Supplementary Materials

Table S1. Kinetic parameters of protein interactions with conventional ('large') NPs.

Entry	Nanoparticle	Size (nm)	Interaction with	Technique	Surface immobilization	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)	Ref.
1	Liposome-PEG 2k	100-150	Albumin	SPR	NP	1.4×10^{5}	2.3×10^{-3}	1.6×10^{-8}	[83]
2	Liposome-PEG 2k	100-150	α2-Macroglobulin	SPR	NP	3.9×10^{4}	5.4×10^{-3}	1.4×10^{-7}	[83]
3	Liposome-PEG 2k	100-150	Clusterin	SPR	NP	4.5×10^{4}	3.2×10^{-3}	7.0×10^{-8}	[83]
4	Liposome-PEG 2k	100-150	Vitronectin	SPR	NP	3.8×10^{4}	2.1×10^{-3}	5.5×10^{-8}	[83]
5	Liposome-PEG 2k	100-150	Ficolin-3	SPR	NP	3.7×10^{4}	2.1×10^{-1}	6.9×10^{-6}	[83]
6	Liposome-PEG 2k	100-150	CD5L	SPR	NP	2.7×10^{5}	2.1×10^{-1}	7.6×10^{-7}	[83]
7	Liposome-PEG 2k	100-150	Complement C3	SPR	NP	1.1×10^{4}	3.9×10^{-3}	3.6×10^{-8}	[83]
8	Liposome without PEG	100-150	Albumin	SPR	NP	1.1×10^{5}	2.1×10^{-3}	1.9×10^{-8}	[83]
9	Liposome without PEG	100-150	α2-Macroglobulin	SPR	NP	5.3×10^{4}	1.1×10^{-2}	2.1×10^{-7}	[83]
10	Liposome without PEG	100-150	Clusterin	SPR	NP	3.5×10^{4}	4.5×10^{-3}	1.3×10^{-7}	[83]
11	Liposome without PEG	100-150	Vitronectin	SPR	NP	5.5×10^{4}	3.8×10^{-3}	7.0×10^{-8}	[83]

12	Liposome without PEG	100-150	Ficolin-3	SPR	NP	4.8×10^{4}	2.4×10^{-1}	5.5×10^{-6}	[83]
13	Liposome without PEG	100-150	CD5L	SPR	NP	2.3×10^{5}	1.3×10^{-1}	5.7×10^{-7}	[83]
14	NIPAM/BAM	70	ApoA-I	SPR	NP	3.0×10^{4}	3.0×10^{-5}	3.0×10^{-5}	[85]
15	NIPAM/BAM	70	HSA	SPR	NP	2.4×10^{3}	2.0×10^{-3}	2.0×10^{-3}	[85]
16	NIPAM/BAM	70	Fibrinogen	SPR	NP	2.0×10^{3}	2.0×10^{-3}	2.0×10^{-3}	[85]
17	Silica with FBS corona	70	Apolipoprotein H	SPR	NP	2.8×10^{3}	4.8×10^{-2}	1.7×10^{-5}	[87]
18	Polymer NP with plasma corona	50	LRP1	SPR	Protein	-	3.3×10^{-4}	-	[79]
19	Polymer NP with plasma corona	50	Anti-ApoE	SPR	Protein	-	4.6×10^{-4}	-	[79]
20	Polymer NP with plasma corona	50	Anti-HSA	SPR	Protein	-	1.0×10^{-5}	-	[79]
21	Liposome-PA 20%	151	Amyloid-β	SPR	Protein	2.6×10^{3}	8.6×10^{-5}	3.3×10^{-8}	[81]

22	PA-SLN Solid Lipid NP	76	Amyloid-β	SPR	Protein	-	9.0×10^{-3} $\leq 7.0 \times 10^{-5}$	2.2×10^{-6} $\leq 1.7 \times 10^{-8}$	[81]
23	Gold	17	ApoA-I	SPR	NP	1.8×10^{4}	1.6×10^{-3}	1.2×10^{-7}	[82]
24	Gold	17	HSA	SPR	NP	4.7×10^{2}	1.8×10^{-3}	4.9×10^{-6}	[82]
25	Gold	17	Fibrinogen	SPR	NP	3.8×10^{3}	2.0×10^{-3}	5.3×10^{-7}	[82]
26	Gold	17	IgG	SPR	NP	2.3×10^{2}	2.3×10^{-3}	1.0×10^{-5}	[82]
27	TiO_2	3.5	Fibrinogen	SPR	NP	3.7×10^{6}	7.6×10^{-4}	2.1×10^{-10}	[78]
28	TiO_2	3.5	HSA	SPR	NP	9.5×10^{3}	9.8×10^{-4}	1.0×10^{-7}	[78]
29	Al_2O_3	13.5	Fibrinogen	SPR	NP	4.3×10^{4}	7.2×10^{-4}	1.7×10^{-8}	[78]
30	Al_2O_3	13.6	HSA	SPR	NP	1.0×10^{3}	1.0×10^{-3}	9.8×10^{-7}	[78]
31	CeO_2	13	Fibrinogen	SPR	NP	5.1×10^{6}	2.2×10^{-4}	4.2×10^{-11}	[78]

32	CeO_2	13	HSA	SPR	NP	1.8×10^{4}	6.8×10^{-4}	3.9×10^{-8}	[78]
33[‖]	Citrate gold NPs	5	αRep (G8)	SPR	Protein	1.6×10^{6}	2.9×10^{-3}	1.8×10^{-9}	[88]
34[‖]	Citrate gold NPs	5	αRep (F5)	SPR	Protein	1.5×10^{6}	5.7×10^{-3}	3.8×10^{-9}	[88]
35[‖]	Citrate gold NPs	5	αRep (A12)	SPR	Protein	1.6×10^{6}	5.1×10^{-3}	3.2×10^{-9}	[88]
36[‖]	Citrate gold NPs	5	αRep (D7)	SPR	Protein	2.1×10^{6}	5.0×10^{-3}	2.4×10^{-9}	[88]
37[‖]	Citrate gold NPs	5	αRep (D5)	SPR	Protein	1.9×10^{6}	3.3×10^{-3}	1.7×10^{-9}	[88]
38	Gold NPs	20	IgG	SPR	Protein	-	2.6×10^{-3}	-	[89]
39	Gold NPs	20	Transferrin	SPR	Protein	-	3.6×10^{-3}	-	[89]
40	Gold NPs	20	HSA	SPR	Protein	-	5.5×10^{-3}	-	[89]
41	Silver NPs	30	IgG	SPR	Protein	-	1.4×10^{-3}	-	[89]

42	Silver NPs	30	Transferrin	SPR	Protein	-	1.5×10^{-3}	-	[89]
43	Silver NPs	30	HSA	SPR	Protein	-	1.6×10^{-3}	-	[89]
44	Polymer-coated FePt	5.6	HSA	Time-resolved fluoresc. quenching	-	2.4×10^{3}	9.0×10^{-3}	3.8×10^{-6}	[84]
45	NIPAM/BAM (85:15)	200	HSA	Size exclusion chromatography	-	-	4.0×10^{-4}	-	[6]
46	Polystyrene	100	Lysozyme	Differential dynamic microscopy	-	5.2×10^{4}	5.2×10^{-2}	1.0×10^{-6}	[119]
47#	Latex particles	80	B1 binding domain of *Streptococcal* protein G	Stopped-flow spectroscopy	-	-	3.8×10^{-1}	-	[86]
48	Lipid nanoparticles	90	Liver fatty acid binding proteins	Time-resolved fluoresc. quenching	-	-	7.1×10^{-1}	-	61]
49	Lipid nanoparticles	90	Liver fatty acid binding proteins	Time-resolved fluoresc. quenching	-	-	1.4×10^{-2}	-	[61]
50†	Gold coated with poly(acrylic acid)	7	Fibrinogen	Manual-mixing technique	-	4.4×10^{4}	2.7×10^{-4}	6.1×10^{-9}	[54]
51†	Gold coated with poly(acrylic acid)	10	Fibrinogen	Manual-mixing technique	-	2.5×10^{4}	1.1×10^{-4}	4.2×10^{-9}	[54]

52†	Gold coated with poly(acrylic acid)	15	Fibrinogen	Manual-mixing technique	-	2.5×10^{4}	5.8×10^{-5}	2.3×10^{-9}	[54]
53†	Gold coated with poly(acrylic acid)	17	Fibrinogen	Manual-mixing technique	-	1.9×10^{4}	3.3×10^{-5}	1.7×10^{-9}	[54]
54†	Gold coated with poly(acrylic acid)	19	Fibrinogen	Manual-mixing technique	-	1.4×10^{4}	2.2×10^{-5}	1.6×10^{-9}	[54]
55†	Gold coated with poly(acrylic acid)	22	Fibrinogen	Manual-mixing technique	-	1.1×10^{4}	1.7×10^{-5}	1.5×10^{-9}	[54]
56&	Sulfonated polystyrene NPs	100	Transferrin / plasma 5%	Fluoresc. correlation spectroscopy	-	-	6.4×10^{-4}	-	[77]
57&	Sulfonated polystyrene NPs	100	Transferrin / plasma 10%	Fluoresc. correlation spectroscopy	-	-	1.4×10^{-3}	-	[77]
58&	Carboxylated polystyrene NPs	100	Transferrin / plasma 5%	Fluoresc. correlation spectroscopy	-	-	1.7×10^{-2}	-	[77]

‖ Experiments in Entries 33 to 37 involved quantifying the interactions of artificial α-helical repeat proteins, which were generated in a phage display system, with citrate-stabilized gold NPs.

In Entry 47, the stopped-flow data were analyzed using a model that considers four rate constants: adsorption rate (18 $M^{-1}s^{-1}$), desorption rate (8.2 s^{-1}), unfolding rate (k_u = 2.24 s^{-1}), and refolding rate (0.38 s^{-1}). Only k_{off} was entered into the Table, and it was assigned the value 0.38 s^{-1}.

† Entries 50 to 55 utilized manual-mixing in combination with NP centrifugation and fluorescence readings of the supernatant to determine k_{off} and K_D values. The k_{on} was subsequently calculated as $k_{on} = k_{off}/K_D$.

& Experiments in Entries 56 to 58 involved evaluating the dissociation rate constant of pre-adsorbed transferrin coronas on NP surfaces through competitive displacement with plasma at concentrations of 5 or 10%.

Table S2. Kinetic parameters of protein interactions with ultrasmall NPs.

Entry	Nanoparticle[&]	Size (nm)[$]	Interaction with	Technique[#]	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})[‡]	K_D (M)	NaCl (M)*	Ref.
1	AuMBA	2	Thrombin	SPR	2.0×10^{6}	6.2×10^{-2}	3.1×10^{-8}	0.15	[103]
2	AuGSH	2	Thrombin	SPR	2.8×10^{4}	5.0×10^{-1}	1.9×10^{-5}	0.15	[103]
3	AuMBA	2	Thrombin	Stopped-flow	6.0×10^{7}	5.0×10^{-2} 2.0×10^{-1} 1.8×10^{0}	-	0.15	[103]
4	AuGSH	2	Thrombin	Stopped-flow	-	1.4×10^{-1} 6.4×10^{-1} 7.9×10^{0}	-	0.15	[103]
5	AuMBA	2	CrataBL	SPR	4.4×10^{5} 2.9×10^{5}	1.5×10^{-2} 3.8×10^{-1}	3.5×10^{-8} 1.7×10^{-6}	0.15	[73]
6	AuGSH	2	CrataBL	SPR	1.7×10^{4}	3.8×10^{-1}	2.7×10^{-5}	0.15	[73]
7	AuMBA	2	CrataBL	SPR	2.2×10^{5}	6.4×10^{-1}	2.9×10^{-6}	0.4	[73]
8	AuGSH	2	CrataBL	SPR	8.1×10^{2}	1.8×10^{-1}	2.2×10^{-4}	0.4	[73]
9†	AuMBA	2	Ubiquitin	Stopped-flow	5.1×10^{7}	2.0×10^{1} 2.8×10^{0} 5.4×10^{-1} 7.7×10^{-2}	1.0×10^{-7}	0.005	[96]

10†	AuMBA	2	Ubiquitin	Stopped-flow	4.3×10^{7}	2.0×10^{1} 2.7×10^{0} 5.0×10^{-1} 7.0×10^{-2}	-	0.02	[96]
11†	AuMBA	2	Ubiquitin	Stopped-flow	2.7×10^{7}	2.0×10^{1} 2.5×10^{0} 4.5×10^{-1} 6.6×10^{-2}	-	0.05	[96]
12	AuMBA	2	Ubiquitin	Stopped-flow	-	2.6×10^{1} 3.1×10^{0} 5.5×10^{-1} 7.3×10^{-2}	-	0.15	[96]
13	AuMBA	2	Ubiquitin	Stopped-flow	-	2.9×10^{1} 3.4×10^{0} 5.6×10^{-1} 7.2×10^{-2}	-	0.3	[96]
14	AuECYN	2	Thrombin	SPR	1.6×10^{6}	2.1×10^{-1}	1.3×10^{-7}	0.15	[104]
15	AuMBA	2	FXIIa	SPR	5.0×10^{5}	1.0×10^{-1}	2.0×10^{-7}	0.15	[106]
16	AuMBA	2	Cytochrome c	SPR	8.6×10^{5}	6.0×10^{-1}	7.2×10^{-7}	0.15	[99]
17‖	Gold NPs decorated with tweezer motifs	2	Survivin	SPR	1.8×10^{5} 1.7×10^{2}	1.3×10^{-1} 1.2×10^{-4}	7.0×10^{-7} 7.0×10^{-7}	0.15	[110]
18‖	Gold NPs decorated with tweezer motifs	2	Survivin	SPR	5.1×10^{2}	6.1×10^{-4}	1.2×10^{-6}	0.15	[110]
19‖	Gold NPs (control)	2	Survivin	SPR	6.3×10^{2}	5.0×10^{-3}	8.0×10^{-6}	0.15	[110]
20	CdTe@TGA	2.6	HSA	SPR	6.9×10^{6}	7.6×10^{-2}	1.1×10^{-8}	0.15	[80]

21	CdTe@MPA	3.0	HSA	SPR	4.4×10^{6}	6.9×10^{-2}	1.6×10^{-8}	0.15	[80]

& AuMBA, AuGSH, and AuECYN refer to NPs coated with *p*-mercaptobenzoic acid, glutathione, and the peptide ECYN, respectively.
$ The size of an ultrasmall NP can be reported in terms of its core diameter or total hydrodynamic diameter. The former can be typically assessed by electron microscopy, while the latter can be assessed by techniques such as dynamic light scattering (DLS), differential centrifugal sedimentation, and DOSY-1H NMR. Due to the variation in measurement methods and the reporting of size, most sizes listed in the table were approximated as 2 nm.
In all SPR experiments, the protein was surface immobilized. For all stopped-flow analyses, fitting of the stopped-flow traces resulted in multiple k_{off} values, preventing the calculation of a single K_D. Additionally, with the exception of Entry 3, all stopped-flow analyses revealed a complex mechanism of NP-protein association involving intermediate reaction steps.
† In Entry 9, the K_D was determined by fluorescence quenching titration; in Entries 9-11, the k_{on} was estimated from $k_{on} = k_2/K_1$ in the stopped-flow analysis.
‖ In Entries 17 to 19, K_D and k_{off} values were estimated from Figure 8 within ref. [110], and k_{on} values were calculated as $k_{on} = k_{off}/K_D$.
‡ Stopped-flow analysis of usNPs resulted in multiple k_{off} values, but only the k_{off} value with the larger corresponding amplitude is plotted in Figure 4 within the main text.
***** Kinetic measurements of usNP interactions with CrataBL and ubiquitin were performed at various salt concentrations, but only data for 150 and 5 mM NaCl (for CrataBL and ubiquitin, respectively) are plotted in Figure 4 within the main text.

Table S3. Kinetic parameters of serum and plasma interactions with conventional NPs.

Entry	Nanoparticle	Size (nm)	Interaction with	Technique†	k_{off} (s^{-1})	K_D (M)	Incubation time (min)*	Ref.
1	NIPAM/BAM (85:15)	70	Plasma	SPR	3.7×10^{-4} 6.1×10^{-5}	-	30	[6]
2	NIPAM/BAM (50:50)	70	Plasma	SPR	2.0×10^{-3} 3.4×10^{-5}	-	30	[6]
3	Gold	50	Serum	Biolayer interferometry	7.4×10^{-3} 1.7×10^{-4}	8.83×10^{-6} 3.43×10^{-3}	10	[69]
4	Gold	50	Serum	Biolayer interferometry	7.4×10^{-3} 6.2×10^{-5}	2.73×10^{-6} 7.76×10^{-9}	20	[69]
5	Gold	50	Serum	Biolayer interferometry	1.8×10^{-3} $< 1.0 \times 10^{-7}$	2.35×10^{-7} $< 1.0 \times 10^{-12}$	40	[69]
6	Gold	50	Serum	Biolayer interferometry	7.61×10^{-4} $< 1.0 \times 10^{-7}$	1.91×10^{-7} $< 1.0 \times 10^{-12}$	60	[69]
7	Gold	50	Serum	Biolayer interferometry	3.4×10^{-4} $< 1.0 \times 10^{-7}$	1.63×10^{-7} $< 1.0 \times 10^{-12}$	120	[69]
8	Liposomes	100	Serum	Biolayer interferometry	2.67×10^{-2} 5.35×10^{-4}	2.75×10^{-5} 3.54×10^{-6}	10	[69]
9	Liposomes	100	Serum	Biolayer interferometry	1.78×10^{-2} 3.10×10^{-4}	2.25×10^{-5} 2.36×10^{-6}	20	[69]

10	Liposomes	100	Serum	Biolayer interferometry	1.5×10^{-2} 3.6×10^{-4}	5.58×10^{-5} 4.05×10^{-6}	40	[69]
11	Liposomes	100	Serum	Biolayer interferometry	9.1×10^{-3} 2.1×10^{-4}	3.28×10^{-5} 2.38×10^{-6}	60	[69]
12	Liposomes	100	Serum	Biolayer interferometry	6.0×10^{-3} 1.4×10^{-5}	3.0×10^{-6} 1.6×10^{-6}	120	[69]
13[#]	PS NPs with labeled serum corona	100	Serum	Differential dynamic microscopy	2.4×10^{-4}	-	-	[119]

† Both SPR and biolayer interferometry experiments were conducted with immobilized NPs. Additionally, in both experiments, the obtained data were best fit assuming two modes of interactions representing weakly and strongly binding proteins.

***** Values of the dissociation rate constants were determined after the indicated incubation time between NPs and serum/plasma.

In Entry 13, the polystyrene NPs were pre-coated with a labeled serum protein corona. The pre-coated NPs were injected into zebrafish larvae, and the dissociation of the labeled corona was monitored by differential dynamic microscopy. k_{off} was estimated as $1/\tau_{desorption}$ from the reported value of $\tau_{desorption}$.