MULTIPLEXED NANOPARTICLES IN CANCER TREATMENT

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Abstract: Cancer affects about seven million people worldwide, and that number is projected to grow to 15 million by 2020. Most of those patients are treated with chemotherapy and/or radiation, which are often effective but can have debilitating side effects because it's difficult to target tumor tissue. Nanotechnology, an interdisciplinary research field involving chemistry, engineering, biology, and medicine, has great potential for early detection, accurate diagnosis, and personalized treatment of cancer. Applications of nanotechnology to medicine and physiology imply materials and devices designed to interact with the body at molecular scales with a high degree of specificity. This can be potentially translated into targeted cellular and tissue-specific clinical applications designed to achieve maximal therapeutic efficacy with minimal side effects.These multiplexed nanoparticles may be capable of identifying malignant cells by means of molecular detection, visualizing their location in the body by providing enhanced contrast in medical imaging techniques, killing diseased cells with minimal side effects through selective drug targeting, and monitoring treatment in real time.This review article highlights the recent progress and the use of therapeutic nanoparticles in the clinic and also discusses the opportunities and challenges faced by therapeutic nanoparticles.

Key words: Nanomedicine, Nanoparticles, Cancer therapy, Drug delivery

Introduction: Despite advancements in treatment, cancer remains one of the leading causes of death worldwide. And it's getting worse: In the year 2030, researchers from the International Agency for Research on Cancer (IARC) expect 22.2 million new cases of cancer worldwide, a 75% rise from 2008[1]. Cancer is caused by damage of genes which control the growth and division of cells. Detection/diagnose/treatment is possible by confirming the growth of the cells and treated by rectifying the damaging mechanism of the genes or by stopping the blood supply to the cells or by destroying it. Nano Particles (NP) being of a few of nano meters size and the cells being of the size of few microns, NP can enter inside the cells and can access the DNA molecules/genes and therefore, there is a possibility that the defect in the genes can be detected. The conventional treatment options of cancer are surgery, radiation therapy and chemo therapy. However, all the these methods have their own limitations (in surgery one loses the organ and the cancer may appear again, in radiation therapy even the healthy cells get burnt, cancerous cells burning is not uniform and the burnt part may become dead and non functional, in chemotherapy treatment is harmful to healthy cells, approach is gross and rarely successful if the cancer is in advanced stage). How it works: The nano-particles invented by Patrick Couvreur measure between only 10 to 1,000 nanometers and are free to travel throughout the body without being absorbed or dissolved like conventional drugs injected into the bloodstream. Instead of releasing their biologically active ingredients right after injection, the drugs inside nano-capsules only deliver their load after the outside coating has dissolved, either because of changes in temperature or of chemical factors such as the biological breakdown of fats in certain body regions. As a result, nano-capsules offer a much longer half-life in the bloodstream compared to conventional injections, and they can take effect in a much more concentrated, spatially condensed fashion. Another advantage of covering drugs with polymers lies in the fact that the human immune system does not recognise the drug before the coating is dissolved. Together with their small size, this 'stealth' coating enables drug-laden nano-particles to travel throughout the body, even crossing the blood-brain barrier.

Recent approaches: The general mechanism is based on the principle that all living cells require folic acid to replicate but cancer cells have particularly strong appetite for it, displaying up to 1000 more docking sites called folate receptors on their membranes. By attaching five folic acid molecules to branches of the dendrimer (NP), the researchers were able to lure the cancer cells into accepting the whole package across the membrane and into the cell including the toxic drug, which then kills of the cell [2].The approaches stated henceforth are the most recent Nano particle advancements used in cancer treatment.

Thermal approach*:* Approaches to nanoparticle-mediated thermal therapy include absorption of infrared light, radio frequency ablation, and magnetically-induced heating. These approaches have demonstrated high efficacy in animal models, and two are already in human clinical trials [3]. In this regard, gold nanoparticles can mediate hyperthermia induction and kill tumor cells upon laser irradiation, thereby functioning as a 'thermal scalpel'. Recent developments in gold nanoparticle

design have resulted in their absorption of energy in the near-infrared wavelength spectrum, which is best suited to tissue penetration and, thus, clinical application. Furthermore, to ensure accumulation of nanoparticles in neoplastic tissue, targeting ligands are being incorporated into the thermal scalpel schema. This method has primary goal of curing cancer growth by producing heat. In this method, particles are administered to cells and/or tissue, which upon their exposure to light, effect the in vitro or in vivo, local heating of their immediate environment. In the preferred embodiment, the particles consist of a dielectric or semiconductor core and a conducting shell, the dimension of the particles is on a scale of tens to hundreds of nanometers, and the radiation used is infrared radiation, this preferred embodiment is used to treat cancer.

Nano emulsion (NEs): Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. NEs are a group of dispersed particles used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of diagnostics and drug therapies.NEs have a much higher surface area and free energy than macro emulsions that make them an effective transport system.NEs are non-toxic and non-irritant hence can be easily applied to skin and mucous membranes. Among the different types of nanoparticles, lipid nanoemulsions and nanoparticles have several advantages for topical delivery of poorly soluble chemotherapeutics. These particles show sustained drug release and protection of loaded drugs from chemical degradation. This technology is promising to enhance the intracellular concentration of drugs and consequently reduce the cytotoxicity of skin chemotherapy.

In the present invention, comparing with nanoparticles prepared by emulsion polymerization, poly (n-butyl cyanoacrylate) (PBCA) nanoparticles prepared by miniemulsion polymerization process are higher loading and encapsulation efficiencies for hydrophobic monomers, such as paclitaxel and flutamide. An advantageous feature of this invention is that therapeutic or diagnostic nanoparticles so produced can be utilized for intravascular injections to treat systemic diseases. Another advantageous feature is that extra vascular injections containing these particles can provide controlled release of the drug at the site of injection for prolonged drug effects, and minimize multiple dosing. A further advantage of this invention is the improved oral bioavailability of poorly absorbed drugs.

PH responsive nanoparticles: Nanoparticles responsive to the pH gradients are promising for cancer drug delivery. Because tumor cells have an altered pH gradient across their cell compartments. Such pH-responsive nanoparticles consist of a corona and a core, one or both of which respond to the external pH to change their soluble/insoluble or charge states.Nanoparticles whose coronas become positively charged or become soluble to make their targeting groups available for binding at the tumor extracellular pH have been developed for promoting cellular targeting and internalization. Nanoparticles whose cores become soluble or change their structures to release the carried drugs at the tumor extracellular pH or lysosomal pH have been developed for fast drug release into the extracellular fluid or cytosol. Such pH-responsive nanoparticles have therapeutic advantages over the conventional pH-insensitive counterparts [4].In addition, a biological signal has been conjugated to the shell of the nanoparticles, which can recognize tumor cells. This system may be able to target drugs to tumor cells and release the drugs intracellularly.

Nanoparticles in Cancer Drug Delivery: Nanomedical approaches to drug delivery center on developing nanoscale particles or molecules to improve drug bioavailability. More than $65 billion are wasted each year due to poor bioavailability. Nanotechnology has provided the possibility of delivering drugs to specific cells using nanoparticles. The overall drug consumption and side-effects may be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach would reduce costs and human suffering. They could hold small drug molecules transporting them to the desired location. A targeted or personalized medicine is intended to reduce the drug consumption and treatment expenses resulting in an overall societal benefit by reducing the costs to the public health system. Nanoparticles used for anticancer drug delivery can be made from a variety of materials, including polymers, dendrimers, liposomes, carbon nanotubes, gold and metals such as iron oxide and gold. So far, almost all the nanoparticle delivery systems which have been approved by the FDA or are currently in clinic trials are based on polymers or liposomes.

Polymeric nanoparticles: Polymeric nanoparticles are nanoparticles which are prepared from polymers. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticles and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in drug targeting to particular organs/tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through a per oral route

of administration. In spite of development of various synthetic and semi synthetic polymers, natural polymers (Ex. Acacia gums, Guar, etc.) Chitosan, Gelatin, Sodium alginate, Albumin etc.) are good in in drug delivery.

Dendrimers: The first Newkome dendrimer was synthesized in 1985. This macromolecule is also commonly known by the name arborol**.** Dendrimers are repetitively branched molecules[5].They are monodisperse and usually highly symmetric, spherical compounds. It is possible to make dendrimers water soluble, unlike most polymers, by functionalizing their outer shell with charged species or other hydrophilic groups. Other controllable properties of dendrimers include toxicity, crystallinity, tecto-dendrimer formation, and chirality[6].

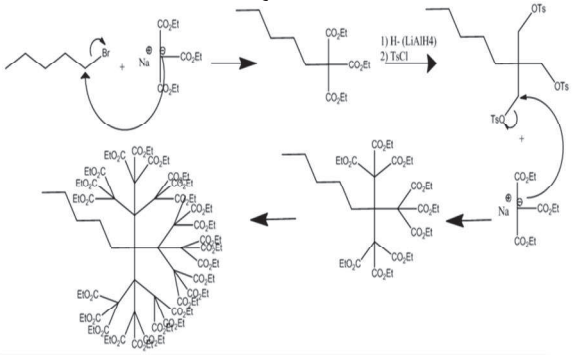

Figure 2.Synthesis to second generation arborol

Anticancer agents can be either encapsulated in or conjugated to dendrimer and be delivered to the tumour *via* enhanced permeability and retention (EPR) effect of the nanoparticle and/or with the help of a targeting moiety such as antibody, peptides, vitamins, and hormones. Imaging agents including MRI contrast agents, radionuclide probes, computed tomography contrast agents, and fluorescent dyes are combined with the multifunctional nanomedicine for targeted therapy with simultaneous cancer diagnosis. However, an important question reported with dendrimer-based therapeutics as well as other nanomedicines to date is the long-term viability and biocompatibility of the nanotherapeutics. Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radio ligands, imaging agents, or pharmaceutically active compounds

Liposomes: Liposomes were first described by British haematologist Alec D Bangham[7].A liposome is an artificially-prepared vesicle composed of a lipid bilayer. The liposome can be used as a vehicle for administration ofnutrients and pharmaceutical drugs[8]. Liposomes can be prepared by disrupting biological membranes (such as bysonication). Liposomes are composite structures made of phospholipids and may contain small amounts of other molecules. Though liposomes can vary in size from low micrometer range to tens of micrometers, unilamellar liposomes (Fig.3) They are typically in the lower size range with various targeting ligands attached to their surface allowing for their surface-attachment and accumulation in pathological areas for treatment of disease [8].

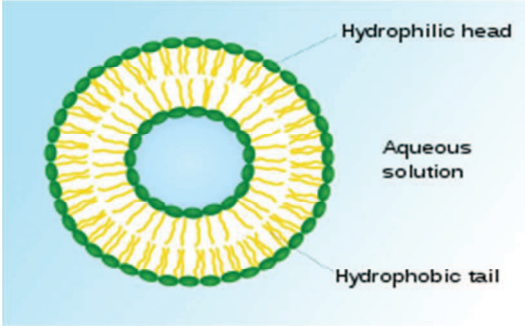

Fig.3. Liposomes

A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane;dissolved hydrophilic solut es cannot readily pass through the lipids. Hydrophobic chemicals can be dissolved into the membrane, and in this way liposome can carry both hydrophobic molecules and hydrophilic molecules. To deliver the molecules to sites of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents. By making liposomes in a solution of DNA or drugs (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer. A liposome does not necessarily have lipophobic contents, such as water, although it usually does [9].

Carbon Nanotubes (CNTs): CNTs are tubular materials with nano meter sized diameters and axial symmetry, giving them unique properties that can be exploited in the diagnosis and treatment of the cancer. Carbon nanotubes (CNTs), with their unique physical and chemical properties, hold great hopes for cancer imaging and treatment [10]. In pharmacological applications, CNTs have primarily been explored as potential drug carriers and delivery vehicles. In particular, recent data suggest that CNTs can deliver intracellularly apoptotic agents [11]. Nevertheless, besides precise tumor targeting and toxicity concerns, drug resistance remains a major obstacle for the treatment of advanced cancerous tumors. [12].Due to diverse surface chemistry and unique thermal properties, CNTs can act as strong

optical absorbers in near infra redlight. The process of laser mediated ablation of cancer cells marked with bio functionalized CNTs frequently termed as nano photo thermolysis [13].

Gold nanoparticles (Au NPs): Gold nanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photo thermal agents, contrast agents and radiosensitisers [14]. Gold nanoparticles are often the first choice for enabling early disease detection. This is due to gold nanoparticles' ability to detect biomarkers at very low concentrations. They undergo intense color changes when in the presence of certain targets.The combination of inertness and low toxicity, easy synthesis, very large surface area, well-established surface functionalization (generally through thiol linkages) and tunable stability provide Au NPs with unique attributes to enable new delivery strategies. Once the Au NPs are targeted to the diseased site, such as a tumor, hyperthermia treatment can be used for tumor destruction.

Quantum dots (QDs): Quantom dots were discovered in the early 1980s by Alexei Ekimov in a glass matrix [15].Quantum dots (QDs) are nanometer-size luminescent semiconductor nanocrystals. Their unique optical properties, such as high brightness, long-term stability, simultaneous detection of multiple signals and tunable emission spectra, make them appealing as potential diagnostic and therapeutic systems in the field of oncology [16]. Bioconjugated QDs can be used to identify potential molecular biomarkers for cancer diagnosis, treatment and prognosis. They may allow the surgeon to map sentinel lymph nodes and perform a complete surgical resection. Their unique optical properties make them ideal donors of fluorescence resonance energy transfer and photodynamic therapy studies. Multifunctional QDs have become effective materials for synchronous cancer diagnosis, targeting and treatment. For QDs, toxicity remains the major barrier to clinical translation.

Disadvantages of Nanomedicine:

- The potential for mass poisoning over a period of time.
- Lack of our own knowledge. We still have to stop and understand the impact of the creation of these products will have on the nanoscale.
- Possible loss of jobs in the traditional farming and manufacturing industry.
- The particles that are created are so incredibly small that they may very well cause eventual health problems in the consumers that use them.
- If nanotechnology can help the human body recovers from illness or injury then it is quite possible that nanotechnology can create an altered human state.
- Since these particles are very small, problems can actually arise from the inhalation of these minute particles, much like the problems a person gets from inhaling minute asbestos particles

Conclusion: The future of nanotechnology is completely new territory. It is almost impossible to predict everything that nanoscience will bring to the world considering that this is such a young science. Ongoing developments have further expanded the boundary of this paradigm in medicine, such as the concept of "theranosis", a system that can be used to perform diagnosis and therapy simultaneously. Although there have been toxicity and safety issues, we believe that we will benefit from the new knowledge of molecular events in cancer gathered by nanoscale drug delivery systems. With the continued discovery of new materials, the establishment of improved designs and considerate efforts for sophisticated optimization, we predict that a "cancer-overcoming era" will emerge. Additional clinical studies on humans and on animal models should be performed to validate their use especially in biomedical imaging using MRI, CT, ultrasound, PET, SERS, and optical imaging.

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