

Supplementary information

Nanoparticle-Proteome *In Vitro* and *In Vivo*

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Table S1. *In vitro* protein corona, extracted from relevant literature as indicated.

Note: Due to space constraint, DOIs were indicated when there were too many types of nanoparticles or conditions used in the studies.

NA indicates no relevant information available.

In vitro (1)

Literature	Dobrovolskaia et al (2009)	Tenzer et al (2011)	Zhang et al (2011)	
Nanoparticle core	Colloidal gold particles (AuNP)	Silica nanoparticles (SiNP)	Polystyrene nanoparticles	
Protein source	Human plasma containing sodium citrate as anticoagulant	Human plasma	Human plasma	
Incubation time	30 min	1 h	5 min, 15 min, 1 h and 5 h	
Techniques for identifying protein corona	Centrifugation followed by 2D-PAGE and in-gel trypsin digest (analysed by IT-MS)	Centrifugation followed by 1D and 2D-PAGE and in-gel trypsin digest (analysed by LC-MS)	SDS buffer elution, acetone precipitation followed by trypsin digest (analysed by LC-MS)	On particle digestion followed by centrifugation (analysed by LC-MS)
Surface chemistry	30 and 50 nm citrate stabilized AuNP	8, 20 and 125 nm amorphous SiNP	50 and 100 nm amine, carboxylated and unmodified polystyrene nanoparticles	
Cell uptake	NA	NA	NA	

Cell toxicity	NA		NA	NA
No. of unique proteins	30 nm AuNP: 34	50 nm AuNP: 7	NA	NA

Top 10 most abundant proteins (1)

Literature	Dobrovolskaia et al (2009)		Tenzer et al (2011)			Zhang et al (2011)
Nanoparticle	30 nm citrate AuNP	50 nm citrate AuNP	8 nm SiNP	20 nm SiNP	125 nm SiNP	See DOI: 10.1002/pmic.201100037
1	Fibrinogen Fibrinogen $\alpha/\alpha E$ precursor	Fibrinogen Fibrinogen $\alpha/\alpha E$ precursor	Complement factor H	Serum albumin	Serum albumin	
2	Fibrinogen β -chain precursor	Fibrinogen β -chain precursor	Serum albumin	Complement factor H	Alpha-2-macroglobulin	
3	Fibrinogen γ -chain precursor	Fibrinogen γ -chain precursor	Apolipoprotein A-I	Complement C ₃	Complement C ₃	
4	Inter- α -trypsin inhibitor heavy-chain H ₄ precursor	Inter- α -trypsin inhibitor heavy-chain H ₄ precursor	Complement C ₃	Apolipoprotein A-I	Ig gamma-1 chain C region	
5	Plasma serine protease inhibitor precursor	Gelsolin precursor	Kininogen-1	Fibronectin	Serotransferrin	
6	Gelsolin precursor	Kininogen precursor	Plasma protease	Apolipoprotein B-100	Alpha-1-antitrypsin	

			C1 inhibitor			
7	Kininogen precursor	α -antitrypsin precursor	Nesprin-1	Nesprin-1	Haptoglobin	
8	α 1-antichymotrypsin precursor	Protocadherin 17	Apolipoprotein B-100	Kininogen-1	Apolipoprotein A-I	
9	Protocadherin 17	Crumbs protein homologue precursor	Clusterin	C4b-binding protein alpha chain	Ig kappa chain C region	
10	Crumbs protein homologue precursor	Tropomyosin 4 chain	C4b-binding protein alpha chain	Plasma protease C1 inhibitor	Ig gamma-2 chain C region	

In vitro (2)

Literature	Shannahan et al (2013)	Cai et al (2013)	Shannahan et al (2013)
Nanoparticle core	Single and multi-walled carbon nanotubes (SWCNT and MWCNT)	Multi-walled carbon nanotubes (MWCNTs) and carbon black (CB)	Silver nanoparticles (AgNP)
Protein source	Fetal bovine serum	Cell lysate prepared from the human cell line Hela	Dulbecco's Modified Eagle's Medium with glutamax and 10% heat inactivated fetal bovine serum
Incubation time	1 h	3 h	1 h
Techniques for	Centrifugation followed by solubilization in situ using a lysis buffer	Proteins pulled down by MWCNTs and CB followed by SDS-PAGE and	Centrifugation followed by solubilization in situ using a lysis buffer (8 M urea, 10

identifying protein corona	(8 M urea, 10 Mm DTT) and digested by trypsin (analysed by LC-MS/MS)							digested by trypsin (analysed by LC-MS)		Mm DTT) and digested by trypsin (analysed by LC-MS/MS)			
Surface chemistry	Na noc lay	M WC NT - pur e	M WC NT - ra w	SW CN T- ra w	M WC NT - PV P	M WC NT - CO OH	SW CN T- CO OH	Pristine MWCNTs with mean diameter of 20-40 nm	Colloidal CB	20 nm AgNP-citrate	110 nm AgNP-citrate	20 nm AgNP-PVP	110 nm AgNP-PVP
Cell uptake	NA							NA		NA			
Cell toxicity	NA							NA		NA			
No. of unique proteins	1	6	7	3	6	16	34	NA		10	1	15	10

Top 10 most abundant proteins (2)

Literature	Shannahan et al (2013)							Cai et al (2013)		Shannahan et al (2013)			
Nanoparticle	Na noc lay	M WC NT - pur e	M WC NT - ra w	SW CN T- ra w	M WC NT - PV P	M WC NT - CO OH	SW CN T- CO OH	NA		20 nm AgNP-citrate	110 nm AgNP-citrate	20 nm AgNP-PVP	110 nm AgNP-PVP
1	TT N	XIR P2	TT N	TT N	XIR P2	TT N	XIR P2			Histone-lysine N-	Serum albumin	Alpha-1-antiprot	Serum albumin

											protein 1		
7	CS N1 S1	P2 RX 5	AT AD 2B	AT AT 1	SE RPI NA 1	AH SG	AL S2			Comple ment C3	Alpha- fetoprot ein	40S ribosom al protein S12	Alpha- fetoprot ein
8	AT AD 2B	SE RPI NA 1	AL S2	AP OA 1	CO L3 A1	SE RPI NA 1	LC T			Thromb ospondi n-1	Apolipo protein B-100	Kalirin	Apolipo protein B-100
9	AH SG	AP OA 1	AP OA 2	CP S1	HB A	AA RS 2	KIF 7			Titin	Alpha- 2- antiplas min	Keratin, type II cytoskel etal 1	Comple ment C3
10	SE RPI NA 1	HB A	CO L6 A6	CS N1 S1	KR T1 0	AT AD 2B	AB CA 1			Tight junction protein ZO-1	Comple ment C3	Titin	Alpha- 2- antiplas min

In vitro (3)

Literature	Tenzer et al (2013)	Walkey et al (2014)	Sakulphu et al (2014)
Nanoparticle core	Commercial and lab-synthesized silica nanoparticles and polystyrene nanoparticles (AmSil, SiNP and PsNP)	Gold nanoparticles (GNP) and silver nanoparticles (SNP)	Superparamagnetic iron oxide nanoparticles (SPION)
Protein source	Human blood plasma	Human serum	Rat blood
Incubation	0.5 min at the earliest, 0.5-480 min for	1 h	15 min

time	prolonged exposure						
Techniques for identifying protein corona	Centrifugation followed by 1D polyacrylamide gel electrophoresis (1D-PAGE), and trypsin digest (analysed by LC-MS)			Centrifugation followed by polyacrylamide gel electrophoresis (PAGE), and trypsin digest (analysed by LC-MS/MS)	Magnetic separator		
Surface chemistry	Silica nanoparticles	Negatively charged polystyrene nanoparticles (nPsNP)	Positively charged polystyrene nanoparticles (pPsNP)	Various surface modifications (67 molecules or combinations of molecules used for surface modification) and sizes (15, 30 or 60 nm)	Positively charged PVA (amino group)	Negatively charged PVA (carboxyl group)	Neutral PVA
Cell uptake	Protein corona formation increased cell uptake for fluorescent silica and pPsNP in endothelial cells. Uptake of nPsNP was less affected by corona formation			Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) was used to measure nanoparticle association with A549 human lung epithelial carcinoma cells. Cationic gold nanoparticles associated with cells greater than anionic or neutral ones	NA		
Cell toxicity	Protein corona prevented haemolysis and reduced primary human endothelial and microvascular endothelial cell death mostly notably for the early corona			NA	No toxicity on RAW 264.7 cells up to 0.8 mg Fe per mL		
No. of unique proteins	Rising: 11	19	19	NA	NA		
	Falling: 8	27	15				
	Peak: 12	16	20				

Top 10 most abundant proteins (3)

Literature	Tenzer et al (2013)			Walkey et al (2014)	Sakulphu et al (2014)		
Nanoparticle	AmSi30 (0.5 min exposure)	nPsNP (0.5 min exposure)	pPsNP (0.5 min exposure)	NA	Positively charged SPION	Negatively charged SPION	Neutral SPION
1	Serum albumin	Serum albumin	Serum albumin		Apolipoprotein A-I	Haptoglobin	Apolipoprotein A-I
2	Apolipoprotein A-I	Complement C3	Apolipoprotein A-I		Apolipoprotein E	Serotransferrin	Apolipoprotein E
3	Complement C3	Complement factor H	Ig γ -1 chain C region		Hemoglobin subunit alpha-1/2	Serum albumin	Serum amyloid P-component
4	Ig γ -1 chain C region	β 2-glycoprotein 1	Inter- α -trypsin inhibitor heavy chain H4		Hemoglobin subunit beta-1	Apolipoprotein A-II	Alpha-2-HS-glycoprotein
5	Complement factor H	Kininogen-1	Ig μ chain C region		Serum amyloid P-component	Apolipoprotein E	Hemoglobin subunit alpha-1/2
6	Kininogen-1	Inter- α -trypsin inhibitor heavy chain H4	Ig γ -3 chain C region		Coagulation factor X	Coagulation factor X	Hemoglobin subunit beta-1

7	Complement C4-A	Ig γ -1 chain C region	Ig κ chain C region		Alpha-2-HS-glycoprotein	Ficolin-1	Coagulation factor X
8	Ig κ chain C region	Vitronectin	Vitronectin		Complement component C9	Secreted phosphoprotein 24	T-Kininogen 2
9	Serotransferrin	Complement C1r subcomponent	Complement C3		Myosin light polypeptide 6	Fibrinogen alpha chain	Serum albumin
10	Gelsolin	Ig γ -3 chain C region	Complement C1r subcomponent		Prothrombin	Glyceraldehyde-3-phosphate dehydrogenase	T-Kininogen 1

In vitro (4)

Literature	Groult et al (2014)	Wan et al (2015)	Hadjidemetriou et al (2015)
Nanoparticle core	Superparamagnetic iron oxide nanoparticles (SPION)	Silica nanoparticles (SiNP)	Liposome
Protein source	Rat serum	Human plasma	CD-1 mouse plasma
Incubation	15, 90 or 180 min	1 h	10 min

time						
Techniques for identifying protein corona	Centrifugation followed by SDS-PAGE and trypsin digest (analysed by LC-MS/MS)		Centrifugation followed by SDS-PAGE and trypsin digest (analysed by LC-MS/MS)	Size exclusion chromatography followed by membrane ultrafiltration		
Surface chemistry	Micellar phosphatidylcholine-coated superparamagnetic iron oxide nanoparticles (PC SPION)	Micellar polysorbate 80-coated superparamagnetic iron oxide nanoparticles (P80 SPION)	FITC	Bare	PEG	Anti-MUC-1 antibody conjugated PEG
Cell uptake	Effective internalization of the nanomicelles into C57BL/6 mouse embryonic fibroblasts in a time and concentration-dependent manner		The deglycosylated (removal of glycan) protein corona coated nanoparticles showed higher cell uptake in M1 and M2 macrophages	Protein corona significantly reduced cell uptake in MCF7 cells (More pronounced than in vivo)	Poor cell uptake with and without protein corona in MCF7 cells	Protein corona significantly reduced cell uptake in MCF7 cells (More pronounced than in vivo)
Cell toxicity	Low toxicity up to 40 µg/mL		NA	NA		
No. of unique proteins	NA		NA	26	24	41

Top 10 most abundant proteins (4)

Literature	Groult et al (2014)	Wan et al (2015)	Hadjidemetrious et al (2015)		
Nanoparticle	See DOI: 10.1002/chem.201404221	SiNP (Deglycosylated proteins after enzymatic deglycosylation reaction)	Bare liposome	PEGylated liposome	Targeted liposome
1		Fibrinogen alpha chain	Apolipoprotein E	Apolipoprotein E	Apolipoprotein E
2		Plasminogen	Alpha-2-macroglobulin	Fibrinogen beta chain	Fibrinogen beta chain
3		Serotransferrin	Fibrinogen beta chain	Alpha-2-macroglobulin	Alpha-2-macroglobulin
4		Kininogen-1	Fibrinogen gamma chain	Fibrinogen gamma chain	Fibrinogen gamma chain
5		Cartilage acidic protein 1	Ig mu chain C region	Protein Fga	Protein Fga
6		Coagulation factor XII	Protein Fga	Ig kappa chain C region	Ig mu chain C region
7		Histidine-rich glycoprotein	Apolipoprotein C-III	Apolipoprotein B-100	Apolipoprotein C-III
8		Plasma protease C1 inhibitor	Apolipoprotein C-I	Apolipoprotein C-III	Apolipoprotein B-100
9		Vitronectin	Apolipoprotein B-100	Ig mu chain C region	Serum albumin

10		Vimentin	Serum albumin	Serum albumin	Ig heavy chain V region
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In vitro (5)

Literature	Pozzi et al (2015)		Sopotnik et al (2015)			Vogt et al (2015)	
Nanoparticle core	Liposome		Carbon black (CB), multi-walled carbon nanotubes (MWCNT) and graphene oxide sheets (GO)			Superparamagnetic iron oxide nanoparticles (SPION)	
Protein source	Fetal bovine serum		Human serum protein			Human plasma	
Incubation time	90 min static incubation	90 min dynamic incubation	1 h			1 h	
Techniques for identifying protein corona	Centrifugation followed by in-solution trypsin digestion and desalting (analysed by NanoLC-MS/MS)		Centrifugation followed by SDS-PAGE and in-gel trypsin digest (analysed by LC-ESI-MS)			Centrifugation followed by in-solution trypsin digestion and desalting (analysed by mass spec)	
Surface chemistry	None		CB	MWCNT	GO	Silica	Dextran
Cell uptake	NA		NA			Protein corona increased primary	Protein corona didn't affect

			human monocyte-derived macrophage (HMDM) cell uptake	HMDM cell uptake
Cell toxicity	NA		NA	Low HMDM cell viability was observed at 100 µg/mL but completely restored with pre-formed hard protein corona
No. of unique proteins	44	48	NA	NA

Top 10 most abundant proteins (5)

Literature	Pozzi et al (2015)		Sopotnik et al (2015)			Vogt et al (2015)	
Nanoparticle	Liposome under static conditions	Liposome under dynamic conditions	CB	MWCNT	GO	Silica	Dextran
1	Apolipoprotein A-II	Apolipoprotein A-II	Complement component C ₃	Transferrin	Complement 9	Fibrinogen beta	Kininogen 1 microtubule associated ser/thr

2	Serum albumin	Serum albumin	Serum albumin	Apolipoprotein A-I precursor	Inter-alpha-trypsin inhibitor heavy chain H4 precursor	Fibrinogen gamma	Kinase-like
3	Alpha-2-HS-glycoprotein	Antitrypsin	Complement C4-A protein	Proapolipoprotein	Complement C3	Fibrinogen alpha	Platelet factor 4
4	Hemoglobin fetal subunit beta	Alpha-2-HS-glycoprotein	Transferrin	Serum albumin	Transferrin	Vitronectin	Actin, beta
5	Antitrypsin	Hemoglobin fetal subunit beta	Ig G1 H Nie	Vitamin K-dependent protein S	Complement component C8 alpha chain	Histidine-rich glycoprotein	Integrin, alpha 2b
6	Inter-alpha-trypsin inhibitor heavy chain H3	Apolipoprotein C-III	Complement component C3	Ig gamma-1 chain C region	Complement component C8 beta chain	Thrombospondin 1	Pro-platelet basic protein
7	Apolipoprotein C-II	Apolipoprotein C-II	Trypsin precursor	Clusterin	Complement C15 subcomponent	Otoferlin	Kallikrein B, plasma 1
8	Apolipoprotein C-III	Apolipoprotein A-I	Complement C1q subcomponent	Inter-alpha-trypsin inhibitor	Complement component C7	Coagulation factor XII	Lactotransferrin

			subunit B	heavy chain H2			
9	Alpha-2-macroglobulin	Hemoglobin subunit beta	Keratin	Trypsin inhibitor	Apolipoprotein E	Complement 4A/4B	Glycoprotein Ib (platelet)
10	Protein AMBP	Hemoglobin subunit alpha	Clusterin	Apolipoprotein J	Complement component C3	Complement factor H-related 1	Integrin, beta 3

In vitro (6)

Literature	Raesch et al (2015)	Schöttler et al (2016)	Saha et al (2016)
Nanoparticle core	Oleic acid-coated primary magnetite nanoparticles	Polystyrene nanoparticle (PS)	Gold nanoparticles (AuNP)
Protein source	Native porcine surfactant	Human plasma	Human serum (10 % and 50 %)
Incubation time	1 h	1 h	1 h
Techniques for identifying protein corona	Repeated magnetic separation and centrifugation followed by 1D polyacrylamide gel electrophoresis (1D-PAGE), and trypsin digest (analysed by LC-MS)	Centrifugation followed by SDS-PAGE and trypsin digest (analysed by LC-MS)	Centrifugation followed by LC-MS/MS procedure

Surface chemistry	PLGA	PEG	Lipid	Amine	PEG (Degree of polymerization: 44 and 110)	PEEP (Degree of polymerization: 49 and 92)	Thiolated ligand with increasing hydrophobicity
Cell uptake	NA			High RAW264.7 cell uptake of PEG and PEEP functionalized nanoparticles without protein corona but no uptake with protein corona. Clusterin reduces RAW264.7 cell uptake		Lower cell (RAW264.7) uptake for hydrophobic NPs compared to hydrophilic NPs with protein corona. High nonspecific uptake for all NPs without protein corona. Specifically, complement proteins in the corona increased cell uptake while immunoglobulins showed the opposite effect	
Cell toxicity	NA			NA		Non-toxic at the concentration of 50 nM for all AuNPs	
No. of unique proteins	NA			NA		NA	

Top 10 most abundant proteins (6)

Literature	Raesch et al (2015)	Schöttler et al (2016)	Saha et al (2016)

Nanoparticle	PLGA-NP	PEG-NP	Lipid-NP	Amine-functionalized PS	PEG ₄₄ -PS	PEEP ₄₉ -PS	See DOI: 10.1021/acsnano.6b00053
1	Tubulin alpha-4A chain	Tubulin alpha-4A chain	Tubulin alpha-4A chain	Serum albumin	Clusterin	Clusterin	
2	Actin, cytoplasmic 1	Actin, cytoplasmic 1	Actin, cytoplasmic 1	Fibrinogen beta chain	Apolipoprotein A-I	Fibronectin	
3	Hemoglobin subunit beta	Hemoglobin subunit beta	Hemoglobin subunit beta	Fibrinogen gamma chain	Vitronectin	Apolipoprotein A-IV	
4	L-xylulose reductase	L-xylulose reductase	L-xylulose reductase	Vitronectin	Apolipoprotein C-III	Serum amyloid P-component	
5	Tubulin beta-4B chain	Tubulin beta-4B chain	Myosin-9	Fibrinogen alpha chain	Fibrinogen beta chain	Apolipoprotein C-III	
6	Tubulin alpha-1A chain	Tubulin alpha-1A chain	Tubulin beta-4B chain	Clusterin	Fibronectin	Vitronectin	
7	Deleted in malignant brain tumors 1 protein	Tubulin beta chain	Pulmonary surfactant-associated protein A	Ig gamma-1 chain C region	Fibrinogen gamma chain	Apolipoprotein D	
8	Tubulin beta chain	Myosin-9	Deleted in malignant brain tumors 1	Ig kappa chain C region	Serum albumin	Component C1q subcomponent	

			protein			subunit B	
9	Pulmonary surfactant-associated protein A	Fibronectin	Tubulin alpha-1A chain	Apolipoprotein C-III	Ig kappa chain C region	Ig mu chain C region	
10	Myosin-9	Glyceraldehyde-3-phosphate dehydrogenase	Tubulin beta chain	Apolipoprotein A-I	Complement C1q subcomponent subunit C	Ig kappa chain C region	

In vitro (7)

Literature	Koshkina et al (2016)	Corbo et al (2016)	Wang et al (2016)
Nanoparticle core	Poly(organosiloxane) nanoparticles (POS)	Liposome	CdSe/ZnS quantum dots (QDs)
Protein source	Fetal calf serum	BALB/C mice blood plasma	PBS solution of human serum
Incubation time	1 h	1 h	10 min
Techniques for identifying protein corona	Centrifugation followed by 1D SDS-PAGE and in-solution trypsin digest (analysed by LC-MS)	Centrifugation followed by 1D SDS-PAGE and in-gel trypsin digest (analysed by LC-MS)	Centrifugation followed by SDS-PAGE and in-gel trypsin digest (analysed by MALDI-ToF/MS)

Surface chemistry	Negatively charged POS (COOH)	Positively charged POS (NEt ₃)	Poly(ethylene glycol) (PEG)	Poly(2-ethyl-2-oxazoline) (PEtOx)	None	Bidentate anionic dihydrolipoic acid (DHLA)	Zwitterionic D-penicillamine (DPA)	Poly(ethylene glycol) with cationic amino group (PEG)
Cell uptake	Cell uptake of POS-PEG and POS-PEtOx was much lower than that of POS-COOH and POS-NEt ₃ . Protein corona decreased cell uptake for all four NPs, and POS-PEtOx was the most efficient to avoid protein bindings				Protein corona facilitated liposome cell uptake by both J774 mouse macrophage and 4T1 mouse mammary tumor cells	NA		
Cell toxicity	NA				NA	NA		
No. of unique proteins	NA				NA	NA		

Top 10 most abundant proteins (7)

Literature	Koshkina et al (2016)				Corbo et al (2016)	Wang et al (2016)
Nanoparticle	POS-COOH	POS-NEt ₃	POS-PEG	POS-PEtOx	Liposome	NA

1	Serum albumin	Apolipoprotein A-II	Serum albumin	Serum albumin	Serum albumin
2	Hemoglobin subunit alpha	Hemoglobin subunit alpha	Hemoglobin subunit alpha	Hemoglobin subunit alpha	Apolipoprotein-E
3	Alpha-2-HS-glycoprotein	Apolipoprotein A-I	Alpha-2-HS-glycoprotein	Alpha-2-HS-glycoprotein	Ig mu chain C region
4	Apolipoprotein A-I	Serum albumin	Alpha-1-antitrypsin	Alpha-1-antitrypsin	Apolipoprotein A-IV
5	Alpha-1-antitrypsin	Alpha-1-antitrypsin	Hemoglobin fetal subunit beta	Hemoglobin fetal subunit beta	Myosin
6	Apolipoprotein A-II	Hemoglobin fetal subunit beta	Actin, cytoplasmic 2	Apolipoprotein A-II	Alpha-2 macroglobulin
7	Hemoglobin fetal subunit beta	Apolipoprotein C-III	Serotransferrin	Serotransferrin	Serotransferrin

8	Beta-2-glycoprotein-1	Apha-2-HS-glycoprotein	Apolipoprotein A-II	Actin, cytoplasmic 2	Apolipoprotein A-I	
9	Vitronectin	Apolipoprotein D	Alpha-2-macroglobulin	Alpha-2-macroglobulin	Phospholipid transfer protein	
10	Serotransferrin	Coagulation factor XIII, B polypeptide	Complement C ₃	Apolipoprotein C-III	Hemoglobin sub beta-1	

In vitro (8)

Literature	Chen et al (2016)		Pisani et al (2017)	Zhu et al (2017)
Nanoparticle core	Superparamagnetic iron oxide (SPIO) nanoworms		Magnetic mesoporous silica NPs (M-MSNs)	Hydroxyapatite (HA) and magnetic hydroxyapatite (MHA) scaffolds
Protein source	Human plasma	Human serum	Human serum and fetal bovine serum	100 % fetal bovine serum (100% FBS), extracellular secretion (ES) of MC ₃ T ₃ -E1 cells and the combination of 10% FBS, and extracellular secretion (FBS+ES)
Incubation time	1 h		From 0.5 min to 7 days	24 h

Techniques for identifying protein corona	Ultracentrifugation followed by SDS-PAGE and trypsin digest (analysed by Nano LC-MS)	NP-protein corona complexes were magnetically separated and followed by NuPAGE gel electrophoresis and trypsin digest (analysed by Nano LC-MS/MS)	Hard corona was collected by SDT lysis buffer, boiled for 10 min at 99 °C. Protein in the supernatant was separated by 1D-SDS-PAGE and followed by trypsin digest (analysed by LC-MS/MS)
Surface chemistry	Dextran	None	With and without magnetic Fe ₃ O ₄ nanoparticles
Cell uptake	Higher cell (leukocyte) uptake of SPIO nanoworms in serum than in plasma. 10 mM EDTA significantly reduced cell uptake in both serum and plasma	NA	NA
Cell toxicity	NA	NA	NA
No. of unique proteins	NA	NA	NA

Top 10 most abundant proteins (8)

Literature	Chen et al (2016)		Pisani et al (2017)	Zhu et al (2017)	
Nanoparticle	SPIO nanoworms in plasma	SPIO nanoworms in serum	See DOI: 10.1039/C6NR04765C	HA in 100% FBS	MHA in 100% FBS
1	Complement C3	Apolipoprotein B-100		Serum albumin	Serum albumin

2	Fibrinogen beta chain	Serum albumin		Serotransferrin	Serotransferrin
3	Fibrinogen alpha chain	Complement C ₃		Alpha-2-HS-glycoprotein	Alpha-2-HS-glycoprotein
4	Fibronectin	Apolipoprotein A		Alpha-1-antiproteinase	Apolipoprotein A-I
5	Myosin-9	Serotransferrin		Alpha-fetoprotein	Alpha-1-antiproteinase
6	Filamin-A	Alpha-2-macroglobulin		Apolipoprotein A-I	Alpha-fetoprotein
7	Talin-1	Fibronectin		Alpha-2-macroglobulin	Alpha-2-macroglobulin
8	Fibrinogen gamma chain	Complement C ₄ -B		Hemoglobin subunit alpha	Vitamin D binding protein
9	Thrombospondin-1	Plasma kallikrein		Vitamin D-binding protein	Transthyretin
10	Serum albumin	Complement factor B		Hemoglobin fetal subunit beta	Antithrombin-III

In vitro (9)

Literature	Gao et al (2017)		Lundqvist et al (2017)				Bonvin et al (2017)	
Nanoparticle core	Silver nanoparticles (AgNPs)		Silica nanoparticles				Iron oxide nanoparticles	
Protein source	Smallmouth bass plasma (male)	Smallmouth bass plasma (female)	Whole blood	Whole blood with EDTA	Plasma	Serum	Human blood (flow rate: 1400 and 20 rpm)	Lymph serum (flow rate: 1400 and 20 rpm)

Incubation time	1 h		24 h		5 min for whole blood and 2 h for other samples	24 h				
Techniques for identifying protein corona	Centrifugation followed by SDS-PAGE and in-gel trypsin digest (analysed by LC-MS/MS)				Centrifugation followed by 1D SDS-PAGE and in-gel trypsin digest (analysed by MALDI-TOF MS)		Magnet to collect nanoparticle-protein corona complexes followed by multiple centrifugation and SDS-PAGE in-gel digest (analysed by LC-MS)			
Surface chemistry	PVP				None		None			
Cell uptake	NA				NA		NA			
Cell toxicity	NA				NA		NA			
No. of unique proteins	Male 1 h: 67	Female 1 h: 19	Male 24 h: 64	Female 24 h: 26	NA		NA			

Top 10 most abundant proteins (9)

Literature	Gao et al (2017)				Lundqvist et al (2017)		Bonvin et al (2017)			
Nanoparticle	AgNP in male plasma for 1 h	AgNP in female plasma for 1 h	AgNP in male plasma for 24 h	AgNP in female plasma for 24 h	NA		Human blood at 1400 rpm	Human blood at 20 rpm	Lymph serum at 1400 rpm	Lymph serum at 20 rpm

1	Immunoglobulin light chain	Immunoglobulin light chain	Immunoglobulin heavy chain variable region	Immunoglobulin light chain			Apolipoprotein B-100	Apolipoprotein B-100	Apolipoprotein B-100	Fibrinogen beta chain
2	Immunoglobulin heavy chain variable region	Hemoglobin embryonic subunit alpha	Immunoglobulin M heavy chain	Immunoglobulin heavy chain variable region			Complement C3	Complement C3	Complement C3	Fibrinogen alpha chain
3	Immunoglobulin M heavy chain	Hemoglobin subunit alpha-1	Immunoglobulin light chain	Immunoglobulin M heavy chain			Serum albumin	Complement C4-A	Serum albumin	Fibrinogen gamma chain
4	Immunoglobulin mu heavy chain	Immunoglobulin M heavy chain	Immunoglobulin mu/tau heavy chain	Immunoglobulin mu heavy chain			Complement C4-A	Apolipoprotein A-I	Complement C4-A	Serum albumin
5	Fibrinogen	Immunoglobulin	Complement	Hemoglobin			Complement	Serum albumin	Alpha-2-	Complement C3

	beta chain	in mu heavy chain	C ₃	subunit alpha-1		C ₄ -B		macroglobulin	
6	Hemoglobin subunit beta	Complement C ₃	Hemoglobin subunit alpha-1	Apolipoprotein E		Apolipoprotein A-I	Prothrombin	Apolipoprotein A-I	Fibrinogen
7	Beta-fibrinogen	Complement C8 beta	Immunoglobulin in mu heavy chain	Immunoglobulin in mu/tau heavy chain		Apolipoprotein E	Apolipoprotein E	Apolipoprotein E	Apolipoprotein B-100
8	Complement C8 beta	Immunoglobulin in heavy chain variable region	Complement C8 beta	Complement C ₃		Antithrombin-III	Antithrombin-III	Antithrombin-III	Complement C ₄ -A
9	Immunoglobulin in kappa chain V region Mem5	Apolipoprotein E	Fibrinogen beta chain	Complement C8 beta		Alpha-2-macroglobulin	Plasminogen	Histidine-rich glycoprotein	Complement factor H
10	Hemoglobin embryonic	Alpha-2-macroglobulin	Apolipoprotein E	Hemoglobin subunit		Histidine-rich glycoprotein	Vitronectin	Plasminogen	Plasminogen

	nic subunit alpha	lobulin		alpha-A		otein			
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In vitro (10)

Literature	Kokkinopoulou et al (2017)			Wang et al (2017)			Müller et al (2017)				
Nanoparticle core	Polystyrene nanoparticles (PS-NP)			Iron oxide nanoparticles (IONPs)			Polystyrene nanoparticles		Magnetite nanoparticles		
Protein source	Human serum			Human plasma			Human plasma	Sheep plasma	Mouse plasma	Rabbit plasma	
Incubation time	1 h, multiple washing			24 h			1 h				
Techniques for identifying protein corona	Multiple centrifugation and wash followed by SDS-PAGE and in-solution trypsin digest (analysed by LC-MS)			Centrifugation followed by 1D SDS-PAGE and in-gel trypsin digest (analysed by LC-MS/MS)			Centrifugation followed by SDS-PAGE and in-gel trypsin digest (analysed by LC-MS)				
Surface chemistry	Unfunctionalized polystyrene nanoparticles (PS)	Negatively charged polystyrene nanoparticles (PS-CCOH)	Positively charged polystyrene nanoparticles (PS-NH ₂)	Bare	Brushed polyethylene glycol (bPEG)	Brushed phosphorylcholine (bPC)	Unfunctionalized (PS)	Carboxyl-end group (PS-COOH)	Amino-end group (PS-NH ₂)	Dextran (M-DEX)	Hydroxyethyl starch (HES)
Cell uptake	Cellular (RAW264.7) uptake of soft corona coated nanoparticles lower			NA			Coated with human plasma proteins, cell (murine macrophage cell line RAW264.7)				

	than hard corona and uncoated nanoparticles. Lower cellular uptake of PS and PS-NH ₂ than PS-COOH				uptake of polystyrene nanoparticles decreased. On the contrary, cell uptake increased when polystyrene nanoparticles were coated with mouse plasma proteins			
Cell toxicity	NA	NA			NA			
No. of unique proteins	NA	13	8	9	PS-NP in human plasma: 48	Sheep plasma: 7	Mouse plasma: 78	Rabbit plasma: 17
					M-DEX in human plasma: 57	Sheep plasma: 14	Mouse plasma: 80	Rabbit plasma: 4

Top 10 most abundant proteins (10)

Literature	Kokkinopoulou et al (2017)	Wang et al (2017)			Müller et al (2017)
Nanoparticle	See DOI: 10.1039/C7NR02977B	Bare IONPs	bPEG-IONPs	bPC-IONPs	See DOI: 10.1021/acs.biomac.7b01472
1		Serum albumin	Serum albumin	Ig heavy constant mu	
2		Complement C ₃	Vitronectin	Apolipoprotein B-100	

3		Vitronectin	Complement C ₃	Serum albumin	
4		Ig heavy constant gamma 1	Fibronectin	Vitronectin	
5		Coagulation factor XI	Ig heavy constant mu	Ig kappa variable 3-1 1	
6		Kininogen-1	Ig heavy constant gamma 1	Apolipoprotein(a)	
7		Complement C1q subcomponent subunit C	Kininogen-1	Complement C ₃	
8		Apolipoprotein B-100	Coagulation factor XI	Ig heavy constant gamma 1	
9		Complement C ₄ -A	Complement C1q subcomponent subunit C	Fibronectin	
10		Ig kappa constant	Histidine-rich glycoprotein	Alpha-2-HS-glycoprotein	

In vitro (11)

Literature	Simon et al (2018)					Wang et al (2018)			Castagnola et al (2018)	
Nanoparticle core	Polystyrene nanoparticles (PS)					Nano-graphene oxide (nGO)			Graphene nanoflakes	
Protein source	Human plasma					Human plasma			Human serum (10 % and 100 %)	Fetal bovine serum (10 % and 100 %)
Incubation time	1 h					24 h			1-4 h under ultrasonication	
Techniques for identifying protein corona	Centrifugation followed by SDS-PAGE and in-solution digest (analysed by LC-MS)					Centrifugation followed by 1D SDS-PAGE and in-gel trypsin digest (analysed by LC-MS/MS)			A series of washing by centrifugation followed by 1D SDS-PAGE and in-gel trypsin digest (analysed by LC-MS/MS)	
Surface chemistry	Amino-functionalized (PS-NH ₂)	PEGylation (PS-PEG)	Hydrophilic polymer (PS-P(1) ₄₅)	Copolymers (PS-P(1) ₄₂ -co-2 ₄)	Hydrophobic copolymers (PS-P(1) ₃₁ -co-2 ₁₅)	Bare	Polyethylene glycol (PEG)	Poly(2-ethyl-2-oxazoline) (PEtOx)	None	
Cell uptake	With plasma protein coatings, strong cellular (RAW 264.7) uptake was observed for positively charged nanocarriers and weaker cellular uptake observed for PS-PEG and PS-P(1) ₄₅ . With increasing polymer					NA			NA	

	hydrophobicity, cellular uptake was strongly enhanced				
Cell toxicity	Non-toxic up to 75 µg/mL in RAW 264.7 cells	Lower toxicity of nGO-PEG and nGO-PEtOx than bare nGO at 100 µg/mL. Non-toxic for all three types of nGO below 100 µg/mL on HEK 293 cells and red blood cells. Protein corona reduced toxicity for all three types of nGO on red blood cells			NA
No. of unique proteins	NA	11	2	4	NA

Top 10 most abundant proteins (11)

Literature	Simon et al (2018)	Wang et al (2018)			Castagnola et al (2018)	
Nanoparticle	See DOI: 10.1002/anie.201800272	Bare nGO	nGO-PEG	nGO-PEtOx	Graphene nanoflakes exfoliated in 100 % human serum	Graphene nanoflakes exfoliated in 100 % fetal bovine serum
1		Serum albumin	Fibrinogen alpha chain	Fibrinogen alpha chain	Serum albumin	Serum albumin
2		Fibrinogen gamma chain	Fibrinogen gamma chain	Fibrinogen beta chain	Apolipoprotein A-I	Hemoglobin subunit alpha
3		Complement C4-B	Fibrinogen beta chain	Fibrinogen gamma chain	Apolipoprotein E	Apolipoprotein A-I

4		Inter-alpha-trypsin inhibitor heavy chain H ₄	Inter-alpha-trypsin inhibitor heavy chain H ₄	Inter-alpha-trypsin inhibitor heavy chain H ₄	Vitronectin	Hemoglobin subunit beta
5		Ig heavy constant gamma 1	Ig heavy constant gamma 1	Ig heavy constant gamma 1	Alpha-1-antitrypsin	Alpha-2-HS-glycoprotein
6		Fibrinogen alpha chain	Apolipoprotein A-I	Kininogen-1	Apolipoprotein A-IV	Histone H ₄
7		Fibrinogen beta chain	Gelsolin	Gelsolin	Hemoglobin subunit beta	Apolipoprotein E
8		Complement C ₃	Serum albumin	Complement C ₃	Apolipoprotein A-II	Alpha-1-antiproteinase
9		Gelsolin	Kininogen-1	Vitronectin	Complement C ₃	Complement C ₃
10		Apolipoprotein B-100	Apolipoprotein B-100	Apolipoprotein B-100	L-lactate dehydrogenase A chain	Alpha-2-macroglobulin

In vitro (12)

Literature	Tavano et al (2018)	
Nanoparticle core	Organically modified silica nanoparticles	
Protein	Human sera	Mouse sera

source			
Incubation time	15 min		
Techniques for identifying protein corona	<p>Shot-gun proteomics: Centrifugation followed by in-solution digest and desalting (analyzed by LC-MS)</p> <p>MS spectrometry analysis: Centrifugation followed by SDS-PAGE and in-gel digest (analyzed by LC-MS)</p>		
Surface chemistry	Uncoated	Poly(ethylene glycol) (PEG)	Poly(2-methyl-2-oxazolin) (PMOXA)
Cell uptake	<p>PMOXA and PEG-coated NPs exhibited higher uptake in blood phagocytes and human macrophages than uncoated NPs. Whereas PMOXA-coated NPs showed lower uptake in mouse monocyte-derived macrophages than uncoated NPs.</p> <p>Human sera from 8 individual donors promoted efficient uptake of PMOXA-coated NPs. Variable macrophage uptake was observed</p>		

	for PEGylated NPs
Cell toxicity	Very low percentage of hemolysis of human erythrocytes and low toxicity on monocyte-derived human macrophages for all three types of NPs
No. of unique proteins	NA

Top 10 most abundant proteins (12)

Literature	Tavano et al (2018)
Nanoparticle	See DOI: 10.1021/acsnano.8b01806
1	
2	
3	
4	
5	
6	
7	
8	

9	
10	

Table S2. *In vivo* protein corona, extracted from relevant literature as indicated.

In vivo (1)

Literature	Sakulkhu et al (2014) (in vitro vs in vivo)	Hadjidemetriou et al (2015) (in vitro vs in vivo)	Hadjidemetriou et al (2016) (in vivo only)		
Nanoparticle core	Superparamagnetic iron oxide nanoparticles (SPION)	Liposome	Liposome		
Protein source	Rat sera	CD-1 mouse plasma	CD-1 mouse plasma		
Incubation time	15 min	10 min	10 min	1 h	3 h
Technique of separating	Magnetic separator	Size exclusion chromatography followed by membrane ultrafiltration	Size exclusion chromatography followed by membrane ultrafiltration		

nanoparticle-PC complex from free proteins									
Surface chemistry	Positively charged PVA (amino group)	Negatively charged PVA (carboxyl group)	Neutral PVA	Bare	PEG	Anti-MUC-1 antibody conjugated PEG	Doxorubicin-encapsulated PEG		
Cell uptake	NA			Protein corona reduced cell uptake in MCF7 cells	Poor cell uptake with and without protein corona in MCF7 cells	Protein corona reduced cell uptake in MCF7 cells	NA		
Cell toxicity	No toxicity on RAW 264.7 cells up to 0.8 mg Fe per mL			NA			NA		
No. of unique proteins	32	51	55	12	18	34	90	25	35

Top 10 most abundant proteins (1)

Literature	Sakulku et al (2014) (in vitro vs in vivo)	Hadjidemetriou et al (2015) (in vitro vs in vivo)	Hadjidemetriou et al (2016) (in vivo only)
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Nanoparticle	Positively charged PVA	Negatively charged PVA	Neutral PVA	Bare liposome	PEGylated liposome	Targeted liposome	10 min Doxorubicin-encapsulated PEGylated liposome	1 h Doxorubicin-encapsulated PEGylated liposome	3 h Doxorubicin-encapsulated PEGylated liposome
1	Hemoglobin subunit beta-2	Hemoglobin subunit beta-2	Fibrinogen alpha chain	Apolipoprotein C-III	Apolipoprotein C-III	Apolipoprotein E	Alpha-2-macroglobulin	Apolipoprotein E (PE=2 SV=1)	Hemoglobin subunit beta-1
2	Hemoglobin subunit alpha-1/2	Hemoglobin subunit alpha-1/2	Fibrinogen beta chain	Apolipoprotein E	Apolipoprotein E	Apolipoprotein C-III	Apolipoprotein C-III	Alpha-2-macroglobulin	Apolipoprotein E (PE=2 SV=1)
3	Hemoglobin subunit beta-1	Hemoglobin subunit beta-1	Hemoglobin subunit alpha-1/2	Haemoglobin subunit beta-1	Hemoglobin subunit beta-1	Alpha-2-macroglobulin	Hemoglobin subunit beta-1	Apolipoprotein C-III	Apolipoprotein C-III
4	Apolipoprotein E	Apolipoprotein A-II	Fibrinogen gamma chain	Beta-globin	Alphaglobin 1	Haemoglobin subunit beta-1	Apolipoprotein E (PE=1 SV=2)	Serum albumin	Alpha-2-macroglobulin
5	Fibrinogen alpha chain	Apolipoprotein E	Hemoglobin subunit beta-1	Alpha-2-macroglobulin	Alpha-2-macroglobulin	Apolipoprotein C-IV	Beta-globin, Hbbt1 (A8DUK2)	Apolipoprotein E (PE=1 SV=2)	Beta-globin, Hbbt1 (A8DUK2)
6	Secreted phosphoprotein 24	Coagulation factor X	Secreted phosphoprotein 24	Alphaglobin 1	Haemoglobin subunit beta-2	Ig mu chain C region	Apolipoprotein A-I	Hemoglobin subunit beta-1	Hemoglobin subunit beta-2

7	Complement C3	Ficolin-1	Apolipoprotein A-II	Ig mu chain C region	Ig mu chain C region	Hemoglobin subunit beta-2	Hemoglobin subunit beta-2	Apolipoprotein A-I	Alpha-globin
8	Fibrinogen beta chain	Secreted phosphoprotein 24	Apolipoprotein A-I	Serum albumin	Beta-globin	Serum albumin	Alpha-globin	Serine protease inhibitor A3K	Apolipoprotein A-I
9	Matrix Gla protein	Fibrinogen alpha chain	Coagulation factor X	Hemoglobin subunit beta-2	Apolipoprotein C-IV	Alphaglobin 1	Ig mu chain C region	Ig mu chain C region	Fibrinogen beta chain
10	Serum albumin	Glyceraldehyde-3-phosphate dehydrogenase	Apolipoprotein E	Apolipoprotein A-I	Ig kappa chain C	Ig kappa chain C	Putative uncharacterized protein	Hemoglobin subunit beta-2	Fibrinogen gamma chain

In vivo (2)

Literature	Corbo et al (2017) (in vivo only)		Zhu et al (2017) (in vitro vs in vivo)	Bertrand et al (2017) (in vivo only)
Nanoparticle core	Liposome	Leukosome	Hydroxyapatite (HA) and magnetic hydroxyapatite (MHA) scaffolds	PEG-PLGA nanoparticles
Protein source	Healthy BALB/c mice blood		Female SD rats blood	Male mice or Sprague-Dawley rats blood
Incubation time	10 min and 1 h		24 h	15 min
Technique of separating	Centrifugation		Boiled in SDT lysis buffer and supernatants collected	Size exclusion chromatography followed by membrane ultrafiltration

nanoparticle-PC complex from free proteins								
Surface chemistry	None				Without magnetic Fe ₃ O ₄ nanoparticles	With magnetic Fe ₃ O ₄ nanoparticles	PEG chains with different density (15, 18, 25 and 45 chains per 100 nm ²)	
Cell uptake	Protein corona increased cell uptake		Protein corona decreased cell uptake		NA		NA	
Cell toxicity	NA				NA		NA	
No. of unique proteins	10 min: 14	1 h: 27	10 min: 11	1 h: 11	99	138	NA	

Top 10 most abundant proteins (2)

Literature	Corbo et al (2017) (in vivo only)				Zhu et al (2017) (in vitro vs in vivo)		Bertrand et al (2017) (in vivo only)
Nanoparticle	10 min Liposome	1h Liposome	10 min Leukosome	10 min Leukosome	HA	MHA	NA

1	Vitronectin	Fibrinogen gamma chain	Vitronectin	Fibrinogen gamma chain	Hemoglobin subunit beta-1	Hemoglobin subunit beta-1	
2	Serum amyloid P-component	Fibrinogen beta chain	Ig mu chain C region	Fibrinogen, alpha polypeptide	Protein Hbb-b1	Protein Hbb-b1	
3	Ig mu chain C region	Ig mu chain C region	Fibrinectin	Fibrinogen beta chain	Protein Hba-a2	Protein Hba-a2	
4	Actin, cytoplasmic 1	Actin, cytoplasmic 1	Serum amyloid P-component	Serum albumin	Hemoglobin subunit beta-2	Hemoglobin subunit beta-2	
5	Fibrinectin	Fibrinogen, alpha polypeptide	Hemoglobin subunit beta-1	Ig mu chain C region	Hemoglobin subunit alpha-1/2	Serum albumin	
6	Serum albumin	Serum albumin	Plasminogen	Actin, cytoplasmic 1	Serum albumin	Hemoglobin subunit alpha-1/2	
7	Hemoglobin subunit alpha	Apolipoprotein A-I	Serum albumin	Vitronectin	Zero beta-globin (Fragment)	Beta-globin	

8	Hemoglobin subunit beta-1	Myosin-9	Fibrinogen gamma chain	Apolipoprotein A-I	Epsilon 1 globin	Epsilon 1 globin	
9	Plasminogen	Hemoglobin subunit beta-1	Hemoglobin subunit beta-2	Serum amyloid P-component	Rat haemoglobin beta-chain	Protein Myh1	
10	Ig kappa chain C region	Plasminogen	Ig heavy chain V regions	Plasminogen	Histone H4	Histone H2A	

In vivo (3)

Literature	Garcia-Alvarez et al (2018) (in vivo only)			
Nanoparticle core	Gold nanorod 40 nm (NR40)	Gold nanostar 40 nm (NS40)	Gold nanorod 70 nm (NR70)	Gold nanostar 70 nm (NS70)
Protein source	CD-1 female mice			
Incubation	10 min			

time				
Technique of separating nanoparticl e-PC complex from free proteins	Size exclusion chromatography followed by membrane ultrafiltration			
Surface chemistry	Polyethylene glycol			
Cell uptake	NA			
Cell toxicity	NA			
No. of unique proteins	(The effect of size) NR40: 95	NS40: 224	NR70: 43	NS70: 33
	(The effect of shape) NR40: 35	NS40: 143	NR 70: 69	NS70: 38

Top 10 most abundant proteins (3)

Literature	Garcia-Alvarez et al (2018) (in vivo only)			
Nanoparticle	NR40	NS40	NR70	NS70
1	Serum albumin	Serum albumin	Serum albumin	Serum albumin
2	Alpha-2-macroglobulin	Alpha-2-macroglobulin	Alpha-2-macroglobulin	Alpha-2-macroglobulin
3	Fibrinogen beta chain	Serine protease inhibitor A3K	Serine protease inhibitor A3K	Serine protease inhibitor A3K
4	Apolipoprotein A-I	Fibrinogen beta chain	Apolipoprotein A-I	Fibrinogen beta chain
5	Complement factor H	Apolipoprotein E	Fibrinogen beta chain	Alpha-1B-glycoprotein
6	Serine protease inhibitor	Fibrinogen gamma chain	Fibrinogen gamma chain	Fibrinogen gamma chain

	r A ₃ K			
7	Ig mu chain C region (fragment)	Apolipo protein A-I	Complement C ₃	Apolipo protein A-I
8	Fibrinogen gamma chain	Ig mu chain C region (fragment)	Apolipo protein E	Apolipo protein E
9	Argininosuccinate synthase	Complement factor H	Muroglobulin-1	Fibrinogen alpha chain
10	Plasminogen	Ig kappa light chain (fragment)	Complement factor H	Muroglobulin-1