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NANOTECHNOLOGY AND CANCER – AN OVERVIEW

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INTRODUCTION

Nanotechnology is a new direction in science and technology, which is intensively developed during the last decade and represents one of the most important directions in the technological developments of the leading countries in 21st century. By analogy with existing microtechnologies the nanotechnologies may be considered as the technologies operating with nanometer objects. These include new nanomaterials: nanotubes, fullerenes, nanocomposites, porous materials, ultra dispersed powders, photon crystals, supramolecular ensembles and constructs, thin films and superficial layers, micellar systems and microemulsions, liquid crystals, liposomes, biomembranes, etc. Employment of nanotechnologies and nanomaterials opens new perspectives in electronics, chemical industry, energetics, biology and medicine, etc

Today nanotechnologies significantly influence all aspects of our life. Their commercial use involves all branches of industry, medicine, agriculture, etc. Transition from the “micro” to the “nano” represents qualitative rather than quantitative transition form manipulation of the matter to controlled manipulation by individual atoms and molecules. Due to their sizes the nanoparticles acquire new physico-chemical properties and functions, which significantly differ from properties and functions of atoms and molecules constituting large sized particles.

The use of nanoparticulate pharmaceutical carriers to enhance the *in vivo* efficiency of many drugs well established itself over the past decade both in pharmaceutical research and clinical setting. The current level of engineering pharmaceutical nanocarriers in some cases allows for drug delivery systems (DDS) to demonstrate a combination of some desired properties. However, looking into the future of the field of drug delivery, we have to think about the development to the next generation of pharmaceutical nanocarriers combining different properties and allowing for multiple functions. Long-circulating immuno liposomes represent a good example of this approach, since they combine the ability to remain in the circulation for along time with the ability to specifically accumulate in target areas. One may add pH-sensitive long-circulating liposomes and micelles, or nanocarriers simultaneously loaded with a drug and an imaging agent to the list. Such nanocarriers belong to the new and smart generation of DDS. We can imagine DDS, which, depending on the immediate

requirements, can simultaneously or sequentially demonstrate the following properties:(1) Circulate long in the blood or, more generally stay long in the body;(2) Specifically target the site of the disease via different mechanisms, such as enhanced permeability and retention effect (EPR) and ligand mediated recognition;(3) Respond local stimuli characteristic of the pathological site, such as abnormal pH values or temperature or respond externally applied stimuli, such a magnetic field, or ultrasound, by, for example, releasing an entrapped drug or facilitating the contact between drug-loaded nanocarriers and target cells;(4) Provide an enhanced intracellular delivery of an entrapped drug in case the drug is expected to exert its action inside the cell;(5) Provide a real-time information about the carrier (and drug) biodistribution and target accumulation as well as about the outcome of the therapy due to the presence within the structure of the carrier of a certain reporter moiety. To be able to meet the medical/clinical requirement, drug carrier should simultaneously carry on its surface various moieties capable of functioning in a certain orchestrated order. We have to agree that systems like this still represent a challenge, although a certain work in this direction already done.

Nanotechnology for Cancer Therapy

Nanoparticles were first developed approximately 35 years ago. They were initially developed as carriers for vaccines and cancer chemotherapy agents. Nanoparticles are stable, solid colloidal particles consisting of biodegradable polymer or lipid materials and range in size from 10 to 1,000 nm. Drugs can be absorbed onto the particle surface, entrapped inside the polymer/lipid, or dissolved within the particle matrix. An example of a DDS is a liposome. Liposomes are closed bilayered phospholipids first designed 40 years ago. These were collectively designed to be taken up and delivered by mononuclear phagocytes (MP).

Although there have been significant advances in defining the fundamentals of cancer biology over the past 25 years, this has not translated into similar clinical advances in cancer therapeutics. One are a that holds great promise for making such advances is the area defined as cancer nanotechnology, which involves the inter section of a variety of disciplines, including engineering, materials science, chemistry, and physics with cancer biology. This multidisciplinary convergence has resulted in the creation of devices and / or materials that are themselves or have essential components in the 1–1000-nm range for at least one dimension and holds the possibility of rapidly advancing the state of cancer therapeutics and tumor imaging. This newly developing area of “nanohealth” may ultimately allow detection of human tumors at the very earliest stages, regardless of the location of the primary tumor and / or metastases, and may provide approaches to more effectively destroy tumors as well as their associated vascular supplies with fewer adverse side effects.

One of the most important characteristics of nanovectors is their ability to be functionalized to overcome barriers that block access of agents used for treatment of tumors and for imaging of tumors and their associated vasculature. These biological barriers are numerous and complex. One such barrier is the blood–brain barrier, which prevents access to brain malignancies, compounding the difficulties in their successful treatment. One example of the potential utility of nanovectors in overcoming this bio barrier, which is critical to treatment of malignant brain tumors, is the use of nanoparticles in combination with boron neutron capture therapy (BCNT).

Additional bio barriers that must be overcome include epithelial–endothelial cell barriers, the barriers presented by the markedly tortuous structures that are characteristic of angiogenic vasculature associated with

tumors, as well as the barrier set up by the rapid uptake of nanovectors by resident macrophages within the reticulo endothelial system (RES) which may prevent nanovectors from reaching their targeted location. To achieve breakthrough advances in cancer therapeutics, there are two related and essential components which must be addressed. The first issue in successful use of nanovectors is recognition of the tumor and the second is the ability of the nanovector for each the site of the tumor and associated blood vessels. The goal is to preferentially achieve high concentrations of a specific chemotherapeutic agent, a tumor imaging agent, and/or gene therapies at the site(s) of tumors and associated vasculature. In addition, nanovectors must be able to deliver an active agent to achieve effective anti tumor treatment, or tumor imaging, which is essential for tumor diagnosis and for monitoring the extent and timing of an individual patient's response to anti-tumor therapy.

Multi-accessibility of Nanotechnology

In the field of cancer biology, intravascularly injectable nanodevices/vectors are the major class of drug delivery systems to the targeted drug delivery system. Some imaging nanovectors are helped a lot to study about the targeted delivery systems as well as to know the traveling pathway of an introduced nanovectros. Targeted delivery of drug leads to decrease the adverse side effects to the normal tissue and increase the bioavailability of the expected drug. So the importance of nanovectors is mandatory in order to improve the life of the drug.

Before entering into the discussion about this topic, it is necessary to have a look on the current nanotechnologies in medical field. This helps to understand the concept further more.

In clinical and research protocol, several types of nanoparticles have been used for the enhancement of MRI contrast. This includes gadolinium-based [1] and iron oxide based nanoparticles and multiple-mode imaging nano agent with magnetic resonance along with biological targeting and optical detection [2-4]. Generally low density lipid nanoparticles have been used to enhance ultrasound imaging. Because of these innovative approaches, a nanoparticle can provide signal enhancement, environmental sensitive as well as biomolecular targeting capabilities [5] and delivery of large amount of therapeutic or imaging agents per targeting biorecognition event and covalently linked to antibodies [6].

1. Nanocryosurgery

Cryosurgery is becoming popular because of less invasive than traditional surgical resection. This technique minimizes pain, bleeding and other complications of surgery and less expensive than other treatments. Nanocryosurgery is a combination of nanotechnologies and this physical therapy. Initially nanoparticles is mixed with functional solution and transferred into the target tissue. Thus addition of metal nanoparticles into wet biological environment will increase the tissue conductivity which turns in significant freezing effects. According to the theory of ice nucleation, massive load of nanoparticle in tumor cells is bound to induce more efficient ice formation, known as probability of intracellular ice formation (PIF), a main reason for cell death in cryosurgery [7-9].

2. Photodynamic Therapy

Photodynamic therapy is a treatment methodology used for the selective destruction of cancerous cells. To produce cytotoxic effects towards the tumorous tissue alone, PDT requires components of oxygen input and a light- activatable chemical sensitize called photosensitizer (PS) [10-13]. Photofrin is an approved PS for clinical use- it's simply an porfimer sodium. This PS specifically used for the treatment of lung

digestive tract cancers [14, 15]. However, photofrin has poor selectively in between tumor and normal tissues, due to its long clearance time [16]. Second generation PS such as verteporfin, [17, 18] have improved tumors selectively and quicker clearance, resulting in less prolonged skin phototoxicity. The selective accumulation of PS towards tumor tissue instead of normal tissues achieved by dissecting light irradiation to tumors.

3. DNA-binding by functionalized Gold nanoparticle

Controlling disease by gene regulation or altering cellular activity has become a realistic goal in the field of medicinal chemistry. Converting of synthetic molecular into capable of DNA binding molecule is a notable success in the creation of DNA transcription regulators [19-23]. Added to this, peptide and saccharide scaffolds that can be a known DNA-binding components to confer the activity of a particular sequences [24-29]. Nuclear delivery via gold nanoparticle-peptide complexes also a challenging task. Because targeted entry into cells is an increasingly important area of research. The nucleus is a desirable target because the genetic information of the cell and transcription machinery resides there. The diagnosis of disease phenotype, the identification of potential drug candidates, and the treatment of disease by novel methods such a antisense therapy would be enhanced greatly by the efficient transport of materials to living cell nuclei. Nuclei probe is having certain qualities like i). enter the cell via receptor-mediated endocytosis (RME), ii) escape endosomal/lysosomal pathways iii) posses a nuclear localization signal (NLS) to interact with the nuclear pore complex iv) small enough (< 30 nm) to cross the nuclear membrane.

The disadvantage of such formulations is that the rupture time cannot be adjusted as it is strongly correlated with the physicochemical properties of the polymer. Very commonly two or more polymers can be used to develop an acceptable product regarding the efficient control release of the active compound. In some cases miscible polymer blends seem to be the most effective drug carriers for pulsatile chromotherapeutics. However, due to thermodynamic restrictions the majority of the polymer blends are immiscible containing two or more different phase. But the mixtures of polymers are inappropriate due to the different erosion rates of the substances, which leads to channeling creation and unrepeatable rupture times [30].

4. Quantum Dots

Quantum dots (QDs) are new semiconductor nanocrystals with sizes ranging from 1 nm to 10 nm in diameter. The special physical composition and size lead to many unique bio- medical properties, such as higher fluorescence intensity, longer fluorescence lifetime, sensitive detection of QDs signals over intrinsic biological fluorescence and simultaneous detection of many biomarkers [31]. Furthermore, appropriate composition and size of QDs can emit near infrared optical spectrum (700–2000 nm) which has low tissue scatter and absorption, so as able to obtain optical signals of maximized penetration depth from biological tissue, and was ideal to deep-tissue imaging, especially *in vivo* imaging [32]. The rapid development of QDs in bio-medical applications was intimately associate with the increasing progresses on the synthesis and bio-conjugation [33-37] of QDs in recent years, especially the application of conjugation by PEG (polyethylene glycol), which not only makes QDs water soluble and stable, but also make them escape recognition and non-specific uptake by reticulo endothelial system (RES), and thereby prolonging [38, 39] the half life of QDs in circulation. Magnetic nanoparticles have been widely used for targeted delivery of chemotherapeutic agents

for the treatment of solid tumors. The drugs are adsorbed or chemically bonded to the particles, and then the system is targeted to the site of choice with the aid of an external magnet, being the drugs eventually desorbed on the desired area over a long period of time [40]. This local treatment improves the efficacy of the chemotherapy, reducing dramatically systemic toxicity.

5. Polymers as Nanovectors

An important and long-term goal of the pharmaceutical industry is to develop therapeutic agents that can be selectively delivered to specific are as in the body to maximize the therapeutic index. Drugs, given systemically, provide a profound beneficial effect but canal so exhibit adverse reactions. Historically, cancer chemotherapy agents have been well-known examples of achieving balance between efficacy and toxicity. Cytotoxic compounds can be highly effective in destroying cancer cells but may also damage normal cells resulting in possible adverse and potentially life-threatening effects. The “magic bullet” concept, first theorized by Paul Ehrlich in 1891 represents the first early description of the drug-targeting paradigm. The aim of drug targeting is to deliver drugs to the right place, at the right concentration, for the right period of time. As drug characteristics differ substantially in chemical composition, molecular size, hydrophilicity, and protein binding, the essential characteristics that identify efficacy are highly complex. All of these are investigated to bring a new compound to market although only a fraction reaches active clinical use [95-97].

In recent years, pH-sensitive polymeric carriers in various forms of micelles [41-43], and nanoparticles [44, 45] have seen rapid development. Particularly, polymeric micelles are being extensively studied as a promising nano scale drug carrier since the pioneering work in early 1990s [46]. Polymeric micelles have many advantages such as small size (10 to 200 nm) for passive accumulation in solid tumors by enhanced permeation and retention (EPR), improved stability, biodegradability and high flexibility for structural and chemical modifications [47,48]. Early generation polymeric micelles simply accumulated on the tumor extra cellular matrix (ECM) and did not provide high enough concentrations of anti cancer drugs to kill the tumors, because most cytotoxic drugs act inside the cells and not on the ECM [49,50]. Therefore, tumor targeting carriers have been modified such that they accumulate by the EPR effect on tumor cells followed by active internalization into tumor cells [51]. Such improved active targeting technology is being developed by using binding characteristics between tumor specific antigens and their monoclonal antibodies (mAb) [52], binding fragments specific to a tumor associated surface antigens [53],or between ligands and their corresponding receptors [54]. Such active targeting carriers show enhanced capability to translocate the micelles into tumor cells [55]

To minimize drug degradation and loss upon administration, prevent harmful or undesirable side-effects, and increase drug bioavailability and the fraction of the drug accumulated in the pathological zone, various drug delivery and drug targeting systems are currently being developed or under development. Among drug carriers one can find soluble polymers, microparticles made of natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes and micelles [56, 57]. Each of those carrier types offers its own advantages and shortcomings, and all those carriers can be made slowly degradable, stimuli reactive (for example, pH or temperature sensitive) and even targeted (for example, by conjugating them with specific antibodies against certain characteristic components of the area of interest). In addition, drug carriers should be

long circulating [58, 59] since prolonged circulation allows for maintaining the required therapeutic level of pharmaceuticals in the blood for extended time intervals. Long-circulating, high molecular weight drugs or drug-containing microparticulates can also slowly accumulate in pathological sites with affected and leaky vasculature (such as tumors, inflammations and infracted areas) via the enhanced permeability and retention effect (EPR) and enhance drug delivery in these areas [60, 61]. In addition, prolonged circulation can help to achieve a better targeting effect for specific ligand-modified drugs and drug carriers since it increases the total quantity of targeted drug/carrier passing through the target, and the number of interactions between targeted drugs and their targets [62].

Micelles represent so-called colloidal dispersions (with particle size normally within the 5–100nm range) that belong to a large family of dispersed systems consisting of particulate matter or dispersed phase, distributed within a continuous phase or dispersion medium. They belong to a group of association or amphiphilic colloids. Such colloids are spontaneously formed under certain concentration and temperature by amphiphilic or surface-active agents (surfactants), molecules of which consist of two clearly distinct regions with opposite affinities toward a given solvent [63]. At low concentrations in aqueous medium, these amphiphilic molecules exist separately; however, as their concentration is increased, aggregation takes place within a rather narrow concentration interval.

Those aggregates, known as micelles, include several dozens of amphiphilic molecules and usually have a shape close to spherical. The concentration of a monomeric amphiphile at which micelles appear is called the critical micelle concentration (CMC), while the temperature below which an amphiphilic molecule exist as unimers and above as aggregates is called the critical micellization temperature (CMT). Hydrophobic fragments of amphiphilic molecules form the core of a micelle, which can solubilized poorly soluble pharmaceuticals, while hydrophilic fragments form the micelle's corona [64, 65]. In aqueous systems, non polar molecules are solubilized within the micelle core, polar molecules will be adsorbed on the micelle surface and substances with intermediate polarity will be distributed along surfactant molecules in intermediate positions.

5.1. Polymeric Micelles

Polymeric micelles represent a class of micelles and are formed from block copolymers consisting of hydrophilic and hydrophobic monomer units. It has repeatedly been shown that amphiphilic block and graft AB-type copolymers with the length of a hydrophilic block exceeding to some extent that of a hydrophobic one can form spherical micelles in aqueous solutions [66]. The particulates are composed of the core of the hydrophobic blocks stabilized by the corona of hydrophilic polymeric chains. If the length of a hydrophilic block is too high, copolymers exist in water as unimers (individual molecules), while molecules with very long hydrophobic blocks form structures with non-micellar morphology, such as rods and lamellae [67]. The major driving force behind self-association of amphiphilic polymers is the decrease of free energy of the system due to removal of hydrophobic fragments from the aqueous surroundings with the formation of a micelle core stabilized with hydrophilic blocks exposed into water [68]. The lower the CMC value of a given amphiphilic polymer, the more stable micelles are even at low net concentration of amphiphile in the medium [69]. This is especially important from the practical point of view, since upon dilution with a large volume of blood, micelles with a high CMC value may dissociate into unimers, and their content may precipitate in the blood.

Numerous studies have been published developing a theoretical description of micelle formation and properties [70].

The core compartment of the pharmaceutical polymeric micelle should demonstrate a high loading capacity, a controlled release profile for the incorporated drug, and good compatibility between the core-forming block and the incorporated drug. The micelle corona should provide effective steric protection for the micelle. It should also determine micelle hydrophilicity, charge, the length and surface density of hydrophilic blocks, and the presence of reactive groups suitable for further micelle derivatization, such as attachment of targeting moieties [71-75]. These properties control important biological characteristics of a micellar carrier, such as its pharmacokinetics, biodistribution, biocompatibility, longevity, surface adsorption of biomacromolecules, adhesion to biosurfaces and targetability [76].

5.2. Polymeric micelles: Enhancing Solubility

Micelles are nano sized, spherical colloidal particles with a hydrophobic interior (core) and a hydrophilic exterior (shell). Their main utility is in the preparation of pharmaceutical formulations, notably agents that are regularly soluble in water (84,85). Drugs or contrast agents may be entrapped within the hydrophobic core or linked covalently to the surface of micelles. Their individual particle size is less than 50 nm in diameter, which provides obvious benefits over liposomes. Polymeric micelles may circulate for prolonged periods in the blood, evading host defenses. With their property of continued stability in the blood, polymeric micelles can be used to gradually release drugs and facilitate in vivo imaging (86,87). To support prolonged systemic circulation, shells of polymeric micelles are designed to be thermodynamically stable and biocompatible (88).

Polymeric micelles provide a safer alternative for parenteral administration of poorly water-soluble drugs like amphotericin B, propofol, paclitaxel, and photosensitizers. For the formation of micelles, amphiphilic molecules must have both hydrophobic and hydrophilic segments, where the hydrophilic fragments form the micelle shell and the hydrophobic fragment forms the core. Thus, in aqueous media, the core of the micelles can solubilize water-insoluble drugs; the surface can adsorb polar molecules, where as drugs with intermediate polarity can be distributed along with the surfactant molecules in intermediate positions (89). The mechanism of solubilization and utilization of micelles has been extensively studied by various researchers. Similar to liposomes, polymeric micelles can be modified using piloting ligand molecules for targeted delivery to specific cells (i.e.,cancercells). pH-sensitive drug-binding linkers can be added for controlled drug release. For that same purpose, micelles can also be formed from stimuli responsive amphiphilic block co-polymers. Multifunctional polymeric micelles can be designed to facilitate simultaneous drug delivery and imaging (90).

5.3. Liposomes

Liposomes are spherical vesicles composed of amphiphilic phospholipids and cholesterol, which self-associate into bilayers to encapsulate an aqueous interior (77). The amphiphilic phospholipid molecules form a closed bilayer sphere in an attempt to shield their hydrophobic groups from the aqueous environment, while still maintaining contact with the aqueous phase via the hydrophilic head group. Drugs with widely vary in glipophilicities can be encapsulated in liposomes, in the phospholipid bilayer, in the entrapped aqueous volume, or at the bilayer interface. Although liposomes vary greatly in size, most are 400 nm or less (77-79). Depending upon their size and number of

bilayers, liposomes can be classified into three categories: multi- lamellar vesicles, large unilamellar vesicles, and small unilamellar vesicles. Liposomes can be classified in terms of composition and mechanism of intracellular delivery into five types: conventional liposomes, pH-sensitive liposomes, cationic liposomes, immunoliposomes, and long-circulating liposomes. Although liposome technology was discovered over 40 years ago, liposome-based drug formulations have not entered the market in great number. Some of the major problems limiting the manufacture and development of liposomes are their stability, poor batch-to-batch reproducibility, difficulties in sterilization, and low drug loading (80-83).

5.4. Dendrimers

Polymer chemistry and technology have traditionally focused on linear polymers, which are widely in use. Linear macromolecules only occasionally contain some smaller or longer branches. In the recent past it has been found that the properties of highly branched macromolecules can be vary from conventional polymers. The Structure of these materials has also a great impact on their applications. First discovered in the early 1980's by Donald Tomalia and co-workers, these hyper branched molecules were called dendrimers [91]. The term originates from 'dendron' meaning a tree in Greek. At the same time, Newkome's group independently reported synthesis of similar macromolecules. They called them arborols from the Latin word 'arbor' also meaning a tree [92]. The term cascade molecule is also used, but 'dendrimer' is the best established one.

Dendrimer technology has become well established in recent years, and has enabled us to build macromolecules with nano-sized defined structures. Macromolecules comprising branched repeat units have globular shaped three-dimensional structures with sole molecular weights [93]. As described in many review articles, many types of dendritic molecules are known, while various synthetic approaches to efficient construction of dendrimers continue to be explored. The functionalizations and application of dendrimers have been investigated in a wide range of research areas based on the uniqueness of their size, shape, and space. In particular, the inner space of a dendrimer surrounded by a shell made of highly dense terminal groups is suitable for the incorporation of guest molecules. Such an isolated space can be used or molecular recognition, catalytic reaction, drug delivery, etc [94].

Recently, much effort has been expended to introduce heterogeneity into dendrimer or dendron structures to obtain more elaborate functions using different types of functional groups in one dendrimer structure. For example, dendrimers containing both hydrophilic and hydrophobic parts dynamically change their structure corresponding to the polarity of the solvent.

When introducing a new class of nanoparticles for medical applications are directed towards the biocompatibility of these particles. In order to be usable in drug delivery applications, dendrimers have to be non-toxic and non-immunogenic. Most of these studies are very recent, and therefore, the cytotoxicity of dendrimers has been primarily evaluated in vitro; however, a few in vivo studies have been published [98-102]. As observed for other cationic macromolecules including liposomes and micelles, dendrimers with positively charged surface groups are prone to destabilize cell membranes and cause cell lysis. Furthermore, the cytotoxicity was found to be generation dependent, with higher generation dendrimers being the most toxic [103]. A similar generation dependency of amino-terminated PAMAM dendrimers was

observed for the haemolytic effect, studied on a solution of blood cells [104]. The biocompatibility of dendrimers is not solely determined by the surface groups. However, the influence of the dendrimer core will diminish with increasing dendrimer size (number of generations) and rigidity of the dendritic branches that form the shell around the core.

The flexible branches of a dendrimer, when constructed appropriately, can provide a tailored sanctuary containing voids that provide a refuge from the outside environment. Encapsulation of hydrophilic, hydrophobic, or even amphiphilic compounds as guest molecules within a dendrimer [105] can be enhanced by providing various degrees of multiple hydrogen bonding sites or ionic interactions [106,107] or highly hydrophobic interior void spaces [108, 109]. A wide variety of molecules have been successfully encapsulated inside dendrimers. For example, actual drugs, including 5-fluorouracil [110], 5-amino salicylic acid, pyridine, mefanminic acid and diclofenac, paclitaxel [111,112], docetaxel [113], as well as the anticancer agent 10-hydroxycamptothecin, have been successfully encapsulated. Together, these results demonstrate that encapsulation is a general strategy for the delivery of low molecular weight compounds by dendrimers. This method is anticipated to be of particular value when display of the bioactive molecule on the surface of the dendrimer induces unwanted immunogenicity or reduces biocompatibility.

The strategy of coupling small molecules to polymeric scaffolds by covalent linkages to improve their pharmacological properties has been under experimental test for over three decades [114-117]. Unfortunately, conventional linear polymers typically used in these efforts are plagued by inherent properties that render them distinctly ‘‘un-drug-like’’, including high polydispersity and size distributions, a lack of defined structure, and a low density of drug payload per unit volume or mass. Properties of dendrimers that overcome these problems include monodispersity that results in the ability to select the precise sizes of nanoparticle required to a specific application, a fully defined structure that allows the presentation of attached conjugates in a defined architecture, a high ratio of drug payload to volume, and enhanced control over drug release rates. Unsurprisingly, based on these many beneficial features, a wide range of biologically active molecules have already been covalently attached to dendrimers. These conjugates range from small molecule drugs, such as ibuprofen [118], fluorescent and radioactive imaging agents, oligonucleotides, oligosaccharides and peptides, as well as much larger molecules such as monoclonal antibodies. Biologically active molecules attached to dendrimers can have two fundamentally different relationships to the host molecule. In some cases, exemplified by vaccine applications, there is no need to liberate active drug from the dendrimer (indeed, the success of antibody production usually depends on the unique display characteristics achieved by conjugation to the dendrimer). In most cases, however, the conjugated dendritic assembly functions as ‘‘pro-drug’’ where, upon internalization into the target cell, the conjugate must be liberated to activate the drug.

CONCLUDING REMARKS

Different applications were envisaged, including vaccination (as immunological adjuvants), cosmetics, imaging (carrying contrasting agents) and for the transport and specific delivery of potent drugs (for cancer, ophthalmic, pulmonary and infectious diseases), as well as of nucleic acids, aiming at cancer therapy applications. The liposomal delivery of highly charged or macromolecular

drugs into cells presents the challenge of penetration through the endosomal membrane. This problem has been resolved partially by the development of pH-sensitive liposomes, and sterically stabilized pH-sensitive liposomes. The use of the latter liposomes, as well as their targeting to specific tissues, is very likely to facilitate the application of ribozymes, antisense oligonucleotides, triple helix forming oligonucleotides, short interfering RNAs and other macromolecular drugs to the therapy of infectious diseases and cancer.

Many believe strongly that nanotechnology will be the next industrial revolution, and is ready to expand into biomedicine. Within a remarkably short period of time, the emergence of nanoparticle tools has matched and even surpassed the capabilities of traditional imaging, delivery, and sensing devices. Nanoparticle vectors can now penetrate endothelial barriers to reach tumor sites, unlike previous micron-scale formulations. Conductivity-based sensing arrays will perform multiplexed detection without probe labeling, which is impossible with current immunoassay or microarray technology. As with many much fledgling technologies, mass adaptation to complement and replace current tools will take time. Cost, ease of integration with current infrastructure, and performance variability are critical factors that will determine not if, but when, nanoparticle systems become standard tools in cancer research.

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