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## NANO THERANOSTICS – A BREAKTHROUGH IN CANCER DIAGNOSIS AND TREATMENT AND REGULATIONS OF NANO TECHNOLOGY PRODUCTS

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**ABSTRACT:** An object with at least one characteristic dimension between 1 and 100 nm can be defined as “nanomaterial”. The unbelievable development of nanotechnology in the last 30 years has allowed the release of new and efficient synthetic routes towards the production and functionalization of different NPs, composed of a variety of materials including noble metals (*e.g.* gold and silver), semiconductors, TiO<sub>2</sub>, magnetic compounds and their combinations, such as core-shell and alloy. Advances in nanoparticle synthesis and engineering have produced nanoscale agents affording both therapeutic and diagnostic functions that are often referred to by the portmanteau 'Nanotheronostics'. The field is associated with many applications in the clinic, especially in cancer management. These include patient stratification, drug-release monitoring, imaging-guided focal therapy and post-treatment response monitoring NPs which is clearly elaborated in this work. Intelligent nanotheronostics based on bio responsive systems have recently emerged and offer the promise of high specificity and efficiency *via* "on-demand" activation of both therapeutic and diagnostic capabilities are being widely used for cancer diagnostics. As this development is very sensitive in terms and diagnosis and treatment proper regulations have been implemented in several countries and the regulations in few of the developed countries have been discussed in this article.

**INTRODUCTION:** Theranostics<sup>1</sup> is a novel multifunctional approach that describes any “material that combines the modalities of therapy and diagnostic imaging” into a single package. Nanotheronostics can deliver treatment while simultaneously monitoring therapy response in real-time, thereby decreasing the potential of over- or under-dosing patients.

Polymer-based nanomaterials, in particular, have been used extensively as carriers for both therapeutic and bioimaging agents and thus hold great promise for the construction of multifunctional theranostic formulations

### Advantages of Nanotechnology in Cancer Treatment:<sup>2</sup>

1. The ultra-small size of the nanoparticles enables them to escape clearance by kidneys
2. They easily permeate through the abnormally leaky blood vessels of tumor tissues and accumulate inside the cells.
3. Their high surface area increases their loading capacity for therapeutic and imaging agents.

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4. They have the ability to selectively accumulate in the diseased tissues.
5. They are safe and can undergo biodegradation into non-toxic by-product<sup>3</sup>.
6. They increase the time period in which a drug remains active in the body.
7. They can also lead to reduction in the drug volume and also site specificity, avoids the problem of accumulation in healthy tissues.
8. They provide the capacity for the personalized medicine, as the drug therapeutic efficacy can be easily monitored as the nanoparticle contains both drug and imaging elements in them<sup>4</sup>.

### Types of Nano Sized Vehicles that are used for Theranostic Applications:

#### 1. Gold and Iron oxide Nanoparticles:<sup>5</sup>

Attractive for their size, stability, and biocompatibility, gold nanoparticles (NPs) continue to gain interest due to their potential to enhance a number of biomedical applications. More importantly, the ability to functionalize the surface of gold with organic molecules allows for the preparation of nanoparticles which can specifically interact with any physiological system polymer-functionalized metallic nanoparticles featuring a gold core are, in fact, suitable for traditional characterization methods in solution and, therefore, present an attractive opportunity for manufacturing drug delivery vehicles with tuneable properties. Jacob *et al.*, developed a 2nm gold nanoparticles of paclitaxel with the attachment of a flexible hexaethylene glycol linker at C-7 position of paclitaxel followed by coupling of the resulting linear analogue to phenol-terminated gold nanocrystals<sup>5</sup>. The synthetic strategy yielded a hybrid structure with an extremely high content of organic shell (67 wt. %), a narrow polydispersity index (1.02), and a well-defined number of drug molecules ( $73 \pm 4$ ) per metallic particle. This well-defined chemical structure of drug-functionalized nanoparticles may allow one to more accurately define their efficacy and therapeutic utility.

2. **Quantum Dots(QD's):**<sup>6</sup> Quantum dots (QD) are very small semiconductor particles, only several nanometres in size, so small that their optical and electronic properties differ from those of larger particles. They are a central

theme in nanotechnology. Many types of quantum dot will emit light of specific frequencies if electricity or light is applied to them, and these frequencies can be precisely tuned by changing the dots' size, shape and material, giving rise to many applications.

Tamara *et al.*, formulated a tumor-targeted, pH-responsive quantum dot-mucin1 aptamer doxorubicin (QD-MUC1-DOX) conjugate for the chemotherapy of ovarian cancer. The conversion of doxorubicin to quantum dots provided the stability of complex in the systemic circulation and drug release in the acidic environment inside cancer cell. As the quantum dots possess fluorescence behaviour, the efficacy of the treatment can be visualized by fluorescence imaging<sup>7</sup>.



FIG. 1: QUANTUM DOTS WITH GRADUALLY STEPPING EMISSION FROM VIOLET TO DEEP RED ARE BEING PRODUCED IN A KG SCALE AT PLASMA CHEM DMBH<sup>8</sup>

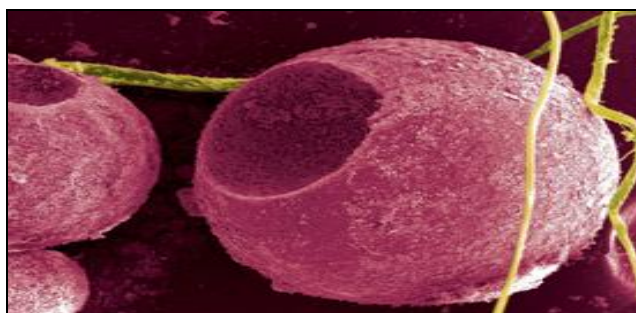


FIG 2: CADMIUM SULPHIDE QUANTUM DOTS ON CELL<sup>9</sup>

3. **Carbon Nanotubes:**<sup>10</sup> A carbon nanotube is a tube-shaped material, made of carbon, having a diameter measuring on the nanometre scale. A nanometre is one-billionth of a meter, or about 10,000 times smaller than a human hair. CNT are unique because the bonding between the atoms is very strong and the tubes can have extreme aspect ratios. A carbon nanotube can be as thin as a few nanometres yet be as long as hundreds of microns. To put this into

perspective, if your hair had the same aspect ratio, a single strand would be over 40 meters long.

There are many different types of carbon nanotubes, but they are normally categorized as either single-walled (SWNT) or multi-walled nanotubes (MWNT). A single-walled carbon nanotube is just like a regular straw. It has only one layer, or wall. Multi-walled carbon nanotubes are a collection of nested tubes of continuously increasing diameters. They can range from one outer and one inner tube (a double-walled nanotube) to as many as 100 tubes (walls) or more. Each tube is held at a certain distance from either of its neighbouring tubes by interatomic forces.

Hongjie *et al.*, formulated a Polyethylene glylated single wall nanotubes loaded with Doxorubicin by supramolecular  $\pi$ - $\pi$  stacking. They found that the use of high pressure carbon monoxide on the single wall nanotubes increased the binding energy of doxorubicin on nanotubes approximately 48 kJ/mol in water and the stacking of carbon nanotubes provided higher drug loading capacity. The increase in the size provided added advantage by reducing the renal clearance of the drug and increase in the residence of drug in the systemic circulation<sup>11</sup>.

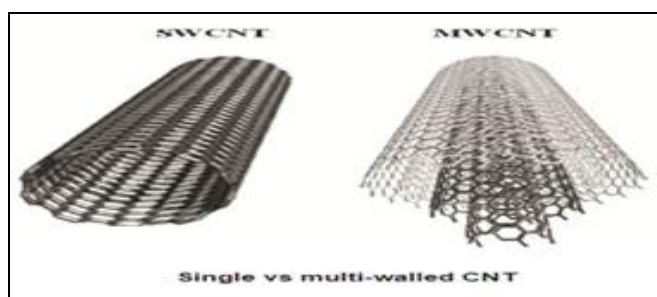


FIG. 3: SINGLE AND MULTIPLIED WALL CARBON NANO TUBES

**4. Liposomes** Liposomes are small spherical shaped vesicles consisting of one or more phospholipid bilayers. The most commonly used phospholipid in the preparation of liposomes are polyethylene glycol and phosphatidylcholine<sup>12</sup>. Polyethylene glycol (PEG) exhibit stealth effect as they are electrically neutral and is not recognized by the

reticuloendothelial cells (RES) of liver or spleen. Due to stealth effect, the liposomal drugs exhibit reduced clearance and prolonged plasma half life<sup>13</sup>.

Yoshihisa *et al.*, studied the stability and biological behaviour of *in vitro* system of doxorubicin entrapped in doxil, polyethylene glycol conjugated liposomes was examined and compared with those of DXR entrapped in the NK911, polymer micelles. According to their findings, the PEG-liposomes localize immediately only around the tumor vessel after extravasation, which was absent in case of normal tissues. Thus the liposomes possess the ability to deliver anticancer drug more efficiently<sup>13</sup>.

#### 5. Polymer Based Nanoparticles:

Polymer is a large molecule composed of repeating units organized in a chain like molecular architecture exhibiting a multiplicity of compositions, structures and properties. Natural polymers such as chitosan, albumin and heparin have been used for the delivery of drugs<sup>14</sup>. The synthetic polymers include polycyanoacrylate (PCA), poly-D,L- glycolide (PLG), poly(lactic acid) (PLA), poly(lactide-co-glycolide) (PLGA), poly(isohexyl cyanoacrylate) (PIHCA) or polybutyl cyanoacrylate (PBCA) are the most commonly used polymers in the synthesis of nanoparticles<sup>12</sup>.

Polymer based nanoparticles are usually preferred as they have good control over size and size distribution. It has low toxicity and provide large surface area for faster dissolution of active agents in aqueous environment<sup>15</sup>.

**6. Solid Lipid Nanoparticles (SLNs):** SLN are particles with a solid lipid matrix with an average diameter in the nanometre range. In addition to lipid and drug, the particle dispersions contain surfactants as stabilisers. SLNs have advantages of protection of liable drugs from degradation, physical stability, easy preparation, maximized drug availability at the site of tumour cell and minimize the systemic drug toxicity<sup>16</sup>. Wong, H. L., *et al.*, published a review which focuses on the current use of SLN

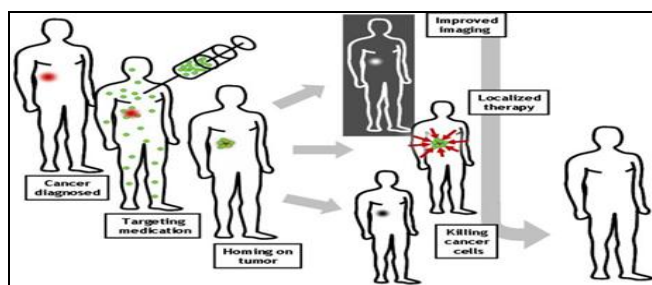


for the encapsulation and delivery of cytotoxic anticancer compounds. It also discusses more recent trends in the use of SLN as vehicles for delivery of chemosensitizers and cytotoxic therapeutic molecules. It is anticipated that, in the near future, SLN will be further improved to deliver anticancer compounds in a more efficient, specific and safer manner<sup>16</sup>.

- 7. Dendrimers:** Dendrimers are nano-sized, hyper branched, radially symmetric molecules with well-defined homogenous and monodisperse structure that has typically symmetric core, an inner shell and an outer shell. Dendrimers having promising potentials to perform controlled and specified drug delivery. The drug dendrimer conjugate has high solubility, reduced systemic toxicity and selective accumulation in the tumour cells<sup>17</sup>.

## Nanotheranostics in Cancer Diagnosis and Treatment:

**1. Molecular Imaging and Therapy:**<sup>18</sup> A sophisticated nano constructs with thousands of pores that can hold the anti-cancer drug molecules were built. The ends of the pores are capped with nano-valves that keep the drug molecules contained until they are activated by light. The nano-particles are made of mesoporous silica and they are fluorescent. Hence, they can be monitored by molecular imaging techniques during their passage towards the tumour cells. When the nano-particles are exposed to the high-power two-photon laser light, the nano-valves open up and release the drug molecules. At the same time, at low power the laser light helps to image the cells. The researchers tested these devices on breast cancer cells in culture and obtained positive results. They reported that this technique would help in targeted treatment of breast cancers, colonic cancers and ovarian cancers with nil effects on healthy tissues.



**FIG. 4: IMAGE DEMONSTRATING MOLECULAR IMAGING AND THERAPY**

**I. Polymer based Nanotheranostics for Cancer Treatment and Diagnosis:**<sup>19</sup> In particular, polymeric nanoparticles are able to enhance drug efficacy compared with free drugs via improved drug encapsulation and delivery, prolonged circulation half-life, and sustained or triggered drug release<sup>20</sup>. Polymeric nanoparticles are also able to accumulate at specific disease sites through passive targeting by the enhanced permeability and retention (EPR) effect, or through active targeting by the incorporation of targeting moieties specific for a receptor or cell surface ligand at the region of interest. As there is a lot of progress that is being made in the therapeutic polymeric nanoparticles, researchers are now incorporating clinically used imaging modalities into therapeutic nanocarriers.

Few of them are:

- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
- Single photon emission computed tomography (SPECT)
- Fluorescent agents for fluorescent imaging
- Nano/ microbubbles for ultrasound imaging

**a) Drug Delivery and MRI:** Most commonly used technique used to analyse the tissues. A magnetic field of appropriate resonant frequency is applied to excite the hydrogen atoms in the tissues. A radiofrequency signal is emitted by the excited hydrogen atom while returning to its ground state. The contrast would be made between the tissues as the hydrogen atoms in different tissues relaxes at different rates various superparamagnetic metals are commonly employed as contrast agents for MRI. SPIO and gadolinium (Gd) are most often utilized. Interaction of SPIO and Gd an external magnetic field to improve the visibility of internal structures by altering the relaxation times of atoms in tissues where they are present. Polymeric nanoparticles have been shown to be effective carriers of both SPIO and Gd<sup>21</sup>.

**Steps:**

1. SPIO is used as a T2-Contrast enhancement agent. The T2 weighed images are the basic

pulse sequences in MRI. It highlights the differences between the relaxation times of the tissues. T2-weighted images are often used to study pathology as fluid appears bright against the darker normal tissues<sup>22</sup>.

2. Several polymer-based SPIO-containing drug delivery systems have been developed as nano spheres, micelles, nanogels, and polymersomes which offer narrow particle size distribution, biocompatibility, good stability, prolonged blood circulation times, high drug loading, and control over drug release rate, in addition to superparamagnetic behaviour for MRI contrast.
3. For example, SPIO and chemotherapy drug doxorubicin (DOX) can both be directly encapsulated by using an amphiphilic block copolymer composed of maleimide-PEG-poly (lactic acid). This block copolymer self-assembles into nanoparticles with functionalize maleimide groups on the surface, which allows for further conjugation of targeting peptides<sup>23</sup>. In tumor-bearing mice, these targeted theranostic nanoparticles showed increased tumor-specific accumulation and enhanced inhibition of tumor growth

#### b) Drug Delivery and Radio Nucleoside Imaging:

- Radio nucleoside imaging is also used in medicine to image the extent of disease development based on cellular metabolism and physiology within the body, instead of than relying on physical changes in tissues like MRI. Similar to MRI, radionuclide imaging has high sensitivity with no tissue penetration limitations.
- Radioisotopes such as <sup>11</sup>C, <sup>18</sup>F, <sup>64</sup>Cu, <sup>76</sup>Br, <sup>99m</sup>Tc, <sup>111</sup>In, and <sup>90</sup>Y are administered intravenously or orally. Gamma cameras are then used to capture and create images from the radiation emitted by the internalized radionuclides.
- Lammers *et al.*, have also taken advantage of HPMA to load <sup>131</sup>I, along with antitumor agent doxorubicin or gemcitabine, to study the dual imaging and therapeutic capabilities of drug- and radionuclide loaded polymeric nanocarriers<sup>24</sup>.

- These polymeric drug carriers demonstrated prolonged circulation time and selective accumulation in the tumor site. The two components acted synergistically to increase the therapeutic efficacy against the tumor.
- As external beam radiotherapy can now a day be delivered with extremely high levels of spatial specificity this is likely mostly due to the low degree of spatial specificity that chemotherapeutic agents generally present upon intravenous (I.V) administration<sup>25</sup>.
- Thus, combining both chemotherapy and radiotherapy into a single nanocarrier can be an effective method to combat solid tumors.

Few other techniques that are being used for diagnosis are:

- c) Drug Delivery and Fluorescence Imaging<sup>26</sup>
- d) Drug Delivery and Ultrasound Photo acoustic Imaging<sup>27</sup>

**3. Combined Gene Therapy and Imaging:**<sup>27</sup> In general, there are two types of polymer systems currently in use for gene delivery. In the first, polymer carries the genetic material (*i.e.*, is loaded within the nanoparticle). In the second, a cationic polymer is complexed with the genetic material to form a polyplex. Ultimately, the genetic material must be able to cross the cell membrane barrier and be transported into the nucleus to have a therapeutic effect.

- a. Gene therapy and MRI
- b. Gene Delivery and Radio Nucleoside Imaging
- c. Gene Delivery and Fluorescence Imaging

**Combined Photo Dynamic Therapy and Imaging:** Unlike gene delivery photodynamic therapy (PDT) achieves its therapeutic effect via a different mechanism. The targets would be destroyed by the anticancer drugs rather than delivering rather than delivering. It kills target cancer cells in the presence of oxygen via the release of reactive oxygen species upon light activation of a photosensitizer and it's a minimally invasive technique. The cancer cells would be destroyed through direct cellular damage, vascular shutdown, and induction of the host immune response against the target cells<sup>28</sup>.

## II. Nanomaterial-based Microfluidic Chips for the Capture and Detection of Circulating Tumor Cells:

Circulating tumor cells (CTCs) are the type of cancer cells that spreads from primary or metastatic tumors into the bloodstream which may lead to a new fatal metastasis. The low sensitivity and selectivity and the high detection cost and complicated detection process made is a big challenge for the capture and detection of CTC<sup>29</sup>.

Hence, it is necessary to perform advanced material interfaces to improve efficient capture and sensitive detection of rare CTCs for clinical cancer studies and applications. Microfluidic chip has become one of the mainstream technologies for CTC study due to some advantages including miniaturization, portability, cost-effectiveness and abilities of single cell analysis and online isolation/detection<sup>31</sup>.

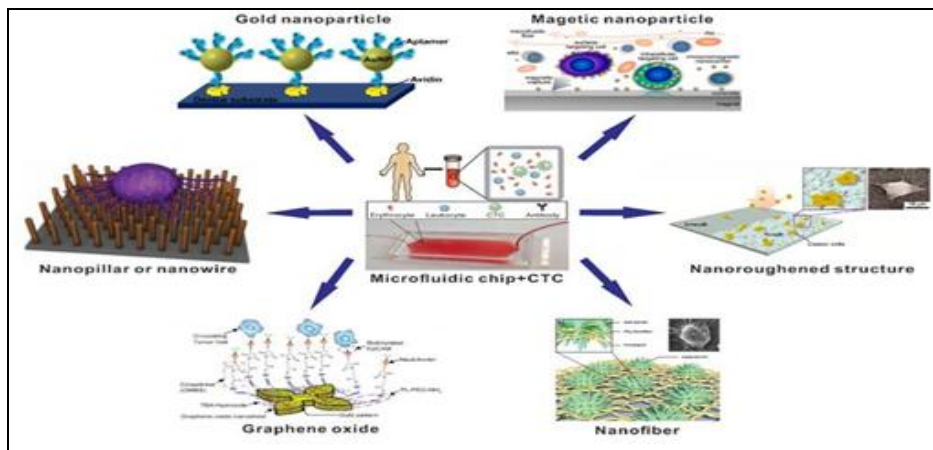


FIG. 5: SCHEMATIC ILLUSTRATION OF NANO-MATERIAL-BASED MICROFLUIDIC CHIPS

### Types of Targeting Agents:

Targeting agents are classified as follows:

1. Proteins (mainly antibodies and their fragments)
2. Nucleic acids (aptamers), or
3. Other receptor ligands (peptides, Vitamins, and carbohydrates).

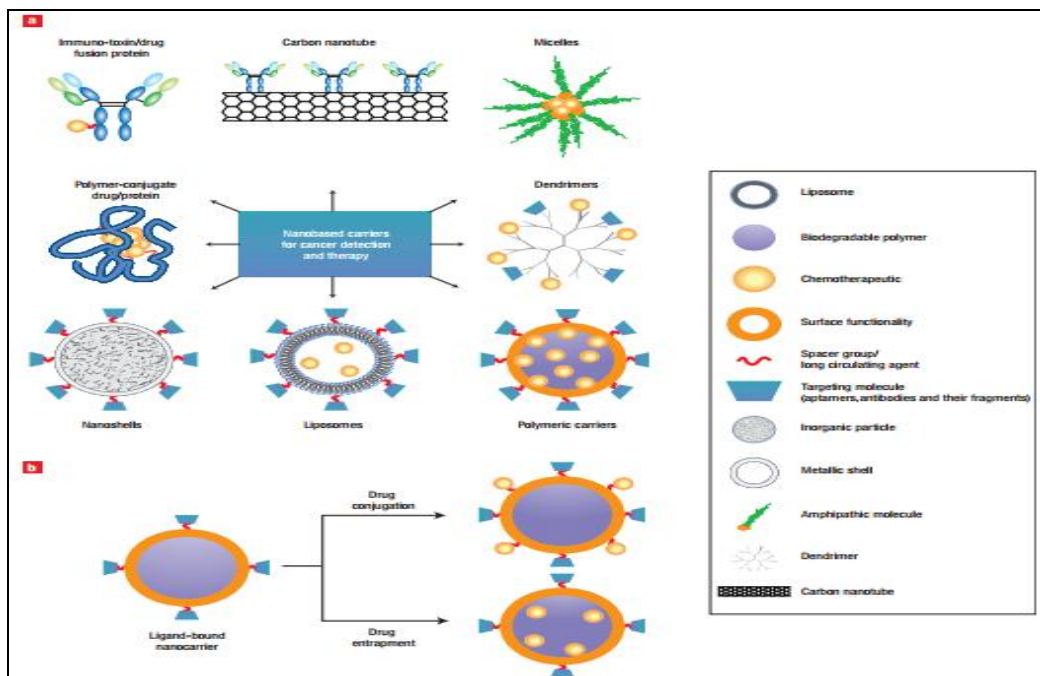


FIG. 6: EXAMPLES OF NANOCARRIERS FOR TARGETING CANCER. A) A WHOLE RANGE OF DELIVERY AGENTS ARE POSSIBLE BUT THE MAIN COMPONENTS TYPICALLY INCLUDE A NANOCARRIERS, A TARGETING MOIETY CONJUGATED TO THE NANOCARRIERS, AND A CARGO (SUCH AS THE DESIRED CHEMOTHERAPEUTIC DRUGS)

Schematic diagram of the drug conjugation and entrapment processes. The chemotherapeutics could be bound to the nanocarriers, as in the use of polymer drug conjugates, dendrimers and some particulate carriers, or they could be entrapped inside the nanocarriers<sup>32</sup>.

**Nanotechnology based Detection and Separation of Circulating Tumor Cells:**<sup>33</sup> Circulating tumor cell (CTC) detection from blood, often as referred to “liquid biopsy”, has attracted a great deal of scientific and clinical interests, particularly because this method can be potentially used to diagnose metastatic cancer and to monitor the disease progress without invasive tissue biopsy.

Cell Search™, ISET™, and CTC-chip are three CTC detection methods that are in advanced stages of clinical translations. In many of the emerging CTC detection techniques, nanomaterials, such as gold nanoparticles, magnetic nanoparticles, quantum dots, graphene's/graphene oxides, and dendrimers/stimuli-responsive polymers, have played a central role in the enhancement of immunoaffinity-based detection of CTCs.

#### **Nanotechnology used in CTC detecting platforms:**

**1. Gold Nano particles:**<sup>34</sup> Enhanced light absorption and scattering properties of gold nanoparticles have been employed in detecting CTCs as the binding between gold nanoparticles and CTCs can be quantitatively measured via photoacoustic signals or surface plasmon resonance (SPR) shifts. A variety of gold nanoparticles, such as gold nanospheres, nanorods, and Nano shells, can be prepared and integrated with targeting ligands, imaging labels, therapeutic drugs, and other functionalities.

**A. Gold nanoparticles for CTC targeting *in vivo*** CTCs in blood stream can be targeted *in vivo* by injecting nanomaterial's targeting CTCs, enabling *in situ* monitoring of the number of CTCs. The real-time CTC monitoring *in vivo* eliminates the necessity of blood sampling, sample preparation, or CTC isolation, and induces the phagocytic clearance of CTCs upon binding.

**B. Gold nanoparticles for CTC capture *ex vivo*:** Nanoparticles functionalized with targeting ligands for CTCs can be used *ex vivo* either to directly bind to and separate the CTCs in blood samples or to functionalize a surface to capture CTCs from blood. The CTC detection *ex vivo* has advantages including the potentially enabled post-capture analysis after cell culture and zero risk of potential toxicity of the CTC-capturing nanoparticles to the patients.

**2. Magnetic nanoparticles (MNPs):**<sup>35</sup> One of the commonly used strategies to isolate CTCs is to utilize MNP complexes that bind to the cells for *in vivo* and *in vitro* separation under a magnetic field. MNPs are composed of magnetic elements, commonly iron, nickel, cobalt and their oxides such as magnetite (Fe<sub>3</sub>O<sub>4</sub>), maghemite (γ-Fe<sub>2</sub>O<sub>3</sub>), cobalt ferrite (Fe<sub>2</sub>CoO<sub>4</sub>), and chromium dioxide (CrO<sub>2</sub>)<sup>1</sup>. Among iron oxide MNPs that are chemically stable, biocompatible MNPs such as magnetite (Fe<sub>3</sub>O<sub>4</sub>) have been most commonly used in biological applications. Superparamagnetic MNPs display the features with a fast response to applied magnetic fields with negligible remanence (residual magnetism), which is attractive for a broad range of biomedical applications to prevent agglomeration at room temperature.

**A. MNPs for CTC capture *ex vivo*:** MNPs containing CTC-targeting molecules have been used for CTC detection upon mixing with blood specimens drawn from patients. Cell Search™ is based on iron oxide (Fe<sub>3</sub>O<sub>4</sub>, Ferrofluid™) MNPs coated with antibodies (anti-EpCAM) against CTC surface markers (EpCAM) through polymeric linkers. Upon binding to CTCs in blood specimens, the MNPs bound to CTCs can be isolated by magnetic active cell sorting (MACS) upon applying an external magnetic field.<sup>36</sup> This Cell Search™ approach has been used as a diagnostic and prognostic test, monitoring CTCs in blood from patients with various types of cancers, such as breast,



prostate, colorectal, pancreatic, gastrointestinal, and small lung cancer<sup>37</sup>.

### B. MNPs combined with Other Strategies for *ex vivo* CTC Capture:

The fluorescent-magnetic bifunctional nanoparticles composed of MNPs and optical components, such as fluorescence dyes, quantum dots (QDs), or X-ray contrast agents, are of particular interest in multimodal imaging. By means of encapsulation, direct reaction, and inorganic synthesis, magnetic-optical bifunctional nanoparticles with different structures have been prepared and successfully applied for multimodal imaging. Fluorescent-MNPs can be used for the simultaneous detection and isolation of multiple types of tumor cells. For instance, anti-CD3- and anti-PSMA-conjugated MNPs were labeled with red and yellow fluorescence dyes to target leukemia Jurkat T cells and prostate LNCaP cancer cells, respectively<sup>38</sup>.

### 3. Quantum Dots(QDs) and Other Fluorescent Nanomaterial's:

QDs, based on their strong fluorescence intensity, present a unique opportunity to isolate CTCs in a quantitative manner. Colloidal QDs made of ZnS, CdS, ZnSe, CdTe and PbSe, emit a wide spectrum of fluorescence ranging from ultraviolet (UV) to infrared (IR). Compared to other fluorescence dyes, QD properties of interest include high quantum yield, high molar extinction coefficients (around 10-100 folds higher), broad absorption with narrow, symmetric photoluminescence spectra, the ability to size-tune the photoluminescence emission, high resistance to photo bleaching, and exceptional resistance to photo- and chemical degradation<sup>39</sup>.

- a. QDs for CTC capture *ex vivo*
- b. Fluorescence-labelled nanoparticles for CTC capture *in vivo*

### 4. Graphene and Graphene oxides:<sup>40</sup> Graphene is an atomically thick, two-dimensional (2-D) sheet of sp<sup>2</sup> hybridized carbon arranged in a honeycomb structure. Graphene is the basic building block for graphitic materials of all other dimensionalities: graphite (3-D carbon allotrope of graphene sheets stacked on top of

each other and separated by 3.37 Å) and carbon nanotubes (CNT, 1-D carbon allotropes). Graphene has numerous extraordinary physicochemical properties, such as high theoretical specific surface area (2,630 m<sup>2</sup>g<sup>-1</sup>), high intrinsic mobility (200,000 cm<sup>2</sup> v<sup>-1</sup>s<sup>-1</sup>), strong mechanical strength (high Young's modulus, ~1.0 TPa), and excellent thermal conductivity (~5,000 Wm<sup>-1</sup>K<sup>-1</sup>), along with its optical transmittance (~97.7% opacity) and electrical conductivity. As charge transfer between the adsorbed molecules and graphene is responsible for the chemical response, graphene has shown excellent performance in electrochemical detection of small biomolecules. As a result, graphenes and its oxidized form graphene oxides (GO) dispersed on materials or devices have been investigated as a platform for electrical detection of CTCs.

### A. Graphene / GO for CTC capture *ex vivo*:

The fluorescence quenching properties of GO have increasingly been used in optical bio sensing applications and applied for the CTC capture. Ionic hydroxyl and carboxyl groups of GO allow for formation of molecular complexes and electrostatic interactions with charged molecules, while its aromatic sp<sup>2</sup> domains facilitate pi-pi stacking and fluorescence quenching. The quenched fluorescence gets recovered upon interaction of a targeting biomolecule with a target protein on a cell membrane, which is the basis of several detection and imaging applications using GO.

### 5. Dendrimers and Stimuli Responsive Polymers:

Recent advances in polymeric nanomaterials have enabled to design biomedical devices with significantly improved functions. For example, multivalent binding that occurs in a variety of physiological processes has been exploited to significantly increase the sensitivity and selectivity of detection assays. Dendrimers offer a unique opportunity to precisely control the multivalent binding effect with their unique properties obtained from their well-defined chemical structure and a high density of peripheral functional groups. Another promising approach is to use stimuli-responsive polymers for CTC capture and release. Stimuli-



responsive polymers have been used to release the captured CTCs upon exposure to various stimuli, such as light, temperature, pH, and physical stress. In this section, these polymer-based approaches in CTC detection will be discussed<sup>41</sup>.

**A. Dendrimers for CTC capture *ex vivo*:** The binding strength between CTCs and a capture surface can be enhanced through dendrimer-mediated multivalent binding effect, which can significantly improve the sensitivity and selectivity of the surfaces for CTC detection. Dendritic nanomaterials, such as poly (amidoamine) (PAMAM) dendrimers, have been demonstrated to effectively mediate multivalent binding effect due to their capability to preorganized/orient ligands, polymer backbone topology, and easy deformability<sup>42</sup>.

#### **Regulation of Nano Medicines:**

**USA:**<sup>43</sup> The nature of nanotechnology makes it difficult for one agency to regulate all nano research and applications. Therefore, multiple federal agencies regulate products that may employ nanotechnology or nanomaterial's, but there is no comprehensive regulatory framework. With this piecemeal approach, it is likely that certain technologies or products will not be fully regulated by any agency. Even though the FDA, for instance, typically regulates cosmetic products "the agency may have limited authority over the use of nanotechnology related to those products"

Though FDA has not identified specific safety issues regarding Nano technology in regulated products, it has an agenda to help understand how the changes in the physical, chemical and biological properties affect the safety, efficacy and performance of a product containing nano materials.

The FDA Nanotechnology Task Force, formed in 2006, had the mandate of identifying and addressing ways to evaluate the potential effects on health of FDA-regulated nanotechnology products. In 2007, the task force recommended that the agency issue guidelines to industry and take steps to address the potential risks and benefits of drugs,

medical devices, cosmetics and other products that incorporate nanotechnology. In June 2011, FDA published a draft guidance, Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, as a starting point for the nanotechnology discussion.<sup>27</sup> Based on its current scientific and technical understanding of nanomaterials and their characteristics, the agency is proposing certain points it will use to determine whether an FDA-regulated product contains nanomaterials or otherwise involves the use of nanotechnology.

FDA has issued several guidance's regarding agency's current thinking regarding the use of nanotechnology or nanomaterials in FDA-regulated products:

1. Final guidance for Industry – considering whether an FDA regulated product involves the application of Nano technology.
2. Final guidance for Industry-Safety of Nano Medicines in Cosmeceutical products
3. Final guidance for Industry-Assessing the effects of significant manufacturing process changes, including emerging technologies in the safety and regulatory status of food ingredients and food contact substances, including food ingredients that are colour additives.

#### **Nano Regulation:**

**2007-** Report on Nanotechnology and Life Cycle Assessment released (2007-03-20)

**2008-** Final framework document for the nanotechnology stewardship program released by EPA (2008-01-28)

ASTM Committee E56 on Nanotechnology (2008-03-15)

**2009** - Research strategy to study nanomaterials announced (2009-09-29)

**2010** - ASTM – E56 American Society for Testing Materials International Committee on Nanotechnology (2010-06-01) Developments in Nanotechnologies Regulation and Standards 2010 (2010-06-01)

Under Toxic Substances Control Act, Nanomaterials classified as new substances are subjected, as any other new chemical, to a pre-manufacture review process (premanufacturing

notification – PMN), to identify and assess risks of the substance considered. (2010-06-01)

**2011** - Significant New Use Rule for Multi-Walled Carbon Nanotubes issued (2011-05-06)  
NNI Releases 2011 EHS Research Strategy (2011-10-20)

SNURs for 17 Chemicals including CNTs proposed (2011-12-28)

**2012** - Draft Guidance Documents on Nanomaterials released by FDA (2012-04-20)  
Federal Advisory Council on Occupational Safety and Health considers Dispersible Engineered Nanomaterials (2012-05-03)

**European Union:** <sup>44</sup> ‘Nanomaterial’ means an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.

There is a wide range of Community legislation related to issues relevant for nanotechnology and nanomaterial’s, currently in existence or being elaborated. These issues primarily have to do with risk assessment.

EMA and the National Agencies provide customized advice sessions for applicants which are dutiable. EMA, for example, has an Innovation Task Force which is happy to learn and discuss about general very new nanotechnological and biomaterial developments.

Medicinal products marketed in the European Union are covered by comprehensive EU legislation: Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2003/94/EC, Directive 2003/63/EC. All medicinal products marketed in the European Union must obtain an EU product authorization. Directive 726/2004 lays down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishes a European Medicines Evaluation Agency (EMA).

The European regulatory system for medicinal products offers two routes for authorizing medicinal products:

A “centralized procedure”

A” mutual recognition” procedure

There is extensive regulation on areas where nanomedicine is used in products. Medicinal products and medical devices are subject to strict rules. Cosmetics are also subject to rules requiring inter alia risk assessment, but without verification of the manufacturer’s risk evaluation. These provisions will probably embrace the products for which nanomedicine is being used.

The European Medicines Agency’s scientific guidelines on nanomedicines help medicine developers prepare marketing authorization applications for human medicines.

#### **EMA has Published 4 Reflection Papers on Nanomedicines:**

1. Data requirements for intravenous iron-based Nano-colloidal products developed with reference to an innovator medicinal product.
2. Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product.
3. Development of block-copolymer-micelle medicinal products.
4. Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products.

**Responsible Nano Code:** The aim of the ‘Responsible Nano Code’ as stated in its text is to “[...] establish a consensus of good practice in the research, production, retail and disposal of products using nanotechnologies and to provide guidance on what organizations can do to demonstrate responsible governance of this dynamic area of technology.

**Code of Conduct for Responsible Nanotechnology:** (‘Responsible Nano Code’) with the following aims

- Establish what is good practice for companies and other organizations involved in nanotechnologies
- Develop a code which is: International in scope, for adoption by companies and other organizations, large and small for adoption by companies and other organizations, large and small.

The resulting Responsible Nano Code consists of 7 key principles:

**EU –Nano Regulations:**

**2005** - Risk assessment methodology for nanomaterials reviewed by the Scientific Committee (2005-04-28)

**2006** - Opinion on nano sciences and nanotechnologies: An action plan for Europe 2005-2009 published

**2008** - Regulation of nanoscale silver products as pesticides demanded (2008-11-19)

**2009** - Report on Nanomaterials under REACH published (2009-11-17)

**2010** - Final SCENIHR opinion for a definition of "nanomaterial" adopted (2010-12-08)

**2011** - National Action Plan to focus on nanomaterials (2011-03-10)

Report on nanomaterials in consumer products released (2011-05-02). European Commission publishes final Reports on REACH Implementation Projects on Nanomaterials (RIP-oN) (2011-10-18) Guidance document on the safety assessment of nanomaterials in cosmetics (2011-10-07) "Nanomaterial" defined (2011-10-20)

2012 - Registration of nanomaterials guided by ECHA (2012-04-30)

Consultation on safety, health and environmental effects of nanosilver launched by SCENIHR (2012-04-01)

**Regulations and Current Initiatives in Japan for Nano Medicines:** “Nanomaterial” refers to, among solid materials manufactured using elements, *etc.* as a raw material, a nano-object with at least one of the three dimensions of approximately 1nm- 100nm and a nano-structured material composed of nano-objects (including matter composed of aggregated /agglomerated nano-objects).

**Regulation by MHLW/PMDA:**

1. Review and confirmation of quality, safety and efficacy for each product. GMP/GLP/GCP/GPSP inspections and conformity audits by PMDA
2. Manufacturing/Distributing business license and approval of manufacture and distribution by MHLW.

3. Report of any adverse events after marketing of the product.
4. Re-examination and re-evaluation.

Nano Medicine have been regulated within a general framework of Pharmaceutical Affairs Law on a product by product basis. At present there are no specially designed regulations for nanomedicines.

The MHLW is supporting the research activities with respect to Nano-Medicines

Science and technology basic law, with an objective of science and technology to contribute to the development of the economy and society of Japan so on.

4 areas of promotion are:

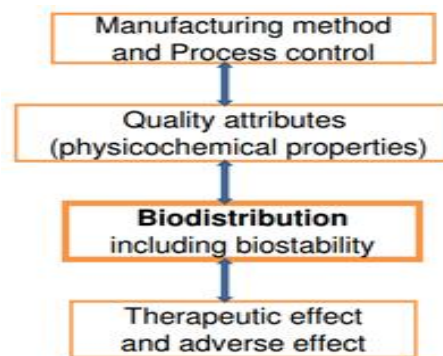
- Nanotechnology and Materials
- Life Science
- IT
- Environment Science

In the Second Science and Technology basic plan: The main objective was the promotion of Nanotechnology application to medicine.

1. Health and Labour sciences grants (2002) For therapeutic and diagnostic applications of Nano Medicine.
2. Collaboration with other ministries concerning to Nano Medicine  
Nanotech DDS Work group  
Council of Science and Technology Policy, Cabinet office inter-ministry projects.

**Research activities of Nano Medicine and Nanomaterials at MHLW/NIHS:**

Nano Medicine are mainly developed for control of bio distribution of APIs



**Japan:**<sup>45</sup>

**2009** – Notification on precautionary measures of exposure *etc.*, to Nanomaterials.

**2010** - JISC/CNSJ - Japan Industrial Standards Committee - Council on Nanotechnology Standards in Japan (2010-06-01): They are drafting an International Standardization Roadmap for Nanotechnology along with the Nanotechnology Business Creation Initiative (NBCI). 2011 5 year project on toxicity test protocols and risk assessment methodologies for manufactured nanomaterials (2010-06-01): At the institutional level, the Ministry of Economy, Trade and Industry (METI) is conducting a 5 year project on toxicity test protocols and risk assessment methodologies for manufactured nanomaterials, coordinated by the National Institute of Advanced Industrial Science and Technology (AIST), and the National Institute of Occupational Safety and Health Japan (JNIOSH) has started a three-year project on exposure to manufactured nanomaterials at the workplace.

**2011:** Discussion committee on chemical substances.

Committee on Safety management for Nanomaterials established.

**China - Nano regulations:** “Nanomaterials” is the material which has structure in the three-dimensional space in at least one dimension in the nanometer scale, or constituted by the Nano-structure unit and a material with special properties.

**2004:** Seven Nano-standard released (2004-10-26): Notice No.2004-10 on Newly Approved National Standards of P.R. China (26 October 2004, Administration of Quality Inspection, Supervision and Quarantine, State Administration of Standardization).

**2010:** National Steering Committee for Nanoscience and Nanotechnology (NSCNN) established (2010-06-01) Nanotechnology Standards are reviewed (2010-12-30): Nanotechnology Standards are reviewed by the National Nanotechnology Standardization Technical Committee (NSTC), the Technical Committee 279, and nanomaterial-specific subcommittee under the Standardization Administration of China (SAC).

**2011:** Notice on Standard Draft Planning on 17 National Standards including "the Standard on the Health and Safety Practices in Occupational

Settings Relevant to Nanotechnologies (22 August 2011, Standardization Administration of China)

**CONCLUSION:** Recent developments of various Theronostic nanomedicines and their preclinical success were discussed. There are more challenges to be faced for their *in vivo* applications to preclinical and clinical level. Various studies on nanomedicine have showcased a foreseeable progress in the field of cancer management. An advantage of this technique is that it provides the capacity for personalized medicine. For cancer patients, this involves the amalgamation of imaging agents with chemo-therapeutic drugs. It should be noted that in terms of the diagnostic element of Theronostics, for the majority of cases a diagnosis has already been performed in order to choose the most appropriate chemo-therapeutic drug. Undoubtedly, nanomedicine will determine the future of personalized and targeted cancer treatment. Quantum dots, gold nanoparticles and iron oxide nanoparticles loaded Theronostic nanomedicines could be potential carrier to address some of these issues in near future. As the proper regulation of nanomedicines is equally important like the other pharmaceuticals, the regulations that are being implemented few countries have also been included in this review article.

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