ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Role of Nanoparticles and Nanodevices in Nanomedicine.

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ABSTRACT

The world wide interest in nanomedicine has led to the development of sophisticated nanomaterials and miniaturisation of devices that are contributing to improved healthcare. Opportunities include superior diagnostics and biosensors, enhanced imaging techniques – from molecules to man – innovative therapeutics and technologies for tissue regeneration, repair and replacement therapy.
Keywords: Nanomedicine, Nanodiagnosis, Nanodevices, Nanosurgery.

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INTRODUCTION

Nanomedicine aims at comprehensive monitoring, control, construction, repair, defence and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures, to achieve medical benefit. The term "Nanomedicine" was first introduced into medical science by Dr.Eric Drexler, Christine Peterson, and Gayle Pergamit in 1991. Nanomedicine an application of nanotechnology is the process of diagnosing, treating, preventing disease, traumatic injury thereby relieving pain, preserving and improving human health [1].

BIO-MEDICAL APPLICATIONS OF NANOMEDICINE

Targeted Drug Delivery

Nanopolymer proteins and drug delivery systems are designed for disease-specific targeting, controlled the drug release , maintaining therapeutic concentration over a prolonged period of time with various routes of administration (e.g. oral, transdermal and pulmonary) that are able to reach even inaccessible areas in the human body(eg-brain). The various nanomaterials and nanodevices available for targeted drug delivery include the following [2].

- Nanopores
- Quantum dots
- Fullerenes and carbon nanotubes
- Nanoshells
- Dendrimers and dendrimer based devices.
- Microscale biological nanorobots.

Nanopores

These devices have surface perforated with nanopores (20nm in diameter permitting passage of oxygen, glucose, insulin) containing drugs developed by Desai and Ferrari in 1997. Nanopore microcapsules containing replacement islets of Langerhans cells—can be implanted beneath the skin of diabetes patients(Leioni et al 2001) to secrete insulin. Nanopore encapsulated neurons implanted in the brain can be electrically stimulated to release neurotransmitters, for treatment of Alzheimer's or Parkinson's diseases. (Tao et al 2003). Nanopore based DNA sequencing by Daniel Branton et al 1998, has shown that the nanopore could be used to rapidly discriminate between pyrimidine and purine segments along a single RNA molecule [3].[3] (figure 1)

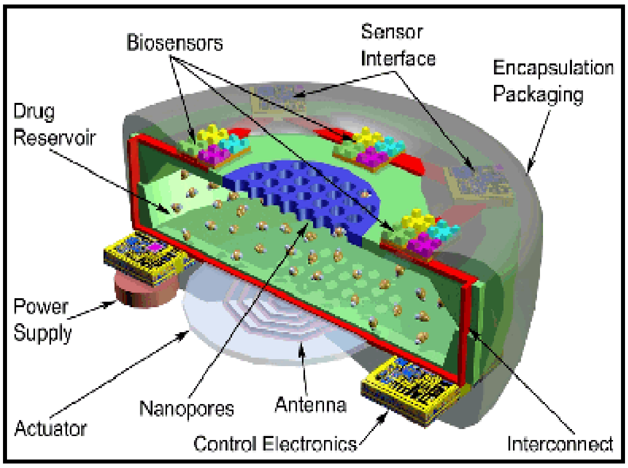


Fig 1: Implantable nanopore drug delivery system (courtesy- leadershipmedica.com)

Quantum Dots & Nanocrystals

Discovered by Louis E. Brus, at Bell Labs quantum dots are semiconductors with conducting characteristics depending on the size and shape of the individual crystal. The nanocrystals are fluorophores (absorb photons of light, then re-emit photons at different wavelengths). Higher frequencies of light, fluorescence are emitted on excitation of the quantum dot with a smaller the crystal size. These quantum dots can contain 100 to 100,000 atoms with a diameter of 15 to 20 nm [4]. (figure 2) They come in sharply defined colours customized by particle size and composition.

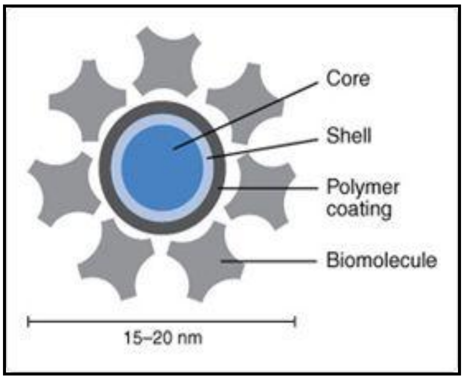


Fig 2: Structural parts of a quatum dot (courtesy-www.qstorm.org)

Due to superior optical properties, they are being researched for use in diode lasers, amplifiers, and biological sensors. The biomedical applications include highly sensitive cellular imaging (quantum dots are 20 times brighter and 100 times more stable than traditional fluorescent dyes) for tumor targeting , in vitro imaging of pre-labeled cells in real time PCR (for research of embryogenesis, cancer metastasis, stem-cell therapeutics, and lymphocyte immunology), for delivering a gene-silencing tool known as siRNA into cells [5].

ISSN: 0975-8585

Quantum dots are being investigated as chemical sensors for cancer cell detection, gene expression studies, gene mapping and DNA microarray analysis, immunocytochemical probes, intracellular organelle markers, live cell labelling, medical diagnostics and drug screening, SNP (Single Nucleotide Polymorphism) genotyping, vascular imaging and many other applications. (Williamson et al 2002, Watson et al 2003, Hanaki et al 2003) [6].

Nanoparticles of cadmium selenide quantum dots glow when exposed to ultraviolet light. When injected, they seep into cancer tumors. The surgeon can visualize the glowing tumor, and use it as a guide for more accurate tumor removal. (figure 3)

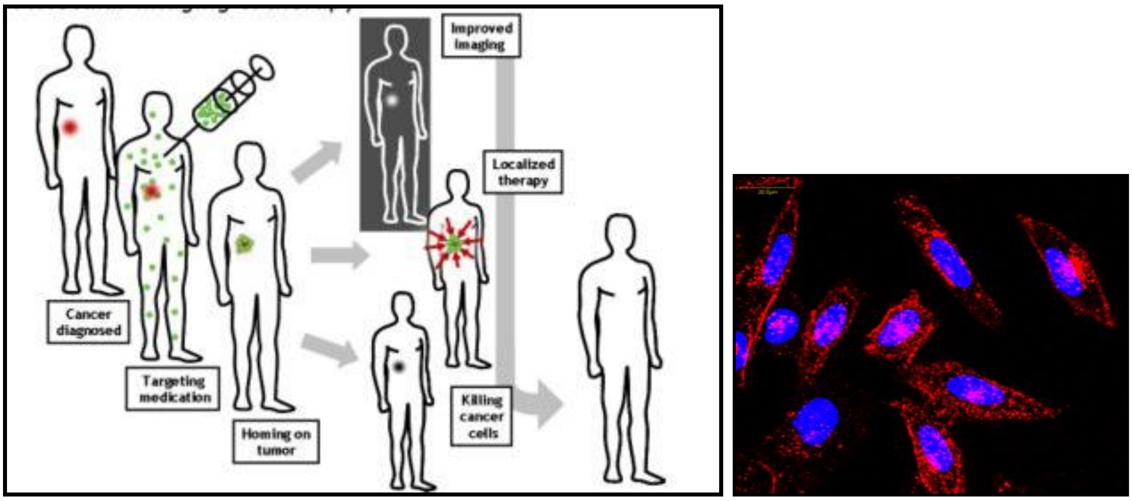


Fig3: Quantum dot Molecular imaging & therapy (courtesy-www.cancer.gov)

Fullerenes and Nanotubes

Carbon nanotubes CNTs (discovered by Iijma in 1991) with a length to diameter ratio greater than 10,000 nm contain sp2 hybridized carbon atoms in the form of two dimensional sheets that curl like cylinders [7]. They have good biocompatibility and low toxicity even at relatively high dosages. Fullerene compounds help in drug delivery- antiviral agent against HIV; antibacterial agents against E. coli, Streptococcus, Mycobacterium tuberculosis; photodynamic antitumor and anticancer therapies; neurobiology to cure neuro degenerative diseases antioxidants, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) and Parkinson's disease. Single-walled and multi-walled carbon nanotubes are being investigated as biosensors to detect glucose, ethanol, hydrogen peroxide, selected proteins such as immunoglobulins and as an electrochemical DNA hybridization biosensor. Carbon nanotubes are promising in radiation oncology for spotting tumors, inflammation and other processes inside the body.

Magnetic nanoparticles and gold-plated carbon nanotubes both target tumour cells. The combination of magnetic enrichment and photoacoustic detection (with the laser and ultrasound receiver) allows *in vivo* detection of circulating tumour cells [8].(figure 4)

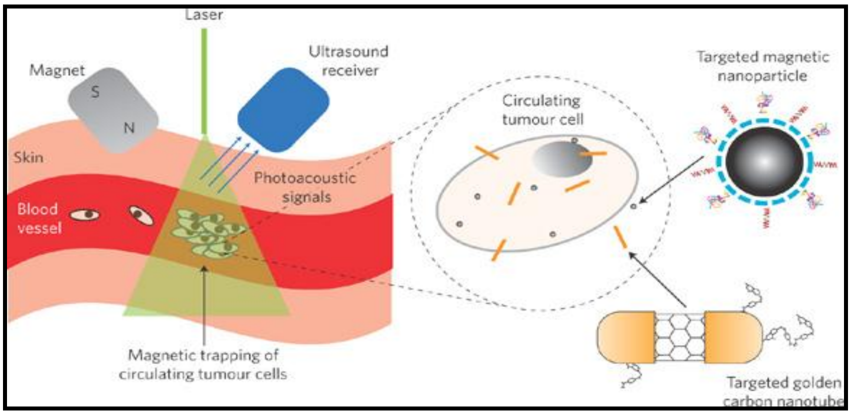


Fig 4: CNTs for cancer diagnosis
(Courtesy –www.nature.com)

Nanoshells

This is a spherical nanoparticle consisting of a dielectric core covered by a thin metallic shell. They are made of drug coated metal nanospheres, typical metals include gold, silver, platinum and palladium. The function is based on the thickness of the shell (1-20nm). When these nanoshells are irradiated with laser of known intensity, it causes release of the drug coat present on the nanoparticle surface. This can have profound implications in cancer detection, protein immunoassay, colorimetric sensing (monitoring changes in color of nanoparticles), drug delivery (gold nanoshells conjugate with enzymes, antibodies) and biosensing [9].(figure 5)

Halas & West et al 2003 used a ballpoint-pen-size infrared laser to heat the skin where the nanoshell polymer (containing insulin) can be injected for treatment of diabetes. Unlike insulin injections, required several times a day, the nanoshell-polymer system could remain in the body for months [10].

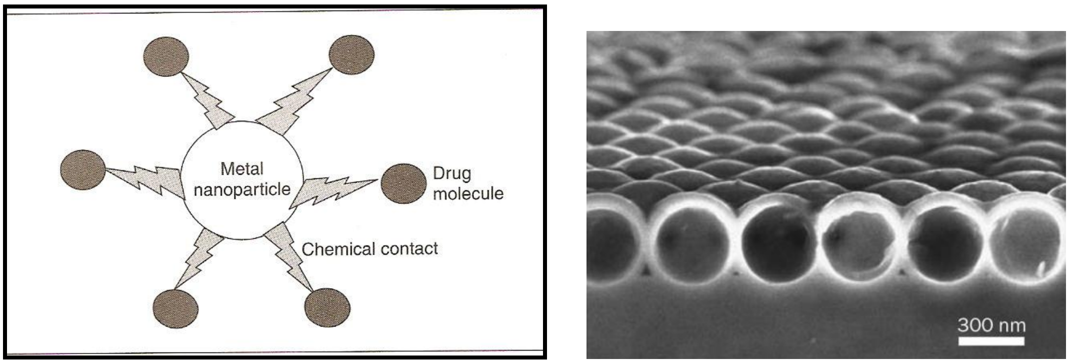


Fig 5: Drug molecule attached to metal nanoparticle nanoshell
(courtesy-physicsworld.com)

Dendrimers

First synthesized by Vogtle in 1978, Dendrimers are tree-shaped molecules with a regular branching structure emanating outward from a core .The peripheral layer contains a dense field of molecular groups that serve as hooks for attaching DNA, to enter cells without triggering an immune response. On contact with living cell, endocytosis is initiated – cell's outer membrane converts into vesicle. The vesicle encloses the dendrimer admitting it into the cell's interior, after which the DNA is released and migrates to the nucleus becoming part of the cell's genome.

They are used in the field of nanobiotechnology for diseased cell recognition, diagnosis of diseased state, drug delivery, reporting location, reporting the outcome of therapy, biomedical imaging for detection of tumour cells (multivalent diagnosis in MRI and CT imaging, changes in structures as small as 15 nm can be accurately detected). The glycodendrimer "nanodecoys" deactivate some strains of influenza virus particles (Landers et al 2002) .Cancer targeting tecto-dendrimers detect the intracellular presence of capase 3(one of the first enzymes released during cell apoptosis, the sign of a radiation damaged-Sparks et al. [11].(figure 6)

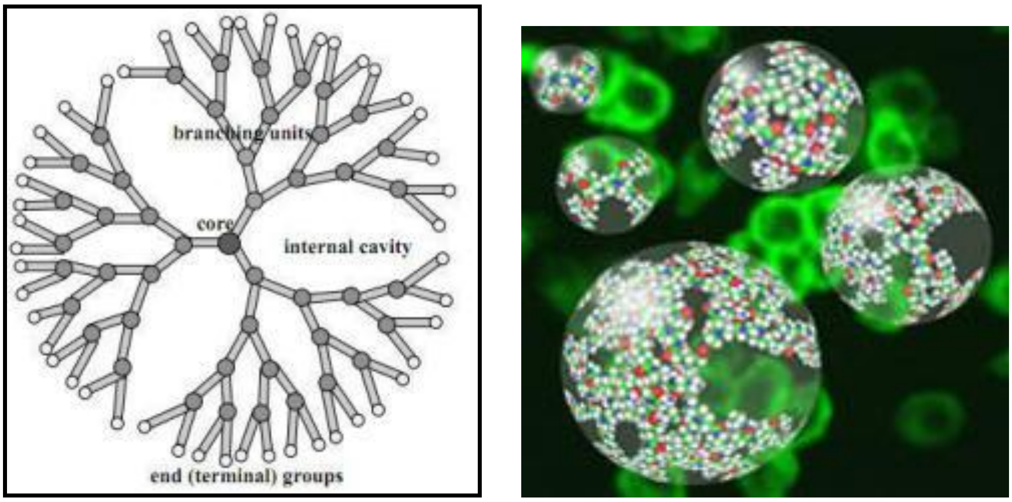


Fig 6: Dendrimer –drug delivery (courtesy- www. Worldofchemicals.com)

Nanorobots

Medical microscopic nanorobots (200 nm) injected into the body are used for drug delivery , perform minimally invasive cell surgery (karyobots), monitor diabetes, destroy cancer cells (Pharmacytes), perform artificial phagocytes (microbivores nanorobots) digesting unwanted pathogens including bacteria, viruses or fungi, for treatment of atherosclerosis, 'Respirocytes' – deliver 236 times more oxygen to body tissues, assist in diagnosis and repair damaged organs [12-14]. (figure 7)

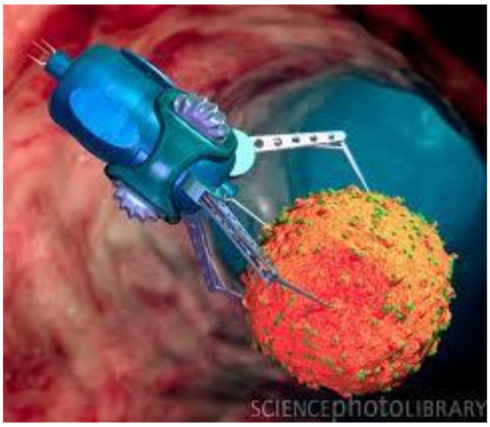


Fig 7: Nanorobot (courtesy-topicideas.net/ science photo library)

NANONEPHROLOGY

Nanonephrology is a branch of nanomedicine and nanotechnology that deals with 1) the study of kidney protein structures at the atomic level; 2) nano-imaging approaches to study cellular processes in kidney cells; and 3) nano medical treatments that utilize nanoparticles and to treat various kidney diseases. Advances in nanonephrology can provide nano-scale information on the cellular molecular machinery involved in normal kidney processes and in pathological states. By understanding the physical and chemical properties of proteins at the atomic level in various cells in the kidney, novel therapeutic approaches can be designed to combat major renal diseases. The nano-scale artificial kidney will permit programmable and controllable nano-scale robots to execute curative and reconstructive procedures in the human kidney at the cellular and molecular levels [15]. (figure 8)

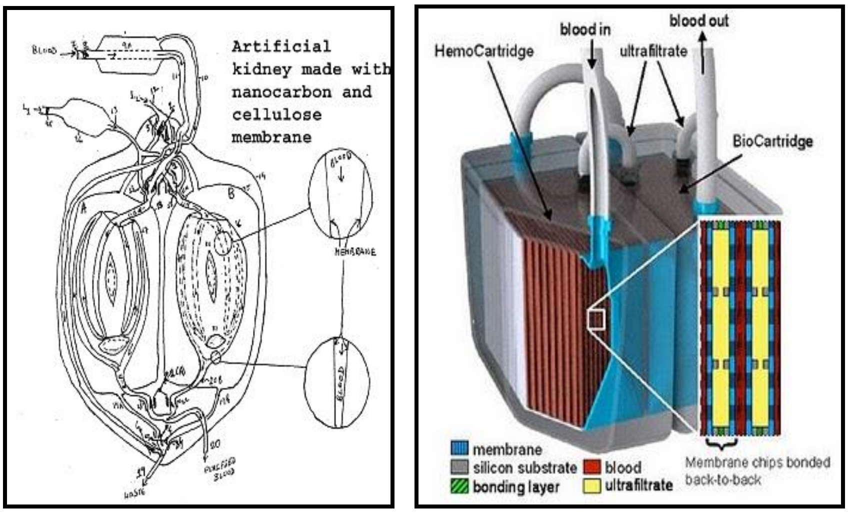


Fig 8: Schematic representation- artificial kidney(courtesy-ucsf.edu)

ISSN: 0975-8585

THERANOSTICS

The term "theranostics," in nanomedicine describes the fusion of therapy and diagnostics, coined originally by Warner.S et al 2004. Theranostic nanomedicine is an integrated nanotherapeutic system, which can diagnose, deliver targeted therapy and monitor the response to therapy. Its core technology is the Reverse Phase Protein Microarray (RPMA) combined with Laser Capture Microdissection (LCM)- first invented by Drs. Emanuel Petricoin and Lance Liotta, in 2001.

Theranostic agents allow detection as well as monitoring of an individual patient's cancer at an early-stage and deliver anticancer agents over an extended period for enhanced therapeutic efficacy. Multifunctional theranostic agents deliver gene therapeutics and provide real-time imaging of therapy response in vivo. This will allow for widespread preclinical and clinical applications of theranostics in cancer, cardiovascular and immune diseases [3].

REGENERATIVE MEDICINE

Regenerative medicine remains as one of nanomedicine's core interests, after diagnostics and theranostics. Regenerative medicine aims at a multidisciplinary approach to strengthen the self-healing processes of the human body either by stimulating or emulating them. Nanomachinery provides precision control in tissue engineering, restore insulin production in diabetics, reconnect severed nerves or restore neural function in neurodegenerative diseases such as Alzheimer's or Parkinson's [16].

IMAGING

In nanoparticulate molecular imaging various biocompatible nanoparticles (like iron oxide nanoparticles, gadolinium nanoparticles, gold nanoparticles, quantum dots etc) are incorporated with the contrast agents or the dyes to provide high resolution images with MRI & fluorescent techniques. Thus imaging is used to track nanoparticles systemically, pre-validate appropriate targeting ,detect therapeutic efficacy, drug distribution and metabolization. (figure 9)

Nanoparticles used in cardiovascular imaging (Sharma et al 2006). The applications include targeted drug delivery; tissue engineering to replace defective valves, damaged heart muscle, clogged blood vessels; molecular imaging to detect artherosclerotic deposits; biosensors for myocardial diagnostics. Several nanoparticles like dendrimers, liposomes, polymer delivery molecules, cantilevers, nanoscaffolds, nanofibres are potential candidates for cardiac visualization [17,18].

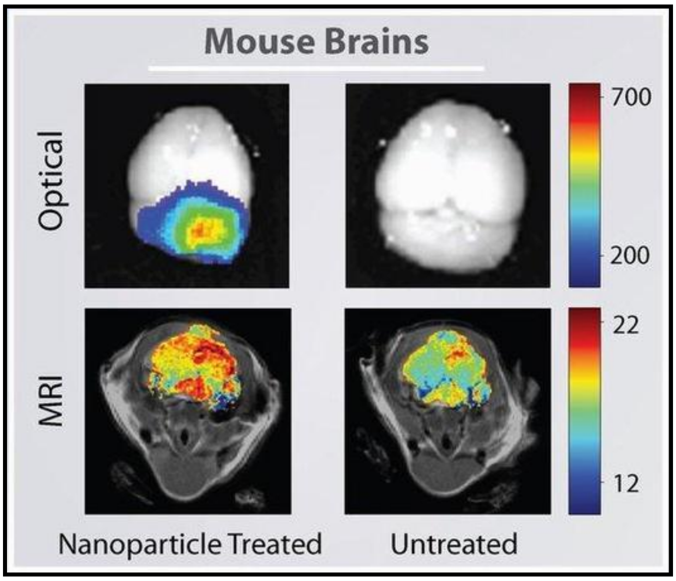
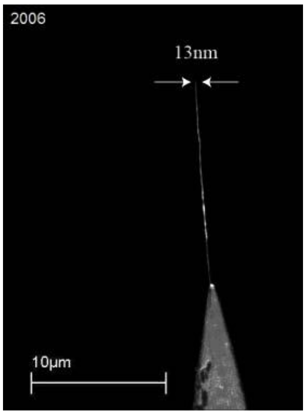


Fig 9: Nanoparticle molecular imaging to detect brain tumor (courtesy-medicalphysicsweb.org)

SURGERY

Nanosurgery enables direct intervention at the cellular level being more precise and less invasive than the traditional methods. Various nanostructures used in nanosurgery include the following:

NANONEEDLES: Obataya et al performed surgery on living cells using atomic force microscopy (AFM) with a nanoneedle (6-8 µm in lenghth and 200-300 nm in diameter). They permit painless injection of the local anesthetic solution at the surgical site. Also used for drug delivery (painless delivery of vaccines into the body), perform laser surgery at the nanoscale with femtosecond near infrared (NIR) laser pulses inside living cells(Tirlapur and Konig et al 2003), enable DNA delivery to human mesenchymal stem cells. Tiny pyramid-shaped 'micro needles' made out of silicon and with a central bore hole allow the passage of any active ingredient, including antigens [19]. (figure 10).



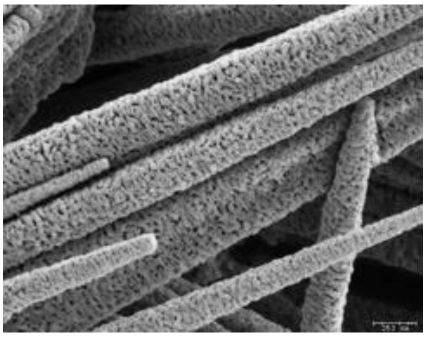


Fig 10: Nanoneedles (courtesy – optobrown.edu)

ISSN: 0975-8585

NANOTWEEZERS: Mc Donald et al fabricated micrometer scale electromechanical tweezers with silicon . The arms made by tungsten deposition (200 µm long and 2.5µm wide) are closed by applying an electrical potential 150 V and can be re-opened by reducing the potential to 0 V. These are ideal materials for manipulation of tissues during surgery, manipulation of bacteria, viruses for measurement of biochemical activity. During surgery they produce separation of non viable cells from viable cells. Eg- breast cancer cells from normal T-lymphocytes, cervical carcinoma cells from peripheral blood cells etc [20].(figure 11)

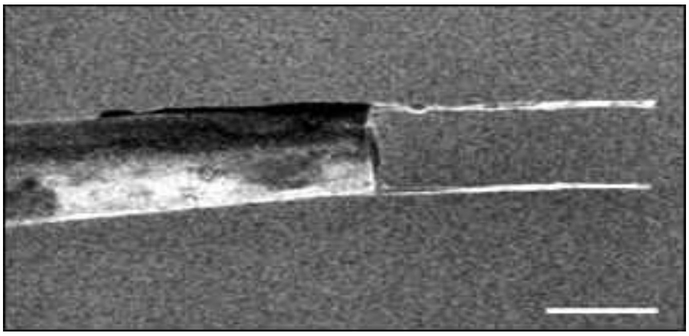


Fig 11: Nanotweezers(courtesy-science willandbeyond.com, news.bbc.co.uk)

NANOSCISSORS: In recombinant DNA technology , nanoscissors are used to cut DNA strands and reassemble them, thus creating reconstruction of new DNA samples in biochemistry. The scissors measures 3 nm in length, small enough to deliver drugs into cells or manipulate genes and other biological molecules. The parts of the nanoscissors includes a pivot (chiral ferrocene, with a spherical iron atom sandwiched between two carbon plates), blades and handles. Attached to the scissors' blades are organometallic units called "zinc porphyrin." When the zinc atom in the zinc porphyrin binds with a nitrogen-containing molecule, such as DNA, the zinc and nitrogen act like magnets, securing a firm grip on the molecule.As the blades open and close, the guest molecules remain attached to the zinc porphyrin, and as a result, they are twisted back and forth. The movement activates the pivot, followed by an opening-closing motion of the blades [21]. (figure 12)

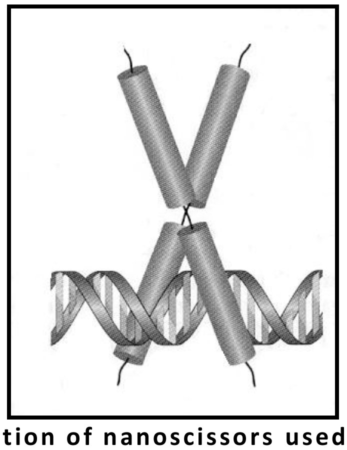


Fig 12: Schematic representation of nanoscissors used to manipulate DNA strands(courtesy-nmstr.org)

ISSN: 0975-8585

CONCLUSION

The application of nanomedicine can revolutionize medicine extending from targeted drug delivery to precision diagnostics & surgery. The ultimate aim is to develop a robust mechanism whereby therapeutic intervention is able to locate the site of infection/disorder, diagnose the level of infection, deliver the drugs in case therapeutic treatment is required and provide metabolic support in the event of impaired functioning. A bright future lies ahead for nanomedicine but all ethical and social concerns need to be overcome to make this dream into true reality!

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