INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A STUDY AND OVERVIEW OF NANOTECHNOLOGY IN THE FIELD OF CANCER TREATMENT

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Accepted Date: 18/06/2020; Published Date: 27/06/2020

Abstract: Nanotechnology has the potential to increase the selectivity and potency of chemical, physical, and biological approaches for eliciting cancer cell death while minimizing collateral toxicity to nonmalignant cells. Materials on the nanoscale are increasingly being targeted to cancer cells with great specificity through both active and passive targeting. In this review, we summarize recent literature that has broken new ground in the use of nanotechnology for cancer treatment with an emphasis on targeted drug delivery.

Keywords: Cancer, Drug-delivery, Nanotechnology

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PAPER-QR CODE

Access Online On:

www.ijprbs.com

How to Cite This Article:

Susmita Talukdar, IJPRBS, 2020; Volume 9(3): 24-42

INTRODUCTION

It's hard to imagine **just how small nanotechnology** is. One nanometer is a billionth of a meter, or 10^{-9} of a meter. Here are a few illustrative examples:

- There are 25,400,000 nanometers in an inch
- A sheet of newspaper is about 100,000 nanometers thick
- On a comparative scale, if a marble were a nanometer, then one meter would be the size of the Earth

Nanoscience and nanotechnology involve the ability to see and to control individual atoms and molecules. Everything on Earth is made up of atoms—the food we eat, the clothes we wear, the buildings and houses we live in, and our own bodies. **Nanotechnology** is a part of science and technology about the control of matter on the atomic and molecular scale - this **means** things that are about 100 nanometers across. **Nanotechnology** includes making products that use parts this small, such as electronic devices, catalysts, sensors, etc. Nanotherapy is a branch of nanomedicine that involves using nanoparticles to deliver a drug to a given target location in the body so as to treat the disease through a process known as targeting. Nanoparticles can be classified into **different types** according to the size, morphology, physical and chemical properties. Some of them are carbon-based nanoparticles, ceramic nanoparticles, metal nanoparticles, semiconductor nanoparticles, polymeric nanoparticles and lipid-based nanoparticles.

Compared to the conventional methods, this method has gained more popularity because it promises high precision when it comes to administering therapeutic formulations. With conventional chemotherapy, there is no targeting, which means that the drug is simply transported by the circulatory system until it reaches and acts upon the affected body part. In the process, the drug is likely to be affected by various molecules or react with other compounds. As a result, this method has been found to present various problems especially when treating cancer. However, with nanotherapy, the carrier is protected from such degradations, which allows it to reach given target cells in the body for a local reaction.

The need for an advanced technology to play an important role for cancer treatment is clearly evident in the statistics indicating that cancer incidence, prevalence, and mortality remain at exceedingly high levels. Cancer is one of the leading causes of deaths worldwide with an estimated 7.6 million individuals lost each year and accounting for 13% of all deaths. Cancer-related mortality is expected to rise to 13.1 million by 2030. Cancer is not a single disease but a multitude of diseases with each organ or system developing a distinct set of diseases. Many instances of cancer could be avoided, with some estimates indicating that about 30% of cancer

deaths are associated with smoking or other lifestyle factors or dietary practices that could potentially be avoided by changes in human behaviour. Nonetheless, the majority of cancers cannot be avoided by simple behavioural changes and require technological innovation to improve outcomes. The developed world has had notable success in limiting cancer caused by viral infections [e.g., human papilloma virus (HPV). This success could be further enhanced by more widespread implementation of existing vaccine technologies and also by using nanotechnology as well as other technologies to improve vaccination efficiency. Nanotechnology may also be able to increase the percentage of cancers that are diagnosed early through improved imaging and this, in conjunction with more aggressive implementation of existing screening technologies, will lead to improved outcomes for cancer patients. Still, for many cancer types, new approaches for treating established disease are required. To address these therapeutic requirements, nano-sized molecular tools capable of distinguishing between malignant and non-malignant cells as well as delivering a lethal payload should be developed. This review summarizes several of the most innovative technologies that have been reported in recent years and that hold promise for improving outcomes for cancer patients.

Cancer nanotechnology is a branch of nanotechnology concerned with the application of both nanomaterials such as nanoparticles for tumor imaging or drug delivery and nanotechnology approaches (such as nanoparticle-based theranostics) to the diagnosis and treatment of cancer. Nanotechnology can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. Nanotechnology also has the potential to generate entirely novel and highly effective therapeutic agents. It has made a great revolution in selective cancer targeting. Nanoparticles (NP's) can be designed through various modifications such as changing their size, shape, chemical and physical properties, and so forth, to program them for targeting the desired cells.

Before moving into the applications of nanotechnology in cancer, a little brief of cancer should be understood.

CANCER

Cancer is one of the most serious fatal diseases in today's world that kills millions of people every year. It is one of the major health concerns of the 21st century which does not have any boundary and can affect any organ of people from any place. Cancer, the uncontrolled proliferation of cells. Because of complexity in genetic and phenotypic levels, it shows clinical diversity and therapeutic resistance. A variety of approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects. Cancer treatment includes surgical removal, chemotherapy, radiation, and hormone therapy.

Chemotherapy, a very common treatment, delivers anticancer drugs systemically to patients quenching the uncontrolled proliferation of cancerous cells. Unfortunately, due to nonspecific targeting by anticancer agents, many side effects occur and poor drug delivery of those agents cannot bring out the desired outcome in most of the cases.

Cancer drug development involves a very complex procedure which is associated with advanced polymer chemistry and electronic engineering. The main challenge of cancer therapeutics is to differentiate the cancerous cells and the normal body cells. That is why the main objective becomes engineering the drug in such a way as it can identify the cancer cells to diminish their growth and proliferation. Chemotherapy fails to target the cancerous cells selectively without interacting with the normal body cells. Thus they cause serious side effects including organ damage resulting in impaired treatment with lower dose and ultimately low survival rates. Hence the nanotechnology was introduced. Nanotechnology is the science that usually deals with the size range from a few nanometers (nm) to several hundred nm, depending on their intended use. It has been the area of interest over the last decade for developing precise drug delivery systems as it offers numerous benefits to overcome the limitations of conventional formulations. It is very promising both in cancer diagnosis and treatment since it can enter the tissues at molecular level. Cancer nanotechnology is being enthusiastically evaluated and implemented in cancer treatment indicating a major advance in detection, diagnosis, and treatment of the disease. Various researches are being carried out in order to discover more accurate nanotechnology based cancer treatment minimizing the side effects of the conventional ones.

NANOTHERAPY (NANOMEDICINE)

Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials and biological devices, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology such as biological machines. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials (materials whose structure is on the scale of nanometres.

MATERIALS USED FOR MAKING NANOPARTICLES:

Nanoparticles used are made from a variety of materials depending on the needs or the researcher. Some of the most common materials used to produce nanoparticles include:

- Dendrimers: Dendrimers are branched with three dimensional structures that make it possible to add more functional groups,

- Liposomes: New polymer-coated liposome are becoming more popular because of their durability. This makes them ideal in targeted delivery systems because they can last longer in the circulation system.

- Metal: Various metal elements have been used to develop nanoparticles. A good example of this is iron oxide, which is used as an imaging agent.

HOW DOES NANOTHERAPY WORKS:

Nanotherapy, which is also referred to as targeted therapy, offers to deliver the molecules to the affected cells in order to help treat the disease without causing other negative effects to the healthy cells.

One of the biggest advantages of nanoparticles used is that they have a larger surface area, which allows for multiple functional groups to be added to the surface. These particles (nanoparticles) are targeted by adding targeting groups onto their surface. These groups are capable of binding onto the receptors or tumor-specific antigen allowing for the molecule to release the drug product. The target group is designed in a manner that only allows the molecule to bind/attach onto the receptors or tumor-specific antigen. This means that the molecule can only get attached to the tumor cells, which is what is meant by targeting. Here, the type of target group on the molecule surface is dependent on the type of cancer cells. Although the nanoparticles (nano containers) have been designed in a manner that allows the drug compound to remain intact until the molecule reaches the target cells, they are also sensitive to the internal environment of the cancerous cells. As a result, they are destroyed once they enter this environment, which causes the drug to be released. Once the drug compound is released, the treatment process begins. Depending on the intended purpose, scientists can easily modify these carriers to either interact with the surface on internal areas of the cell. This therefore gives scientists a lot of options when it comes to treating cancers. The passive & active targeting is discussed further.

APPROACHES AND RECENT DEVELOPMENT TOWARDS THE NANOTECHNOLOGY USED IN CANCER:

Recent advances have led to development of bio affinity of Nano Particles probes for molecular and cellular imaging, targeted Nano particles drugs for cancer therapy, and integrated nanodevices for early screening and detection of cancer. 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. However, several barriers do exist for in vivo applications of nanodevices in preclinical and clinical use of nanotechnology. Amongst them are biocompatibility, in vivo kinetics, tumor-targeting efficacy,

acute and chronic toxicity, ability to escape the reticule endothelial system, and cost-effectiveness.

SOME OF THE RECENT RESEARCH AND THEIR REVIEWS:

A MICRO FLUIDIC PLATFORM TO DESIGN MULTIMODAL PEG - CROSS LINKED HYALURONIC ACID NANOPARTICLES (PEG-CHANPS) FOR DIAGNOSTIC APPLICATIONS**:** Multimodal Imaging is a promising approach that allows the combination of different imaging techniques, overcoming limitations proper of every single modality. For example, recently, Magnetic Resonance Imaging (MRI) and Optical imaging (OI) have been used in combination to obtain the excellent sensitivity of the OI with the high spatial resolution of the MRI.

SET-UP OF THE MICRO FLUIDIC PLATFORM FOR PEG-CHANPS PRODUCTION. Hydrodynamic Flow-Focusing (HFF) nano precipitation is a consolidate method for the production of nanoparticles. The regimen of hydrodynamic flow focusing ensures uniform reaction conditions and particle formation kinetics. A study about the feasibility of the particle production process is conducted to evaluate the effect of the flow rate ratio on the obtaining of the nanoparticle and their properties such as composition, size, shape and superficial charge. Moreover, optimized conditions for the micro fluidic translation of the nucleophilic attack reaction are evaluated both in terms of total polymer concentration and of molar ratio between functional groups.

The below schematic illustration presents the nanoprecipitation process implemented in micro fluidics through an HFF approach for Gd-DTPA and ATTO 488 co-loaded PEG-cHANPs production.

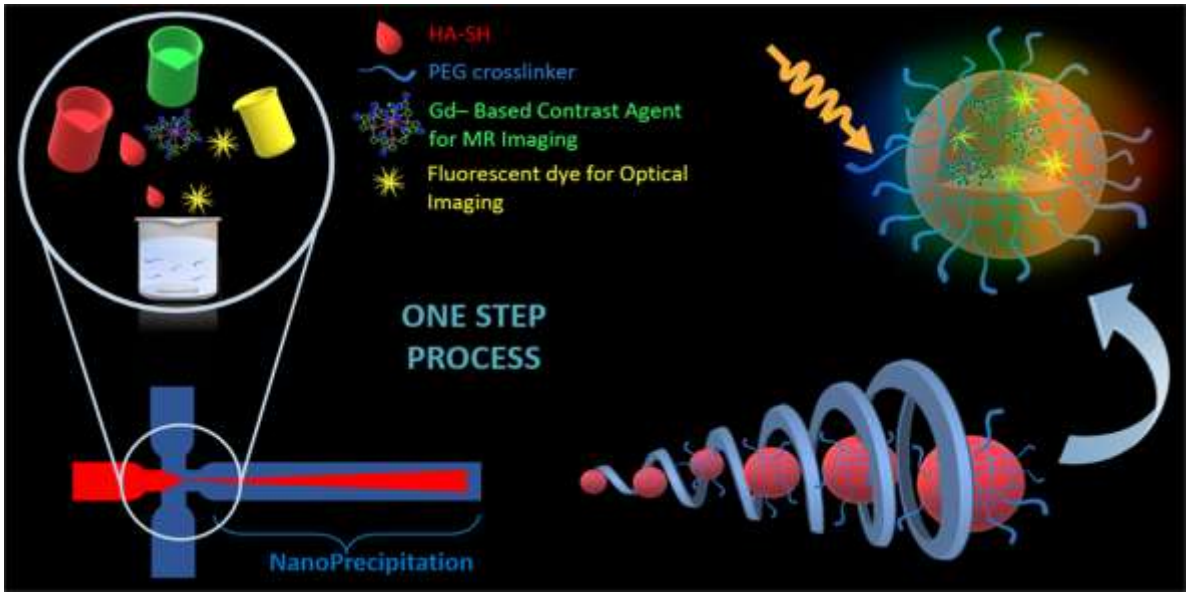

Figure-1: Nanotechnology one step process

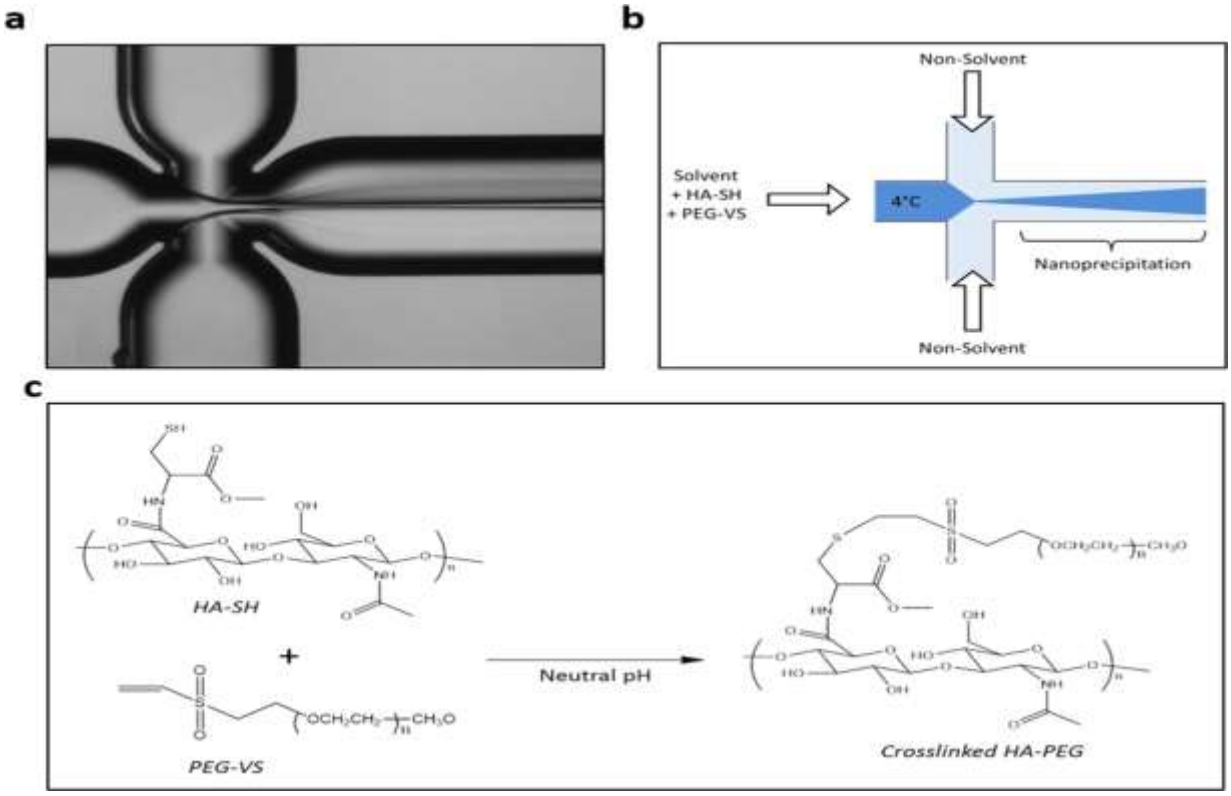

Figure-2: Microfluidic experiment

The process provides biocompatible and ready-to-use nanoprobes for Multimodal applications. This strategy condenses in a ONE-STEP process, a complex synthesis usually realized in batch mode through many different steps with significantly reduced controllability. The encapsulation of Gd-DTPA in the polymeric matrix provides a boosting of the MR signal in accordance with the Hydrodenticity theory. The nanoprecipitation process is implemented in a micro fluidic chip with an X-junction configuration ("Droplet - Junction Chip", depth x width: 190 µm x 390 µm) where particle formation occurs by diffusion and nanoprecipitation. The middle channel is injected with an aqueous solution composed of thiolated hyaluronic acid (HA-SH) and polyethylene glycol- vinyl sulfone (PEG-VS); the side channels are injected with pure acetone to provide the extraction of the water phase. **Schematic illustration of Micro fluidic experimental set-up**. (**a**) Optical Fluorescence Microscopy Image of Flow-Focusing pattern; (**b**) Qualitative Illustration of cross-linking strategies processed in our micro fluidic device; (**c**) Cross linking reaction of HA thiol groups with the terminal double bond of PEG-VS.

CONCLUSIONS OBTAINED:

Micro fluidics is considered a disruptive technology for pharmaceutical manufacturing and is becoming a gold standard in the production of nanoparticles for drug delivery. Here, a ONE-STEP microfluidic synthesis of *pegylated* cross linked Hyaluronic Acid Nano Particles (PEG-

cHANPs) has been investigated for the production of multimodal nanoparticle for potential Multimodal Imaging application. A feasibility study has been conducted exploiting all the process parameters such as FR^2, Temperature, and SH/VS ratio. Results have shown the ability of the microfluidic platform to tune the properties and control the size of the particles from 30 nm up to 800 nm. Moreover, it has been proved that the reaction conditions in the microfluidic device are less prohibitive than in a batch mode; indeed, we are able to stabilize the nanoparticles at an SH/VS ratio several orders of magnitude lower than the value reported in the literature. These conditions are able to guarantee particle stability in water. Furthermore, the proposed strategy allows co-encapsulating in a one-step process two different diagnostic compounds, Gd-DTPA and ATTO 488, to produce a probe for Multimodal applications. The designed probe is able to boost the MR signal thanks to the unique effect of the Hydrodenticity, furthermore amplifying the T1 up to 5 times in presence of the ATTO 488. This result could potentially lead to a reduction of the administered dose of CA safekeeping high quality images.

TARGETED CRYSTALLIZATION OF MIXED-CHARGE NANOPARTICLES IN LYSOSOMES INDUCES SELECTIVE DEATH OF CANCER CELLS

Lysosomal organelles comprise a dynamic system of acidic vesicular compartments (pH ≈ 4.8) receiving cargoes from the plasma membrane via endocytosis and from the cytoplasm through autophagy, all ultimately destined for degradation and/or recycling. In cancer cells, these degradation pathways are deregulated, causing various alterations in the structure and function of lysosomal membranes and ultimately rendering these cells more susceptible to lysosomal membrane permeabilization (LMP) by various endogenous (p53 activation, oxidative stress) and exogenous (cationic amphiphilic drugs, CADs) triggers. Importantly, lysosomal cell death (LCD) triggered by LMP commonly bypasses the classical caspase-dependent apoptosis pathway, opening up a new strategy for targeting apoptosis- and drug-resistant cancers. A handful of small molecules—repurposed antimalarial, antihistamine and anticancer drugs as well as leads from LMP screening assays (for example, thioridazine, fluphenazine or toremifene) are under clinical trials and are also known to accumulate in lysosomes and cause LMP. None of them, however, were specifically designed to target the LCD pathway; most have low cancer selectivity and their effects are not always lysosomes-specific.

Here, we demonstrate selective lysosomes targeting (Fig 1)

In which [+/−] NPs (Fig 2) gradually disrupt the integrity of lysosomal membranes, ultimately triggering lysosomes-dependent cell death selectively in cancerous cells (Figs 3&4). These effects emerge from a remarkable succession of transport and aggregation phenomena: NP clustering at the cell surface and internalization of ~50–100 nm NP clusters via endocytosis, their gradual accumulation in multi vesicular endosomes followed by transport to the

lysosomes, further pH-dependent assembly into ordered [+/−] NP supra crystals inside lysosomes, induction of osmotic flows and lysosomal swelling, gradual loss of the integrity of lysosomal membranes and, finally, cell death. In contrast, in normal cells, [+/−] NP aggregation is limited and they are excluded from cells via exocytosis, causing these cells little harm. Overall, these results demonstrate how the propensity of a cancerous cell to act as a 'nanoscale assembly line', meticulously constructing NP crystals that ultimately cause its own demise, can be harnessed for selective in-cell intervention with therapeutic potential.

FIG. 1: SUMMARY OF HOW CRYSTALLIZATION OF MIXED-CHARGE NPS IN CANCER LYSOSOMES LEADS TO SELECTIVE KILLING OF CANCER CELLS.

FIG. 2: STRUCTURE AND PH-DEPENDENT AGGREGATION OF MIXED-CHARGE NPS.

FIG. 3: ENGINEERING CANCER-SPECIFIC CYTOTOXICITY BY TUNING THE BALANCE OF SURFACE CHARGES ON MIXED-CHARGE NPS.

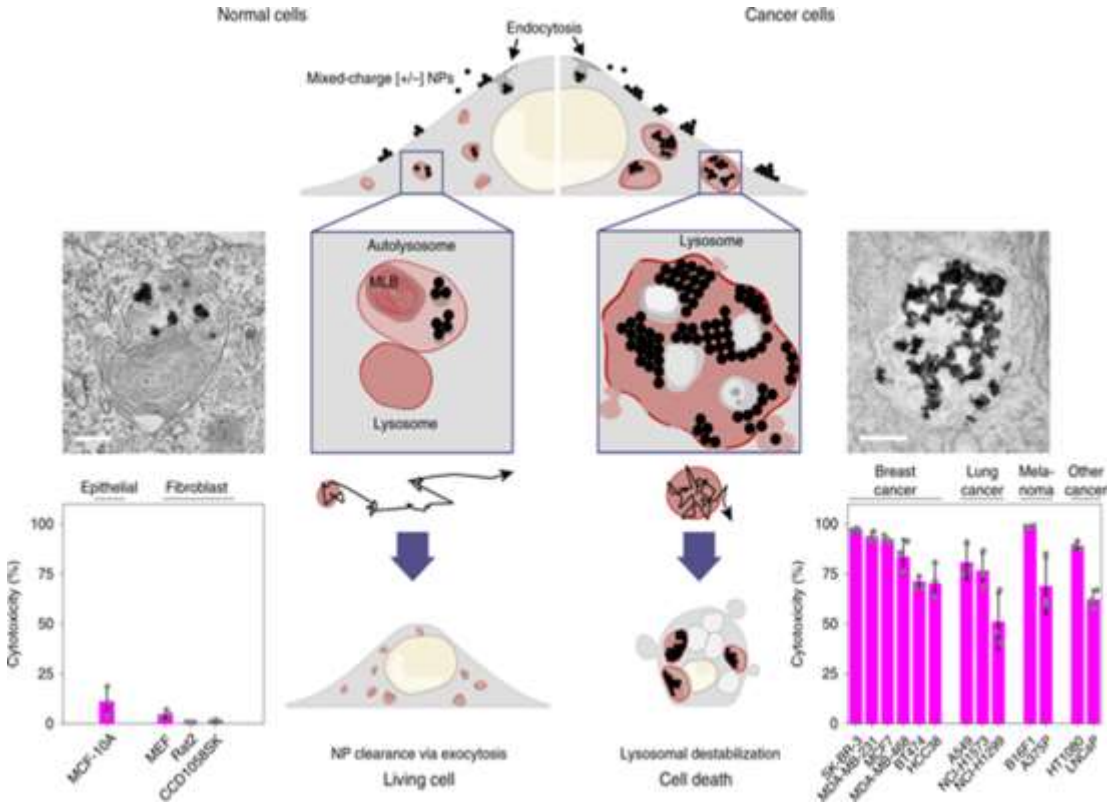

Figure-3: Cancer specific cytotoxicity study

FIG. 4: CELLULAR UPTAKE AND DIFFERENTIAL INTRACELLULAR AGGREGATION OF MIXED-CHARGE NPS IN CANCEROUS VERSUS NORMAL CELLS.

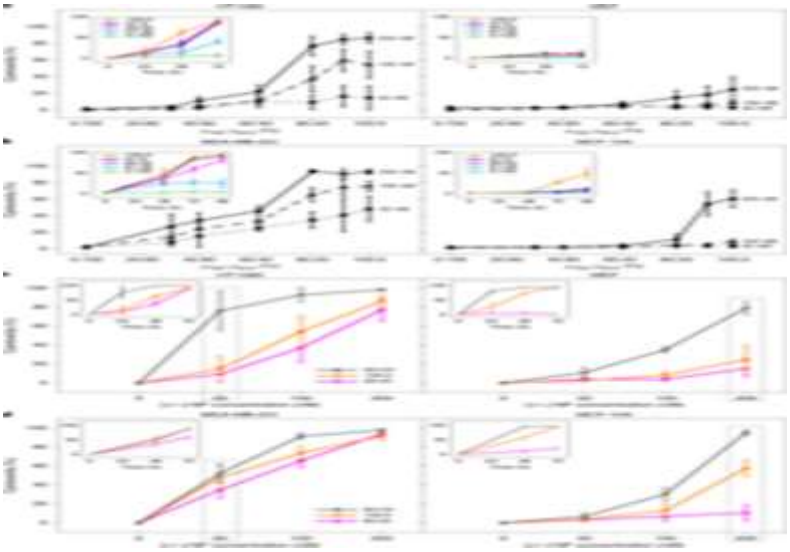

Figure-4: Cellular uptake of intracellular mixed charge NPS

DRUG DELIVERY:

One of the most important applications of nanotechnology in medicine which is currently being tested involves employing nanoparticles to deliver drugs or other substances to specific types of cells, in particular to cancer cells. One of the most important applications of nanotechnology in medicine which is currently being tested involves employing nanoparticles to deliver drugs or other substances to specific types of cells, in particular to cancer cells.

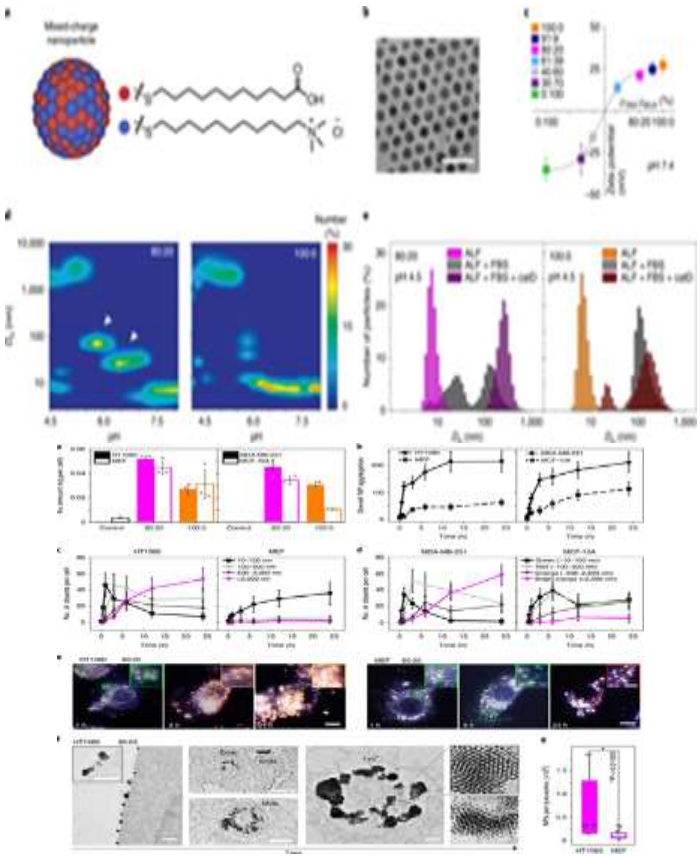

Figure-5: Drug delivery by nanotechnology

Particles are engineered so that they are attracted to diseased cells, which then allow direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. One treatment involves targeted chemotherapy that delivers a tumor-killing agent called tumor necrosis factor alpha (TNF) to cancer tumors. One of the major flaws of our body's immune system is that is "oversensitive". It will attack almost anything foreign that enters our body. TNF is attached to a gold nano particle along with a chemical (Thiol-derivatised polyethylene glycol) which "hides" the TNF possessing nano particle from our immune system. This method to deliver TNF and other chemotherapy drugs. One of the most important applications of nanotechnology in medicine which is currently being tested involves employing nano particles to deliver drugs or other substances to specific types of cells, in particular to cancer cells. Particles are engineered so that they are attracted to diseased cells, which then allow direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. One treatment involves targeted chemotherapy that delivers a tumor killing agent called tumor necrosis factor alpha (TNF) to cancer tumors. One of the major flaws of our body's immune system is that is "oversensitive". It will attack almost anything foreign that enters our body. TNF is attached to a gold nanoparticle along with a chemical (Thio l-derivatised polyethylene glycol) which "hides" the TNF possessing

nanoparticle from our immune system. This method to deliver TNF and other chemotherapy drugs Particles are engineered so that they are attracted to diseased cells, which then allow direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. One treatment involves targeted chemotherapy that delivers a tumor-killing agent called tumor necrosis factor alpha (TNF) to cancer tumors. One of the major flaws of our body's immune system is that is "oversensitive". It will attack almost anything foreign that enters our body. TNF is attached to a gold nanoparticle along with a chemical (Thiol-derivatised polyethylene glycol) which "hides" the TNF possessing nano particle from our immune system. This method to deliver TNF and other chemotherapy drugs to cancer tumors is called cytimmune. An alternative approach uses nano particles constructed from carbon. The value of nano particles made of diamond is multifaceted. Very recent studies report that tiny flecks of carbon can shrink tumors in mice by delivering chemotherapy drugs to cancer cells. Made of carbon, they're non-toxic, and the body's immune system doesn't attack them. They can bind tightly to a variety of molecules and deliver them right into a tumor. And because they are only 2 to 8 nanometers in diameter, they are easy for the kidneys to clear from the body before they block up blood vessels, a long-standing problem in nano particle therapy.

A study done for the use of Nano diamonds in cancer treatment, doxorubicin, a standard chemotherapy drug, was injected into mice with drug-resistant breast and liver cancer. With the help of the diamonds, the drug stayed in the bloodstream 10 times longer than usual, making it much more effective. As a result, the tumors shrank significantly, as reported in Science Translational Medicine. This technique also decreased the toxicity of the drug.

BENEFITS OF NANOTECHNOLOGY IN CANCER:

Nanoscale devices are one hundred to ten thousand times smaller than human cells. They are similar in size to large biological molecules ("bimolecules") such as enzymes and receptors. As an example, hemoglobin that carries oxygen in red blood cells, is approximately 5 nanometers in diameter. Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can move out of blood vessels as they circulate through the body. Because of their small size, nanoscale devices can readily interact with biomolecules on both the surface and inside cells. By gaining access to so many areas of the body, they have the potential to detect disease and deliver treatment in ways unimagined before now. Nanotechnology provides researchers with the opportunity to study and manipulate macromolecules in real time and during the earliest stages of cancer progression. Nanotechnology can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes even when they occur only in a small

percentage of cells. Nanotechnology also has the potential to generate entirely novel and highly effective therapeutic agents.

Ultimately and uniquely, the use of nanoscale materials for cancer, comes down to its ability to be readily functionalized and easily tuned; its ability to deliver and / or act as the therapeutic, diagnostic, or both; and its ability to passively accumulate at the tumor site, to be actively targeted to cancer cells, and to be delivered across traditional biological barriers in the body such as dense stromal tissue of the pancreas or the blood-brain barrier that highly regulates delivery of biomolecules to / from, our central nervous system.

PASSIVE TUMOUR ACCUMULATION: An effective cancer drug delivery should achieve high accumulation in tumor and spare the surrounding healthy tissues. The passive localization of many drugs and drug carriers due to their extravasations through leaky vasculature (named the Enhanced Permeability and Retention [EPR] effect) works very well for tumors. As tumor mass grows rapidly, a network of blood vessels needs to expand quickly to accommodate tumor cells need for oxygen and nutrient. This abnormal and poorly regulated vessel generation (i.e. angiogenesis) results in vessel walls with large pores (40 nm to 1 um); these leaky vessels allow relatively large nanoparticles to extravasate. (Let or force out) into tumor masses. As fast-growing tumor mass lacks a functioning lymphatic system, clearance of these nanoparticles is limited and further enhances the accumulation. Through the EPR effect, nanoparticles larger than 8 nm (between 8-100 nm) can passively target tumors by freely pass through large pores and achieve higher intra tumoral accumulation. The majority of current nanomedicines for solid tumor treatment relies on EPR effect to ensure high drug accumulation thereby improve treatment efficacy. Without targeting cell types expressing targeting ligand of interest, this drug delivery system is called passive targeting. Before reaching to the proximity of tumor site for EPR effect to take place, passive targeting requires drug delivery system to be long-circulating to allow sufficient level of drug to the target area. To design. Nano-drugs that can stay in blood longer, one can “mask” these nano-drugs by modifying the surface with water-soluble polymers such as polyethylene glycol (PEG). PEG is often used to make water-insoluble nanoparticles to be water-soluble in many pre-clinical research laboratories. PEG-coated liposomal doxorubicin (Doxil) is used clinically for breast cancer leveraging passive tumor accumulation. Passive accumulation through EPR effect is the most acceptable drug delivery system for solid tumor treatment. However, size or molecular weight of the nanoparticles is not the sole determinant of the EPR effect, other factors such as surface charge, biocompatibility and *in-vivo* surveillance system for macromolecules should not be ignored in designing the nanomedicine for efficient passive tumor accumulation.

ACTIVE TUMOUR TARGETING: Active targeting is considered an essential feature for next generation nanoparticle therapeutics. It will enable certain modalities of therapies not

achievable with EPR and improve effectiveness of treatments which can be accomplished using EPR, but with less than satisfactory effect. Active targeting of nanoparticles to tumor cells, microenvironment or vasculature, as well as directed delivery to intracellular compartments, can be attained through nanoparticle surface modification with small molecules, antibodies.

Active targeting is expected to enhance nanoparticle/drug accumulation in tumor and also promote their prospective cell uptake through receptor mediated endocytosis. The particles, which are engineered for vascular targeting, incorporate ligands that bind to endothelial cell-surface receptors. The vascular targeting is expected to provide synergistic strategy utilizing both targeting of vascular tissue and cells within the diseased tissue. Most of the nanotechnology-based strategies which are approved for clinical use or are in advanced clinical trials rely on EPR effect. It is expected that next generation nanotherapies will use targeting to enable and enhance intracellular uptake, intracellular trafficking, and penetration of physiological barriers which block drug access to some tumors.

TRANSPORT ACROSS TISSUE BARRIERS

Nano-drug delivery is hampered by tissue barriers before the drug can reach the tumor site. Tissue barriers for efficient transporting of nano-drugs to tumor sites include tumor stroma (e.g. biological barriers) and tumor endothelium barriers (e.g. functional barriers). Biological barriers are physical constructs or cell formation that restricts the movement of nanoparticles. Functional barriers can affect the transport of intact nanoparticles or nanomedicine into the tumor mass: elevated interstitial fluid pressure and acidic environment for examples. It is important to design nanoparticles and strategies to overcome these barriers to improve cancer treatment efficacy. For example the most notorious biological barrier to cancer treatment is pancreatic stroma in pancreatic ductal adenocarcinoma (PADC). Pancreatic cancer stroma has the characteristics of an abnormal and poorly functioning vasculature, altered extracellular matrix, infiltrating macrophages and proliferation of fibroblasts. Not only tumor-stroma interactions have been shown to promote pancreatic cancer cell invasion and metastasis, but TME and tumor stroma also create an unfavourable environment for drug delivery and other forms of cancer treatments.

Because EPR effect is a clinically relevant phenomenon for nano-carriers' tumor penetration, strategies have been developed to address the tumor endothelium barrier. Strategies to reduce interstitial fluid pressure to improve tumor penetration include ECM-targeting pharmacological interventions to normalize vasculature within TME; hypertonic solutions to shrink ECM cells; hyperthermia, radiofrequency (RF) or high-intensity focused ultrasound (HIFU) to enhance nano-drug transport and accumulation. These strategies can also alleviate hypoxic conditions in larger tumor mass. Another formidable tissue barrier for drugs and nanoparticle delivery is the

blood-brain barrier (BBB). BBB is a physical barrier in the central nervous system to prevent harmful substances from entering the brain. It consists of endothelial cells which are sealed in continuous tight junction around the capillaries. Outside the layer of epithelial cell is covered by astrocytes that further contribute to the selectivity of substance passage. As BBB keeps harmful substances from the brain, it also restricts the delivery of therapeutics for brain diseases, such as brain tumors and other neurological diseases. There have been tremendous efforts in overcoming the BBB for drug delivery in general. The multi-talent feature of nanoparticles makes nano-carriers appealing in designing BBB-crossing delivering strategies. One promising nanoparticle design has transferring receptor-targeting moiety to facilitate transportation of these nanoparticles across the BBB.

DRAWBACKS OF NANOTECHNOLOGY IN CANCER:

Despite its varied applications and several benefits, nanomedicine cannot be termed as flawless. A very cogent reason for this assessment is that as the transition from micro particles to nano particles begins, the size range decreases to a large extent and the number of surface atoms increase. As the surface area becomes larger, the problems like inter particular friction and sticking become significant. Also, being so small in size, the nanoparticles may have their clearance rate from the body high enough to preclude their use in diagnosis or drug delivery.

The increased surface area of the nanoparticles results in an augmented chemical reactivity of these particles leading to a pressing uncertainty as to how these particles will react under different conditions and whether they will be able to cross cell membranes and enter cells. The increased chemical reactivity of nanoparticles brings about the production of reactive oxygen species (ROS), which may cause oxidative stress, inflammation, and damage to DNA, proteins and membranes, ultimately leading to toxicity.

Nanoparticles produce ROS and oxidative stress, which may cause neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, tendency of nanoparticles to cause damage to the lungs. Nanoparticles may cause pulmonary inflammation, immune effects and systemic effects. Uptake of the nanoparticles through the olfactory epithelium can also take place, leading to epithelial cell injury, which can compromise the basic functions of the nose

Other than the evident risks to the patient, nanoparticles may perhaps be toxic to the environment too, and may require prior processing before disposal. The non-biodegradable ones are likely to cause land, water or air pollution.

Another limitation of using nanotechnology in medicine is its high expense. The use of nanomedicine would increase the cost of health care, which would make its access difficult to the poor.

CURRENT RESEARCH:

While nanotherapy has been shown to present significant advantages in the treatment of cancer among a number of other diseases, research studies continue to be conducted in a bid to enhance its efficiency. Currently, a great deal of research is going towards multi functionality of nanoparticles for nanotherapy.

Researchers agree that multi functionality of nanoparticles would make them ideal in nanotherapy given that they would be able to not only carry more drug compound, but also have the following advantages:

- Void being destroyed by macrophages
- Efficiently permeate biological barriers
- Selectively target the desired sub cellular objects,
- Deliver its components in a controlled way once it gets to the target cells/tissue

To achieve this, most studies focus on making modifications on the surface of the nanoparticles by adding various groups such as alkyl chains to add to the functionality of the particles; In doing so, it will not only be possible to enhance delivery, but also have better control of the system.

Research is also being directed towards completely eliminating the side-effects of nanotherapy. While it has been shown that the carriers can be used to target specific cells, this is yet to be achieved with the bioactive agents.

Given that the bioactive agents are unable to solely target cancerous cells, they end up affecting some of the nearby healthy cells where they cause irreparable effects. Therefore, research is also being geared towards associating the bioactive components with the target-specific nanocarrier system.

In 2015, researchers successfully developed a nanoparticle-based therapy (nanotherapy) that could treat multiple myeloma in mice. From the results, researchers were positive that this form of therapy can be used to treat cancer of the immune cells in the bone marrow in human beings.

In their study, the researchers found out that while this method of delivery presents a significant advantage in treating cancers, there is a need to improve on targeting, protecting the bioactive compound (drug product) and enhance delivery.

Using nanotherapy, researchers hope to block Myc, which has been found to be active in most cancers. However, Myc inhibitors have been shown to be highly potent, which means that they are highly reactive. As a result, there is a great need to improve the nanotherapy technology in order to ensure that the inhibitor is efficiently transported to the target cells without undergoing degradation. Given that the inhibitor has been shown to be very effective in animals, only an effective vehicle is required in humans to ensure the same efficiency.

Apart from the treatment of cancer, research is also being directed towards the treatment of a number of other disease including heart diseases and ischemia. For instance, researchers have been working with nanoparticles loaded with a hepatocyte growth factor protein (1K1) in therapeutic angiogenesis. This is seen as one of the ways through which researchers can grow new blood vessels in a bid to improve the supply of blood to some organs/tissues that do not receive sufficient amounts.

Studies have shown that this treatment method has the potential to help patients with the disease and aims to start new trials using another protein (1K1-NP) that has been shown to be better in the production of new blood cells compared to 1K1.

Other studies have shown that nanotherapy has the potential to help prevent repeated heart attacks among patients. Researchers used a high-density lipoprotein nanoparticle that was loaded with a statin drug in mice and discovered that the treatment helped target and lower inflammations in blood vessels. In human beings, this treatment method is expected to help patients by preventing new heart attacks by controlling inflammation in the arteries.

CHALLENGES:

Although nanotherapy presents many advantages in the treatment of diseases like cancer, it faces a number of challenges that are yet to be overcome.

The body's defence system is one of the challenges faced in nanotherapy. As is the case with other foreign substances (bacteria, foreign proteins etc) nanoparticles are identified as foreign and cleared by the body. This has been shown to reduce the efficiency of nanotherapy. For this reason, researchers are working to develop long lasting drugs or control nanocarrier so that they avoid certain routes in the body. The surface area of nanoparticles in nanotherapy has also been shown to be a problem. While it presents a big advantage in that more functional groups can be added, this is also a problem given that the surface area results in high surface energy, which encourages binding of other proteins.

Some of the proteins that bind the surface have been shown to signal MPS macrophages, which in turn engulfs the nanoparticles. While these issues prevent nanotherapy from being the ideal form of therapy, research studies are being conducted to overcome these challenges.

CURRENT SITUATION:

Currently, the researches on nanoparticle drug delivery system focus on: (1) the selecting and combination of carrier materials to obtain suitable drug release speed; (2) the surface modification of nanoparticles to improve their targeting ability; (3) the optimization of the preparation of nanoparticles to increase their drug delivery capability, their application in clinics and the possibility of industrial production; (4) the investigation of in vivo dynamic process to disclose the interaction of nanoparticles with blood and targeting tissues and organs, etc. One type of nanoparticle, which is differentiated from any of the above terms, is a solid lipid covalently attached. The distinct advantages offered by solid nanoparticles in drug development can be ascribed to their physical stability and the possibility of modifying the formulating materials in order to achieve controlled release characteristics. The ability to formulate nanoparticles to achieve sustained release offers an opportunity for product life cycle management by developing formulations with decreased dosing frequency for drugs that are going off patent. There has been a variety of materials used to engineer solid nanoparticles both with and without surface functionality. Perhaps the most widely used are the aliphatic polyesters such as poly (lactic acid) (PLA), the more hydrophilic poly (glycolic acid) (PGA) and their copolymers poly (lactide-coglycolide) (PLGA). The degradation rate of these polymers and often the corresponding drug release rate can vary from days (PGA) to months (PLA). The effectiveness of nanoparticles in drug delivery can be attributed to many factors such as physical and biological stability, good tolerability of the components, simplicity of the manufacturing process, possibility of facile scale-up of the manufacturing process, amenability to freeze drying and sterilization. Nanoparticle (SLN) with a lipid core that is solid at room temperature. During formation of SLNs the solid lipid is first melted, then emulsified as a liquid to form an o/w emulsion, and cooled to allow the lipid to solidify. Due to the similarity in formation and content, these particles have been referred to as ‘‘emulsions with solid fat globules’’.

SUMMARY AND FUTURE PERSPECTIVE:

Nanotechnology is playing an increasingly important role in cancer diagnosis and treatment. The size regime of NPs is small compared to cells and cellular organelles permitting NPs to interact with specific features of cells and allowing for tumor cell localization through active targeting. The size regime of NPs is also appropriate for passive targeting to tumor tissue via the EPR. Thus, nano-sized materials have particular advantages for cancer treatment with distinct features relative to low molecular weight drugs. These properties are being effectively exploited for improved delivery of chemotherapeutic drugs resulting in both enhanced anticancer activity and reduced systemic toxicity.

The chemical diversity of NPs allows for interactions with magnetic fields, NIR irradiation, and other external fields to provide a conduit for highly specific interactions between external fields with tumor tissue and potentially with individual malignant cells *in-vivo*. The diverse material composition of NPs also permits perturbation of external fields providing enhanced contrast for imaging applications. The unparalleled specificity of coupling between external fields and malignant cells in the context of normal tissue provided by appropriate NPs is expected to lead to more accurate and earlier diagnoses and improved treatment outcomes. One concern potentially limiting the applicability of some NPs for cancer treatment is the toxicity of nanomaterials that requires further investigation. Nonetheless, improved cancer treatments using nanotechnology will continue to be developed and result in improved treatment outcomes.

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