

Figure 1

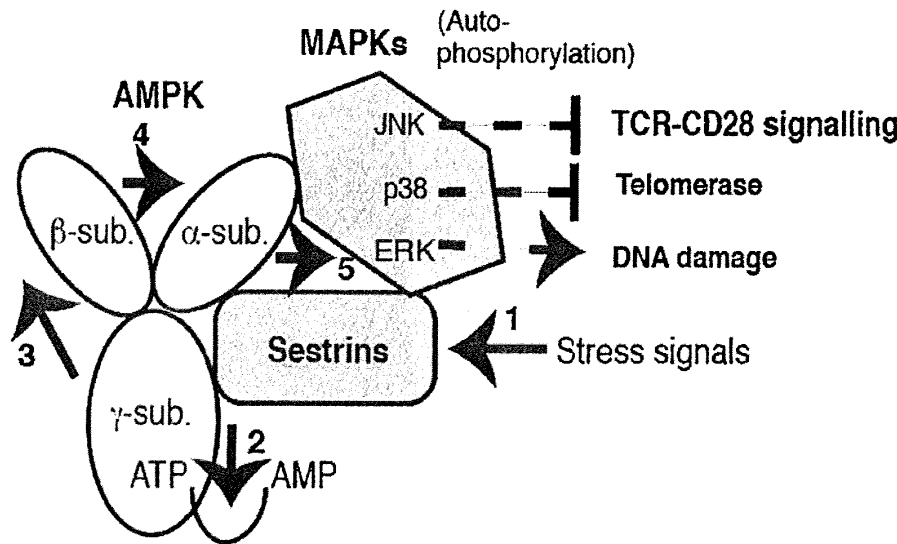


Figure 2

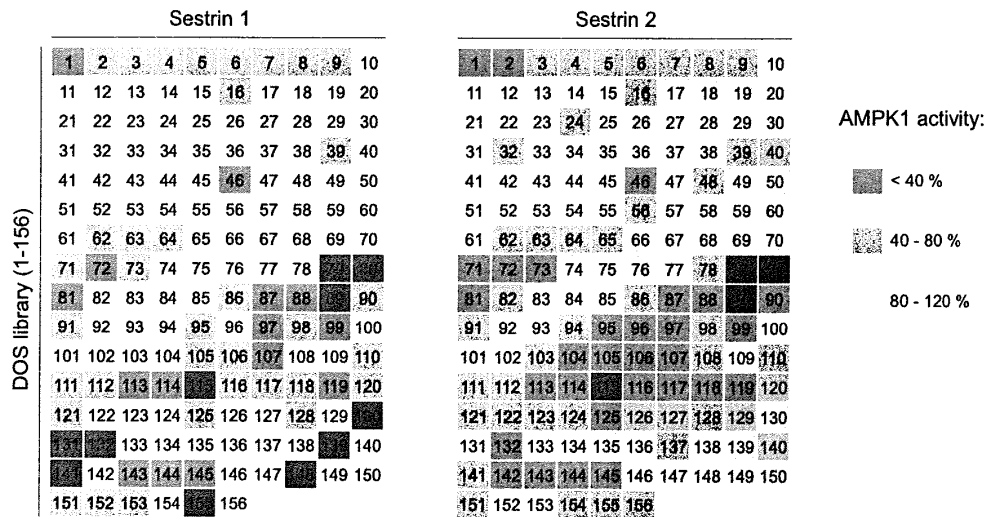


Figure 3

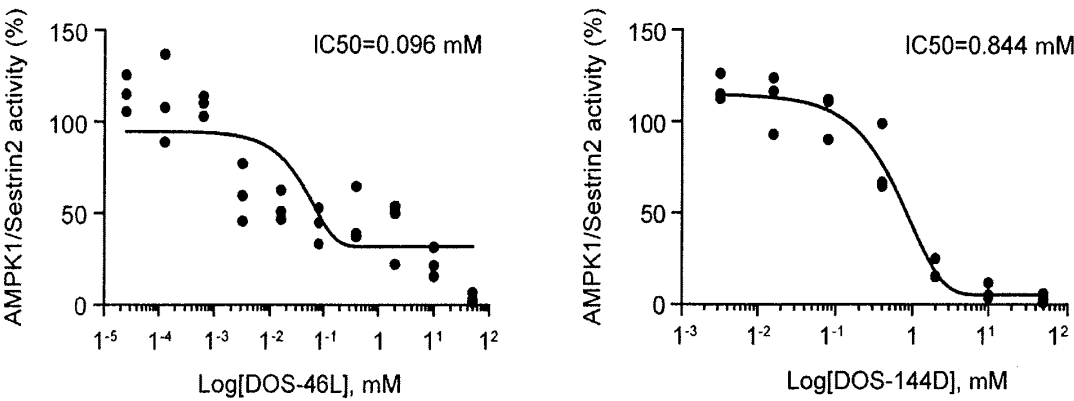
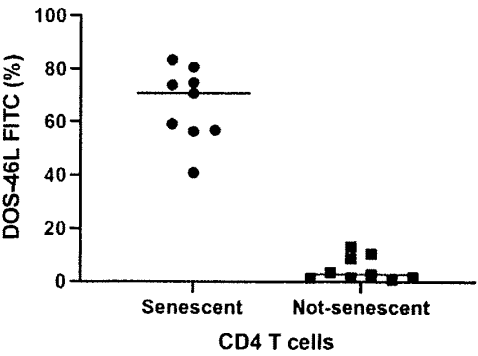


Figure 4

A



B



C

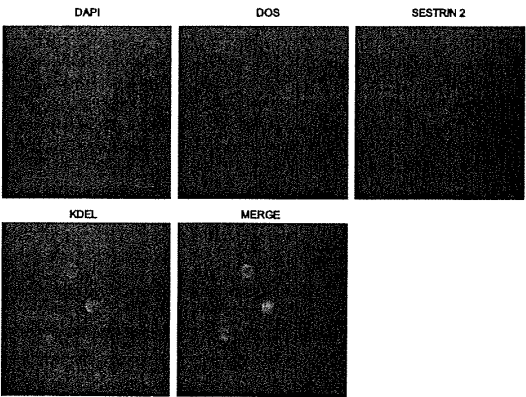


Figure 5

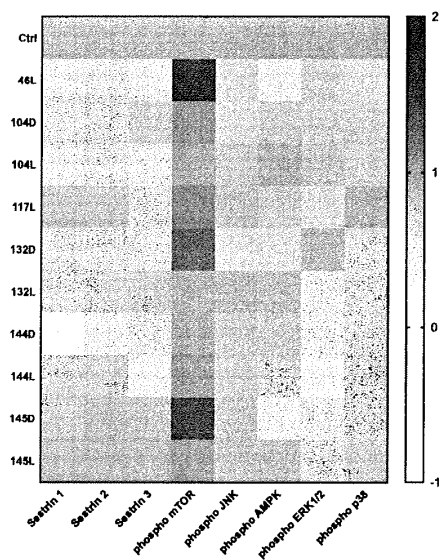


Figure 6

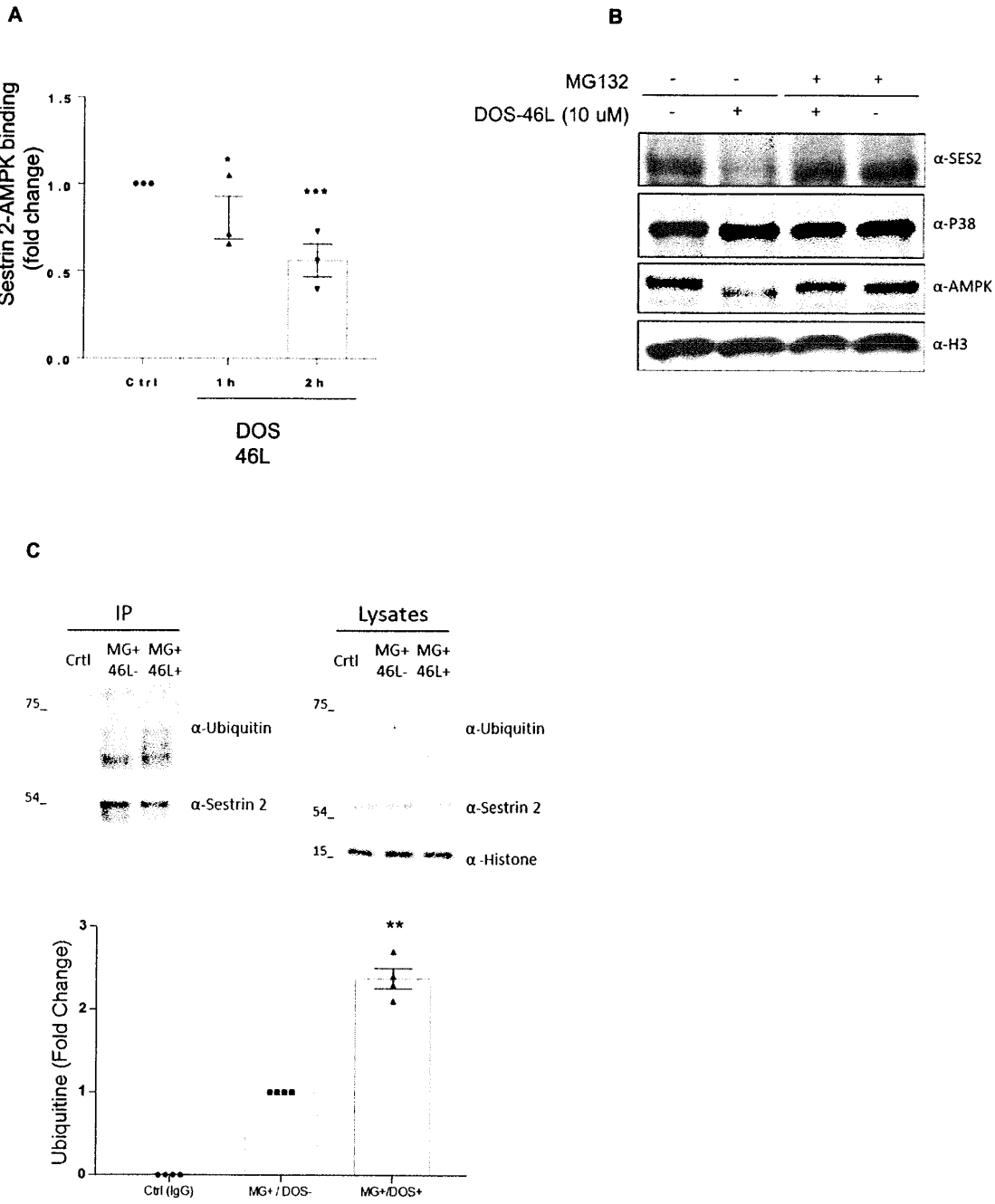


Figure 7

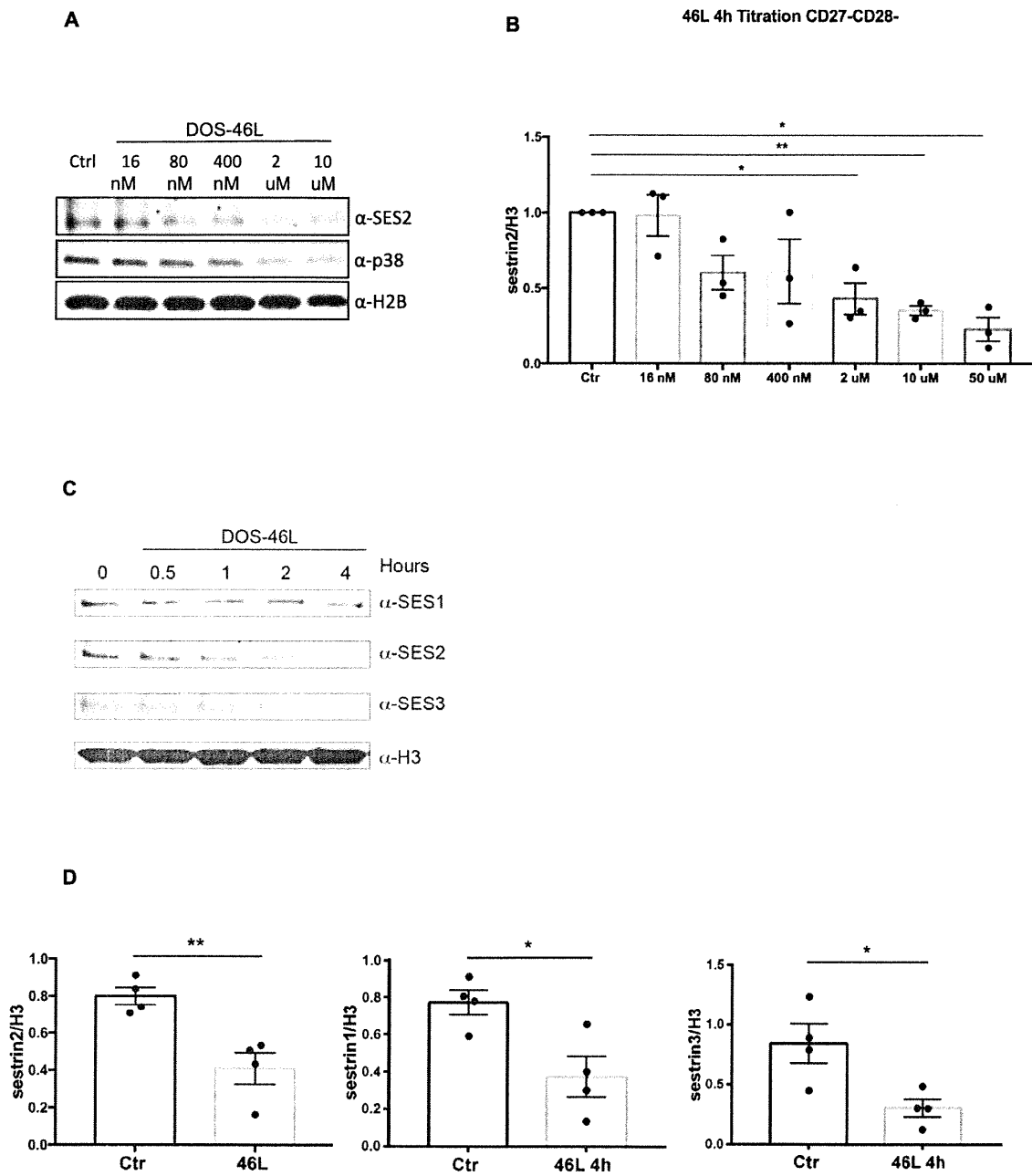


Figure 8

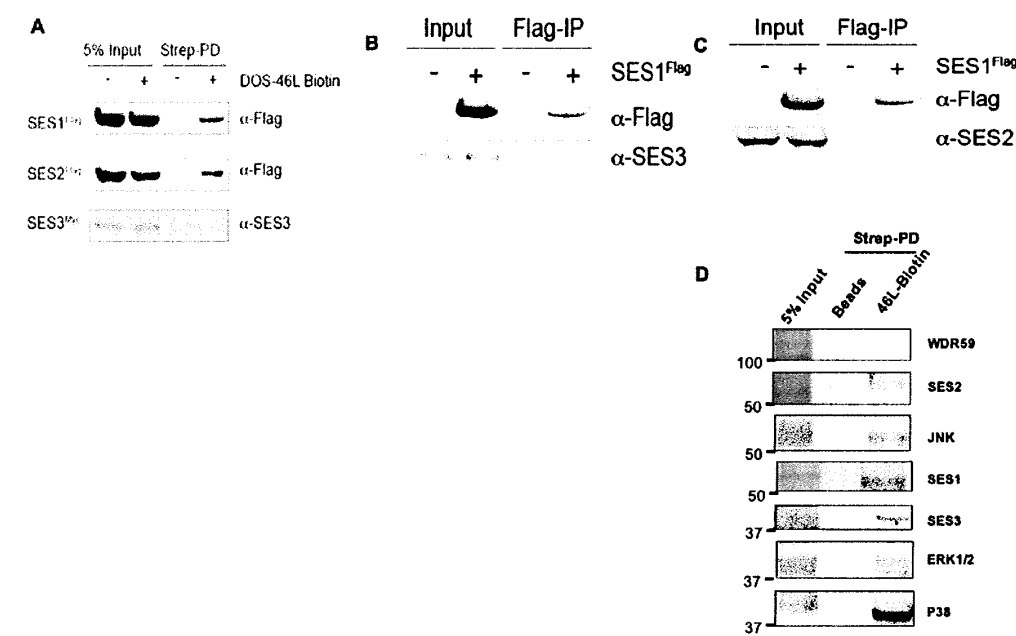


Figure 9

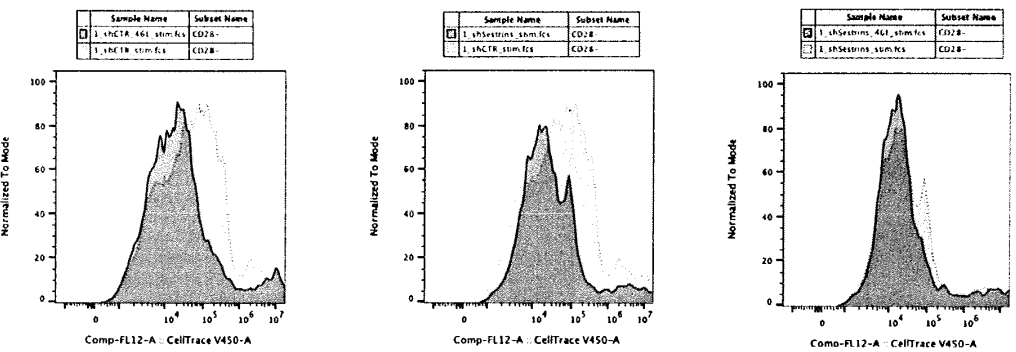


Figure 10

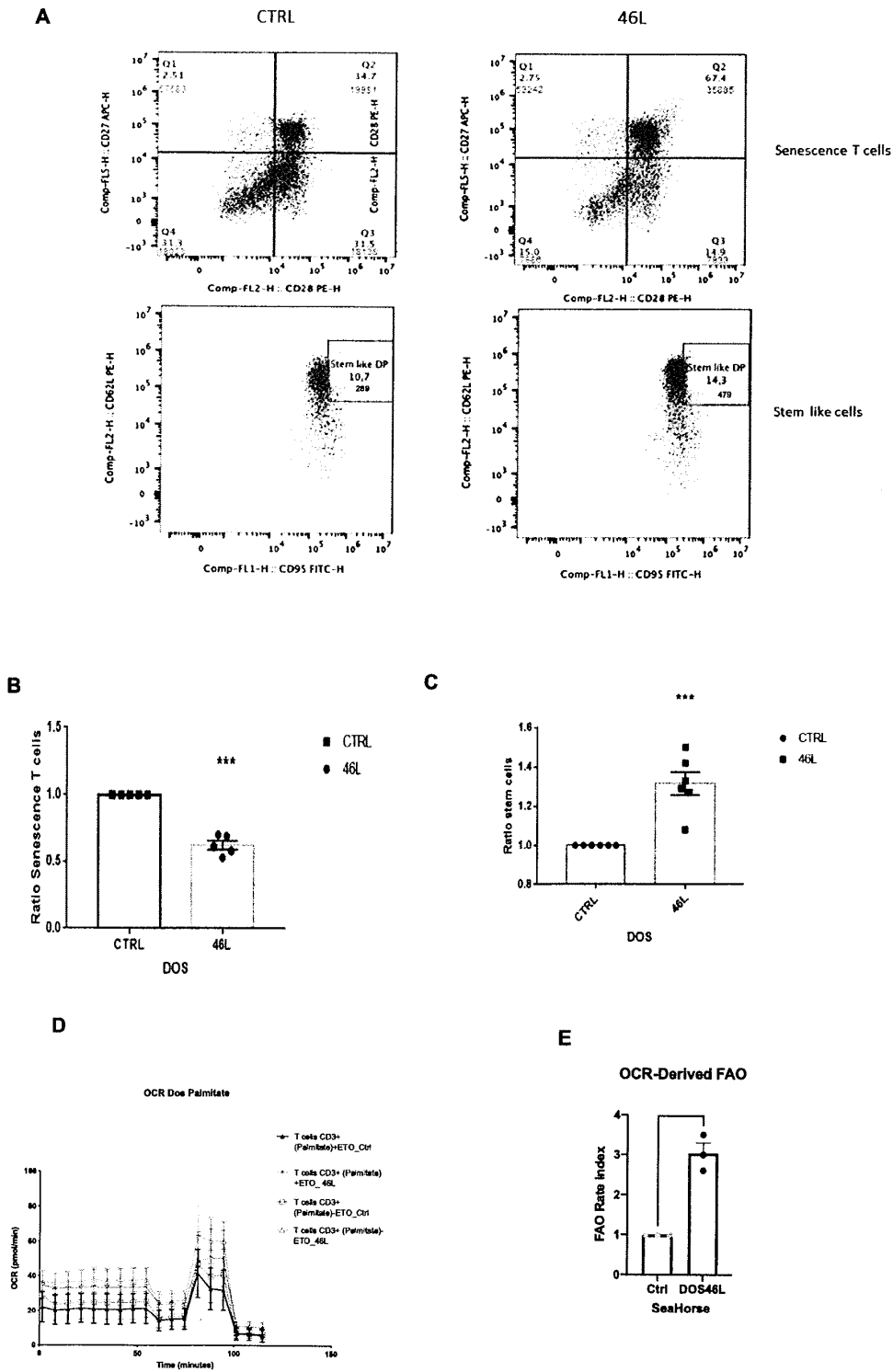


Figure 11

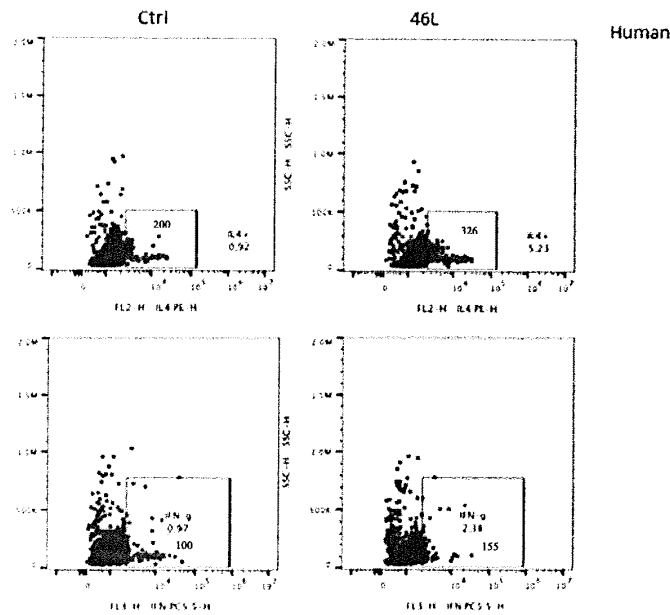


Figure 12

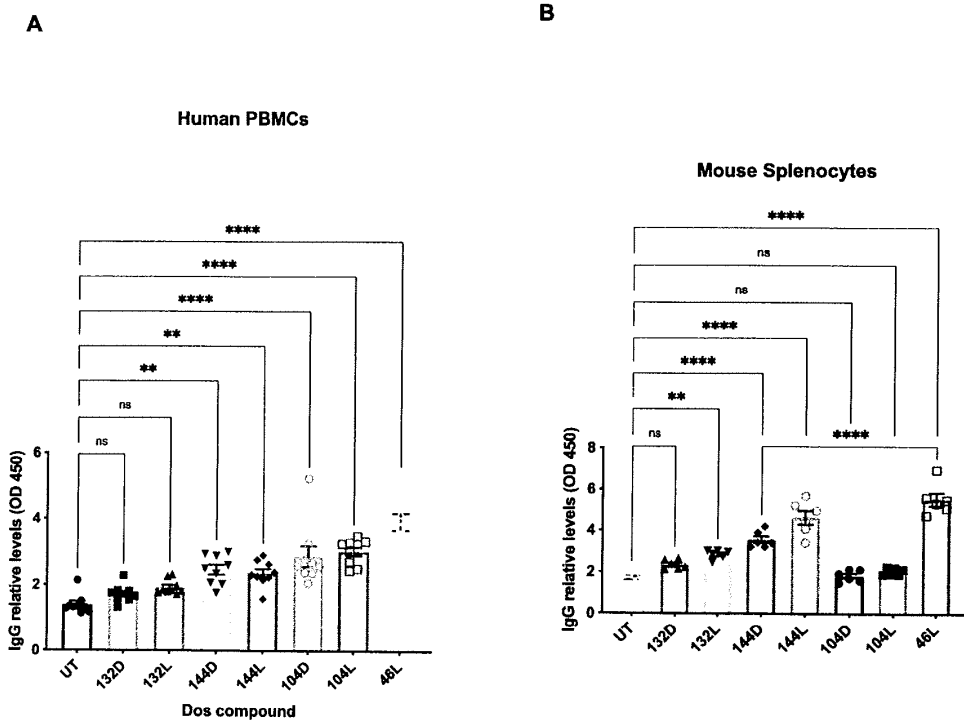


Figure 13

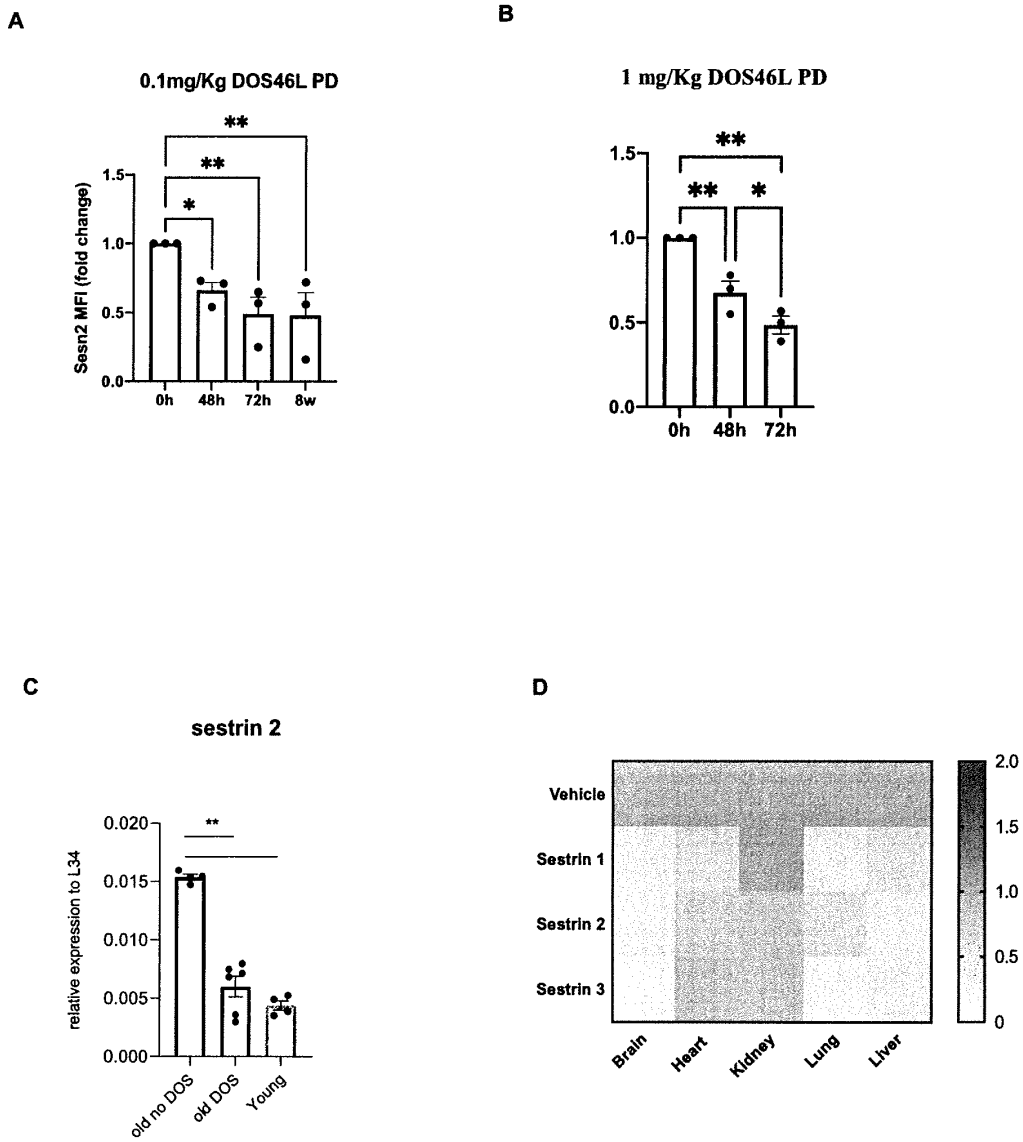


Figure 14

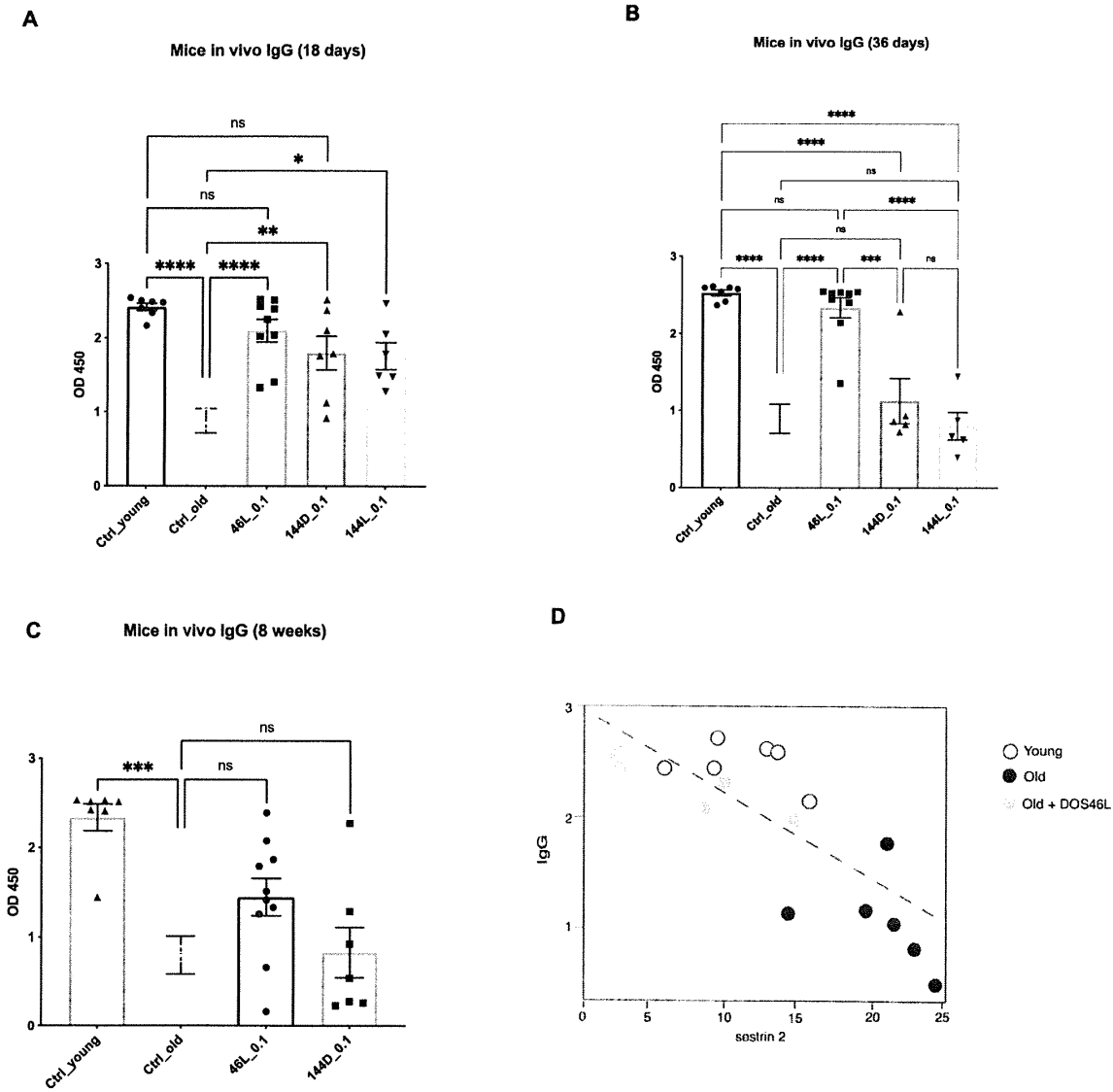


Figure 15

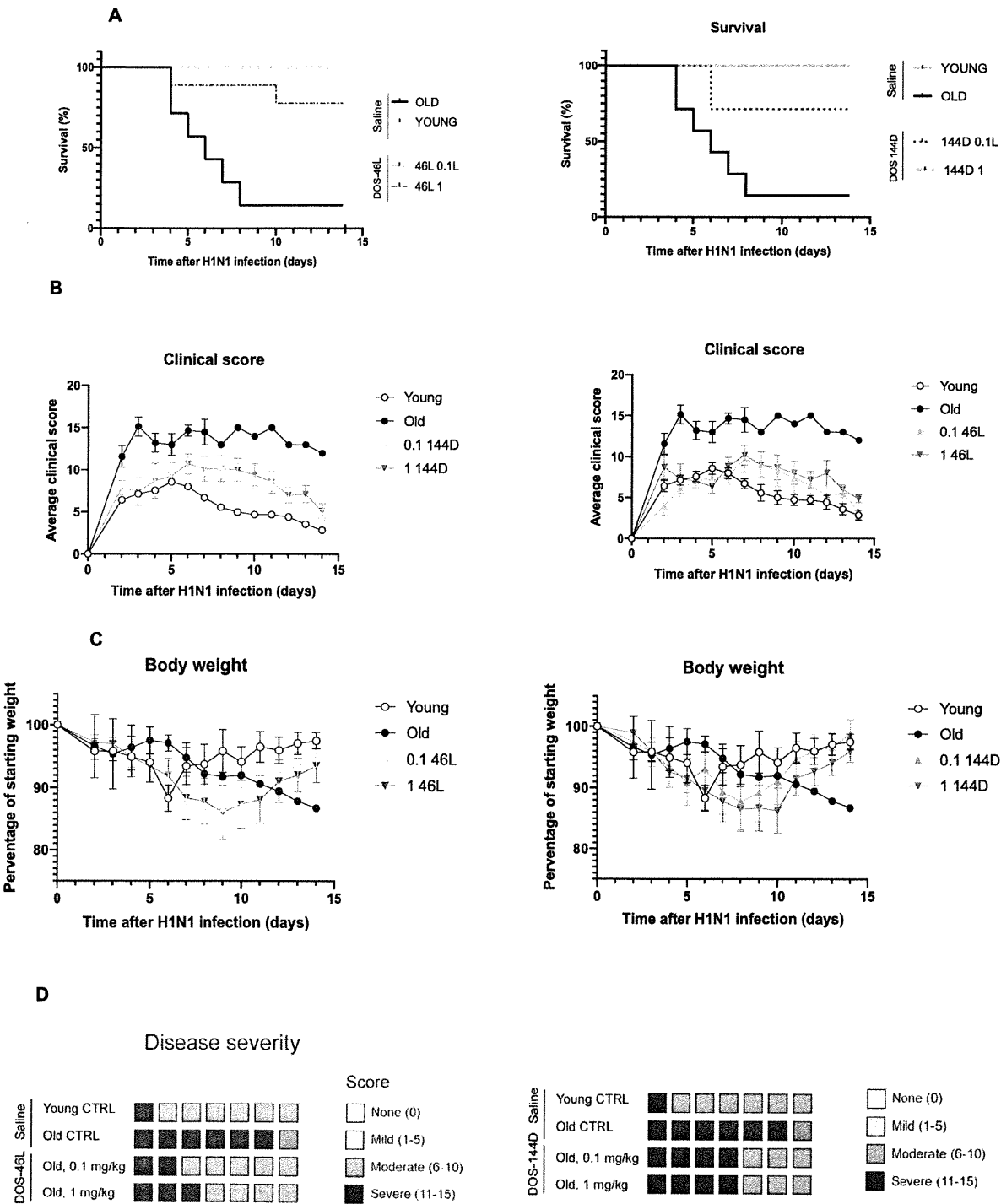


Figure 16

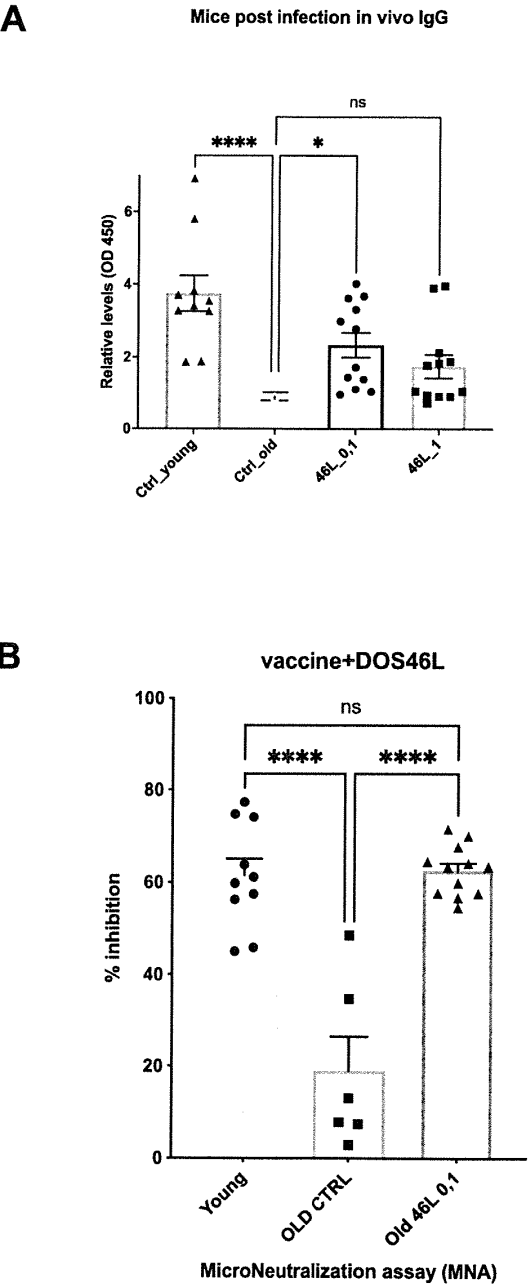
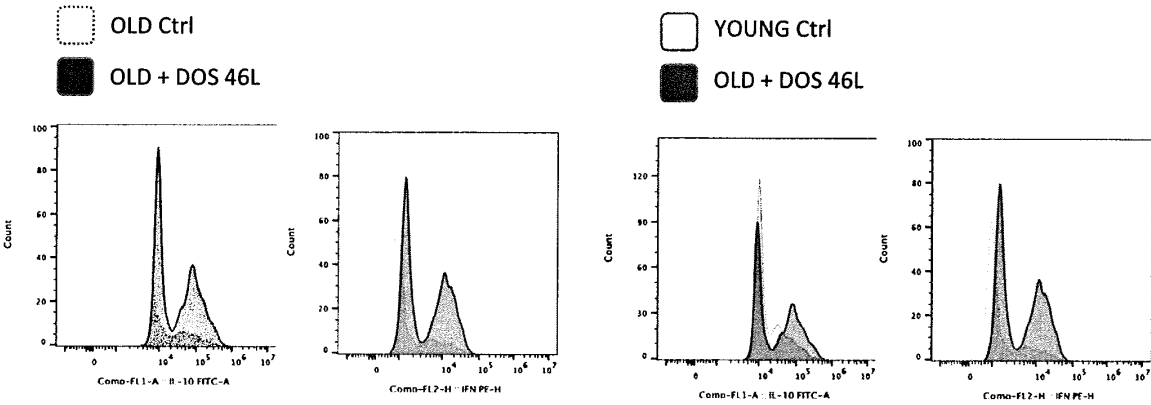


Figure 17

CD4+ T cells



CD8+ T

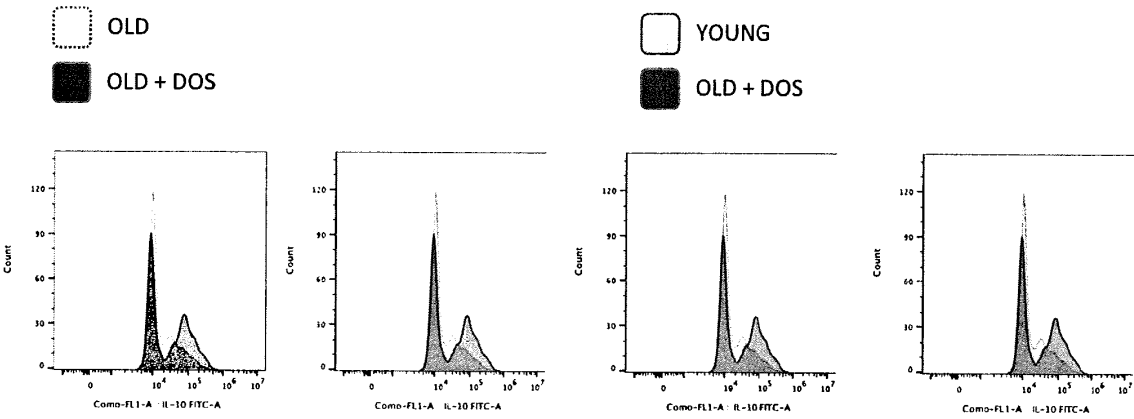


Figure 18

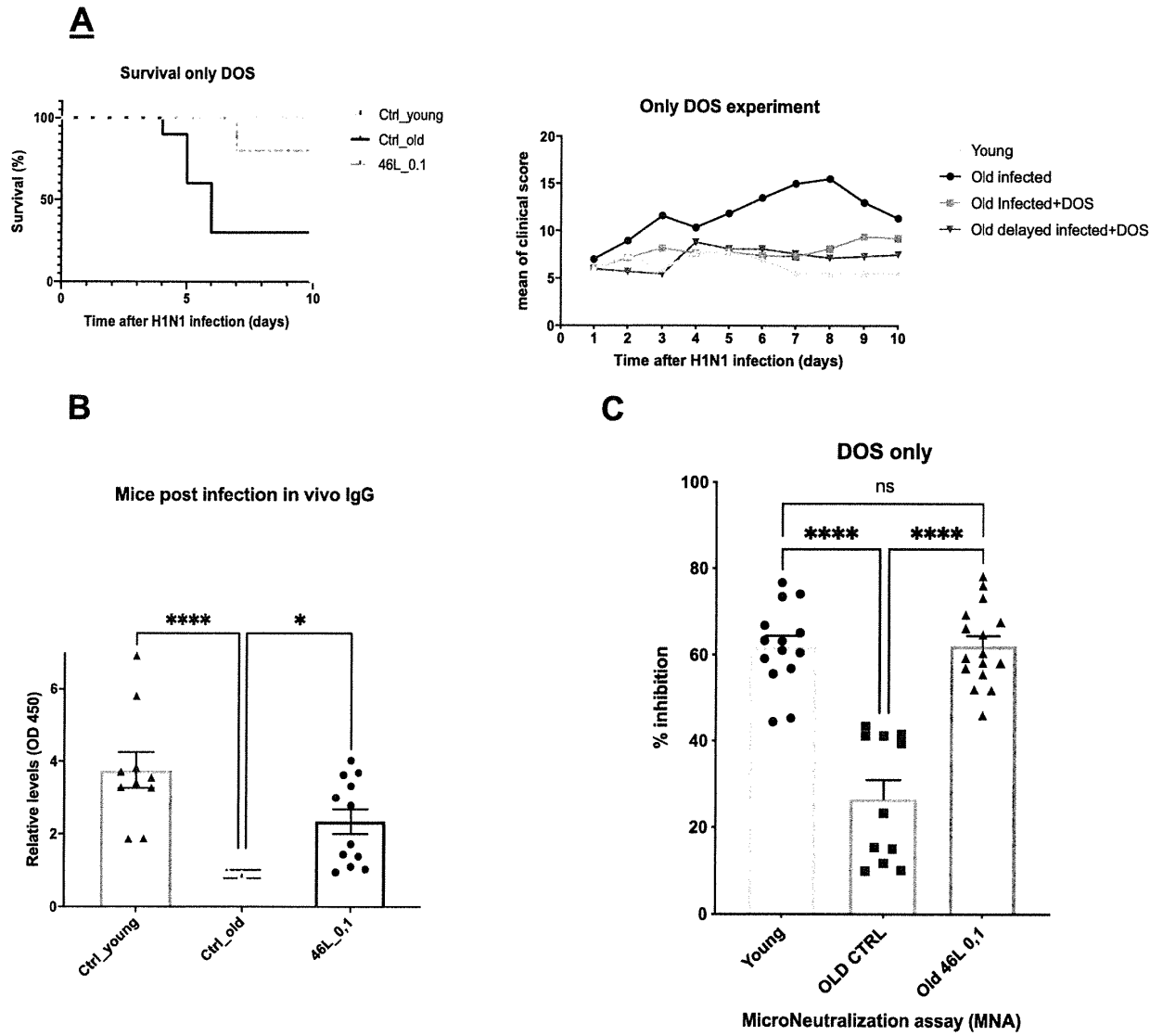


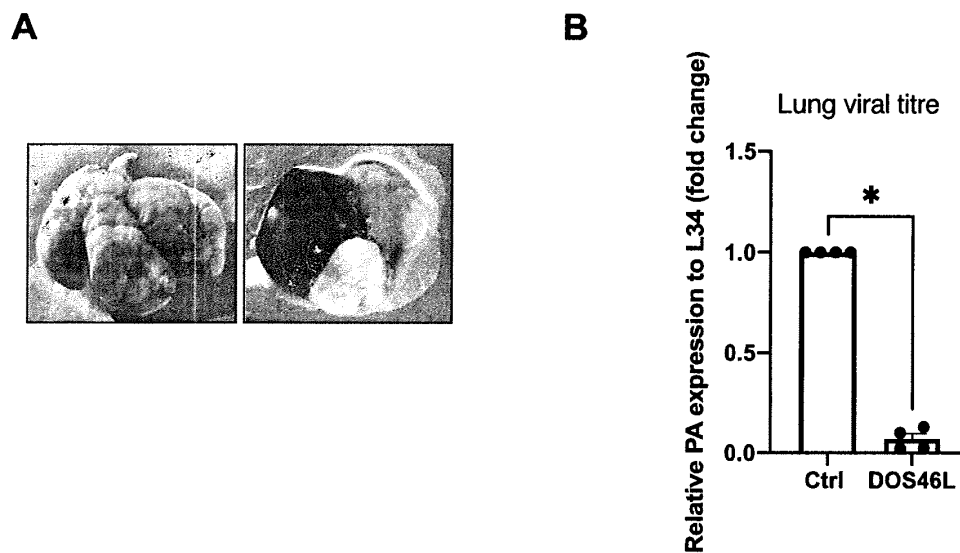
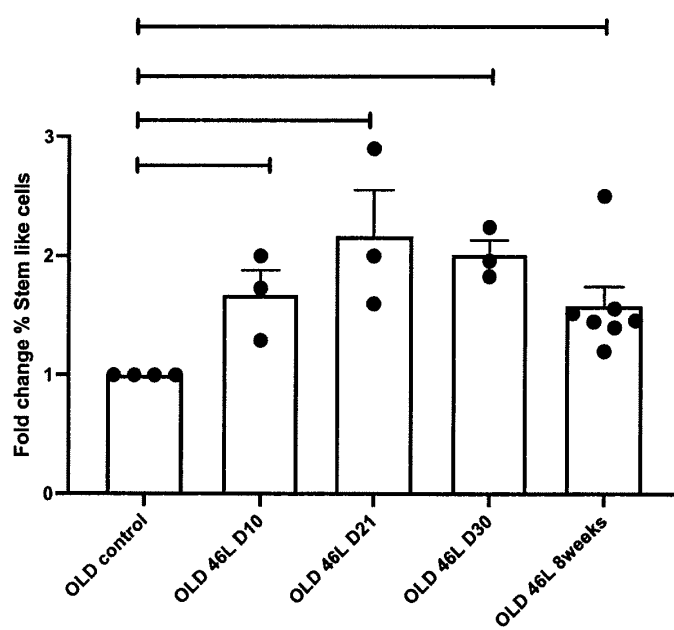
Figure 19**Figure 20**

Figure 21

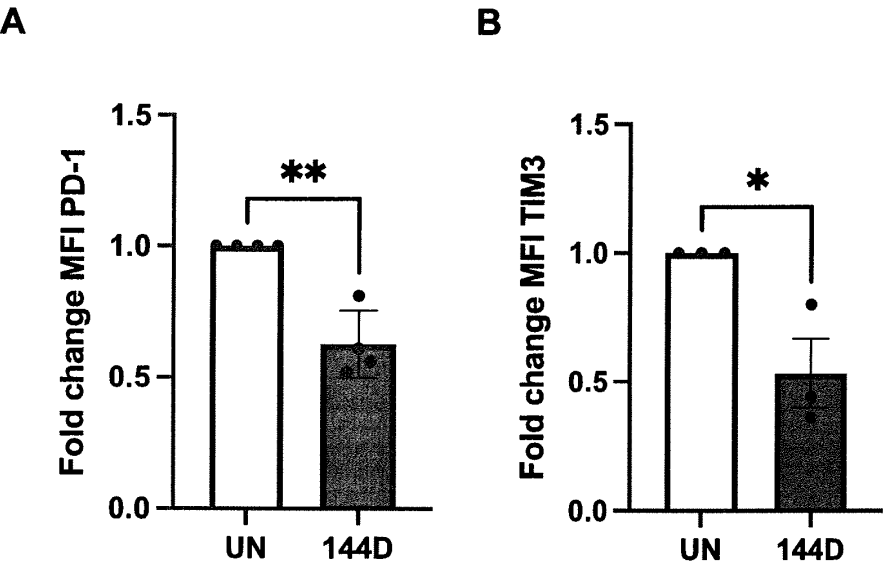
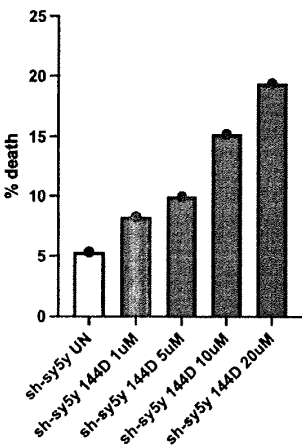


Figure 22

Death sh-sy5y Neuroblastoma cell line 48hr



Death MCF-7 Breast cancer cell line 48hr

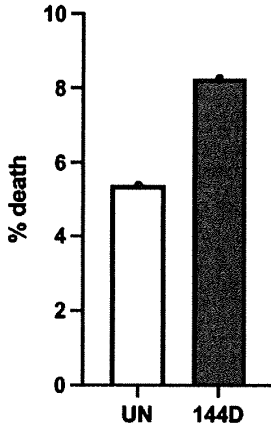


Figure 23

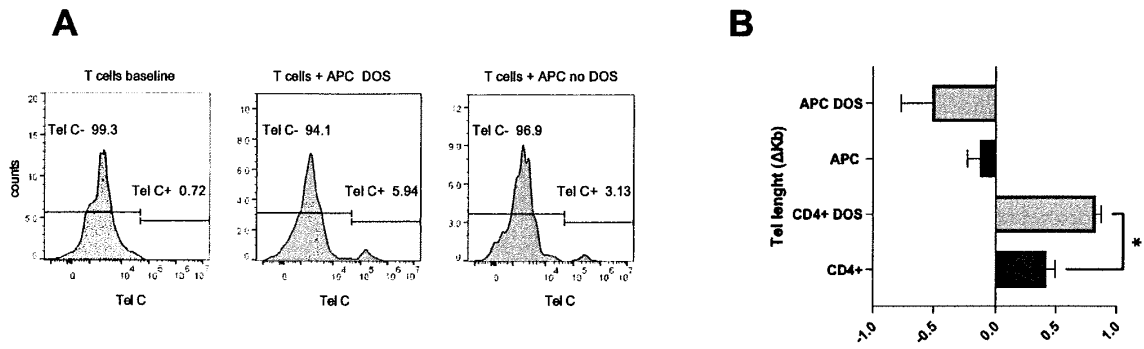


Figure 24

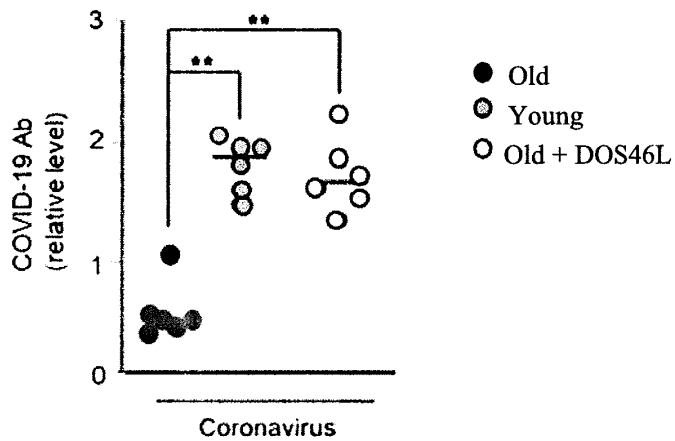


Figure 25

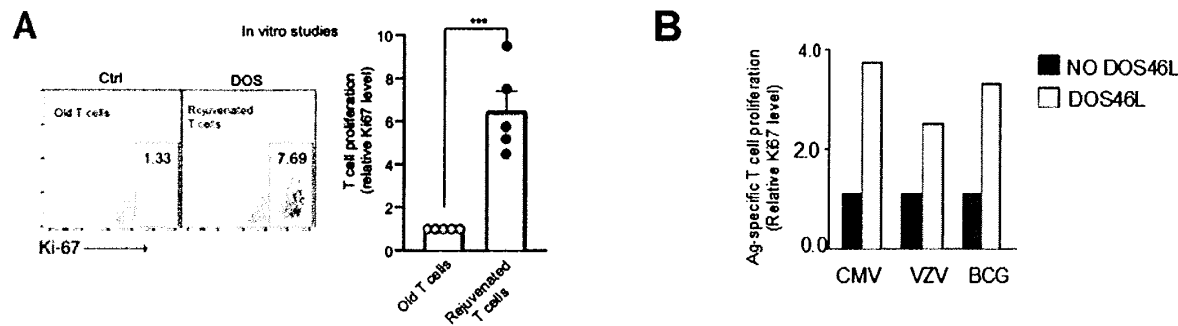


Figure 26

Formula (I):

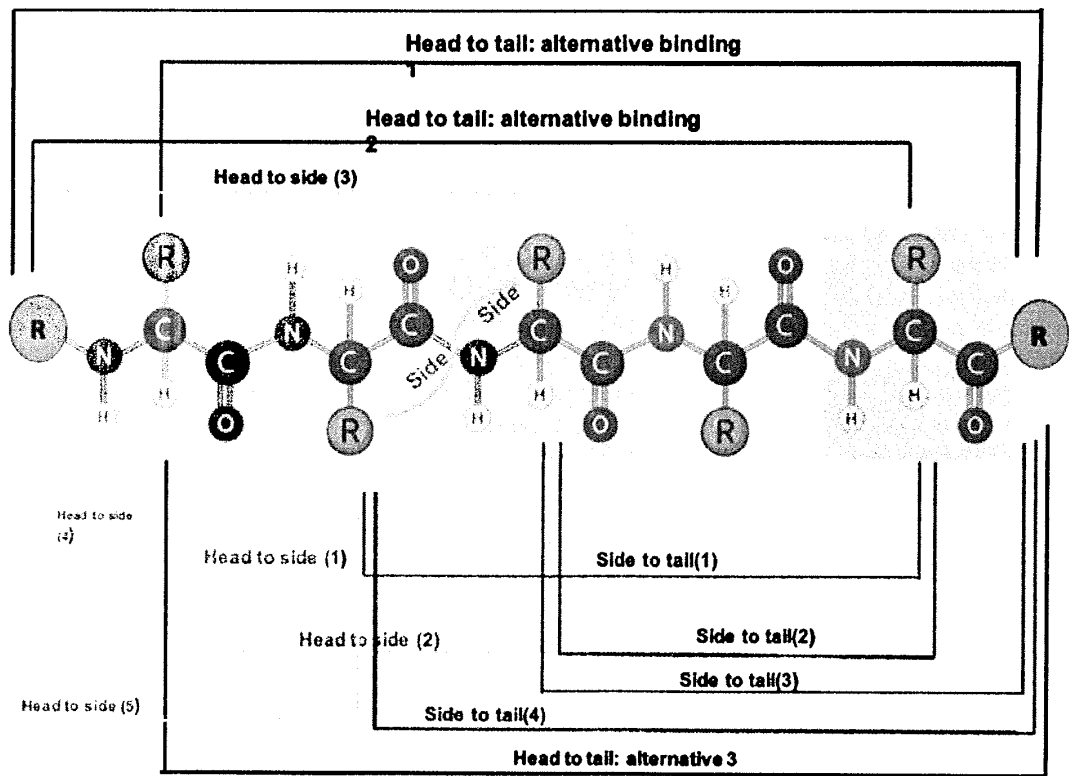
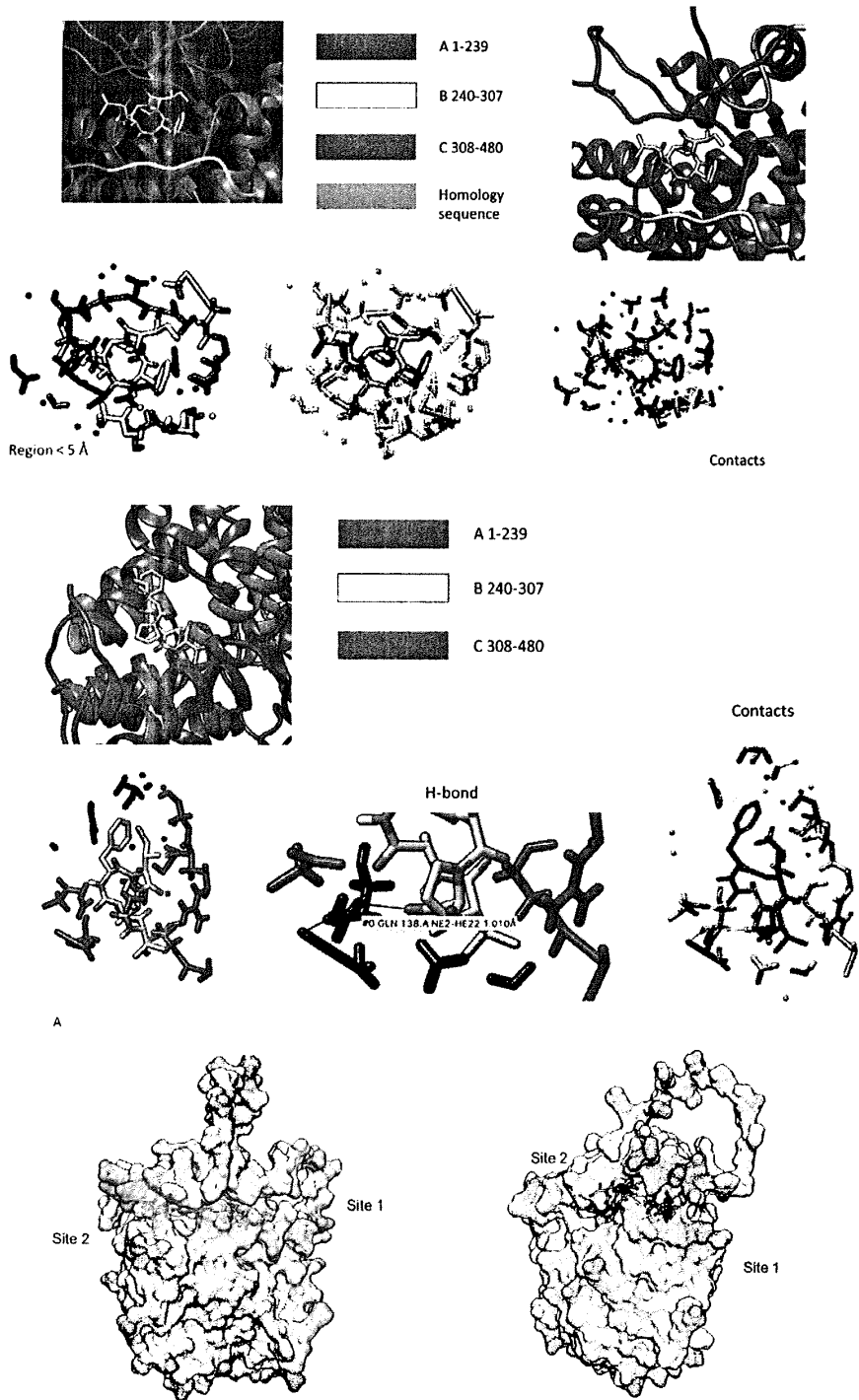
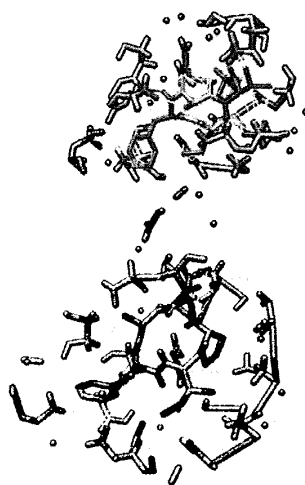


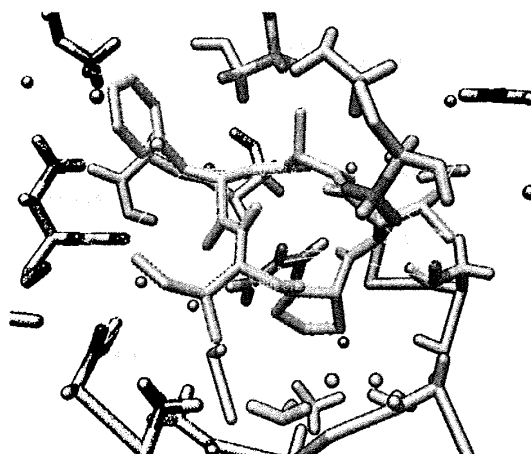
Figure 27



SITE 1



SITE 1



SITE 2

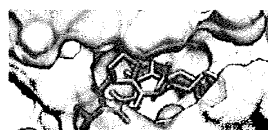
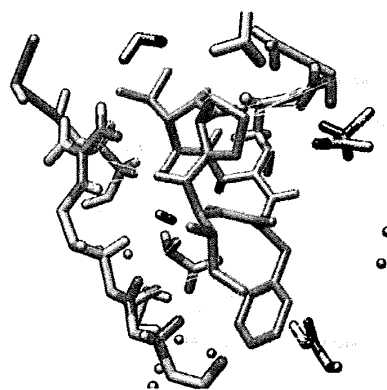


Figure 28**Alignment human Sestrin 2 vs human Sestrin 1*****conserved**

Sestrin2	-----	0
Sestrin1	maegenevrdgclsrddstretalenirqttilrkteylrsvkethrpsdglstntessd	60
Sestrin2	-----mivadsecra-elkdylrfapggvgdsgpgeeqresrarrgprgpsafipve	51
Sestrin1	glnkllahlmlskrcpfkdvreksefilksiqel-----giriprplgqgpsrfipek	114
	::: ...* :::: .* : : *	
Sestrin2	evlregaesleqhl-glealmssgrvndlavvmglhpdiftsfwrhlhllhtdgpllass	110
Sestrin1	eilqvgsedaqmhalafadsfaalgrldnitlvmvfhpqylesflktqhyllqmdgplplh	174
	: :*: . : * :: : **:*::** :*: : * : : ** : ***	
Sestrin2	wrhyiaimaaarhqcsylvgshmaeflqtggdpewllglhrapeklrklseinkllahrp	170
Sestrin1	yrhyigimaaarhqcsylvnlhvndflhvvgdgpklwnglenapqklqnlgeinlvahrp	234
	:****.*****. * :*: :***:* **..*:*:*.*.*:*****	
Sestrin2	wlitkehiqallktgehtwslaeliqalvllthchslssfvfgcgilpegdadgspapqa	230
Sestrin1	wlitkehiqgllkaehswslaelvhavvllthyhslasftfgcgispeihcdgghtfrp	294
	*****.***: **:*****:*:***** **:*.****** ** ..**. : :	
Sestrin2	ptppseqs-----spsrdpln---nsggfesardvealmermqqlqesllrdegtsq	280
Sestrin1	psvsnycicditngnhsvdempvnsaenvsvdsffevealmekmrqlqecr-deeeasq	353
	: . ..: * . :* :*****:*:*****. * : **	
Sestrin2	eemesrfelekseallvtpsadilepsphpdmlcfvedptfgyedftrrgaqapptfra	340
Sestrin1	eemasrfeiekresmfvfssdde-evtparavsrhfedtsygykdfsrhgmh-vptfrvq	411
	*** ***:** **:* * * * : * : ..** :*:***:* : ***:**	
Sestrin2	dwtwedhgysliqrlypeggqlldekfqaaysltyntiamhsgvdtsvlrraiwnyihcv	400
Sestrin1	dycwedhgyslvnrlypdvgqlidekfhiaynltyntmamhkdvdtsmlrraiwnyihcm	471
	** *****:****: **:*****: **.*****:***..*****:*****:	
Sestrin2	fgiryddydygevnqllernlkvyiktvacypekttrrmynlfrhfrhsekvhnllli	460
Sestrin1	fgiryddydygeinqlldrsfkvyiktvtvctpekvtkrmysfwrqfkhsekvhnllli	531
	*****:****:*.*****.* ***.*:***: ***:*****:*****:	
Sestrin2	earmqaallyalraitrymt	480
Sestrin1	earmqaallyalraitrymt	551
	***** *****	

Figure 29**Alignment human Sestrin 2 vs human Sestrin 3*****conserved**

Sestrin2	-----mivadsecraelkdylrfapggvgdsgpgeeqresrarrgprgpsafi	48
Sestrin3	mnrgggspsaanyllctncrkvlr-----kdkrirvsqpltrgpsafi	44
	: :** * : :*: : : *****	
Sestrin2	pveevlregaesleqhlglealmssgrvndlavvmglhpdiftsfwrhlhllhtdgpla	108
Sestrin3	pekevqvantvdertnflveeystsgrlnditqvmshltqylesflrsqfymrlrmdgplp	104
	* :***: . : . : : * :***:*::**.* : * : * : : * : *	
Sestrin2	sswrhyiaimaaarhqcsylvgshmaeflqtggdpewllglhrapeklrklseinkllah	168
Sestrin3	lpyrhyiaimaaarhqcsylinmhvdeflktggiaewlnglelyvpqrlnlneinkllah	164
	:*****:*****. * :*:*** ** **..*:*:*.*.*:*****	
Sestrin2	rpwlitkehiqallktgehtwslaeliqalvllthchslssfvfgcgilpegdadgspap	228
Sestrin3	rpwlitkehiqklvtgenwnslpelvhavvllahyhalasfvfgsginperdpaisngf	224

	*****:***:.* ** :*:.*:.*:.*:.*:.* ** * : *	
Sestrin2	qaptpps-----eqssppsrldplnnsggfesardvealmermqqlqesllrdegtsq	280
Sestrin3	rliisvnnfcvcdlandnnienaslsnsgnfgivdlslealmermkrlqeer-edeeasq	283
	: : . :. : . * * :.* :*****:***. . ** : **	
Sestrin2	eemesrfelekseqlvtpsadilepsph-----pdlmcfvedptfgyedftrrg	330
Sestrin3	eemstrfekekkeslfvvsugd-tfhfsfhpsdfeddmitsdvsryiedpgfgyedfarrg	342
	: **.**:.*. . :. ** *: :*** *****.*	
Sestrin2	aqapptfraqdytwedhgyqliqrlypeggqlldekfgaaysltyntiamhsgvdtsvlr	390
Sestrin3	eehlptfraqdytwenhgfslvnrlsldighlldekfrmyvnltyntmathevdvtmlr	402
	: *****:*.*:.*:*** : *:*****: .*.*****:* *.***:***	
Sestrin2	raiwnyihcvfgiriyddydygevnqllernlkvyiktvacypekttrrmynlfrwrhfrhs	450
Sestrin3	ralfnvyhcmfgiriyddydygevnqllerslkvyiktvtcyperttkrmysdywrqfks	462
	::*.*****.*****.*****.***.***: .**.*:.*	
Sestrin2	ekvhvnl1llllearnmqaalylalraitrymt	480
Sestrin3	ekvhvnl1llllearnmqaalylalraitrhlt	492
	*****.***** *****.*****:.*	

Figure 30

	SESTRIN 2		SESTRIN 1		
Dos number	Sequence	SEQ ID No	Sequence	SEQ ID No	
1	MIVAD	<u>8</u>	<u>MRLAA</u>	86	DOSalt1
2	IVADS	9	<u>RLAAA</u>	87	DOSalt2
46	AFIPV	22	QGPSR	88	DOSsel46
71	MSSGR	29	FADSF	89	DOSsel71
72	SSGRV	30	ADSFA	90	DOSsel72
73	SGRVD	31	DSFAA	91	DOSsel73
87	PDYFT	36	<u>VMVEH</u>	92	DOSalt87
88	DYFTS	37	MVFHP	93	DOSsel88
90	FTSFW	<u>39</u>	<u>FHPQY</u>	94	DOSalt90
96	LHYLL	42	<u>ESFLK</u>	95	DOSalt96
97	HYLLL	43	<u>SFLKT</u>	96	DOSalt97
99	LLLHT	<u>45</u>	<u>LKTQH</u>	97	DOSalt99
104	DGPLA	47	YLLQM	98	DOSsel104
105	GPLAS	48	LLQMD	99	DOSsel105
106	PLASS	49	LQMDG	100	DOSsel106
107	LASSW	50	QMDGP	101	DOSsel107
113	HYIAI	55	PLHYR	102	DOSsel113
114	YIAIM	56	LHYRH	103	DOSsel114
117	IMAAA	58	RHYIG	104	DOSsel117
118	MAAAR	59	HYIGI	105	DOSsel118
119	AAARH	60	YIGIM	106	DOSsel119
125	CSYLV	66	AARHQ	107	DOSsel125
132	HMAEF	71	YLVNL	108	DOSsel132
142	DPEWL	75	LHVGG	109	DOSsel142
143	PEWLL	76	HVGGD	110	DOSsel143
144	EWLLG	77	VGGDP	111	DOSsel144
145	WLLGL	78	GGDPK	112	DOSsel145

	SESTRIN 2		SESTRIN 1		
Dos number	Sequence	SEQ ID No	Sequence	SEQ ID No	
3	VADSE	10	LAAAA	113	DOSalt3
4	ADSEC	11	AAAAAN	114	DOSalt4
5	DSECR	12	AAANE	115	DOSsel5
6	SECRA	13	AANE A	116	DOSalt6
7	ECRAE	14	ANE A Y	117	DOSalt7
8	CRAEL	15	NE A YT	118	DOSalt8
9	RAELK	16	E A YTA	119	DOSalt9
16	LRFAP	17	AVSGL	120	DOSsel16
24	GDSGP	18	KQCGG	121	DOSalt24
32	QRESR	19	QDEEL	122	DOSalt32
39	RGPRG	20	R I PRP	123	DOSalt39
40	GPRGP	21	I P RPL	124	DOSalt40
48	IPVEE	23	PSRFI	125	DOSsel48
56	EGAES	24	E I LQV	126	DOSalt56
62	EQHLG	25	SEDAQ	127	DOSsel62
63	QHLGL	26	EDAQM	128	DOSsel63
64	HLGLE	27	DAQMH	129	DOSsel64
65	LGLEA	28	AQMHA	130	DOSalt65
78	NLAVV	32	LGRLD	131	DOSsel78
82	VMGLH	34	DNITL	132	DOSsel82
86	HPDYF	35	LVMV F	133	DOSalt86
91	TSFWR	39	HPQYL	134	DOSsel91
98	YLLH	44	FLKTQ	135	DOSsel98
103	TDGPL	46	HYLLQ	136	DOSsel103
110	SWRHY	52	GPLPL	137	DOSsel110
111	WRHYI	53	PLPLH	138	DOSsel111
112	RHYIA	54	LPLHY	139	DOSsel112
120	AARHQ	107	IGIMA	140	DOSsel120
121	ARHQC	62	GIMAA	141	DOSsel121
122	RHQCS	63	IMAAA	58	DOSsel122
123	HQCSY	64	MAAAR	59	DOSsel123
124	QCSYL	65	AAARH	60	DOSsel124
126	SYLVG	67	ARHQC	62	DOSsel126
127	YLVGS	68	RHQCS	63	DOSalt127
128	LVGSH	69	HQCSY	64	DOSsel128
129	VGSHM	70	QCSYL	65	DOSalt129
137	LQTGG	72	HVNDF	142	DOSsel137
140	GGDPE	73	DFLHV	143	DOSsel140
141	GDPEW	74	FLHVG	144	DOSsel141

154	EKL ⁸² RK	82	LENAP	145	DOSsel154
155	KLRKL	83	ENAPQ	146	DOSsel155
156	LRKLS	84	NAPQK	147	DOSsel156

Figure 31

Dos number	SESTRIN 2		SESTRIN 3		
	Sequence	SEQ ID No	Sequence	SEQ ID No	
1	MIVAD	<u>8</u>	<u>M</u> NRGG	148	DOSalt1
2	IVADS	9	NRGGG	149	DOSsel2
46	AFIPV	22	EKEV <u>V</u>	150	DOSalt46
73	SGRVD	31	DNITQ	151	DOSsel73
81	VVMGL	33	LHTQY	152	DOSsel81
87	PDYFT	36	ESFLR	153	DOSsel87
88	DYFTS	37	SFLR <u>S</u>	154	DOSalt88
90	FTSFW	<u>39</u>	RSQFY	155	DOSalt90
95	RLHYL	41	YMLRM	156	DOSsel95
96	LHYLL	42	MLRMD	157	DOSsel96
97	HYLLL	43	LRMDG	158	DOSsel97
104	DGPLA	47	PLP <u>Y</u> R	159	DOSalt104
105	GPLAS	48	LP <u>Y</u> RH	160	DOSalt105
106	PLASS	49	P <u>Y</u> RHY	161	DOSalt106
113	HYIAI	55	IMAA <u>A</u>	58	DOSalt113
114	YIAIM	56	MAA <u>A</u> R	59	DOSalt114
116	AIMAA	57	<u>A</u> ARHQ	107	DOSalt116
117	IMAAA	58	ARHQC	62	DOSsel117
118	MAAAR	59	RHQCS	63	DOSsel118
119	AAARH	60	HQCSY	64	DOSsel119
125	CSYLV	66	INMH <u>V</u>	162	DOSalt125
132	HMAEF	71	FLKTG	163	DOSsel132
143	PEWLL	76	NGLEY	164	DOSsel143
144	EWLLG	77	GLEYV	165	DOSsel144
145	WLLGL	78	LEYVP	166	DOSsel145

Dos number	SESTRIN 2		SESTRIN 3		
	Sequence	SEQ ID No	Sequence	SEQ ID No	
3	VADSE	10	RGGGS	167	DOSsel3
4	ADSEC	<u>11</u>	GGGSP	168	DOSsel4
5	DSECR	12	GGSPS	169	DOSsel5
6	SECRA	13	GSPSA	170	DOSalt6
7	ECRAE	14	SPSAA	171	DOSalt7
8	CRAEL	15	PSAAA	172	DOSalt8
9	RAELK	16	SAAAN	173	DOSsel9
16	LRFAP	17	<u>L</u> CTNC	174	DOSalt16
24	GDSGP	18	LRKDK	175	DOSsel24
32	QRESR	<u>19</u>	VSQPL	176	DOSsel32
39	RGPRG	<u>20</u>	GPSAF	177	DOScon*****39
40	GPRGP	21	PSAFI	178	DOScon*****40
48	IPVEE	23	EVVQA	179	DOSalt48
56	EGAES	<u>24</u>	DEFTN	180	DOSsel56
62	EQHLG	25	LVEEY	181	DOSsel62
63	QHLGL	26	VEEYS	182	DOSsel63
64	HLGLE	27	EEYST	183	DOSsel64
65	LGLEA	28	EYSTS	184	DOSsel65
78	NLAVV	32	VMSLH	185	DOSsel78
82	VMGLH	34	HTQYL	186	DOSsel82
91	TSFWR	39	<u>R</u> SQFY	187	DOSalt91
94	WRLHY	40	FYMLR	188	DOSsel94
98	YLLH	44	RMDGP	189	DOSsel98
103	TDGPL	46	LPLPY	190	DOSalt103
108	ASSWR	51	RHYIA	54	DOScon*****108
110	SWRHY	52	YIAIM	56	DOScon*****110
111	WRHYI	53	IAIMA	191	DOSsel111
112	RHYIA	54	AIMAA	57	DOScon*****112
120	AARHQ	107	QCSYL	65	DOSsel120
121	ARHQC	62	CSYLI	192	DOSsel121
122	RHQCS	63	SYLIN	193	DOSsel122
123	HQCSY	64	YLINM	194	DOSsel123
124	QCSYL	65	LINMH	195	DOSsel124
126	SYLVG	67	NMHVD	196	DOSalt126
127	YLVGS	68	MHVDE	197	DOSalt127
128	LVGSH	69	HVDEF	198	DOSalt128
129	VGSHM	70	VDEFLL	199	DOSalt129

137	LQTGG	72	GIAEW	200	DOSsel137
140	GGDPE	73	EWLNG	201	DOSsel140
151	RAPEK	79	RLKNL	202	DOSalt151
154	EKLRK	82	NLNEI	203	DOSsel154
155	KLRKL	83	LNEIN	204	DOSsel155
156	LRKLS	84	NEINK	205	DOSsel156

Figure 32

Sestrin 1

DOS compound	Sequence	SEQ ID No
DOSsim1	LLMLS	206
DOSsim2	LMLSK	207
DOSsim3	MLSKR	208
DOSsim9	PF(K)DVR	209
DOSsim10	F(K)DVRE	210
DOSsim11	DVREK	211
DOSsim12	VREKS	212
DOSsim13	REKSE	213
DOSsim19	ILKSI	214
DOSsim33	GIRIP	215
DOSsim65	A(L)FAD	216
DOSsim66	FADSF	89
DOSsim67	ADSFA	90
DOSsim68	DSFAA	91
DOSsim69	SFAAL	217
DOSsim94	LKTQH	97
DOSsim95	KTQHY	218

Figure 33**Sestrin 3**

DOS compound	Sequence	SEQ ID No
DOSsim1	NYLLC	219
DOSsim2	YLLCT	220
DOSsim3	LLCTN	221
DOSsim34	IRVSQ	222
DOSsim35	RVSQP	223
DOSsim36	VSQPL	176
DOSsim37	SQPLT	224
DOSsim54	VQANT	225
DOSsim55	QANTV	226
DOSsim56	ANTVD	227
DOSsim57	NTVDE	228
DOSsim58	TVDER	229
DOSsim59	VDERT	230
DOSsim60	DERTN	180
DOSsim61	ERTNF	231
DOSsim62	RTNFL	232
DOSsim63	TNFLV	233
DOSsim96	SQFYM	234

Figure 34

From the sequence alignment Sestrin 1 vs Sestrin 2

Sequence	SEQ ID No	Name
GPS	235	DOScon1/1
FIP	236	DOScon2/1
E-L	237	DOScon3/1
G-E	238	DOScon4/1
GR-DN	239	DOScon5/1
HP-Y	240	DOScon6/1
DGPL	241	DOScon7/1
RHYI	242	DOScon8/1
IMAA	243	DOScon9/1
ARHQ	244	DOScon10/1
CSYL	245	DOScon11/1
GGDP	246	DOScon12/1
AP-KL	247	DOScon13/1

Figure 35

From the sequence alignment Sestrin 3 vs Sestrin 2

Sequence	SEQ ID No	Name
RGPS	248	DOScon1/3
AFIP	249	DOScon2/3
SGR	250	DOScon3/3
VM-LH	251	DOScon4/3
SF-R	252	DOScon5/3
DGPL	253	DOScon6/3
RHYI	254	DOScon7/3
AIMA	255	DOScon8/3
AARH	256	DOScon9/3
QCSY	257	DOScon10/3
EFL	258	DOScon11/3
TGG	259	DOScon12/3
EWL	260	DOScon13/3

Figure 36

Sequences conserved between sestrin 1, sestrin2 and sestrin 3

Sequence	SEQ ID No	Sestrin 1	Sestrin 2	Sestrin 3	DOS Name
AARHQ	107	X	X	X	DOSsupercon1
IMAAA	58	X	X	X	DOSsupercon2
MAAAR	59	X	X	X	DOSsupercon3
ARHQC	62	X	X	X	DOSsupercon4
RHQCS	63	X	X	X	DOSsupercon5
HQCSY	64	X	X	X	DOSsupercon6
QCSYL	65	X	X	X	DOSsupercon7
LDNIT	261	X		X	DOScon1
LESFL	262	X		X	DOScon2
YRHYI	263	X		X	DOScon3
YLESF	264	X		X	DOScon4
MDGPL	265	X		X	DOScon5
LNGLE	266	X		X	DOScon6
RLDNI	267	X		X	DOScon7
DGPLP	268	X		X	DOScon8
WLNGL	269	X		X	DOScon9