design for therapeutic efficacy



Using iterative control of the Nano/bio Interface to Develop new Cancer treatment

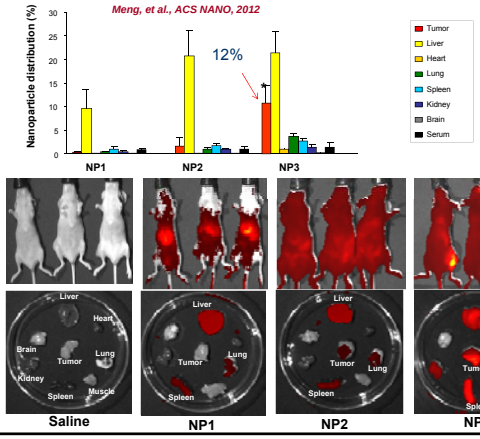


Improved Biodistribution and enhancing tumor retention through Size Tuning and Surface Functionalization

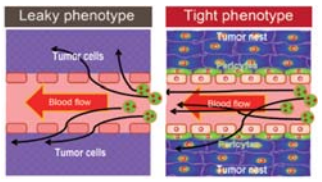


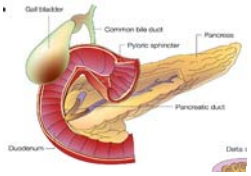
Iterative Design to achieve a 12% EPR effect

Meng, et al., ACS NANO, 2012



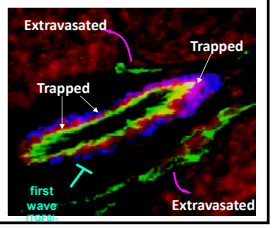
Additional Obstacles at the Cancer Site



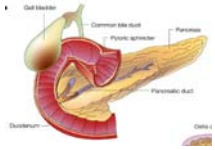


Pericyte coverage in different cancer types

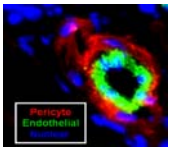
-Pancreatic cancer	+++++
-Colon cancer	+
-Ovarian cancer	+
-Prostate cancer	++
-Glioblastomas	++
-Breast cancer	++



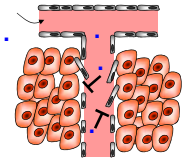
Pancreatic Cancer Exhibit a prominent Dysplastic Stroma: Introduction of an Engineered Rx Approach



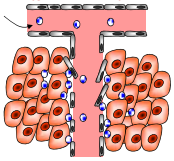
Erkan et al. Nature Reviews



Wave 1: Stromal targeting (to enhance particle access)



Wave 2: Chemotherapy (gemcitabine)



Huan Meng
Medicine/CNSI

Jeffrey Zink
Chem & Biochem

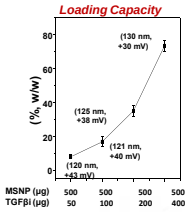
Andre Nel
Nanomedicine

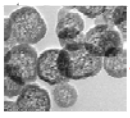
Timothy Donahue
Surgery

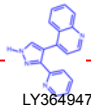
Choice of a MSNP to deliver the TGFβ inhibitor

Meng, et al., ACS NANO, 2013

Loading Capacity







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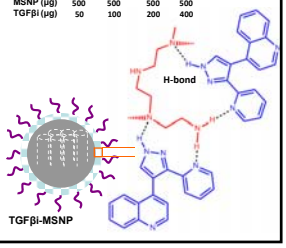
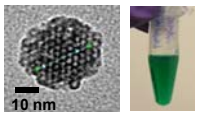


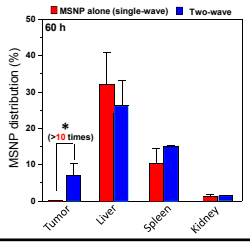
TGFβi-MSNP

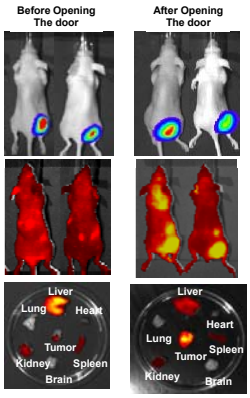
Engineered Vascular Access using two MSNP Waves

Meng, et al., ACS NANO, 2013

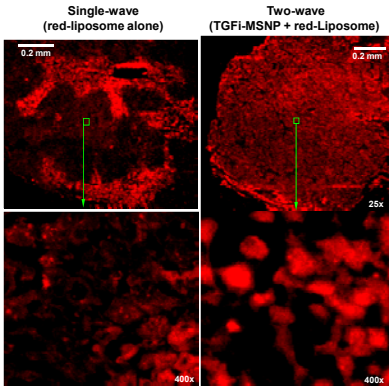
Second Wave NIR-labeled NP





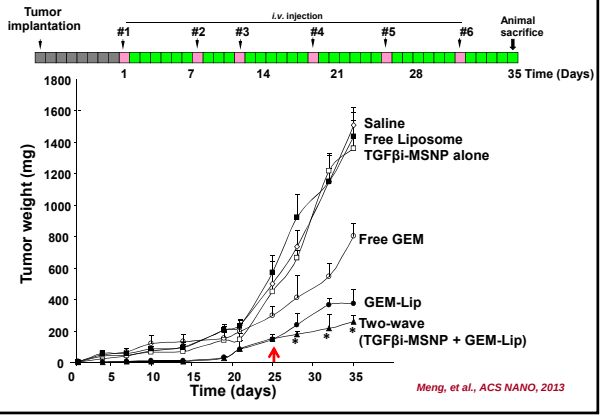


2nd wave Liposome access to tumor tissue after 1st wave Rx



Meng, et al., ACS NANO, 2013

Two wave Therapy becomes effective in a Xenograft after 25 days



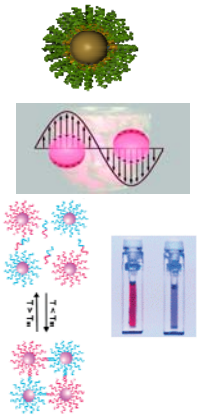
Meng, et al., ACS NANO, 2013

New fMol and aMol Diagnostics

Table 1 | Detection of protein biomolecules

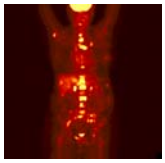
Tool or technique	Read-out	Illustration	Detection limit*	Molecules per drop (60 µl)	In clinical use
Colorimetry	Visual		150 pM	10^8	Yes
Carbon nanotubes	Electrical		100 pM	10^8	No
Chemi-luminescence	Luminescence		30 pM	10^8	Yes
ELISA	Luminescence		1–10 pM	10^7	Yes
Quantum dots	Fluorescence		500 fM	10^7	No
Silicon nanowires	Electrical		1 fM	10^4	No
Metal nano-particles (bio-barcode)	Scanometric and/or light scattering		30 aM	900	Yes

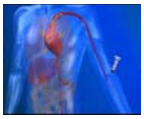
Barcode Assay



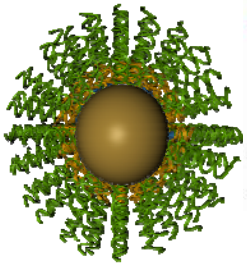
Imaging and Nanotechnology

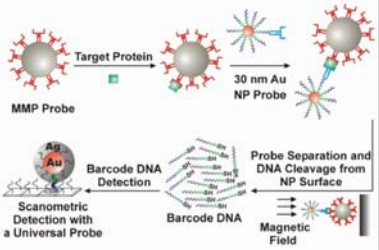
- Image structure and function
- Whole body imaging
- Improved spatial and temporal resolution
- Capability to probe tumor microenvironment – information on tumor mass and its biochemical signatures
- Theranostic constructs allow for tumor recognition and subsequent treatment – image-guided therapy
- Intra-operative techniques to monitor margins of surgically removed issue in real-time





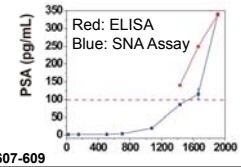
Spherical Nucleic Acids (SNAs)





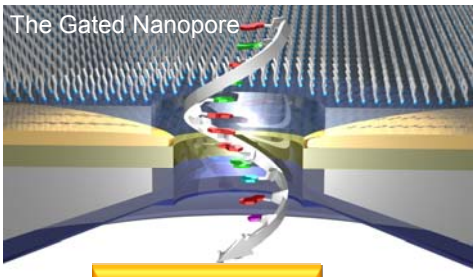
13 nm Au NP
~67,500 atoms

40-mer Oligo-Nucleotide 1400 atoms



Mirkin *et al, Nature* 1996 (382) 607-609

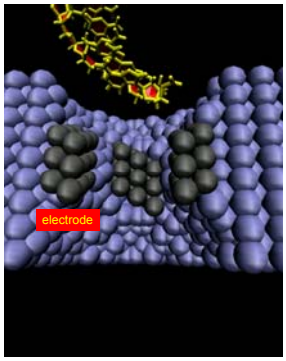
DNA Sequencing Technology beyond the Sanger Chain termination being carried out by Capillary Electrophoresis



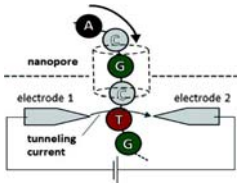
Requirements:
- Nanopore
- Nanogap electrode
- DNA transport physics
- Base pair discrimination

..to the $1000 personal genome

Current Status of Nanopore DNA Sequencer



Status:
- Nanopore ☺
- Nanogap electrode ☺
- DNA transport physics ☺
- Single base pair discrimination ☺



Pipeline for New Antibiotics Running empty: Antimicrobial Mechanisms of Nanomaterials

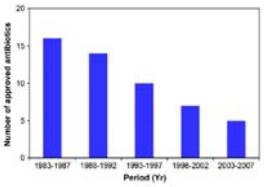
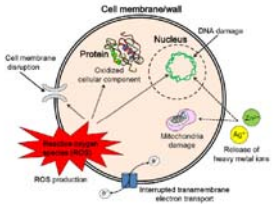


Fig. 1. FDA approval on new antibiotics [13].



1) Semiconductor/photocatalytic production of ROS that damage cellular and viral components,
2) Compromising the bacterial cell wall/membrane,
3) Interruption of energy transduction
4) inhibition of enzyme activity and DNA synthesis

Antimicrobial NP

Nanomaterial	Antimicrobial mechanism
Ag NPs	Release of Ag^+ ions; disruption of cell membrane and electron transport; DNA damage
ZnO NPs	Intracellular accumulation of NPs; cell membrane damage; H_2O_2 production; release of Zn^{2+} ions
TiO_2 NPs	Production of ROS; cell membrane and wall damage
Au NPs	Interaction with cell membranes; strong electrostatic attraction
Chitosan	Increased permeability and rupture of membrane; chelation of trace metals; enzyme inactivation
Fullerenes	Destruction of cell membrane integrity; enhancing activity of infiltrating neutrophil
CNTs	Cell membrane damage by ROS; oxidation of cell membrane proteins and lipids
NO-releasing NPs	NO release and production of ROS
Nanoemulsion	Membrane disruption; disruption of the spore coat

Antibacterial Effects of Carbon Nanotubes: Size Does Matter!

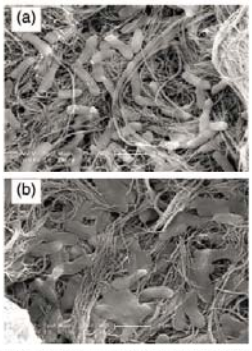
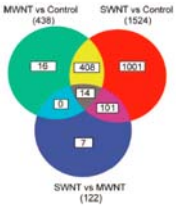


Figure 3. Scanning electron microscopy (SEM) images of *E. coli* cells exposed to CNTs. (a) Cells incubated with MWNTs for 60 min. (b) Cells incubated with SWNTs for 60 min. The bars in both images represent 2 μm.

Kang et al. Langmuir. 2008



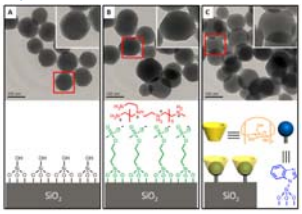
SWNTs exhibit the strongest antimicrobial activity via combination of membrane and oxidative stress, in three-steps:

- Initial SWNT bacteria contact
- Membrane perturbation
- Membrane oxidation in an electronic structure (i.e., metallic vs. semiconducting) dependent manner.

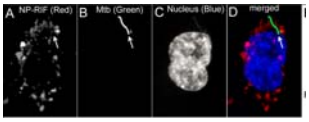
Biofilm formation and subsequent biofouling of surfaces may be sufficiently prevented by SWNTs

Targeted Intracellular Delivery of Anti-Tuberculosis Drugs to *Mycobacterium tuberculosis*-Infected Macrophages via Functionalized Mesoporous Silica Nanoparticles

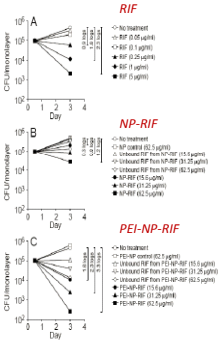
Clemens. Antimicrob. Agents Chemother. 2012, 56(5):2535.



TEM images of **A)** MSNP, **B)** PEI-coated MSNP and **C)** MSNP equipped with pH operated nanovalves.

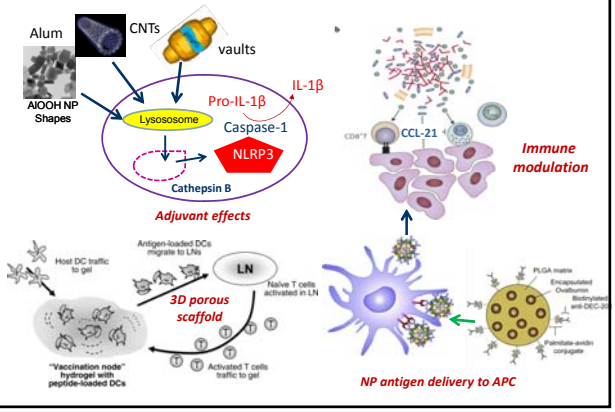


Anti-tuberculosis drug loaded MSNP are internalized efficiently by human macrophages infected with *M. tuberculosis* (A-D)



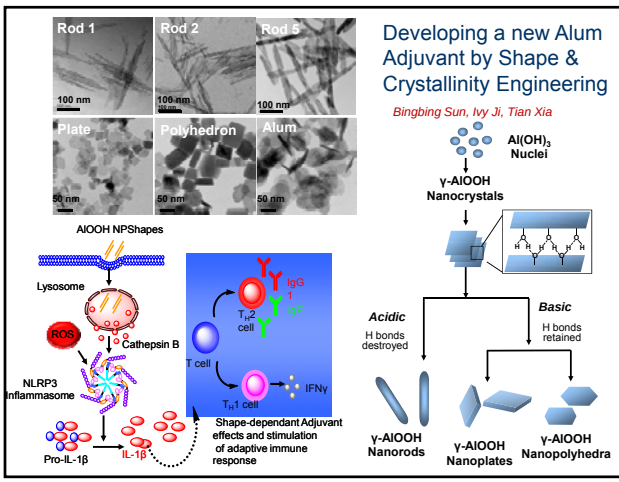
PEI coating on MSNP enhances the delivery of RIF to *M. tuberculosis*-infected human macrophages.

Use of Nanotechnology to boost Immune Responses and to make Vaccines



Developing a new Alum Adjuvant by Shape & Crystallinity Engineering

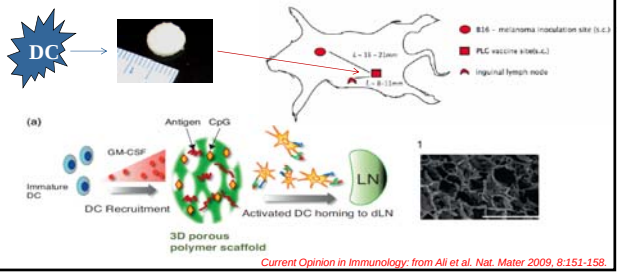
Bingbing Sun, Ivy Ji, Tian Xia



A Nano-Immunotherapy Strategy for Cancer: 3D Porous Scaffolds

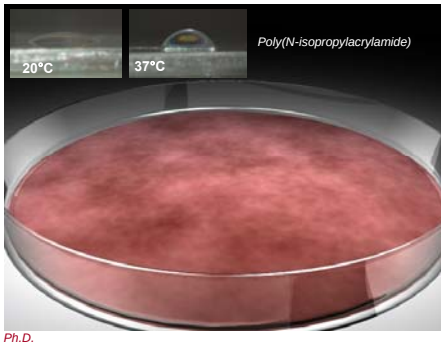
EXAMPLE: PLG loaded with GM-CSF, and decorated with condensed CpG. Melanoma tumor lysate was utilized as the cancer antigen.

- GMCSF recruited DCs to the scaffold, DCs were activated by CpG, they processed the tumor antigen. Activated DCs homed to the draining lymph nodes (dLNs) and primed naive T cells.
- This vaccine induced 90% prophylactic tumor protection and generated complete regression of established melanoma in a fraction of the animals.



Current Opinion in Immunology: from Ali et al. Nat. Mater 2009, 8:151-158.

Regenerative Medicine: Cell Sheet Engineering for Patch-repair and reconstruction of damaged organs



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Director and Professor
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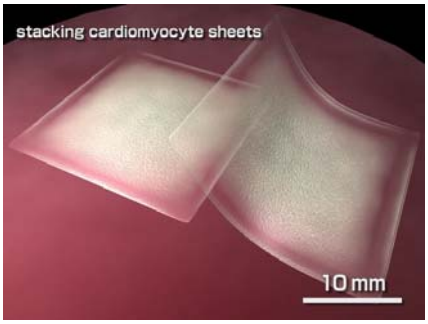
Tokyo Women's Medical University

Masuda et al. Adv Drug Deliv Reviews 60 (2008) 277–285

A Cell Sheet of Primary Cardiac Myocytes …the beat goes on

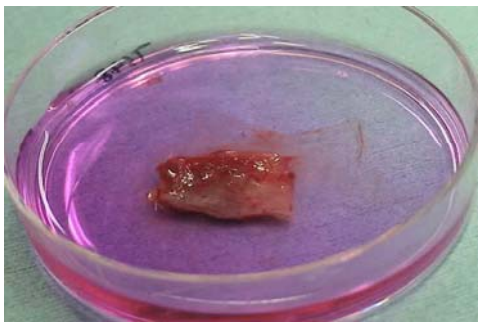
Courtesy Teruo Okano, Ph.D.

Stacking Cardiomyocyte Sheets creates a Contractile Tissue



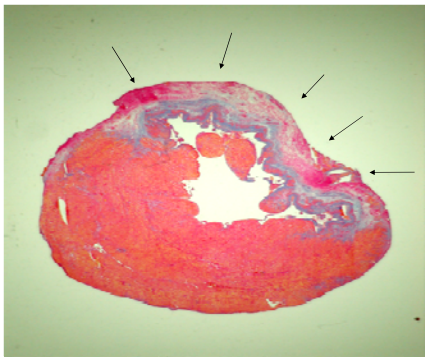
Courtesy Teruo Okano, Ph.D.

Stacking Cardiomyocyte Sheets creates a Contractile Tissue



Courtesy Teruo Okano, Ph.D.

Patching a dyskinetic myocardial wall

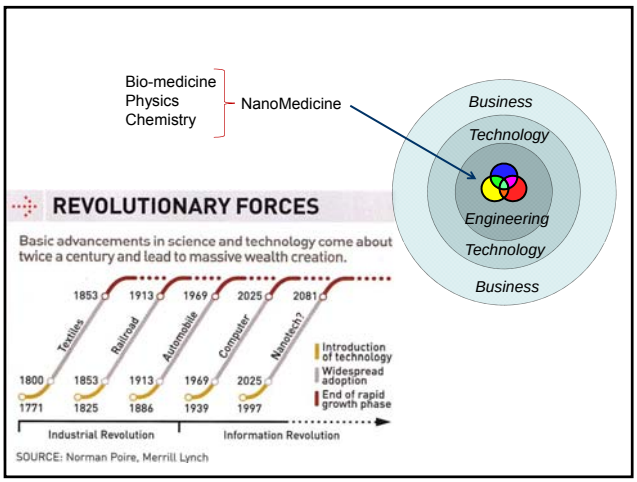


Courtesy Teruo Okano, Ph.D.

Promises of Nanomedicine

	Screening	Diagnosis & Staging	Treatment & Monitoring
Current	• Relative low sensitivity • Macroscale imaging of organs and regions • Established disease	• Macroscale imaging • Invasive approaches, e.g., surgery/biopsy • Batch testing • Individual biomarkers	• Surgery • Radiation • Debilitating chemo • Total body effects
Nano Impact	• Million fold ↑ in sensitivity • Whole body imaging • Disease inception	• Image structure & function • Whole body/Non-invasive • Multiple biomarkers lab-on- a-chip	• Targeted drug delivery • On-demand drug delivery • Imaged drug delivery

nano2 *Nanotechnology Long-term Impacts and Research Directions: 2000 – 2020*



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