Internet Journal of Medical Update

Journal home page: http://www.akspublication.com/ijmu

Review

Cancer Nanotechnology: Recent Trends and Developments

Mr. Hardik R Mody[Ψ], B.Pharm

Project Assistant, Department of Biosciences and Bioengineering, Centre for Research in Nanotechnology and Science, IIT Bombay, Powai, Mumbai 400076, India

ABSTRACT: Cancer is one of the leading causes of death worldwide. Deaths from cancer are continuously rising worldwide with a projection of about 12 million deaths from cancer in 2030. Hence, over the past few years, tremendous attention has been given to the cancer related research and there has been an outstanding progress in the basic cancer biology. The present article deals with the recent developments in cancer nanotechnologies and its potential application in cancer therapeutics. Nanotechnology is one of the most rapidly growing fields in the 21st century. It may be defined as the creation of materials, drugs and devices that are used to manipulate matter of size in the range of 1-100nm. Nanotechnology has found its applications in many fields related to medicine including novel drug delivery systems, biotechnology to name a few. Many different types of nanosystems have been utilized in diagnostics and therapeutics of various diseases. To subside the disadvantages of conventional cancer therapeutics, nanotechnology has been given considerable attention. In this paper, the current nanotechnologies that can be utilized in oncological interventions will be discussed. These mainly include arrays of nanocantilevers, nanotubes and nanowires for multiplexing detection, multifunctional injectable nanovectors for therapeutics and diagnostics.

KEY WORDS: *Nanotechnology; Cancer; Nanoparticles; Nanovectors; Liposomes; Nanobiosensors*

INTRODUCTION

Cancer is one of the leading causes of death worldwide especially in low income and middle income countries. As we all know, cancer is malignant neoplasm. There is uncontrolled division of cells which enter into normal adjacent tissues and destroy them. Often the abnormal cells also spread into other parts of the body via lymph or blood, popularly the situation known as metastasis. According to WHO (World Health Organization), cancer accounted for 7.4 million deaths in 2004 which extended to 7.6 million which was about 13% of all human cell deaths in 2007. Breast cancer, colorectal cancer, lung cancer, liver cancer and stomach cancer are some of the major types of cancer existing today. Deaths from cancer are continuously rising worldwide with a projection of about 12 million deaths from cancer in 2030. Thereby, over the past few years, tremendous attention has been given to the cancer related research and developments. There has been an outstanding progress in the basic cancer biology. Many institutions, pharmaceutical and biotechnological industries have focused on cancer as their main target in their research and development departments. However, in spite of this progress in cancer research, comparable advances in cancer therapeutics have not taken place. The main reason for this failure was inability to deliver therapeutic moieties that selectively reach the desired targets which also resulted in unintended effects[1,2]. In addition to this, inability of a therapeutic formulation to cross biological barriers has also been one of the main hindrances. To overcome above mentioned obstacles in cancer therapeutics, Nanotechnology seems to be a promising tool.

Nanotechnology is one of the most rapidly growing and developing fields in the 21st century.

[Ψ]**Correspondence at:** Department of Biosciences and Bioengineering, Centre for Research in Nanotechnology and Science, IIT Bombay, Powai, Mumbai 400076, India; Telephone: +91 9773551938; Email: hardik_2504@yahoo.co.in

Nanotechnology may be defined as the creation of materials, drugs and devices that are used to manipulate matter that are of size in the range of 1-100nm[3]. It has found applications in various fields including electronics, energy production, medicine, pharmaceutical industries to name a few. A nanometer is 1/50,000 times of the width of an average human hair. Moreover, the dimensions of a DNA strand are also in the range of nanometer. Similarly, a variety of biological processes takes place at nanometer scales. Thus, in order to communicate with these natural nanoclusters, a moiety with nanoscale dimensions would be appropriate. As a result, nanoparticles can offer some unique advantages in the field of biotechnology and medicine. Nanomaterials, due to their extremely small size, are readily taken up by the human body. In contrast to normal larger sized particles, they can cross the biological membranes and reach the cells, tissues and organs with ease. Mostly, biodegradable polymers are utilized in the preparation of the colloidal dispersions of nanoparticles. Drugs can be enclosed, entrapped or adsorbed onto the particle surface or dissolved within the matrix. Moreover, they have large surface area to volume ratio that aids in their diffusion through the membranes[4]. Surface area to volume ratio is an important factor that governs the rate and the extent of absorption/diffusion of a chemical moiety across the biological membrane. It is the amount of surface area per unit volume of a substance and is inversely related with size. Thus, smaller the size as in case of nanoparticles, greater the surface area to volume ratio, greater the rate and extent of absorption/diffusion across the biological membranes. Nanotechnology has found its applications in many fields related to medicine including novel drug delivery systems, biotechnology to name a few. Many different types of nanosystems have been utilized in diagnostics and therapeutics of various diseases. These may include silicon and silica based nanoparticles[5], gold nanoparticles[6], polymer based nanoparticles[7], dendrimers[8], liposomes[9], paramagnetic nanoparticles. In addition multifunctional nanoparticles have been also tested for their oncological applications. An example of their application is liposomal based drug delivery system of Doxorubin for the treatment of breast and ovarian cancer[9]. The present article deals with the recent developments in cancer nanotechnologies and its potential application in cancer therapeutics.

CURRENT CANCER NANOTECHNOLOGIES

To subside the disadvantages of conventional cancer therapeutics, nanotechnology has been given considerable attention[5-9]. In this section, the current nanotechnologies that can be utilized in oncological interventions will be discussed. These mainly include arrays of nanocantilevers, nanotubes and nanowires for multiplexing detection, multifunctional injectable nanovectors for therapeutics and diagnostics. The effective utilization of nanosized, targeted MRI (Magnetic Resonance Imaging) contrast agents for oncological detection has been known for quite some time.

Nanoparticles

As compared to large sized particles, nanoparticles exhibit new or enhanced size dependant properties. They serve as the raw materials, ingredients or additives in various products[10]. The control of cell and tissue distribution of anticancer agents is the biggest advantage of such nanoparticulate systems. Several types of nanoparticles have been developed and utilized in MRI (Magnetic Resonance Imaging) contrast. These include iron oxide based nanoparticles[11], gadolinium based nanoparticles[12] to name a few. Local biology and pathology condition information can be obtained with the help of MRI. These are based on the nuclear magnetic resonance signals which are based on the hydrogen nuclei present in different pathological conditions in an organism[13].

In addition to these, antibody conjugated gold nanoparticles have also been utilized for cancer diagnostics. Ivan *et al* have shown that with the aid of the unique optical properties of gold nanoparticles, such systems can have effective applications in cancer therapeutics. Such gold nanoparticles conjugated with monoclonal antibodies can be used in biosensor techniques in oral cancer diagnostics[14]. Low density lipid nanoparticles have been developed to increase ultrasound imaging. Multimode imaging contrast nanoagents have also been developed combining biological targeting and magnetic resonance.

Nanovectors

Nanovectors are hollow or solid structured nanoparticles which can be filled with various anticancer drugs, targeting moieties and detection agents. The presence of targeting moieties attributes to their specificity; thereby reduction in toxic effects may be seen. These have been interest of use as nanotechnological devices in cancer. They are intravascular injectables considered for drug delivery and imaging in cancer.

Nanovectors may be classified into different generation nanovectors-namely, first generation, second generation and third generation nanovectors[15].

The first generation nanovectors are not targeted specifically against any biological molecule on the tumor cells[16]. An example of this would be albumin

bound Paclitaxel. It has found its application in breast cancer chemotherapy. This chemotherapy enabled to overcome solubility problems related to Paclitaxel and improve the toxicity profile of conventional Paclitaxel therapy which was formulated with chemophor[17].

The second generation of nanovectors was evolved for specific targeting. These nanovectors were developed to recognize and target specific biological molecules on the cancer cells (active targeting). Active targeting is one in which the therapeutic moiety or the drug is able to recognize and target specific moieties to the desired target on its own. This reduces the toxicity and would also improve therapeutic index. Coupling of high affinity ligands and specific antigens on the surfaces of nanoparticles[18] is an example of this generation of nanovectors. As compared to the first generation, they have improved biodistribution and reduced toxicity profile. The antigens on the cancer cells allow efficient uptake of targeted drugs through endocytosis (receptor mediated). The active drug delivery consists of several components like drug conjugated polymer and ligands/antibodies which are specific and bind to the specific tumor antigens/receptors. An example of this generation of nanovectors is liposome-entrapped drugs with phospholipid-anchored folic acid-PEG conjugates put forth by Gabizon *et al*[19]. However, further studies need to be carried out for its effective application in cancer therapeutics.

The third generation of nanovectors is currently under development which is multi stage strategy based[20]. The first stage particle can be biodegradable silicon microparticles which are having pores within them. They are designed to pass through the circulatory system and recognize the disease specific endothelium. The second stage particles are multitypes of nanoparticle which are loaded within the first stage particles. They are within the pores of the first stage particles and are set free towards the tumor mass. They are small enough (less than 20nm) to easily cross the inter-endothelial junctions. They contain different payloads for therapy and imaging. They can effectively be utilized for cancer in future.

Certain anticancer nanovectors have been developed which are targeted to tumors with the help of external magnetic field. Laurance *et al* have demonstrated their work on anticancer nanovectors based on superparamagnetic iron oxide nanoparticles[21]. Nanovectors were designed with iron oxide nanoparticles constituting the core. Coating of the nanoparticles was carried out by incorporation of the nanoparticles in the polymer matrix or their surface was functionalized with polymers. They concluded that such nanovectors can be applied in cases when the solid tumor is close to the body surface. In addition, highly flexible nanovectors have also been developed with

the aid of adhesion controlling and improving drug targeting and drug delivery[22].

Liposomes

Liposomes are the simplest forms of nanovectors which are made up of lipids enclosing water core. They have found applications in various cancer indications[23]. With the aid of over expression of fenestrations in cancer neovasculature, they increase the drug concentration at the tumor sites (passive targeting). In passive targeting, the drug is targeted to the target site passively owing to the physiological conditions of the body. Various Doxorubin encapsulated liposomal formulations have been clinically utilized for the treatment of Kaposi's sarcoma, breast cancer and refractory ovarian cancer[9]. They were developed to improve therapeutic index of the conventional Doxorubin chemotherapy while maintaining its antitumor activity. Similarly, S. Kommareddy *et al* have shown effective utilization of gelatin based nanovectors in tumors. Here, PEG modified gelatin based nanovectors were used as safe and effective vehicle for the delivery of systemically administered genes for tumors. Ruthenium and complexes of several other heavy metals have shown potential applications in cancer therapeutics. Lipid based nanovectors containing such complexes have also been put forth as a potential route in cancer[24].

Dendrimers

Another type of nanoparticle, Dendrimers have also been of interest in cancer. They are self assembling synthetic polymers which were used in the MRI of lymphatic drainage in mouse model of breast cancer[25]. Majoros *et al* have shown the synthesis, characterization and functionality of Poly (Amidoamine) (PAMAM) dendrimer based anticancer therapeutics. Such dendrimer based anticancer systems have found applications for targeted delivery in cancer (13). In addition to this, AK Patri *et al* have shown the synthesis and application of an antibody-dendrimer based conjugate system. Such systems have found applications in targeted delivery in prostate cancer therapeutics[26]. Xiangyang *et al* have demonstrated that dendrimer-entrapped gold nanoparticles can be effectively utilized for cancer cell targeting and imaging purposes[27].

Nanoshells

Nanoshells are other nanoparticles which are being lined up in cancer therapeutics and diagnostics. They are composed of a gold shell surrounding a semiconductor. When they reach the cancer cells, they can be irradiated. These irradiations make

5

them hot which ultimately kill the cancer cells. This technique has been successfully utilized in veneral tumours in mice[28].

Nanobiosensors

Varied types of novel devices are emerging with potential applications in cancer. Nanobiosensors have been developed for cancer diagnostics. Nanobiosensors are useful for early diagnosis of cancer. They can also effectively be utilized for the detection of cancer agents such as environmental pollutants, pathogens and carcinogenic gases. A device used for detection of an analyte through combination of a sensitive biological component, transducer along with a detector component is termed as a biosensor. These nanoscale sensors comprise of cancer specific antibody or ligands so that they can selectively capture cancer cells or target proteins. This yields mechanical, optical or electrical signals which can be detected by the detector. The use of nanobiosensors in cancer clinical testing have been increased due to high speed and reduced cost for diagnosis, automation and multi target analysis[29,30]. For detection of DNA, Quantum dots based sensor has also been developed.

Nanocantilevers

Multimolecular mechanical sensing devices like nanocantilevers have also been emerged as one of the promising approaches. Nanocantilevers comprise of large number of beams. When specific biomolecules bind, deflection of beam takes place which is observed by laser light or other methods. The flexible beams are coated with molecules capable of binding to cancer biomarkers.

Nanowires, Fullerenes and Nanotubes

Nanowires, fullerenes and nanotubes are amongst others which are considered for cancer therapeutics and diagnostics. Fullerenes are nanostructured arrangement of carbon atoms in specific soccer like architecture. They may also form nanotubes which are cylindrical carbon atom assemblies. Nanotubes and fullerenes have found several specific sensing applications. For instance, Nanotubes have been developed as high specificity sensors of antibody signatures of autoimmune disease and SNPs (single nucleotide polymorphism). Nanowires are other class of nanotechnology that has been developed. They are sensing wires coated with antibodies like molecules to bind to proteins of interest. Silicon nanowires are one such real time detectors for simultaneous molecular binding effects.

PRESENT CHALLENGES AND FUTURE PROSPECTS

The application of nanotechnology in clinical use in cancer has found several drawbacks and challenges. Endothelial cell barriers on vessels, cellular uptake of therapeutic agent, clearance of drugs from circulation, heterogeneity among tumors are the present challenges.

To conclude, the present cancer therapy needs advancement. However, cancer nanotechnology definitely can provide a breakthrough to eradicate cancer related death. Varied types of nanodevices have been developed which can effectively be applied in cancer therapeutics and diagnostics. Still extensive research needs to be carried out for effective utilization of cancer nanotechnology in clinic. There is need to identify favorable physiochemical properties and favorable nanodevices that will help to overcome multiple barriers.

REFERENCES

1. Langer R. Drug delivery and targeting. *Nature*. 1998 Apr;392(6679 Suppl):5-10.
2. Duncan R. The dawning era of polymer therapeutics. *Nat Rev Drug Discov*. 2003 May;2(5:347-60.
3. Feynman R. There's plenty of room at the bottom. *Science*. 1991;254:1300-1.
4. Pathak P, Katiyar VK. Multi-functional nanoparticles and their role in cancer drug delivery - a review. *Journal of Nanotechnology online*. 2007;3:1-17.
5. Martin FJ, Melnik K, West T, *et al*. Acute toxicity of intravenously administered microfabricated silicon dioxide drug delivery particles in mice: preliminary findings. *Drugs R D*. 2005;6(2):71-81.
6. Loo A, Lowery N, Halas J, *et al*. Immunotargeted nanoshells for integrated cancer imaging and therapy. *Nano Lett*. 2005 Apr;5(4):709-11.
7. Green E, Chiu ES, Leshchiner J, *et al*. Electrostatic ligand coatings of nanoparticles enable ligand-specific gene delivery to human primary cells. *Nano Lett*. 2007 Apr;7(4):874-9.
8. Pan D, Cui Y, Sheng C, *et al*. Dendrimer-modified magnetic nanoparticles enhance efficiency of gene delivery system. *Cancer Res*. 2007 Sep;67(17):8156-63.
9. Paolo D. Liposomal anticancer therapy: pharmacokinetic and clinical aspects. *J. Chemother*. 2004 Nov;16 Suppl 4:90-3.
10. Mohanraj VJ, Chen Y. Nanoparticles: A Review. *Tropical Journal of Pharmaceutical Research*. 2006;1-5:561-73.
11. Yan F, Xu H, Anker J, et al. Synthesis and characterization of silica-embedded iron oxide

6

nanoparticles for magnetic resonance imaging. *J. Nanosci. Nanotechnol.* 2004 Jan-Feb;4(1-2):72-6.

12. Oyewumi MO, Yokel RA, Jay M, et al. Comparison of cell uptake, biodistribution and tumor retention of folate-coated and PEG-coated gadolinium nanoparticles in tumor-bearing mice. *J.Control. Rel.* 2004 Mar;24(3):613-26.

13. Majoros IJ, Myc A, Thomas T, *et al.* PAMAM dendrimer-based multifunctional conjugate for cancer therapy: synthesis, characterization, and functionality. *Biomacromolecules.* 2006 Feb;7(2):572-9.

14. El-Sayed IH, Huang X, El-Sayed MA. Surface plasmon resonance scattering and absorption of anti-EGFR antibody conjugated gold nanoparticles in cancer diagnostics: applications in oral cancer. *Nano Lett.* 2005 May;5(5)*:*829-34.

15. Kommareddy S, Amiji M. Antiangiogenic gene therapy with systemically administered sFlt-1 plasmid DNA in engineered gelatin-based nanovectors gelatin-based nanovectors. *Cancer Gene Ther*. 2007 May;14(5):488-98.

16. Ferrari M. Nanogeometry: beyond drug delivery. *Nat Nanotechnol.* 2008 Mar;3(3):131-2.

17. Nyman DW, Campbell KJ, Hersh E, *et al.* Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. *J Clin Oncol.* 2005 Nov;23(31):7785-93.

18. Farokhzad OC, Cheng J, Teply BA, *et al.* Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. *Proc Natl Acad Sci* U S A. 2006 Apr;103(16):6315-20.

19. Gabizon A, Shmeeda H, Horowitz AT, *et al.* Tumor cell targeting of liposome-entrapped drugs with phospholipid-anchored folic acid-PEG conjugates. *Adv Drug Deliv Rev.* 2004 Apr; 56(8):1177-92.

20. Tasciotti E, Liu XW, Bhavane R, *et al.*, Mesoporous silicon particles as a multistage delivery system for imaging and therapeutic applications. *Nat. Nanotechnol.* 2008 Mar;3(3):151-7.

21. Eyrolles LD, Marchais H, Hervé K, *et al.* Nanovectors for anticancer agents based on superparamagnetic iron oxide nanoparticles. *Int J Nanomedicine.* 2007;2(4):541-50.

22. Pugno NM. Flexible Nanovectors. *J Phys Condens Matter* 2008;20:474205.

23. Park JW. Liposome-based drug delivery in breast cancer treatment. *Breast Cancer Res.* 2002;4(3):95-9.

24. Vaccaro M, Litto RD, Mangiapia G, *et al.* Lipid based nanovectors containing ruthenium complexes: a potential route in cancer therapy. *Chem Commun.* 2009 Mar;11:1404-6.

25. Kobayashi H, Kawamoto S, Sakai Y, et al. Lymphatic drainage imaging of breast cancer in mice by micro-magnetic resonance lymphangiography using a nano-size paramagnetic contrast agent. *J Natl Cancer Inst.* 2004 May;96(9):703-8.

26. Patri AK, Myc A, Beals J, *et al.* Synthesis and in vitro testing of J591 antibody-dendrimer conjugates for targeted prostate cancer therapy. *Bioconjug Chem.* 2004 Nov-Dec*;*15 (6):1174-81.

27. Shi X, Wang S, Meshinchi S, *et al.* Dendrimer-entrapped gold nanoparticles as a platform for cancer-cell targeting and imaging. *Small.* 2007 Jul;3(7):1245-52.

28. Hirsch LR, Stafford RJ, Bankson JA, et al. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc Natl Acad Sci U S A.* 2003 Nov;100(23):13549-54.

29. Rasooly A. Moving biosensors to point-of-care cancer diagnostics. *Biosens Bioelectron.* 2006 Apr;21(10):1847-50.

30. Wang J. Electrochemical biosensors: towards point-of-care cancer diagnostics. *Biosens Bioelectron.* 2006 Apr;21(10):1887-92.

7