ECE 370
Introduction to Biomedical Engineering

Nanomedicine and Personalized Medicine

Nano… What???

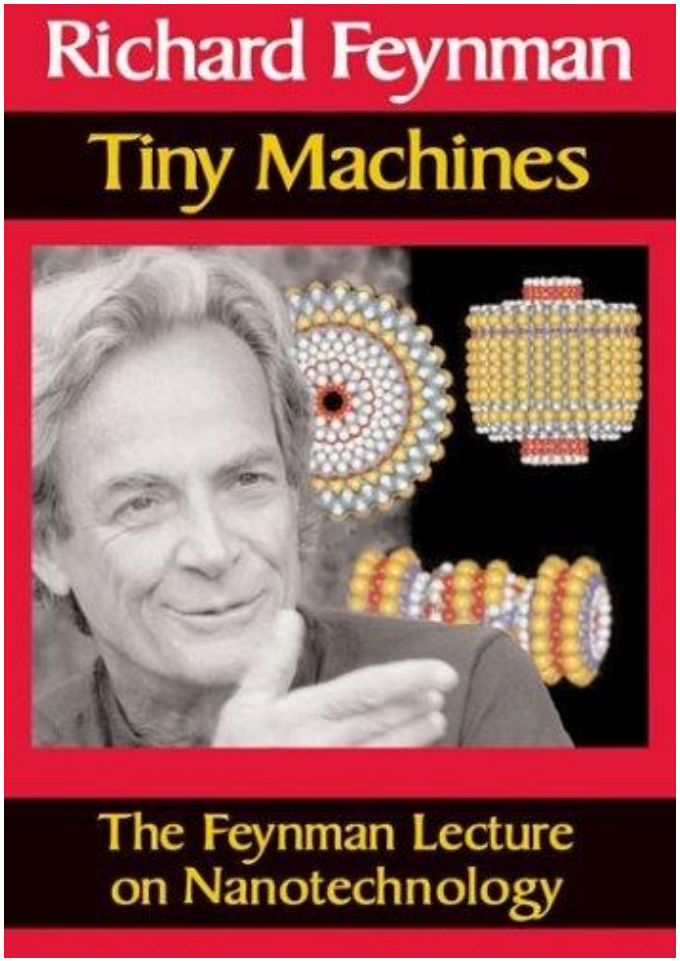
Heigh Ho…

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

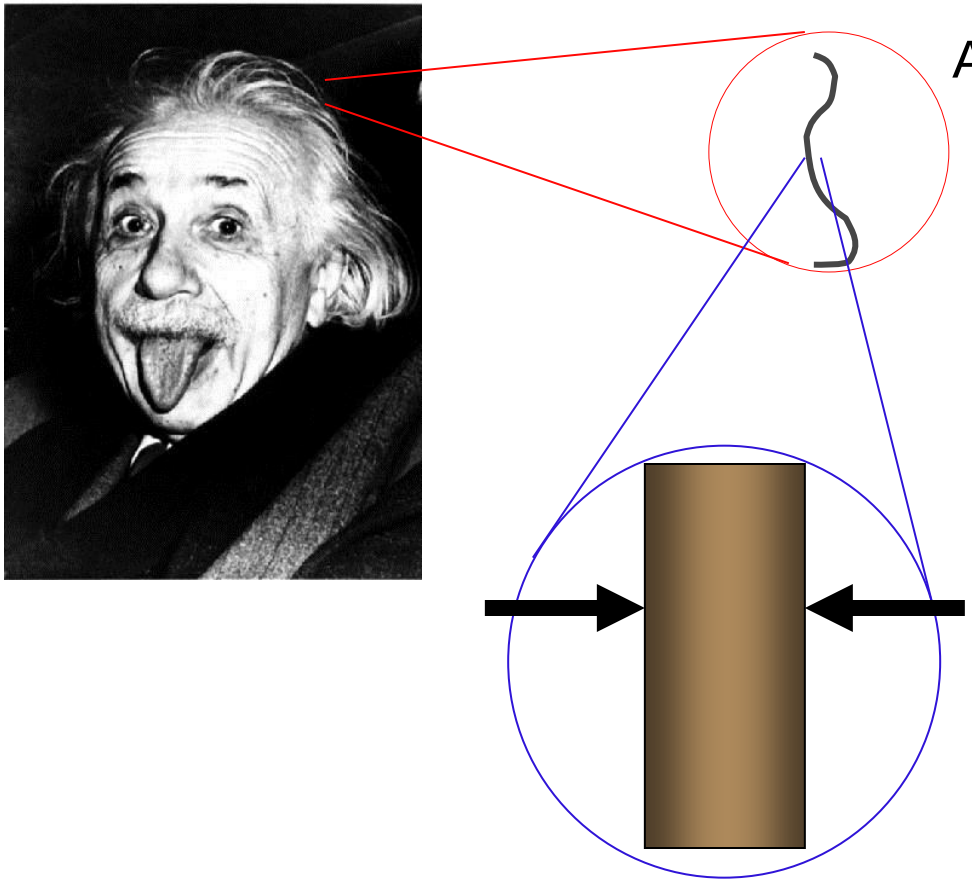
- **Nanotechnology**
  - The study of the control of matter at the atomic/molecular level
  - Structures < 100 nm



Nano… What???

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

Nano… What???

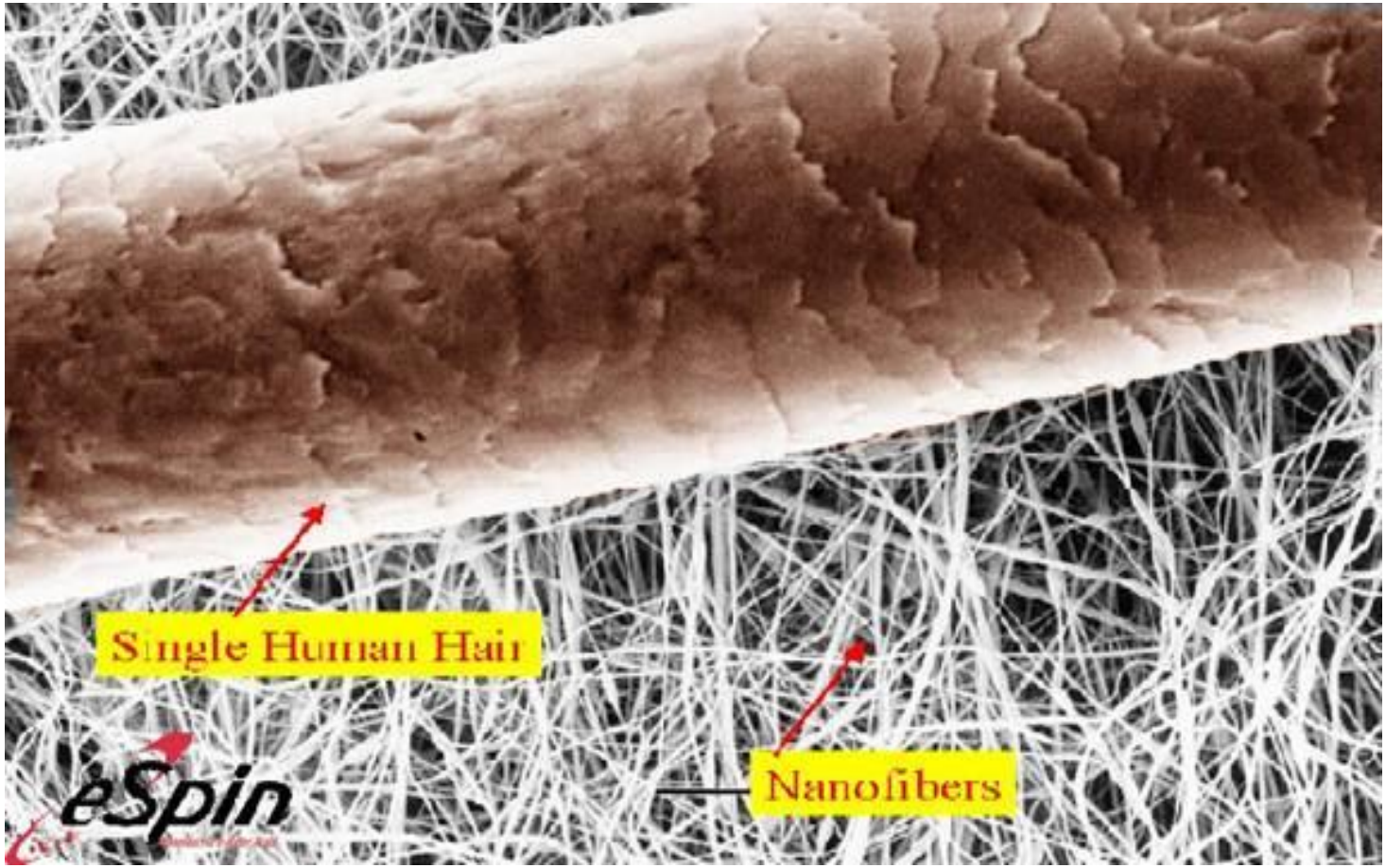


Diameter = 0.1 mm

= 100 micrometers

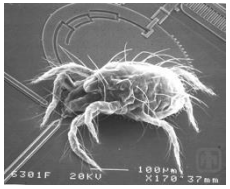
= 100,000 nanometers!

Nano… What???



The Scale of Things – Nanometers and Beyond

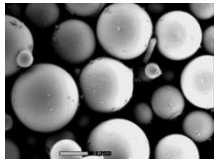
Natural Structures



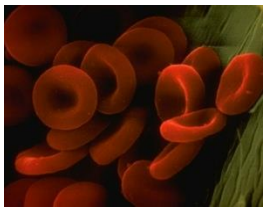
Dust mite
200 μm

Ant
~ 5 mm

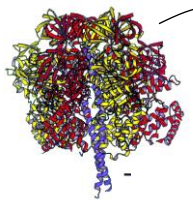
Human hair
~ 60-120 μm wide



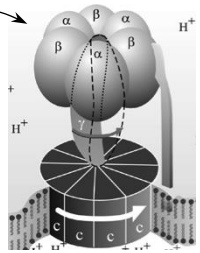
Fly ash
~ 10-20 μm



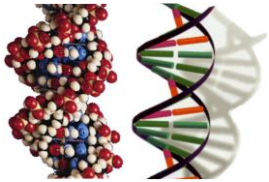
Red blood cells
(~7-8 μm)



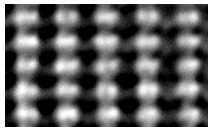
~10 nm diameter



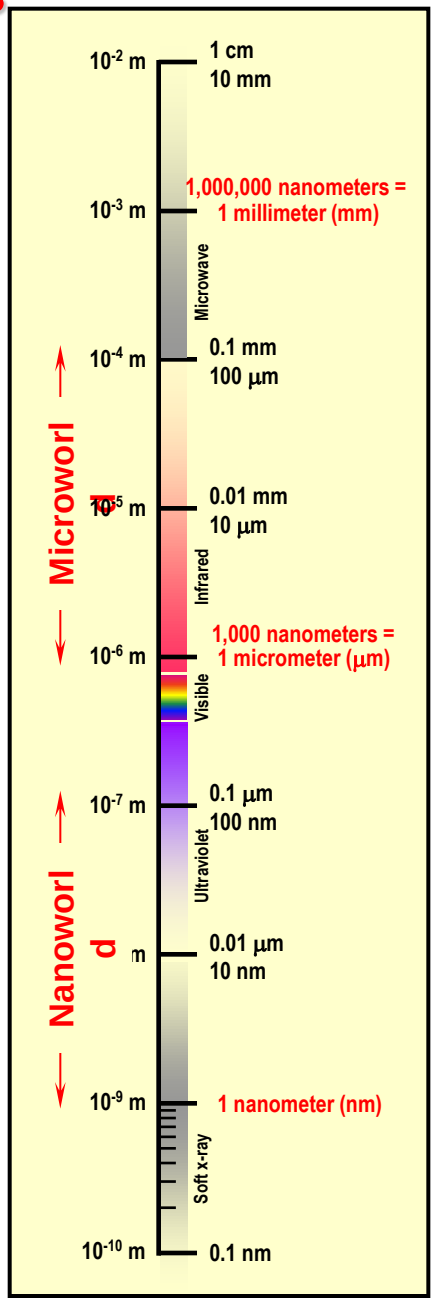
ATP synthase



DNA
~2-1/2 nm diameter

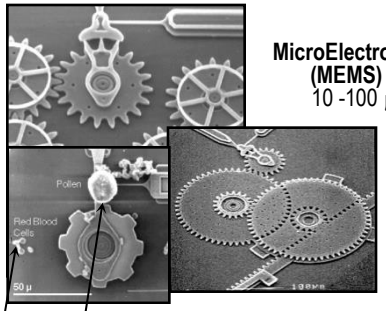


Atoms of silicon
spacing 0.078 nm



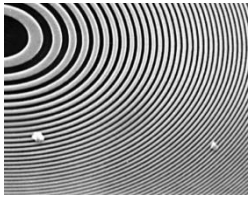
Artificial Structures

Head of a pin
1-2 mm

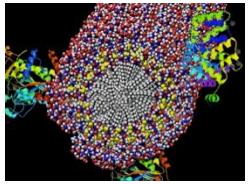


MicroElectroMechanical (MEMS) devices
10 -100 μm wide

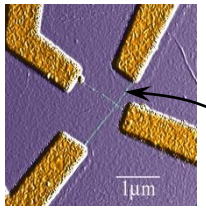
Pollen grain
Red blood cells



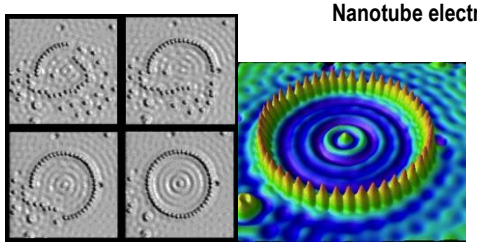
Zone plate x-ray "lens"
Outer ring spacing ~35 nm



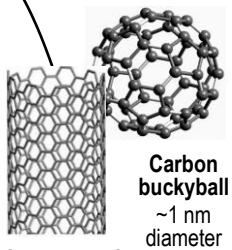
Self-assembled,
Nature-inspired structure
Many 10s of nm



Nanotube electrode



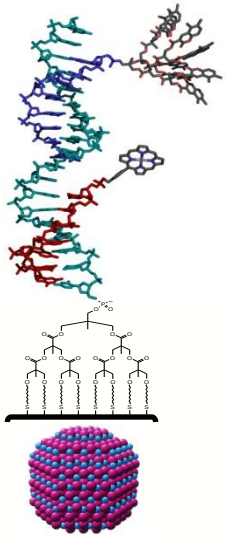
Quantum corral of 48 iron atoms on copper surface positioned one at a time with an STM tip
Corral diameter 14 nm



Carbon buckyball
~1 nm diameter

Carbon nanotube
~1.3 nm diameter

The Challenge



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

Office of Basic Energy Sciences
Office of Science, U.S. DOE
Version 05-26-06, pmd

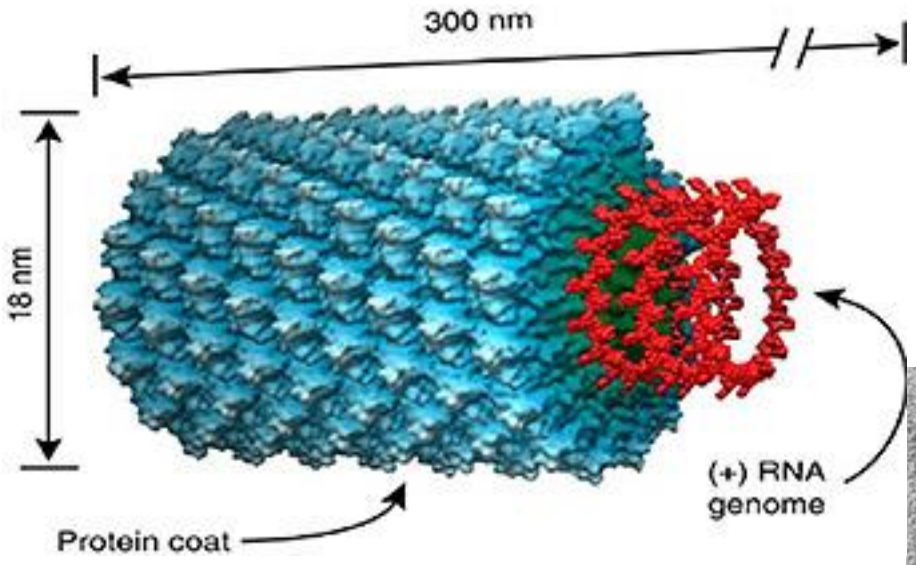
Why Nanoscale?

- **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.)

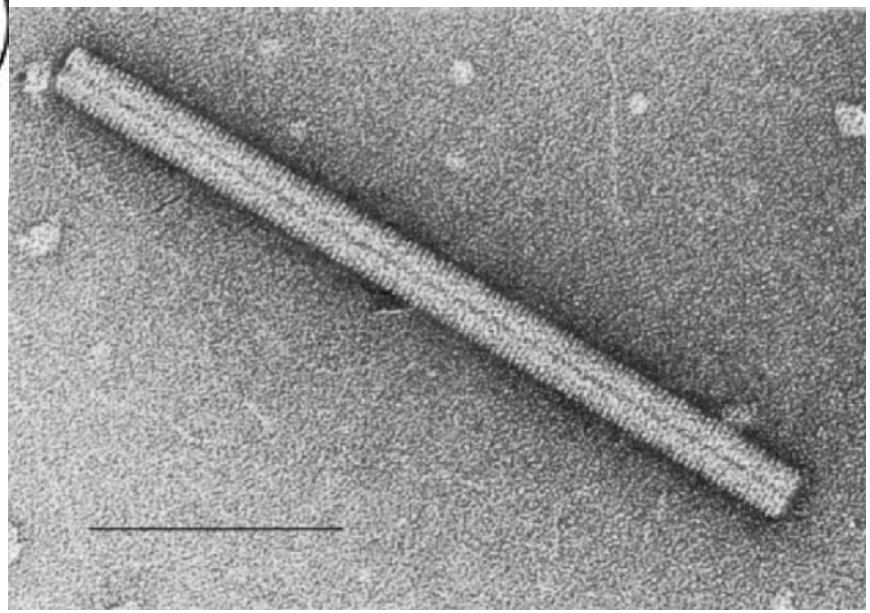
  - To take advantage of new physical phenomena in science and technology. (Quantum behavior, etc)

Nature's Lessons



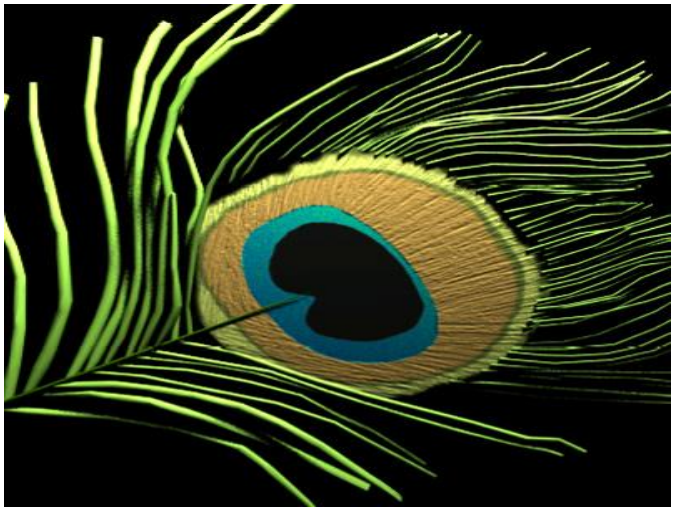
wisc.edu

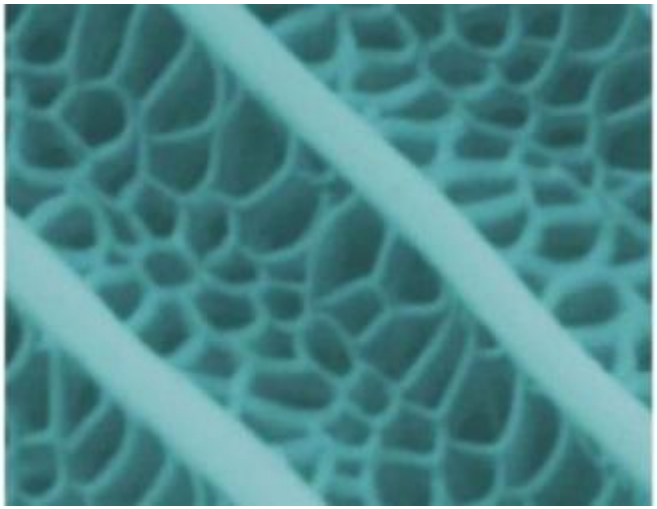
Ioí (Tobacco Mosaic)

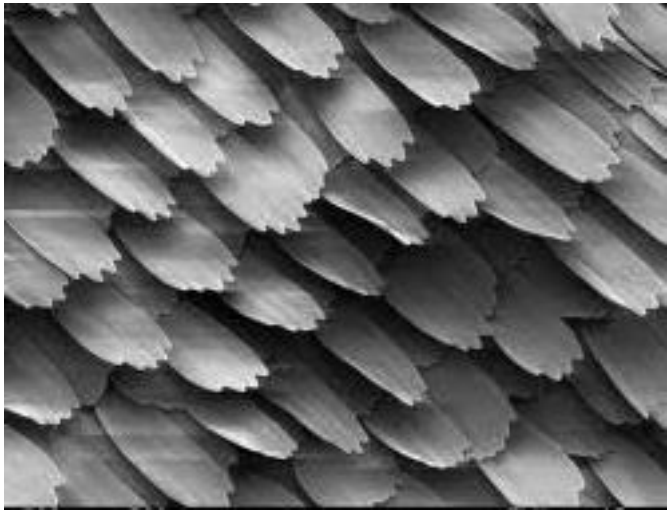


nih.gov

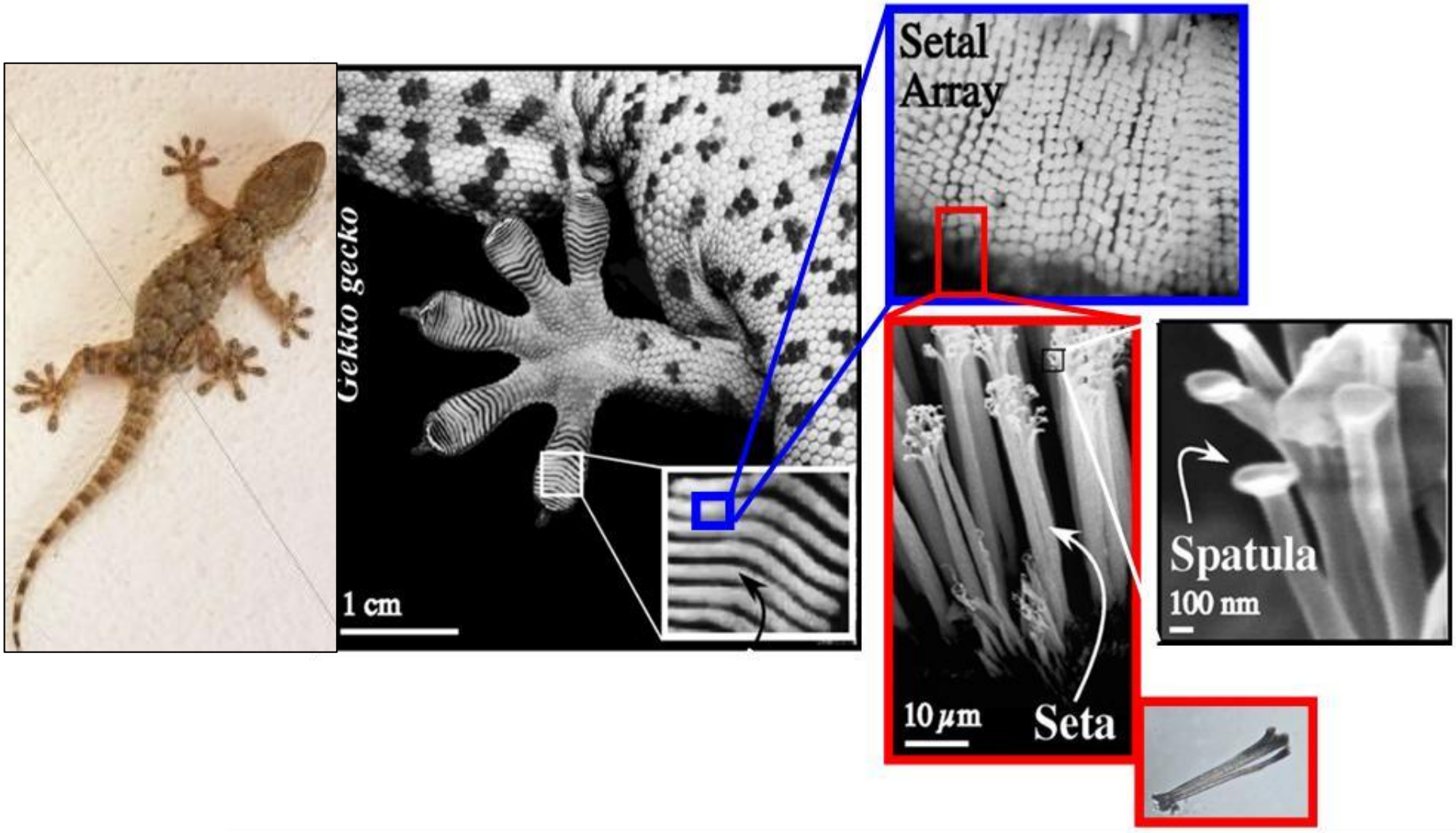
Nature's Lessons



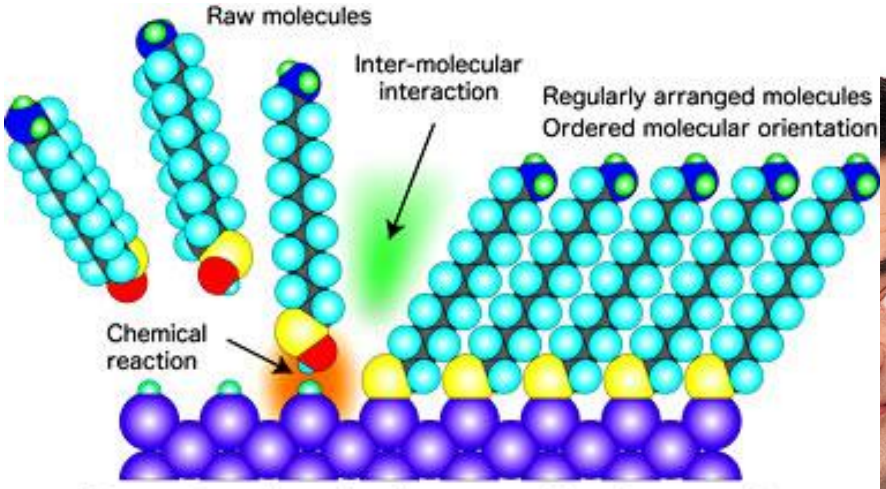


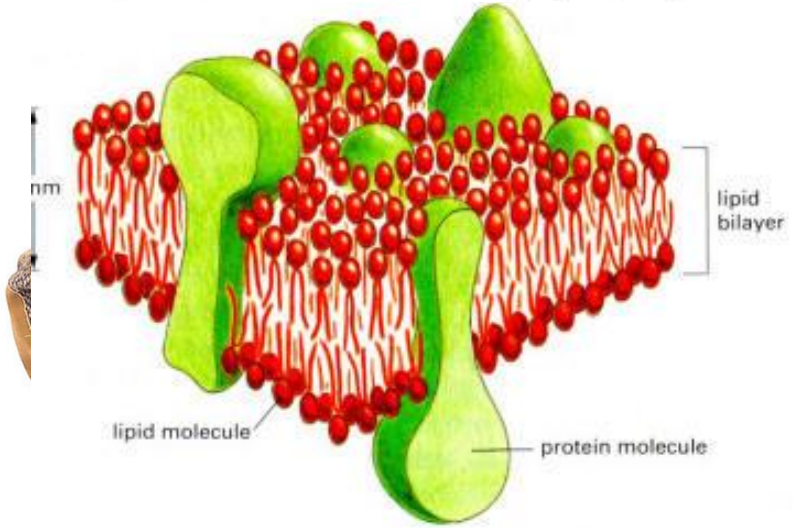


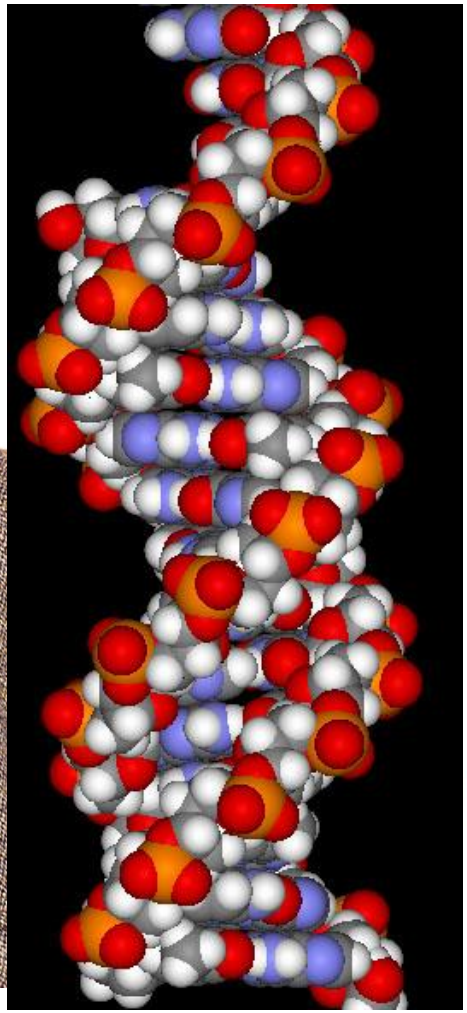
Nature's Lessons



Nature's Lessons





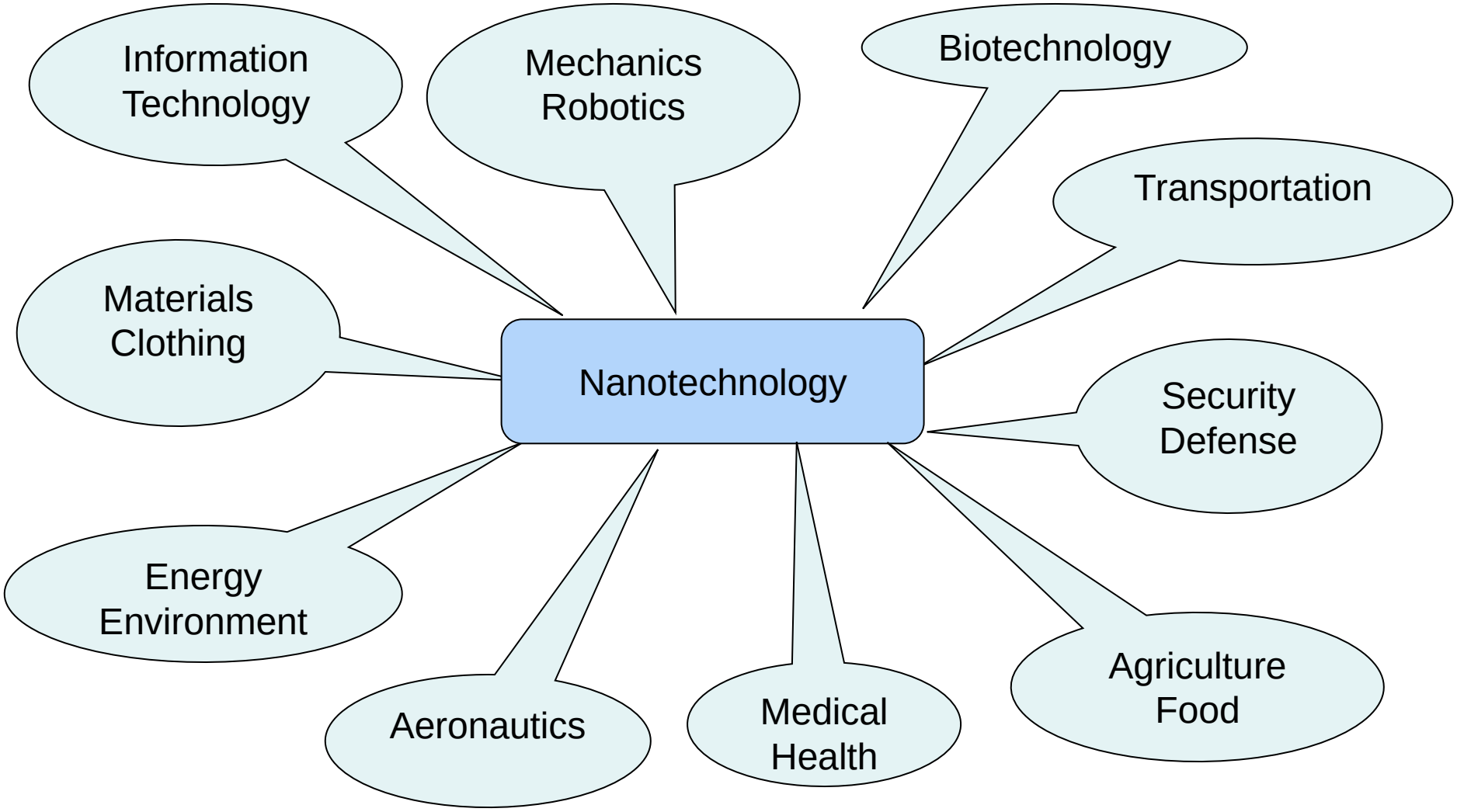


Self-assembling nanotechnology factory!

Nature's Lessons

- **Since when do we have nanotechnology applications?**

The Many Effects of Nanotechnology



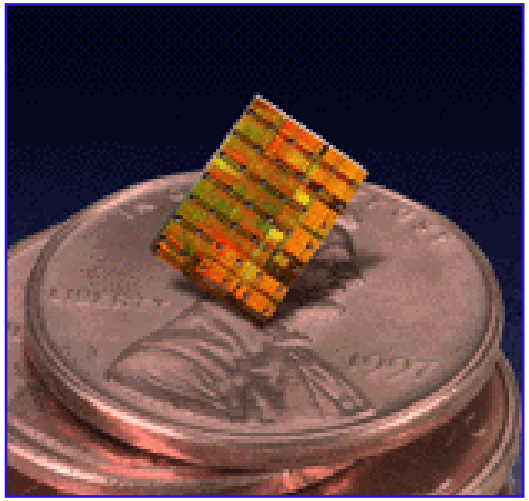
Nanotechnology in the Market

- **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

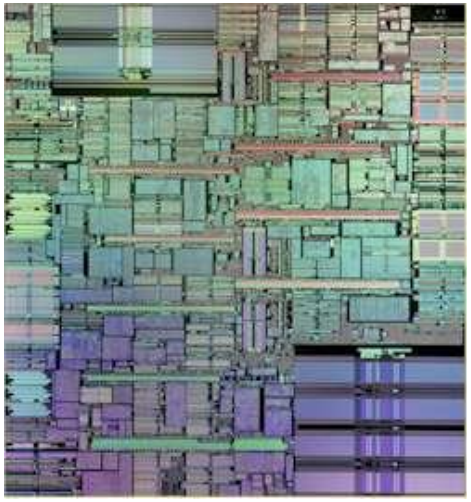
160 GB

Nanotechnology in the Market

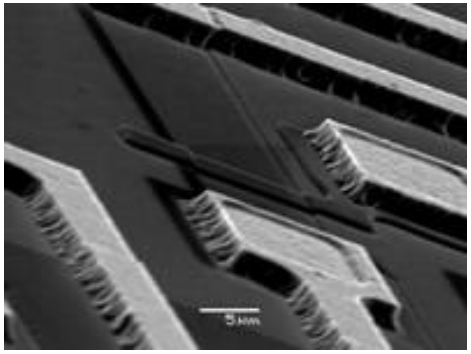
- **Electronics and micro-processors**
  - Getting smaller and smaller → 180 nm technology



Μακρο-κλίμακα



Μίκρο-κλίμακα

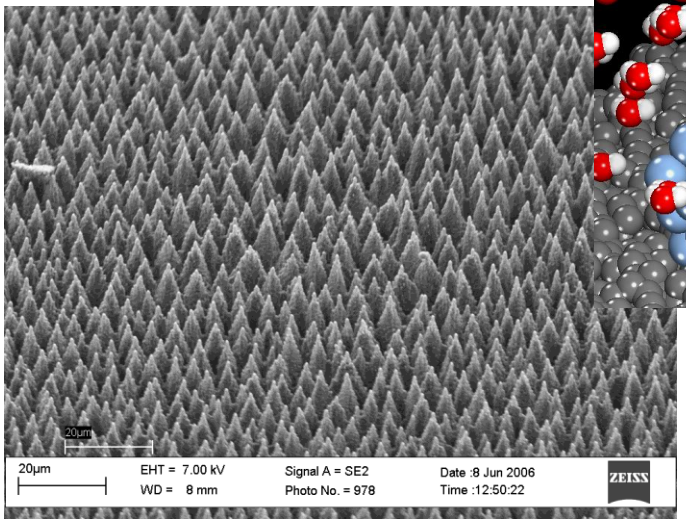


Νανο-κλίμακα

ibm.com

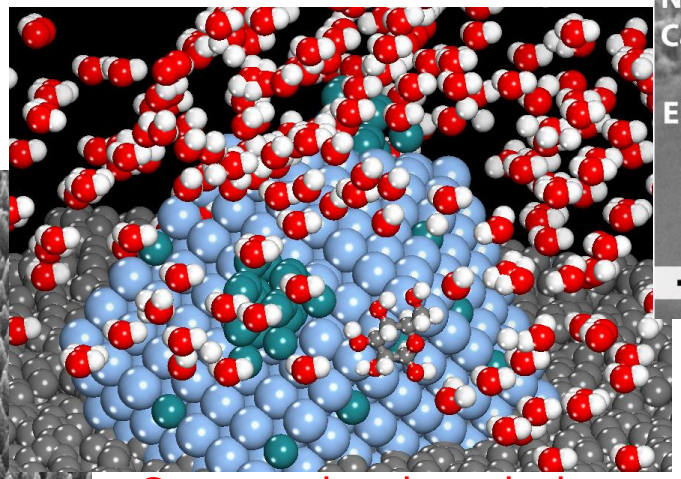
Nanotechnology Prospects

- **Cleaner and cheaper energy**



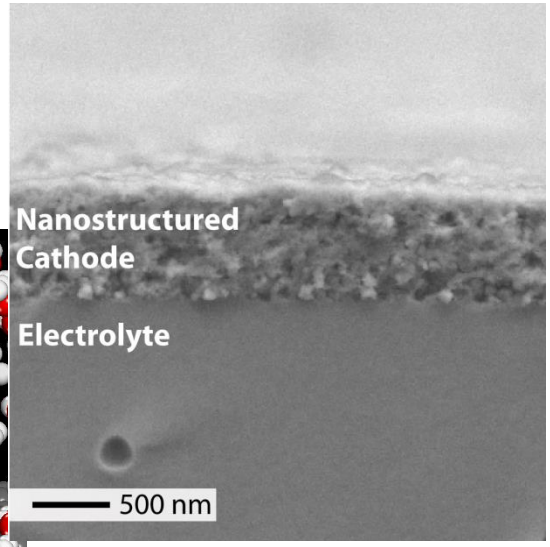
Laser-textured silicon for solar cells

Courtesy: Mool Gupta, UVA



Computational catalysis

Courtesy: Matthew Neurock, UVA

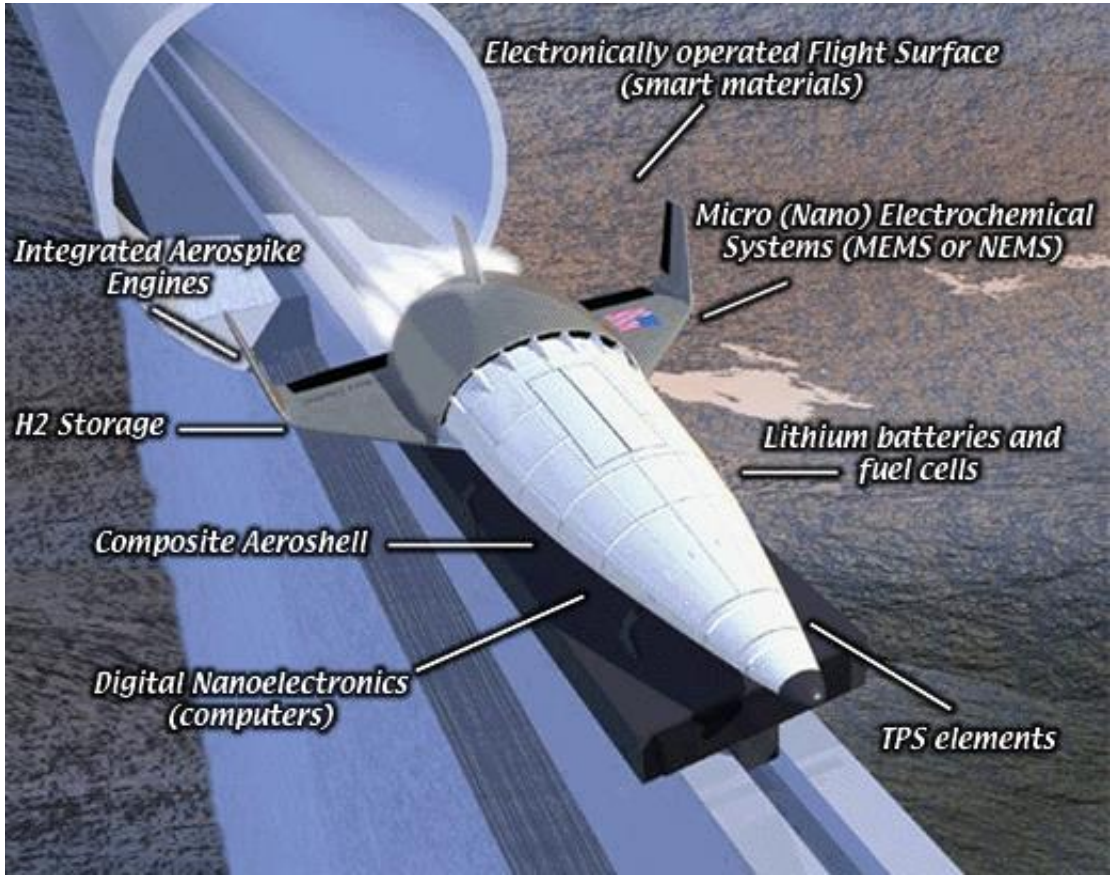


Solid oxide fuel cell

Courtesy: Steve McIntosh, UVA

Nanotechnology Prospects

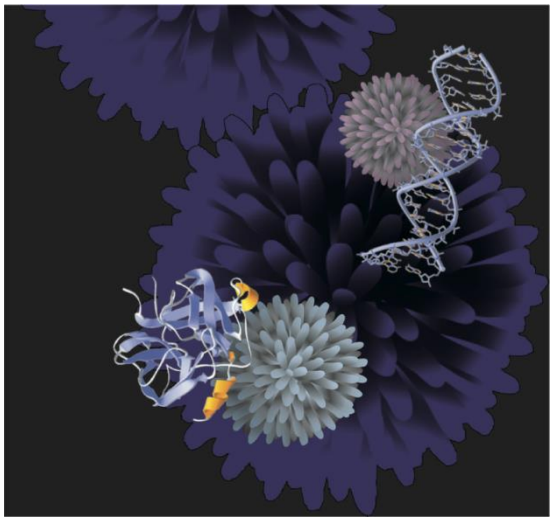
- **Nanotubes for faster, better, and cheaper space flight!**

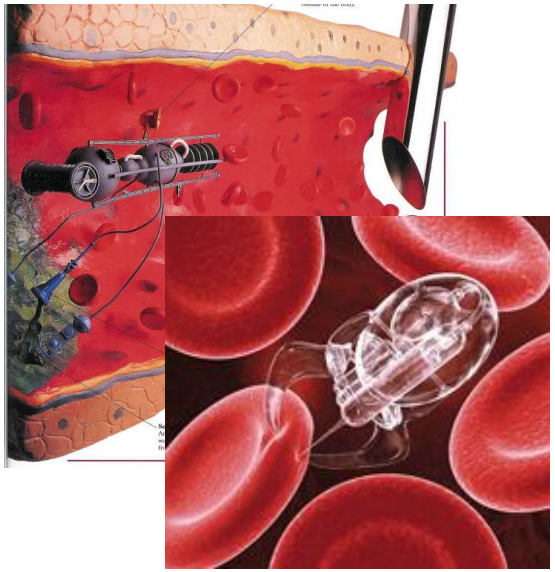


Courtesy of NASA

Nanomedicine

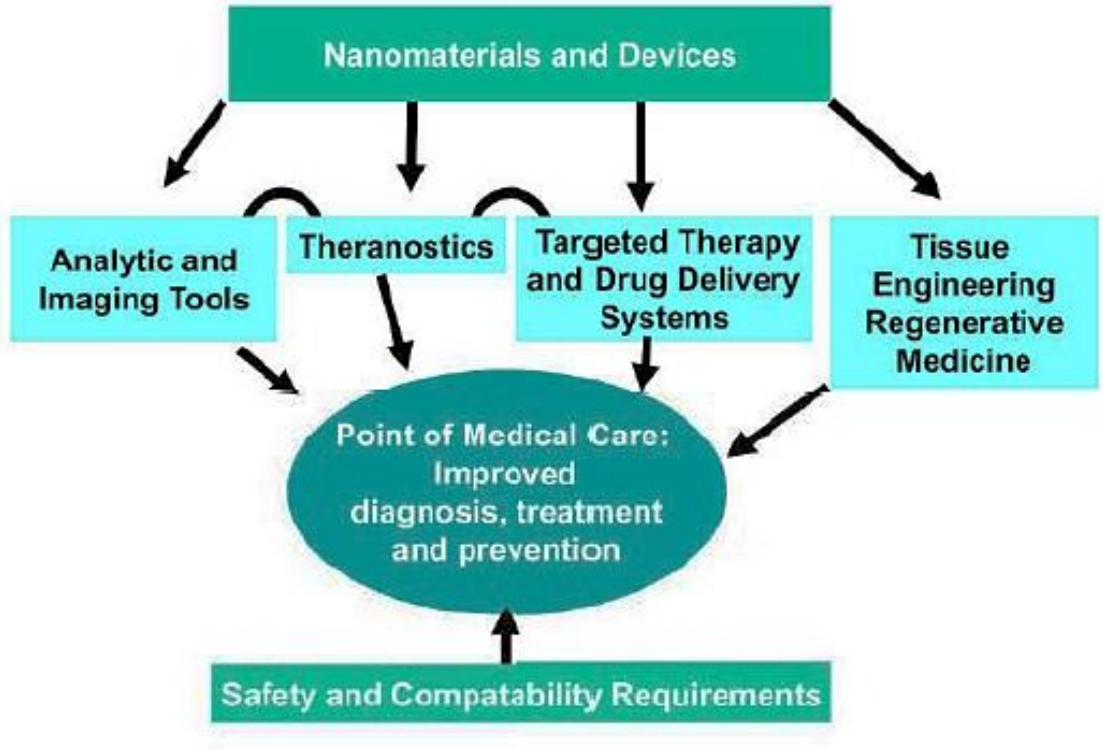
- **Medical application of nanotechnology**
- **Potential impact on**
  - Diagnosis
  - Therapy
  - “Theranostics” and Personalized medicine
- **What isn’t nanomedicine?**
  - Flesh eating/repairing nanorobots
  - Not yet!!!





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

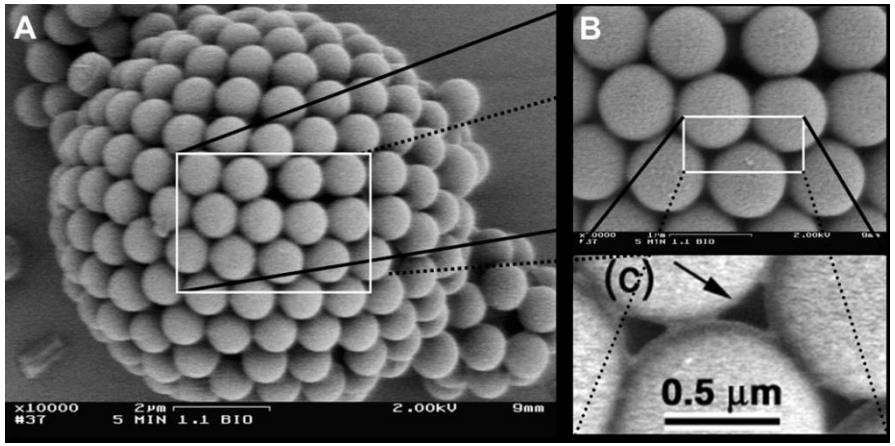
- **Nanomedicine has the potential to provide**
  - Advanced drug delivery systems
  - New therapies
  - In vivo imaging
  - neuro-electronic interfaces (biosensors)$
  - Perhaps even….cell repair machines
- **Nanomedicine research**
  - Prevention and control:
    - Developing nanoscale devices cancer 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

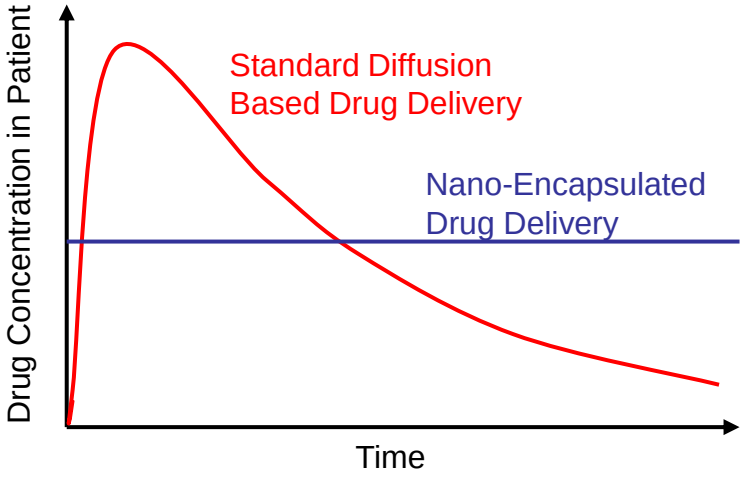
- **Drug delivery**
  - Nanoparticles are easily taken up by cells because of their size
    - Can also deliver hydrophobic/hydrophylic drugs to opposite environment
  - Targeted nanoscale particles could improve the availability of the drug to cells that most need it
    - Targeting is a huge issue: $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
    - A.D. Dinsmore, et al., Science 298, 1006 (2002), Y. Lin, et al., Science 299, 226 (2003)
  - 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.



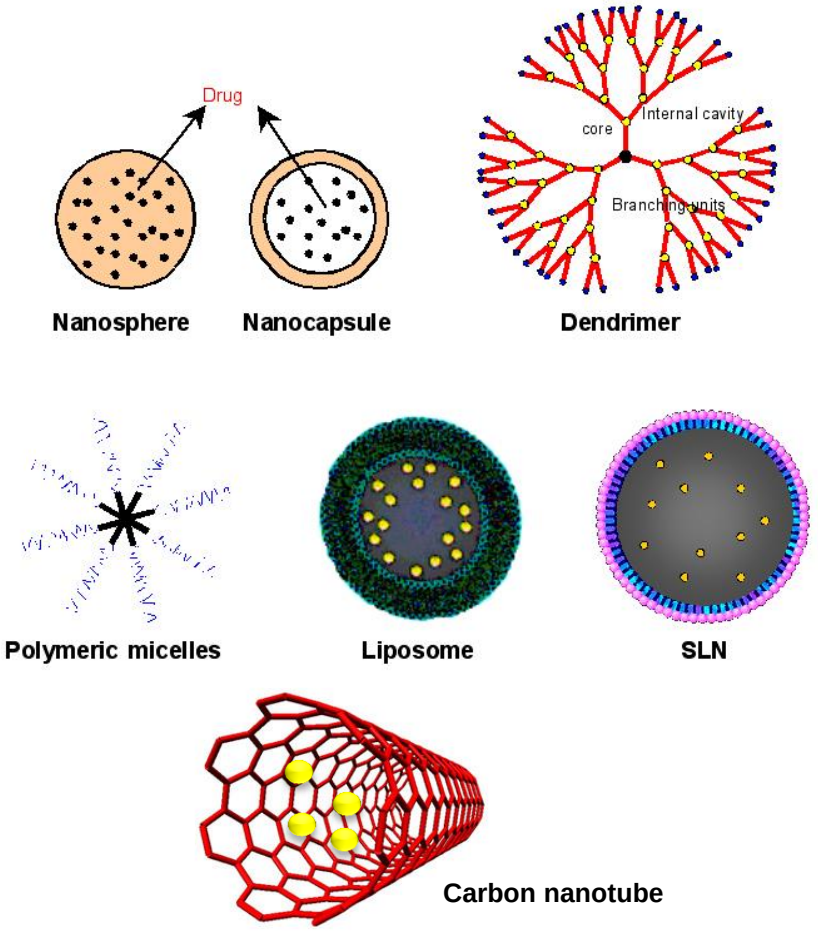
A: Scanning electron microscope of a dried 10-µm-diameter colloidosome composed of 0.9- µm-diameter polystyrene spheres.



Medical Uses: Drug Delivery

- **Nanotechnology Based Drug Delivery Systems for Cancer Therapy**

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

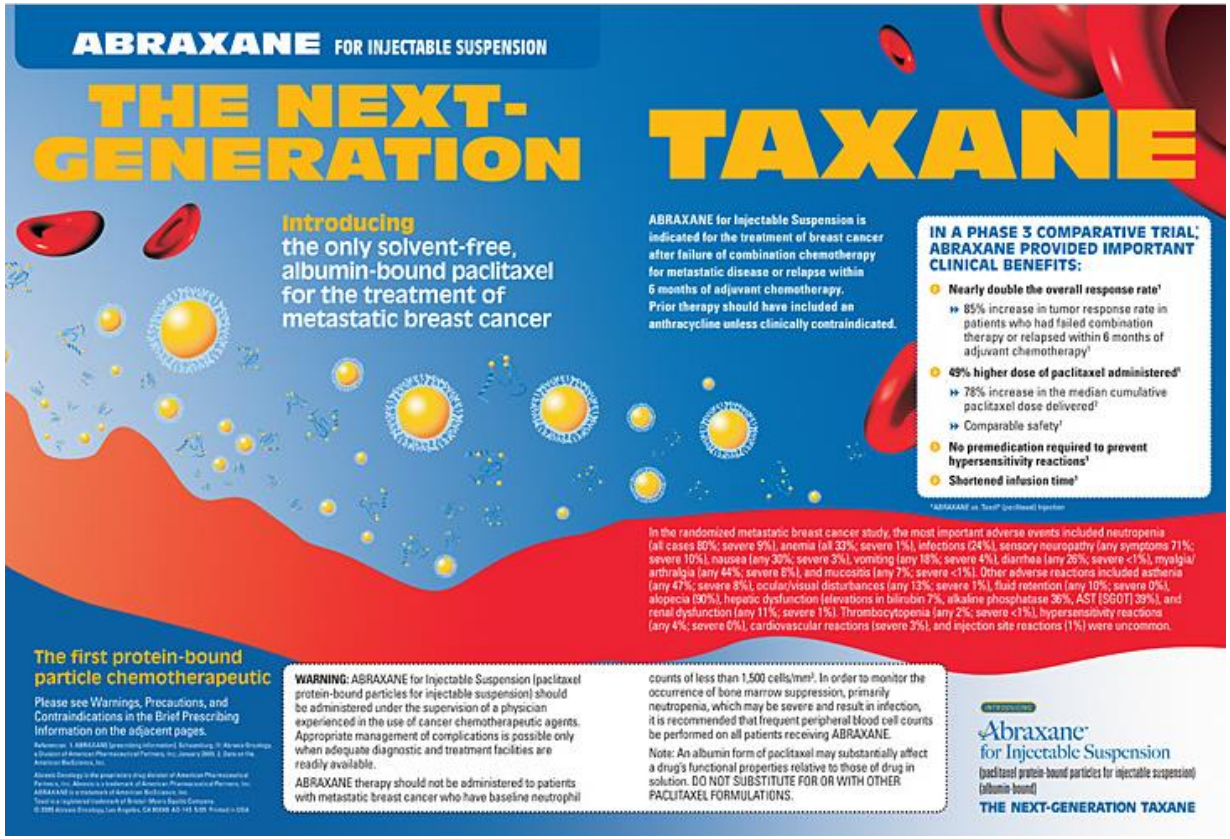


Schematics - Reproduced from Sahoo and Labhasetwar, 2003

http://cancer-therapy.org / CT /v3 / A / 13.%20Orive%20et%20al,%20131-138.p%20copy

Medical Uses: Drug Delivery

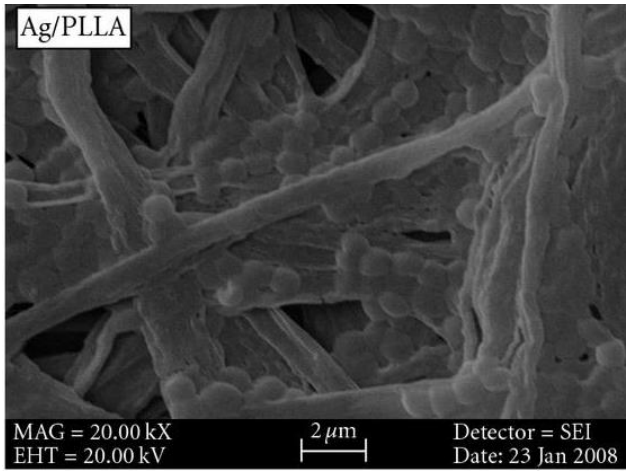
- **First Approved Nanomedicine for Cancer - Abraxane**

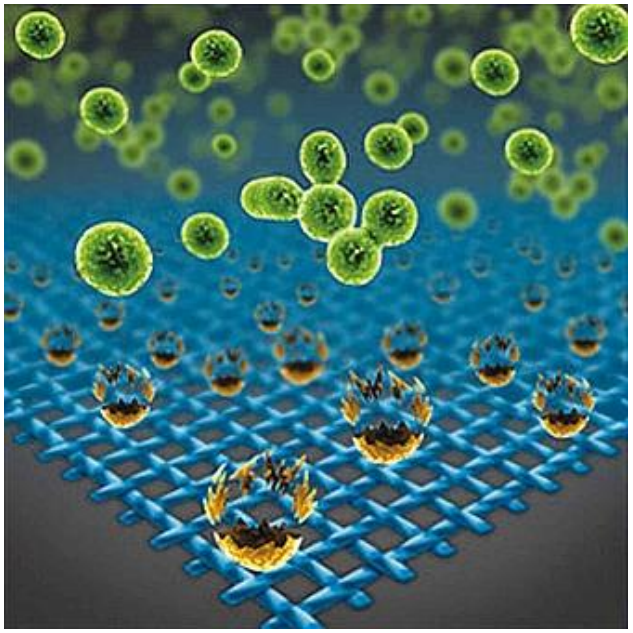


- Approved for Breast Cancer
- Albumin-bound Paclitaxel
- Paclitaxel – powerful anticancer drug – not water soluble
- Abraxane is water soluble – reduces treatment to 30 min from 3 hrs
- Increases dose and reduces side effects
- ~130 nm

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-extruded with a polymer like PLLA, the silver is released slowly over time and has been shown to effectively kill bacteria



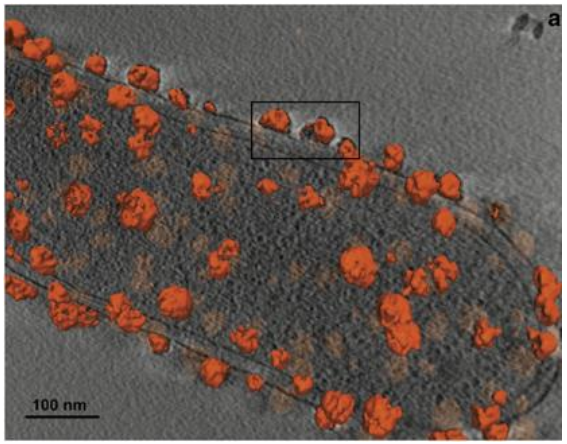


Medical Uses: Diagnostics

- **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

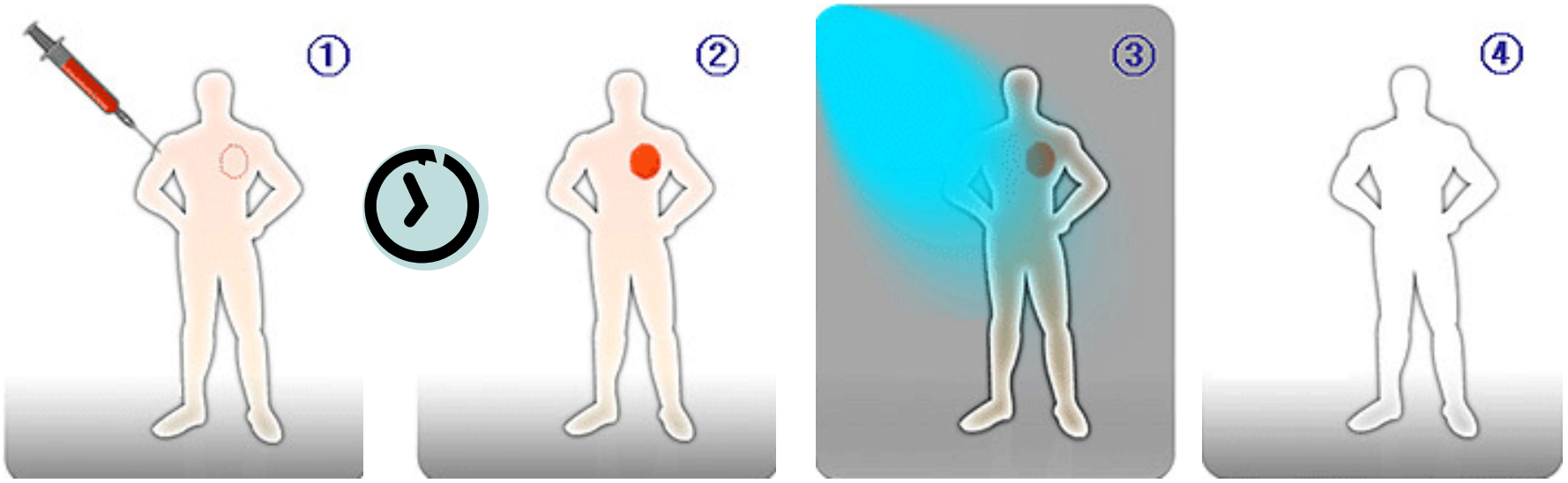
Medical Uses: Diagnostics

- **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



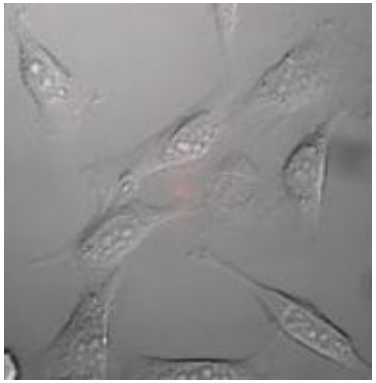
Medical Uses: Surgical Applications

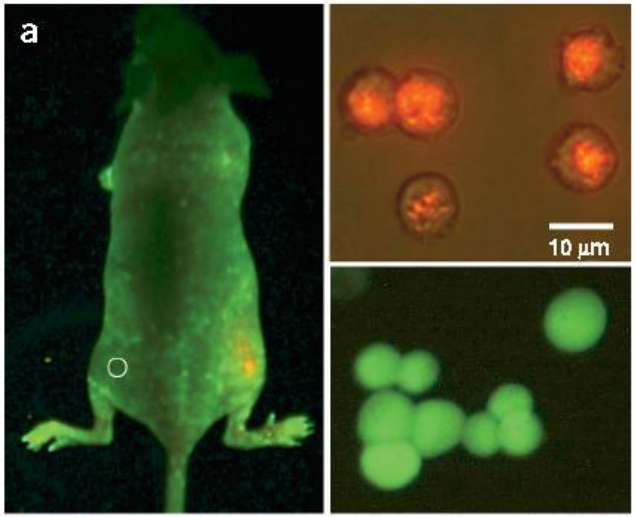
- **Photodynamic therapy:**
  - Nanoparticles localized to cancer cells could “melt them” when heated using a light source.
  - Noninvasive
  - Not toxic to other tissues, like chemotherapy

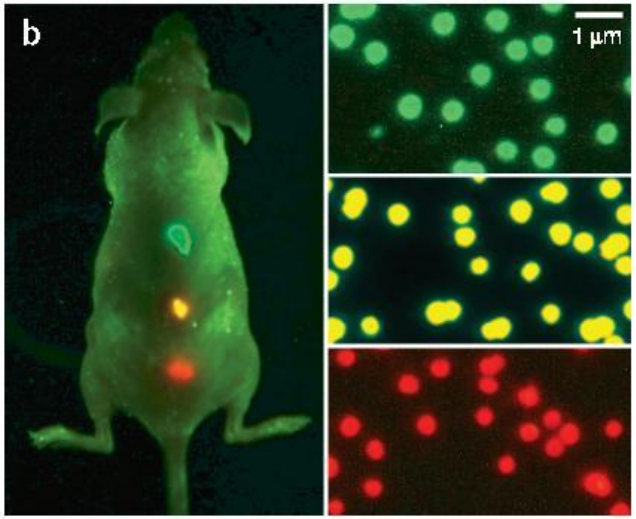


Medical Uses: In vivo Imaging

- **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 …

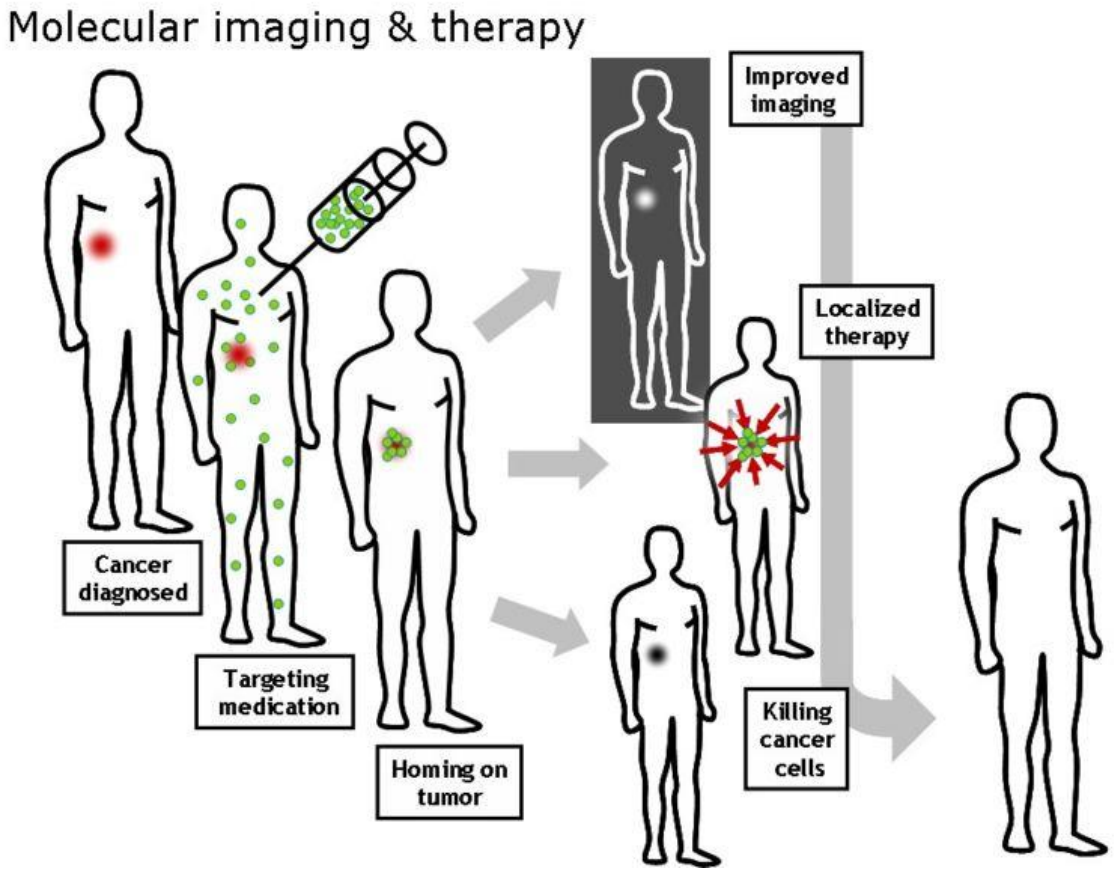






Theranostics and Personalized Medicine

- **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

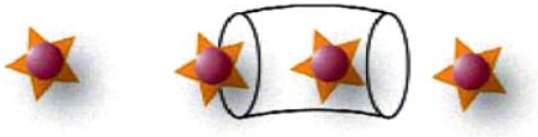
- **Identification of a marker of disease**
  - Such markers can be genes expressed or activated, cytoplasmic or free proteins, enzymes produced at the site of disease etc.
  - These markers can be specific
    - to the disease (e.g. type, sub-type, sub-sub-type of cancer)
    - to the patient (avoid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

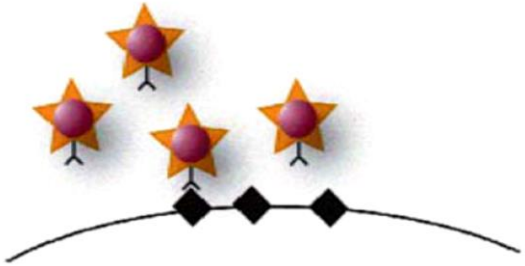
Molecular Imaging & Therapy

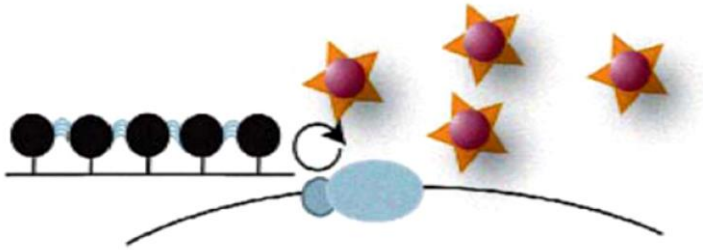
- **Attaching an appropriate beacon to the marker**
  - Such a beacon can be a fluorescent or bioluminescent molecule, a metallic nanoparticle or nanoshell, or a quantum dot or a radioactive nucleotide.
  - Depending on the marker and its location, issues such as beacon uptake by the tissue and intracellular 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

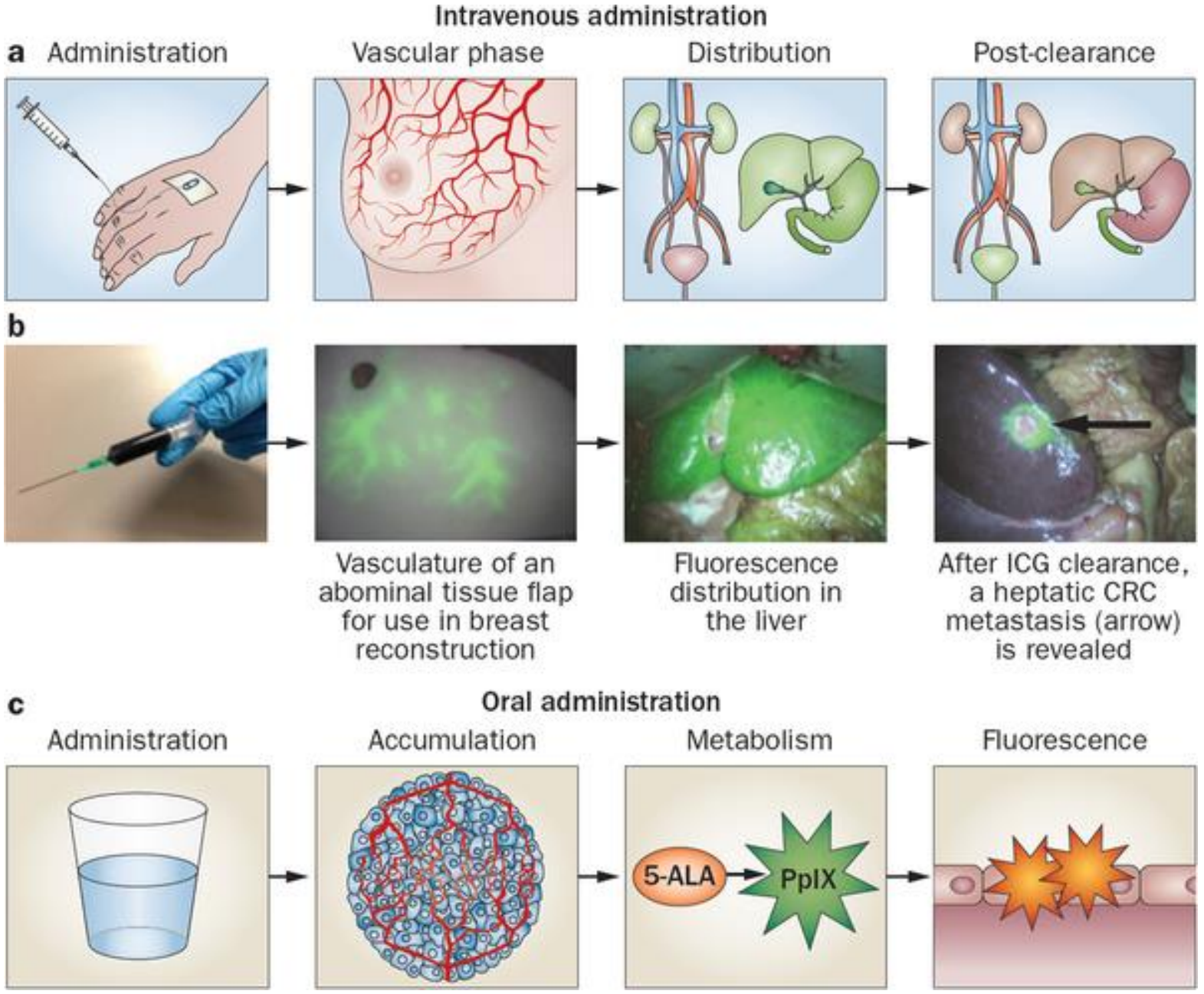
Contrast Agents

- **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





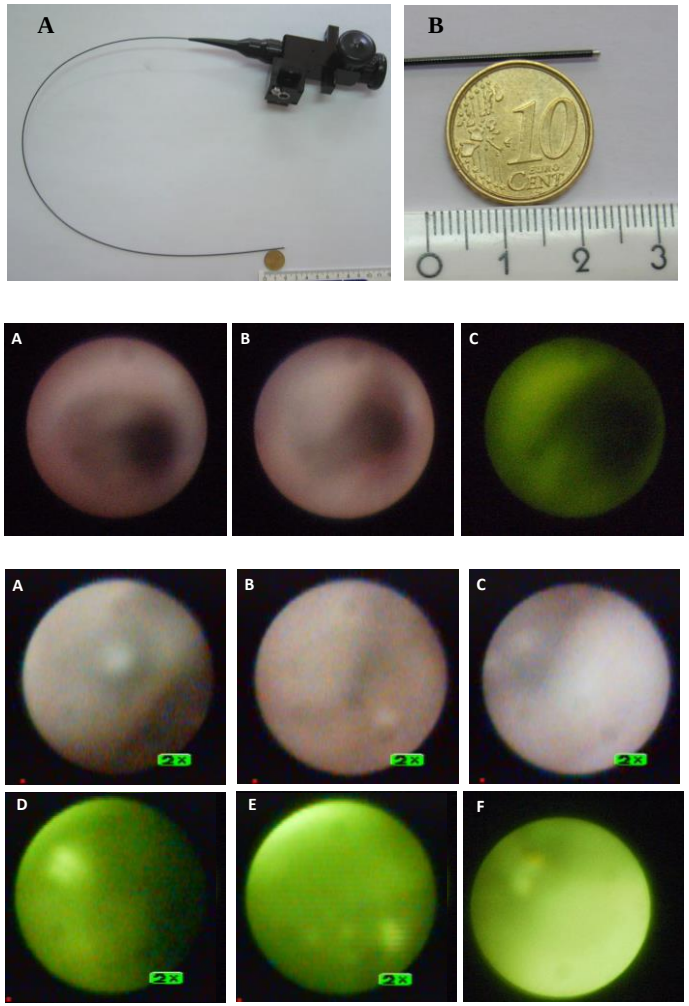



Intravenous administration
a
Administration
Vascular phase
Distribution
Post-clearance
b
Vasculature of an abominal tissue flap for use in breast reconstruction
Fluorescence distribution in the liver
After ICG clearance, a heptatic CRC metastasis (arrow) is revealed
c
Oral administration
Administration
Accumulation
Metabolism
Fluorescence
5-ALA
PpIX

Theranostics

Research at UCY

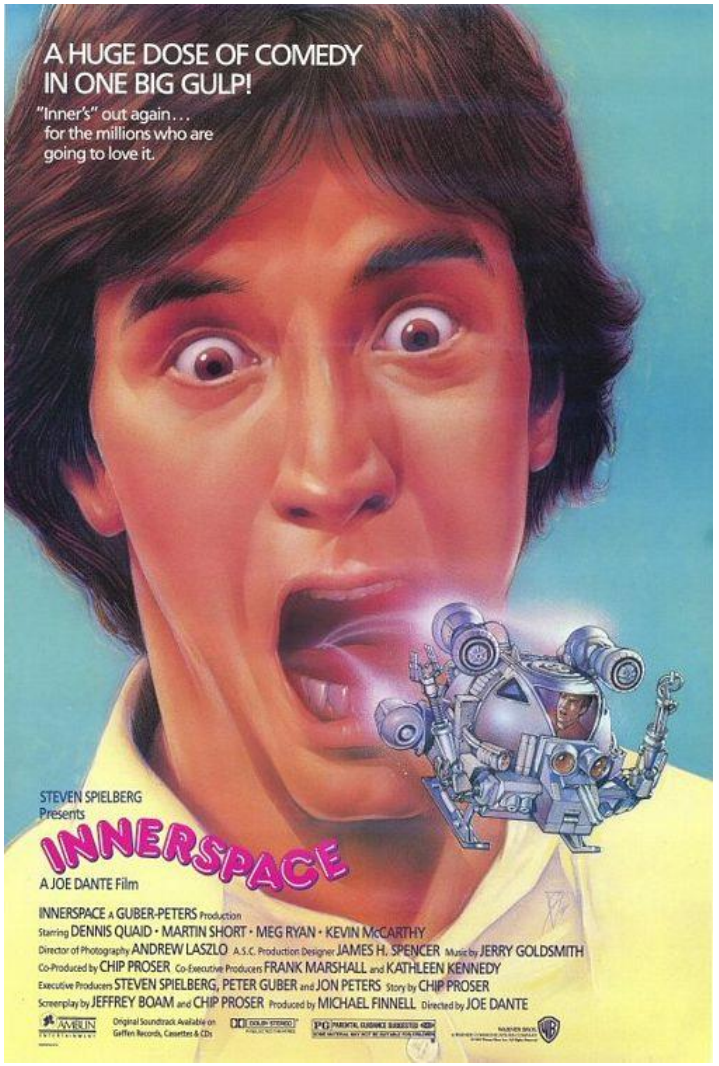
- **Multipotent Theranostic Metal-Based Scaffolds for Molecular Targeting of Colorectsl Cancer**
  - A novel system of targeted molecular imaging and therapeutic (theranostic) agents for the management of colorectal cancer
  - Optical and MRI beacons with therapeutic effect
  - Earlier diagnosis and 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…



FDA Approved

Table 1 Examples of FDA-Approved Agents Utilizing Nanomedicine

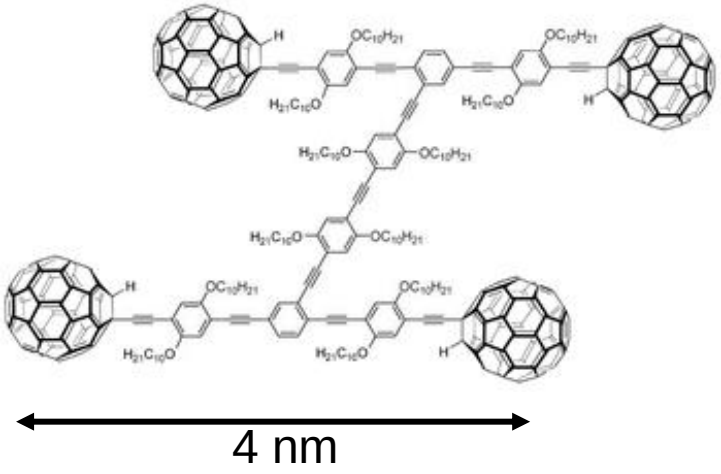
Trade Name	Active Ingredient	Indication*	Manufacturer	Approval
Abelcet	Liposomal amphotericin B	Invasive fungal infections	Sigma Tau	1995
Abraxane	Albumin protein-bound paclitaxel	Metastatic breast cancer	Celgene	2005
Adagen	Pegylated adenosine deaminase enzyme	Severe combined immunodeficiency disease	Sigma Tau	1990
Alimta	Pemetrexed	Nonsquamous NSCLC, malignant pleural mesothelioma		
AmBisome	Liposomal amphotericin B	Fungal infections, leishmaniasis		
Amphotec	Liposomal amphotericin B	Invasive aspergillosis		
Cimzia	Pegylated Fab´ fragment of a humanized anti–TNF-alpha antibody	Crohn's disease, rheumatoid arthritis		
Copaxone	Glatiramer acetate (copolymer composed of L-glutamic acid, L-alanine, L-lysine, and L-tyrosine)	Multiple sclerosis		
DaunoXome	Liposomal daunorubicin citrate	HIV-associated Kaposi's sarcoma		
Depocyt(e)	Liposomal cytosine arabinoside	Lymphomatous meningitis		
Doxil	Pegylated-stabilized liposomal doxorubicin	AIDS-related Kaposi's sarcoma, refractor ovarian cancer, multiple myeloma		
Eligard	Leuprolide acetate and PLGH polymer formulation	Advanced prostate cancer		
Emend	Aprepitant nanocrystal particles	Chemotherapy-related nausea and vomi		
Macugen	Pegaptanib (PEG-anti-VEGF aptamer)	Wet age–related macular degeneration		
Mircera	Methoxy PEG-epoetin beta	Symptomatic anemia associated with CK		
Neulasta	Pegfilgrastim	Chemotherapy-associated neutropenia		
Oncaspar	PEG-asparaginase	Acute lymphocytic leukemia		
Ontak	Interleukin-2 diphtheria toxin fusion protein	Cutaneous T-cell lymphoma		
Pegasys	Peginterferon alpha-2a	Hepatitis B and C		
PegIntron	Peginterferon alfa-2b	Hepatitis C		
Renagel	Amine-loaded polymer	Serum phosphorus control in patients with CKD on dialysis	Genzyme	2000
Somavert	Pegylated human growth hormone receptor antagonist	Acromegaly	Pfizer	2003
Tricor	Fenofibrate	Hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia	Abbott	2004
Visudyne	Liposomal verteporfin	Wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome	QLT Ophthalmics	2000

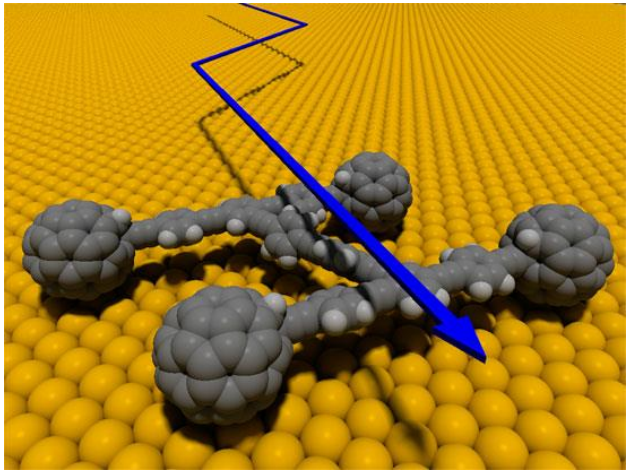
Table 2 Examples of Medical Devices and Diagnostics Utilizing Nanomedicine

Name	Device/Diagnostic Type	Application	Manufacturer	Year Approved
FDA-Approved				
CellSearch	Antibodies bound to IO NPs	CTC detection	Veridex	2004
DNAarray	Lab-on-a-chip	DNA-based tests	CombiMatrix	2005
Gastromark	Silicone-coated ferumoxsil SPIOs	MRI contrast agent	AMAG Pharmaceuticals	1996
MultiHance	Gadolinium-based NPs	MRI contrast agent	Bracco Group	2004
Optimark	Gadolinium-based NPs	MRI contrast agent	Mallinckrodt	1999
Omniscan	Gadolinium-based NPs	MRI contrast agent	General Electric Healthcare	1993
Silvagard	Silver NP solution	Anti-infective coating for medical devices	AcryMed, Inc.	2005
Verigene	Functionalized gold NPs	Diagnostic tests	Nanosphere	2007
Vitoss	Ultraporous beta-TCP NPs	Bone-replacement scaffold	Orthovita	2000
Investigational				**Status (U.S.)**
Combidex	Dextran-coated ferumoxtran-10 USPIOs	MRI contrast agent	Advanced Magnetics	Phase 1, 2, 4
MagProbe	CD34 antibody-linked NPs/magnetic biopsy needle	Leukemia diagnosis	Senior Scientific	Phase 1
NanoTherm therapy	Aminosaline-coated IO NPs	Thermal ablation/hyperthermia therapy for liver, pancreatic cancer	MagForce AG	Preclinical

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 → A threat to the existence of human beings