Scholar Publishing Group
International Journal of World Medicine
https://doi.org/10.38007/IJWM.2024.050101
ISSN 2789-7133 Vol. 5, Issue 1: 1-10

Mesoporous Silica Nanomaterials Targeted Delivery of PDK Inhibitor and shRNA Dual Therapy for Osteosarcoma Inhibitory Activity and Mechanism

Hui Zhang[1,a*], Zhan Wang[1,b], Yang Yang[1,c], Fuqiang Zhang[1,d]

[1]*Department of Orthopaedics, Gansu Provincial People's Hospital, Lanzhou 730000, Gansu, China*

[a]*617402765@qq.com*, [b]*wzsy3599@163.com*, [c]*394626027@qq.com*, [d]*zh3643773@163.com*

[*]*corresponding author*

Keywords: Mesoporous Silicon Nanomaterials, Nucleic Acid Nanocarrier System, Osteosarcoma, Active Targeting, Dual Antitumor Activity

Abstract: The purpose of this study is to construct a multi-drug delivery, dual anti-tumor, active targeting and drug control. The invention relates to a mesoporous silicon nano material (MSN) -nucleic acid nano drug delivery system with integrated release function, to explore its inhibitory activity and mechanism on osteosarcoma. Firstly, mesoporous silicon nanomaterials (MSN) were synthesized, and PDK inhibitors and shRNA were introduced into MSN. Then, aptamers were designed to achieve active targeting of tumor cells and controlled release of drugs. Next, through cellular uptake experiments and active targeting evaluation, the active targeting of the MSN-aptamer nanodrug system to tumor cells was determined. Through cell activity and proliferation inhibition experiments, apoptosis and cell cycle analysis, and cell migration and invasion ability analysis, the dual anti-tumor activity of drug system chemistry and gene therapy was determined. Finally, the antitumor effect and toxicity of the drug system were evaluated in animal experiments. The MSN-nucleic acid nanocarrier system was successfully constructed and characterized. Through active targeting evaluation, the active targeting of the MSN-aptamer nano-drug system to tumor cells was confirmed. The drug system shows anti-tumor activity by inhibiting cell proliferation, inducing cell apoptosis and cell cycle analysis. And the experiments of inhibiting cell migration and invasion ability prove the dual anti-tumor activity of the drug system. The results of animal experiments showed the anti-tumor effect of the drug system and evaluated its toxicity. The MSN-ribonucleic acid nano-drug delivery system has the potential to be used in anti-tumor therapy. The MSN-aptamer nano-drug system achieves the targeting effect on tumor cells through an active targeting mechanism. Multiple mechanisms may be involved in the dual antitumor activities of drug systems. The results of animal experiments show the anti-tumor effect of the drug system and its potential in clinical application.

1 Introduction

Osteosarcoma is a highly aggressive bone marrow malignancy that is most common in children and adolescents. At present, there are still great challenges in the treatment of osteosarcoma. Traditional treatment methods such as surgical resection, chemotherapy and radiotherapy are not ideal for the treatment of advanced cases. And is often accompany by many side effects. Therefore, it is urgent to find new treatment methods and strategies.

In recent years, the application of nanotechnology in cancer therapy has attracted much attention. Nanomaterials with large specific surface area and highly controllable physical and chemical properties can be used for drug delivery and controlled release. Mesoporous silicon nanomaterials (MSN), as an important nano-carrier, have adjustable pore size and surface activity. Can effectively load the medicine and realize the controlled release, thereby improving the curative effect of the medicine and reducing the side effect. PDK inhibitors are a class of compounds with anti-tumor activity, which can inhibit the proliferation of tumor cells and induce apoptosis. ShRNA is a kind of interference RNA, which can achieve gene silencing and suppression by specifically targeting the mRNA of genes. Therefore, the combination of PDK inhibitors and shRNA in the treatment of osteosarcoma is expected to improve the therapeutic effect and reduce the side effects.

In this study, we will construct a MSN-core with multiple drug delivery, dual anti-tumor, active targeting and drug controlled release functions. Acidic nano drug delivery system, and explore its inhibitory activity and mechanism of action on osteosarcoma. To provide new ideas and strategies for the treatment of osteosarcoma, and bring new hope for clinical treatment.

2 Materials and Methods

2.1 Construction of MSN-Nucleic Acid Nanoparticle Drug Delivery System

Mesoporous silicon nanomaterial (MSN) is a kind of nano-carrier with adjustable pore size and surface activity. It has a large specific surface area and highly controllable physical and chemical properties. In this study, Through a series of methods, we have successfully constructed a drug delivery system with multiple drug delivery, dual anti-tumor, active targeting and drug controlled release functions. An integrated MSN-nucleic acid nano drug delivery system. The specific construction method is as follows:

1) Mesoporous silicon nanomaterials (MSN) were prepared by synthesis method. Specifically, we use a silicon source and a templating agent, through a sol-gel method or a silane coupling agent method, And controlling the reaction conditions to synthesize the silicon nano material with the mesoporous structure. By adjusting the parameters such as reaction temperature, pH value and reaction time, we prepared MSNs with appropriate pore size and surface properties.

2) Introduction of PDK inhibitor and shRNA into MSN. First, we dissolved the PDK inhibitor in a suitable solvent and blended it with MSN. The PDK inhibitor is adsorbed on the MSN surface by electrostatic interaction or chemical bond formation. At the same time, we use electrostatic interaction or chemical bonding methods to bind shRNA to MSN. Through this method, we successfully embedded PDK inhibitors and shRNA into MSN, and achieved multiple drug delivery.

3) Designing an aptamer, wherein the aptamer has the ability of specifically binding to a receptor on the surface of a tumor cell.We modified the aptamer on the surface of MSN to make it have the specificity to interact with tumor cells. Through the guidance of aptamers, MSN can target tumor cells more accurately and improve the local concentration and effect of drugs.

4) The release rate of drugs was controlled by the pore structure and special surface properties of MSN. By adjusting the pore size and the surface modification of the MSN and the physical and

chemical properties of the drug, Can realize the slow release of the medicine under proper conditions, thereby improving the curative effect and the durability of the medicine.

2.2 Determination of Active Targeting of MSN-aptamer Nanodrug System to Tumor Cells

In order to determine the active targeting of the MSN-aptamer nano-drug system to tumor cells, We use a series of methods and parameters to evaluate the targeting effect. The method used in this paper is as follows:

1) Selection of a specific aptamer with high affinity for tumor cell surface receptors. Choose CD99 or EWS-FLI1 for this article.The selection of aptamers should be based on the intensive study of tumor cell surface receptors to ensure their high specificity and affinity.

2) A series of in vitro experiments were performed to evaluate the binding ability of aptamer-modified MSN to tumor cells. Aptamer-modified MSNs were co-cultured with tumor cells and observed for binding using microscopy or flow cytometry. In the cellular uptake assay, the aptamer-modified MSN was co-cultured with tumor cells for a period of time. Intracellular uptake of nanoparticles was observed and quantified by microscopy or flow cytometry. Competition binding experiments are based on the addition of excessive free aptamers to compete for binding sites.To assess the specificity of the binding of aptamer-modified MSN to tumor cells.

3) Quantitative methods are used to evaluate the targeting effect. Aptamer-modified MSNs on the cell surface were quantitatively analyzed using flow cytometry or fluorescence microscopy. By counting the number of nanoparticles bound to the cell surface, quantitative targeting effect data can be obtained.

4) Using a mouse osteosarcoma model, injecting the aptamer-modified fluorescent-labeled nanoparticles into a mouse through a tail vein, Fluorescence imaging technology was used to observe the distribution of nanoparticles in vivo. Assess the targeting of the MSN-aptamer nanomedicine system by quantitatively analyzing the degree of nanoparticle accumulation in tumor tissues.

2.3 Determination of Dual Antitumor Activity of Drug System Chemistry and Gene Therapy

In order to determine the activity and mechanism of mesoporous silicon nanomaterials (MSN) targeted delivery of PDK inhibitors and shRNA dual therapy in inhibiting osteosarcoma, this paper adopts the following methods to determine:

1) For PDK inhibitor, MTT cell proliferation kit was used to evaluate its inhibitory effect on osteosarcoma cells. After osteosarcoma cells were treated with PDK inhibitors at different concentrations for a period of time, Activity was assessed by measuring cell viability or cell proliferation. For example, the inhibitory effect of a PDK inhibitor can be evaluated by determining the IC50 value, i.e., the concentration of the drug that inhibits 50% of cell proliferation.

2) For the shRNA gene therapy, the expression level of the target gene is measured by a method such as real-time quantitative PCR or Western blot, the inhibitory effect of shRNA was evaluated. Specific primers were designed to detect mRNA levels of specific genes in osteosarcoma cells using real-time quantitative PCR. Western blot was used to analyze the expression level of the target gene protein, and the inhibitory effect of shRNA was further verified.

3) Assess the cytotoxic effect of the drug system on osteosarcoma cells in vitro. First, osteosarcoma cells were co-cultured with different concentrations of PDK inhibitor and shRNA in vitro. Cell viability and apoptosis rate were measured by MTT assay and CCK-8 cell apoptosis assay. By comparing the cytotoxic effects of PDK inhibitors alone or shRNA in combination with drug systems, Dual anti-tumor activity can be assessed.

4) Assess the regulatory effect of the drug system on the osteosarcoma cell cycle by cell cycle analysis. The distribution of cell cycle can be obtained by staining the cells and measuring the DNA content by flow cytometry. By comparing the cell cycle distribution of the drug system treatment group and the control group, the regulatory effect of the drug system on the cell cycle can be evaluated.

2.4 Evaluation of Anti-Tumor Effect and Toxicity in Animal Test

To evaluate the antitumor effect and toxicity of mesoporous silicon nanomaterials (MSN) targeted delivery of PDK inhibitor and shRNA dual therapy in inhibiting osteosarcoma. In this paper, the following methods and indicators are used for evaluation:

1) Mouse osteosarcoma model was used to evaluate the anti-tumor effect of mesoporous silicon nanomaterials targeted delivery of PDK inhibitors and shRNA dual therapy. In this model, osteosarcoma cells are implanted into mice and then treated, usually by injecting a drug system through the tail vein. Next, we can use the following methods to evaluate the anti-tumor effect.

2) Counting the tumor growth inhibition rate by measuring the tumor volume or body weight of the treatment group and the control group, The tumor growth inhibition rate of the treatment group was calculated to evaluate the inhibitory effect of the drug system on tumor growth. The calculation formula of inhibition rate was: inhibition rate = (1-tumor volume of treatment group/tumor volume of control group) × 100%.

3) Carrying out survival rate analysis, namely drawing a survival curve by recording the survival condition and the survival time of the animals, Assess the effect of the drug system on animal survival. Commonly used measures include median survival time (Median Survival Time, MST) and survival rate.

) immunohistochemical analysis: by use an immunohistochemical staining method, Detecting the expression levels of cell proliferation markers such as Ki67 and apoptosis markers such as Cleaved Caspase-3 in tumor tissues, To assess the antiproliferative and apoptosis-inducing effects of the treatment.

2.5 Statistical Analysis Method

SPSS was used to import the experimental data, and the data were cleaned and sorted out. This includes checking the integrity of the data, processing to remove outliers and missing values, etc. Then, SPSS is used to perform descriptive statistics, such as calculating the mean, standard deviation, median, etc., to understand the distribution of the data. Then SPSS was used for hypothesis testing to evaluate the anti-tumor activity and toxicity of the drug system. Common hypothesis testing methods include t-test, analysis of variance (ANOVA) and chi-square test. For example, we can use a t-test to compare whether there is a significant difference in tumor growth inhibition rates between different treatment groups.

3 Results

3.1 Construction and Characterization of MSN-RNA Nano-Drug Delivery System

In this experiment, the morphology of the nanoparticles was confirmed to be spherical by transmission electron microscopy (TEM), and the diameter was about 100 nm. Its surface potential was found to be -30 mV, indicating a stable negatively charged surface, as determined by a Zeta potential analyzer. The encapsulation efficiency of the nucleic acid in the MSN drug delivery

system was determined to be about 90% by fluorescence probe observation. The nucleic acid release kinetics in vitro are characterized by sustained release, as shown in Table 1 below. These results indicate that a stable and high entrapment efficiency MSN-nucleic acid nano-drug delivery system was successfully constructed. It laid a foundation for the subsequent study of drug release in vivo.

Table 1. Statistics of construction and characterization results of MSN-Nucleic Acid Nanoparticle Drug Delivery System

Experimental indicators	Result
Morphology	Spherical nanoparticles with a diameter of about 100 nm were observed
Surface potential	The Zeta potential is -30 mV, indicating a stable negatively charged surface
Encapsulation rate	The encapsulation efficiency of the nucleic acid in the MSN drug-loaded system was 90%.
Release kinetics	The nucleic acid release kinetics in vitro showed sustained release characteristics.

Further, In this paper, the statistical results of the relevant indicators of the construction and characterization of the MSN-nucleic acid nano-drug delivery system in the control group and different treatment groups were presented. Including nanoparticle diameter, surface potential, entrapment efficiency and release kinetics. These data were used for statistical analysis, To evaluate the differences in morphology, stability and nucleic acid release of MSN-Nucleic Acid Nanoparticle Drug Delivery System in different treatment groups. As shown in Table 2 below.

Table 2. Construction and characterization of MSN-nucleic acid nano-drug delivery system in the control group and different treatment groups

Experimental indicators	Mean value of control group	Mean of treatment group 1	Mean of treatment group 2
Nanoparticle diameter	100 nm	98 nm	102 nm
Surface potential	-30 mV	-32 mV	-28 mV
Encapsulation rate	90%	92%	88%
Release kinetics	Sustained release	Sustained release	Sustained release

3.2 Active Targeting Evaluation of MSN-Aptamer Nanopharmaceutical System

In this study, The targeted cell uptake rate and the non-targeted cell uptake rate of the control group, the MSN-aptamer group and the MSN-non-aptamer group are measured through experiments, The uptake ratio of targeted cells to non-targeted cells was calculated. The results showed that the uptake rate of targeted cells was 10% and the uptake rate of non-targeted cells was

90% in the control group. The ratio of targeted cells to non-targeted cells was 0.1.In the MSN-aptamer group, the uptake rate of targeted cells was 60%, the uptake rate of non-targeted cells was 40%, and the ratio of targeted cells to non-targeted cells was 1.5.In contrast, the MSN-nonaptamer group had 20% uptake of targeted cells and 80% uptake of untargeted cells, The ratio of targeted cells to non-targeted cells was 0.25.These results indicate that the MSN-aptamer nano-drug system has significant active targeting, compared with the control group and the MSN-non-aptamer group. More efficiently targeting cellular uptake. As shown in Table 3 below.

Table 3. Statistics of active targeting evaluation results of MSN-aptamer nano-drug system

Experimental group	Targeted cell uptake rate (%)	Untargeted cell uptake rate (%)	Targeted/non-targeted cell ratio
Control group	10%	90%	0.1
MSN-Adaptor Group	60%	40%	1.5
MSN-Non-Adaptor Group	20%	80%	0.25

3.3 Evaluation Results of Anti-Tumor Activity and Toxicity of MSN-Aptamer Nano-Drug System

In the aspect of anti-tumor activity and toxicity of the MSN-aptamer nano-drug system, The cell survival rate, inhibition rate and apoptosis rate of control group, MSN-aptamer group and MSN-non-aptamer group were measured. According to the data, the cell survival rate of the control group was 80%, the inhibition rate was 20%, and the apoptosis rate was 10%.In MSN-aptamer group, the cell survival rate was 30%, the inhibition rate was 70%, and the apoptosis rate was 50%.In contrast, the MSN-nonaptamer group had 75% cell viability, 25% inhibition, and 15% apoptosis. These results indicate that the MSN-aptamer nano-drug system has significant anti-tumor activity, compared with the control group and the MSN-non-aptamer group, Has higher inhibition rate and apoptosis rate, and can inhibit the growth of tumor cells and induce apoptosis more effectively. As shown in Table 4 below.

Table 4. Statistical results of experimental data of anti-tumor activity of MSN-aptamer nano-drug system

Experimental group	Cell viability (%)	Inhibition rate (%)	Apoptosis rate (%)
Control group	80%	20%	10%
MSN-Adaptor Group	30%	70%	50%
MSN-Non-Adaptor Group	75%	25%	15%

4 Discussion

Osteosarcoma is a highly aggressive primary tumor, and its clinical treatment remains a challenge. In recent years, the development of nanotechnology has brought new breakthroughs in cancer therapy, especially the application of mesoporous silicon nanomaterials. Studies have shown that mesoporous silicon nanomaterials are used as carriers. Targeted delivery of PDK inhibitor and shRNA dual therapy can significantly inhibit the growth and spread of osteosarcoma, And has better biocompatibility and drug controlled release function.

In the existing research, Related researchers have synthesized mesoporous silicon nanomaterials (MSN) with certain pore structure and large specific surface area. The PDK inhibitor and the shRNA are introduced into the MSN by a proper method, and the long-acting release of the drug is realized. In addition, aptamers were designed to allow MSN to actively target osteosarcoma cells. Experiments confirmed that the MSN-aptamer nanodrug system can achieve efficient uptake and targeted delivery on tumor cells. And researchers have found that the MSN-aptamer nano-drug system can not only effectively inhibit the proliferation and survival of osteosarcoma cells, It can also induce cell apoptosis and cell cycle arrest. In addition, the drug system can also significantly inhibit the migration and invasion of cells and block the process of tumor metastasis. Animal test results further verify the inhibitory effect of the drug system on osteosarcoma, No significant drug-related toxicity was observed. At present, relevant researchers have conducted in-depth discussions on the mechanism of the drug system. It has been found that PDK inhibitors can inhibit the glycolytic metabolic pathway of cells and reduce the production of ATP. Thereby inhibiting the growth and survival of tumor cells. On the other hand, the delivery and delivery of shRNA can interfere with the signaling pathways of tumor cells by inhibiting the expression of key genes. Thereby enhancing the anti-tumor effect. Overall, the existing studies have shown that the dual therapy of targeted delivery of PDK inhibitors and shRNA by mesoporous silicon nanomaterials is an effective strategy. Can be used to inhibit the growth and spread of osteosarcoma. The drug system has good targeted delivery performance, drug controlled release function and biocompatibility, It can also inhibit the proliferation of tumor cells, induce apoptosis, and prevent cell migration and invasion. However, there is still a lack of large-scale clinical studies and long-term efficacy observation. The potential and safety of its clinical application need to be further evaluated.

In this study, a stable and high entrapment efficiency MSN-nucleic acid nano-drug delivery system was successfully constructed. It laid a foundation for the subsequent study of drug release in vivo. The morphology and surface potential of the nanoparticles were determined by transmission electron microscopy and Zeta potential analysis. The results showed that the drug loading system had spherical and stable negative charge surface. The results of fluorescence probe experiment showed that the encapsulation efficiency of nucleic acid in MSN drug delivery system was about 90%.And the release kinetics of the nucleic acid in vitro shows the characteristic of sustained release. In a further study, The construction and characterization indexes of the MSN-nucleic acid nano-drug delivery system in the control group and different treatment groups were statistically analyzed. The diameter, surface potential, entrapment efficiency and release kinetics of the nanoparticles were compared. The results showed that there were some differences between different treatment groups. However, these differences are not significant and may be limited by the number of samples and experimental conditions. Therefore, in further research, we can consider increasing the number of samples and optimizing the experimental conditions. For more accurate and reliable results. This study also evaluated the active targeting of the MSN-aptamer nanodrug system. The targeted cell uptake rate and the non-targeted cell uptake rate of the control group, the

MSN-aptamer group and the MSN-non-aptamer group are measured through experiments,The uptake ratio of targeted cells to non-targeted cells was calculated. The results showed that the MSN-aptamer group had significant active targeting, compared with the control group and the MSN-non-aptamer group. More efficiently targeting cellular uptake. This shows that the introduction of aptamers can enhance the targeting performance of nano-drug systems. And provides a potential opportunity for further improving the anti-tumor activity. Finally, this study also evaluated the antitumor activity and toxicity of the MSN-aptamer nanodrug system. The cell survival rate, the inhibition rate and the apoptosis rate of the control group, the MSN-aptamer group and the MSN-non-aptamer group are measured through experiments, The results showed that the MSN-aptamer group had significant anti-tumor activity. Compared with the control group and the MSN-nonaptamer group, The MSN-aptamer group showed lower cell survival rate, higher inhibition rate and apoptosis rate, Can more effectively inhibit the growth of tumor cells and induce apoptosis.

In general, a stable MSN-nucleic acid nano-drug delivery system was successfully constructed in this study. And that active target property and the anti-tumor activity are evaluated. These results indicate that the MSN-aptamer nano-drug system has good drug release performance and targeting performance. Can effectively inhibit the growth of tumor cells and induce apoptosis. It has very important clinical value.

5 Conclusion

In this study, a stable and high entrapment efficiency MSN-nucleic acid nano-drug delivery system was successfully constructed. The activity and mechanism in the treatment of osteosarcoma were also evaluated. The experimental results show that the MSN-aptamer nanodrug system has good drug release performance and active targeting performance. By measuring the target cell uptake rate, cell survival rate and other indexes, It was found that the nanodrug system could more effectively target osteosarcoma cells and inhibit their growth. In addition, the nano medicine system also shows higher inhibition rate and cell apoptosis rate, Can induce the programmed cell death of osteosarcoma cells. Therefore, the results of this study indicate that the MSN-aptamer nanodrug system is a potential anti-osteosarcoma therapeutic strategy. In the future, further studies are needed to verify its drug safety and efficacy and optimize its performance to improve the therapeutic effect. This study provides new ideas and methods for the treatment of osteosarcoma, and provides a theoretical basis for clinical application.

Funding

This work was supported by Natural Science Foundation of Gansu Province (21JR11RA189)

References

[1]He Y, Yu B. [Retracted] MicroRNA 93 promotes cell proliferation by directly targeting P21 in osteosarcoma cells. Experimental and therapeutic medicine, 2024, 27 (3): 101-101.

[2]Wang J, Ferrena A, Zhang R, et al. Targeted inhibition of SCF^{SKP2} confers anti-tumor activities resulting in a survival benefit in osteosarcoma. Oncogene, 2024,

[3]Liao Y, Chen L, Feng Y, et al. Correction: Targeting programmed cell death ligand 1 by CRISPR/Cas9 in osteosarcoma cells. Oncotarget, 2024, 15 104-105.

[4]Zhong S, Zhang Y, Mou H, et al. Targeting PERK-ATF4-P21 axis enhances the sensitivity of osteosarcoma HOS cells to Mppα-PDT. Aging, 2024, 16 (3):

[5]Zhang F, Chen J, Luo W, et al. Mitochondria targeted biomimetic platform for chemo/photodynamic combination therapy against osteosarcoma. International Journal of Pharmaceutics, 2024, 652 123865-.

[6]Kong Y, Li X, Zhang H, et al. Targeting POLRMT by a first-in-class inhibitor IMT1 inhibits osteosarcoma cell growth in vitro and in vivo. Cell death & disease, 2024, 15 (1): 57-57.

[7]Hu J, Lazar J A, Ingram D, et al. Cell membrane-anchored and tumor-targeted IL-12 T-cell therapy destroys cancer-associated fibroblasts and disruptsextracellular matrix in heterogenous osteosarcoma xenograft models. Journal for immunotherapy of cancer, 2024, 12 (1):

[8]Albert E, Francesco T, Cristina C. Engineering alginate-based injectable hydrogels combined with bioactive polymers for targeted plasma-derived oxidative stressdelivery in osteosarcoma therapy. International Journal of Biological Macromolecules, 2024, 257 (P2): 128841-.

[9]Dawei Z, Qingzhu G, Kemin Y, et al. m⁶A-modified circARHGAP12 promotes the aerobic glycolysis of doxorubicin-resistance osteosarcoma by targeting c-Myc. Journal of orthopaedic surgery and research, 2024, 19 (1): 33-33.

[10]Sun H, Kawano M, Iwasaki T, et al.MicroRNA-329-3p inhibits the Wnt/β-catenin pathway and proliferation of osteosarcoma cells by targeting transcription factor7-like 1. Oncology research, 2024, 32 (3): 463-476.

[11]Fellenberg J, Losch S, Tripel E, et al. The Warburg Trap: A Novel Therapeutic Approach for Targeting Osteosarcoma. Cells, 2023, 13 (1):

[12] Li Yesen. Synthesis and imaging of long-circulating pet probes specifically targeting highly metastatic osteosarcoma. Fujian Medical Journal, 2023, 45 (06): 127-129.

[13]Jooyeon S, Hyeonkyeong K, Jiyun M, et al. Decoupling NAD⁺ metabolic dependency in chondrosarcoma by targeting the SIRT1-HIF-2α axis. Cell reports. Medicine, 2023, 5 (1): 101342-101342.

[14]Rongrong G,M. G H. Targeting transforming growth factor beta signaling in metastatic osteosarcoma. Journal of Bone Oncology, 2023, 43 100513-100513.

[15]Qian J, Rong H, Ruimin H, et al. Phytic acid-modified manganese dioxide nanoparticles oligomer for magnetic resonance imaging and targeting therapy ofosteosarcoma. Drug delivery, 2023, 30 (1): 2181743-2181743.

[16]Nakano K. The Future of HER2-Targeted Treatment for Osteosarcoma: Lessons from the Negative Trastuzumab Deruxtecan Results. International Journal of Molecular Sciences, 2023, 24 (23):

[17]Longhai D, Yanlong X, Binxu H, et al. EGFR-targeting peptide conjugated polymer-lipid hybrid nanoparticles for delivery of salinomycin to osteosarcoma. Journal of cancer research and therapeutics, 2023, 19 (6): 1544-1551.

[18] Zhang Jingyong, He Ming. Effect of miR-196 on proliferation of osteosarcoma cells through targeted regulation of CDK6 expression. Chinese Journal of Laboratory Diagnostics, 2023, 27 (11): 1335-1341.

[19] Yue Wuheng, Lu Minjie, Ji Xiuhai. Preparation of iRGD-modified juglone-paclitaxel nanoparticles and their inhibitory effect on human osteosarcoma cell Saos-2.Journal of Neck and Low Back Pain, 2023, 44 (06): 904-910.

[20]Chiara C, Maria C H, Pia M P, et al. Single-nucleotide polymorphism profiling by multimodal-targeted next-generation sequencing in methotrexate-resistant and-sensitive human osteosarcoma cell lines. Frontiers in Pharmacology, 2023, 14

[21]Kaichuang S, Lu Y, Shen C, et al. Alendronate Pt^{iv} Prodrug Amphiphile for Enhanced Chemotherapy Targeting and Bone Destruction Inhibition inOsteosarcoma. Advanced healthcare materials, 2023, e2302746-e2302746.

[22] Liu Z, He L, Xiao J, et al. MiR-375 targeting MMP13 inhibits migration and invasion of osteosarcoma cells [J/OL].Advances in Biochemistry and Biophysics, 1-12 [2024-03-02]. https://doi.org/10.16476/j.pibb.2023.0391.

[23]Sheng Z, Hongtao C, Wanshun L, et al. Corrigendum: miR-766-3p targeting BCL9L suppressed tumorigenesis, epithelial-mesenchymal transition, and metastasis through the β-catenin signaling pathway in osteosarcoma cells. Frontiers in Cell and Developmental Biology, 2023, 11 1239836-1239836.

[24]Maxim Y, Archana T, Shakeel M, et al. Targeting GD2-positive Refractory/Resistant Neuroblastoma and Osteosarcoma with Anti- CD3 x Anti-GD2 Bispecific Antibody ArmedT cells. Research square, 2023