ECE 370
Introduction to Biomedical Engineering

Nanomedicine and Personalized Medicine
Nano... What???

Heigh Ho...
Nano... What???

Richard Feinman

• “There is plenty of room at the bottom”
• … microscopic (molecular) machines which can self-replicate and self-repair and manipulate materials one atom at a time …
• … it’s not impossible, we haven’t succeeded because we are too big ..
• Nobel Prize in Physics 1965

• Nanotechnology
  • The study of the control of matter at the atomic/molecular level
  • Structures < 100 nm
Nano... What???

• Nanotechnology: Technology with dimensions 1-100 nm
• Nanometer = 10^{-9} m (1 billionth)
Nano... What???

A hair

Diameter = 0.1 mm

= 100 micrometers

= 100,000 nanometers!
Nano... What???
**The Scale of Things – Nanometers and Beyond**

### Natural Structures

- **Dust mite**: 200 μm
- **Ant**: ~ 5 mm
- **Human hair**: ~ 60-120 μm wide
- **Fly ash**: ~ 10-20 μm
- **Red blood cells**: ~7-8 μm
- **DNA**: ~2-1/2 nm diameter
- **Atoms of silicon spacing**: 0.078 nm
- **ATP synthase**: ~10 nm diameter

### Artificial Structures

- **Head of a pin**: 1-2 mm
- **MicroElectroMechanical (MEMS) devices**: 10-100 μm wide
- **Pollen grain**: Red blood cells
- **Zone plate x-ray “lens”**: Outer ring spacing ~35 nm
- **Self-assembled, Nature-inspired structure**: Many 10s of nm
- **Nanotube electrode**: Outer ring spacing ~35 nm
- **Quantum corral of 48 iron atoms on copper surface**: Positioned one at a time with an STM tip, Corral diameter 14 nm

### The Challenge

Fabricate and combine nanoscale building blocks to make useful devices, e.g., a photosynthetic reaction center with integral semiconductor storage.

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**Visible**

- 1,000 nanometers = ~100 μm

**Infrared**

- 1,000,000,000 nanometers = ~1 μm

**Ultraviolet**

- 1,000,000,000,000 nanometers = ~1 mm

**Microwave**

- 1,000,000,000,000,000,000 nanometers = ~1 cm

**Soft x-ray**

- 1,000,000,000,000,000,000,000,000 nanometers = ~1 m

**Outer ring spacing**

- ~35 nm

**Carbon nanotube**

- ~1 nm diameter

**Carbon buckyball**

- ~1.3 nm diameter
Why Nanoscale?

• Why do we want to make things this small?

  • To make better products: Smaller, cheaper, faster, and more efficient. (Electronics, Chemicals, Water purification, Photovoltaics, medical diagnoses and treatment, etc.)

  • To take advantage of new physical phenomena in science and technology. (Quantum behavior, etc)
Nature’s Lessons

Ioí (Tobacco Mosaic)

wisc.edu

nih.gov
Nature’s Lessons
Nature’s Lessons

Self-assembling nanotechnology factory!
Nature’s Lessons

• Since when do we have nanotechnology applications?
The Many Effects of Nanotechnology

- Information Technology
- Mechanics Robotics
- Biotechnology
- Transportation
- Security Defense
- Agriculture Food
- Energy Environment
- Aeronautics
- Medical Health
- Materials Clothing
Nanotechnology in the Market

• How much do we spend for "nanotech" products?
  • Approximately $ 80B worth of products using nanotechnology in the U.S. in 2009.
  • The main category is:
    • Consumer Products

• Forbes Top 10 Nanotechnology Products for 2005
  • iPod Nano
  • Canola Active
  • O’Lala Foods Choco’la Chewing Gum
  • Zelens Fullerene C-60 Face Cream
  • Easton Sports Stealth CNT Bat
  • Casual Apparel-Nanotex
  • ArcticShield Socks- odor and fungus resistant
  • Behr NanoGuard Paint
  • Pilkington Active Glass
  • NanoBreeze Air Purifier
Nanotechnology in the Market

- Electronics and micro-processors
  - Getting smaller and smaller $\rightarrow$ 180 nm technology

[Image of electronics and micro-processors]

Mακρο-κλίμακα
Μίκρο-κλίμακα
Νανο-κλίμακα

ibm.com
Nanotechnology Prospects

• Cleaner and cheaper energy

Laser-textured silicon for solar cells
Courtesy: Mool Gupta, UVA

Computational catalysis
Courtesy: Matthew Neurock, UVA

Solid oxide fuel cell
Courtesy: Steve McIntosh, UVA
Nanotechnology Prospects

• Nanotubes for faster, better, and cheaper space flight!

 Courtesy of NASA
Nanomedicine

- Medical application of nanotechnology
- Potential impact on
  - Diagnosis
  - Therapy
  - “Theranostics” and Personalized medicine
- What isn’t nanomedicine?
  - Flesh eating/repairing nanorobots
  - Not yet!!!
Goals of Nanomedicine

- End goal of nanomedicine is improved diagnostics, treatment and prevention of disease

For a great review see http://www.wtec.org/nano2/Nanotechnology_Research_Directions_to_2020/
Nanomedicine

- Nanomedicine has the potential to provide
  - Advanced drug delivery systems
  - New therapies
  - In vivo imaging
  - neuro-electronic interfaces (biosensors)$
  - Perhaps even….cell repair machines

- Nanomedicine research
  - Prevention and control:
    - Developing nanoscale devices cancer prevention agents and designing multicomponent anticancer vaccines.
  - Early detection:
    - Developing “smart” collection platforms for simultaneous mass analysis of cancer-associated markers
  - Imaging diagnostics:
    - Designing targeted contrast agents that improve the resolution of cancer to a single cell
  - Multifunctional Therapeutics:
    - Creating therapeutic devices that can control the release of cancer fighting drugs and optimally deliver medication
Medical Uses: Drug Delivery

• **Drug delivery**
  
  • Nanoparticles are easily taken up by cells because of their size
    • Can also deliver hydrophobic/hydrophylic drugs to opposite environment
  
  • Targeted nanoscale particles could improve the availability of the drug to cells that most need it
    • Targeting is a huge issue: $65 billion are lost each year due to poor targeting
    • More on targeting later …
  
  • Could allow for lower doses that are much more effective because of targeting
    • Less toxic (less side effects)
    • Less costly
Medical Uses: Drug Delivery

- Nanshells for more efficient drug delivery
  - Nanoparticle shells can be formed around spherical droplets
  - By making the holes between nanoparticles approximately the same size as the drug you want to administer you can get a constant release rate – avoids spikes in dosage.
  - Can also allow encapsulation of hydrophobic drugs which are difficult to get into you mostly water body.

A: Scanning electron microscope of a dried 10-μm-diameter colloidosome composed of 0.9- μm-diameter polystyrene spheres.

Drug Concentration in Patient

Time

Standard Diffusion Based Drug Delivery

Nano-Encapsulated Drug Delivery
## Medical Uses: Drug Delivery

### Nanotechnology Based Drug Delivery Systems for Cancer Therapy

<table>
<thead>
<tr>
<th>Nanoparticle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanocapsules</td>
<td>Vesicular systems in which the drug is surrounded by a polymeric membrane</td>
</tr>
<tr>
<td>Nanospheres</td>
<td>Matrix systems in which the drug is physically and uniformly dispersed</td>
</tr>
<tr>
<td>Micelles</td>
<td>Amphiphilic block copolymers that can self-associate in aqueous solution</td>
</tr>
<tr>
<td>Ceramic nanoparticles</td>
<td>Nanoparticles fabricated using inorganic compounds including silica, titania…</td>
</tr>
<tr>
<td>Liposomes</td>
<td>Artificial spherical vesicles produced from natural phospholipids and cholesterol</td>
</tr>
<tr>
<td>Dendrimers</td>
<td>Macromolecular compound that comprise a series of branches around an inner core</td>
</tr>
<tr>
<td>SLN particles</td>
<td>Nanoparticles made from solid lipids</td>
</tr>
<tr>
<td>Carbon Nanotubes</td>
<td>Allotropes of carbon with a cylindrical nanostructure. Intracellular delivery and bypassing resistance</td>
</tr>
</tbody>
</table>

Schematics - Reproduced from Sahoo and Labhasetwar, 2003

Medical Uses: Drug Delivery

• First Approved Nanomedicine for Cancer - Abraxane

- Approved for Breast Cancer
- Albumin-bound Paclitaxel
- Paclitaxel – powerful anticancer drug – not water soluble
- Abraxane is water soluble – reduces treatment to 30 min from 3 hrs
- Increases dose and reduces side effects
- ~130 nm
Medical Uses: Antimicrobial Surfaces

• Keeping Things Clean – Antimicrobial Surfaces

  • Silver is an excellent anti-microbial agent
  
  • Silver nanoparticles are now being added to fibers of clothing and bandages as well as being incorporated into surfaces in hospitals to reduce the rate of bacterial infections
  
  • When co-extracted with a polymer like PLLA, the silver is released slowly over time and has been shown to effectively kill bacteria
Medical Uses: Diagnostics

- **Lab-on-a-chip**
  - Goal is to develop handheld diagnostic devices for personalized medical testing and treatment
  - Combinations of
    - Microfluidics
    - MEMS
    - Micro-Array
    - Lasers
    - Detectors
    - etc
Medical Uses: Diagnostics

• Research at UCY
  • Surface Enhanced Raman Spectroscopy
    • Use of nanoparticles to perform sensitive spectroscopy measurements of chemical bonds
  • Projects
  • UTI infection diagnosis and antibiotic sensitivity
    • In 2 hrs instead of 2 days
    • 93.75% correct classification rate
    • 90% correct antibiotic testing
  • Food Analysis
    • Identification of nutritional facts (15 % error)
    • Identification of contamination
Medical Uses: Surgical Applications

- Photodynamic therapy:
  - Nanoparticles localized to cancer cells could “melt them” when heated using a light source.
  - Noninvasive
  - Not toxic to other tissues, like chemotherapy
Medical Uses: In vivo Imaging

- **Nanoparticles for cancer diagnosis**
  - Specifically attaching to certain molecules characteristic of cancer
    - Specific DNA, RNA, or protein sequences known to exist in a certain cancers.
  - Provide better contrast
    - Optical
    - MRI
    - Ultrasound
  - More on targeting later …
Theranostics and Personalized Medicine

- **Theranostics**
  - All-in-one (diagnosis, therapy, monitoring)

- **Personalized Therapy**
  - Personalized to the characteristics of the cancer (or other disease) and of the patient
Molecular Imaging & Therapy

• Identification of a marker of disease
  • Such markers can be genes expressed or activated, cytoplasmic or free proteins, enzymes produced at the site of disease etc.
  • These markers can be specific
    • to the disease (e.g. type, sub-type, sub-sub-type of cancer)
    • to the patient (avoid side effects)

• Targeting of the marker
  • Targeting provides a means to concentrating the contrast agent/pharmaceutical at the disease with high disease specificity
  • Monoclonal antibodies, antibody fragments, peptides, etc. are all suitable targeting agents
• **Attaching an appropriate beacon to the marker**
  - Such a beacon can be a fluorescent or bioluminescent molecule, a metallic nanoparticle or nanoshell, or a quantum dot or a radioactive nucleotide.
  - Depending on the marker and its location, issues such as beacon uptake by the tissue and intracellular penetration may have to be considered.

• **Detection of the beacon**
  - The presence or absence of the marker can be detected indirectly by using optical, ultrasound, MRI, or nuclear techniques to identify the beacon’s presence and concentration.
  - The detection can be quantitative.

• **Therapy**
  - Activation or release of the pharmaceutical
  - Localized effect
    - Lower dose, more effective
    - Less side effects
Contrast Agents

• **Non-specific contrast agents**
  • Non-specific distribution pattern
  • An important tool for depicting tumor physiology: perfusion, vessel permeability, tissue blood volume

• **Targeted / active contrast agents**
  • Combining efficient targeting strategies with sensitive beacons
    • Antibodies or antibody fragments
    • Small peptide derivatives
    • etc
  • Resolves molecular targets in the nM range in vivo

• **Smart/ activatable contrast agents**
  • Alter their signal characteristics upon interaction with the specific target
    • Very little signal in the native stage/ strong after enzymatic cleavage
    • They provide the highest SNR
  • More complex probe design and synthesis
Intravenous administration

(a) Administration
Vascular phase
Distribution
Post-clearance

(b) Vasculature of an abdominal tissue flap for use in breast reconstruction
Fluorescence distribution in the liver
After ICG clearance, a hepatic CRC metastasis (arrow) is revealed

Oral administration

(c) Administration
Accumulation
Metabolism
Fluorescence

5-ALA
PpIX
Theranostics

Research at UCY

• **Multipotent Theranostic Metal-Based Scaffolds for Molecular Targeting of Colorectal Cancer**
  
  • A novel system of targeted molecular imaging and therapeutic (theranostic) agents for the management of colorectal cancer
  
  • Optical and MRI beacons with therapeutic effect
  
  • Earlier diagnosis and better prognosis
  
  • Reduced side effects
Nanomedicine Market

• Global nanomedicine market
  • $43.2 billion in 2010
  • $50.1 billion in 2011
  • $96.9 billion by 2016
  • Annual growth rate of 14.1% between years 2011 and 2016.

• Anticancer products market
  • $4.7 billion in 2010
  • $5.5 billion in 2011
  • $12.7 billion by 2016
  • Annual growth rate of 18.2% between years 2011 and 2016.

• > 200 companies
• > 130 drug delivery systems are under development…
Table 1: Examples of FDA-Approved Agents Utilizing Nanomedicine

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active ingredient</th>
<th>Indication*</th>
<th>Manufacturer</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abicil</td>
<td>Liposomal amphotericin B</td>
<td>Invasive fungal infections</td>
<td>Sigma Tau</td>
<td>1995</td>
</tr>
<tr>
<td>Abraxane</td>
<td>Albumin-protein-bound paclitaxel</td>
<td>Metastatic breast cancer</td>
<td>Celgene</td>
<td>2005</td>
</tr>
<tr>
<td>Adagen</td>
<td>Pegylated adenosine deaminase enzyme</td>
<td>Severe combined immunodeficiency disease</td>
<td>Sigma Tau</td>
<td>1990</td>
</tr>
<tr>
<td>Alimta</td>
<td>Pemetrexed</td>
<td>Non-small cell NSCLC, malignant pleural mesothelioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambisome</td>
<td>Liposomal amphotericin B</td>
<td>Fungal infections, leishmaniasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotec</td>
<td>Liposomal amphotericin B</td>
<td>Invasive aspergillosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimzia</td>
<td>Pegylated Fab’ fragment of a humanized anti-17-70a antibody</td>
<td>Crohn’s disease, rheumatoid arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capoxone</td>
<td>Glutamer acetate (copolymer composed of L-glutamic acid, L-alanine, L-lysine, and L-tyrosine)</td>
<td>Multiple sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DaunoXome</td>
<td>Liposomal daunorubicin citrate</td>
<td>HIV-associated Kaposi’s sarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depocyt(e)</td>
<td>Liposomal cytosine arabinoside</td>
<td>Lymphomatous meningiitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docxil</td>
<td>Pegylated-stabilized liposomal doxorubicin</td>
<td>AIDS-related Kaposi’s sarcoma, refractory ovarian cancer, multiple myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligard</td>
<td>Leuprolide acetate and PLGH polymer formulation</td>
<td>Advanced prostate cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emend</td>
<td>Aprepitant nanocrystal particles</td>
<td>Chemotherapy-related nausea and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macugen</td>
<td>Pegaptanib (PEG-anti-VEGF aptamer)</td>
<td>Wet age-related macular degeneration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miracar</td>
<td>Methoxy PEG-eotin beta</td>
<td>Symptomatic anemia associated with CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nolleva</td>
<td>Pegfilgrastim</td>
<td>Chemotherapy-associated neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncaspargi</td>
<td>Peg-asparaginase</td>
<td>Acute lymphocytic leukemia</td>
<td></td>
<td></td>
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<tr>
<td>Ontak</td>
<td>Interleukin-2 in interferon fusion protein</td>
<td>Cutaneous T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegaseq</td>
<td>Peginterferon alpha-2a</td>
<td>Hepatitis B and C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peglatron</td>
<td>Peginterferon alpha-2b</td>
<td>Hepatitis C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renagel</td>
<td>Amine-loaded polymer</td>
<td>Serum phosphorus control in patients with CKD on dialysis</td>
<td>Genzyme</td>
<td>2000</td>
</tr>
<tr>
<td>Somavert</td>
<td>Pegylated human growth hormone receptor antagonist</td>
<td>Acromegaly</td>
<td>Pfizer</td>
<td>2003</td>
</tr>
<tr>
<td>Tricor</td>
<td>Fenofibrate</td>
<td>Hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia</td>
<td>Abbott</td>
<td>2004</td>
</tr>
<tr>
<td>Visudyne</td>
<td>Liposomal verteporfin</td>
<td>Wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome</td>
<td>OLT Ophthalmics</td>
<td>2000</td>
</tr>
</tbody>
</table>

Table 2: Examples of Medical Devices and Diagnostics Utilizing Nanomedicine

<table>
<thead>
<tr>
<th>Name</th>
<th>Device/Diagnostic Type</th>
<th>Application</th>
<th>Manufacturer</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA-Approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CellSearch</td>
<td>Antibodies bound to IO NPs</td>
<td>CTC detection</td>
<td>Veridex</td>
<td>2004</td>
</tr>
<tr>
<td>DNAarray</td>
<td>Lab-on-a-chip</td>
<td>DNA-based tests</td>
<td>CombiMatrix</td>
<td>2005</td>
</tr>
<tr>
<td>Gastronark</td>
<td>Silicone-coated ferumoxsil SPIOs</td>
<td>MRI contrast agent</td>
<td>AMAG Pharmaceuticals</td>
<td>1996</td>
</tr>
<tr>
<td>MultiHance</td>
<td>Gadolinium-based NPs</td>
<td>MRI contrast agent</td>
<td>Bracco Group</td>
<td>2004</td>
</tr>
<tr>
<td>Optmark</td>
<td>Gadolinium-based NPs</td>
<td>MRI contrast agent</td>
<td>Mallinckrodt</td>
<td>1999</td>
</tr>
<tr>
<td>Omniscan</td>
<td>Gadolinium-based NPs</td>
<td>MRI contrast agent</td>
<td>General Electric Healthcare</td>
<td>1993</td>
</tr>
<tr>
<td>Silvagard</td>
<td>Silver NP solution</td>
<td>Anti-infective coating for medical devices</td>
<td>AcryMed, Inc.</td>
<td>2005</td>
</tr>
<tr>
<td>Verigene</td>
<td>Functionalized gold NPs</td>
<td>Diagnostic tests</td>
<td>Nanosphere</td>
<td>2007</td>
</tr>
<tr>
<td>Vitoss</td>
<td>Ultrapermeable beta-TCP NPs</td>
<td>Bone-replacement scaffold</td>
<td>Orthovita</td>
<td>2000</td>
</tr>
<tr>
<td><strong>Investigational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combidx</td>
<td>Dextran-coated ferumoxtran-10 USPIOs</td>
<td>MRI contrast agent</td>
<td>Advanced Magnetics</td>
<td>Phase 1, 2, 4</td>
</tr>
<tr>
<td>MagProbe</td>
<td>CD34 antibody-linked NPs/magnetic biopsy needle</td>
<td>Leukemia diagnostics</td>
<td>Senior Scientific</td>
<td>Phase 1</td>
</tr>
<tr>
<td>NanoTherm therapy</td>
<td>Aminosilane-coated IO NPs</td>
<td>Thermal ablation/hyperthermia therapy for liver, pancreatic cancer</td>
<td>MagForce AG</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
What the future holds?

• Nanorobots?
  • Nanosize machines that could be activated by light to do things inside our bodies…
  • ex. Nanocar
Concerns and Ethical Issues

• Concerns/Dangers
  • Chemical Disagreements
  • Toxicity
  • Immune Rejection
  • Control Issues

• Ethical issues
  • Potential Medical Breakthrough - Risks
  • Possible Scientific/Societal Dud
  • How do we weigh out nanomedicine’s costs and benefits towards society?

• Nano Horrors
  • Superhumans
  • Self replicating Nano Robots \( \rightarrow \) A threat to the existence of human beings