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Original Article

Nanoparticle-Based Targeted Drug Delivery in Cancer Therapy: Mechanisms, Advances, and Challenges

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ABSTRACT

Cancer remains a major cause of death worldwide, mostly because of the shortcomings of conventional chemotherapy, including non-specific distribution, systemic toxicity, and multidrug resistance. Targeted drug delivery systems (TDDS) based on nanoparticles have become a viable approach to maximize treatment effectiveness while reducing side effects. Through active targeting via ligand–receptor interactions and passive targeting via the increased permeability and retention (EPR) effect, these systems facilitate better drug accumulation at tumor locations. Numerous nanocarriers have been thoroughly studied for cancer treatment, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and metallic nanoparticles. The main mechanisms behind nanoparticle-mediated targeting are outlined in this overview, along with recent developments in clinical translation and nanocarrier design and contemporary issues such biological obstacles, toxicity issues, and large-scale manufacturing. Future directions for enhancing the clinical applicability, safety, and effectiveness of cancer treatments based on nanoparticles are also discussed.

Keywords: Nanoparticles, Targeted Drug Delivery, Cancer Therapy, EPR Effect and Active Targeting, Theranostics and Multidrug Resistance

INTRODUCTION

The word "cancer" refers to a broad category of over 100 diseases that are defined by unchecked cell division and proliferation brought on by genetic and cellular changes. Every type of cancer has unique biological and molecular characteristics, and it can arise in almost every tissue in the body. Cancer starts when a cell divides continuously and uncontrollably instead of adhering to the normal regulatory systems that govern proliferation. Hippocrates used the Greek word "Karkinoma," which was ultimately translated into the Latin word "cancer," to describe the disease more than 2,300 years ago. [1,2] The incidence of cancer is still rising, making it the second most common cause of death globally. About 1,665,540 new instances of cancer were diagnosed in the US in 2014 alone, and 585,720 fatalities were recorded. Prostate, lung, colon, and bladder cancers are the most common cancers in males, whereas breast, lung, colon, uterine, and thyroid cancers are the most common in women. The most common malignancies in children are lymphatic, brain, and hematological. The illness arises from a series of genetic mutations that change regular cellular processes, frequently brought on by chemical and environmental influences. [3] The intricate and varied nature of cancer presents considerable difficulties in achieving precise diagnoses and effective treatments. Traditional chemotherapy is still a fundamental aspect of cancer treatment; however, it does not differentiate well, as cancer cells have many biological traits in common with normal cells. Consequently, chemotherapy can harm healthy tissues, resulting in significant side effects and reduced treatment effectiveness. To address these restrictions, targeted drug delivery systems (DDS) have arisen as a hopeful treatment approach. Targeted DDS facilitate the accurate delivery of therapeutic agents straight to cancer cells, reducing systemic toxicity. These systems improve treatment effectiveness by utilizing particular cellular and molecular processes, such as inducing cell cycle arrest, promoting apoptosis, inhibiting proliferation, and disrupting metabolic reprogramming. Moreover, focusing on and altering the tumor microenvironment (TM) has emerged as a significant complementary

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approach, enabling treatments to operate more efficiently within the intricate tumor setting.

In contrast to traditional chemotherapy, targeted therapies focus on specifically targeting cancerous cells while preserving healthy tissues through unique molecular mechanisms [4,5] Nanotechnology has greatly improved the creation of targeted drug delivery systems. It entails the deliberate design of materials at the nanoscale (1–100 nm), allowing for the development of nanosystems with improved or unique functional characteristics. Nanoparticles, created via molecular-level fabrication, exhibit distinct physicochemical properties including a large surface-area-to-volume ratio, enhanced reactivity, structural integrity, ability to modify surfaces, and potential for self-assembly. These characteristics render them especially appropriate for cancer treatment. Their diminutive size permits infiltration through biological barriers, and their customizable surfaces allow for the attachment of targeting ligands, promoting targeted drug accumulation within tumor tissues. [6]

3. Types of Nanoparticles Used in Targeted Drug Delivery

3.1 Liposomes:

Liposomes are round, self-contained entities created by self-organizing lipid bilayers that encapsulate a central aqueous core. This lipid-centered method is becoming more common for administering different cancer medications using various preparation techniques. Significant instances comprise anthracyclines such as doxorubicin (available as Doxil or Myocet) for Kaposi's sarcoma and daunorubicin (DaunoXome) for metastatic breast cancer. These liposomes provide a significant benefit compared to other nanocarriers by improving the selectivity, bioavailability, and biocompatibility of anticancer medications. Researchers use specific types like pH-sensitive liposomes and immunoliposomes to accomplish this. Liposomes coated with polyethylene glycol (PEG) are notable for their exceptional drug-trapping capability; they selectively attach to tumor cells in targeted scenarios, facilitating effective absorption and destruction of the cells [7,8]

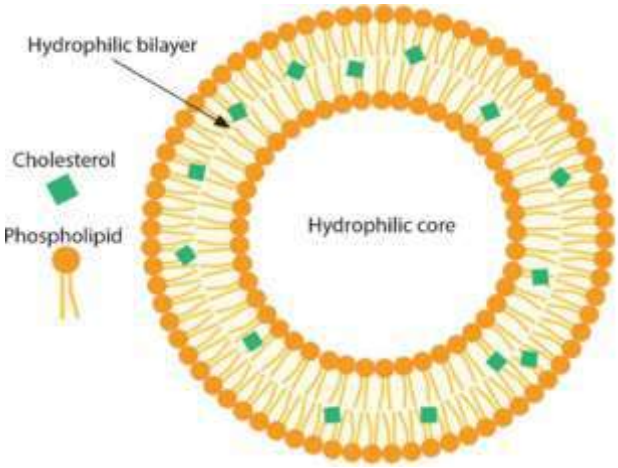

Fig:1 Liposome structure with hydrophilic core and hydrophobic bilayer. [9]

3.2 Polymeric Nanoparticles:

Researchers are currently studying biodegradable and biocompatible polymeric nanoparticles as efficient carriers for targeted drug delivery. Different varieties, including those derived from polymers like PLGA, PLA, and chitosan, have been thoroughly assessed in both preclinical and clinical studies, demonstrating their safety and efficacy. These nanoparticles enable controlled drug release and can be altered on the surface for specific delivery. Polymers derived from natural sources, such as albumin, chitosan, and heparin, have historically served as carriers for medications, oligonucleotides, DNA, and proteins. A prime example is paclitaxel attached to albumin at the nanometer scale, which was recently employed for treating metastatic breast cancer, utilizing serum albumin as its transport mechanism. The hydrophobic core of these nanoparticles contains substantial drug loads, while the hydrophilic surface provides steric

protection. Furthermore, they are capable of encapsulating both micro- and macromolecules, whether hydrophilic or hydrophobic, such as proteins and nucleic acids, increasing their therapeutic potential. [8,9,10]

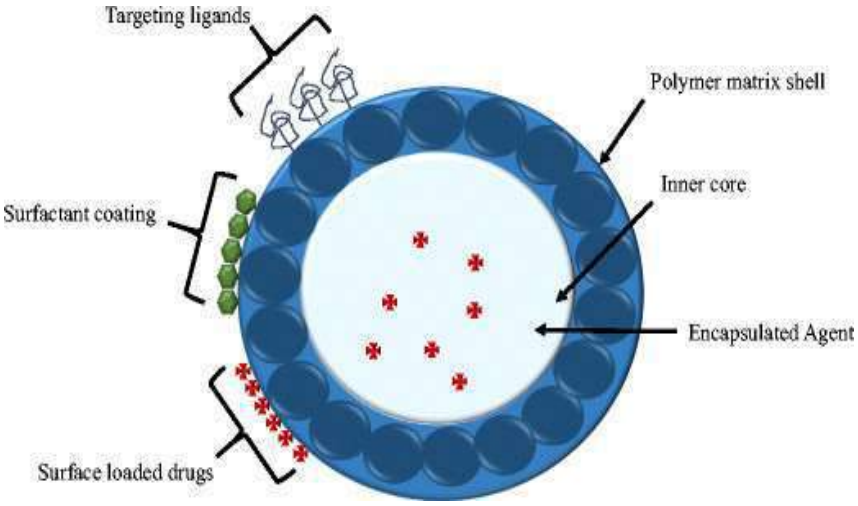

Fig:2 Basic structure of polymeric nanoparticles.

3.3 Dendrimers:

Dendrimers are a novel category of nanoparticles created particularly as carriers for delivering drugs in cancer treatment. These clearly structured, branched spherical macromolecules are created via a sequential and repetitive process, leading to an accurate design. Dendrimers fundamentally consist of a central core encased in concentric layers of branched repeating units, possessing functional groups on the outer layer that allow for diverse modifications. Typically obtained from synthetic or natural components like nucleotides, sugars, and amino acids, these nanoparticles enable simple conjugation of therapeutics onto their surface. Moreover, drugs can be incorporated into the cavities or "spaces" inside their cores through hydrophobic forces, hydrogen bonding, or chemical linkage, increasing payload capacity. The clearly defined surface groups enhance conjugation with a variety of biomolecules, such as antibodies, aptamers, nucleic acids, targeting ligands, imaging probes, drugs, and biosensing agents. In addition to direct drug delivery, dendrimers act as efficient surface-functionalizing or coating agents for dendrimer-based inorganic nanoparticles, broadening their applicability in diverse biomedical applications for cancer therapy. [11,10]

3.4 Solid Lipid Nanoparticles (SLNs):

Solid lipid nanoparticles (SLNs) have become a potential nanocarrier system for cancer therapy. These colloidal carriers are made of solid lipids (stable at ambient temperature) with particle sizes between 50 to 500 nm, acting as a viable substitute for conventional systems such as oil-in-water emulsions, liposomes, and polymeric micro- or nanoparticles. SLNs draw interest because of their round shape, tiny nano-scale diameter, large specific surface area, and advantageous zeta potential. They consist of a core of crystallized lipids blended with emulsifiers and surfactants that facilitate effective drug encapsulation. SLNs are superior in regulated and specific drug delivery by encapsulating active substances within their solid lipid framework. A stabilizing layer created by a single surfactant or a combination of surfactants guarantees reduced particle sizes and improved storage stability. In contrast to traditional colloidal carriers, SLNs provide reduced toxicity, increased surface area for drug incorporation, extended-release profiles, enhanced cellular absorption, and better drug solubility and bioavailability. [12,13]

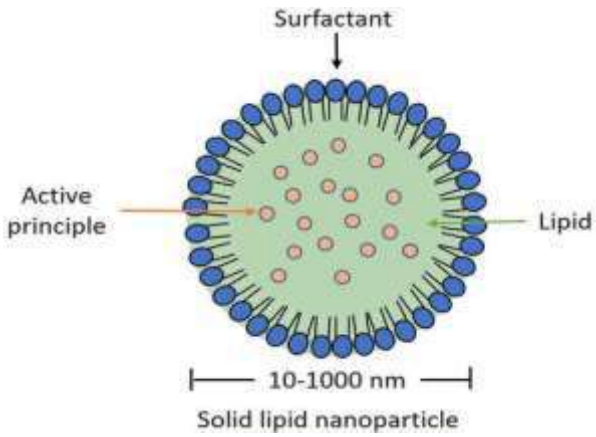

Fig:3 General diagram of Solid lipid nanoparticles [14]

3.5 Metallic Nanoparticles:

Metallic nanoparticles such as AuNPs, AgNPs, and IONPs (e.g., SPIONs) facilitate targeted drug delivery due to specific characteristics and mechanisms designed for cancer treatment. Gold nanoparticles (AuNPs) are highly effective in cancer targeting due to their adjustable plasmon resonance properties, which enhance imaging capabilities and enable efficient ligand functionalization. (e.g., folate/HER2). AgNPs provide antimicrobial and anticancer benefits via ROS production. IONPs facilitate magnetic targeting, improving EPR accumulation through external fields. [15]

Targeting Mechanisms:

Passive EPR and active receptor targeting (e.g., EGFR using peptides/aptamers); IONPs utilize magnetic gradients and pH-sensitive release (~6.5 pH) to reduce off-target effects.

Cancer Applications:

AuNPs/IONPs provide doxorubicin with 5-10 times greater tumor accumulation compared to the free drug in breast/prostate models, along with photothermal synergy.

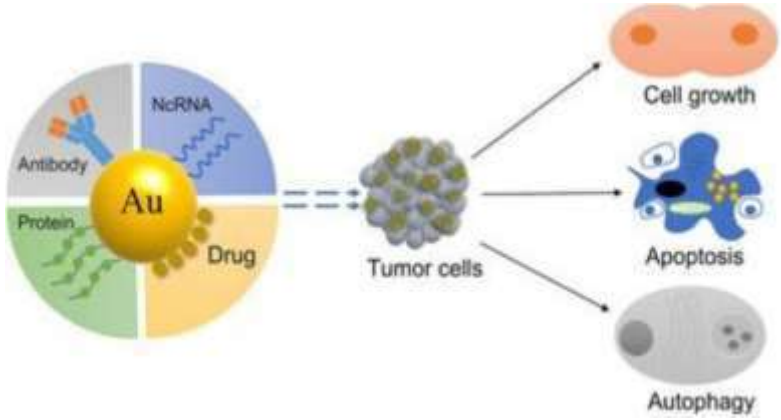

Fig:4 AuNPs delivery for cancer treatment [15]

4. Mechanisms of Targeted Delivery:

4.1 Passive Targeting — EPR Effect:

The Enhanced Permeability and Retention (EPR) effect supports passive targeting of tumors, allowing for the preferential gathering of therapeutic nanoparticles (generally 50–200 nm) in solid tumors because of their faulty, disordered blood vessels and impaired lymphatic drainage. This occurrence was first clinically confirmed approximately 30 years ago with the authorization of DOXIL, a PEGylated liposomal formulation of doxorubicin. Nanocarriers take advantage of these tumor pathophysiological traits mainly through a diffusion-driven process to enhance selective intratumoral buildup, delivering the drug or drug-carrier complex to the target location via physicochemical and pharmacological influences.

Nonetheless, the effectiveness of EPR depends on several factors, such as circulation duration, dimensions, morphology, surface characteristics, and the capacity to overcome biological obstacles, with accumulation differing greatly among patients and tumor classifications.

Key factors influencing EPR-based delivery include:

- **Size**: Nanoparticles measuring 40–400 nm enhances prolonged circulation, tumor escape, and retention, while reducing renal clearance; sizes between 50–200 nm are optimal for balancing these factors.
- **Shape and morphology**: Sturdy, spherical particles sized between 50–200 nm show the longest circulation durations, avoiding capture by the liver and spleen while being too large for swift renal elimination.
- **Surface properties**: PEGylation and various alterations prolong half-life, decrease opsonization, and improve permeability across tumor endothelium. [16,17]

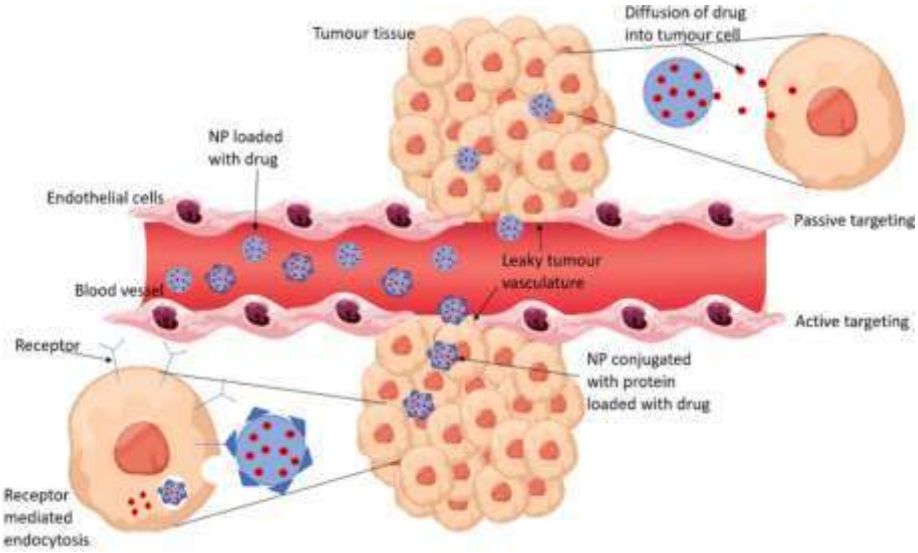

Fig:5 EPR effect illustration showing accumulation in tumor tissue. [18]

4.2 Active Targeting:

In contrast to passive targeting, active targeting depends on distinct biological interactions between ligands present on the nanoparticle (NP) surface and receptors on the target cell. A broad array of biological ligands such as monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates has been recognized and investigated to support this process. These ligands specifically attach to receptors that are overexpressed on target cells, including the transferrin receptor, folate receptor, glycoproteins, and epidermal growth factor receptor (EGFR), which improves the cellular absorption of drug-loaded nanoparticles through receptor-mediated endocytosis. NPs can be modified with these ligands in two primary methods: via chemical conjugation or physical adsorption after NP creation, or by attaching them to NP elements (such as polymers) before assembly. This focused strategy enhances drug retention in cancer cells, improves treatment effectiveness, and reduces unintended side effects, thereby making it particularly ideal for administering macromolecular therapies such as proteins and siRNAs. Various NP formulations featuring these ligands have been created to realize these advantages. [19,20,21]

Tabel: Active targeting offers enhanced accuracy compared to passive simplicity for macromolecules such as siRNAs.

Aspect	Passive Targeting	Active Targeting
Mechanism	EPR phenomenon (leakage due to size)	Ligand-receptor interaction + endocytosis
Specificity	Reduced (influenced by the tumor microenvironment)	Elevated (cell-type specific)
NP Design	Stealth coating (e.g., PEG)	Surface ligands (antibodies, peptides)
Efficacy	~0.6-0.9% ID/g tumor; variable by patient	Often 2-5x higher uptake; reduces off-target.

4.3 Stimuli-Responsive Release:

Stimuli-responsive nanocarriers have been systematically created and engineered by utilizing unique pathological characteristics in healthy tissues, intracellular areas, and the tumor microenvironment to enhance drug delivery precision, effectiveness, and biological function. These sophisticated systems deliver therapeutic agents in reaction to particular internal (endogenous) stimuli such as pH variations, temperature fluctuations, enzymes, or redox states, as well as external (exogenous) influences like light, magnetic fields, or ultrasound. The inherent characteristics of unhealthy tissues significantly contrast with those of normal cells, facilitating the development of endostimuli-responsive nanocarriers for accurate delivery and targeting of drug payloads. In the meantime, external stimuli serve as energy sources that effectively activate drug release from nanocarriers at specific locations. These systems provide regulated, targeted release that improves treatment results, reduces side effects, increases targeting precision by activating exclusively at disease locations, stops early leakage, and boosts solubility and stability, particularly for hydrophobic medications. [22,23,24]

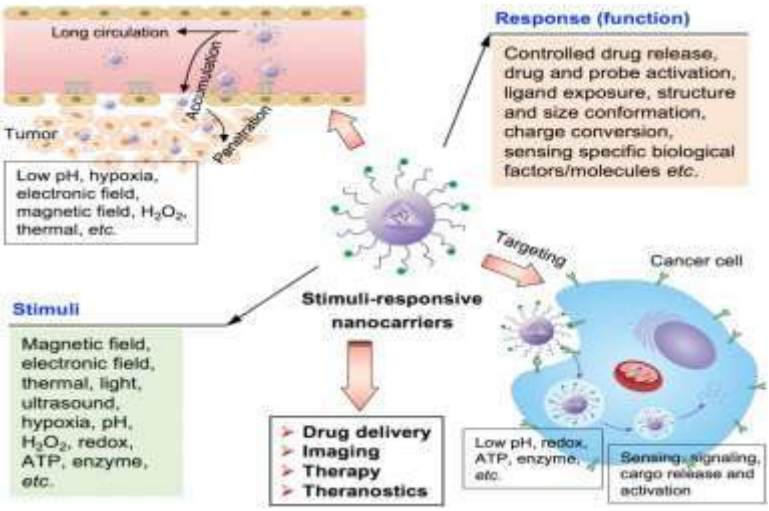

Fig:7 Stimuli-responsive nanocarriers utilize pathological variations in tissues, compartments, and tumor microenvironments for targeted drug delivery [22]

5. Advantages of Nanoparticle-Based Targeted Delivery:

- **Enhanced Tumor Accumulation**: Nanoparticles take advantage of the enhanced permeability and retention (EPR) effect, enabling passive accumulation in the defective blood vessels of tumors while avoiding healthy tissues. Ligand modification allows for active targeting of cancer cell receptors, increasing drug delivery at the location.
- **Reduced Systemic Toxicity:** Site-targeted delivery restricts cytotoxic medications to tumors, reducing exposure to essential organs and decreasing side effects such as nausea or cardiotoxicity. This enables increased effective doses while enhancing patient tolerance.
- **Controlled and sustained release:** Stimuli-responsive nanoparticles (triggered by pH, temperature, or enzymes) enable sustained, on-demand drug release, extending circulation and

enhancing pharmacokinetics compared to bolus dosing. [25]

- **Overcoming multidrug resistance:** Nanoparticles evade efflux pumps such as P-glycoprotein through direct cytosolic entry or by co-delivering resistance inhibitors, reinstating sensitivity in resistant tumors. [26]

- **Possibility of theranostics:** Multifunctional nanoparticles merge treatment with diagnostics (such as imaging agents), allowing for real-time observation of treatment outcomes and individualized dosing. [27]

6. Challenges and Limitations:

1. **Biological barriers**: Nanoparticles undergo swift immune clearance through opsonization and RES uptake, restricting tumor accumulation even with approaches such as PEGylation. The variability in tumor microenvironments undermines the consistency of the EPR effect. [28,29]

2. **Toxicity and safety concerns:** Metal and polymeric nanoparticles pose risks of cytotoxicity, organ buildup, and inflammation, making long-term safety more complex. [30]

3. **Heterogeneity of tumor microenvironment:** Differences in vascular supply, pH levels, and oxygen availability result in inconsistent delivery among patients.

Tabel: Challenges, Causes, and Solutions in Nanoparticle-Based Cancer Drug Delivery

Challenge	Cause	Possible Solution
Biological Barriers	Quick immune removal through opsonization and RES absorption; anti-PEG antibodies shorten circulation duration.	Alternatives to PEGylation (e.g., zwitterionic surfaces); stealth polymers such as PMPC
Toxicity and Safety Concerns	Toxic effects from metals/polymers; accumulation in organs (liver/spleen); chronic inflammation.	Biodegradable substances (PLGA); surface modification for compatibility with biological systems. Compatibility with biological systems.
Tumor Heterogeneity	Differences in vascularization, pH levels, hypoxia, and extracellular matrix density hinder the EPR effect.	Ligands with active targeting capabilities (e.g., antibodies); nanoparticles that respond to stimuli

7. Recent Advances and Trends:

7.1 Theranostics:

- Metallic nanoparticles (gold, iron oxide) facilitate multimodal imaging and regulated drug release through stimuli such as pH or light, enhancing tumor-targeted "see-and-treat" features.
- Designs that respond to stimuli improve spatiotemporal specificity and decrease resistance. [31]

7.2 Multifunctional Nanocarriers:

- Surface-engineered systems combine targeting ligands, imaging agents, and therapeutics (e.g., liposomes with doxorubicin).
- All-in-one platforms address pharmacokinetics challenges for combined functions. [32]

7.3 Clinical Translation

- Systems such as Abraxane demonstrate enhanced trial success with superior safety and survival results; recent approvals indicate improved profiles.

CONCLUSION:

In conclusion, targeted drug delivery using nanoparticles has transformed cancer treatment by utilizing advanced mechanisms such as the EPR effect, specific ligand-receptor interactions, and stimuli-responsive release to provide accurate, effective therapy while minimizing systemic toxicity. Various nanocarriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and metallic nanoparticles, provide flexible platforms that improve tumor accumulation, tackle multidrug

resistance, and facilitate theranostic integration, as demonstrated by clinical achievements such as Doxil and Abraxane. Despite ongoing challenges like biological obstacles, toxicity issues, and tumor variability, recent progress in multifunctional designs, stealth coatings, and tailored stimuli-responsive systems indicates a promising direction for wider clinical application. Future interdisciplinary advancements in nanotechnology, combined with thorough preclinical validation and patient-stratified studies, are expected to address these challenges, ultimately enhancing survival rates and quality of life for cancer patients globally.

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