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NANO-BASED DRUG DELIVERY SYSTEMS FOR CHEMOIMMUNOTHERAPY: A NOVEL APPROACH

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ABSTRACT

In spite of significant advancements in cancer treatment, patients with cancer still have a poor prognosis and poor therapeutic outcomes. Combining chemotherapy and immunotherapy drugs, called chemo-immunotherapy, offers promise by harnessing the synergistic effects of these two treatments. In addition to reducing drug dosages, this strategy optimizes therapeutic efficacy, making it a viable option for treating cancer.A nano-based drug delivery system (NDDS) was developed as a result of nanotechnology integration into cancer therapy. Chemotherapeutic agents are encapsulated within nanocarriers, offering advantages such as site-specific release of drugs and responsiveness to the tumor microenvironment.Many nanocarriers have been approved to treat cancer, including liposomes, nanoparticles, and micelles. Comparatively to traditional formulations, they have demonstrated significant improvements in therapeutic efficacy.Cancer treatment could be revolutionized with the application of NDDS to chemoimmunotherapy. Cancer patients can benefit from this approach by improving therapeutic outcomes, minimizing adverse side effects, and optimizing clinical outcomes. Recent advancements in NDDS tailored for chemoimmunotherapy are discussed in this discussion of the current landscape of cancer immunotherapy and chemoimmunotherapy.

KEYWORDS: Nano-drug delivery, cancer therapy, liposomes, nanocarriers, dermal delivery

INTRODUCTION

Every year, millions of people are killed by cancer, a devastating and lethal disease. No matter what one's origin or organ it targets, it ranks as one of the foremost global health challenges of the 21st century [1].A multifaceted approach is required to treat cancer, which is characterized by unregulated cell growth and an impaired ability to apoptosis.Cancer is being treated using multiple approaches, each with its own limitations and potential side effects [2].Radiation therapy, chemotherapy, and hormone therapy are all available treatments for cancer. A common approach to treating cancer is chemotherapy, which administers anti-cancer medications systematically to patients in order to stem unbridled cancer cell growth [3].Anticancer agents suffer from numerous side effects due to their nonspecific nature, and their ineffective delivery makes them difficult to use.Differentiating cancerous cells from healthy body cells is one of the greatest challenges in cancer therapeutics. As a result, the primary focus is on developing drugs capable of recognizing cancerous cells and thereby stopping their growth and proliferation.It is impossible to selectively target cancerous cells with conventional chemotherapy without damaging healthy cells as well. This may negatively impact the effectiveness of treatment at lower doses by causing significant side effects, such as organ damage [4].A nanotechnology device typically consists of dimensions between a few nanometers (nm) and several hundred nanometers (nm), depending on its use [5].A precise drug delivery system has emerged as one of the most compelling areas of interest in nanotechnology in the last decade. As a result, it provides numerous advantages over traditional formulations in overcoming constraints [6,7].Since it penetrates tissues at the molecular level, it holds great promise for both cancer diagnosis and treatment.A significant leap forward has been made in cancer detection, diagnosis, and treatment through the application of cancer nanotechnology. In order to reduce conventional side effects associated with cancer treatments, different research efforts are underway to explore increasingly precise cancer treatments based on nanotechnology [5].Liposomes, polymeric micelles, dendrimers, nanospheres, nanocapsules, and nanotubes are some of the nanotechnology-based cancer treatment systems available today [8,9].

Immunotherapy

During the past few years, cancer immunotherapy has rapidly advanced as a treatment option. A cancer-immunity cycle entails a number of critical stages. As part of these stages, cancer cell antigens are released, antigen-presenting cells (APCs) present cancer antigens, T cells are initiated and activated, and T cells migrate to tumors and are infiltrated, followed by cytotoxic T cells that identify and eliminate tumor cells[10].

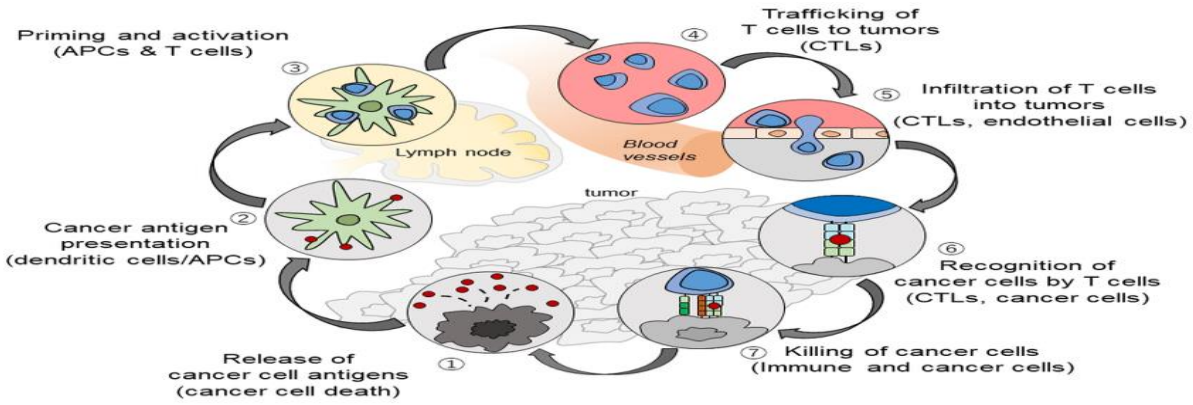

Fig.1 Cancer Immunity Cycle

Adoptive cell therapy

In adoptive cell therapy (ACT), potent and tumor-specific lymphocytes are ex vivo cultivated, followed by significant quantities of these lymphocytes being administered to the same individual (autologous host) for cancer treatment [11].In comparison with other cancer immunotherapeutic methods, ACT offers several advantages. A large number of antitumor lymphocytes can be efficiently cultivated in vitro, which recognize the tumor specifically and help stimulate an effective immune response against it [12].B-cell non-Hodgkin lymphoma and B-cell acute lymphoblastic leukemia (B-ALL) patients have shown remarkable anti-tumor effectiveness with anti-CD19 CAR-T cells. In multiple trials, between 70% and 94% of patients responded completely [13].Comparatively to macrophages treated with free cytokines, backpack-loaded macrophages displayed enhanced anti-tumor effects for up to 5 days.

Nanocarriers for cancer Chemoimmunotherapy

A new avenue for cancer immunotherapy is available through nanoparticle drug delivery systems (NDDSs). The TME (Tumor Microenvironment) can be re-educated by these systems that are readily internalized by immune cells and have unique chemical and physical properties. This enhances the immune function of the body as a result of these systems [14].By enhancing solubility and bioavailability, extending agent circulation time, and enhancing in vivo pharmacokinetic profiles, NDDS can significantly enhance drug delivery. By combining these effects, therapeutic outcomes are improved and side effects are reduced [15-18].Chemoimmunotherapy can be achieved using NDDS via several flexible approaches [19,20].

Various techniques can be used to combine multiple agents in chemoimmunotherapy: one agent is administered free of charge and another via NDDS (Free drug + Nano), both agents are delivered via the same or different NDDS (Nano + Nano), or both agents are co-encapsulated in a single NDDS (co-encapsulation).

Several advantages can be derived from the "Free drug + Nano" approach, including customizable prescription, manageable administration intervals, straightforward preparation, and ease of industrial scale-up [21].

Poly(lactic-co-glycolic acid) nanoparticles (NPs) containing the chemotherapy drug paclitaxel (PTX) were developed . There are two types of PLGA NPs—CpG-loaded NPs (called PCNs) and PCNs for stimulating BMDCs. Also known as PINs, these PLGA NPs contain IL-10 small interfering RNA that is intended to silence IL-10 expression [22].

As compared to PTX alone, sequential treatment of melanoma-bearing mice (B16-F10) with PCNs and PINs improved anti-tumor effects and prolonged survival rates ($p<0.05$). NDDS was encapsulated within immunotherapy agents in a free form while chemotherapy drugs were in a nano form. This was referred to as the "Free drug + Nano" approach [23].

According to a study [24], they have developed an oxaliplatin (OXA)-prodrug vesicle that can be loaded with a photosensitizer (PS) and activated by the tumor microenvironment. Tumor cells are induced to die because of this combination.

By combining two agents in a nano + nano formulation, you can adjust the dosage and coordinate their distribution [25,26].For the "co-encapsulation" approach of

chemoimmunotherapy, nanoparticle drug delivery systems (NDDS) have been developed. In addition to liposomes, polymer micelles, dendrimers, metallic and inorganic nanoparticles, nanogels, and biomimetic nanoparticles, there are also nanogels and nanoparticles in biomaterials.

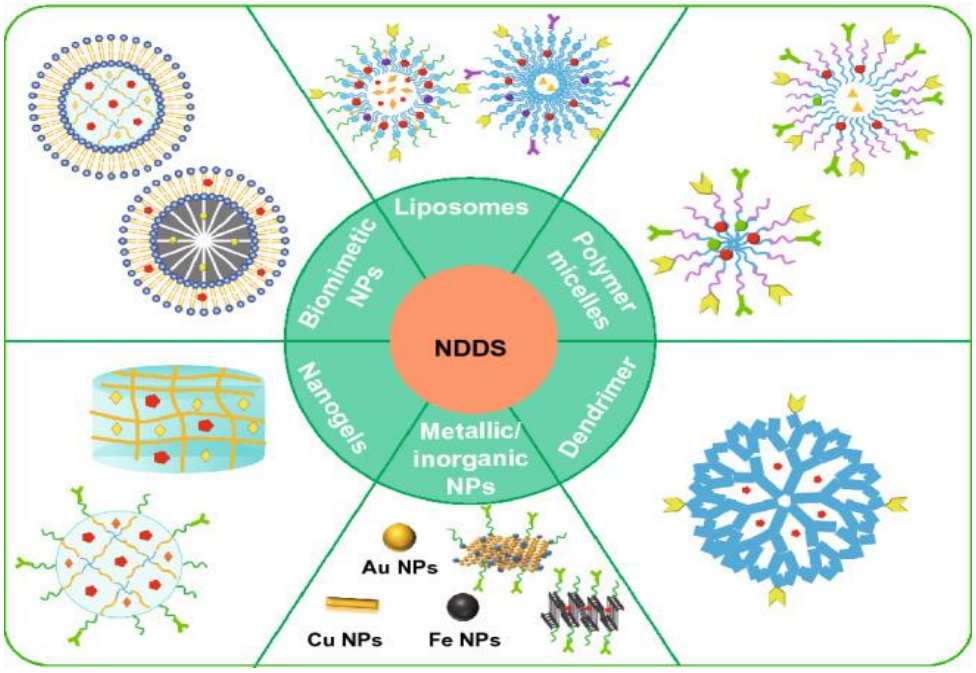

Fig.**Nanocarriers for cancer Chemoimmunotherapy**

Liposomes

Liposomes enable high encapsulation efficiency, targetability, and low toxicity. Liposomes are bilayer vesicles made of phospholipids and cholesterol. Industrial production would benefit greatly from their properties. Adjuvants and antigens attached to liposomes can either be encapsulated within the hydrophobic core or be adsorbate onto the lipid surface by charge interactions with lipids [27].

The interior aqueous cores of liposomes can also be used to encapsulate hydrophilic small-molecule chemotherapeutic agents, whereas the lipid bilayers can encapsulate hydrophobic agents [28].

Numerous liposomal products have been approved for cancer therapy using liposomes. The use of liposomes for chemoimmunotherapy has also been extensively researched. In one study, Chen et al. developed dual-responsive liposomes (LPDp) that were pH- and MMP-responsive. A combination of PD-L1 inhibitor conjugates and low-dose chemotherapy drug, doxorubicin (DOX), in LPDp liposomes resulted in significant antitumor activity [29].A remarkable 78.7% tumor suppression rate was achieved with the LPDp formulation. Immune checkpoint blockade and synergistic effects of chemotherapeutic agents contributed to this remarkable result.As a result of self-assembly of phospholipid-conjugated IND, a DOX/IND-liposome was then assembled from a distance before DOX was loaded onto it.

A comparison of DOX-liposomes and DOX/IND-liposomes showed that DOX/IND-liposomes significantly increased the immune response against breast cancer.

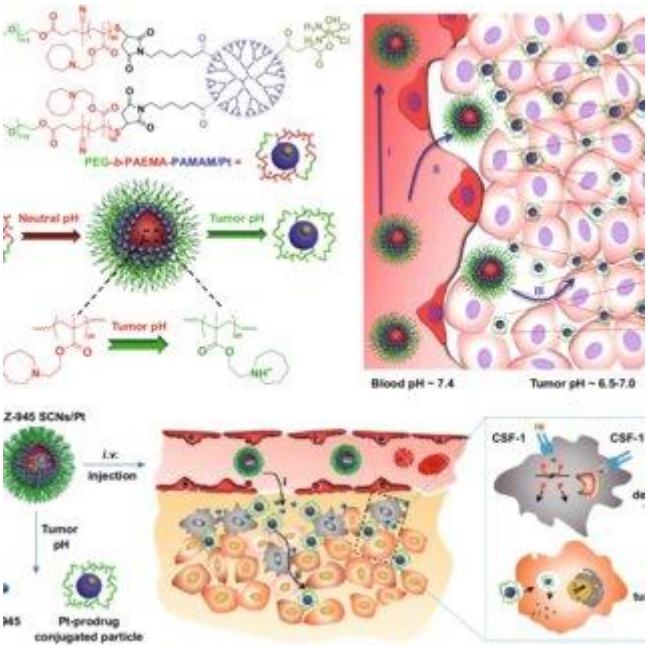

Fig. 3 DOX/IND Liposome synthesis

Polymer Micelles

A polymer micelle is an amphiphilic block copolymer that self-assemblies to produce a stable colloid solution [30].Physicochemical interactions or chemical conjugation enable the encapsulation of hydrophobic medicines into micelles, while hydrophilic medications can be loaded into them physically [31].

Nanoxel®-loaded docetaxel (DTX) and Genexol®-loaded paclitaxel (PTX) are examples of polymer micelles approved for cancer treatment. Cancer chemoimmunotherapy makes extensive use of these versatile micelles. In addition, by surface-modifying polymeric materials, multifunctional polymer micelles can be created that provide effective packaging of hydrophilic and hydrophobic drugs while preventing degradation in vitro and in vivo.

It has been demonstrated that polymer micelles derived from PLGA/PLA can be used in chemoimmunotherapy as drug carriers [32-34].After treatment with ATRA-PLGA-PEG-PD-L1, a greater number of CD8+ T cells were activated in the tumor microenvironment compared to free ATRA in in vivo antitumor assays.

In a synergistic cancer immunotherapy, designed micelles that can be triggered by both pH and MMP-2 [35].

PEGylated phospholipid micelles modified with Pt(IV) prodrugs have been reported. In these micelles, iron oxide nanoparticles (IONPs) are encapsulated with poly (I:C), which is then functionalized with platinum (IV) in order to achieve chemoimmunotherapy [36].

Several studies have demonstrated that PCPCD inhibits in vivo tumor growth, metastasis, and recurrence. The synergistic effects of chemotherapy enhanced immunogenicity and IDO-blocking immunotherapy induced by NLG919 allowed this to be achieved.

Dendrimers

Dendrimers as spherical polymers with a hydrophobic core, branched monomers, and functional peripheral groups, they are composed of a hyperbranched structure with hydrophobic monomers in the middle [37].

A number of innovative nanoparticles based on dendrimers have been developed and have gained significant scientific interest due to their distinctive structural characteristics, such as well-defined structure, near-monodispersity, ease of incorporation of multiple functionalities, and multivalency [38-40].

Small molecular drugs can be accommodated in the hydrophobic central core, while immunotherapy agents such as therapeutic antibodies can be chemically bonded to the functional peripheral groups. Most dendrimers currently employed in pharmaceutical applications are polyamidoamine (PAMAM), polypropyleneimine (PEI), and peptide dendrimers.The field of chemoimmunotherapy is currently showing significant promise with several dendrimers undergoing clinical trials–[41-43].

Chemoimmunotherapy with enhanced drug penetration has been enhanced by using novel dendrimer-based nanoparticles (NPs) [44].

Nanogels

There is great promise in nanogels as chemoimmunotherapy delivery systems because of their nano-sized hydrogel scaffolds, excellent biocompatibility, high water content, and compatibility with a variety of therapeutic agents, including small-molecule drugs and biocompatible macromolecules. In addition to incorporating targeting ligands and synthesizing responsive functional bonds, multifunctional nanogels can be intelligently designed for chemo-immunotherapy applications [45-49].

Immune stimulation can be achieved through the use of certain hydrogel systems. One example is the discovery that a melittin-RADA32 hydrogel containing DOX (MRD) is an effective chemoimmunotherapy that actively modulates the tumor microenvironment [50].

A combination of MRD and innate immune cell modulation was found to be more effective at eliminating melanoma tumors via medication delivery, modulation of innate immune cells, and depletion of M2-type tumor-associated macrophages.

Biomimetic NPs

Through the incorporation or encapsulation of biocompatible materials, biomimetic nanoparticles (NPs) mimic the characteristics of natural organisms and structures. It also helps them evade immune system clearance by making them look like autologous components. Red blood cells and exosomes are natural structures with similar morphology, surface characteristics, and size. Through this innovative design, drugs are delivered to specific cells or tissues, biocompatibility is excellent, treatment effectiveness is improved, and side effects are minimized.In HDL, cholesterol and molecules are transport by high-density lipoproteins (HDL), which allows them to reach specific cells. DTX-sHDL-CpG was developed to treat glioblastomamultiforme (GBM) with nano-discs that mimic HDL. A combination of DTX-sHDL-CpG and radiation therapy reduced tumor growth and prolonged survival in mice with GBM tumors [51].

The most important component of cell membrane biomimetic nanoparticles is the coating of nanoparticles with the cell membrane. These cell membranes contain proteins that originate from several kinds of cells and retain their bioactivity. They achieve immune evasion, prolong their circulation time, and target tumors efficiently because of this unique feature [52,53].

Enhanced biocompatibility, biodegradability, and extended blood circulation potential can be achieved by erythrocyte membrane biomimetic nanoparticles [54].

The inner core of the nanogels consisted of two oppositely charged chitosan derivatives and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), which was used for loading and controlled release of PTX. Nanogels could be altered to respond precisely to tumor microenvironments (TMEs), which are acidic. In addition, IL-2 was delivered through the nanogel by coating it with erythrocyte membranes. In the TME, PTX was released in a pH-responsive manner by HP-β-CD and chitosan.

As a result of their homologous targeting and homology adhesion properties, tumor cell membrane biomimetic nanoparticles are recognized and aggregated in tumor tissue specifically [55].An extended circulation time within the body can be achieved by lymphocyte membrane biomimetic nanoparticles [56].

Nanoparticles based technology for dermal delivery

Topical drug delivery through the skin with nanoparticle-based systems has been extensively studied over the years, both in vitro and in vivo. Nanoparticles have been shown to be capable of penetrating skin layers effectively, enabling bioactive molecules to be delivered to tumor sites. It also reduces the required dosage and minimizes toxicity risks, which ultimately improves patient compliance by enhancing drug retention in the skin and tumor [57].

It is still too early for nanoparticle-based topical therapies to be commercially approved. A review of the different topical systems that have been studied for the topical treatment of skin cancers is provided here to identify the key parameters influencing the formulation of an optimal formulation [58].

Niosomes

Nonionic surfactants make up niosomes, which are similar to liposomes. Compared to liposomes, these are highly stable and cost-effective [59].

In addition to modifying the subcutaneous barrier, niosomes can also interact with lipid molecules. By restoring lost lipids and enhancing the smoothness of the subcutaneous layer, these particles can decrease transepidermal water loss.

Transferosomes

Cevc and Blume introduced Transferosomes in 1992, which are highly efficient vesicles that deliver drugs topically and transdermally [60].This provides enhanced SC penetration of Transferosomes via the intercellular route, which enables them to deliver drugs deep within the skin. [61] A phospholipid bilayer surrounds the aqueous core and an edge activator activates the edges.

Ethosomes

The ethanolosome is a vesicle that contains phospholipids, cholesterol, water, and a majority of ethanol. [62] Ethosomes are elasticity-based molecules, which are introduced by Touitou et al as a result of ethanol and cholesterol effects on the phase transition temperature of phosphatidylcholine. [63] Drugs delivered by ethosomes reach systemic circulation more easily and are delivered deeper into skin layers. A controlled-release method was used in clinical studies to provide better antifungal activity with ethosomes. [64]

Transethosomes

This lipid vesicle is made by combining the features of both Transfersomes and Ethosomes, which was first introduced [65] About 30% ethanol was present in Transethosomes along with edge activators. Transethosomes penetrate deeper into the skin with the help of edge activators. In chemotherapeutic treatment of many skin diseases, transethosomes proved effective due to their better penetration through skin. [66]

Nanostructured Lipid carriers (NLCs)

These molecules do not acquire the perfect crystalline structure of molecules because they are made up of solid lipids and liquid lipids in combination.Surfactant layers enclose lipids and lipids are located inside solid lipid matrixes. [67] There is a decrease in water content in the liquid phase of NLCs, as well as high drug loading in these formulations. Controlled drug release is achieved by using these particles. [68]

Previously, NLCs were found to significantly improve the bioavailability and penetration of drugs through the deeper side of skin by improving the efficacy and delivery of drugs. As a result, drugs will be able to enhance anti-inflammatory effects with reduced doses without causing irritation to the site of delivery. [69]

Natural polymeric nanoparticle

There has been extensive research on natural polymers that can be made from Chitosan nanoparticles for dermal drug delivery. [70]

This biodegradable cationic derivative of chitin is made up of N-deacetylated chitosan. By interacting with negative charges on the surface of skin, nanoparticles will enhance their ability to modify the barrier and deliver drugs, because of their positive charge [71].

Synthetic Polymeric nanoparticle

There have been reports of the preparation of synthetic polymeric nanoparticles using biodegradable polymers (lactide-co-glycolide), copolymers (PLGA), and polylactic acid (PLA). Sun et al demonstrated the effectiveness of curcumin-loaded PLGA with particle sizes ranging from 50-150 nm. In another study, hydrogel formulations of curcumin were compared to imiquimod (IMQ)-induced psoriasis mice. [72] Because they are small, they can deposit on the skin surface by attaching to hair follicles. Depending on the application, these polymers may contain paramagnetic metals such as gadolinium (Gd) or manganese (Mn), which are used for topical diagnosis as image contrast agents.

Recent Nano-formulation in clinical trials

As antineoplastic agents or in combination with existing anticancer drugs, nanomaterials can enhance the therapeutic efficacy of existing drugs. A limited number of nanotechnology-based formulations have advanced to clinical trials, despite numerous descriptions in the literature. Recently, researchers have been interested in repurposing FDA-approved nanodrugs, such as Abraxane® (nab-paclitaxel) and Genexol-PM®, as adjuvants in combination cancer therapies.Designed to treat metastatic breast cancer, Abraxane® contains paclitaxel albumin-stabilized nanoparticles. Genexol-PM is composed of a poly(ethylene glycol)-poly(D,L-lactide) copolymer, and is a biodegradable polymeric micelle formulation of paclitaxel that does not contain cremophor EL. Due to its enhanced solubility in water, this formulation enhances its delivery efficiency and allows for higher doses of paclitaxel than paclitaxel free. An improved pre-clinical in vivo study using Genexol-PM has demonstrated a three-fold increase in the Maximum Tolerated Dose (MTD) as well as significantly reduced tumor growth. The effectiveness and safety of Genexol-PM have been demonstrated in phase II clinical trials in patients with metastatic breast cancer [73-75].

CONCLUSION

Recently, nanotechnology has emerged as a breakthrough field that has successfully treated a number of diseases, including skin cancer. Skin cancer and a variety of other types of carcinoma can be effectively managed with nanomedicine, particularly in the context of dermal carcinomas. Molecular targets and therapeutic agents are delivered by nanoparticles through a variety of routes for cancer treatment. Individual variations in response can be reduced as a result of this approach, which enables personalized and targeted therapies.As a result of the integration of nanoparticles with a variety of therapeutic modalities such as chemotherapy, immunotherapy, gene therapy, and nano-carriers, along with laser radiation and physical methods, cancer treatments have been significantly enhanced. This advancement has the potential to lower cancer treatment costs as well. In order to ensure optimal outcomes for patients, ongoing research is essential to improve the safety and effectiveness of treatments for carcinoma.

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AUTHORS CONTRIBUTIONS

Lokeshvar R: Writing – original draft, review & editing

Ramaiyan Velmurugan: Writing – original draft, Methodology, Investigation, Conceptualization, Supervision.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this article.

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