



## Supporting Information

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The Impact of Protein Corona Formation on the Macrophage Cellular Uptake and Biodistribution of Spherical Nucleic Acids

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## Supporting Information

**The Impact of Protein Corona Formation on the Macrophage Cellular Uptake and Biodistribution of Spherical Nucleic Acids***Alyssa B. Chinen, Chenxia M. Guan, Caroline H. Ko, and Chad A. Mirkin\****General Information****Table S1.** DNA Sequences Used

Name	Sequence (5'-3')
G-rich	(GGT) <sub>4</sub> TGT(GGT) <sub>4</sub> T <sub>13</sub> -SH
Poly-T	T <sub>40</sub> -SH

**Methods*****Quantification of Au Content in Tissues by ICP-MS***

Tissue and blood samples collected from mice were prepared for determination of Au content by ICP-MS by first weighing the tissue. Samples were dried in an oven at 65°C overnight. Samples were weighed again and digested in 3% HCl in HNO<sub>3</sub> using a Milestone EthosEZ Microwave Digestion System. Samples were diluted in ICP wash solution (2% HNO<sub>3</sub> and 2% HCl in water) and analyzed using a ThermoFisher X Series II ICP-MS and 5% In, 5% Bi, and 5% Ho as internal standards.

***Pharmacokinetic Modeling***

To calculate pharmacokinetic parameters, the data were fit to a one-compartment model using non-linear regression analysis in GraphPad Prism. This model assumes that NPs are transported between the central and peripheral compartments with first-order kinetics and that NPs are eliminated from the central compartment with first-order kinetics. The data were fit to equation S1, where Cp is the concentration of the particles in blood; A and B are hybrid coefficients;  $\alpha$  and  $\beta$  are rate constants for the distribution and elimination processes, respectively; and t is the time component.

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (\text{Eqn. S1})$$

Pharmacokinetic parameters were estimated using standard calculations. An initial data point at t=0 was included representing 100% of the injected dose in the blood.

***Circular Dichroism***

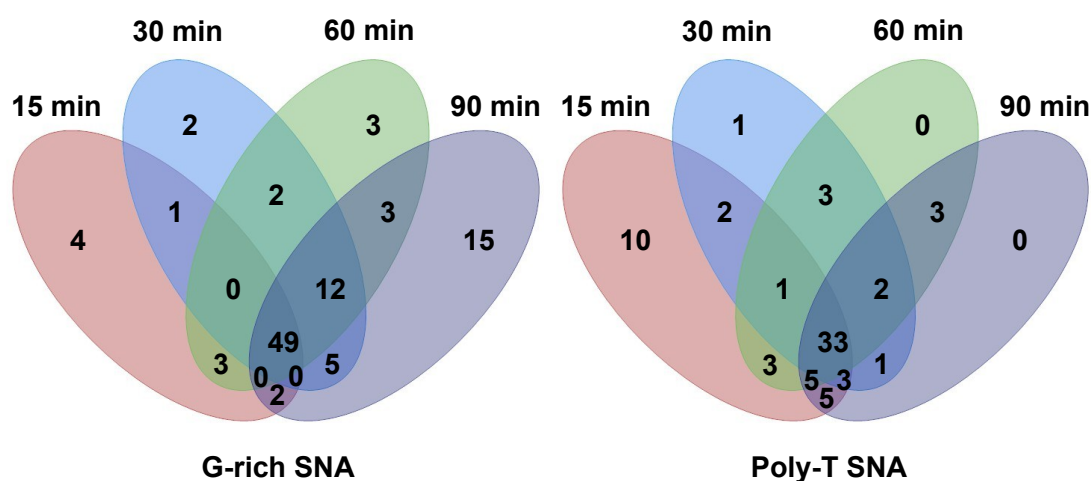
Free DNA and SNAs were prepared in 1X PBS at a concentration of 7.5 $\mu$ M and 50nM, respectively to normalize the measurement by oligonucleotide concentration. Samples were measured using a JASCO J-815 CD Spectrometer. Scans were taken from 230-300 nm with a 2nm bandwidth and a scanning speed of 100nm/minute. The data integration

time was set to 2 seconds and measurements were made every 0.025nm. The spectra shown are the results of averaging 20 runs.

**Results**

**Table S2.** Characterization of SNA loading

	Diameter (nm)	Zeta Potential (mV)	DNA Strands/AuNP
G-rich SNA	54±8	-21.1±0.6	134±17
Poly-T SNA	56±3	-23.2±0.8	132±18



**Figure S1.** Four-unit venn diagram depicting the number of unique proteins that bind to SNAs over time for (A) G-rich SNAs and (B) poly-T SNAs over time. The plot suggests that more types of proteins bind to G-rich SNAs, and that a protein exchange is occurring on the nanoparticle over time. This trend is not followed by poly-T SNAs, which has fewer proteins binding, and very little evidence of an exchange occurring on the nanoparticle.

**Table S3.** List of proteins bound to G-rich SNAs after a 15-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P01008	Antithrombin-III	62.28	27	27	543	52.6
P02768	Serum albumin	70.94	37	37	303	69.3

P04114	Apolipoprotein B-100	36.64	99	99	231	515.3
P01024	Complement C3	50.63	57	57	218	187.0
P00734	Prothrombin	45.02	23	23	163	70.0
P02647	Apolipoprotein A-I	60.30	20	20	105	30.8
P04264	Keratin, type II cytoskeletal 1	45.19	18	21	88	66.0
P08603	Complement factor H	40.78	28	32	84	139.0
P04004	Vitronectin	31.59	11	12	63	54.3
P01009	Alpha-1-antitrypsin	47.13	16	16	61	46.7
P13645	Keratin, type I cytoskeletal 10	40.24	15	16	60	58.8
P35527	Keratin, type I cytoskeletal 9	56.02	18	18	54	62.0
P0COL5	Complement C4-B	22.42	22	22	46	192.6
P01042	Kininogen-1	21.12	12	12	45	71.9
P01871	Ig mu chain C region	30.31	3	9	45	49.3
P01023	Alpha-2-macroglobulin	25.85	22	22	44	163.2
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	23.44	13	13	43	103.3
P02652	Apolipoprotein A-II	57.00	5	5	40	11.2
P10909	Clusterin	28.73	11	11	37	52.5
P27169	Serum paraoxonase/arylesterase 1	45.35	9	9	36	39.7
P02787	Serotransferrin	34.81	16	16	35	77.0
P35908	Keratin, type II cytoskeletal 2 epidermal	33.96	12	14	34	65.4
P01834	Ig kappa chain C region	80.19	6	6	32	11.6
P02765	Alpha-2-HS-glycoprotein	40.87	7	7	31	39.3
P02655	Apolipoprotein C-II	52.48	5	5	31	11.3
Q9BXR6	Complement factor H-related protein 5	33.39	10	11	30	64.4
P0CG05	Ig lambda-2 chain C regions	65.09	4	4	30	11.3
P04003	C4b-binding protein alpha chain	32.33	12	12	27	67.0
P02649	Apolipoprotein E	37.22	8	8	20	36.1
P06727	Apolipoprotein A-IV	25.25	8	8	20	45.4
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	17.11	8	8	17	105.2
P02766	Transthyretin	59.86	7	7	16	15.9
P04196	Histidine-rich glycoprotein	13.52	6	6	16	59.5
P00739	Haptoglobin-related protein	41.95	6	8	16	39.0
P01876	Ig alpha-1 chain C region	37.96	7	7	15	37.6
P01857	Ig gamma-1 chain C region	27.27	3	6	15	36.1
P05546	Heparin cofactor 2	17.84	6	6	14	57.0
P02760	Protein AMBP	25.00	6	6	14	39.0
G5E9F8	Protein S (Alpha), isoform CRA_b	21.47	7	7	13	60.3
P08697	Alpha-2-antiplasmin	25.05	6	6	13	54.5
K7ERI9	Truncated apolipoprotein C-I (Fragment)	31.17	4	4	13	8.6
D6RBJ7	Vitamin D-binding protein	18.39	3	3	12	38.8
J3QLC9	Haptoglobin (Fragment)	25.21	3	5	12	40.8
P07996	Thrombospondin-1	8.21	6	6	11	129.3

F5H7E1	Uncharacterized protein	10.85	5	5	11	72.1
O95445	Apolipoprotein M	32.98	4	4	11	21.2
P08779	Keratin, type I cytoskeletal 16	12.68	4	5	10	51.2
P12259	Coagulation factor V	2.65	4	4	10	251.5
B4E1H2	Plasma protease C1 inhibitor	12.95	4	4	9	49.7
P02749	Beta-2-glycoprotein 1	22.32	4	4	8	38.3
P01019	Angiotensinogen	11.34	3	3	8	53.1
P02790	Hemopexin	13.85	4	4	7	51.6
P18428	Lipopolysaccharide-binding protein	9.77	3	3	7	53.3
P02656	Apolipoprotein C-III	46.46	3	3	7	10.8
O75636	Ficolin-3	21.07	3	3	6	32.9
P09871	Complement C1s subcomponent	6.69	3	3	6	76.6
Q16610	Extracellular matrix protein 1	12.59	3	3	6	60.6
O43866	CD5 antigen-like	17.00	3	3	6	38.1
F5GXS5	Apolipoprotein F	26.95	3	3	4	33.4

**Table S4.** List of proteins bound to G-rich SNAs after a 30-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P01008	Antithrombin-III	66.16	31	31	647	52.6
P04114	Apolipoprotein B-100	41.99	126	126	352	515.3
P01024	Complement C3	54.30	64	64	255	187.0
P02647	Apolipoprotein A-I	71.91	26	26	251	30.8
P00734	Prothrombin	48.07	25	25	209	70.0
P02768	Serum albumin	73.56	40	40	175	69.3
P13645	Keratin, type I cytoskeletal 10	53.60	25	27	105	58.8
P04264	Keratin, type II cytoskeletal 1	48.45	20	23	101	66.0
P08603	Complement factor H	41.27	33	36	95	139.0
K7ER74	Protein APOC4-APOC2	37.08	6	8	88	20.0
P35908	Keratin, type II cytoskeletal 2 epidermal	60.09	22	26	76	65.4
P04004	Vitronectin	22.38	8	9	73	54.3
P10909	Clusterin	33.18	16	16	65	52.5
P01871	Ig mu chain C region	36.73	12	12	62	49.3
F5GXS0	Complement C4-B	21.08	3	23	62	187.6
P01009	Alpha-1-antitrypsin	50.24	18	18	57	46.7
P01042	Kininogen-1	25.62	14	14	57	71.9
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	25.91	15	15	56	103.3
P02652	Apolipoprotein A-II	57.00	5	5	56	11.2
P35527	Keratin, type I cytoskeletal 9	57.14	20	21	54	62.0

P01023	Alpha-2-macroglobulin	27.48	24	24	52	163.2
P06727	Apolipoprotein A-IV	55.81	21	21	50	45.4
P02649	Apolipoprotein E	54.89	14	14	49	36.1
P02765	Alpha-2-HS-glycoprotein	42.78	8	8	45	39.3
P01834	Ig kappa chain C region	80.19	6	6	45	11.6
P27169	Serum paraoxonase/arylesterase I	47.89	10	10	38	39.7
P04003	C4b-binding protein alpha chain	32.83	13	13	34	67.0
Q9BXR6	Complement factor H-related protein 5	39.72	11	12	31	64.4
P02787	Serotransferrin	32.81	15	15	30	77.0
P05546	Heparin cofactor 2	28.66	13	13	29	57.0
K7ER19	Truncated apolipoprotein C-I (Fragment)	31.17	5	5	28	8.6
O95445	Apolipoprotein M	52.13	7	7	24	21.2
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	19.47	10	10	23	105.2
P07996	Thrombospondin-1	14.96	10	10	22	129.3
P04196	Histidine-rich glycoprotein	20.19	8	8	22	59.5
P08697	Alpha-2-antiplasmin	32.18	9	9	21	54.5
P02760	Protein AMBP	34.94	8	8	21	39.0
P02766	Transthyretin	68.03	7	7	21	15.9
P01876	Ig alpha-1 chain C region	37.96	3	7	21	37.6
P07225	Vitamin K-dependent protein S	16.12	7	7	18	75.1
P02774	Vitamin D-binding protein	24.26	6	6	18	52.9
Q03591	Complement factor H-related protein 1	31.82	3	7	18	37.6
P00739	Haptoglobin-related protein	34.77	5	8	17	39.0
P02656	Apolipoprotein C-III	48.48	4	4	17	10.8
P05090	Apolipoprotein D	25.93	4	4	17	21.3
F5H7E1	Uncharacterized protein	18.29	8	8	14	72.1
P02749	Beta-2-glycoprotein 1	33.91	7	7	14	38.3
F5GXS5	Apolipoprotein F	26.95	3	3	14	33.4
P01857	Ig gamma-1 chain C region	29.09	3	6	14	36.1
O14791	Apolipoprotein L1	18.34	4	4	13	43.9
P08519	Apolipoprotein(a)	19.24	4	4	13	501.0
P18428	Lipopolysaccharide-binding protein	16.84	6	6	12	53.3
P35542	Serum amyloid A-4 protein	26.92	3	3	12	14.7
D6R934	Complement C1q subcomponent subunit B	17.13	3	3	11	26.4
P02776	Platelet factor 4	26.73	3	3	11	10.8
P00736	Complement C1r subcomponent	11.35	5	5	10	80.1
P02533	Keratin, type I cytoskeletal 14	16.95	5	7	10	51.5
O75636	Ficolin-3	24.08	4	4	10	32.9
P00747	Plasminogen	12.59	5	5	9	90.5
O43866	CD5 antigen-like	21.04	4	4	9	38.1
P09871	Complement C1s subcomponent	10.17	4	4	8	76.6

P12259	Coagulation factor V	2.65	4	4	8	251.5
B4E1H2	Plasma protease C1 inhibitor	12.95	4	4	8	49.7
P02747	Complement C1q subcomponent subunit C	16.33	3	3	8	25.8
P04180	Phosphatidylcholine-sterol acyltransferase	17.73	4	4	7	49.5
P01019	Angiotensinogen	11.34	3	3	7	53.1
B7Z8Q5	Hyaluronan-binding protein 2 50 kDa heavy chain	15.71	3	3	7	31.7
P01031	Complement C5	2.92	3	3	6	188.2
F8W6P5	LVV-hemorphin-7 (Fragment)	53.33	3	3	6	9.7
Q9UGM5	Fetuin-B	19.11	3	3	5	42.0
P23142	Fibulin-1	7.54	3	3	4	77.2
P02748	Complement component C9	9.12	3	3	4	63.1

**Table S5.** List of proteins bound to G-rich SNAs after a 60-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P01008	Antithrombin-III	64.66	29	29	577	52.6
P04114	Apolipoprotein B-100	46.33	142	142	445	515.3
P01024	Complement C3	62.30	72	72	332	187.0
P02768	Serum albumin	74.55	42	42	311	69.3
P02647	Apolipoprotein A-I	73.41	30	30	277	30.8
P00734	Prothrombin	50.96	25	25	169	70.0
K7ER74	Protein APOC4-APOC2	39.89	7	8	115	20.0
P08603	Complement factor H	40.94	28	31	85	139.0
P13645	Keratin, type I cytoskeletal 10	49.66	21	22	82	58.8
P01009	Alpha-1-antitrypsin	48.33	18	18	80	46.7
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	33.12	18	18	75	103.3
P04264	Keratin, type II cytoskeletal 1	43.32	17	20	75	66.0
P04004	Vitronectin	33.68	9	11	72	54.3
P02652	Apolipoprotein A-II	72.00	7	7	68	11.2
P0C0L5	Complement C4-B	23.97	3	24	64	192.6
P10909	Clusterin	32.96	14	14	61	52.5
P01023	Alpha-2-macroglobulin	27.95	24	24	56	163.2
P01042	Kininogen-1	25.62	14	14	56	71.9
P02765	Alpha-2-HS-glycoprotein	44.69	9	9	53	39.3
P06727	Apolipoprotein A-IV	51.77	18	18	52	45.4
P01871	Ig mu chain C region	32.08	3	10	46	49.3
P02649	Apolipoprotein E	55.52	14	14	43	36.1
P05546	Heparin cofactor 2	53.31	18	18	41	57.0
P35527	Keratin, type I cytoskeletal 9	51.85	16	16	39	62.0
P35908	Keratin, type II cytoskeletal 2 epidermal	42.72	13	17	39	65.4

P01834	Ig kappa chain C region	80.19	6	6	38	11.6
P27169	Serum paraoxonase/arylesterase 1	45.35	9	9	36	39.7
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	25.78	13	13	35	105.2
K7ER19	Truncated apolipoprotein C-I (Fragment)	31.17	5	5	32	8.6
P04003	C4b-binding protein alpha chain	36.35	13	13	31	67.0
P08779	Keratin, type I cytoskeletal 16	39.75	8	14	31	51.2
P02787	Serotransferrin	30.23	14	14	30	77.0
F5H7E1	Uncharacterized protein	19.84	9	9	29	72.1
O95445	Apolipoprotein M	52.13	7	7	29	21.2
P02538	Keratin, type II cytoskeletal 6A	25.18	6	10	27	60.0
P02766	Transthyretin	68.71	8	8	26	15.9
P02533	Keratin, type I cytoskeletal 14	26.69	5	11	25	51.5
P08697	Alpha-2-antiplasmin	34.22	8	8	23	54.5
Q9BXR6	Complement factor H-related protein 5	25.48	7	8	23	64.4
P01857	Ig gamma-1 chain C region	33.94	3	7	23	36.1
P06396	Gelsolin	23.27	9	9	22	85.6
P07225	Vitamin K-dependent protein S	18.93	8	8	22	75.1
P02656	Apolipoprotein C-III	48.48	4	4	22	10.8
P02760	Protein AMBP	34.94	9	9	21	39.0
O14791	Apolipoprotein L1	27.39	6	6	21	43.9
P00739	Haptoglobin-related protein	41.95	6	8	19	39.0
P01876	Ig alpha-1 chain C region	38.81	3	8	18	37.6
P02749	Beta-2-glycoprotein 1	33.91	7	7	16	38.3
P18428	Lipopolysaccharide-binding protein	26.61	7	7	16	53.3
P04196	Histidine-rich glycoprotein	16.38	6	6	16	59.5
P02774	Vitamin D-binding protein	19.62	5	5	16	52.9
P08519	Apolipoprotein(a)	26.01	5	5	16	501.0
P00747	Plasminogen	20.49	8	8	15	90.5
Q04695	Keratin, type I cytoskeletal 17	14.81	3	7	15	48.1
P05090	Apolipoprotein D	23.28	4	4	14	21.3
F5GXS5	Apolipoprotein F	26.95	3	3	14	33.4
P01860	Ig gamma-3 chain C region	23.61	3	6	14	41.3
B4E1H2	Plasma protease C1 inhibitor	15.40	5	5	13	49.7
P35542	Serum amyloid A-4 protein	26.92	3	3	12	14.7
P55056	Apolipoprotein C-IV	33.86	3	4	12	14.5
P01019	Angiotensinogen	11.34	3	3	11	53.1
J3QLC9	Haptoglobin (Fragment)	19.45	3	5	11	40.8
P12259	Coagulation factor V	3.46	6	6	10	251.5
P07996	Thrombospondin-1	8.21	6	6	10	129.3
P04180	Phosphatidylcholine-sterol acyltransferase	19.32	5	5	10	49.5
P00736	Complement C1r subcomponent	11.35	5	5	10	80.1
P02748	Complement component C9	15.56	6	6	8	63.1
P09871	Complement C1s subcomponent	12.65	5	5	7	76.6



O43866	CD5 antigen-like	17.00	3	3	6	38.1
P02747	Complement C1q subcomponent subunit C	16.33	3	3	6	25.8
B7Z8Q5	Hyaluronan-binding protein 2 50 kDa heavy chain	15.71	3	3	5	31.7
Q9UGM5	Fetuin-B	18.59	3	3	5	42.0
Q96PD5	N-acetylmuramoyl-L-alanine amidase	11.46	3	3	4	62.2

**Table S6.** List of proteins bound to G-rich SNAs after a 90-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P01008	Antithrombin-III	65.09	30	30	670	52.6
P02647	Apolipoprotein A-I	78.28	29	29	480	30.8
P04114	Apolipoprotein B-100	43.79	146	146	440	515.3
P01024	Complement C3	62.78	81	81	338	187.0
P02768	Serum albumin	73.73	45	45	259	69.3
P00734	Prothrombin	50.96	26	26	205	70.0
K7ER74	Protein APOC4-APOC2	39.89	7	9	119	20.0
P08603	Complement factor H	45.74	36	39	118	139.0
P04004	Vitronectin	32.43	10	12	94	54.3
P02652	Apolipoprotein A-II	69.00	8	8	90	11.2
P10909	Clusterin	38.08	18	18	84	52.5
P01009	Alpha-1-antitrypsin	57.42	21	21	80	46.7
F5GXS0	Complement C4-B	24.68	29	29	79	187.6
P06727	Apolipoprotein A-IV	65.40	26	26	77	45.4
P01042	Kininogen-1	31.21	19	19	74	71.9
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	32.26	20	20	71	103.3
P13645	Keratin, type I cytoskeletal 10	45.03	20	22	70	58.8
P01871	Ig mu chain C region	38.50	14	14	70	49.3
P01023	Alpha-2-macroglobulin	29.10	27	27	67	163.2
P02649	Apolipoprotein E	58.99	17	17	66	36.1
P02787	Serotransferrin	46.99	27	27	62	77.0
P02765	Alpha-2-HS-glycoprotein	45.50	10	10	60	39.3
P04264	Keratin, type II cytoskeletal 1	44.57	22	25	56	66.0
K7ER19	Truncated apolipoprotein C-I (Fragment)	37.66	5	5	55	8.6
P01834	Ig kappa chain C region	80.19	6	6	45	11.6
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	28.56	17	17	43	105.2
P04003	C4b-binding protein alpha chain	32.83	13	13	43	67.0
P35527	Keratin, type I cytoskeletal 9	46.23	15	15	39	62.0
Q9BXR6	Complement factor H-related protein 5	39.72	13	14	39	64.4
P02760	Protein AMBP	40.63	11	11	39	39.0
P05546	Heparin cofactor 2	33.47	14	14	38	57.0

P27169	Serum paraoxonase/arylesterase I	45.35	9	9	35	39.7
P04196	Histidine-rich glycoprotein	24.00	11	11	33	59.5
P02656	Apolipoprotein C-III	55.56	6	6	32	10.8
P07225	Vitamin K-dependent protein S	29.44	15	15	29	75.1
P06396	Gelsolin	21.99	10	10	28	85.6
P05090	Apolipoprotein D	29.63	6	6	28	21.3
P00738	Haptoglobin	36.21	5	11	27	45.2
P35908	Keratin, type II cytoskeletal 2 epidermal	37.56	11	14	26	65.4
O95445	Apolipoprotein M	60.64	8	8	25	21.2
P07996	Thrombospondin-1	16.67	12	12	23	129.3
P02766	Transthyretin	53.06	7	7	23	15.9
Q03591	Complement factor H-related protein 1	38.79	5	9	23	37.6
P00739	Haptoglobin-related protein	40.80	5	11	23	39.0
P00736	Complement C1r subcomponent	19.72	10	10	22	80.1
P00747	Plasminogen	21.11	10	10	22	90.5
P01876	Ig alpha-1 chain C region	47.31	4	9	22	37.6
O14791	Apolipoprotein L1	41.21	8	8	21	43.9
F5H7E1	Uncharacterized protein	17.21	8	8	21	72.1
P01857	Ig gamma-1 chain C region	41.82	4	8	21	36.1
P55056	Apolipoprotein C-IV	33.86	3	5	21	14.5
B4E1H2	Plasma protease C1 inhibitor	24.11	10	10	20	49.7
P08697	Alpha-2-antiplasmin	31.57	9	9	20	54.5
P02749	Beta-2-glycoprotein 1	37.97	8	8	20	38.3
P02774	Vitamin D-binding protein	24.26	6	6	20	52.9
P08519	Apolipoprotein(a)	36.59	8	8	18	501.0
P01031	Complement C5	6.92	8	8	15	188.2
O43866	CD5 antigen-like	29.39	7	7	14	38.1
P09871	Complement C1s subcomponent	21.22	8	8	13	76.6
D6R934	Complement C1q subcomponent subunit B	17.13	3	3	13	26.4
P02790	Hemopexin	24.68	6	6	12	51.6
P02748	Complement component C9	12.70	5	5	12	63.1
P02776	Platelet factor 4	26.73	3	3	12	10.8
P35542	Serum amyloid A-4 protein	26.92	3	3	12	14.7
F5GXS5	Apolipoprotein F	26.95	3	3	12	33.4
P0DJI8	Serum amyloid A-1 protein	66.39	6	6	11	13.5
P12259	Coagulation factor V	2.65	5	5	11	251.5
P19652	Alpha-1-acid glycoprotein 2	21.89	3	4	11	23.6
P04180	Phosphatidylcholine-sterol acyltransferase	22.50	5	5	10	49.5
P48740	Mannan-binding lectin serine protease 1	9.44	5	5	10	79.2
Q96PD5	N-acetylmuramoyl-L-alanine amidase	13.72	4	4	10	62.2
P01019	Angiotensinogen	17.32	5	5	9	53.1
P68871	Hemoglobin subunit beta	52.38	5	5	9	16.0
D6REX5	Selenoprotein P (Fragment)	17.10	4	4	9	35.1
F8W7G7	Ugl-Y3	3.62	5	5	8	243.1

Q14520	Hyaluronan-binding protein 2	9.64	4	4	8	62.6
H7C5R1	Ceruloplasmin (Fragment)	8.45	4	4	8	97.7
P02747	Complement C1q subcomponent subunit C	16.33	3	3	8	25.8
Q16610	Extracellular matrix protein 1	10.00	4	4	7	60.6
P03952	Plasma kallikrein	9.56	4	4	7	71.3
G3XAM2	Complement factor I light chain	8.33	3	3	7	65.0
D6RD17	Immunoglobulin J chain (Fragment)	28.66	4	4	6	18.0
B1AHL4	Fibulin-1	11.98	4	4	6	65.4
P18428	Lipopolysaccharide-binding protein	9.77	3	3	6	53.3
P04217	Alpha-1B-glycoprotein	10.30	3	3	4	54.2
E7EUT5	Glyceraldehyde-3-phosphate dehydrogenase	16.54	3	3	4	27.9

**Table S7.** List of proteins bound to poly-T SNAs after a 15-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P02768	Serum albumin	74.88	43	43	294	69.3
P04264	Keratin, type II cytoskeletal 1	56.52	31	35	288	66.0
P04114	Apolipoprotein B-100	34.30	98	98	241	515.3
P35527	Keratin, type I cytoskeletal 9	66.29	33	34	212	62.0
P01024	Complement C3	48.71	52	52	196	187.0
P13645	Keratin, type I cytoskeletal 10	59.42	29	32	174	58.8
P01008	Antithrombin-III	40.95	15	15	173	52.6
P02647	Apolipoprotein A-I	71.91	28	28	150	30.8
P08603	Complement factor H	49.63	40	43	127	139.0
P35908	Keratin, type II cytoskeletal 2 epidermal	59.00	21	29	78	65.4
P02655	Apolipoprotein C-II	52.48	5	5	66	11.3
P01871	Ig mu chain C region	33.85	11	11	57	49.3
P02652	Apolipoprotein A-II	67.00	6	6	53	11.2
P01009	Alpha-1-antitrypsin	44.74	15	15	50	46.7
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	27.63	13	13	46	103.3
P01023	Alpha-2-macroglobulin	22.93	21	21	45	163.2
P08779	Keratin, type I cytoskeletal 16	42.49	7	16	45	51.2
P01834	Ig kappa chain C region	80.19	6	6	44	11.6
P02533	Keratin, type I cytoskeletal 14	40.47	6	15	42	51.5
P02765	Alpha-2-HS-glycoprotein	44.69	9	9	41	39.3
P02787	Serotransferrin	41.40	20	20	40	77.0
P02649	Apolipoprotein E	53.63	15	15	38	36.1
P06727	Apolipoprotein A-IV	45.71	15	15	37	45.4
P10909	Clusterin	30.96	12	12	37	52.5
P04004	Vitronectin	20.29	7	7	37	54.3
P00734	Prothrombin	37.30	15	15	36	70.0

P13647	Keratin, type II cytoskeletal 5	30.34	8	15	35	62.3
P0C0L5	Complement C4-B	15.19	14	14	32	192.6
P01042	Kininogen-1	21.27	12	12	32	71.9
P04259	Keratin, type II cytoskeletal 6B	22.34	3	12	32	60.0
P01857	Ig gamma-1 chain C region	37.58	5	8	23	36.1
K7ER19	Truncated apolipoprotein C-I (Fragment)	31.17	4	4	21	8.6
Q08380	Galectin-3-binding protein	17.78	6	6	17	65.3
Q03591	Complement factor H-related protein 1	41.52	4	7	17	37.6
P01876	Ig alpha-1 chain C region	47.31	4	9	17	37.6
P04003	C4b-binding protein alpha chain	20.60	8	8	16	67.0
P00739	Haptoglobin-related protein	45.40	6	9	16	39.0
P02766	Transferrin	59.18	6	6	16	15.9
O14791	Apolipoprotein L1	25.38	5	5	16	43.9
P27169	Serum paraoxonase/arylesterase 1	23.94	5	5	16	39.7
J3QLC9	Haptoglobin (Fragment)	31.23	4	7	15	40.8
Q5T749	Keratinocyte proline-rich protein	22.11	6	6	12	64.1
O95445	Apolipoprotein M	39.89	5	5	12	21.2
P02774	Vitamin D-binding protein	12.45	3	3	12	52.9
D6R934	Complement C1q subcomponent subunit B	21.12	3	3	12	26.4
P08519	Apolipoprotein(a)	18.84	3	3	11	501.0
P14923	Junction plakoglobin	8.72	4	4	10	81.7
P02656	Apolipoprotein C-III	46.46	3	3	10	10.8
P07225	Vitamin K-dependent protein S	12.28	5	5	9	75.1
F5H7E1	Uncharacterized protein	8.37	4	4	9	72.1
P35542	Serum amyloid A-4 protein	24.62	3	3	9	14.7
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	13.48	6	6	8	105.2
P09871	Complement C1s subcomponent	10.47	4	4	8	76.6
P81605	Dermcidin	22.73	3	3	8	11.3
P02760	Protein AMBP	16.76	4	4	7	39.0
O43866	CD5 antigen-like	20.17	4	4	7	38.1
P05090	Apolipoprotein D	20.11	3	3	7	21.3
P04196	Histidine-rich glycoprotein	8.00	3	3	6	59.5
P08697	Alpha-2-antiplasmin	14.26	3	3	4	54.5
P02749	Beta-2-glycoprotein 1	15.36	3	3	4	38.3
P05546	Heparin cofactor 2	10.22	3	3	3	57.0
P04180	Phosphatidylcholine-sterol acyltransferase	12.05	3	3	3	49.5

**Table S8.** List of proteins bound to poly-T SNAs after a 30-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P02768	Serum albumin	74.22	44	44	338	69.3
P02647	Apolipoprotein A-I	80.15	29	29	140	30.8

P01008	Antithrombin-III	51.29	17	17	112	52.6
P04114	Apolipoprotein B-100	20.03	51	51	111	515.3
P08603	Complement factor H	42.65	33	36	95	139.0
P01024	Complement C3	34.46	34	34	89	187.0
P02787	Serotransferrin	45.99	24	24	60	77.0
P13645	Keratin, type I cytoskeletal 10	39.55	16	17	57	58.8
P04264	Keratin, type II cytoskeletal 1	44.41	19	21	53	66.0
P01009	Alpha-1-antitrypsin	39.00	14	14	45	46.7
P02652	Apolipoprotein A-II	59.00	6	6	39	11.2
P35527	Keratin, type I cytoskeletal 9	48.64	14	14	35	62.0
P01023	Alpha-2-macroglobulin	20.90	18	18	34	163.2
P02649	Apolipoprotein E	43.85	12	12	33	36.1
P02655	Apolipoprotein C-II	52.48	5	5	32	11.3
P35908	Keratin, type II cytoskeletal 2 epidermal	43.35	13	15	31	65.4
P06727	Apolipoprotein A-IV	43.69	13	13	31	45.4
P10909	Clusterin	28.73	10	10	31	52.5
P01834	Ig kappa chain C region	80.19	6	6	26	11.6
P00734	Prothrombin	29.74	12	12	25	70.0
P0CG05	Ig lambda-2 chain C regions	65.09	4	4	24	11.3
P04004	Vitronectin	14.23	5	5	22	54.3
J3QLC9	Haptoglobin (Fragment)	34.79	5	8	22	40.8
F5GXS0	Complement C4-B	11.19	9	9	20	187.6
P01042	Kininogen-1	16.61	8	8	20	71.9
P02765	Alpha-2-HS-glycoprotein	40.87	7	7	20	39.3
F5GXQ1	35 kDa inter-alpha-trypsin inhibitor heavy chain H4	14.29	4	4	20	62.1
K7ER19	Truncated apolipoprotein C-I (Fragment)	31.17	5	5	17	8.6
P02766	Transthyretin	68.71	7	7	16	15.9
P27169	Serum paraoxonase/arylesterase 1	25.63	5	5	16	39.7
P02774	Vitamin D-binding protein	19.62	5	5	14	52.9
O14791	Apolipoprotein L1	19.35	4	4	14	43.9
Q08380	Galectin-3-binding protein	17.09	6	6	13	65.3
P00739	Haptoglobin-related protein	28.45	3	6	13	39.0
Q03591	Complement factor H-related protein 1	33.64	3	6	13	37.6
P02656	Apolipoprotein C-III	46.46	3	3	12	10.8
P08519	Apolipoprotein(a)	18.84	3	3	10	501.0
P01876	Ig alpha-1 chain C region	21.81	3	5	10	37.6
P04003	C4b-binding protein alpha chain	10.22	4	4	9	67.0
O95445	Apolipoprotein M	22.34	3	3	9	21.2
P08697	Alpha-2-antiplasmin	13.85	3	3	8	54.5
B4E1H2	Plasma protease C1 inhibitor	11.16	3	3	8	49.7
P01857	Ig gamma-1 chain C region	14.85	3	3	7	36.1
P02790	Hemopexin	19.91	5	5	6	51.6
P07225	Vitamin K-dependent protein S	9.47	3	3	6	75.1
D6RD17	Immunoglobulin J chain (Fragment)	23.57	3	3	6	18.0

**Table S9.** List of proteins bound to poly-T SNAs after a 60-min incubation in human serum

Accession	Description	Coverage	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P02768	Serum albumin	71.26	39	39	276	69.3
P02647	Apolipoprotein A-I	79.40	34	34	256	30.8
P04114	Apolipoprotein B-100	20.40	50	50	124	515.3
P01024	Complement C3	33.97	34	34	103	187.0
P01008	Antithrombin-III	52.59	18	18	98	52.6
P02655	Apolipoprotein C-II	54.46	7	7	79	11.3
P13645	Keratin, type I cytoskeletal 10	36.13	15	16	73	58.8
P02652	Apolipoprotein A-II	59.00	6	6	69	11.2
P08603	Complement factor H	35.50	25	27	66	139.0
P04264	Keratin, type II cytoskeletal 1	38.04	16	20	60	66.0
P01009	Alpha-1-antitrypsin	42.58	15	15	48	46.7
P02649	Apolipoprotein E	53.63	15	15	43	36.1
P35527	Keratin, type I cytoskeletal 9	48.80	16	16	41	62.0
P35908	Keratin, type II cytoskeletal 2 epidermal	44.91	13	17	41	65.4
P02787	Serotransferrin	30.80	15	15	39	77.0
P02765	Alpha-2-HS-glycoprotein	42.78	8	8	38	39.3
P01023	Alpha-2-macroglobulin	17.03	14	14	31	163.2
P00734	Prothrombin	29.42	12	12	29	70.0
P06727	Apolipoprotein A-IV	38.89	12	12	29	45.4
P10909	Clusterin	24.72	8	8	29	52.5
P0CG05	Ig lambda-2 chain C regions	65.09	4	4	29	11.3
F5GXQ1	35 kDa inter-alpha-trypsin inhibitor heavy chain H4	14.29	4	4	25	62.1
F5GXS5	Apolipoprotein F	26.95	3	3	24	33.4
K7ER19	Truncated apolipoprotein C-I (Fragment)	42.86	6	6	23	8.6
P01042	Kininogen-1	18.01	10	10	22	71.9
P02766	Transthyretin	68.71	8	8	21	15.9
P01834	Ig kappa chain C region	63.21	4	4	21	11.6
P0COL5	Complement C4-B	11.35	9	9	19	192.6
P04004	Vitronectin	14.23	4	4	19	54.3

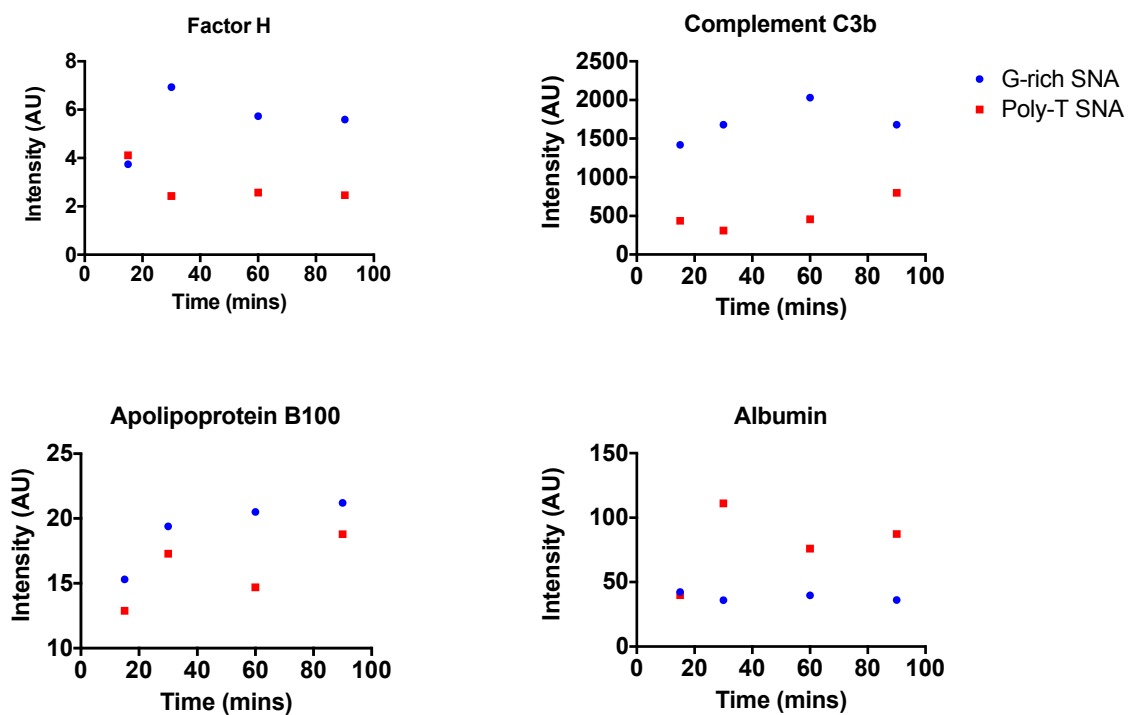
P00739	Haptoglobin-related protein	41.95	6	8	18	39.0
Q08380	Galectin-3-binding protein	20.51	7	7	16	65.3
P02656	Apolipoprotein C-III	58.59	6	6	16	10.8
P27169	Serum paraoxonase/arylesterase 1	25.63	5	5	16	39.7
O95445	Apolipoprotein M	45.21	5	5	16	21.2
P08779	Keratin, type I cytoskeletal 16	16.70	3	5	14	51.2
O14791	Apolipoprotein L1	22.36	3	3	13	43.9
P35542	Serum amyloid A-4 protein	44.62	4	4	11	14.7
P08697	Alpha-2-antiplasmin	19.14	4	4	10	54.5
P01876	Ig alpha-1 chain C region	24.93	5	5	9	37.6
P08519	Apolipoprotein(a)	18.84	3	3	9	501.0
O43866	CD5 antigen-like	17.00	3	3	9	38.1
P04003	C4b-binding protein alpha chain	11.06	4	4	7	67.0
P05090	Apolipoprotein D	19.58	3	3	7	21.3
P68871	Hemoglobin subunit beta	34.69	3	3	7	16.0
P02749	Beta-2-glycoprotein 1	22.90	4	4	6	38.3
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	9.09	4	4	6	105.2
D6RD17	Immunoglobulin J chain (Fragment)	38.85	3	3	6	18.0
P02760	Protein AMBP	12.50	3	3	5	39.0
B4E1H2	Plasma protease C1 inhibitor	9.38	3	3	5	49.7
F8WCZ6	Complement C1s subcomponent	12.67	3	3	4	57.5

**Table S10.** List of proteins bound to poly-T SNAs after a 90-min incubation in human serum

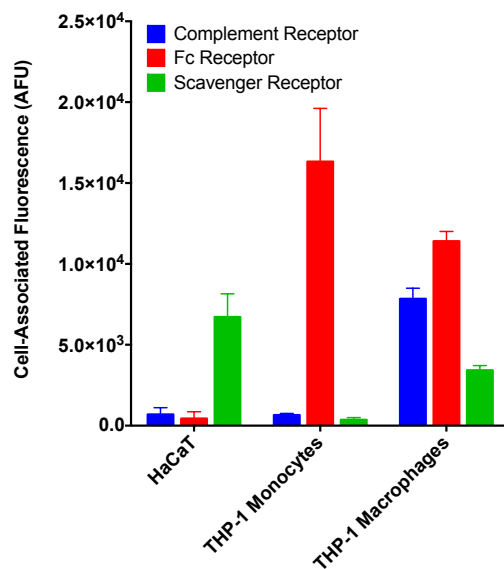
Accession	Description	Coverage	# Proteins	# Unique Peptides	# Peptides	# PSMs	MW [kDa]
P02647	Apolipoprotein A-I	78.65	2	33	33	312	30.8
P02768	Serum albumin	65.19	6	35	35	281	69.3
P04114	Apolipoprotein B-100	30.59	2	85	85	201	515.3
P02655	Apolipoprotein C-II	54.46	4	7	7	191	11.3
P01024	Complement C3	35.96	5	36	36	126	187.0
P02652	Apolipoprotein A-II	74.00	6	8	8	109	11.2
P01008	Antithrombin-III	47.20	1	16	16	83	52.6
P13645	Keratin, type I cytoskeletal 10	41.61	11	19	19	75	58.8
P04264	Keratin, type II cytoskeletal 1	35.87	10	15	19	65	66.0
P08603	Complement factor H	35.74	5	23	26	59	139.0
P02765	Alpha-2-HS-glycoprotein	42.78	2	8	8	58	39.3
P01009	Alpha-1-antitrypsin	42.58	5	14	14	47	46.7
P02649	Apolipoprotein E	48.58	4	13	13	46	36.1
P10909	Clusterin	34.30	10	14	14	44	52.5
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	28.71	4	14	14	41	103.3
P06727	Apolipoprotein A-IV	51.01	1	14	14	37	45.4

P02787	Serotransferrin	31.95	7	15	15	35	77.0
P35908	Keratin, type II cytoskeletal 2 epidermal	43.04	10	11	16	35	65.4
P01871	Ig mu chain C region	30.97	1	3	10	34	49.3
K7ER19	Truncated apolipoprotein C-I (Fragment)	42.86	6	6	6	33	8.6
P01023	Alpha-2-macroglobulin	17.10	4	15	15	32	163.2
P01834	Ig kappa chain C region	80.19	1	6	6	31	11.6
P01042	Kininogen-1	22.05	1	12	12	30	71.9
P35527	Keratin, type I cytoskeletal 9	38.36	2	12	12	28	62.0
F5GXS5	Apolipoprotein F	26.95	2	3	3	28	33.4
P00734	Prothrombin	29.42	3	11	11	25	70.0
F5GXS0	Complement C4-B	10.48	3	10	10	24	187.6
O14791	Apolipoprotein L1	35.18	4	6	6	23	43.9
P02766	Transthyretin	68.71	1	8	8	22	15.9
P02656	Apolipoprotein C-III	58.59	2	6	6	21	10.8
P04004	Vitronectin	12.13	1	4	4	19	54.3
Q5T985	Inter-alpha-trypsin inhibitor heavy chain H2	20.96	3	10	10	17	105.2
P27169	Serum paraoxonase/arylesterase 1	25.63	3	5	5	17	39.7
B4E1H2	Plasma protease C1 inhibitor	25.67	6	7	7	15	49.7
P00739	Haptoglobin-related protein	32.76	2	5	6	15	39.0
P01876	Ig alpha-1 chain C region	36.26	1	4	7	14	37.6
P35542	Serum amyloid A-4 protein	26.92	1	3	3	14	14.7
F5H7E1	Uncharacterized protein	14.88	4	7	7	11	72.1
P04003	C4b-binding protein alpha chain	17.59	2	6	6	11	67.0
P02749	Beta-2-glycoprotein 1	21.74	4	5	5	11	38.3
P05090	Apolipoprotein D	26.46	4	4	4	11	21.3
P01857	Ig gamma-1 chain C region	29.70	3	4	6	11	36.1
P08697	Alpha-2-antiplasmin	25.46	3	5	5	10	54.5
P07225	Vitamin K-dependent protein S	10.36	3	4	4	9	75.1
Q08380	Galectin-3-binding protein	17.78	9	6	6	8	65.3
P08519	Apolipoprotein(a)	18.84	1	3	3	8	501.0
J3QLC9	Haptoglobin (Fragment)	21.92	5	3	4	8	40.8
P05546	Heparin cofactor 2	12.42	1	4	4	6	57.0
P02760	Protein AMBP	12.22	2	3	3	6	39.0
P68871	Hemoglobin subunit beta	34.69	5	3	3	6	16.0
P04180	Phosphatidylcholine-sterol acyltransferase	13.64	3	3	3	6	49.5
F8WCZ6	Complement C1s subcomponent	8.83	4	3	3	5	57.5

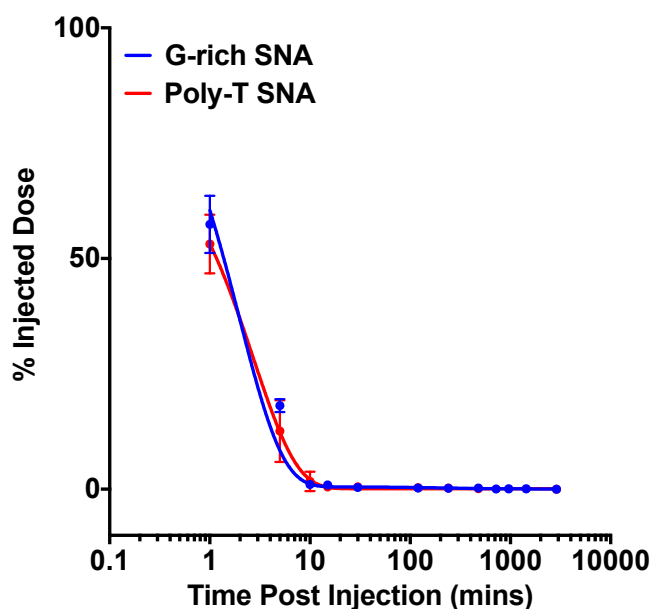




**Figure S2.** Relative quantification of proteins associated with G-rich and poly-T SNAs following incubation in 10% human serum.



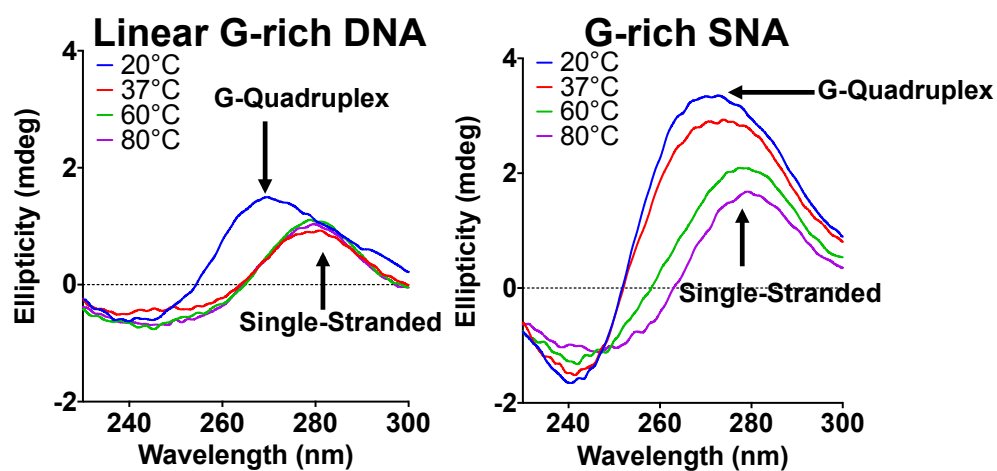
**Figure S3.** Flow cytometry of cells treated with fluorophore-tagged antibodies recognizing class A scavenger receptors, Fc receptors, and complement receptors. The cell-associated fluorescence of THP-1 (monocytes, and differentiated macrophages) and HaCaT cells is shown.



**Figure S4.** Pharmacokinetic analysis of G-rich (blue dots) and poly-T (red dots) SNA content in blood of CD57BL/6 mice following intravenous injection via the tail vein. A line of best fit (plotted as solid lines) was used to determine pharmacokinetic parameters.

**Table S11.** Pharmacokinetic parameters of G-rich and poly-T SNAs.

	G-rich SNAs	Poly-T SNAs
$t_{1/2}$ fast (min)	1.368	1.647
$t_{1/2}$ slow (min)	400.6	429.2

**Figure S5.** Circular dichroism spectra of G-rich SNAs and G-rich DNA showing the formation of parallel G-quadruplexes templated on the SNA surface.