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NANOMEDICINE: APPLICATION OF NANOTECHNOLOGY

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ABSTRACT
This paper highlights the applications of nanotechnology in medicine termed "Nanomedicine". Advances in nanomedicine centre on diagnosis (invitro and invivo), pharmaceuticals and therapeutics. Nanobiotechnology utilizing nano-based particles (1-100nanometers) offers miniaturization biosensors, enabling high throughput (smaller samples to be used for different biochemical analysis) and point-of-care diagnostics. Nanopharmaceutics are optimized in drug delivery systems with increased bioavailiablity of the drug to the target site. This has resulted in the increased efficacy of drugs and with a reduction in the side effects. Nanoparticles are applied in therapeutic areas such as treatment of HIV related Kaposi sarcoma, cancer (ovarian, breast, pancreatic and non small cell cancer), Antifungal and anti-leishmanial agent. Nanomedicine offers a wide prospect for the early detection and treatment of diseases but safety is the watchword.

KEYWORDS: Nanomedicine, Nanotechnology, Nanopharmaceutics, Theranostics.

1.0 INTRODUCTION
Nanotechnology is the study and the use of matter at nanoscopic scale (1-100nm).[1,2] Nanomedicine involves the application of nanotechnology to medicine.[3] Nanomedicine is an emerging field comprising of diagnosis, therapeutics,[2] prophylaxis and understanding of the molecular basis of the human body. It also covers theranostics (diagnostics and therapy) and nanopharmaceutics.[4] According to European Science Foundation's forward Look Nanomedicine, (2005): "Nanomedicine uses nano-sized tools for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying pathophysiology of disease.[5] The ultimate goal is to improve quality of life."

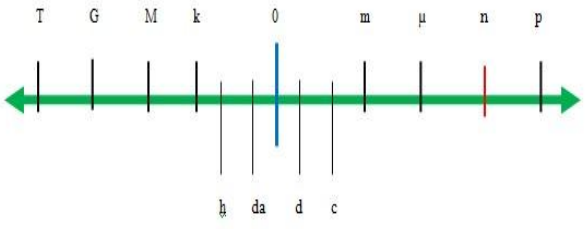

Figure I: Metric scale.

T: tera (10^{12}), giga (10^{9}), mega (10^{6}), kilo (10^{3}), hecto (10^{2}), deca (10^{1}), deci (10^{-1}), centi (10^{-2}), mili (10^{-3}), micro (10^{-6}), nano (10^{-9}), pico (10^{-12}).

Applications of nanotechnology
Nanotechnology can simply be applied into the following areas:
a. Diagnosis
b. Pharmaceuticals/Therapeutics

2.0 Diagnosis
Nanostructures (1-100nm) are employed in nanodiagnostics. Nanostructures exists in zero dimension, one dimension and two dimension.[6] The nanostructure dimensions play a role in showing the range of size in which biomolecules such as nucleic acid, proteins and viruses exist in the nanoscale. Invitro diagnostics involves the use of material to detect biochemical changes, activity and concentration of specific substance in biological solution.[6] Also a single biosensor or an integrated device containing many biosensors can detect such biochemical changes and convert it into a biochemical signal; a transducer converts the biochemical signal into a quantifiable signal.[6] The quantified signal now will reflect the concentration or activity of the substance in the

biological solution. Nanomaterials used for this purpose include metallic nanoparticles, quantum dots, silica nanospheres, magnetic nanoparticles, DNA-protein and nanoparticle conjugates.[7]

2.1 Metallic nanoparticles

Gold nanoparticles are widely used due to noncytotoxicity, high biocompatibility, low non-specific binding in control cells, broad-based optical properties.[7]

The applications of metallic nanoparticles are:

Gold nanoparticles are used as a suitable stain for samples (tissue samples) with poor contrast in transmission electron microscopy because of its strong electron absorbing properties.[7] Also, gold nanoparticles are used in immunostaining because of its small size and the ability to specifically combine with antibodies.[7,8] Gold and other metals exhibit surface plasmon resonance under specific wavelengths.[8,9,10] This feature allows them to be combined with colorimetry or absorption spectroscopy, photothermal or photoacoustic imaging. Nanoparticles particularly gold are used as a color marker in rapid test such as pregnancy test kits.[6] Metallic nanoparticles produce Raman signal, making them suitable for surface-enhanced Raman spectroscopy (SERS).[6] SERS is used as a biomarker for the detection of bacillus spores.[6,11,12] Another example is the molecular sentinels, which are comprised of metal NPs decorated with a Raman label conjugated stem loop DNA.[6] Gold nanoparticles is useful in the detection of Amyloid-derived diffusible ligands,[13] Avian influenza H5N1 and differentiate from other major influenza A virus strains (H1N1, H3N2),[14,15] ultrasensitive detection of HIV-1 p24 antigen (hybrid nanomechanicaloptoplasmonic platform),[16] Extracellular adherence protein (EAP)/PSA, Squamous cell carcinoma antigen, α-fetoprotein (AFP)/PSA, Microalbuminuria,[17] p53 mutation,[18,19] NADH, Nucleic Acid,[20,21] miRNA,[22,23] DNA,[24] Single nucleotide polymorphisms (SNPs).[25] Silver nanoparticles can be used to detect Human epididymis secretory protein 4, IgG.[26] Also silver nanoparticles can be employed to detect miRNA.[23]

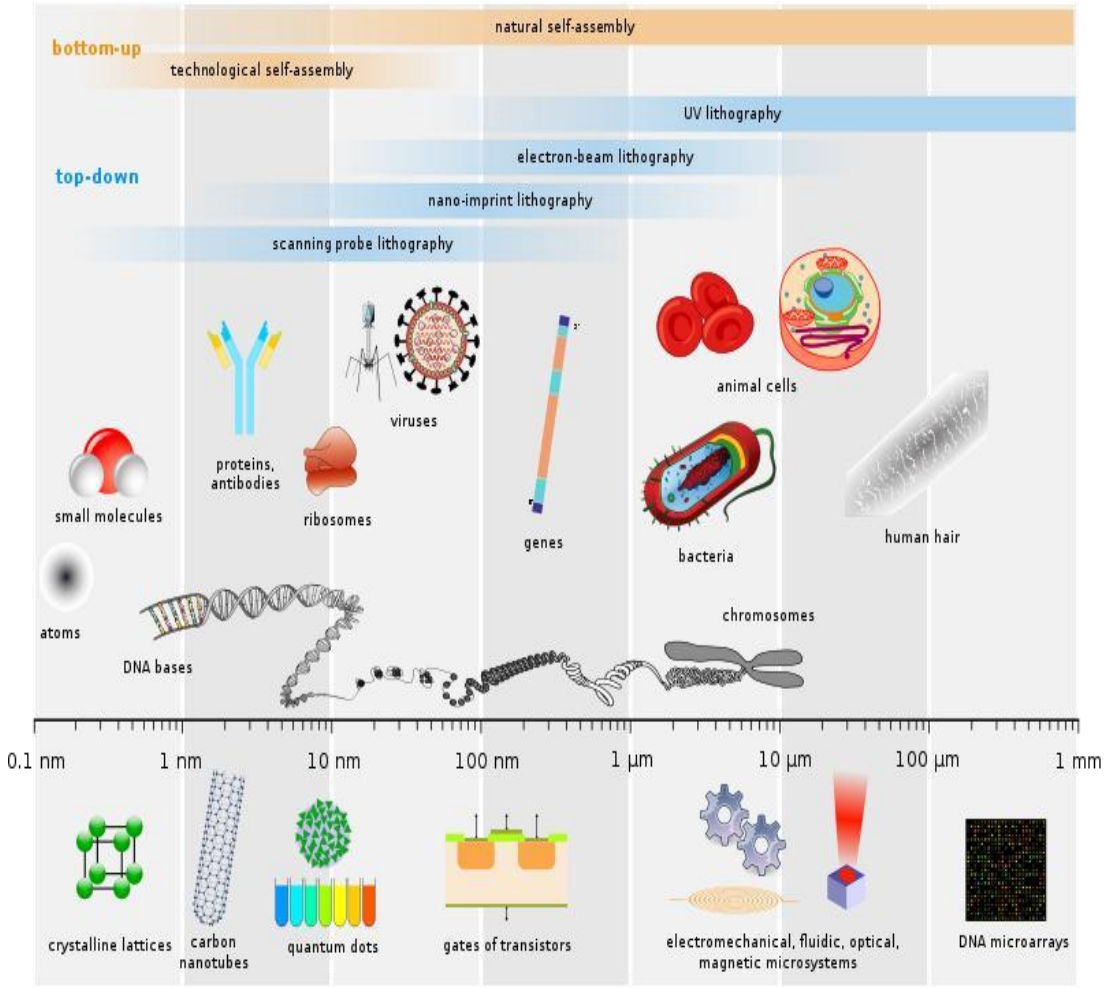

Figure II: Biological and technological scales.[27]

Table I: Shows various applications of metallic nanoparticles.

Name	Method	Principle	Uses	Detection limit
[28]	SRP biosensor	Immobilizing AuNPs onto a SiO2 layer on a gold electrode	Detection of PSA	0.1 ng/mL
[29]	SRP biosensor	Anti-IMA is assembled onto an AuNPs modified gold chip.	Myocardial ischemia	10 ng/mL
[30]	Ultrasensitive SPR inhibition immunoassay using a mixed selfassembled monolayer (mSAM) surface	Progesterone was conjugated to ovalbumin with an oligoethylene glycol linker to form a protein conjugate, immobilized onto the mSAM surface	Detection of progesterone	4.9 ng/mL
[31]	Bifunctional hydroxyl/thiolfunctionalized fourthgeneration polyamidoamine dendrimer to encapsulate AuNPs	Encapsulation of the particles into dendrimers. The resulting AuNPs dendrimer-modified surface is a good support for insulin immobilization.	Detection of insulin in human serum	0.5 pM
[32]	Molecularly imprinted polymer with embedded AuNPs, immobilized on a decanethiol-modified Au chip	It is based on swelling of the imprinted polymer gel triggered by the analyte binding within the polymer gel, which increases the distance between AuNPs embedded in the film resulting in a change of the SPR signal.	Detection of dopamine	
[33]	Ultrasensitive SPR affinity device	The conjugation of AuNPs and the polyclonal antibody	Detection of PSA	300 fM
[34]	AuNPs modified SPR biosensor based on a reverse sandwich assay	A first monoclonal anti-cMB antibody was covalently immobilized on the sensor surface and then AuNPs were covalently immobilized to the second monoclonal anti-cMb antibody.	Detection of human cardiac myoglobin (cMb)	10 pM
[35]	SPR affinity biosensor based on a new biofunctionalization of AuNPs.	Sandwich assay format using a primary antibody immobilized on the surface, the antigen CEA with different concentrations, and the biotinylated secondary antibody bound with the bio-AuNPs.	Detect low levels of carcinoembryonic antigen (CEA) in human blood plasma	0.1 ng mL−1
[36]	A sandwich format with aptamer/thrombin/aptamerAuNPs system on an SPR sensor	It is based on the simultaneous binding of thrombin to different aptamers at two exosites.	For subnanomolar detection of thrombin	0.1 nM
[37]	A “sandwich assay” DNA aptamer-biomarkerantibody.	Chemical binding of DNA aptamer on the surface by self-assembling, followed by the affinity recognition with BNP and antibody labeled gold nanocubes (AuNCs).	Cardiac biomarker	
[38]	A gold sensor chip modified with 3-mercaptopropionic acid (MPA) self-assembled monolayer	Immunoreaction between the antigen, TNF-α, and the secondary antibody bioconjugated with gold nanorods	Detection of progesterone	0.5 ng mL−1
[39]	Rolling circle amplification (RCA)	Detected human thrombin using SPR and quartz crystal microbalance (QCM) sensing platforms in combination with aptamer-based rolling circle amplification and bio-bar-coded AuNPs enhancement.	Detection of human thrombin	0.78 aM

2.2 Qantum dot (QD)

Quantum dots are tiny particles (nanocrystals) of a semiconductor that are in the range of 2-10nm, proportional to 50 atoms.[7,40] They possess optoelectronic properties and can emit light of specific frequency when excited by light or electricity.[41] The color produced is dependent on the size of the particles; small dots emit blue or green while larger dots emit orange or red.[40] The applications of quantum dot include (a) Detection of malignant cells.

(b) Antibody labeling
(c) Genotyping
(d) Multiplexed diagnostics (e) Specific DNA sequence
(f) Imaging cellular structures.
(g) Immunoassays
(h) Detection of pathogenic microorganisms
(i) Inorganic fluorophores

2.3 Silica nanospheres

Silica nanoparticles possess biocompatibility, low toxicity, controllable size and shape.[42] These properties make silica nanoparticles important in nanotechnology. The application of silica and multifunctional silica nanoparticles include bioimaging or molecular imaging, ultrasensitive single bacterium detection, DNA and microarray detection, barcoding signatures.[43]

2.4 Magnetic nanoparticles

These are nanoparticles manipulated by means of magnetic field. Magnetic nanoparticles consist of two components: magnetic material (iron, nickel, cobalt) and a chemical component.[7] Magnetic nanoparticles show superparamagnetism,[44,45] also the physical and chemical properties depend on the method of synthesis. Magnetic nanoparticles have in-vitro and in-vivo applications. Invitro include bioseparation and selection, detection of bacteria like *Escherichia coli* and *Streptococcus suis*, magnetic immunoassay, biosensors, catalysis and cancer detection (using microfludic chip).[45,46,47]

In-vivo applications include nuclear magnetic resonance imaging, drug delivery and magnetic hyperthermia for destruction of pathological cells (tumor destruction by heat).[48,49]

2.5 Carbon nanotubes

These are cylindrical nanostructures that possess optical, electrical, mechanical and thermal conductivity properties.[50] Carbon nanotubes or nanopores can detect a single molecule when this passes through the tube or pore, which is dependent on the change of the ionic current of the electrolyte solution containing the molecules of interest, which results in a change of the electrical current.[7] CNTs are currently investigated in areas such as drugs, biosensors, antibodies, genes and vaccines though there toxicity is a major concern.[51]

2.6 Silicon nanowires and molecular nanowires

Silicon nanowires are formed from silicon (semiconductor) while molecular nanowires are made of repeating molecular units of DNA or Moybdenum-based subnanometre diameter nanowires ($Mo_6S_{9-x}I_x$: molybdenum_sulfur_iodine_based nanowire).[52] Nanowires are important because of their electrical controllability and chemical-friendly surface, therefore their applications include the detection of viruses, biomarkers, and DNA.[53]

2.7 Nanofludics

Nanofludics is the study of fluids that are confined to nanostructures. Nanostructures contain small size of fluidic channels; hence they are used when samples are required in very small quantities such as coulter counting.[54] Nanofludics are applied in areas including analytical separation, determination of proteins and DNA.[55] The prospect of nanofludics is its integration into microfludic systems (micrototal analytical systems or lab-on-a-chip devices for PCR).[56]

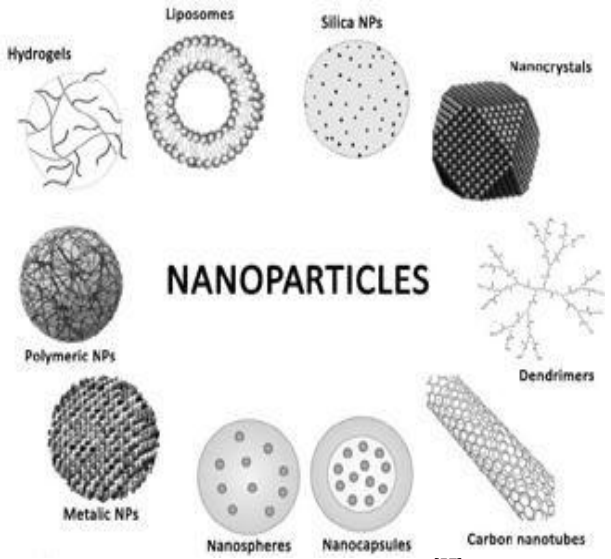

Figure III: Nanoparticles.[57]

3.0 Pharmaceuticals/Therapeutics

Nanotechnology has made it possible for drugs to be delivered directly to the target pathological site with the use of nanoparticles.[58] This has optimized therapeutic efficacy, elimination of drug resistance, reduction of unwanted side effects and toxicity.[59] Classes of drug delivery systems include water-soluble polymer, emulsion (oil droplets stabilised by amphiphilic surface coatings), nanosphere, liposome (vesicle with bilayer wall similar to normal cell wall) and polymeric micelle (assembly of polymers with spherical inner core and outer shell).[60]

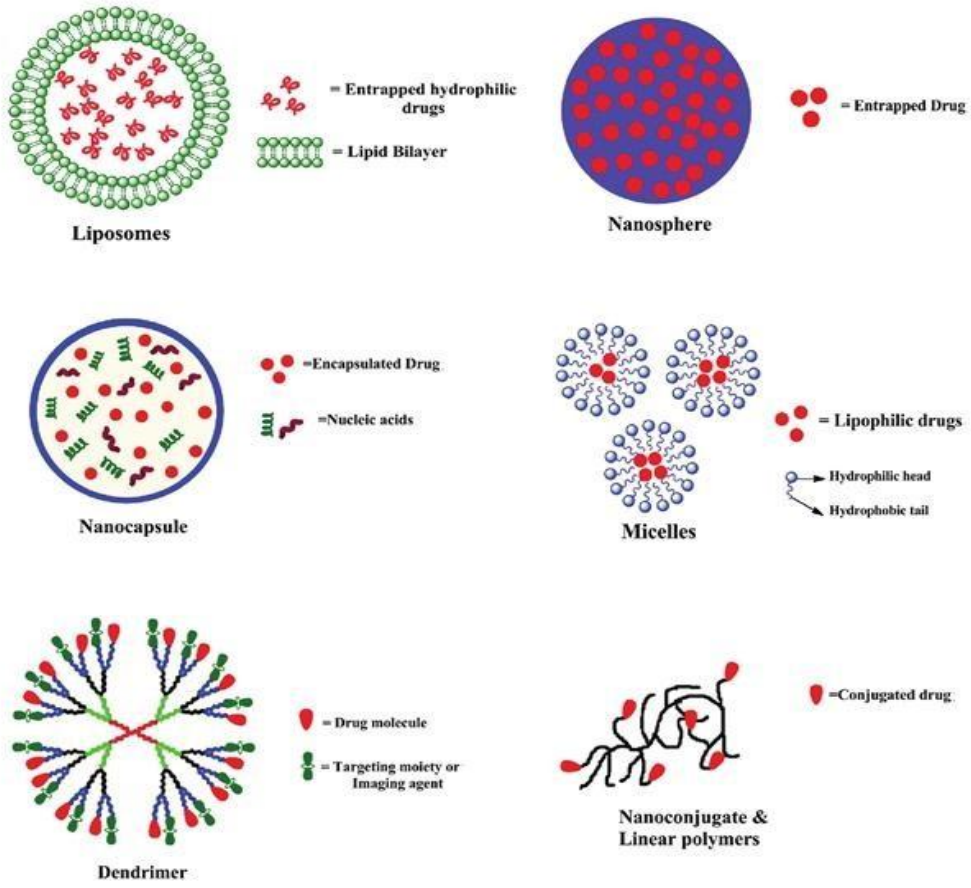

Figure IV: Drug delivery nanoparticles.[61]

The applications of nanotechnology in pharmaceuticals include:

a. Nanoparticle albumin bound paclitaxel (Abraxane) is used in the treatment of breast cancer, non-small-cell lung cancer and pancreatic cancer.[62,63]
b. Doxil (encased in liposomes) for the use on HIV-related Kaposi's sarcoma, ovarian cancer and multiple myeloma.[64]
c. Onivyde (liposome encapsulated irinotecan) used to treat metastatic pancreatic cancer.[65]
d. Polyalkylcyanoacrylates (PACA) nanoparticles have been used as a carrier for targeting antileishmanial drugs into macrophages.[66]
e. Antifungal and anti-leishmanial agent amphotericin B has been complexed with lipids-based nanotubes to develop a less toxic formulation.[67]
f. Polyethylene glycol (PEG) nano particles carrying payload of antibiotics at its core can be used to treat multi-resistant bacterial infections.[68]
g. Loteprednol etabonate for treating inflammation and pain after cataract surgery and dry eye disease. (under clinical trial).[69]
h. Photodynamic therapy can be used for treating malignant cancers including cancer of the skin.[70]
i. Photoimmunotherapy combines photodynamic therapy and immunotherapy for the treatment of metastatic cancer.[71]

Currently, nanotechnology hold immense potential in targeting cancer cells, neovascularization, inflammation and inflammatory molecules.

CONCLUSION

Nanomedicine is a promising field with an expectation of having an immense impact in diagnosis and treatment of diseases. Many nanoparticles used in drug delivery systems are still in their clinical trial. However, it is important that their toxicity is adequately assessed for safety.

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