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RESEARCH PAPER

A novel biocompatible nanoprobe based on lipoproteins for breast cancer cell imaging

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ABSTRACT

Objective(s): Contrast-enhanced magnetic resonance imaging (MRI) of breast cancer provides valuable data on the disease state of patients. Biocompatible nanoprobes are expected to play a pivotal role in medical diagnosis in the future owing to their prominent advantages. The present study aimed to introduce a novel biocompatible nanoprobe based on lipoproteins for breast cancer cell imaging.

Materials and Methods: In this study, a biocompatible nanoprobe based on high-density lipoprotein was synthesized successfully. Scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), and dynamic light scattering (DLS) were used for material characterization, and cellular uptake and in-vitro and in-vivo imaging were investigated using the nanoprobe.

Results: The nanoprobe could significantly reduce the relaxation time in the phantom and cancer cells with no toxicity in the studied cells. In addition, the nanoprobe demonstrated proper cellular uptake in the cancer cells. The in-vivo tumor images were obtained 30, 60, and 120 minutes after the injection of the nanoprobe (5.0 µmol/kg) via the tail vein, and the results indicated that the synthesized nanoprobe could be introduced as a potential MRI contrast agent.

Conclusion: Future developments may allow the application of this nanoparticle to be used in pathological and physiological processes in preclinical models.

Keywords: *Breast Cancer, Contrast Agent, High-density Lipoprotein, Nanoprobe*

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INTRODUCTION

Cancer is considered to be a global, complex disease associated with high mortality in different countries. According to the World Health Organization (WHO), 17 million individuals are expected to be at the risk of cancer by 2020 [1-2].

Diagnosis of cancer in the early stages is highly effective in the prevention of disease expansion, and diagnostic methods play a pivotal role in the successful treatment of cancer [3-4]. Despite the availability of numerous diagnostic techniques, magnetic resonance imaging (MRI) has gained special attention in clinical and research settings as a noninvasive and relatively inexpensive modality. MRI has numerous benefits, while it requires proper contrast agents to compensate for its low sensitivity and increase its relaxation time.

Nanotechnology has unique properties and is effective in the signal enhancement of various imaging modalities. The nanoparticles that are based on natural materials for biocompatibility could be considered a major strategy for the elimination of the restrictions that are detected in the other contrast agents used for imaging [5-8].

Among various properties that are considered in the design of appropriate nanoprobes, the main influential factors include a proper complex with high stability in the circulatory system and ability to deliver large amounts of ion-targeted

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gadolinium-based MRI toward cancer cells [9-10] .

Lipoproteins are composed of one water-soluble protein and other water-insoluble lipids, which lead to the selectivity of the behavior of the cell membrane. High-density lipoprotein (HDL) is composed of smaller lipid nanoparticles (diameters: 5-112 nm) compared to low-density lipoprotein (LDL). HDL becomes stable through interacting with apolipoprotein A-1 proteins, which contains 243 amino acids and two amphipathic α-helix structures [11] . To date, HDL has been used to convey various types of drugs [12-15]. One of the first studies using HDL as a nanocarrier for disease treatment was conducted at Van Berkel Laboratory in the Netherlands [16]. According to the obtained results, lipophilic antiviruses and the analogous of dioleyl iododeoxyuridine and 9-(2-phosphonylmethoxyethyl) adenine could be delivered to liver cells. The other studies in this regard have employed HDL as a nanocarrier for chemotherapy [17-24]. In the present study, a human HDL nanoprobe was synthesized successfully, and the obtained results indicated that the nanoprobe had a spherical shape with the proper size to enter cells with no cell toxicity. Moreover, cell reabsorption and relaxation time were evaluated in an animal model at various times. The synthesized nanoprobe could be introduced as an appropriate biocompatible contrast agent for breast cancer cell imaging.

MATERIALS AND METHODS

Experimental materials

The experimental materials required for this study were obtained from Sigma-Aldrich Chemical Co. (USA), including HDL (high-density from human plasma lyophilized powder; Sigma-Aldrich Co., USA), 3-(trimethoxysilylpropyl)diethylenetriamine, bromoacetic acid (≥99.0%), ethanol, oleic acid (≥99.0%), ethyl(dimethylaminopropyl)carbodiimide (EDC)/N-hydroxysulfosuccinimide (Sulfo-NHS) (≥98.0%), gadolinium(III) chloride ($GdCl_3$) (3-aminopropyl) triethoxysilane (APTES) (99%), dimethyl sulfoxide (DMSO), and sodium hydroxide (NaOH). Neuberger chambers and dialysis bags (cutoff: 12,000 Da) were also obtained from the Spectrum Lab (USA). MCF-7 (human breast cancer cell) and MCF-10A cell lines (non-tumorigenic epithelial cell) were purchased from Pasteur Institute (Tehran, Iran), and BALB/c mice were supplied from the Cancer Research Center at Tehran University of Medical Sciences (Tehran, Iran).

Synthesis of the nanoprobe, chelator, and Si-DTTA

For the synthesis of the chelator, 0.4 gram of 3-(trimethoxysilylpropyl)diethylenetriamine and one gram of bromoacetic acid were dissolved in two milliliters of distilled water, and two molar of sodium chloride (NaOH) solution was added to the the resultant solution, with the temperature increased to 50°C. Following that, NaOH (6 ml; 2 M) was added and stirred for three hours at the same temperature. Afterwards, the solvent was removed under pressure, and an oily substance was obtained and washed three times with distilled water and ethanol (compound A).

Conjugation of Si-DTTA to oleic acid

Initially, a mixture of oleic acid in distilled water was obtained and stirred for 15 minutes. Following that, the crosslinker agents (EDC/sulfo-NHS) were added to the resultant structure, and compound B was obtained with the addition of APTES and after stirring for two hours. Compound A was added to compound B, and the mixture was stirred for one hour. The final stages involved centrifugation and dialysis (cutoff: 12,000 Da).

Conjugation of HDL to the chelator

After the dissolution of compound C in DMSO, HDL (500:1) was added to the obtained solution and stirred for four hours. After 16 hours of dialysis, compound D was obtained.

Synthesis of the nanoprobe

To synthesize the nanoprobe, 100 grams of compound D was dissolved in distilled water and stirred at room temperature. Afterwards, 0.5 molar of gadolinium chlorides was added to the solution, and the pH of the medium was set at nine. After stirring for three hours at room temperature, the solution was dialyzed in order to separate the unloaded Gd^{3+}.

Characterization

The morphology, size, and zeta potential of the synthesized nanoprobe were characterized using SEM (HITACHI S-4160), DLS and a zeta potentiometer (Malvern Instruments, UK), respectively. In addition, FTIR (Thermo Nicolet, Nexus 870 FTIR, USA) was utilized to determine the chemical structure, and Gd^{3+} concentration was detected by inductively coupled plasma optical emission spectrometry (ICP-AES; Optima 2300, Perkin-Elmer).

In-vitro analysis

MTT assay

The MTT assay was used to evaluate the cytotoxicity of the nanoprobe on the MCF-10A and MCF-7 cell lines. In total, 5×10^5 MCF-10A

and MCF-7 cells were cultured in 200 microliters of Dulbecco's modified eagle medium and 10% of fetal bovine serum (FBS). After 24 hours, the culture medium was replaced with 10% FBS. Following that, 10, 50, and 100 µg/ml of the nanoprobe and 100 µg/ml of HDL were incubated for 48 hours. At the next stage, 20 microliters of the MTT solution was added to each well and incubated at the temperature of 37°C with 5% CO_2 for four hours. During incubation, MTT reduced by the mitochondrial dehydrogenase enzyme, and blue formazan crystals were produced. The absorbance of the specimen was read using the ELISA reader (ELX800, Biotek, USA) at the wavelength of 570 nanometers [25].

Cellular uptake

Initially, the cells were put in contact with a specific concentration of the nanoprobe at 0.5, two, four, and six hours at the temperature of 37°C. Following that, various concentrations of the nanoprobe were added to each well, and the cells were incubated for six hours in the same conditions.

The cells were washed with phosphate buffered saline (PBS; 500 µl) and centrifuged at 1,000 rpm for four minutes in 100 microliters of PBS. The cell reabsorption of the Gd^{3+} ions was determined via ICP-AES. Based on the concentrations of the Gd^{3+} ions and total cell count, the mean cellular absorption of the Gd^{3+} ions was calculated by the counting of each cell. The measurements were performed in triplicate, and the obtained mean values were reported.

Relaxation time (T_1 and T_2)

Protocol

At this stage, MRI (1.5 T) with the head coil located in Vali-e Asr Hospital Imaging Center of Tehran University of Medical Sciences was applied for the evaluation of the relaxation time. In order to obtain T_2, a multipoint method was applied. The T_E exponential curve was achieved in terms of the intensity of the signal in the echoes of an ecosystem 32 (1st echo) echo sequence with equivalents (2 ms) and 3,000 ms (matrix=256×256, slice thickness=1.5 mm, non-averaged). By fitting a linear curve on the logarithm, the intensity of the signal was calculated in terms of T_E, with the slope of the line or $-1/T_2$ assessed in the Excel environment. In addition, T_1 maps were achieved using a flash protocol with the repeated times of 20, 50, 100, 200, 400, 600, 1,000, 2,000, and 3,000 milliseconds (TE: 12 ms; matrix=256×256; slice thickness=1.5 mm, non-averaged).

In-vitro studies

At this stage, 2×10^5 MCF-7 cells were cultured at the temperature of 37°C and 5% CO_2 for 24 hours.

The culture medium was discarded afterwards, and the nanoprobes with various concentrations of Gd^{+3} (0.086, 0.0645, 0.043, 0.0215, 0.01075, and 0.00535 mM) was added to each well and incubated for two hours. The cells were washed twice with PBS (0.5 ml), and 0.5 milliliter of trypsin was added to each well; after 5-10 minutes, the cells were detached and suspended. MRI was performed, and image analysis was analyzed in the DICOM software version 1.3.0.5. (MEDAV GmbH Company). In addition, the ICP method was used to determine the gadolinium concentration in the cell. To this end, the cell was dissolved in concentrated nitric acid (1 ml). After centrifugation (1,500 rpm) for five minutes at the temperature of -7°C, the cell was diluted to distilled water (1:5), and after 10 minutes of sonication, ICP was applied.

In-vivo studies

To evaluate the efficacy of the synthesized nanoprobe in animal breast cancer cell imaging, *in-vivo* tests were carried out. Each BALB/c rat was anesthetized via the intraperitoneal injection of ketamine/xylazine (10 mg/kg of body weight), and Murine mammary adenocarcinoma cells were injected intraperitoneally at the right flank. After approximately four weeks, tumor growth was tracked. To this end, the nanoprobe was injected into normal and cancerous animals at the desired concentration, and images were obtained based on the T1-weighted sequence using an MRI (1.5 T) device. The process was performed immediately after the injection (repetition time: 1,120 ms, echo time: 24 ms, field of view: 60×60 mm, matrix size: 512×512, contiguous slice thickness: 2 mm).

Statistical analysis

Multigroup comparison of the means was performed using one-way analysis of variance (ANOVA). In all the statistical analyses, the P-value of less than 0.05 was considered significant, and the obtained results were expressed as mean and standard deviation (n=3-5).

Table 1. Properties of Synthesized Nanoprobe and HDL (Zeta Potential and DLS)

Sample	Zeta Potential (mV)	Average Diameter (nm)	PDI
HDL	-8.88	12	0.4
Nanoprobe	-18.4	55	0.43

RESULTS

Synthesis of the nanoprobe

Fig 1 depicts the SEM results of the synthesized HDL and spherical morphology of the nanoprobe. As can be seen, the spherical shape of HDL had no changes after the synthesis of the nanoprobe. Table 1 shows the mean diameter and zeta potential of HDL and the nanoprobe. Accordingly, the mean diameter of HDL and the nanoprobe was 12 and 55 nanometers, while the zeta potential was estimated at -8.88 and -18.4 mV, respectively.

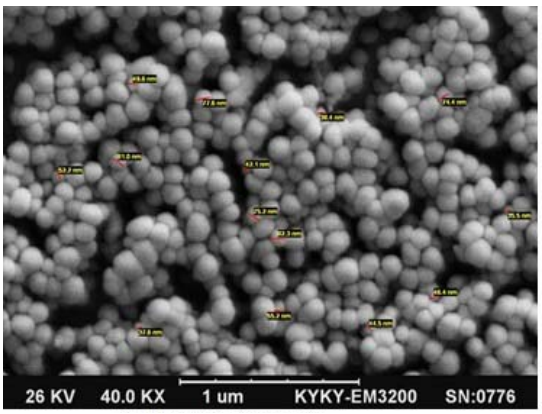

Fig 1. SEM Image of Synthesized Nanoprobe with Spherical Shape

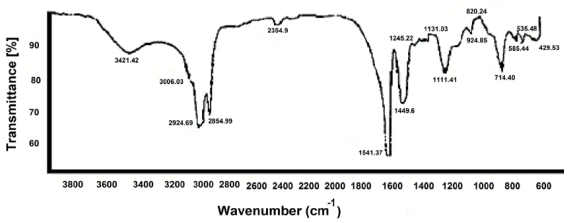

Fig 2. FTIR Spectrum of Synthesized Nanoprobe

Fig 2 shows the FTIR spectrum of the nanoprobe and its absorbance peaks. As is depicted, the peak in the region of 3,421 cm^{-1} was attributed to the amin group, while the peak in the region of 1,561 cm^{-1} represented the formation of the carbonyl group. In addition, the strong peak associated with the Si-O-Si absorption band was observed within the range of 11,000-1,200 cm^{-1}, while OH-silane was within the range of 3,000-3,400 cm^{-1}.

In-vitro studies

MTT assay

The cytotoxicity studies of the nanoprobe on normal and cancer cells are shown in Fig 3. As is observed, the diverse concentrations of the nanoprobe had no toxicity on either of the mentioned cells; therefore, it could be concluded that these nanocarriers were compatible with the cells (P<0.05).

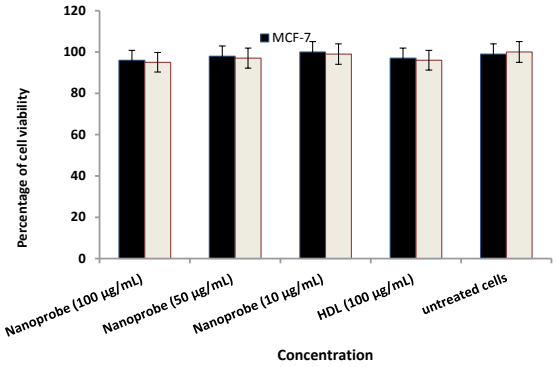

Fig 3. MTT Results of Nanoprobe, HDL Exposure to Human Breast Cancer Cell Lines (MCF-7), and Non-tumorigenic Epithelial Cells (MCF-10A) (No significant toxic effects observed; P<0.05)

Cellular uptake of the nanoprobe

Figs 4 and 5 depict the cellular uptake of the synthesized nanoprobe at various times (0.5, 2, 4, and 6 hours) and its concentration at six hours, respectively. According to the obtained results, cellular uptake increased with time, with a regular trend achieved with concentration.

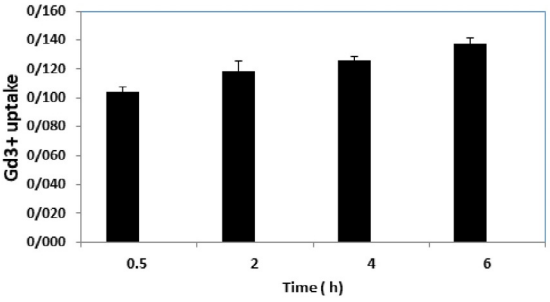

Fig 4. Cellular Uptake of Nanoprobe at Various Times

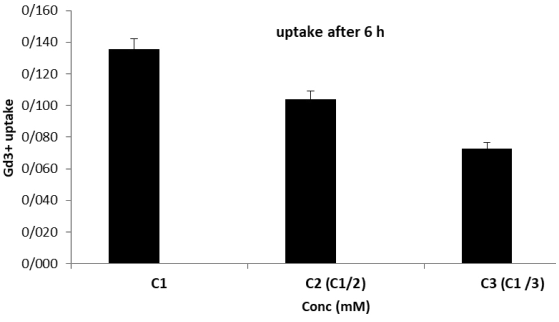

Fig 5. Intra-cellular Uptake of Nanoprobe after Six Hours

In-vitro MRI experiment

An *in-vitro* MRI experiment was performed in order to achieve adequate concentrations of the internalized nanoprobe for the MRI visualization of the cancer cells. To this end, the MCF-7 cells were incubated for one hour in the presence of the nanoprobe (100 µM). According to the findings, the cells that were labeled with the nanoprobe displayed a strong, intense signal on the T1-weighted spin-echo image. On the other hand, the untreated cells demonstrated the efficient uptake of the nanoprobe.

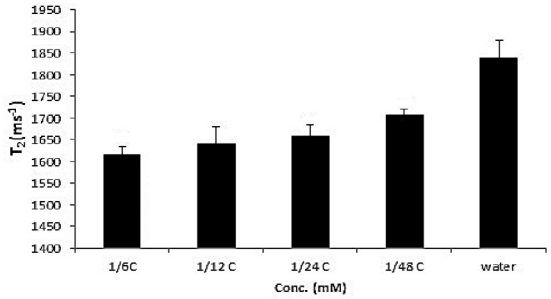

Fig 6. T2 Data Based on Spin-echo and Gradient-echo Protocols

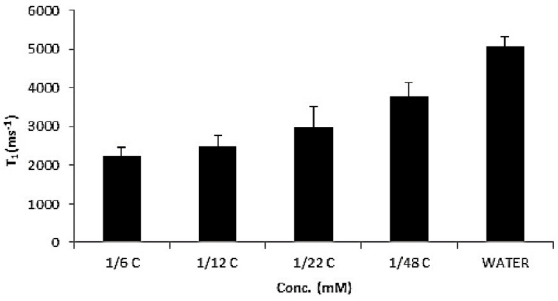

Fig 7. T1 Data Based on Spin-echo and Gradient-echo Protocol

Figs 6 and 7 show the findings of the current research on T_1/T_2 relaxation times. It is notable that the spin-echo and gradient-echo protocol results needed to be further processed in order to derive the data in Tables 1-B and 1-C. Accordingly, the synthesized nanoprobe significant decreased the T_1 and T_2 relaxation times compared to water ($P<0.001$).

In-vivo tumor imaging

The efficacy of the synthesized nanoprobe as an *in-vivo* MRI contrast agent was evaluated, and the tumor images were obtained 30, 60, and 120 minutes after the injection of the nanoprobe (5.0 µmol/kg) via the tail vein. In addition, the *in-vivo* imaging indicated that the synthesized nanoprobe could be introduced as a potential MRI contrast agent (Fig 8).

DISCUSSION

The present study aimed to synthesize a novel nanoprobe as an invasive contrast agent for MRI imaging. To this end, a biocompatible lipoprotein nanoprobe was selected as a carrier of Gd^{+3} in breast cancer diagnosis. The morphology and size of the synthesized nanoprobe were characterized using SEM (Fig 1) and DLS (Fig 2). The SEM results confirmed the spherical shape of the nanoparticles, while DLS determined the average diameter to be 50 nanometers. Moreover, the surface charge of -18.4 mV was obtained using the zeta potentiometer.

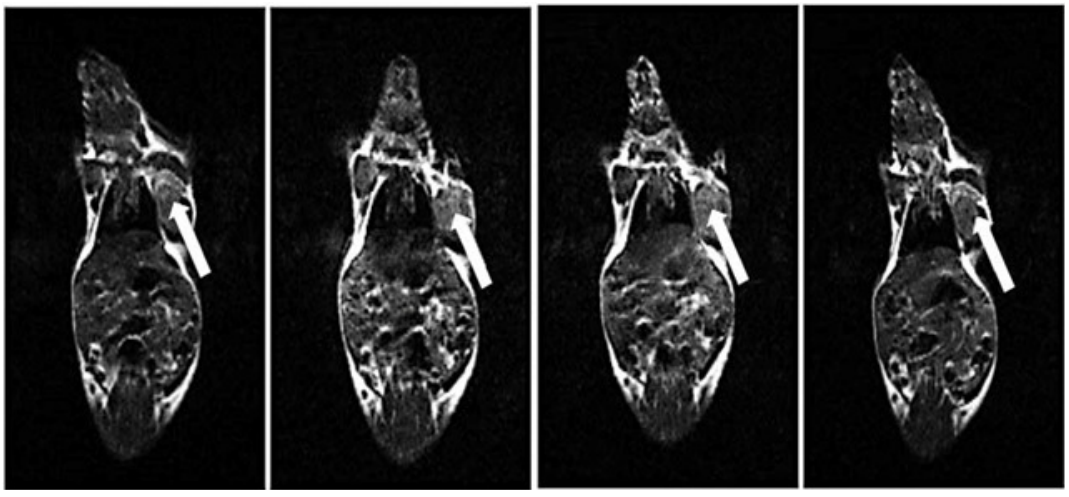

Fig 8. MRI Image of Cancerous Animal Model at Various Times (30, 60, and 120 minutes)

Biocompatibility and cytotoxicity are important parameters in the investigation of nanoscale compounds. The cytotoxic activity of the HDL nanoparticles loaded with Gd^{+3} (nanoprobe) on the MCF-7 and MCF-10A cells was also investigated. According to the obtained results, the nanoprobe caused no toxicity in the normal and cancer breast cells (concentration up to 100 µg/ml) (Fig 3).

Nanoprobe reabsorption in cancer cells is considered critical in the design of nanoprobes for imaging processes. As can be seen in Fig 4, the absorption rate of the synthesized nanoprobe in the cancer cells was high and had an increasing trend with time. As is depicted in Fig 5, the absorption rate of the nanoprobe increased at higher concentrations. Furthermore, the ICP test results indicated that the intracellular penetration of the synthesized nanoprobe was high, resulting in the high accumulation of the nanoprobe inside the cells. Previous findings have indicated that the HDL carriers of Gd^{+3} could successfully target the cancer cells, thereby leading to the release of Gd^{+3} into malignant tumor cells [26].

The main objectives of the current research were MRI imaging using HDL nanoparticles and determining the efficacy of the applied nanoprobe. MRI imaging was performed with T_1 and T_2 relaxation times after tumor growth. Excellent contrast and high-resolution images were observed owing to the higher accumulation of this compound in the cancer cells compared to the normal cells. Moreover, the obtained results indicated that the synthesized nanoprobe reduced T_1 and T_2 relaxation times more significantly compared to water, thereby increasing the contrast (Figs 6 & 7).

The *in-vitro* studies of the BALB/c mice demonstrated the distinct increment of the contrast and high resolution in the treatment of the Gd^{+3}-loaded HDL nanoparticles. Furthermore, the intravenous injection of the nanoprobe in the cancer model of mice showed that this substance could provide appropriate contrast between the tumor and surrounding tissues, with the tumor detected visibly. This phenomenon was attributed to the ability of the nanoprobe to enter the cancer cells due to the high expression of its receptors in these cells (Fig 8).

According to the findings of the current research, the synthesized nanoprobe was well adapted to the body, and the molecules of contrast compositions were largely accumulated in the cancer tissues, representing proper performance in the selective imaging of breast cancer cells. Use of HDL nanoparticles as a molecular contrast agent is a noninvasive approach to investigating the changes on a molecular level, which is a promising and highly sensitive method. In the present study, the tumor-oriented MRI contrast agent based on the nanoprobe targeted to the HDL receptors, which were overexpressed in the tumor cells, indicating the ability of the nanoprobe to enhance the T_1-weighted images.

In a study in this regard, the efficacy of a nanoprobe was evaluated as an *in-vivo* MRI contrast agent, and the tumor images were obtained a few minutes after the tail vein injection of the nanoprobe at the concentration of 5.0 µmol/kg. In another research conducted by Rijpkema et al., the MRI data were obtained from the HDL-containing contrast compositions for the detection of human tumors. According to the results of the mentioned study, the rate of the contrast absorbance after transfusion increased significantly by HDL and was clearly visible after the injection [27]. This finding is consistent with the results of the present study.

CONCLUSION

In this study, an HDL-based nanostructure system was successfully designed as a probe for the detection of breast cancer. In general, HDL nanoparticles in the form of a nanoprobe could be a promising protocol for cancer diagnosis *in-vivo*.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin. 2012; 62(1): 10-29.
2. Mousavi SM, Mohagheghi MA, Mousavi-Jerrahi A, Nahvijou A, Seddighi Z. Outcome of breast cancer in Iran: a study of Tehran Cancer Registry data. Asian Pac J Cancer Prev. 2008; 9(2): 275-278.
3.Raymond KN, Pierre VC. Next generation, high relaxivity

gadolinium MRI agents. Bioconjug Chem. 2005; 16(1): 3-8.
4.Loomans-Kropp HA, Umar A, Cancer prevention and screening: the next step in the era of precision medicine. NPJ Precis Oncol. 2019; 3: 3.
5.Shahbazi-Gahrouei D, Moradi Khaniabadi P, Moradi Khaniabadi B, Shahbazi-Gahrouei S. Medical imaging modalities using nanoprobes for cancer diagnosis. A literature review on recent findings. J Res Med Sci. 2019; 24: 38.
6.Joan Estelrich, María Jesús Sánchez-Martín, Maria Antònia Busquets. Nanoparticles in magnetic resonance imaging: from simple to dual contrast agents. Int J Nanomedicine. 2015; 10: 1727–1741.
7.Zhang Z, Chen J, Ding L, Jin H, Lovell JF, Corbin IR, Cao W, Lo PC, Yang M, Tsao MS, Luo Q, Zheng G. HDL-mimicking peptide-lipid nanoparticles with improved tumor targeting. Small. 2010; 6(3): 430-437.
8.Koning GA, Krijger GC. Targeted multifunctional lipid-based nanocarriers for image-guided drug delivery. Anticancer Agents Med Chem. 2007; 7(4): 425-440.
9.Shahbazi-Gahrouei D, Williams M, Rizvi S, Allen BJ. In vivo studies of Gd-DTPA-monoclonal antibody and Gd-porphyrins: potential MR imaging contrast agents for cancer. J Magn Reson Imaging. 2001; 14(2):169-174.
10.Monika A. Cywińska, Ireneusz P. Grudziński, Andrzej Cieszanowski, Michał Bystrzejewski, Magdalena Popławska. Pol J Radiol. 2011; 76(2): 28–36.
11.Luke J. Leman, Bruce E. Maryanoff, and M. Reza Ghadiri. Molecules that Mimic Apolipoprotein A-I: Potential Agents for Treating Atherosclerosis. J Med Chem. 2014; 57(6): 2169–2196.
12.Sangram Raut, Linda Mooberry, Nirupama Sabnis, Ashwini Garud, Akpedje Serena Dossou, and Andras Lacko, Reconstituted HDL: Drug Delivery Platform for Overcoming Biological Barriers to Cancer Therapy. Front Pharmacol. 2018; 9: 1154.
13.Alan T Remaley, Marcelo Amar, Dmitri Sviridov. HDL-replacement therapy: mechanism of action, types of agents and potential clinical indications. Expert Rev Cardiovasc Ther. 2008; 6(9): 1203–1215.
14. Lacko AG, Sabnis NA, Nagarajan B, McConathy WJ. HDL as a drug and nucleic acid delivery vehicle. Front Pharmacol. 2015; 6: 247.
15.Ma X, Song Q, Gao X. Reconstituted high-density lipoproteins: novel biomimetic nanocarriers for drug delivery. Acta Pharm Sin B. 2018; 8(1): 51-63.
16.Bijsterbosch MK, Van Berkel TJ. Lactosylated high density lipoprotein: a potential carrier for the site-specific delivery of drugs to parenchymal liver cells. Mol Pharmacol. 1992; 41(2): 404-411.
17.McConathy WJ, Nair MP, Paranjape S, Mooberry L, Lacko AG. Evaluation of synthetic/reconstituted high-density lipoproteins as delivery vehicles for paclitaxel. Anticancer Drugs. 2008; 19(2): 183-188.
18.Corbin IR, Ng KK, Ding L, Jurisicova A, Zheng G. Near-infrared fluorescent imaging of metastatic ovarian cancer using folate receptor-targeted high-density lipoprotein nanocarriers. Nanomedicine (Lond). 2013; 8(6): 875-890.
19.Gong M, Zhang Q, Zhao Q, Zheng J, Li Y, Wang S, Yuan Y. Development of synthetic high-density lipoprotein-based ApoA-I mimetic peptide-loaded docetaxel as a drug delivery nanocarrier for breast cancer chemotherapy. Drug Deliv. 2019; 26(1): 708-716.
20.Wang T, Subramanian C, Yu M, White PT, Kuai R, Sanchez J, Moon JJ, Timmermann BN, Schwendeman A, Cohen MS. Mimetic sHDL nanoparticles: A novel drug-delivery strategy to target triple-negative breast cancer. Surgery. 2019. pii: S0039-6060(19)30349-30356.
21.Emily E. Morin, Xiang-An Li, Anna Schwendeman. HDL in Endocrine Carcinomas: Biomarker, Drug Carrier, and Potential Therapeutic. Front Endocrinol (Lausanne). 2018; 9: 715.
22.Lacko AG, Nair M, Paranjape S, Johnso S, McConathy WJ. High density lipoprotein complexes as delivery vehicles for anticancer drugs. Anticancer Res. 2002; 22(4): 2045-2049.
23.Kenneth K. Ng, Jonathan F. Lovell, Gang Zheng. Lipoprotein-Inspired Nanoparticles for Cancer Theranostics. Acc Chem Res. 2011; 44(10): 1105–1113.
24.Yang M, Chen J, Cao W, Ding L, Ng KK, Jin H, Zhang Z, Zheng G. Attenuation of nontargeted cell-kill using a high-density lipoprotein-mimicking peptide-phospholipid nanoscaffold. Nanomedicine (Lond). 2011; 6(4): 631-641.
25. Mirzaei M, Mehravi B, Ardestani MS, Ziaee SA, Pourghasem p. In Vitro Evaluation of Gd^{3+}-Anionic Linear Globular Dendrimer-Monoclonal Antibody: Potential Magnetic Resonance Imaging Contrast Agents for Prostate Cancer Cell Imaging. Mol Imaging Biol. 2015; 17(6): 770-776.
26.Rui M, Guo W, Ding Q, Wei X, Xu J, Xu Y. Recombinant high-density lipoprotein nanoparticles containing gadolinium-labeled cholesterol for morphologic and functional magnetic resonance imaging of the liver. Int J Nanomedicine. 2012; 7: 3751-3768.
27.Rijpkema M, Kaanders JH, Joosten FB, van der Kogel AJ, Heerschap A. Method for quantitative mapping of dynamic MRI contrast agent uptake in human tumors. J Magn Reson Imaging. 2001; 14(4): 457-463.