CURRENT CONCEPTS AND NEWER DEVELOPMENTS IN CANCER

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ABSTRACT

Nanotechnology is multidisciplinary field that involves the design and engineering of objects <500 nanometers (nm) in size. These have been applied to improve drug delivery and to overcome some of the problems of drug delivery in cancer. These can be classified into many categories that include use of various nanoparticles, nanoencapsulation, targeted delivery to tumors of various organs, and combination with other methods of treatment of cancer such as radiotherapy. Nanoparticles are also used for gene therapy for cancer. This review explores recent work directed towards more targeted treatment of cancer, whether through more specific anti-cancer agents or through methods of delivery. A part of these, Sonophoresis is also a tool to enhance bioavailability and solubility of drug and also a useful tool to enhance permeability of anticancer agents.

Keywords: Nanotechnology, Cancer, Sonophoresis, Fluorescent nanoparticles

INTRODUCTION

Nanotechnology is the scientific field that deals with the creation, manipulation, and utilization of engineered, manmade, functional particles at the nanoscale dimension (10^{-9}m). Nanoparticles as colloidal systems can be fabricated from a multitude of materials in a variety of compositions, including quantum dots (QDs), polymeric nanoparticles, gold nanoparticles, paramagnetic nanoparticles etc. Since these nanoparticles are 100-10000-fold smaller than cancer cells, they can easily pass through cell barriers. In addition, they preferentially accumulate at the tumor sites because of hallmarks of tumors such as the fenestrated vasculature and poorly lymphatic drainage, resulting in an enhanced permeability and retention (EPR) effect.

NANOTECHNOLOGY IN CANCER

Tremendous opportunities exist for using micro and nanoparticles as controlled drug delivery systems for cancer treatment[1,2,3]. Nanoparticles are on the same size scale as receptors, channels, ligands, effectors, and nucleic acids and can be modified and further engineered to achieve a particular physiological effect, such as increased biocompatibility. Drugs found to be efficacious under in vitro conditions, such as in high-throughput screening studies, are often insoluble—and are rapidly cleared from the bloodstream when injected invivo. Hydrophilic molecules such as polyethylene glycol (PEG) can be bound to nanoparticle surfaces, which greatly increase their solubility and biocompatibility, Candidate drugs that were previously discarded because of insolubility or high molecular weight can be attached to this nanoparticle 'platform'. Albumin, the most plentiful protein in human serum, turns out to be a natural 'solvent' for paclitaxel. In addition, experimental data suggest that the albumin nanoparticles (i.e., Abraxane) interact with tumor blood vessel receptors that transport the nanoparticles into tumors. This interactivity may account for the increased levels of paclitaxel seen in tumors treated with Abraxane compared with legacy paclitaxel [4]. When attached to an engineered nanoparticle, a drug's solubility, half-life, and general biocompatibility depend on the tailorable properties of the nanoparticle, other than the intrinsic properties. The preferential delivery of nanoparticulate drugs to tumors allows lower dosages to be effective and reduces the adverse side effects of chemotherapeutics of the drug itself. Table 1 lists nanotech-based constructs currently in clinical or preclinical development.

Polymeric Nanoparticles in Cancer Therapy

Polymeric nanoparticles can be used in nanoparticle therapeutics containing small-molecule drugs, peptides, proteins, and nucleic acids. Compared to conventional therapeutic strategies, they can improve the solubility of poorly soluble drugs and increase drug half-life and specificity to the target sites. Furthermore, most nanoparticles preferentially accumulate within tumors via the EPR effect (enhanced permeability and retention effect.) Thus, polymeric nanoparticles allow for enhancing the intracellular drug concentration in cancer cells while avoiding toxicity in normal cells, resulting in potent therapeutic effects.

SYSTEMATIC DELIEVERY SYSTEM

Passive Targeting: Passive targeting takes advantage of the inherent size of nanoparticles and the unique properties of tumor vasculature, such as the enhanced permeability and retention (EPR) effect and the tumor microenvironment. This approach can effectively enhance drug bioavailability and efficacy.

Tumor Microenvironment: Hyperproliferative cancer cells have profound effects on their surrounding microenvironment. Tumors should accept to use glycolysis (hypoxic metabolism) to obtain excessive energy, resulting in an acidic microenvironment. In addition, cancer cells overexpress and release some enzymes that are crucial to tumor migration, invasion, and metastasis, including matrix metalloproteinases (MMPs). Tumor activated prodrug therapy is an example of passive targeting that takes advantage of this characteristic of the tumor-

associated microenvironment. A nanoparticle conjugating an albumin-bound form of DOX with an MMP-2–specific peptide sequence (Gly-Pro-Leu-Gly-Ile-Ala-Gly-Gln) was efficiently and specifically cleaved by MMP-2

Active Targeting: These drug delivery systems using a binary structure conjugate inevitably have intrinsic limitations to the degree of targeting specificity they can achieve. In the case of the EPR effect, while poor lymphatic drainage on the one hand helps the extravasated drugs to be enriched in the tumor interstitium, A part of these, it induces drug outflow from the cells as a result of higher osmotic pressure in the interstitium, which eventually leads to drug redistribution in some portions of the cancer tissue. To resolve these limitation incorporation a targeting molecule that specifically binds an antigen or receptor that is either uniquely expressed or overexpressed on the tumor cell surface, the ligand-targeted approach is expected to selectively deliver drugs to tumor tissues with greater efficiency. Such targeted nanoparticles may constitute the next generation of polymeric nanoparticle drug delivery systems.

MULTIFUNCTIONAL NANOPARTICLES FOR TUMOR IMAGING

Tumor imaging plays a key role in clinical oncology, with radiological examinations able to detect solid tumors, determine recurrence, and monitor therapeutic responses. Current molecular imaging approaches, including PET, single-photon emission tomography, and optical imaging including fluorescence-mediated tomography and near-infrared fluorescence reflectance (NIRF) imaging, have shown a high sensitivity in noninvasive tumor imaging. A commonly used PET imaging probe, ^{18}F-labeled fluorodeoxyglucose (FDG) can only localize tumors by identifying cells in the body that have increased glucose uptake and metabolism, allowing for the detection of those tumors. However, it is not suitable for tumor types with a low glucose uptake. One molecular imaging strategy to improve the specificity of cancer detection is target specific imaging of biomarker molecules specifically produced by cancer cells, coupled with imaging probes guided by ligands that can recognize and interact with target molecules. Recently, tumor-targeted optical, radioactive, or magnetic probes have been generated and their feasibility examined in animal tumor models and in very limited clinical studies.

Table 1: Nanoparticles in cancer treatment according to FDA

Product	Nanoparticles as drug	Disease	Company/ Refenences
Megace ES	Nanocrystal/megestrol acetate	Breast Cancer	Par Pharmaceutical
INGN-401	Liposomal	Lung cancer	Introgen
Combidex	Iron oxide	Tumour imaging	Advanced Magnetics
Aurimune	Colloidal gold/TNF	Solid tumors	CytImmune Sciences
SGT-53	Liposome Tf antibody/p53 gene	Solid tumors	SynerGene Therapeutics
Doxil	PEGylated liposome/doxorubicin hydrochloride	Ovarian cancer	OrthoBiotech
Abraxane	Nanoparticulate albumin/paclitaxe	Various cancer	American Pharmaceutical Partners
Cyclosert	Cyclodextrin Nanoparticle	Solid tumors	Insert Therapeutics

Source: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Table 2: Different properties of fluorescent nanoparticles

Parameter	QDs	organic dye doped NPs	UCNs (upconversion Nanoparticles)
Size	2–10 nm	50-500 nm	50-200 nm
Autofluorescence	High	High	Low
Cytotoxicity	High	Medium	Low
Biocompatibility	Good	Good	Good
Light penetration depth	High	High	High

Table 3: Marketed pharmaceutical products containing nanocrystals used in Skin

Product	Drug	Dosage form	Manufacturer	Market introduction
Rapamune	Sirolimus	Tablet	Wyeth Pharma	August 2000.
Emed	Aprepitant	Capsule	Merck	March 2003.
Tricor	Fenofibrat	Capsule	Abbott	December 2004.
Megace ES	Megestrol	Suspension	Par Pharmaceuticals	June 2005.

FLUORESCENT NANOPARTICLES

Conventional fluorophores such as fluorescent dyes, bioluminescent proteins and fluorescent proteins were used initially. But the recent advancements in the development of fluorescent NPs have made them potential candidates for imaging-guided therapy and they have a lot of advantages over their predecessors.

Quantum dots (QDs): QDs are semiconductor crystals composed of elements from groups II to VI, III to IV or IV to VI from the periodic table. The size of the QD is usually from 2 to 10 nm, which gives them special properties not seen at a macro-level owing to the effect of quantum confinement. QDs have a broad absorption spectrum, i.e. they can be excited by a wide range of wavelengths and they have a narrow emission spectrum.

Synthesis: QDs are usually synthesized by heating the precursors dissolved in organic solvents at high temperatures of about 300°C. The size of the QDs can be varied by varying the concentration of the precursors and the crystal growth time. The nanocrystals thus formed have a hydrophobic core and are thus insoluble in water. So various surface modifications such as silica encapsulation, ligand exchange, conjugation to mercaptohydrocarbonic acids, dithiothretol and oligomeric ligands are carried out to make them soluble in water, which is essential for biological applications. QDs are very bright, photostable and thermostable. They are quite resistant to photobleachin.

Important Properties regarding Properties of different Fluorescent Nanoparticle are summerised on table 2.

Gold nanoparticles:

- The first trial of gold nanoshells in hyperthermal therapy was introduced by Hirsh et al. The average temperature of tumor cells treated with gold nanoshells and NIR light increased up to 38.8°C at a depth of 2.5mm beneath the dermal surface and irreversible photothermal destruction was observed and confined to the tumor area. As follow-up work by Halas and co-workers, gold nanoshells were conjugated with the HER2 antibody to actively target breast carcinoma cells. In this study, NIR irradiation caused a rise in the temperature of the target regions of between 40 to 50ºC, which selectively destructed the carcinomas. In addition, the survival rate of mice treated with HER-gold nanoshells and NIR irradiation was excellent compared with the controls (non-specific antibody or NIR light alone).
- Colloidal gold nanoparticles are another attractive platform for cancer diagnosis and therapy**.**
- Gold nanoparticles also have been used as a platform for novel experimental cancer therapy. In a subcutaneous model of colon cancer, it was demonstrated that systemically delivered gold nanoparticles (size, approximately 33 nm) conjugated to tumor necrosis factor (TNF) accumulated in tumors [13].
- In these approach Mice that were treated with TNF-conjugated gold nanoparticles had improved survival compared with mice that were treated with native TNF alone.
- Gold particles also have been used to enhance sensitivity to external beam radiation [14].
- Systemically administered gold nanoparticles (size, 1.9 nm) accumulated in a murine subcutaneous tumor model and greatly enhanced local X-ray therapy and overall survival compared with mice that received radiation alone.
- Gold nanocages, a new type of gold nanoparticle, recently have been described [15].
- These particles have been used to detect c-erbB2 and EGFR in vitro assays by using NIR and optical coherence tomography [16].
- Gold nanocages may be constructed to generate heat in response to NIR light and, thus, also may have a potential application in photothermal ablation.

Paramagnetic nanoparticles:

- Superparamagnetic iron oxide contrast agents consisting of 50-nm to 100-nm.
- These agents are attractive because they have much greater magnetic susceptibility than traditional MR contrast agents, such as gadolinium. Such particles have rapid hepatic uptake after intravenous administration, which makes them useful for the characterization of hepatic tumors.
- Ultrasmall, superparamagnetic iron oxide nanoparticles have been used clinically in humans to characterize lymph node status in patients with breast cancer [17].

Nanoshells

- Nanoshells (appproximately 10–300 nm in dimension) are composed of a dielectric core, usually

silica, surrounded by a thin metal shell, typically gold [18]. The optical properties of nanoshells are different from quantum dots. Nanoshells rely on the plasmon-mediated conversion of electrical energy into light.

- Nanoshells have been used in vivo as a contrast agent for imaging with optical coherence tomography and photoacoustic tomography.

OTHER APPLICATIONS

Nanotechnology-based preventive HIV/AIDS vaccine: [19, 20]

- Generation of an effective HIV/AIDS vaccine has been notoriously diffcult and new approaches are always sought.
- Nanoparticles have various advantages in improving delivery of antigens to enhance the immune response. They can be used both for encapsulating antigens in their core from which antigen presenting cells can process and present and cross-present antigen to CD4+ and CD8+ T cells respectively, or absorbing the antigens on their surfaces, allowing B cells to generate humoral responses. Nanoparticle vaccines can also be optimized for various routes of administration.
- Various polymeric and lipid-based nanoparticles have been used to deliver DNA-, protein- or peptide-based antigens in vivo, eliciting strong cellular, humoral and mucosal immune responses.

Nanotechnology-based intravaginal microbicides:

- Intravaginal microbicides are preventive agents that are topically applied to the vagina to prevent the transmission of HIV/AIDS or other sexually transmitted diseases.
- Nanotechnology-based approaches are being developed to use dendrimers, siRNA and nanoparticles for microbicidal functions.
- VivaGel is a dendrimer-based microbicide gel that has been shown to be safe in humans in Phase I clinical trials.
- Polymeric nanoparticles have been used to deliver the CCR5 inhibitor PSC-RANTES and HIV-specifc siRNA as microbicides.

SONOPHORESIS

- Ultrasound, particularly at low frequencies (20–100 kHz), has been shown to greatly enhance the permeability of skin, a phenomenon termed as sonophoresis. The efficacy of low- frequency sonophoresis (LFS) in delivering large-molecular weight substances, for example, insulin through the skin, has been shown through both in vitro and in vivo studies. These are a technique which involves the use of ultrasonic energy to enhance skin penetration of active substances. Ultrasound is best known for its imaging capability in diagnostic medicine. However, there have been considerable efforts recently to develop therapeutic uses for it. The purpose of this review is to summarize some of the recent advances made in the area of therapeutic ultrasound as they relate to drug delivery. These technologies will focus on the applications of ultrasound to enhance the delivery and effect of three distinctive therapeutic drug classes: chemotherapeutic, thrombolytic, and gene-based drugs. In addition, ultrasound contrast agents have been recently developed for diagnostic ultrasound. New experimental evidence suggests that these contrast agents can be used as exogenous cavitation nuclei for enhancement of drug and gene delivery
- A good candidate for Sonophoresis is 5-Fluorouracil (5-Fu). This anticancer agent has been used either alone or in combination with other drugs, for treating solid tumors such as breast and gastrointestinal cancers [21]. Although oral administration has also been used for convenience, this route has the disadvantage of the oral bioavailability of 5-Fu being low and erratic, making this therapy less efficient and more difficult to control [22]. Hence, Sonophoresis is a suitable choice for 5-Fu to produce better bioavailability and control the delivery rate.
- Gomez et al., in 2008 studied laser ablation of stratum corneum (SC) enhances transdermal delivery of hydrophilic drugs [23].

CONCLUSION

Nanoparticle appear to be a unique viable approach for combating problems such as poor bioavailability,and to achieve site specific delivery to the tumour site. The present paper reviews the use of nanotechnology as strategies to deliver existing chemotherapies and novel therapeutic molecules in a controlled manner to malignancies. A part of these, Sonophoresis is also a tool to enhance bioavailability and solubility of drug and also a useful tool to enhance permeability of anticancer agents.

REFERENCES

1. Panyam J, Labhasetwar V, Biodegradable nanoparticles for drug and gene delivery to cells and tissue, Adv Drug Deliv Rev, 55, 2003,329-347.
2. Birnbaum DT, Brannon-Peppas L, Microparticle drug delivery systems. In Drug delivery systems in cancer therapy, Ed. Brown DM, Humana Press, 2004, 117-135.
3. Harris JM, Chess RB, Effect of pegylation on pharmaceuticals, Nat Rev Drug Discov 2003, 2,214–221.
4. Desai N, Trieu V, Yao Z, Louie L, Ci S, et al., Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel, Clin Cancer Res, 2006, 12,1317–1324.
5. Fassas A, Anagnostopoulos A, The use of liposomal daunorubicin (DaunoXome) in acute myeloid leukemia, Leuk Lymphoma, 2005, 46, 795–802.

6. Dragovich T, Mendelson D, Kurtin S, et al, A Phase 2 trial of the liposomal DACH platinum L-NDDP in patients with therapy-refractory advanced colorectal cancer, Cancer Chemother Pharmacol, 2006,58,759–764.
7. Sapra P, Tyagi P, Allen TM, Ligand-targeted liposomes for cancer treatment, Curr Drug Deliv, 2005,2,369–381.
8. White SC, Lorigan P, Margison GP, et al., Phase II study of SPI-77 (sterically stabilised liposomal cisplatin) in advanced non-small-cell lung cancer, Br J Cancer, 2006, 95, 822–828.
9. Rosenthal DI, Yom SS, Liu L, et al. A phase I study of SPI-077 (Stealth liposomal cisplatin) concurrent with radiation therapy for locally advanced head and neck cancer, Invest New Drugs, 2002, 20, 343–349.
10. Harrington KJ, Lewanski CR, Northcote AD, et al., Phase I-II study of pegylated liposomal cisplatin (SPI-077) in patients with inoperable headand neck cancer, Ann Oncol, 2001, 12, 493–496.
11. Ciuleanu T, Diculescu M, Hoepffner NM, et al. A randomised phase II study of OSI-7904Lversus 5-fluorouracil (FU)/leucovorin (LV) as first-line treatment in patients with advanced biliary cancers, Invest New Drugs, 2007,25,385–390.
12. Clamp AR, Schöffski P, Valle JW, et al., A phase I and pharmacokinetic study of OSI-7904L, a liposomal thymidylate synthase inhibitor in combination with oxaliplatin in patients with advanced colorectal cancer, Cancer Chemother Pharmacol, 2007, 23,[Epub ahead of print] PMID:17520255.
13. Paciotti GF, Myer L, Weinreich D, et al. Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery, Drug Deliv, 2004, 11, 169–183.
14. Hainfeld JF, Slatkin DN, Smilowitz HM, The use of gold nanoparticles to enhance radiotherapy in mice, Phys Med Biol, 2004,49,N309–N315.
15. Chen J, Saeki F, Wiley BJ, et al. Gold nanocages: bioconjugation and their potential use as optical imaging contrast agents, Nano Lett, 2005,5, 473–477.
16. Michel SC, Keller TM, Frohlich JM, et al., Preoperative breast cancer staging: MR imaging of the axilla with ultrasmall superparamagnetic iron oxide enhancement, Radiology, 2002, 225, 527–536.
17. Hirsch LR, Stafford RJ, Bankson JA, et al., Nanoshell- mediated near-infrared thermal therapy of tumors under magnetic resonance guidance, Proc Natl Acad Sci USA, 2003,100,13549–13554.
18. Michel SC, Keller TM, Frohlich JM, et al. Preoperative breast cancer staging: MR imaging of the axilla with ultra small superparamagnetic iron oxide enhancement, Radiology, 2002,225,527–536
19. Vyas TK, Shah L, Amiji MM, Nanoparticulate drug carriers for delivery of HIV/AIDS therapy to viral reservoir sites, Expert Opin. Drug Deliv, 2006, 3(5), 613–628.
20. Wan L, Pooyan S, Hu P, Leibowitz MJ, Stein S, Sinko PJ, Peritoneal macrophage uptake, pharmacokinetics and biodistribution of macrophage-targeted peg-fmlf (n-formyl-methionyl-leucyl-phenylalanine) nanocarriers for improving HIV drug delivery, Pharm. Res,2007, 24(11), 2110–2119.
21. Diasio RB, Harris BE, Clinical pharmacology of 5-fluorouracil, Clin Pharmacokinet, 1989, 16, 215–237.
22. Yuasa H, Gu J, Hayashi Y, Watanabe J. First-pass metabolism of 5-fluorouracil in rats, J Pharm Pharmacol, 1998, 50, 1019–1025.
23. Go´mez et al., Laser Treatments on Skin Enhancing and Controlling Transdermal Delivery of 5-Fluorouracil, Lasers in Surgery and Medicine, 2008, 40, 6–12.

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