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Revolutionary Advances in Red Blood Cell-Based Nano carrier Drug Delivery Systems for Specific Tumor Therapy: Progresses, Challenges, and Research Directions

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Abstract

Red blood cell (RBC)-based nanocarrier drug delivery systems have emerged as a promising avenue for targeted tumor therapy, leveraging the natural biocompatibility, long circulation time, and unique targeting capabilities of RBCs. This review comprehensively examines recent revolutionary advances in the development of RBC-based nanocarriers, focusing on their design, functionalization, and therapeutic applications in specific tumor types. It discuss the progress made in enhancing drug loading capacity, optimizing release profiles, and achieving targeted delivery to tumor sites. However, several challenges remain, including the complex biophysical properties of RBCs, immunogenicity concerns, and the need for precise control over drug release mechanisms. Additionally, it highlights potential research directions that could address these challenges and improve the efficacy and safety of RBC-based nanocarriers in cancer therapy. By bridging the gap between nanotechnology and biomedicine, RBC-based drug delivery systems hold significant promise for advancing personalized cancer treatment strategies.

Keywords: Red blood cells; Nanocarrier systems; Drug delivery; Tumor therapy; Cancer treatment

Introduction

Fundamentals of Tumor Treatment

The application of nanotechnology in medicine represents a paradigm leap in the field, providing previously unheard-of chances to solve persistent problems with extraordinary accuracy and effectiveness. Through nanoscale material manipulation, scientists have opened up a wide range of applications, including personalized medicine, cancer treatment, drug delivery, and diagnostic imaging [1]. The rapid advancement of nanotechnology has created new opportunities for anticancer therapy, as malignant tumors are one of the primary diseases that cause death. In order to improve the curative effect and lessen toxic and side effects, researchers are currently working to promote the research and development of new nano-drugs and nano-drug carriers in an effort to address the biomedical challenges related to conventional anti-tumor medical methods [2]. Particulate drug carriers, also known as active targeting of particulates carrying physically entrapped pharmaceuticals, can transport drugs to target cells in vivo, increasing the treatment's therapeutic efficacy and minimizing systemic side effects. Due to the limited therapeutic index of the majority of anticancer medications, targeted drug delivery is urgently needed

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in medicine [3]. Tumor therapy is the primary application of this method. For cancer treatment, nanomedicines are being investigated in great detail. To enhance the balance between treatment efficacy and toxicity, nanomedicine formulations strive to deliver drug molecules more efficiently to diseased areas while also reducing their accumulation in healthy organs and tissues. Hundreds of formulations and more than 20 cancer medications are authorized for clinical usage [4].

The development of several novel drug-delivery systems for solid tumor targeting has been facilitated by technological developments in the fields of biomaterials, polymer chemistry, and drug-delivery techniques. Several research teams have investigated the potential of employing nanoparticle-based tumor-specific medication delivery systems. The accomplishments of several research concepts related to nanoparticulate drug delivery systems have been attempted to be highlighted in this review [5]. To treat cancer, nanomedicine frequently employs passive targeting techniques like the increased permeability and retention (EPR) effect. It was recently shown that the EPR effect causes tumors to absorb just a very small percentage (3%) of nanoparticles. The remaining 97% of the nanoparticles are absorbed through active targeting. which make actively targeted therapy necessary. Active targeting techniques that conjugate nanoparticles with specific biomolecules and antibodies are the focus of studies [6].

The Importance of Targeted Drug Delivery

In addition to enhancing a medicine's therapeutic potential, targeted drug delivery, or the controlled release of a drug at the intended location, also reduces the total dosage and undesirable side effects. Improvements in this area will significantly affect the treatment of illnesses and the standard of living for patients. The biggest opportunity and problem at the same time is targeted drug delivery, which calls for integrated techniques involving several disciplines, including physiology, molecular biology, pharmacology, and nanotechnology, in order to be translated into clinical settings [7]. With an emphasis on peptide-drug conjugates (PDCs), especially those found using combinatorial peptide libraries, we address the benefits of alternative drug carriers and when they should be used in conjunction with the acknowledged significance of targeted drug delivery systems for cancer therapy. It should be feasible to create a more logical method of applying targeted drug delivery techniques in various contexts and, eventually, to a wider range of more potent treatments for cancer patients by outlining the benefits and drawbacks of naked TMAs, ADCs, and PDCs [8]. The landscape of cancer treatment has evolved as a result of advances in precision medicine. Technologies that facilitate genomic sequencing, molecular profiling, and optimal drug creation to customize patient treatments are the driving forces behind precision medicine. While there have been some clinical triumphs with precision medicines, pharmacological problems such as toxicities and drug resistance have prevented the implementation of many promising treatments [9]. Recent years have seen an increase in interest in microbubbles as drug delivery vehicles, partly because of their desirable properties and partly because of the requirement for localized drug administration in a variety of applications. Microbubbles can be functionalized for targeted adhesion, are naturally small enough to allow transvascular transit, and can be acoustically driven, which makes it easier to detect ultrasound, produce bioeffects, and release the cargo in a controlled manner [10].

Thanks to advancements in drug delivery materials and techniques, it is now possible to modify a drug's pharmacological characteristics without sacrificing the intended impact on molecular targets. More specifically, they can help administer synergistic drug combinations and alter a drug's pharmacokinetics, stability, absorption, and exposure to tumors and healthy tissues. In addition to highlighting current advancements in drug transport and precision therapies, this review proposes potential tactics to raise the therapeutic index of cancer medications and, as a result, clinical outcomes [11]. Nanotechnology in the health sciences is being effectively utilized by the rapidly expanding field of nanomedicine. Enhanced solubility, higher efficacy, reduced toxicity, increased tissue selectivity, and the ability to traverse the blood-brain barrier are just a few of the many benefits of nano drug formulations. To guarantee better pharmacokinetic and pharmacodynamic qualities as well as successful treatment results, nanoparticles are essentially already-approved conventional medications conjugated to NPs [12].

Summary of Nano carrier Systems

For anterior eye disorders, traditional pharmacological preparations such eye drops work well, but they have drawbacks like poor permeability, frequent drug administration, and low bioavailability.For posterior eye disorders, intravitreal injection of medications crosses the ocular barrier and produces a therapeutic impact; however, it carries a high risk of complications and unpleasant responses, which has made disease treatment extremely difficult. To improve drug delivery to the eyes and increase the amount of time that pharmaceuticals remain in the eyes, research and development of novel DDSs are therefore required.

[13]. Drug distribution is a significant problem, particularly with new treatments that are either insoluble in water, unstable in the biological milieu, have poor transport characteristics across biological membranes, or have extremely low bioavailability. Some of the aforementioned problems can be resolved and their therapeutic efficacy increased by using drug carriers that are nanosized. Various nano-sized carriers, including dendrimers, nanowires,

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nanoparticles, and nanocages, are being developed for a range of drug delivery applications. The problem is figuring out the therapeutic dosage of the drug that is formed in a system, which may differ greatly from the drug nanocarrier's dosage [14]. The creation of nanocontainer systems for the treatment of different illnesses is a cutting-edge, exciting, and rapidly developing scientific topic. Agents for the treatment of neuropsychiatric disorders are among the substances found in nanoparticles. Long-term treatment is necessary for all mental diseases, and patients may require months or even years of continuous medication. This makes it crucial to administer the medication through nanocontainer technologies that allow for a prolonged release of the medication. Many nanocontainers are creating opportunities for novel drug delivery methods, including "patches" that deliver drugs subcutaneously [15]. In response to consumers' increasing need for more nutrient-dense and healthful food products, the food industry has been developing functional foods more frequently in recent years, moving from a trend to a reality. The data that researchers and industrial food workers collected was crucial to completing this evolutionary stage. Thus, certain significant trends pertaining to the application and manufacturing may be identified during this research [16].

Red Blood Cell (erythrocyte)-Based Novel Drug Delivery Systems

History and Evolution

In the 17th century, Dutch scientist Lee Van Hock described red blood cells (RBCs) in human blood samples. Howson discovered that RBCs had a flat disc shape instead of a spherical one a century later. A whole new field of drug delivery techniques was made possible by Gardos' 1953 attempt to load the "erythrocyte ghosts" with ATP. This approach also laid the groundwork for later coatings of the erythrocyte membrane with different active substances. Dextrans was found to be trapped in erythrocytes by Marsden and Ostling in 1959. Ihler et al. then used RBC loading with medicinal drugs for administration. The phrase "carrier red blood cells" was then coined in 1979[17]. Red blood cells (RBCs) are unquestionably one of the best-studied natural carrier systems in drug delivery history; yet, pre-clinical use of RBC-based delivery systems is currently limited by a number of fundamental issues that have not yet been resolved. According to more sophisticated evaluations, the physical interaction of medications and nanocarriers with red blood cells can really alter their pharmacokinetics, biodistribution, clearance, and metabolism in unfavorable ways [18]. From a practical perspective that is really simplistic, an RBC is similar to a sturdy sac-voyage composed of elastic material. Drug encapsulation inside RBC ghosts may be the reason why research into RBC carrying capabilities in the drug delivery sector began. The earliest clinically tested RBC-based medication delivery systems were developed in this field of study, which has drawn a lot of attention since the early 1970s. More than 200 papers, monographs, and proceedings chapters have been published on various facets of drug encapsulation into carrier red blood cells; readers seeking a more comprehensive list of literature references and a more detailed explanation of drug encapsulation techniques into carrier red blood cells are advised to consult the earlier inclusive reviews [19]. Patients with beta-thalassemia who have premature stop codons in their beta-globin gene may benefit from medications that enable stop codon readthrough, as the new understanding that RBCs perform low levels of protein synthesis may also be therapeutically advantageous. Similar to this, indications of channel transfer in RBCs may offer treatment approaches that target channelopathies with promise. Furthermore, the protective function of particular RBC miRNAs in malaria and the part RBC GTPases play in the invasion process point to new therapeutic targets [20].

Benefits Compared to Other Nanocarriers

RBCs are widely accessible, incredibly abundant, and reasonably, to some extent, expendable. The diameter and thickness of RBC biconcave discs are approximately 6–7 μm and 2 μm, respectively, making them very simple and uniform when compared to other cells. Over the length of a person's life, which is about 120 days, each of 1013 red blood cells (about 4–5 million per microliter of blood) travels about 250 kilometers. In the arterial vasculature, an RBC goes through millions of cycles of incredibly rapid flow before squeezing into capillaries. The polymer and durability of the RBC membrane and cytoskeleton, the absence of nuclei and organelles, and the molecular characteristics of the RBC surface give them an unmatched level of endurance, tensile strength, and deformability. RBCs naturally developed into transport oxygen and carbon dioxide into the bloodstream, and they appear to be a good fit for vascular medication delivery [21]. RBCs naturally circulate for a long time in the circulatory system, delivering "cargoes" like oxygen throughout the body. RBCs circulate in mice for approximately 40 days and in humans for approximately 3 months. Because red blood cells (RBCs) are biconcave and lack organelles, their full inner volume and expanded surface can be employed to carry a variety of substances. RBCs are the most readily available, biocompatible, reasonably priced, and manageable biological carrier for DDSs from a practical perspective [22]. Blood cell-based carriers are among the many cell-based drug delivery technologies; they are also highly effective and have many uses. The three primary types of blood cells are leukocytes, platelets, and erythrocytes. Because of their many advantageous characteristics, blood cell-based carriers—including those formed from their membranes are perfect for the delivery of drugs. The following is a description of these attributes [23]. Juliano and Stamp removed sialoglycoproteins from erythrocyte membranes and combined them with liposomes to create the first report

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of loading nanoparticles onto the surface of red blood cells, which was published forty-five years ago. Following their in vitro binding to the RBC surface, the authors hypothesized that this strategy would prove helpful in the creation of tailored liposomes. The Papahadjopoulos group established the first description of antibody-based liposome coupling to the RBC surface using [24].

Types of Red Blood Cell -Based Nanocarriers

Juliano and Stamp removed sialoglycoproteins from erythrocyte membranes and combined them with liposomes to create the first report of loading nanoparticles onto the surface of red blood cells, which was published forty-five years ago. Following their in vitro binding to the RBC surface, the authors hypothesized that this strategy would prove helpful in the creation of tailored liposomes. The Papahadjopoulos group established the first description of antibody-based liposome coupling to the RBC surface using [25]. Given the leaky structure of the tumoral neovasculature, nanosized drug delivery systems (NDDS) have the potential to significantly increase the dispersity of water-insoluble anticancer medications and deliver them to solid tumors efficiently through the increased penetration and retention (EPR) effect. Due to two inherent limitations of nanodrugs, the therapeutic efficacy of existing NDDS against metastatic tumors was significantly compromised despite their promise. The first is that they have limited blood circulation, mostly because of identification by the reticule endothelial system (RES) [26]. This may lead to the anticancer medications' sublethal tumor spread. The standard NDDS's limited tumor penetration is

Table 1: Mechanism of Red Blood Cell -Based Novel Drug Delivery Systems.

Mechanism	Description	Advantages	Challenges
Passive Loading	Drugs diffuse into RBCs by soaking cells in a drug-containing solution, allowing uptake.	Simple, does not require advanced technology	Low drug loading capacity, risk of drug leakage
Hypotonic Dialysis	RBCs are exposed to a hypotonic solution, creating pores for drug entry. They are then resealed.	High drug loading, suitable for hydrophilic drugs	Possible hemolysis, limited repeatability
Electroporation	Application of an electric field temporarily opens pores in RBC membrane for drug loading.	Effective for macromolecules, controlled pore formation	May damage RBCs, requires precise control
Endocytosis or Phagocytosis	Inducing RBCs to engulf nanoparticles or other drug carriers into their structure.	Enhanced stability, prolonged circulation time	Complex process, requires RBC preservation
Membrane Fusion	Fusion of drug-loaded liposomes or nanoparticles with RBC membranes to achieve direct drug transfer.	Enhanced loading efficiency, good biocompatibility	Complex fusion process, stability issues
Receptor-Mediated Binding	Surface modification of RBCs with ligands or antibodies for receptor-targeted delivery.	High specificity, ideal for targeting specific cells	Risk of immunogenicity, stability concerns

Table 2: Drug Delivery Mechanisms for Red Blood Cell (RBC)-Based Cancer Therapies.

Aspect	Mechanism	Description	Advantages	Challenges
Drug Releasing Mechanisms	Controlled Release via pH Change	Drugs are released from RBCs in acidic tumor environments.	Targeted release at cancer sites	Requires precise pH sensitivity
	Enzyme-Triggered Release	Enzyme-sensitive linkers allow drug release in environments with specific enzymes.	High specificity, effective for tumor-associated enzymes	Linker stability, enzymatic specificity concerns
	Magnetically Controlled Release	Magnetic nanoparticles in RBCs release drugs when exposed to an external magnetic field.	Non-invasive, targeted release	Potential toxicity of magnetic particles, control issues
Association with Cancerous Cells	Receptor-Mediated Targeting	RBC surface modified with ligands or antibodies that bind specifically to cancer cell receptors.	High specificity to cancer cells, minimal off-target effects	Risk of immunogenicity, receptor selection
	Passive Targeting through EPR Effect	Exploits enhanced permeability and retention (EPR) in tumor vasculature to accumulate drugs.	Effective for solid tumors, passive targeting	Limited to tumors with EPR effect, not suitable for all types

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	Functionalization with Targeting Ligands	Modifying RBCs with peptides or aptamers that selectively bind cancer cell markers.	High affinity to cancer cells, improved uptake	Complexity in ligand attachment, potential immune response
	Nano-RBC Conjugates	Nano-sized RBC fragments combined with nanoparticles for enhanced tumor penetration.	Greater penetration, effective delivery to dense tumors	Production challenges, nanoparticle stability

another. The presence of the dense extracellular matrix (ECM) and the high interstitial fluid pressure are two biological and pathological obstacles that prevent nanoparticles (NP) from penetrating tumors. A lot of work has gone into improving the blood circulation of NDDS by altering its surface with hydrophilic polymers, such polysaccharides, poly(ethylene glycol) (PEG), or PEG analogs (like poloxamines and poloxamers) [27]. By using PEG for surface shielding, NP aggregation and protein absorption may be avoided. Thus, by the EPR effect, it can somewhat slow down the NPs' rapid circulation clearance and cause preferred storage in the main tumors. Everything has two sides, though, as the dense PEG corona may impede NDDS's ability to interact with the tumoral milieu by reducing their mobility and flexibility. This may lead to inadequate NP tumor penetration. It was discovered that by coating RVs, PNs may more easily permeate the area surrounding metastases with a higher level of anti-metastasis efficacy, hence improving the intratumoral penetration ability of NDDS. Our findings indicated the significant potential of coadministration of iRGD and RVPNs as a novel strategy for effectiveness.PEG-based surface shielding may stop NP aggregation and prevent protein absorption. Thus, it can somewhat slow down the NPs' quick blood clearance and, through the EPR effect, cause preferential accumulation in the main tumors. Everything has two sides, though, and the dense PEG corona can decrease the mobility and flexibility of NDDS and interfere with their interactions with effective drug delivery in the treatment of metastatic breast cancer. This also highlighted the significance of penetration and long circulating ability when designing a nanodrug delivery system to fight against metastatic cancer [28].

Targeting Strategies

The endothelium of blood vessels is known to become more susceptible to certain situations, such as inflammation or hypoxia, which is common in tumors. Compared to the healthy state, tumor medication targeting via nano-carrier permeability [29]. Under hypoxic conditions, tumors that are growing quickly either engulf or recruit new blood vessels. Selective improved penetration of nanosystems and macromolecules greater than 40 kDa into the tumor stroma is made possible by these recently created leaky capillaries. Additionally, one factor contributing to the retention of NPs is the tumor's lack of normal lymphatic outflow. However, this special characteristic does not apply to small molecule medications, which have a very short half-life and rapidly wash out of tumors. As a result, encapsulating small-molecule medications in nanodevice carriers improves their pharmacokinetics (longer systemic circulation), offers some tumor selectivity, and reduces adverse effects. Although this "passive" kind of tumor targeting lacks a ligand for a particular tissue or organ, it depends on carrier properties (size, circulation time) and tumor biology (vascularity, leakiness, etc.) organ binding [30]. It suggests an overall plan that depicts this occurrence and the active targeting that will be covered later. Since Maeda et al. discovered the EPR effect in the 1980s, a lot of work has been done to comprehend the phenomenon's importance in tumor targeting and create suitable DDS. Some of these nanocarriers, such the commercially available Doxil© and Caelyx©, are currently being employed in clinics with success, and the EPR effect has emerged as the gold standard for designing passive tumor-targeted devices [31].

In order to deliver medications, genes, and theranostics to the desired site while avoiding normal tissues, active targeting is crucial. This improves therapeutic efficacy and reduces adverse effects. When compared to passively targeted nanosystems or free drug, active targeting can dramatically boost the amount of drug delivered to the target cell. Once the medicine has accumulated in the tumor area, so-called active targeting can further boost its effectiveness. To do this, ligands that bind to receptors that are overexpressed on tumor cells are used to decorate the surfaces of the nanocarriers. This tactic will increase the drug's penetration by improving the nanocarriers' affinities for the cancer cell surface.

In 1980, the first proof of this phenomena was put out using antibodies grafted onto the liposome surface [32]. followed by other various kinds of ligands like for instance peptides, nucleic acids, aptamers. Among the classical targets, we can cite the transferrin receptors (TfR) or nicotinic acetylcholine receptors that allow the reach the environment of brain tumours.

In this case, the mechanism concerns targeting if endothelial cells, that is vascular targeting. Applied to target glioma, for drug delivery or biomedical imaging, transferrin ligands were grafted on solid lipid nanoparticles (SLNPs), micelles, dendrimers [33].The nanoparticles of superparamagnetic iron oxide (SPIONPs). Additionally, the literature provides examples of how nicotinic acetylcholine has been targeted with micelles to reach the central nervous system (CNS) and glioblastoma. In addition to the successful synthesis and in vitro and in vivo investigation of their antibodies, a large number of receptors have been identified.

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Nano-carrier ligand/receptor binding for tumor therapeutic targeting, making them viable models to advance active targeting technology. It has been discovered that aVb3 integrin interacts to the RGD peptide. The TME's glioma cells and vasculature both have high expression levels of these receptors [34] . In the TME, it was discovered that the F3 peptide bound to the nucleolin receptor expressed on angiogenic endothelial cells. Similarly, a tripeptide (Asn-Gly-Arg (NGR) peptide) has been demonstrated to bind aminopeptidase N (CD 13), a putative receptor in the TME. One of the more well-known examples of a ligand is folic acid (FA), which is found in TME and binds specifically to the folate receptor (FAR). In that situation, various approaches have been documented, including the manufacture of FA-drug conjugates and FA-grafting onto nanocarriers to encourage the endocytosis of cancer cells. Table 2 shows examples of often targeted ligands. In conclusion, there are several ways to actively target tumors: directly attacking tumor cells, targeting the slightly acidic TME, focusing on the tumor nucleus and TME vascularization, as detailed in the sections that follow [35].

Drug Loading and Encapsulation

Setting up the NP core and loading DOX First, acetonitrile was used to dissolve the DOX–PLA conjugate, creating a 1 mg/ml solution. One milliliter of this solution was added dropwise to three milliliters of water. After that, the mixture was agitated for two hours outside to allow the acetonitrile to evaporate. To get rid of any organic solvent residues, the resultant NP core solution was cleaned using Amicon Ultra-4 Centrifugal Filters (Millipore, CA, USA; 10 kDa cut-off). Another suspension of the particles was made in 1 milliliter of distilled water [36]. The physical encapsulation of DOX was achieved by dissolving 1 mg of poly(lactic-co-glycolic acid [PLGA]; 0.67 dl/g, carboxy-terminated, LACTEL Absorbable Polymers, CA, USA) in 1 ml of acetonitrile, and then adding DOX that had been predissolved in 25 µl of dimethyl sulfoxide. Suspensions containing NP cores were created using the same methods as previously mentioned. Combining NP cores with vesicles generated from RBCm RBCm-derived vesicles made from 1 milliliter of whole blood were first combined with a suspension containing 1 milligram of NP cores in order to fuse the RBCm-derived vesicles with the previously described NP cores. An Avanti small extruder was then used to extrude the mixture eleven times through a 100 nm polycarbonate porous membrane. An excess of blood was employed to make up for the membrane loss during RBC ghost derivation and extrusion in order to completely coat 1 mg of NP cores [37]. PEGylated NP preparation The following steps were taken to create the future science group: first, the DOX–PLA conjugate and PLA-PEG-COOH (MW = 10 kDa, polydispersity index = 1.12; PEG = 3.5 kDa, PLA = 6.5 kDa) [13] at a weight ratio of 1:1 were dissolved in acetonitrile at a concentration of 1 mg/ml. Future Medicine doi: 10.2217/NNM.12.153 RResea esearchch AArrticle ticle NP solutions of polymeric nanoparticles enveloped in erythrocyte membranes. 100 µg of DOX diluted in 25 µl of dimethyl sulfoxide was added after 1 mg of PLGA (0.67 dl/g, MW = 40 kDa, carboxy-terminated, LACTEL Absorbable Polymers) had been dissolved in 1 ml of acetonitrile in order to physically encapsulate DOX into PEGylated NPs. NP suspensions were created using the above-described methods [38].

Table 3: Medicinal Applications of RBC-Based Drug Delivery Systems.

Application Area	Mechanism	Description	Advantages	Challenges
Cancer Therapy	Targeted Drug Delivery	RBCs loaded with anticancer drugs for selective tumor targeting	Reduces off-target toxicity	Requires precise targeting mechanisms
Anti-inflammatory Treatment	Controlled Drug Release	RBCs deliver anti-inflammatory agents to inflamed tissues	Sustained release reduces dosing frequency	Ensuring controlled release in inflamed areas
Infectious Disease Treatment	Pathogen Targeting	RBCs deliver antibiotics or antiviral agents directly to infection sites	Increased drug efficacy	Pathogen-specific targeting is challenging
Pain Management	Sustained Release of Analgesics	RBCs carry and gradually release pain-relief medications	Provides prolonged pain relief	Avoiding overdose, controlling release timing
Chemotherapy	Controlled Drug Release	RBCs deliver chemotherapeutic agents directly to cancer cells	Minimizes systemic toxicity, targets tumor cells	Maintaining controlled release and dosage
Vaccine Delivery	Antigen Presentation	RBCs present specific antigens to the immune system, acting as a vaccine carrier	Enhances immune response, stable antigen delivery	Achieving precise antigen loading and release
Gene Therapy	Nucleic Acid Delivery	RBCs transport genetic material (e.g., mRNA) to specific tissues	Safe delivery with reduced immune response	Ensuring genetic material stability

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Clinical Trials and Studies

Preclinical studies are essential for translation to disease treatments and effective use in clinical practice. An undue emphasis on single approaches to Alzheimer's disease (AD) appears to have retarded the pace of translation in the field, and there is much frustration in the public about the lack of an effective treatment. We critically reviewed past literature (1990–2014), analyzed numerous data, and discussed key issues at a consensus conference on Brain Ageing and Dementia to identify and overcome roadblocks in studies intended for translation[39]. We highlight various factors that influence the translation of preclinical research and highlight specific preclinical strategies that have failed to demonstrate efficacy in clinical trials. The field has been hindered by the domination of the amyloid hypothesis in AD pathogenesis while the causative pathways in disease pathology are widely considered to be multifactorial. Understanding the causative events and mechanisms in the pathogenesis are equally important for translation. Greater efforts are necessary to fill in the gaps and overcome a variety of confounds in the generation, study design, testing, and evaluation of animal models and the application to future novel anti-dementia drug trials. A greater variety of potential disease mechanisms must be entertained to enhance progress [40].

Limitations and Challenges

Nanomedicine will play an increasing role in prevention and treatment across the entire healthcare spectrum. However, their precise market size, economic value and areas of application remain unclear. This opacity, including the question of what constitutes nanomedicine matters, especially when considered alongside the key regulatory questions and concerns [41]. This article begins by placing these key questions into context in relation to the current scientific state of the art, focusing particular attention on the human health and safety context. In exploring these central questions surrounding the regulation of nanomedicine, this perspective also explores existing and suggested frameworks that aim to deal with emerging technologies more generally. It then outlines priority areas for action and general conclusions specific to nanomedicine [42].

Commercialization and Market Potential

The development and commercialization of red blood cell (RBC)-based nanomedicine is an exciting frontier in the pharmaceutical and healthcare industries. RBC-based nanomedicines leverage the natural properties of red blood cells to deliver drugs, genes, or other therapeutic agents to specific targets in the body. Their biocompatibility, long circulation time, and ability to avoid immune system detection offer significant advantages in drug delivery systems. ndustry Trends [43].

Nanomedicine is becoming a rapidly growing sector within the pharmaceutical and biotechnology industries. RBC-based drug delivery systems are part of this broader trend, as they offer a platform for more targeted, efficient, and less toxic therapies compared to traditional drug delivery methods. As of now, RBC-based nanomedicines are still in the research and early clinical trial phases. Regulatory frameworks for nanomedicines, including RBC-based technologies, are being updated to address their unique characteristics. The FDA and EMA are both involved in developing specific guidelines for nanomedicine, which will likely expedite their path to commercialization once these products prove efficacy and safety [44].

Table 4: Comparative Analysis of RBC-Based Drug Delivery with Other Nanocarriers.

Nanocarrier Type	Composition & Structure	Drug Loading & Release Mechanism	Advantages	Challenges
RBC-Based Carriers	Natural cell membrane structure, biocompatible	Drug encapsulation within RBCs, release triggered by pH, enzymes, or magnetic fields	High biocompatibility, long circulation time, immune evasion	Complex preparation, maintaining RBC integrity
Liposomes	Phospholipid bilayer, aqueous core	Drugs encapsulated within lipid bilayer, released via fusion or degradation	Biocompatible, flexible surface modification	Rapid clearance by RES, stability issues
Polymer-Based Systems	Synthetic or natural polymers, core-shell structure	Drugs loaded within polymer matrix, released via diffusion, degradation	Controlled release, tunable properties	Potential toxicity, complex synthesis
Inorganic Nanoparticles	Metal or metal oxide cores (e.g., gold, iron oxide)	Drug adsorbed or conjugated onto surface, release by external triggers (e.g., light, magnetic field)	High stability, easy functionalization	Toxicity concerns, limited biodegradability

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Personalized or precision medicine is another trend influencing RBC-based nanomedicine. These nanocarriers can be engineered to deliver therapies tailored to a patient's genetic profile, which can dramatically improve treatment outcomes, particularly in oncology and rare genetic diseases. Many pharmaceutical companies are entering partnerships with biotechnology startups or academic research centers to develop RBC-based drug delivery systems. This trend is driving innovation and accelerating the pace of commercialization. In particular, collaborations are becoming more common in oncology, infectious diseases, and autoimmune disorders [45].

Table 5: Future Research Directions in RBC-Based Drug Delivery Systems.

Research Direction	Description	Potential Impact	Challenges
Innovations in Design	Development of advanced RBC engineering techniques, such as synthetic RBCs or hybrid carriers	Enhanced drug loading capacity and controlled release profiles	Complexity of manufacturing and scalability
New Targeting Strategies	Exploration of novel ligands and antibodies for precise targeting of specific cancer cells or tissues	Improved specificity and reduced off-target effects	Identifying and validating effective targeting moieties
Emerging Therapeutic Applications	Investigating RBC-based delivery for new therapies, including gene editing, immunotherapy, and vaccines	Broader application in various diseases, including rare and chronic conditions	Regulatory hurdles and ensuring safety and efficacy

Conclusion

In conclusion, the revolutionary advances in red blood cell-based nanocarrier drug delivery systems have showcased significant potential for targeted tumor therapy, enhancing therapeutic efficacy while minimizing systemic side effects. Key progress includes improved biocompatibility, controlled release mechanisms, and the ability to navigate the tumor microenvironment effectively. However, challenges such as scalability, regulatory hurdles, and the need for comprehensive in vivo studies remain critical barriers to overcome. Future research directions should focus on optimizing carrier designs, enhancing targeting strategies, and exploring combination therapies to maximize treatment outcomes. Ultimately, these innovations promise to transform cancer therapy, offering hope for more effective and personalized treatment options.

Author's contributions

All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interest.

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