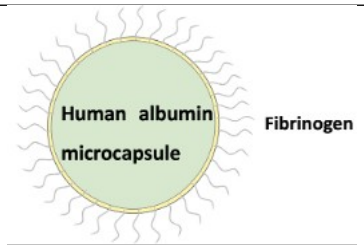
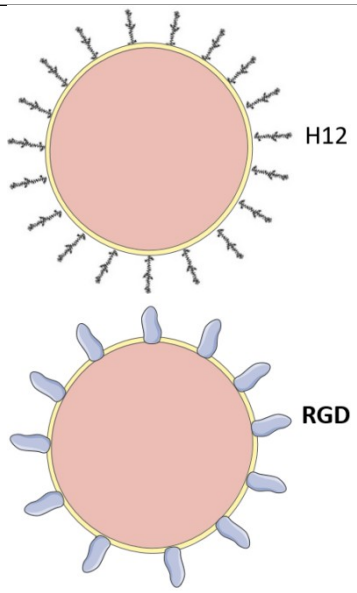
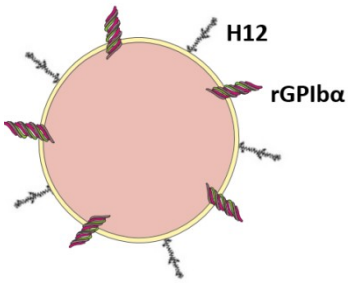
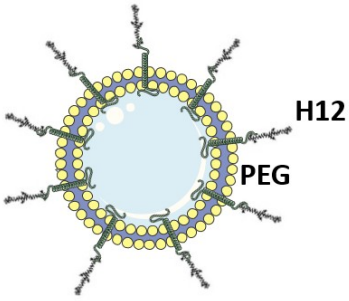
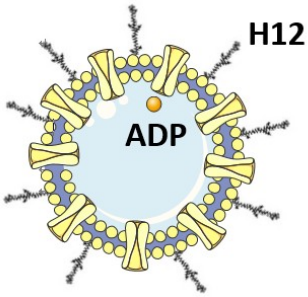
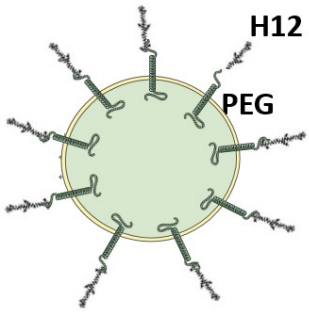
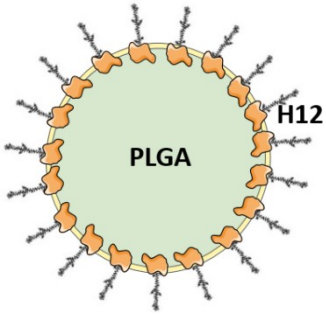
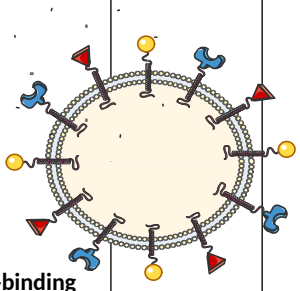
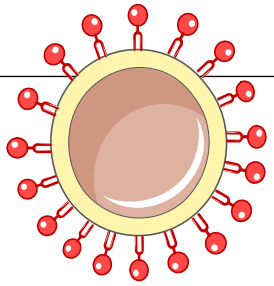
Table 1. Classification of platelet subsititues

Classification of platelet subsititues	Specific subsititutes
Platelet-based products(*85*)	● Platelet membrane microparticles ● Insoluble platelet membrane microparticles ● Frozen platelets ● Cold-stored(4℃)platelets ● Lyophilized platelets
Coated/Conjugated polymers(*43-53*, *77*, *86*)	● Albumin granule ● Latex beads ● Phospholipid vesicles ● Polymerized particles
Reconstitution of platelet glycoproteins(*54*, *55*, *57-61*, *87*)	● Lipid vesicles ● liposomes
Nanoparticles/nanosheets(*25*, *26*, *62-65*, *70-75*)	● Platelet-like nanoparticles (PLNs) ● Polymerized particles (PLGA-PLL-PEG, Synthetic particles, et al) ● Ultralow crosslinked particles of microgels ● Cell membrane coating technology
Other analogues(*66-68*)	● polyphosphate nanoparticle (ployP NP)

Table 2. The main representatives of H12/RGD-coated platelet substitutes

Name	Diameter	Important factors of design	Simple structure	Reference

Synthocytes	3.5-4.5um	human albumin microcapsule coated with fibrinogen		(*43*)
H12- or RGD-conjugated latex beads	200nm or 1 µm	Latex beads coated with human serum albumin (rHSA) and conjugated with H12 or RGD		(*47*)
H12/rGPIbα-latex beads		Latex beads coated with human serum albumin (rHSA) and conjugated with H12 and rGPIbα		(*48*)
H12-PEG-vesicles	220 nm	phospholipid vesicle conjugated with H12 and PEG		(*52*)

H12-(14C-ADP)-(3Hvesicles	-	Phospholipid vesicle conjugated with H12 and then ADP was encapsulated in		(*51*)
H12-polyAlb , H12-PEG-polyAlb	260±60 nm, 200 - 80 nm ,	polymerized albumin particles conjugated with H12 or H12/PEG		(*50*, *53*)
H12-PLGA microparticles	2.2 ± 0.5 µm	Nanosheets prepared by biodegradable poly(D,L-lactide-co-glycolide) (PLGA) and H12 was conjugated on the surface		(*77*)
liposome model	150nm **vWF-binding VBP**	conjugated with von Willebrand Factor (VWF)-binding peptide (VBP), a collagen binding peptide (CBP) and an active platelet GPIIb-IIIa-binding cyclic RGD-based fibrinogen-mimetic peptide (FMP)	**Active GpIIb-IIIa binding cRGD**  **Collagen-binding CBP**	(*59*)
synthetic particle (SP)	1-1.5µm **vWF-A1**	coated with VWF-A1		(*25*)

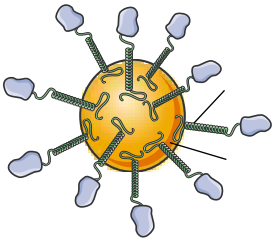
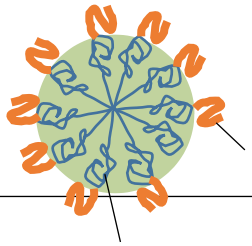
Drug Reservoir Protein shell		targeting drug delivery to platelets		
PLGA-PLL-PEG	1500RGD (SEM 178 ±68nm,DLS 326±45nm); 4600RGD (SEM 154 ±36nm,DLS 345±81nm)	PLGA-PLL core with PEG arms terminated with the RGD moiety		(*63*)
PLP	~1 µm	H6 sdFvs were conjugated to ULC µgels		(*70*)

Table 3. Animal models for platelet analogues

Experimental subject	Advantages	Disadvantage	Basic condition	Injured part	Main measurement index	Reference
Porcine	1.highly sensitive to nanoparticles;2.most resemble to humans(hemodynamic, respiratory, skin);3.sensitive to complement activation and related pseudoallergy (CARPA);4.morphological similarity to human	1.pulmonary hypertension in response;2. low specificity to some liposomes	15-40kg	not mentioned	C activation-related pseudoallergy(CARPA) test (cardiopulmonary, hemodynamic, skin, hematological and blood	92,93
			≤26kg	muscle crush injury	hemorrhage volume	94
			30-40kg	vena caval injury	hemorrhage volume	95
			28-35kg	hepatic injury bolt gun	intra-abdominal hemorrhage volume(main index)	96
			45-55kg,3 to 4 months	spleen injury by wires	intra-abdominal hemorrhage volume	97
			Female	left midshaft femur	blood loss	98
				rectus abdominus muscle soft tissue crush injury	blood loss	99
			≤25kg	liver injury	blood loss	100
			40–50 kg	liver and spleen injury	blood loss	101
			not mentioned	femoral artery injury	blood loss, hematological index, biodistribution analysis	102
Nonhuman primates	similar to human body	1.complex anaesthetic process;2.lack of animal source	macaque	liver injury	blood loss	103
			baboons,23-33kg,AM	resection of the proximal clavicle plus a laparotomy	the biologic activity of thoracic duct lymph	104
Rats	1. small size;2. low cost;3. ease of handling;4. ethical acceptance;5. availability;6. easier operation than mice;7. share 90% of genome with human		250-280g	51Cr-activity of labeled platelets was injected into the tail vein	Platelet count, fibrinogen, fibrin monomer, and plasma hemoglobin	105,106
			230-250g,M	tail injury	bleeding time(tail)	107
			400-475g	tail injury	bleeding time(tail);blood loss(tail)	108
			400-475g	liver injury	blood loss	109
			200-250g,F	tail injury	bleeding time(tail);blood loss(tail)	110
			200-250g,M	tail injury	bleeding time(tail)	111
			300g, M	tail injury	bleeding time(tail)	63
			not mentioned	major femoral artery injury	bleeding time	43
Rabbits	1.decreases the variance and permits greater reproducibility of results	1.the vessel damage sustained during the isolation of the jugular veins;2.small vessels were disrupted	not mentioned	ear injury	blood loss	112
			2.5kg, 11 weeks old,F/M	ear injury	bleeding time(ear),PT, APTT and Fbg	113
			2.5-3kg	ear injury	bleedig time(ear)	114
			2.5-3kg;equal F/M,Thr(irradiation)	jugular veins	bleeding time	115
			2.5-3.5kg;AM;Thr(irradiation, heterologous platelet antiserum infusion, or a combination of both.)	Jugular Vein, Microvascular	bleeding time	43
			approximately 2.5 kg,Thr(busulfan-induced)	ear injury	bleeding time,blood loss(ear)	116
			2.5-3.5 kg,Thr(combination of irradiation and heterologous platelet antiserum infusion)	ear injury	bleeding time	118
Mouse	1.small size;2.low cost;3.easily handing;4.ethical acceptance	1.lack of standardized model;2.unstable;3.low matching rate of gene(80%);4.difficult operation;5.limitations of perianaesthetic management	not mentioned	tail veins	1.blood loss;2.hemoglobin concentration;3.the ability to survive the tail bleed	106,109
			C57BL/6 WT mice (8-12 weeks, male)	lacerted liver injury	blood loss, bleeding time	117

Table 4. Current Research Patents of Platelet production

Title	Inventor	Patent Application	filing date	Country
platelet-like proteo-microparticles and method of using such in drug delivery	Hsieh; Patrick C.H; ; Cheng; Bill	20180092846-A1	20 Apr 2016	Taipei
CROSS-LINKED PLATELET MATERIAL	DIETZ; Allan B.; (Rochester, MN) ; KNUTSON; Gaylord J.; (Rochester, MN)	20160206783-A1	27 Aug 2013	United States
PLATELET PRODUCTION METHODS	Lasky; Larry C.; (Columbus, OH) ; Sullenbarger; Brent; (Dayton, OH) ; Kotov; Nicholas A.; (Ypsilanti, MI)	20100248361-A1	24 Mar 2010	United States
Method for preparing silver-loaded mesoporous silica nanoparticle carrying platelet-derived growth factor for preparing tissue engineered bone, involves placing silver-loaded mesoporous silica nanoparticles in phosphate buffer solution	MA C, CHENG X, SUN X, PU H, WEI Q, REHEMUTULA A, DENG Q	CN108371726-A	07 Aug 2018	Chinese
Microfluidic proplatelet and platelet-like particle production chamber device comprises multiple of slit channels including one or more microfluidic proplatelet/platelet-like particle production slits configured to expose megakaryocyte	MILLER W M, MCMAHON R, MARTINEZ A	WO2018237061-A1	27 Dec 2018	English
Synthetic platelet comprises biocompatible flexible nanoparticle including outer surface and multiple of site targeted peptides conjugated to surface and therapeutic agent, where therapeutic agent is conjugated to nanoparticle	SEN G A, PAWLOSKI C	US2019054151-A1	21 Feb 2019	English