Nanomedicine : A Promising Tool for the Treatment of Cancer

SUNITA JAIN*[1] and SC JOSHI[2]

*1 Reader, Lal Bahadur Shastri College of Pharmacy
Udai Marg,Tilak Nagar, Jaipur - 302004 Rajasthan (India)
Phone : 91-141- 2620517 (O)
91-141- 2295138 (R)
E-mail : sunitajain_30@yahoo.com

2 Dy. Director, UGC Academic Staff College and Associate Professor
Department of Zoology, University of Rajasthan, Jaipur - 302004 Rajasthan (India)
Phone : 91-141- 2710925 (O)
91-141- 2762525 (R)
Telefax : 91-141- 2740141
E-mail : s_c_joshi2003@rediffmail.com

Summary

The application of nanotechnology to biomedical research is expected to have a major impact leading to the development of new types of diagnostic and therapeutic tools.Nanotechnology offers a vision for smart drug approach involving the design ,synthesis and characterization of materials and devices that have a functional association in nanometer scale.

Nanomedicine will benefit from stem cell research, tissue engineering research and device miniaturization. There are opportunities to design nanosized bioresponsive systems able to diagnose and then deliver drugs and system able to promote tissue regeneration and repair, circumventing chemotherapy. The present review throws light on application of nanoscience in cancer treatment

The use of nanotechnology in oncology offers exciting possibilities and is regarded an area of interest for various scientist .The use of nanoparticles conjugated to antibodies allow the possibility of simultaneously detecting multiple molecular targets in small tumor samples on which treatment decisions can be made . Protein and gene expression in an individual tumor can be correlated using nanoparticle tags. Nanoparticles offer a new method of tumor targeting already available in clinical practice which can concomitantly improve the efficacy and decrease the toxicity of existing or novel anticancer drugs.

Key Words: Nanotechnology, nanomedicine, nanoparticles, cancer , anticancer drugs

Introduction

Nanotechnology is a revolutionary field of micro manufacturing involving manipulation by chemical or physical processes of individual atoms and molecules. Current and potential applications of nanotechnology in medicine (nanomedicine) range from research involving diagnostic devices ,drug delivery, areas of gene therapy ,imaging and novel drug discovery techniques.The market of nanobiotechnology has existed for only a few years, but it is expected to exceed $3 billion by 2008, reflecting on annual growth rate of 28. By 2014 ,16% of goods in health care and life sciences (by revenue)will incorporate emerging nanotechnologies.[1,2]Bawa and Colleagues define nanotechnology as the design ,characterization, production and application of structures devices and system by controlled manipulation of size and shape at the nanometer scale with at least one novel /superior characteristic or property .[3]

Nanomedicine offers many benefits such as ;

- Targeted delivery of ingredients to a particular cell type or receptor.
- Longer duration of action due to extended release of ingredients.
- Capable of heat triggered local release.
- Enhanced stability .
- Enhanced bioavailability.
- Minimize side effects.
- Increase patient compliance.
- Ability to cross blood brain barrier and other crucial system.
- Cost effectiveness

There is a lot of opportunities in developing nanotechnology based efficient drug delivery systems in all therapeutic classes of pharmaceuticals such as anticancer drugs, hypolipidemic drugs antiatherosclerotic drugs, hormones vaccines, etc. because of safety and efficacy shortcomings in their conventional administration modalities (table 1).[4-8]

Table 1: Type of Nanoparticles in Nanotherapeutics

S. No.	**Type of Nanoparticles**	**Material used**	**Applications**
1	Polymeric Nanoparticles	Biodegradable Polymers	Controlled and targeted drug delivery
2	Solid Lipid Nanoparticles	Melted lipid dispersed in an aqueous surfactant	Least toxic and more stable colloidal carrier systems as alternative materials to polymers
3	Nanosuspensions and Nanocystals	Drug powder is dispersed in a surfactant solution	Stable system for controlled delivery of poorly soluble drugs
4	Ceramic Nanoparticles	Silica Alumina Titania	Drug targeting , Biomolecules delivery
5	Liposomes	Phospholipid Vesicles	Controlled and targeted drug delivery
6	Dendrimers	Polymers	Carriers for site specific drug delivery
7	Polymeric Micelles	Amphiphillic block copolymers	Systemic and Controlled water insoluble drug delivery
8	Magnetic nanoparticles	An inorganic core of iron oxide coated with polymer	Drug targeting ; Diagnostic tool in biology and medicine
9	Nanoshells coated with gold	Dielectric core and a metal shell	Tumor targeting
10	Nanowires or carbon nanotubes	Metals , semiconductors or carbon	Gene and DNA Delivery
11	Nanopores	Aerogel(sol-gel chemistry)	Controlled release drug carrier
12	Quantum Dots	CdSe-CdS core shell	Targeting, imaging agent

CANCER

Cancer is the second common cause of death in the developed countries next to cardiovascular (heart and blood vessel) diseases. According to WHO, out of an estimated total of 50 million deaths annually in the world, more than 5 million deaths are attributed to cancer. In Europe and North America, approximately one in five die of cancer. The figures given by Indian Cancer Society State that about 1.5 million people suffer from cancer at any point of time in India. According to Dr. D. J. Jussawalla, founder secretary of Indian Cancer Society, "Cancer is one of the 10 leading causes of death today in India, and is advancing in rank year by year." Approximately five Lac new cases of cancer occur every year in India and the no. of deaths from cancer is increasing.

Cancer is a disease of cells characterized by reduction or loss of normal cellular control and maturation mechanisms. In the early stages after a cell becomes cancerous it multiplies at feverish rates in one place; at this point it is considered benign. However, if left untreated the cancer becomes malignant and begins to spread through the circulatory system embedding itself wherever it sees fit. Smoking, tobacco chewing, industrial/vehicular pollution, asbestos, exposure to frequent X-rays ,oral contraceptives, different sexual partners, menopause, early marriage and frequent pregnancies are some of the risk factors for cancer. Four primary modalities are employed in the approach to cancer treatment : surgery, radiation, chemotherapy and biologic therapy. Each having its limitations hence it is required to look forward for new technologies.[9]

CANCER NANOTECHNOLOGY

Cancer Nanotechnology is an interdisciplinary area of research in science, engineering and medicine with broad applications for molecular imaging, molecular diagnosis and targeted therapy. The basic rationale is that nanometer-sized particles, in size range of 5-100nm diameter, have large surface areas and functional groups for conjugating to multiple diagnostic (e.g. optical, radio isotopic or magnetic) and therapeutic (e.g. anticancer) agents. Recent advances have led to bioaffinity nanoparticle probes for molecular and cellular imaging, targeted nanoparticle drugs for cancer therapy, and integrated nanodevices for early cancer detection and screening. These developments raise exciting opportunities for personalized oncology in which genetic and protein

biomarkers are used to diagnose and treat cancer based on the molecular profiles of individual patients.[10,11]

TOOLS OF NANOTECHNOLOGY [12-18]

NANOCANTILEVERS

These are helpful in early molecular diagnosis of cancer. Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. These molecules may bind to altered DNA proteins that are present in certain types of cancer. This will change the surface tension and cause the cantilevers to bend. By monitoring the bending of cantilevers, it would be possible to tell whether the cancer molecules are present. (Fig. 1)

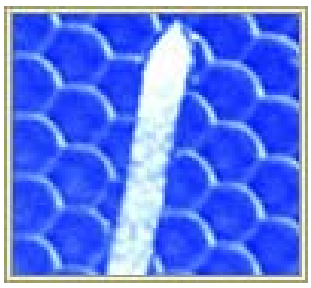

Fig. 1: NANOCANTILEVERS

NANOPORES

A small electric potential draws a charged strand of DNA through a pore of 1-2nm in diameter in a complex which is inserted into a lipid bilayer separating two conductive compartments. The passage of DNA through a nanopore can be used to decipher the encoded information, including errors in the code known to be associated with cancer. (Fig. 2)

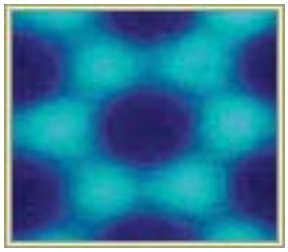

Fig. 2: NANOPORES

NANOTUBES

Nanotubes are hollow cylinders made of carbon and boron nitride.An electrode with single stranded DNA probes attach to their open end They will help identify DNA changes associated with cancer. It helps to exactly pin point location of the changes. (Fig. 3)

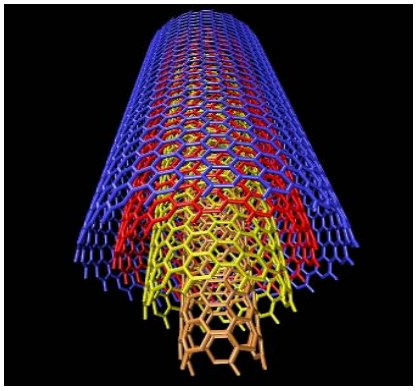

Fig. 3: NANOTUBES

QUANTUM DOTS

Quantum dots, nanoscale crystals of a semiconductor material such as cadmium selenide, cadmium sulphide and cadmium telluride . Quantum dots can be linked to antibodies and combined to create assays that are capable of detecting multiple substances simultaneously. Quantum dots are robust and very stable light emitters. The emission of different wavelengths of radiation depends on the type of cadmium used in their cores: cadmium sulfide for ultraviolet to blue, cadmium selenide for most of the visible spectrum, and cadmium telluride for the far red and near infrared. (Fig. 4)

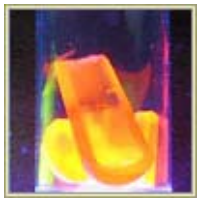

Fig.4 : QUANTUM DOTS

NANOSHELLS

Nanoshells are miniscule beads or hollow silica spheres coated with gold. By manipulating the thickness of the layers making up the NS, the beads can be designed that absorb specific wavelength of light. Nanoshell-assisted photo-thermal therapy (NAPT), is a simple, non invasive procedure for selective photo-thermal tumor removal. It makes use of nanoshells that absorb light in the near infrared(NIR) region. Nanoshells for cancer therapeutic purposes have been designed to have a peak optical absorption in the NIR, as this is the wavelength that optimally penetrates tissue.The metal shell converts the absorbed light into heat with great efficacy and stability. In addition, biomaterial nanoshells are composed of elements that are biocompatible. Due to their small size, nanoshells are preferentially concentrated in cancer cells by EPR or enhanced permeation retention. Further specificity can be engineered by attaching antigens on the nanoshells which are specifically recognized by the cancer cells. (Fig. 5)

Fig. 5: NANOSHELLS

NANOWIRE SENSORS

Researchers have developed coated nanowires that bind to certain proteins that can indicate the presence of prostate cancer before conventional tests can. Other potential applications for nanowires include the early sensing of breast and ovarian malignancies. Nanowires are so small that doctors could implant them into the body as permanent health detectives that continuously monitor molecular levels. (Fig. 6)

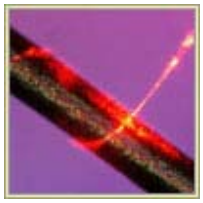

Fig. 6: NANOWIRE SENSORS

LIPOSOMES

Liposomes are small artificial vesicles of spherical shape that can be produced from natural nontoxic phospholipids and cholesterol. Their exterior lipid bilayer is very chemically reactive, thereby providing a means to conveniently couple "tags" on a covalent basis. Such "tags" can be antibodies, antigens, cell receptors, nucleic acid probe, etc. This provides significant versatility in assay formats (i.e. immunoassay, receptor based, nucleic acid probe, etc.) possible. Drugs associated with Liposomes have markedly altered pharmacokinetic properties compared to drugs in solution. They are also effective in reducing systemic toxicity and preventing early degradation of the encapsulated drug after introduction to the target organism. (Fig. 7)

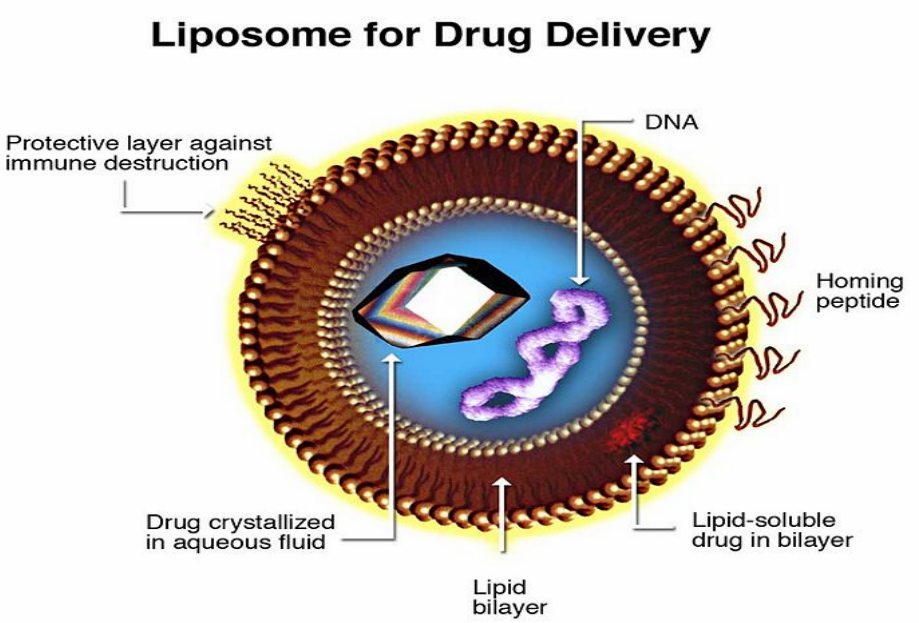

Fig. 7: LIPOSOMES

FULLERENES

These are a form of carbon atom whose molecular architecture is arranged in a soccer ball-like structur known as buckyballs. They are crystalline in nature and used for delivery of anticancer drugs. Fullerenes don't break down in the body and are excreted intact. This is beneficial for some anticancer drugs that are dangerous to healthy cells. For example, delivery of radioactive atoms through would allow for the complete removal of radiation from the body following treatment. (Fig. 8)

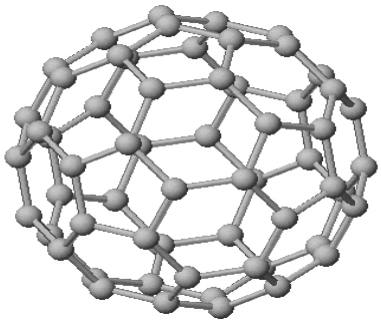

Fig. 8: FULLERENCES

POLYMERIC NANOPARTICLES

Nanoparticles can be in the form of nanospheres(matrix systems in which drugs are dispersed throughout the particle) and nanocapsules (drug is confined in an aqueous or oily cavity surrounded by a single polymeric membrane). Nanoparticles have the potential to overcome biological, biophysical and biomedical barriers currently faced by conventional administration of cancer drugs. If designed appropriately, nanoparticles may selectively target tumors, while protecting the drug from inactivation during transport.4 Poly(isobutylcyanoacrylate) has been used to make nanocapsules with an oily core for hydrophobic drugs. Nanospheres loaded with anticancer drugs successfully increase drug concentration in cancer tissues. (Fig. 9)

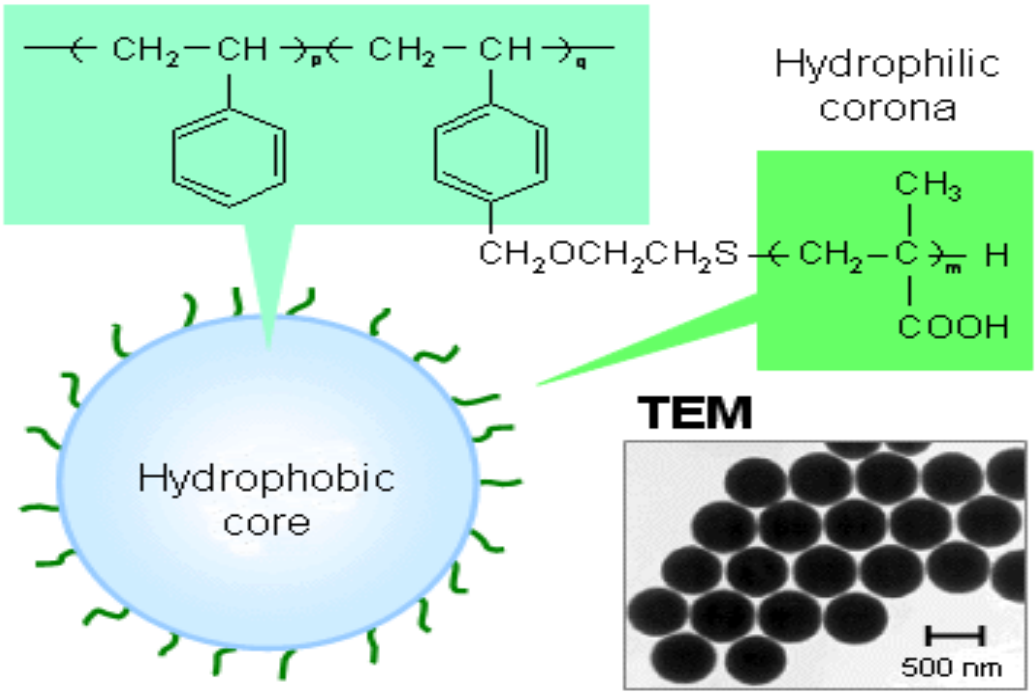

Fig. 9: POLYMERIC NANOPARTICLES

SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) are one of the potential colloidal carrier systems for lipophilic drugs. They show good biocompatibility, low toxicity, and are more stable. They can be prepared by homogenization of melted lipid dispersed in an aqueous surfactant solution and their size ranges from 100 to 150nm.They show promising result in sustaining and targeting the release of antitumor drugs such as Camptothecin and Doxorubicin .They might be used as a CNS MRI contrast agents also. (Fig. 10)

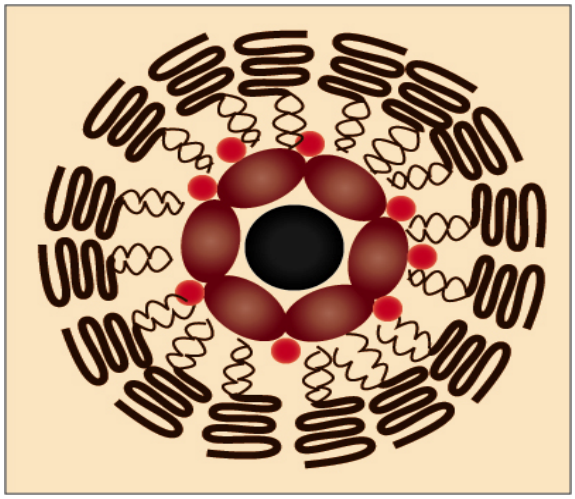

Fig. 10: SOLID LIPID NANOPARTICLES

CERAMIC NANOPARTICLES

These are inorganic particles made up of silica, alumina and titania entrapping biomolecules in a range of 50 nm. Theresize shape and porosity can be varied with different functional groups.They can be conjugated to various monoclonal antibodies or ligands for targeting the delivery. (Fig11)

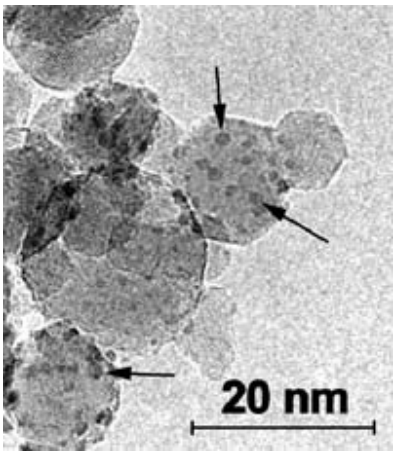

Fig. 11: CERAMIC NANOPARTICLES

MAGNETIC NANOPARTICLES

Super paramagnetic nanoparticles are used for magnetic resonance imaging (MRI).5 They consist of an inorganic core of iron oxide coated or not with polymers like dextran. There are two main groups of nanoparticles:

1) superparamagnetic iron oxides whose diameter size is greater than 50nm,

2) ultrasmall superparamagnetic iron oxides whose nanoparticles are smaller than 50nm.

DENDRIMERS

They are highly branched macromolecules possessing three dimensional architecture emerging from central core .Polymer growth starts from a central core and extends in an outward direction by polymerization reaction resulting in formation of cavities .With the help of chemical modification a number of diagnostic agents and anticancer drugs can be attached to surface groups on dendrimers. (Fig. 12)

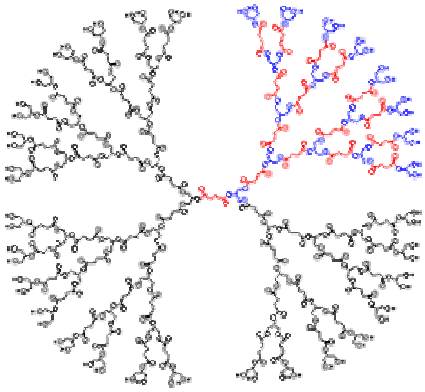

Fig. 12: DENDRIMERS

NANOGELS

These are made from a network of crosslinked ionic polyethylenimine and non ionic PEG chains using theemulsification solvent evaporation method.They are used to encapsulate N-hexylcarbamoyl-5-fluorocil(HCFU),a prodrug of 5-FU,and have been targeted to brain tissue across blood brain barrier after coating with polysorbate 80.

ERADICATION OF CANCER USING NANOTOOLS

NANOTECHNOLOGY DETECTION

Nanodevices can provide rapid and sensitive detection of cancer-related molecules by enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. This would allow early detection of cancer – a critical step in improving cancer treatment. Conventional methods such as X-rays ,CT Scans and biopsy through cell culture are not very sensitive and the detection is possible only after substantial growth of the cancerous cells. Nanoparticles are of very small in size so they can enter inside the cells and

can access the DNA molecules/ genes .Hence they can detect the defect in the genes in their incipient stage. Targeted QDs and other bioengineered nanoparticles provide several unique features and capabilities.

Their size-dependent optical and electronic properties can be tuned continuously by changing the particle size. There size effect provides a broad range of nanoparticles for simultaneous detection of multiple cancer biomarkers.

They have more surface area to accommodate a large number or different types of functional groups that can be linked with multiple diagnostic (e.g., radioisotopic or magnetic) and therapeutic (e.g., anticancer) agents. Hence they can be utilised for integrated imaging and therapy.

Nanoparticles in the size range of 10–100 nm are accumulated preferentially at tumor sites through an effect called enhanced permeability and retention (EPR). This causes tumor-associated neovasculatures to be highly permeable, allowing the leakage of circulating macromolecules and nanoparticles into the tumor interstitium.

MOLECULAR CANCER DIAGNOSIS

Significant opportunities exist at the interface between biomarkers and nanotechnology for molecular cancer diagnosis. Nanomedicine can be used to quantify a panel of biomarkers on intact cancer cells and tissue specimens, allowing a correlation of traditional histopathology and molecular signatures for the same material.[19-22]

TARGETED CANCER THERAPY

Anticancer agents do not greatly differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. They are widely distributed in non targeted organs and tissues and eliminated rapidly. Therefore a large dose is required for treatment. Nanotechnology offers a more targeted approach and could thus provide significant benefits to cancer patients. There are different targeting strategies for nanoscale drug delivery systems.

Passive Targeting

Rapid vascularization in fast-growing cancerous tissues is known to result in leaky, defective architecture and impaired lymphatic drainage. This structure allows an EPR effect, resulting

in the accumulation of nanoparticles at the tumor site. For such a passive targeting mechanism to work, the size and surface properties of drug delivery nanoparticles must be controlled to avoid uptake by the reticuloendothelial system (RES). To maximize circulation times and targeting ability, the optimal size should be less than 100 nm in diameter and the surface should be hydrophilic to circumvent clearance by macrophages. A hydrophilic surface of the nanoparticles safeguards against plasma protein adsorption and can be achieved through hydrophilic polymer coatings such as PEG, poloxamines, poloxamers, polysaccharides, or through the use of branched or block amphiphilic copolymers. The covalent linkage of amphiphilic copolymers (polylactic acid, polycaprolactone, polycyanonacrylate chemically coupled to PEG) is generally preferred, as it avoids aggregation and ligand desorption when in contact with blood components. (Fig. 13)

An alternative passive targeting strategy is to utilize the unique tumor environment in a scheme called tumor-activated prodrug therapy. The drug is conjugated to a tumor-specific molecule and remains inactive until it reaches the target.

Another passive targeting method is the direct local delivery of anticancer agents to tumors. This approach has the obvious advantage of excluding the drug from the systemic circulation.

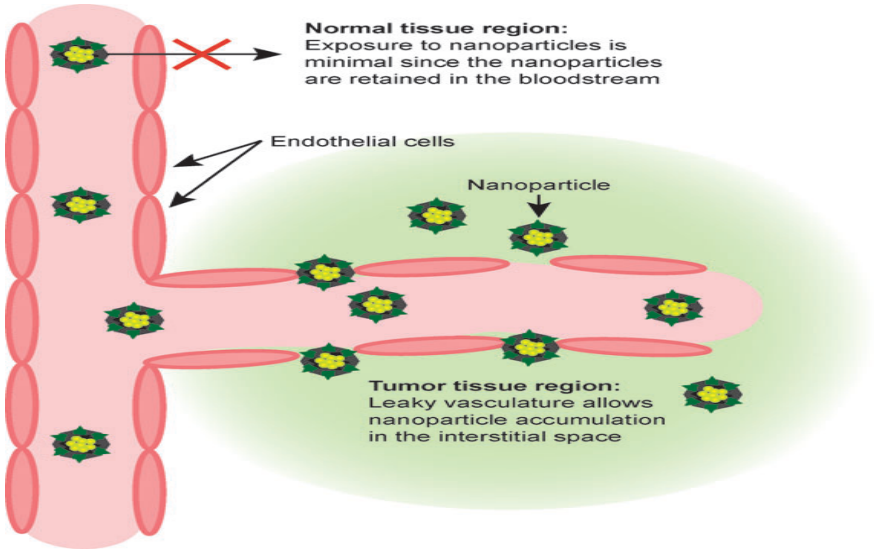

Fig. 13: PASSIVE TARGETING

Active Targeting

Active targeting is usually achieved by conjugating to the nanoparticle a targeting component that provides preferential accumulation of nanoparticles in the tumor bearing organ, in the tumor itself, individual cancer cells, or intracellular organelles inside cancer cells. In most cases the targeting moiety is directed toward specific receptors or antigens expressed on the plasma membrane or elsewhere at the tumor site. Interest in exploiting folate receptor targeting in cancer therapy and diagnosis has rapidly increased, as attested by many conjugated systems, including proteins, liposomes, imaging agents, and neutron activation compounds.

Anticancer Drugs

For decades, researchers have been developing new anticancer agents and new formulations for delivering chemotherapy drugs. Paclitaxel (Taxol^{TM}) is one of the most widely used anticancer drugs in the clinic. In a new formulation approach used in Abraxane^{TM}, recently approved by the FDA to treat metastatic breast cancer, Paclitaxel was conjugated to albumin nanoparticles. The formulation is very effective in circumventing side effects of the highly toxic Chremophor EL, which include hypersensitivity reactions, nephrotoxicity, and neurotoxicity. Carrier design and targeting strategies may vary according to the type, developmental stage, and location of cancer.(Fig.14)[23-30]

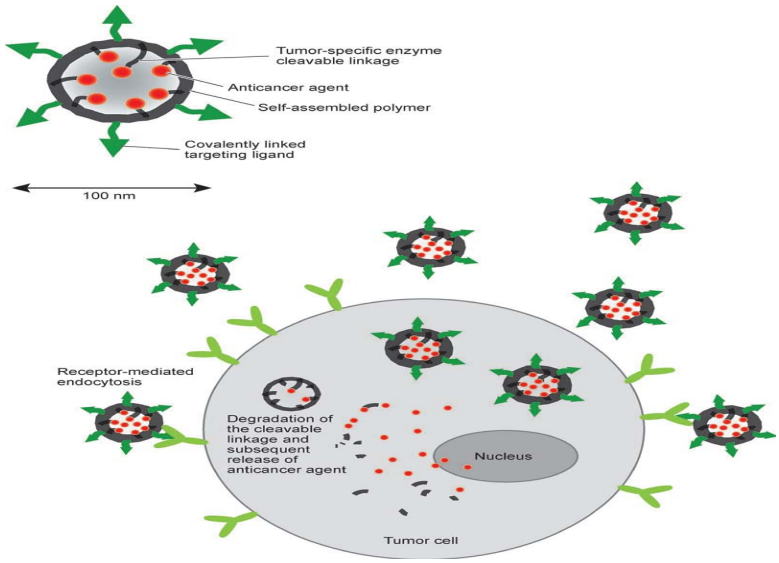

Fig. 14: EFFECT OF ANTICANCER AGENTS ON TUMOR CELL

Conclusion

Nanomedicine is a powerful and revolutionary development that is likely to have significant impact on society, the economy and life in general. Nanomedicine for cancer has the ability to improve health care by leaps and bounds. Nanotechnology will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. Nanotechnology can provide the technical power and tools that will enable those developing new diagnostics, therapeutics, and preventives to keep pace with today's explosion in knowledge. With nanomedicine, we might be able to stop cancer even before it develops.

References

1. Dua K, Sharma V K, Sara U V S and Pabreja K,Nanotechnology :An emerging field in targeted drug delivery. *Pharma Buzz,* 4(5), (2009)6
2. Kumar R , Nanotherapy-Present status. *Pharma Buzz,* 4(5) (2009) 30
3. Bawa R, Bawa S R, Maebius et al ,Protecting new ideas and innovations in nanomedicine via patents. *Nanomedicine,* 1(2) (2005)150.
4. Karanth Hand Murthy R S R, Nanotechnology in brain targeting. *Int J Pharma Sci Nanotech,* 1(1) (2008) 9.
5. Gopal V S, Karthik A, Ranjith Kumar A and Udupa N, Regulatory considerations of Nanotechnological Products in developed countries:Acritical Review. *Int J Pharma Sci Nanotech,* 1(1) (2008)25
6. Jain S, Shukla K, Jain V, Sarf S and Saraf S. Nanoparticles : Emerging carriers in delivery of bioactive agents.. *Pharma Times* 39(1) (2007)30-35.
7. NSF and NIH Commit $213 Million to Nanotech, *State Science and Technology Institute Weekly Digest*, *November 1, 2004*
8. Mnyusiwalla A, Daar A S & Singer P A, 'Mind the gap': science and ethics in nanotechnology, *Nanotechnology,* 14 (2003) 9.
9. von Eschenbach A C, A vision for the National Cancer Program in the United States, *Nature*,4 (2004) 820.
10. National Cancer Institute, *Cancer Nanotechnology: Going small for big advances,* NIH publication, Jan 2004
11. Zandonella C, *The tiny toolkit*, Nature, 423 (2003) 10.
12. Wang S G, Wang R., Sellin P J & Zhang Q, DNA biosensors based on self-assembled carbonnanotubes, *Biochem Biophys Res. Comm.,* 325 (2004)1433.
13. Bradbury J, *Nanoshell destruction of inoperable tumors,* Lancet Oncology, 4 (2003) 711.
14. Torchilin V P, Weissing V, editors. *Liposomes: a practical approach.* 2nd ed. New York: Oxford University Press; 2003.

15. Kojima C, Kono K, Maruyama K, Takagishi T. Synthesis of polyamidoamine dendrimers having poly(ethylene glycol) grafts and their ability to encapsulate anticancer drugs. *Bioconjug Chem* ,1(2000)910.
16. Brigger I, Dubernet C & Couvreur P, Nanoparticles in cancer therapy and diagnosis, *Advanced Drug Delivery Reviews*, 54 (2002) 631.
17. Fundaro A, Cavalli R, Bargoni A, Vighetto D, Zara G P, Gasco M R. Non-stealth and stealth solid lipid nanoparticles (SLN) carrying doxorubicin: pharmacokinetics and tissue distribution after i.v. administration to rats. *Pharmacol Res* ,42(2000) 337.
18. Bonnemain B, Superparamagnetic agents in magnetic resonance imaging: physiochemical characteristics and clinical applications – a review, *J. Drug Target*, 6(1998) 167.
19. Fahmy T M, Fong P M, Park J, Constable T, Saltzman W M. Nanosystems for simultaneous imaging and drug delivery to T cells. *AAPS J* ,9(2007),E171.
20. Venditto VJ, Regino CA, Brechbiel MW. PAMAM dendrimer based macromolecules as improved contrast agents. *Mol Pharm* ,2(2005): 302
21. Bagalkot V, Zhang L, Levy-Nissenbaum E, Jon S, Kantoff P W, Langer R, et al. Quantum dot-aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on bi-fluorescence resonance energy transfer. *Nano Lett*,7(20007),3065.
22. Gao X, Cui Y, Levenson RM, Chung LW, Nie S. In vivo cancer targeting and imaging with semiconductor quantum dots. *Nat Biotechnol* ,22(2004) 969
23. Koch A M, Reynolds F, Merkle H P, Weissleder R & Josephson L, Transport of surface modified nanoparticles through cell monolayers, *Chem Bio Chem*, 6 (2005) 337.
24. O'Neal D P, Hirsch L R, Halas N J, Payne J D & West J L, Photo-thermal tumor ablation in mice using near infared-absorbing nanoparticles, *Cancer letters*, 209 (2004) 171.
25. Brongersma M L, Nanoshells: Gifts in a gold wrapper, *Nature materials*, 2 (2003) 296.
26. LaVan D A, McGuire T & Langer R, Small-scale systems for *in vivo* drug delivery, *Nature Biotechnology*, 21(10) (2003) 1184.
27. Couzin J, Nanoparticles cut tumors' supply lines, *Science*, 296(5577) (2002) 2314.
6. Torchilin V P. Targeted pharmaceutical nanocarriers for cancer therapy and imaging. *AAPS J* 9(2007) ,E128.
28. Sparreboom A, Scripture C D, Trieu V, Williams P J, De T, Yang A, et al. Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). *Clin Cancer Res* ,11(2005) 4136
29. Zara G P, Cavalli R, Bargoni A, Fundaro A, Vighetto D, Gasco M R. Intravenous administration to rabbits of non-stealth and stealth doxorubicin-loaded solid lipid nanoparticles at increasing concentrations of stealth agent: pharmacokinetics and distribution of doxorubicin in brain and other tissues. *J Drug Target* ,10(2002) 327
30. Shvedova A A, Castranova V, Kisin E R, Schwegler-Berry D, Murray A R, Gandelsman V Z, et al. Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells. *J Toxicol Environ Health A* ,66(2003)1909