

SUPPLEMENTAL TABLES

<i>Subject</i>	A31P Genotype	Disease Status	Treatment Group	Given Dose	Sex	Age
<i>Cat 1</i>	Heterozygous	HCM ACVIM stage B1	HCM control	-	M	9.99
<i>Cat 2</i>	Wildtype	HCM ACVIM stage B1	HCM control	-	M	9.97
<i>Cat 3</i>	Heterozygous	HCM ACVIM stage B1	HCM control	-	M	11.11
<i>Cat 4</i>	Heterozygous	HCM ACVIM stage B1	High-Dose	0.24mg/kg	M	1.92
<i>Cat 5</i>	Homozygous	HCM ACVIM stage B1	High-Dose	0.31mg/kg	M	1.87
<i>Cat 6</i>	Homozygous	HCM ACVIM stage B1	High-Dose	0.30mg/kg	F	1.47
<i>Cat 7</i>	Homozygous	HCM ACVIM stage B1	Low-Dose	0.13mg/kg	F	3.39
<i>Cat 8</i>	Homozygous	HCM ACVIM stage B1	Low-Dose	0.13mg/kg	M	1.47
<i>Cat 9</i>	Homozygous	HCM ACVIM stage B1	Low-Dose	0.15mg/kg	F	1.67

Supplemental Table S1. Subject information and affection status. The *MYBPC3* A31P genotype, disease status, treatment allocation, DR rapamycin dose, sex, and age for each cat used in this study are presented.

Abbreviations: *MYBPC3* = *myosin-binding protein C3*, DR = delayed-release, HCM = hypertrophic cardiomyopathy, ACVIM = American college of veterinary internal medicine.

<i>Event</i>	Screening	Day 0	Day 1-55; 57, 58, 59	Day 56	Day 60	Post In-Life
<i>Physical Exam</i>	X			X		
<i>Echocardiogram</i>	X			X		
<i>Electrocardiogram</i>	X			X		
<i>Clinical Pathology</i>	X			X		
<i>Urinalysis</i>	X			X		
<i>Blood Collection (Proteomics)</i>	X			X		
<i>Urine Collection (Proteomics)</i>	X			X		
<i>Randomization</i>		X				
<i>Weekly Dosing</i>		X	X	X		
<i>Body Weight</i>	X			X	X	X
<i>Daily Observations</i>			X			
<i>Euthanasia</i>					X	
<i>Necropsy</i>					X	
<i>Proteomics & RNA-Seq Analysis</i>						X

Supplemental Table S2. Study design and schedule of events. Events for each study timepoint are presented.

<i>Subject</i>	<i>Treatment Group</i>	<i>Age (yrs)</i>	<i>Screening BW (kg)</i>	<i>Day 56 BW (kg)</i>		<i>Screening HR</i>	<i>Day 56 HR</i>		<i>Screening RR</i>	<i>Day 56 RR</i>		<i>Screening BP</i>	<i>Day 56 BP</i>	
<i>Cat 1</i>	HCM	9.99		5.7			238						WNL	
<i>Cat 2</i>	HCM	9.97		7.5			245						WNL	
<i>Cat 3</i>	HCM	11.11		4.61			172						WNL	
<i>Cat 4</i>	High-Dose	1.92	6.39	6.74	0.25	132	190	1	20	50	0.75	86	126	0.25
<i>Cat 5</i>	High-Dose	1.87	4.96	5.04		168	180		20	34		99	102	
<i>Cat 6</i>	High-Dose	1.47	2.7	2.89		216	130		48	32		121	128	
<i>Cat 7</i>	Low-Dose	3.39	5.34	5.64	0.25	208	170	0.25	28	36	0.75	120	111	1
<i>Cat 8</i>	Low-Dose	1.47	5.15	5.46		208	150		56	40		97	112	
<i>Cat 9</i>	Low-Dose	1.67	2.78	2.93		168	150		48	40		95	95	
<i>Pooled Statistics</i>		1.77(1.47-3.39)	5.06(2.70-6.39)	5.25(2.89-6.74)	0.03*	188 (132-216)	160(130-190)	0.34	38(20-56)	38(32-50)	1	98(86-121)	112(95-128)	0.31

Supplemental Table S3. Age and physical exam findings. Descriptive statistics for age and pertinent physical exam variables are provided for all cats used in this study at available time points. For the HCM control group (Cat 1, 2, and 3) the blood pressure was deemed within normal limits as a component of a prior study through confirmation of a Doppler systolic blood pressure <160mmHg, no evidence of abnormality on fundic examination, and no evidence of renal disease via routine serum biochemical profile. Blood pressure and respiratory rate were not recorded for the purposes of this study in the HCM control group. Results from a Wilcoxon matched-pairs signed rank test between pre- (Screening) and post-treatment (Day 56) variables are presented for individual treatment groups (low- or high-dose) as well as for pooled treatment groups (low- + high-dose); only BW was statistically significant between timepoints in the pooled comparison. * $P<0.05$.

Abbreviations: yrs = years, BW = bodyweight, kg = kilogram, HR = heart rate, RR = respiration rate, BP = blood pressure, WNL = within normal limits.

<i>Subject</i>	<i>Treatment Group</i>	<i>Screening Crystals</i>	<i>Day 56 Crystals</i>		<i>Screening pH</i>	<i>Day 56 pH</i>		<i>Screening [Protein]</i>	<i>Day 56 [Protein]</i>		<i>Screening Specific Gravity</i>	<i>Day 56 Specific Gravity</i>		<i>Screening WBC</i>	<i>Day 56 WBC</i>	
<i>Cat 4</i>	High-Dose	2	0	1	7.5	7.0	0.50	0	1	0.50	1.048	1.041	0.75	2	2	1
<i>Cat 5</i>	High-Dose	1	5		7.0	7.0		1	1		1.055	1.058		2	2	
<i>Cat 6</i>	High-Dose	1	0		7	6.5		0	1		1.059	1.058		2	5	
<i>Cat 7</i>	Low-Dose	2	1	1	7.5	6.0	0.50	0	0	1	1.044	1.056	0.25	2	2	1
<i>Cat 8</i>	Low-Dose	1	0		8.0	6.0		1	1		1.034	1.070		2	2	
<i>Cat 9</i>	Low-Dose	0	1		6.5	6.5		1	1		1.053	1.056		2	2	
<i>Pooled Statistics</i>				0.78			0.13			0.50			0.31			1

Supplemental Table S4. Urinalysis findings on rapamycin-treated cats. Results from urinalysis of HCM cats receiving low- or high-dose DR rapamycin are presented. Results from a Wilcoxon matched-pairs signed rank test between pre- (Screening) and post-treatment (Day 56) variables are presented for individual treatment groups (low- or high-dose) as well as for pooled treatment groups (low- + high-dose); no statistically significant variables between timepoints were found in any of the comparisons. * $P < 0.05$. Abbreviations: HCM = hypertrophic cardiomyopathy, DR = delayed-release, WBC= white blood cell.

Subject	Treatment Group	Screening ALT	Day 56 ALT		Screening Bicarbonate	Day 56 Bicarbonate		Screening BUN	Day 56 BUN		Screening Creatinine	Day 56 Creatinine		Screening Fructosamine	Day 56 Fructosamine		Screening Glucose	Day 56 Glucose		Screening NTproBNP	Day 56 NTproBNP		Screening SDMA	Day 56 SDMA		Screening T4	Day 56 T4	
Cat 4	High-Dose	40	60	0.75	21	20	0.25	21	20	0.50	1.3	1.1	0.25	193	209	0.50	80	94	0.75	24	55	0.75	18	13	0.75	1.9	2.2	0.25
Cat 5	High-Dose	54	63		21	19		21	19		1.3	1.0		190	185		100	84		1500	1426		13	11		2.0	2.4	
Cat 6	High-Dose	82	67		17	15		23	23		1.1	1.0		184	191		68	97		1070	1500		9	11		2.5	2.6	
Cat 7	Low-Dose	36	33	0.50	18	17	0.25	19	19	1	1.1	0.9	0.50	182	169	0.25	94	88	0.50	124	106	0.50	14	12	1	2.9	1.9	0.25
Cat 8	Low-Dose	35	55		18	17		18	22		1.0	0.9		219	174		103	112		774	1353		5	9		1.4	1.0	
Cat 9	Low-Dose	62	82		15	14		26	20		1.3	1.3		199	184		97	158		123	179		16	12		2.0	1.8	
Pooled Statistics		47(35-82)	61.5(33-82)	0.19	18(15-21)	17(14-20)	0.03*	21(18-26)	20(19-23)	0.63	1.2(1-1.3)	1(0.9-1.3)	0.06	191.5(182-219)	184.5(169-209)	0.56	95.5(68-103)	95.5(84-158)	0.31	449(24-1500)	766(55-1500)	0.31	13.5(5-18)	11.5(9-13)	0.53	2(1.4-2.9)	2.05(1-2.6)	0.72

Supplemental Table S5. Biochemistry findings on rapamycin-treated cats. Results from pertinent biochemistry measures of HCM cats receiving low- or high-dose DR rapamycin are presented. Results from a Wilcoxon matched-pairs signed rank test between pre- (Screening) and post-treatment (Day 56) variables are presented for individual treatment groups (low- or high-dose) as well as for pooled treatment groups (low- + high-dose); only bicarbonate/total CO₂ measures were statistically significant between timepoints in the pooled comparison. * $P < 0.05$.

Abbreviations: HCM = hypertrophic cardiomyopathy, DR = delayed-release, ALT = alanine transaminase, BUN = blood urea nitrogen, NTproBNP = N-terminal prohormone of brain natriuretic peptide, SDMA = symmetric dimethylarginine, T4 = total thyroxine.

Subject	Treatment Group	Screening [EOS]	Day 56 [EOS]		Screening HCT (%)	Day 56 HCT (%)		Screening [HGB]	Day 56 [HGB]		Screening [LYMPH]	Day 56 [LYMPH]		Screening MCH	Day 56 MCH		Screening MCV	Day 56 MCV		Screening [MONO]	Day 56 [MONO]		Screening [NEUT]	Day 56 [NEUT]		Screening [Platelet]	Day 56 [Platelet]		Screening [RBC]	Day 56 [RBC]		Screening [WBC]	Day 56 [WBC]	
Cat 4	High-Dose	800	959	0.50	30.0	44.2	0.25	9.7	15.2	0.25	1950	3128	1	14.3	14.6	0.75	44	42	0.50	50	140	0.50	2200	3565	0.25	359	141	1	6.76	10.42	0.25	5.0	7.8	0.25
	High-Dose	686	393		30.3	41.1		10.5	13.7		5684	6747		14.1	13.9		41	42		196	288		3234	5672		252	232		7.43	9.86		9.8	13.1	
Cat 6	High-Dose	750	323		30	39.5		9.9	13.8		3450	1856		14.1	13.4		43	39		300	277		3000	5244		33	328		7.04	10.27		7.5	7.7	
Cat 7	Low-Dose	258	148	1	44.0	29.7	0.25	13.7	10.4	0.25	2387	1685	0.75	14.6	14.2	0.50	47	41	0.75	170	159	0.75	3978	3307	0.75	358	211	0.75	9.36	7.33	0.50	6.8	5.3	0.75
	Low-Dose	283	441		50.0	33.2		15.7	11.8		2707	2608		13.5	13.5		43	38		707	290		16503	9261		139	91		11.62	8.76		20.2	12.6	
Cat 9	Low-Dose	476	356		45.0	41.1		14.1	13.6		1768	2261		14.5	13.9		46	42		136	249		4352	6034		27	151		9.70	9.75		6.8	8.9	
Pooled Statistics		581(256-800)	374.5(148-959)	0.56	37.15(30-50)	40.3(29.7-44.2)	0.84	12.1(8.7-15.7)	13.6(10.4-15.2)	0.72	2547(1768-5684)	2439(1685-6747)	1	14.2(13.5-14.6)	13.9(13.4-14.6)	0.19	43.5(41-47)	41.5(38-42)	0.06	183(50-707)	263(140-290)	0.84	3608(2360-16503)	5438(3307-9261)	0.56	195.5(27-359)	181(91-328)	0.84	8.39(6.76-11.62)	9.80(5.73-10.42)	0.44	7.1(5-20.2)	8.35(5.3-13.1)	0.69

Supplemental Table S6. Hematology findings on rapamycin-treated cats. Results from pertinent hematology measures of HCM cats receiving low- or high-dose DR rapamycin are presented. Results from a Wilcoxon matched-pairs signed rank test between pre- (Screening) and post-treatment (Day 56) variables are presented for individual treatment groups (low- or high-dose) as well as for pooled treatment groups (low- + high-dose); no statistically significant variables between timepoints were found in any of the comparisons. * $P < 0.05$.

Abbreviations: HCM = hypertrophic cardiomyopathy, DR = delayed-release, [EOS] = eosinophil concentration, HCT = hematocrit, [HGB] = hemoglobin concentration, [LYMPH] = lymphocyte concentration, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, [MONO] = monocyte concentration, [NEUT] = neutrophil concentration, [RBC] = red blood cell concentration, [WBC] = white blood cell concentration.

Subjects	Treatment Group	LVEF	MD	CH	IF	CVR	CVN	NSPC
<i>Cat 1</i>	HCM	1	1	1	1	1	1	11
<i>Cat 2</i>	HCM	2	2	1	0	3	0	9
<i>Cat 3</i>	HCM	2	1	1	1	1	1	6
<i>Cat 4</i>	High-Dose	3	1	1	0	0	1	5
<i>Cat 5</i>	High-Dose	2	3	2	0	1	1	4
<i>Cat 6</i>	High-Dose	3	2	2	1	1	1	5
<i>Cat 7</i>	Low-Dose	2	1	1	0	1	1	6
<i>Cat 8</i>	Low-Dose	3	2	3	2	1	1	3
<i>Cat 9</i>	Low-Dose	2	1	2	1	1	1	6
<i>P-value</i>		0.36	0.68	0.36	0.87	0.75	1	0.11

Supplemental Table S7. Histopathologic findings for treatment and HCM control cats. Histopathologic scores from HCM control and DR-rapamycin-treated cats are presented. Results from a Kruskal-Wallis test followed by Dunn's multiple comparisons correction are reported; no statistically significant variables between and within groups were identified. * $P < 0.05$. Abbreviations: HCM = hypertrophic cardiomyopathy, DR = delayed release, LVEF = left ventricular endocardial fibrosis, MD = myocardial disarray, CH = cellular hypertrophy, IF = interstitial fibrosis, CVR = coronary vessel remodeling, CVN = coronary vessel narrowing, NSPC = number of perimysial collagen.

Subject	Treatment Group	Screening RPSA Lx/Ao	Day 56 RPSA Lx/Ao	Screening RPLA Lx	Day 56 RPLA Lx	Screening IVSd Max	Day 56 IVSd Max	Screening LVPWd Max	Day 56 LVPWd Max	Screening LVIDd Sx	Day 56 LVIDd Sx	Screening LVIDs Sx	Day 56 LVIDs Sx	Screening FS%	Day 56 FS%	Screening LVOT maxPG	Day 56 LVOT maxPG	Screening LAF	Day 56 LAF	Screening MWT	Day 56 MWT										
Cat 1	HCM		1.48		1.43		6.46		5.57		1.42		0.40		71.5		5.10		57.0		6.46										
Cat 2	HCM		1.18		1.25		7.10		6.17		1.29		0.33		74.6		7.73		31.59		7.10										
Cat 3	HCM		1.31		1.46		6.55		5.70		1.34		0.73		45.2		1.59		70.2		6.55										
Cat 4	High-Dose	1.87	1.5	1	1.59	1.43	1	6.93	7.18	0.5	6.49	5.2	1	1.47	1.73	0.8	0.72	0.91	0.5	51	47.4	0.3	2.36	2.41	0.3	56.07	52.66	0.8	6.93	7.18	0.3
Cat 5	High-Dose	1.34	1.58		1.31	1.69		6.04	6.92		7.71	8.24		1.27	1.3		0.42	0.56		67	56.9		2.33	3.22		42.2	70.58		7.71	8.24	
Cat 6	High-Dose	1.36	1.52		1.31	1.06		7.11	9.97		6.41	7.24		1.26	1.09		0.43	0.41		65.5	62		3.08	3.55		74.55	38.82		7.11	7.24	
Cat 7	Low-Dose	1.1	1.34	0.8	1.28	1.08	0.8	6.67	6.61	0.8	4.42	4.7	0.8	1.43	1.28	0.5	0.52	0.69	1	63.4	46.2	1	2.8	1.28	0.3	83.38	37.98	0.5	6.67	6.61	0.3
Cat 8	Low-Dose	1.42	1.44		1.34	1.94		8.54	7.3		8.13	7.85		1.5	1.26		0.47	0.33		68.3	73.7		4.5	4.23		43.23	58.67		8.54	7.85	
Cat 9	Low-Dose	1.59	1.41		1.22	1.24		4.74	5.71		6.05	5.04		1.01	1.08		0.49	0.48		50.8	55.8		3.19	0.75		75.44	34.59		6.05	5.71	
Pooled Statistics		1.45(1.1-1.87)	1.47(1.34-1.58)	0.8	1.34(1.22-1.59)	1.41(1.06-1.94)	0.8	6.67(4.74-8.54)	7.28(5.71-9.97)	0.8	6.54(4.42-8.13)	6.38(4.7-8.24)	0.7	1.32(1.01-1.5)	1.28(1.08-1.73)	0.8	0.51(0.42-0.72)	0.56(0.33-0.91)	0.5	61(50.8-68.3)	57(46.2-73.7)	0.6	3.04(2.33-4.5)	2.57(0.75-4.23)	0.7	62.48(42.2-83.38)	48.88(34.5-97.058)	0.3	7.17(6.05-8.54)	7.14(5.71-8.24)	1

Supplemental Table S8. Echocardiographic findings for treatment cats. Results from echocardiographic measures of HCM cats receiving low- or high-dose DR rapamycin are presented. Results from a Wilcoxon matched-pairs signed rank test between pre- (Screening) and post-treatment (Day 56) variables are presented for individual treatment groups (low- or high-dose) as well as for pooled treatment groups (low- + high-dose); no statistically significant variables between timepoints were found in any of the comparisons. Raw values from the control HCM group are provided; descriptive statistics and statistical comparisons for the control group were not performed as no Day 56 is available.

Abbreviations: RPSA = right parasternal short-axis, RPLA = right parasternal long-axis, LA/Ao = left atrial to aortic root diameter, LA = left atrial diameter (cm), IVSd = interventricular septum diameter in diastole (mm), LVPWd Max = maximum left ventricular posterior wall diameter in diastole (mm), LVIdd = left ventricular internal diameter in diastole (cm), LVIDs = left ventricular internal diameter in systole (cm), Sx = short-axis, FS% = percent fractional shortening, LVOT maxPG = left ventricular outflow tract maximum pressure gradient (mmHg), LAF = left auricular flow velocity (cm/s), MWT = maximal wall thickness (mm).

Comparison	Downregulated	Upregulated
<i>Low-Dose* vs HCM</i>	<i>ECRG4, P2RX1, TAAR1</i> (n=3)	<i>DCLK1, KERA, MYL1, VTN</i> (n=4)
<i>High-Dose* vs HCM</i>	<i>AS3MT, FAM177B, HSD17B8, PPDPFL</i> (n=4)	<i>CNGA1, FREM1, GRAP2, ITGB8, KIT</i> (n=5)
<i>All Doses* vs HCM</i>	- (n=0)	<i>FBLN5, FREM1, ITGB8</i> (n=3)
<i>Low-* vs High-Dose</i>	- (n=0)	<i>DIPK1A</i> (n=1)

Supplemental Table S9. Shared down- and upregulated DEGs between LV and IVS tissues. Total number of shared DEGs between LV and IVS tissues are presented for each group comparison. *Down-/upregulation was assigned respective to the asterisk-marked groups in the comparison column.

Abbreviations: HCM = hypertrophic cardiomyopathy, DEG = differentially expressed gene(s), LV = left ventricle, IVS = interventricular septum.

	TBCB, TMEM161A, TSEN15, TWFI (n=99)	RPL27A, RPL28, RPL30, RPL31, RPL32, RPL35A, RPL36, RPL39, RPL4, RPL7A, RPL8, RPS11, RPS12, RPS13, RPS15, RPS15A, RPS18, RPS18, RPS20, RPS21, RPS23, RPS24, RPS25, RPS27A, RPS6, RPS6KA3, RPS8, RRAD, RRBPI, RTN4, RUVBL2, S100A10, SAFB, SAR1A, SDCBP, SEC22B, SEMA3C, SEPTIN9, SERBP1, SERPINF1, SERPINH1, SF1, SF3B1, SGCD, SGTA, SH3GLB1, SIRT2, SLC2A1, SLC44A2, SLIRP, SMIM20, SNRNP70, SNRPC, SNRPDI, SNRPE, SORBS1, SORBS1, SORBS2, SORT1, SPARCL1, SPG7, SRPRA, SRSF1, SSPN, SSR4, STBD1, SUCLG2, SUN2, SVIL, SYNCRIP, SYNPO, SYNPO2L, TARS1, TBCA, TGFBI, TGM2, THBS4, TIMM29, TINAGL1, TLN2, TMED10, TMED2, TMEM11, TMX4, TNKS1BP1, TNXB, TOMM20, TOMM22, TRIM54, TRIM63, TRIP6, TSPAN9, TTN, TUBB, TUBB6, TXNDC5, U2AF1, UBE2L3, USP28, VASP, VCAN, VNN1, WASL, WDR61, WFS1, XIRP1, XIRP2, YBX1, ZMPSTE24, ZYX (n=432)		RPS23, RPS24, RPS28, RPS3A, RPS5, RPS6, RPS6KA3, RPS8, RRAD, RRAGC, RRBPI, RSF1, RTN3, RUVBL2, S100A11, SAFB, SARS2, SBSPOP, SCN7A, SDCBP, SEC31A, SEC61A1, SELENOO, SEMA3C, SEPTIN1, SEPTIN8, SERBP1, SERPINC1, SF1, SFXN3, SH3GL1, SHC1, SIRT2, SLC20A2, SLC25A22, SLC25A3, SLC2A1, SLC30A9, SLC9A3R1, SMC1A, SMYD2, SNAP23, SNRNP200, SNRNP70, SNRPA1, SNRPDI, SNRPD3, SNRPE, SNX6, SOD3, SORBS1, SORBS2, SORT1, SPCS2, SRI, SRSF1, SSPN, ST13, STAT3, STBD1, STOML2, STRN3, SUGCT, SUN1, SUN2, SVIL, SYNCRIP, SYNE1, SYNPO, SYNPO2L, TARDBP, TBCB, TBRG4, TGFBI, THBD, THNSL1, TIMM29, TIMMDC1, TINAGL1, TIPRL, TLN2, TMED2, TMEM120A, TMEM201, TMPO, TNKS1BP1, TNPO1, TNPO2, TNXB, TOMM20, TOMM7, TRA2B, TRIM28, TRIM54, TRIM63, TRIP6, TUBB, TXNDC5, U2AF1, UAPIL1, UBA7, UBE2G2, UBXN1, UCHL5, UPF1, USP13, USP28, USP7, VAPB, VASP, VCAN, VDAC3, VLDLR, VNN1, VPS36, VTA1, WDR82, XIRP1, XIRP2, XPO7, YBX1, YBX3 (n=460)
Low- ^a vs High-Dose	- (n=0)	FBP2, USP15 (n=2)	NADPH (n=1)	AFP, PPM1K, ZBED8 (n=3)

Supplemental Table S10. Total global DAPs of LV and IVS tissues. Global LV and IVS DAPs of all study comparisons are reported. Bolded protein symbols represent shared DAPs between low-dose vs HCM and high-dose vs HCM comparisons per tissue type. All under- (log2FoldChange<-1) and overabundant (log2FoldChange>1) DAPs reported here were statistically significant (P -value_{adjusted}<0.05). *Under-/overabundance was assigned respective to the asterisk-marked groups in the comparison column. Abbreviations: HCM = hypertrophic cardiomyopathy, DAP = differentially abundant peptide(s), LV = left ventricle, IVS = interventricular septum.

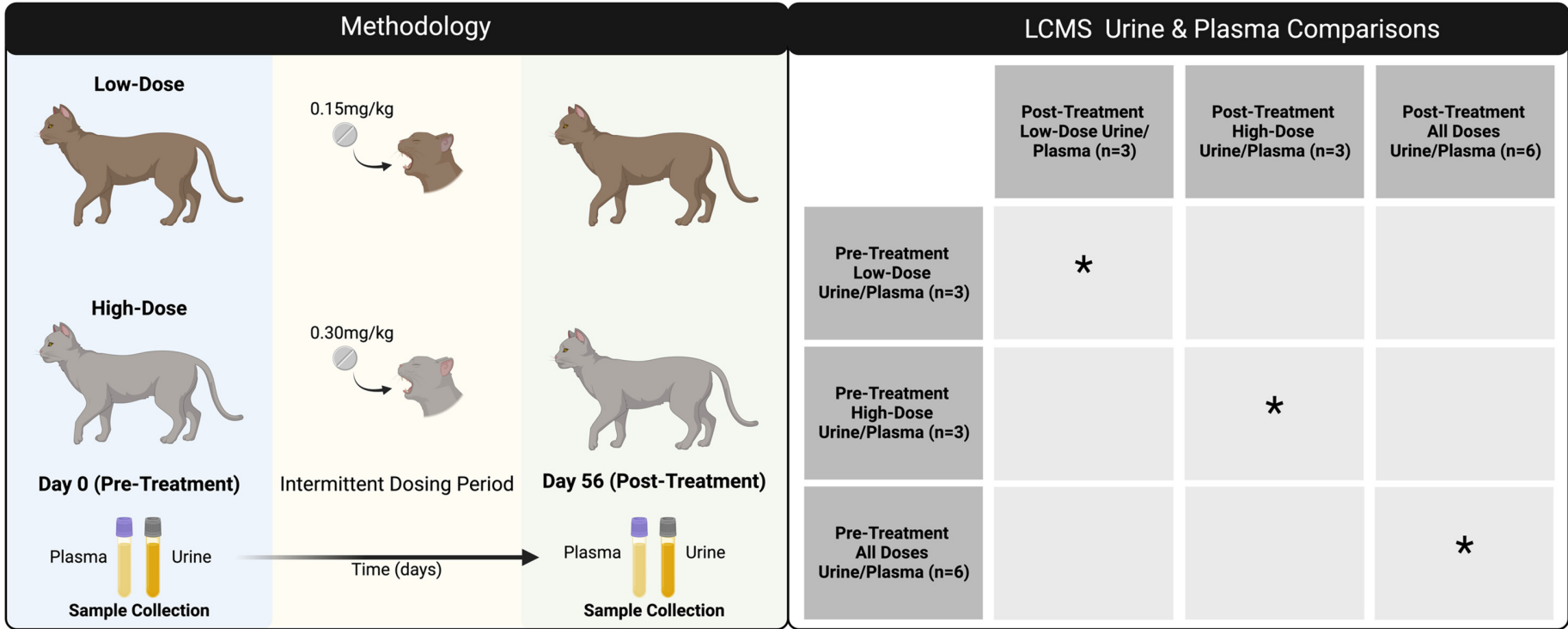
<i>Comparison</i>	Plasma		Urine	
	Underabundant	Overabundant	Underabundant	Overabundant
<i>Low-Dose (pre) vs Low-Dose (post)*</i>	- (n=0)	- (n=0)	ALDOB, AQP2, ATP1B1, ATP5F1B, B3GNT2, CDH11, COL18A1, CRYZ, FES, H2B, HSPA5, IL1RAP, ISLR, LOC101091370, LOC101098453, MYL1, NIT2, NUTF2, PGK1, PODXL, PPIA, PRSS53, PRSS8, RAB7A, SLC5A10, TREML1 (n=26)	ASGR1, FSTL3, NPC1L1, PRNP, VASN (n=5)
<i>High-Dose (pre) vs High-Dose (post)*</i>	- (n=0)	- (n=0)	- (n=0)	- (n=0)
<i>All Doses (pre) vs All Doses (post)*</i>	ACE2, CXC, IGFBP7, LOC101080826, THBS1, TIMP2, VWF (n=7)	APOA1, APOA4, APOC4, VNN1 (n=4)	AGA, AQP2, ARSA, B3GNT2, CD300LG, CD63, CHMP2B, CILP, CRYZ, EFNB2, FABP3, FES, GALC, GBA3, H2B, HAAO, IDH1, IGFBP1, IL1RAP, IL4R, ISLR, KCNJ15, LBP, LOC101091370, LRRC19, MTA2, NEU1, NUTF2, OLFM1, PBLD, PLA2G15, PMM2, PODXL, PPIA, PPIB, RAC1, RHBG, RRAS2, SELENBP1, SHISA7, SLC25A3, SLC3A1, SLC5A10, SORT1, SPON1, TMEM123, TREML1, TTN, TUBB, TUBB4B (n=50)	AFM, ALB, ANGPTL2, ANGPTL3, ANXA6, APBB1, APOH, ASGR1, C4A, C4BPA, C4BPA, CD27, CD55, CFI, DSC1, ELANE, EPS8, FABP5, FBLN1, GC, GOLM1, GPR108, GSN, HRG, ICOSLG, ITIH4, KRT10, KRT18, KRT2, LACTB2, NPC1L1, PEAR1, PLG, PZP, SIAE, STC1, TF, VASN, WFDC2 (n=39)

Supplemental Table S11. Total global DAPs of plasma and urine samples. Global plasma and urine DAPs of all study comparisons are reported. All under- ($\log_2\text{FoldChange} < -1$) and overabundant ($\log_2\text{FoldChange} > 1$) DAPs reported here were statistically significant ($P\text{-value}_{\text{adjusted}} < 0.05$). *Under-/overabundance was assigned respective to the asterisk-marked groups in the comparison column. Abbreviations: HCM = hypertrophic cardiomyopathy, DAP = differentially abundant peptide(s).

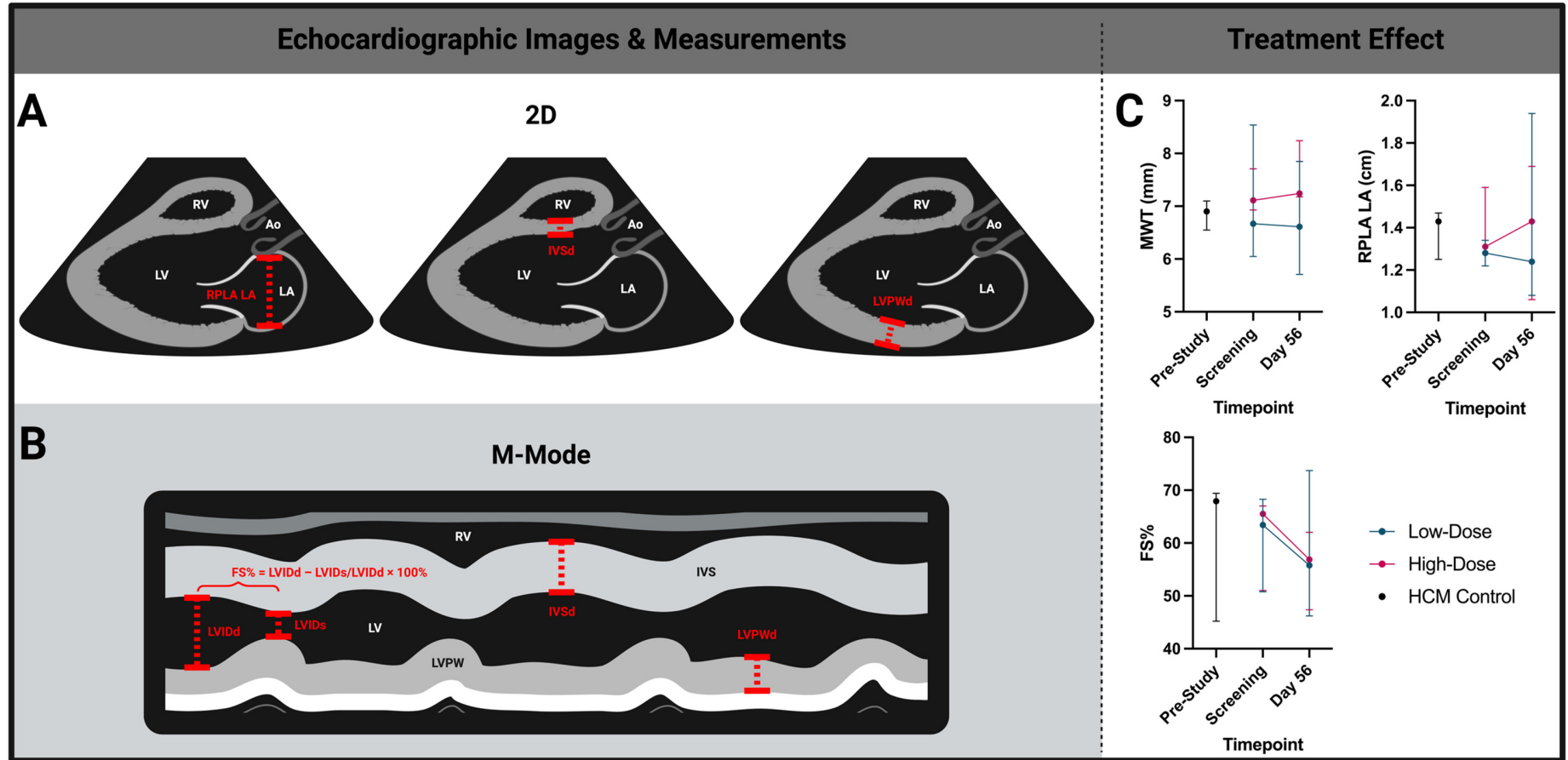
<i>Method</i>	Enrichment Analysis			Specimen	Comparison	Regulation
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	Low-Dose vs HCM	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	Low-Dose vs HCM	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	High-Dose vs HCM	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	High-Dose vs HCM	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	All Doses vs HCM	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	All Doses vs HCM	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	Low- vs High-Dose	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	LV	Low- vs High-Dose	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	Low-Dose vs HCM	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	Low-Dose vs HCM	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	High-Dose vs HCM	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	High-Dose vs HCM	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	All Doses vs HCM	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	All Doses vs HCM	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	Low- vs High-Dose	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	IVS	Low- vs High-Dose	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	Plasma	Low-Dose Pre vs Post	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	Plasma	Low-Dose Pre vs Post	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	Plasma	High-Dose Pre vs Post	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	Plasma	High-Dose Pre vs Post	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	Plasma	All Doses Pre vs Post	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	Plasma	All Doses Pre vs Post	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	Urine	Low-Dose Pre vs Post	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	Urine	Low-Dose Pre vs Post	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	Urine	High-Dose Pre vs Post	UA
<i>LCMS</i>	GO CC	GO BP	KEGG	Urine	High-Dose Pre vs Post	OA
<i>LCMS</i>	GO CC	GO BP	KEGG	Urine	All Doses Pre vs Post	UA

<i>LCMS</i>	GO CC	GO BP	KEGG	Urine	All Doses Pre vs Post	OA
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	Low-Dose vs HCM	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	Low-Dose vs HCM	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	High-Dose vs HCM	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	High-Dose vs HCM	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	All Doses vs HCM	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	All Doses vs HCM	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	Low- vs High-Dose	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	LV	Low- vs High-Dose	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	Low-Dose vs HCM	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	Low-Dose vs HCM	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	High-Dose vs HCM	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	High-Dose vs HCM	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	All Doses vs HCM	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	All Doses vs HCM	UR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	Low- vs High-Dose	DR
<i>RNA-Seq</i>	GO CC	GO BP	KEGG	IVS	Low- vs High-Dose	UR

Supplemental Table S12. Total GO and KEGG term analyses on proteomic and transcriptomic comparisons. All possible cellular component and biological processes GO and KEGG pathway term analyses are listed (n=132). Results from identified enriched genes/proteins for proteomic (n=39) and transcriptomic (n=23) GO and/or KEGG term analyses are bolded. Abbreviations: LCMS = liquid mass spectrometry, GO = gene ontology, CC = cellular component, BP = biological processes, LV = left ventricle, IVS = interventricular septum, HCM = hypertrophic cardiomyopathy, UA = underabundant, OA = overabundant, DR = downregulated, UR = upregulated.

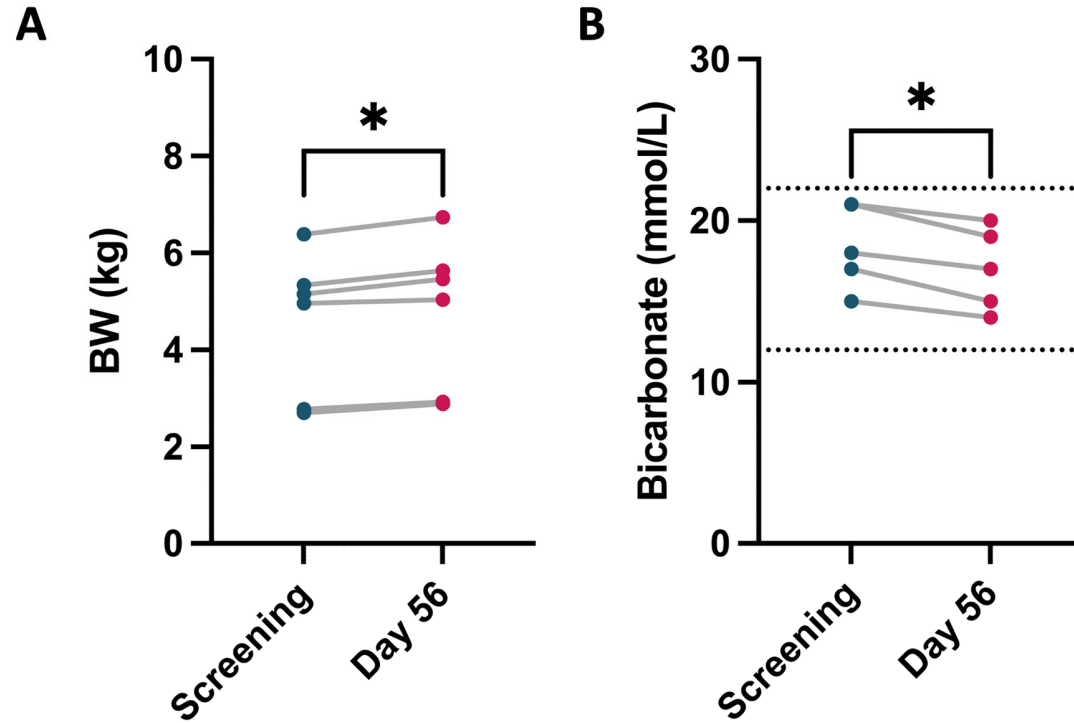


Supplemental Figure S1. Methodology and proteomic comparisons of pre- and post-treatment urine and plasma samples. Illustrative description of LCMS methods and sample collection specification are illustrated. LCMS proteomic comparisons between the pre- and post-treatment of low-, high-, and pooled all dose (low- & high-dose) groups are presented for urine and plasma samples. *Asterisks in the above chart denote comparisons that were performed in this study.



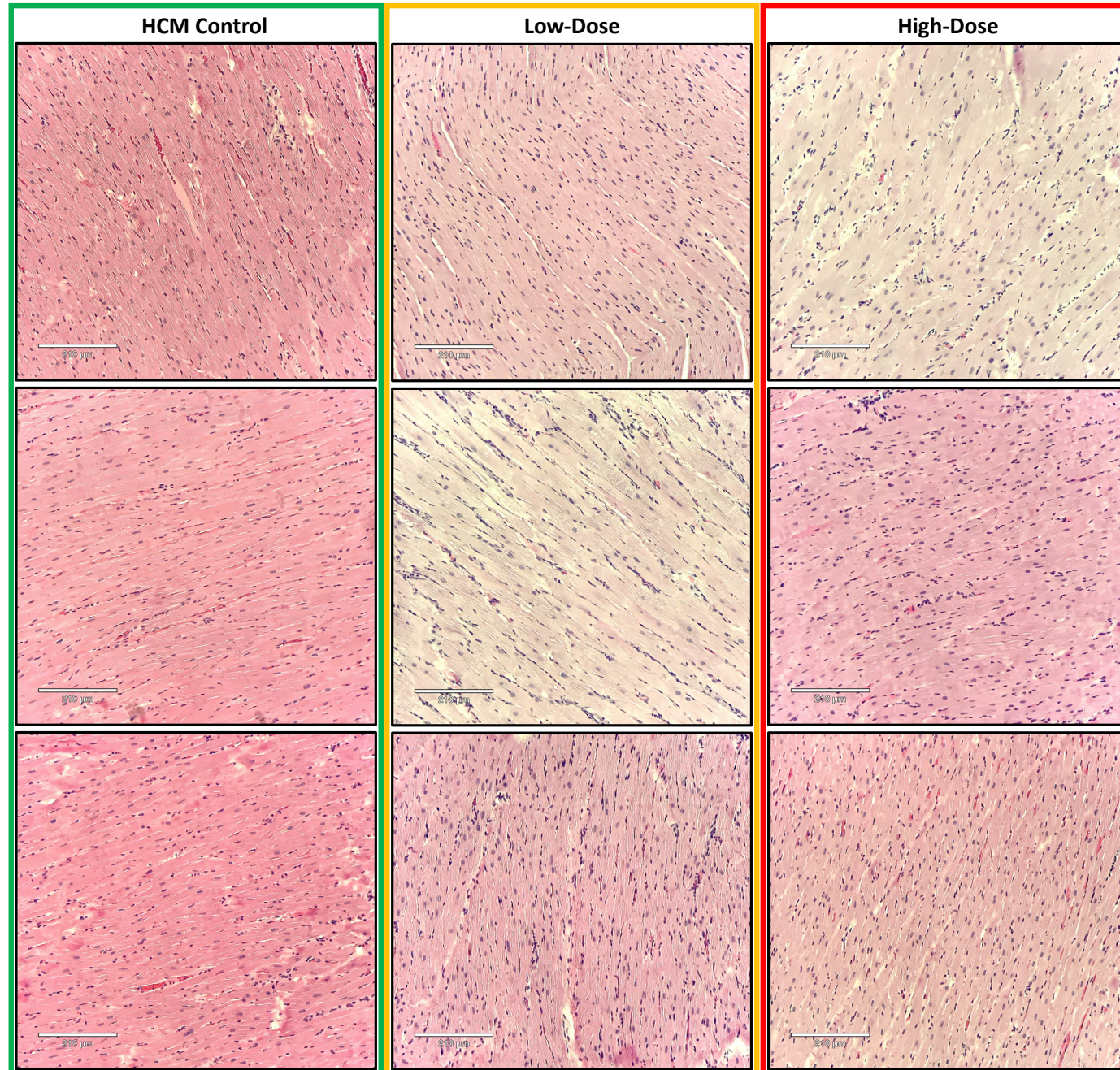
Supplemental Figure S2. Key echocardiographic measurements and treatment-related changes. Representative illustrations of echocardiographic images obtained in 2D right parasternal long-axis (A) and M-mode right parasternal short-axis (B) for the measurement of diastolic maximum wall thickness (MWT) from the IVSd or LVPWd, LA maximal diameter (RPLA LA), and percent LV fractional shortening (FS%) obtained from LV internal diameter measures in diastole and systole (LVIDd and LVIDs, respectively). Screening and Day 56 timepoint echocardiographic measurements are reported for HCM control (single timepoint pre-study) and low- and high-dose treated cats (for Screening and Day 56). In these graphs the median is shown with error bars representing the minimum and maximum values (C); note, the single echocardiographic assessment of untreated HCM controls shows that control cats were well-matched phenotypically to the treated cats.

Abbreviations: LV = left ventricle, RV = right ventricle, LA = left atrium, Ao = aorta, RPLA = right parasternal long-axis, RPLA LA = right parasternal long-axis LA diameter, IVS = interventricular septum, IVSd = diastolic interventricular septum thickness, LVPW = left ventricular posterior wall, LVPWd = diastolic left ventricular posterior wall thickness, FS% = percent fractional shortening, LVIDd = diastolic left ventricular internal diameter, LVIDs = systolic left ventricular internal diameter, MWT = maximum wall thickness, HCM = hypertrophic cardiomyopathy.

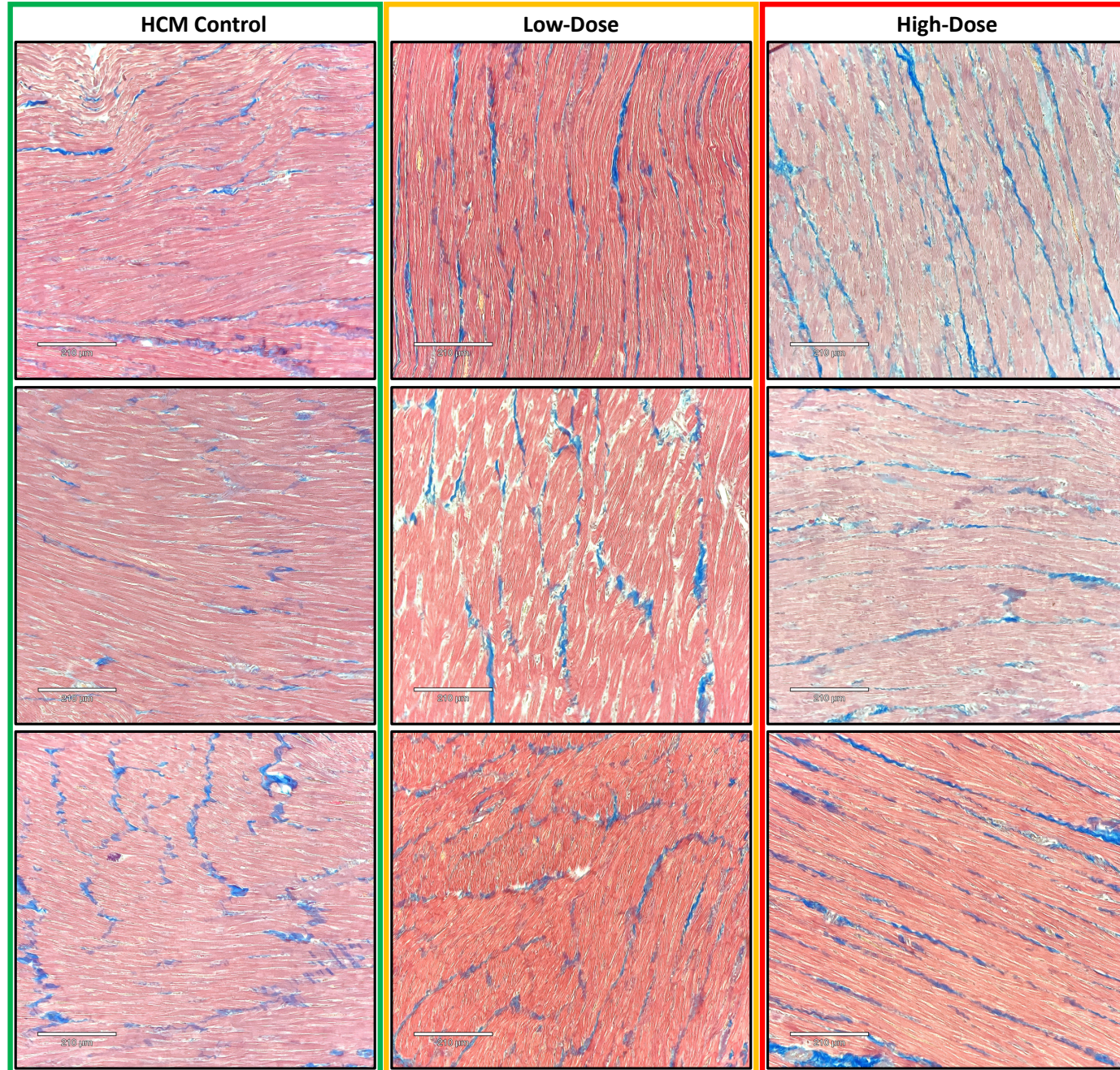


Supplemental Figure S3. Statistically significant physical exam and biochemistry variables. Data points depicting a statistically significant increase in BW (A) and a decrease in blood bicarbonate/total CO₂ levels (B) from pre- (teal) to post-treatment (pink) timepoints for pooled treatment groups (low- + high-dose) are shown ($P<0.03$ and $P<0.03$, respectively). Normal reference range values (12-22mmol/L) for blood bicarbonate/total CO₂ are plotted (dotted lines). * $P<0.05$.

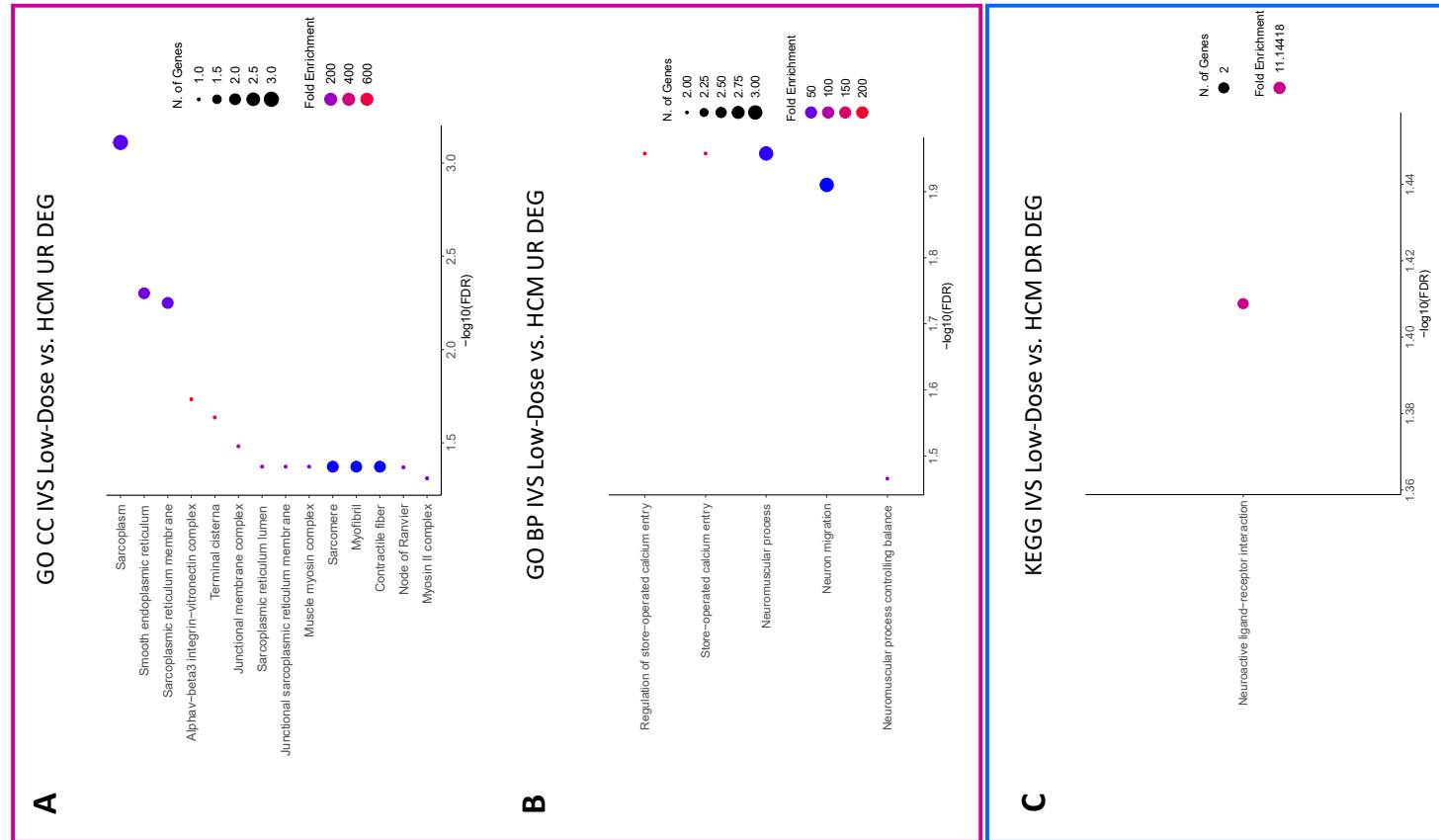
Abbreviations: BW = body weight.



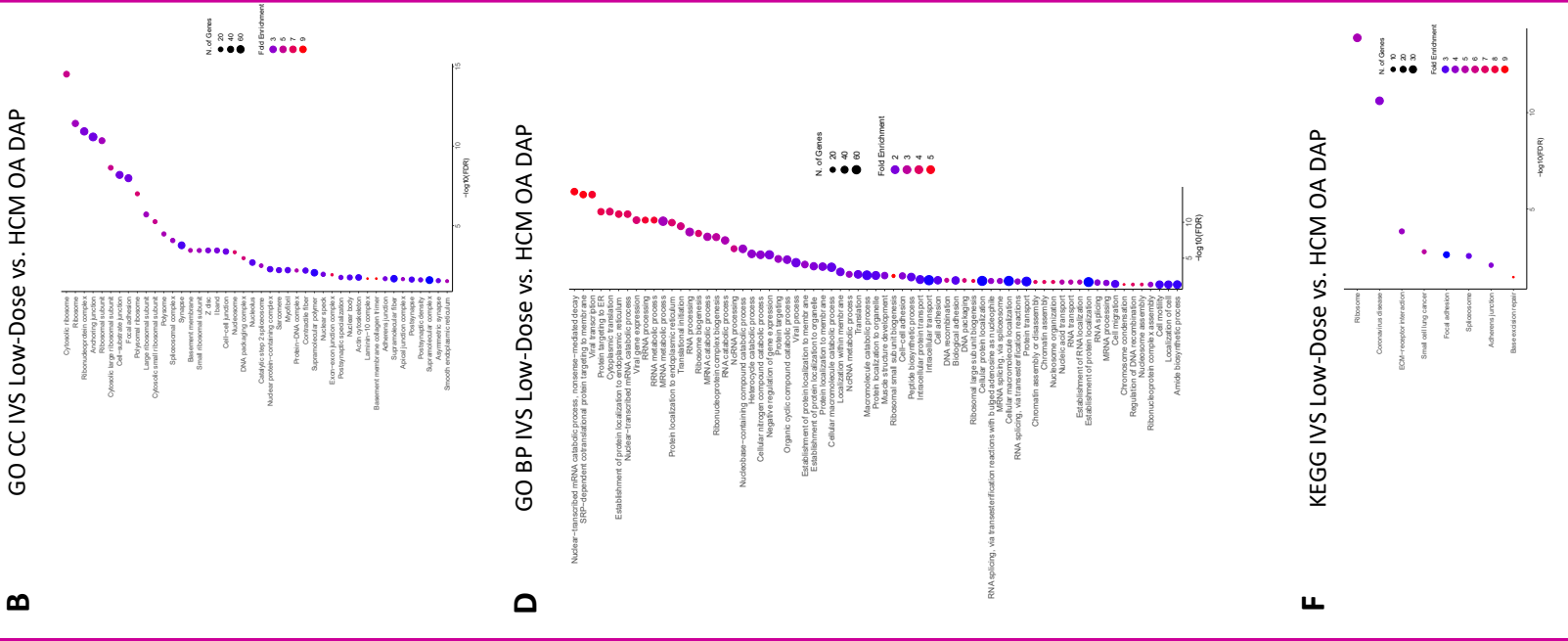
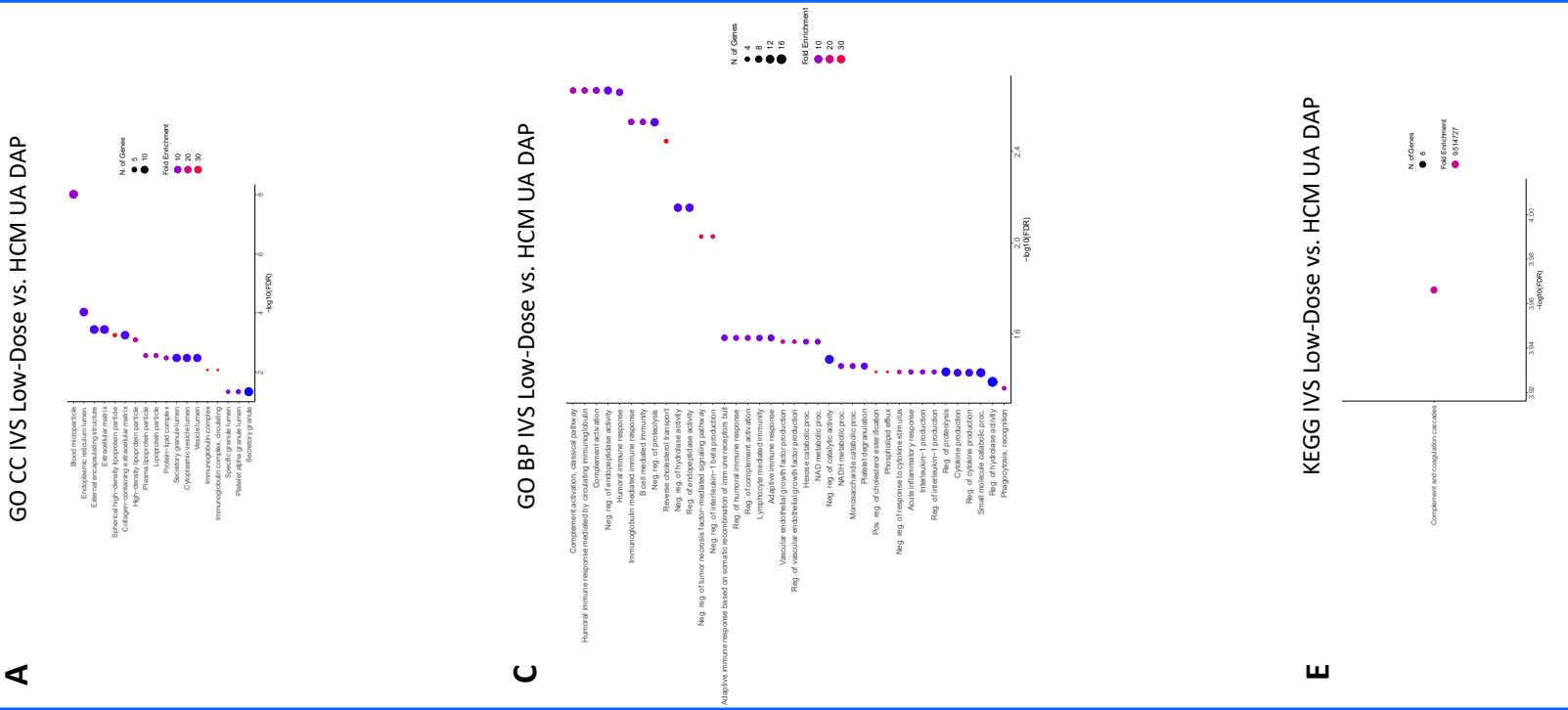
Supplemental Figure S4. Representative H&E staining of all nine study cats. Histopathologic hematoxylin and eosin (H&E) slide images via light microscopy for all three cats in the HCM control (green box), all three cats in the low-dose (yellow box), and all three cats in the high-dose group (red box) are provided. Images were obtained on the posterior wall of the LV adjacent to papillary muscles. White scale bar=210µm.
Abbreviations: HCM = hypertrophic cardiomyopathy.



Supplemental Figure S5. Representative Masson's trichrome staining of all nine study cats. Histopathologic Masson's trichrome slide images via light microscopy for all three cats in the HCM control (green box), all three cats in the low-dose (yellow box), and all three cats in the high-dose group (red box) are provided. Images were obtained on the posterior wall of the LV adjacent to papillary muscles. White scale bar=210µm.
Abbreviations: HCM = hypertrophic cardiomyopathy.

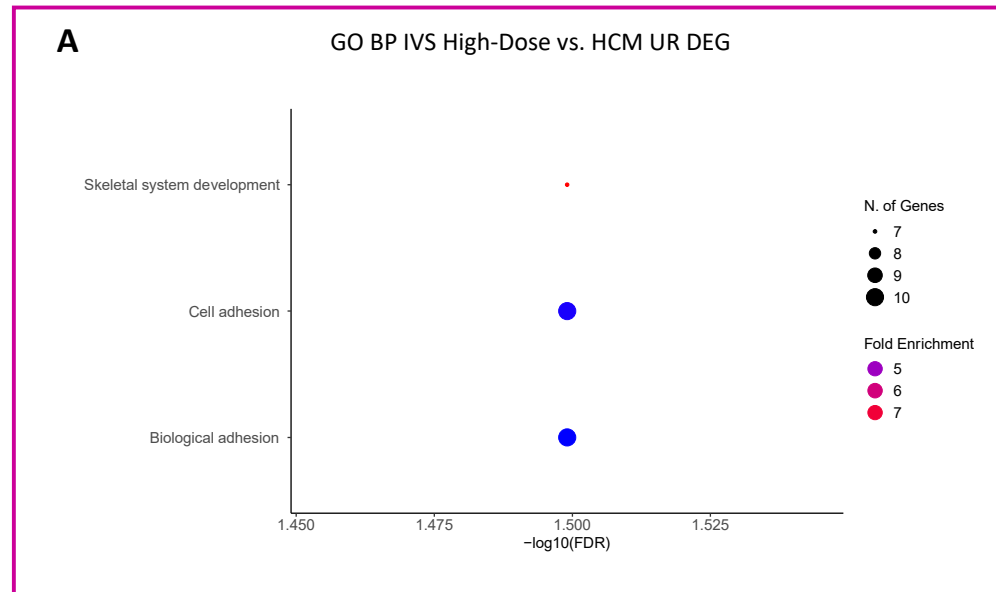


Supplemental Figure S6. Enriched terms for IVS DEGs in the low-dose vs HCM comparison. Enrichment plots for GO CC (A), GO BP (C), and KEGG pathway (C) term analyses are presented for down- (blue box) and upregulated (pink box) DEGs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of genes binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively. Abbreviations: HCM = hypertrophic cardiomyopathy, IVS = interventricular septum, GO = gene ontology, CC = cellular components, BP = biological processes, UR = upregulated, DR = downregulated, DEG = differentially expressed gene(s).



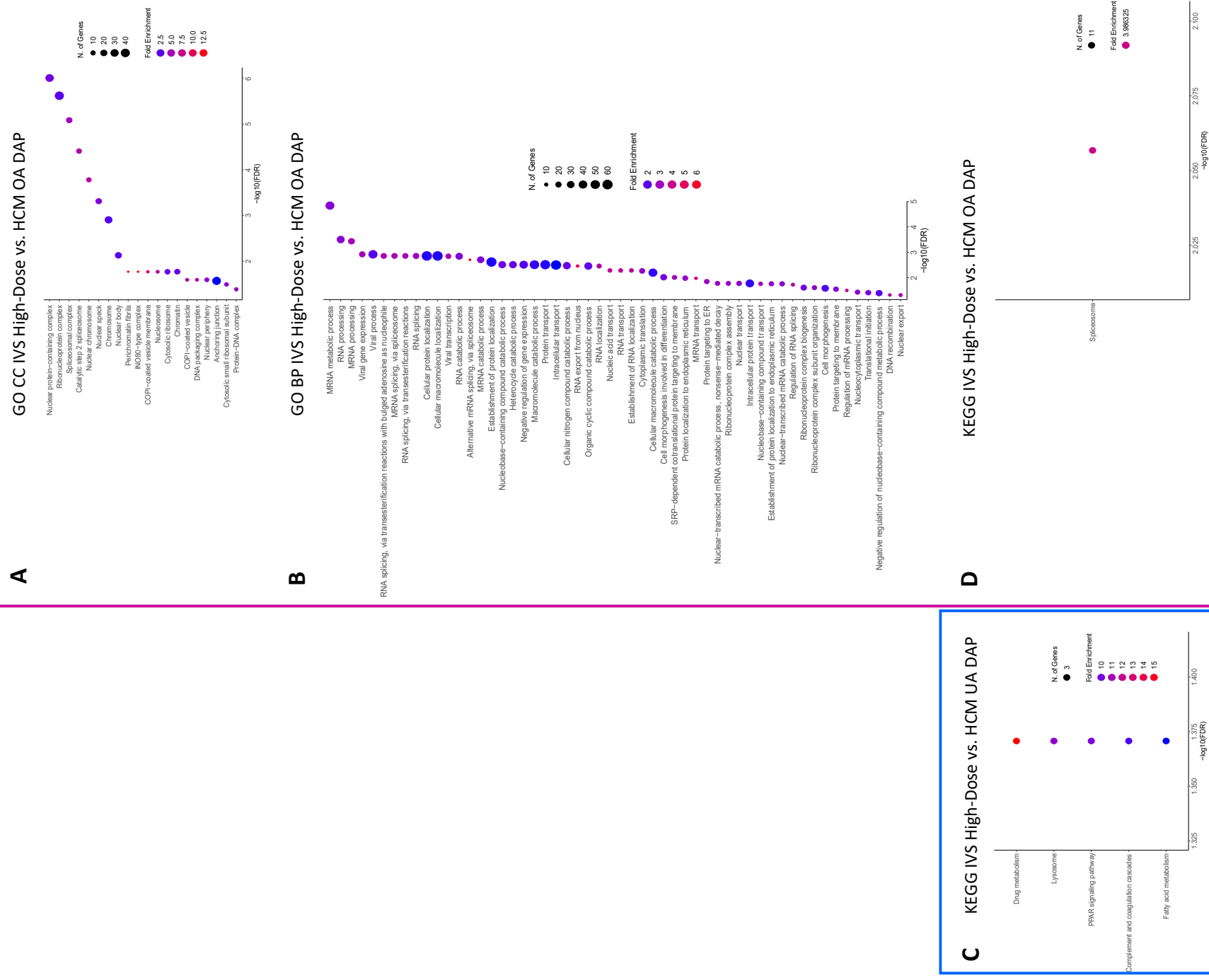
Supplemental Figure S7. Enriched terms for IVS DAPs in the low-dose vs HCM comparison. Enrichment plots for GO CC (A & B), GO BP (C & D), and KEGG pathway (E & F) term analyses are presented for under- (blue box) and overabundant (pink box) DAPs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of proteins binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

Abbreviations: HCM = hypertrophic cardiomyopathy, IVS = interventricular septum, GO = gene ontology, CC = cellular components, BP = biological processes, UA = underabundant, OA = overabundant, DAP = differentially abundant peptide(s).



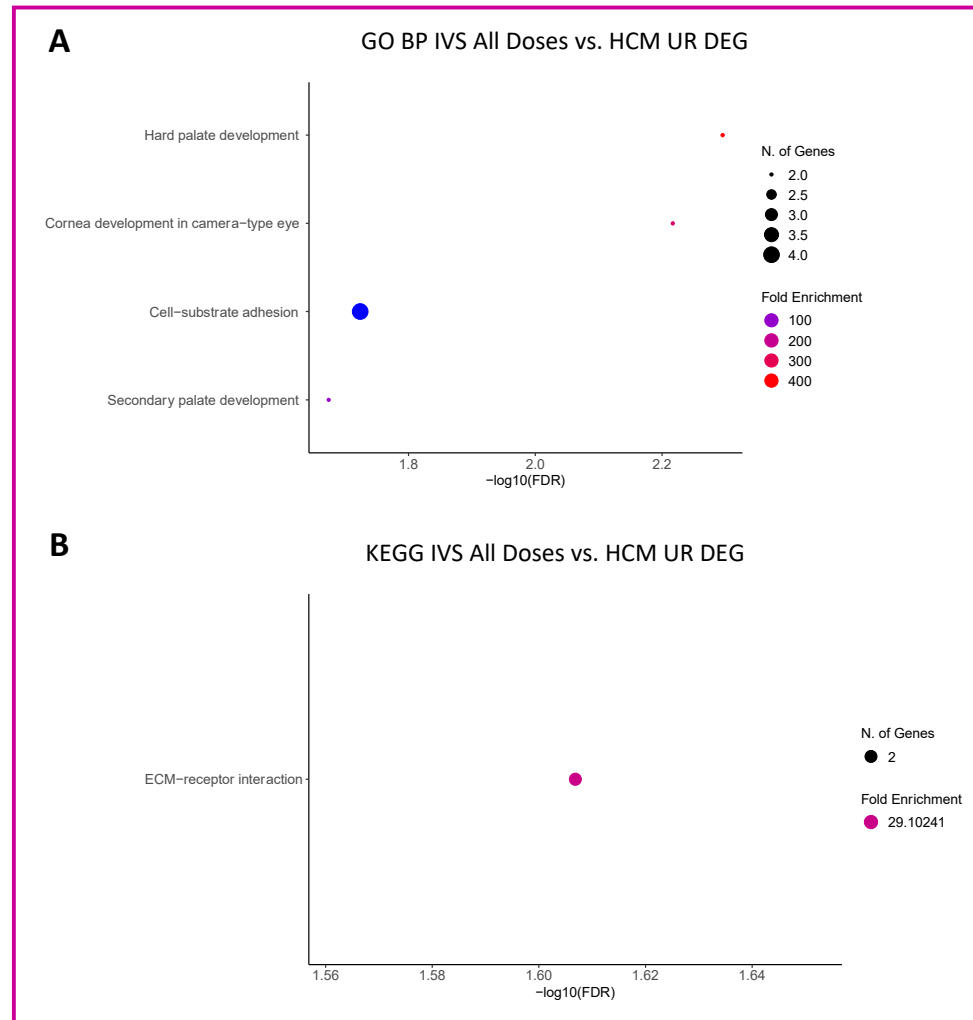
Supplemental Figure S8. Enriched terms for IVS DEGs in the high-dose vs HCM comparison. Enrichment plot for GO CC (A) term analysis are presented for upregulated (pink box) DEGs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of genes binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

Abbreviations: HCM = hypertrophic cardiomyopathy, IVS = interventricular septum, GO = gene ontology, BP = biological processes, UR = upregulated, DEG = differentially expressed gene(s).



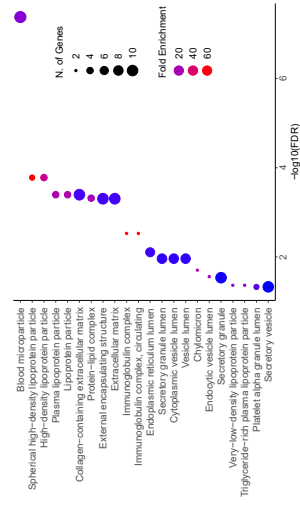
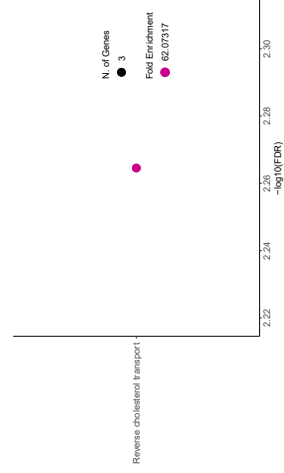
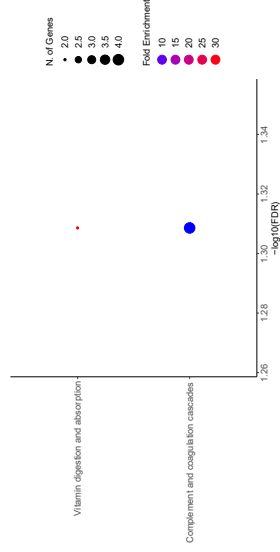
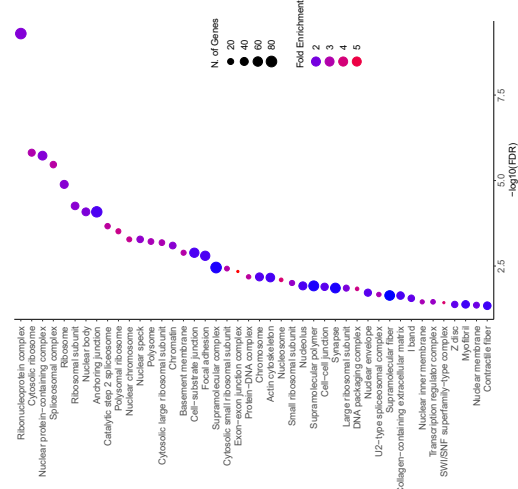
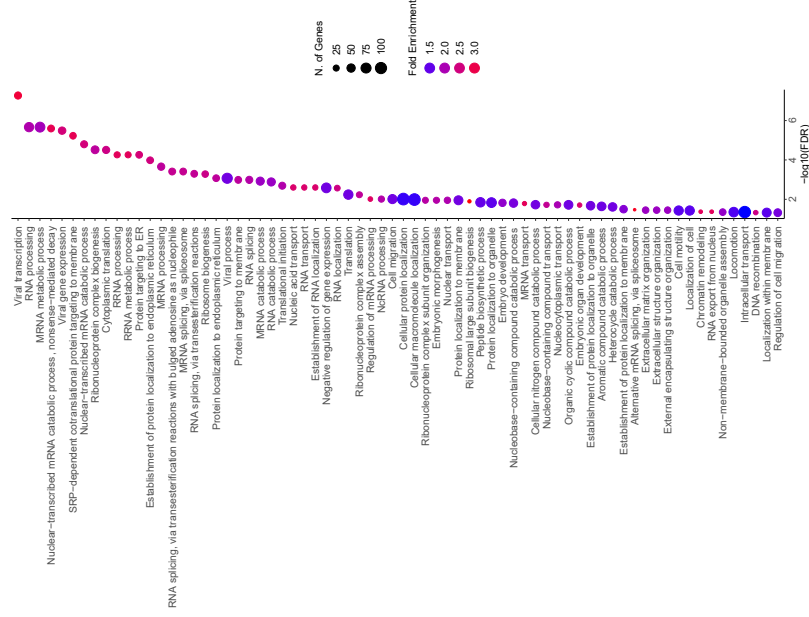
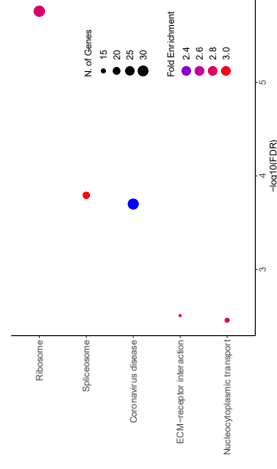
Supplemental Figure S9. Enriched terms for IVS DAPs in the high-dose vs HCM comparison. Enrichment plots for GO CC (A), GO BP (C), and KEGG pathway (C & D) term analyses are presented for under- (blue box) and overabundant (pink box) DAPs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of proteins binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

Abbreviations: HCM = hypertrophic cardiomyopathy, IVS = interventricular septum, GO = gene ontology, CC = cellular components, BP = biological processes, UA = underabundant, OA = overabundant, DAP = differentially abundant peptide(s).



Supplemental Figure S10. Enriched terms for IVS DEGs in the pooled all dose vs HCM comparison. Enrichment plot for GO BP (A) and KEGG pathway (B) term analyses are presented for upregulated (pink box) DEGs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of genes binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

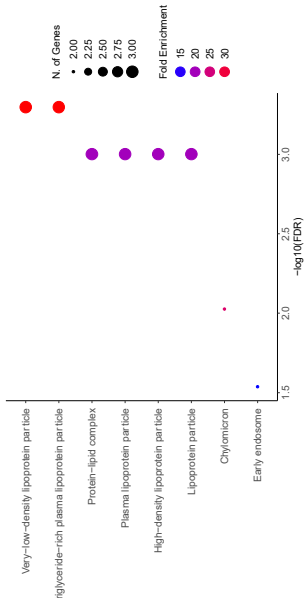
Abbreviations: HCM = hypertrophic cardiomyopathy, IVS = interventricular septum, GO = gene ontology, BP = biological processes,
UR = upregulated, DEG = differentially expressed gene(s).

A GO CC IVS All-Doses vs. HCM UA DAP**C** GO BP IVS All Doses vs. HCM UA DAP**E** KEGG IVS All Doses vs. HCM UA DAP**B** GO CC IVS All Doses vs. HCM OA DAP**D** GO BP IVS All Doses vs. HCM OA DAP**F** KEGG IVS All Doses vs. HCM OA DAP

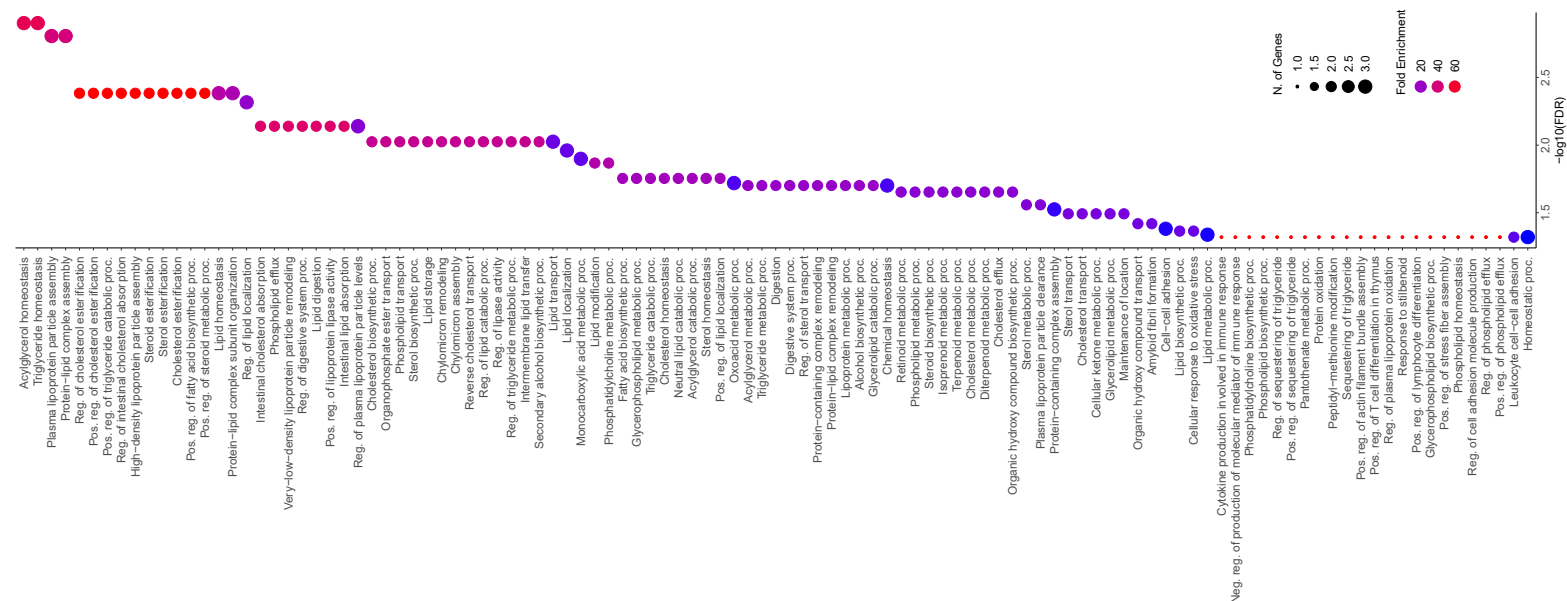
Supplemental Figure S11. Enriched terms for IVS DAPs in the pooled all doses vs HCM comparison. Enrichment plots for GO CC (A & B), GO BP (C & D), and KEGG pathway (E & F) term analyses are presented for under- (blue box) and overabundant (pink box) DAPs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of proteins binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

Abbreviations: HCM = hypertrophic cardiomyopathy, IVS = interventricular septum, GO = gene ontology, CC = cellular components, BP = biological processes, UA = underabundant, OA = overabundant, DAP = differentially abundant peptide(s).

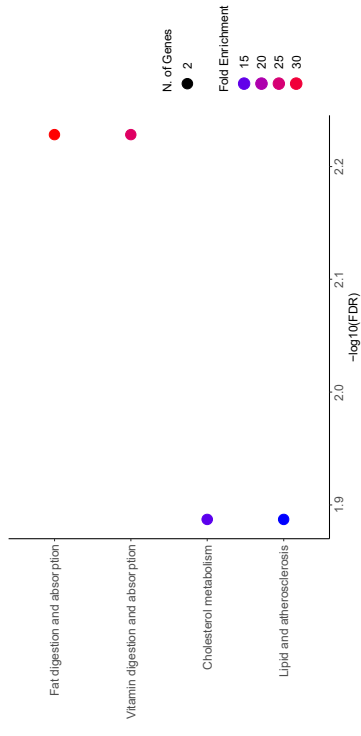
A GO CC Plasma All Doses Pre- vs. Post-Treatment OA DAP



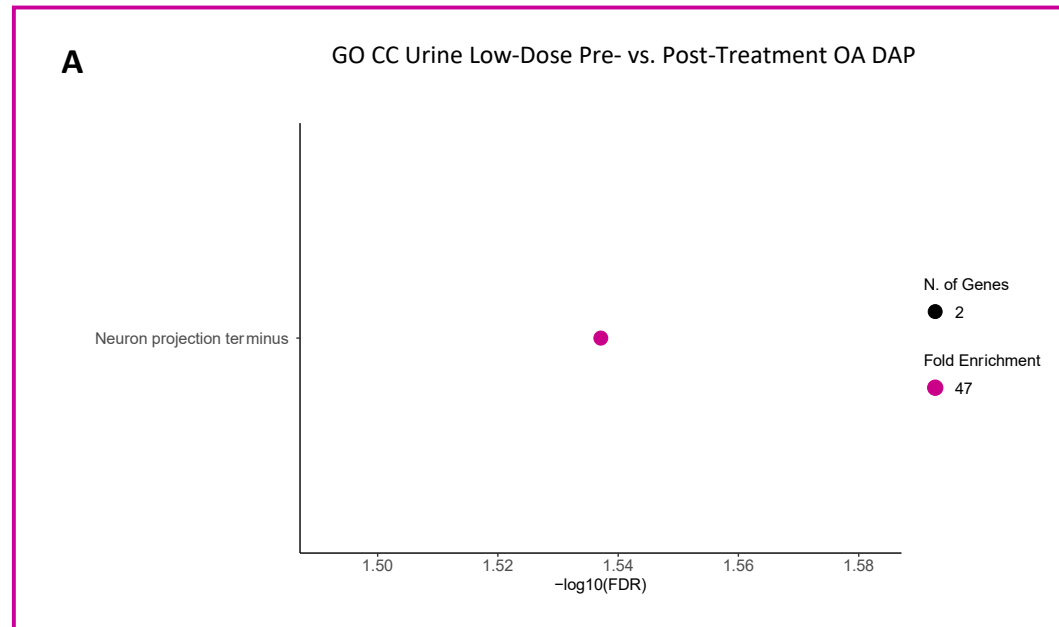
B GO BP Plasma All Doses Pre- vs. Post-Treatment OA DAP



C KEGG Plasma All Doses Pre- vs. Post-Treatment OA DAP

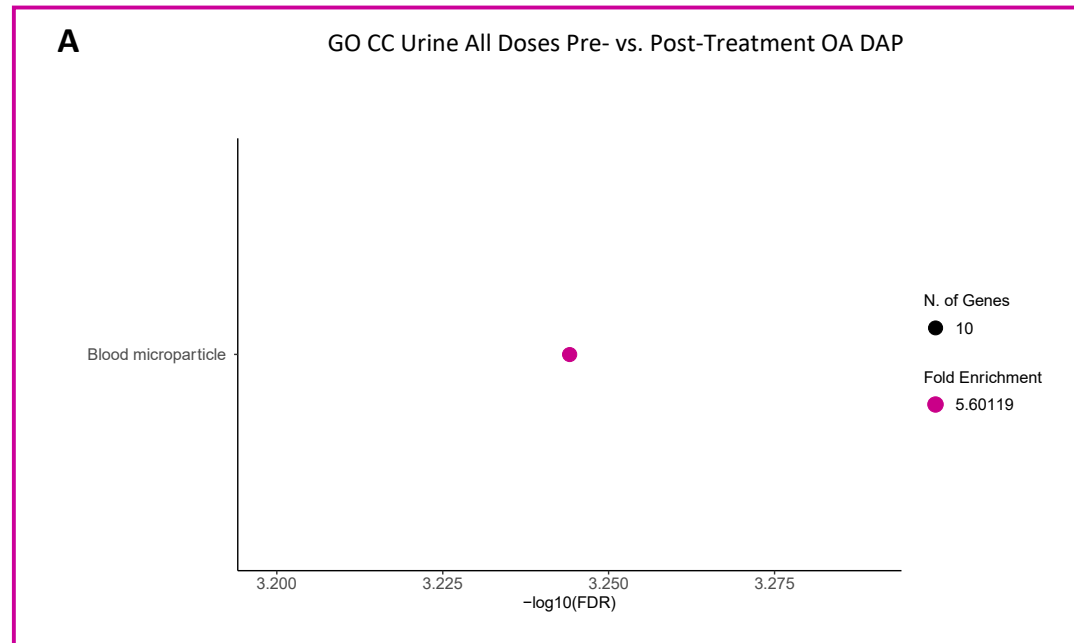


Supplemental Figure S12. Enriched terms for plasma pre- and post-treatment DAPs in the pooled all doses group. Enrichment plots for GO CC (A), GO BP (B), and KEGG pathway (C) term analyses are presented for overabundant (pink box) DAPs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of proteins binned to a given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively. Abbreviations: GO = gene ontology, CC = cellular components, BP = biological processes, OA = overabundant, DAP = differentially abundant peptide(s).



Supplemental Figure S13. Enriched term for urine pre- and post-treatment DAPs in the low-dose group. Enrichment plot for the GO CC (A) term analysis is presented for overabundant (pink box) DAPs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Size of individual points depict the total number of proteins binned to the given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

Abbreviations: GO = gene ontology, CC = cellular components, OA = overabundant, DAP = differentially abundant peptide(s).



Supplemental Figure S14. Enriched term for urine pre- and post-treatment DAPs in the pooled all doses group. Enrichment plot for the GO CC (A) term analysis is presented for overabundant (pink box) DAPs. The y-axis depicts identified enriched terms, whereas the x-axis depicts the terms' significance ($-\log_{10}[\text{FDR}]$). Terms are sorted according to statistical significance; the top-most terms on the y-axis constitute the most statistically significant of terms. Size of individual points depict the total number of proteins binned to the given enriched term; high or low fold enrichment is represented by red or blue coloring, respectively.

Abbreviations: GO = gene ontology, CC = cellular components, OA = overabundant, DAP = differentially abundant peptide(s).