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Nanotechnology in Diagnosis: A Review

Tenderwealth Clement Jackson[1*], Bernard Opatimidi Patani[2], Daniel Effiong Ekpa[1]

[1]Department of Pharmaceutics & Pharmaceutical Technology, University of Uyo, Uyo, Nigeria
[2]Medical Department, Nigerian Agip Oil Company, Port Harcourt, Nigeria
Email: *clementjackson1@gmail.com

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Abstract

The fast pace of today's world has presented several challenges in the area of healthcare. Depression, hypertension, diabetes, cancers and several infectious diseases are just some of the common outcomes associated with the high speed stress-filled lifestyle. Early diagnosis has been the goal for prompt arrest and management of these health conditions. This has been a challenge in recent times. However, great scientific advancement with improved potential in medical diagnosis has equally been a giant stride in times like these. Early disease detection even before symptoms' presentation, improved imaging of internal body structure, as well as ease of diagnostic procedures, have been developed with the help of a new branch of laboratory medicine termed nanodiagnostics. Use of microchips, biosensors, nanorobots, nano identification of single celled structures, and microelectromechanical systems are current techniques being developed for use in nanodiagnostics. This piece of write up takes a panoramic view of available nanotechnological advances in current use for medical diagnosis and projecting into future possibilities and potentials for an improved health care delivery.

Keywords

Nanodiagnostics, Biosensors, Microelectromechanical Systems

1. Introduction

Although the production and use of the tiniest particles invisible to the naked eye are not really a new invention, the concept of nanotechnology has been in the front burner of scientific research in recent times. Colloidal nanoparticles of silver and gold contained in the antique Roman glass cup have been found to be responsible for the phenomenon that makes it reflect different colours, when illuminated. The elasticity and resistance noticed in the legendary Damascene Sword have been described to be due to nanometer sized particles of carbon discovered to be present in them [1]. From the physical, to environmental and even the life sciences, the use of particles at the nanoscale to achieve results, monitor processes and take part in reactions has not only been explorative but also interesting. In the life sciences, nanotechnology becomes ever relevant specifically as components of functional biological unit such as Deoxyribonucleic acid (DNA), Ribosomes, ribonucleic acids in living cells, for example, are mainly of nanoscale sizes. This presents a potential for the application of nanotechnology in affecting these cell components; to screen, detect any defect, improve, incorporate or knock them off.

Nanotechnology, according to the United State Environmental Protection Agency involves creating and using structures, devices, and systems that have novel properties and functions as a result of their small and/ or intermediate size; it is the branch of science that employs the use of nanoscale particles, studying its peculiar characteristics and employing these to obtain desired outcomes in the fields of Engineering, Medicine, Agriculture, or Pharmaceuticals (http://www.epa.gov/). Nanotechnology deals with nanoparticles. Any material with dimensions of less than 1 μm is described as a Nanoparticle. Nanotechnology has provided many useful tools that can be applied for the detection of biomolecules and analytes relevant for diagnosis purposes–nanodiagnostics [2]. A good understanding of nanoparticles and their unique properties gives insight to the peculiar reasons for their application in different fields, specifically in medical diagnosis.

Medical diagnostics has been described using different catchy expressions by various textbooks on medicine. But capturing the main concept, the homepage of the website of journal of medical diagnostic methods, with slight modification, defines it as the discipline or practise of diagnosis which involves determining and describing of a disease state and its causative factors responsible, using signs, symptoms obtained from patient history or from physical examination of patients or their specimen with the help of several diagnostic techniques. The essence is to ascertain what medical condition is being treated, managed or endured. This is especially true considering that any attempt in treating, or managing a medical condition begins with identifying the disease condition. Thus, from the crude method of organoleptic assessment of body samples through the era of use of microscopy and now employing of biosensors and body imaging, medical diagnosis has a long history. So inclusion of nanotechnology to improve diagnosis is not only a positive step but also a welcome one.

Nanodiagnostics is the new term that describes use of methods and techniques of nanotechnology and its principles for diagnostics purposes. It includes, although not limited to, the manipulation and assessment of single molecule, size reduction of systems and platforms to make use of nanoscale properties obtainable from interactions between surfaces and biomolecules. Nanodiagnostics is an evolving application of nanoscale technology to meet the demand of clinical diagnostics, determining disease state, any predisposition to such, the pathology of the condition and the identification of causative organisms. With nanotechnol-

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ogy, diagnosis is being carried out on a nano-scale leading to a trend of the use of hand held devices that are easy to use and marketable [2] [3]. Nanodiagnostics as surging new field of molecular diagnostics, have been positively changing laboratory procedures, providing new ways for patient's sample assessment and early detection of disease biomarkers with increased sensitivity and specificity. Nanoparticle platforms have been developed and optimized for the detection of pathogens and cancer biomarkers such that diagnostic proceedures now become less cumbersome but more sensitive because most of the complex proceedures are now integrated onto a simple device having the capacity to be used for on the spot diagnosis. The economic implications of these notable developments can be graphically illustrated below (**Figure 1**).

1.1. Nanoparticle (Nanomaterials) Classification

1.1.1. Nano Tube

These are cylindrical carbon molecule with novel properties which make them potentially useful in many applications in nanotechnology, electronics, and the material sciences. They exhibit extraordinary strength and unique electrical properties and are good conductors of thermal energy; this is because the chemical bonding is in line with sp^2 orbital hybridization. Examples include fullerene, an allotrope of carbon. A research team at the University of Connecticut has reportedly used a sensor made from densely packed carbon nanotubes coated with gold nanoparticles, to develop a device capable of detecting oral cancer from samples [5]. Carbon nanotubes and Silicon nanowires have been utilized for detection of various volatile organic compounds present in breath samples of lung and gastric cancer patients respectively [6].

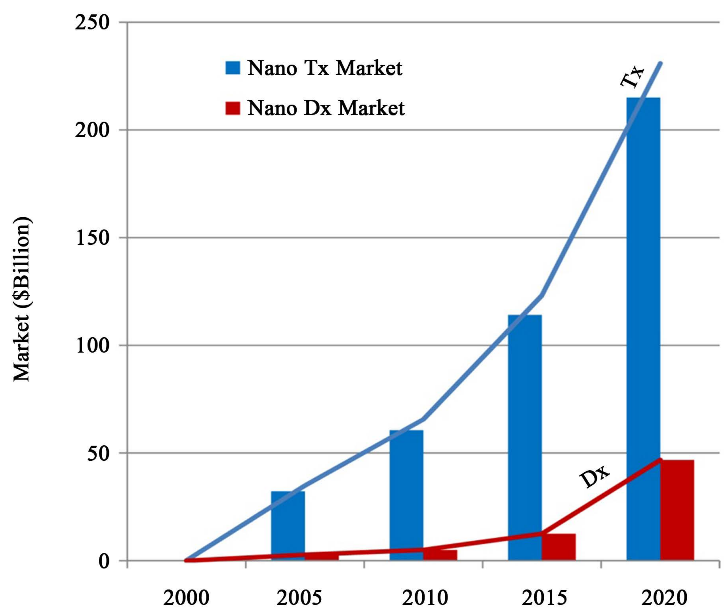

Figure 1. Graphical representation of historical and projected records of nanodiagnostic (Dx) and nanotherapeutics (Tx). Source: (Baseline data and compounded annual growth rates are based on BCC Research 2010 [4]).

1.1.2. Nano Crystal

They are crystalline materials with at least one dimension being less than 1μm and their properties, both electrical and thermodynamic, are size dependent. An example of these crystals is that of Elan pharma International Limited based in Ireland involved in nanoparticle drug formulation. Nanocrystals are good semi-conductor in the 10 nm and show a loose microstructure, with nanopores situated between the crystals. The surfaces of the pores are modified such that they could adsorb protein, due to the addition of silica molecules. Bone defects can be treated by using these hydroxyapatite nanoparticles [7]. An international co-funding arrangement in nano drug development will equally be a good step in expanding treatment [8].

1.1.3. Nanobots

Also known as nanorobotics, are robots of nanometer (10^{-9} m) scale, that has been applied in medicine for early diagnosis as well as targeted drug-delivery for treatment of cancer, pharmacokinetic monitoring of diabetes and healthcare. Nanobots dentrifices (dentifrobots), for instance, when used as mouthwash or toothpaste can cover all subgingival surfaces, thereby metabolizing any trapped organic matter into harmless and odourless vapors. Pathogenic bacteria that exist in dental plaque are identified and destroyed, using properly configured dentifrobots [9]. In fact, nanobots have been predicted to be injected into patients so as to perform work at the cellular level. Biochips and nubots are good examples of nanobots.

1.1.4. Nanowires

Nanowires (NW) are nanosized channels that allows passage of electrical current at very low amplitude and can be constructed from carbon nanotubes, metal oxides or silicon. Their very small size and minute diameter, usually 10nm, makes them sensitive to any minute change in electrical properties at any slight adjustment for example when an additional molecule is bonded to it. Antibodies could be attached to surface of nanowires and used as detectors such that when the antibodies interact with biomolecules of target, they undergo a conformational change which is picked up as electrical signal on the nanowire. Thus when several nanowires with different antibodies attached are integrated into a single device, they can be employed as detectors for diseases like cancers. Examples include Silicon nanowire (SiNW) used in sensors as Field Effect Transistors [10]. FET-SiNWs have been reportedly used to detect several prostate cancer biomarkers, such as PSA (Prostate-Specific Antigen) at very minute level and for monitoring prostate cancer, predicting earlier, before full manifestation, the risk of biochemical relapse. Furthermore, as published in literatures, using nanowire technology (seen in nCounter Analysis System), ribonucleic acid (RNA) expression levels of CTAs (cancer-testis antigens) have been measured, as biomarkers for aggressive prostate cancer. Nanowires of Silicon and Zinc oxide have also been used to detect ssDNA, because the binding of this negatively charged polyanionic macromolecule to p-type NW surfaces leads to an increase in conductance. These DNA biosensors have been used to detect mutations related with cancer types. For example, a nanowire platform functionalized with ssDNA detected the BRAF mutation for breast cancer [11] [12].

1.1.5. Quantum Dots

These are inorganic crystalline nanomaterials that are fluorescent. When irradiated with low energy light, quantum dots emit fluorescent light whose colour (or frequency) depends on the size of the dot. These dots of different size could be embedded into a given microbead, producing distinct spectrum of colours once excited. With just such simple excitation, high sensitivity and broad spectra of excitation is achieved which makes it quite useful in genotype determination, image guided surgery and molecular diagnostics. Quantum dots have been conjugated with other diagnostic techniques bringing together diagnostics and therapeutics. For instance, quantum dot can be linked covalently with fluorescence microscopy to observe cells in living animals; immunofluorescent labelling of breast cancer marker Her2 have been achieved with the specific cancer antibodies covalently linked to quantum dots covered by polyacrilate cap and quantum dots with detectable luminescence encapsulated in carbohydrate are useful in cancer imaging [13].

2. Available Nanoparticle-Based Platforms Employed in Nanodiagnostics

2.1. Nanotechnology Based Biochips; Nanofluidics Microarrays

Also called "lab on a chip", it is a modern technology of the severals for nanodiagnostics. It is a simple device (usually made of glass or silicon base) combining many processes for DNA analysis. The device is particularly designed to interact with cellular components with high level of specificity.

Composition: Lab-on-chip device usually consists of microfluidic channels that provide paths for biomolecules to flow to individual sensors or biosensors. Mainly it is composed of heater sensors for temperature, electrophoretic chamber, fluorescence detectors and fluidic channels that are microfabricated for analysing DNA samples of nano-litre size It is often used as a tool to analyse small and low concentration samples in order to achieve a complex laboratory function in biomedical applications..

Capability and Possiblities: Generally the DNA samples to be analysed may be completely unknown. Nanofluidics can analyse, measure biomolecules such as DNA from their containing solutions, mix the solutions, digest the DNA, forming discrete products and then separating (isolating) and detecting the products [3]. It is often used for analyzing small and low concentration samples to achieve complex laboratory information in biomedical applications [14] This new method of detection has driven the world economy for a decade and is still growing [15]. Systems biology, personalized medicines, detection of disease causing organisms and development of medicines are unique possibilities of nanofuidic technique [13].

Workings: On introduction of a DNA containing solution onto a fluid entry port, using a pipette and a reagent-containing solution on the other port, both solutions are drawn into the device by capillary action but are stopped by hydrophobic patches placed just beyond the point of vent in each injection channel. Air pressure lines placed throughout the device are necessary for measuring correct amount of DNA or reagent. The device can specifically separate cell contents, analysing any cell component present provided sample is fluid using the change in the current in the device as the DNA moves (Figure 2).

2.1.1. Protein Nanobiochips

These are based on protein binding silica-nanoparticles. Though still at the developmental stage, protein chips offer a lot of potentials.

Composition: protein nanochips capture proteins configured onto thin silica nano-particles, which may be arranged on layers.

Workings: protein antibodies and enzymes are immobilized as an array on glass slide by robot. The surface of the slide is probed with a sample of interest which binds to relevant antibody on the chips then analysed by a relevant method of detection. Molecular diagnostics and personalized medicine have been made possible with the help of miniature micro arrays which is a product of nanotechnology. Proteins on arrays on being profiled will be used to distinguish normal cell proteins from those of cancer cells at an early stage or those of metastatic malignant [13].

2.1.2. Microelectromechanical Systems (MEMS)

This nanodiagnostic tool is related to the microfluidics but does not require reagents or fluidy substrate as a base. Mainly, MEMS are used in recent drug deliveries but also employed in diagnostics as "smart" capsular pills to give the image of lumen of the gastrointestinal tract allowing medical practitioners to see the structures of the tract for possible diagnosis of bleeding, its site and potential cause.

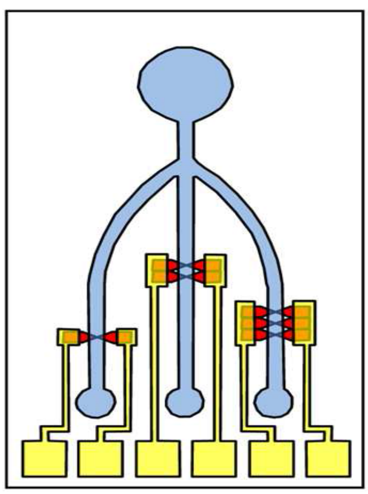

Figure 2. A lab-on-a-chip microfluidic device showing the inlet and outlets. (Source: Sharma *et al*., 2013 [15]).

Composition: MEMS come as capsules containing a light emitting diode, complementary metal oxide semi-conductor (CMOS) video camera, battery, and a transmitter.

Capability: with the aid of the capsular camera, image of the gastrointestinal lumen is taken and presented as moving pictures. A specific diagnosis of condition of the internal structures could be achieved with non-invasive methods. Gastric ulcers and tumors could be easily seen at their specific locations even at the stage of minute development.

Workings: A patient wears a belt which serves as a receiver for the transmission of images taken by the capsular camera that the patient must have swallowed. Movement of the capsule through the GIT is accompanied by pictures of the lumen taken by the 'smart' capsule and transmitted to the worn belt receiver. The images are projected on the screen to be seen by the expert. On seeing this, the medical Doctor can make inferences for possible diagnosis.

2.1.3. Nano Biosensors

These find a useful role in medical diagnosis because nanomaterials are chemically and biologically sensitive and have the ability to identify certain cells or some areas of the body.

Composition: these are made up of mainly a biological element (used for sampling), and physical element,(transducer for processing of sampling result).

Workings: Nanobiosensors, using indicators, are able to distinguish between cells and recognise certain cells especially cancer cells using perculiar biomolecules released or produced by such cells so that the rate of growth and development of such regions of the body is monitored as well as deliver specific medicines to such regions. Nanobiosensors could even work from outside the body, detecting large sized variations and signals are related to similar products within the body.

Capabilities: Using florescence properties of quantum dots of some metals such as Cadmium Selenide and Zinc sulphide, tumors within the body could be located by a medical practitioner by finding the fluoresced nanodot that was earlier injected. Cancerous tumors could be detected earlier by mere distinguishing between cells having a morphological or biochemical deviation from normalcy. Genetic defects could be recognized specifically and earlier due to its potential of detecting particular DNA. Literature has reported that researchers at Massachausset institute of technology (MIT) have discovered how to amplify weak biomarkers–peptides coated on nanoparticles which were released into the bloodstream by certain proteases that are often produced by cancer cells and then detected in urine [5].

2.1.4. Nanoscale Single-Cell Identification

This is an added application of nanotechnology. Employing nanolaser scanning confocal spectroscopy which has high single cell resolution, cancer cells having properties closely related to normal cells could be distinguished. Single cell protein could be detected using nanobiotechnology. Even little amounts of proteins in body fluids not identified by conventional methods could be identified by biobarcode assays.

3. Future of Nanotechnology Application in Medical Diagnosis

The constant giant strides recorded in the field of nanodiagnostics gives heightened hope for more possibilities. Such possibilities which are due to highly reduced-size particles, the high sensitivity of nanodiagnostics platforms, early detection of diseases and genetic dispositions at the molecular level using simple inexpensive rapid tests, and accurate imaging methods, have triggered the development of devices that can be used for accurate molecular diagnosis at point-of-care (POC). At present, available diagnostic technologies employ the principle of detecting biomarkers of various diseases. Hand held devices are in vogue, which are portable and easy to use, for instance Gluco-watch which can be used as a wrist watch has nano-chip biosensors that helps in monitoring of blood glucose. With such devices easily usable by some patients, hospital visits are reduced, physicians are eased, being under less pressure to concentrate with consequent improved practice. Medical practice is made easier with nanodiagnostics. Unlike now that Doctors have to order for medical tests to ascertain their educated guesses of a possible ailment, they can proactively prevent possible disease presentations employing the nanodiagnostic–based differentiation of diseases using DNA sequence analysis [3].

The avalanche techniques in Nanotechnology reveals how biological information can be acquired easily, quickly and inexpensively, then analyzed, thus enormously increasing the possibilities of achieving preventive medicine. With such move in medical diagnosis, therapy is becoming more specific and individualized with positive outcomes. In fact, therapy and diagnostics are increasingly fast becoming fused into a new specialist medical field designated *theranostics*; because the nanotechnology methods and medicines serve diagnostic and therapeutic purposes concomitantly. Examples are the contrast medium, made from nanoparticles, which brings with it directly the active substance in the event of a pathological tissue change and carrier systems which circulate preventively in the organism reacting to endogenous signals and automatically secrete active substances if needed. The production of nanomaterials which recognize cells and cell constituents, including individual genes, of impaired function and repair them of their own accord in the organism is also being researched [16].

Targeted transport of active substances can be used to introduce nucleic acids, DNA fragments and individual genes into tissue and cells by means of nanoparticles. In a cutting-edge animal study using rats biodegradable, polymeric gene delivery nanoparticles have been shown to effectively kill glioma cells in the brain and extend the survival of the animals [17]. This discovery makes possible for further early diagnosis of medical conditions having genetic predispositions

The advances in the unending possibilities of nanotechnology in diagnostic approaches however raise ethical concerns. One of such being, who should be in possession of the records of the total genetic sequence of an individual as analysed by nanodiagnostics? Should a medical practitioner or institution have in possession all the genetic information about an individual? What about Issues of leakage of medical information as an angle to be considered. Also what of cases of unscrupulous individuals having access to such genetic information? The use of MEMS device within the body is another area to be looked at. Should the capsule with the miniature nanotechnology embedded in it break down in the body, of what fate is the metal oxide with high risk of free radical released in the gastrointestinal tract?

4. Conclusions

There is more to nanotechnology and nanodiagnostics than mere discoveries in the laboratories and approvals by health institutions and authorities for use by consumers. Global coordination will be needed for establishing and maintaining international standards and nomenclature, toxicity testing, risk assessment and mitigation as well as public participation in achieving both benefits and safety, while reducing the gap between developing and developed countries is a necessity. This will enable internationally agreed concrete standardized characterization protocols for nanoscale items and products that can then be used with biological systems. Global coordination will also ensure monitoring for strict compliance with approved existing detailed well-established guidelines and specifications.

The future of nanotechnology and particularly nanodiagnostics is here! With proper attention to the associated ethical concerns and a global direction in establishment of international standards, the possibilities in this sphere of healthcare delivery will continue being in leaps and bounds.

Conflict of Interest

The authors declared no conflict of interest.

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