International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

# Recent Advances in Targeted Therapies for Infantile Hemangiomas

Tiantian Liang[1,*], Xianbin Liu[1,*], Yujun Tong[2], Qian Ding[3], Min Yang[1], Hong Ning[1]

[1]Department of Pharmacy, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, Sichuan, People's Republic of China; [2]Department of Breast Surgery, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, Sichuan, People's Republic of China; [3]Department of Clinical Pharmacy, The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang, Sichuan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hong Ning; Min Yang, Department of Pharmacy, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, No. 12, Changjia Alley, Jingzhong Street, Mianyang, Sichuan, 621000, People's Republic of China, Email ninghong555@126.com; ym8710@126.com



**Abstract:** Targeted therapy for infantile hemangiomas (IHs) has been extensively studied as they can concentrate drugs, increase therapeutic efficacy and reduce drug dosage. Meanwhile, they can extend drug release times, enhance drug stability, decrease dosing frequency, and improve patient compliance. Moreover, carriers made from biocompatible materials reduced drug immunogenicity, minimizing adverse reactions. However, current targeted formulations still face numerous challenges such as the non-absolute safety of carrier materials; the need to further increase drug loading capacity; the limitation of animal hemangioma models in fully replicating the biological properties of human infantile hemangiomas; the establishment of models for deep-seated hemangiomas with high incidence rates; and the development of more specific targets or markers. In this review, we provided a brief overview of the characteristics of IHs and summarized the past decade's advances, advantages, and targeting strategies of targeted drug delivery systems for IHs and discussed their applications in the treatment of IHs. Furthermore, the goal is to provide a reference for further research and application in this field.

**Keywords:** targeting, targeted therapies, infantile hemangiomas, drug delivery systems, nanoparticle

## Introduction

IHs are benign tumors characterized by abnormal proliferation of endothelial cells and extensive vascular growth within the hemangioma in infants and young children.[1] The global incidence of IHs is approximately 4% to 10%.[2] Most IHs do not require special treatment and resolve with infant growth, but 10% to 15% of patients will have high-risk complications, such as possible malformations, major structural obstructions, persistent ulcers, organ dysfunction, disfigurement, and even life-threatening conditions.[3,4] IHs with high-risk complications not only affect the external appearance, anatomical structures, and physiological functions of the body but also impose significant psychological stress and may lead to psychological disorders in affected patients. Therefore, active intervention is required, and the earlier the better, to intervene at the source and prevent irreversible physical and psychological damage to infants and young children.

Currently, the primary treatment modality for IHs is pharmacotherapy, with secondary treatment options including non-pharmacological approaches such as laser therapy, surgical excision, and cryotherapy.[5,6] However, laser therapy can easily cause pigmentation, blistering, and even tissue necrosis. The timing of surgical excision is crucial, as the scars produced by surgery ares usually suboptimal in children over 1.5 years old.[7] Additionally, the abundant and intricate vasculatures surrounding the hemangioma result in a high risk of bleeding during surgery. Also, cryotherapy has a narrow range of indications. The β-receptor blocker propranolol is the only drug approved by the United States Food and Drug Administration (FDA) for the treatment of IHs.[8] The oral liquid formulation of propranolol suitable for pediatric patients is currently available on the market. Meanwhile, safer β-receptor blockers, such as Nadolol and Atenolol, are currently

Received: 8 February 2024
Accepted: 2 June 2024
Published: 19 June 2024

undergoing clinical trials.[9,10] However, the β-receptor blockers may have adverse effects including sleep disturbances, hypoglycemia, hypotension, bradycardia, and bronchospasm.[11–13] These adverse effects could potentially cause secondary harm to infants and young children. Therefore, close monitoring of the patient's blood pressure and heart rate is necessary during clinical use.

To overcome these challenges, researchers are continuously exploring new drug delivery methods and materials to safely and efficiently deliver drugs to the targeted areas. Targeted drug delivery systems have always been a research hotspot in the field of biomedicine. They are the novel drug delivery systems that use special carriers or drug delivery technologies to selectively concentrate drugs at the site of lesions, organs, cells, or intracellular structures through local administration or systemic circulation.[14] These systems offer advantages such as good biocompatibility, low toxicity, controlling in vivo release and easily crossing various biological barriers.[14] In recent years, they have been mainly introduced into passive and active targeting therapeutic systems, which have found extensive applications in the delivery of drugs, genes, and vaccines.[15–17] Various targeted drug carriers, including liposomes,[18] micelles,[19] nanoemulsions,[20] dendrimers,[21] metal nanoparticles,[22] and microspheres,[23] have been applied in various cancer treatments, such as breast cancer, liver cancer, and prostate cancer, showing excellent anti-tumor effects and low toxicity.[24] Although targeted formulations of propranolol and other targeted drugs for IHs have not yet been marketed, it is encouraging that there have been numerous reports on the basic research of targeted therapy for infantile hemangiomas. Therefore, we provided a brief overview of the characteristics of IHs and reviewed the development, advantages, and application of targeting strategies for targeted agents in IHs over the past decade. The intention is to provide valuable insights and references for further research in this field.

## Overview of IHs

The pathogenesis of IHs is considered to be multifactorial. The primary risk factors include female, Caucasians, premature infants with low birth weights, multiple gestation pregnancy, older maternal age, and so on.[25,26] It is currently believed that IHs may develop from intrinsic endothelial progenitor cells (EPCs) or angioblasts of placental origin. Additionally, the growth of IHs is influenced by both intrinsic factors (angiogenesis and angiogenic factors) and external factors (tissue hypoxia and developmental field disruption).[27] IHs are categorized based on soft tissue depth into superficial ("strawberry" type), deep ("cavernous" type), and mixed types, and based on anatomical appearance into localized, multifocal, or segmental.[5,27] The histological characteristics of proliferative-phase IHs are quite typical. They consist of clusters of plump endothelial cells and pericytes, forming capillaries with small round lumens. Over time, the basement membrane becomes increasingly multilayered, and the proliferating capillaries are arranged within lobules, separated by thin fibrous septa or normal intervening tissue (as shown in Figure 1).[28] Most IHs can be clinically diagnosed by clinicians based on medical history and physical examination. In very few uncertain cases, ultrasound examination may be required for further confirmation (as shown in Figure 2).[5] Currently, treatment strategies of IHs can be divided into two types: systemic treatment and local treatment. Each patient is individually evaluated according to the type of IHs, local or regional involvement, and his or her own functional status to determine the appropriate treatment.[25] According to the guidelines from the American Academy of Pediatrics,[5,27] the β-receptor blocker propranolol is the first-line drug for IHs. For children with β-receptor blockers intolerance, glucocorticoids, vincristine, interferon-α, and imiquimod are also clinical options, but their utility may be limited by their safety. Surgical resection and laser therapy are also recommended by the guidelines, but their use is limited by strict indications and adverse reactions. Therefore, the development of targeted drug delivery systems for IHs, which can passively or actively target hemangioma cells, while overcoming the limitations of current treatment modalities, would be desirable.

## Development of Drug Delivery Systems for Targeted Therapy of IHs Over the Past Decade

Traditional drugs for the treatment of IHs have the disadvantages of short half-life, poor bioavailability, poor patient compliance, and adverse drug reaction. With the continuous development of pharmaceutics and materials science, a variety of new types of carriers have been reported for the treatment of IHs in the past decade. They can

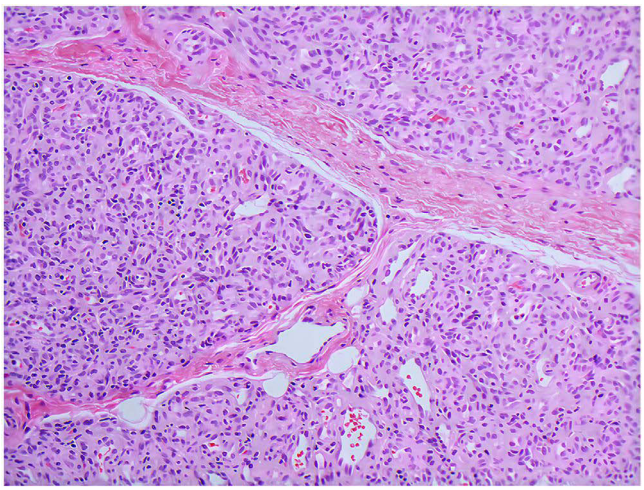

**Figure 1** The pathological imaging of IHs of proliferative phase.
**Notes**: Used with permission of Elsevier Science & Technology Journals, from North PE. *Surg Pathol Clin*. 2010;3(3):455–494; Copyright © 2010 Elsevier Inc;[28] permission conveyed through Copyright Clearance Center, Inc.

improve drug efficacy by delivering higher drug concentrations to the lesion, thereby reducing drug side effects. In 2013, researchers prepared urea liposomes by reverse phase evaporation method, and further generated urea immunoliposomes by coupling urea liposomes with vascular endothelial growth factor receptor-2 (VEGFR2) monoclonal antibody to preliminarily explore their effects on hemangioma vascular endothelial cells (HVECs).[29] In 2015, it was reported that glucose transporter protein 1 (GLUT1), a surface-specific antibody of IHs, was conjugated to $Fe_3O_4$ nanoparticles to differentiate IHs from vascular malformations.[30] In 2017, there were multiple reports of the common drugs loaded on PLGA nanoparticles for targeted therapy of IHs.[31–33] As shown in Figure 3, Table 1, the exploration of targeted agents for the treatment of IHs has increased significantly over the past 10 years.

## Advantages of the Targeted Treatment of IHs

### Locating Concentration to Increase the Therapeutic Effect of the Drug

The drugs commonly used to treat IHs are not targeted and can easily cause many toxic side effects. The most commonly used clinical drug is propranolol hydrochloride, often prepared as conventional formulations such as oral tablets or liquid preparations, which can easily lead to adverse reactions such as dizziness, bradycardia, hypotension, and bronchospasm.[11,49] Although topically applied propranolol can avoid some adverse reactions, ordinary topical emulsions or gels have poor transdermal efficacy and cannot ensure prolonged retention of the drug in the different layers of the skin (stratum corneum, epidermis, dermis).[50] Topical targeted formulations have opened new perspectives in the treatment of IHs.[51,52] Rawia M. Khalil et al used a nano-gel prepared by loading propranolol into phospholipid/chitosan. When applied topically to the surface of vascular hemangiomas in rats, drug deposition in the skin was found to be 1.56–1.91 times higher than that of the drug solution alone. This takes advantage of the sufficiently small size of the nanoparticles, allowing full contact with the skin surface. It is selectively located in different layers of the skin (stratum corneum, epidermis, dermis). In addition, the positively charged nature of the carriers, phospholipid/chitosan nanovesicles, allows them to adhere to the negatively charged skin, enhancing drug deposition and accumulation. This allows the drug to localize and concentrate at the lesion site, enhancing its targeting ability.[41] Guan et al prepared propranolol hydrochloride (PRO) liposome gel by exploiting the properties of liposomes with a lipid bilayer structure similar to that of the skin. Tissue distribution studies showed that PRO liposome gel significantly increased the drug concentration in the skin by about 74 times compared with PRO gel.[34]

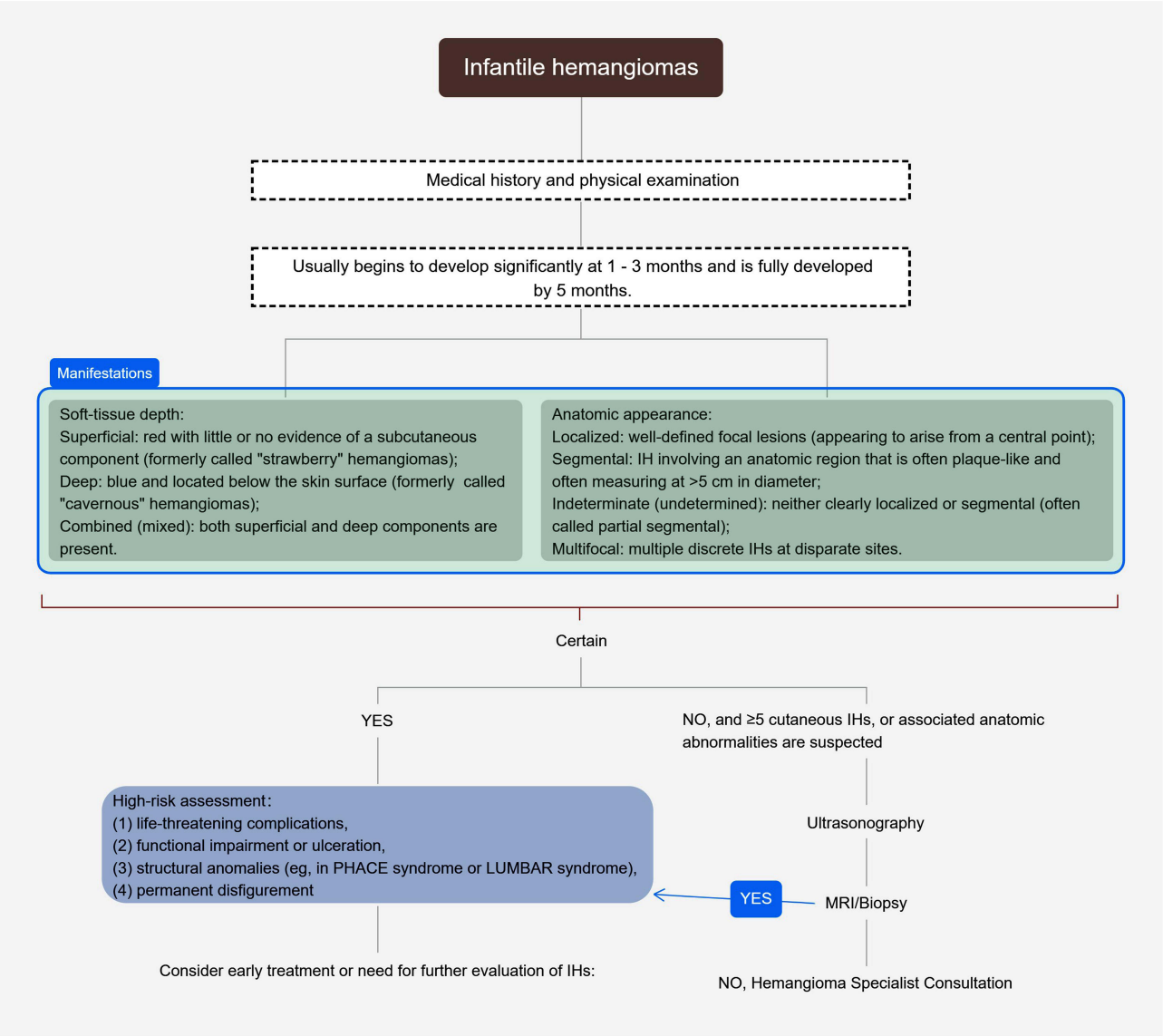


**Figure 2** The diagnostic workflow for IHs.

## Prolonging the Drug Release Time, Reducing Administration Frequency, and Improving Patient Compliance

In addition to the inherent nature of the drugs, poor treatment outcomes for IHs can also be attributed to challenges with patient compliance. Due to the unique nature of infants and young children, the doses may not be correct when taking traditional oral preparations, and they are susceptible to choking or even suffocation. In addition, frequent administration can lead to resistance and poor compliance, resulting in suboptimal treatment outcomes. Loading drugs into polymeric materials in targeted formulations can achieve slow and sustained release, leading to a controlled release effect and reducing the frequency of administration.[14] Poly (lactic-co-glycolic acid) (PLGA) has a certain rigidity and can effectively prolong drug release time. And it has been widely used in various drug delivery systems.[53,54] Existing studies have reported that loading drugs into lipid-based PLGA microspheres can achieve drug release for up to 40 days, thereby significantly inhibiting the growth of IHs.[36] Similarly, Li et al demonstrated that rapamycin-encapsulated exosome-mimetic nanoparticles-in-PLGA microspheres (RNM) could achieve a release time of up to 40 days in PBS at different pH levels (as shown in Figure 4).[45] Therefore, using polymeric materials as drug carriers to prepare targeted

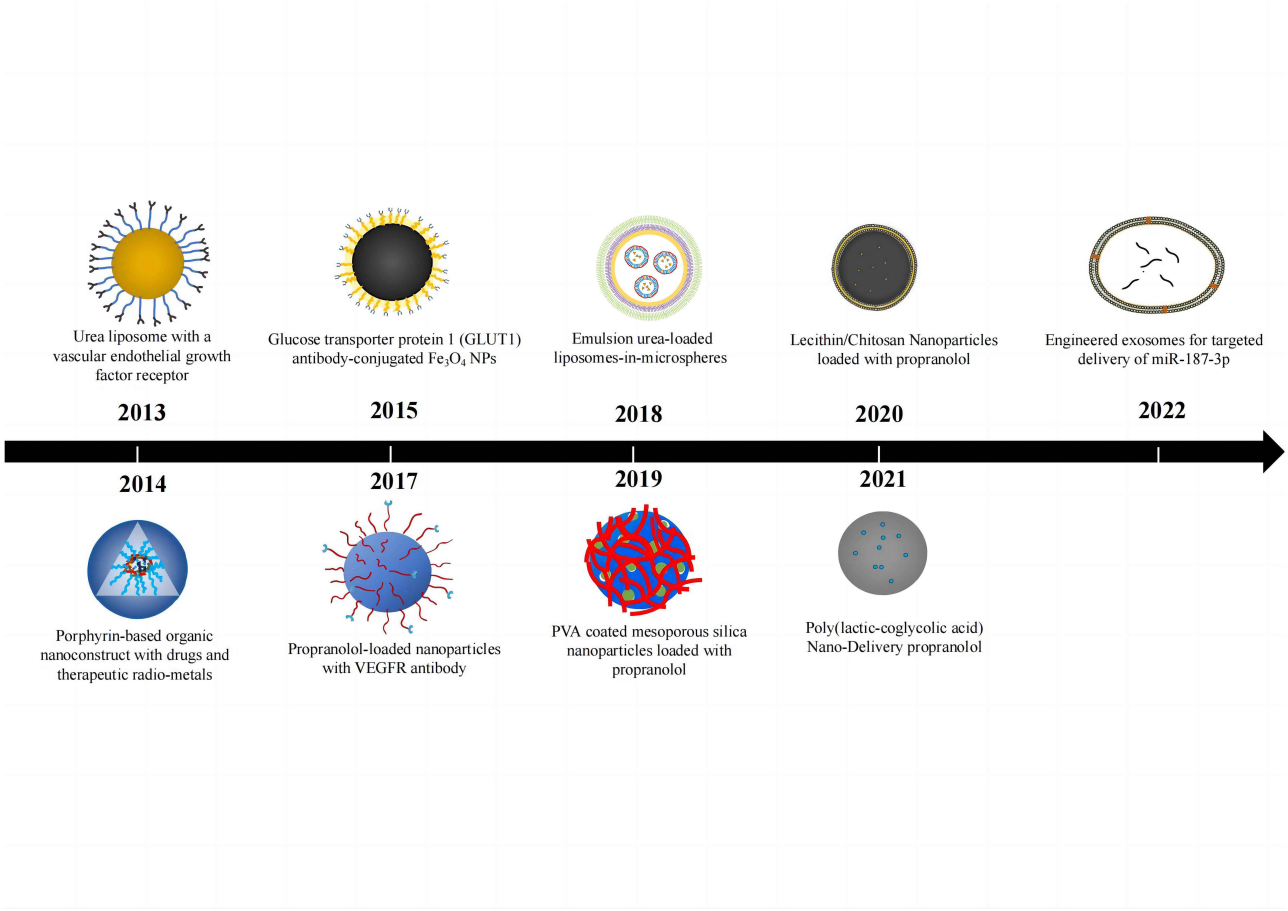


**Figure 3** A variety of representative targeted agents used in the last decade for targeted delivery of drugs for the treatment of IHs.

formulations for sustained drug release not only reduces the frequency of drug administration but also significantly improves patient compliance.

## Good Biocompatibility and Enhancing Drug Effectiveness

Biocompatibility and in vivo degradability of polymeric carriers are also key concerns.[55] When targeted formulations enter the body, they must evade clearance by the body's reticuloendothelial system (RES),[56] perform specific functions, target lesions, avoid drug effects at other sites, and reduce side effects. Cell cytotoxicity tests have shown that blank nanoparticles and microspheres do not exhibit significant toxicity, confirming the excellent biocompatibility of the nanoparticles and microspheres in hemangioma stem cells (HemSCs), thereby reducing adverse reactions of the drug in the circulation of the body.[45] To bypass RES clearance, Zhu et al first loaded propranolol onto conventional nanoparticle carriers to obtain propranolol-loaded nanoparticles (PNPs). Subsequently, the VEGFR antibody was used as a targeting moiety to bind with nanoparticles to prepare PNP-VEGFR. In vitro cell experiments showed that in human umbilical vein endothelial cells (HUVECs), the efficacy of PNP-VEGFR at 72 hours was 2.4 times and 3.8 times that of PNPs and propranolol, respectively. At 120 hours, the efficacy was 2.9 times and 4.8 times that of PNPs and propranolol, respectively. Similar results were obtained in Human hemangioma endothelial cells (HemECs). The efficacy of PNP-VEGFR at 72 hours was 2.6 times and 4.1 times that of PNPs and propranolol, respectively. At 120 hours, the efficacy was 2.4 times and 4.6 times, respectively. In conclusion, after combining nanoparticles with the VEGFR antibody, the toxic effects induced by propranolol on HUVECs and HemECs were significantly increased, thereby enhancing the efficacy of the drug.[32]

**Table 1** Summary of Targeted Agents for IHs in the Past Decade

| Targeting Strategy | Model Drug | Materials | Preparation Methods | Connecting the Target | Method of Administration | Main Effects | Year[Ref] |
|---|---|---|---|---|---|---|---|
| Passive targeted agents | Propranolol hydrochloride | Propranolol; Phosphatidyl ethanolamine (PE); Cholesterol | The film dispersion method | - | Transdermal application | Prolonged the drug release time; reduced administration frequency; improved patient compliance | 2015[34] |
| | Propranolol hydrochloride | Propranolol hydrochloride; PLGA-PEG -PLGA; PVA; DSPC; Cholesterol; Chitosan | The film hydration method; Membrane extrusion; The modified double emulsion method | - | Intratumoral injections | Sustained release; achieved superior therapeutic efficacy; reduced the frequency of administration | 2017[35] |
| | Rapamycin | Rapamycin; PLGA; DSPE; PEG2000; Soybean lecithin | Nanoprecipitation | - | Intratumor injections | Achieved local and sustained drug release; improved the effect of drug treatment; reduce the frequency of drug administration | 2017[33] |
| | Urea | Urea; PLGA-PEG-PLGA; HSPC; Cholesterol; Chitosan | The reverse evaporization method and vortex mixing | - | Intratumoral injections | Reduced the frequency of drug administration; achieved sustained drug release; enhanced the effect of drug therapy | 2018[36] |
| | Propranolol hydrochloride | Propranolol hydrochloride; Mesoporous silica; PVA; MCM-41 | Physisorption | - | Intraperitoneal injection | Enhanced the efficacy of drugs; reduced drug toxicity; reduced the number of doses administered | 2019[37] |
| | Propranolol hydrochloride | Propranolol hydrochloride; Mesoporous silica; PVA; MCM-41 | Physisorption | - | Intratumoral injection | Improved the bioavailability; improved the therapeutic efficacy and the safety | 2020[38] |
| | HIF-1α-shRNA pDNA | HIF-1α-shRNA pDNA; Branched polyethylenimine; Triethylamine; HFAA | Synthesis conjugation and mixed incubation method | - | Tumor subcutaneous injection | Improved biocompatibility and efficient delivery; improve delivery efficiency and treatment effectiveness | 2020[39] |
| | Propranolol hydrochloride | Propranolol hydrochloride; Glycerol monooleate (GMO); Phytantriol; Pluronic F127. | Remote drug loading method based on a transmembrane pH gradient process | - | Transdermal delivery | Reduces drug toxicity; enhances stability; enhanced skin permeation; enhanced antitumor effect | 2020[40] |
| | Propranolol hydrochloride | Propranolol hydrochloride; Lecithin; Chitosan | w/o/w type double emulsification method | - | Transdermal patch | Located concentration to increase the therapeutic effect of the drug; minimized systemic side effects | 2021[41] |
| | Propranolol hydrochloride | Propranolol hydrochloride; PLGA; PVA | Double emulsion emulsification solvent evaporation | - | Tail vein injection | Increased the stability of the drug and reduced the immunogenicity of the drug; prolonged the circulation time of drugs in the body; increased the concentration of drugs in the tumor site; reduced the systemic side effects of drugs and improved the therapeutic effect of drugs | 2021[42] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Antibody-modified active targeting agents | Urea | Urea; Soybean phospholipid; Cholesterol; Anti-VEGFR2 | Reverse phase evaporation | Anti-VEGFR2 | - | Enhanced drug targeting; prolonged drug treatment | 2013[29] |
| | - | $Fe_3O_4$;1,2-distearoyl-sn-glycero -3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000] | High temperature heating, mixing, solvent evaporation; Incubation | GLUT1 antibody | Intravenous injection | Location aggregation; enhanced drug targeting and therapeutic effect | 2015[30] |
| | Propranolol hydrochloride | Propranolol hydrochloride; PLGA-PEG -MAL; PVA; Anti-VEGFR Antibody | Double emulsion approach | Anti-VEGFR Antibody | Intratumoral injection | Provided targeted delivery and sustained release | 2017[32] |
| | Sodium morrhuate | Sodium morrhuate; SPDP; Anti-human KDR monoclonal antibody; VEGFR2/ KDR; Egg yolk phosphatidyl Choline; Cholesterol | Antibody-thiolated, blowing film, hydration, and filtration. | Anti-VEGFR2 /KDR antibody | - | Location concentration; Increased drug targeting; Increased the therapeutic effect of drugs | 2017[43] |
| | Rapamycin | Rapamycin; PLGA; DSPE-PEG2000-Mal; Soybean lecithin; Anti-VEGFR2 antibody | One-step nanoprecipitation approach and incubated | Anti-VEGFR2 antibody | Intratumoral injections | Facilitated targeted delivery and sustained release | 2018[44] |
| Ligand-modified active targeting agents | Propranolol hydrochloride | Propranolol hydrochloride; PLGA (17 kDa)-PEG (3.4kDa)-COOH; PVA; CD133 Aptamers (A15) | Double emulsion method and an EDC/NHS technique | A15 (CD133 aptamers) | Inrtratumoral injection | Targeted delivery and sustained release | 2017[31] |
| The bionic targeted agents | Rapamycin | Rapamycin; Chitosan; PLGA-PEG-PLGA; exosome | The extrusion-based method and the double emulsion approach | - | Intratumoral injections | Extend the release time; the targeting activity; good biocompatibility and enhanced drug effectiveness | 2022[45] |
| | MiR-187-3p | MiR-187-3p; hAMSC-exos | Electroporation | - | - | Good biocompatibility; increase the therapeutic effect of drugs | 2022[46] |
| Physical and chemical targeting agents | - | Linear polyethylene glycol; Dendritic oligomers of pyropheophorbide-a (Por, aporphyrin analogue); CA; PEG5k-Por4-CA4 | Self-assembly | Copper-64–labeled | Tail vein injections | Enhanced targeting and therapeutic efficacy | 2014[47] 2016[48] |

**Abbreviations**: PLGA-PEG-PLGA, poly(lactic-co-glycolic acid)-b-poly (ethylene glycol)-b-poly(lactic-co-glycolic acid; hAMSC-exos, human adipose mesenchymal stem cellderived exosomes; PLGA, Poly(lactic-co-glycolic acid; DSPE-PEG2000-Mal,1,2-distearoyl-sn-glycero-3- phosphoethanolamine-N-(maleimide (polyethylene glycol)-2000); SPDP, N-succinimidyl-3- (2-pyridyldithio)propionate; DSPC, Distearoyl-l-phosphatidylcholine; CA, cholic acid; GLUT1, Glucose transporter protein 1; PVA, polyvinyl alcohol; HSPC, Hydro soyphosphatidyl choline; HFAA, heptafluorobutyric anhydride.


https://doi.org/10.2147/IJN.S463119 DovePress

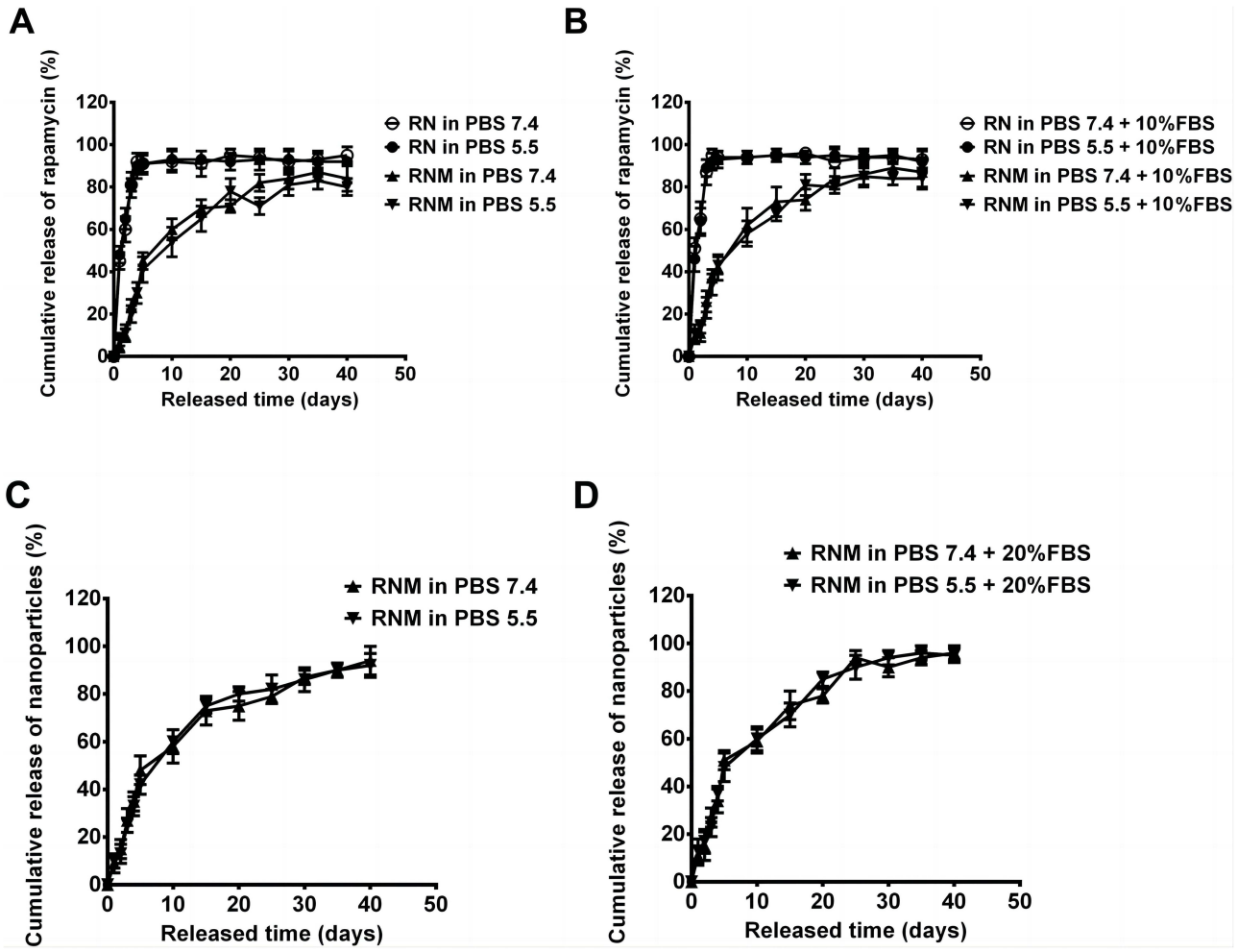


**Figure 4 (A)** The in vitro release profile of rapamycin in PBS. **(B) T**he in vitro release profile of rapamycin in PBS with 10% FBS. **(C)** The in vitro release profile of nanoparticles in PBS. **(D)** The in vitro release profile of nanoparticles in PBS with FBS.

**Notes**: Reproduced from Li H, Wang X, Guo X, Wan Q, Teng Y, Liu J. Development of rapamycin-encapsulated exosome-mimetic nanoparticles-in-PLGA microspheres for treatment of hemangiomas. *Biomed Pharmacother.* 2022;148:112,737. Creative Commons.[45]

**Abbreviations**: RN, rapamycin-encapsulated exosome-mimetic nanoparticles; RNM, rapamycin-encapsulated exosome-mimetic nanoparticles-in-poly (lactic-co-glycolic acid) microspheres; FBS, fetal bovine serum; PBS, phosphate buffered saline.

## Increasing the Stability of Drugs and Reducing the Immunogenicity of Drugs

To prevent drugs from entering the body directly and being affected by the body's internal environment, researchers are using nanocarriers to encapsulate drugs. The carrier itself can form an isolation space to protect the drug from premature inactivation and degradation by the body's factors and improve the stability of the drug in the body. The use of PLGA nanoparticles as drug carriers has many advantages such as low toxicity, good stability, and sustained release. They can also prevent enzyme-induced degradation to enhance the clinical efficacy of drugs, improve drug permeability to vascular tumors, and prolong the retention time of drugs in the tumor.[42]

In recent years, there have been increasing reports on the use of nucleic acid drugs for gene therapy in tumors.[57,58] However, nucleic acids need to enter cells to exert their therapeutic effects, and cell entry is challenging because nucleic acids are prone to degradation by nucleases during the delivery process, making it difficult to maintain a stable and intact structure before entering cells. Therefore, in gene therapy, it is necessary to prepare safe and efficient delivery vehicles to protect nucleic acids from degradation, increase the delivery efficiency of nucleic acids, and improve targeting to enrich the functions of gene therapy. Guo et al used fluorine-modified novel cationic polymer FPEI to electrostatically compress and condense HIF-1α shRNA pDNA into nano complexes. This process facilitated the escape of HIF-1α shRNA pDNA

from endosomes, reduced its immunogenicity, completed the nucleic acid delivery process, and inhibited the expression of HIF-1α protein in IHs, thereby achieving the therapeutic effect of inhibiting hemangioma growth.[39]

# Targeting Strategy and Application of Targeted Agents in IHs

## Passive Targeted Agents

Passive targeted agents are formulations that are designed based on the differential retention of particles by organs and tissues, resulting in differential drug distribution in the body. The distribution primarily relies on factors such as the particle size and surface charge.[59] The structural basis of passive targeted agents is the Enhanced Permeability and Retention (EPR) effect of tumor tissue. The EPR effect is attributed to the larger intercellular gaps in the endothelial cells of tumor blood vessels compared to normal blood vessels. This allows drugs and particles with larger molecular weights to permeate into the tumor tissue through these gaps.[60,61] Currently, an increasing number of polymeric materials, such as nanoparticles, liposomes, micelles, polymeric nanoparticles, dendritic polymers and so on, are being developed as targeted agents that utilize this effect for the targeted therapy of IHs.

### Nanoparticles

Nanotechnology is currently a focus of attention for scientists both domestically and internationally. It has become a tool for developing multifunctional drug delivery systems for various disease treatments and diagnostics.[62] Currently, there are a plethora of reports on drug-loaded Nanoparticles for targeted treatment of vascular tumors. Liao et al used PLGA as a drug carrier to load propranolol hydrochloride (PLGA-PP) and found that compared with free propranolol, the stability of PLGA-PP in vivo was significantly improved and the circulation time in vivo was prolonged. It can not only reduce the systemic side effects of PP but also increase the accumulation of PP in hemangioma due to the EPR effect. In addition, the experiment showed that the mechanism of PLGA-PP in the treatment of hemangioma involves the downregulation of the Id-1 gene, thereby inhibiting the colonization of HemECs and promoting its apoptosis effect.[42]

To improve the transdermal delivery of propranolol hydrochloride (PRH), researchers loaded PRH into cubic liquid crystal nanoparticles (PRH-CNPs) with a cubic structure similar to the cell membrane. Compared to the PRH solution, PRH-CNPs showed significantly increased skin permeability and higher cytotoxicity against mouse hemangioendothelioma (EOMA) cells.[40]

In recent years, another novel type of nanoshell has also attracted the attention of researchers. Mesoporous silica nanoparticles (MSN), due to their unique high pore volume, ordered channels, large surface area, and abundant surface functional groups, are considered one of the most promising drug carriers.[63,64] Haiwei Wu et al used its high pore volume and ordered channels as a carrier for propranolol to prepare mesoporous silica nanoparticles (PVA-MSN-PRN), which have the advantages of good therapeutic effect, low toxicity, and low administration frequency. They can significantly inhibit the proliferation of HemECs, promote HemECs apoptosis in vitro, and inhibit the growth of transplanted tumors in vivo.[37] Following that, the research team discovered that PVA-MSN-PRN could induce autophagy dysfunction with excessive autophagosome accumulation to promote the therapeutic efficacy of PRN therapy.[38]

### Polyplexes

To maintain stability, high transfection efficiency and safety of gene delivery, the choice of gene carrier is particularly critical. Gene vectors are usually divided into viral vectors and non-viral vectors. Due to the antigenicity and immunogenicity of viral vectors, non-viral vectors are widely selected.[65–67] Polyethylenimine (PEI) is one of the most classic non-viral vectors, and fluorination on polyethylenimine as a gene delivery vector has the advantages of stability, low toxicity, high efficiency and good biocompatibility.[68] During the progression of hemangioma, the rapid proliferation of endothelial cells can lead to hypoxia within the tumor, creating a hypoxic microenvironment.[69] Hypoxia-inducible factor-1 alpha (HIF-1α) is an important cytokine that regulates the response of cells to hypoxia and plays an important role in tumor initiation, growth, and angiogenesis.[70] Research has shown that HIF-1α is highly expressed in HemECs and correlates with the expression levels of VEGF, making it a potential therapeutic target for IHs.[71,72] The RNA interference (RNAi) technique can inhibit the expression of target proteins and has higher specificity, safety and efficacy.[73] The use of RNAi technology to transduce the HIF-1α gene into HemECs provides a new approach for the treatment of hemangioma. Guo chose heptafluorobutyric

anhydride (HFAA) to modify PEI, obtaining fluorinated low molecular weight PEI (FPEI). FPEI compacted HIF-1α -shRNA pDNA through electrostatic interactions, forming structurally stable nanocomplexes, namely FPEI Polyplexes (as shown in Figure 5). Thus, RNAi technology was successfully used to efficiently and stably deliver the HIF-1α gene into hemangiomas. The polymeric nanoparticles exhibit low cytotoxicity and high serum stability both in vitro and in vivo. In addition, the cellular endocytosis, transfection and silencing efficiencies were all satisfactory.[39]

## Liposomes

Liposomes are primarily composed of phospholipids and cholesterol, and exhibit a structure similar to biological membranes, often referred to as artificial biomembranes. Due to the presence of phospholipids and cholesterol as natural components of cell membranes, liposomes are generally non-immunogenic and non-pyrogenic, and exhibit excellent biocompatibility.[74] Studies suggest that liposomes can enhance skin permeability, making them effective carriers for local drug delivery.[75] Researchers loaded propranolol into liposomes and added an appropriate amount of bioadhesive carbomer to prepare a propranolol hydrochloride (PRO) liposomal gel for the treatment of IHs. A comparison between PRO liposomal gel and PRO gel was conducted, and the in vivo skin deposition study showed that the maximum drug concentration in the skin with PRO liposomes was 123.34 μg/g, significantly higher than that of PRO gel (75.65 μg/g). The tissue distribution study showed that the PRO liposomal gel significantly improved drug distribution in the body, resulting in a 74-fold relative increase in drug concentration in the skin compared to the PRO gel. Meanwhile, drug concentrations in other tissues decreased, reducing adverse effects on organs, especially the heart. Therefore, liposomal gel stands out as a promising carrier for transdermal drug delivery.[34]

## Hybrid Particles

With the deepening research and optimization of drug carriers, the development of hybrid carrier systems that can combine different organic-organic and organic-inorganic materials can achieve superior drug loading characteristics, so they can play an important role in various fields such as biomedical applications.[76] They are optimized on the original carrier materials, which are more economical, efficient and environmentally friendly. Due to the soft and fragile nature of liposomal membranes, the cholesterol and phospholipids in the structure are easily exchanged with other membranes, resulting in instability and suboptimal

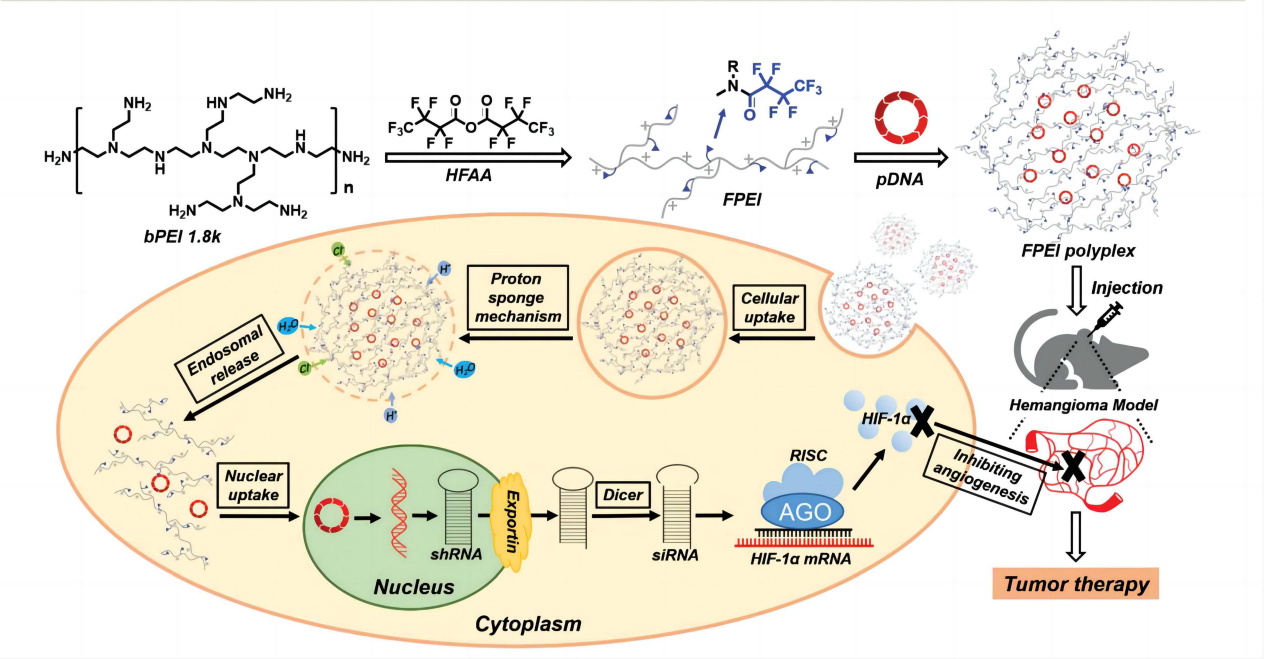


**Figure 5** Schematic illustration showing the formation and intracellular process of fluorinated PEI (FPEI) polyplexes and their effects in tumor angiogenesis.
**Notes**: Used with permission from Guo X, Yuan Z, Xu Y, Wei M, Fang Z, Yuan WE. A fluorinated low-molecular-weight PEI/HIF-1α shRNA polyplex system for hemangioma therapy. *Biomater Sci*. 2020;8(8):2129–2142; Copyright © 2020 Royal Society of Chemistry;[39] permission conveyed through Copyright Clearance Center, Inc.
**Abbreviation**: HFAA, heptafluorobutyric anhydride.

sustained drug release. Biodegradable polymeric carriers, such as PLGA, offer structural rigidity, sustained release capabilities, and superior drug loading capacity.[77] In recent years, there have been an increasing number of reports on the hybridization of liposomes and polymeric carriers. Compared to other carrier systems, the combination of liposomes and polymers offers several advantages, such as structural reliability, storage stability, and controlled release capabilities.[78,79] To mitigate the side effects and high dosing frequency associated with propranolol therapy for IHs, Guo et al encapsulated propranolol liposomes (PLs) within liposomal microspheres composed of poly(lactic-co-glycolic acid)-polyethylene glycol-poly(lactic-co-glycolic acid) (PLGA-PEG-PLGA) (as shown in Figure 6). PLGA-PEG-PLGA liposomal microspheres (PLIMs) provided sustained release of propranolol for up to 40 days, significantly reducing the frequency of propranolol administration. PLIMs showed superior therapeutic effects on hemangiomas compared to propranolol alone and PLs.[35] The following year, a similar method was reported to encapsulate urea liposomes within microspheres made of PLGA-PEG-PLGA copolymers, resulting in urea liposomal microspheres (ULIMs). ULIMs were introduced as a novel local controlled release system for the sustained release of urea. This approach further improved the drug encapsulation efficiency, which reached up to approximately 51.5%. Sustained drug release lasted for 40 days. ULIMs demonstrated superior therapeutic effects on IHs compared to propranolol, urea, urea liposomes and urea microspheres. Specifically, there were significant reductions in hemangioma weight, volume, and microvascular density. In addition, ULIM demonstrated improved safety.[36] The two formulations mentioned above both involve coating the surface of liposomes with PLGA polymer to increase stability and prolong release, but the microsphere diameters formed in both cases reach the micron range. To control particle size for better targeting effects, researchers have continued to refine their methods. They found that using the nanoprecipitation method by dissolving rapamycin in PLGA solution (1 mg/mL), forming the polymer first, and rapidly adding it to an aqueous lipid solution, rapamycin-loaded PLGA nanoparticles (Rapamycin-PLNPs) were obtained with the particle size of only 129.1 nm and the encapsulation efficiency of 63.7%. These nanoparticles effectively inhibited the proliferation of HemECs, reduced the expression of angiogenic factors in HemECs, and demonstrated superior therapeutic effects on IHs compared to free rapamycin.[33]

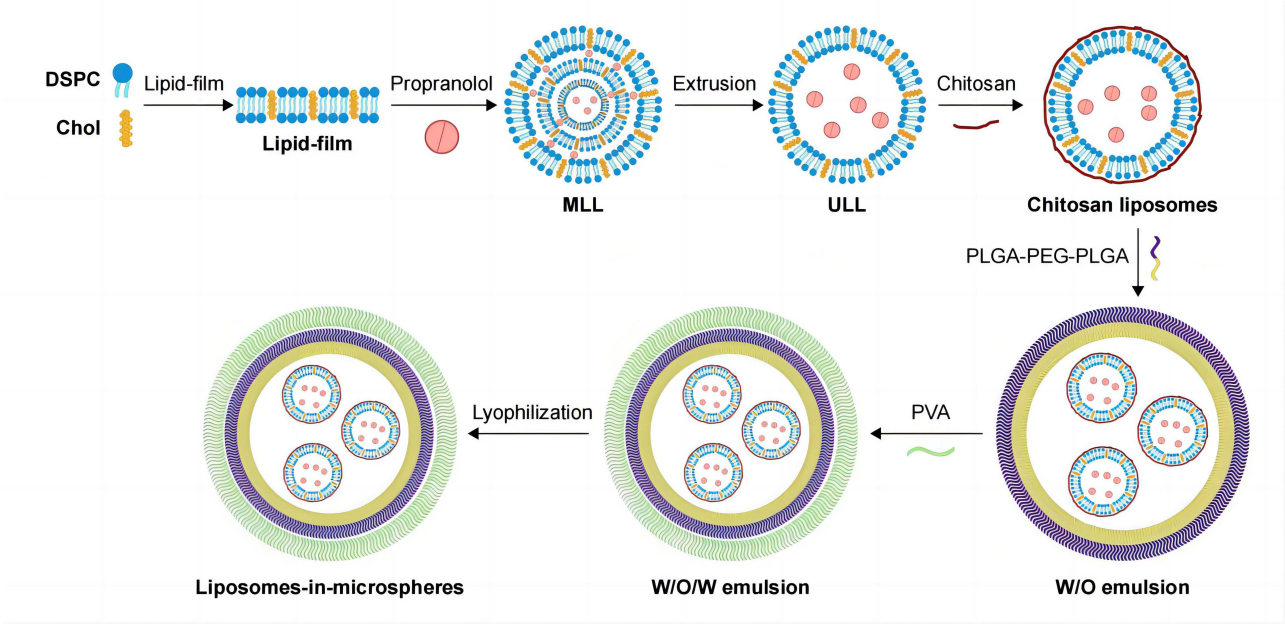


**Figure 6** The detailed preparation procedure for PL and PLIM.
**Notes**: Reproduced with permission from Guo X, Zhu X, Liu D, Gong Y, Sun J, Dong C. Continuous delivery of propranolol from liposomes-in-microspheres significantly inhibits infantile hemangioma growth. *Int J Nanomedicine*. 2017;12:6923–6936.[35]
**Abbreviations**: Chol, cholesterol; DSPC, distearoyl-L-phosphatidylcholine; MLL, multilamellar liposome; O, oil; PL, propranolol-loaded liposome; PLGA-PEG-PLGA, poly (lactic-co-glycolic acid)-b-poly(ethyleneglycol)-b-poly(lactic-co-glycolic acid); PLIM, porpranolol-loaded liposomes-in-microsphere; PVA, poly (vinyl alcohol); ULL, unilamellar liposome; W, water.

## Active Targeting Agents

Active targeting agents are drug formulations that combine with ligands or antibodies, taking advantage of the specific binding between certain receptors or antigens in organs and tissues and their corresponding ligands or antibodies, to achieve the purpose of active targeting. Active targeting agents overcome the drawbacks of passive targeting agents, enhance the specificity of drug formulations, reduce drug toxicity, minimize side effects, and further improve the safety and efficacy of drugs.[80,81] There are also increasing reports of active targeting agents in the treatment of IHs, including the use of receptor-ligand interactions, antigen-antibody binding, and biomimetic nanoparticles.

### Ligand-Modified Active Targeting Agents

CD133 is a normal stem cell/progenitor cell and cancer stem cell surface marker.[82] In IHs tissue, a population of stem cells expressing CD133+ can be isolated. Injection of these 'hemangioma stem cells' into nude mice results in the development of hemangioma-like lesions. Therefore, CD133+ stem cells are considered to be the origin of IHs.[1,83] The researchers exploited the specificity of the aptamer A15 to selectively bind to HemSCs overexpressing CD133 to prepare PP-PLGA nanoparticles containing a CD133 aptamer, termed PPN-CD133. PPN-CD133 exhibited a suitable particle size of 143.7 nm. In vitro, uptake experiments demonstrated that PPN-CD133 could deliver higher concentrations of propranolol to HemSCs via the CD133 aptamer compared to PPN. PPN-CD133 effectively bound to CD133+ hemangioma stem cells and demonstrated superior inhibition of VEGF-A and bFGF mRNA and protein expression in hemangiomas compared to propranolol and PPN. PPN-CD133 exhibited excellent therapeutic effects on IHs, with no significant changes in mouse body weight during treatment, indicating its safety and efficacy.[31]

### Antibody-Modified Active Targeting Agents

VEGF is an endothelial cell growth factor composed of three tyrosine kinase receptors: VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR-2 is the critical receptor for the development of the blood vasculature. Alterations in the VEGF-2 signaling pathway within endothelial cells (EC) can lead to the formation of IHs.[84–86] In 2013, researchers developed an immune liposome loaded with urea and combined with an anti-VEGFR antibody. In vitro experiments, it was observed that urea-immune liposomes could significantly inhibit the proliferation of HVECs, showing both time- and dose-dependency.[29] Because of its ability to disrupt endothelial cells and promote coagulation and thrombosis, sodium morrhuate has been used to treat hemangiomas.[87] Sodium morrhuate immunoliposomes were prepared by coupling sodium morrhuate ordinary liposomes with anti-VEGFR2 /KDR antibody, which have an increased capacity to target HECs and promote mitochondrial apoptosis.[43] Similarly, enhanced rapamycin delivery to hemangiomas by lipid polymer nanoparticles conjugated with anti-VEGFR antibodies has been reported.[44]

Researchers have discovered that glucose transporter 1 (GLUT1) is continuously overexpressed in the endothelial cells of hemangiomas and persists until regression, whereas it is not expressed in other benign vascular tumors and vascular malformations. Therefore, Choi et al used GLUT1 antibodies as the targeting component of iron oxide nanoparticles ($Fe_3O_4$-NPs) for molecular MRI imaging in an animal model of hemangiomas, aiming to differentiate between IHs and vascular malformations. Histological examination using GLUT1 antibody-$Fe_3O_4$-NPs revealed Prussian blue-stained nanoparticles in CD133-positive endothelial cells of hemangiomas. When treated with $Fe_3O_4$-NPs without coupled antibodies, Prussian blue-stained nanoparticles were found in macrophages rather than endothelial cells. The low signal pixel percentages in mouse hemangiomas treated with $Fe_3O_4$-NPs and GLUT1-$Fe_3O_4$-NPs were 8.3% and 56.6%, respectively. The signal intensity produced by GLUT1-$Fe_3O_4$-NPs MRI imaging was significantly lower than that of $Fe_3O_4$-NPs without coupled antibodies. This aids in more accurate differentiation and diagnosis of IHs and vascular malformations through MRI.[30]

### The Bionic Targeted Agents

Biomimetic drug delivery systems deliver drugs through cells, cell membranes, or cell-produced drug-loaded exosome vesicles or ordinary nanoparticles. By exploiting the intrinsic immunogenicity of cells and surface effectors such as proteins, messenger RNA, or microRNA (miRNA) to mediate cell communication, evade phagocytosis by the reticuloendothelial system, and deliver drugs to target cells, biomimetic drug delivery systems demonstrate robust delivery and

targeting capabilities.[88,89] Zheng et al isolated extracellular vesicles (EVs) from human adipose-derived mesenchymal stem cells (hAMSCs), termed hAMSC-exos. Then, the tumor suppressor gene miR-187-3p was introduced into hAMSC-exos by electroporation to obtain engineered exosomes E-exos. Experimental results showed that E-exos showed no significant changes in morphology, particle size, or surface markers compared with hAMSC-exos. E-exos were efficiently internalized by HemSCs. After internalization, E-exos suppressed the Notch signaling pathway through the inhibition of miR-187-3p, thereby inhibiting the proliferation of HemSCs and providing a new research avenue for the treatment of IHs.[46] In the same year, based on the specific binding interaction between integrin α4β1 on the cell membrane of macrophages and vascular cell adhesion molecule-1 (VCAM-1), which is highly expressed on endothelial cells,[90] researchers co-incubated rapamycin with macrophage-derived exosomes and used extrusion to prepare drug-loaded particles (RNs). These particles were then encapsulated with PLGA microspheres to obtain rapamycin-encapsulated exosome-mimetic nanoparticles-in-PLGA microspheres (RNM). The results showed that RNM exhibited excellent sustained release, with drug release lasting up to 40 days. RNM effectively inhibited the proliferation of HemSCs, significantly suppressed apoptosis, and inhibited the expression of vascular growth factors, thereby achieving the therapeutic goal for IHs.[45]

## Physical and Chemical Targeting Agents

Photothermal therapy (PTT) and photodynamic therapy (PDT) are at the forefront of current cancer treatment. The basic principle involves the use of photosensitizers that, when stimulated by light, generate heat and reactive oxygen species, effectively damaging cancer cells.[91,92] Yuanpei Li et al utilized the principles of photodynamic therapy, which used the combination of a photosensitizer such as porphyrin with laser light, to develop a novel, locally active, non-toxic nano-photothermal treatment system for the treatment of IHs.[47] The nano-porphyrin accumulated at high levels in the vascular hemangioma through enhanced permeability and retention effects, and exhibits cytotoxicity upon laser irradiation. One day after treatment, the hemangioma began to regress, and by the 21st day, it was completely gone. The difference in tumor volume between the treatment and control groups was significantly different at day 17 and day 21 ($p < 0.05$). By activating porphyrin only within the hemangioma under laser irradiation, while remaining inactive in other organs, systemic side effects of the treatment were avoided.[48]

# Summary and Outlook

In this study, we summarized various types of targeted formulations for IHs as the target site. Compared with traditional therapeutic drugs, targeted formulations have several advantages: targeted carriers enable drug localization and concentration, thereby enhancing therapeutic efficacy while reducing drug dosage; specific carrier materials can prolong drug release, increase drug stability, reduce dosing frequency, and improve patient compliance; carriers made of biocompatible materials reduce drug immunogenicity, thereby minimizing the occurrence of adverse reactions. An increasing number of researchers are focusing on the design and development of targeted drug delivery systems for the treatment of vascular tumors. While the proposed strategies for targeting IHs show promising applications, there are still several issues that require further investigation, including the safety of carrier materials. Currently, targeted formulations are considered relatively safe rather than completely non-toxic. Although existing biomaterials do not pose a significant risk to humans, they can induce immune responses. To further increase drug loading and reduce dosing frequency, research efforts should focus on optimizing formulations and delivery systems. In addition, the commonly used vascular tumor model involves subcutaneous implantation of tumors in nude mice to establish a hemangioma model. However, this model may not fully reflect the identical biological behavior seen in human infantile hemangiomas. Currently, there are no reports on the establishment of deep vascular hemangioma models, despite the high incidence of deep vascular tumors. Suboptimal therapeutic outcomes and side effects often result from a lack of specificity in treatment. Specificity in treatment depends on the advancement of basic research. Combining the microenvironment of IHs with the study of specific proteins or markers on the tumor surface could lead to the discovery of more specific and effective targets or markers.

The targeted agents and treatment strategies mentioned in this study are still in the preclinical stage. Although numerable preclinical drugs have been researched and documented, Unfortunately, none of these agents has been used or prepare to use in clinical trials. Faced with numerous challenges, the development of sustained, efficient drug delivery

systems that exert anti-tumor effects without toxic side effects has become a research hotspot. It is believed that with a deeper understanding of the pathological mechanisms of IHs and the rapid development of targeted drug formulations, these challenges are likely to be overcome in the future.[93,94] Targeted drug formulations for IHs are expected to have broader prospects.

## Funding

This work was supported by Sichuan Hospital Association Young Pharmacists Research Special Fund Project (22004).

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Sun Y, Qiu F, Hu C, Guo Y, Lei S. Hemangioma endothelial cells and hemangioma stem cells in infantile hemangioma. *Ann Plast Surg*. 2022;88(2):244–249. doi:10.1097/SAP.0000000000002835
2. Olsen GM, Nackers A, Drolet BA. Infantile and congenital hemangiomas. *Semin Pediatr Surg*. 2020;29(5):150969. doi:10.1016/j.sempedsurg.2020.150969
3. Hasbani DJ, Hamie L. Infantile Hemangiomas. *Dermatol Clin*. 2022;40(4):383–392. doi:10.1016/j.det.2022.06.004
4. Briones M, Adams D. Neonatal vascular tumors. *Clin Perinatol*. 2021;48(1):181–198. doi:10.1016/j.clp.2020.11.011
5. Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics*. 2019;143(1). doi:10.1542/peds.2018-3475
6. Sebaratnam DF, Rodríguez Bandera AL, Wong LF, Wargon O. Infantile hemangioma. Part 2: management. *J Am Acad Dermatol*. 2021;85(6):1395–1404. doi:10.1016/j.jaad.2021.08.020
7. Waner M. The surgical management of infantile hemangiomas. *Otolaryngol Clin North Am*. 2018;51(1):125–131. doi:10.1016/j.otc.2017.09.011
8. Castaneda S, Melendez-Lopez S, Garcia E, De la Cruz H, Sanchez-Palacio J. The role of the pharmacist in the treatment of patients with infantile hemangioma using propranolol. *Adv Ther*. 2016;33(10):1831–1839. doi:10.1007/s12325-016-0391-9
9. Ji Y, Chen S, Yang K, et al. Efficacy and safety of propranolol vs atenolol in infants with problematic infantile hemangiomas: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2021;147(7):599–607. doi:10.1001/jamaoto.2021.0454
10. Pope E, Lara-Corrales I, Sibbald C, et al. Noninferiority and safety of nadolol vs propranolol in infants with infantile hemangioma: a randomized clinical trial. *JAMA Pediatr*. 2022;176(1):34–41. doi:10.1001/jamapediatrics.2021.4565
11. Droitcourt C, Kerbrat S, Rault C, et al. Safety of oral propranolol for infantile hemangioma. *Pediatrics*. 2018;141(6). doi:10.1542/peds.2017-3783
12. Raphael MF, Breur JMPJ, Vlasveld FAE, et al. Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events – a review of the literature. *Expert Opin Drug Saf*. 2016;15(2):199–214. doi:10.1517/14740338.2016.1130125
13. Koh SP, Leadbitter P, Smithers F, Tan ST. β-blocker therapy for infantile hemangioma. *Expert Rev Clin Pharmacol*. 2020;13(8):899–915. doi:10.1080/17512433.2020.1788938
14. Ashique S, Sandhu NK, Chawla V, Chawla PA. Targeted drug delivery: trends and perspectives. *Curr Drug Deliv*. 2021;18(10):1435–1455. doi:10.2174/1567201818666210609161301
15. Alsaggar M, Liu D. Organ-based drug delivery. *J Drug Target*. 2018;26(5–6):385–397. doi:10.1080/1061186X.2018.1437919
16. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009;3(1):16–20. doi:10.1021/nn900002m
17. Björnmalm M, Thurecht KJ, Michael M, Scott AM, Caruso F. Bridging bio-nano science and cancer nanomedicine. *ACS Nano*. 2017;11(10):9594–9613. doi:10.1021/acsnano.7b04855
18. Alavi M, Hamidi M. Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles. *Drug Metab Pers Ther*. 2019;34(1). doi:10.1515/dmpt-2018-0032
19. Aqeel R, Srivastava N, Kushwaha P. Micelles in cancer therapy: an update on preclinical and clinical status. *Recent Pat Nanotechnol*. 2022;16(4):283–294. doi:10.2174/1872210515666210720125717
20. Dartora VFC, Salata GC, Passos JS, et al. Hyaluronic acid nanoemulsions improve piplartine cytotoxicity in 2D and 3D breast cancer models and reduce tumor development after intraductal administration. *Int J Biol Macromol*. 2022;219:84–95. doi:10.1016/j.ijbiomac.2022.07.162
21. Grześkowiak BF, Maziukiewicz D, Kozłowska A, Kertmen A, Coy E, Mrówczyński R. Polyamidoamine dendrimers decorated multifunctional polydopamine nanoparticles for targeted chemo- and photothermal therapy of liver cancer model. *Int J Mol Sci*. 2021;22(2):738. doi:10.3390/ijms22020738
22. Chen Z, Zeng Y, Chen N, et al. A facile and universal method for preparing polyethylene glycol-metal hybrid nanoparticles and their application in tumor theranostics. *Adv Healthc Mater*. 2022;11(12):e2200044. doi:10.1002/adhm.202200044
23. Xu Y, Liu Y, Liu Q, et al. Co-delivery of bufalin and nintedanib via albumin sub-microspheres for synergistic cancer therapy. *J Control Release*. 2021;338:705–718. doi:10.1016/j.jconrel.2021.08.049
24. Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y. Engineered nanoparticles for drug delivery in cancer therapy. *Angew Chem Int Ed Engl*. 2014;53(46):12320–12364. doi:10.1002/anie.201403036
25. Leung AKC, Lam JM, Leong KF, Hon KL. Infantile hemangioma: an updated review. *Curr Pediatr Rev*. 2021;17(1):55–69. doi:10.2174/1573396316666200508100038
26. Goelz R, Poets CF. Incidence and treatment of infantile haemangioma in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(1):F85–91. doi:10.1136/archdischild-2014-306197
27. Darrow DH, Greene AK, Mancini AJ, Nopper AJ. Diagnosis and management of infantile hemangioma. *Pediatrics*. 2015;136(4):e1060–1104. doi:10.1542/peds.2015-2485
28. North PE. Pediatric vascular tumors and malformations. *Surg Pathol Clin*. 2010;3(3):455–494. doi:10.1016/j.path.2010.07.002

29. Wang Z, Li J, Xu X, Duan X, Cao G. Urea immunoliposome inhibits human vascular endothelial cell proliferation for hemangioma treatment. *World J Surg Oncol*. 2013;11(1):300. doi:10.1186/1477-7819-11-300
30. Sohn CH, Park SP, Choi SH, et al. MRI molecular imaging using GLUT1 antibody-$Fe_3O_4$ nanoparticles in the hemangioma animal model for differentiating infantile hemangioma from vascular malformation. *Nanomedicine*. 2015;11(1):127–135. doi:10.1016/j.nano.2014.08.003
31. Guo X, Zhu X, Gao J, Liu D, Dong C, Jin X. PLGA nanoparticles with CD133 aptamers for targeted delivery and sustained release of propranolol to hemangioma. *Nanomedicine*. 2017;12(21):2611–2624. doi:10.2217/nnm-2017-0130
32. Zhu X, Guo X, Liu D, Gong Y, Sun J, Dong C. Promotion of propranolol delivery to hemangiomas by using anti-vegfr antibody-conjugated poly (lactic-co-glycolic acid) nanoparticles. *J Biomed Nanotechnol*. 2017;13(12):1694–1705. doi:10.1166/jbn.2017.2449
33. Li H, Teng Y, Sun J, Liu J. Inhibition of hemangioma growth using polymer-lipid hybrid nanoparticles for delivery of rapamycin. *Biomed Pharmacother*. 2017;95:875–884. doi:10.1016/j.biopha.2017.08.035
34. Guan Y, Zuo T, Chang M, et al. Propranolol hydrochloride-loaded liposomal gel for transdermal delivery: characterization and in vivo evaluation. *Int J Pharm*. 2015;487(1–2):135–141. doi:10.1016/j.ijpharm.2015.04.023
35. Guo X, Zhu X, Liu D, Gong Y, Sun J, Dong C. Continuous delivery of propranolol from liposomes-in-microspheres significantly inhibits infantile hemangioma growth. *Int J Nanomed*. 2017;12:6923–6936. doi:10.2147/IJN.S137634
36. Zhu X, Guo X, Liu D, Gong Y, Sun J, Dong C. Significant inhibition of infantile hemangioma growth by sustained delivery of urea from liposomes-in-microspheres. *Oncol Rep*. 2018;39(1):109–118. doi:10.3892/or.2017.6103
37. Wu H, Wang X, Zheng J, et al. Propranolol-loaded mesoporous silica nanoparticles for treatment of infantile hemangiomas. *Adv Healthc Mater*. 2019;8(9):e1801261. doi:10.1002/adhm.201801261
38. Wu H, Wang X, Liang H, Zheng J, Huang S, Zhang D. Enhanced efficacy of propranolol therapy for infantile hemangiomas based on a mesoporous silica nanoplatform through mediating autophagy dysfunction. *Acta Biomater*. 2020;107:272–285. doi:10.1016/j.actbio.2020.02.033
39. Guo X, Yuan Z, Xu Y, Wei M, Fang Z, Yuan WE. A fluorinated low-molecular-weight PEI/HIF-1α shRNA polyplex system for hemangioma therapy. *Biomater Sci*. 2020;8(8):2129–2142. doi:10.1039/D0BM00171F
40. Zeng L, Tao C, Liu Z, et al. Preparation and evaluation of cubic nanoparticles for improved transdermal delivery of propranolol hydrochloride. *AAPS Pharm Sci Tech*. 2020;21(7):266. doi:10.1208/s12249-020-01809-7
41. Khalil RM, El Arini SK, AbouSamra MM, Zaki HS, El-Gazaerly ON, Elbary AA. Development of lecithin/chitosan nanoparticles for promoting topical delivery of propranolol hydrochloride: design, optimization and in-vivo evaluation. *J Pharm Sci*. 2021;110(3):1337–1348. doi:10.1016/j.xphs.2020.11.025
42. Liao S, Wu J, Li Z, et al. Study on the mechanism of targeted poly(lactic-coglycolic acid) nano-delivery carriers in the treatment of hemangiomas. *J Nanosci Nanotechnol*. 2021;21(2):1236–1243. doi:10.1166/jnn.2021.18689
43. Li X, Ren X, Liang J, Ma W, Wang Z, Yang Z. Delivery of sodium morrhuate to hemangioma endothelial cells using immunoliposomes conjugated with anti-VEGFR2/KDR antibody. *Int J Nanomed*. 2017;12:6963–6972. doi:10.2147/IJN.S144056
44. Li H, Teng Y, Xu X, Liu J. Enhanced rapamycin delivery to hemangiomas by lipid polymer nanoparticles coupled with anti-VEGFR antibody. *Int J Mol Med*. 2018;41(6):3586–3596. doi:10.3892/ijmm.2018.3518
45. Li H, Wang X, Guo X, Wan Q, Teng Y, Liu J. Development of rapamycin-encapsulated exosome-mimetic nanoparticles-in-PLGA microspheres for treatment of hemangiomas. *Biomed Pharmacother*. 2022;148:112737. doi:10.1016/j.biopha.2022.112737
46. Zhao ZL, Liu C, Wang QZ, Wu HW, Zheng JW. Engineered exosomes for targeted delivery of miR-187-3p suppress the viability of hemangioma stem cells by targeting Notch signaling. *Ann Transl Med*. 2022;10(11):621. doi:10.21037/atm-21-4138
47. Li Y, Lin TY, Luo Y, et al. A smart and versatile theranostic nanomedicine platform based on nanoporphyrin. *Nat Commun*. 2014;5(1):4712. doi:10.1038/ncomms5712
48. Orbay H, Li Y, Xiao W, Cherry SR, Lam K, Sahar DE. Developing a nanoparticle-delivered high-efficacy treatment for infantile hemangiomas using a mouse hemangioendothelioma model. *Plast Reconstr Surg*. 2016;138(2):410–417. doi:10.1097/PRS.0000000000002403
49. Wu W, Wang H, Hao J, Gao Z, Li F, Chen Y. Therapeutic efficacy of propranolol for infantile hemangiomas. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;128(2):132–138. doi:10.1016/j.oooo.2019.04.014
50. Tang YJ, Zhang ZZ, Chen SQ, et al. Effect of topical propranolol gel on plasma renin, angiotensin II and vascular endothelial growth factor in superficial infantile hemangiomas. *J Huazhong Univ Sci Technolog Med Sci*. 2015;35(5):759–762. doi:10.1007/s11596-015-1503-5
51. Baveloni FG, Riccio BVF, Di Filippo LD, Fernandes MA, Meneguin AB, Chorilli M. Nanotechnology-based drug delivery systems as potential for skin application: a review. *Curr Med Chem*. 2021;28(16):3216–3248. doi:10.2174/0929867327666200831125656
52. Sharma G, Thakur K, Raza K, Singh B, Katare OP. Nanostructured lipid carriers: a new paradigm in topical delivery for dermal and transdermal applications. *Crit Rev Ther Drug Carrier Syst*. 2017;34(4):355–386. doi:10.1615/CritRevTherDrugCarrierSyst.2017019047
53. Shive MS, Anderson JM. Biodegradation and biocompatibility of PLA and PLGA microspheres. *Adv Drug Deliv Rev*. 1997;28(1):5–24. doi:10.1016/S0169-409X(97)00048-3
54. Swider E, Koshkina O, Tel J, Cruz LJ, de Vries IJM, Srinivas M. Customizing poly(lactic-co-glycolic acid) particles for biomedical applications. *Acta Biomater*. 2018;73:38–51. doi:10.1016/j.actbio.2018.04.006
55. Su H, Wang Y, Gu Y, Bowman L, Zhao J, Ding M. Potential applications and human biosafety of nanomaterials used in nanomedicine. *J Appl Toxicol*. 2018;38(1):3–24. doi:10.1002/jat.3476
56. Brouwer A, Knook DL. The reticuloendothelial system and aging: a review. *Mech Ageing Dev*. 1983;21(3–4):205–228. doi:10.1016/0047-6374(83)90042-8
57. Zhang Y, Liu Q, Zhang X, et al. Recent advances in exosome-mediated nucleic acid delivery for cancer therapy. *J Nanobiotechnology*. 2022;20(1):279. doi:10.1186/s12951-022-01472-z
58. Hager S, Fittler FJ, Wagner E, Bros M. Nucleic acid-based approaches for tumor therapy. *Cells*. 2020;9(9):2061. doi:10.3390/cells9092061
59. Zhang J, Tang H, Liu Z, Chen B. Effects of major parameters of nanoparticles on their physical and chemical properties and recent application of nanodrug delivery system in targeted chemotherapy. *Int J Nanomed*. 2017;12:8483–8493. doi:10.2147/IJN.S148359
60. Mattheolabakis G, Rigas B, Constantinides PP. Nanodelivery strategies in cancer chemotherapy: biological rationale and pharmaceutical perspectives. *Nanomedicine*. 2012;7(10):1577–1590. doi:10.2217/nnm.12.128
61. Shi Y, van der Meel R, Chen X, Lammers T. The EPR effect and beyond: strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics*. 2020;10(17):7921–7924. doi:10.7150/thno.49577

62. Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnology*. 2018;16(1):71. doi:10.1186/s12951-018-0392-8
63. Liu J, Luo Z, Zhang J, et al. Hollow mesoporous silica nanoparticles facilitated drug delivery via cascade pH stimuli in tumor microenvironment for tumor therapy. *Biomaterials*. 2016;83:51–65. doi:10.1016/j.biomaterials.2016.01.008
64. Watermann A, Brieger J. Mesoporous silica nanoparticles as drug delivery vehicles in cancer. *Nanomaterials*. 2017;7(7):189. doi:10.3390/nano7070189
65. Rajagopal P, Duraiswamy S, Sethuraman S, Giridhara Rao J, Krishnan UM. Polymer-coated viral vectors: hybrid nanosystems for gene therapy. *J Gene Med*. 2018;20(4):e3011. doi:10.1002/jgm.3011
66. Zu H, Gao D. Non-viral vectors in gene therapy: recent development, challenges, and prospects. *Aaps j*. 2021;23(4):78. doi:10.1208/s12248-021-00608-7
67. Yin H, Kanasty RL, Eltoukhy AA, Vegas AJ, Dorkin JR, Anderson DG. Non-viral vectors for gene-based therapy. *Nat Rev Genet*. 2014;15(8):541–555. doi:10.1038/nrg3763
68. Jiang HL, Islam MA, Xing L, et al. Degradable polyethylenimine-based gene carriers for cancer therapy. *Top Curr Chem*. 2017;375(2):34. doi:10.1007/s41061-017-0124-9
69. de Jong S, Itinteang T, Withers AH, Davis PF, Tan ST. Does hypoxia play a role in infantile hemangioma? *Arch Dermatol Res*. 2016;308(4):219–227. doi:10.1007/s00403-016-1635-x
70. Sharp FR, Lu A, Tang Y, Millhorn DE. Multiple molecular penumbras after focal cerebral ischemia. *J Cereb Blood Flow Metab*. 2000;20(7):1011–1032. doi:10.1097/00004647-200007000-00001
71. Zhang W, Sun L, Gao H, Wang S. Mechanism of the HIF-1α/VEGF/VEGFR-2 pathway in the proliferation and apoptosis of human haemangioma endothelial cells. *Int J Exp Pathol*. 2023;104(5):258–268. doi:10.1111/iep.12485
72. Chim H, Armijo BS, Miller E, Gliniak C, Serret MA, Gosain AK. Propranolol induces regression of hemangioma cells through HIF-1α-mediated inhibition of VEGF-A. *Ann Surg*. 2012;256(1):146–156. doi:10.1097/SLA.0b013e318254ce7a
73. Patil YB, Swaminathan SK, Sadhukha T, Ma L, Panyam J. The use of nanoparticle-mediated targeted gene silencing and drug delivery to overcome tumor drug resistance. *Biomaterials*. 2010;31(2):358–365. doi:10.1016/j.biomaterials.2009.09.048
74. Guimarães D, Cavaco-Paulo A, Nogueira E. Design of liposomes as drug delivery system for therapeutic applications. *Int J Pharm*. 2021;601:120571. doi:10.1016/j.ijpharm.2021.120571
75. Carita AC, Eloy JO, Chorilli M, Lee RJ, Leonardi GR. Recent advances and perspectives in liposomes for cutaneous drug delivery. *Curr Med Chem*. 2018;25(5):606–635. doi:10.2174/0929867324666171009120154
76. Ferreira Soares DC, Domingues SC, Viana DB, Tebaldi ML. Polymer-hybrid nanoparticles: current advances in biomedical applications. *Biomed Pharmacother*. 2020;131:110695. doi:10.1016/j.biopha.2020.110695
77. Narmani A, Jahedi R, Bakhshian-Dehkordi E, et al. Biomedical applications of PLGA nanoparticles in nanomedicine: advances in drug delivery systems and cancer therapy. *Expert Opin Drug Deliv*. 2023;20(7):937–954. doi:10.1080/17425247.2023.2223941
78. Dave V, Tak K, Sohgaura A, Gupta A, Sadhu V, Reddy KR. Lipid-polymer hybrid nanoparticles: synthesis strategies and biomedical applications. *J Microbiol Methods*. 2019;160:130–142. doi:10.1016/j.mimet.2019.03.017
79. Go YK, Leal C. Polymer-lipid hybrid materials. *Chem Rev*. 2021;121(22):13996–14030. doi:10.1021/acs.chemrev.1c00755
80. Tan KX, Danquah MK, Sidhu A, Yon LS, Ongkudon CM. Aptamer-mediated polymeric vehicles for enhanced cell-targeted drug delivery. *Curr Drug Targets*. 2018;19(3):248–258. doi:10.2174/1389450117666160617120926
81. Novio F. Design of targeted nanostructured coordination polymers (NCPs) for cancer therapy. *Molecules*. 2020;25(15):3449. doi:10.3390/molecules25153449
82. Mizrak D, Brittan M, Alison M. CD133: molecule of the moment. *J Pathol*. 2008;214(1):3–9. doi:10.1002/path.2283
83. Khan ZA, Boscolo E, Picard A, et al. Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. *J Clin Invest*. 2008;118(7):2592–2599. doi:10.1172/JCI33493
84. Oszajca K, Szemraj J, Wyrzykowski D, Chrzanowska B, Salamon A, Przewratil P. Single-nucleotide polymorphisms of VEGF-A and VEGFR-2 genes and risk of infantile hemangioma. *Int J Dermatol*. 2018;57(10):1201–1207. doi:10.1111/ijd.14127
85. Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. *Eur J Cancer*. 2006;42(18):3127–3139. doi:10.1016/j.ejca.2006.09.015
86. Tugues S, Koch S, Gualandi L, Li X, Claesson-Welsh L. Vascular endothelial growth factors and receptors: anti-angiogenic therapy in the treatment of cancer. *Mol Aspects Med*. 2011;32(2):88–111. doi:10.1016/j.mam.2011.04.004
87. Tu JB, Dong Q, Hu XY, et al. Proteomic analysis of mitochondria from infantile hemangioma endothelial cells treated with sodium morrhuate and its liposomal formulation. *J Biochem Mol Toxicol*. 2012;26(9):374–380. doi:10.1002/jbt.21436
88. Fukuta T, Kogure K. Biomimetic nanoparticle drug delivery systems to overcome biological barriers for therapeutic applications. *Chem Pharm Bull*. 2022;70(5):334–340. doi:10.1248/cpb.c21-00961
89. Wang R, Sha X. Biomimetic drug delivery systems oriented by biological function in tumor targeting. *Curr Drug Targets*. 2021;22(8):882–895. doi:10.2174/1389450122666210114095859
90. Liang T, Zhang R, Liu X, et al. Recent advances in macrophage-mediated drug delivery systems. *Int J Nanomed*. 2021;16:2703–2714. doi:10.2147/IJN.S298159
91. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer*. 2017;17(1):20–37. doi:10.1038/nrc.2016.108
92. Kadkhoda J, Tarighatnia A, Barar J, Aghanejad A, Davaran S. Recent advances and trends in nanoparticles based photothermal and photodynamic therapy. *Photodiagnosis Photodyn Ther*. 2022;37:102697. doi:10.1016/j.pdpdt.2021.102697
93. Li Z, Cao Z, Li N, et al. M2 macrophage-derived exosomal lncrna lncRNA MIR4435-2HG progression of infantile hemangiomas by targeting HNRNPA1. *Int J Nanomed*. 2023;18:5943–5960. doi:10.2147/IJN.S435132
94. Wu Y, Li H, Xie J, Wang F, Cao D, Lou Y. MiR-139-5p affects cell proliferation, migration and adipogenesis by targeting insulin-like growth factor 1 receptor in hemangioma stem cells. *Int J Mol Med*. 2020;45(2):569–577. doi:10.3892/ijmm.2019.4430