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^-9m). 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. 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. 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 DELIVERY 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

<table>
<thead>
<tr>
<th>Product</th>
<th>Nanoparticles as drug</th>
<th>Disease</th>
<th>Company/ References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megace ES</td>
<td>Nanocystal/megestrol acetate</td>
<td>Breast Cancer</td>
<td>Par Pharmaceutical</td>
</tr>
<tr>
<td>INGN-401</td>
<td>Liposomal</td>
<td>Lung cancer</td>
<td>Introgen</td>
</tr>
<tr>
<td>Combidex</td>
<td>Iron oxide</td>
<td>Tumour imaging</td>
<td>Advanced Magnetics</td>
</tr>
<tr>
<td>Aurimune</td>
<td>Colloidal gold/TNF</td>
<td>Solid tumors</td>
<td>CyImmun Sciences</td>
</tr>
<tr>
<td>SGT-53</td>
<td>Liposome Tf antibody/p53 gene</td>
<td>Solid tumors</td>
<td>SynerGene Therapeutics</td>
</tr>
<tr>
<td>Doxil</td>
<td>PEGylated liposome/doxorubicin hydrochloride</td>
<td>Ovarian cancer</td>
<td>OrthoBiotech</td>
</tr>
<tr>
<td>Abraxane</td>
<td>Nanoparticulate albumin/paclitaxae</td>
<td>Various cancer</td>
<td>American Pharmaceutical Partners</td>
</tr>
<tr>
<td>Cyclosert</td>
<td>Cyclodextrin Nanoparticle</td>
<td>Solid tumors</td>
<td>Insert Therapeutics</td>
</tr>
</tbody>
</table>

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

### Table 2: Different properties of fluorescent nanoparticles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>QDs</th>
<th>organic dye doped NPs</th>
<th>UCNs (upconversion Nanoparticles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>2–10 nm</td>
<td>50-500 nm</td>
<td>50-200 nm</td>
</tr>
<tr>
<td>Autofluorescence</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Biocompatibility</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Light penetration depth</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
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 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 mercaptophenolic 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 photobleaching.

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

Gold nanoparticles:

- The first trial of gold nanoshells in hyperthermia 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 50°C, 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.
- 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.
- 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 irradiation alone.
- Gold nanocages, a new type of gold nanoparticle, recently have been described.
- These particles have been used to detect c-erbB2 and EGFR in vitro assays by using NIR and optical coherence tomography.
- 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.

Nanoshells

- Nanoshells (approximately 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 difficult 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-specific 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-Fluourouracil (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


