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A CONCISE REVIEW ON NANOPARTICLES USED IN DIAGNOSTIC AND SCREENING PURPOSES

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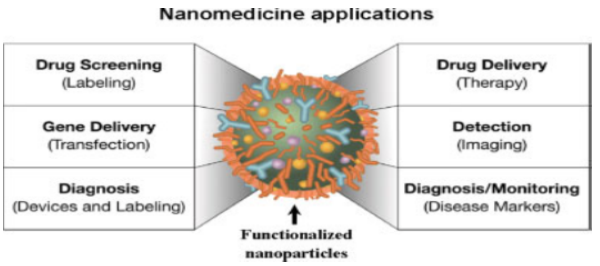
ABSTRACT The genesis of nanotechnology can be traced to the promise of revolutionary advances across medicine, communications, genomics and robotics. Nanoparticles can attach to proteins or other molecules, allowing detection of disease indicators in a lab sample at a very early stage. There are several efforts to develop nanoparticle disease detection systems underway. Several nanoparticles have been used for diagnostics, most commonly gold nanoparticles, quantum dots (QDs) and magnetic nanoparticles. This review focuses on the potential of nanomedicine as it specifically relates to developing novel and more effective diagnostic and screening techniques to extend the limits of molecular diagnostics providing point-of-care diagnosis and more personalized medicine.

KEYWORDS : Nanoparticle; Molecular diagnosis; Targeted Drug delivery; Personalized medicine



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Categories of nanodiagnostic technologies.

1. Nanoscale visualization, e.g., atomic force microscopy, scanning
2. Probe microscopy
3. Nanoparticle biolabels
4. Nanotechnology-based biochips/microarrays
5. Nanoparticle-based nucleic acid diagnostics
6. Nanoproteomic-based diagnostics
7. Biobarcode assays
8. Nanopore technology
9. DNA nanomachines for molecular diagnostics
10. Nanoparticle-based immunoassays
11. Nanobiosensors
12. Combinations of multiple diagnostic technologies

A. Clinical Applications of Nanodiagnostics

a) Applications of Nanodiagnostics in Management of Cancer

Bioconjugated QDs, collections of differently sized nanoparticles embedded in tiny polymer beads, provide a new class of biological labels for evaluating biomarkers on intact cells and tissue specimens (Zhao et al., 2004).

Bioconjugated QDs can be used for multiplexed profiling of biomarkers, and ultimately for correlation with disease progression and response to therapy. These applications will increase the clinician's ability to predict the likely outcomes of drug therapy in a personalized approach to disease management.

Bioinformatics and systems biology are used to link each patient's molecule profile with disease diagnosis and treatment decisions (Jain,2005).

Efficient conversion of strongly absorbed light by plasmonic gold nanoparticles to heat energy and their easy bioconjugation suggest their use as selective photothermal agents in molecular cancer cell targeting (Sayed et al.,2006).

b) Application of Nanodiagnostics in Infectious Diseases

A bioconjugated nanoparticle-based bioassay for in situ pathogen quantification can detect a single bacterium within 20-min (Zhao et al., 2004).

A spectroscopic assay based on SERS (surface enhanced Raman spectroscopy) using silver nanorods, which significantly amplify the signal, has been developed for rapid detection of trace levels of viruses with a high degree of sensitivity and specificity(Shanmukh et al., 2006).

The technique measures the change in frequency of a near infrared laser as it scatters viral DNA or RNA. That change in frequency is as distinct as a fingerprint. This novel SERS assay can detect spectral differences between viruses, viral strains, and viruses with gene deletions in biological media. The method provides rapid diagnostics (60 s) for detection and characterization of viruses generating reproducible spectra without viral manipulation.This method is also inexpensive and easily reproducible.

c) Applications of Nanodiagnostics in Neurological Disorders

Nanoparticle contrast agents are in development to enhance MRI. A new MRI contrast agent using manganese oxide nanoparticles to visualize the anatomic structures of mouse brain produces images that are as clear as those obtained by histological examination which will enable better research and diagnosis of neurological disorders such as Alzheimer disease, Parkinson disease, and stroke (Ramos-Cabrer and Campos, 2013).

B. Nanomolecular Diagnostics - Applications

1.Nanotechnology-Based Biochips and Microarrays

Nanotechnology on a chip is a new paradigm for total chemical analysis systems (Zhang et al.,2008). The ability to make chemical and biological information easier and less costly to obtainwill impact molecular diagnostics and healthcare. Some examples of devices that incorporate nanotechnology- based biochips and microarrays are nanofluidic arrays and protein nanobiochips.

2.Nanotechnology-Based Cytogenetics

Cytogenetics has been used mainly to describe the chromosome structure and identify abnormalities related to disease. Molecular cytogenetics in now enhanced by use of nanobiotechnology,e.g., atomic force microscopy and quantum dot (QD), FISH(fluorescent in situ hybridization) (Ioannou and Griffin,2010).This method is also focused on the combination of biochemical and nanomanipulation techniques, which enable both nanodissection and nanoextraction of chromosomal DNA.

3.Application of Nanoparticles for Tracking Stem Cells

A superparamagnetic iron oxide (SPIO) nanoparticle is emerging as an ideal probefor noninvasive cell tracking (Lisa et al., 2016).These methods could soon enable researchers and physicians to use unique signatures from the ingested nanoparticle beacons to directly track cells used in medical treatments. The use of 200-nm perfluorocarbon nanoparticles to label endothelial progenitor cells taken from human umbilical cord blood enables in vivo progenitor cell detection by MRI.Such tracking ability could prove useful for monitoring tumors and diagnosing as well as treating cardiovascular problems.

4. Nanoscale Single-Cell or Molecule Identification

Nanotechnology has facilitated the development of methods for detection of single cells or a few molecules (Gourley et al.,2005). Nanolaser scanning confocal spectroscopy, with the capability of single-cell resolution, can be used to identify previously unknown properties of certain cancer cells that distinguishes them from closely related nonpathogenic cells.

The detection of single molecule of protein is also enabled by the application of nanobiotechnology to proteomics called Nanoproteomics (Cheng et al.,2010).

5. Application of Nanoparticles for Discovery of Biomarkers

The physicochemical characteristics and high surface areas of nanoparticles make them ideal candidates for developing biomarker-harvesting platforms.It is feasible to tailor nanoparticle surfaces to selectively bind a subset of biomarkers and sequester them for later study using high-sensitivity proteomic tests (Noelia et al.,2012). Functional polymer coated nanoparticles can be used for quick detection of biomarkers and DNA separation.

6. Nanoparticles for Molecular Diagnostics

Nanoparticles are most frequently used used for diagnostics Ex., are gold nanoparticles, QDs, and magnetic nanoparticles

a. Gold Nanoparticles for Diagnostics

- Small pieces of DNA can be attached to gold particles no larger than 13 nm in diameter.
- Gold nanoparticles are particularly good labels for sensors because a variety of analytical techniques can be used to detect them (Aneta et al., 2013).

b. Quantum Dots

- QDs are inorganic fluorophores that have high sensitivity, broad excitation spectra,stable fluorescence with simple excitation, and no need for lasers. Their red/infrared colors enable whole blood assays.
- QDs have a wide range of applications for molecular diagnostics and genotyping. QDs also enable multiplexed diagnosticsand integration of diagnostics with therapeutics (Lin et al., 2014).
- The most important potential applications of QDs are for cancer diagnosis. Luminescent and stable QD bioconjugates enable visualization of cancer cellsin living animals.
- Another application of QDs is for viral diagnosis

c. Magnetic Nanoparticles

- Iron nanoparticles, 15–20 nm in size and having saturation magnetization, have been synthesized and embedded in copolymer beads of styrene and glycidyl methacrylate (GMA), which were coated with polyGMA by seed polymerization.
- Nanoparticles are used as labeling molecules for bioscreening (McBain et al 2008).
- Superparamagnetic nanoparticles are useful for cell-tracking cells and for calcium sensing.
- Superparamagnetic nanoparticles measuring 2–3 nm have been used in conjunction with MRI to reveal small and otherwise undetectable lymph-node metastases.
- Ultrasmall SPIO (super paramagnetic iron oxide)enhances MRI for imaging cerebral ischemic lesions.
- A dextran-coated iron oxide nanoparticle enhances MRI visualization of intracranial tumors for more than 24 h.

II. Ultra-fast DNA sequencing using nanopores

Ultra-fast DNA sequencing using nanoporesis used to sequence a complete codon in an individual DNA strand tethered to a nanopore. In principle, nanopore detection and characterization of single molecules represents a new method for directly reading information encoded in linear polymers (Soni and Meller , 2007).

III. Drug delivery

Microsphere formulations have been successfully used to protectagents susceptible to degradation or denaturation, while prolonging the duration of action of a drug by increasing systemic exposure or retention of the formulation through bioadhesion. Another broad application of nanosphere uptake is the delivery of antigens for vaccination.

I. Nanoencapsulation

- Other approaches to drug delivery that merit attention include the integration of controlled-release drug reservoirs with microchips. These devices have unlimited potential for modulation of release, with the ability to combine modalities within each reservoir, as well as the control of each individual pulse of drug release (Reis et al., 2006).
- Nanotubes have large relative internal volumes, can be functionalised either on the internal or external surface, soluble derivatives of fullerenes have good biocompatibility and low toxicity, are under investigation as antiviral agents, antibacterial agents, anticancer therapies, antioxidants and antiapoptosis agents for potentially treating amyotropic lateral sclerosis and Parkinson's disease.

ii. Nanoshells

One exciting area of potential use for nanoshellsis the delivery of chemotherapeutics to tumours. Nanoshells, embedded in a drug-containing polymer and then injected into the body, accumulate near tumour cells (Loo et al., 2004). When heated with an infrared laser, the nanoshells selectively absorb a specific infrared frequency, melting the polymer and releasing the drug at a specific site.

IV. Single-virus detection

Single virus particles could be detected with high selectivity using nanowire field-effect transistors to measure discrete conductance changes characteristic of binding and unbinding on nanowire arrays modified with viral antibodies (Chen et al., 2009). Real-time detection of individual viruses would greatly impact our ability to diagnose and provide early intervention to a wide range of diseases which would have been traditionally impossible.

V. Nanorobots

a. Nanorobotic microbivores

Artificial phagocytes called microbivores could patrol the bloodstream, seeking out and digesting unwanted pathogens.With the alarming rise in antibacterial resistance, developing nanorobotical capabilities to battle infection may open promising avenues for treatment of infection (Freitas Jr., 1998). These robots would be designed to have a large number of customizable binding sites on their external surface, for antigens or pathogens for anything from HIV to E. coli. Microbivores are theorized to be as much as 80 times more effective than our physiologic phagocytic capabilities, and could have the potential to clear septicemia within hours of administration.

b. Surgical nanorobot

A surgical nanorobot, programmed or guided by a human surgeon, could act as a semiautonomous on site surgeon inside the human body (Song et al., 2012), when introduced into the body through vascular system or cavities. Such a device could perform various functions such as searching for pathology and then diagnosing and correcting lesions by nanomanipulation, coordinated by an onboard computer while maintaining contact with the supervising surgeon via coded ultrasound signals.

c. Intra Vascular therapy

- The use of nanorobots intravascularly greatly expands the potential for screening and monitoring for life-threatening health conditions, as well as monitoring the development and progression of chronic diseases (Wicklin et al.,2006). Screening for brain aneurysms, lung cancer, and unstable atherosclerotic lesions.
- The monitoring of chronic health conditions such as diabetes increases the capability for optimally managing chronic diseases.
- nanorobots can be developed for the application of direct intravascular therapy, in the case of coronary artery stenosis, nanorobots could provide direct therapy to the target area either mechanically or with pharmacologic treatment.
- The intravascular navigational ability of a nanorobot can allow localized drug delivery to reduce the amount of bleeding, as well as a localization tool as an adjunct to imaging.
- Additionally, nanorobots can be used for the detection and direct treatment of cancer, constant tumor surveillance.
- Nanorobot can be used for direct local treatment delivery resulting in lower potential toxicity.

d. Oncology

- Nanotechnology is promising in the management of cancer, increasing the sensitivity of cancer imaging tools, overcoming drug resistance, and improved treatment of metastasis.
- The development of a nanorobot that can autonomously detect cancerous cells, and release treatment agents at the site of these cancerous cells has been successfully developed.
- This nanorobot can be constructed to respond to a number of different cell surface receptors, and the payload it releases upon activation can also be changed as necessary. This nanorobot has been constructed using engineered DNA strands that have been made to fold into a desired tertiary structure. Upon binding the desired target, the conformation of the DNA nanorobot undergoes a structural reconfiguration and shifts from a closed to an open state, releasing the stored therapy (Douglas et al., 2012).
- There has been developments in the potential incorporation of nanorobots in tumor resection surgeries, to improve the detection and mapping of tumor margins intraoperatively.

e. Neurosurgery

- Improved detection of pathology, minimally invasive intracranial monitoring, and pharmaceutical delivery, one of the most effective ways to prevent morbidity and mortality in the field of neurosurgery is the treatment of cerebral aneurysms before rupture.These nanorobots have the capability to wirelessly communicate information about pertinent vascular changes potentially decreasing screening costs of imaging and frequent follow up visits.
- Importantly, developing the platform required for this device will also enable horizontal expansion of the idea for many other uses, such as tumor detection or ischemic changes.The topic of spinal cord injury and nerve damage is an important area of concern within neurosurgery as a field, and as a significant life-altering event for affected patients.Restoring connectivity to transected axons is an integral step to the restoration of function. The ability to do this is limited by technical limitations to surgery on that scale.
- Advancements in technology have led to the development of devices on the nanoscale which allow manipulation of individual axons. A Nanoknife with a 40 nanometer diameter has been developed and found to be effective for axon surgery (Elder, et al., 2008).
- Following controlled transection of axons and maneuvering them into position using dielectrophoresis, fusion between the two ends can be induced via electrofusion, polyethylene glycol, or laser-induced cell fusion, amongst other methods. Nanodevices are enabling a new dimension of precision and control with the reconnection of nerves.

f. Dentistry

- Nanorobots can have significant routine and specialized use is the field of dentistry, ranging from a routine cleaning, to cosmetics and teeth whitening, hypersensitivity, and even orthodontics (Babel and Mathur, 2011). Nanorobots can be incorporated into almost every aspect of dental care, including the initial analgesia a dentist may give at the start of a visit.
- A suspension containing millions of nanorobots is administered orally to the patient enter the gingival sulcus, and eventually travel through the micron sized dental tubules to reach the pulp. Central control of these nanorobots would allow activation of analgesic activity in highly specific areas in proximity to where the dentist will be providing care. Use of nanorobots in procedures such as root canal fillings or in the treatment of infection is also plausible.

g. Hematology

- Uses ranging to emergency transfusions of non-blood oxygen carrying compounds to restoring primary hemostasis, a nanorobot dubbed "Respirocyte", equipped to have three functions as it travels through the bloodstream. First, collecting oxygen as it passes through the respiratory system for distribution throughout the bloodstream. Second, collecting carbon dioxide from tissues for release into the lungs. And finally, metabolizing circulating glucose to power its own functions. Development and use of this technology could provide an effective and lower risk alternative to blood transfusions (Hassouna, 2000).
- The process of hemostasis is another area where nanorobotics may have applicability, natural limitations to physiologic hemostasis, can be improved upon by nanorobotics. "Clottocyte", which is inundated with hemostasis promoting proteins, is fired at areas of vessel injury to carry out hemostasis.

VI. Nanogenerators

Nanogenerators that can convert mechanical energy to electrical energy for powering devices inside the body. This could open up tremendous possibilities for self-powered implantable medical devices (Wang, 2008).

VII. Nanoassemblers

- Could be smaller than a cell nucleus so that they could fit into places that are hard to reach by hand or with other technology.
- Used to destroy bacteria in the mouth that cause dental caries or even repair spots on the teeth where decay has set in and could be controlled by computer to perform specialized jobs.

VIII. Nanobiosensors

Nanobiosensors are nanosensors used for detection of chemical or biological materials. They are of many kinds,viz.,

i. Electronic nanobiosensors
ii. Electrochemical nanobiosensors
iii. Ion channel switch biosensor technology
iv. Nanowire biosensors
v. Cantilevers as biosensors
vi. Carbon nanotube biosensors
vii. FRET-based DNA nanosensor
viii. Optical biosensors using laser, nanoshell, SPR, SERS, mRNA
ix. PEBBLE (Probes Encapsulated by Biologically Localized Embedding)
x. Quartz nanobalance DNA sensor
xi. Viral nanosensor

Implications

One of the best applications of nanomedicine will be improved fluorescent markers for diagnostic and screening purposes like use of 'quantum dots', PEBBLES (probes encapsulated by biologically localized embedding) and perfluorocarbon particles, Gold nanoparticles for DNA diagnostics and DNA microarrays for genotypic analysis and assessment of drug responses Nanoparticles are being used to monitor glucose concentrations and also for simultaneous tagging of multiple biomolecules, both outside and inside cells, as well as to monitor disease progression.

They can be inserted into living cells as magnetic resonance contrast agents.

Polymeric nanospheres can selectively target different tissues for imaging purposes which can be injected systemically to target the liver, spleen and lymph nodes.

Safety Issues of Nanoparticles for Diagnostics

Potential toxic effects are a major concern with the in vivo use of nanoparticles which is a must in majority of laboratory diagnostics. There are environmental concerns about the release of nanoparticles during manufacturing of nanoparticles and the environmental effects. There are still many unanswered questions about the fate of nanoparticles introduced into the living body. Because of the huge diversity of the materials used and the wide range of size of nanoparticles, these effects will vary considerably. It is conceivable that particular sizes of some materials may have a bearing on toxic effects, nanoparticles smaller than 20 nm in diameter can penetrate the cells and hence there is a premiere concern that the mere presence of these potentially toxic sentinels disrupts cell function. One other major limitation is the approval of *in vivo* use of nanomaterials for human diagnostics and the demonstration of safety of nanoparticles in intact human systems. Though a number of studies have been done, presently no precise conclusions can be drawn about the safety of nanoparticles in this regard.

CONCLUSION

The major advantages provided by the Nanotechnology based diagnosis techniques are:

- Rapid testing, which allows complete diagnosis and start of treatment rather than the need for a follow-up visit to the doctor after a lab test is completed.
- The detection of diseases at an earlier stage provides the potential of curing the disease in the initial stages with potentially less risk to the patient.

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