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NANOTECHNOLOGY IN CANCER TREATMENT: REVIEW OF RESEARCH, CHALLENGES, MERITS AND FUTURE SCOPE.

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Abstract: The cancer therapies used today mainly involve damage to normal tissues. However**,** with the advancement in nanotechnology new methods of delivering drugs targeted at the cancer cells has become possible. Nanomaterials are also being used to develop new therapeutics which could enhance cancer treatment. This report focuses on review of some techniques used to deliver drug at targeted sites using nano carriers, the barriers and challenges involved**,** and the results obtained by this approach.

Index Terms **– Nanotechnology, Cancer, Nanoparticles. Nanopolymers, targeted drug delivery**

I. INTRODUCTION

The current techniques of fighting cancer run the risk of not eradicating the cancer completely or damaging healthy cells. The three common techniques are Chemotherapy, radiation, and surgery. With the advancements of Nanotechnology, cancer can be completely fought and destroyed with minimum invasion and targeted drug delivery. Nano-sized molecular tools capable of distinguishing between malignant and non-malignant cells as well as delivering drugs at the target site are being developed. The use of tumor necrosis factor alpha (TNF) for targeted chemotherapy is one such treatment under development which uses Nanoparticles to destroy cancer tumors. Another targeted chemotherapy treatment under development uses polyethylene glycol (PEG) polymers to prevent non-specific binding of nanoparticle (NP) surfaces to blood components and reduce their rapid uptake. Application of Nanoparticle in cancer treatment extends beyond targeted drug delivery to the development of new therapeutics which might help in fighting cancer. Nanoparticles are small in comparison to the human cell but large enough to encapsulate various molecules that have cancer treating abilities like pDOX.
However, there are various biological, immunological, transitional, and economical barriers in the use of the advancements in Nanotechnology for cancer treatment. The study about the challenges faced integrated with the technologies being developed would provide new insights on cancer treatment and could go a long way in eradicating it completely.

II. METHODS AND TECHNIQUES

2.1 Polymeric nanoparticles:

Nanomaterials have found their way in medicine in the past few decades. The role of nanotechnology in targeted drug delivery and cancer treatment has proved to be an especially important find. The nano carriers coated with PEG polymers were found to prevent binding of nanoparticles to blood components and hence increase their circulation time. The image below shows a timeline for the development of several distinct nano particles, which have either been approved for human use or are undergoing clinical trials.

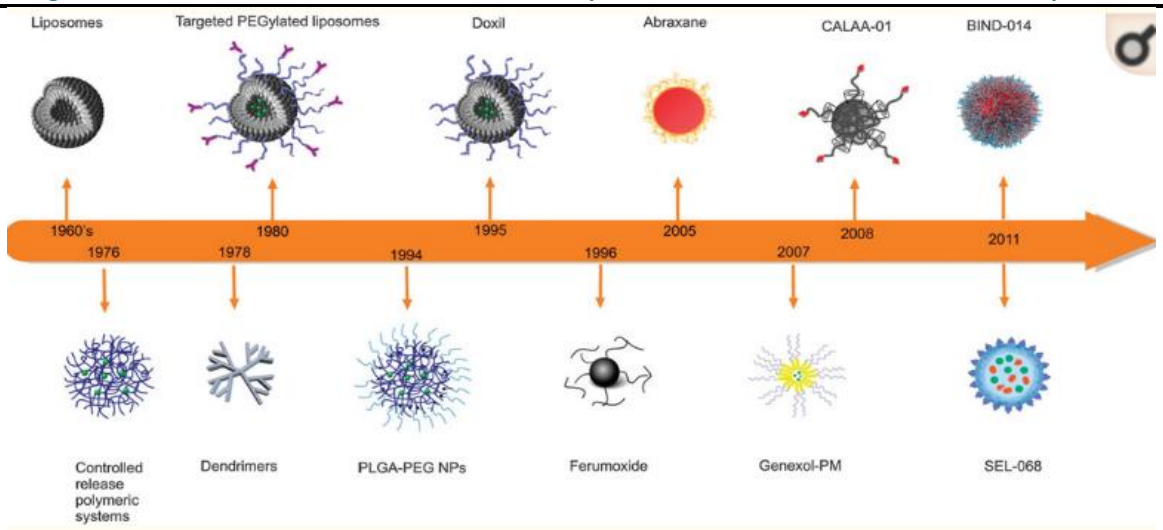


Fig1: Timeline of clinical stage nanomedicine

The first generation clinically approved NP drug delivery technologies (liposomes, micelles, proteins etc.) lacked controlled release and active targeting properties and were able to generally improve the safety and efficacy of the active drugs they carried. A higher tumor does accumulation of DOX was possible as DOXIL altered the pharmacokinetics (PK) and biodistribution (BD) leading to longer circulation half-life. This enhancement was since the cardiotoxicity associated with the free drug (Dox) was reduced and efficacy was demonstrated in taxane/platinum-resistant ovarian cancers. They usually lack controlled release properties that can control the kinetics of drug exposure at the target tissue. Liposomes are also comparatively less stable in comparison. If the NP platform can predictably alter the BD, PK, and tissue exposure kinetics only then will the NP platform be said to have exponentially improve drug pharmaceutical and pharmacological properties. The combination of one or more drugs with controlled release polymeric biomaterials for tunable drug exposure, and molecular targeting for differential delivery has the potential to create novel therapeutic NPs for a range of medical applications. Polymeric NPs have the capability to:

- release drugs at an experimentally predetermined rate over a prolonged period,
- release drugs preferentially at target sites with the possibility of controlled release rates,
- maintain drug concentrations within therapeutically appropriate ranges in circulation and within tissues and.

The Polymeric NPs can encapsulate the drug and releasing them in a regulated manner via diffusion through the polymeric matrix or through differential surface and bulk erosion rates. The having targeting ligands on NPs can increase their uptake and active agents, thus improving therapeutic outcomes. Further, the therapeutic efficacy can be maximized by overcoming drug resistance mediated by multidrug resistance (MDR) proteins using targeted polymeric NPs.

Controlled release systems generally refer to technologies or biomaterials that can be engineered to release drugs at predetermined and/or tunable rates, or in response to external stimuli and triggers. Using well-established techniques to manipulate the physicochemical, synthetic, biocompatibility, and degradation properties make Polymeric materials important control release systems. Poly-d,l-lactide-co-glycolide, polyglutamic acid, polycaprolactone, polylactic acid, and polyamino acids are the most commonly used targeted drug release polymers today.

2.2 Passive and Active targeting:

Nanoparticle targeting is mainly done by one of the 2 approaches: passive targeting, active targeting. Passive targeting refers to the accumulation of Nanoparticles at active sites by the inherent biophysiochemical properties of the NP (size, shape, charge, flexibility). NPs with surface modification to incorporate affinity ligands which are specific to disease tissues and cells to target specific cancer cells is termed active targeting. These NPs differentially bind to target molecules because of the binding properties of the ligands on the NP surface.

All clinically validated therapeutic and imaging NPs are currently passively targeted nanomedicines. Tumor tissue is highly heterogeneous and is perfused by an aberrant and leaky microvasculature. Indeed, tumor microvasculature has been shown to be characterized by excessive branching, chaotic structures, enlarged inter-endothelial gaps with associated break-down of tight junctions between endothelial cells, and a disrupted basement membrane. The gaps between endothelial cells cause the particulate material from the surrounding vessels to leak into the tumor, however the size cut-off varies based on type of tumor cell. Extravasation and permeability of NPs up to 400 nm has been observed through these gaps. Most passively targeted NPs possess a surface coated with PEG polymer for biocompatibility; however, this highly hydrophilic surface does not result in optimal endocytic uptake by cancer cells within the tumor. This problem leads to hamper efficient drug delivery in tumors as passively targeted NPs end up releasing their therapeutic payload into the tumor milieu rather than within cancer cells. Extracellular drug release is inefficient at maintaining a high tumor drug concentration over an extended period for drugs that are not readily retained in tumors or cancer cells. This can become even more complicated by using NP systems that lack controlled drug release properties. Having long circulating half-lives will provide more opportunities for the NPs in systemic circulation into the disordered and permeable regions of tumor and thus help to achieve effective EPR mediated targeting.

Active targeting uses ligand affinity to bind the NPs to antigens, differentially overexpressed on the plasma membrane of diseased cells or to the extracellular proteins that are overexpressed in the damaged tissue. Applications where drug release is either intracellular or extracellular can make use of actively targeted NPs. Targeted NPs are most efficient in delivering therapies that act on intracellular sites of action. The biodistribution is decided by the colloidal properties of NPs, while the cellular uptake at targeted site is enhanced by the targeting ligand. NP internalization into cells can significantly enhance treatment efficacy which can be obtained by a variety of different targeting ligands.

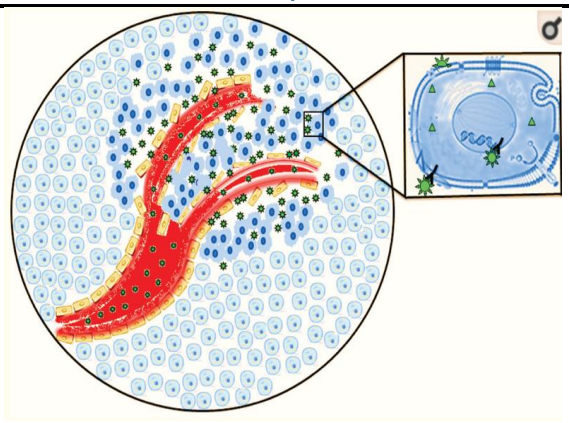


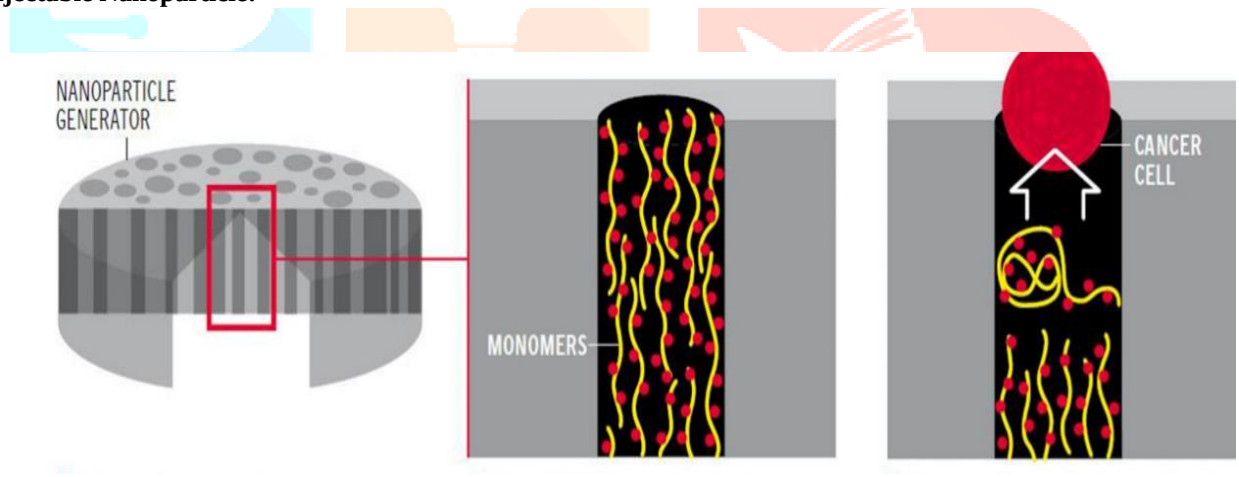
Fig 2: Depiction of Nanoparticle targeting of malignant cells through both active and passive targeting.

2.3 Nanoparticles for imaging:

NPs may be incredibly useful for imaging applications because of the chemical modifications that can be used to amplify imaging sensitivity and the high surface area-to-volume ratio. The avoidance of macrophage uptake is important for NPs, however the ability of NPs to undergo macrophage-mediated phagocytosis can prove to be beneficial for the application of NPs in imaging. Superparamagnetic iron oxide NPs (IONPs) have been used for MR Thermal ablative approaches to cancer imaging of lymph nodes following macrophage uptake, which may be beneficial for detecting metastatic disease.

NPs can be used for treatment as well as imaging applications for cancer treatment. The TiO2 NPs area good example as they can be used to enhance CT scans contrast and can also be used as sensitizers for photodynamic therapy. Magnetic NPs can be used for hyperthermia applications and improved MR imaging for cancer detection and treatment. The IONPs are directed to malignant cells for both enhancing contrast as well as hyperthermia-based therapy. Paclitaxel, methotrexate, or other anticancer drugs for therapeutic and diagnostic applications can be conjugated with IONPs. Potential therapeutic and diagnostic applications also make use of modified Gold NPs, quantum dots, and cNTs.

2.4 Injectable Nanoparticle:



- *The anti-cancer drug doxorubicin (pDOX) is held within an injectable nanoparticle generator (iNPG), a nanoporous silicon material that naturally degrades in the body after it is injected.*
- *The iNPG is composed of a plymer, a biodegradable substance that can absorb sub microscopic particles. The polymer is made up of strands or "monomers" that contain the ant-cancer drug pDOX*
- *Once released, these single strands curl up into nanoparticles that get taken up by the cancer cells. Once inside the cell, they cross into the inner nucleus where the drug is released, and the cell dies.*

Fig 3. The efficacy of cancer drugs is hindered as only a small fraction of the intended medicine accumulates in tumors. An injectable nanoparticle generator (iNPG) can be used overcomes multiple biological barriers to cancer drug delivery.

Nanoporous silicon particles encapsulating pDOX which can self-assemble into nanoparticles contribute to iNPG-pDox. Due to favorable vascular dynamics and natural tropism iNPG-pDox localizes to tumor tissues. pDox molecules then assemble into nanoparticles and are released in a sustained manner. pDox NP undergo trafficking to perinuclear regions of the cell on internalization in the tumor cells. A pH-sensitive linker connecting the polymer to Dox is split in the acidic environment created by the endosomes. This causes high intracellular concentrations of Dox in the targeted cell which is beyond the reach of cell surface drug methods.

pDox is made by covalently conjugating Dox to glutamic acid side chains of polyL-glutamic acid. This is done via a pH-sensitive hydrazone linker. 40–80 nm-sized pores of discoidal silicon carrier particles measuring 2.5 µm in diameter were used to load pDox. These had geometries and dimensions which had previously shown to optimize the concentration of NPs in metastases. Confocal microscopy was used to confirm pDox had been loading in to nanopores of the silicon-carrier. According to the

research, pDox accounted for 25% of the total weight of iNPG-pDox. Upon loading, pDox distributed homogeneously throughout the nanopores across all levels of the construct from lower to top planes. Cross-sectional examination using confocal microscopy of iNPG-pDox , focusing on the region of the particles showed the release of pDox NPs from the silicon carrier. Thus, this is one of the most important recent developments in the use of NPs in the treatment of cancer and the researchers have demonstrated a novel method to use pDOX in silicon structures to combat cancer.

III. BARRIERS FOR NANOMEDICINE:

The success of NPs clinically is hindered by: (1) bio-barriers in route to the affected cell in the tissue (2) the effect of the NPs at the disease site, and (3) toxicity and safety concerns.

NPs activate immunity responses which is a group of more than 30 soluble and membrane-bound proteins that function to neutralize invading microorganisms. The activation by nanosurfaces cause the uncontrolled release of highly pro-inflammatory mediators such as anaphylatoxins which may induce adverse reactions in some individuals. Whereas opsonization of nanoparticles may cause them to be absorbed by phagocytic cells. Avoidance of complement activation by nanomedicines should be ensured even though a complement activation related pseudo allergy (CARPA) induced by NPs is a concern

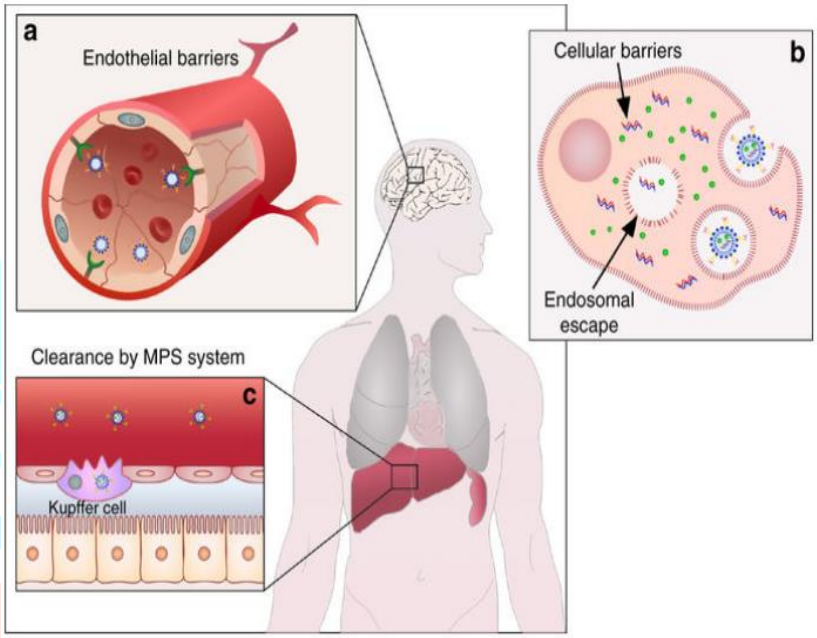


Fig 4. Main physiological barriers faced by passive and active targeted NCs. ***a*** *NCs face endothelial barriers;* ***b*** *Uptake of NCs by the target cells and their escape are the major cellular barriers.* ***c*** *Mononuclear phagocytic system (MPS), which results in the clearance of systemically administered NCs*

With the aim to eliminate potential danger and to signal required immune response tissue-resident macrophages and peripheral blood leukocytes take up materials entering the body. For the nanocarriers to reach their targeted site, it is desirable to avoid premature clearance of nanocarriers/nanodrugs by the MPS. This is especially important in the liver and spleen. The leukocytes can act as transporters and hence NPs uptake by leukocytes could be beneficial. The interaction of nanocarriers with leukocytes can have some unaccounted effects on tumor progression such as, they can trigger inflammatory reactions or change the normal immune response.

Designing supramolecular carriers that can stick to the tumor endothelium and release nanomedicine over time is one solution to overcome the tumor endothelium barrier. Various studies demonstrate that passive targeting is useful but does not cause drastic improvements in cancer therapeutics. The high tumor interstitial fluid pressure and the effect of dense extracellular matrix in reducing convection flow are among the main reasons for the inefficiency of passive targeting as these reduce the intratumoral distribution of the NPs.

Macrophages are recruited to the tumor as an immune reaction to a damage event. Hence, they represent a prominent cell population in the micro-environment of many tumors. As macrophage infiltrate is abundant and is a sign of aggressive cancers, targeting tumor-associated macrophages cells could be a major advantage. The disparity between the reduced blood flow but increase in TAMs can be used as a strategy to localize therapeutics and imaging agents within the tumor.

For vascular transport the shape, size, mechanical stiffness, and surface properties of nanoparticles are very important factors for MPS avoidance. Nonspherical NPs have shown resistance to MPS sequestration more efficiently. Modulating the mechanical stiffness of nanoparticles is also an important way of avoiding MPS. For instance, soft nanoconstructs show longer circulation half-lives and lower accumulation in the liver, spleen, and lungs.

Financial, clinical, and safety are also various barriers faced in the development of nanomedicine for cancer treatment apart from biological barriers.

Three properties of nanomedicines need to be understood better:
(1) interaction of immune system with nanoparticles
(2) Role of EPR in the performance of nanopharmaceuticals and its effect on human cancer
(3) Amount of active drug that reaches the targeted cells.

The future of NPs in medicine may include the combination of NPs that can achieve targeted drug delivery while avoiding the MPS and help in the imaging and treatment of cancer. However, the future NPs medicines should also consider the effects on toxicity and safety when making a drug that can treat cancer. Thus, it is important to discuss the Merits and Demerits of the NPs in cancer treatment.

IV. Merits and limitations:

Nanotechnology is playing a vital role in cancer detection and treatment. NPs are small in comparison to cells and cellular organelles allowing them to interact with specific features of cells, thereby permitting tumor cell localization by active targeting. Passive targeting to tumor tissue via the EPR is also possible given the size regime of NPs. Thus, nano-sized materials have advantages for cancer treatment with distinct features relative to low molecular weight drugs.
Potential advantages of therapeutic NPs include:

1. Without the need to alter drug molecules NPs can improve the pharmaceutical and pharmacological properties of drugs
2. Increase efficiency in therapeutic targeted delivery of drugs in a tissue or cell specific manner,
3. NPs can supply drug through a range of biological barriers such as endothelial and epithelial barriers,
4. Delivering therapeutic drugs to intracellular sites
5. Delivering multiple types of therapeutics with different physicochemical properties,
6. Combining imaging and therapeutic agents for real time monitoring of drug action
7. Nanotechnology can make the diagnosis and treatment of cancer efficient, easy, and safe.
8. The number of effective therapeutic agents is exponentially increased.
9. Nanotechnology can enhance the absorption of drugs into tumors by protecting drugs from being degraded in the body before they reach their target.

One concern potentially limiting the applicability of some NPs for cancer treatment is the toxicity of nanomaterials that requires further investigation. Nonetheless, nanotechnology in cancer treatment will continue to be developed and will eventually result in improved treatment outcomes

Some of the disadvantages involved with the use of nanotechnology are:

1. As with any new technology, the safety of nanotechnology is continuously being tested. The unique tensile and magnetic properties, size, and high reactivity have raised concerns about their effects on the environment, health, and safety. The potential toxicity of a specific nanomaterial, carbon nanotubes, has been associated with tissue damage in animals. However, most data indicate that NPs are not uniquely toxic in nature.
2. Cancer targeting depends on surface chemistry and hence, any nanoparticle does not work. The solution is to use different nanoparticles for different types of cancer. However, cancer cells mutate rapidly and regularly and this can mean urgent changes in the structure of the nanoparticle for its efficacy. This might be very time consuming and extremely costly.
3. Nanoparticles that are biocompatible need to be designed to reduce the side effects and toxicity.

IV. Future scope and Conclusion:

The characteristics that are imperative for successful implementation of NPs as therapeutic agents like MPS avoidance and passive and active targeting have been developed. NP therapeutics have entered clinical trials and are displaying significant improvements in toxicity profiles and drug release as compared to conventional chemotherapy. One treatment under development by CytImmune involves targeted chemotherapy. They deliver a cancer killing agent- tumor necrosis factor alpha (TNF) to cancer tumors using NPs. On the other hand, Cerulean Pharma uses another target treatment using a nanoparticle called CRLX101.
A method using infrared light to trigger the release of two anticancer drugs to tumors is being developed by researchers at Massachusetts General Hospital. The effectiveness of nanoparticles that carry precise ratios of three different drugs on ovarian cancer cells is being researched at MIT. A method to fight pancreatic cancer using two different nanoparticles is being studied at UCLA. The two nanoparticles work in conjunction where the first NP removes material that block the entry of chemotherapy drugs on the exterior of the cancer cells, on the other hand the second nanoparticle carries the chemotherapy drug. The tests on mice showed positive results as the tumors shrunk faster than conventional medicines. Sustained drug delivery using hydrogel is another research that is being undertaken by researchers at the Institute of Bioengineering and Nanotechnology and IBM. Just one injection is required to inject the hydrogel under the skin which allows continuous drug release for weeks. UC San Diego researchers are working to encapsulate cancer killing drug in liposome NPs called Staurosporine, which was effective in suppressing tumors in mice without side effects.
This review paper thus provides insights on the developments in Nanotechnology and related techniques for cancer treatment. A few important research findings have been mentioned above. The merits and demerits of Nanotechnology in cancer treatment are also discussed briefly. Further, current research and potential for future scope of the topic is shown. It is important to understand that though nanotechnology shows great potential in cancer treatment more tests and research need to be caried out to obtain any substantial results. A systematic research incorporating the nanopolymers, targeted drug delivery, nanomedicine, and the barriers can help in understanding and finding solution to the problem.

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