

---

**REVIEW**

**NANOPARTICLES IN DRUG DELIVERY FOR THE TREATMENT OF CANCER**

**M. SAEED ARAYNE AND NAJMA SULTANA\***

*Department of Chemistry, University of Karachi, Karachi-75270, Pakistan*

*\*Department of Pharmaceutical Chemistry, Research Institute of Pharmaceutical Sciences,  
Faculty of Pharmacy, University of Karachi, Pakistan*

**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.

---

*Corresponding author:* E-mail: arayne@gawab.com

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, nanomedicine 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 nanomedicine 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. 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.

**Keywords:** Nanoparticles, cancer, chemotherapy.

## 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.

The completion of the human genome sequence in 2001 (International Human Genome Sequencing Consortium 2001; Venter *et al.* 2001) and subsequent improvements in the sequence data (International Human Genome Sequencing Consortium 2004) are important steps to fully comprehend cancer cell biology. We are now closer to being able to fully characterize the differences between the normal and the tumor cell. Coupled with the use of microdissection techniques (Player 2004), 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 (Sahoo and Labhassetwar 2003; Vasir *et al.*, 2005). Some drugs that have previously failed clinical trials might also be re-examined using nanotechnological approaches. A number of obstacles may be overcome with various novel applications

of nanodrug delivery. For example, many drugs are not very soluble, making it difficult to administer therapeutic doses (Kipp 2004; Muller and Keck 2004; Rabinow 2004). These compounds can be "solubilized" by formulating them into crystalline nanosuspensions that are stabilized by surfactants (Rabinow 2004), or by combining them with organic or lipid nanoparticles that keep them in circulation for longer periods (Horn and Rieger 2001; Torchilin 2005; Wissing *et al.*, 2004). 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 (Torchilin 2005). 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 (Koziara *et al.*, 2004; Steiniger *et al.*, 2004).

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 (Vasir *et al.*, 2005; Brannon-Peppas and Blanchette 2004). 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 (Hood *et al.*, 2002).

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 (Dubin 2004; Dass and Su 2001). Nanoscale drug delivery systems can be

implemented within pulmonary therapies (Courrier *et al.*, 2002), as gene delivery vectors (Senior 1998), and in stabilization of drug molecules that would otherwise degrade too rapidly (LaVan *et al.* 2002; LaVan *et al.*, 2003). Additional benefits of using targeted nanoscale drug carriers are reduced drug toxicity and more efficient drug distribution (Ravi Kumar 2000).

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. Courrier *et al* (Courrier *et al.*, 2002) have shown that the greatest efficiency for delivery into the pulmonary system is achieved for particle diameters of <100 nm. Greater uptake efficiency has also been shown for gastrointestinal absorption (Desai 1996; Hussain *et al.*, 2001) and transcutaneous permeation (Kohli and Alpar 2004), 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 (Brzoska *et al.*, 2004).

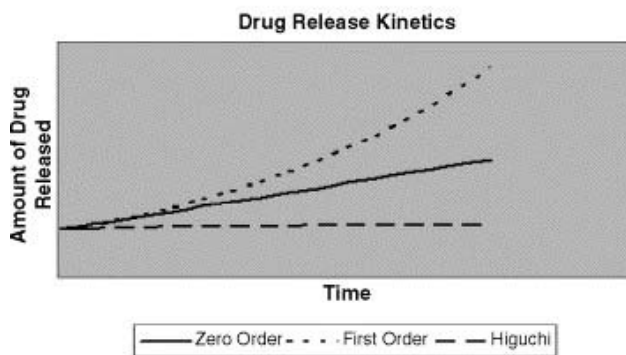
Advantages of nanostructure-mediated drug delivery include the ability to deliver drug molecules directly into cells (Martin and Kohli, 2003) and the capacity to target tumors within healthy tissue (Drummond *et al.*, 1999). For example, DNA and RNA that is packaged within a nanoscale delivery system 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 (Moselhy *et al.*, 2000).

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 (Costa and Sousa Lobo 2003). As shown subsequently, nanostructured polymeric and silica nanoparticles are being developed as drug carriers which achieve near zero-order kinetics.

$$\begin{aligned} \text{Zero order:} \quad D_t &= D_0 + K_0t \\ \text{First order:} \quad \ln D_t &= \ln D_0 + K_1t \\ \text{Higuchi order:} \quad D_t &= D_0 = K_Ht^{1/2} \end{aligned}$$

where  $D_t$  is the amount of drug released at time  $t$ ,  $D_0$  is the initial amount of drug released, result of initial rapid release,  $k_0$  is the zero-order release constant,  $k_1$  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 (Zhang 2002), bioaggregation (Mirkin *et al.*, 1996), nanomanipulation (Hansma *et al.*, 2004), photochemical patterning (Cui 2003), molecular imprinting (Cui 2003), layer-by-layer electrostatic deposition (Ai 2003; Ai 2002), and vapor deposition (Mamalis *et al.*, 2004).

Liposomes (phospholipid spheres of ~100 nm in diameter that are bi-layered in structure) are excellent carriers for a

variety of drugs (Torchilin 2005) 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 (Yu *et al.*, 2004). This protocol was shown to improve the transfection efficiency in prostate and pancreatic cancer cell lines by 39-fold, 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 bioconjugates 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 (Farokhzad *et al.*, 2004). There are numerous examples of similar type targeting of nanoparticles (Vasir *et al.*, 2005; Brannon-Peppas and Blanchette 2004; Cortez-Retamozo *et al.*, 2004; Gillies and Frechet 2005; and (Schiffelers *et al.*, 2004), 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 (Xie and Gao 2005). 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 (Shi *et al.*, 2005) 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

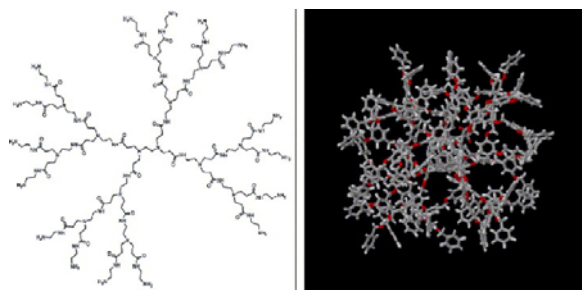
without damaging the surrounding healthy cells (West and Halas 2003).

Nanoparticles have already been used for targeted drug delivery, which enables much earlier detection (Karhanek *et al.*, 2005) and immediate treatment of cancer. Nanoparticles attached to chemotherapeutic drugs allow them to traverse the blood-brain barrier for brain tumor treatment (Lockman *et al.*, 2002). 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.

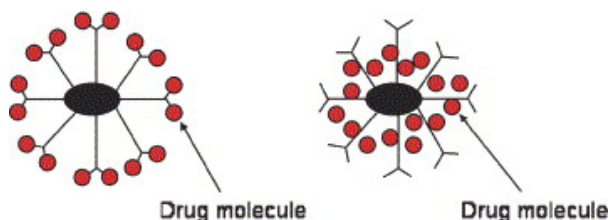
### **Polymer materials**

A review of biodegradable polymeric materials that show promise for drug delivery applications is compiled in Ulrich *et al.* (Ulrich *et al.*, 1999). 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 (Panyam and Labhassetwar 2003; Panyam *et al.*, 2003), vaccines (Nugent *et al.*, 1998; Katare *et al.*, 2003) and anticancer drugs (Lee *et al.*, 2002; Brannon-Peppas and Blanchette 2004; Rosiak *et al.*, 2003).

Dendrimers, a unique class of polymers, are highly branched macromolecules whose size and shape can be precisely controlled (Pricl *et al.*, 2003; Namazi and Adeli 2004). 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 (Cloninger 2002; Hussain *et al.*, 2004), as carriers for penicillin (Yang and Lopina 2003; Xike *et al.*, 2005), and for use in anticancer therapy (Quintana *et al.*, 2002; Meijer and Van Genderen 2003). Dendrimers used in drug delivery studies typically incorporate one or more of the following polymers: polyamidoamine (PAMAM) (Kannan *et al.*, 2004; Jevprasesphant *et al.*, 2004), melamine (Neerman *et al.*, 2004), poly(L-glutamic acid) (PG) (Tansey *et al.*, 2004), polyethyleneimine (PEI) (Tansey *et al.*, 2004), poly(propylene imine) (Paleos *et al.*, 2004), and poly(ethylene glycol) (PEG) (Paleos *et al.*, 2004). Chitin and chitosan have also been incorporated with dendrimers (Sashiwa and Aiba 2004).



**Fig. 2:** Example chemical structure of a polyamidoamine dendrimer (*left*). Stick model representation of a polyamidoamine dendrimer (*right*) (Hughes 2005).



**Fig. 3:** Schematic of incorporation of drug within a dendrimer structure. Complexation—covalent attachment to end groups (*left*). Encapsulation—trapment inside dendrimer core (*right*) (Hughes 2005).

### Silicon-based structures

Silicon-based structures can be fabricated by photolithography, etching, and deposition techniques 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 (Prinz *et al.* 2003; Tao and Desai 2003). 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 (Chen *et al.*, 2004). 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 (Chen *et al.*, 2004).

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 (Li *et al.*, 2004).

Examples of therapies being investigated for use with silicon-based delivery systems include porous silicon embedded with platinum as an antitumor agent (Li *et al.* 2000), calcified porous silicon designed as an artificial growth factor (Weis *et al.*, 2002), silicon nanopores for antibody delivery (Tao and Desai 2003; Leoni and Desai (2004) and porous silica nanoparticles containing antibiotics (Chen *et al.* 2004), enzymes (Jain *et al.* 1998) and DNA (Sameti *et al.*, 2003).

### Metal structures

Hollow metal nanoshells are being investigated for drug delivery applications (Sun *et al.*, 2002). 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 (Rösler *et al.*, 2001). Biomolecular conjugation methods of metals include bifunctional linkages, lipophilic interaction, silanization, electrostatic attraction, and nanobead interactions (Bagwe *et al.*, 2003).

### 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 (Whitesides 2003). 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 “nanopacking” in a 2- to 5- $\mu\text{m}$ -diameter nucleus.

Medicinal and structural chemists have been creating and manipulating nanometer- and subnanometer- 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* (Sun *et al.*, 2004), 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” (Hood *et al.*, 2004; Hood and Perlmutter 2004).

What are the requirements for an effective and safe cancer drug (Kamb 2005)? 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 (Ferrara *et al.*, 2004; Groner *et al.*, 2004; Von Eschenbach 2004), 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 cytotoxicity; complement-dependent cellular cytotoxicity; 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 (Arkin and Wells 2004; Brooijmans and Kuntz 2003; Card *et al.*, 2005; Erlanson *et al.*, 2004; Lipinski and Hopkins 2004; Rees *et al.*, 2004; Shoichet 2004). 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 (Capdeville *et al.*, 2002; Druker 2004). 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 (Burgess *et al.*, 2005; Gumireddy *et al.*, 2005; Shah *et al.*, 2004). The two drugs are reported to work synergistically, which will, hopefully, result in a complete cure of CML.

Drugs derived from nucleic acids are beginning to make an impact on the nanomedicine scene. Antisense technology (Crooke 2004) 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 nanoliposomes to target and deliver the nucleic acids to the cancer cells (Jhaveri *et al.*, 2004) 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 (Dorsett and Tuschl 2004; Downward 2004; Fuchs *et al.* 2004), 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 (Schiffelers *et al.*, 2004).

A fascinating approach for eradicating tumors is through the application of cancer immunotherapy or vaccines (Gilboa 2004; Pardoll 2003; Rosenberg *et al.* 2004). 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 (Fifis *et al.*, 2004). 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 (Stauffer and Goldberg 2004), 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 (Brongersma 2003; Hirsch *et al.* 2003; O'Neal *et al.* 2004). 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 nanoshells 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 nanomedicinal 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 nanotechnological and other

medical advances could create the same laudable statistic for cancer as heart disease in the next decade.

Nanotechnological studies are not new. In essence, all drug molecules can be considered as nanoengineered 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.

### **REFERENCES**

- Ai H (2002). Electrostatic layer-by-layer nanoassembly on biological microtemplates: platelets. *Biomacromolecules*, **3**: 560-564.
- Ai H (2003). Biomedical applications of electrostatic layer-by-layer nano-assembly of polymers, enzymes, and nanoparticles, *Cell Biochem. Biophys.*, **39**: 23-43.
- Arkin MR and Wells JA (2004). Small-molecule inhibitors of protein-protein interactions: progressing towards the dream, *Nat. Rev. Drug Discov.*, **3**: 301-317.
- Bagwe RP, Zhao X and Tan W (2003). Bioconjugated luminescent nanoparticles for biological applications, *J. Dispersion Sci. Technol.*, **24**: 453-464.
- Brannon-Peppas L and Blanchette JO (2004). Nanoparticle and targeted systems for cancer therapy, *Adv. Drug Deliv. Rev.*, **56**: 1649-1659.
- Brannon-Peppas L and Blanchette JO (2004). Nanoparticle and targeted systems for cancer therapy, *Adv. Drug Delivery Rev.*, **56**: 1649-1659.
- Brongersma ML (2003). Nanoscale photonics: nanoshells: gifts in a gold wrapper, *Nat. Mater.*, **2**: 296-297.
- Brooijmans N and Kuntz ID (2003). Molecular recognition and docking algorithms, *Annu. Rev. Biophys. Biomol. Struct.*, **32**: 335-373.
- Brzoska M, LangerK, Coester C, Loitsch S, Wagner TOF and Mallinckrodt CV (2004). Incorporation of biodegradable nanoparticles into human airway epithelial cells-in vitro study of the suitability as a vehicle for drug or gene delivery in pulmonary diseases, *Biochem Biophys Res. Commun.*, **318**: 562-570.
- Burgess MR, Skaggs BJ, Shah NP, Lee FY and Sawyers CL (2005). Comparative analysis of two clinically active

- BCR-ABL kinase inhibitors reveals the role of conformation-specific binding in resistance, *Proc. Natl. Acad. Sci., USA*.
- Capdeville R, Buchdunger E, Zimmermann J and Matter A (2002). Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug, *Nat. Rev. Drug Discov.*, **1**: 493-502.
- Card GL, Blasdel L, England BP, Zhang C, Suzuki Y and Gillette Y (2005). A family of phosphodiesterase inhibitors discovered by cocrystallography and scaffold-based drug design, *Nat. Biotechnol.*, **23**: 201-207.
- Chen JF, Ding HM, Wang JX and Shao L (2004). Preparation and characterization of porous hollow silica nanoparticles for drug delivery application, *Biomaterials*, **25**: 723-727.
- Chen JF, Ding HM, Wang JX and L. Shao L (2004). Preparation and characterization of porous hollow silica nanoparticles for drug delivery application, *Biomaterials*, **25**: 723-727.
- Cloninger MJ (2002). Biological applications of dendrimers, *Curr. Opin. Chem. Biol.*, **6**: 742-746.
- Cortez-Retamozo V, Backmann N, Senter PD, Wernery U, De Baetselier P and Muylldermans S *et al.* (2004). Efficient cancer therapy with a nanobody-based conjugate, *Cancer Res.* **64**: 2853-2857.
- Costa P and Sousa Lobo JM (2003). Evaluation of mathematical models describing drug release from estradiol transdermal systems, *Drug Dev. Ind. Pharm.*, **29**: 89-97.
- Courrier HM, Butz N and Vandamme TF (2002). Pulmonary drug delivery systems: recent developments and prospects, *Crit. Rev. Ther. Drug Carrier Syst.*, **19**: 425-498.
- Crooke ST (2004). Antisense strategies, *Curr. Mol. Med.*, **4**: 465-487.
- Cui D (2003). Advance and prospect of bionanomaterials, *Biotechnol Prog.*, **19**: 683-692.
- Dass CR and Su T (2001). Particle-mediated intravascular delivery of oligonucleotides to tumors: associated biology and lessons from gene therapy. *Drug Delivery*, **8**: 191-213.
- Desai MP (1996). Gastrointestinal uptake of biodegradable microparticles: effect of particle size, *Pharm. Res.*, **13**: 1838-1845.
- Dorsett Y. and Tuschl T (2004). siRNAs: applications in functional genomics and potential as therapeutics, *Nat. Rev. Drug Discov.*, **3**: 318-329.
- Downward J (2004). Use of RNA interference libraries to investigate oncogenic signalling in mammalian cells, *Oncogene*, **23**: 8376-8383.
- Druker BJ (2004). Imatinib as a paradigm of targeted therapies, *Adv. Cancer Res.*, **91**: 1-30.
- Drummond DC, Meyer O, Hong K and Kirpotin DB (1999). Papahadjopoulos. Optimizing liposomes for delivery of chemotherapeutic agents to solid tumors, *Pharmacol Rev.*, **51**: 691-743.
- Dubin CH (2004). Special delivery: pharmaceutical companies aim to target their drugs with nano precision, *Mech. Eng. Nanotechnol.*, **126**(Suppl.): 10-12.
- Erlanson DA, Wells JA and Braisted AC (2004). Tethering: fragment-based drug discovery, *Annu. Rev. Biophys. Biomol. Struct.*, **33**: 199-223.
- Farokhzad OC, Jon S, Khademhosseini A, Tran TN, Lavan DA and Langer R (2004). Nanoparticle-aptamer bioconjugates: a new approach for targeting prostate cancer cells. *Cancer Res.*, **64**: 7668-7672.
- Ferrara N, Hillan KJ, Gerber HP and Novotny W (2004). Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer, *Nat. Rev. Drug Discov.*, **3**: 391-400.
- Fifis T, Gamvrellis A, Crimeen-Irwin B, Pietersz GA, Li J and Mottram PL (2004). Size-dependent immunogenicity: therapeutic and protective properties of nano-vaccines against tumors. *J. Immunol.*, **173**: 3148-3154.
- Fuchs U, Damm-Welk C and A. Borkhardt A (2004). Silencing of disease-related genes by small interfering RNAs, *Curr. Mol. Med.*, **4**: 507-517.
- Gilboa E (2004). The promise of cancer vaccines, *Nat. Rev. Cancer*, **4**: 401-411.
- Gillies ER and Frechet J.M. (2005). Dendrimers and dendritic polymers in drug delivery. *Drug Discov. Today*, **10**: 35-43.
- Groner, Hartmann C and Wels W (2004). Therapeutic antibodies. *Curr. Mol. Med.*, **4**: 539-547.
- Gumireddy K, Baker SJ, Cosenza SC, John P, Kang AD and Robell KA (2005). A non-ATP-competitive inhibitor of BCR-ABL overrides imatinib resistance, *Proc. Natl. Acad. Sci., USA*, **102**: 1992-1997.
- Hansma HG, Kasuya K and Oroudjev E (2004). Atomic force microscopy imaging and pulling of nucleic acids, *Curr. Opin. Struct. Biol.*, **14**: 380-385.
- Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B and Price RE (2003). Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance, *Proc. Natl. Acad. Sci. USA* **100**: 13549-13554.
- Hood JD, Bednarski M, Frausto R, Guccione S, Reisfeld RA and Xiang R *et al.* (2002). Tumor regression by targeted gene delivery to the neovasculature, *Science*, **296**: 2404-2407.
- Hood L and Perlmutter RM (2004). The impact of systems approaches on biological problems in drug discovery. *Nat. Biotechnol.*, **22**: 1215-1217.
- Hood L, Heath JR, Phelps ME and Lin B (2004). Systems biology and new technologies enable predictive and preventative medicine, *Science*, **306**(2004): 640-643.
- Horn D and Rieger J (2001). Organic nanoparticles in the aqueous phase-theory, experiment, and use. *Angew. Chem. Int. Ed.*, **40**: 4330-4361.
- Hughes G. A. (2005) Nanostructure-mediated drug delivery Nanomedicine: Nanotechnology, Biology and Medicine **1**(1): 22-30.

- Hussain M, Shchepinov M, Sohail M, Benter IF, Hollins AJ and Southern EM (2004). A novel anionic dendrimer for improved cellular delivery of antisense oligonucleotides, *J. Controlled Release*, **99**: 139-155.
- Hussain N, Jaitley V and Florence AT (2001). Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lymphatics. *Adv. Drug Delivery Rev.*, **50**: 107-142.
- International Human Genome Sequencing Consortium, Finishing the euchromatic sequence of the human genome. *Nature*, **431**(2004): 931-945.
- International Human Genome Sequencing Consortium, Initial sequencing and analysis of the human genome. *Nature* **409**(2001): 860-921.
- Jain TK, Roy I, De TK and Maitra AN (1998). Nanometer silica particles encapsulating active compounds: a novel ceramic drug carrier. *J. Am. Chem. Soc.*, **120**: 11092-11095.
- Jevprasesphant R, Penny J, Attwood D and D'Emanuele A (2004). Transport of dendrimer nanocarriers through epithelial cells via the transcellular route. *J. Controlled Release*, **97**: 259-267.
- Jhaveri MS, Rait AS, Chung KN, Trepel JB and Chang EH (2004). Antisense oligonucleotides targeted to the human alpha folate receptor inhibit breast cancer cell growth and sensitize the cells to doxorubicin treatment, *Mol. Cancer Ther.*, **3**: 1505-1512.
- Kamb A (2005). Opinion: what's wrong with our cancer models? *Nat. Rev. Drug Discov.*, **4**: 161-165.
- Kannan S, Kolhe P, Raykova V, Glibatec M, Kannan RM and Lih-Lai M (2004). Dynamics of cellular entry and drug delivery by dendritic polymers into human lung epithelial carcinoma cells, *J. Biomat. Sci. Polymer Ed.*, **15**: 311-330.
- Karhanek M, Kemp JT, Pourmand N, Davis RW and Webb CD (2005). Single DNA molecule detection using nanopipettes and nanoparticles. *Nano Lett.*, **5**: 403-407.
- Katare YK, Panda AK, Lalwani K, Haque IU and Ali MM (2003). Potentiation of immune response from polymer-entrapped antigen: toward development of single dose tetanus toxoid vaccine. *Drug Delivery*, **10**: 231-238.
- Kipp JE (2004). The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. *Int. J. Pharm.*, **284**: 109-122.
- Kohli AK and Alpar HO (2004). Potential use of nanoparticles for transcutaneous vaccine delivery: effect of particle size and charge. *Int. J. Pharm.*, **275**: 13-17.
- Koziara JM, Lockman PR, Allen DD and Mumper RJ (2004). Paclitaxel nanoparticles for the potential treatment of brain tumors. *J. Control Release*, **99**: 259-269.
- LaVan DA, Lynn DM and Langer R (2002). Moving smaller in drug discovery and delivery. *Nat. Rev. Drug Discovery*, **1**: 77-84.
- LaVan DA, McGuire T and Langer R (2003). Small-scale systems for in vivo drug delivery. *Nat. Biotechnol.*, **21**: 1184-1191.
- Lee KE, Kim BK and Yuk SH (2002). Biodegradable polymeric nanospheres formed by temperature-induced phase transition in a mixture of poly(lactide-co-glycolide) and poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer. *Biomacromolecules*, **3**: 1115-1119.
- Leoni L and Desai TA (2004). Micromachined biocapsules for cell-based sensing and delivery. *Adv. Drug Delivery Rev.*, **56**: 211-229.
- Li X, St John J, Coffey JL, Chen Y, Pinizzotto RF and Newey J *et al.* (2000). Porosified silicon wafer structures impregnated with platinum anti-tumor compounds: Fabrication, characterization, and diffusion studies, *Biomed. Microdevices*, **2**: 265-272.
- Li ZZ, Wen LX, Shao L and Chen JF (2004). Fabrication of porous hollow silica nanoparticles and their applications in drug release control. *J. Controlled Release*, **98**: 245-254.
- Lipinski C and Hopkins A (2004). Navigating chemical space for biology and medicine. *Nature*, **432**: 855-861.
- Lockman PR, Mumper RJ, Khan MA and Allen DD (2002). Nanoparticle technology for drug delivery across the blood-brain barrier. *Drug Dev. Indust. Pharm.*, **28**: 1-13.
- Mamalis AG, Vogtländer LOG and Markopoulos A (2004). Nanotechnology and nanostructured materials: trends in carbon nanotubes. *Precision Eng.*, **28**: 16-30.
- Martin CR and Kohli P (2003). The emerging field of nanotube biotechnology. *Nat. Rev. Drug Discovery*, **2**: 29-37.
- Meijer EW and Van Genderen MHP (2003). Chemistry: dendrimers set to self-destruct. *Nature*, **426**: 128-129.
- Mirkin CA, Letsinger RL, Mucic RC and Storhoff JJ (1996). A DNA method for rationally assembling nanoparticles into macroscopic materials. *Nature*, **382**: 607-609.
- Moselhy J, Wu XY, Nicholov R and Kodaria K (2000). *In vitro* studies of the interaction of poly(NIPAm/MAA) nanoparticles with proteins and cells. *J. Biomat. Sci. Polymer Ed.*, **11**: 123-147.
- Muller RH and Keck CM (2004). Challenges and solutions for the delivery of biotech drugs—a review of drug nanocrystal technology and lipid nanoparticles. *J. Biotechnol.*, **113**: 151-170.
- Namazi H and Adeli M (2004). Dendrimers of citric acid and poly(ethylene glycol) as the new drug-delivery agents. *Biomaterials*, **26**: 1175-1183.
- Neerman MF, Zhang W, Parrish AR and Simanek EE (2004). *In vitro* and *in vivo* evaluation of a melamine dendrimer as a vehicle for drug delivery, *Int. J. Pharm.*, **281**: 129-132.
- Nugent J, Wan Po A.L. and Scott EM (1998). Design and delivery of non-parenteral vaccines, *J. Clin. Pharm. Ther.*, **23**: 257-285.
- O'Neal DP, Hirsch LR, Halas NJ, Payne JD and West JL (2004). Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles. *Cancer Lett.*, **209**: 171-176.

- Paleos CM, Tsiourvas D, Sideratou Z and Tziveleka L (2004). Acid- and salt-triggered multifunctional poly(propylene imine) dendrimer as a prospective drug delivery system. *Biomacromolecules*, **5**: 524-529.
- Panyam J and Labhasetwar V (2003). Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv. Drug Delivery Rev.*, **55**: 329-347.
- Panyam J, Dali MM, Sahoo SK, Ma W, Chakravarthi SS and Amidon GL *et al.* (2003). Polymer degradation and in vitro release of a model protein from poly(D,L-lactide-co-glycolide) nano- and microparticles. *J. Controlled Release*, **92**: 173-187.
- Pardoll D (2003). Does the immune system see tumors as foreign or self? *Annu. Rev. Immunol.*, **21**: 807-839.
- Player A, Barrett JC and Kawasaki ES (2004). Laser capture microdissection, microarrays and the precise definition of a cancer cell. *Expert Rev. Mol. Diagn.*, **4**: 831-840.
- Priel S, Fermiglia M, Ferrone M and Asquini A (2003). Scaling properties in the molecular structure of three-dimensional, nanosized phenylene-based dendrimers as studied by atomistic molecular dynamics simulations. *Carbon*, **41**: 2269-2283.
- Prinz AV, Prinz V Ya and Seleznev VA (2003). Semiconductor micro- and nanoneedles for microinjections and ink-jet printing. *Microelectronic Eng.*, **67-68**: 782-788.
- Quintana A, Raczka E, Piehler L, Lee I, Myc and Majoros I (2002). Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. *Pharm. Res.*, **19**: 1310-1316.
- Rabinow BE (2004). Nanosuspensions in drug delivery. *Nat. Rev. Drug Discov.*, **3**: 785-796.
- Ravi Kumar MN (2000). Nano and microparticles as controlled drug delivery devices. *J. Pharm. Pharm. Sci.*, **3**: 234-258.
- Rees DC, Congreve M, Murray CW and Carr R (2004). Fragment-based lead discovery. *Nat. Rev. Drug Discov.*, **3**: 660-672.
- Rosenberg SA, Yang JC and Restifo NP (2004). Cancer immunotherapy: moving beyond current vaccines. *Nat. Med.*, **10**: 909-915.
- Rosiak JM, Janik I, Kadlubowski S, Kozicki M, Kujawa P and Stasica P (2003). Nano-, micro- and macroscopic hydrogels synthesized by radiation technique. *Nucl. Instruments Methods Phys. Res. B.*, **208**: 325-330.
- Rösler A, Vandermeulen GW and Klok HA (2001). Advanced drug delivery devices via self-assembly of amphiphilic block copolymers. *Adv. Drug Delivery Rev.*, **53**: 95-108.
- Sahoo SK and Labhasetwar V (2003). Nanotech approaches to drug delivery and imaging. *Drug Discov. Today*, **8**: 1112-1120.
- Sameti M, Bohr G, Ravi Kumar MN, Kneuer C, Bakowsky U and Nacken M (2003). Stabilisation by freeze-drying of cationically modified silica nanoparticles for gene delivery. *Int. J. Pharm.*, **266**: 51-60.
- Sashiwa H and Aiba S-I (2004). Chemically modified chitin and chitosan as biomaterials. *Prog. Polymer Sci.*, **29**: 887-908.
- Schiffelers RM, Ansari A, Xu J, Zhou Q, Tang Q and Storm G (2004). Cancer siRNA therapy by tumor selective delivery with ligand-targeted sterically stabilized nanoparticle. *Nucleic Acids Res.*, **32**: e149.
- Schiffelers RM, Ansari A, Xu J, Zhou Q, Tang Q and Storm G *et al.* (2004). Cancer siRNA therapy by tumor selective delivery with ligand-targeted sterically stabilized nanoparticle. *Nucleic Acids Res.*, **32**: e149.
- Senior K (1998). Nano-dumpling" with drug delivery potential. *Mol. Med. Today*, **4**: 321.
- Shah NP, Tran C, Lee FY, Chen P, Norris D and Sawyers CL (2004). Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science*, **305**: 399-401.
- Shi W, Sahoo Y, Swihart MT and Prasad PN (2005). Gold nanoshells on polystyrene cores for control of surface plasmon resonance. *Langmuir*, **21**: 1610-1617.
- Shoichet BK (2004). Virtual screening of chemical libraries. *Nature*, **432**: 862-865.
- Stauffer PR and S.N. Goldberg SN (2004). Introduction: thermal ablation therapy. *Int. J. Hyperthermia.*, **20**: 671-677.
- Steiniger SC, Kreuter J, Khalansky AS, Skidan IN, Bobruskin AI and Smirnova ZS *et al.* (2004). Chemotherapy of glioblastoma in rats using doxorubicin-loaded nanoparticles. *Int. J. Cancer*, **109**: 759-767.
- Sun Q, Wang Q, Rao BK and Jena P (2004). Electronic structure and bonding of Au on a SiO<sub>2</sub> cluster: a nanobullet for tumors. *Phys. Rev. Lett.*, **93**: 186803/1-186803/4.
- Sun Y, Mayers BT and Xia Y (2002). Template-engaged replacement reaction: a one-step approach to the large scale synthesis of metal nanostructures with hollow interiors. *Nano. Lett.*, **2**: 481-485.
- Tansey W, Ke S, Cao XY, Pasuelo MJ, Wallace S and Li C (2004). Synthesis and characterization of branched poly(L-glutamic acid) as a biodegradable drug carrier. *J. Controlled Release*, **94**: 39-51.
- Tao SL and Desai TA (2003). Microfabricated drug delivery systems: from particles to pores. *Adv. Drug Delivery Rev.*, **55**: 315-328.
- Torchilin VP (2005). Recent advances with liposomes as pharmaceutical carriers. *Nat. Rev. Drug Discov.*, **4**: 145-160.
- Ulrich KE, Cannizzaro SM, Langer RS and Shakeshelf KM (1999). Polymeric systems for controlled drug release. *Chem. Rev.*, **99**: 3181-3198.
- Vasir JK, Reddy MK and Labhasetwar V (2005). Nanosystems in drug targeting: opportunities and challenges. *Curr. Nanosci.*, **1**: 47-64.
- Venter JC, Adams EW, Myers PW, Li RJ, Mural and Sutton GG (2001). The sequence of the human genome. *Science*, **291**: 1304-1351.

- Von Eschenbach AC (2004). A vision for the National Cancer Program in the United States. *Nat. Rev. Cancer*, **4**: 820-828.
- Weis RP, Montchamp JL, Coffey JL, Attiah DG and Desai TA (2002). Calcified nanostructured silicon wafer surfaces for biosensing: effects of surface modification on bioactivity. *Dis. Markers*, **18**: 159-165.
- West JL and Halas NJ (2003). Engineered nanomaterials for biophotonics applications: improving sensing, imaging, and therapeutics. *Annu. Rev. Biomed. Eng.*, **5**: 285-292.
- Whitesides GM (2003). The "right" size in nanobiotechnology. *Nat. Biotechnol.*, **21**: 1161-1165.
- Wissing SA, Kayser O and Muller RH (2004). Solid lipid nanoparticles for parenteral drug delivery. *Adv. Drug Deliv. Rev.*, **56**: 1257-1272.
- Xie Y and Gao Y (2005). Controlled transdermal delivery of model drug compounds by MEMS microneedle array. *Nanomedicine*, **1**: 184-190.
- Xike T, Jinbo F, Zhenbang P, Chao Y and Dongyue L (2005). Synthesis and characterization of amoxicillin nanostructures. *Nanomedicine: Nanotechnology, Biology and Medicine*, **1**(4): 323-325.
- Yang H and Lopina ST (2003). Penicillin V-conjugated PEG-PAMAM star polymers. *J. Biomat. Sci. Polymer Ed.*, **14**: 1043-1056.
- Yu W, Pirollo KF, Yu B, Rait A, Xiang L and Huang *et al.* W (2004). Enhanced transfection efficiency of a systemically delivered tumor-targeting immunolipoplex by inclusion of a pH-sensitive histidylated oligolysine peptide. *Nucleic Acids Res.*, **32**: e48.
- Zhang S (2002). Emerging biological materials through molecular self-assembly. *Biotechnol. Adv.*, **20**: 321-339.

Received: 15-05-2006 – Accepted: 30-06-2006