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Research Article

NANO-PARTICULATE TECHNOLOGY: A PROMISING TECHNOLOGY IN THE FIELD OF CANCER TREATMENT THERAPIES IN RECENT SCENARIO

Neetu Singh*

Department of Chemistry, PSIT. College of Engineering, Bhauti, Kanpur, UP, India

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ABSTRACT

Advances in technology mean that scientists are able for the first time to apply statistical genetics and molecular pathology techniques to epidemiological studies on a large scale. It will also help us investigate preventative triggers in the patient microbiome and immune response. This review provides an overview on gene therapeutics and gene delivery technologies, and highlight recent advances, challenges and insights into the design and the utility of nanoparticles in various therapies for cancer treatment and comprehensive summary on how nanotechnology can improve various cancer therapies in aspects of treatment delivery and monitoring as well as diagnosis. This study describes the progress that has been made in the field of polymeric nanomedicine that brings the science closer to clinical realization of nanopolymeric therapeutics for its application in cancer treatment. In recent years, nanomedicine has exhibited strong promise and progress in radically changing the approach to cancer detection and treatment.

INTRODUCTION

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter).[1,2]. Nanotechnology is an exciting and rapidly developing field with ramifications in engineering, material science, biology and medicine.

The term nanomedicine was coined by the National Institutes of Health to recognize the fast-growing field and its potential to fundamentally change the way diseases are diagnosed, treated and prevented.[3] Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three methods risk damage to normal tissues or incomplete eradication of the cancer.

Nanotechnology offers the means to target chemotherapies directly and selectively to cancerous cells and neoplasms, guide in surgical resection of tumors, and enhance the therapeutic efficacy of radiation-based and other current treatment modalities.[4] All of this can add up to a decreased risk to the patient and an increased probability of survival. The use of nanotechnology in cancer treatment offers some exciting possibilities, including the possibility of destroying cancer tumors with minimal damage to healthy tissue and organs, as well as the detection and elimination of cancer cells before they form tumors. Promoting research on cancer prevention and early detection, there has been a revolution in cancer medicine over the last 10 years, with many new targeted therapies developed and released and improved survival rates for many patients, particularly in later stages of the disease.[5] Compared to conventional treatments, gene therapy offers a variety of advantages for cancer treatment including high potency and specificity, low off-target toxicity, and delivery of multiple genes that concurrently target cancer tumorigenesis, recurrence, and drug resistance. In the past decades, gene therapy has undergone remarkable progress, and is now poised to become a first line therapy for cancer. Among various gene delivery systems, nanoparticles have attracted much attention because of their desirable characteristics including low toxicity profiles, well-controlled and high gene delivery efficiency, and multi-functionalities.[6] The advantage of nanosized carriers is that they can increase the delivered drug's overall therapeutic index through nanoformulations in with chemotherapeutics are either encapsulated or conjugated to the surfaces of nanoparticles. This capability is largely due to their tunable size and surface properties. Size is a major factor in the delivery of nanotechnology-based therapeutics to tumor tissues. Selective delivery of nanotherapeutic platforms depends primarily on the passive targeting of tumors through the enhanced permeability and retention (EPR) effect. This phenomenon relies on defects specific to tumor microenvironment such as defects in

Corresponding author:* **Neetu Singh
Department of Chemistry PSIT. College of Engineering, Bhauti, Kanpur, UP, India

lymphatic drainage, along with increased tumor vasculature permeability, to allow nanoparticles (<200 nm) to accumulate in the tumor microenvironment. Furthermore, the timing or site of drug release can be controlled by triggered events, such as ultrasound, pH, heat, or by material composition.[7]

Cancer therapeutic resistance occurs as cancers develop resistance to treatments such as chemotherapy and targeted therapies, through many different mechanisms. These include specific genetic and epigenetic changes in the cancer cell and/ or the microenvironment in which the cancer cell resides.

Well-controlled Applications of nano-particles in different Cancer therapies

Radiation therapy

Radiotherapy has been an integral treatment modality for cancer.[8,9] Radiotherapy is used to treat approximately 80% of patients with cancer of the head and neck. The main problem with using radiation therapy against liver cancer is that it also damages healthy liver tissue. Researchers are now working on ways to focus radiation therapy more narrowly on the cancer, sparing the nearby normal liver tissue. One approach being studied is called brachytherapy. In this treatment, catheters (thin tubes) are placed in the tumor and then pellets that give off radiation are put into the catheters for a short time. After the treatment, both the pellets and the catheters are removed. This allows radiation to be targeted to the cancer with less harm to the normal liver.

A new area of science that possesses the ability to impact radiation oncology is nanomedicine. Materials on the nanoscale provide many unique properties such as enhanced permeability and retention effect and super paramagnetism that are well suited for applications in radiation oncology.[10]

Formulation of wortmannin with nanoparticles, which is composed of a DSPE-PEG lipid shell and a PLGA polymer core, solved these problems (Fig. 1). The nanoradiosensitizer was demonstrated to be more effective than 5-FU on mice bearing KB cell xenografts and its MTD was three to five times greater than that of wortmannin.[11]

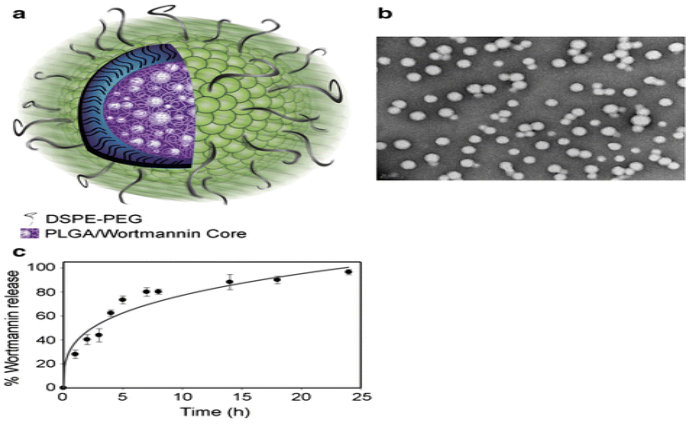

Fig 1 Characterization of NP Wtmn. a Cartoon of NP Wtmn depicting a PLGA core containing Wtmn surrounded by a lipid monolayer (green head groups) and a PEG shell. b TEM image of NP Wtmn. cRelease profile of NP Wtmn in PBS at 37 °C. *Error bars* correspond to SD of three separate sample preparations with duplicate samples per data point (Karve *et al*. 2012)

Targeted therapy

Novel technology in the nanomedicine field is expected to develop innovative products as targeted drug delivery approaches. Targeted drug delivery of various drugs for the treatment of cancer, AIDS and brain disorders is the primary research area in which nanomedicines have a major role and need.[12] New drugs are being developed that work differently from standard chemotherapy drugs. These newer targeted drugs act on specific parts of cancer cells or their surrounding environments.[13] The "drug-targeting" paradigm can be exploited to finally formulate therapeutic carriers that can selectively treat neoplastic tissues without affecting normal cells. The use of targeted nanoparticles in the treatment of cancer, developed in the pioneering work of Farokhzad and Langer, has been validated by the Phase II clinically used prototype BIND-014 (marketed by BIND Therapeutics under the brand name Accurins™), a polymeric drug delivery nanovehicle containing the chemotherapeutic agent docetaxel, which is approved for use in the treatment of several common cancers, including breast, lung, and prostate.[14] Other complex targeted nanosystems addressed to various cancers, also combining diagnostic and therapeutic agents, or that can trigger drug release at the target site when exposed to external stimuli, are currently in clinical development. At this stage, BIND-014 can reasonably be seen as representing an evolution of the "magic bullet" concept, the first description of the drug-targeting paradigm that can also be used to develop programmable and personalized nanomedicine for routine use in clinic practice.[15] s

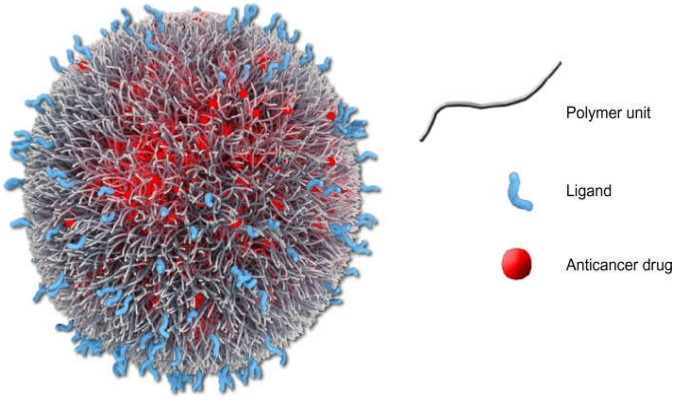

Fig 2 Graphic representation of BIND-014 composed of a biodegradable and hydrophobic PLA polymeric core and a hydrophilic PEG corona decorated with small-molecule (a pseudomimetic PSMA-directed dipeptide) targeting ligands, and a semisynthetic taxane (docetaxel) as an encapsulated anticancer drug.

Tumor blood vessels are the target of several newer drugs. Liver tumors need new blood vessels to grow beyond a certain size. The drug sorafenib (Nexavar), which is already used for some liver cancers that can't be removed surgically, works in part by hindering new blood vessel growth. This drug is now being studied for use earlier in the course of the disease, such as after surgery or trans-arterial chemoembolization (TACE). Researchers are also studying whether combining it with chemotherapy may make it more effective.

Regorafenib (Stivarga) is a targeted drug that has shown promise in treating liver cancers that are no longer responding to sorafenib.

Chemotherapy

Cancer is one of the major causes of death worldwide and chemotherapy is a major therapeutic approach for the treatment which may be used alone or combined with other forms of therapy. At the same time, newer types of drugs are continually being developed that work in different ways to attack cancer cells. Research on nanotechnology cancer therapy extends beyond drug delivery into the creation of new therapeutics available only through use of nanomaterial properties.[16] However, conventional chemotherapy suffers lack of aqueous solubility, lack of selectivity and multidrug resistance. Nanotherapeutics is rapidly progressing aimed to solve several limitations of conventional drug delivery systems.[17,18,19] Nonspecific target of cancer chemotherapy leads to damage rapidly proliferating normal cells and can be significantly reduced through folate and transferrin mediated nanotherapeutics which are aimed to target cancerous cells.[20] One treatment under development involves targeted chemotherapy that delivers a tumor killing agent agent called tumor necrosis factor alpha(TNF) to cancer tumors. TNF is attached to a gold nanoparticle along with Thiol-derivatized polythene glycol (PEG-THIOL), which hides the TNF bearing nanoparticle from the immune system. This allows the nanoparticle to flow through the blood stream without being attacked. One chemotherapy drugs to cancer tumor is called Cytlmmune and another targeted chemotherapy treatment under development uses a nanoparticle called CRLX101. Researchers are developing grapheme strips to deliver different drugs to specific regions of cancer cells. When the graphene strip reaches the cancer cell one drug separates from the grapheme and attacks the cell membrane while the grapheme strip enters the cell and delivers the second dug to the cell nucleus. Multidrug resistance is challenge in cancer chemotherapy which can be significantly reversed by solid lipid nanoparticles, polymeric nanoparticles, mesoporous silica nanoparticles, nanoparticulated chemo-sensitizer, nanoparticluated poloxamer and magnetic nanoparticles.[21]

Virus therapy

Oncolytic viruses are defined as genetically engineered or naturally occurring viruses that selectively replicate in and kill cancer cells without harming the normal tissues. A newer approach to treatment is the use of a virus, known as *JX-594*. This started as the same virus that was used to make the smallpox vaccine, but it has been altered in the lab so that it mainly infects cancer cells and not normal cells. A solution containing the virus is injected into liver cancers, and the virus can enter the cancer cells, where it causes them to die or to make proteins that result in them being attacked by the body's immune system. Early results of this treatment against advanced liver cancer have been promising, even in patients who have already had other treatments.[22]

Nano-enabled Immunotherapy

Immunotherapy is a promising new front in cancer treatment encompassing a number of approaches, including checkpoint inhibition and cellular therapies. Although results for some patients have been spectacular, only a minority of patients being treated for just a subset of cancers experience durable responses to these therapies. Expanding the benefits of immunotherapy requires a greater understanding of tumor-host immune system interactions.[24] Nanotechnologies are also being investigated to deliver immunotherapy. This includes use of nanoparticles for delivery of immunostimulatory or immunomodulatory molecules in combination with chemo- or radiotherapy or as adjuvants to other immunotherapies.[25] New technologies for molecular and functional analysis of single cells are being used to interrogate tumor and immune cells and elucidate molecular indicators and functional immune responses to therapy. Fig-3

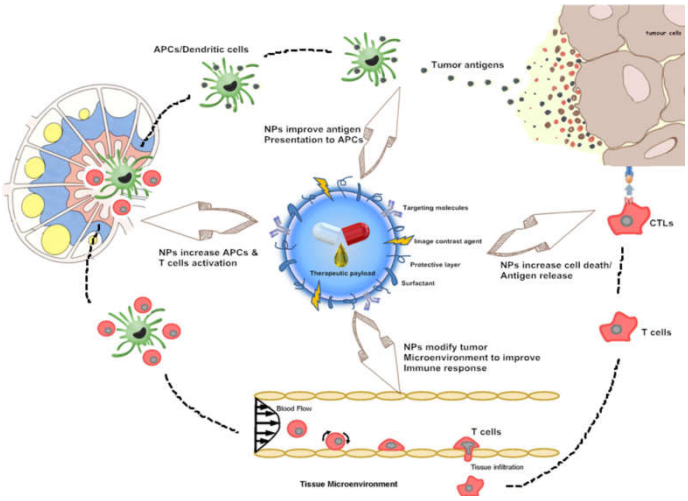

Fig 3 Depiction of the complex pathway involved in cancer immunotherapy. Nanoparticle delivery vehicles can play a role at multiple points along this pathway.(National Cancer Institue)

Additional uses of nanotechnology for immunotherapy include immune depots placed in or near tumors for in situ vaccination and artificial antigen presenting cells. These and other approaches will advance and be refined as our understanding of cancer immunotherapy deepens.[26]

Delivering Gene Therapy

This sort of treatment uses the viruses to kill cancer cells directly rather than to deliver genes. So it is not cancer gene therapy in the true sense of the word. But doctors sometimes refer to it as gene therapy. A drug called T-VEC (talimogene laherparepvec) is now available as a treatment for melanoma skin cancer. The value of nanomaterial-based delivery has become apparent for new types of therapeutics such as those using nucleic acids, which are highly unstable in systemic circulation and sensitive to degradation. These include DNA and RNA-based genetic therapeutics such as small interfering RNAs (siRNAs), and microRNAs (miRNAs). Gene silencing therapeutics, siRNAs, have been reported to have significantly extended half-lives when delivered either encapsulated or conjugated to the surface of nanoparticles. These therapeutics are used in many cases to target 'undruggable' cancer proteins. Additionally, the increased stability of genetic therapies delivered by nanocarriers, and often combined with controlled release, has been shown to prolong their effects. It is anticipated that gene therapy will play an important role in future cancer therapy as part of a multimodality treatment, in combination with, or following other forms of cancer therapy, such as surgery, radiation and chemotherapy. The type and mode of gene therapy will be determined based on an individual's genomic constituents, as well as his or her tumor specifics, genetics, and host immune status, to design a

multimodality treatment that is unique to each individual's specific needs.[27]

CONCLUSION

Nanoparticles offer characteristics for designing and exhibiting properties that may not be feasible with conventional pharmaceutical agents. They show promise in both cancer diagnosis and therapy. There is continued progress on immuno-oncology and targeted therapy across many tumour types, with basic discoveries now translating into real benefit for many cancer patients. Nanotechnology can be used to potentiate the delivery and/or concentration of radiosensitizers or radioisotopes, thus enhancing their anti-tumor activity. Nanotechnology may provide an alternative means to overcome the limitation of dose escalation (radiosensitizers, radioisotopes) and physical-technical features that can be manipulated to further improve treatment efficacy. As cancer is one of the most serious lethal diseases, the contribution of nanotechnology in precise treatment avoiding the life threatening side effects can potentially contribute to a positive movement in clinical practice for life saving approach.

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