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Nuclear Medicine In 21st Millennium: An Approach Via Nanotechnology

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Abstract : 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. 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. Clinical schemes of radiation therapy result from many decades of experimentation and empirical development of most effective regimes, both by laboratory researchers and clinicians. In radiotherapy, the role of nanotechnology is in offing because nanoparticles can be targeted to tumors. Thus, researchers have seized on the idea of using **nanoparticles** to deliver radionuclides to tumors and sparing healthy tissues from radiation-induced damage. The role of **dendrimer nanocomposites** in radiotherapy and imaging of the tumor microvasculature has recently been realized. Carbon nanoparticles, C-60 called buckyballs, being only a nanometer 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. It is speculated that the electron clouds that surround buckyballs might immerse up these free radicals. Looking at several such recent developments the emerging role of nanotechnology conjointly radiation biology is quite promising.

Key words : Buckyballs, Dendrimer nanocomposites, Radionuclides

Introduction

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 a yearly basis, 0.5% of the population is diagnosed with cancer. Although diagnostic and therapeutic advances have made it possible to detect cancer in earlier stages and hence treat such cases more effectively, current diagnostic and treatment procedures are far from ideal and there is an urgent need to address the many shortcomings. Given cancer's natural history, the time of diagnosis heavily influences the prognosis, with early detection significantly reducing the risk of morbidity and mortality.

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. So targeted drug delivery will be more advantageous. Recently, a series of exciting experiments revealed nanoparticles hold great promise, as nanoparticles can be targeted to tumors, researchers have seized on the idea of using nanoparticles to deliver radionuclides to tumors, thus sparing healthy tissues from radiation-induced damage. It is an important step toward realizing the potential of radionuclide-loaded nanoparticles as radiotherapeutic agents.

Development and application of nano-scaled products for cancer treatment show promise of increased efficiency with reduced, or may be even eliminated side-effects. Doctors and scientists throughout the country have been working on different methods for early cancer detection and elimination. Early detection of cancer cells plays a vital role in cancer prevention and treatment. Therefore, the federal government and organizations such as the National Cancer Institute (NCI) and NASA have funded the research of nanotechnology use in battling cancer. With increased funding from the government and private organizations, many nanoscale devices were developed to aid in cancer detection and elimination, namely nanoscale cantilevers, dendrimers, and gold nanoshells.

Nanotechnology offers extraordinary opportunity to study and interact with normal and cancer cells at molecular and cellular levels, and during the earliest stages of cancer process. Nanoscale devices due to their extreme small size can readily interact with biomolecules and can gain access to human cells, hence they possess the ability to detect disease and deliver treatment in ways unknown before.

Following are the arenas where nanotechnology can be applied successfully: Diagnosing cancerous cells in its initial stages, delivery of therapeutic agents effective against cancer, monitoring the molecular changes and preventing normal cells from becoming malignant, managing symptoms of cancer. Nanoscale devices have the potential to

radically change cancer therapy for the better and to dramatically increase the number of highly effective therapeutic agents. Nanoscale constructs can serve as customizable, targeted drug delivery vehicles capable of ferrying large doses of radiation into malignant cells while sparing healthy cells, greatly reducing or eliminating the often unpalatable side effects that accompany radiation therapy.

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, release a therapeutic agent, and then monitor the effectiveness of the intervention, thus enhancing the subsequent effect of radiation therapy. Nanomaterials have garnered increasing interest recently as potential therapeutic drug-delivery vehicles. Among the existing nanomaterials are the pure carbon-based particles, such as fullerenes and nanotubes, various organic dendrimers, liposomes and other polymeric compounds. These vehicles have been decorated with a wide spectrum of target-reactive ligands, such as antibodies and peptides, which interact with cell-surface tumor antigens or vascular epitopes. Once targeted, these new nanomaterials can then deliver radioisotopes or isotope generators to the cancer cells. Here, we will review some of the more common nanomaterials under investigation and their current and future applications as drug-delivery scaffolds with particular emphasis on targeted cancer radiotherapy.

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 (CCNE-TR), 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).

Nanocrystals or 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, mutivalency, globular architecture and well defined molecular weight, make them promising new scaffolds for drug delivery. Recent 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 photodynamics 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. 1). 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

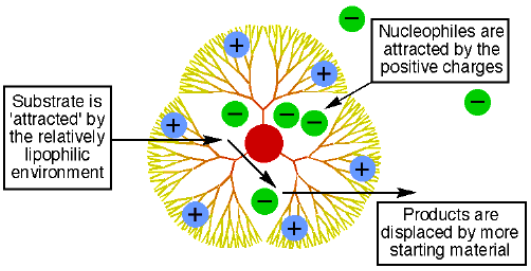


Fig. 1 : A Dendritic Catalyst for Reactions of Anionic Nucleophiles in Water

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 pro-angiogenic 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).

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 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. 2). Zebrafish usually have most of their organs formed by day three of life,

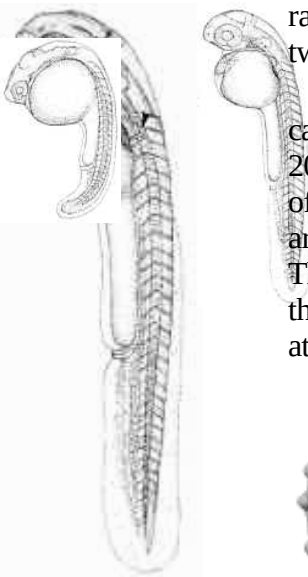


Fig. 2 : Zebrafish Embryo

allowing the researchers to quickly and inexpensively conduct their research. The researchers found that buckyballs given before or immediately after exposure to X-rays 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 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.

Fig. 3 : Bucky Balls

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.

The Nano-metamorphoses of Gold

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

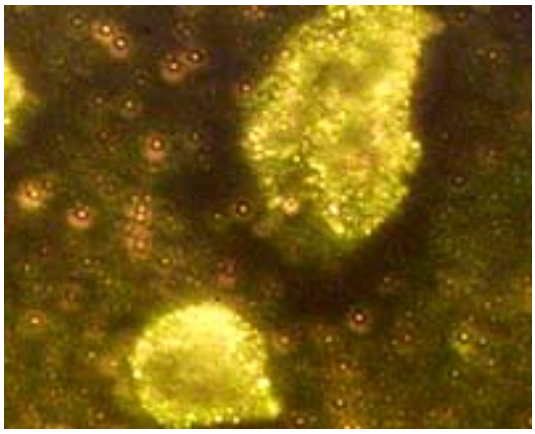


Fig. 4 : Gold nanoparticles stick to cancer cells and make them shine.

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 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 by short laser pulses, get hot so quickly that 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.

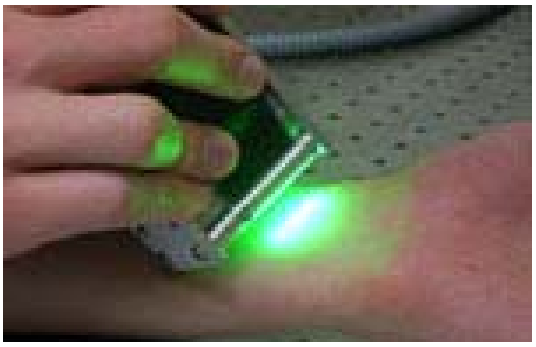
Gold nanoparticles are the most promising candidates for photothermolysis since they are strong absorbers, photostable, nontoxic, easily conjugated to antibodies or proteins and have adjustable optical properties.

Nanoshell-assisted photo-thermal therapy (NAPT):

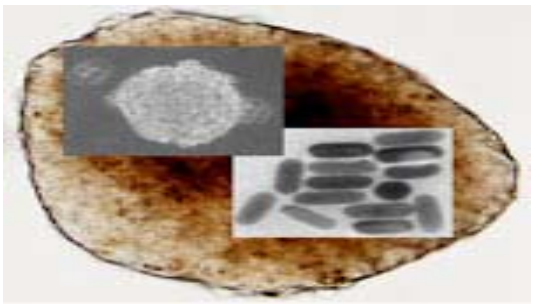
Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles was studied. Nanoshell-assisted photo-thermal therapy (NAPT) is the technique which takes advantage of the strong near infrared (NIR) absorption of nanoshells, a new class of gold nanoparticles with tunable optical absorptivities that can undergo passive extravasation from the abnormal tumor vasculature due to their nanoscale size. By adjusting the relative core and shell thickness, nanoshells can be manufactured to absorb or scatter light at a desired wavelength across visible and NIR wavelengths. In the study tumors were grown in immune-competent mice by subcutaneous injection of murine colon carcinoma cells (CT26.WT). Polyethylene glycol (PEG) coated nanoshells (<130 nm diameter) with peak optical absorption in the NIR were intravenously injected and allowed to circulate for 6 h. Tumors were then illuminated with a diode laser (808 nm, 4 W/cm2, 3 min). All such treated tumors abated and treated mice appeared healthy and tumor free 90 days later. Control animals and additional sham-treatment animals (laser treatment without nanoshell injection) were euthanized when tumors grew to a predetermined size, which occurred 6-19 days post-treatment. This simple, non-invasive procedure shows great promise as a technique for selective photo-thermal tumor ablation (O'Neal *et al*., 2004).

Sound and light against cancer

Whilst being yellow in its solid state, gold turns red, purple and even blue when it



An optoacoustic excitation process in which biofunctionalised gold nanoparticles are attached to certain target cells generates ultrasounds that reveal pathological cellular configurations. Institute of Applied Physics - University of Bern (CH)
(Courtesy : Adonis project)



The Adonis Project - At the nanoparticle level, gold can be bio-functionalised, or linked to the antibody's organic matter, as it has the property of binding itself to certain cells in living tissue.
(A Mass Spectrometry Laboratory - University of Liège (BE))

is reduced to nanometric particles. This property, acknowledged for centuries by craftsmen using fine gold powders to make the colour of glass change with the light, is used these days to detect cancerous cells. At very precise dimensions (from 5 to 10 nm), gold particles react to infrared laser emissions by reflecting part of the energy in light form, while the rest is converted into heat. After having biofunctionalised them with specialised antibodies to target specific antigens in diseased cells, it is then possible to 'illuminate' them, thanks to the infrared light that passes through the biological tissue. They can thereby be detected with the help of magnetic resonance imagery.

This year-old European project also uses ultrasound to locate gold nanoparticles. When subjected to certain infrared frequencies, they emit a sound resulting from the expansion or contraction of the material. 'The coupling of optical and acoustic detectors offers greater accuracy; acoustic methods penetrate the tissue far more deeply.

But detection is simply the first stage, as the consortium also envisages therapeutic procedures. By fine-tuning the light's wavelength, as well as the size and shape of the nanoparticles, the thermal part of the energy restored relative to the light emission can be increased. While attached to the cancer cell, the particle is heated. At under 60º C, the membrane's permeability is altered, thereby destroying the cell. This procedure, which is currently undergoing in vitro testing, could be applied to various tumors by identifying good targets for each one to which gold nanoparticles could be attached.

Cerium oxide (Nanoceria)

Nanocrystalline cerium oxide (nanoceria) possesses some unique properties: blue shift in ultra violet absorption spectrum, shifting and broadening in Raman allowed modes and lattice expansion. It is observed that Cerium oxide nanoparticles increase the neuronal lifespan in culture. The biological activity of the cerium oxide

nanoparticles was assessed in an organotypic tissue culture model of rat cells, and it was observed that cerium oxide nanoparticles prolong brain cell longevity in culture, by two- to threefold or more (Singh *et al*., 2007). Further, cerium oxide nanoparticles reduced hydrogen peroxide (H_2O_2) and UV-light-induced cell injury by over 60%. The unique structure of cerium oxide nanoparticles, with respect to valence and oxygen defects, promotes cell longevity and decreases toxic insults by virtue of its antioxidant properties. Because of the potential of free-radical-scavenging compounds to act as radioprotectants, cerium oxide nanoparticles can be seen to confer radio-resistance to normal cells during ionizing radiation treatment. Ceria nanoparticles prepared by the microemulsion process result in ultrafine nonagglomerated particles in the range of 2-5 nm.

Cerium oxide is a rare earth oxide material from the lanthanide series of the periodic table. It is used in various applications, electrolytes for solid oxide fuel cells (SOFC) (Eguchi*et al*, 1992), ultraviolet absorbents (Tsunekawa*et al*, 1999), oxygen sensors (Izu eat al, 2004; Jasinski *et al*, 2003) and automotive catalytic converters (Masui 2000). Nanocrystalline cerium oxide (nanoceria) possesses some unique properties: blue shift in ultra violet absorption spectrum (Tsunekawa *et al*, 1999) shifting and broadening in Raman allowed modes,9 and lattice expansion. (Tsunekawa *et al*, 1999; Feng *et al*., 2002).

These unique properties of nanoceria are proven to be beneficial in the present applications and open avenues for a plethora of newer applications. We have observed that cerium oxide nanoparticles increase the neuronal lifespan in culture (Clark *et al*., 2003). Its micrometer counterpart does not have any effect on cell survival. The biological activity of the cerium oxide nanoparticles was assessed in an organotypic tissue culture model of rat cells, and it was observed that cerium oxide nanoparticles prolong brain cell longevity in culture, by two- to threefold or more. Further, cerium oxide nanoparticles reduced hydrogen peroxide (H_2O_2) and UV-light-induced cell injury by over 60%. We hypothesize that the unique structure of cerium oxide nanoparticles, with respect to valence and oxygen defects, promotes cell longevity and decreases toxic insults by virtue of its antioxidant properties. Because of the potential of free-radical-scavenging compounds to act as radioprotectants, cerium oxide nanoparticles could confer radio-resistance to normal cells during ionizing radiation treatment. The ability of engineered cerium oxide nanoparticles to confer radioprotection was examined in a study. Human normal and tumor cells were treated with nanoceria and irradiated, and cell survival was measured. Treatment of normal cells conferred almost 99% protection from radiation-induced cell death, whereas the same concentration showed almost no protection of tumor cells. For the first time, nanoceria are shown to confer radioprotection to a normal human breast line but not to a human breast tumor line, MCF-7 (Tarnuzzer *et al*., 2005). Thus, nanoceria could reduce the side effects of radiotherapy.

Cerium oxide nanoparticles have very low or no toxicity based on the cell culture data as well as the available literature(Health Effects Institute, 2001; *Development of Reference Doses and Reference*

Concentrations forLanthanides 1999). Furthermore, cerium oxide nanoparticles are long-lived and can confer their beneficial effect for extended periods of time without redosing. Although not known at present for nanoceria *in vivo*, shortcomings of amifostine are the following: very short half-live of less than 10 min in serum, toxicity at higher doses, and toxicity based on the route of administration (Nair *et al*., 2001). Taken together, these data suggest that cerium oxide nanoparticles could have a role as effective radioprotectants for normal tissues as well as show a differential protection in normal cells as compared to tumor cells. Further studies will determine the mechanism of this differential effect as well as determine the *in vivo* efficacy of nanoceria both for general radioprotection as well as for radiation oncology applications.

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.

References

American Cancer Society (2007): Report sees 7.6 million global 2007 cancer deaths. Reuters. Retrieved on 2007-12-17.

Bergey E.J., Levy L., Wang X., Krebs L.J., Lal M. and Kim K.S. (2002): DC Magnetic field induced magnetocytolysis of cancer cells targeted by LHRH magnetic nanoparticles *in vitro*. *Biomed Microdevices* , **4**, 293-299.

Cancer Research UK (2007): UK cancer incidence statistics by age. Retrieved on 2007-06-25.

Clark A., Ellison A., Fry R., Merchant S., Kuiry S., Patil S., Seal S., Rzigalinski B. Program no. 878.2. (2003) : Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience 2003, Online.

Cohen-Jonathan E., Bernhard E.J. and McKenna W.G. (1999) : How does radiation kill cells. *Curr Opin Chem Biol*, **3**, 77-83

Dicker A. (2006): Nanoparticle Shows Promise in Reducing Radiation Side Effects. Annual Meeting of the American Society for Therapeutic Radiology and Oncology in Philadelphia, November 7, 2006.

Eguchi K., Setoguchi T., Inoue T. and Arai H. (1992): *Solid State Ionics*, **52**, 165.

Feng Z., Zhang F., Chan S. W., Spanier J. E., Apak E., Jin Q., Robinson R. D. and Herman I. P. (2002) : Cerium Oxide Nanoparticles: Size-selective Formation and Structure Analysis, *Appl. Phys. Lett*., **80**, 127-129.

Gao X., Cui Y., Levenson R.M., Chung L.W. and Nie S. (2004): *In vivo* cancer targeting and imaging with semiconductor quantum dots. *Nat Biotechnol*, **22(8)**, 969-976.

Gillies R. and Fréchet J. M. J. (2005): Dendrimers and dendritic polymers in drug delivery. *Drug Discovery Today*, **10(1)**, 35-43.

Grdina D.J., Murley J.S. and Kataoka Y. (2002): Radioprotectants: current status and new directions. *Oncology*.,**63(2)**, 2-10.

Hardman R.(2006): A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factors. Environ Health Perspect , 114: 165-172.

Hirsch L. R., Stafford R. J., Bankson J. A., Sershen S. R., Rivera B., Price R. E., Hazle J. D., Halas N. J. and West J. L.(2003): Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance, PNAS, **100(23)**, 13549-13554.

Izu N., Shin W., Matsubara I. and Murayama N. J. (2004): Development of resistive ... based on cerium oxide thick film, *J Electroceram*, **13**, 703-706.

Jain K. K. (2005) : Targeted Drug Delivery for Cancer, TCRT.

Jasinski P., Suzuki T. and Anderson H. U. (2003): Nanocrystalline undoped ceria oxygen sensor, Sens. *Actuators* B 95, pp. 73-77.

Jemal A., Murray T., Ward E., Samuels A., Tiwari R.C., Ghafoor A., Feuer E.J. and Thun M.J. (2005). "Cancer statistics, 2005". CA Cancer *J Clin*. **55 (1)**, 10-30.

Khan M. K., Shraddha S., Nigavekar, Minc L. D., Kariapper, M. S. T., Nair B. M., Lesniak W.G. and Balogh L.P. (2005): *In Vivo* Biodistribution of Dendrimers and Dendrimer Nanocomposites - Implications for Cancer Imaging and Therapy, *Technology in Cancer Research and Treatment*, **4 (6)**, 603-613.

Khan M.K., Miller M.W., Taylor J., Gill N.K., Dick R.D., Van Golen K., Brewer G.J. and Merajver S.D.(2002): Radiotherapy and antiangiogenic TM in lung cancer. *Neoplasia*, **4(2)**,164-70.

Khan M.K., Mamou F., Schipper M.J., May K.S., Kwitny A., Warnat A., Bolton B., Nair B.M., Kariapper M.S. T., Miller M., Brewer G., Normolle D., Merajver S. and Teknos T. (2006): Combination of Tetrathiomolybdate and Radiation in a Mouse Model of HNSCC. *Arch Otolaryngol Head Neck Surg*., **132 (3)**, 333-338.

Klajnert B. and Bryszewska M. (2001): Dendrimers: properties and applications, *Acta Biochimica polonica*, **48**, 199-208.

Klein K. M., Zheng J., Gewirtz A., Sarma D. S., Rajalakshmi S., Sitaraman S. K. (2005) : Array of Nano-Cantilevers as a Bio-Assay for Cancer Diagnosis, Electronic Components and Technology Conference, 2005.

Mamou F., May K. S., Schipper M. J., Gill N., Kariapper M. S. T., Nair B. M., Brewer, G., Normolle D. and Khan M. K. (2006): Tetrathiomolybdate Blocks bFGF- but not VEGF- Induced Incipient Angiogenesis in vitro. *Anticancer Research*, **26**, 1753-1758.

Masui T, Ozaki T, Machida K, Adachi G. (2000): Preparation of ceria-zirconia sub-catalysts for automotive exhaust cleaning. *Journal of Alloys and Compounds*, **303**, 49-55.

NCI (2006): Alliance for Nanotechnology in Cancer. Nanotechnology in cancer. Tools to relieve human cancer. Technology backgrounder [Web page]. National Cancer Institute. [updated 2006; cited 2006 Oct. 16]. Available at: http://nano.cancer.gov/resource_center/tech_backgrounder.asp

NCI (National Cancer Institute) (2005a): Slide 13. Nanotubes: marking mutations [Web page]. [updated 2005 Jan. 28; cited 2006 June 6]. Available at: http://cancer.gov/cancertopics/understandingcancer

NCI (National Cancer Institute) (2005b): Slide 14. Nanotubes: mapping mutations [Web page]. U.S. National Institutes of Health. [updated 2005 Jan. 28; cited 2006 Sept. 15]. Available at:http://www.cancer.gov/cancertopics/understandingcancer/nanodevices/Slide14

O'Neal L.R., Hirsch N.J., Halas J.D. and Payne J.L. (2004): Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles D.P. West, *Cancer Letters*, **209**, 171-176.

Sahoo S.K. and Labhasetwar V. (2003): Nanotech approaches to drug delivery and imaging. *Drug Discov Today*, **8**, 1112-1120.

Singh N., Courtney, Cohen A. and Rzigalinski B. A. (2007): Treatment of Neurodegenerative Disorders with Radical Nanomedicine. *Ann. N.Y. Acad. Sci*., **1122**, 219-230

Spanier J. E. Zhang F., Robinson R. D., Chan S.-W. and Herman I. P. (2001) : Size-Dependent Properties of CeO2-y Nanoparticles as Studied by Raman Scattering, *Phys. Rev. B 64*, 245407(1-8).

Tarnuzzer R.W., Colon J., Patil S. and Seal S. (2005): Vacancy engineered ceria nanostructures for protection from radiation-induced cellular damage. *Nano letters*, **5(12)**, 2573-2577.

Tomalia D.A., Baker H., Dewald J.R., Hall M., Kallos G., Martin S., Roeck J., Ryder J., Smith P. (1985): A new class of polymers: Starburst-dendritic macromolecules , *Polym. J*., **17**, 117-132.

Tsunekawa S., Sivamohan R., Ohsuna T., Kasuya A., Takahashi H. and Tohji K. (1999) : Ultraviolet Absorption Spectra of CeO_2 Nano-Particles. Materials Science Forum, 315-317

WHO (2006) : Cancer. World Health Organization. Retrieved on 2007-06-25.