Nuclear Medicine: An Approach Via Nanotechnology

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Abstract

The birth of nanotechnology in human society was around 2000 years ago and soon found applications in various fields and with nanotechnology nuclear medicine (radiation techniques) are an important tool in fighting against cancer and are used to treat for a variety of malignant tumors of different origins and stage; it is used in the treatment of as many as 50% of all cancer patients and other then cancer infection/inflammation, and brain and heart diseases also treated with it. Every day in the clinic, nuclear physicians work with nuclear biologists, chemists, and physicists to practise nuclear medicine. Nanomedicine is a medical use of nanomaterials, biologic and nanoelectronics devices, biosensors, and possibly molecular nanotechnology. The fact that radiation dose can be supplied locally and that cells within the radiation nanoparticles transfer radionuclides to tumours while sparing healthy tissues from radiation induced damage account for radiation's efficacy as a cancer treatment technique. Because nanoparticles can be targeted to malignancies, nanotechnology has a promising future in radiotherapy. As a result, scientists have seized on the notion of employing nanoparticles to deliver radionuclides to tumours while avoiding radiation damage to healthy cells. Dendrimer nanocomposites have recently been discovered to be useful in radiation and imaging of tumour microvasculature. Carbon nanoparticles, also known as buckyballs, are barely a nanometer in diameter and could be used as antiradiation medications in the future to assist protect against the negative effects of cancer therapies or dirty bombs. Radiation therapy and chemotherapy frequently harm cells and tissues by releasing potentially harmful reactive oxygen species such as free radicals, oxygen ions, and peroxides. The electron clouds that surround buckyballs are thought to be capable of absorbing these free radicals. In light of a number of recent breakthroughs, the emerging role of nanotechnology in conjunction with radiation biology appears to be highly promising.

Introduction

nanotechnology is the manipulation of matter on an atomic and molecular scale to prepare new structures, devices and materials. In general, nanotechnology uses materials sized between 1 and 100 nanometres [1] .

The interdisciplinary nature of nanotechnology has given it a fundamental influence in various fields, especially medical science. Nanomedicine is defined as the knowledge and skill of manipulating and exploiting the unique chemical, physical, electrical, optical, and biological attributes of natural or synthesized material at the Nano-sized scale for various medical

purposes, such as opportune prevention, early detection, and targeted treatment of disease [2-7].

Applications of nanotechnology in nuclear medicine can be found in areas of diagnostics, therapeutics, theragnostic, and regenerative medicine, as described below (Fig. 1).

1.1 Cancer Application

The mere thought of cancer can be sufficient to elicit images of pain, loss, and adverse side effects. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age (Cancer Research UK, 2007). Cancer causes about 13% of all deaths (WHO, 2006). According to the American Cancer Society, 7.6 million people died from cancer in the world during 2007 (American Cancer Society, 2007). In the U.S. and other developed countries, cancer is presently responsible for about 25% of all deaths (Jemal *et al*., 2005).

On an annual basis, cancer affects 0.5 percent of the population. Although developments in diagnostic and therapeutic technology have made it possible to detect cancer at an earlier stage and so treat instances more successfully, present diagnostic and treatment processes are far from ideal, and there is an urgent need to address the numerous flaws. Given the natural history of cancer, the time of diagnosis has a substantial impact on the prognosis, with early detection lowering the risk of morbidity and mortality.

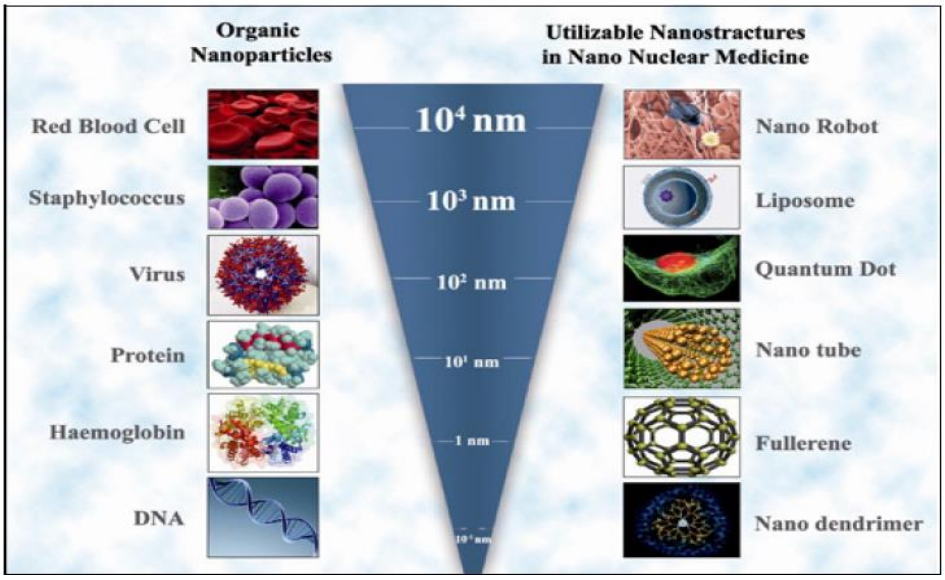

Figure 1 The Organic nanoparticle as compared with utilizable nanostructures in nano-nuclear medicine

Radiation therapy

is now commonly accepted as one of the most effective forms of cancer treatment, and used for a variety of malignant tumors of different origins and stage. Radiotherapy uses a special kind of energy, ionizing energy, which is applied over a certain area that contains the tumor. The ionizing energy damages the nuclear genetic material of the cancer cell, thereby preventing it from properly multiplying. The success of radiation as a cancer treatment modality stems from the facts that radiation dose can be delivered locally and that cells within the radiation field can be

killed effectively. Effectiveness of the radiation therapy is low if the tumor is located in vital regions of the body. The treatment is intrinsically toxic to the body and targets rapidly dividing cells such as those in a tumor. However, treatment is not selective and rapidly dividing cells (i.e. hair, intestinal lining, and bone-marrow) are also killed in the process. Thus, the main limitation of radiation therapy is that they kill healthy cells almost as easily as they do tumors.

Such limitations warrant the need for novel cancer imaging and therapeutic modalities that are increasingly safer and more specific for their cancerous targets. The current focus in development of cancer therapies (Jain, 2005) is on targeted drug delivery to provide therapeutic concentrations of anticancer agents at the site of action and to spare the normal tissues. Targeted drug delivery to tumors can increase the selectivity for killing cancer cells, decrease the peripheral/systemic toxicity and can permit a dose escalation. This will more advantageous then earlier. Now days the drug delivery system uses nanoparticale based transportation of drugs that helps to target cancerous tumors only. It increases the efficiency of cancer treatment.

Nanotechnology can be advantageously used to eradicate cancer cells without harming healthy ones. Scientists hope to use nanotechnology to create therapeutic agents that target specific cancer cells and deliver the toxin and radiation in a controlled, time release manner. The ultimate goal of this research is nanoparticles that will circulate through the body, detect cancer-associated molecular changes, assist with imaging,

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Nanowire Sensors

Nanowires are made of carbon, silicon and other materials that have unique properties (NCI, 2006). When used as a sensor, nanowires lay across a small fluid channel. As particles flow through the channel (e.g., from blood), the nanowire sensors pick up the molecular signatures of the particles and relay this information

through a connection of electrodes outside the body. Nanowires have potential to be used to detect the presence of altered genes associated with cancer (NCI, 2006).

Cantilevers

Nanoscaled cantilevers like springs are being developed using electron-beam lithography for an ultra sensitive bioassay. The flexible nature of the technology has the potential to offer high-throughput detection of proteins, DNA and RNA for a broad range of applications ranging from disease diagnosis to biological weapons detection. through e-beam lithography (Klein et al.2005). Nano-scale cantilevers resemble an everyday comb with evenly spaced teeth. The cantilevers possess conductive properties and are coated with specific antibodies responsive to cancer proteins (NCI). Protein secreted from cancerous cells attaches to the antibodies bonded to the cantilevers and actually cause the teeth to bend. This deformation creates a change in conductivity in the cantilever. This change can be measured in real time and the concentration of different molecular secretions determined (NCI, 2006), alerting doctors to the presence of cancer within a patient (NCI). This is much more effective than traditional detection methods because it allows doctors to detect cancer before tumor formation, and could in fact allow for the prevention of tumors if the disease is treated appropriately.

Nanotubes

Nanotubes are carbon rods that can detect the presence of altered genes and may help pinpoint the exact location of the changes. Carbon nanotubes (CNTs) are remarkable solid state nanomaterials (Teker et al., 2004), due to their unique electrical (Bockrath et al., 1997) and mechanical properties (Ruoff et al., 1995). The electronic properties of nanotubes combined with biological molecules such as proteins could make miniature devices for biological sensing applications. The research of carbon nanotube functionalization has intensified due to their great potential for biomedical and biotechnological applications. Organic modification of carbon nanotubes generates multiple sites for the attachment of bioactive molecules, and the modified nanotube could be used as a biosensor or a novel delivery system. Carbon Nanotubes Target Tumors (Liu et al., 2007) in the first experiment of its kind, investigators at the Center for Cancer Nanotechnology Response (CCNETR), based at Stanford University. Experiments have shown that single-walled carbon nanotubes (SWCNTs) wrapped in poly (ethylene glycol), or PEG, can successfully target tumors in living animals.

To prepare DNA for nanotube analysis, a bulky molecule must be attached to regions of DNA that are associated with cancer. Designer tags can be used to target specific mutations in the DNA. A nanotube tip is then used to trace the physical shape of the DNA and pinpoint the mutated regions. Since the location of mutations can influence the effects they have on a cell, nanotubes may be important in predicting disease (NCI, 2006a, b).

Quantum Dots

Quantum dots (QDs) are nanometer sized semiconductor crystals that glow when they are stimulated by ultraviolet light. The wavelength or colour of the light emitted from a QD depends on the size of the crystal Structurally, QDs consist of a metalloid crystalline core and a "cap" or "shell" that shields the core and renders the QD bioavailable. QDs consist of a variety of metal complexes such as semiconductors, noble metals and magnetic transition metals

(e.g., indium arsenate, gallium arsenate, zinc selenium, cadmium selenium, cadmium tellurium and lead selenium) (Hardman, 2006). Biocompatible coatings or functional groups are added to the QD core-shell to improve water solubility, QD core durability and suspension characteristics, and assigns a desired bioactivity (e.g., drug delivery or molecular imaging). Compromise of the coating may reveal the metalloid core, which may be toxic either as a composite core (e.g., cadmium telluride) or upon dissolution of the QD core to constituent metals (e.g.,cadmium) (Hardman, 2006).

Compared to organic dyes and fluorescent proteins, QDs have unique optical and electronic properties such as size and composition-tunable fluorescence emission from visible to infrared wavelengths, large absorption coefficients across a wide spectral range and very high levels of brightness and photo stability. Due to the broad excitation profiles, QDs are well suited to optical multiplexing in which multiple colours and intensities are combined to encode genes, proteins and small molecule libraries (Gao *et al*., 2004).

Gao et al. (2004) created QD conjugates containing a special polymer coating (including a QD capping ligand) for in vivo protection, targeting ligands for tumour recognition, and several molecules (poly ethylene glycol) for improved biocompatibility and circulation.

Dendrimers

Highly branched, monodisperse macromolecules (Klajnert *et al*., 2001). (Hyperbranched molecules) or "Dendrimers" were discovered in the early 1980's by D. Tomalia and co-workers (Tomalia *et al*., 1985). Dendrimers are man-made macromolecular compounds that comprise a series of branches around an inner core (Sahoo and Labhasetwar, 2003). The interaction of dendrimer macromolecules with the molecular environment is mainly controlled by their terminal groups. Due to their globular shape and internal cavities, dendrimers can encapsulate therapeutic agents within the macromolecule interior as well as attach to surface groups.

The unique properties (Gillies and Fréchet, 2005) of dendrimers, such as their high degree of branching, multi valency, globular architecture and well defined molecular weight, make them promising new scaffolds for drug delivery. Progress has been made in the application of biocompatible dendrimers to cancer treatment, including their use as delivery systems for potent anticancer drugs such as cisplatin and doxorubicin, as wall as agents for both boron neutron capture therapy and photo-dynamics therapy. One of the advantages of using nanoparticles as delivery devices for therapeutic and imaging agents is their ability to attach tumour-targeting molecules to the nanoparticle surface.

Nanoshells

Nanoshells are layered colloids with a nonconducting nanoparticles (Hirsch et al., 2003) core covered by a thin metal shell, whose thickness can be changed to precisely tune the plasmon resonance. Proteins that bind only with tumor cells can be attached to the surface, creating tumor-seeking nanoparticles. By tuning the shells to strongly absorb 820 nm NIR light, where optical transmission through body tissue is optimal and harmless, low-power extracorporeally applied laser light shone at the patient induces a response signal from injected nanoshells clustered around a tumor. Increasing the laser power to a still moderately low exposure heats the nanoshells just enough to destroy the tumor without harming healthy tissue. Nanoshells have been applied in a number of biological applications such as detection of immunoglobulins in whole blood and for thermal ablation of cancerous cells both in

vitro and in vivo (Hirsch *et al*., 2003). Nanoshells can be conjugated to antibodies that recognize cancer cells. In vitro studies have examined the use of magnetic fields to create magnetocytolysis (lysis of cells in a magnetic field) of cancer cells that were targeted by specific peptides. Bergey *et al*. (2002) demonstrated that a multifunctional nanoparticle (composed of an iron oxide core, a fluorescent probe to aid in optical tracking Nanotechnology and a peptide to target specific cancer cells) can destroy in vitro cancer cells upon exposure to a magnetic field similar to that used for MRI in diagnostic settings.

Dendrimer Nanocomposites in Radiotherapy and Imaging of the Tumor Microvasculature

Nanotechnology is by its nature very multidisciplinary. Researchers focussed on both tumor imaging and therapy using composite nanodevices (CNDs) that exploit differences between the normal and tumor microvasculature. The composite nanodevices have a dendrimer 3-D polymer component with an external surface that can be use for targeting or placement of agents to attack cancer, and the "inner" region traps inorganic materials again that can be used for imaging and therapy (for example the CNDs can deliver radiation dose at level at least a log fold more that that seen with radioactive antibody therapies) (Fig. 2). One set of experiments in the laboratory attempts to send nanocomposites through the leaky tumor microvasculature and into cancer tissue in mouse tumor mouse tumor model systems, and examines important effects produced by small changes in nanodevice size or charge. The second major area is attempting to design and test nanocomposites targeted directly at the leaky tumor microvasculature, and to utilize this for multi-level imaging (whole animal, intra-tumoral, intracellular) using the same nanodevice. These are also being developed for therapy, as the metal (or Isotopes) carried by the nanodevices can be used for the delivery of radiation dose to the tumor microvasculature (Khan et al., 2005).

Tetrathiomolybdate (TM) and Radiotherapy

Laboratories are completed preclinical experiments demonstrating that the combination a novel anti-angiogenic agent (tetrathiomolybdate or TM) with radiation therapy will slow tumor growth better that either therapy used alone in mouse model (Khan et al., 2002). TM is an orally administered agent was shown to reduce copper levels in patients safely. Copper reduction has been shown to block angiogenesis, by affecting multiple proangiogenic molecules (bFGF, VEGF, IL-6, IL-8, angiogenic) (Mamou et al., 2006), making it a "multi-hit" anti-angiogenic agent. It has also been shown to slow tumor growth Khan et al., 2006).

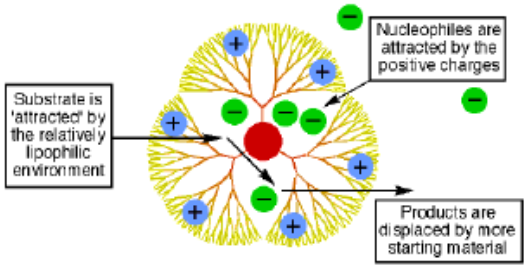

Figure 2. A Dendritic Catalyst for Reactions of Anionic Nucleophiles in Water

Nano-based antiradiation drug

Balls of carbon atoms called buckyballs only a nanometer or billionth of a meter in diameter could serve as future antiradiation drugs to help protect against the side effects of cancer therapies or against dirty bombs. One way that radiation therapy and chemotherapy frequently injures cells and tissues are by producing damaging "reactive oxygen species," such as free radicals, oxygen ions and peroxides. These free radicals induce a cascade of deleterious biological events that cause further destruction to the organism in the days and

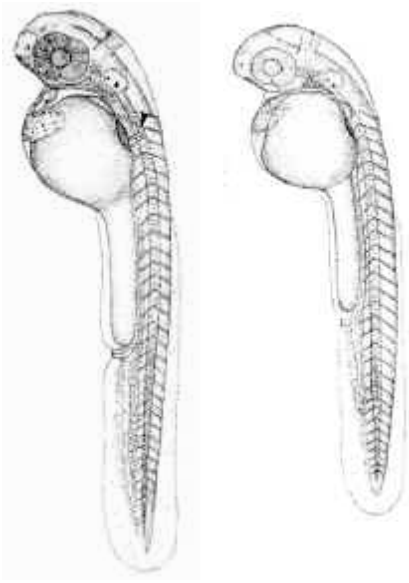

Figure 3. Zebrafish Embryo

weeks after the initial radiation exposure event. The researchers and their collaborators at Houston-based nanotechnology firm C Sixty speculated the electron clouds that surround buckyballs might "soak up these free radicals. To investigate how well buckyballs protect against radiation, the scientists used zebrafish embryos, which are transparent, helping scientists to closely observe damage produced by radiation treatments against organs (Fig. 4). Zebrafish usually have most of their organs formed by day three of life, allowing the researchers to quickly and inexpensively conduct their research. The researchers found that buckyballs given before or immediately after exposure to Xrays reduced organ damage by one-half to two-thirds (Dicker, 2006).

C60 is a molecule that consists of 60 carbon atoms, arranged as 12 pentagons and 20

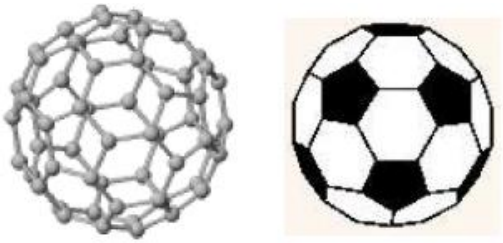

Figure 4. Bucky balls

hexagons. The shape is the same as that of a soccer ball: The black pieces of leather are the pentagons, the hexagons are white. There are 60 different points where three of the leather patches meet. Imagine a carbon atom sitting at each of these points, and you have a model of the C60 molecule. That model, however, is vastly out of scale: If the C60 molecule were the size of a soccer ball, then the soccer ball in turn would be roughly the size of the earth.

The most striking property of the C60 molecule is its high symmetry. There are 120 symmetry operations, like rotations around an axis or reflections in a plane, which map the molecule onto itself. This makes C60 the molecule with the largest number of symmetry operations, the most symmetric molecule. They are called Fullerenes, after the American architect Richard Buckminster Fuller. Fuller, who is shown here on the cover of Time Magazine of January 10, 1964, was renowned for his geodesic domes, that are based on hexagons and pentagons. An even earlier example of such a construction was the dome of the first planetarium, built by Zeiss in 1922

Killing cancer with gold nanobullets and nanobombs

Binding gold nanoparticles to a specific antibody for cancer cells could make cancer detection much easier. Gold nanoparticles are very good at scattering and absorbing light. Many cancer cells have a protein, known as Epidermal Growth Factor Receptor (EFGR), all over their surface, while healthy cells typically do not express

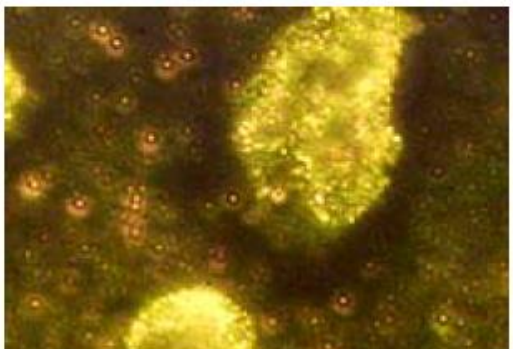

Figure 5. Gold nanoparticles stick to cancer cells and make them shine.

the protein as strongly. By conjugating, or binding, the gold nanoparticles to an antibody for EFGR, suitably named anti-EFGR, researchers were able to get the nanoparticles to attach themselves to the cancer cells. In one study, researchers found that the gold nanoparticles have 600 percent greater affinity for cancer cells than for noncancerous cells. If conjugated nanoparticle solution is added to healthy cells and cancerous cells and it is found that the whole cancer cell is shining. The healthy cell doesn't bind to the nanoparticles specifically.

When these nano particles are irradiated |they explode. The process which is known as nanophotothermolysis, is used to kill the cancer cells. This thermal explosion of nanoparticles (nanobombs) may be accompanied by optical plasma, generation of shock waves with supersonic expansion and particle fragmentation with fragments of high kinetic energy, all of which can contribute to the killing of cancer cells they are attached to. By engineering the laser wavelength, pulse duration and particle size and shape, this technology can provide highly localized damage in a controlled manner, potentially varying from a few nanometers (for DNA) to tens of microns (the size of a single cancer cell) without damaging the surrounding tissue.

Gold nanoparticles are the most promising candidates for photothermolysis since they are strong absorbers, photostable, nontoxic, easily conjugated to antibodies or proteins and have adjustable optical properties.

CHALLENGES FOR NANOTECHNOLOGY: TARGETING THERAPY TO TUMORS

In directing therapeutic molecules to tumors, it has been determined that three major limiting factors contribute challenges that nanotechnology must overcome on a systematic scale. The first of these factors is an uneven distribution of a drug molecule in the organs of the body, where kidney and liver have the most concentrated levels of drug because they are highly vascular organs. Secondly, small molecules are readily excreted, and therefore have a short circulation times. The third factor is drug inactivation by irreversible binding to proteins, while larger particles are retained in the spleen [13].

The tumor itself provides many hurdles. The largest challenge is presented by the spatial and temporal heterogeneity of tumor vasculature [14, 15]; this includes vessel diameter, length, permeability, integrin expression, density, and spatial distribution. A recent approach to improve therapeutic delivery is priming the tumor tissue with a course of treatment that changes tumor properties, such as interstitial pressure, to favor diffusion and convection to carry the therapeutic payload to its destination [14].

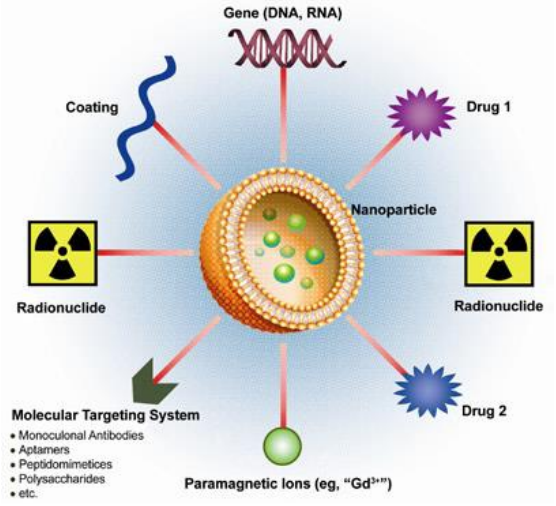

Figure 6 A multifunctional nanoplatform including multimodality imaging, multiple targeting system and multiple therapeutic item

Conclusion

Nanotechnology may prove definitely a medical boon for diagnosis, treatment and prevention of cancer disease. It will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. Keeping in view several such recent developments, the emerging role of nanotechnology in nuclear medicine is quite promising. Dynamic imaging elegantly quantifies molecular uptake of radiolabelled substances within tumors and organs of interest over time. radiotherapies using nanotechnology are on the rise including new chelating agents and novel methods for anti-body and peptide targeting of nanoparticles carrying radiotherapeutic payloads.

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