



A REVIEW ON NANO MEDICINE FOR CANCER TREATMENT

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ABSTRACT

Novel technologies in the nanomedicine field are expected to develop innovative products as targeted drug-delivery approaches. Nanomedicines currently being developed for the treatment of cancer, although diverse in chemical composition, size and shape. The potential for using nanotechnology in medicine and especially in the area of cancer is vast. Nanoparticles target (passive and active targeting) tumor cells, to deliver therapy specifically to the tumor while reducing unwanted side effects. Nanodevices like nanowires, nanotubes, nanoshells, gold nanorods, dendrimers and quantum dots are capable of doing one or more clinically important functions, including detecting cancer at its earliest stages, pinpointing its location within the body, delivering anticancer drugs specifically to malignant cells, and determining if these drugs are killing malignant cells. The use of nanoparticles as drug delivery vehicles for anticancer therapeutics has great potential to revolutionize the future of cancer therapy.

Keywords: Cancer, Nanowires, Gold nanorods, Nanoshells, Dendrimers, Quantum dots.

INTRODUCTION

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes.¹⁻²

Nanomedicines, for the medical applications of nanotechnology, are promising candidates for targeted drug delivery. Novel targeted drug-delivery approaches using nanomedicines are changing the future of therapy.³⁻⁴

The most advanced nanomedicines are multifunctional nanomedicines, capable of simultaneously diagnosing and targeting drug to specific molecular targets by incorporating active molecules, targeting ligands and imaging agents.⁵

Particles larger than 200 nm can activate the human complement system and can be cleared from the blood by Kupffer cells. Additionally, splenic filtration captures particles that exceed slit size (200-250 nm) and liver filtration captures particles greater than 150 nm. Also, tumor capillaries rarely exceed 300 nm in diameter.⁶

Cancer

Cancer remains one of the most complex diseases affecting humans and, despite the impressive advances that have been made in molecular and cell biology, how cancer cells progress through carcinogenesis and acquire their metastatic ability is still widely debated.

At its heart, cancer is the result of uncontrolled cell growth. Our bodies are composed of trillions of cells, all working together. In cancer, one of those cells stops paying attention to the normal signals that tell cells to grow, stop growing or even to die. Cancer cells still share many of the same needs and properties of normal cells but they become independent of the controls that make our body function smoothly. The process by which a normal cell changes into one that behaves so abnormally can take a long time and is often triggered by outside influences.

Cancer is actually a general term that describes a large group of related diseases. Every case of cancer is unique, with its own set of genetic changes and growth properties. Some cancers grow quickly while others can take years to become dangerous to the patient.⁷

Nanotechnology vs cancer

Nanomedicine is the application of nanotechnology to medicine. It is the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body. Present-day nanomedicine exploits carefully structured nanoparticles such as dendrimers, carbon nanotubes and nanoshells to target specific tissues and organs. These nanoparticles may serve as diagnostic and therapeutic antiviral, antitumor or anticancer agents.⁸



Conventional drug delivery systems or dosage forms suffer from many limitations such as lack of target specificity, high rate of drug metabolism, cytotoxicity, high dose requirement, poor patient compliance etc.

Some nanobased drug delivery tools are polymeric nanoparticles, liposome, dendrimer, polymeric micelles, polymer-drug conjugates, antibody-drug conjugates, which can broadly be classify as (i) sustained and controlled delivery system, (ii) stimuli sensitive delivery system, (iii) functional system for delivery of bioactives, (iii) multifunctional system for combined delivery of therapeutics, biosensing and diagnostic, and (iv) site specific targeting (intracellular, cellular, tissue).⁹

Targeting cancer cells

Currently, cancer fight drugs are toxic to both tumor and normal cells, thus the efficacy of chemotherapy is often limited by the side-effects of the drug. Some Nano scale delivery devices, such as dendrimers (spherical, branched polymers), silica-coated micelles, ceramic nanoparticles, and cross-linked liposomes can be targeted to cancer cells. This increase selectivity of drugs towards cancer cells and will reduce the toxicity to normal tissue.¹⁰ This is done by attaching monoclonal antibodies or cell surface receptor ligands that bind specifically to the cancer cells.¹¹

Targeted delivery can be achieved by either passive or active targeting.

Passive Targeting

Passive targeting is achieved by loading drug into a nanocarrier that reaches the target organ passively. Passive targeting of tumors takes advantage of hyper-permeable cells owing to their rapid vascularization. This rapid vascularization results in leaky, defective cells and impaired lymphatic drainage. Nanoparticles ranging from 10 to 100 nm then begin to accumulate within tumors because of their ineffective lymphatic drainage. This results in a phenomenon known as the enhanced permeation and retention (EPR) effect (figure 1).¹²

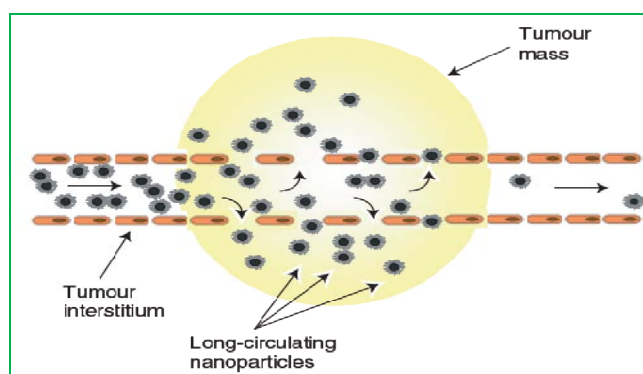


Figure 1: A schematic representation of the nanoparticle localization in solid tumors' by the enhanced permeability and retention effect. Long-circulating nanoparticles, shielded by water-soluble polymer such as poly (ethylene glycol), preferentially accumulate in the tumour mass by extravasation through the fenestrated tumor interstitium.

Active Targeting or synaphic targeting or pathotropic targeting

Recent advances have led to the transformation from passive to active targeting. Active targeting of a drug is achieved by conjugating a Nano carrier system (drug loaded) to a tissue- or cell-specific targeting ligand. Active targeting has raised the importance of nanomedicine and this can now be achieved by a number of specific interactions, such as ligand-receptor and antibody-antigen binding. These specific interactions result in preferential accumulation of nanomedicine into molecular targets.¹³ Leukemia and lymphoma treatments with antibodies conjugated to a radioisotope have been in clinical use for several years.¹⁴ However, this approach has not been as successful with solid tumors. The apparent reason is the difficulty in delivering drugs into these tumors; drugs only penetrate a few cell diameters into the extravascular tumor tissue from blood vessels.¹⁵ This low penetration appears to arise from two main factors: first, tumor vessels are poorly perfused with blood and are dysfunctional, which limits the delivery of blood-borne compounds to tumors.¹⁶ Second, tumors have a high interstitial pressure thought to result from dysfunctional lymphatic's, which causes tissue fluid to flow out of the tumor, working against diffusion of drugs from the blood vessels into the tumor.¹⁷ The luminal side of tumor vessels is fully accessible to compounds circulating in the blood, and the vessels can serve as a gateway to the tumor interior for compounds concentrated in the vessels. Using a targeting probe with tumor-penetrating properties and a receptor that is shared between tumor vessels and tumor cells provides additional advantages (figure 2).

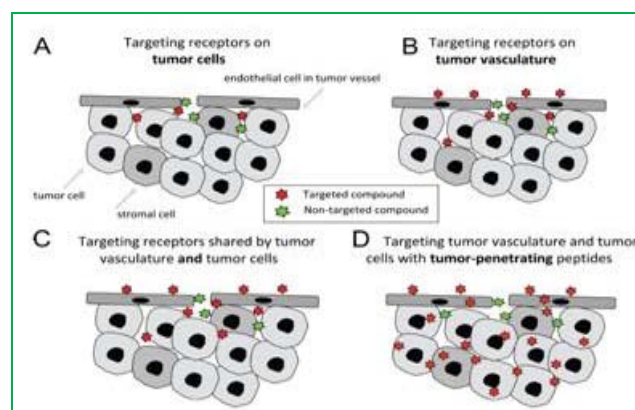


Figure 2: Synaphic targeting of tumors. The targeted receptors can be on tumor cells, tumor vessels, or shared by both. (A) Probes that recognize solely tumor cells provide little improvement of tumor accumulation over a nontargeted probe. (B) Probes that recognize tumor vessels accumulate in the tumor, but entry into tumor tissue relies on passive mechanisms. (C) Probes that recognize both the vessels and tumor cells combine the (limited) efficiency of the two targeting mechanisms. (D) Tumor-penetrating targeting probes (so far only peptides with such characteristics are known) provide a particularly potent targeting system.

By gold Nano rods

It would be advantageous to create more binding sites for targeted delivery in a tumor, particularly if they are within the vascular space. Recently a system was constructed that leverages a biological cascade in vivo to increase the available binding sites for targeted delivery. Plasmonic nanomaterials, such as gold Nano rods, present exciting opportunities for such targeting combinations. These materials are metallic structures that efficiently convert optical radiation into heat by coupling into one or more Plasmon modes.¹⁸ It was shown that photo thermal heating mediated by tumor-targeted gold Nano rods can increase binding sites for targeted delivery with thermosensitive drug carriers (Figure 3).¹⁹

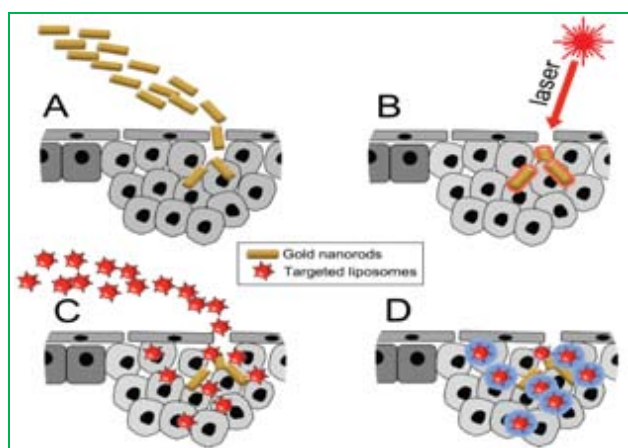


Figure 3: Treating tumors with cooperative nanoparticles. This scheme illustrates a method to induce cooperative nanoparticle behavior that results in more effective delivery of treatments to tumors. This example uses a two component system consisting of gold Nano rods and targeted, thermally sensitive liposomes. (A) Passive accumulation of gold Nano rods. The circulating Nano rods passively accumulate in the tumor as a result of leakiness of the tumor vasculature (the EPR effect). (B) Laser irradiation of nanorods activates tumor cells. The gold nanorods absorb laser energy, heating the surrounding tissue. This localized rise in temperature increases tissue permeability and induces expression of receptor proteins on the surface of the tumor cells. (C) Targeted nanoparticles (liposomes) bind to tumor. Receptor-specific targeting peptides attached onto the secondary nanoparticles allow these particles to bind to the overexpressed receptor proteins on the heat-activated tumor cells. (D) Activation of targeted liposomes releases drug. In this example, thermally responsive liposomes containing a drug payload are heated with a second laser pulse, inducing rupture of the liposome shell and release of its contents.

NANODEVICES/NONOTOOLS

Nanotechnology can have a revolutionary impact on cancer diagnosis and therapy. Available therapies commonly employed in cancer treatment include surgery, chemotherapy, immunotherapy, and radiotherapy. Nanotechnology offers tremendous opportunities to aid and improve these conventional therapies by virtue of its nano tools.

- ❖ Nanowires
- ❖ Nanoshells

- ❖ Carbon nanotubes
- ❖ Dendrimers
- ❖ Quantum dots²⁰

Nanowires

Nanowires by nature have incredible properties of selectivity and specificity. Nanowires can be engineered to sense and pick up molecular markers of cancer cells. By laying down nanowires across a microfluidic channel and allowing cells or particles to flow through it. The wires can detect the presence of genes and relay the information via electrical connections to doctors and researchers (figure 4). This technology can help pinpoint the changes in the genetics of cancer. Nanowires can be coated with a probe such as an antibody that binds to a target protein. Proteins that bind to the antibody will change the nanowire's electrical conductance and this can be measured by a detector. Each nanowire bears a different antibody or oligonucleotide, a short stretch of DNA that can be used to recognize specific RNA sequences. They have begun testing the chip on proteins secreted by cancer cells.²¹

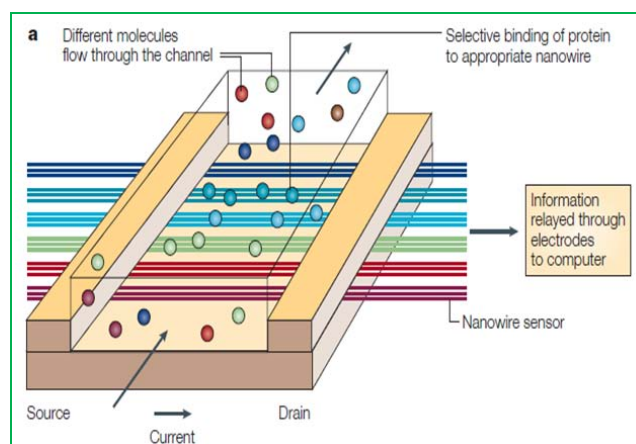


Figure 4: Nanowires deployed within a microfluidic system. Different colors indicate that different molecules (coloured circles) adsorb or affinity-bind to different nanowire sensors. The binding causes a change in conductance of the wires, which can be electronically and quantitatively detected in real time. The working principle is that of a (biologically gated) transistor and is illustrated in the insert. The charges of the binding protein disrupt electrical conduction in the underlying nanowire. The 'nano' size of the wire is required to attain high signal-to-noise ratios.

Cantilevers

Nanoscale cantilevers are built using semiconductor lithographic techniques. These can be coated with molecules (like antibodies) capable of binding to specific molecules that only cancer cells secrete. When the target molecule binds to the antibody on the cantilever, a physical property of the cantilever changes and the change can be detected (figure 5). Researchers can study the binding real time and the information may also allow quantitative analysis. The nanometer-sized cantilevers are extremely sensitive and can detect single molecules of

DNA or protein. Thus providing fast and sensitive detection methods for cancer related molecules.²²

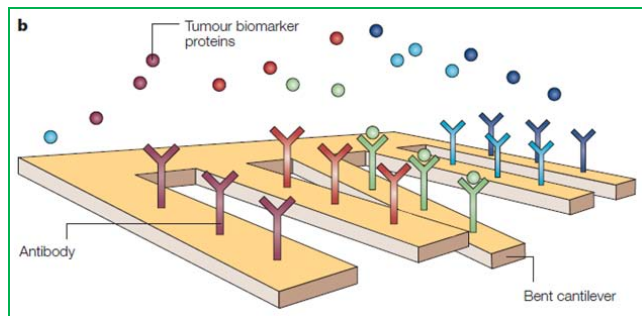


Figure 5: Nanocantilever array. The biomarker proteins are affinity-bound to the cantilevers and cause them to deflect. The deflections can be directly observed with lasers. Alternatively, the shift in resonant frequencies caused by the binding can be electronically detected. As for nanowire sensors, the breakthrough potential in nanocantilever technology is the ability to sense a large number of different proteins at the same time, in real time.

Nanoshells

With the goal to improve the safety and efficacy of systemically administered tumor necrosis factor alpha (TNF), TNF is bound to the surface of 27nm PEGylated colloidal gold particles (figure 6). The binding of TNF and thiol-derivatized polyethylene glycol (PEG-THIOL) is through available thiols/sulfhydryls, forming a covalent bond with the nanoparticles. Both TNF and PEG-Thiol retain their biologic activity when coupled to the surface of colloidal gold nanoparticles and each component of this nanomedicine serves a specific function in achieving tumor-targeted drug delivery, limiting the bio-distribution of TNF to solid tumors:

- PEG-Thiol hydrates the colloidal gold nanoparticles, surrounding each nanoparticle with water that prevents recognition, uptake and clearance by the reticuloendothelial system.
- At 27nm, the gold nanoparticles are small enough to circulate safely through the body, but too large to exit the circulation, except at solid tumors where the new blood vessels that support tumor growth are leaky.
- TNF molecules on the surface of the gold nanoparticles act as a tumor-targeting ligand, binding to receptors at the tumor site, pulling gold-bound TNF out of the circulation and accumulating this anti-cancer drug in and around solid tumors, thereby limiting the bio-distribution of TNF primarily to tumors and avoiding uptake by healthy organs and tissues.

CYT-6091 is a first-generation nanomedicine that is currently being evaluated in a Phase I clinical trial at the National Cancer Institute (NCI, USA). This nanotherapeutic is manufactured on a pegylated colloidal gold (Au) nanoparticle platform and is designed to target the delivery of human TNF- α to solid tumors. The

nanomedicine sequesters within solid tumors by passively extravasating from the leaky tumor vasculature and by actively binding to TNF- α receptors on the cells present in the tumor interstitium. In preclinical models, CYT-6091 has been shown to improve the therapeutic index of TNF- α treatment by increasing the safety and efficacy of TNF- α treatment.²³⁻²⁴

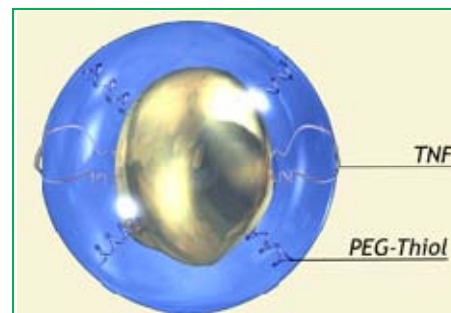


Figure 6: CYT-6091

Carbon Nanotubes

Carbon nanotubes are hexagonal networks of carbon atoms, 1 nm in diameter and 1–100 nm in length, as a layer of graphite rolled up into a cylinder. There are two types of nanotubes: single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs), which differ in the arrangement of their graphene cylinders (figure 7, 8).

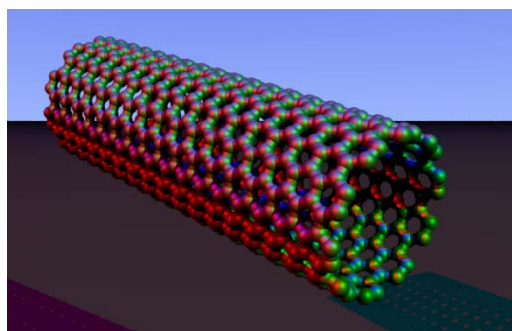


Figure 7: single walled (SWNTs)

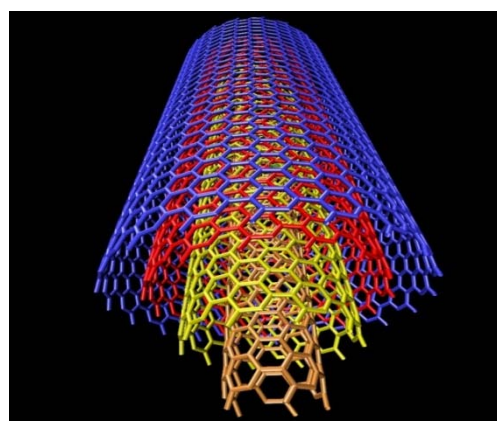


Figure 8: Multi walled (MWNTs)

SWNTs functionalized for biological systems have an interesting relationship with cells. Somatic cells naturally internalize these specialized carbon nanotubes (at 12% to 15%) through CNT-cell interactions. They move into cells through the process of endocytosis or penetrate the cell

membrane by piercing it like a needle. They are then able to enter the cytoplasm and nucleus. While this is a useful ability, in order to fight cancer, functionalized SWNTs must be targeted specifically to malignant tumor cells, ensuring that healthy cells are not adversely affected by the treatment.²⁵

Treatment using functionalized SWNTs can begin after they make their way inside the tumor. Floating in the cytoplasm and nucleus they are harmless. No effects will be seen until the patient is placed inside a radiofrequency or NIR field. These two types of radiation were chosen for their ability to pass through the body without damaging body tissue.

Radiofrequency waves have the tendency to penetrate further into the body. Once inside the field, SWNTs can effectively convert radiofrequency energy or NIR into heat. They absorb the arriving waves of radiation, giving them energy and, in turn, causing them to vibrate. The vibrational movement causes heat to be produced and thermal properties to activate. Vibration of the lattice structure releases phonons which transfer the heat energy throughout the length of the nanotube. Heat is then dispersed inside the tumor from the entire surface area of the SWNTs causing overheating, protein denaturation and eventually malignant cell death.²⁶

Dendrimers

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches. Starburst1 clusters, made of poly(amidoamine) (PAMAM) units, are arguably the most-thoroughly characterized and extensively utilized dendrimers. A basic characteristic of these molecules is their layered composition – known as “cascades” or “generations”. The overall shapes of dendrimers range from spheres to flattened spheroids (disks) to amoeba-like structures, especially in cases where surface charges exist and give the macromolecule a “starfish”-like shape.

The exact morphology of a dendrimer depends both on its chemical composition (the chemical composition of PAMAM dendrimers is shown in Figure 9) as well as on the generation number, as exemplified by PAMAM where the lowest generation.²⁷

Polymer-based drug delivery systems are designed to improve the pharmacokinetics and biodistribution of a drug and/or provide controlled release kinetics to the intended target. The ideal dendrimer carrier should exhibit high aqueous solubility and drug-loading capacity, biodegradability, low toxicity, favorable retention and biodistribution characteristics, specificity, and appropriate bioavailability. In dendrimer-based drug delivery, a drug is either non-covalently encapsulated in the interior of the dendrimer or covalently conjugated to form macromolecular prodrugs. Poly(glycerol succinic acid) dendrimers, or PGLSA dendrimers, were investigated as delivery vehicles for camptothecins, a

group of naturally-derived hydrophobic compounds with anti-cancer activity.

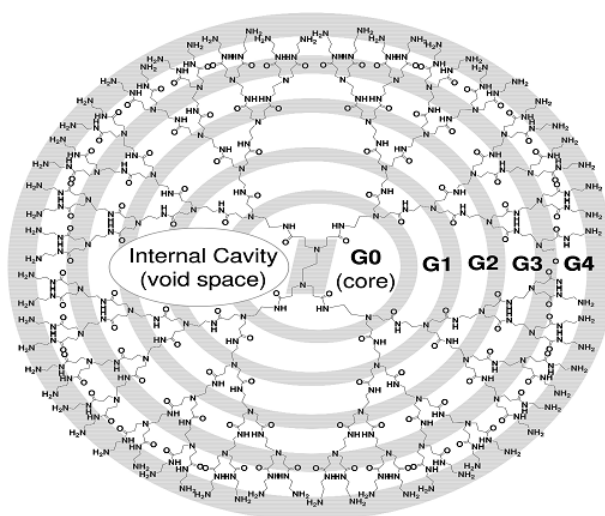


Figure 9: Schematic representation of a generation G4 dendrimer with 64 amino groups at the periphery. This dendrimer starts from an ethylene diamine core; the branches or arms were attached by exhaustive Michael addition to methyl acrylate followed by exhaustive aminolysis of the resulting methyl ester using ethylene diamine. This sequence of reactions was applied in an iterative fashion to increase the level of generations. The periphery of successive generations is marked by grey circles, starting from G0, G1, G2, G3 and G4. Of note, distinctive features of dendrimers, including the densely-packed membrane-like arrangement of surface functional groups, the formation of internal cavities, and the condensation into globular structures (not shown), are typically manifest at the G4 stage.

The cytotoxicity and encapsulation efficiency of star amphiphilic PAMAM block copolymers containing poly(γ -caprolactone) and PEG arms has also been assessed. The polymer forms micelles in solution which were non-cytotoxic. The anti-cancer drugs doxorubicin and etoposide were encapsulated within the micelles. Doxorubicin showed low encapsulation efficiency while the more lipophilic etoposide achieved a loading capacity of approximately 22% by weight.

Unloaded dendrimer was non-cytotoxic to porcine kidney epithelial cells, while etoposide-encapsulated dendrimers showed comparable toxicity to free etoposide at similar drug concentrations.²⁸

Quantum dots (tumor imaging)

Current methods of tumor imaging include the use of organic and radiolabeled dyes that fluoresce in the UV spectrum. These methods lack the ability to penetrate deep into tissues, only allowing for detection of near surface tumors. Additionally, these methods are susceptible to photobleaching and chemical degradation. Quantum dots, consisting of semiconductor core molecules surrounded by metal shells and biocompatible protein coatings, are arising as a new method of tumor imaging. These nanoparticles have been shown to penetrate tissues deeper, resist photobleaching, and



resist chemical degradation for longer time spans than traditional methods, making them candidates for long-range tumor tracking. However, many cytotoxicity factors remain under investigation, making quantum dots only suitable for current *in vitro* human studies. Although quantum dots can be used for a wide range of things, a major focus of use in recent years has been on tumor imaging of cancerous cells. Although QDs hold so much potential for tumor imaging and cancer research, toxicity is still a major issue when dealing with semiconductors. Quantum dot nanocrystals are most commonly made from cadmium selenide, a highly toxic metal, capped with zinc sulfide. Because of this, current study of QDs is restricted to *in vitro* human research, as well as *in vivo* research in animals. Different coating techniques are under investigation to help make QDs safe for use in humans.²⁹

APPLICATIONS OF NANOMEDICINE

In cardiovascular disease, nanomedicine applications are based on recognition and therapy of early atherosclerosis before myocardial infarction, discovery of unstable carotid plaques before the onset of stroke, prevention of restenosis following angioplasty without impaired vessel healing, and early delivery of thrombolytic enzymes to intravascular thrombi with less risk for adverse events.³⁰

Nanotechnology applications are being used to protect the CNS from free-radical damage, which plays a significant role in various pathologies, including trauma and degenerating neurologic disorders.³¹

Nanotechnology has provided the means of producing pure silver nanoparticles (SNPs), markedly increasing the rate of silver ion release. SNPs have been shown to destroy Gram-negative bacteria more effectively than Gram-positive bacteria. They also exhibit good antifungal activity, synergism when associated with commonly used antibiotics such as ceftazidime, additive effects when associated with streptomycin, kanamycin, ampiclox, polymyxin B, as well as antagonistic effects with chloramphenicol.³²

The development of nanoparticle-based vaccines for HIV/AIDS is at an early stage, there has been recent progress. Nanotechnology can impact the treatment and prevention of HIV/AIDS with various innovative approaches. Treatment options may be improved using nanotechnology platforms for delivery of antiretroviral drugs.

In addition to delivering antiviral drugs, nanomaterials have shown their ability to inhibit viral replication by themselves. Fullerenes, dendrimers and inorganic nanoparticles such as silver have antiviral effects or improve antiviral effects of other molecules, as in the case of gold nanoparticles.³³

CONCLUSION

The biology of cancer, as well as the demands of clinical oncology, will likely serve as drivers for the further development of micro/nano technologies. As representative examples, drivers include protein biomarker development, understanding the tumor microenvironment, interrogating the functional status of the immune system of cancer patients, interrogating the interrelationship between the immune system and cancer and stratifying patients and patient responses for molecularly targeted therapies. The best technology solutions will be cost effective, rapid, highly multiplex, and of course robust.

Furthermore developments in cancer treatment using nanomedicine is achieved by:

(1) Identifying appropriate ligands specific to cancer cells from different tissue types and to metastatic, recurrent, and drug-resistant cancer populations. Of particular interest would be to identify ligands that can target both tumor cells and the tumor microenvironment simultaneously; (2) Developing organ-specific orthotopic animal models including those of metastasis and drug resistance, which are essential to evaluate TNPs in the treatment of specific phenotypes; (3) Conducting pre-clinical PD/PK and toxicology studies for Investigational New Drug (IND) filing and (4) Collaborating with FDA to conduct the relevant clinical trials.

In near future nanomedicine applications will be including activity monitors, chemotherapy, biochips, insulin pumps, needle less injectors, medical flow sensors and blood pressure, glucose monitoring devices and drug injecting systems. At its best nanomedical machine may replicate back to them and could cover up the deficiencies by replacing or improving the DNA molecules of body.

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