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Platelets and their biomimetics for regenerative medicine and cancer therapies

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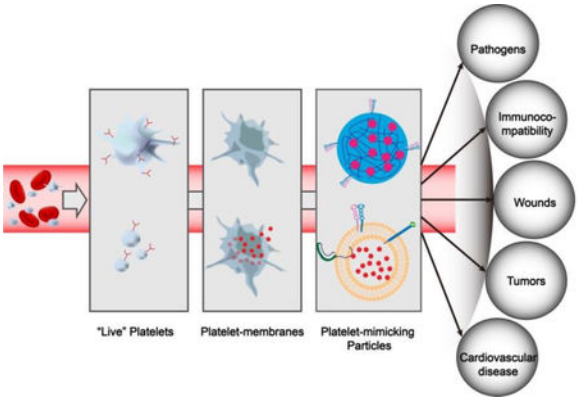
Abstract

Platelets, circulating blood cells derived from megakaryocytes, play a key role in various physical activities, including coagulation, hemostasis, the body's innate immune response, and cancer metastasis. By taking advantage of their key traits, researchers have developed strategies to exploit platelets and platelet-mimicking nanoassemblies to treat a number of conditions, including wounds, cancers, and bacterial infections. Compared to traditional polymer, lipsosome, and inorganic nanoparticles-based delivery systems, platelets and platelet-mimicking vehicles hold many advantages. Among these are their enhanced circulation time, their large volumes and surface areas for drug loading or conjugation, and their inherent ability to target some diseases. In this review, we will highlight the recent progress made in the development of disease-targeting platelets- and platelet-mimicking-vehicles as therapeutic platforms.

Graphical Abstract



In this review, we will focus on the recent progress made in the development of platelet and platelet-mimicking delivery systems for the treatment of disease.

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1. Introduction

Nanomedicine has emerged as a new field in medical science that seeks to apply the recent breakthroughs made in nanotechnology to advance human health, driven by the intrinsic physicochemical properties of nanoparticles.[1–6] Despite the continuous progress in recent decades, important insights are still lacking, such as the pharmacokinetics, pharmacodynamics, and safety of many nanomaterials.[7–9] To address the above nanotechnology challenges, researchers are developing drug carriers using the body's own circulatory cells.[10, 11]

Circulatory cells have a number of advantages over nanoparticles. They are highly biocompatible and mobile, have a longer circulation lifespan, are inherently biodegradable, naturally target cells/tissues, have a high drug-loading capacity, are remarkably stable in circulation, and they are able to cross biological barriers.[12] Various cell types have been studied for drug delivery applications, including macrophages,[13–15] T cells,[16–18] neutrophils,[19–21] stem cells,[22–26] red blood cells,[27–32] and platelets.[33] Among these, platelet-based systems have gained more attention, and have a wide range of applications, because of their key roles in coagulation and hemostasis, the body's innate immune response, and cancer metastasis.[34] Due to the applicability of their biological functions, the development of a platelet-based drug delivery system has been widely favored by researchers. In this review, we will narrow our focus to the recent progress made in the development of platelet and platelet-mimicking delivery systems for the treatment of disease (Fig. 1 and Table 1).

2. Natural platelet vehicle

2.1. The inherent properties of platelets

Platelets are small, discoid-shaped, non-nucleated blood cells with diameters between 2–4 μm, derived from megakaryocytes in the bone marrow.[35] They are unstable and easily damaged or activated during the process of isolation. Centrifugation is the most commonly used method for isolating platelets.[36] They can be stored at room temperature with maximized viability. Once refrigerated, the platelets only remain viable for 24–48 hours.[37, 38]

Compared to red blood cells (RBCs) and white blood cells (WBCs), platelets show more complexity and multifactorial functionality (Fig. 2). There are more receptors on the surface of platelets, including GPIb/IX/V complex, GPVI and α2β1, β1, and β3 integrins which are responsible for interactions with the cellular microenvironment and biological ligands.[39, 40] For example, platelets can bind to exposed sub-endothelial collagen at the site of injury in blood vessels, via the interaction between GPIb/IX/V complexes with the von Willebrand factor (VWF). Platelet αIIbβ3, P-selectin, and α6β1 can mediate the binding of platelets to tumour cells. In addition, the circulatory lifespan of platelets is 8–10 days, which is short enough to make them suitable drug carriers. In addition, platelets are large in volume and surface area, which facilitate drug loading and conjugation (Fig. 3A). The loaded drugs can naturally be released upon platelet activation. On these bases, platelet-based drug delivery

systems have been developed for basic research and clinical applications, yielding promising results.

2.2 Platelet-based delivery system

2.2.1 In the treatment of tumor and tumor metastasis—Tumor cell membranes express many receptors for platelet binding.[41, 42] The interactions between tumor and platelet cells induce transformations and mediate functional changes in both cell types. For example, platelets play a significant role in facilitating tumor metastasis and host defense invasion. They help circulating tumor cells (CTCs) survive in the blood stream and spread to new tissues by promoting epithelial-to-mesenchymal cell transition, and by secreting matrix degrading proteases.[43, 44] Therefore, platelets can be regarded as ideal targets for tumor microenvironments and CTCs. By taking advantage of their specific targeting ability to vascular disorders, Xu *et al.* and Sarkar *et al.* utilized platelets to transport doxorubicin (DOX) to treat lymphoma and A549 adenocarcinoma human alveolar epithelial cells.[45, 46] As a result of the "tumor cell-induced platelet aggregation" phenomenon, DOX-loaded, activated platelets were able to target cancer cells and release DOX in a pH-mediated process. The growth inhibition of cancer cells was enhanced and the cardiotoxicity of DOX was reduced. To avoid chemo-drug induced multi-drug resistance, Rao *et al.* combined photothermal therapy (PTT) with tumor cell-targeted platelets to construct a platelet-facilitated photothermal tumor therapy system (Fig. 4).[47] Intriguingly, photothermal therapy damaged the tumor tissues, which subsequently enhanced the accumulation of gold nanorod-loaded platelets (PLT-AuNRs), due to their natural ability to home to damaged tissue. The accumulating PLT-AuNRs further improved the PTT efficiency, which then led to further accumulation of PLT-AuNRs in a positive feedback loop. Their results showed that this cascading process gave an efficacious PTT treatment and effectively inhibited the growth of head and neck squamous cell carcinoma, demonstrating the unique self-reinforcing characteristic of their delivery system in the treatment of cancer. Although nanoparticle-based nanomedicine has provided an improvement in cancer treatment, inorganic and polymer nanoparticles offer low efficacy in the treatment of metastatic cells, resulting in tumor reoccurrence. Platelets proved to be highly applicable in the treatment of cancer metastasis owing to their inherent ability to bind to circulating tumor cells (CTCs) *via* several cell-surface proteins. Inspired by this, Jing *et al.* reported a platelet-based melanin nanoparticles (MNPs) and DOX co-loaded delivery system to inhibit tumor growth and metastasis.[48] To further enhance their accumulation, the RGD peptide (c (RGDyC)) was chosen to modify the platelets. Results showed that platelet-based carriers evaded immune clearance, targeted cancer cells, as well as tumor vasculatures, and effectively removed drug-resistant tumors through PTT. In addition to PTT, T-cell-mediated cancer immunotherapy is an effective method to treat metastatic tumors because of its high specificity, minimal side effects, and the production of memory cells that against cancer recurrence during immunotherapy. On this basis, inspired by the intrinsic properties of platelets in recognizing and interacting with CTCs, Wang *et al.* conjugated anti-PD-L1 (antibodies against PD-L1; hereafter, aPDL1) antibodies to the surface of platelets as a preventative treatment for post-surgical tumor recurrence.[49] They found that aPDL1-modified platelets were highly stable and anti-PDL1 antibodies could be released upon their activation. These, in turn, were recruited by T-cells in the tumor microenvironment, which triggered immunotherapy. A

major limitation to the platelet-mediated delivery of proteins on the surface of T cells is the inability to genetically induce the production of said proteins by the platelets. This is due to the fact that platelets do no possess nuclei. To circumvent this drawback, megakaryocyte (MK) progenitor cells, which are responsible for producing platelets, were genetically engineered to express PD-1. Further, a small amount of cyclophosphamide (CP) was encapsulated into engineered platelets for simultaneously depleting the immune suppressive effects of PD-L1 and Tregs in the surgical tumor microenvironment.[50] Results showed that a large number of CD8+ T lymphocytes infiltrated the tumor microenvironment and prevented tumor relapse.

2.2.2 Applications in wound healing—Wound healing, an important but complicated physiological process, involves four phases: hemostasis, inflammation, proliferation, and remodeling.[51] The exposure of extracellular matrix proteins and intracellular components occurs after wounding.[52] Normally, platelets are critical for the formation of clots during the hemostatic phase. The extracellular matrix mediated platelets adhesion and then induced the platelets activated to further trigger a series of physiological responses including release of platelet-derived growth factor. The growth factors played an important role in accelerating and directing healing processes. Given their key function in wound healing, platelets have been widely used in regenerative medicine. A common method used to activate and apply these platelets to wound site is through the formulation of platelet gels (Fig. 3B). Kazakos *et al.* studied the enhanced wound healing ability of autologous, platelet-rich plasma (PRP) gel in clinical applications.[53] Traditional therapy strategies for wound healing included antibiotic ointments and occlusive dressings. Compared with conventional dressings, the wound healing rate was significantly higher in dressings modified with platelet gel. In addition, to demonstrate the advantages of platelet gel-based therapy, Hom *et al.* synthesized platelet gels and compared their effects on the healing rates of acute human skin wounds.[54] Over a 42-day period, increased wound closure was found on platelet gel-treated sites compared to the control group. Although promising, platelet gel-based wound healing still suffers from limitations that hinder its widespread application, including the lack of controlled release behavior, easy degradation, and poor mechanical properties. To overcome these limitations, Pallotta *et al.* introduced silk to the platelet gels, demonstrating that the could improve the gel's properties without affecting the gelation process.[55] The swelling properties of the silk extended the release of growth factors, which translated to improved wound healing. They then showed that the silk enhanced the stability of the gels but had no effect on their proliferative properties. Finally, they studied the systemic degradation and therapeutic efficacy of injected gels in athymic nude rats. Results showed that the concentration of silk in the platelet gels effected their stability and drug releasing behavior, which translated to changes in the degradation rate and the efficacy of the wound healing process.

3. Platelet-mimicking delivery system

We have summarized some of the live platelet-based delivery systems for cancer treatment and wound healing. The application of live platelets as drug carriers, however, only accounts for a small fraction of the area, since platelets are much more complex and have more

multifactorial functionality compared to other types of blood cells, such as red blood cells. Previous reports have indicated that some platelet glycoproteins are responsible for adhesion, aggregation, and hemostasis. Along with more and more nanocarriers have been employed and proved to be efficient in cancer, cardiovascular, and some other disease therapies, such as PLGA, micelles, and other inorganic nanoparticles. Researchers designed biomimetic nanoparticles by taking advantages of nanotechnology and biological structures, such as functional peptides, mimicking cell membrane receptors, or whole-cell membranes themselves for the treatment of disease (Fig. 5).[56, 57]

3.1 Platelet binding molecule-linked particles

The bioinspired design strategy has recently emerged as a novel paradigm to overcome the limitations of traditional nanocarriers. To mimic the platelete's innate ability of migrating to the vascular wall, Anselmo *et al.* developed a platelet-mimicking nanoassembly similar to platelets in shape, flexibility, surface biology, and function, for the application of wound-triggered hemostasis.[58] The nanoassemblies were designed to target and bind to injured blood vessels in the injured site. Then, they investigated the effects of shape on the platelet-mimicking functions of the nanoparticles. They first placed differently shaped nanoparticles in an assembly that mimicked blood flow conditions. Results showed that, compared with other types of nanoparticles, the platelet-like nanocarriers demonstrated enhanced surface-binding, site-selective adhesion, and platelet-aggregatory properties. After having demonstrated their platelet-mimicking functions *in vitro*, they tested them *in vivo*. The results showed that platelet-mimicking nanocarriers targeted the injured site and induced a 65% reduction in bleeding time. Previous studies have indicated that thrombosis, inflammation, and restenosis would induce the expression of endothelial cell adhesion molecules. Platelet glycoprotein Iba (GP Iba) is capable of targeting the overexpressed P-selectin on the surface of active endothelial cells (ECs). Inspired by this, Lin *et al.* employed GP Iba to modify carboxylated polystyrene and fabricated biodegradable nanoparticles for the targeted delivery of therapeutic agents to inflamed ECs after angioplasty and/or stenting treatments.[59] They indicated that the synthesized nanoparticles were an efficient drug delivery system, capable of targeting and sustained releasing. In addition, Kona *et al.* also confirmed the targeted binding of GP Iba-conjugated PLGA nanoparticles to injured vasculatures.[60] Furthermore, the results of parallel flow chamber studies demonstrated that the size of the nanoparticles and the shear stress caused by the blood flow had an effect on their adhesion efficiency. Another example was the application of platelet-like nanoparticles in cardiovascular diseases that involved vascular injury and inflammation. The traditional delivery strategies for cardioprotective drugs still rely on enhanced permeability and retention (EPR) effects. Since the EPR effect is so limited in ischemic hearts, cardioprotective drugs have a low targeting efficiency. Previous reports have indicated that monocytes are activated and migrate to the infarct area. Moreover, platelets would interact with the activated monocytes and home to the infarcted area. To this end, nanocarriers that possess platelet membrane proteins also possess the ability to migrate to the infarcted heart, which enhances the drug delivery efficiency. Thus, Cheng et al. collected the platelet membrane proteome and integrated into liposome membranes to fabricate platelet-like proteoliposomes (PLP).[61] The PLPs were able to specifically bind to monocytes, and target the injured tissue rather than endothelial cells, compared to liposomes without platelet

membrane protein modification. Finally, enhanced targeting and improved cardiac function were achieved by inducing HO-1 overexpression and downregulating several proinflammatory genes in a murine ischemia–reperfusion model.

3.2 Platelet membrane-cloaked nanoplatforms

Platelets mimicking systems that use biological structures usually require the conjugation of membrane proteins with the surface of nanoparticles. However, the complicated chemical modifications needed to achieve the conjugations can damage the proteins' structure. Furthermore, since a large array of proteins are needed for proper protein interactions, conjugating just one or a few types of proteins isn't capable of fully mimicking the biofunctions of the cells.[62] Cell membranes play an important role in various physiological processes, such as intercellular recognition, adhesion, and cell-cell communication.[63] In addition, cell membranes express several specialized proteins which have important functions, such as the capability of crossing biological barriers, migrating to specific sites, avoiding rapid phagocytic clearance, and prolonging the circulation time.[64] On the basis of these properties, researchers introduced cell membranes to nanoparticle surfaces to construct biomimetic nanomaterials. Red blood cell membranes were the first to be used for encapsulating nanoparticles with coating technique developed by Zhang *et al.*.[65] Thereafter, membranes from stem cells, cancer cells and platelets have been used to design membrane-cloaked nanoplatforms for disease treatment.[66–70] Platelet membrane-coated nanoparticles, especially, hold great promise for the treatment of disease because of their important roles in wound repair, immune response, and tumor metastasis.

3.2.1 Platelet membrane-coated particles acted as detoxicating agents—After having demonstrated the first red blood cell membrane-coated PLGA nanoparticles, Zhang *et al.* developed platelet membrane-cloaking nanoparticles.[71] They first confirmed the integrity of the platelet membrane proteins after cloaking (Fig. 6). Then they made sure that platelet functions, such as the specific binding to injured vasculatures or pathogens were preserved after membrane-coating. Finally, to study their possible applications, these membrane-cloaked nanocarriers were administrated to two animal disease models (rat coronary restenosis and mouse systemic bacterial infection). The study showed that platelet-mimetic nanoparticles enhanced therapeutic efficacy.

Inspired by their preliminary work, they developed different platelet membrane-cloaking nanoassemblies for various applications. Immune thrombocytopenic purpura (ITP) is characterized by early platelet destruction due to the presence of anti-platelet autoantibodies. ITP is an autoimmune disease in which the body produces antibodies against several platelet surface antigens. These platelets are then destroyed by the reticuloendothelial system. Treatment strategies may follow several routes, including medications to elicit a rebound in platelet levels, or surgery to remove the spleen. However, most patients that receive these treatments report that the side effects are more burdensome than the disease itself. Previously, Zhang *et al.* have demonstrated the applicability of red blood cells as detoxicating agents as a result of their membranes' ability to bind toxins. They then developed platelet membrane-coated PLGA nanoparticles as a natural detoxification for the neutralization of anti-platelet autoantibodies to anti-platelet autoantibodies ITP.[72] These

platelet-derived nanoparticles showed a high binding affinity to anti-platelet antibodies both *in vitro* and *in vivo*. They also employed this platelet membrane-coated poly(DL-lactic-co-glycolic acid) (PLGA) to target and detect atherosclerosis after encapsulating an MRI contrast agent.[73] Since the platelets have the ability to strongly adhere to exposed subendothelial matrices, the platelet nanoparticles (PNPs) also retained the ability to target the sites of plaque rupture. The resulting PNP showed a high binding affinity to atherosclerotic plaques both *in vitro* and *in vivo*. Furthermore, PNPs loading with MRI contrast agents help to distinguish the presence of plaque during live imaging. In addition, as a result of a collaboration between Zhang et al. and Wang et al. novel platelet-membrane-coated nanorobots were designed to recognize and remove Shiga toxin and *Staphylococcus aureus* (Fig. 7).[74] Their nanomotors were made from nickel and gold-coated palladium nanohelices that utilized magnetic-mediated propulsion to provide fuel-free remote actuation. Finally, taking advantage of the platelet membrane's high binding affinity to toxin and bacteria, these biomimetic nanomotors have the potential to evade the body's immune system, mimic the natural movement of motile cells for the adsorption and removal of some biological threats. With the development of cell-membrane-coating technology, membrane-based delivery systems often need to introduce multifunctionality specific to each application. With this idea in mind, recently, Zhang et al. further developed red blood cell and platelet fusion membrane-cloaked nanoparticles.[75] These hybrid membrane-coated nanoparticles retained the functionality of each individual cell type. Their application *in vivo* showed circulation and biodistribution profiles similar to nanoparticles coated with either red blood cell membranes or platelet membranes. Additionally, they retained the biological functions of both red blood cells and platelets.

3.2.2 Platelet-mimicking particles in cancer treatment—Platelets have also been recognized for promoting tumor growth and tumor metastasis by inducing epithelial to mesenchymal transitions. On this basis, the Hu *et al.* exploited a platelet-mimicking nanovehicle (PM-NV) to sequentially transport tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and DOX.[76] The PM-NV was fabricated from cloaking the platelet membranes onto the surface of DOX-loaded nanogels by a "top-down" method. PM-NV was further chemically modified with TRAIL to induce cell death. After administration, P-selectin specifically interacts with CD44 receptors on the cancer cells. This binding would further induce apoptosis of the tumor cells, mediated by the binding of death receptors with TRAIL. Furthermore, thanks to the acid-responsive cross-linkers within the nanogels, PM-NV releases the loaded DOX upon internalization by acidic endosomes. The combined chemo-immunotherapy induced a synergistic cytotoxicity to MDA-MB-231 tumor cells. More importantly, the co-delivery of DOX and TRAIL significantly reduced the number of CTCs, as evidenced by decreased lung metastasis. As a further extension, they developed another platelet-membrane-cloaked nanocarrier to deliver bortezomib for the enhanced therapy of multiple myeloma (Fig. 8).[77] The nanoassemblies were further functionalized with plasminogen activator (tPA) and alendronate to bestow clot lysing and bone-targeting functionalities. With the help of platelet membranes and alendronate, the nanoassemblies can home to and internalize myeloma cells, and then release the encapsulated bortezomib, leading to enhanced therapy efficacy. Moreover, the tPA-

containing formulation effectively dissolves the thrombus, demonstrating the benefit of combined treatment.

In another example of cancer treatment, Li et al. coated synthetic silica particles with platelet membranes to deliver TRAIL for capturing and killing CTCs (Fig. 1).[78] As expected, the platelet membrane-based nanocarriers showed reduced phagocytic uptake owing to the preservation of CD47 protein, and efficient elimination capability of CTCs due to the specific binding of platelet membrane to CTCs. The capacity of nanoparticles to target many disease sites makes them incredibly useful for disease-imaging applications. Rao et al. collected platelet membranes and used them to coat Fe_3O_4 magnetic nanoparticles for enhanced tumor magnetic resonance imaging (MRI) and photothermal therapy (PTT).[79] They illustrated the immune evasion and improved cancer cell targeting ability of their designed nanoparticles. Meanwhile, magnetic nanoparticles with the magnetic and optical absorption properties endowed the ability of MRI-guided PTT.

3.2.3 Platelet membrane-cloaked system for treating cardiovascular disease

—In the final example, our group further expanded the application of platelet membranes (Fig. 10). We fused platelet membranes onto the surface of cardiac stem cells (CSCs) for the targeted repair of heart injury.[80] Cardiovascular disease is the leading cause of mortality in the world and stem cell transplantation is regarded as one of the most promising therapeutic strategy for cardiac regeneration. However, a major limitation is the low efficiency of integration and retention of the injected cells with the injured myocardium. Thus, by taking advantage of the natural infarct-homing ability of platelet membranes and the regenerative potential of cardiosphere-derived CSCs, our group decorated the surface of CSCs (PNV-CSCs) with platelet nanovesicles (PNV) for targeted repair of injured heart. *In vitro*, we confirmed that PNV-CSCs showed an enhanced binding affinity to collagen surfaces and denuded aortas, owing to the presence of the platelet membranes. *In vivo*, using mice and porcine models of ischaemia/reperfusion, we demonstrated that PNV-CSCs efficiently accumulated onto the injured heart and enhanced the proliferation of cardiomyocytes, reduced the scar tissue, and improved the heart function. Furthermore, we investigated the mechanisms underlying the therapeutic benefits of PNV-CSCs. Our design represents a promising therapy delivery platform for treating I/R injury.

4. Conclusions and perspectives

This review has highlighted the recent progress made in the construction of platelet and platelet-mimicking, nanomaterials-based drug delivery systems, as well as their practical applications in the treatment of disease (Table 1). Platelets play an important role in adhesion, aggregation, hemostasis, and tumor metastasis. Thus, various platelet-mimicking nanomaterials have been developed. In contrast to the traditional nanoparticles-based drug delivery systems, this emerging platelet and platelet-mimicking paradigm has shown high biocompatibility, high mobility, a longer circulation lifespan, inherent biodegradability, and the natural capability of cell/tissue targeting. In this review, we summarized three drug delivery strategies that take advantage of the biological function of platelets: 1) live platelets; 2) platelet-mimicking nanoparticles with platelet specific protein modifications, and 3) platelet membrane-cloaked nanoparticles. Since the body must maintain a balance in the

number of platelets circulating at any given time, the injection of platelet-based carriers may alter the body's homeostasis, resulting in unexpected side effects. In addition, storage and transportation issues are obstacles in the way of the practical application of the live platelets. Thus, few studies have reported the use of living platelets as drug carriers. As for the platelet-like nanocarriers, partial proteome modifications can't totally mimic the biofunctions of live platelets, which limits their practical applications as well. In contrast, the direct use of cell membranes as nanomaterials has proven to be particularly effective. Membrane-coating methods translocate all the membrane-associated proteins to the nanocarriers, which gives them an integrity and functionality similar to actual platelets. In addition to their vital role in coagulation and hemostasis, platelet-mimicking materials have been widely used in the treatment cancer metastasis, toxicity, and myocardial infarction. Along with the development of sophisticated strategies for mimicking platelet features and functions, more platelet-based biomimetic materials will be constructed in the future for additional applications.

Although promising results have been achieved under laboratory conditions, there are still several issues that need to be addressed before clinical applications. Given the relatively low concentration of platelets in the blood, the first is the large scale manufacture of platelet-based, low cost, biomimetic materials that meet the commercial and regulatory requirements. To that end, simpler, more cost effective production methods will need to be developed. One caveat for clinical translation is that it has been reported that platelets facilitate tumour growth and metastasis by forming aggregates with tumor cells. Anti-platelet medications including aspirin have been used for cancer therapy. Therefore, higher risk in tumor metastasis may occur if we use platelet-based materials for cancer therapy. However, most of the previous studies indicate that only activated platelets can act as culprits in cancer growth and metastasis. Thus, the use de-activated platelets or platelet mimics, which are unlikely to collaborate with cancer cells. As for the membrane-coating materials, the assurance of the biocompatibility and safety of the membrane-cloaking systems that introduce synthetic and biological components into the body. In addition, maintaining stability of live platelets during storage and transportation is no easy feat. The platelet-mimicking materials also run into the same problem, owing to the relatively low stability and degradable nature of their biological membranes. More studies that focus on the stability of synthetic biomaterials will be required. Moreover, the tendency of platelets and their membranes to undergo aggregation during manufacturing, processing, and while in blood vessels is a natural trait that limits their functional applicability and needs to be addressed.

The use of platelets and their mimics has emerged as a robust and versatile platform technology for various drug delivery and regenerative medicine applications. Looking forward to the future, more works related to the safety, pharmacokinetics and the interaction with substances in the body should be concerned to accelerate clinical translation. As researchers continue to develop more sophisticated strategies to transform platelets and mimics and utilize their functions, we will undoubtedly see broader applications of those agents, including a move into the space of diagnostics and immune modulation. With more efforts being made, we are optimistic that platelet-based delivery system will be a promising next-generation drug carrier for broad medical applications.

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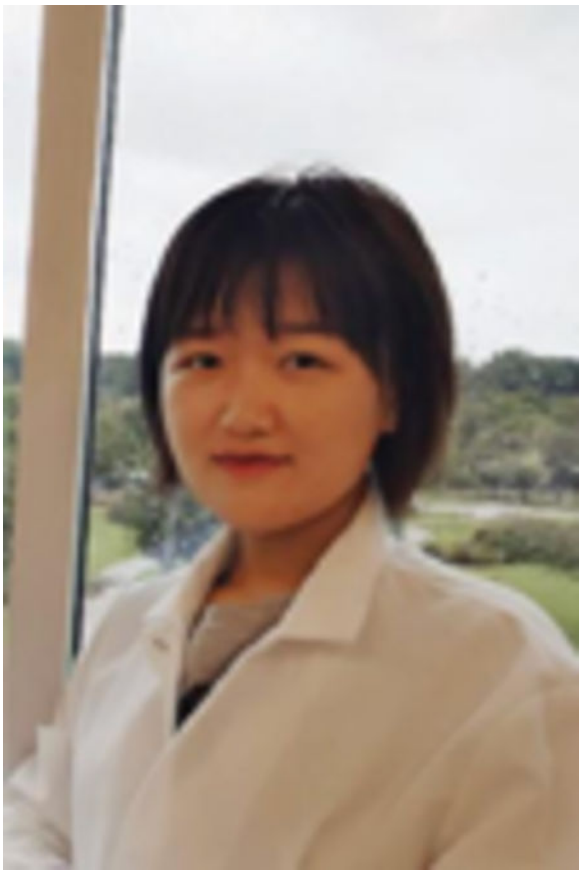

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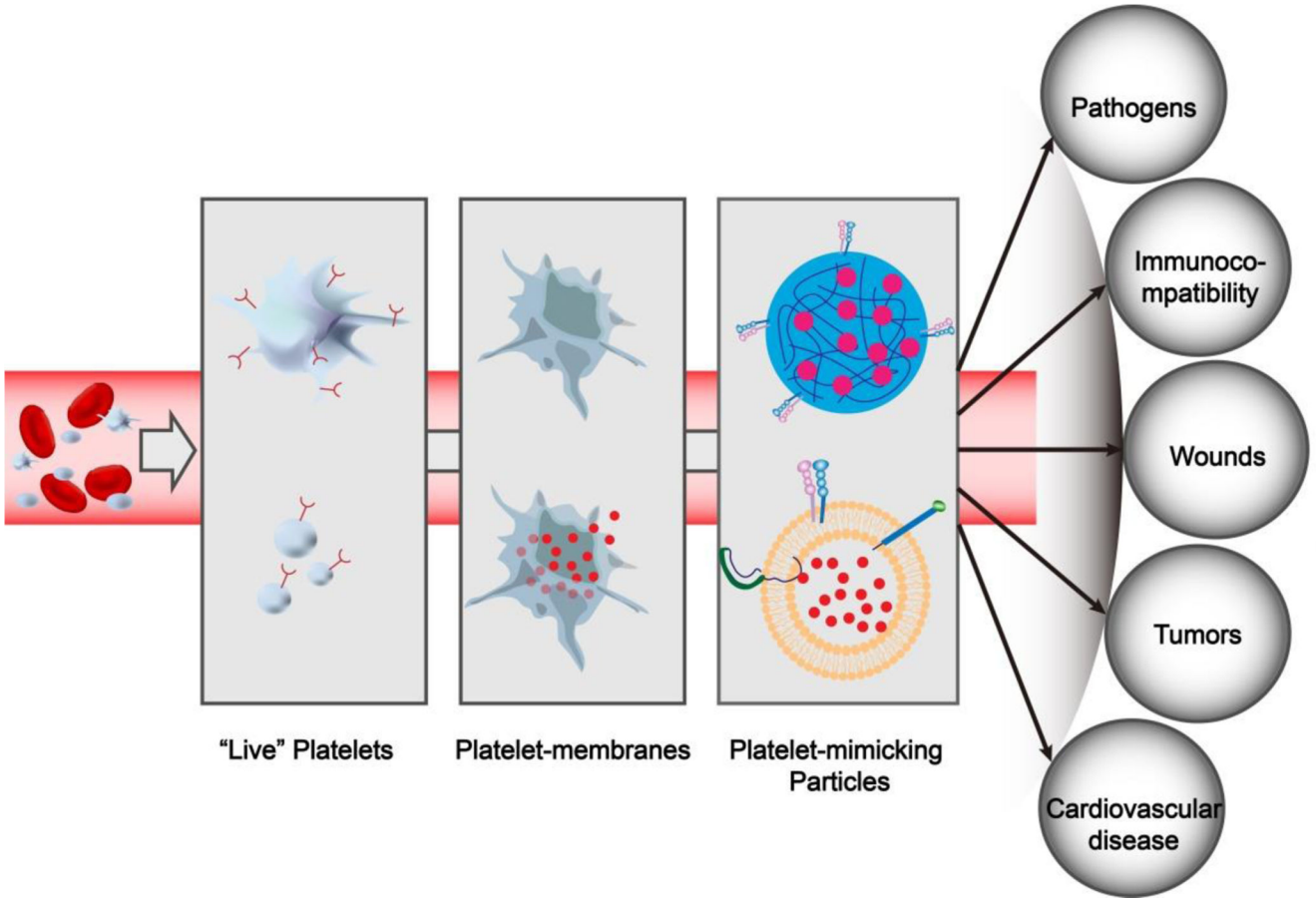

Fig. 1.
Schematic illustration of the key functions of platelets in various diseases.

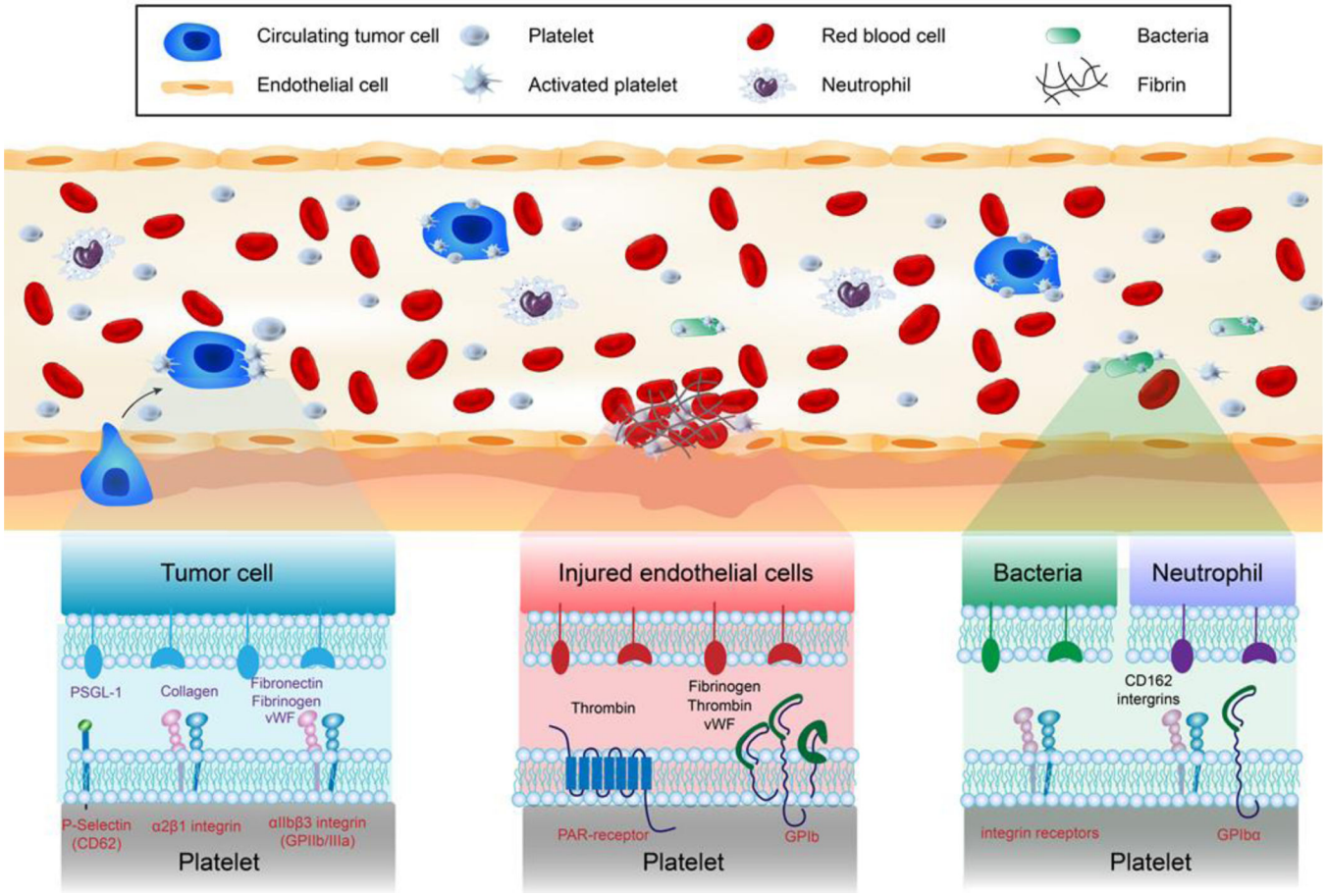

Fig. 2. A diagram showed the interaction mechanism to bind to different cells.

The interaction of platelet membranes with different cells types: cancer cells, injured endothelial cells, bacteria, and neutrophils.

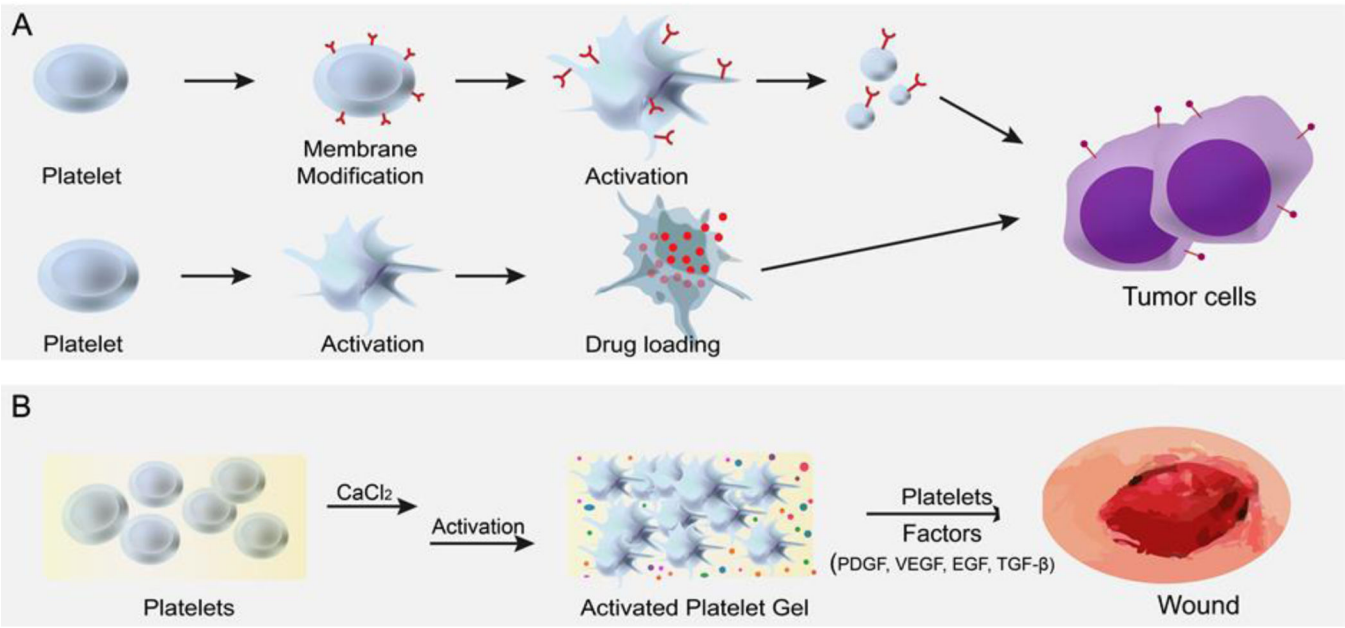

Fig. 3. The use of "live" platelets.

A) Antibody-conjugated platelets and drug loaded platelets for enhanced cancer therapy. B) The preparation and application of platelets gel for wound healing.

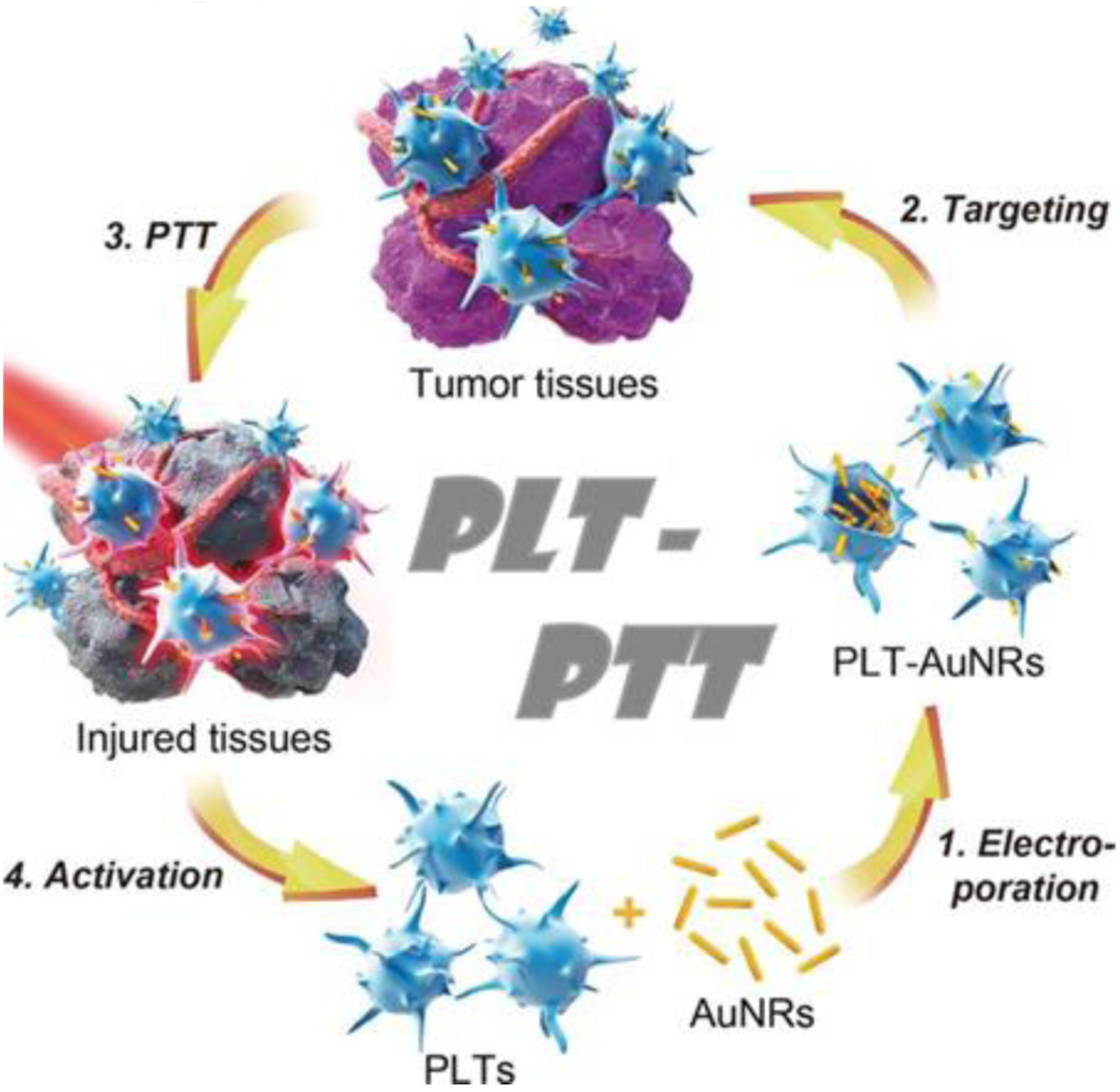

Fig. 4. Platelet-facilitated photothermal tumor therapy (PLT-PTT).

Platelets (PLTs) were first separated from blood and then mixed with gold nanorods (AuNRs). After an electroporation process, AuNRs were loaded into PLTs. The resulting AuNR-loaded PLTs (PLT-AuNRs), which inherited the cancer targeting characteristics from the PLTs and photothermal properties from the AuNRs, were used for enhanced *in vivo* photothermal tumor therapy (PTT). Moreover, PTT, which injures the tissues adjacent to tumors, would activate PLTs and recruit them to the tumor sites, and enhance the PTT effect in a feedback manner. Adapted from ref. 47.

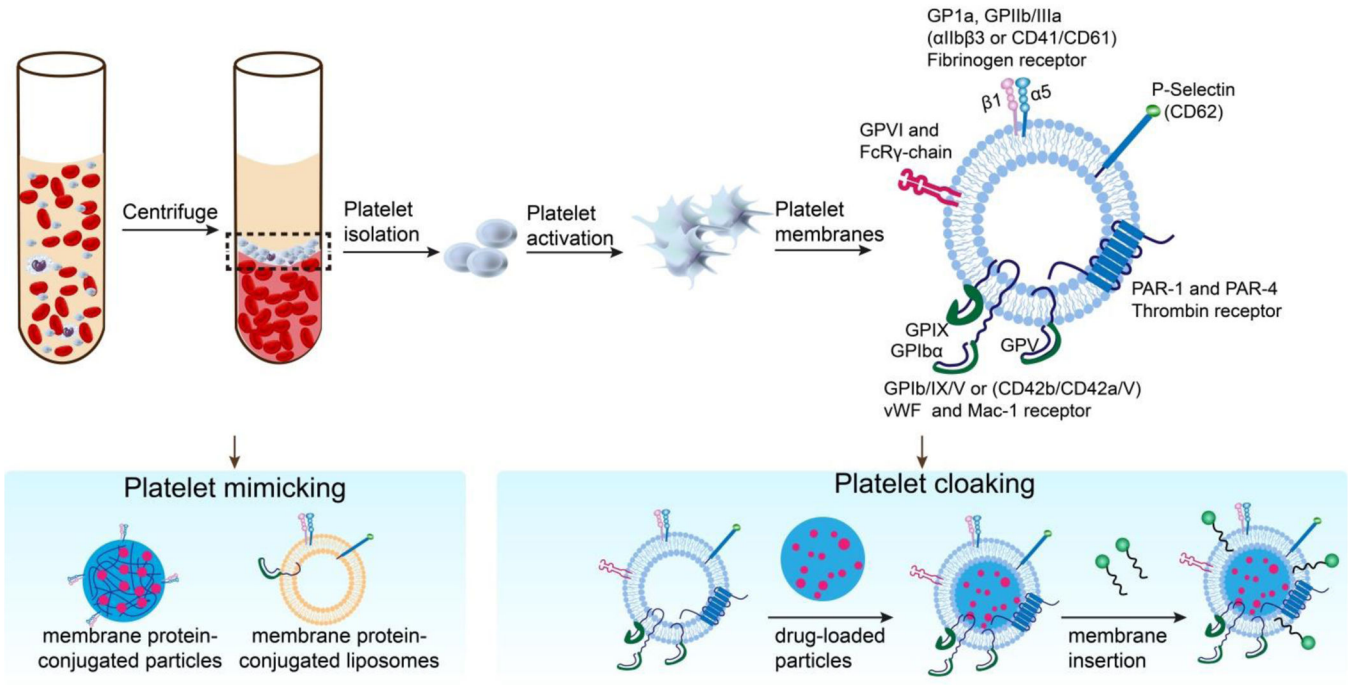

Fig. 5. The fabrication of platelets-like nanoparticles for diseases treatment.

Platelets were collected by centrifugation and activated, the membranes of platelets were prepared for further usage.

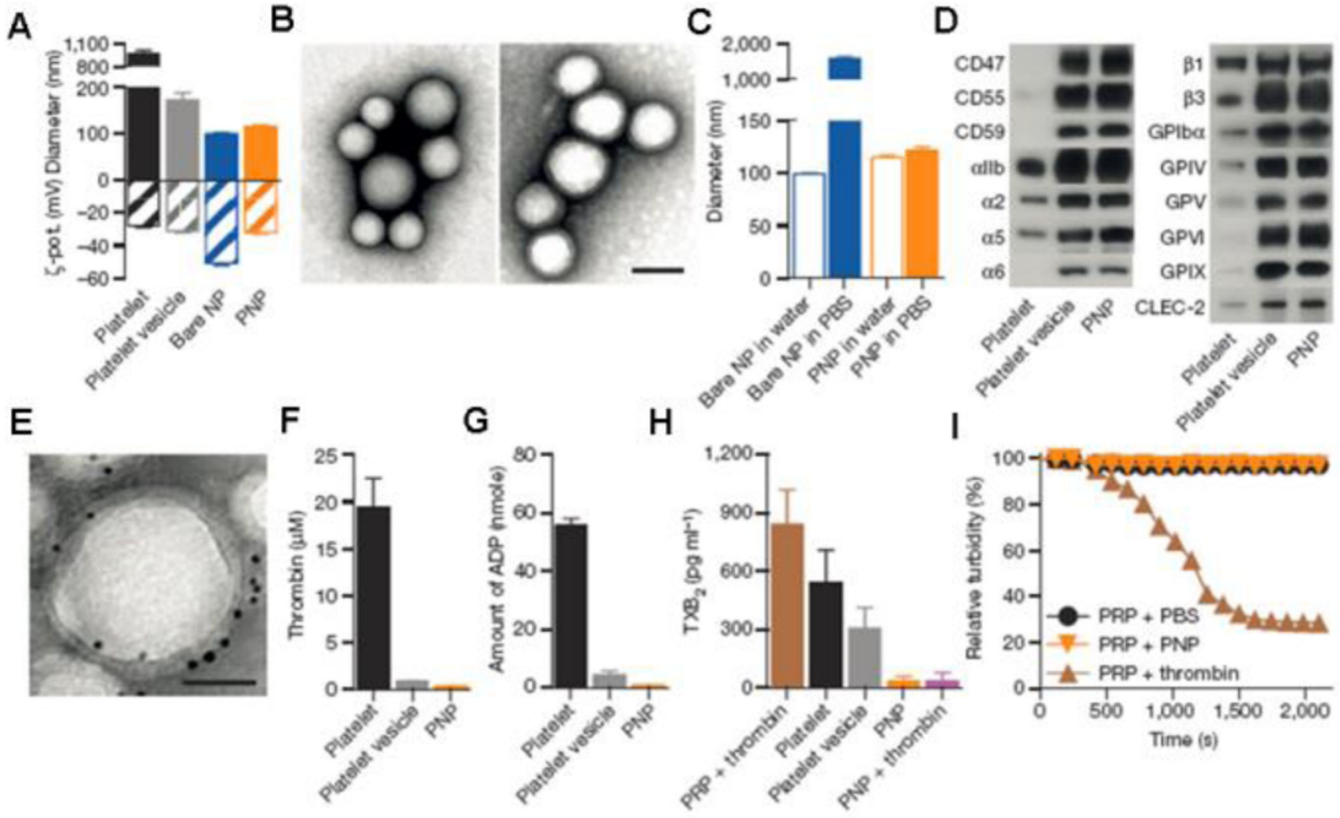

Fig. 6.

Preparation and characterization of PNPs. (A) Physicochemical characterization of platelets, platelet vesicles, bare NPs, and PNPs. (B) TEM images ofbare NPs (left) and PNPs (right) negatively stained with uranyl acetate. Scale bar, 100nm. (C) Particlediameter of bare NPs and PNPs in water and in PBS. (D) Representative protein bands resolved using western blotting. (E) TEM image of PNPs primary-stained with extracellular-domainspecific anti-CD47, and secondary-stained by an immunogold conjugate. Scale bar, 40 nm. F–H, Platelet-activating contents including thrombin (F), ADP (G) and thromboxane (H) in platelets, platelet vesicles, and PNPs were quantified. (I) Platelet aggregation assay. All bars represent means ± s.d. Adapted from ref. 71.

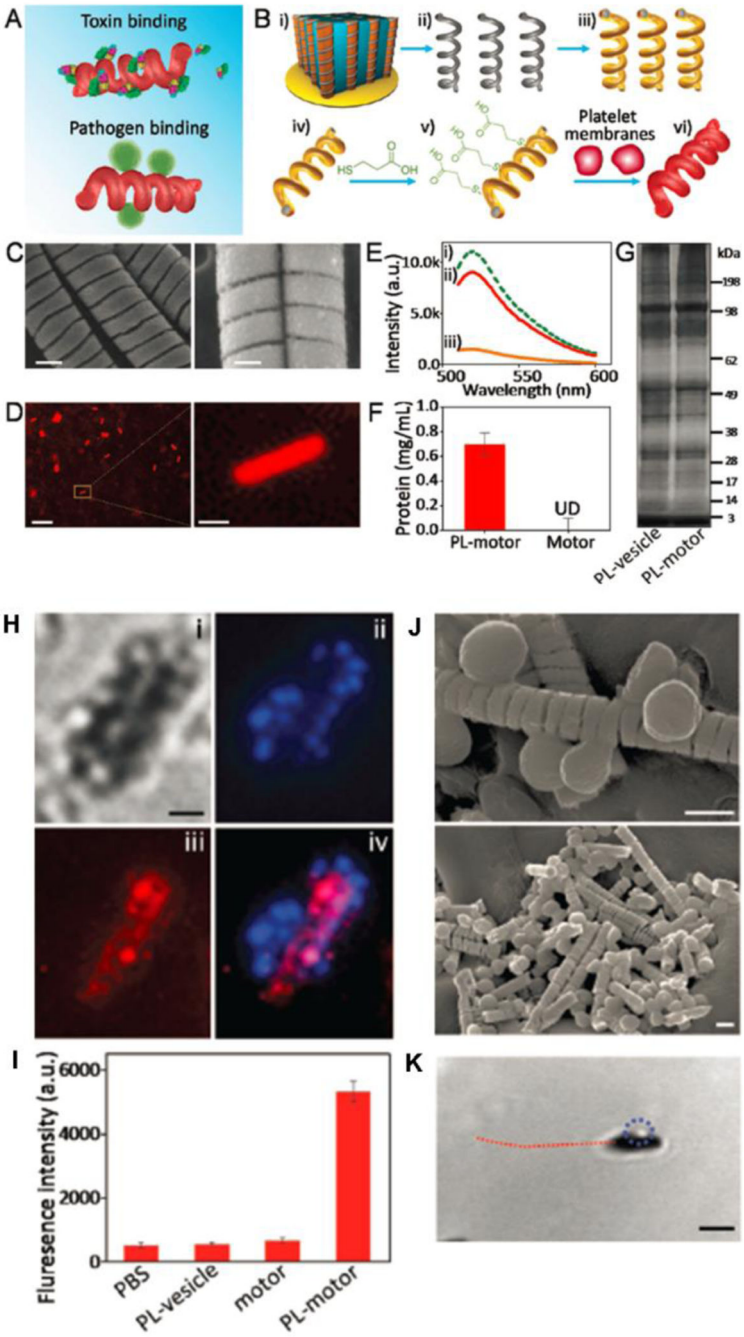

Fig. 7. Preparation and characterization of platelet-membrane-cloaked magnetic helical nanomotors (denoted "PL-motors").

(A) Schematic of PL-motors for binding and isolation of platelet-specific toxins and pathogens. (B) Preparation of PL-motors. (C) Representative SEM images of the fabricated bare nanomotors without platelet coating (left) and PL-motors (right). Scale bars, 100 nm. (D) Fluorescent images of PL-motors covered with rhodamine-labeled platelet membranes. Scale bars, 20 μm (left) and 1 μm (right). (E) Fluorescence quenching assay to determine the platelet membrane coverage of the PL-motors. (F) The measured weight of protein content on bare motors and PL-motors. (G) Sodium dodecyl sulfate polyacrylamide gel

electrophoresis (SDS–PAGE) analysis of proteins presents on the PL-vesicles and the PL-motors. (H) Microscopic images showing the binding of MRSA252 bacteria with PL-motors. (I) Normalized fluorescence intensity of DAPI stained MRSA252 bacteria retained on the PL-motors ($n = 3$). Scale bars, 500 nm. (J) SEM images of MRSA252 bacteria attached to PL-motors. Scale bars, 500 nm. (K) Microscopy image showing one-the-fly isolation of a bacterium (labeled with blue circle) with a PL-motor. Scale bar, 2 μm. Adapted from ref. 74.

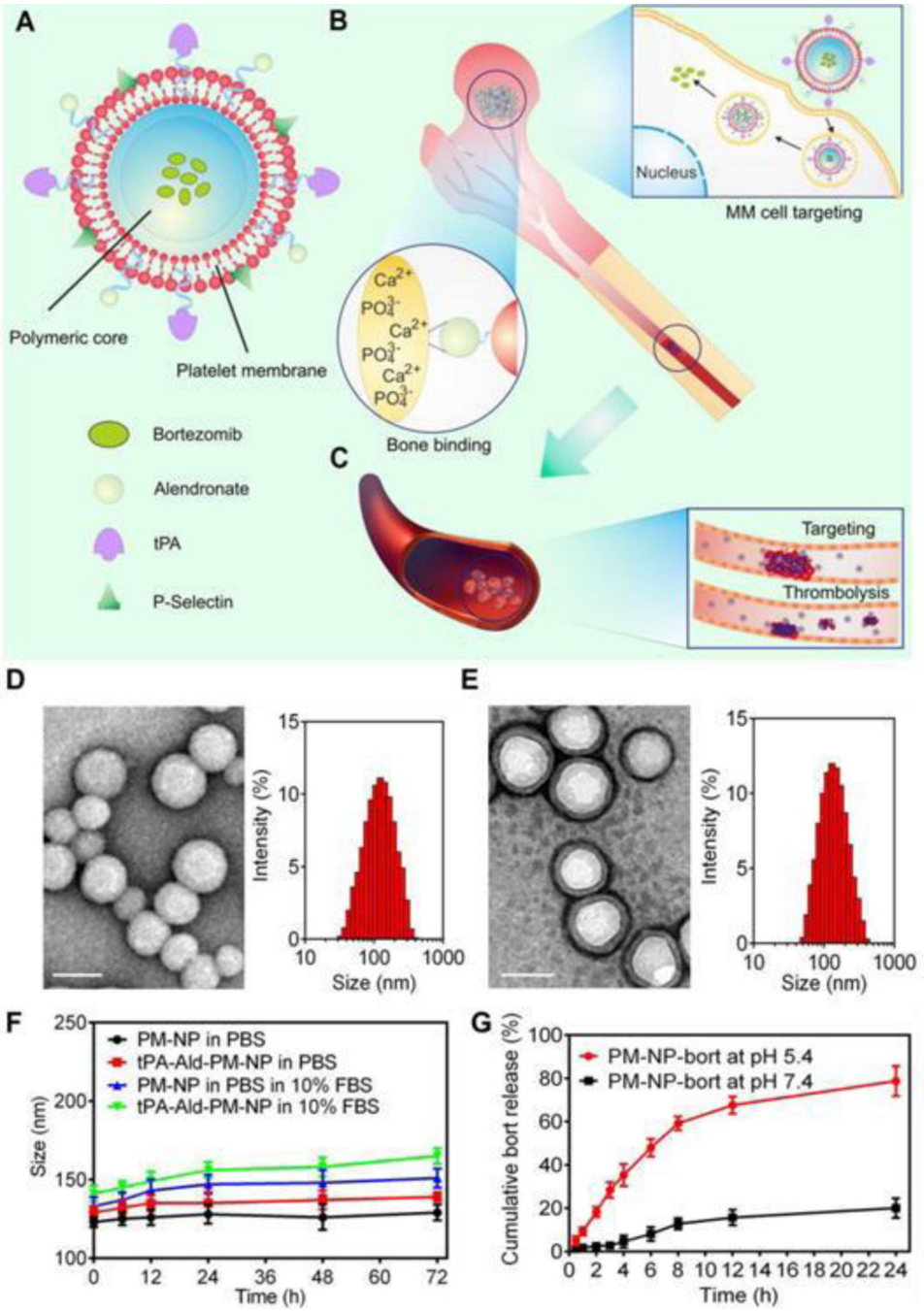

Fig. 8.

(A) The main components of tPA-Ald-PM-NP-bort. (B) After intravenous injection, tPA-Ald-PM-NP-bort sequentially targets the bone microenvironment through efficient binding between Ald and calcium ions, and homes to MM cells *via* specific affinity of P-Selectin and overexpressed CD44 receptors. After internalization, the matrix of tPA-Ald-PM-NP-bort is dissociated by the acidity of lyso-endosomes, releasing the encapsulated bortezomib. (C) tPA-Ald-PM-NP-bort further targets the thrombus that forms during the anti-MM treatment and dissolves it readily and effectively. (D) The TEM image and hydrodynamic size

distribution of bare *m*-dextran NP. Scale bar: 100 nm. (E) The TEM image and hydrodynamic size distribution of PM-NP. Scale bar: 100 nm. (F) *In vitro* stability of PM-NP and tPA-Ald-PM-NP in PBS and 10% FBS. Error bars indicate s.d. (n=3). (G) Cumulative release of bortezomib from PM-NP in PBS with different pH levels. Error bars indicate s.d. (n=3). Adapted from ref. 77.

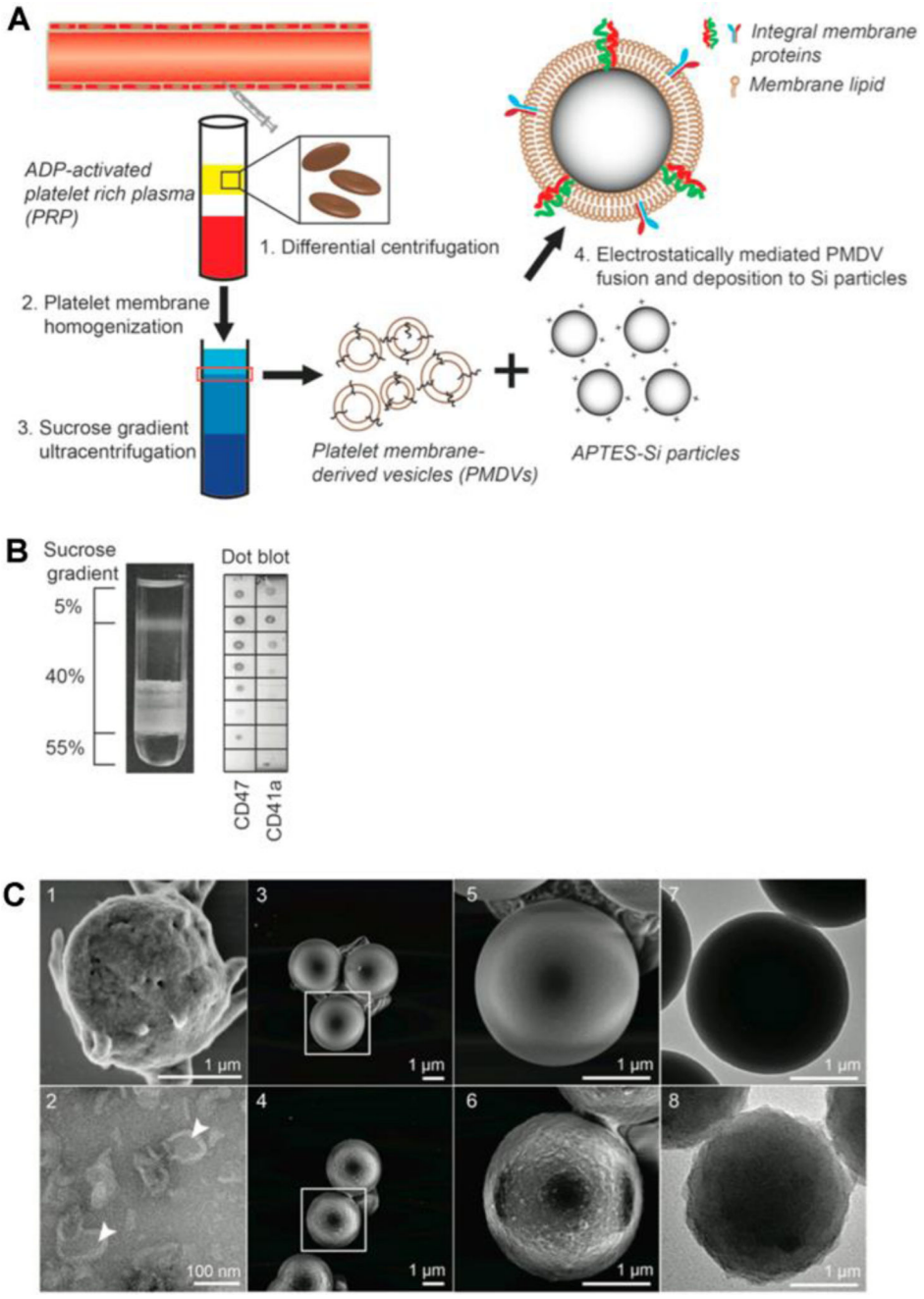

Fig.9. Functionalization and characterization of PMDV-coated Si particles.

(A) Schematic of preparing platelet membrane-coated Si particles. (B) Detection of membrane proteinassociated lipid layer in discontinuous sucrose gradient solution by dot blot assay. Lipid fractions were identified as translucent layers in between two sucrose concentrations. (C) SEM and TEM characterization. SEM images: (1) Activated platelets, (3, 5) APTES-Si particles, (4, 6) PMDV-coated Si particles. TEM images: (2) PMDVs, (7) APTES-Si particles, (8) PMDV-coated Si particles. Arrow head identifies the hollow structure of PMDVs. Adapted from ref. 78

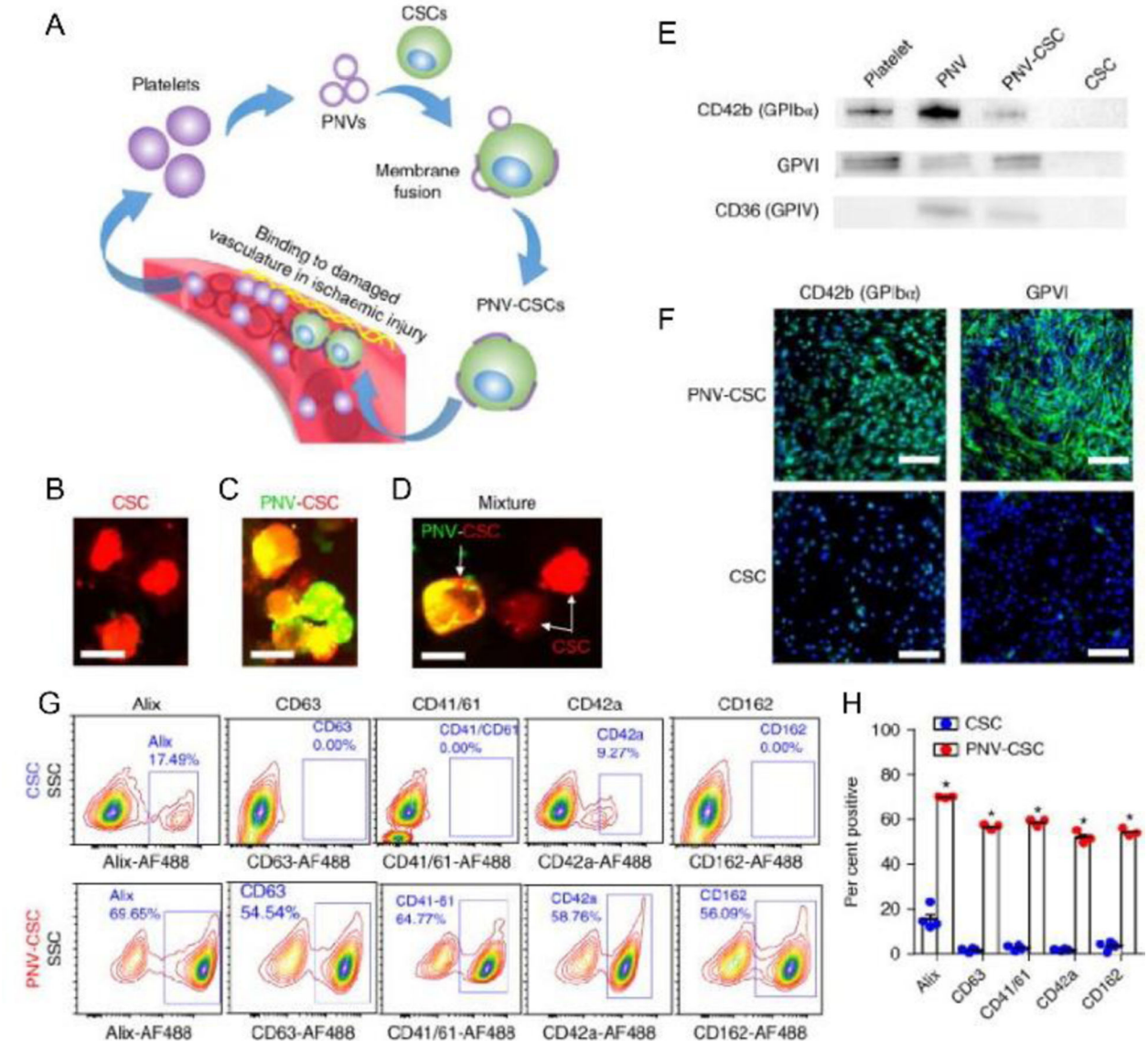

Fig. 10. Generation and characterization of PNV-CSCs.

(A) A schematic showing the overview of PNV decoration and PNV-CSC therapy. (B-C) Red fluorescent DiI-labelled CSCs (B) were fused with green fluorescent DiO-labelled PNVs to form PNV-CSCs (C). (D) Co-incubation of CSCs (red) with PNV-CSCs (yellow). Scale bar: 20 μm. (E) Western blot analysis revealed the expressions of platelet-specific markers including CD42b (GPIbα), GPVI, and CD36 (GPIV) in platelets, PNVs, and PNV-CSCs, but not in CSCs. (F) Immunocytochemistry staining confirmed CD42b (GPIbα) and GPVI expression in PNV-CSCs (top), but not in CSCs (bottom). Scale bars: 200 μm. (G-H) Flow cytometric analysis of platelet and exosome surface marker expressions on PNV-CSCs (n = 3) and CSCs (n = 4). Adapted from ref. 80.

Table 1.

Platelet- and platelet mimic-based drug delivery systems and their applications.

TYPE	TARGET DISEASE	NANOPARTICLES CORE	THERAPEUTICS	REFS
Live Platelets	Cancer	--	DOX	45,46,48
		--	AuNRs	47
		--	Anti-PD-L1 antibodies	49
		--	PD-1 antibodies	50
	Wounds	--	PRP gel	53,54,55
Platelet binding molecule-linked particles	Wounds	PAH-BSA crosslinking	--	58
	Endothelial Cells	Fluorescent-carboxylated Polystyrene Nanoparticles	--	59
	Injured Rat Artery	PLGA	Dexamethasone	60
	Heart Disease	Liposomes	Cobalt Protoporphyrin	61
Platelet membrane-cloaked nanoplatfor ms	Coronary Restenosis Bacterial Infection	PLGA	Docetaxel and Vancomycin	71
	Immune Thrombocytopenia	PLGA	--	72
	Atherosclerosis	PLGA	MRI Contrast Agents	73
	Biological Threats	Nanorobots	--	74
	Cancer	polyacrylamide	DOX & TRAIL	76
	Multiple Myeloma and Thrombus	m-Dextran Nanoparticle	tPA	77
	Cancer	Biocompatible Silica (Si) Particles	TRAIL	78
	Cancer	Fe_3O_4 Magnetic Nanoparticles	Fe_3O_4-based PTT	79
	Injured Heart	Cardiac Stem Cells	--	80