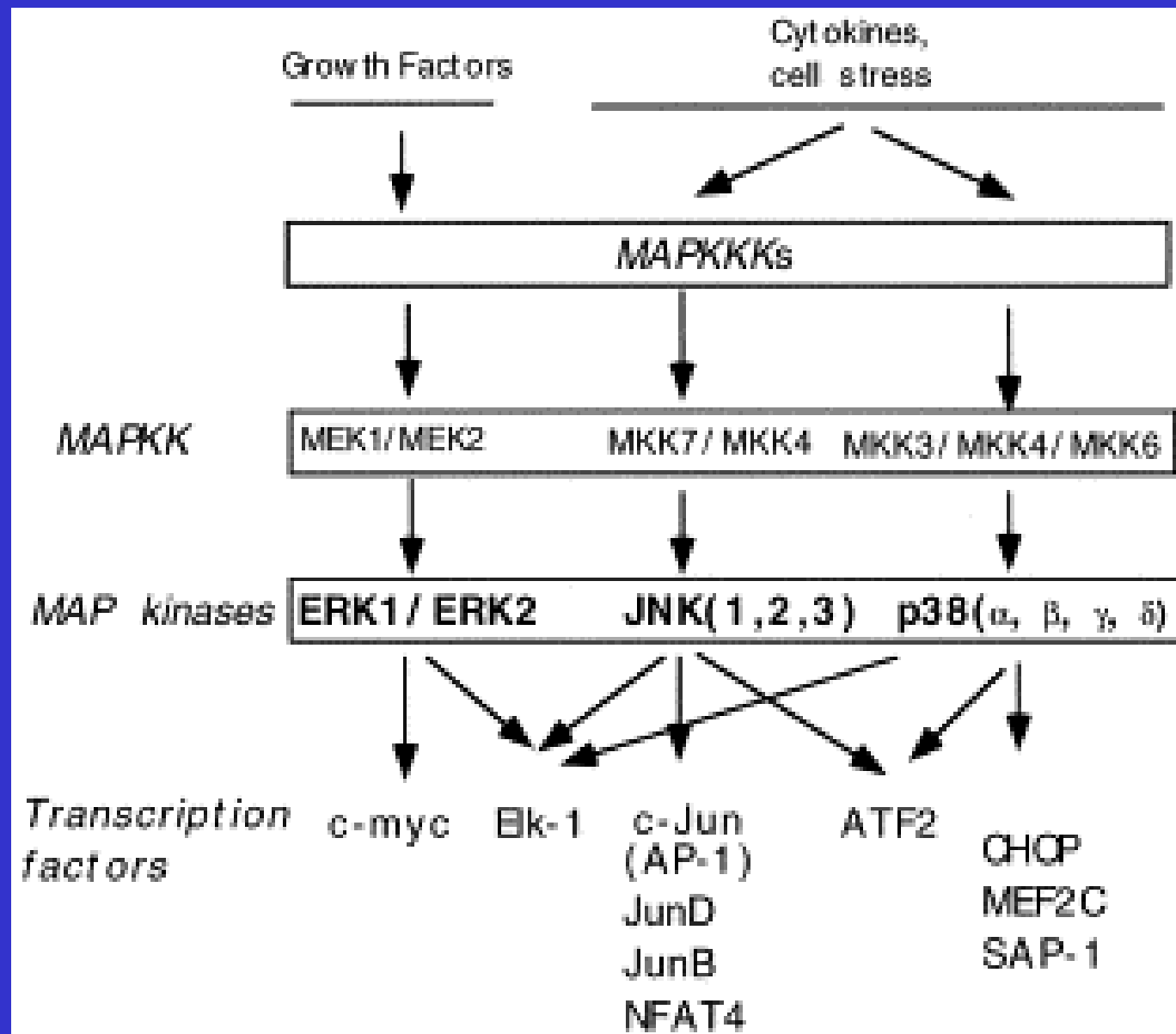


**DIFFERENCES AND SIMILARITIES
AMONG THE MAPK:
ERK2, p38 and JNK**

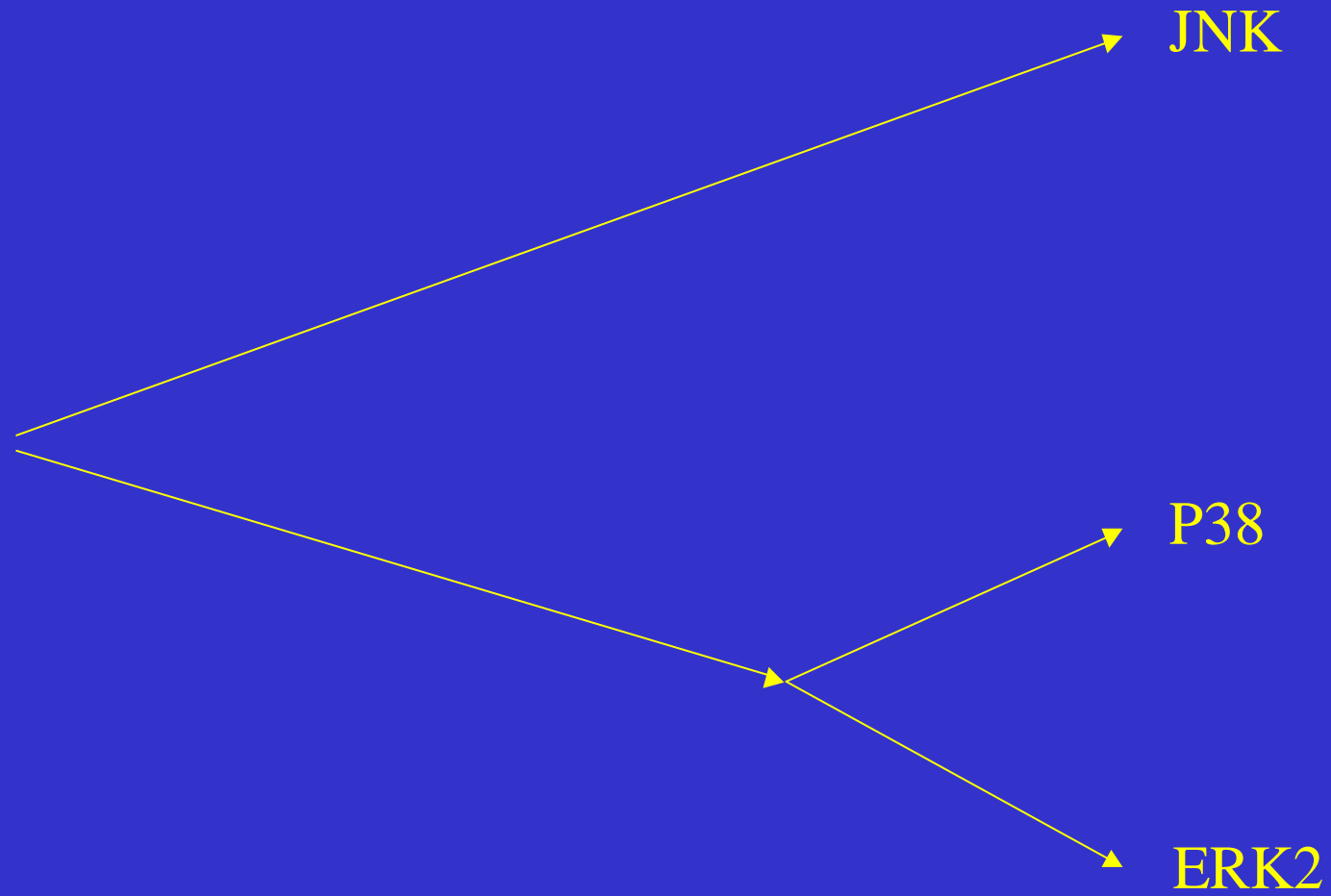


Comparison of ERK2, JNK3s and p38beta

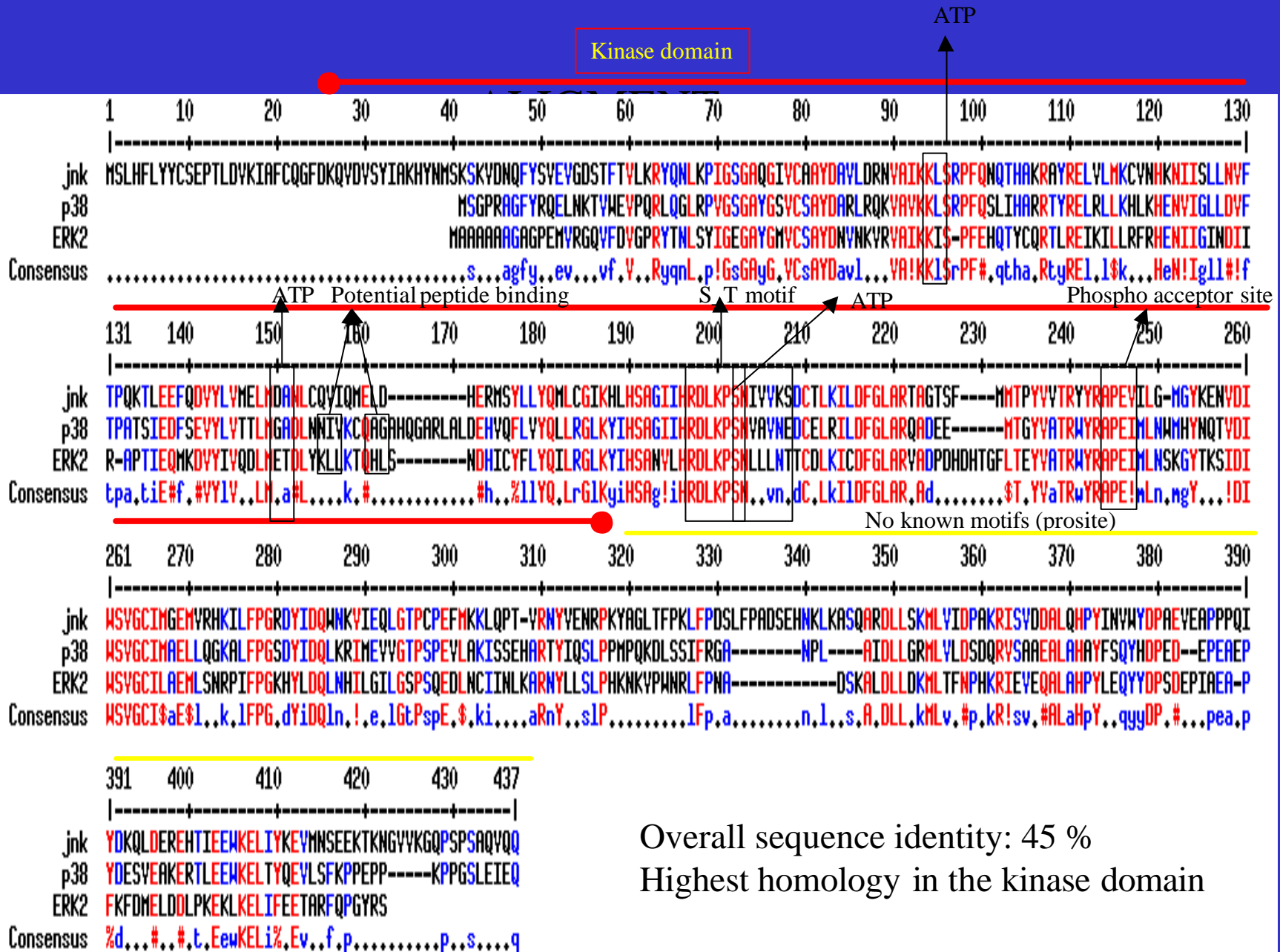
DIFFERENCES AND SIMILARITIES AMONG THE MAPK: ERK2, p38 and JNK

- Phylogenetic tree
- Alignment
- ERK substrates
- JNK substrates
- p38 substrates

PHYLOGENETIC TREE



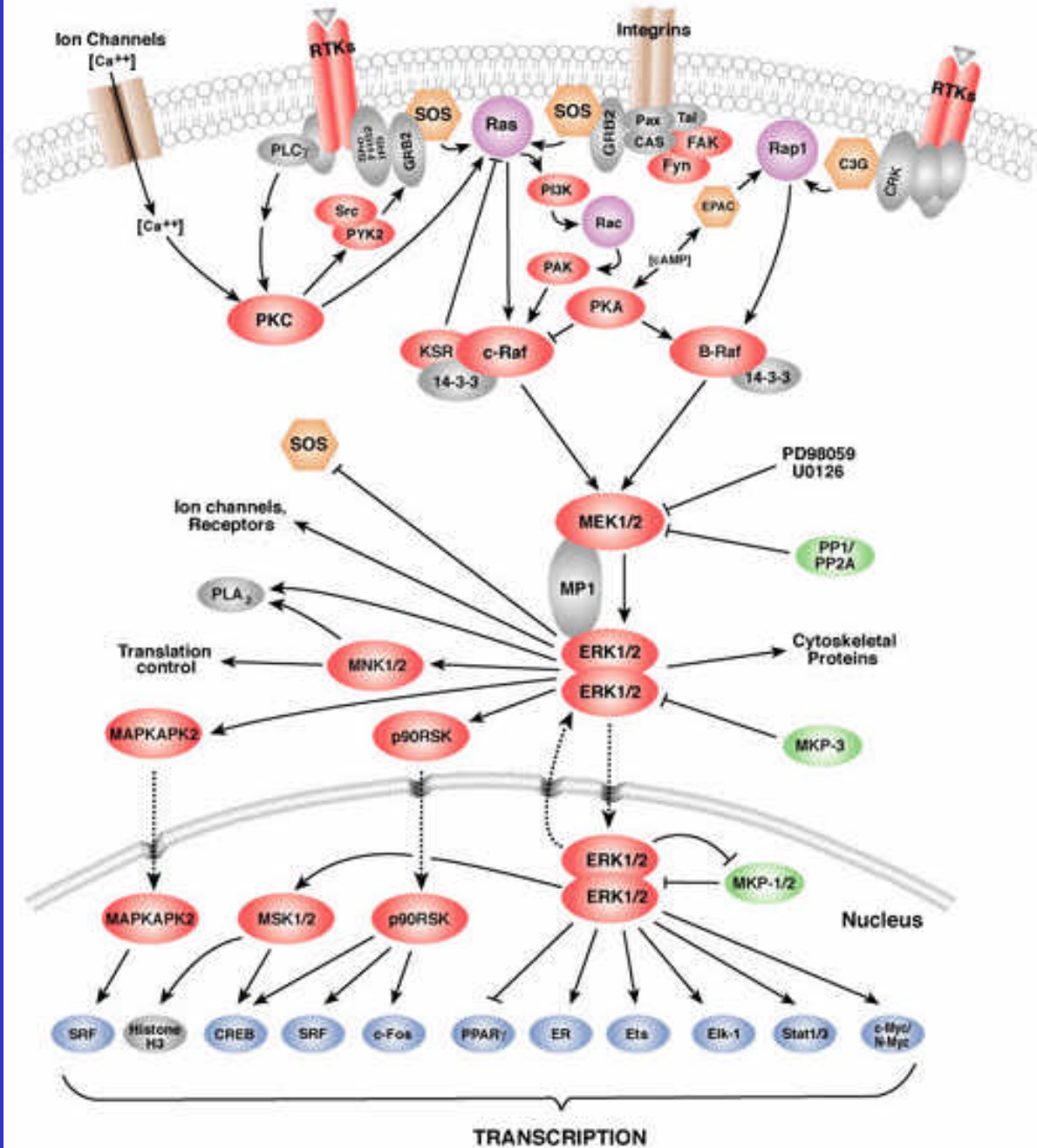
Mapkinase Sequence alignment



Overall sequence identity: 45 %

Highest homology in the kinase domain

MAPK/ERK in Growth and Differentiation



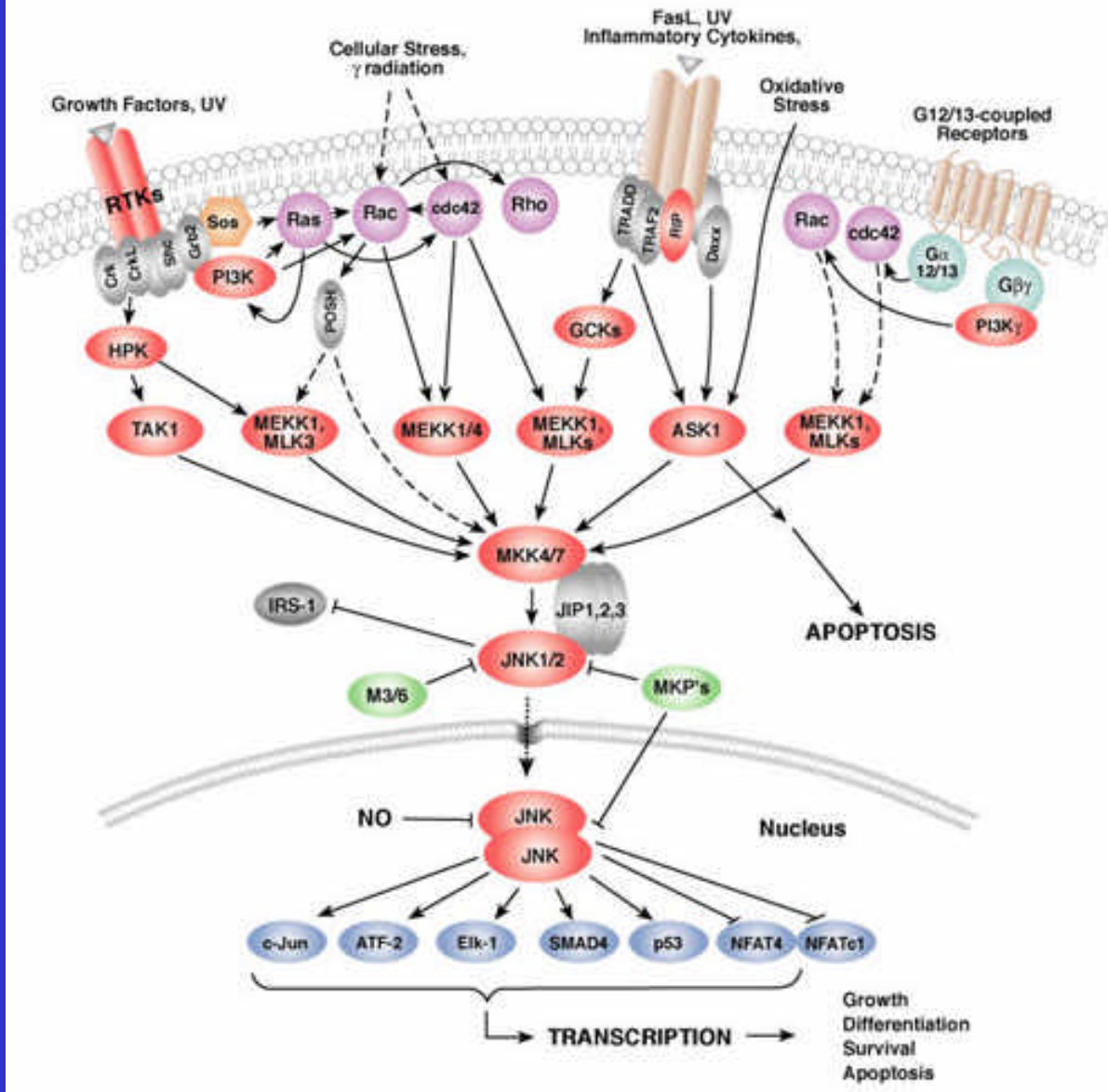
ERK2 known substrates

	Full name	Function	Phosphorylation site
MARCKS	Myristoylated Alanine-Rich C-Kinase Substrate	Calmodulin interacting	S113
c-myc	Cellular homolog of v-myc	Proto-oncogene	S62
EIk1		Transcription factor	S383
TH	Tyrosine Hydroxylase	Enzyme involved in catecholamine biosynthesis	S31

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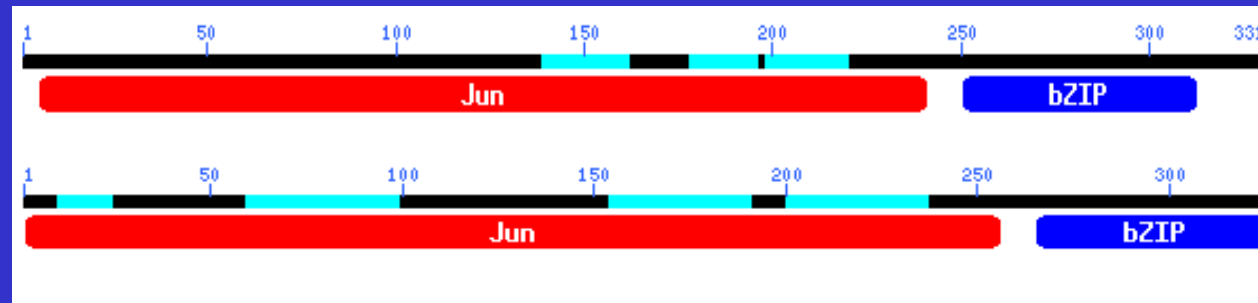
      1      10      20      30 34
      |-----+-----+-----+---|
MARCKS PAEPSPAAEAEGASASSTS-SPKAEDGATPSPS
c-myc  PTPPLSPRRSGLCSPSYVAVTPFSLRGDNDGG
EIk1   FWTLSPIAPRSPAKLSFQFPSSGSAQVHIPSI
TH     AEAIMSPRFIGRRQSLIEDARKEREAAVAAAAA
Consensus ....LSP.a.....asls..a.s..sa.va.ps..
    
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SAPK/JNK Signaling Cascades

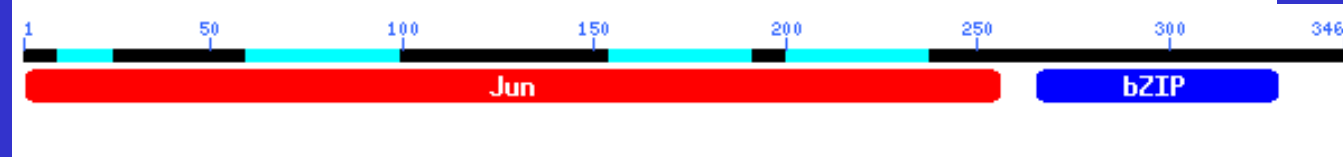


JNK3 substrates (TFs)

AP-1



JunD



Jun domain with activation loop

DNA binding domain
(leucine zipper)

ATF2
JNK1 and
p38
phosphorylation site
(Thr 51 & 55)

Characterised JNK substrates

JNK3

Phosphorylation site
(Ser 140 & 150)

	1	10	20	30	40	50	60	70	80	90	100	110	120	130
AP-1										MTAKMETTFYDDALNASFLPSESGPYGYSNPKILKQSMTLNLADPVGS-LKPH				LRAKNSD
JunD								METPFYGD	EARL	SGLGGASGSGGSFASPGRLFP	APPTAAGSMKKDALTL	SLSEQVAALKPA	AAPPPTPL	RADGAP
JunB										MCTKMEQPFYHDDSYTATGYGRAPGGLSLHDKYKLLKPSLAVNLADPYRSLKAPGARGP	PEGGGGSSY			
ATF-2	MSDDKPFLCTAPGCGQRFTNEDHLAVHKHKHEHTLKFGRARND	SVIVADQ	TPTPT	FLKNCEEVGLFNELASPFENEFKASEDDIKKMP	LDL	SPLATPIIRSKIEEP	SVVETTHQDSPLHP	ESTSD						
Consensus
	131	140	150	160	170	180	190	200	210	220	230	240	250	260
AP-1	LLTSPDVGLLKLASPELER	VIQSSNGHIT	TTPTPT	QFLCPKNVTDEQE	GF	AEGFYRALAELHSQNTLPSYTSAAQPVNGAGMVA	PAVASVAGGSGSGGFSASLHSEPPVYANLSNF							
JunD	SAAPPDL	LLASPD	LGLKLASPELER	IIQS	NGLVT	TTPTSS	QFLYPKVAASEEQ	EF	AEGFYKAL	EDLHKQNLGAGAAAAA	AGGPGSGTATGSAPP	GELAPAAAP	EA	PVYANLSSY
JunB	L	AGSD	TGASLKLASSELER	I	VPNSNGVIT	TTPTPP	QYFYPRGGGSGGG	AGGAGGGVTEEQEGFADGF	VKALD	DHLKMNHVTPPNVSLGATGGPP	AGPGG	YAGPEPP	PPVY	TNLSSY
ATF-2	EKEYPLAQTAQPTSAIVRPASLQV	PNVLLTSSDSSV	IIQAVPSPTSS	VITQAPSSNRPIV	VPVPGFPLLLHL	PNGQTHPVAIPASITSSNVHVPA	AVPLVRPVTHVPSVPGIPGSSPQPVQSEAKMR							
Consensus
	261	270	280	290	300	310	320	330	340	350	360	370	380	390
AP-1	NPGALSSGGGAPSYGAAGLAFPAQPQQQQ	PPHHL	PQMPYQHPR	LQAL	KEEPQTVPEMP	GETPPLSPIDHESQERIK	AERKRMNR	IAASKCRKRKLERIARLEEKVTKLKAQNS	ELASTANML					
JunD	AGGAGGAGG	AATVAF	AAEPVPFP	PP	PPGALGPPR	LAAL	KDEPQTVDPV	SFGES	PPLSPIDHDTQERIK	AERKRLNR	IAASKCRKRKLERI	SRLEEKVTKLKSQNT	ELASTASLL	
JunB	SPASASSGGAGAAVGTGS	SYPTT	ISYLPHAPPFAGGHPAQLGL	GRGASTF	KEEPQTVPEAR	SRDATPPVSPINMEDQERIK	VERKRLNR	LAATKCRKRKLERIARLEEKVTKLKAENAGL	SSTAGLL					
ATF-2	LKAAL	TQQHPPVTNGD	VKGHGSGLV	RTQS	EESR	PQSLQQPATSTTET	PASPAHTPQT	STSGRRRRRA	NEPDEKRRK	FLE	RNR	AAASKCRKRKLERI	rLE	KvktLks.N.L.Sta.\$L
Consensus
	391	400	410	420	430	440	450	460	470	480	490	494		
AP-1	REQVAQLKQKYMNHVNSGCQLMLTQQLQTF													
JunD	REQVAQLKQKYL	SHVNSGCQLLPQHQPAY												
JunB	REQVAQLKQKYMTHVNSGCQLLLGVKGFHAF													
ATF-2	RNEVAQLKQLLLAHKDCPYTAMQKKS	GYHTADKDDSS	EDISVPSSPHT	EAIQHS	VSTSN	GVSSSTSKAEAVATSVLTQ	MADQSTEPALS	SQIYMAPSSQSPSGS						
Consensus	R#	VAQLKQkv\$.Hv..gcqI\$.g		

Predicted phosphorylation sites

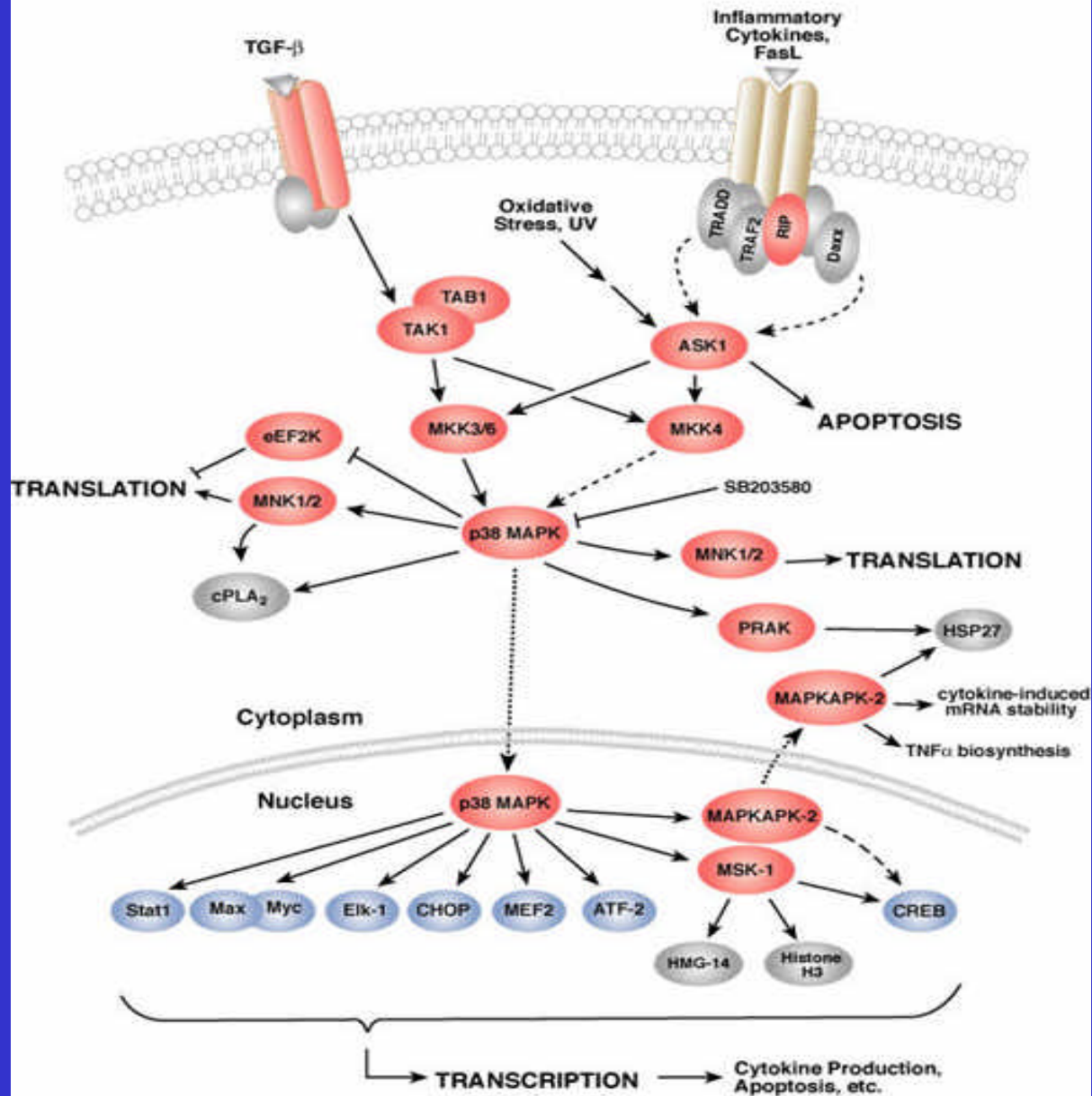
JunD T267, S257, S261

ATF-2 T 37, S167, S251

API T10, T95, Y172, T233, T241, S251, S245

94-100 % conservation/identity of JNK phosphorylation domain of AP-1 (19 aa containing Ser^{150, 153}) between human, mouse and chicken.

p38 MAPK Signaling Pathways



	1	10	20	30	40	50	60	70	80	90	100	110	120	130
E1k1	----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- -----													
MEF2c	MGRKKIQITRIMDE--RNRQVFTFKRKFGL--MKKAYELSVLDCCEIALIIFNSTNK--LFQYASTDMQVLLKYTEYNPEPHESTRNSQIVETLRKKG----LN													
nsk1human	MEEEGSSGGGAAGTSADGGDGGELLTYKHELTRANLTGHAKEVGTENFELLKVLGTGAYGKVLVYRKISGHD--TGKLYAMKVLKKAIIYQKAKTTEHTRTERQVLEHIRQSPFLVTLH													
ATF2	MSDDKPFLECTAPGCGQRFTNEDHLAVHKHKHEHTLKFGPARNDSYIVADQTPTRFLKNCEEVGLFNE--LASPFENEFKKAEDDIKKMPLDLSPLATPIIRSKIEEPSVYETT													
napkap2	MLSNSQGGQSPVPFPAPAPPPQPTPALPHPPAQPFPFQFHVKSGLQIKKNAIIDDYKVTSQLVGLGTINGKVLQIFNKRQTQEFALKMLQDCPKARREVELHWRASQCPIHIVRIVDVYENLYAG													
Consensust.....g.....t.....n.....k.....s.t.....													
	131	140	150	160	170	180	190	200	210	220	230	240	250	260
E1k1	----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- -----													
MEF2c	SMTSRDGGFEKLVDAEEYARL----MGLRKNKTNMNYDKLSRALRYYYDKNIIRKYSGQKFVYKFSYPE--VAGCSTEDCPQPPEVSVTSTMPNVAPAAIHAAAPGDTYSGKPGTPKGGMAGPGLARSS													
nsk1human	GCDSPDPDADDSVGHSPSE----DKYRKINEDIDLHISRQLCAVPPPNFEMPYSIPVSSHNSLYYSNPVSSLGNPNLLP--LAHPSLQRNSMSPGVTHRPPS---AGNTGGLMGGDLTS--GAGTSAG													
ATF2	YAFQTETKLHLILDYINGGELFTHLSQRERFTEHEVQIYVGEIVLLEHLHLKGIYRDIKLENILLDSNGHVVLTDGFLSKEFVADETERAYSFCGTIEYMAPDIVRGDSGHDKAVDMSLGLVLYEL													
napkap2	HQDSPLPHPESTTSDEKEVPL----AQTAQPTSATVIRPNSLQVPMVLLTSSDSSVIQAVPSPSTSVITQAPSSNRPIVVPVGPFPPLLHLPLNGQTHPVAIIPASITSSNVHVPAAVPLVVPVTHVPSV													
Consensus	...s.....l.....l.....n.....n.....l.....p.....l.....p.....aP.....g..g..k..d..s.g.....													
	261	270	280	290	300	310	320	330	340	350	360	370	380	390
E1k1	----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- -----													
MEF2c	R---NEYMRSGLYSTFTTIQSLQPPPPHPRPAVVLPNAPAGAAAPPSSGRSTSPSPLEACLEAE-----AGLPLQVILTPPEAPNLKSEELNVEPGLGRALPPEVKVEG--PKEELEVA													
nsk1human	NGYGNPRNSPGLLVSPGNLNKNHAKSPPHNLGNMNRKPDRLVLPVGGKNTMPSVSEVDVL-----LLNQRIN--NSQSAQSLATPVVSVATPTLPQQGMGGYPSAISTTYG--TEYSLSSADLS													
ATF2	LTGASPFYVDGKNSQAEISRRLKSEPPYPQEMSAKADLIQRLLMKDPKKRLGCGPRDADEIKE-----HLFFQKINMDDLAAKKVPAFPKPVIRDELQVSNFAEEFTENDPTYSAPALPQSEKLF													
napkap2	PGIPGPPSSPQPVSQAKMRLKAALTQQHPPYVNGDVTYKGGHGLVRTQSEESRQSLQQPATSTTETPASPAHTTPTQSTSGRRRRRAEDPDEKRRKFLERNRAASRCRQKRKYVQVQSLKKAEDLS													
Consensus	...P.....g.....p.p.....l.....k.....s.....e.....q.....tp.....l.....l.....													
	391	400	410	420	430	440	450	460	470	480	490	500	510	520
E1k1	----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- ----- -----													
MEF2c	GERGFVPEITTKAEPEVPPQEGVPARLPVYMDTAGQAGGHAASSPEISQPQKGR---KPRDLELPLSPSLLGGPGPERTPGSGSGSGL--QAPGPALTPSLLPHTLTPVLLTPSSLPPSIHFHSTLSPI													
nsk1human	SLSGFNTASALHL--GSYTGHQQLHNMPPSA--LSQLGACTSTHLSQSSNLSL--PSTQLNLIKSEPVSPPRDRITTPSRYPQHTR--HEAGRSPVDSLSSCSSSYDGS--REDHRNEFHSPIGLTRP													
ATF2	QGYSFVAPSILFKRNAAYIDPLQFHMGVERPGVTVNVARSAMMKDPPFYQHYDLDLKDQPLGEGSFSICRKCVMKSNQAFAYKIIISKRM--EANTQKEITALKCEGHPNIVKLHEVFDHQLHTFLVMELL													
napkap2	SLNGQLQSEVTLRNEVAQLKQLLLAHKDCPVTAHQKSGYHTADKDDSEDISVPSPPHTEAIQHSVSYSTNGVSYSTSKAREAVATSVLTMADQSTEPALSQIYMAPSSSQSPSGS													
Consensus	...gf.....l..r.....h.....p.....q.....P.....l.....h.....													
	521	530	540	550	560	568								
E1k1	----- ----- ----- ----- ----- -----													
MEF2c	AP---RSPAKLSFQFPSSGSAQVHIPISVDGLSTPVVLSPGPQKP													
nsk1human	SPDERESPSVKRMRLSEGMA													
ATF2	NGGELFERIKKKHFSETEASYIMRKLVSAYSHMHADVGVVHRDLKPEV													
napkap2														
Consensus													

Phosphorylation sites of known p38 substrates :

ELK1: T368

Mef2: T292

Mapkap2:T334

ATF2:S173, S72,S310

MSK1:S111

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1      10      20      30      40      50      60      70      80      90      100     110     120     130
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
p53
FLIPc
Bc12
A1human
bin
Consensus
MSAEVIHQVEEALDTEKEMLLFLCRDVAIDVYPPNVRDLLDILRERGKLSVGDLAELLYRVRRFDLLKRILKMDRKAVETHLLRNPHLVSDYRVLMAEIGEDLDKSDVSSLIFLHKDYMGRGKISKEKS
.....
MAKQPSDVSSECDREGRQLQPAERPPQLRPGAPATSLQTEPQGNPEGNHGGEGDSCPHGSPQ6GLAPPASPGPFATRSPLEFIFHRRSSLLSRSSSGYFSFDTORSPAPM5CDKSTQTPSPPCQAFNHLYLS
.....
131     140     150     160     170     180     190     200     210     220     230     240     250     260
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
p53
FLIPc
Bc12
A1human
bin
Consensus
FLDLVVELEKLNLYAPDQDLLEKCLKNIHRIDLKTKIQKYKQSVQ6AGT5SYRNVLQAARIQKSLKDP5NNFRLNHNGRSKEQRLKEQLGAQQEPYKKSIESEAFLPQ5IPEERYKHKSKPLGICLIIDCI
.....
AMEEQRQAEPADH--RPEIWIQAQLRRIGDEFNAYYARRVFLNNYQAEDHPRHVILRLLRYIVRLV---WRMH
.....
261     270     280     290     300     310     320     330     340     350     360     370     380     390
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
p53
FLIPc
Bc12
A1human
bin
Consensus
LSPDDIEQWFTEDPGDEAPRMP---EAAPRVAPAPAPPTPAAPAPAP5MPLSS5VPSQKTYQGSYGFRGLGFLHSGTAKSV--TCTYSPALNKHFCQLAKTCPVQLHVDST---PPP6TRVRAHAIYKQSQ
GNETELLRDTFTSLGYEVQKFLHLSNHGISQILGQFACHPEHRDYDSFVCVLVSRGG5QSVY6VDQTHSGLPLHAIIRMFHNGD5CPYL6GPKPMFFIQNYVV5EGQLED5SLL5VDG6PANKNVEFKAKQR
.....
391     400     410     420     430     440     450     460     470     480     490     500     510     520
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
p53
FLIPc
Bc12
A1human
bin
Consensus
HMTEVYRR---CPHHERCSDSDGLAPPQHLIRVEGNLRVEY---LDDRNTFRHSVYVYEPPEV6SDCTTIHYNHMCN5SCMG6NRRPILTIITLED5SGNLL-GRNSFEYRVCACPGDRDRTEE
GLCTVHREADFFMSLCTADM5LLEQSHSSPSLYLQCL5QKLRQERKRPLLDLHIELNGYMYDMNSRVS5AKEKYVVLQHTLRKKLILSYTBCLXLH5MANSQ5NREL5VD5FLSYKLSQKGY5S4QF5DVE
MAHAGRTGYDNREIVMKYIHYKLSQRGYENDAGDVGA
.....
521     530     540     550     560     570     580     590     600     610     620     630     640     650
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
p53
FLIPc
Bc12
A1human
bin
Consensus
ENLRKKGEPHHELPPG5TKRALPNMT5SS5PQKKKPLDGEYFTLQIRGRERFENFRELNEALELKDQAQ6KEPPG5SRAH5SHLKS5KKGQ5TS
EN---RTEAPEGT5ESEHETPSAINGNPS5HLAD5PAVNGATGH5SSLDAREVIPHAAVYKQALREAGDEFELRYRRAF5DLT5QLHITP6TAYQ5FEQV5VNELFRDGV-NMGRIVAF5FFG6ALCV5E5VDKE
APPGAAPAPGIF55QPGHTPHPAASRDPVART5PLQTPAAPGAAGPAL5PV5PVVHLT-LRQAGDD5FR5RYRRDFAEM5SQLHLTPFARGRFATVVEELFRDGV-NMGRIVAF5FFG6VHC5E5V5NRE
HTDCEFGYIYRLAQDYLCVYLQIPQ6SGSPK5TSRVLQNVAF5VQKEVEKNLKSCLDNV5V5VD5TARTL5NMQVMEKEFEDG5I5MGRIVTIFAFEG5ILIKKLLRQQ
.....
P.....P.....a.d.....s.l.....ta...f.v...f.dg..nugriv..f.f.g.....
651     660     670     680     690     700     710     720     728
|-----|-----|-----|-----|-----|-----|-----|
p53
FLIPc
Bc12
A1human
bin
Consensus
MQVLVS---RIAAHMATYLN5DLEPHIQENGGHD-TFV5ELYGNNAAR5ESRKGQERLEHHHHHH
MSPLVD---NIALMHT5EYLN5RHLHTI5QDNGGHD-AFV5ELYG5PSMRPL5DFSML5LKTLL5LAL5VGACITL5GAYL5GHK
IAPD5D5TYKEISYFVAEF5HNT5GEH5IRQNGG5MENG5FVKKFEPK5G5MHT5FLEVT5GKICEML5LLKQYCL
.....
v.....i.....wi..nggu..fv.....

```

Phosphorylation sites of predicted substrates :

A1: S28 by ERK1/2, close to a proline

FLIP: lots of basophilic STK, S419 proline-dep. STK

Bim: high stringency for ERK1 phosphorylation at S69

Bcl2: S70, S87, S167 for p38 MAPK

