

# Vascular embolic nanobiomaterials for efficient tumor treatment

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## ABSTRACT

Embolization is a minimally invasive cancer treatment method. Embolization involves artificially blocking blood flow using an embolic agent to block abnormal blood vessels that supply nutrients or oxygen to a specific lesion, thereby killing the lesion, inhibiting its growth, and stopping bleeding. Currently, polyvinyl alcohol (PVA) and gelatin are the most popular embolic agents. These substances are available in various sizes and shapes that physically obstruct blood flow to cause vascular embolization. They are commonly used due to their ease of use and low cost. However, they can cause side-effect such as bleeding and potential complications related to catheter- and insertion-related complications. Recently, nanobiomaterials have been explored as embolization agents with high biocompatibility, such as liquid metals, and can be used with autologous blood. In this review, we cover the types of embolic agents currently used in cancer treatment and focus on those with fewer adverse effects and minimal vascular damage, followed by discussions on new embolic agents under development. Additionally, we explore potential future research directions for developing better embolic agents.

## 1. Introduction

### 1.1. Embolization and embolic agents

Minimally invasive cancer treatment methods require minimal incisions with embolization being one of the most common approaches (Hu et al., 2019a). Embolization involves using an embolic agent to block blood flow to abnormal blood vessels that supply nutrients or oxygen to a specific lesion. This blockage either kills the lesion, inhibits its growth, or stops bleeding (Wang et al., 2020). Early embolization utilized muscle fragments, blood clots, and stainless steel pellets. Since the 1970s, embolization methods have significantly evolved with the advent of imaging and catheterization technologies. Compared with invasive incision surgery, embolization is less risky as it involves less blood loss and typically local anesthesia (de Castro et al., 2005). The procedure involves X-ray imaging and contrast agents to visualize the blood vessels. A catheter is then inserted through the skin into the blood vessel and guided to the target area. Drugs and embolic agents are then introduced through the catheter to embolize the blood vessels (Bartling

et al., 2011). Vascular embolization is used to manage potentially fatal acute bleeding in more chronic situations, including aneurysms and vascular malformations. They are also used in targeted oncological applications, such as the embolization of blood vessels supplying tumors (Duffis et al., 2012).

Materials currently used as embolic agents include PVA, gelatin microspheres, and various types of metal coils, such as platinum, tungsten, nickel, and stainless steel (Bellamkonda et al., 2021 Byrne et al., 1997 Prasad et al., 2004). Embolic agents are categorized according to their persistence in the blood (Fig. 1). (Vaidya et al., 2008) In this review, we discuss the trend of nanobiomaterial embolic agents that have been recently explored for cancer treatment (Scheme 1).

### 1.2. Embolization for cancer treatment

Embolization is most often used when surgery is not an option or as a pre-surgical step to reduce tumor size. Embolization is particularly effective in treating liver cancers such as hepatocellular carcinoma (HCC) and certain types of kidney, lung, and bone tumors (Wallace et al.,

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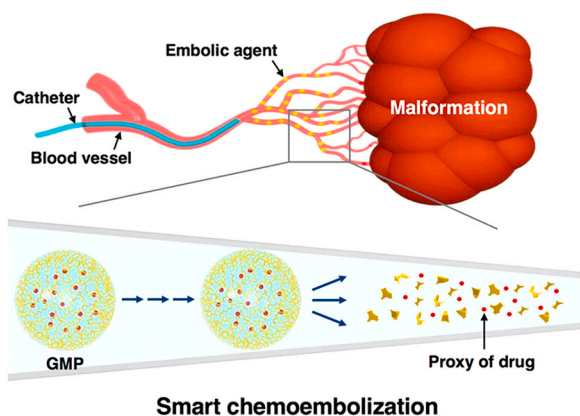
E-mail addresses: [hysshr@kumoh.ac.kr](mailto:hysshr@kumoh.ac.kr) (H.-Y. Lee), [nanomed@cau.ac.kr](mailto:nanomed@cau.ac.kr) (J. Choi).

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**Fig. 1.** Schematic diagram of monodisperse gelatin microparticles (GMPs) designed to block blood vessels and control drug release. Kim, B., et al. utilized a microfluidic approach to fabricate GMPs with a microshell structure, demonstrating that this structure enables controlled rupturing and drug release under temporary chemoembolic conditions. Reproduced with permission from (Kim et al., 2018). Copyright (2018) American Chemical Society.

1984). The technique can be combined with chemotherapy (chemoembolization) or radiation (radioembolization) to enhance its effectiveness.

Chemoembolization is a representative example of active embolization, in which chemotherapeutic drugs are actively loaded and delivered directly to a tumor through its feeding blood vessels, followed by embolization to block the vessels. This contrasts with conventional inert embolization, which relies solely on physical occlusion of the vasculature without additional therapeutic effects. Chemoembolization is primarily used for treating liver cancers, such as hepatocellular carcinoma (Ramsey et al., 2002). The advantages of chemoembolization include targeted delivery of chemotherapeutic agent directly to the tumor, while sparing healthy tissues, and reducing the adverse effects; in addition, lower systemic exposure reduces the side effects of chemotherapy (Lencioni, 2012). Chemoembolization can also be effective in treating inoperable tumors (Takayasu et al., 1989). Not only limited to drug delivery, Rong-guang Luo et al. and Yang-feng Lv et al. have demonstrated

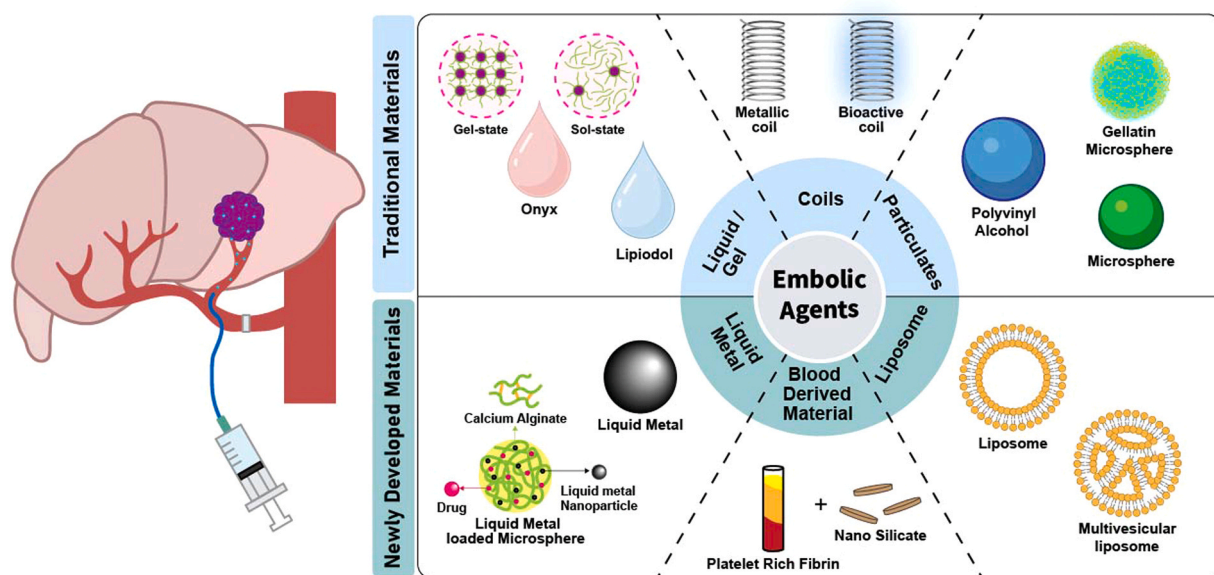
innovative forms of active embolization, where inorganic phosphate binders and intratumoral phosphate deprivation were utilized to modulate tumor immunity and enhance intracellular doxorubicin accumulation, respectively (Luo et al., 2025; Lv et al., 2022).

However, chemoembolization may pose procedure-related risks since it involves the risk of bleeding, infection, and liver damage (Son et al., 2018). Furthermore, it is not a curative method and is generally aimed at suppressing tumor growth or relieving symptoms. Besides, it is usually only effective for certain types of cancers with an abundant blood supply, such as liver tumors (Jin et al., 2024). It is predominantly used in the treatment of HCC and has been shown to significantly improve survival rates. Since large HCC tumors are almost entirely dependent on the hepatic artery for their primary blood supply, chemoembolization, which occludes the artery, proves to be an effective treatment (Bruix et al., 2004).

Radioembolization is a treatment where radioactive particles are delivered directly to a tumor through the bloodstream. It is commonly used for the treatment of liver cancers such as hepatocellular carcinoma. The procedure involves injecting small beads containing a radioactive isotope (usually yttrium-90) into the blood vessels that supply the tumor (Sangro et al., 2012). Radioembolization has the advantage of targeting as it delivers radiation only to the tumor, thus minimizing damage to the surrounding healthy tissue. It is also effective against inoperable tumors or tumors resistant to chemotherapy (Lau et al., 1994). However, one limitation of radioembolization is its restricted applicability to only certain types of cancer, primarily those with a highly vascularized structure, such as HCC. Tumors with poor vascularity or diffuse infiltration are less responsive to this therapy, as the radioactive particles may not be delivered efficiently or uniformly throughout the tumor tissue (Sangro et al., 2012). It can also cause adverse effects, such as fatigue, abdominal pain, nausea, and possible liver damage. As with any invasive procedure, other risks including bleeding and infection (Carr, 2004).

### 1.3. Limitations of embolization therapy and embolic agents

Embolic therapy and agents have several limitations. As mentioned earlier, embolization is most effective for tumors with a rich blood supply, limiting its use for other types of tumors (Moustafa et al., 2017).



**Scheme 1.** Schematic illustration of embolic agents based on nanobiomaterials. Traditional and newly developed materials embolic agent materials are compared. Top: Traditional embolic agents. Liposome / Gel - Onyx and Lipiodol. Coils - Metallic coil and Bioactive coil. Particulate - PVA, Gelatin microsphere, microsphere. Bottom: Newly developed embolic agents. Liquid metal - Bi-based liquid metal, magnetic liquid metal nanoparticle (Fe@EGaIn NP) loaded calcium alginate (CA) microspheres. Blood derived material - Platelet rich fibrin loaded Nanosilicate. Liposome - pH-responsive Liposome, and Multivesicular liposome.

Moreover, it may not completely eradicate the tumor, often serving more as a control measure rather than as a curative approach. Risks associated with this procedure include bleeding, infection, and damage to blood vessels (Ashrafmansouri et al., 2024). Post-embolization syndrome, which includes symptoms such as pain, fever, and nausea, is common after the procedure (Mason et al., 2015). Additionally, the delivery of embolic agent through surgery, may not effectively target small or poorly vascularized parts of the tumor (Kabakov and Yakimova, 2021).

Additionally, several disadvantages have been reported with the materials currently in use as embolic agents. Catheter delivery of the embolic agent or the insertion process can lead to several complications. For example, skin prolapse (Talaie et al., 2022) or catheter-related bloodstream infection (CRBSI) may occur, as much as blockage of the catheter by a blood clot (Vanholder et al., 2010). Additionally, pneumothorax may occur if the needle punctures the lung during insertion. Air embolization can cause mild symptoms, such as cough, chest pain, and tachycardia, and severe symptoms, such as right ventricular outlet obstruction, decreased blood flow to the left atrium, hypotension, coronary ischemia, and cardiovascular collapse (Renier et al., 2020). Addressing these complications remains challenging and novel nanobiomaterial are being developed to overcome these limitations.

## 2. Currently used vascular embolization materials & devices

This section outlines the types of embolic agents currently used in clinical practice, detailing their characteristics, advantages, and disadvantages. We also review recent advancements in nanobiomaterial agents and discuss current research trends in this field.

### 2.1. Mechanical occlusion devices

Mechanical occlusion devices are typically made from biocompatible materials such as platinum, stainless steel, nitinol (a nickel-titanium alloy), and various polymers (Pal et al., 2023; Salaskar et al., 2020). The sizes and dimensions of these devices vary depending on their specific application and the target vessel size. Coils generally range from 2 mm to 10 mm in diameter and can be up to 20 cm in length. Vascular plugs are available in diameters from 4 mm to 20 mm (Medsing et al., 2014; Rossi et al., 2006). Stents used for embolization purposes typically range from 2 mm to 5 mm in diameter and 10 mm to 40 mm in length (Tähtinen et al., 2013). Detachable balloons, when inflated, can vary from 2 mm to 15 mm in diameter (White et al., 1980). These devices physically obstruct blood flow, leading to thrombus formation and complete embolization (Kasirajan et al., 2001). The Guglielmi detachable coils (GDC), approved by the FDA (Food and Drug Administration) in 1995, were the first coil embolization device for treating aneurysms. These coils are soft, flexible, and made of a platinum alloy, typically consisting of 92 % platinum and 8 % tungsten. GDCs are available in various sizes, with diameters ranging from 2 mm to 10 mm and lengths up to 20 cm (Murayama et al., 2003). They function by applying a weak electric current of 1.0 mA to the delivery wire. This current causes electrolytic dissolution of the detachment zone. The detachment process typically takes approximately 4–12 minutes to complete. During this process, gas bubbles are generated at the detachment zone, particularly in GDC coils. The electrolytic detachment also promotes localized thrombus formation around the detachment zone, which may contribute to the coil's effectiveness in occluding the aneurysm (Lauzier et al., 2023; Padolecchia et al., 2001).

Metallic coils, primarily made of platinum, platinum-tungsten alloys, and stainless steel, enable high-precision placement in embolization procedures. Their accuracy is attributed to several key features: detachable mechanisms for repositioning, availability in various sizes and shapes, soft and flexible designs for navigating tortuous vessels, controlled release mechanisms, and placement under fluoroscopic guidance. These characteristics collectively allow for precise targeting of

specific vessels while minimizing impact on adjacent areas, making metallic coils effective for various clinical applications in embolization. Metallic coils provide immediate blood flow occlusion, which is essential in cases of aneurysms or bleeding vessels (Gianturco et al., 1975). The mechanism of action involves both mechanical obstruction and thrombogenesis. When deployed, the coils physically obstruct blood flow within the target vessel or aneurysm sac, while their metal surface promotes platelet aggregation and activates the coagulation cascade, leading to rapid thrombus formation (Padolecchia et al., 2001). This dual mechanism ensures swift and effective occlusion, which is critical in emergency situations where rapid hemostasis is required. They provide a long-term solution as they remain indefinitely in the body. Owing to their design and the way they conform to the shape of the vessel, there is a reduced risk of migration compared with other embolic agents. Metallic coils can be used in conjunction with other embolic agents, particularly liquid embolic agents such as Onyx (ethylene-vinyl alcohol copolymer), to enhance their efficacy and achieve more complete occlusion in complex vascular abnormalities. This combination technique has shown promising results, especially in the treatment of intracranial aneurysms where either coil embolization or liquid embolic agent alone might be insufficient. The synergistic effect of coils and liquid embolic can provide more durable aneurysm occlusion in selected cases (Cekirge et al., 2006).

However, there is a risk of coil compaction over time, which may lead to recanalization (reopening of the vessel). This risk is typically assessed at 6 months post-procedure, as many studies use follow-up angiography currently point as a standard protocol. Navigating the catheter for coil placement may be challenging in some cases, particularly in tortuous or small vessels. There is also a risk that the coil may not completely occlude the vessel, particularly in large or complex vascular structures, potentially necessitating additional treatment (Wiśniewski et al., 2021). Although rare, allergic reactions or inflammatory responses to metals can also occur. Additionally, some coils may be incompatible with MRI procedures, posing a limitation for patients who require regular imaging (Bussmann et al., 2018).

Metallic coils have been developed into bioactive coils by modifying their surfaces in various ways. These modifications include coating with bioactive materials or incorporating bioactive substances into the coil structure. Bioactive metallic coils, such as Matrix, HydroCoil, Cerecyte, and Nexus, are designed not only to mechanically occlude blood vessels but also to promote biological healing processes. They are often used in endovascular treatment of aneurysms or vascular malformations (Vance and Welch, 2014).

Matrix coils are coated with polyglycolic-lactic acid (PGLA), which is designed to induce an inflammatory response and promote healing (Murayama et al., 2006). HydroCoils consist of an expandable hydrogel coupled to a platinum coil, which can undergo a three- to ninefold increase in size upon contact with blood (Cantón et al., 2005). Cerecyte coils have PGLA incorporated within the coil lumen, while Nexus coils also utilize PGLA technology (Killer et al., 2009).

These bioactive coils are designed to promote cellular growth and healing around the coil, leading to a more stable and permanent occlusion as the body's own tissues integrate with the coil. Due to their bioactive properties, these coils can minimize the risk of vessel recanalization over time, which is a significant issue for standard metallic coils. Bioactive materials can encourage clot formation and endothelialization, resulting in a more complete and rapid vessel occlusion compared to non-bioactive coils. Additionally, the incorporation of fibers or bioactive coatings increases the immediate thrombogenicity of coils, potentially reducing the number of coils required to achieve vessel occlusion. This enhanced effectiveness may lead to quicker and less complex procedures (Broeders et al., 2016).

However, bioactive coils are typically more expensive than standard metallic coils, with costs ranging from \$1984 to \$172,179 for bioactive coils compared to \$714 to \$113,009 for standard small diameter helical coils, which is a significant factor in healthcare settings with limited

resources(Simon et al., 2010). As a relatively new technology, there may be limited long-term data on its efficacy and safety compared with standard coils(Jana, 2019). Despite their bioactive properties, there remains a risk that the coil may not completely occlude the vessel, especially in large or complex vascular structures. The deployment and positioning of bioactive coils can be technically challenging, requiring skilled operators and sometimes more complex procedures. Additionally, excessive tissue growth around the coil could lead to complications or need for further intervention(Apostolovic et al., 2010).

Bioactive metallic coils represent a significant advancement in embolic therapy, offering the potential for improvements in biological integration and more stable long-term results. However, their higher cost, need for more data on long-term outcomes, and technical challenges in their use should be weighed against their benefits. The choice of bioactive metallic coils should be based on individual patient needs, the medical condition being treated, and the expertise available at the treatment facility(Parkinson et al., 2008).

## 2.2. Liquid/gel embolic agents

Liquid/gel embolic agents have garnered significant attention because of their ability to achieve deep vascular penetration and complete occlusion of vascular structures, independent of thrombus formation, which depends on the patient's coagulation system. Liquid/gel embolic agents are fluids that can be delivered rapidly through microcatheters. Common clinical liquid/gel embolic agents include sclerosants, Lipiodol, cyanoacrylate adhesives, and onyx(Ko et al., 2022).

Lipiodol, a contrast agent composed of ethyl esters of iodized poppy seed oil, has been used since 1901 for lymphangiography(Gough et al., 1963). The ethiodized oil is often used in combination with the anticancer drug doxorubicin or other chemotherapeutic agents. Embolization using cocktail therapy with lipiodol and other embolization devices can improve tumor response rates compared to treatment with lipiodol alone(Simon et al., 2009).

Onyx is an embolic agent composed of an ethylene-vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Approved by the FDA in 2005 for embolization of cerebral Arteriovenous malformations, it is available in various viscosities, including Onyx-18, Onyx-20, Onyx-34, and OnyxHD-500 (Ayad et al., 2006). Physicians can select the appropriate onyx viscosity for different embolization purposes. Onyx coagulates externally, and when delivered to the blood vessel, DMSO rapidly diffuses into the blood, causing EVOH to precipitate and harden into a sponge-like gel within five minutes of injection, that captures the tantalum powder, an X-ray contrast agent. Unlike n-butyl cyanoacrylate (NBCA), onyx is not an adhesive and has minimal risk of clogging or sticking to the microcatheter (Poursaid et al., 2016). However, removing the microcatheter can be challenging when the long segment is within a tortuous artery. Onyx creates a permanent occlusion and exerts a mild inflammatory effect on the endothelium. The DMSO dose used is well below the toxic level; however, the injection rate should not exceed a certain level to avoid vasospasm(Koçer et al., 2016).

Liquid/gel embolic agents can conform to the shapes of irregular and complex vascular structures, providing more complete embolization of the target area. These agents can penetrate smaller and more distal vessels that may be inaccessible to coils, making them ideal for certain types of vascular malformations(Lanzino et al., 2005). The application of liquid/gel agents can be faster than the placement of multiple coils, especially in complex vascular networks. Many liquid/gel embolic allow for controlled and precise delivery, which is critical for avoiding non-target embolization. Liquid/gel agents do not rely on the patient's clotting ability, making them useful for patients with coagulopathies (Kilani et al., 2017).

Owing to their fluid nature, these agents carry a risk of migrating to non-target areas, which can lead to complications. Administering liquid/gel embolic requires a high level of skill and experience because of the risk of unintended embolization and need for precise control.

Once solidified, they can be difficult to remove and can penetrate deeper with further intervention, making retreatment more challenging (Ganguli et al., 2021). Some liquid agents may cause inflammatory responses or allergic reactions in certain cases. Additionally, liquid/gel embolisms can be expensive, and their cost-effectiveness must be considered, particularly in settings with limited resources. Visualization under imaging during their deployment can also be limited, necessary adjunctive imaging techniques or contrast mixing.

Liquid/ gel embolic agents offer unique advantages by filling complex vascular spaces and penetrating small vessels. However, their use requires careful consideration owing to risks such as non-target embolization and the technical skills, and the need for their safe and effective deployment. The decision to use these agents should be based on the specific medical condition, the anatomy of the vascular structure to be embolized, the experience of the medical team, and available resources.

## 2.3. Particulate embolic agents

Embolic particulates were the first embolic agents to be developed and are currently the most used. Particulates can be temporary (biodegradable) or permanent (non-biodegradable), and their origins can be natural or synthetic. They can be loaded chemotherapeutically or radioactively for targeted tumor delivery. These diverse properties allow them to be applied in clinical scenarios and they are primarily designed to embolize tissues at the arteriolar and capillary levels(Asah et al., 2018).

Polyvinyl alcohol (PVA) is a biocompatible polymer that has been used in various medical procedures since the 1950s. It was initially used as a filler after pneumonectomy. PVA particles are considered biocompatible permanent embolization agents that are not absorbed in vivo. PVA particles tend to aggregate owing to their surface charge and are characterized by aggregation in physiological solutions owing to their surface hydrophobicity. These properties cause immediate mechanical occlusion of the vessels, leading to thrombus formation. However, despite these characteristics, due to the way the particles are manufactured, the size and shape of the particles are irregular and can lead to unintended occlusion of larger vessels during the embolization process. This has impacted the use of particle injections, and several studies have reported high rates of adverse events and complications(Sheth et al., 2017).

Gelatin-based systems are commercially available biodegradable embolic agents used for temporary embolization. These systems come in various forms, including gelatin microspheres (GMS), Gelpart, sponges, and powders. GMS typically range from 35 to 100  $\mu\text{m}$  in diameter, while Gelpart is larger at about 1 mm. (Ohta et al., 2010) When injected into blood vessels, these particles cause terminal vessel occlusion and promote thrombus formation. The porous structure of gelatin particles acts as a scaffold, encouraging cell adhesion and tissue regeneration. The size of the particles influences their level of embolization; smaller GMS can reach interlobular arteries, while larger Gelpart tends to occlude interlobular arteries. This difference affects the extent of embolization, with GMS often resulting in smaller areas of occlusion compared to Gelpart. Gelatin-based particles typically degrade within several weeks to months, making them suitable for temporary embolization procedures. Their degradation rate can be influenced by factors such as cross-linking and particle size. The degradable nature of the gelatin-based embolic agent is advantageous for certain functions such as embolization of the internal iliac artery and occlusion of the hepatic artery during chemoembolization. Recent studies have shown that GMS can be effectively loaded with anticancer drugs, allowing for controlled release during chemoembolization procedures, which enhances the therapeutic efficacy of the treatment (Kim et al., 2018). Microspheres used for embolization are manufactured to have a consistent size (generally ranging from 1 to 1000  $\mu\text{m}$ ) and homogeneous shape, ensuring predictable and uniform embolization (Lee et al., 2024a). This homogeneity is crucial for controlling the degree of vessel occlusion. Specific products offer

narrower size ranges, such as LC Bead, which is available in 70–150  $\mu\text{m}$ , 100–300  $\mu\text{m}$ , 300–500  $\mu\text{m}$ , and 500–700  $\mu\text{m}$  sizes. Other products, like Embosphere, are available in ranges including 40–120  $\mu\text{m}$ , 100–300  $\mu\text{m}$ , 300–500  $\mu\text{m}$ , 500–700  $\mu\text{m}$ , 700–900  $\mu\text{m}$ , and 900–1200  $\mu\text{m}$  (Caine et al., 2017). Because of their small size, microspheres can penetrate deep into the vascular bed of the target tissue, making them effective for the treatment of tumors or vascular malformations. The size of the microspheres can be selected based on the desired level of embolization, providing a high degree of control over the procedure. Compared with liquid agents, microspheres have a lower risk of migrating to non-target areas when properly selected and administered. Additionally, microspheres can often be visualized using imaging modalities, aiding in precise delivery and assessment of treatment efficacy (Nosrati et al., 2018).

However, the microspheres may not completely occlude the target vessel, particularly in cases with high-flow vessels or complex vascular networks (Nam et al., 2024). If not administered carefully, they can occlude non-target vessels, leading to tissue ischemia or necrosis. Once deployed, the microspheres cannot be repositioned or easily retrieved, making the procedure irreversible (Caine et al., 2017). The precise delivery of microspheres requires technical expertise and careful planning, making the procedure operator-dependent. Additionally, microspheres are more expensive than other embolic agents, which may limit their use in budget-constrained settings. Some types of microspheres may also induce an inflammatory response in tissues that must be managed appropriately.

Microspheres are a valuable tool in the embolization arsenal, offering advantages such as deep-tissue penetration and controlled embolization. However, their use requires careful patient selection, meticulous planning, and skilled execution to minimize risks such as inadequate occlusion or non-target embolization. The decision to use microspheres should be based on a thorough evaluation of the clinical scenario, anatomy of the target vessels, and experience of the medical team.

Particulate embolic agents represent a diverse and essential category of embolic materials, offering a range of options for various clinical scenarios. These agents, which include polyvinyl alcohol (PVA) particles, gelatin-based systems, and calibrated microspheres, have evolved significantly since their introduction. Each type offers unique advantages and limitations. PVA particles, while biocompatible and permanent, face challenges due to their irregular shape and tendency to aggregate. Gelatin-based agents provide temporary embolization with controllable degradation rates, making them suitable for specific procedures and drug delivery applications. Calibrated microspheres offer precise control over embolization depth and uniformity, enhancing predictability in treatment outcomes. However, they require careful selection and administration to avoid complications. The choice of particulate embolic agent depends on factors such as the desired duration of embolization, target vessel size, and specific clinical requirements. As research continues, these agents are likely to see further refinements in their properties and applications, potentially improving their efficacy and safety profiles in interventional radiology procedures. (Table 1)

### 3. Newly developed embolic agents

Traditional embolic agents have primarily been developed to achieve vessel occlusion. However, these materials face significant limitations, including unpredictable degradation profiles, adverse effects on non-target tissues, and a lack of multifunctionality. These limitations can lead to complications such as premature restoration of blood flow or permanent occlusion, depending on the physiological conditions of the patient. These challenges have driven the development of new embolic agents that incorporate advanced functionalities, moving beyond the conventional approach. Innovations in nanomedicine and advanced materials have spurred the creation of more versatile and effective embolic agents, aiming to overcome the limitations of traditional

materials (Hu et al., 2019a).

In response to the clinical requests for embolic materials, an ideal embolic agent should not only achieve vessel occlusion but also combine multiple characteristics that enhance therapeutic efficiency, safety, and ease of use. It must exhibit high biocompatibility to prevent adverse reactions such as inflammation or toxicity, be capable of delivering therapeutic payloads like drugs (e.g., doxorubicin, cisplatin, irinotecan, mitomycin C, or gemcitabine, which are clinically used in chemo-embolization protocols for liver cancer) or radiation and allow precise control over the embolization process to minimize non-target effects (Hu et al., 2019b; Wáng et al., 2015). Additionally, it should be clearly visible under imaging techniques (e.g., fluoroscopy, CT, or MRI) for accurate placement and continuous monitoring, provide stable occlusion that resists migration or dissolution, and be adaptable in size and shape to treat various vascular lesions (Ierardi et al., 2020). Ease of handling, minimal preparation time, and straightforward deployment are crucial, and while reversibility can be beneficial for some cases, permanent occlusion is often necessary (Senturk et al., 2010).

Recent advances have led to the development of various new embolic agents, some of which include liquid metals (Fan et al., 2020), blood-derived materials (Liu et al., 2020), and liposomes (Wang et al., 2022). Each of these agents brings unique characteristics and functionalities, addressing some of the limitations that traditional embolic agents cannot resolve. Ongoing research in nanomedicine and biomaterials is likely to further advance the development of multifunctional embolic agents, tailored to meet the specific clinical needs of various conditions. Such innovations hold great promise for the future of embolization therapies and may eventually close the gap between current limitations and clinical demands (Lv et al., 2021).

#### 3.1. Liquid metals

Liquid metals, particularly gallium-based alloys, are a unique class of materials that remain in a liquid state at or near room temperature. These materials offer a combination of metallic and fluidic properties, making them highly versatile for various applications, especially in the biomedical field. Liquid metals exhibit several advantageous characteristics, including low toxicity, high thermal and electrical conductivity, and excellent deformability (Fan et al., 2020). Recently, clinically used microsphere embolic agents have limited therapeutic efficacy and lack real-time imaging capabilities. Magnetic liquid metal nanoparticles, specifically those based on gallium alloys like eutectic gallium-indium (EGaIn), offer several benefits by integrating CT/MR dual-modality imaging and photothermal/optical functions. They also combine integrated embolization and drug loading functions and can be used as flexible agents for smart chemoembolization (Li et al., 2020). Gallium-based liquid metals (LMs) exhibit numerous basic, amorphous, and physicochemical properties (Tang et al., 2021). In recent years, liquid-metal micro/nanomaterials have been innovated through micro/nanotechnology to impart different performance-related parameters and have shown potential in various biomedical applications, including drug delivery (Li et al., 2020), molecular imaging (Gao et al., 2022), cancer therapy (Li et al., 2020), and biomedical devices (Yan et al., 2018).

As embolic agents, liquid metals undergo rapid transition from liquid to solid state in the body, allowing prompt vessel occlusion. Their fluid nature enables them to penetrate deeply into targeted vascular beds. They often provide better visibility in imaging modalities, aiding in precise placement (Wang et al., 2014). However, the administration of liquid-metal embolic agents requires high precision and skill to avoid non-target embolization. Moreover, information on their long-term safety and efficacy is limited. In addition, there is a risk of the liquid metal migrating to non-target areas before solidification.

Calcium alginate (CA) acts as a carrier for Fe@EGaIn and as a matrix embolization material (Qu et al., 2022). It integrates dual-modality diagnostics to meet various diagnostic needs and enhance the efficacy of

**Table 1**  
**Summary of currently used vascular embolization materials and devices.**

Category	Embolic Agent	Form	Features	Clinical Stage	References
Mechanical Occlusion Devices	Metallic Coils	Solid (Platinum, Stainless Steel, Nitinol)	<ul style="list-style-type: none"> <li>- Physically obstructs blood flow.</li> <li>- Promotes thrombus formation.</li> <li>- Provides long-term embolization with minimal migration risk.</li> <li>- May compact overtime, leading to vessel recanalization.</li> </ul>	Fully established in clinical practice; widely used for vascular embolization and aneurysm treatment.	Platinum(Yang et al., 1988), Stainless Steel(Prasad et al., 2004), Nitinol(Melzer and Stoeckel, 2010)
	Guglielmi Detachable Coils (GDC)	Solid (Platinum alloy)	<ul style="list-style-type: none"> <li>- Utilizes electrolytic detachment for precise placement.</li> <li>- Flexible for navigating tortuous vessels.</li> <li>- Detachment process using electric current can be technically demanding.</li> </ul>	FDA-approved; extensively used for aneurysm treatment with robust clinical evidence.	(Murayama et al., 2003; Murayama et al., 1999; Padolecchia et al., 2001)
	Bioactive Metallic Coils (e.g., Matrix, HydroCoil, Cerecyte, Nexus)	Solid (Platinum with bioactive coatings)	<ul style="list-style-type: none"> <li>- Facilitates clot formation and vessel healing.</li> <li>- HydroCoil expands upon contact with blood, enhancing occlusion.</li> <li>- Reduces the risk of recanalization.</li> </ul>	Established in clinical practice; ongoing studies to optimize outcomes and reduce recanalization risks.	Matrix(Murayama et al., 2006), HydroCoil(Cantón et al., 2005), Cerecyte(Killer et al., 2009), Nexus(Kang et al., 2008)
	Detachable Balloons	Solid	<ul style="list-style-type: none"> <li>- Provides temporary occlusion.</li> <li>- Adjustable size through inflation.</li> <li>- Applied for larger arteries.</li> <li>- Risk of balloon deflation or migration after placement.</li> </ul>	Clinically used for temporary occlusion of larger arteries; less common compared to coils.	(DeSouza and Reidy, 1992; Higashida et al., 1989; White et al., 1980)
Liquid/Gel Embolic Agents	Onyx	Liquid/Gel	<ul style="list-style-type: none"> <li>- Non-adhesive EVOH copolymer.</li> <li>- Solidifies into a permanent, sponge-like structure.</li> <li>- Minimizes the risk of catheter clogging.</li> <li>- DMSO delivery can cause vasospasm.</li> </ul>	FDA-approved; widely applied clinically for arteriovenous malformations and tumors.	(Ayad et al., 2006; Cekirge et al., 2006; Kilani et al., 2017)
	Lipiodol	Liquid	<ul style="list-style-type: none"> <li>- Iodized oil used as a contrast agent.</li> <li>- Frequently combined with chemotherapeutic agents.</li> <li>- Enhances tumor response rates.</li> <li>- May persist in the body for extended periods and cause toxicity.</li> </ul>	Long-standing clinical use as a contrast agent and for chemoembolization in liver cancer.	(Gough et al., 1963; Ko et al., 2022; Simon et al., 2009)
	Cyanoacrylate Adhesives	Liquid	<ul style="list-style-type: none"> <li>- Rapid solidification upon application.</li> <li>- Exhibits strong adhesive properties.</li> <li>- Commonly applied for vascular malformations.</li> <li>- Risk of catheter sticking</li> <li>- Permanent embolization agent.</li> <li>- Biocompatible material.</li> <li>- Irregular particle shapes can cause non-target embolization.</li> </ul>	Fully established in clinical practice for vascular malformations and preoperative embolization.	(García Cerdá et al., 2015; Petrie and adhesives, 2015; Pollak et al., 2001)
Particulate Embolic Agents	Polyvinyl Alcohol (PVA)	Particulate	<ul style="list-style-type: none"> <li>- Biodegradable and used for temporary embolization.</li> <li>- Exhibits a controllable degradation rate.</li> <li>- Capable of delivering therapeutic agents.</li> <li>- Variable degradation rate may reduce embolization consistency.</li> </ul>	Fully established in clinical use for permanent embolization, including cancer treatment.	(Bendszus et al., 2000; Laurent and radiology, 2007; Sheth et al., 2017)
	Gelatin-Based Systems	Particulate (Gelatin microspheres, Gelpart)	<ul style="list-style-type: none"> <li>- Biodegradable and used for temporary embolization.</li> <li>- Exhibits a controllable degradation rate.</li> <li>- Capable of delivering therapeutic agents.</li> <li>- Variable degradation rate may reduce embolization consistency.</li> </ul>	Fully established in clinical practice for temporary embolization; biodegradable with controllable degradation rates.	Gelatin microspheres (Bendszus et al., 2000; Kim et al., 2018; Laurent et al., 1996), Gelpart (Miyayama et al., 2014; Nitta et al., 2013; Ohta et al., 2010)

(continued on next page)

**Table 1** (continued)

Category	Embolitic Agent	Form	Features	Clinical Stage	References
	Microspheres (e.g., Embosphere, LC Bead)	Particulate	<ul style="list-style-type: none"> <li>- Provides predictable and uniform embolization.</li> <li>- Available in various size ranges.</li> <li>- Capable of deep vascular penetration for targeted embolization.</li> <li>- Irreversible once deployed; risk of non-target embolization.</li> </ul>	Fully integrated into clinical practice for targeted embolization in uterine fibroids and liver cancer treatment.	Embosphere (Caine et al., 2017; Rodiek et al., 2004), LC Bead (Caine et al., 2018; Levy et al., 2016)

the three therapeutic modalities: embolization, chemotherapy, and photothermal/photodynamic therapy. This approach has successfully achieved enhanced chemoembolization when using a near-infrared (NIR) laser. Specifically, an NIR laser with a wavelength of 808 nm was applied at a power density of 1.5 W/cm<sup>2</sup>, leading to a localized temperature increase of up to 60°C within 50 seconds. This induced both photothermal and photodynamic effects, optimizing drug release and tumor ablation. The agent shows potential improvements in radiopacity, enabling better visualization during procedures. In terms of therapeutic efficacy, the system demonstrated a tumor growth inhibition (TGI) of 98 % when combined with NIR laser assistance, compared to 62 % with NIR laser alone and 78–84 % with conventional embolization methods. This innovative approach offers significant advantages over traditional embolic materials, particularly in terms of imaging precision and targeted delivery control (Wang et al., 2021).

Recent advancements in bismuth (Bi)-based liquid metal (LM) embolic agents have shown promising results in the field of embolotherapy. One of the most significant advantages of these agents is their ability to undergo a rapid liquid-solid phase transition, enabling fast and effective embolization in clinical settings. Bismuth, while solid at room temperature, can transition to a liquid state under specific conditions and then rapidly solidify again, ensuring quick vascular occlusion. These agents offer complete vascular blockage upon embolization and provide excellent multimodal imaging capabilities, such as visibility under CT and MRI, which greatly enhances both therapeutic and diagnostic applications. Moreover, the ability to induce magnetic hyperthermia under an alternating magnetic field adds a novel dimension to treatment, supporting the theranostic approach by integrating both therapy and diagnosis (Duan et al., 2022).

Bismuth-based embolic agents have been developed in various forms and compositions, with bismuth liquid metal (LM) and solid bismuth-based embolic agents being the most notable examples. Solid bismuth-based embolic agents, such as Bismuth Beads and Bi2S3@SH microspheres, are primarily used for vascular occlusion in their solid state, where they embolize blood vessels effectively after delivery. These solid agents provide radiopacity, which is crucial for image-guided

procedures, but they lack the rapid phase transition capabilities of bismuth liquid metal (LM), which allows for quicker embolization by injecting in liquid form and solidifying within the vasculature (Shen et al., 2023).

While solid bismuth-based embolic agents play an essential role in embolotherapy by providing excellent imaging contrast and effective embolization, bismuth liquid metal (LM)-based agents offer unique advantages that are unmatched. Their ability to undergo a rapid liquid-solid phase transition enables immediate embolization, and their combined magnetic hyperthermia and multimodal imaging capabilities allow for more versatile and effective treatment within the theranostic framework. These distinctive features make bismuth liquid metal a powerful tool for future advancements in embolotherapy, with significant potential to revolutionize tumor therapy and diagnosis. (Table 2)

### 3.2. Blood-derived materials

As embolic agents, blood-derived materials are either derived from or mimic components of blood and are utilized for embolization in medical procedures. These materials typically harness the natural clotting or occlusive properties of the blood. They are often preferred in scenarios in which biocompatibility and natural integration with the body's systems are paramount. Potential benefits include a reduced risk of foreign body reactions and compatibility with the body's natural healing processes (Altun et al., 2020). However, challenges include ensuring consistent performance, managing the risk of unintended clotting, and potential variability in preparation and application. The development and use of blood-derived materials for embolization represent an evolving area in medical research, focusing on leveraging the body's intrinsic properties for therapeutic purposes.

Novel blood-derived embolic materials have shown promising results in catheter-directed arterial embolization. Made from platelet-rich fibrin, these materials exhibit shear-thinning properties, making it easier to inject them through catheters (Liu et al., 2020). Research has highlighted their potential for instant, effective, and durable intra-arterial hemostasis, regardless of the patient's coagulopathy status. Animal

**Table 2**  
Summary of bismuth-based embolic agents.

Embolitic agents	Composition	Form	Features	Embolization Efficacy	Author, year
BBM (Bismuth-based metal)	Bi 32.8 %, In 46.8 %, Sn 15.7 %, Zn 0.4 %, Ga 3.8 %	Liquid (at high temperature) and solid (after cooling)	<ul style="list-style-type: none"> <li>- Rapid solidification after injection- Visible in CT and MRI- Generate heat under magnetic fields for hyperthermia- Biocompatible</li> </ul>	<ul style="list-style-type: none"> <li>- Effective for vascular and tumor embolization- Block both veins and arteries- Complete tumor necrosis with combined hyperthermia</li> </ul>	Duan et al., 2022 (Duan et al., 2022)
Bismuth Beads	Bismuth, polyvinyl alcohol (PVA)	Spherical beads (100–600 μm)	<ul style="list-style-type: none"> <li>- Radiopaque (visible on DECT)- Homogeneous bismuth distribution - Compatible with microcatheters for delivery</li> </ul>	<ul style="list-style-type: none"> <li>- Delivered through standard clinical microcatheters- Radiopaque beads distinguishable from iodine contrast</li> </ul>	Negussie et al., 2021 (Negussie et al., 2021)
Bi2S3@SH Microspheres	Sodium hyaluronate, bismuth sulfide (Bi2S3) nanorods (NRs)	Spherical microspheres (87 μm)	<ul style="list-style-type: none"> <li>- Radiopaque (visible under Micro-CT)- Good biocompatibility and mechanical properties- Uniform size and good dispersibility due to microfluidic fabrication</li> </ul>	<ul style="list-style-type: none"> <li>- High embolization efficacy for small-sized blood vessels (500–300 μm)- Effective in simulated in vitro embolization models</li> </ul>	Shen et al., 2023 (Shen et al., 2023)
PLGA-Bismuth Oxychloride Composite	PLGA with 50 % Bismuth Oxychloride	Biodegradable filament	<ul style="list-style-type: none"> <li>- Shape memory polymer composite with water-induced buckling- Fully biodegradable with radiopaque properties- Programmable shape memory</li> </ul>	<ul style="list-style-type: none"> <li>- Complete occlusion in less than 2 minutes in in-vitro and in-vivo rabbit models- Water-induced swelling enhances occlusion</li> </ul>	Salvekar et al., 2018 (Salvekar, 2018)

models have demonstrated their efficacy in occluding arteries and their ability to induce a histologic response while integrating with the surrounding tissue. This innovative embolotherapy approach, which leverages the properties of blood-derived materials, offers a potentially safer and more effective alternative to traditional embolic agents. Being derived from blood, blood-originating embolic agents are naturally

compatible with the body, reducing the risk of adverse reactions and potentially promoting healing and integration with surrounding tissues. Additionally, blood-derived materials may cause lesser inflammation than synthetic agents(Weng et al., 2013).

However, there could be variability in functional properties owing to differences in individual blood samples. Additionally, there is a potential

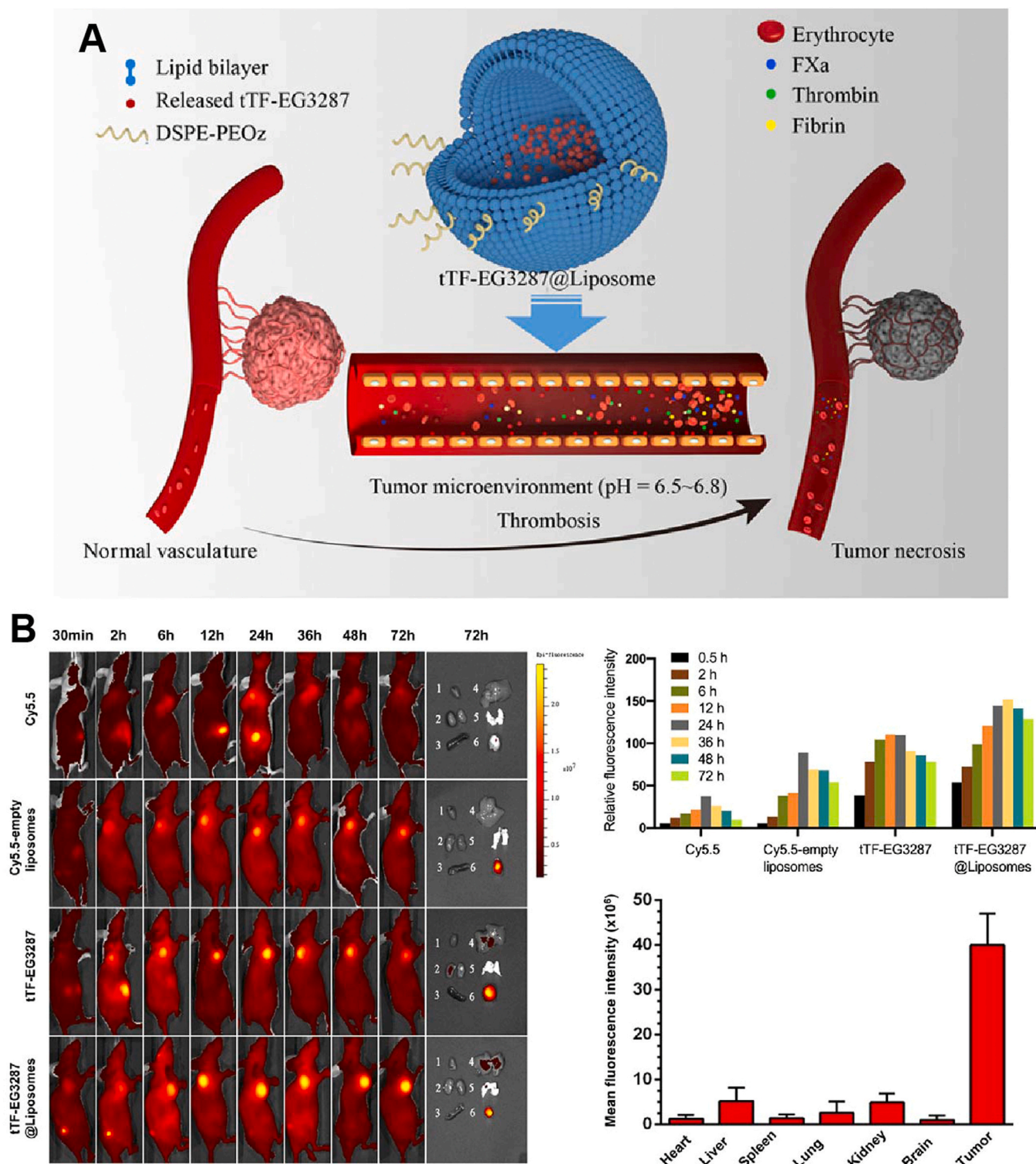


Fig. 2. A) Schematic diagram of pH-responsive liposomes. Wang, L., et al. encapsulated tTF-EG3287, a procoagulant protein-targeting agent, into poly(2-ethyl-2-oxazoline)-distearoyl phosphatidyl ethanolamine (PEOz-DSPE) modified liposomes to create tTF-EG3287@liposomes. B) In a mouse model of HCC, tTF-EG3287@liposomes demonstrated prolonged retention and increased tumor accumulation compared to tTF-EG3287 alone, leading to superior antitumor efficacy. Reproduced with permission from(Wang et al., 2022). Copyright (2022) American Chemical Society.

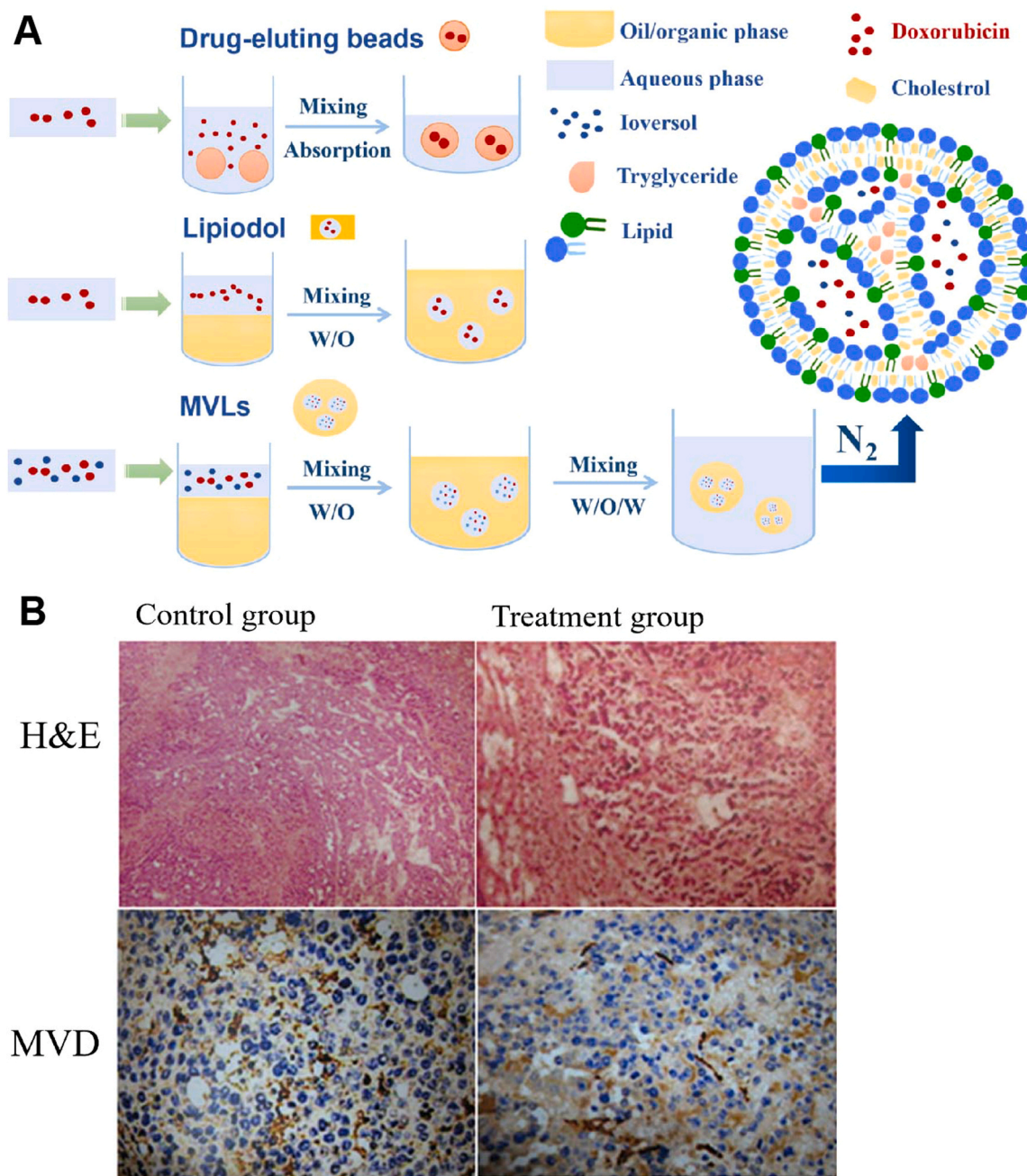
risk of unintended clotting during the preparation or application of these materials. Furthermore, insufficient long-term data are available on the efficacy and safety of these materials compared to those for more established embolic agents.

### 3.3. Liposome

Liposomes have also been explored as potential embolic agents for targeted cancer therapy. One study evaluated the use of pH-responsive liposomes loaded with targeted procoagulant proteins (Wang et al., 2022). These liposomes were designed to selectively induce tumor thrombosis and subsequent necrosis, which is a novel strategy for anti-tumor therapy. Liposomes encapsulating a targeted procoagulant protein, tTF-EG3287, demonstrated considerable drug-loading capacity,

encapsulation efficiency, and biocompatibility. In acidic microenvironments (pH 6.5–6.8, typical of the tumor microenvironment), these liposomes effectively release their contents and show promise as novel vascular embolization agents, particularly for solid tumors. The pH adjustment was typically achieved using phosphate-buffered saline (PBS) or HEPES buffer, with the addition of small amounts of hydrochloric acid (HCl) to reach the desired acidic pH. This approach provides a novel strategy for tumor-targeted infarction therapy. (Fig. 2)

Another example involves the use of multivesicular liposomes (MVLs) in a rabbit model of VX2 liver tumors. These liposomes were investigated for their embolic and therapeutic effects, demonstrating their potential for transcatheter arterial chemoembolization (TACE). The study examined the influence of liposome particle size on embolic efficacy and treatment outcomes. Specifically, the researchers used



**Fig. 3.** A) The preparation process and structure of MVLs, compared with conventional drug-eluting beads and Lipiodol. B) The therapeutic effect was evaluated in a rabbit model of VX-2 tumor. The results show a decrease in necrosis degree and micro vessel density (MVD). The reduction in MVD indicates the anti-angiogenic and therapeutic efficacy of MVLs in treating VX2 liver tumors. Reproduced with permission from. (Tang et al., 2023) Copyright (2022) Drug Delivery.

MVLs with sizes ranging from 20 to 80 μm, with a mean diameter of 35.6 ± 15.8 μm. The embolic efficacy was evaluated through angiography, which showed that the MVLs achieved complete embolization of the tumor-feeding arteries in all treated rabbits (100 % efficacy). In terms of treatment outcomes, the MVL-TACE group showed significantly reduced tumor growth rates compared to the control group, with a tumor growth inhibition rate of 86.7 % at 14 days post-treatment. These findings highlight the potential of liposomes as embolic agents, particularly in the context of cancer therapy (Tang et al., 2023). (Fig. 3)

Research on liposomes for cancer therapy has undergone significant advancements (Lee et al., 2024b). The exploration of liposomes and bioengineered hybrid nanovesicles for cancer detection and therapy has been the focus of several recent studies (Mukherjee et al., 2022). These investigations aim to leverage the unique properties of liposomes for targeted drug delivery, improving treatment efficacy, while minimizing side effects.

These examples underscore the growing interest in using liposomes as embolic agents, particularly in oncology, where targeted delivery and controlled release of therapeutic agents can significantly enhance treatment outcomes. Liposomes are generally well-tolerated by the body. They can encapsulate and deliver therapeutic agents directly to the target sites (Kim et al., 2025). Liposomes allow controlled release of encapsulated substances (Saraf et al., 2020). However, liposomes may have stability issues in the bloodstream. Liposomes may not be as effective in creating complete and stable vessel occlusion as other embolic agents. Besides, preparing liposomes with the appropriate characteristics can be technically challenging. (Table 3)

#### 4. Conclusion

This review has highlighted the potential of various embolic agents, particularly those incorporating nanotechnology, in enhancing the efficacy of tumor treatment. Current clinical embolic materials, while widely used, are limited by issues such as unpredictable degradation profiles, the risk of premature restoration of blood flow, and incomplete tumor eradication. Examples such as liquid metals, which allow simultaneous imaging and embolization, and blood-derived materials, offering enhanced biocompatibility, illustrate promising advancements. Liposomes provide another example of innovation, delivering chemotherapeutic agents precisely to tumor sites while minimizing systemic toxicity. Nanotechnology-based embolic agents offer promising alternatives, with the potential to overcome these limitations through improved targeting, biocompatibility, and multifunctionality. The integration of nanomedicine into embolization strategies represents significant advancement, especially in addressing challenges such as hypoxia, chemotherapy resistance, and angiogenesis associated with tumor recurrence. By enabling the precise delivery of chemotherapeutic agents with reduced systemic toxicity, nanotechnology holds the potential to transform current therapeutic approaches (Wang et al., 2024).

**Table 3**  
Summary of newly developed embolic agents.

Category	Embolic Agent	Form	Features	References
Liquid Metals	Gallium-Based Liquid Metals	Liquid/Solid transition	- Rapid phase transition from liquid to solid. - Enhances visualization in CT/MRI. - Possesses photothermal and drug delivery capabilities.	(Qu et al., 2022; Wang et al., 2021; Wang et al., 2014) (Duan et al., 2022)
	Bismuth-Based Liquid Metals	Liquid/Solid transition	- Quick liquid-to-solid transformation for occlusion. - Provides imaging contrast in multiple modalities. - Enables magnetic hyperthermia for theranostic applications.	
Blood-Derived Materials	Blood-Derived Materials (Platelet-Rich Fibrin)	Gel/Solid transition	- Easily injectable due to shear-thinning, transitioning from gel to solid upon blood contact. - Forms a stable solid structure for vessel occlusion and tissue integration. - Enhances fibrin interaction and collagen deposition, promoting histologic response.	(Altun et al., 2020)
Liposomes	pH-Responsive Liposomes	Particulate	- Induces tumor thrombosis selectively in acidic environments. - Encapsulates procoagulant proteins. - Targets solid tumor embolization.	(Wang et al., 2022)
	Multivesicular Liposomes (MVLs) -	Particulate	- Provides both embolic and therapeutic effects. - Allows for controlled drug release. - Achieves complete embolization in tumor-feeding arteries.	(Tang et al., 2023)

Recent research suggests that we may soon see the integration of new technologies that go beyond the traditional role of embolic agents in tumor treatment. The development of active and multifunctional embolic agents is paving the way for therapies that combine diagnosis and treatment (Li et al., 2024). These advancements will enable the precise delivery of immune checkpoint inhibitors, immunotherapy, and gene therapy based on individual biomarkers, creating a new era of nanomedicine systems (Kong et al., 2024). Moreover, lipid nanoparticle-based gene therapies are rapidly advancing and could combine with lipid-based contrast agents to go beyond simple targeting (Mehta et al., 2023). By incorporating immune checkpoint inhibitors and gene therapy, these systems will enable multi-faceted approaches to cancer treatment, opening new possibilities for more effective and personalized care (Ashrafmansouri et al., 2024; Lee et al., 2024a).

However, challenges remain. The unpredictable degradation behavior of embolic materials and the need for more precise control over the timing of embolic dissolution require further investigation. Additionally, translating these advanced materials from the laboratory to clinical practice remains a critical hurdle that must be addressed through rigorous testing and development (Ahn et al., 2023). Future research should focus on the development of embolic agents that incorporate peptides, genes, or radiopharmaceuticals, alongside the potential for integration with immunotherapy. These multifunctional agents could provide enhanced therapeutic outcomes while minimizing adverse effects. Moreover, advancements in imaging capabilities will be essential for real-time monitoring of embolization procedures and improving overall treatment precision.

In conclusion, nanotechnology-based embolic agents represent a critical step forward in the treatment of tumors. Ongoing research in this field will likely lead to the development of more effective, targeted, and safer embolic materials, with the potential to significantly improve clinical outcomes in cancer therapy.

#### Author contributions

Jonghoon Choi and Hee-Young Lee supervised the study. Jihyuk Yang, Yonghyun Choi, Suyeon Ahn, Jiwon Kim, Heejin Ha, Jaehee Jang, and Jonghoon Choi designed the study and conducted the literature survey. Jihyuk Yang, Yonghyun Choi, Suyeon Ahn, Heejin Ha, Masayoshi Tanaka, Hee-young Lee and Jonghoon Choi wrote and revised the manuscript.

#### CRediT authorship contribution statement

**Jihyuk Yang:** Writing – original draft, review & editing, Visualization, Conceptualization, Investigation. **Yonghyun Choi:** Writing – review & editing, Conceptualization, Investigation. **Suyeon Ahn:** Writing – original draft, Conceptualization, Investigation. **Heejin Ha:** Writing – original draft, Conceptualization, Investigation. **Jiwon Kim:** Writing –

review & editing, Conceptualization, Investigation. **Jaehae Jang:** Writing – review & editing, Conceptualization, Investigation. **Masayoshi Tanaka:** Supervision. **Hee-Young Lee:** Supervision. **Jonghoon Choi:** Conceptualization, Supervision.

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## Declaration of Competing Interest

Dr. Jonghoon Choi is the CEO/founder, and Dr. Yonghyun Choi is the CTO of the Feynman Institute of Technology at the Nanomedicine Corporation.

## Data availability

Data will be made available on request.

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