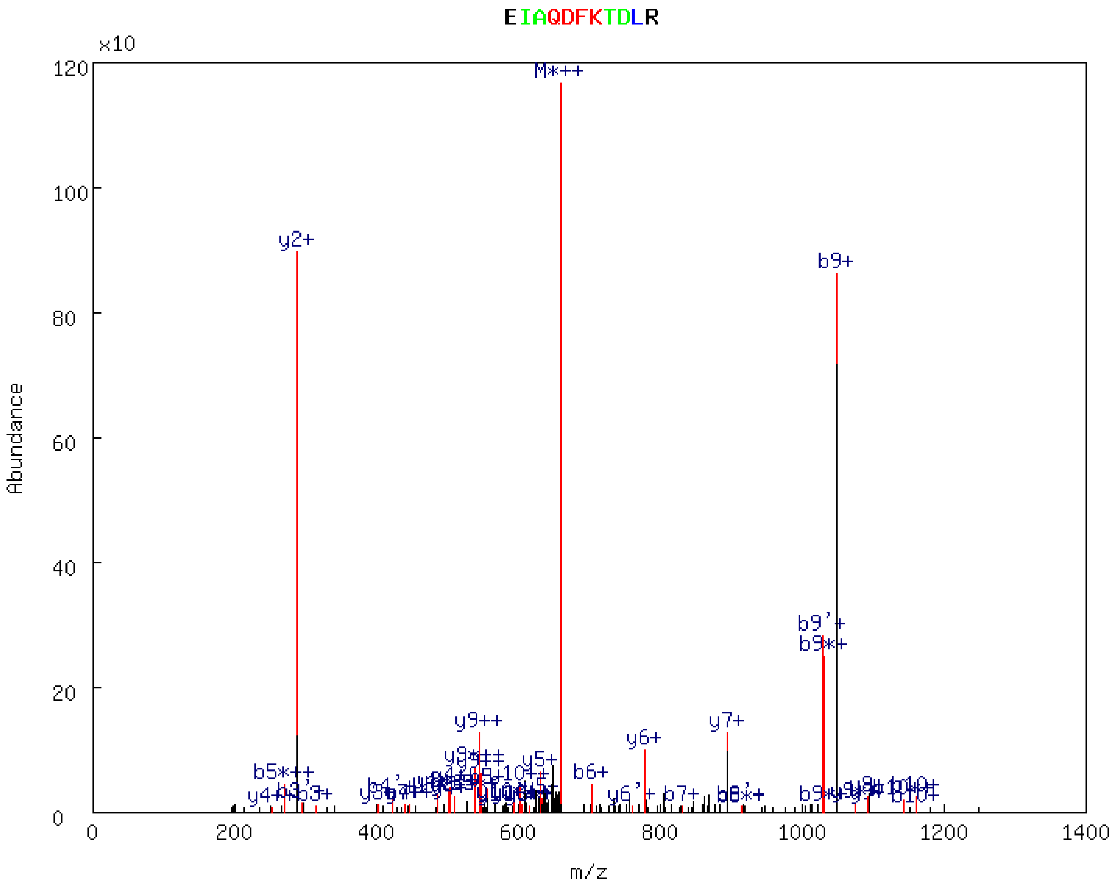
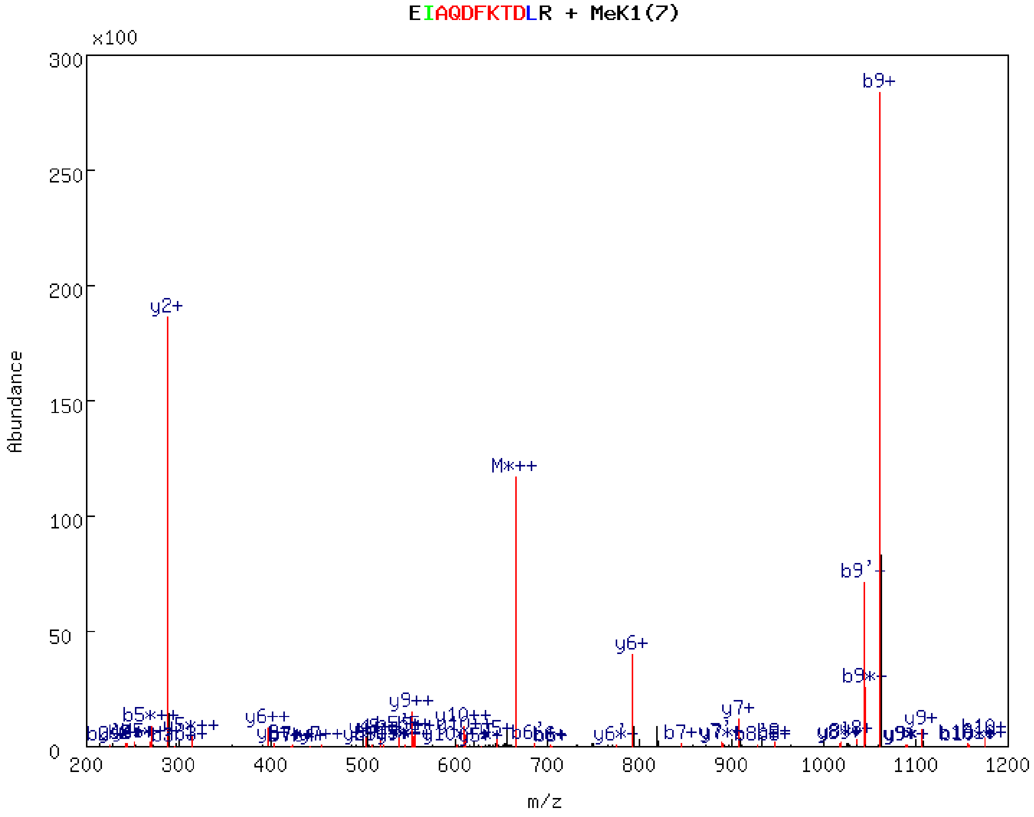
Supplemental Figure 1A. H3 EIAQDF^{79}K(Me$_0$)TDLR Peptide fragment



Index	scan#	charge	score	pp	pp_2	pp_{tag}	m/z	MW(obs)	MW	delta	miss	Unique sequence + modifications
1080	2480	+2	47	11.0	8.4	5.3	668.3484	1335.6895	1335.6903	-0.0008	0	× EIAQDFKTDLR

#	b'^{++}	b^{*++}	b^{++}	b'^{+}	b^{*+}	b^{+}	seq	y'^{++}	y^{*++}	y^{++}	y'^{+}	y^{*+}	y^{+}	#
1	56.52	--	65.53	112.04	--	130.05	**E**	**659.34**	**659.84**	668.35	1317.68	1318.66	1335.69	**M**
2	113.07	--	122.07	225.12	--	243.13	**I**	**594.82**	**595.31**	**603.83**	1188.64	1189.62	1206.65	**10**
3	148.58	--	157.59	**296.16**	--	**314.17**	**A**	**538.28**	**538.77**	**547.29**	1075.55	**1076.54**	**1093.56**	**9**
4	212.61	213.11	221.62	**424.22**	425.20	**442.23**	**Q**	**502.76**	**503.25**	**511.77**	1004.52	1005.50	1022.53	**8**
5	270.13	**270.62**	279.13	**539.25**	**540.23**	**557.26**	**D**	438.73	439.22	**447.74**	876.46	877.44	**894.47**	**7**
6	343.66	344.15	352.67	686.31	687.30	**704.32**	**F**	381.22	381.71	390.22	**761.43**	762.41	**779.44**	**6**
7	407.71	408.20	416.71	814.41	815.39	**832.42**	**K**	307.68	308.18	316.69	614.36	**615.35**	**632.37**	**5**
8	458.23	458.72	467.24	**915.46**	**916.44**	933.47	**T**	243.64	244.13	**252.64**	486.27	**487.25**	**504.28**	**4**
9	515.75	516.24	524.75	**1030.48**	**1031.47**	**1048.49**	**D**	193.11	193.61	202.12	385.22	386.20	**403.23**	**3**
10	572.29	572.78	581.29	1143.57	**1144.55**	**1161.58**	**L**	135.60	136.09	144.61	270.19	**271.18**	**288.20**	**2**
	--	--	--	--	--	--	**R**	79.06	79.55	88.06	157.11	158.09	175.12	**1**

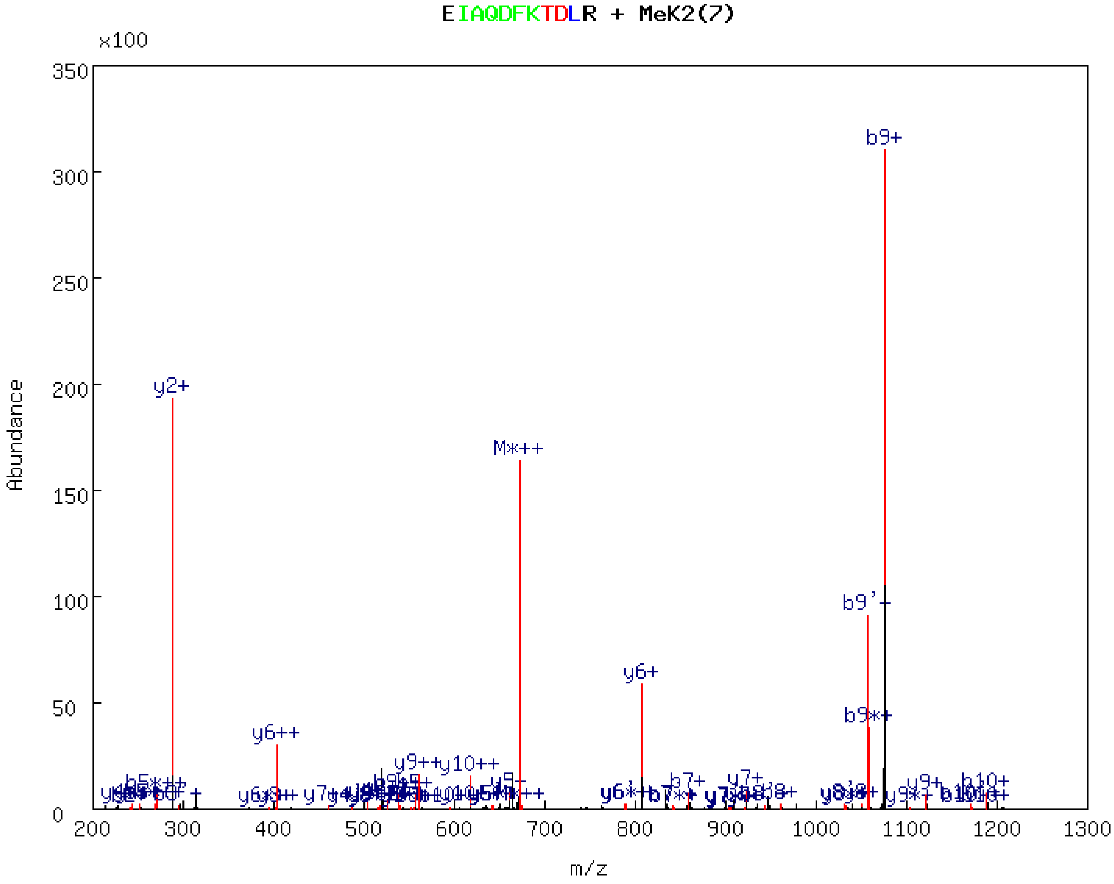
Supplemental Figure 1B. H3 EIAQDF^{79}K(Me$_1$)TDLR Peptide fragment



Index	scan#	charge	score	pp	pp_2	pp_{tag}	m/z	MW(obs)	MW	delta	miss	Unique sequence + modifications
893	1563	+2	56	**21.5**	**8.3**	**10.9**	675.3580	1349.7088	1349.7060	0.0028	0	× **EIAQDFKTDLR** + MeK1(7)

#	$b^{\prime++}$	b^{*++}	b^{++}	$b^{\prime+}$	b^{*+}	b^{+}	seq	$y^{\prime++}$	y^{*++}	y^{++}	$y^{\prime+}$	y^{*+}	y^{+}	#
1	56.52	--	65.53	112.04	--	130.05	**E**	**666.35**	**666.84**	675.36	1331.70	1332.68	1349.71	**M**
2	113.07	--	122.07	**225.12**	--	**243.13**	**I**	**601.83**	**602.32**	**610.84**	1202.65	1203.64	1220.66	**10**
3	148.58	--	157.59	**296.16**	--	**314.17**	**A**	**545.29**	**545.78**	**554.29**	**1089.57**	**1090.55**	**1107.58**	**9**
4	212.61	213.11	221.62	**424.22**	425.20	**442.23**	**Q**	**509.77**	**510.26**	**518.77**	**1018.53**	**1019.52**	**1036.54**	**8**
5	**270.13**	**270.62**	279.13	**539.25**	**540.23**	**557.26**	**D**	445.74	446.23	**454.75**	**890.47**	**891.46**	**908.48**	**7**
6	343.66	344.15	352.67	**686.31**	687.30	**704.32**	**F**	388.23	388.72	**397.23**	**775.45**	**776.43**	**793.46**	**6**
7	414.72	415.21	**423.72**	828.43	829.41	**846.44**	**K**	**314.69**	**315.18**	323.70	628.38	**629.36**	**646.39**	**5**
8	465.24	465.73	474.25	**929.47**	930.46	**947.48**	**T**	**243.64**	**244.13**	**252.64**	486.27	487.25	**504.28**	**4**
9	**522.75**	523.25	531.76	**1044.50**	**1045.48**	**1062.51**	**D**	193.11	193.61	202.12	385.22	386.20	**403.23**	**3**
10	579.30	579.79	588.30	**1157.58**	**1158.57**	**1175.59**	**L**	135.60	136.09	144.61	**270.19**	**271.18**	**288.20**	**2**
	--	--	--	--	--	--	**R**	79.06	79.55	88.06	157.11	158.09	175.12	**1**

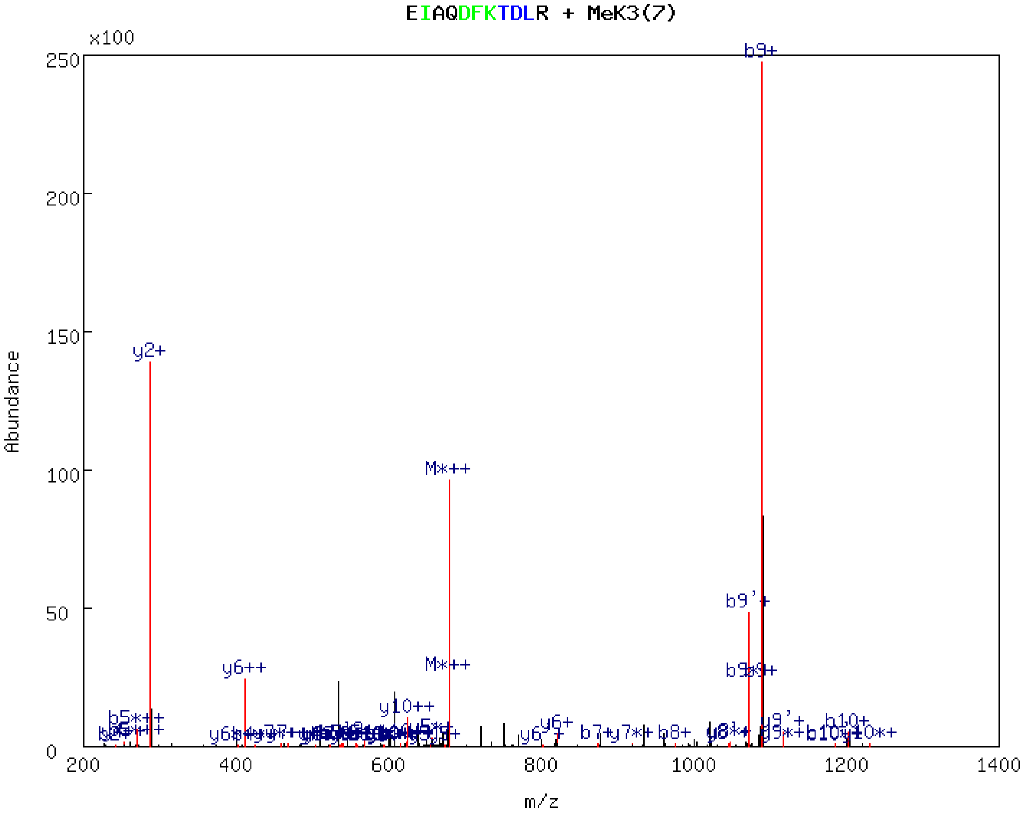
Supplemental Figure 1C. H3 EIAQDF^{79}K(Me$_2$)TDLR Peptide fragment



Index	scan#	charge	score	pp	pp_2	pp_{tag}	m/z	MW(obs)	MW	delta	miss	Unique sequence + modifications
917	1570	+2	55	**18.4**	**8.7**	**6.9**	682.3644	1363.7216	1363.7216	-0.0000	0	× **EIAQDFKTDLR** + MeK2(7)

#	$b^{\prime ++}$	b^{*++}	b^{++}	$b^{\prime +}$	b^{*+}	b^{+}	seq	$y^{\prime ++}$	y^{*++}	y^{++}	$y^{\prime +}$	y^{*+}	y^{+}	#
1	56.52	--	65.53	112.04	--	130.05	**E**	**673.36**	**673.85**	682.36	1345.71	1346.70	1363.72	**M**
2	113.07	--	122.07	225.12	--	**243.13**	**I**	608.84	609.33	**617.84**	1216.67	1217.65	1234.68	**10**
3	148.58	--	157.59	**296.16**	--	314.17	**A**	**552.30**	**552.79**	**561.30**	**1103.58**	**1104.57**	**1121.59**	**9**
4	212.61	213.11	221.62	424.22	425.20	442.23	**Q**	**516.78**	**517.27**	**525.78**	**1032.55**	**1033.53**	**1050.56**	**8**
5	**270.13**	**270.62**	279.13	**539.25**	**540.23**	**557.26**	**D**	452.75	453.24	**461.75**	**904.49**	**905.47**	**922.50**	**7**
6	343.66	344.15	352.67	686.31	687.30	704.32	**F**	**395.23**	**395.73**	**404.24**	**789.46**	**790.45**	**807.47**	**6**
7	421.72	422.22	430.73	**842.44**	**843.42**	**860.45**	**K**	321.70	322.19	330.71	**642.39**	**643.38**	**660.40**	**5**
8	472.25	472.74	481.25	**943.49**	944.47	**961.50**	**T**	**243.64**	**244.13**	**252.64**	**486.27**	487.25	**504.28**	**4**
9	529.76	530.25	**538.77**	**1058.52**	**1059.50**	**1076.53**	**D**	193.11	193.61	202.12	385.22	386.20	**403.23**	**3**
10	586.30	586.80	**595.31**	**1171.60**	**1172.58**	**1189.61**	**L**	135.60	136.09	144.61	**270.19**	**271.18**	**288.20**	**2**
	--	--	--	--	--	--	**R**	79.06	79.55	88.06	157.11	158.09	175.12	**1**

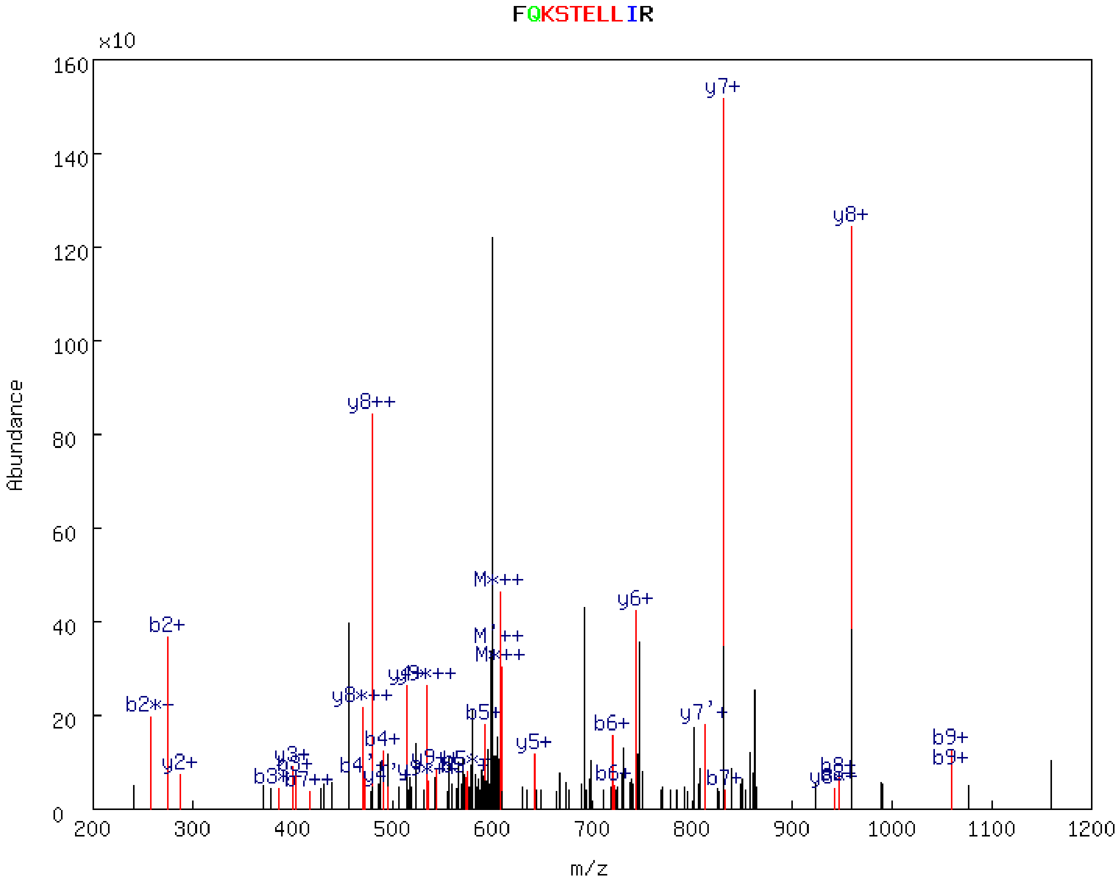
Supplemental Figure 1D. H3 EIAQDF^{79}K(Me$_3$)TDLR Peptide fragment



Index	scan#	charge	score	pp	pp$_2$	pp$_{tag}$	m/z	MW(obs)	MW	delta	miss	Unique	sequence + modifications
941	1569	+2	37	**12.3**	**7.3**	**1.6**	689.3741	1377.7410	1377.7373	0.0038	0	×	**EIAQDFKTDLR** + MeK3(7)

#	b'$^{++}$	b*$^{++}$	b^{++}	b'$^{+}$	b*$^{+}$	b^{+}	seq	y'$^{++}$	y*$^{++}$	y^{++}	y'$^{+}$	y*$^{+}$	y^{+}	#
1	56.52	--	65.53	112.04	--	130.05	**E**	**680.37**	**680.86**	689.37	1359.73	1360.71	1377.74	**M**
2	113.07	--	122.07	225.12	--	**243.13**	**I**	**615.85**	**616.34**	**624.85**	**1230.68**	**1231.67**	1248.69	**10**
3	148.58	--	157.59	296.16	--	314.17	**A**	**559.30**	**559.80**	**568.31**	**1117.60**	**1118.58**	1135.61	**9**
4	212.61	213.11	221.62	424.22	**425.20**	442.23	**Q**	**523.79**	**524.28**	532.79	**1046.56**	**1047.55**	1064.57	**8**
5	**270.13**	**270.62**	279.13	**539.25**	**540.23**	**557.26**	**D**	**459.76**	**460.25**	**468.76**	918.50	**919.49**	936.51	**7**
6	343.66	344.15	352.67	686.31	687.30	704.32	**F**	**402.24**	**402.73**	**411.25**	**803.48**	804.46	**821.49**	**6**
7	428.73	429.22	437.74	856.46	857.44	**874.47**	**K**	328.71	329.20	337.71	**656.41**	**657.39**	**674.42**	**5**
8	479.26	479.75	488.26	957.50	958.49	**975.51**	**T**	**243.64**	244.13	**252.64**	486.27	487.25	**504.28**	**4**
9	**536.77**	**537.26**	545.77	**1072.53**	**1073.51**	**1090.54**	**D**	193.11	193.61	202.12	385.22	386.20	403.23	**3**
10	**593.31**	**593.80**	602.32	**1185.62**	**1186.60**	**1203.63**	**L**	135.60	136.09	144.61	**270.19**	**271.18**	**288.20**	**2**
	--	--	--	--	--	--	**R**	79.06	79.55	88.06	157.11	158.09	175.12	**1**

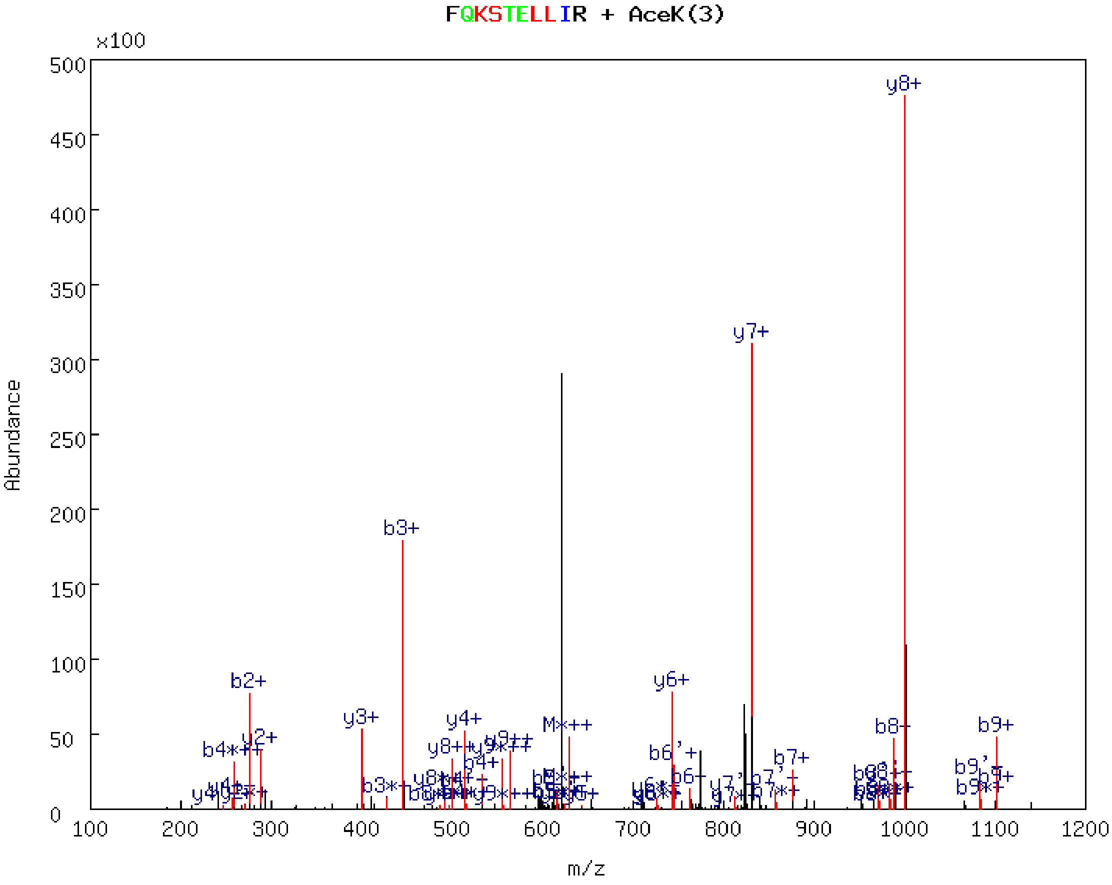
Supplemental Figure 1E. H3 FQ^{56}K(Ace$_0$)STELLIR Peptide fragment



Index	scan#	charge	score	pp	pp$_2$	pp$_{tag}$	m/z	MW(obs)	MW	delta	miss	Unique sequence + modifications
666	1512	+2	30	7.3	9.7	6.8	617.8636	1234.7200	1234.7154	0.0046	0	× FQKSTELLIR

#	$b^{\prime++}$	b^{*++}	b^{++}	$b^{\prime+}$	b^{*+}	b^{+}	seq	$y^{\prime++}$	y^{*++}	y^{++}	$y^{\prime+}$	y^{*+}	y^{+}	#
1	--	--	74.54	--	--	148.08	**F**	**608.86**	**609.35**	617.86	1216.70	1217.69	1234.72	**M**
2	--	130.06	138.57	--	**259.11**	**276.13**	**Q**	**535.32**	**535.81**	**544.33**	1069.64	1070.62	1087.65	**9**
3	--	194.10	202.62	--	**387.20**	**404.23**	**K**	**471.29**	**471.78**	**480.30**	941.58	**942.56**	**959.59**	**8**
4	237.13	237.62	246.13	**473.25**	474.23	**491.26**	**S**	407.25	407.74	416.25	**813.48**	814.47	**831.49**	**7**
5	**287.65**	**288.14**	296.66	**574.30**	**575.28**	**592.31**	**T**	363.73	364.22	372.73	726.45	727.43	**744.46**	**6**
6	352.17	352.67	361.18	703.34	704.32	**721.35**	**E**	313.21	313.70	322.21	625.40	626.39	**643.41**	**5**
7	408.72	409.21	**417.72**	816.43	817.41	**834.44**	**L**	248.68	249.18	257.69	**496.36**	497.34	**514.37**	**4**
8	465.26	465.75	474.26	929.51	930.49	**947.52**	**L**	192.14	192.63	201.15	383.28	384.26	**401.29**	**3**
9	521.80	522.29	530.81	1042.59	1043.58	**1060.60**	**I**	135.60	136.09	144.61	270.19	271.18	**288.20**	**2**
	--	--	--	--	--	--	**R**	79.06	79.55	88.06	157.11	158.09	175.12	**1**

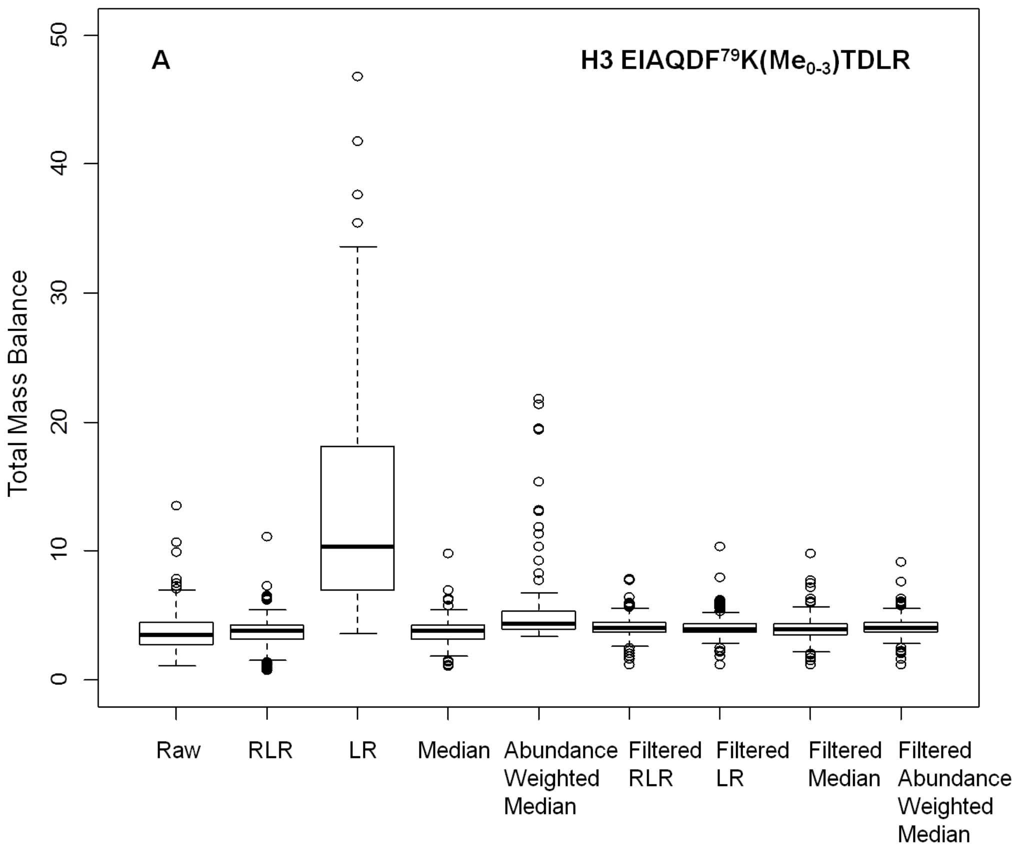
Supplemental Figure 1F. H3 FQ^{56}K(Ace$_1$)STELLIR Peptide fragment

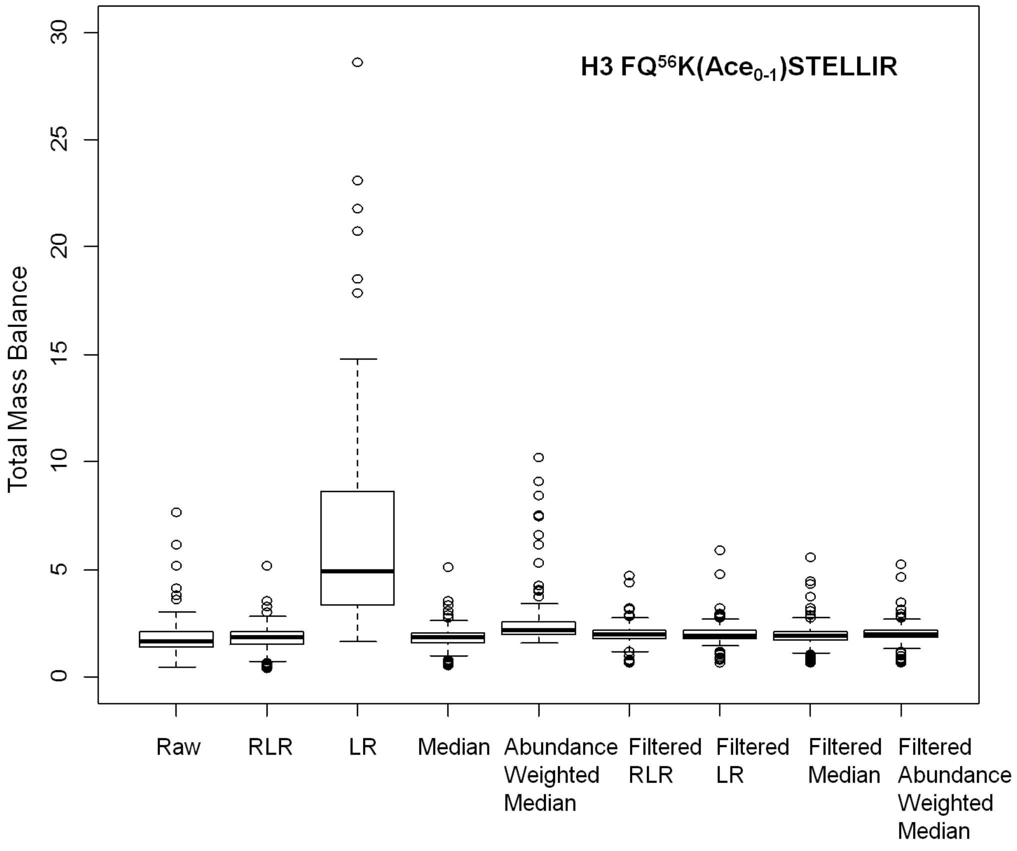


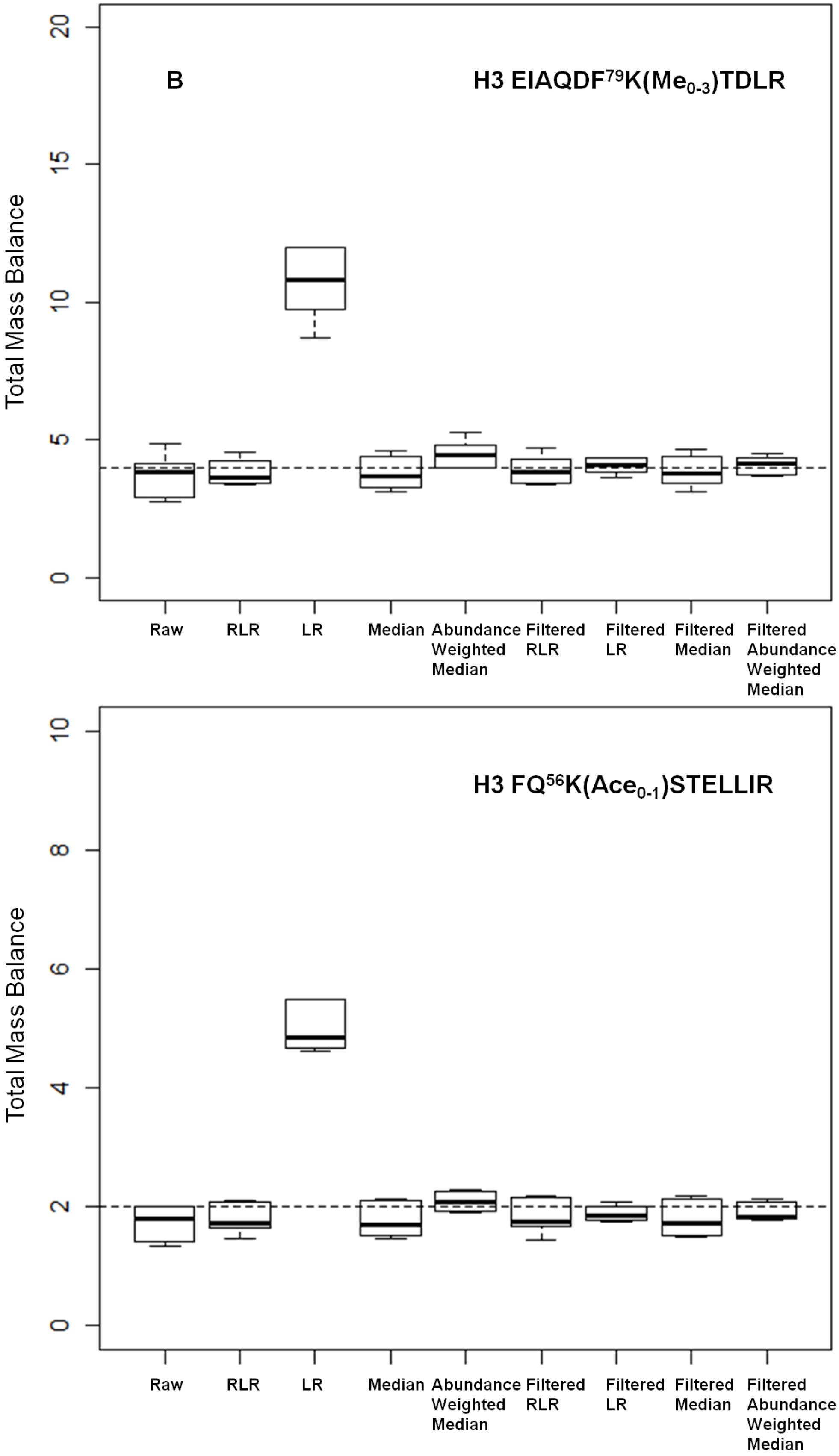
Index	scan#	charge	score	pp	pp$_2$	pp$_{tag}$	m/z	MW(obs)	MW	delta	miss	Unique sequence + modifications
759	2091	+2	46	**16.7**	**9.9**	**5.1**	638.8677	1276.7282	1276.7260	0.0022	0	× **FQKSTELLIR** + AceK(3)

#	$b^{\prime++}$	b^{*++}	b^{++}	$b^{\prime+}$	b^{*+}	b^{+}	seq	$y^{\prime++}$	y^{*++}	y^{++}	$y^{\prime+}$	y^{*+}	y^{+}	#
1	--	--	74.54	--	--	148.08	**F**	**629.86**	**630.35**	638.87	1258.72	1259.70	1276.73	**M**
2	--	130.06	138.57	--	**259.11**	**276.13**	**Q**	**556.33**	**556.82**	**565.33**	1111.65	1112.63	1129.66	**9**
3	--	215.11	223.62	--	**429.21**	**446.24**	**K**	**492.30**	**492.79**	**501.30**	**983.59**	**984.57**	**1001.60**	**8**
4	**258.13**	**258.63**	267.14	**515.26**	**516.25**	**533.27**	**S**	407.25	407.74	416.25	**813.48**	**814.47**	**831.49**	**7**
5	308.66	309.15	317.66	**616.31**	**617.29**	634.32	**T**	363.73	364.22	372.73	**726.45**	**727.43**	**744.46**	**6**
6	373.18	373.67	382.18	**745.35**	746.34	**763.36**	**E**	313.21	313.70	322.21	**625.40**	626.39	**643.41**	**5**
7	**429.72**	430.21	438.73	**858.44**	**859.42**	**876.45**	**L**	**248.68**	249.18	**257.69**	496.36	**497.34**	**514.37**	**4**
8	**486.26**	**486.76**	495.27	**971.52**	**972.50**	**989.53**	**L**	192.14	192.63	201.15	383.28	384.26	**401.29**	**3**
9	542.81	543.30	551.81	**1084.60**	**1085.59**	**1102.61**	**I**	135.60	136.09	144.61	270.19	**271.18**	**288.20**	**2**
	--	--	--	--	--	--	**R**	79.06	79.55	88.06	157.11	158.09	175.12	**1**

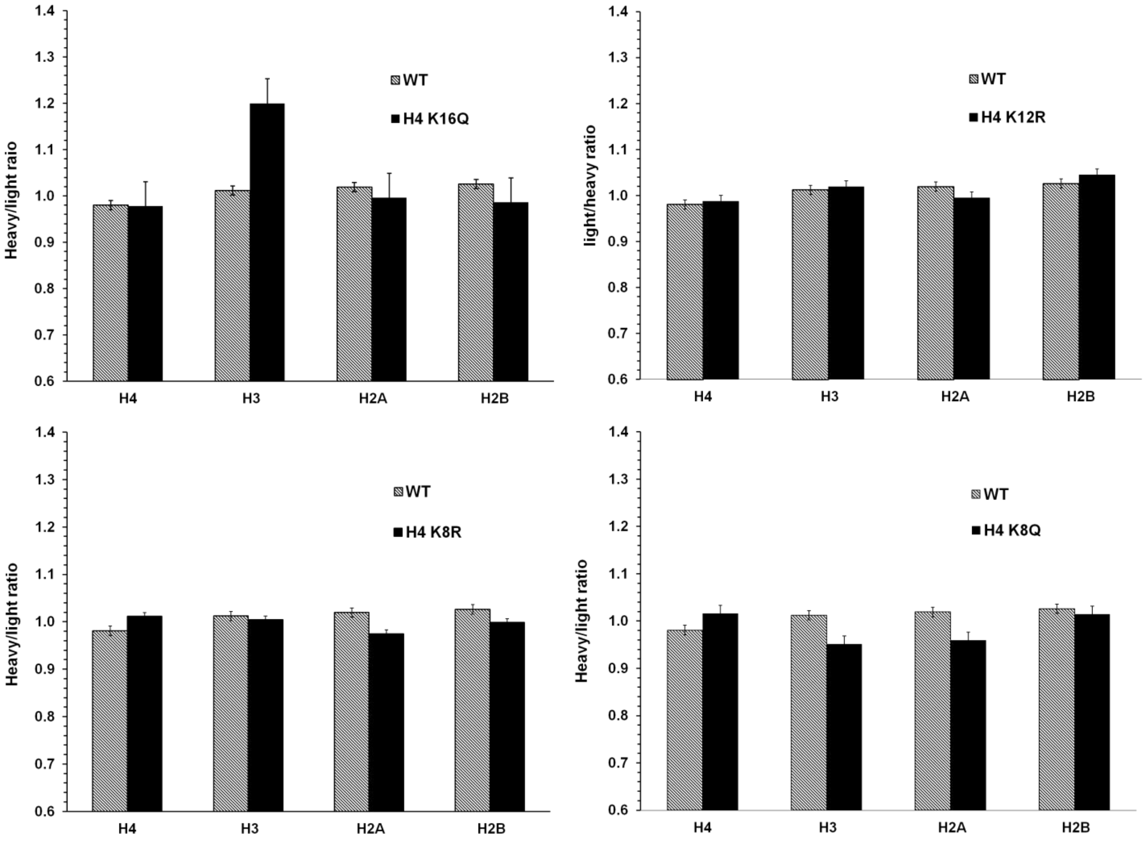
Supplemental Figures 1A-F. A-D) MS/MS spectra of the H3 K79 peptide $EIAQDF^{79}K(Me_{0\text{-}3})TDLR^{2+}$ and E&F) MS/MS spectra of the H3 K56 peptide of $FQ^{56}K(Ace_{0\text{-}1})STELLIR$ from SILAC light wild type:heavy mutant H4 K16Q


A
H3 EIAQDF^{79}K(Me$_{0-3}$)TDLR
Total Mass Balance
0
10
20
30
40
50
Raw
RLR
LR
Median
Abundance Weighted Median
Filtered RLR
Filtered LR
Filtered Median
Filtered Abundance Weighted Median

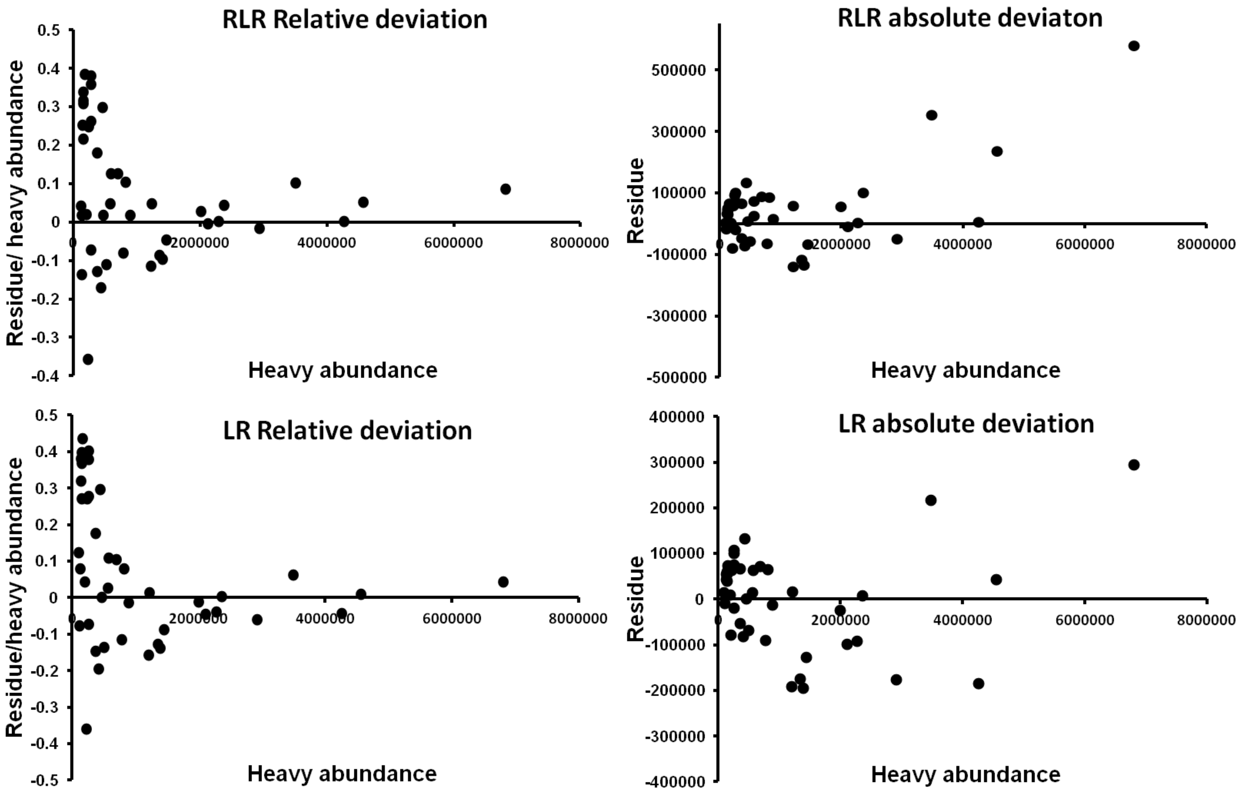

H3 FQ^{56}K(Ace$_{0-1}$)STELLIR
Total Mass Balance
0
5
10
15
20
25
30
Raw
RLR
LR
Median
Abundance Weighted Median
Filtered RLR
Filtered LR
Filtered Median
Filtered Abundance Weighted Median


B
H3 EIAQDF^{79}K(Me$_{0-3}$)TDLR
Total Mass Balance
0
5
10
15
20
Raw
RLR
LR
Median
Abundance Weighted Median
Filtered RLR
Filtered LR
Filtered Median
Filtered Abundance Weighted Median
H3 FQ^{56}K(Ace$_{0-1}$)STELLIR
Total Mass Balance
0
2
4
6
8
10
Raw
RLR
LR
Median
Abundance Weighted Median
Filtered RLR
Filtered LR
Filtered Median
Filtered Abundance Weighted Median

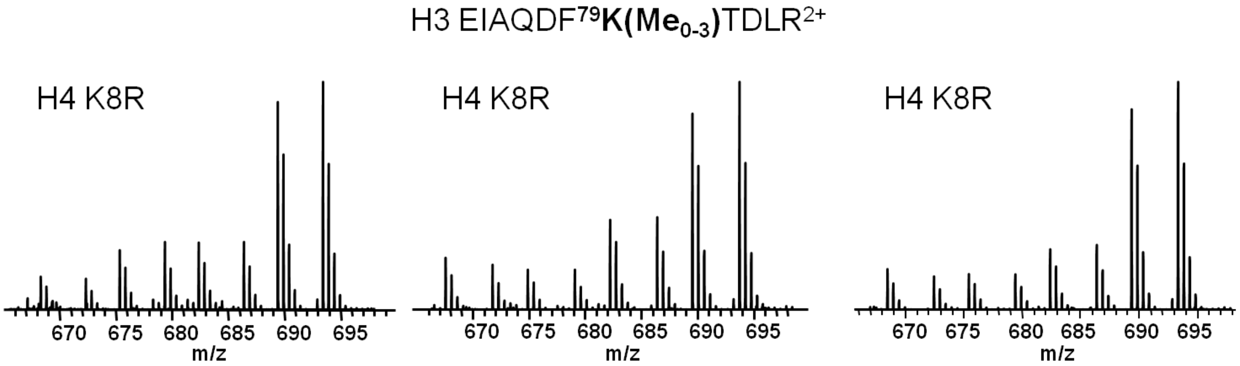
Supplemental Figure 2. Boxplot summarizing the effect of different normalization strategies on mass balance (sum of all isoform ratios) for: A) H3 EIAQDF^{79}K(Me$_{0\text{-}3)}$TDLR and H3 FQ^{56}K(Ace$_{0\text{-}1}$)STELLIR in 44 mutants and B) H3 EIAQDF^{79}K(Me$_{0\text{-}3)}$TDLR and H3 FQ^{56}K(Ace$_{0\text{-}1}$)STELLIR in wild type only. On the x axis, from left to right, is the raw, robust linear regression (RLR), linear regression (LR), median and abundance weighted median, filtered (0.5≤ratio≤2) robust linear regression, filtered linear regression, filtered median and filtered abundance weighted median. The y axis is for the total mass balance for the target peptides.



Supplemental Figure 3. Representative SILAC derived protein ratios for the core histone in the mixture of light WT and heavy mutants: H4 K16Q, K12R, K8R and K8Q, respectively. Error bars correspond to two standard errors.



Supplemental Figure 4. Relative and absolute residual plots for SILAC peptide ratio determined for the H3 K79Me$_0$ peptide in a light WT: heavy WT mixture by the robust linear regression (RLR)(top panel) and linear regression (LR)(bottom panel). Both approaches show that the absolute deviation for ratios at high abundance is large, however, they have relatively less relative deviation compared to ratios at low abundance.



Supplemental Figure 5. MS/MS spectra of H3 EIAQDF^{79}K(Me$_{0\text{-}3}$)TDLR^{2+} from the light WT: heavy mutant H4 K8R mixture. Three biological replicates are presented to demonstrate the reproducibility of SILAC labeling.