Nanomedicine – an emerging and expanding field

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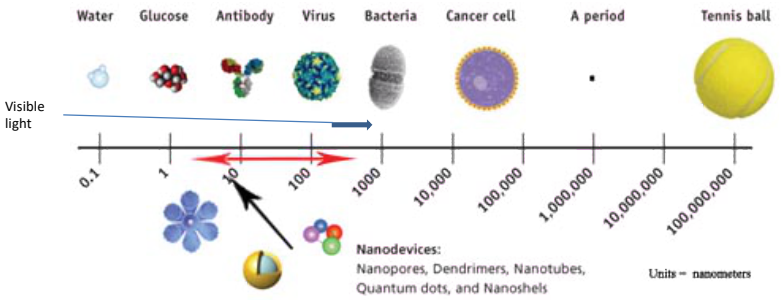
Nanoscience basics



- Nanotechnology- materials at scale of 1 to 100 nanometres. Visible light wavelength 400 to 700 nm; atomic radius 0.03 to 0.3 nm. Much of biological activity is at nanoscale.
- Nanostructures have large surface area and reactivity, quantum effects important as size diminishes. Unusual properties result.

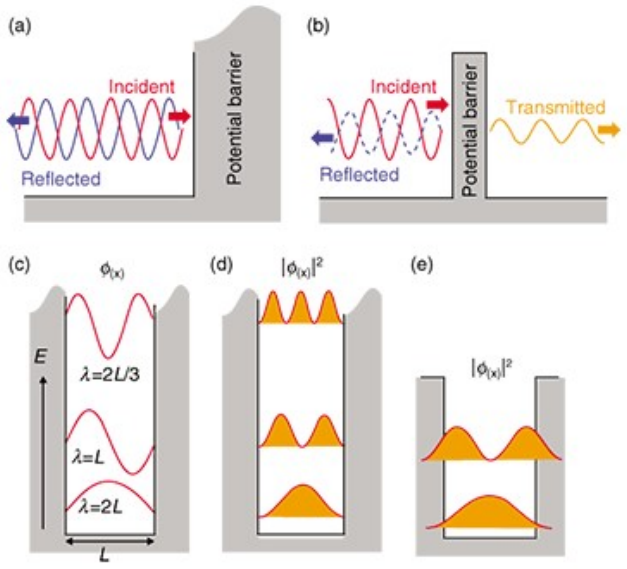
Nanomaterials

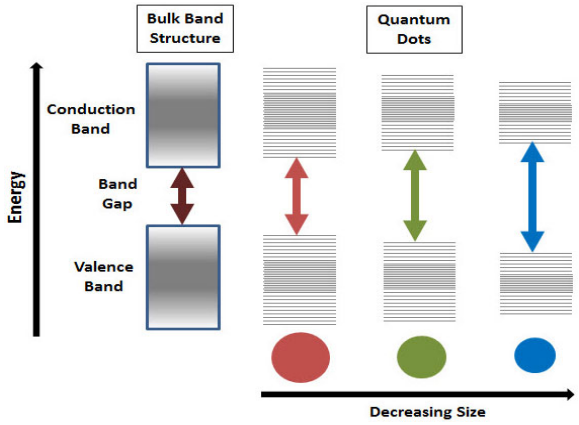
- Nanostructures can be in one dimension (films), two dimensions (dots), or three dimensions (nanoparticles),
- Also nanoporous materials, consisting of pores of less than 100 nm in size in a regular inorganic or organic framework. Generally classified as bulk material.
- Nanotechnology involves diverse fields such as physics, chemistry, biology, materials science, and engineering.

Nanostructure physics

- Small size implies large surface area ratio to mass and volume. Surface properties dominate.Higher reactivity due to large surface area.
- Properties such as melting point, fluorescence, electrical conductivity, magnetic permeability, and chemical reactivity change as a function of the size of the particle.
- Quantum affects significant. Momentum and energy restricted to discrete allowed values – “quantum confinement”. Tunneling through barriers can occur.
- Intermolecular forces become important.

Tunneling and Quantum confinement

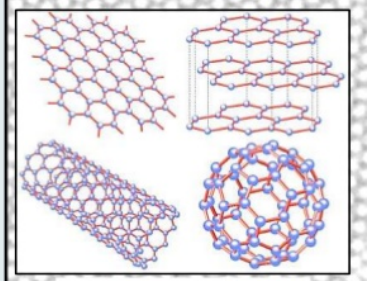




Quantum dots are tiny particles of a semiconducting material with diameters in the range of 2-10 nanometres (10-50 atoms).
There is quantization of the energy levels depending in the size of the crystal
They can emit any colour of light from the same material simply by changing the dot size.
They can be tuned during manufacturing to emit any colour of light.
They can be core, core shell, or alloyed types.

Carbon Nanostructures

- sp^2 Carbon Allotropes
  - Elemental carbon
  - Each atom bonded to three others
- Graphene
  - Hexagonal lattice in a single sheet
- Graphite
  - Parallel sheets of graphene
- Nanotubes
  - Cylindrical, rolled up graphene
- Fullerenes
  - Carbon polyhedra



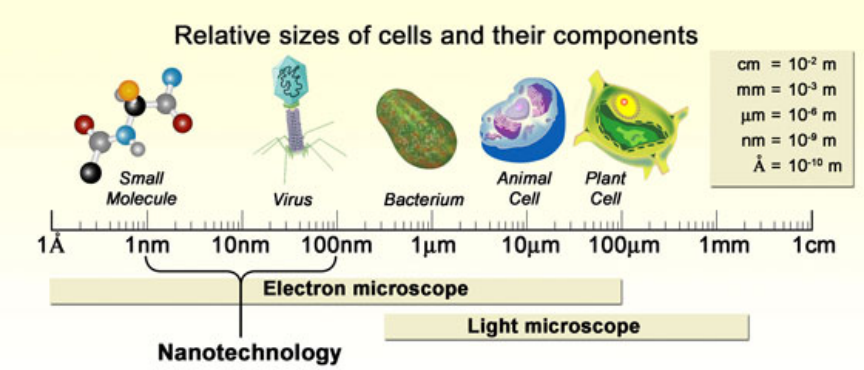
http://uef.saske.sk/en/dtp/research/

Nobel prizes

- Nanotechnology related research has won three Nobel prizes already.
- 1996 Chemistry – fullerenes discovery in 1985 by Kroto, Smalley and Curl.
- 2010 Physics – graphene discovery 2004 – Geim and Novoselov
- 2016 Chemistry – molecular nanomachines – Sauvage 1983, Stoddart 1991, Feringa 1999

Nano in biology

- Many of the inner workings of cells naturally occur at the nanoscale.
- For example, hemoglobin, the protein that carries oxygen through the body, is 5.5 nanometers in diameter.
- A strand of DNA, one of the building blocks of human life, is only about 2 nanometres in diameter.

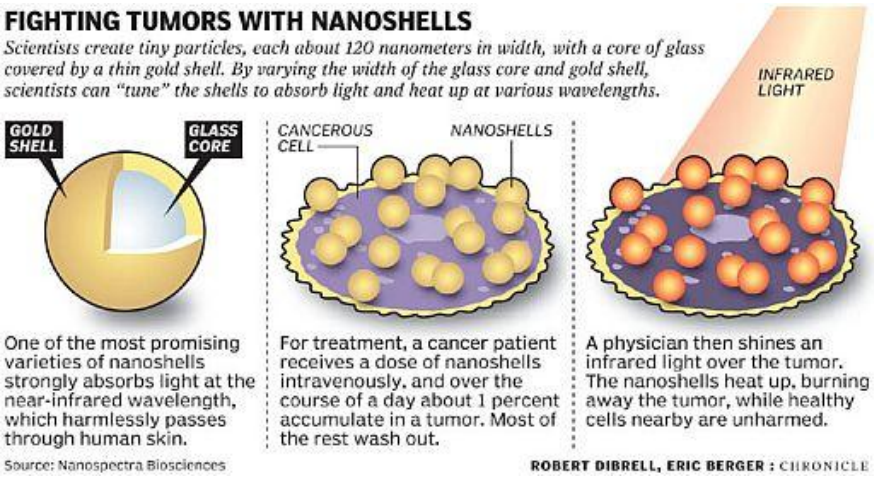


Small size of nanomaterials provides unique functional capabilities in biological systems.
Pores in the blood vessels size 50nM. Space in between cells 60 nM.

Nanomedicine areas

- **Drug delivery** -Deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, which allows direct treatment of those cells. This reduces damage to healthy cells in the body and allows for earlier detection of disease.
- **Therapy techniques** - "nanosponges" that absorb toxins and remove them from the bloodstream, generate intense focused sound waves for noninvasive surgery, concentrate radiation used to treat cancer tumors, targeted heat therapy, etc.
- **Diagnostics** - measure level of nitric oxide, detection of cancer cells, early diagnosis of infectious disease, early detection of kidney damage, etc.
- **Anti microbials-** cleaning of instruments in hospitals, antibiotic resistant infections, chronic bacterial infections, treatment of wounds and burns, etc.
- **Cell repair** – nanorobots,
- **Nanosensors**
- **Tissue engineering**
- **Medical nano devices**

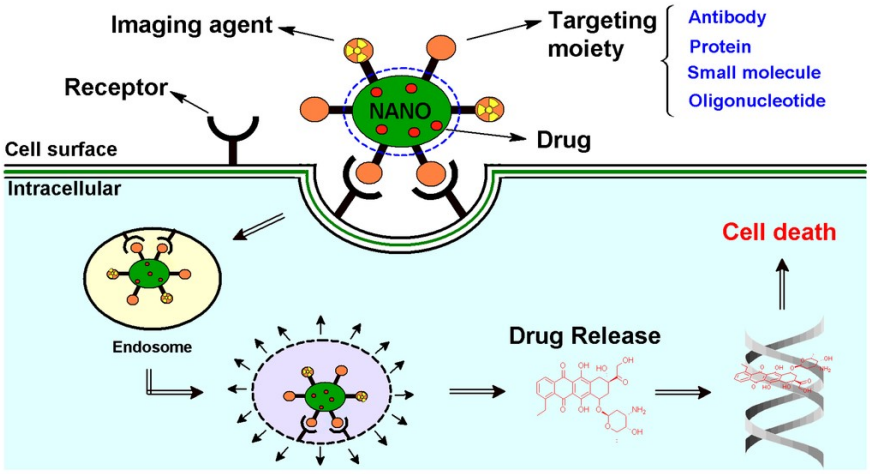
Example – cancer treatment



GNPs can have molecules attached which can attach to cancer cell receptors.
Energy can be fed via IR, microwaves, etc to heat up the GNP and destroy the cell

Gold nanoshells for cancer

- By increasing the radius of the core and decreasing the thickness of the shell to 5 nm, the nanoshells are able to absorb infrared.
- Nanoshells can naturally buildup in tumors sites as tumors have many defective blood vessels that nanoshells are able to slip through and accumulate in.
- An infrared light can then be applied to heat the nanoshellls killing the tumor. Also RF energy for heating.
- Nanoshells can also be used as a contrasting agent to allow for high resolution imaging in vascular systems due to their scattering cross-section.
- Since gold is known for its biocompatibility, proteins, antibodies, and drugs can be attached to it and be used in treatment of other diseases.
- Liver cancer - Nanoshells can be coated with an anticancer drug, eg. doxorubicin and peptide A54 which adheres preferentially (3 times) to cancer cells

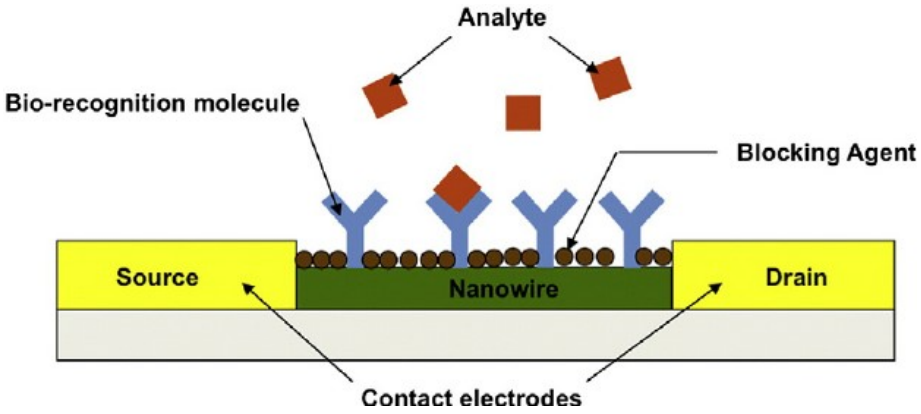


The Nanoparticle (NP) containing a chemotherapy drug gets attached to the cancer cell surface by the cancer cell-specific ligand. The NP binds to the cancer cell surface by recognizing the receptor, resulting in internalization of the NP by endocytosis. Inside the cancer cell, the NP undergoes endosomal escape, leading to the release of the treatment cytotoxic drug, resulting in cell death.

Nano Biosensors

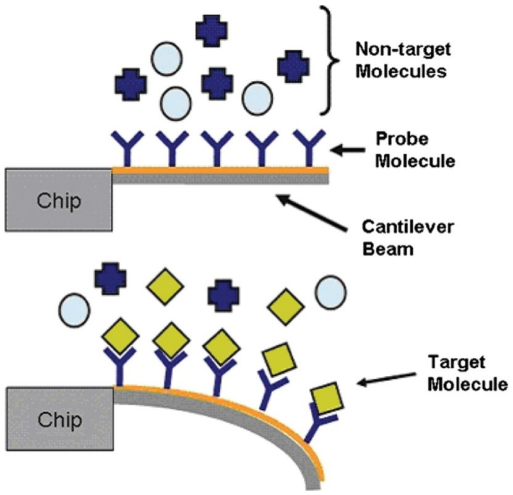
- Large potential applications – disease detection, biological molecule detection, environmentat monitoring, etc.
- Samples can be air, liquid, etc. Derived from human sources or from environment.
- Various detection technologies – optical, piezoresistance, electrical, etc.
- Various nanostructures can be used – nanotubes, nanowires, with various coatings, etc.
- Challenges – reliability, calibration, fabrication, reusability,cost
- Rapid growth expected in this field.

Example - Conducting polymer nanowire-based biosensor

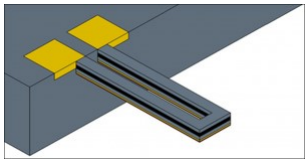


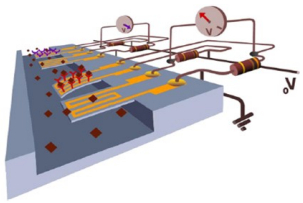
Appropriate bio-recognition molecules either on the surface or in the polymer matrix. Specific bio-interaction between recognition molecule and the analyte, changes electrical properties (e.g. conductance) of the nanowire enabling sensing.

Example – cantilever type biosensors



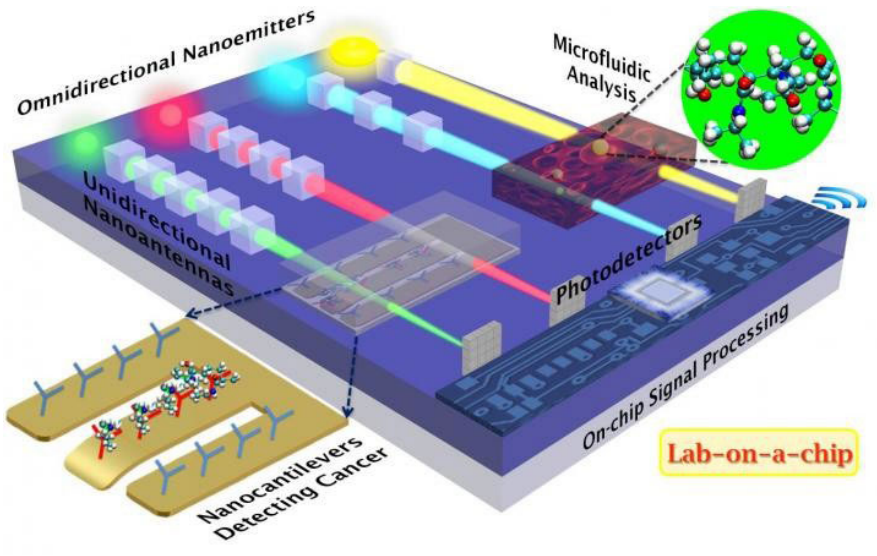
Nano-Sniff Technologies Pvt Ltd Mumbai

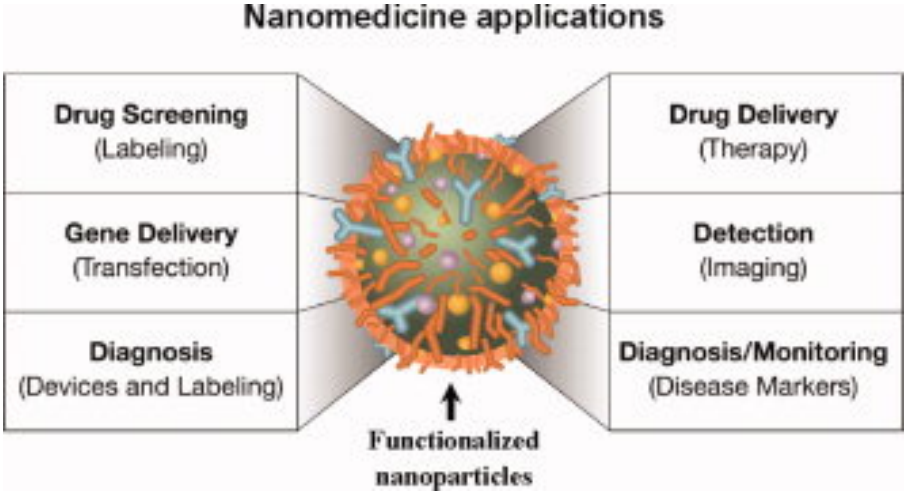




Device Micro Cantilever NMC60
The cantilever stack comprises of piezo-resistive Boron doped poly silicon, encapsulated by layers of silicon dioxide. The thickness of the micro cantilever stack is 650 nm and its length is 200 µm. It can be used in chemical and biochemical sensing applications.

- Diving board like structure.
- Deflects both upwards and downwards due to compressive and tensile stresses leading to strain in the whole structure.
- Piezo-Resistive structure enables measurement of strain in the form of change in resis-tance between two conducting points at the base of the cantilever.
- Therefore, the Piezo-Resistive MEMS Cantilever is capable of transducing a nano-mechanical motion into an electrical signal.


Omnidirectional Nanoemitters
Microfluidic Analysis
Unidirectional Nanoantennas
Photodetectors
On-chip Signal Processing
Lab-on-a-chip
Nanocantilevers Detecting Cancer


Nanomedicine applications
Drug Screening
(Labeling)
Gene Delivery
(Transfection)
Diagnosis
(Devices and Labeling)
Drug Delivery
(Therapy)
Detection
(Imaging)
Diagnosis/Monitoring
(Disease Markers)
Functionalized
nanoparticles

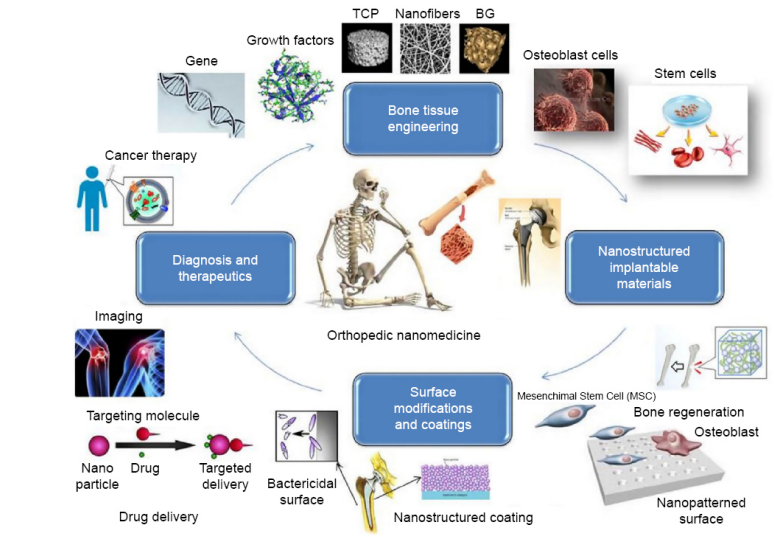
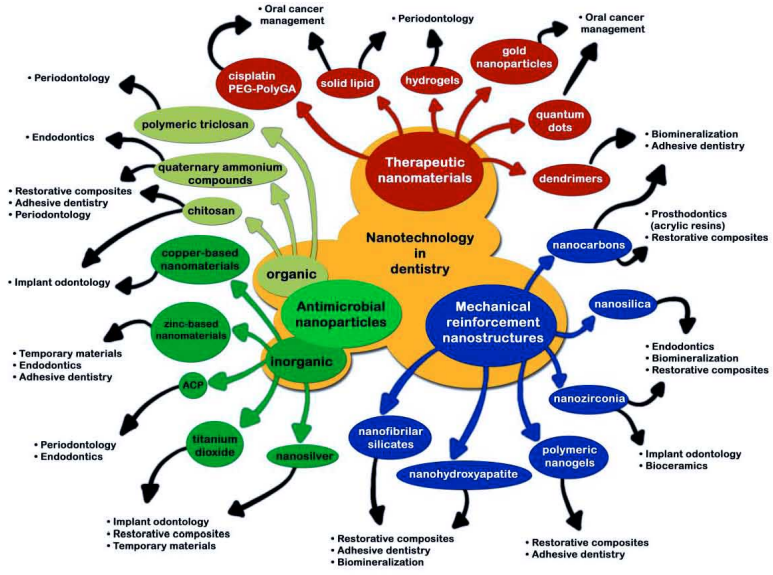


Figure 1 Scheme shows potential applications of nanomedicine in orthopedic medicine.
Abbreviations: BG, bioactive glass; TCP, tricalcium phosphate.

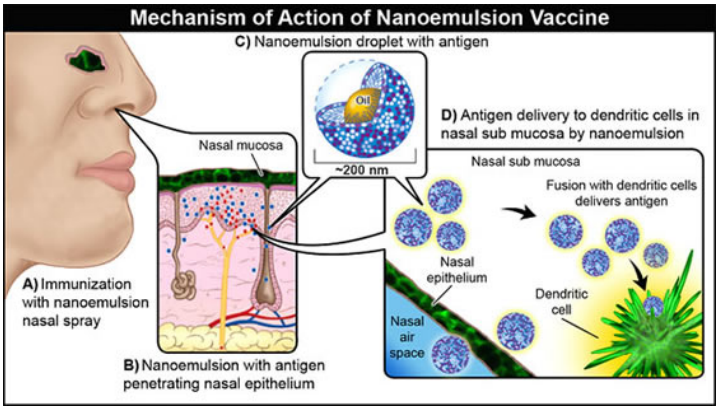
Nanomedicine in orthopedics



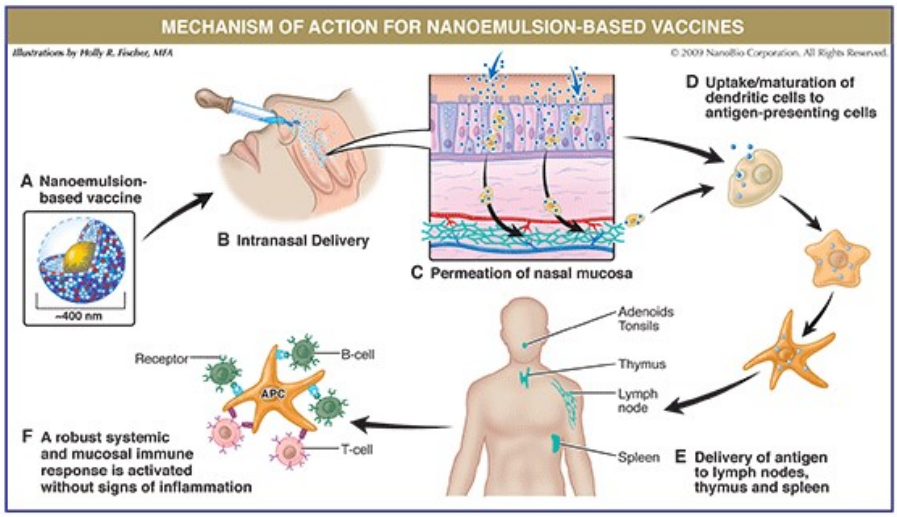
Nanotechnology in dentistry

Nano-emulsions

- Antimicrobial nanoemulsions are oil-in-water droplets that range from 200-600 nm composed of oil and water and are stabilized by surfactants and alcohol.
- The nanoemulsion has a broad spectrum activity against bacteria (e.g., E. coli, Salmonella, S. aureus), enveloped viruses (e.g., HIV, Herpes simplex), fungi (e.g., Candida, Dermatophytes), and spores (e.g., anthrax).
- The nanoemulsion particles are thermodynamically driven to fuse with lipid-containing organisms. This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen.
- When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion.
- Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death.
- Uses - as disinfectant or as vaccines



Mechanism of Action of Nanoemulsion Vaccine
A. Nasal spray nanoemulsion vaccine sprayed into a nostril.
B. Nanoemulsion droplets with antigen penetrate the nasal mucosa.
C. Diagram of nanoemulsion droplet with antigen in its interface. Blue dots are antigen present in emulsion.
D. Antigen delivery by nanoemulsion into nasal submucosa where fusion with dendritic cells delivers the antigen to the immune system. Dendritic cells can then transport the antigen to other parts of the body to trigger the desired immune response.



Dendrimers

- Dendrimers consist of a series of chemical shells built on a small core molecule. Each shell consists of two chemicals, always in the same order.
- Ends of dendrimers are active groups such as amines or acids, to which various molecules of interest can be attached.
- Multifunctional dendrimers can be formed with attached molecules for detection, treatment, etc.

Dendrimer structures

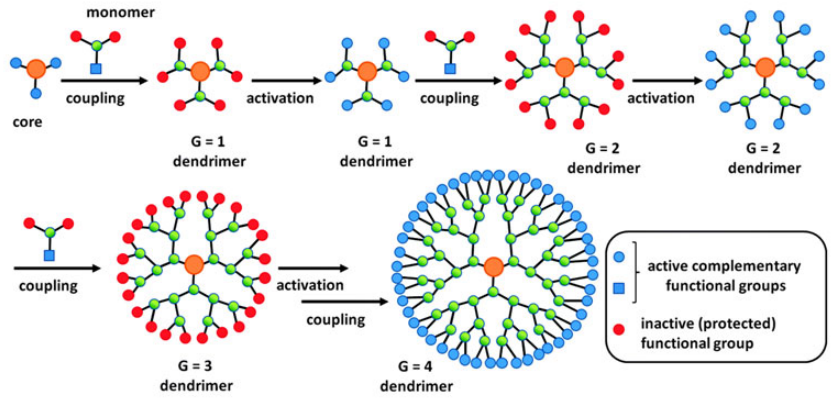
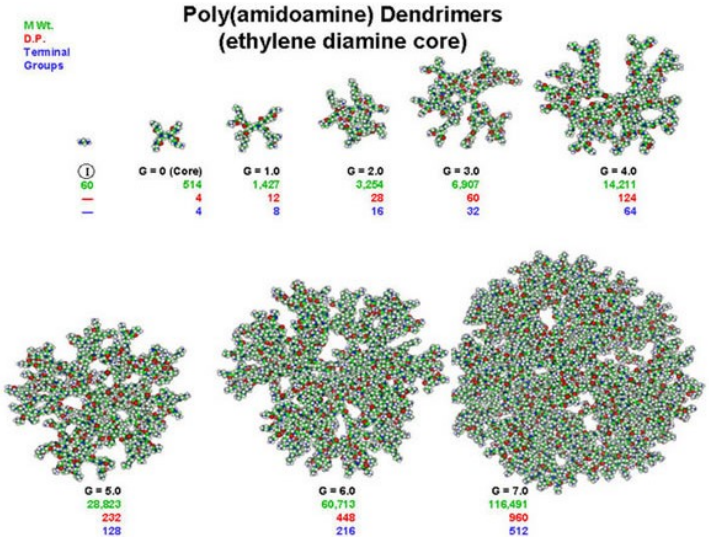
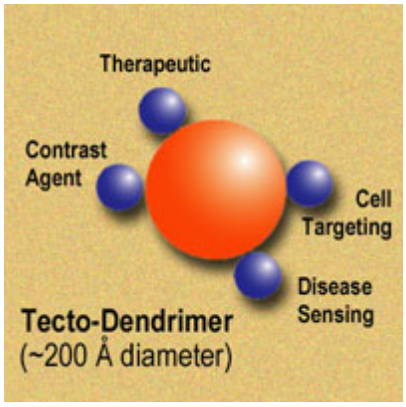
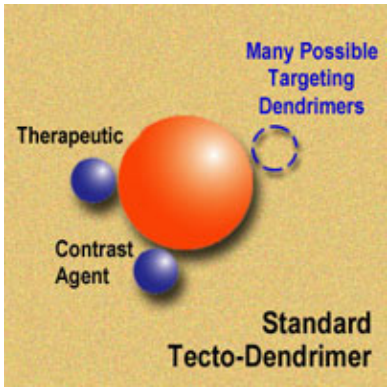


Fig.5: Divergent Growth Method [advances in the chemistry of dendrimers, **Marta Sowinska and Zofia Urbanczyk-Lipkowska,** *New J. Chem.*, 2014, **38**, 2168-2203]



Multifunctional Dendrimers





Dendrimers can be multifunctional, with possibility of targeting various sites on cells for different disease conditions.

Dendrimer applications

- Dendritic polymers are analogous to proteins, enzymes, and viruses, and are easily functionalized
- Other molecules can either be attached to the periphery or can be encapsulated in their interior voids
- Anticancer drugs
- Drug delivery, including transdermal, better solubility.
- Dendrimers as magnetic resonance imaging contrast agents.
- Dendritic sensors
- Photodynamic therapy
- Gene therapy (non-viral transfection agents)
- Dendrimer-based vaccines
- Antiviral and antibacterial agents, Anti-inflammatory agents

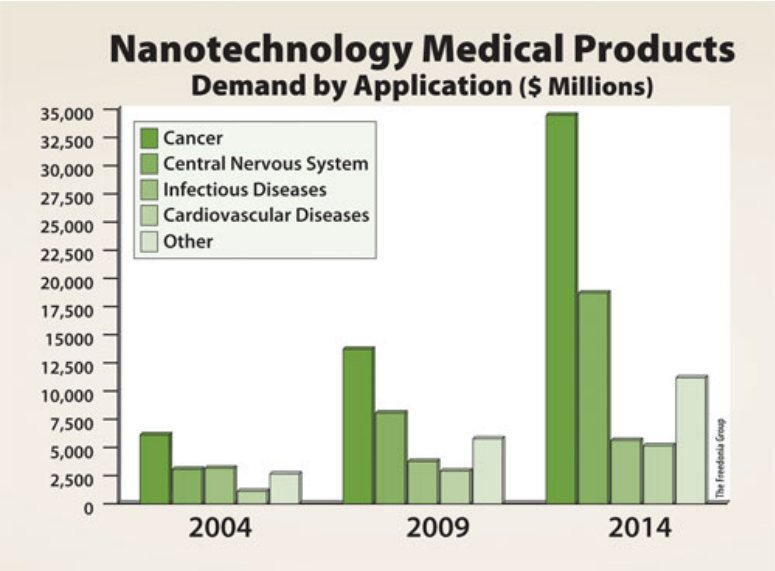
Nanoporous materials medical applications

- DNA sequencing – as the DNA passes through a nanopore, different bases generate different electrical signals which can be read off.
- Nanoporous membranes – have various useful applications ;like filtration, etc.
- Nanoporous composites – useful for bone implants and repairs

Table 1. Select FDA-Approved Agents Utilizing Nanomedicine

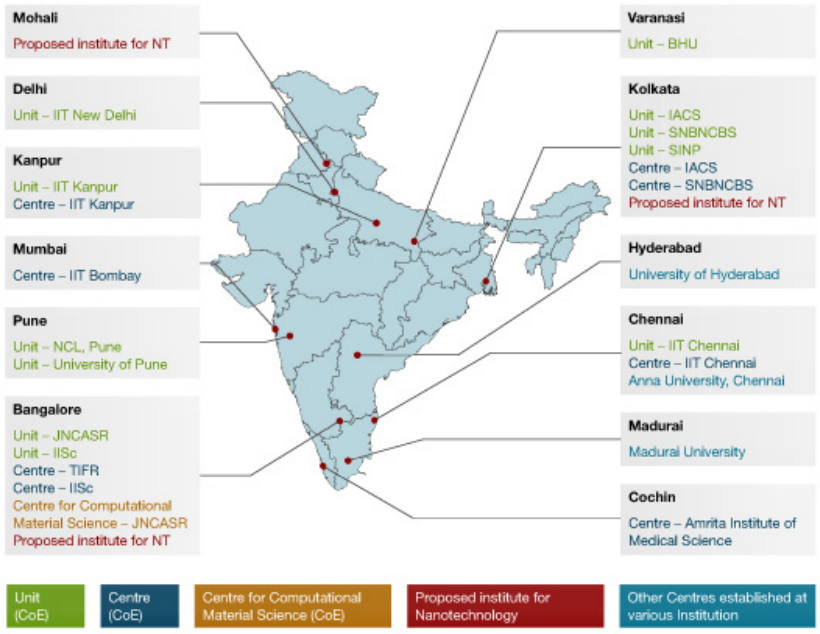
PRODUCT	COMPOSITION	INDICATION	APPROVED
	Lipid-Based Nanoparticles		
Abelcet	Lipid complex formulation of amphotericin B	Invasive fungal infections	1995
AmBisome	Liposomal preparation of amphotericin B	Fungal and protozoal infections	1997
DaunoXome	Liposomal preparation of daunorubicin	HIV-related Kaposi's sarcoma	1996
DepoCyt	Liposomal formulation of cytarabine	Lymphomatous meningitis	1999
DepoDur	Liposomal formulation of morphine sulfate	Relief of postsurgical pain	2004
Doxil/Caelyx	PEGylated liposomal formulation of doxorubicin	Various cancers	1995
Inflexal V	Liposomal influenza vaccine	Influenza	1997
Visudyne	Liposomal formulation of verteporfin	Wet age-related macular degeneration	2000
	Polymer-Based Nanoparticles		
Adagen	PEGylated adenosine deaminase enzyme	Severe combined immunodeficiency disease	1990
Cimzia	PEGlyated Fab' fragment of a humanized anti-TNF-alpha antibody	Crohn's disease, rheumatoid arthritis	2008
Copaxone	Polymer composed of L-glutamic acid, L-alanine, L-lysine, and L-tyrosine	Multiple sclerosis	1996
Eligard	Leuprolide acetate and PLGH polymer formulation	Advanced prostate cancer	2002
Macugen	PEG-anti-VEGF aptamer	Neovascular age-related macular degeneration	2004
Mircera	Chemically synthesized ESA, methoxy PEG-epoetin beta	Symptomatic anemia associated with chronic kidney disease	2007
Neulasta	Conjugate of PEG and filgrastim	Chemotherapy-induced neutropenia	2002
Oncaspar	PEGylated formulation of L-asparaginase	Acute lymphoblastic leukemia	1994
Pegasys	PEGylated interferon alfa-2a	Hepatitis C	2002
PegIntron	PEGylated interferon alfa-2b	Hepatitis C	2001
Renagel	Polyamine (polymer loaded with amine groups)	Chronic kidney disease	2000
Somavert	PEGylated human growth hormone receptor antagonist	Acromegaly	2003
	Protein-Based Nanoparticles		
Abraxane	Albumin-bound paclitaxel (*nab*-paclitaxel)	Breast cancer	2005

ESA: erythropoiesis-stimulating agent; PEG: polyethylene-glycol; PLGH: poly (DL-lactide-co-glycolide); TNF-alpha: recombinant human tumor necrosis factor-alpha.
Source: Reference 7.



India major activities

- Bangalore India Nano Conference (annual)
- Nanomission Ph II under the DST, 2012-2017, Rs 650 crore funding.
- Programmes by DBT, DEITY, etc.
- Indian Society of Nanomedicine (ISNM), located in AIIMS, New Delhi



Conclusion

- Nanomedicine is an exciting and rapidly growing area of knowledge
- There are large potential benefits for human health.
- It requires good collaboration among experts in many disciplines – physics, chemistry, biology, engineering, and medicine.

Thank you