Biomedicine Applications of Nanotechnology towards Sustainable Public Health

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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

- Electronic states
- Hydrophobic/philic
- Curvature
- Charge & Surface functions

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
   - Nanowire 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
   - Nanocomposites for hydrogen generation
   - Hybrid polymer-polymer nanocomposites

2. Agricultural productivity and fertilizer
   - Nanoporous zeolites for slow-release and efficient distribution of water and nutrients for plants and elements and drugs for livestock
   - Nanocomposites for seed quality and for plant health monitoring
   - Nanocomposites for removal of soil contaminants

3. Water treatment and remediation
   - Nanomembranes for water purification, deionization, and desalination
   - Nanomaterials for the detection of contaminants and pathogens
   - Nanoscale filters, nanoporous polymers, and attoliter chips for water purification
   - Magnetic nanoparticles for water treatment and remediation
   - TiO₂ nanoparticles for the catalytic degradation of water pollutants

4. Disease diagnosis and screening
   - Nanobiosensors (Lab-on-a-chip)
   - Nanoparticle arrays based on carbon nanotubes
   - Quantum dots for disease diagnosis
   - Nanomaterials as medical image enhancers
   - Antibody-antigen conjugates for diagnosis of HIV and cancer
   - Nanocomposites for disease diagnosis

5. Drug delivery
   - Nanospheres, liposomes, emulsions, buckytubes, nanorobots, and nanobots

6. Food processing and storage
   - Nanocomposites for plastic film coatings used in food packaging
   - Antimicrobial nanomaterials for applications in disinfection of food equipment, packaging, or food
   - Nanotechnology-based xerogel-entraping biosensors for identification of pathogen contamination

7. Air pollution and remediation
   - TiO₂ nanoparticles for photocatalytic degradation of air pollutants in self-cleaning systems
   - Nanomaterials for more efficient, cheaper, and better-controlled catalytic converters
   - Nanomaterials for detection of toxic materials and leaks
   - Gas separation nanomaterials

8. Construction
   - Nanomaterials for the creation of asphalt and concrete more robust to water and weathering
   - Nanomaterials for cheaper and durable housing, surfaces, coatings, plastics, concrete, and heat and light insulation
   - Self-cleaning surfaces (e.g., windows, mirrors, toilets) with bioactive coatings

9. Health monitoring
   - Nanotubes and nanoparticles for glucose, CO₂, and cholesterol sensors
   - In vivo monitoring of homeostasis

10. Vector and pest detection and control
    - Nanosensors for pest detection
    - Nanoparticles for new pesticides, insecticides, and insect repellents

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

Seven Billion people living in the equivalent of an apple skin

Google Images
Climate Change and 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

1. Hydrophobic and hydrophilic drugs
2. Surface functionalization
3. Magnetically activated
4. Metal/Metal oxide core
5. Nanovalve

CTAB

Self assembly of surfactant

Condensation of Si source

Removal of surfactant

Drug

Imaging Probe

Targeting epitope

Paramagnetic FeO

Motorized Bifunctional valve

Stopper


Liong, et al., ACS NANO, 2008

Meng, et al., ACS NANO, 2010

Xia, et al., ACS NANO, 2009

Meng, et al., ACS NANO, 2011

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Meng, et al., ACS NANO, 2011
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

Additional Obstacles at the Cancer Site

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

Choice of a MSNP to deliver the TGFβ inhibitor
Engineered Vascular Access using two MSNP Waves

Meng, et al., ACS NANO, 2013

Second Wave NIR-labeled NP

Before Opening
After Opening

The door
The door

Liver
Heart
Spleen
Brain
Kidney
Lung
Tumor
Liver
Heart
Spleen
Brain
Kidney
Lung
Tumor

MSNP alone (single-wave)

Two-wave (TGFi-MSNP + red-Liposome)

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

Barcode Assay

New fMol and aMol Diagnostics

| Test | Method | Minimum Detection Limit | Molecular Type | In Vivo | Amplification
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<tr>
<td>Coloremetry</td>
<td>Visual</td>
<td>Yes</td>
<td>Tumor</td>
<td>1000 mg</td>
<td>No</td>
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<tr>
<td>Cells</td>
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<td>Electrical</td>
<td>Tumor</td>
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<td>Chemiluminescence</td>
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<td>Tumor</td>
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<td>Tumor</td>
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<td>Luminescence</td>
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<td>Tumor</td>
<td>10 mg</td>
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Meng, et al., ACS NANO, 2013
**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**

- The Gated Nanopore

**Current Status of Nanopore DNA Sequencer**

- Nanopore
- Nanogap electrode
- DNA transport physics
- Single base pair discrimination

..to the $1000 personal genome
Pipeline for New Antibiotics Running empty: Antimicrobial Mechanisms of Nanomaterials

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

<table>
<thead>
<tr>
<th>Nanomaterial</th>
<th>Antimicrobial mechanism</th>
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<tbody>
<tr>
<td>Ag NPs</td>
<td>Release of Ag⁺ ions; disruption of cell membrane and electron transport; DNA damage</td>
</tr>
<tr>
<td>ZnO NPs</td>
<td>Intracellular accumulation of NPs; cell membrane damage; H₂O₂ production; release of Zn²⁺ ions</td>
</tr>
<tr>
<td>TiO₂ NPs</td>
<td>Production of ROS; cell membrane and wall damage</td>
</tr>
<tr>
<td>Au NPs</td>
<td>Interaction with cell membranes; strong electronic attraction</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Increased permeability and rupture of membrane; chelation of trace metals; enzyme inactivation</td>
</tr>
<tr>
<td>CNTs</td>
<td>Destruction of cell membrane integrity; enhancing activity of infiltrating neutrophils</td>
</tr>
<tr>
<td>Cell membrane damage by ROS; oxidation of cell membrane proteins and lipids</td>
<td></td>
</tr>
<tr>
<td>NO releasing</td>
<td>NO release and production of ROS</td>
</tr>
<tr>
<td>NPs</td>
<td>Nanomutation Membrane disruption; disruption of the spore coat</td>
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</table>

Antibacterial Effects of Carbon Nanotubes: Size Does Matter!

SWNTs exhibit the strongest antimicrobial activity via combination of membrane and oxidative stress, in three-steps:
1. Initial SWNT bacteria contact
2. Membrane perturbation
3. Membrane oxidation in an electronic structure (i.e., metallic vs. semiconducting) dependent manner.

Biofilm formation and subsequent fouling 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

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

Adjuvant effects

NP antigen delivery to APC

Developing a new Alum Adjuvant by Shape & Crystallinity Engineering

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.

GM-CSF recruited DCs to the scaffold. DCs were activated by CpG, they processed the tumor antigen. Activated DCs homed to the draining lymph nodes (dLNcs) 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.

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

Teruo Okano, Ph.D.
Director and Professor
Tokyo Women’s Medical University

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

Stacking Cardiomyocyte Sheets creates a Contractile Tissue

Patching a dyskinetic myocardial wall

Courtesy Teruo Okano, Ph.D.
Promises of Nanomedicine

Current
- Relative low sensitivity
- Macroscale imaging of organs and regions
- Established disease

Nanophase Impact
- Million fold↑ in sensitivity
- Whole body imaging
- Disease inception

Screening
- Macroscale imaging
- Invasive approaches, e.g., surgery/biopsy
- Batch testing
- Individual biomarkers

Diagnosis & Staging
- Surgery
- Radiation
- Debilitating chemo
- Total body effects

Treatment & Monitoring
- Targeted drug delivery
- On-demand drug delivery
- Imaged drug delivery
- Image structure & function
- Whole body/Non-invasive
- Multiple biomarkers lab-on-a-chip

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Rui Lui
Rober Rallo

CEIN MEMBERS

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