Journal of Advanced Scientific Research
Available online through https://sciensage.info
ISSN 0976-9595
Review Article

# NANOPARTICLE AIDED TUMOR TARGETING AND CANCER DETECTION

**Charu Jaiswal[1], Medha Chakraborty[1], Kushal Kant Pant[2], Vikas Chandra*[2], Devendra Singh Porte[3]**
[1]*Dr. D.Y. Patil Biotechnology and Bioinformatics Institute, Pune, Maharashtra, India*
[2]*Department of Biotechnology, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh, India*
[3]*Department of Rural Technology and Social Development, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh, India*
**Corresponding author: digvijay.chandra@gmail.com*
*Received: 30-08-2022; Accepted: 07-10-2022; Published: 31-10-2022*
 https://doi.org/10.55218/JASR.202213901

## ABSTRACT
Cancer refers to a collective group of diseases involving abnormal, uncontrolled cell proliferation with the potential to spread to the other tissues from the location of origin. Various modes of treatments such as radiotherapy, chemotherapy, surgical methods, etc. are commonly available. However, these approaches are not very cost-effective and are accompanied by side effects. An emerging approach of targeted drug delivery or smart drug delivery with the assistance of nanoparticles (NPs) and also in combination with immunological therapies has proven to show great potential in cancer treatment with an additional advantage of having the least side effects. Stimulus-sensitive smart nanomaterials have been designed to specifically target the cancer cells, causing no damage to the healthy cells. This is attained using Poly (lactic-co-glycolic acid) (PLGA), PEGylated NPs, αvβ3-integrin-specific lipid NPs, NP-based radiosensitizers (NBRs), and NP drones. Moreover, not only the specific targeting but the advances allow the detection of these drug-loaded NPs with the help of plasmonic Biosensor and fluorescence nanoprobes that emits fluorescence as it comes in contact with the target. This article describes the application of NPs in targeting the tumor cells as well as the recent researches going on to facilitate easier & cheaper modes of treatment using nanotechnology.

**Keywords:** Nanoparticles, Radiosensitizers, Radiotherapy, Nanoparticle drones, Smart nanomaterials, Plasmonic Biosensor.

## 1. INTRODUCTION
Cancer presents a major concern worldwide despite the availability of numerous treatments. The usability is limited due to the side effects it causes by destroying other cells along with the tumor cells. Nanomedicine is an advancement that opens a way for the effective treatment of various cancers with the least side effects. Nanomedicines confers a significant advantage over that of conventional medicine because of the enhanced permeability as well as the retention effect allowing favourable delivery of payload (drugs encapsulated in polymeric nanoparticles) at the site of the tumor and the ability for the continual release of payloads overtime as soon as they encounter the tumor [1, 2].

This review deals with the nanoparticles (NPs) or nanomaterials (NMs) that can be modified in a way to target the tumor cells/tissues. Some of the NPs present in nature already possess therapeutic properties while the others are being modified to serve the desired effect. This review also deals with how these targeted NMs can be detected using different strategies. The different nanoparticles and nanoparticle based methods involved in tumor targeting and treatment of cancer are described in table 1.

Smart NMs have been designed that are stimulus-specific hence undergo a dynamic change in their property in contact with the stimuli, this is how they specifically target the drugs to the destined cell/organ. Cancer cells overexpress some of the specific enzymes/proteins that serve as a reliable modality for designing a smart delivery system. Furthermore, Cell-Penetrating Peptide (CPP) can help the cargos to easily penetrate the target. Hence CPP in combination with targeting molecule is an effective modality for the treatment [3].

PEGylation can often improve the carrier's stability and can extend the retention time. mPEG-Peptide-PCL reconfigures because of Matrix metallopeptidases (MMPs), to control therapeutic targeting. It often

increases the retention time and improves the stability of the targeted drugs [3].

Enhanced plasmonic biosensor for detection is another approach that deals with the interactivity among incident light and combined oscillation of the unbound electrons that give rise to localized surface plasmon resonance over the surface of the NPs. The receptors present over surface of such NPs help to bind accurately with the target biomolecules that falls under the visible range and are concerned with the real-time measurements [10-13].

Exosomes are developing drug carriers for cancer therapy [14-16]. They are small cell-derived natural nanometric vesicles that are produced mostly by all body cells and can be found throughout body fluids, this facilitates them to escape the lung clearance and cross the blood-brain barrier. Moreover, they accumulate in tumor tissues having abnormally formed blood vessels, therefore the exosomes can reach the solid tumors [17] enhancing the efficiency of the drug delivery.

**Table 1**: **Mechanism of nanoparticles used for targeting tumor cells**

| Nanoparticle | Application/mechanism | Main Drug target/ cancer type/ | Ref |
|---|---|---|---|
| PEGylated self- assembled enzyme- responsive nanoparticle | Matrix metalloproteinases (MMPs) that are over-expressed in many types of cancer serve as appropriate targets for enzyme-induced therapeutics. MMP targeting peptides (mPEG-Peptide-PCL) realign after contact with MMPs that actively guide the therapeutic targeting. | Lung cancer | [3] |
| Nanoparticle-based radiosensitizers (NBRs) | It helps to acquire a higher radiotherapeutic ratio by increasing the susceptibility of tumor cells to ionizing radiation as well as by enhancing DNA damage. They also result in the creation of free radicals in contact with ionizing radiation. | Localized solid tumors (lung cancer) | [4] |
| Poly (lactic-co-glycolic acid) PLGA-based nanoparticles | Encapsulation of various anti-cancer drugs (Doxorubicin, Cisplatin, Nitrocamptothecin, etc.) and their successful delivery. | Microtubules, DNA adducts, Topo II, Cytoplasmic proteins, Cytoplasmic receptors | [3] |
| Nanoparticle Drones | Nanoparticle drones particularly are loaded with drug payloads such as cannabinoids. | Lung cancer | [5] |
| αvβ3-Integrin-Specific Lipid Nanoparticles | cRGD-fabricated NPs have applications for clinical purposes targeted for the delivery of desired drugs to tumors. | Various cancer cells | [6] |
| Exosomes Nanoparticles | Extends the bulk of the solid tumors to surge the efficiency of their drug delivery due to increased permeability and retention effect. Anti-CD44 antibody-covered exosome is capable of initiating CSC death. | Cancer stem cells | [7, 8] |
| Manganese ferrite NPs | Easy synthesis, high stability, minimum toxicity, adjustable magnetic properties & temperature as well as easy fluctuation on the appliance of the external magnetic field. | Breast cancer, other types of cancer | [9] |

Poly (lactic-co-glycolic acid) (PLGA) are polymeric NPs that are biodegradable and hence linked with lower or no risk of side effects. It generates monomers of biodegradable metabolite, lactic acid, and glycolic acid upon hydrolysis that can be metabolized easily to release carbon dioxide and water via the Krebs cycle in the body [18-20] therefore is an efficient polymer for nanomedicines.

αvβ3-Integrin-specific lipid nanoparticles are other entities used in tumortargeting such as immunotherapy approaches involve the interactions between immune cells and NPs. In this approach lipid-based NPs are surface-functionalized using αvβ3-integrin-specific cyclic arginine-glycine-aspartate peptides (cRGD) for therapeutic purpose targeted to deliver drugs to tumours and angiogenic vasculature. An elevated cRGD

-NP interaction with phagocytes was observed to be associated with an αvβ3-integrin expression on these cells [21].

Therapeutic tumor vaccines (for e.g.; Provenge for prostate cancer) are also available in addition to the aforementioned techniques that are proven to be effective against solid tumors due to their high specific ability to induce T cells to attack tumors. They stimulate an effective immune response by activation and hence the destruction of the tumor [22].

Along with the aforementioned approaches, Manganese ferrite NPs also serves as a great way for cancer therapy due to properties like the ease of synthesis, high stability, minimum toxicity, adjustable magnetic properties as well as temperature [9] along with the easy fluctuation on the appliance of the external magnetic field [23-26]. The nanoparticles, due to their small size and large surface area, become a good delivery system for delivering medicines and therapeutics. Nano-materials can be developed as stimulus sensitive and as a targeted delivery system and they also increase the therapeutic ratio. So nanomaterials can be good candidates for cancer treatment. Some other applications of nanomaterials are depicted in fig. 1. Moreover, in this article, we have discussed a few major nanoparticle-mediated strategies and new advances that have shown great promise in the field of cancer therapeutics among the many that are available and yet advancing.

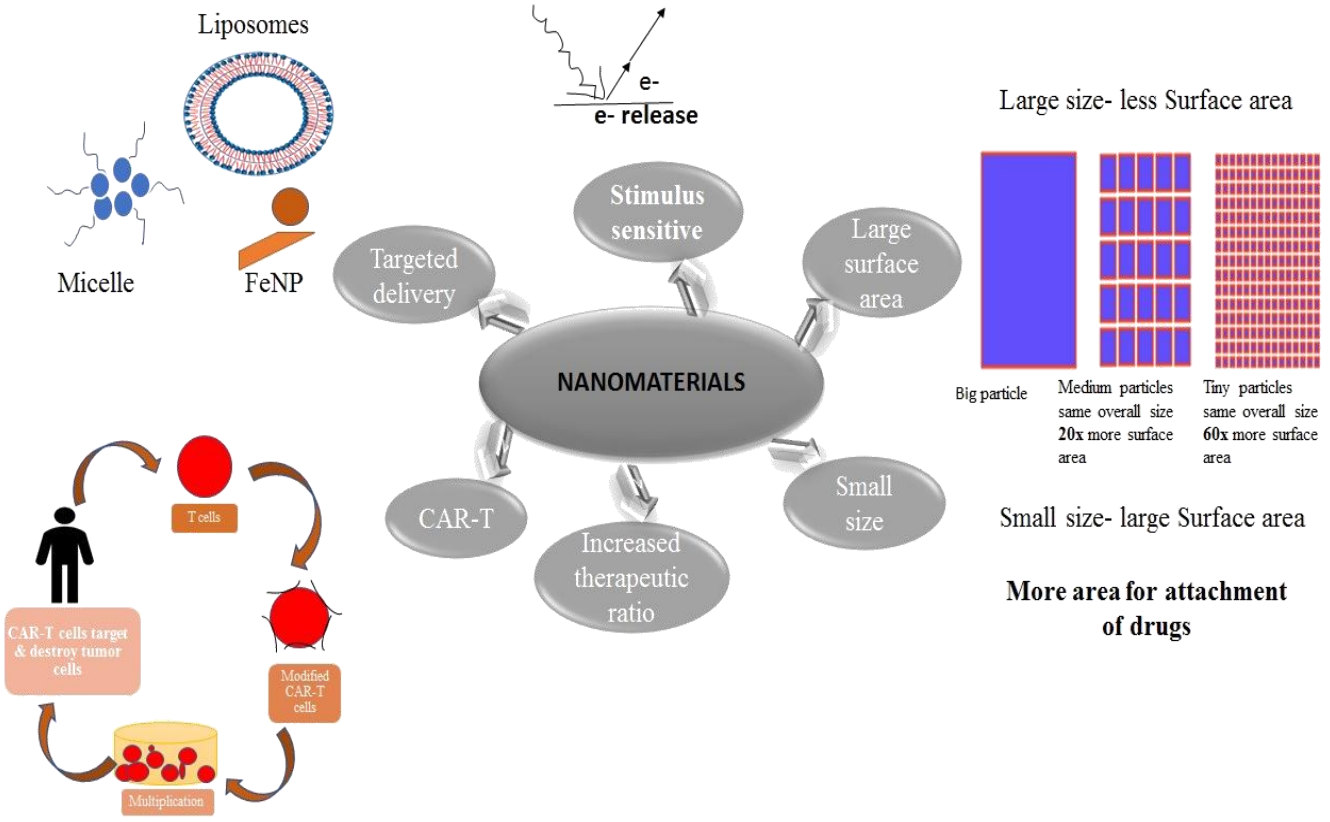


**Fig. 1: Applications of nanomaterials in tumor targeting**

## 2. SMART NANOMATERIALS FOR CANCER THERAPY

Smart nanomaterials (NMs) are designed to be stimulus sensitive (such as responsive to pH, temperature, magnetic field, etc.). On contact with the stimuli, they undergo a dynamic change in their property, and the changes being produced, are reversible as well. This property of the smart NMs contributed to a wide range of applications that includes imaging technologies, specific drug delivery, and self-healing materialsas well [27].

Cancer cells over express some of the specific enzymes hence the development of enzyme-responsive NPscan serve as a reliable modality for designing a smart delivery system. The ability of cell penetration in cargo delivery can further be enhanced by CPP. Therefore, a

combination of the targeting peptides and CPPs is among the effective tactics being developed for improving the efficacy of cancer therapy [3].

Smart radiotherapy biomaterials (SRBs) are found to replace conventional inert radiotherapy biomaterials (IRBs) as it enhances the radiotherapeutic index. They are made up of NP-based radiosensitizers (NBRs) loaded in biodegradable or bioerodible polymers for enhancing the radio therapeutic index. SBRs when administered to patients during regular radiotherapy (RT), as the encapsulating polymer erodes or degrades the NP being inserted start releasing when it comes in contact with the biological fluid within the tumor, this released NPs make tumor cells more susceptible to radiation, as the dose to the tumor is being enhanced by the interaction of the NPs with the ionizing radiation [28]. Similarly, another material made from biodegradable or bioerodible polymers are implants that are loaded with anticancer drugs and facilitate direct drug delivery into the tumor volume [29].

Smart NMs (NP drones) have been constructed that can be activated remotely with the radiation-emitting micrometer range missiles such as electrons that facilitate the destruction of the tumor cells hence specifically target the tumor cells [5]. They can even provide a therapeutic efficacy to deliver the therapeutic payloads as well as can be conferred with image contrast enhancement potency for techniques like computed tomography (CT) and magnetic resonance imaging (MRI) [30]. Furthermore, NP drones can be often loaded with the drug payloads such as cannabinoids to exert palliative effect by minimizing the symptoms of cancer. It prevents nausea, vomiting, and pain as well as stimulates appetite in the cancer patient; it is also known to restrict tumor growth [5]. Cannabinoids along with radiotherapy potentially enhance tumor cell damage (particularly in lung tumor cells) [31, 32]. Recently extensive research has been done on nanoparticle-aided radiotherapy (NRT). This approach of diagnostics endowed with the therapeutics known as theranostics is significant in tumor targeting. Gold NPs (GNPs) are the ones known to exhibit theranostic capability [33]. GNPs provide CT as well as photoacoustic imaging contrast and often a satisfactory drug loading and attracting targeting moieties hence it serves as a splendid prototype for the construction of such NP. They even have radiosensitizers that are biocompatible ensuring no or less toxicity. By the photoelectric effect, they can promptly interact with photons to emit missile-like photoelectrons (Auger electrons) in the range of few micrometers to enhance Radiotherapy (RT) damage to cancer cells [34]. The vacancy created on the emission of the photoelectron is filled by high linear energy transfer hence leading to highly localized damage [5].

NP-based radiosensitization is another technique being developed to enhance the therapeutic ratio of cancer cells by increasing the susceptibility of tumor cells to ionizing radiations by enhancing damage to DNA and also through the creation of the free radicals on contact with the ionizing radiations and is also an effective tool for concomitant chemoradiotherapy [35].

## 3. NANOPARTICLES USED FOR RADIO-SENSITIZATION

Radiosensitizing NPs can be drug-based NPs (such aspolymeric NPs& platinum-based NPs) or inert therapeutic agents (such as GNP) [5]. Some of the therapeutic NPs (e.g. cisplatin, oxaliplatin, or carboplatin NPs) can increase the therapeutic ratio due to the high atomic mass. On exposure to ionizing radiation, they can often sensitize and destroy tumor cells [36]. Such NPs are designed either through encapsulation or by attachment of drugs NP with high atomic number NPs (such as GNPs) [37] where the therapeutic agents are the drugs, and the NPs with high atomic mass (Z) results in dose enhancement on interaction with the ionizing radiation. Auger electrons are released on the interaction of NPs of higher Z value with the ionizing radiation and absorption of photoelectrons by such NPs. Auger electrons hike the dose in the radio therapeutic (RT) window and due to lower energy with a shorter-range result in energy deposition at proximity within the tumor [17, 28, 36, 38, 39]. GNPs are present in nature in chemically inert form but on interaction with the ionizing radiation, they become potent [28]. The surface properties of GNPs can be engineered for making them suitable radiosensitizers for RT [17]. PEGylated GNPs can enhance the cellular uptake of GNPs. GNPs can also be complexed with the targeting agents for precise access to the desired location in the body [39].

Matrix metalloproteinases (MMPs) are the enzyme being overexpressed in numerous kinds of cancers [40]. An enzyme responsive NP dependent on a functionalized copolymer (mPEG-Peptide-PCL) designed to frame work MMPs, serve as SMART medication vesicles for upgraded specificity and diminished side-effects [3]. The carrier's stability, as well as the retention time, can be enhanced through

PEGylation *in vivo*. mPEG-Peptide-PCL gets reconfigured due to the enzymatic action of MMPs. This controls therapeutic targeting. mPEG-Peptide-PCLpolymer self-assembled and they form NPs with a hydrophilic shell & hydrophobic core. These NPs being formed are biodegradable. PCL (Poly-caprolactone) here is used for loading of drugs while the targeting peptide Anticancer Peptide (ACP) was designed to be degraded by MMP-2 and the cell-penetrating peptide enhanced the cellular uptake of NPs [40]. PEGylation often increases the retention time and improves the stability of the carrier as well [3].

## 4. ENHANCED PLASMONIC BIOSENSOR FOR DETECTION

The interactivity among incident light and combined oscillation of the unbound electrons present over the NPs surface gives rise to localized surface plasmon resonance and possesses the attribute that is seen in the wavelength of the visible region [10]. Localized surface plasmonic resonance [11-13] surface-enhanced infrared adsorption [41, 42] and other biosensors utilizing plasmonic NPs have drawn in much attention due to its label-free and real-time measurements properties. Fiber-optic-based localized surface plasmon resonance (FO-LSPR) sensors with three-dimensional (3D) nanostructures have been established. For highly sensitive plasmonic biosensing, modelings of these sensors using zinc oxide (ZnO) nanowires and gold nanoparticles (AuNps) have been evolved [43]. Due to the capacity of receiving and delivering light across an optical-fiber, down-scaling of the measurement system, effortless set-up of the optical arrangement, easy handling and freedom from the reactions of electromagnetic (EM) waves allowing the small loss of signal and facilitating remote sensing makes FO-LSPR sensors favourable aspirant for biosensor applications [44-46].

Nowadays, prostate cancer is a vital cause contributing to the death of almost 10% of all patients having various types of cancers [47]. Prostate-specific antigen (PSA) is reckoned as asignificant biomarker for the detection of cancer along with its application in early- diagnosis as well as in post-care of prostate cancer [48]. Biosensor used for detectionof such biomarkers must be highly sensitive [43]. Measuring the PSA is clinically advantageous asprostate cancer can be more effectively treated if detected in the early stages [49]. Performance of PSA immunoassay with different concentrations utilizing 2D and 3D FO-LSPR sensors was evaluated. 3D FO-LSPR sensors demonstrated satisfactory results for common applications in the biosensing field with diseases that require early detection [43]. The surface of an optical fiber acts as supporting material for the synthesis of ZnO nanowires. This enables the three-dimensional (3D) distribution of NPs [43]. Nanowires of ZnO are developed using hydrothermal synthesis [50] Gold nanoparticles (AuNPs) are fabricated on these nanowires [43]. This is the method being used frequently for attachment of AuNPs on substrates [51-53]. The sensor based on the ZnO nanowires fabricated with AuNPs demonstrated an enhancement in sensitivity by approximately 171%, proving potential applications in high sensitivity real-time label-free biosensors [43].

## 5. EXOSOME NANOPARTICLES FOR DETECTION AND TARGETING

Exosomes are natural nanometric vesicles that are derived from cells and are produced by almost all types of body cells and can be found throughout body fluids such as synovial fluid, saliva, urine, breast milk, semen, and blood and involved in various disease processes, including the formation of cancer. Specific drug delivery to cancer stem cells (CSC) is a pressing need in cancer therapy as multiple mechanisms for drug resistance in CSCs. Drug efflux, slow cell cycle advancement, increased efficiency of DNA repair, amplified anti-apoptotic capacity, and detoxification enzyme expression are altogether responsible for drug resistance of CSCs [54-58]. Thus nanotechnology-based delivery methods may be potentially implemented in cancer therapy. Owning to their capacity of slow drug-release nanoparticles instigate an enhanced local drug concentration at the vicinity of the tumor and exhibit high anti-cancer activity [59, 60]. Exosomes, secreted from living cells are biologically compatible, non-cytotoxic, low immunogenic, effortlessly producible, easy to load, possess a long-shelf lifeduration, and elevated cargo loading capacity [61-63]. The small size of exosomes facilitates them to easily pass through the blood-brain barrier (BBB) and slip away from lung clearance [64, 65]. As a result of the increased permeability and retention effect, nanometric exosomes are inclined to agglomerate in tumor tissues having unusually formed blood vessels than that of the normal tissues, therefore exosomes are capable of simply reaching the bulk of the solid tumors to surge their drug delivery efficiency [17] making exosomes a budding drug carrier for the treatment of cancer [14-16]. Various techniques have evolved to segregate exosomes

from body fluids. Such techniques include immunoaffinity capture, size exclusion chromatography, differential ultracentrifugation, density gradient centrifugation, and polyethylene glycol (PEG)-mediated precipitation [66]. Qi *et al*. linked transferrin receptor-positive blood exosomes to superparamagnetic-conjugated transferrin. An external magnet was attached to the site of the tumor *in vivo*; this permitted the magnetic exosomes to be administered to the target tumors cells to actively restrain the tumor growth. Thus, engineering magnetic exosomes can improve tumor targeting specificity [67]. Multiple cancer gene suppressors and anticancer drugs, along with functional RNAs, were utilized for exosome-based tumor treatment [68, 69]. One study reported that exosome-delivered doxorubicin decreased the size of the tumor with much greater efficiency than free or liposome-delivered doxorubicin, in a colon adenocarcinoma mouse model [70]. Drastic reduction in cardiotoxicity was observed when doxorubicin was delivered through exosome in αv integrin-positive breast cancer cells. Cardiotoxicity is thought to be the crucial side effect of doxorubicin in clinical applications [71]. Due to the benefit of this delivery system, larger concentrations of doxorubicin can be used to treat breast and ovarian tumors while reducing off-target effects [72]. Exosomes filled with celastrol, a triterpenoid derived from plants [73] also demonstrated a more prominent anti-tumor effect compared to free celastrol in the xenograft model of human lung cancer cell [74].

Drug resistance, trouble in specific targeting, and the self-renewal capacity of CSCs all give rise to failure as well as the relapse of cancer treatment. The present exosome engineering techniques can be refined with the help of identified cancer stem cell features, to allow more precise targeting. Divisibly, an anti-CD44 antibody-covered exosome could directly deliver drug to the target CSC and initiate CSC death, including their drug delivery role [75].

Upon intradermal and subcutaneous administration of exosomes acquired from autologous dendritic cells (DCs) and combined with the melanoma antigen gene (MAGE) tumor antigens over a period of 4 weeks in a phase I Clinical trial in metastatic melanoma patients the practicality and also safety of exosome administration have been established [76]. Another phase I clinical trial in progress is trying to assist the ability of plant exosomes to deliver curcumin to colon tumors [77].

Exosomes obtained from cancer cells bear functional cargos that mediate tumor cell growth either directly or indirectly [7, 8, 78]. Therefore, identifying as well as removing those tumor reinforcing elements from exosomes is vital for exosome-mediated cancer therapy, and stab to uplift the efficiency of exosomes to load cargo.

Utilizing helpful exosomes to encourage immuno-therapy is a favourable remedy for the treatment of cancer as theexosomes are more steady than initiated antigen (Ag) introducing cells and can be conveniently designed [17]. Exosome-based frameworks are perhaps the most convenient methodologies for targeting CSC for the treatment of cancer.

## 6. PLGA & OTHER POLYMER BASED NANOPARTICLES AS CANCER DRUG DELIVERY SYSTEMS

Poly (lactic-co-glycolic acid) (PLGA) possesses some properties such as it gets released on contact with the target, and low toxicity that are significant in the delivery of drugs. They are biologically compatible with the cells and tissues as well [79], hence linked with lower or no risk of side effects. The therapeutic drug is encapsulated inside the polymeric particle or is adsorbed on its surface [79-81].

Polyamides, poly (amino acids), poly (alkyl-α-cyanoacrylates), polyesters, poly orthoesters, polyurethanes, and polyacrylamides are some other polymeric materials that can act as a device for targeting [18, 82, 83]. PLGA is associated with minimal toxicity [84]. As upon hydrolysis, it produces monomers *viz*. lactic acid and glycolic acid that are non- toxic metabolites [84] and can be further metabolized easily to release carbon dioxide ($CO_2$) and water via the Krebs cycle in the body [18-20]. This PGLA is an efficient polymer for nanomedicines.

## 7. αvβ3-INTEGRIN-SPECIfiC LIPID NANO-PARTICLES IN TUMOR TARGETING

Elevated drug levels at pathological sites without systemic off-target exposure can be achieved by drugs encased in NPs [21]. Real-time targeting kinetics of NPs and phagocytes contribution to active targeting of the NP is yet to be explored in detail. Lack of a profound understanding of *in vivo* behaviour of NP is one of the hurdles for their extensive use in treatment [85-87]. One of the most commonly used NP ligands in the arena is, Cyclic arginine-glycine-aspartate cRGD peptides [88] which is a ligand for αvβ3-integrin, that is upregulated

on angiogenic tumor vascular endothelium and various types of cancer cells [88-90]. These lipid-based NPs are surface-functionalized using αvβ3-integrin-specific cyclic arginine-alanine-aspartate peptides (cRGD) [91]. cRAD peptides are used as non-specific control peptide [92]. Sudden binding of cRGD-NP-positive cells to tumor vasculature has been observed with the help of intravital microscopy which was failed to be seen in cRAD-NPs demonstrating the vital role of immune cells in cRGD-NPs' distribution through the tumor interstitium [21]. cRGD-fabricated NPs may be applied for therapeutic targeted transfer of drugs to tumors [88, 93,94]. Disclosure of high coexpression of the αv and β3 integrin subunits occurred due to the staining of immune cells with these integrins. Therefore, the elevated cRGD-NP interaction with phagocytes was associated with the expression of anαvβ3-integrin on these cells [21]. Cyclic arginine-glycine-aspartate targeting αvβ3-integrin fabricated oil-in-water nanoemulsions and liposomes in tumor mouse models were studied along with the observation of "NP hitchhiking" via flow cytometric analysis with phagocytes and ligand-mediated build-up in cancerous lesions [21]. With evolving immunotherapy and its current rise, generating interactions between immune cells and NPs can become an applicable approach in developing immunomodulating nanomedicines.

## 8. FLUORESCENCE-MEDIATED SURGERY

Surgery is a successful procedure to ablate solid tumors, and 50 percent of patients having cancer go through surgery every year globally. Surgical methods, however, present various obstacles, including identification of small lesions, detecting metastases, and achieving complete tumor resection. To enhance the precision of surgery, fluorescence guidance is an advantageous method. Intraoperative tissue fluorescence imaging (FI) with the help of nanoprobes emitting fluorescence has proven to become the facilitator of tumor surgery therapy, due to the speedy development of nanotechnology, which could highly help in improving the accuracy of ablation and surgical success rate. FI technology has been known to evolve as a greatly applicable imaging technique in the case of clinical tumor detection and image-mediated surgery due to the advantage of strong real-time performance, high safety and, high spatial resolution [95]. As of now, the treatment of metastatic peritoneal carcinoma is yet a vital challenge and is directly corresponds with the complete ablation of the primary tumor. Recently, for the up-gradation of the image-guided surgery for metastatic ovarian cancer and solve the local frequency at which it occurs, Wang et al in 2018 modelled the second near-infrared window (NIR-II) emitting downconversion nanoparticles (DCNPs), which is superior to Indocyanine green (ICG) with quality photostability and deep tissue penetration [96]. With various approaches ranging from passive andactive targeting of cell surface receptors to tumor microenvironment (TME) responsive targeting, escalating taking up of a cell through cleavable proteins, preclinical development of fibroin nanoparticles (FNPs) formulations has made huge progress [97]. These attempts together may lead to clinical trials with the use of FNPs in the upcoming future.

## 9. MAGNETIC NANOPARTICLES BASED CANCER THERAPY

Cancer cells can be destroyed by the application of hyperthermia [24, 25]. The heat is produced by the magnetic NPs on exposure to the exterior magnetic field, which allows the destruction of the cancer cells. Such magnetic NPs can be introduced either through intravascular or through local regions facilitating specific targeting to tumor cells [98].

For the application in cancer therapy, the substance should have magnetization with an elevated saturation; this property is being posed by the ferrite NPs [24, 25].

Manganese ferrite NPs due to ease in synthesis, great stability, minimum toxicity, adjustable magnetic properties as well as temperature as per the therapy [9] along with the easy fluctuation on the appliance of the external magnetic field can serve a wide range application in cancer therapy, acting as a valuable implant for facilitating cancer treatment [23-27, 99].

An exceptionally enhanced therapeutic effectiveness has been achieved, for the treatment of pancreatic cancer using gemcitabine and pH insertion peptide magnetic nanoparticles (GEM-MNP-pHLIP) targeted delivery through pancreatic stellate cells (PSCs) guided desmoplastic reactions leading to the formation of α-smooth muscle actin and inhibition of collagen [99]. Metformin (MET) was also given during this process of delivery for repressing the activity of PSCs, promoting effective delivery of GEM-MNP-pHLIP [100].

Magnetic nanoparticles continue to show promising efficacy in the treatment of cancer through selective targeting to the attempted location via exercising *in vivo*

techniques with the application of an external magnetic field [101].

## 10. CONCLUSION & FUTURE PROSPECTS

This review gives insight into emerging technologies for targeting and detection of tumors using nanoparticle (NP)-mediated strategies as novel therapeutics for treating cancer. NP drones have been constructed that can be slightly activated via radiation to emit micrometer range missiles like electrons for the destruction of tumor cells. The struggle to distribute strong concentrations of drug payloads with minimal side effects is of especial concern for the delivery of drugs like cannabinoids whose clinical adaptation has suffered negatively by the psychotic side effects [34]. With the current fundamental intravenous conveyance of a drug, even focused on NPs with the incredible possibility of arriving at aimed distant tumor positions, the arrival of just a part of the directed nanoparticles/drug dosage at the tumor takes place, regardless of the improved EPR impact. The remainder of the targeted NPs/drugs stay in circulation, bringing about systemic toxicity, which can diminish the overall strength of affected patients. Conveyance of adequate concentration of NPs or NBRs to the targeted tumor without or with restricted systemic reactions on healthy tissues/organs continues to be a challenge that numerous specialists keep on investigating. Various researchers have revealed that neoangiogenesis is an altogether negative prognostic factor in solid tumors. Hence, a constructive strategy against angiogenesis, treatment of solid tumors needs critical attention [102, 103]. Curcumin, an active ingredient removed from turmeric, has been broadly studied for its various effects one of that includes anti-cancer effects [104]. Moreover, Curcumin can invert chemo-obstruction by restraining numerous flagging pathways, and one such phase I clinical trial in progress is under the processof governing the capability of plant exosomes to deliver curcumin to colon tumors [78]. A relatively unventured field of immunomodulating nanomedicines has to be further investigated to generate immune cell-NP interactions as a feasible strategy and "phagocyte hitchhiking" as a crucial mechanism for cRGD-NP active tumor targeting has been established by Sofias *et al.*, 2020. Extensive research on these approaches along with other various novel strategies will prove to be very vital in the development of targeted therapeutics against cancer [21].

As per an article from Vanderbilt University, the drug delivery system using nanosponge (NS) has been demonstrated to be more effective than direct injection. NSs share the advantages including NS particles being soluble in water [105]. The encapsulation of the anti-cancer drug in the NS permits the use of hydrophobic drugs that do not dissolve freely in the water. Also, the particle size of NS can be controlled by varying the proportion of the cross-linker of the polymer. As nanosized material serves as better drug delivery agents. Another approach is the use of Nano Robots that can be so small to walk inside blood when hit with Lasers, using these approach smallest controllable nanomachines, portable enough to someday even go through blood vessels, may be designed [106].

### *Conflicts of Interest*

The authors declare no conflict of interest.

## 11. REFERENCES


1. Maeda H, Sawa T, Konno T. *J Control Release*, 2001; **74:**47-61.
2. Maeda H, Bharate GY. *Eur J Pharm Biopharm*, 2009; **71:**409-419.
3. Guo F, Wu J, Wu W, Huang D, Yan Q, Yang Q. et al. *J Nanobiotechnol*. 2018; **16(1):**1-13.
4. Wang P, Fan Y, Lu L, Liu L, Fan L, Zhao M. *Nat. Commun*. 2018; **9:**1-10.
5. Ngwa W, Kumar R, Moreau M, Dabney R, Herman A. *Front Oncol.* 2017; **7:**208.
6. Duro-Castano A, Gallon E, Decker C, Vicent MJ. *Adv. Drug Delivery Rev.* 2017; **119:**101-119.
7. Wang J, De Veirman K, De Beule N, Maes K, De Bruyne E, Van Valckenborgh E, et al. *Oncotarget*. 2015; **6:**43992-44004.
8. Wang J, Faict S, Maes K, De Bruyne E, Van Valckenborgh E, Schots R, et al. *Oncotarget*. 2016; **7:**38927-38945.
9. Topkaya R, Kurtan U, Baykal A, Toprak MS. *Ceram. Int.* 2013; **39(5):**5651-5658.
10. Jatschka J, Dathe A, Csáki A, Fritzsche W, Stranik, O. *Sens. Biosensing Res*. 2016; **7:**62-70.
11. Unser S, Bruzas I, He J, Sagle L. *Sens*. 2015; **15:**15684-15716.
12. Manzano M, Vizzini P, Jia K, Adam PM, Ionescu RE. Sens. Actuators B: *Chem.* 2016; **223:**295-300.
13. Hao F, Sonnefraud Y, Dorpe PV, Maier SA, Halas NJ, Nordlander P. *Nano Lett.* 2008; **8:**3983-3988.
14. Tian X, Zhu M, Nie G. *Hum. Vaccin. Immunother.* 2013; **9:**222-225.

15. Tang XJ, Sun XY, Huang KM, Zhang L, Yang ZS, Zou DD, et al. *Oncotarget*., 2015; **6:**44179-44190.
16. Pitt JM, André F, Amigorena S, Soria JC, Eggermont A, Kroemer G, et al. *J. Clin. Invest.,* 2016; **126:**1224-1232.
17. Wang J, Zheng Y, Zhao M. *Front.Pharmacol.* 2017; **7:**533.
18. Jain RA. *Biomaterials,* 2001; **21:**2475-2490.
19. Panyam J, Zhou WENZ, Prabha S, Sahoo SK, Labhasetwar V. *The FASEB J*, 2002; **16:**1217-1226.
20. Dinarvand R, Sepehri N, Manoochehri S, Rouhani H, Atyabi F. *Int J Nanomedicine,* 2011; **6:**877.
21. Sofias AM, Toner YC, Meerwaldt AE, van Leent MM, Soultanidis G, Elschot M. et al. *ACS Nano*, 2020; **14 (7):**7832-7846.
22. Karlou M, Tzelepi V, Efstathiou E. *Nat Rev Urol.* 2010; **7:**494-509.
23. Patade SR, Andhare DD, Kharat PB, Humbe AV, Jadhav KM. *Chem. Phys. Lett.* 2020; **745:**137240.
24. Patade SR, Andhare DD, Somvanshi SB, Jadhav SA, Khedkar MV, Jadhav KM. *Cera. Int.*, 2020; **46(16):**25576-25583.
25. Mendo SG, Alves AF, Ferreira LP, Cruz MM, Mendonça MH, Godinho M. *New J. Chem.* 2015; **39(9):**7182-7193.
26. Khot VM, Salunkhe AB, Thorat ND, Ningthoujam RS, Pawar SH. *Dalton Trans.* 2013; **42(4):**1249-1258.
27. Yoshida M, &Lahann J. *ACS Nano*, 2008; **2:**1101-1107.
28. Boateng F, Ngwa W. *Br. J. Radiol.* 2017; **90:**20170069.
29. Kumar N, Langer RS, Domb AJ. *Adv. Drug. Deliv. Rev*. 2002; **54:**889-910.
30. McCarthy JR, Weissleder R. *Adv Drug Deliv Rev*. 2008; **60:**1241-1251.
31. Guzman M. *Nat. Rev. Cancer*. 2003; **3(10):**745-755.
32. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV. et al., *JAMA,* 2015; **313:**2456-2473.
33. Cifter G, Altundal Y, Detappe A, Sajo E, Berbeco R, Makrigiorgos M. et al., *Springer,* 2015; 1723-1726.
34. Ngwa W, Kumar R, Sridhar S, Korideck H, Zygmanski P, Cormack RA. et al. *Nanomedicine (Lond),* 2014; **9:**1063-1082.
35. Boateng F, Ngwa W. *Int. J. Mol.Sci*., 2020; **21:**273.
36. Altundal Y, Cifter G, Detappe A, Sajo E, Tsiamas P, Zygmanski P. et al. *Phys Med,* 2015; **31:**25-30.
37. Cooper DR, Bekah D, Nadeau JL. *Front. Chem*, 2014; **2:**86.
38. Rosa S, Connolly C, Schettino G, Butterworth, KT, Prise KM. *Cancer Nanotechnol*., 2017; **8:**2.
39. Guo F, Guo D, Zhang W, Yan Q, Yang Y, Hong W, et al. *Eur J Pharm Sci*., 2017; **99:**328-336.
40. Kratz F, Drevs J, Bing G, Stockmar C, Scheuermann K, Lazar P. *Bioorg Med ChemLett,* 2001; **11:**2001-2006.
41. Liu N, Mesch M, Weiss T, Hentschel M, Giessen H. *Nano Lett.,* 2010; **10:**2342-2348.
42. Limaj O, Etezadi D, Wittenberg NJ, Rodrigo D, Yoo D, Oh SH. *Nano Lett.* 2016; **16:**1502-1508.
43. Kim HM, Park JH, Lee SK. *Scientific Reports*, 2019; **9(1):**1-9.
44. Jeong HH, Erdene N, Park JH, Jeong DH, Lee HY, Lee SK. *Biosens. Bioelectron*. 2013; **39:**346-351.
45. Arghir I, Delport F, Spasic D, Lammertyn J. *N. Biotechnol*. 2015; **32:**473-484.
46. Lee B, Park JH, Byun JY, Kim JH, Kim MG. *Biosens. Bioelectron*. 2018; **102:**504-509.
47. Najeeb MA, Ahmad Z, Shakoor RA, Mohamed AMA, Kahraman R. *Talanta.* 2017; **168:**52-61.
48. Thaxton CS, Elghanian R, Thomas AD, Stoeva SI, Lee JS, Smith ND. *Proc. Natl. Acad. Sci. USA.* 2009; **106:**18437-18442.
49. Dey A, Kaushik A, Arya SK, Bhansali S. *J. Mater. Chem*. 2012; **22:**14763-14772.
50. Shin, YM, Lee SK, Jang S, Park JH. *Curr. Appl. Phys.* 2014; **14:**665-671(2014).
51. Xie L, Yan X, Du Y. *Biosens. Bioelectron.* 2014; **53:**58-64.
52. Chauhan SK, Punjabi N, Sharma DK, Mukherji S. *Sens. Actuators B:Chem*. 2016; **222:**1240-1250.
53. Gowri A, Sai VVR. Sens. *Actuators B:Chem*. 2016; **230:**536-543.
54. Marhaba R, Klingbeil P, Nuebel T, Nazarenko I, Buechler MW, Zoeller M. *Curr. Mol. Med.* 2008; **8:**784-804.
55. Saha S, Adhikary A, Bhattacharyya P, Das T, Sa G. *Anticancer Res*. 2012; **32:**2567-2584.
56. Colak S, Medema JP. *FEBS J.*2014;**281:**4779-4791.
57. Sotiropoulou PA, Christodoulou MS, Silvani A, Herold-Mende C, Passarella D. *Drug Discov.Today*. 2014; **19:**1547-1562.
58. Lu B, Huang X, Mo J, Zhao W. *Front. Pharmacol.* 2016; **7:**84.
59. Ahmad J, Akhter S, Khan MA, Wahajuddin M, Greig NH, Kamal MA. et al. *Curr. Pharm. Des.* 2016; **22:**4360-4373.

60. Piktel E, Niemirowicz K, Watek M, Wollny T, Deptula P, Bucki, R. J. *Nanobiotechnology*. 2016; **14:**39.
61. Munagala R, Aqil F, Jeyabalan J, Gupta RC. *Cancer Lett*. 2016; **371:**48-61.
62. Srivastava A, Babu A, Filant J, Moxley KM, Ruskin R, Dhanasekaran D. et al. *J. Biomed. Nanotechnol.* 2016; **12:**1159-1173.
63. Wang J, De Veirman K, Faict S, Frassanito, MA, Ribatti D, Vacca A. et al. *J. Pathol.* 2016; **239:**162-173.
64. Kawikova I, Askenase PW. *Brain Res.* 2015; **1617:**63–71.
65. Li X, Tsibouklis J, Weng T, Zhang B, Yin G, Feng G, et al. *J. Drug Target*. 2016; **11:**1-12.
66. Tauro BJ, Greening DW, Mathias RA, Ji H, Mathivanan S, Scott AM, et al., *Methods.* 2012; **56:**293-304.
67. Qi H, Liu C, Long L, Ren Y, Zhang S, Chang X, et al., *ACS nano*. 2016; **10(3):**3323-3333.
68. Seow Y, Wood MJ. *Mol.Ther.* 2009; 17:767–777.
69. Camussi G, Quesenberry PJ. *Microvesicles.* 2013; **1:**1-14.
70. Jang SC, Kim OY, Yoon CM, Choi DS, Roh TY, Park J, et al. *ACS Nano*. 2013; **7:**7698-7710.
71. To H, Liu C, Long L, Ren Y, Zhang S, Chang X, et al. *ACS Nano*, 2016; **10:**3323-3333.
72. Hadla M, Palazzolo S, Corona G, Caligiuri I, Canzonieri V, Toffoli G, et al., *Nanomedicine*. 2016; **11:**2431-2441.
73. Chang FR, Hayashi K, Chen IH, Liaw CC, Bastow KF, Nakanishi Y, et al. *J. Nat. Prod*. 2003; **66:**1416-1420.
74. Aqil F, Kausar H, Agrawal AK, Jeyabalan J, Kyakulaga AH, Munagala R, et al. *Exp. Mol. Pathol.* 2016; **101:**12-21.
75. Wang YF, Liu L, Xue X, Liang XJ. *F1000Research*, 2017; **6:**681.
76. Escudier B, Dorval T, Chaput N, Andre F, Caby MP, Novault S, et al. *J. Transl. Med.* 2005; **3:**10.
77. Study investigating the ability of plant Exosomes to deliver curcumin to normal and colon cancer tissue. (n.d.). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01294072.
78. Wang J, Hendrix A, Hernot S, Lemaire M, De Bruyne E, Van Valckenborgh E, et al. *Blood*, 2014; **124:**555-566.
79. TabatabaeiMirakabad FS, Nejati-Koshki K, Akbarzadeh A, Yamchi MR, Milani M, Zarghami N. *Asian Pac J Cancer Prev*, 2014; **15(2):**517-535.
80. Labhasetwar V, Song C, Levy RJ. Nanoparticle drug delivery system for restenosis.*Advanc Drug Deliv Rev*, 1997; **24:**63-85.
81. Mahapatro A, Singh J. *Nanobiotechnol,* 2011; **9:**55.
82. Lü JM, Wang X, Marin-Muller C, et al., *Expert Rev MolDiagn*, 2009; **9:**325-341.
83. Panyam J, Labhasetwar V. *Adv Drug Deliv Rev*, 2012, **55:**29-47.
84. Acharya S, Sahoo SK. *Adv Drug Deliv Rev*, 2011; **63:**170-183.
85. Van der Meel R, Vehmeijer LJC, Kok RJ, Storm G, van Gaal EVB. *Adv. Drug Delivery Rev*. 2013; **65:**1284-1298.
86. Witzigmann D, Hak S, van der Meel R. *J. Controlled Release*, 2018; **290:**138-140.
87. Hua S, de Matos MBC, Metselaar JM, Storm G. *Front. Pharmacol.* 2018; **9:**790.
88. Duro-Castano A, Gallon E, Decker C, Vicent MJ. *Adv. Drug Delivery Rev.* 2017; **119:**101-119.
89. Wu PH, Onodera Y, Ichikawa Y, Rankin E, Giaccia A, Watanabe Y, Qian W, Hashimoto T, Shirato H, Nam JM. *Int. J. Nanomed*. 2017; **12:**5069-5085.
90. Ng QKT, Olariu CI, Yaffee M, Taelman VF, Marincek N, Krause T, Meier L, Walter MA. *Biomaterials* 2014; **35:**7050-7057.
91. Danhier F, Le Breton A, Préat V. *Mol. Pharm.*, 2012; **9(11):**2961-2973.
92. Dubey PK, Mishra V, Jain S, Mahor S, Vyas SP. *J. Drug Target*. 2004; **12:**257-264.
93. Schiffelers, RM, Koning GA, ten Hagen TL, Fens MHA, Schraa AJ, Janssen APC, Kok RJ, Molema G, Storm G. *J. Controlled Release*, 2003;**91:**115-122.
94. Koning G A, Schiffelers R M, Wauben MHM, Kok R J, Mastrobattista E, Molema G, et al., *Arthritis Rheum.* 2006; **54:**1198-1208.
95. Cheever MA, Higano CS. *Clin Cancer Res.* 2011; **17:**3520-3526.
96. He J, Li C, Ding L, Huang Y, Yin X, Zhang J, Zhang J, et al., *Adv. Mater.* 2013., 2019; **31(40):**1902409.
97. Kelderhouse LE, Chelvam V, Wayua C, Mahalingam S, Poh S, Kularatne SA, et. al., *Bioconjugate Chem*. 2013; **24:**1075-1080.
98. Hedayatnasab Z, Abnisa F, Daud WM. *Mater. Des*, 2017; **123:**174-196
99. Makridis A, Topouridou K, Tziomaki M, Sakellari D, Simeonidis K, Angelakeris M. *J. Mater. Chem. B*, 2014; **2:**28390–8398.

100. Han H, Hou Y, Chen X, Zhang P, Kang M, Jin Q, et al. *J. Am. Chem. Soc*. 2020; **142(10):**4944-4954.
101. Hosu O, Tertis M, Cristea C. *Magnetochemistry*, 2019; **5:**55.
102. Bremnes RM, Camps C, Sirera R. *Lung Cancer*, 2006; **51:**143-158.
103. Farhat FS, Tfayli A, Fakhruddin N, Mahfouz R, Otrock ZK, Alameddine RS, et. al., *Crit Rev OncolHematol*. 2012; **84:**149-160.
104. Gupta SC, Patchva S, Aggarwal BB. *AAPS J.* 2013; **15:**195-218.
105. Nanosponge drug delivery system more effective than direct injection. (2010, June 1). Vanderbilt University. Available from:https://news.vanderbilt.edu/2010/06/01/nanosponge-drug-delivery-system-more-effective-than-direct-injection-116839/.
106. Nano Robots Walk Inside Blood When Hit With Lasers. (2020, August 31). Available from:https://www.forbes.com/sites/kelseyatherton/2020/08/31/nano-robots-walk-inside-blood-when-hit-with-lasers/#12cb24251010.