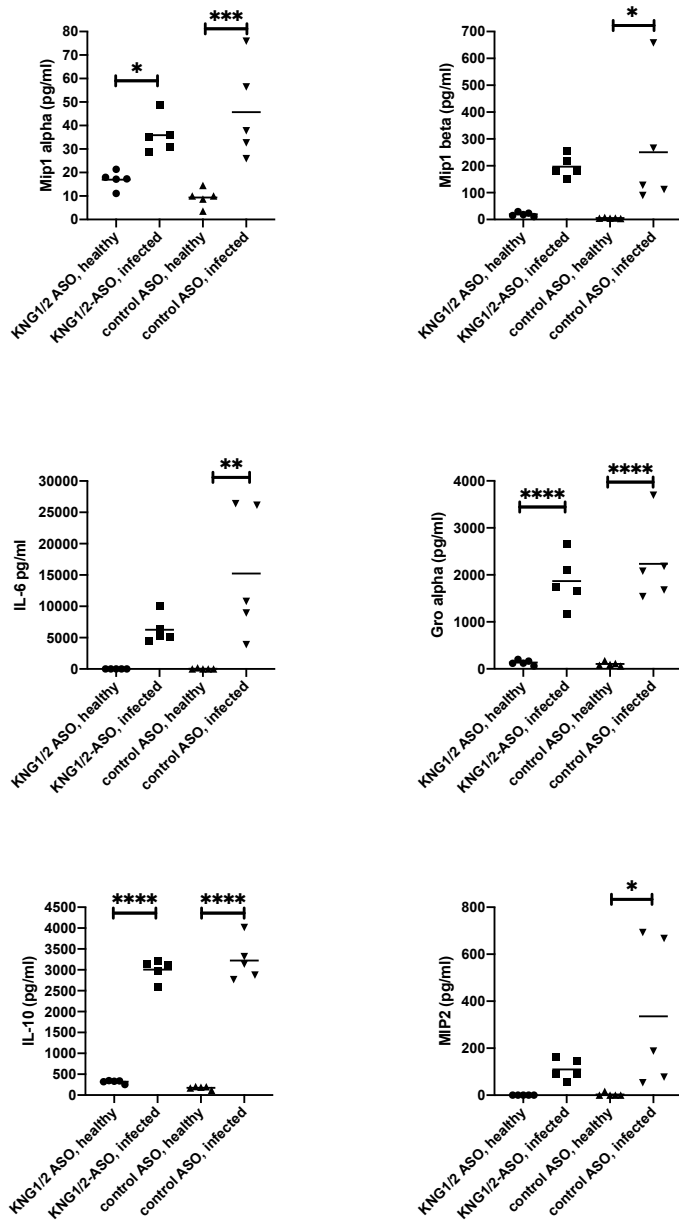


Supplemental Table 1. Mass spectrometric quantification of plasma proteins from control-ASO treated mice compared to KNG1/2-ASO treated mice

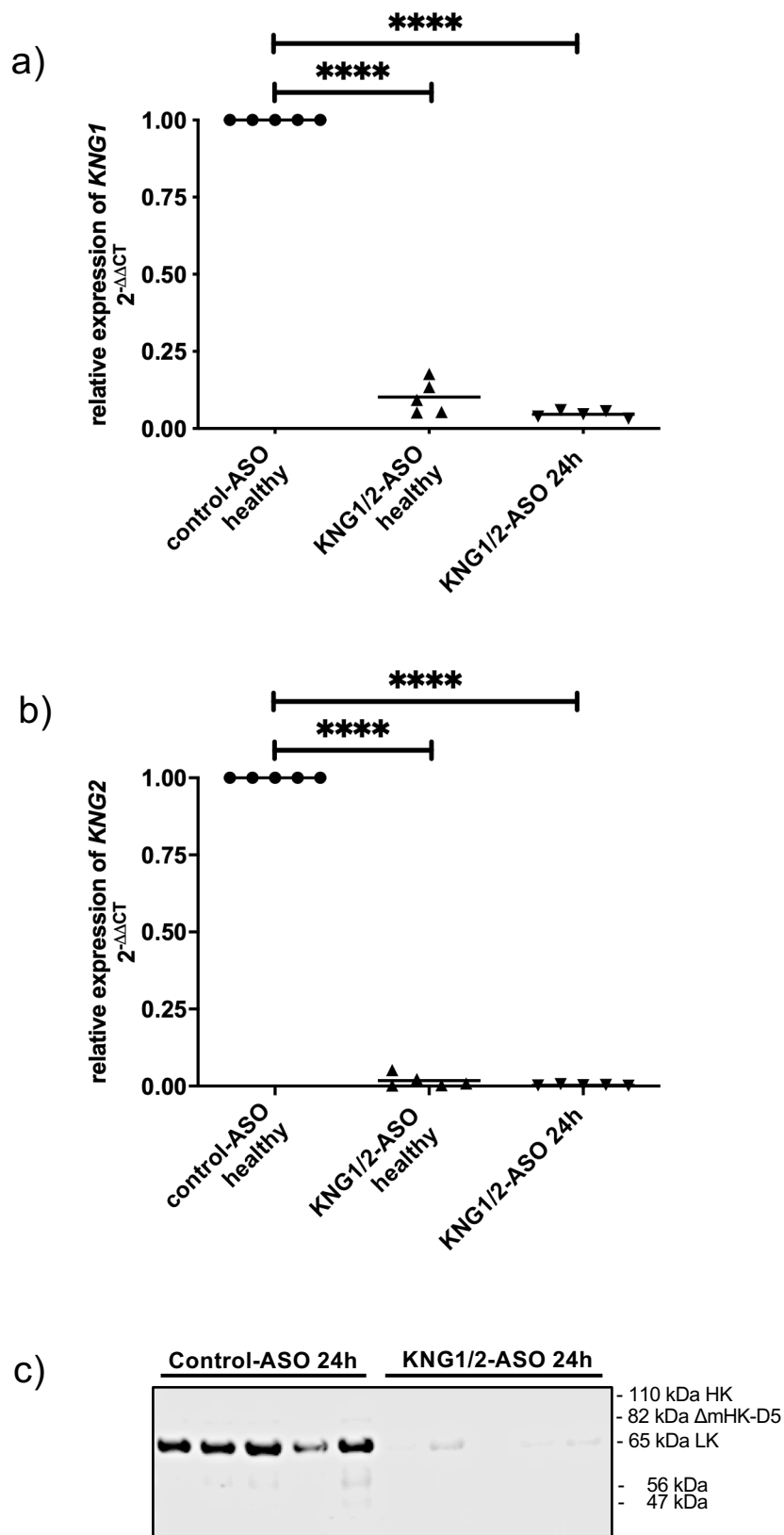
Protein name	Unique peptides	Protein abundance (fmol on column)						Comparative analysis	
		Control-ASO animals (n = 5)			KNG1/2-ASO animals (n = 5)			Fold Change control/KNG	Anova (p)
		Mean	SD	CV	Mean	SD	CV		
Actin cytoplasmic 1	8	1.73	0.64	36.85	2.22	0.41	18.65	0.78	1.65E-01
Adiponectin	3	1.94	0.36	18.55	1.94	0.30	15.58	1.00	9.85E-01
Afamin	22	13.59	1.07	7.87	15.17	0.94	6.21	0.90	4.12E-02
Alpha-1-acid glycoprotein 1	4	4.90	2.04	41.66	6.29	1.74	27.67	0.78	2.85E-01
Alpha-1-antitrypsin 1-1	7	53.39	7.69	14.41	45.92	2.80	6.10	1.16	7.72E-02
Alpha-1-antitrypsin 1-2	8	45.72	4.79	10.47	41.40	2.42	5.83	1.10	1.19E-01
Alpha-2-antiplasmin	17	9.95	0.62	6.26	10.10	0.40	3.94	0.99	6.41E-01
Alpha-2-HS-glycoprotein	11	82.83	17.94	21.66	81.88	5.72	6.98	1.01	9.64E-01
Angiotensinogen	6	1.91	0.46	24.28	1.62	0.28	17.54	1.18	2.79E-01
Antithrombin-III	29	19.21	5.22	27.17	21.64	2.10	9.69	0.89	3.49E-01
Apolipoprotein A-I	36	152.45	31.61	20.73	150.54	18.89	12.55	1.01	9.86E-01
Apolipoprotein A-IV	28	31.34	4.79	15.29	26.66	2.47	9.27	1.18	8.19E-02
Apolipoprotein C-I	2	6.82	0.90	13.17	6.33	0.65	10.30	1.08	3.79E-01
Apolipoprotein C-III	4	18.63	7.33	39.35	13.84	3.25	23.49	1.35	2.21E-01
Apolipoprotein D	5	1.42	0.14	9.94	1.68	0.16	9.80	0.85	2.59E-02
Apolipoprotein E	17	7.05	1.62	22.97	6.60	0.74	11.25	1.07	6.69E-01
Apolipoprotein M	4	0.95	0.14	15.09	0.83	0.09	11.04	1.15	1.43E-01
Band 3 anion transport protein	2	0.50	0.45	91.16	0.51	0.23	45.15	0.97	8.76E-01
Beta-2-glycoprotein 1	23	15.65	2.02	12.90	15.66	1.27	8.14	1.00	9.49E-01
Beta-2-microglobulin	3	3.04	0.47	15.54	3.64	0.34	9.45	0.84	5.38E-02
C4b-binding protein	5	2.22	0.30	13.71	3.10	0.39	12.73	0.72	4.48E-03
Carbonic anhydrase 1	5	1.05	0.47	45.26	0.94	0.28	29.87	1.11	7.83E-01
Carbonic anhydrase 2	6	4.85	1.70	35.11	4.48	1.40	31.30	1.08	8.05E-01
Carboxylesterase 1C	15	70.80	5.71	8.06	69.26	7.90	11.40	1.02	7.03E-01
Carboxypeptidase N catalytic chain	8	2.05	0.14	6.84	2.21	0.23	10.32	0.93	2.27E-01
Carboxypeptidase N subunit 2	13	5.11	0.81	15.80	5.25	0.38	7.18	0.97	6.68E-01
CD5 antigen-like	13	1.31	0.20	15.33	1.57	0.22	14.04	0.84	8.97E-02
Ceruloplasmin	43	12.17	2.13	17.51	12.27	1.86	15.12	0.99	9.16E-01
Clusterin	16	8.56	1.76	20.60	8.91	0.79	8.90	0.96	6.26E-01
Coagulation factor X	9	2.04	0.38	18.41	2.02	0.04	2.12	1.01	9.88E-01
Coagulation factor XII	3	0.63	0.22	35.09	0.66	0.07	10.32	0.96	7.38E-01
Coagulation factor XIII B chain	2	0.37	0.18	48.11	0.30	0.08	27.26	1.24	4.45E-01
Complement C1q subcomponent subunit B	2	1.01	0.20	19.58	1.16	0.17	14.30	0.87	2.28E-01
Complement C3	106	33.88	3.36	9.92	26.73	1.32	4.95	1.27	1.44E-03
Complement C4-B	33	18.28	1.09	5.97	18.82	0.36	1.93	0.97	3.11E-01
Complement C5	27	1.63	0.23	13.88	1.59	0.16	10.09	1.03	7.39E-01
Complement component C8 alpha chain	4	0.36	0.14	38.27	0.40	0.09	23.31	0.91	6.49E-01
Complement component C8 gamma chain	3	0.65	0.18	27.99	0.70	0.14	19.64	0.92	5.62E-01
Complement factor B	24	8.21	0.93	11.28	7.28	0.38	5.26	1.13	6.81E-02
Complement factor D	5	5.62	2.87	50.96	5.20	1.54	29.54	1.08	8.92E-01
Complement factor H	47	13.66	5.98	43.76	10.59	1.76	16.59	1.29	4.05E-01
Complement factor I	17	6.34	0.95	14.99	5.95	0.39	6.61	1.06	4.73E-01
Corticosteroid-binding globulin	10	13.71	2.10	15.35	15.77	3.56	22.58	0.87	3.51E-01
C-reactive protein	2	0.50	0.07	14.38	0.51	0.02	4.46	0.98	7.22E-01
Extracellular matrix protein 1	3	0.58	0.06	9.77	0.55	0.07	12.77	1.06	4.44E-01
Fetuin-B	8	5.95	0.92	15.37	6.26	0.63	10.11	0.95	5.23E-01
Fibrinogen alpha chain	28	47.22	5.62	11.91	42.58	1.93	4.54	1.11	1.33E-01
Fibrinogen beta chain	43	48.43	7.26	14.98	47.27	4.18	8.84	1.02	8.26E-01
Fibrinogen gamma chain	32	66.33	11.84	17.85	65.37	7.54	11.54	1.01	9.42E-01
Flavin reductase (NADPH)	6	0.94	0.37	39.02	0.84	0.10	11.79	1.11	6.63E-01
Gelsolin	29	13.30	1.91	14.35	12.99	1.47	11.33	1.02	7.97E-01
Glutathione peroxidase 3	8	6.28	1.13	17.92	6.22	0.88	14.16	1.01	9.68E-01
H-2 class I histocompatibility antigen_Q10 alpha chain	12	3.98	0.43	10.76	4.85	0.50	10.29	0.82	1.85E-02
Hemoglobin subunit alpha	10	179.44	51.57	28.74	183.94	34.40	18.70	0.98	7.72E-01
Hemoglobin subunit beta-1	9	279.39	94.43	33.80	267.99	64.70	24.14	1.04	9.39E-01

Hemoglobin subunit beta-2	9	123.31	36.35	29.48	119.80	27.03	22.56	1.03	9.46E-01
Hemopexin	33	41.52	5.16	12.41	46.09	5.53	12.00	0.90	2.01E-01
Heparin cofactor 2	8	71.35	8.56	12.00	66.66	10.28	15.42	1.07	4.32E-01
Hepatocyte growth factor activator	4	1.39	0.13	9.33	1.30	0.23	18.02	1.07	4.44E-01
Histidine-rich glycoprotein	14	4.57	0.39	8.56	4.55	0.51	11.30	1.00	9.25E-01
Ig alpha chain C region	6	1.38	0.26	18.57	1.69	0.33	19.32	0.82	1.30E-01
Ig gamma-1 chain C region secreted form	8	24.06	5.41	22.50	25.88	3.09	11.94	0.93	4.83E-01
Ig gamma-2A chain C region A allele	7	2.66	1.23	46.05	2.84	1.23	43.38	0.94	8.19E-01
Ig gamma-2B chain C region	9	6.66	1.47	22.05	7.52	1.71	22.68	0.89	4.04E-01
Ig gamma-3 chain C region	10	8.46	1.42	16.79	7.97	3.02	37.84	1.06	5.92E-01
Ig heavy chain V region AC38 205.12	3	2.31	0.41	17.79	2.33	0.30	13.00	0.99	8.96E-01
Ig heavy chain V-III region A4	3	0.74	0.14	19.03	0.92	0.20	22.11	0.80	1.38E-01
Ig kappa chain V19-17	2	0.96	0.11	11.61	1.00	0.23	23.20	0.97	8.14E-01
Ig kappa chain V-II region 26-10	2	0.57	0.13	23.50	0.62	0.17	27.73	0.91	5.92E-01
Ig kappa chain V-V region K2 (Fragment)	2	0.77	0.21	27.42	0.83	0.11	13.47	0.92	5.15E-01
Ig kappa chain V-VI region XRPC 44	4	1.28	0.40	31.08	0.88	0.16	17.73	1.46	7.17E-02
Ig lambda-1 chain C region	2	1.05	0.30	29.04	1.21	0.29	24.34	0.86	4.11E-01
Ig lambda-1 chain V region	2	1.72	0.84	48.75	1.68	0.64	37.95	1.02	9.85E-01
Immunoglobulin heavy constant mu	21	31.33	4.61	14.71	30.35	4.18	13.77	1.03	7.39E-01
Immunoglobulin J chain	3	1.44	0.27	19.00	1.67	0.23	14.07	0.86	1.83E-01
Immunoglobulin kappa constant	4	5.37	0.63	11.75	5.46	1.97	36.14	0.98	8.79E-01
Inhibitor of carbonic anhydrase	23	6.65	1.34	20.22	6.44	0.95	14.75	1.03	8.52E-01
Insulin-like growth factor-binding protein complex acid labile subunit	5	1.00	0.49	49.22	0.75	0.27	35.53	1.33	3.70E-01
Inter alpha-trypsin inhibitor heavy chain 4	25	5.93	0.56	9.52	5.88	0.47	7.96	1.01	8.99E-01
Inter-alpha-trypsin inhibitor heavy chain H1	16	3.70	0.70	18.82	3.60	0.20	5.59	1.03	8.74E-01
Inter-alpha-trypsin inhibitor heavy chain H2	19	10.25	2.92	28.47	8.33	1.15	13.85	1.23	2.13E-01
Inter-alpha-trypsin inhibitor heavy chain H3	12	2.46	0.51	20.88	2.83	0.18	6.33	0.87	1.65E-01
Interleukin-1 receptor accessory protein	8	3.89	1.84	47.44	3.73	0.44	11.66	1.04	8.54E-01
Kininogen-1	21	41.06	6.10	14.86	3.16	1.02	32.09	12.97	2.54E-07
Leukemia inhibitory factor receptor	8	1.61	0.51	31.36	1.36	0.17	12.25	1.19	3.73E-01
Lumican	11	1.97	0.60	30.21	2.01	0.45	22.16	0.98	8.50E-01
Mannan-binding lectin serine protease 2	2	0.31	0.03	9.48	0.34	0.04	11.27	0.91	1.94E-01
Mannose-binding protein A	3	0.88	0.14	15.87	0.83	0.07	8.23	1.05	5.66E-01
Mannose-binding protein C	6	2.89	0.16	5.40	3.35	0.23	6.92	0.86	5.51E-03
Murinoglobulin-1	40	49.89	16.33	32.74	51.55	7.46	14.47	0.97	6.82E-01
N-acetylmuramoyl-L-alanine amidase	3	0.73	0.11	15.06	0.75	0.06	7.67	0.97	6.74E-01
Odorant-binding protein 1b	2	0.22	0.18	84.96	0.22	0.20	91.68	1.00	9.98E-01
Peroxiredoxin-2	9	3.61	1.59	44.20	3.50	1.19	33.85	1.03	9.75E-01
Phosphatidylcholine-sterol acyltransferase	5	1.29	0.16	12.13	1.38	0.08	5.92	0.94	2.86E-01
Phosphatidylinositol-glycan-specific phospholipase D	10	1.26	0.14	10.85	1.14	0.19	16.93	1.11	2.73E-01
Pigment epithelium-derived factor	2	0.55	0.17	30.47	0.53	0.07	12.41	1.03	8.61E-01
Plasma kallikrein	18	2.89	0.25	8.75	0.98	0.06	5.65	2.95	1.59E-08
Plasma protease C1 inhibitor	14	5.69	0.86	15.12	5.63	0.98	17.33	1.01	8.92E-01
Plasminogen	51	17.31	2.96	17.10	18.66	1.55	8.30	0.93	3.73E-01
Pregnancy zone protein	84	145.63	23.71	16.28	143.70	7.16	4.98	1.01	9.53E-01
Properdin	3	1.57	0.16	10.20	1.66	0.18	10.57	0.94	3.91E-01
Protein AMBP	7	7.69	0.89	11.52	7.51	0.52	6.90	1.02	7.54E-01

Protein Z-dependent protease inhibitor	3	0.67	0.09	13.07	0.73	0.06	8.65	0.92	2.42E-01
Prothrombin	33	10.29	1.97	19.17	10.12	1.08	10.67	1.02	9.56E-01
Retinol-binding protein 4	8	3.00	0.75	25.03	3.30	0.78	23.76	0.91	5.71E-01
Secreted phosphoprotein 24	2	0.52	0.02	3.67	0.60	0.07	12.08	0.86	3.60E-02
Selenoprotein P	4	1.26	0.25	19.86	1.15	0.28	24.85	1.10	5.42E-01
Serine protease inhibitor A3K	16	135.52	42.58	31.42	111.10	32.00	28.80	1.22	3.37E-01
Serine protease inhibitor A3N	12	2.06	0.26	12.46	2.23	0.19	8.36	0.92	2.62E-01
Serotransferrin	69	240.49	22.51	9.36	285.82	14.29	5.00	0.84	6.36E-03
Serum albumin	74	1218.42	159.30	13.07	1207.37	124.03	10.27	1.01	9.30E-01
Serum amyloid A-4 protein	7	1.43	0.41	28.86	1.62	0.20	12.67	0.88	3.53E-01
Serum amyloid P-component	7	7.36	0.89	12.06	8.04	1.27	15.83	0.91	3.95E-01
Serum paraoxonase/arylesterase 1	9	7.46	1.70	22.78	8.09	1.42	17.50	0.92	5.32E-01
Sulfhydryl oxidase 1	14	1.81	0.27	15.15	1.74	0.32	18.23	1.04	7.03E-01
Transthyretin	11	13.88	2.76	19.89	16.52	2.54	15.40	0.84	1.33E-01
Vitamin D-binding protein	36	28.60	11.01	38.49	26.03	5.41	20.78	1.10	8.04E-01
Vitronectin	8	6.25	0.86	13.76	6.30	0.48	7.68	0.99	8.51E-01
Zinc-alpha-2-glycoprotein	11	2.41	0.21	8.60	2.31	0.32	13.73	1.04	5.33E-01



suppl. Fig. 1. Proinflammatory response of control- and kininogen-depleted mice infected with *S. pyogenes*. Mice (n=5/group) were injected sc. with 2×10^7 CFU/mouse *S. pyogenes* AP1. 24 hours after infection animals were collected and EDTA plasma was analyzed for Mip1 alpha, Mip1 beta, IL6, Gro alpha, IL10, and MIP2, using a Multi-Plex immunoassay. One-way ANOVA * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.0002$, **** $p \leq 0.0001$.



Suppl. Figure 2: Analysis of kininogen gene expression and protein levels after KNG1/2-ASO treatment and infection. Groups of mice were treated with KNG1/2-ASO or control-ASO through intraperitoneal injections, with a dose of 800 $\mu\text{g}/\text{mouse}$, twice per week for 3 weeks (total 7 injections, each with 800 μg ASO/mouse). Thereafter mice were injected sc. with $1.5 - 2 \times 10^7$ CFU/mouse *S. pyogenes* AP1. a, b) 24 hours after infection liver tissue was collected for total RNA isolation and gene expression analysis of *KNG1/2*. One sample t-test, **** $p \leq 0.0001$ c) Western Blot analysis of mouse plasma, 24h after infection, with an antibody against kininogen.