International Journal of Drug Development & Research
| January-March 2012 | Vol. 4 | Issue 1 | ISSN 0975-9344 |
Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03,& H index 2

Review Paper
Covered in Index Copernicus with IC Value 4.68 for 2010

Treatment of cancer by using Nanoparticles as a Drug Delivery

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Abstract

Although the "war on cancer" is now in its fourth decade and despite much progress has been made in categorizing the environmental causes and cellular and molecular biological basis for this dreaded disease, we still do not have a precise understanding of the differences between a cancer cell and its normal counterpart. If we do not understand cancer, we cannot control, conquer, and eliminate it. The completion of the human genome sequence and its subsequent improvements in the sequence data are important steps to fully comprehend cancer cell biology.

Nanotechnology, a new, novel focus of research evolved from the convergence and coalescence of many diverse scientific disciplines and as a general term for the creation, manipulation, and application of structures in the nanometer size range. In this article, Nano medicine aspects of nanotechnology will be stressed and will cover areas such as drug delivery systems and new drug therapies as they relate to cancer. One of the ultimate goals of Nano medicine is to create medically useful Nano devices that can function inside the body. It is envisioned that Nano devices will be hybrids of biologic molecules and synthetic polymers that can enter cells and the organelles to interact directly with DNA and proteins. Additionally, Nano medicine will have an impact on the key challenges in cancer therapy: localized drug delivery and specific targeting. Among the newly developed Nano medicine and Nano devices such as quantum dots, nanowires, nanotubes, Nano cantilevers, and Nano pores, Nano shells and nanoparticles are the most promising applications for various cancer treatments.

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Key words:

Nanoparticles, cancer, chemotherapy

***How to Cite this Paper*:**

Dimendra J Patel*, Pratik A Mistri, Jatin J Prajapati "Treatment of cancer by using Nanoparticles as a Drug Delivery", Int. J. Drug Dev. & Res., Jan-March 2012, 4(1): 14-27

Article History:----------
Date of Submission: 29-11-2011
Date of Acceptance: 06-12-2011
Conflict of Interest: NIL
Source of Support: NONE

INTRODUCTION

Nanoscale devices are 100 to 10,000 times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body. Nanodevices are suitable to serve as customized, targeted drug delivery vehicles to carry large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing

healthy cells. Nanodevices can be constructed by the molding or etching, top-down approach, or by assembling structures atom by atom or molecule by molecule, bottom-up approach. [1] [2]

We are now closer to being able to fully characterize the differences between the normal and the tumor cell. Coupled with the use of micro dissection techniques [3], it is also possible to interrogate the genetic make-up of individual cell types. The hope is that use of such technologies will accelerate the progress in identifying the differences between normal and tumor cells, which in turn will lead to development of new therapies that will specifically target the cancer. The ultimate goal of these strategies is to eliminate the tumor with limited effect on normal tissue.

NANOTECHNOLOGY AND TARGETED DRUG DELIVERY

The greatest immediate impact of nanotechnologies in cancer therapy is in drug delivery. The therapeutic index of nearly all drugs currently being used can be improved if they are more efficiently delivered to their biological targets through appropriate application of nanotechnologies [4] [5]. Some drugs that have previously failed clinical trials might also be re examined using Nano technological approaches. A number of obstacles may be overcome with various novel applications of Nano drug delivery. For example, many drugs are not very soluble, making it difficult to administer therapeutic doses [6] [7]. These compounds can be "solubilized" by formulating them into crystalline Nano suspensions that are stabilized by surfactants [7], or by combining them with organic or lipid nanoparticles that keep them in circulation for longer periods [8] [9] [10]. If an efficacious compound has a short half-life in the circulation, its stability can be increased tremendously by encasing it within nanosized liposomes as a drug carrier [9]. In the case of central nervous system cancers, many drugs have difficulty in crossing the blood– brain barrier to attack the tumor. Drug-loaded nanoparticles are able to penetrate this barrier, and have been shown to greatly increase therapeutic concentrations of anticancer drugs in brain tumors [11] [12].

The best way to increase the efficacy and reduce the toxicity of a cancer drug is to direct the drug to its target and maintain its concentration at the site for a sufficient time for therapeutic action to take effect [13]. For example, lipid cationic nanoparticles coupled to an integrin-targeting ligand were shown to deliver genes selectively to angiogenic blood vessels in tumor-bearing mice. As the therapeutic part of the nanocomplex, a mutant RAF gene was coupled to the particle for transfection and expression in the tumor cells; expression of this mutant gene was shown to block angiogenesis in this model. The directed nanoparticle caused apoptosis in the tumors and a sustained regression of established primary and metastatic tumors [14]. The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure-mediated drug delivery, a key technology for the realization of nanomedicine, has the potential to enhance drug bioavailability, improve the timed release of drug molecules, and enable precision drug targeting [15] [16]. Nanoscale drug delivery systems can be implemented within pulmonary therapies [17], as gene delivery vectors [18], and in stabilization of drug molecules that would otherwise degrade too rapidly [19] [20].Additional benefits of using targeted Nano scale drug carriers are reduced drug toxicity and more efficient drug distribution [21].

Anatomic features such as the blood brain barrier, the branching pathways of the pulmonary system, and the tight epithelial junctions of the skin make it difficult for drugs to reach many desired physiologic targets. Nanostructured drug carriers help to penetrate or overcome these barriers to drug delivery. The greatest efficiency for delivery into the

pulmonary system is achieved for particle diameters of <100 nm. [17] Greater uptake efficiency has also been shown for gastrointestinal absorption [22] [23] and transcutaneous permeation [24], with particles around 100 nm and 50 nm in size, respectively. However, such small particles traveling in the pulmonary tract may also have a greater chance of being exhaled. Larger, compartmental or multilayered drug carrier architectures may help with delivery to the pulmonary extremities. For instance, the outer layers of the carrier architecture may be formulated to biodegrade as the carrier travels through the pulmonary tract. As the drug carrier penetrates further into the lung, additional shedding will allow the encapsulated drug to be released. Biodegradable nanoparticles of gelatin and human serum albumin show promise as pulmonary drug carriers [25].

Advantages of nanostructure-mediated drug delivery include the ability to deliver drug molecules directly into cells [26] and the capacity to target tumors within healthy tissue [27].

For example, DNA and RNA that is packaged within a nanoscale delivery system can be transported into the cell to fix genetic mutations or alter gene expression profiles. The mechanisms of cellular uptake of external particulates include clathrin-and caveoli-mediated endocytosis, pinocytosis, and phagocytosis. However, phagocytosis may not play a role in the uptake of nanoscale particles because of the small size of such particles [28].

Nanoscale drug delivery architectures are able to penetrate tumors due to the discontinuous, or "leaky," nature of the tumor microvasculature, which typically contains pores ranging from 100 to 1000 nm in diameter. The microvasculature of healthy tissue varies by tissue type, but in most tissues including the heart, brain, and lung, there are tight intercellular junctions less than 10 nm. Therefore, tumors within these tissue types can be selectively targeted by creating drug delivery nanostructures greater than the intercellular gap of the healthy tissue but smaller than the pores found within the tumor vasculature.

Through precise control of the drug carrier architecture, the release of the drug can be tuned to achieve a desired kinetic profile. Three of the most common kinetic profiles are zero order, first order, and Higuchi; these are depicted in figure 1 and expressed mathematically in the following equations. The delivery of most drugs is accomplished through oral administration or by injection and follows first-order kinetics. The ideal release profile for most drugs would follow a steady release rate so that the drug levels in the body remain constant while the drug is being administered. More recent transdermal drug delivery mechanisms follow the Higuchi model [29]. As shown subsequently, nanostructured polymeric and silica nanoparticles are being developed as drug carriers which achieve near zero-order kinetics.

Zero order: $D_t = D_o + K_o t$

First order: $\ln D_t = \ln D_o + K_1 t$

Higuchi order: $D_t = D_o = K_H t^{1/2}$

Where D_t is the amount of drug released at time *t*, D_o is the initial amount of drug released, result of initial rapid release,

k_o is the zero-order release constant,
k_t is the first-order release constant, and
k_H is the Higuchi release constant.

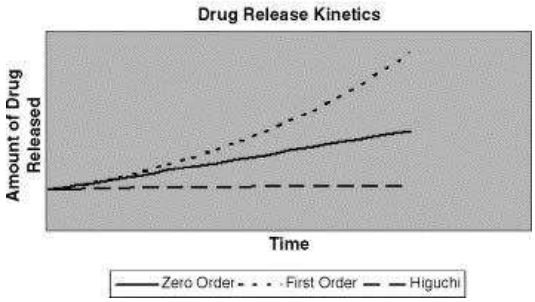

Fig. 1: Drug release profiles from zero order, first order, and Higuchi kinetics.

Various nanoscale architectures can be realized including solid spheres, hollow spheres, tubes, porous particles, solid particles, and branched structures. To achieve such nanostructures, different fabrication methods are used depending on the type of material. The methods used for nanoscale assembly include molecular self-assembly [30], bio aggregation [31], nanomani- pulation [32], photochemical patterning [33], molecular imprinting [33], layer-by-layer electrostatic deposition [34] [35], and vapor deposition [36].

Liposomes (phospholipid spheres of ~100 nm in diameter that are bi-layered in structure) are excellent carriers for a variety of drugs [9] and are being tested extensively for use in gene therapy protocols and targeted drug delivery in cancer. With current liposome technologies it is not difficult to transfect a cell for purposes of gene therapy, but the therapeutic gene may be degraded if it is not able to traffic out of the endosome. To enhance the efficacy of gene therapy, synthetic pH-sensitive histidylated oligolysine can be added to a drug-liposome complex to aid in escaping from the endosome [37]. This protocol was shown to improve the transfection efficiency in prostate and pancreatic cancer cell lines by 39 mfold, and elevated the expression of the transgene in a human prostate cancer xenograft model in athymic nude mice without increasing toxicity.

Monoclonal antibodies are good targeting vehicles for nanoparticles but other bio conjugates are being tested with varying degrees of success. Nucleic acid ligands called aptamers that mimic antibodies are potential replacements because they can be designed to bind to practically any antigen in an in vitro system. The aptamers are generated by evolutionary methods in vitro, and the molecules with high affinity are used for targeting antigens in vivo. This strategy has been applied to directing PEG-coated nanoparticles to home in on prostate-specific membrane antigen in prostate cancer cells. The aptamer conjugated particles were shown to have a 77-fold increase in binding versus the control particles, and a large increase in uptake of drug-encapsulated particles [38]. There are numerous examples of similar type targeting of nanoparticles [5] [13] [39] [40] [41], and this area of research promises to provide important weapons in the arsenal for developing a cure for cancer.

One of the ultimate goals of nanotechnology is to create medically useful nanodevices that can function inside the body. It is envisioned that nanodevices will be hybrids of biologic molecules and synthetic polymers that can enter cells and the organelles to interact directly with DNA and proteins [42]. Additionally, nanomedicine will have an impact on the key challenges in cancer therapy: localized drug delivery and specific targeting. Among the newly developed nanomedicine and nanodevices such as quantum dots, nanowires, nanotubes, nanocantilevers, and nanopores, nanoshells and nanoparticles are the most promising applications for various cancer treatments.

The gold nanoshell-antibody complex can be used to ablate breast cancer cells. Nanoshells [43] have a core of silica and a metal outer layer. They can preferentially concentrate in cancer lesion sites through enhanced permeation retention. A near-infrared laser illuminates the tissue, and the light will be absorbed by the nanoshells to generate an intense heat that destroys only the cancer cells without damaging the surrounding healthy cells [44]. Nanoparticles have already been used for targeted drug delivery, which enables much earlier detection [45] and immediate treatment of cancer.

Nanoparticles attached to chemotherapeutic drugs allow them to traverse the blood-brain barrier for brain tumor treatment [46]. In January 2005, a nanoparticle-based drug called Abraxane (paclitaxel protein- bound particles, Abraxis Oncology) was approved by the Food and Drug Administration for

breast cancer treatment. Abraxane uses nanoscaled particles of the natural protein albumin that can be delivered in the body without the use of solvents.

POLYMER MATERIALS

A review of biodegradable polymeric materials that show promise for drug delivery applications is compiled in Ulrich *et al* [47]. Biodegradable polymer nanoparticles, typically consisting of polylactic acid (PLA), polyglycolic acid (PGA), or a copolymer of PLA and PGA, are being investigated for the delivery of proteins and genes [48] [49], vaccines [50] [51] and anticancer drugs [52] [13] [53].

Dendrimers, a unique class of polymers, are highly branched macromolecules whose size and shape can be precisely controlled [54] [55]. Dendrimers are fabricated from monomers using either convergent or divergent step-growth polymerization.

Two representations of polyamidoamine-based Dendrimers are shown in figure 2. The well-defined structure, monodispersity of size, surface functionalization capability, and stability are properties of dendrimers that make them attractive drug carrier candidates. Drug molecules can be incorporated into dendrimers via either complexation or encapsulation as shown in figure 3. Dendrimers are being investigated for both drug and gene delivery [56] [57], as carriers for penicillin [58] [59], and for use in anticancer therapy [60] [61]. Dendrimers used in drug delivery studies typically incorporate one or more of the following polymers: polyamidoamine (PAMAM) [62] [63], melamine [64], poly (L-glutamic acid) (PG) [65], polyethyleneimine (PEI) [65], poly (propylene imine) [66], and poly (ethylene glycol) (PEG) [66]. Chitin and chitosan have also been incorporated with dendrimers [67].

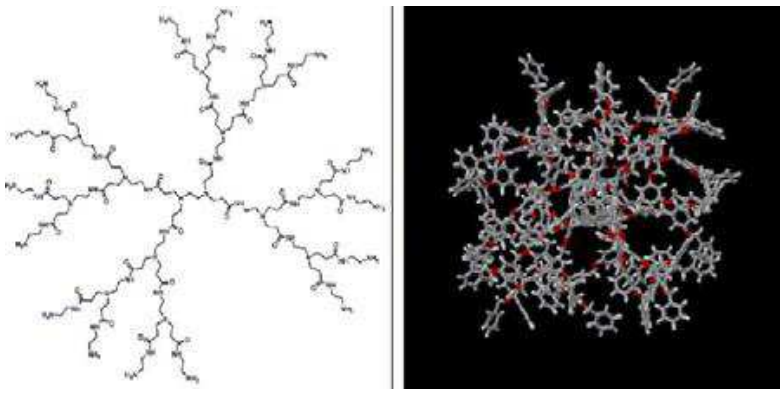

Fig. 2: Example chemical structure of a polyamidoamine dendrimer *(left)*. Stick model representation of a polyamidoamine dendrimer *(right)* [68]

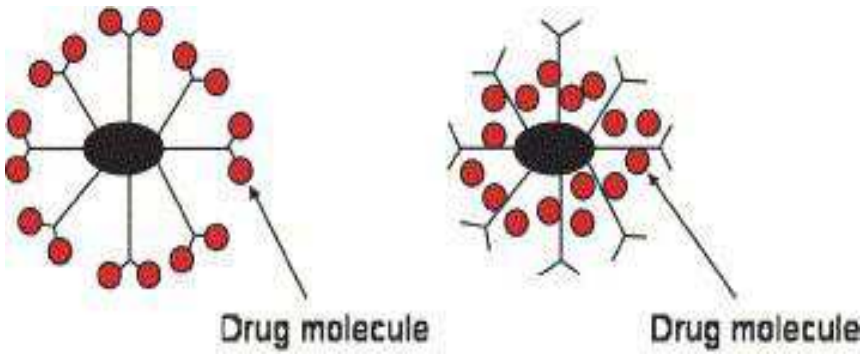

Fig. 3: Schematic of incorporation of drug within a dendrimer structure. Complexation—covalent attachment to End groups *(left)*. Encapsulation—entrapment inside dendrimer core *(right)* [68].

SILICON-BASED STRUCTURES

Silicon-based structures can be fabricated by photolithography, etching, and deposition technique commonly used in the manufacture of semiconductors and microelectromechanical systems (MEMS). The most commonly investigated silicon-based materials for drug delivery are porous silicon and silica, or silicon dioxide. Architectures include calcified nanopores, platinum- containing nanopores, porous nanoparticles, and nanoneedles [69] [70]. The density and diameter of the nanopores can be accurately controlled to achieve a constant drug delivery rate through the pores.

Porous hollow silica nanoparticles (PHSNP) are fabricated in a suspension containing sacrificial nanoscale templates such as calcium carbonate [71]. Silica precursors, such as sodium silicate, are added into the suspension, which is then dried and calcinated creating a core of the template material coated with a porous silica shell. The template material is then dissolved in a wet etch bath, leaving behind the porous silica shell. Creation of drug carriers involves the mixing of the PHSNPs with the drug molecule and subsequently drying the mixture to coalesce the drug molecules to the surface of the silica nanoparticles [71].

Through controlling the pore size and the particle diameter, the release kinetics approach near zero-order, where the release behavior of conventional silica nanoparticles is compared with that of porous hollow silica nanoparticles. As shown, the porous hollow nanoparticles exhibit a much more desirable gradual release [72].

Examples of therapies being investigated for use with silicon-based delivery systems include porous silicon embedded with platinum as an antitumor agent [73], calcified porous silicon designed as an artificial growth factor [74], silicon nanopores for antibody delivery [70] [75] and porous silica nanoparticles containing antibiotics [71], enzymes [76] and DNA [77].

METAL STRUCTURES

Hollow metal nanoshells are being investigated for drug delivery applications [78]. Typical fabrication methods involve templating of the thin metal shell around a core material such as a silica nanoparticle. Typical metals include gold, silver, platinum, and palladium. When linked to or embedded within polymeric drug carriers, metal nanoparticles can be used as thermal release triggers when irradiated with infrared light or excited by an alternating magnetic field [79]. Bimolecular conjugation methods of metals include bifunctional linkages, lipophilic interaction, silanization, electrostatic attraction, and nanobead interactions [80].

NANOMEDICINE AND NEW DRUG THERAPIES FOR CANCER

All drug molecules are, in essence, products of natural or synthetic nanoengineering. For example, the most widely used and effective drug, the common aspirin, is only about 0.6 nm [81]. On the “large” side are therapeutic monoclonal antibodies that are approximately 30 nm in length. Many of the globular proteins, such as hemoglobin, are 5 nm in diameter, and natural proteins of similar size may be used as a therapeutic. Double-stranded DNA in the nucleus is about 2.5 nm in width, but totals 2 meters in length in the mammalian cell, an astounding example of “Nano packing” in a 2- to 5-µm–diameter nucleus.

Medicinal and structural chemists have been creating and manipulating nanometer and sub nanometer sized components of drugs for decades, and will continue to do so into the foreseeable future. The difference is that they will now be joined by a wide variety of scientists from a number of disciplines normally not involved in drug research.

A recent article written by physicists in *Physical Review Letters* [82], titled “Electronic Structure and Bonding of Au on a Si Oh, not zero 2 Cluster: A Nanobullet for Tumors,” is a good example of how research from diverse sources can and should be

brought to bear on the problem of cancer. Success in this endeavor, however, will require a concerted effort to integrate and coordinate the research in an approach that might now be described as "systems biology" [83] [84].

What are the requirements for an effective and safe cancer drug [85]?

There must be an adequate drug concentration in the body to allow for an effective dose at the tumor site. The target must be strongly inhibited, with the target's function essential for tumor cell viability. The drug must have a high differential toxicity toward the tumor or a favorable therapeutic window.

Research in nanomedicine will be addressing all these points, and a few examples in the drug development arena will be given below.

Monoclonal antibodies will be an essential component of the new wave of cancer treatments developed through nanotechnologies. They are being used as imaging vehicles, for drug targeting, as drug carriers, and as the drug itself. There are 9 or more FDA-approved antibodies approved for clinical use in cancer [86] [87] [88], and many more are being evaluated in clinical trials. The mechanism of action of the antibodies includes receptor ligand binding competition; interference with receptor function; antibody-dependent, cell-mediated cytoxicity; complement-dependent cellular cytoxicity; or, perhaps, a combination of the above. This activity can also be combined with toxins directed at the cancer cell to produce an even more efficacious drug.

One of the holy grails of drug research is to be able to rationally design and produce effective small-molecule inhibitors of protein function [89] [90] [91] [92] [93] [94] [95]. Development of many drugs will be the result of application of nanotechnologies that have been in place for many years. For example, nuclear magnetic resonance and x-ray crystal structures of target proteins and their ligands or substrates are being used as the template for rational design of new drugs. The target may be enzymes or receptor–ligand proteins. Inhibitors of enzymatic activity are, in general, easier to design than blockers of protein–protein interactions. As an example, the first successful drug approved for the treatment of chronic myeloid leukemia (CML), Gleevec, is an inhibitor of the tyrosine kinase mutant, BCR-ABL [96] [97].

In many patients, administration of the drug results in what appears to be complete remission, but Gleevec-resistant leukemia often returns through mutations in the active site. By careful study of the mutations and the structure of the kinase, new small molecular inhibitors were designed that could block the mutant strains and appear to be more efficacious than the original drug [98] [99] [100]. The two drugs are reported to work synergistically, which will, hopefully, result in a complete cure of chronic myeloid leukemia.

Drugs derived from nucleic acids are beginning to make an impact on the nanomedicine scene. Antisense technology [101] exploits the use of oligonucleotides in the range of 15 to 20 nucleotides to block the function of an RNA target. This technology has made rapid progress after experiencing initial difficulties in showing efficacy for in vivo models of disease. Ongoing clinical trials using antisense drugs include prostate, breast, pancreatic, lung, colorectal, melanoma, and brain cancers.

A novel approach for this technology is to use oligonucleotides for sensitizing tumor cells to chemotherapy. The oligonucleotides are being combined with Nano liposomes to target and deliver the nucleic acids to the cancer cells [102] and block production of the alpha folate receptor. This block was shown to decrease cell survival of breast cancer cell lines, and sensitized a cell line by 5-fold to doxorubicin. This is a good example of how nanotechnologies can be used to increase the effectiveness of existing drugs, facilitating the use of lower dosages to decrease toxicity.

The latest additions to the repertoire of gene-specific silencing agents are the "small interfering" RNAs or siRNAs [103] [104] [105], which are the effector molecules of the RNA interference (RNAi) pathways found in most eukaryotes. The siRNAs are small double-stranded molecules of about 21 nucleotides in length that result in specific degradation of mRNAs containing the complementary sequence. This specificity makes siRNAs attractive candidates as nanodrugs for blocking the expression of wayward genes in cancer, but their application can be hindered by instability in the blood and poor uptake into the target cells. To overcome these problems, siRNA has been complexed with nanoparticles containing a homing sequence that directs the complex to the tumor site [41].

A fascinating approach for eradicating tumors is through the application of cancer immunotherapy or vaccines [106] [107] [108]. It is thought that the body can eliminate small tumors by an appropriate immune response, but at some point a malignant cancer is able to evade the response by developing mechanisms that blind the host to its presence. If methods can be found to activate the immune system against these tumors, the body should be able to destroy the cancer, and all forms of cancer might be susceptible to this type of immunotherapy. Tumor antigens by themselves are not very immunogenic and require some type of adjuvant to boost the immune response against the cancer. A new vaccine design has been developed that couples the antigens to solid-core nanobeads [109]. For effectiveness, the beads have to be of narrowly defined size (40 nm to 50 nm), which allows them to localize to dendritic cells in the draining lymph nodes.

Conjugation of the antigens to the nanobeads induced responses that were 2 to 10 fold higher than other bead sizes, and higher than currently used immunizing adjuvants were tested. A single dose of the antigen-coated beads protected mice from tumors in 2 different model challenges, and was even able to cause rapid clearance of established tumors. This is a good example of how nanotechnologies may provide a major breakthrough in cancer therapy and the effectiveness of vaccines in general.

Cancer immunotherapy may provide a relatively benign, nonchemotherapeutic method of destroying tumors. Another promising and, perhaps, complementary approach is the thermal ablation method of tumor destruction. Treatment of solid tumors with hyperthermia has been an option for some time [110], but has some drawbacks. For deep, underlying tumors, the energy source can harm the intervening and surrounding healthy tissue even when focused beam are used. To overcome this problem methods have been developed to selectively heat the tumors using near-infrared–absorbing gold nanoparticles called nanoshells [111] [112] [113]. Nanoshells, in this case, are composed of a silica core surrounded by a thin gold metal shell, and will absorb energy (heat up) when exposed to the appropriate wavelength of light. The near-infrared characteristics were chosen because absorption by tissues is minimal and penetration of the light is optimal at this wavelength. The nanoshells were injected into mice, and the nanoparticles were simply allowed to accumulate in implanted tumors. This can occur as most tumor vasculature is "leaky," and will allow nanosized particles to penetrate into the tumor while normal tissue or organs are not affected. The tumors are then illuminated with a near infrared diode laser to heat the tumor and cause cellular destruction. By this protocol all the tumors were ablated, and the mice remained tumor-free for many months.

Although not used in these studies, the efficacy of the procedure could be improved by attachment of tumor homing or -targeting molecules to the Nano shells for increasing concentration at the site of heating. In appropriate settings, thermal ablation methods could be used to replace surgical resection of tumors, and targeted therapies and immunotherapy as a

substitute for toxic chemotherapy. It is becoming increasingly clear that a "one-two punch" is needed to eradicate tumors, and the Nano medicinal methods being developed have a good chance of achieving this goal with much less damage to normal tissue than existing therapeutic protocols.

SUMMARY

If the incidence of deaths from cancer had dropped as much as heart disease, cancer would be approaching the status of a rare disease. Instead, overall cancer mortality has changed little during the last decade, while deaths from heart disease have plummeted almost by half. Although cancer may be more complex than cardiovascular disease, it is not inconceivable that lifestyle changes (smoking cessation) and new drugs developed from Nano technological and other medical advances could create the same laudable statistic for cancer as heart disease in the next decade.

Nano technological studies are not new. In essence, all drug molecules can be considered as Nano engineered structures. What is new is the inclusion of a number of other Nano- based approaches to medicinal studies. For example, the antibody-conjugated nanosized liposomes demonstrate significant improvement over conventional, less-directed drug delivery protocols. Monoclonal antibodies and vaccines directed against tumors have been extensively studied, while antisense oligonucleotides and siRNAs are more recent additions to the nanomedicine repertoire. Tumor destruction via the use of nanoshells for thermal ablation is also being examined and shows promise as a nonsurgical method for tumor removal. Precise knowledge of the normal and cancer genome is at hand, and the structure and function of all genes are now within grasp of the medicinal chemist and drug developers. This will allow the creation of nontoxic, targeted small-molecule drugs for use in the oncology clinic. Due to the complexity of cancers, a combination of approaches will likely be needed for the effective elimination of all tumor cells.

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