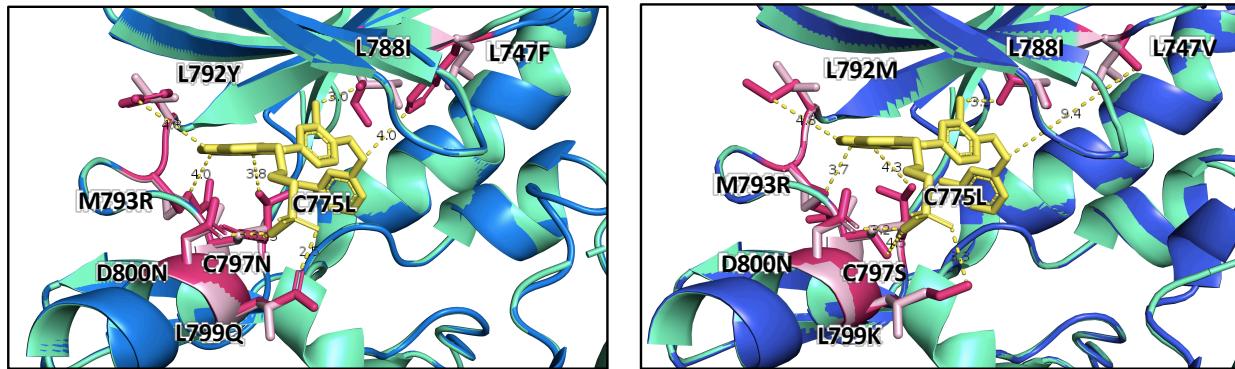


Supplementary Figure 1. Structural comparison of EGFR/LET-23 homology model and LET-23 crystal structure. (A) Homology model of only the *C. elegans* LET-23, which is modeled after an EGFR crystal structure complexed with AMP-PNP (PDB: 2ITX, AMP-PNP in yellow). The *C. elegans* LET-23 residues that diverge from Human EGFR that also have side chains oriented towards the active site are highlighted in dark pink. Residues are labeled according to position in human EGFR, with the first letter indicating the identity of the human residue and the latter indicating the identity of the *C. elegans* residue. (B) The crystal structure of only the LET-23 kinase domain complexed with AMP-PNP (PDB: 5WNO, AMP-PNP in yellow) with the same residues highlighted in (A) here are highlighted in light pink. The orientation of these key residues towards the active site is consistent between the LET-23 homology model and crystal structure. The homology model and crystal structure of LET-23 are overlaid in (C).

Supplementary Figure 2. Structures and alignments for druggable nematode essential kinase targets. In all alignments, residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment. Grey residues were examined but do not differ between *C. elegans* and humans. Divergent residues are highlighted in dark pink (*C. elegans* residue) and light pink (human residue). Yellow highlights those residues from different species that differ in identity from both the *C. elegans* kinase and the human ortholog of interest in these key positions. Some alignments include additional human paralogs where we also color residues yellow that differ from *C. elegans* and the relevant human ortholog. Residues of interest that differ between nematodes and vertebrates are labeled with their position in the human kinase on the alignment and shown in dark and light pink on the structure above. Those residues of interest indicated with a star on the alignment are located within 5Å of the bound inhibitor in any of the *C. elegans* models examined.

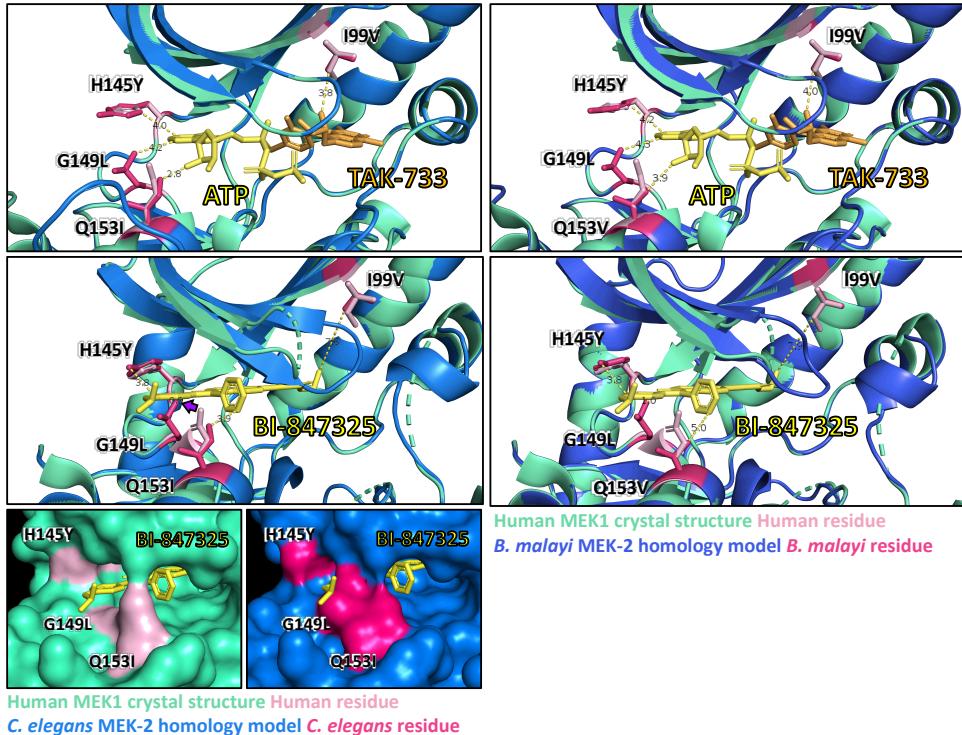


Human EGFR crystal structure Human residue
C. elegans LET-23 homology model *C. elegans* residue

Human EGFR crystal structure Human residue
B. malayi LET-23 homology model *B. malayi* residue

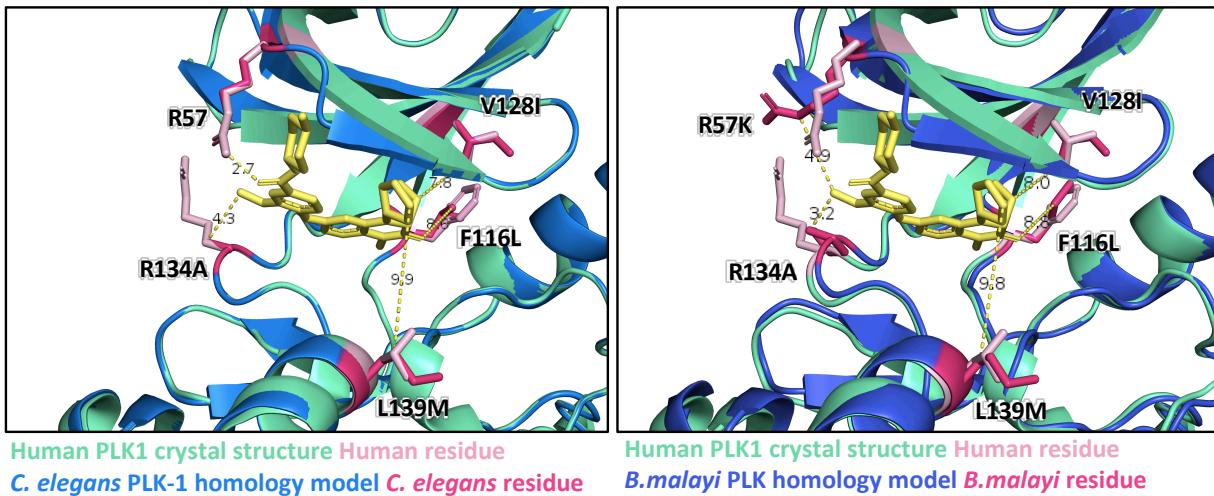
	<i>C. elegans</i> LET-23	<i>C. briggsae</i>	<i>P. pacificus</i>	<i>H. contortus</i>	<i>N. americanus</i>	<i>A. duodenale</i>	<i>A. ceylanicum</i>	<i>S. ratti</i>	<i>B. malayi</i>	<i>O. ochengi</i>	<i>L. loa</i>	<i>T. suis</i>	<i>D. rerio</i>	<i>G. gallus</i>	<i>M. musculus</i>	<i>R. norvegicus</i>	<i>C. familiaris</i>	<i>O. aries</i>	<i>B. taurus</i>	<i>H. sapiens</i> EGFR	<i>H. sapiens</i> ERBB2	<i>H. sapiens</i> ERBB3	<i>H. sapiens</i> ERBB4			
Nematodes	KKLGAGAFGTWFGAIIYPKPRA--KNVKIPVAIKVQTQDS--QTDEMLEEATNMFR--LRHDNLKRIIGFCMHDDGLKIVTIIPLGNLQFLKLHKENLG	KKLGAGAFGTWFGAIIYPKPRA--KNVKIPVAIKV EQVGQS --QTDEM EATNMFR --LRHEHLKRIIGFCIHDDGLKIVT IVPLGDLH STFLQLHKETLG	RELGSGAGFVVYAGCWMVPVSAGKPKVPAV VVRDPS --GRAQSEMLDEAKMTM--MRHENL IVGVCLSGDDLQ VLVTLLEPLGNLREFLQKHKGKLS	TQLGAGAFGVVYAGFWFPKGK-GK- IKV PVAIKLV K GTC TGKEESEM LNEMAMQMS--LRHEHL IVVGICL HEEGIQ IVQ VLLEPLGNLNF LKKHKAHL C	TQLGAGAFGVVYAGFWFPKGK-GK- IKV PVAIKLV K GTC TGKEESEM LNEMAMQMS--LRHEHL IVVGICL HEEGIQ IVQ VLLEPLGNLNF LKKHKAHL C	TQLGAGAFGVVYAGFWFPKGK-GK- IKV PVAIKLV K GTC TGKEESEM LNEMAMQMS--LRHEHL IVVGICL HEEGIQ IVQ VLLEPLGNLNF LKKHKAHL C	QII GGQA FGVVYAGKWKNP IK -DC-KNV V PAIKV MAKITS -IDS KE EAGMM QAVSGGH KHL Y IGICFC-DTVQ V VLLEPLGSLLHFLKKHDKD KL G	QSLGGQAFGTWFL Y WPKGK-DE GEK KLAV A IKV W HD GS GT-AHQ EMLQ EAGIMAC-MR REH LL IVVG CLS-DGM QVTPM PLGS IK N LKKYRQ KLG	QSLGGQAFGTWFL Y WPKGK-DD GEK KLAV A IKV V ND GS STA AAH Q EMLQ EAGIMAC-MR REH LL IVVG V CLS -NG MCQVTPM PLGS IK N LKKHQR Q KL G	QSLGGQAFGTWFL Y WPKGK-DD GEK KLAV A IKV V ND GS STA AAH Q EMLQ EAGIMAC-MR REH LL IVVG V CLS -NG MCQVTPM PLGS IK N LKKHQR Q KL G	QVLGYGAFGTW Y KG I W PEKE -- KV KIPVAIKV W HE AN A-SAQ QET LE BAR IAS--MS HPH V O LG CVG Q OMM V T PL PL G Y DD Y VN NR S K G	KVLGSGAGFTV H KL W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REN K D R I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT Q L MP Y G C LL D V REH K D N I G	KVLGSGAGFTV Y KG W P EGE -- NV KIPVAIK V T EAT SP KAN KE IMD E A Y MAS -- VE PH H V C RL LG ICL T -ST VQ I IT
Vertebrates																										
Nematodes																										

(A) **Structure and alignment of EGFR and LET-23.** Structure of PDB:1XKK (Human EGFR) in green with Lapatinib bound (in yellow), aligned to *C. elegans* LET-23 homology model in blue. The human and *C. elegans* kinase domains share 44% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 1XKK, 2ITX, 3W2S, 4G5J and associated *C. elegans* homology models). The orthologous LET-23 sequence from the parasitic nematode *B. malayi* was modeled to the human EGFR structure (PDB: 1XKK) to confirm the favourable position of the identified divergent residues within the inhibitor binding site. Residues of interest are indicated on the structures in dark pink (nematode residue) and light pink (human residue).



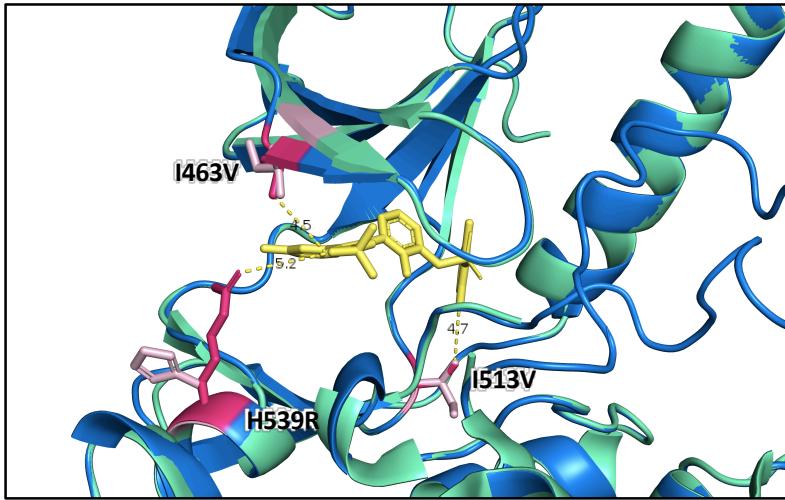
		99	145	149	*	*	*	*
Nematodes	<i>C. elegans</i> MEK-2	LQTGEGLCHGNGGVVNKCVRHKRGIVM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]V[D]NN--D[SI]CME[MO]GSLD[V]LKKVGR[L]PEKFV						
	<i>C. briggsae</i>	LQTGEGLCHGNGGVVNKCVRHKRGIVM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]V[D]NN--D[SI]CME[MO]GSLD[V]LKKVGR[L]PEKFV						
	<i>P. pacificus</i>	LHQ[G]EGLCHGNGGV[V]KQHKGIVM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]V[D]NN--D[SI]CME[MO]GSLD[V]LKKVTRI[Q]ENFI						
	<i>H. contortus</i>	LNEHQ[G]EGLCHGNGGV[V]KQHKGIVM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]V[D]NN--D[SI]CME[MO]GSLD[V]LKKVTRI[Q]ENFI						
	<i>D. viviparus</i>	LNEHQ[G]EGLCHGNGGV[V]KQHKGIVM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]V[D]NN--D[SI]CME[MO]GSLD[V]LKKVGR[L]PEKFV						
	<i>N. americanus</i>	LNLHQ[G]EGLCHGNGGV[V]KQHKGIVM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]V[D]NN--D[SI]CME[MO]GSLD[V]NMKVGR[L]PEKFV						
	<i>A. ceylanicum</i>	LЕНГЕГЛЧГНГГВ[V]КВХККНГУТМ[R]КУХЛЕВРПСВРQОИКЕЛАВЛ[H]КНСНСРПИ[V]Г[F]YГА[F]V[D]NN--D[SI]CME[MO]GSLD[V]НМКВГР[L]ПЕКФВ						
	<i>S. ratti</i>	VEIIEQLGQNGGVVNKLRLH1PTNVINM[R]KUHLEI[K]PSPV[P]QQVKE[L]AV[H]CNNSPF[V]G[F]YGA[F]T[D]NN--D[SI]CME[MO]GSLD[V]VQ[SG]R1HENIT						
	<i>B. malayi</i>	LERKMC[E]LCHGNGGV[S]KV[M]HKS[KL]I[M]ARKL[L]HLEVRPSPVRSQILKEELVLNKNCNSP[V]I[V]G[F]YGA[F]T[D]NN--D[SI]CME[MO]GSLD[V]LKKVGK[L]KESRV						
	<i>O. ochengi</i>	LERKMC[E]LCHGNGGV[S]KV[M]HKS[KL]I[M]ARKL[L]HLEVRPSPVRSQILKEELVLNKNCNSP[V]I[V]G[F]YGA[F]T[D]NN--D[SI]CME[MO]GSLD[V]LKKVGK[L]KESRV						
	<i>L. loa</i>	LERKMC[E]LCHGNGGV[S]KV[M]HKS[KL]I[M]ARKL[L]HLEVRPSPVRSQILKEELVLNKNCNSP[V]I[V]G[F]YGA[F]T[D]NN--D[SI]CME[MO]GSLD[V]LKKVGK[L]KESRV						
	<i>T. trichiura</i>	HLKISELGAGANGGV[M]KVRB[K]SGL1[M]ARKL[L]HLEVRPSPTRNQI[K]ELKLVHYCNSP[V]I[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]LKKTGTRFABQ[Q]						
Vertebrates	<i>D. rerio</i>	FEKISELGAGANGGV[F]KVLB[R]PGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>G. gallus</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>M. musculus</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>R. norvegicus</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>C. familiaris</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>O. aries</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>B. taurus</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>H. sapiens MAP2K1</i>	FEKISELGAGANGGV[F]KVKSH[P]RGL1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]CLLKAGK[R]P[E]QIL						
	<i>H. sapiens MAP2K2</i>	FERISELGAGANGGV[V]KQR[P]G1[M]ARKL[L]HLEI[K]PAI[R]NQI[I]RELQ[V]LHECNCSPI[V]G[F]YGA[F]SDG--E[SI]CME[MO]GSLD[V]LKEAKR1P[E]EIL						
Nematodes	<i>C. elegans</i> MEK-2	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>C. briggsae</i>	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>P. pacificus</i>	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>H. contortus</i>	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>D. viviparus</i>	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>N. americanus</i>	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>A. ceylanicum</i>	GRISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSNGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>S. ratti</i>	GRKISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>B. malayi</i>	GRIAIAVVRGLYSYL[K]DEHR1LRDVKPSNM1VNSGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>O. ochengi</i>	GRIAIAVVRGLYSYL[K]DEHR1LRDVKPSNM1VNSGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>L. loa</i>	GRIAIAVVRGLYSYL[K]DEHR1LRDVKPSNM1VNSGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
	<i>T. trichiura</i>	GRKISAVAVVRGLAYLTKDEIKILHRDVKPSNM1VNSGEIKLCDFGVGS[G]MLIDSMANSP[V]GTRS						
Vertebrates	<i>D. rerio</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>G. gallus</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>M. musculus</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>R. norvegicus</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>C. familiaris</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>O. aries</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>B. taurus</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>H. sapiens MAP2K1</i>	GRKVSIAVVRGLYSYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						
	<i>H. sapiens MAP2K2</i>	GRKVSIAVVRGLAYLREKHH1MHRDVRPSN1LVSNSGEIKLCDFGVGS[G]QLIDSMANSP[V]GTRS						

(B) Structure and alignment of MEK1 and MEK-2. Structure of PDB: 3PP1 (Human MEK1) in green with allosteric inhibitor TAK-733 bound (in orange) aligned to *C. elegans* MEK-2 homology model in blue above. Structure of PDB:5EYM (Human MEK1) with ATP-competitive inhibitor BI-847325 bound (in yellow) aligned to *C. elegans* MEK-2 homology model below. The purple arrow in the BI-847325-bound structure alignment highlights the *C. elegans* leucine residue that may sterically hinder BI-847325 from binding *C. elegans* MEK-2. This steric hindrance is further visualized in the surface representations of the Human MEK1 crystal structure and *C. elegans* kinase domains share 60% identity. All residues proximal to the ATP-competitive inhibitor binding site (identified in PDB structures 5EYM, 5HZE) and allosteric site (identified from PDB structures 3EQH, 3PP1) with side-chains facing inwards are highlighted on the alignment. The orthologous MEK-2 sequence from the parasitic nematode *B. malayi* was modeled to the human MEK-1 structures (PDB: 3PP1 above, PDB: 5EYM below) to confirm the favourable position of the identified divergent residues within the inhibitor binding site. Residues of interest are indicated on the structures in dark pink (nematode residue) and light pink (human residue).



	Nematodes	Vertebrates
<i>C. elegans</i> PLK-1	YEKGRFLGKGGFAHQYELTNRATREVAGKVVPKSMLVKQYQRDKMTQEYVQIHLRELGHINIVK*	YEKGRFLGKGGFAHQYELTNRATREVAGKVVPKSMLVKQYQRDKMTQEYVQIHLRELGHINIVK*
<i>C. elegans</i> PLK-2	YEKCKFLGKGGFAHQYELRNKSTGELFKAGKVVPKALLIKQYQRDKMAQEYVQIHLRNQHNRNVK*	YEKCKFLGKGGFAHQYELRNKSTGELFKAGKVVPKALLIKQYQRDKMAQEYVQIHLRNQHNRNVK*
<i>C. briggsae</i>	YEKCRFLGKGGFAHQYELRNKSTGELFKAGKVVPKALLIKQYQRDKMAQEYVQIHLRNQHNRNVK*	YEKCRFLGKGGFAHQYELRNKSTGELFKAGKVVPKALLIKQYQRDKMAQEYVQIHLRNQHNRNVK*
<i>P. pacificus</i>	YARGRFLGKGGFARCYELNDTNTGAVAGVKVSKQLLQKSQYQDKMVQEIQIHLRLSHEHVVK*	YARGRFLGKGGFARCYELNDTNTGAVAGVKVSKQLLQKSQYQDKMVQEIQIHLRLSHEHVVK*
<i>H. contortus</i>	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*
<i>N. americanus</i>	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*
<i>A. duodenale</i>	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*
<i>D. viviparus</i>	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*
<i>A. ceylanicum</i>	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*	YIRGKFLGKGGFARCYELTNAAATNEVFGAKIVSKTLLIKPQYQREKMTQEYVHILHRLSLSPHVVQ*
<i>S. ratti</i>	YIRGKFLGKGGFARCYELDNK1GE1IVAGVKVVKALTRPKQDKMAQEIDIQ*SLNHPHVVK*	YIRGKFLGKGGFARCYELDNK1GE1IVAGVKVVKALTRPKQDKMAQEIDIQ*SLNHPHVVK*
<i>B. malayi</i>	YKKGKFLGKGGFARCYELTDIKDQRFYIAGKVSFKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*	YKKGKFLGKGGFARCYELTDIKDQRFYIAGKVSFKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*
<i>O. ochengei</i>	YKKGKFLGKGGFARCYELTDIKDQRFYIAGKVSFKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*	YKKGKFLGKGGFARCYELTDIKDQRFYIAGKVSFKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*
<i>L. loa</i>	YKKGKFLGKGGFARCYELTSATNQKLYAGKVSFKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*	YKKGKFLGKGGFARCYELTSATNQKLYAGKVSFKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*
<i>T. suis</i>	YKKGKFLGKGGFARCYELTSATNQKLYAGKVSFKSKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*	YKKGKFLGKGGFARCYELTSATNQKLYAGKVSFKSKLLLKNHQRDKMAQEIRIHLRTQKHHTIVRM*
<i>D. rerio</i>	YMRGRFLGKGGFAKCYEITMDTKEVFRAGKVVPKSMLLKPHQKEKMSTEIAIHKLSDNPVVHGFEDDDFV*	YMRGRFLGKGGFAKCYEITMDTKEVFRAGKVVPKSMLLKPHQKEKMSTEIAIHKLSDNPVVHGFEDDDFV*
<i>G. gallus</i>	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHRHVVGQSFFEDDFV*	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHRHVVGQSFFEDDFV*
<i>M. musculus</i>	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
<i>R. norvegicus</i>	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
<i>C. familiaris</i>	YLRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	YLRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
<i>O. aries</i>	YLRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	YLRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
<i>B. taurus</i>	YLRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	YLRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
<i>H. sapiens</i> PLK1	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	YVRGRFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
	Nematodes	Vertebrates
<i>C. elegans</i> PLK-1	ARYFTHQIVDGVLYLHDLNIHRDMLKGNLFLNDDLTVVKIGDFGLA	ARYFTHQIVDGVLYLHDLNIHRDMLKGNLFLNDDLTVVKIGDFGLA
<i>C. elegans</i> PLK-2	ARYFTYQIVEGVLYLHNLKIVHDLKLGNLFLNDELQVKIGDFGLA	ARYFTYQIVEGVLYLHNLKIVHDLKLGNLFLNDDLTVVKIGDFGLA
<i>C. briggsae</i>	ARYFTHQFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*	ARYFTHQFLGKGGFAKCEISADTKEVFRAGKVVPKSMLLKPHQKEKMSMEIAIHRSLAHQHVVGHDFFEDDSFV*
<i>P. pacificus</i>	ARYFTYQVDAVEYIHAQKIIHDLKLGNLFLINNDMALIKIDFGLA	ARYFTYQVDAVEYIHAQKIIHDLKLGNLFLINNDMALIKIDFGLA
<i>H. contortus</i>	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA
<i>N. americanus</i>	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA
<i>A. duodenale</i>	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA
<i>D. viviparus</i>	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA
<i>A. ceylanicum</i>	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA	ARYFTHQVCLAVDYLHDKVIIHDLKLGNLFLNGLQVKIGDFGLA
<i>S. ratti</i>	ARYFTKQIVDAVSYLVHGRNVIHDLKLGNLFLSELMDVKVGDGLA	ARYFTKQIVDAVSYLVHGRNVIHDLKLGNLFLSELMDVKVGDGLA
<i>B. malayi</i>	ARYFTKQIVDAVSYLVHGRNVIHDLKLGNLFLSELMDVKVGDGLA	ARYFTKQIVDAVSYLVHGRNVIHDLKLGNLFLSELMDVKVGDGLA
<i>O. ochengei</i>	ARYFTKQIVDAVSYLVHGRNVIHDLKLGNLFLSELMDVKVGDGLA	ARYFTKQIVDAVSYLVHGRNVIHDLKLGNLFLSELMDVKVGDGLA
<i>L. loa</i>	SRYFTKQIVACEAYLHENKNIHDLKLGNLFLNEEMEIKVGDGLA	SRYFTKQIVACEAYLHENKNIHDLKLGNLFLNEEMEIKVGDGLA
<i>T. suis</i>	ARYFTKQIVACEAYLHENKNIHDLKLGNLFLNEEMEIKVGDGLA	ARYFTKQIVACEAYLHENKNIHDLKLGNLFLNEEMEIKVGDGLA
<i>D. rerio</i>	ARYFMQTQGVQYLNHNRRVIIHDLKLGNLFLNDMDVVKIGDFGLA	ARYFMQTQGVQYLNHNRRVIIHDLKLGNLFLNDMDVVKIGDFGLA
<i>G. gallus</i>	VRYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLSDDMEVKIGDFGLA	VRYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLSDDMEVKIGDFGLA
<i>M. musculus</i>	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA
<i>R. norvegicus</i>	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA
<i>C. familiaris</i>	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA
<i>O. aries</i>	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA
<i>B. taurus</i>	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA
<i>H. sapiens</i> PLK1	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA	ARYYLRLQIVLGQQYLHNRNQVIHDLKLGNLFLNEDLEVKIGDFGLA

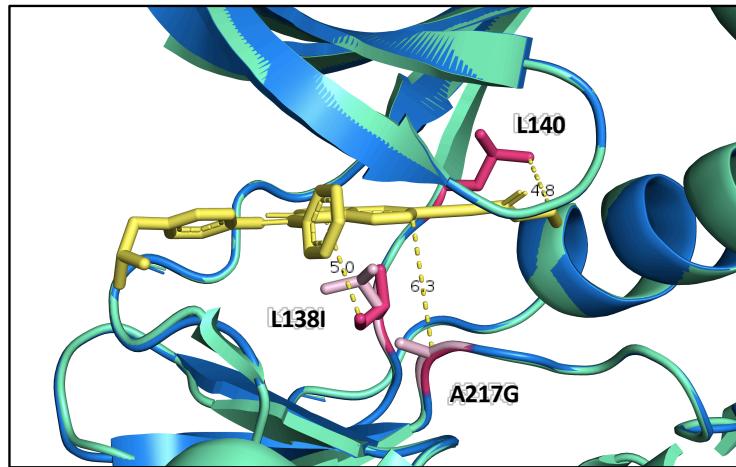
(C) Structure and alignment of PLK1 and PLK-1. Structure of PDB: 2RKU (Human PLK1) in green with BI2536 bound (in yellow), aligned to *C. elegans* PLK-1 homology model in blue. The human and *C. elegans* kinase domains share 64% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 2RKU, 3FC2, 2YAC, 4J52 and associated *C. elegans* homology models). The orthologous PLK-1 sequence from the parasitic nematode *B. malayi* was modeled to the human PLK1 structure (PDB:2RKU) to confirm the favourable position of the identified divergent residues within the inhibitor binding site. Residues of interest are indicated on the structures in dark pink (nematode residue) and light pink (human residue).



Human BRAF crystal structure Human residue *C. elegans* LIN-45 homology model *C. elegans* residue

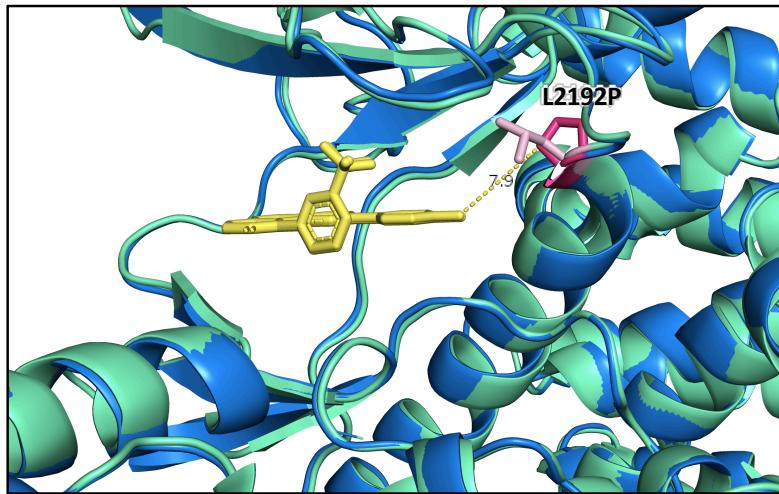
Nematodes		463	*	513		539
<i>C. elegans</i> LIN-45	FIIQYKIGSSGSGFVTYRGEEFGTVAIKKLNV-VDPTPSQMAAFKNEVAVLKKTRHNLVLLFMGWVRPEIATITQWCEGSSLYRHHHVQEPRVEFEMGA					
<i>C. briggsae</i>	FVIHYKIGSSGSGFVTYRGEEFGTVAIKKLNV-VDPTPSQMAAFKNEVAVLKKTRHNLVLLFMGWVRPEIATITQWCEGSSLYRHHHVQEPRVEFEMSA					
<i>H. contortus</i>	ITLQCKIGSSGSGFVTYRGEEFGLVAVKKLNV-GEPTLQLQAFKNEVAVLKKTRHNLVLLFMGWVRPESLATIVTQWCEGSSLYKHHHVPEPRVEFEMST					
<i>N. americanus</i>	ITLQCKIGSSGSGFVTYRGEEFGLVAVKKLNV-GEPTLQLQAFKNEVAVLKKTRHNLVLLFMGWVRPESLATIVTQWCEGSSLYKHHHVPEPRVEFEMST					
<i>D. viviparus</i>	ITLQCKIGSSGSGFVTYRGEEFGLVAVKKLNV-GEPTLQLQAFKNEVAVLKKTRHNLVLLFMGWVRPESLATIVTQWCEGSSLYKHHHVPEPRVEFEMST					
<i>A. ceylanicum</i>	ITLQCKIGSSGSGFVTYRGEEFGLVAVKKLNV-GEPTLQLQAFKNEVAVLKKTRHNLVLLFMGWVRPESLATIVTQWCEGSSLYKHHHVPEPRVEFEMST					
<i>S. ratti</i>	VEFGAKIGSSGSGFVTYRGHGYCPVAIKKINTRGEPESEAQLVAFKNEVAVALKYIIRHGNVLLFMGWCRTPELCIVITQWCEGSSLYKHLHVNEPKWELDIPK					
<i>B. malayi</i>	VTYYYKIGSSGSGFVTYVLGSYFGKVAIKKLNV-GEPSPAQLQAFKNEVGVLKKTRHNVLLFMGWLRPEPLAIVTQWCEGSSLYQIHVNEPRVDFEISS					
<i>O. ochengi</i>	VTYHKKIGSSGSGFVTYVLGSYFGKVAIKKLNV-GEPSPAQLQAFKNEVGVLKKTRHNVLLFMGWLRPEPLAIVTQWCEGSSLYQIHVNEPRVDFEISS					
<i>L. loa</i>	VTYHKKIGSSGSGFVTYVLGSYFGKVAIKKLNV-GEPSPAQLQAFKNEVGVLKKTRHNVLLFMGWLRPEPLAIVTQWCEGSSLYQIHVNEPRVDFEISS					
<i>T. trichiura</i>	VRFGRKIGSSGSGFVTYKGHWGPVAIKKLN-GEPSPAQLQAFKNEVGVLKKTRHNVLLFMGWLRPEPLAIVTQWCEGSSLYQIHVNEPRVDFEISS					
Vertebrates						
<i>D. rerio</i>	ITLGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYTTKPQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>G. gallus</i>	ITVGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>M. musculus</i>	ITVGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>R. norvegicus</i>	ITVGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>C. familiaris</i>	ITVGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>O. aries</i>	ITVGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>B. taurus</i>	ITVGQRIGSSGSGFVTYKGKWHGDVAVKMLNV-TAPTPQQLQAFKNEVGVLKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>H. sapiens</i> BRAF	VQLLRIGTGSFSGTIVYKGKWHGDVAVKMLKV-SQPTAQAAQKNEQMVKRTRHNVLLFMGYSTKPKQLAITVQWCEGSSLYHHLHIIET--KFEMIK					
<i>H. sapiens</i> ARAF						
<i>H. sapiens</i> RAF1	VMLSTRIGSSGSGFVTYKGKWHGDVAVKMLKV-DTPTPQEFQAFKNEVAVLKRTRHNVLLFMGYMTKDNLAITVQWCEGSSLYKHLHVNEQT-KFQMFQ					
Nematodes						
<i>C. elegans</i> LIN-45	IIDILKQVSLGMNYLHSKNI ¹ IRDLKTNNI ¹ FLMDDMSTVKIGDFGLA					
<i>C. briggsae</i>	VIDILKQVSLGMNYLHSKNI ¹ IRDLKTNNI ¹ FLMDDMSTVKIGDFGLA					
<i>H. contortus</i>	ILDIFKQITLGMNYLHSKNI ¹ IRDLKTNNI ¹ FLMDDMSTVKIGDFGLA					
<i>N. americanus</i>	ILDIFKQITLGMNYLHSKNI ¹ IRDLKTNNI ¹ FLMDDMSTVKIGDFGLA					
<i>D. viviparus</i>	ILDIFKQITLGMNYLHSKNI ¹ IRDLKTNNI ¹ FLMDDMSTVKIGDFGLA					
<i>A. ceylanicum</i>	ILDIFKQITLGMNYLHSKNI ¹ IRDLKTNNI ¹ FLMDDMSTVKIGDFGLA					
<i>S. ratti</i>	IIDISKQVNSGMGYLHSKGI ¹ IRDLKSNNI ¹ FITSD-GTVKIGDFGLA					
<i>B. malayi</i>	VIDICKQIAQGMNYLHSRH ¹ IIRDLKTNNI ¹ LFTDD-GTVKIGDFGLA					
<i>O. ochengi</i>	VIDICKQIAQGMNYLHSRH ¹ IIRDLKTNNI ¹ LFTDD-GTVKIGDFGLA					
<i>L. loa</i>	VIDICKQIAQGMNYLHSRH ¹ IIRDLKTNNI ¹ LFTDD-GTVKIGDFGLA					
<i>T. trichiura</i>	VIDIARQTAQGMNYLHSKNI ¹ IRDLKSNNI ¹ LFTDD-LTVKGDFGLA					
Vertebrates						
<i>D. rerio</i>	LIDIARQTAQGMNYLHSKHS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>G. gallus</i>	LIDIARQTAQGMNYLHSKHS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>M. musculus</i>	LIDIARQTAQGMNYLHAKS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>R. norvegicus</i>	LIDIARQTAQGMNYLHAKS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>C. familiaris</i>	LIDIARQTAQGMNYLHAKS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>O. aries</i>	LIDIARQTAQGMNYLHAKS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>B. taurus</i>	LIDIARQTAQGMNYLHAKS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>H. sapiens</i> BRAF	LIDIARQTAQGMNYLHAKS ¹ IIRDLKSNNI ¹ LFTED-LTVKGDFGLA					
<i>H. sapiens</i> ARAF	LIDVARQTAQGMNYLHAKN ¹ IIRDLKSNNI ¹ LHEG-LTVKGDFGLA					
<i>H. sapiens</i> RAF1	LIDIARQTAQGMNYLHAKN ¹ IIRDLKSNNI ¹ LHEG-LTVKGDFGLA					

(D) Structure and alignment of BRAF and LIN-45. Structure of PDB: 5CSW (Human BRAF) in green with dabrafenib bound (in yellow), aligned to *C. elegans* LIN-45 homology model in blue. The human and *C. elegans* kinase domains share 62% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 5CSW, 5CT7 and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



X. laevis AURKB crystal structure *X. laevis* residue
C. elegans AIR-2 homology model *C. elegans* residue

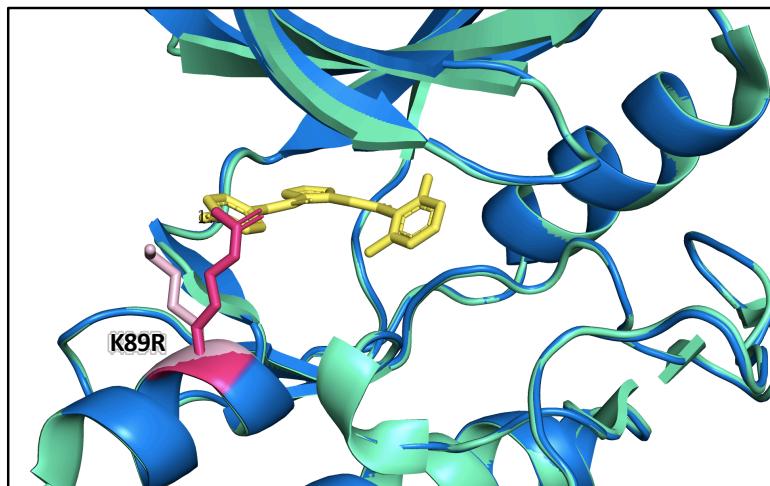
(E) Structure and alignment of AURKB and AIR-2. Structure of PDB: 5EYK (*Xenopus laevis* AURKB) in green with BI-847325 bound (in yellow), aligned to *C. elegans* AIR-2 homology model in blue. The human and *C. elegans* kinase domains share 64% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from human structure PDB: 4AF3 and *X. laevis* structure PDB: 5EYK and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (*X. laevis* residue).



**Human MTOR crystal structure Human residue
C. elegans LET-363 homology model *C. elegans* residue**

		2192
Nematodes		YQFLLKGHEDEPQDERVMQLFGLVNTLLANNSETCRRLNLTIQRYRYSIVALSKDSGLIGWVNCDTLHSLVKEYREKKAKIPLSIEHKTLQKLSLETEHHTL
<i>C. elegans</i>	LET-363	YQFLLKGHEDEPQDERVMQLFGLVNTLLANNSETCRRLNLTIQRYRYSIVALSKDSGLIGWVNCDTLHSLVKEYREKKAKIPLSIEHKTLQKLTQDTERLTT
<i>C. briggsae</i>		YSFLLKGHEDEPQDERVMQFFGLINTLLLHNQDTSSRNVTIERYSITALSQKSGLIGWVPDCDTLHSLSIKEYRERK-KVDLLMEHKIMTSSTIHLDNLT
<i>P. pacificus</i>		YAFLLKGHEDEPQDERVMQLFGLVNTLLVNAETCRRLNLTIQRYRYSIVALSHNSGLIGWVPDCDTLHSLSLVRDYRDKK-KVSLSLERHKVMSLAQDTEQVTL
<i>H. contortus</i>		YAFLLKGHEDEPQDERVMQLFGLVNTLLVNAETCRRLNLTIQRYRYSIVALSHNSGLIGWVPDCDTLHSLSLVRDYRDKK-KVSLSLERHKVMSLAQDTEQVTL
<i>A. duodenale</i>		YAFLLKGHEDEPQDERVMQLFGLVNTLLVNAETCRRLNLTIQRYRYSIVALSHNSGLIGWVPDCDTLHSLSLVRDYRDKK-KVSLSLERHKVMSLAQDTEQVTL
<i>A. ceylanicum</i>		YAFLLKGHEDEPQDERVMQLFGLVNTLLVNAETCRRLNLTIQRYRYSIVALSHNSGLIGWVPDCDTLHSLSLVRDYRDKK-KVSLSLERHKVMSLAQDTEQVTL
<i>S. ratti</i>		YCFLLKGHEDEPQDERVMQLFGLVNTLLVNAETCRRLNLTIQRYRYSIVALSHNSGLIGWVPDCDTLHSLSLVRDYRDKD-NINISAETTAMQSYVIDLEKCNL
<i>B. malayi</i>		YIFLLKGHEDEPQDERVMQLFGLVNTLLLHQGDTSSRNLTIQRYRYSIALNQNSGLIGWVNCDTLHSLSLIRDYREKK-GILLSMEHKIMQNFANDLDQMTL
<i>O. ochengi</i>		YIFLLKGHEDEPQDERVMQLFGLVNTLLLHQGDTSSRNLTIQRYRYSIALNQNSGLIGWVNCDTLHSLSLIRDYREKK-GILLSMEHKIMQNFANDLDQMTL
<i>L. loa</i>		YIFLLKGHEDEPQDERVMQLFGLVNTLLLHQGDTSSRNLTIQRYRYSIALNQNSGLIGWVNCDTLHSLSLIRDYREKK-GILLSMEHKIMQNFANDLDQMTL
<i>T. trichiura</i>		YWFLKGHEDEPQDERVMQLFGLVNTMLLENPMTCRRNLITISRYSIILPSQNSGLIGWMNPNCDTLHSLSLIRDYREKK-KILLNIERHKLQMRSPDFEHLTV
Vertebrates		MFVLLKGHEDLRQDERVMQLFGLVNTLLANDPASLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>D. rerio</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>G. gallus</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>M. musculus</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>R. norvegicus</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>C. familiaris</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>O. aries</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>B. taurus</i>		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
<i>H. sapiens</i> MTOR		FVFLLKGHEDLRQDERVMQLFGLVNTLLANDPDTSLRKNLTSIQRYAVIPNSTNSLIGWVPHCDTLHALIRDYREKK-KILLNIERHIMLRMAPDYDHHTL
Nematodes		MQKVLQLFESALSVTOGEDLRLWLPSPSEWFDRRTNYTRSVACMSMVGYILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>C. elegans</i>	LET-363	MQKVLQCFESALATQGEDLRLQWLKPSPSEWFDRRTNYTRSVACMSMVGYILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>C. briggsae</i>		PQKIQLFEMSLRTSNGEELADILWLKPSPSEWFDRRTNYTRSMACMSMVGHILGLGDRPSNLMDLRESCKIVHHIDFGD
<i>P. pacificus</i>		MQKVLQFLERALA LASTTGDDLQHILWLKPSPSEWFDRRTNYTRSMACMSMVGHILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>H. contortus</i>		MQKVLQFLERALA LASTTGDDLQHILWLKPSPSEWFDRRTNYTRSMACMSMVGHILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>A. duodenale</i>		MQKVLQFLERALA LASTTGDDLQHILWLKPSPSEWFDRRTNYTRSMACMSMVGHILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>A. ceylanicum</i>		MQKVLQFLERALA LASTTGDDLQHILWLKPSPSEWFDRRTNYTRSMACMSMVGHILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>S. ratti</i>		MMKVEAFKNAITATSGDEDLRLQTLWLKPSPSEWFDRRTNYTRSMACMSMVGYILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>B. malayi</i>		LQKVQVFHHALEMTSGNDLQOILWLKPSPSEWFDRRTNYTRSMACMSMVGYILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>O. ochengi</i>		LQK--VFQHALEMSTSNDLQQIWLKPSPSEWFDRRTNYTRSMACMSMVGYILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>L. loa</i>		LQKVQVFQHALEMSTSNDLQQIWLKPSPSEWFDRRTNYTRSMACMSMVGYILGLGDRPSNLMDLRLTGKVHHIDFGD
<i>T. trichiura</i>		VQKLEVFEHALEHTTGDDLRLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLMSCKMVHHIDFGD
Vertebrates		MEKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>D. rerio</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>G. gallus</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>M. musculus</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>R. norvegicus</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>C. familiaris</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>O. aries</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>B. taurus</i>		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD
<i>H. sapiens</i> MTOR		MQKVEVFEHAVNNTAGDDLAKLWLKPSPSEWFDRRTNYTRSLAVMSMVGYILGLGDRPSNLMDLRLSGKILHHIDFGD

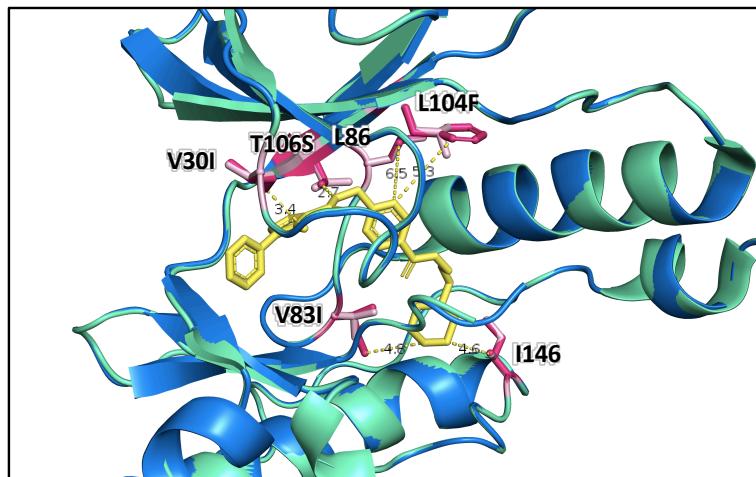
(F) Structure and alignment of MTOR and LET-363. Structure of PDB: 4JSX (Human MTOR) in green with Torin 2 bound (in yellow), aligned to *C. elegans* LET-363 homology model in blue. The human and *C. elegans* kinase domains share 62% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 4JSX, 4JSV and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



Human CDK1 crystal structure Human residue
***C. elegans* CDK-1 homology model *C. elegans* residue**

Nematodes		
<i>C. elegans</i>	CDK-1	FTKLKIGEGTYGVVYKGKNRRTNAMVAMKKIRLESEDEGVPTAVREISLLKEL-QHPNVVGLEAVIMQENRLFLIFEFLSFDLKYMDSLKYMQLGKDEYLPL
<i>C. briggsae</i>		FTKLEKIGEGTYGVVYKGNRRTQAMVAMKKIRLESEDEGVPTAVREISLLKEL-QHPNVVGLEAVIMQENRLYLIFEFSLYSDLKYMPLTSKEYLPL
<i>P. pacificus</i>		FVKIEKIGEGTYGVVYKGNRRTQNLVAMKKIRLESEDEGVPTAVREISLLREL-RHPNIVNLEDVIMQENRLYLIFEFSLMDLKYLDLTKSDEFSL
<i>H. contortus</i>		FVKLDKIGEGTYGVVYKGKKTKNLVAMKKIRLEGEDEGVPTAIREISLLKEL-THPNVALEDVIMQENRLYLIFEFSLMDLKYLQDLPADKRLPP
<i>N. americanus</i>		FADLRKIGEGTYGVFVGVRHRSKGLVALKISLERNEGVPTCIRECLLKKL-NHRNIVRLYDVHSGMQLYLVFEEFIDRBLKYLGLPKR-RLPV
<i>A. duodenale</i>		YVVLKDCKIGEGTYGVVYKAHEKTRQLVIAKIRLEDEGPIPATRALREISLLREL-DHPNIVKLIGISIQESRLYLIFEFVPMFLDLFKFLDLPNGHVP
<i>D. viviparus</i>		FIKLDKIGEGTYGVVYKGKHRTNKLVAMKKIRLEGEDEGVPTAIREISLLKEL-KHPNIVVELEDVIMQENRLYLIFEFSLMDLKYLQDQLPSDKRLPA
<i>A. ceylanicum</i>		FVKLDKIGEGTYGVVYKGKKTKNLVAMKKIRLEGEDEGVPTAIREISLLREL-KHPNIVVALEDVIMQENRLYLIFEFSLMDLKYLQDQLPSDKQLPL
<i>S. ratti</i>		YLKLEKIGEGTYGVVYKARDVTRNTEVALKKIRLEGEDEGVPTAVREISLLREL-QHPNIVFLKAIMEEMKRLLYLFVYLTMDLKYLQIPDDKTMK
<i>B. malayi</i>		YSRKEKIGEGTYGVVYKGIDDRSKGMVAMKKIRLENEDEGVPTAIREISLLREL-THPNIVALEEILLENRLYLIFEFFLYMLDKYIDTVPDSELMNK
<i>O. ochengi</i>		YSRKEKIGEGTYGVVYKGIDDRSKGMVAMKKIRLENEDEGVPTAIREISLLREL-THPNIVGLEEILLENRLYLIFEFHMLDKYIDTIPSELDMN
<i>L. loa</i>		YSRKEKIGEGTYGVVYKGIDDRSKGMVAMKKIRLENEDEGVPTAIREISLLREL-THPNIVALEEILLENRLYLIFEFFLYMLDKYIDTVPDCELMNK
<i>T. trichiura</i>		IQKLEKIGEGTYGVVYKGIDSTRQVALKIRLENEDEGPISTALREICLQEDLGHPNVNLKQVIMEENRLYLIFEFYLSMDLRLKYMPLSPGKMLDK
<i>D. rerio</i>		YTKIEKIGEGTYGVVYKGRRNKTQVQVAMKKIRLESEEEGVPTAVREISLLKEL-QHPNIVRLVLDLQMBSKLYLFEFSLMDLKYLDSIPSGEFMDP
<i>G. gallus</i>		YTKIEKIGEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-HHPNIVCLQDVLQMQRARLYLIFEFSLMDLKYLDTIPSGQYLD
<i>M. musculus</i>		YIKEKIEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-RHPNIVLSQDVLQMDSRLYLIFEFSLMDLKYLDSIPPGQFMDS
<i>R. norvegicus</i>		YIKEKIEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-RHPNIVLSQDVLQMDSRLYLIFEFSLMDLKYLDSIPPGQFMDS
<i>C. familiaris</i>		YIKEKIEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-RHPNIVLSQDVLQMDSRLYLIFEFSLMDLKYLDSIPPGQFMDS
<i>O. aries</i>		YIKEKIEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-RHPNIVLSQDVLQMDSRLYLIFEFSLMDLKYLDSIPPGQFMDS
<i>B. taurus</i>		YIKEKIEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-RHPNIVLSQDVLQMDSRLYLIFEFSLMDLKYLDSIPPGQFMDS
<i>H. sapiens</i>	CDK1	YIKEKIEGTYGVVYKGRRHTTQVQVAMKKIRLESEEEGVPTAIREISLLKEL-RHPNIVLSQDVLQMDSRLYLIFEFSLMDLKYLDSIPPGQYMDMS
Nematodes		
<i>C. elegans</i>	CDK-1	ETLKS-YTFQIQLQACMFCHQRRVIHSDLKPQNLLVDNNNGAIKLAQDFGLARAIGIPIRVYTHEVVTWLWRAPEILMGAQRY
<i>C. briggsae</i>		ETLKS-YTFQIQLQACMFCHQRRVIHSDLKPQNLLVDENKEGAIKLAQDFGLARAIGIPIRVYTHEVVTWLWRAPEILMGAQRY
<i>P. pacificus</i>		ATLKS-YLMQICQACMFCHQRRVIHSDLKPQNLLVDGKGTIKLAQDFGLARAIGIPVRYVTHEVVTWLWRAPEVLLGGQRY
<i>H. contortus</i>		AECKS-YMFQICQATCFAHQRRVIHSDLKPQNLLVDGKGAIKLAQDFGLARAIGIPVRYVTHEVVTWLWRAPEIILGGRYY
<i>N. americanus</i>		RHAKS-FLWQLQLQALAYCHTRRVLHSDLKPQNLLVDNSGVKLAQDFGLARNFSIPSRYVTHEVVTWLWRAPEIILGGRYY
<i>A. duodenale</i>		STVKR-TAFQTQCAFCMFMHQRRVIHSDLKPQNLLVDENGVQKIAFDGFLRSRNSINPVIRVYTHEVVTWLWRAPEILLGANRY
<i>D. viviparus</i>		ABCKS-YMFQICQACIAFCAHQRRVIHSDLKPQNLLVDGKGAIKLAQDFGLARAIGIPVRYVTHEVVTWLWRAPEILLGTRQY
<i>A. ceylanicum</i>		ABCKS-YMFQICQACIAFCAHQRRVIHSDLKPQNLLVDGKGAIKLAQDFGLARAIGIPVRYVTHEVVTWLWRAPEILLGTRQY
<i>S. ratti</i>		YLMKS-YLQLCQGMCFAHQRRVIHSDLKPQNLLVDSSGLCKVADDFGLARSIGIPLRAYTHEIWTWLWRAPEIILGVRVRY
<i>B. malayi</i>		ELQKS-YLQLQIAQCFCHQRRVLHSDLKPQNLLVDQNGAIKLAQDFGLARAIGIPRAYTHEIWTWLWRAPEVLLGATRY
<i>O. ochengi</i>		TLQKS-YLQLQIAQCFCHQRRVLHSDLKPQNLLVDQNGAIKLAQDFGLARAIGIPRAYTHEIWTWLWRAPEVLLGATRY
<i>L. loa</i>		ELQKS-YLQLQIAQCFCHQRRVLHSDLKPQNLLVDQNGAIKLAQDFGLARAIGIPRAYTHEIWTWLWRAPEVLLGATRY
<i>T. trichiura</i>		DLVKAYYLLQITDQGICFCHMRRIMHSDLKPQNLLIDEKGTKIKAQDFGLARCVGVPPRVYTHEVVTWLWRAPEVLLGCQRY
<i>D. rerio</i>		MLVKS-YLQIQLLEGFLCHQRRVLHSDLKPQNLLDNGKVIKAQDFGLARAFGVPPRVYTHEVVTWLWRAPEVLLGASRY
<i>G. gallus</i>		SRVKS-YLQIQLQGVCFHSRVLHSDLKPQNLLIDDGKVIAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
<i>M. musculus</i>		SLVKS-YLHQIQLQGVCFHSRVLHSDLKPQNLLIDDGKTIKAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
<i>R. norvegicus</i>		SLVKS-YLQIQLQGVCFHSRVLHSDLKPQNLLIDDGKTIKAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
<i>C. familiaris</i>		SLVKS-YLQIQLQGVCFHSRVLHSDLKPQNLLIDDGKTIKAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
<i>O. aries</i>		SLVKS-YLQIQLQGVCFHSRVLHSDLKPQNLLIDDGKTIKAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
<i>B. taurus</i>		SLVKS-YLQIQLQGVCFHSRVLHSDLKPQNLLIDDGKTIKAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
<i>H. sapiens</i>	CDK1	SLVKS-YLQIQLQGVCFHSRVLHSDLKPQNLLIDDGKTIKAQDFGLARAFGPVRYVTHEVVTWLWRSPEVLLGASRY
Vertebrates		

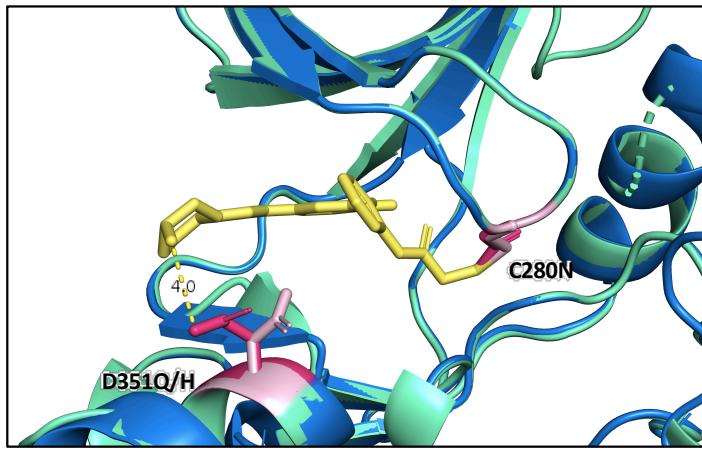
(G) Structure and alignment of CDK1 and CDK-1 Structure of PDB: 4Y72 (Human CDK1) in green with inhibitor bound (in yellow), aligned to *C. elegans* CDK-1 homology model in blue. The human and *C. elegans* kinase domains share 67% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 4Y72, 6GU4 and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



Human MAPK14 crystal structure Human residue
C. elegans PMK-1 homology model *C. elegans* residue

		30	33	36	104	106
Nematodes	<i>C. elegans</i> PMK-1	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	ELRLLCRMCHENI [*] DL [*] LDVFTP [*] NENVNNDIEDVY [*] VSNLMG			
	<i>C. briggsae</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	ELRLLCRMCHENI [*] DL [*] LDVFTP [*] NENVNNDIEDVY [*] VSNLMG			
	<i>P. pacificus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	ELRLLCRMHEHENI [*] DL [*] DCFTPNISATLDDDVY [*] VSNLMG			
	<i>H. contortus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	ELRLLCRMHEHENI [*] DL [*] DCFTPNISATLDDDVY [*] VSNLMG			
	<i>N. americanus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	ELRLLCRMGDHENI [*] DL [*] LDVFTP [*] DASCEQLTDVY [*] VSNLMG			
	<i>A. duodenale</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>D. viviparus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>A. ceylanicum</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>S. ratti</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>B. malayi</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>O. ochengi</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>L. loa</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
	<i>T. trichiura</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLTP [*] G [*] TG [*] GA [*] YGTVC [*] AEC [*] CLRTNTRVAIKKFSRPQSVI [*] IHARRTYRCRTES-----			
Vertebrates	<i>D. rerio</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>G. gallus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>M. musculus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>R. norvegicus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>C. familiaris</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>O. aries</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>B. taurus</i>	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>H. sapiens</i> MAPK14	YINLTPEGTGAYGTVC [*] AEC [*] TRSGTRVAIKKFNRPQSI [*] IHARRTYR-----	YQNLSPV [*] GSGA [*] YGSVCSAFDGKAGL [*] RVA [*] VKKL [*] SRPQSI [*] IHARRTYR-----			
	<i>H. sapiens</i> MAPK11	YEDMLPV [*] G [*] H [*] GA [*] YGSVCSAVDSATGEKVA [*] KKFSRPQSAI [*] HAKRT [*] HR-----	YEDMLPV [*] G [*] H [*] GA [*] YGSVCSAVDSATGEKVA [*] KKFSRPQSAI [*] HAKRT [*] HR-----			
		EVK [*] VL [*] R [*] H [*] MD [*] HM [*] DN [*] HE [*] N [*] EV [*] VL [*] T [*] LM [*]	EVK [*] VL [*] R [*] H [*] MD [*] HM [*] DN [*] HE [*] N [*] EV [*] VL [*] T [*] LM [*]			
		----- [*] MD [*] HM [*] DN [*] HE [*] N [*] EV [*] VL [*] T [*] LM [*]	----- [*] MD [*] HM [*] DN [*] HE [*] N [*] EV [*] VL [*] T [*] LM [*]			
		----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
Nematodes	<i>C. elegans</i> PMK-1	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>C. briggsae</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>P. pacificus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>H. contortus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>N. americanus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>A. duodenale</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>D. viviparus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>A. ceylanicum</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>S. ratti</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>B. malayi</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>O. ochengi</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>L. loa</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>T. trichiura</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
Vertebrates	<i>D. rerio</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>G. gallus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>M. musculus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>R. norvegicus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>C. familiaris</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>O. aries</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>B. taurus</i>	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>H. sapiens</i> MAPK14	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			
	<i>H. sapiens</i> MAPK11	----- [*] EV [*] VL [*] T [*] LM [*]	----- [*] EV [*] VL [*] T [*] LM [*]			

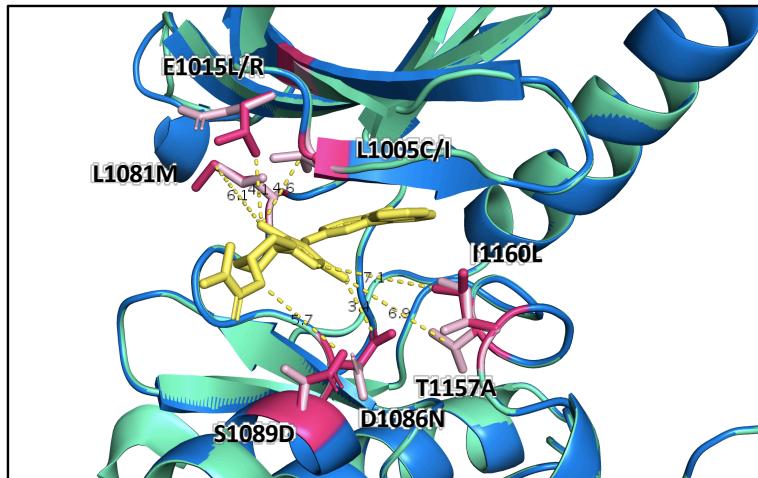
(H) Structure and alignment of MAPK14 and PMK-1. Structure of PDB: 6SFO (Human MAPK14) in green with SR-318 bound (in yellow), aligned to *C. elegans* PMK-1 homology model in blue. The human and *C. elegans* kinase domains share 71% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 6SFO, 3Z55, 1DI9, 1KV2 and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



**Human SRC crystal structure Human residue
C. elegans SRC-1 homology model *C. elegans* residue**

	Nematodes	Vertebrates
		280
		*
<i>C. elegans</i> SRC-1	LHLKRKLGDG[FGEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRIT--D-GSTLGIQALV	
<i>C. briggsae</i>	LHLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEASIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--D-GSTLGIQALV	
<i>P. pacificus</i>	LHLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAAII[KRCRDPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--D-GSTLGIQALV	
<i>H. contortus</i>	LHLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GAALGIQALV	
<i>N. americanus</i>	LHLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GAALGIQALV	
<i>A. duodenale</i>	-----[EVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GAALGIQALV	
<i>D. viviparus</i>	LQLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GAALGIQALV	
<i>A. ceylanicum</i>	LQLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAAII[KRCRDPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GAALGIQALV	
<i>S. ratti</i>	LQLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--Q-TNQISLQASV	
<i>B. malayi</i>	LQLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GS1LTLQALV	
<i>O. ochengi</i>	LQLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GS1LALQALV	
<i>L. loa</i>	LQLKRKLGDG[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GS1LTLQALV	
<i>T. trichiura</i>	LQFGHHLQGQ[GFEVWYGKWRGI-VEVAIKTMKPGTMSPEAFLQEAQIMKQCDHPNLVLYAVCTREEPFYIITEYMINGSLLHVRN--E-GS1LTLQALV	
<i>D. rerio</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--DMGKMLRLPQLV	
<i>G. gallus</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--EMGKYLRLPQLV	
<i>M. musculus</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--ETGKYLRLPQLV	
<i>R. norvegicus</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--E-GS1LTLQALV	
<i>C. familiaris</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--E-GS1LALQALV	
<i>O. aries</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--ETGKYLRLPQLV	
<i>B. taurus</i>	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--ETGKYLRLPQLV	
<i>H. sapiens</i> SRC	LRLEVKLQGGFGEVWYGTWNNGT-TRVAIKTLKPGTMSPEAFLQEAQVMKLRHEKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKG--ETGKYLRLPQLV	
<i>H. sapiens</i> FYN	LQLIKRGLGN[GFEVWYGTWNNGT-TKVAIKTLKPGTMS[PESFLEEAQIMKLLKHDKL[VQLYAVVSE-EPIYIVITEYMGQSLLDFLKD--GEGRALKLPNV	
<i>H. sapiens</i> LCK	LKLVERLQAGG[GFEVWYGMYNGH-TKVA[SKLQGSMS[PDAFLEA[NLMKLQHQHQLRVL[VYAVVTTQ-EPIYIVITEYMGSLVDFLKT--PSGIKLTINKLL	
		357
		*
<i>C. elegans</i> SRC-1	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>C. briggsae</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>P. pacificus</i>	DMAAQIANGMMAYERVNRVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>H. contortus</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>N. americanus</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>A. duodenale</i>	EIAAQVAAGMAYLEEMNFVHDLRAARNILTKNNL---NVKIADFGLARLKENLYEARVGPFRPIKWTAPEEAANFN	
<i>D. viviparus</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>A. ceylanicum</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>S. ratti</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>B. malayi</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>O. ochengi</i>	DMAAQIANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>L. loa</i>	DMAAQVANGMMYLEERKLVHRDLAARNVLVGDKISGV[PVVKADFGLARKLMEEDIYEARTGAKFFIKWTAPEEAATCG	
<i>T. trichiura</i>	DMAAQIANGMAYLEEHHRMVRHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>D. rerio</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>G. gallus</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>M. musculus</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>R. norvegicus</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>C. familiaris</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>O. aries</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGESL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>B. taurus</i>	DMAAQIAGSMAYVERMNVHDLRAANILVGESL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>H. sapiens</i> SRC	DMAAQIAGSMAYVERMNVHDLRAANILVGENL---VCKVADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>H. sapiens</i> FYN	DMAAQVAGMAYIERMNYIHRDLRSANILVGNGL---ICKIADFGLARLIE-DNEYTARQGAKFFIKWTAPEEAALYG	
<i>H. sapiens</i> LCK	DMAAQIAEGMAFEERNYIHRDLRAANILVSDTL---SCKIADFGLARLIE-DNEYTAREGAKFFIKWTAPEAINYG	

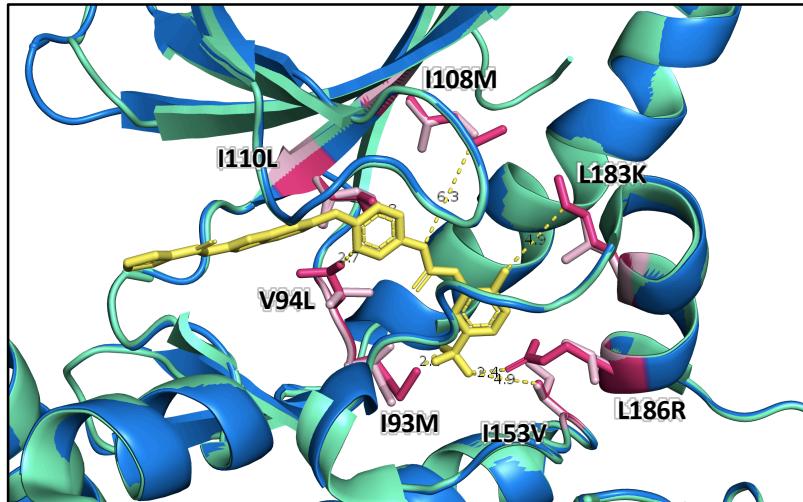
(I) Structure and alignment of SRC and SRC-1. Structure of PDB: 6ATE (Human SRC) in green with inhibitor bound (in yellow), aligned to *C. elegans* SRC-1 homology model in blue. The human and *C. elegans* kinase domains share 63% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 6ATE, 4MXO and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



Human IGF1R crystal structure Human residue
C. elegans DAF-2 homology model *C. elegans* residue

		1005	1015	1081	1086	1089	
Nematodes	<i>C. elegans</i> DAF-2	VVLGQQEGGSFGKVY*	STGNNNVSLMGRDFGPKCAIKINVDDPA-STEINLYLMEANIMKNFK-TNFIVKLYGVISTVQPMVMP	MDLGILR*	YLRSKR		
	<i>C. briggsae</i>	VTLGEVIGQGTGKVY*	SRGKNCVSLRGAFCVAKINTEEAESLENKNGK-TFFIVKLFGVSSVHPAWVME	MELGMLRL*	YLRAKR		
	<i>H. contortus</i>	LTLECEIGRGTGKVY*	RGYGNNVLSRCGDTFGCAIKTVT-ETANSERHLHFLLEANVMKSFAEAFIVKLYGVSDGPQLVVM	MEKGMLRL*	YLRSRR		
	<i>N. americanus</i>	LTLECEIGRGTGKVY*	RGYGNNVLSKC GDTFGCAIKTVT-ETANSERHLHFLLEANVMKSFAEAFIVKLYGVSDGPQLVVM	MEKGMLRL*	YLRSRR		
	<i>A. duodenale</i>			MKSFAEAFIVKLYGVSDGPQLVVM	MEKGMLRL*	YLRSRR	
	<i>D. viviparus</i>	LTLLEYEIGRGTGKVY*	RGYGNNVHSRCGDTFGCAIKTVT-ETANSERHLHFLLEANVMKSFAEAFIVKLYGVSDGPQLVVM	MEKGMLRL*	YLRSRR		
	<i>A. ceylanicum</i>	VVLEEQIGQSGTGFVN	YKGYGNNVFTSGIKFGPCAIKTVR-ESATPAEKLHFLFEASVMKFH-TSFIVKLYGVSEGPQLVVM	MEKGMLRL*	FRLSHR		
	<i>S. ratti</i>	IHLDEEIGRGTGKVY*	RGYGDNCKSYLGVTFGECAIKTVS-ETANSERHLHFLIEASVMQFN-TFFIVKLYGVSDGPQLVVM	MMKGMLRL*	YLRSRR		
	<i>B. malayi</i>	IHLDEEIGRGTGKVY*	RGYGDNCKSYLGVTFGECAIKTVS-ETANSERHLHFLIEASVMQFN-TAFIVKLYGVSDGPQLVVM	MMKGMLRL*	YLRSRR		
	<i>O. chengi</i>	IHLDEEIGRGTGKVY*	RGYGDNCKSYLGVTFGECAIKTVS-ETANSERHLHFLIEASVMQFN-TAFIVKLYGVSDGPQLVVM	MMKGMLRL*	YLRSRR		
	<i>L. loa</i>	IHLDEEIGRGTGKVY*	RGYGDNCKSYLGVTFGECAIKTVS-ETANSERHLHFLIEASVMQFN-TAFIVKLYGVSDGPQLVVM	MMKGMLRL*	YLRSRR		
	<i>T. suis</i>	IELINEIGRGTGTVY*	AGRAKNVRSVCVGVGECAVKTS-EKASIYDRWHFLIEASVMKF D-TAFIVKLYGVSEGPALVVM	MACGDLK*	YLPLARR		
Vertebrates	<i>D. rerio</i>	ITMCRELGGQSFGMVY*	EIGAKGVV--KDEPETRVAIKTVN-EASASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SHLRSLR		
	<i>G. gallus</i>	ITMCRELGGQSFGMVY*	EIGAKGVV--KDEPETRVAIKTVN-EASASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>M. musculus</i>	ITMNRELGGQSFGMVY*	EVGAKGVV--KDEPETRVAIKTVN-EASASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>R. norvegicus</i>	ITMNRELGGQSFGMVY*	EVGAKGVV--KDEPETRVAIKTVN-EASASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>C. familiaris</i>	ITMSRELGGQSFGMVY*	EVGAKGVV--KDEPETRVAIKTVN-EAASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>O. aries</i>	ITMSRELGGQSFGMVY*	EVGAKGVV--KDEPETRVAIKTVN-EAASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>B. taurus</i>	ITMSRELGGQSFGMVY*	EVGAKGVV--KDEPETRVAIKTVN-EAASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>H. sapiens</i> IGF1R	ITMSRELGGQSFGMVY*	EVGAKGVV--KDEPETRVAIKTVN-EAASMRERIEFLNEASVMKEFN-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SYLRSLR		
	<i>H. sapiens</i> INSR	ITLLRELGGQSFGMVY*	EQNARDI--KGEAE TRAVAKTVN-ESASLRERIEFLNEASVMKGFT-CHHVVRLLGVSSQGQPTLV	MAHGDLK*	SYLRSLR		
	<i>H. sapiens</i> INSRR	ITSIIRELGQGSFGMVY*	EGLARGLE--AGEESTPVALKTVN-ELASPRECIEFLKEASVMKAKF-CHHVVRLLGVSSQGQPTLV	IMELMTRGDLK*	SHLRSLR		
Nematodes	<i>C. elegans</i> DAF-2	EDEVFNEDTCNFFDIPIRDKFH	WEAAQICDGMAYLESLKFCHRLDAARNCMINRDET	TK1KIDFGM	TRD	FYHDYYPKSG	
	<i>C. briggsae</i>	EEEVFDENNCNFY	NVPREKICEWAAQICDGMAYLESLKFCHRLDAARNCMIDKTEL	TK1KIDFGM	TRD	FYHDYYPKSG	
	<i>H. contortus</i>	PGAAE--	NVLNPVPTTAEYEWAAQIA	IDGMAYLESIRFC	CHRN	CMVHANNTVK1KIDFGM	
	<i>N. americanus</i>	PGAAE--	NVNLNPVPTTAEYEWAAQIA	IDGMAYLESIRFC	CHRN	CMVHANNTVK1KIDFGM	
	<i>A. duodenale</i>	PGAAE--	NVNLNPVPTTAEYEWAAQIA	IDGMAYLESIRFC	CHRN	CMVHANNTVK1KIDFGM	
	<i>D. viviparus</i>	PGAAE--	NVNLNPVPTTAEYEWAAQIA	IDGMAYLESIRFC	CHRN	CMVHANNTVK1KIDFGM	
	<i>A. ceylanicum</i>	PGAAE--	NVNLNPVPTTAEYEWAAQIA	IDGMAYLESIRFC	CHRN	CMVHANNTVK1KIDFGM	
	<i>S. ratti</i>	PNSED--	NVNDKPKIPSSQQLTNWAAQIA	IDGMAYLESIRFC	CHRN	CMVHANNTVK1KIDFGM	
	<i>B. malayi</i>	PNAEE--	NVNDLPVPGAIDFFR	WMAQSQVADGMAYLES	TKFC	CHRN	
	<i>O. chengi</i>	PNAEE--	NVNDLPVPGAIDFFR	WMAQSQVADGMAYLES	TKFC	CHRN	
	<i>L. loa</i>	PNAEE--	NVNDLPVPGAIDFFR	WMAQSQVADGMAYLES	TKFC	CHRN	
	<i>T. suis</i>	PDSED--	NENHLPPPTKEEMFOFA	EADGMAYLE	AI	KFC	
Vertebrates	<i>D. rerio</i>	SKEQG--	SS-SQSLPLKKMIQMAGEI	ADGMAYLNANKFV	HRL	DAARNCMVAD	
	<i>G. gallus</i>	PDTES--	NP-QOAPTLKKMIQMAGEI	ADGMAYLNANKFV	HRL	DAARNCMVAD	
	<i>M. musculus</i>	PEVEQ--	NNLVLI	PSL	SKM	IQMAGEI	
	<i>R. norvegicus</i>	PEVEQ--	NNLVLI	PSL	SKM	IQMAGEI	
	<i>C. familiaris</i>	PEIEN--	-NPVLAPPSSLSKM	IQMAGEI	ADGMAYLNANKFV	HRL	
	<i>O. aries</i>	PEMEN---	-NPVLAPPSSLSKM	IQMAGEI	ADGMAYLNANKFV	HRL	
	<i>B. taurus</i>	PEMEN---	-NPVLAPPSSLSKM	IQMAGEI	ADGMAYLNANKFV	HRL	
	<i>H. sapiens</i> IGF1R	PEMEN---	-NPVLAPPSSLSKM	IQMAGEI	ADGMAYLNANKFV	HRL	
	<i>H. sapiens</i> INSR	PEAEN--	-NP-GRPFPTLQEMI	QMAAEI	ADGMAYLNANKFV	HRL	
	<i>H. sapiens</i> INSRR	PEAEN--	-NP-GLPQPALGEMI	QMAE	ADGMAYLA	ANKFV	

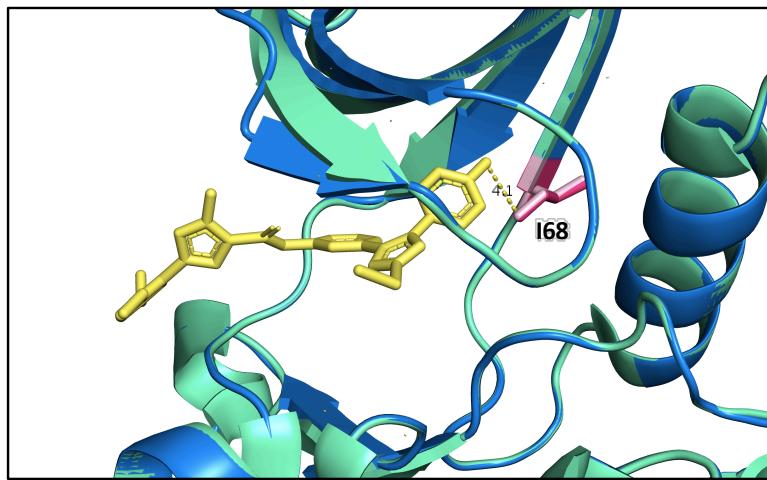
(J) Structure and alignment of IGF1R and DAF-2. Structure of PDB: 5FXS (Human IGF1R) in green with inhibitor bound (in yellow), aligned to *C. elegans* DAF-2 homology model in blue. The human and *C. elegans* kinase domains share 47% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 5FXS, 4D2R and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



**Human STK10 crystal structure Human residue
C. elegans GCK-4 homology model *C. elegans* residue**

		934	108	110
	Nematodes			
<i>C. elegans</i> GCK-4	WNIIGELGDGAFGVKEAVSRSTDPKLFAASKSIEIQLGEELEDFLVIEILSECKGHPMGLYSS-TYFFENKLITMLIEFCGGGAVDNIMELGHPLK			
<i>C. briggsae</i>	WNIIGELGDGAFGVKEAVSRSTDPKLFAASKSIEIQLGEELEDFLVIEILSECKGHPMGLYSS-TYFFENKLITMLIEFCGGGAVDNIMELGHPLK			
<i>P. pacificus</i>	WDIVGELGDGAFGVKEAVSRADPRRVAACKACITMEE-GEELEDFLVIEILVACS-HPNIVGLYA--CYYHDHKLSMLIEFCGGGAVDGMIELEKPLT			
<i>H. contortus</i>	WDIVGELGDGAFGVKEAVSKAQDSLAAAKAIEVQE-GEELEDFLVIEILTSCK-HANIVNLYA--CYYFENKLHMLIEFCGGGAVDAIMIELEKPLT			
<i>N. americanus</i>	WDIVGELGDGAFGVKEAVSKSDKNLYAAAKAIEVQE-GEELEDFLVIEILTSCK-HNIVGLYA--CYYCENKLHMLIEFCGGGAVDAIMIELEKPLT			
<i>A. duodenale</i>	WEIVGELGDGAFGVKEAVSKSDRLYAAAKAIEVQE-GELEDFLVIEILTSCK-HANIVNLYA--CYYFENKLHMLIEFCGGGAVDAIMIELEKPLT			
<i>D. viviparus</i>	WEIVGELGDGAFGVKEAVSKTDRNLLAAAKAIEVQE-GELEDFLVIEILTSCK-HINIVNLYA--CYYFENKLHMLIEFCGGGAVDAIMIELEKPLT			
<i>A. ceylanicum</i>	WEIVGELGDGAFGVKEAVSKSDRLYAAAKAIEVQE-GELEDFLVIEILTSCK-HINIVNLYA--CYYCENKLHMLIEFCGGGAVDAIMIELEKPLT			
<i>S. ratti</i>	WTIGELGDGAFGVKEVENIKNPFLAAAKHIEFD-GEIDDYIPEVILETCK-HENIVNLYA--CYYQKNQLSILIEFCSGGAIDNIMELNSRLT			
<i>B. malayi</i>	WILDEVIGDGAFGVNVYKARSKLKFPTVAAAAMALED-DE-SQDMVVEVSILTQCK-HPNIVELYD-AFTMGRNRTIYLGYGGGAVDSIMMELSRHLS			
<i>O. ochengi</i>	FTRQEKGGRGSFGEVFKGIDNR-TGQVVAIKIIDLEKAEDIEDIQEQQEMLVSYLSCQD-SPYVTKYYG-SYLYKESKLWIIMEYLGGGSALD--LTCKGKLE			
<i>L. loa</i>	WILDEVIGDGAFGVNVYKARSKLKFPTVAAAAMALED-DE-SQDMVVEVSILTQCK-HPNIVELYD-AFTMGRNRTIYLGYGGGAVDSIMMELSRHLS			
<i>T. trichiura</i>	WDVVSDLGDGAFGVQKVIHKE-NGTCAAAKAIELQS-EEEIDEYLVIEILTSQCD-HNIVNLYFVSYNIVLIEFCGGGAVDSIMMELSRHLS			
<i>D. rerio</i>	WEIIGELGDGAFGVYKAQNKE-TGVLAAAKVIETKS-EEELEDYMVIEIDILASCN-HQYIVKLDD-AFFFDNLKSMIEFCPGGAVDAIMLELDRGQL			
<i>G. gallus</i>	WEVVGELGDGAFGVYKAQNKE-TGALAAAAKVIETKS-EDELEDYMVIEIATCD-HPHIVKLGG-AFYWEKGKLWMIIEFCPGGAVDATMLELDRGLT			
<i>M. musculus</i>	WEIVGELGDGAFGVYKAQNKE-TGALAAAAKVIETKS-EEELEDYIIVEIEILATCD-HPYIVKLGG-AYYYDGKLWMIIEFCPGGAVDAIMLELDRGLT			
<i>R. norvegicus</i>	WEILGELGDGAFGVYKAQNKE-TGALAAAAKVIETKS-EEELEDYIIVEIEILATCD-HPYIVKLGG-AYYYDGKLWMIIEFCPGGAVDAIMLELDRGLT			
<i>C. familiaris</i>	WEIVGELGDGAFGVYKAQNKE-TGALAAAAKVIETKS-EEELEDYIIVEIEILATCD-HPYIVKLGG-AYYYDGKLWMIIEFCPGGAVDAIMLELDRGLT			
<i>O. aries</i>	WEIVGELGDGAFGVYKAQNKE-TGALAAAAKVIETNS-EEELEDYIIVEIEILATCD-HPYIVKLGG-AYYYDGKLWMIIEFCPGGAVDAIMLELDRGLT			
<i>B. taurus</i>	WEIVGELGDGAFGVYKAQNKE-TGALAAAAKVIETNS-EEELEDYIIVEIEILATCD-HPYIVKLGG-AYYYDGKLWMIIEFCPGGAVDAIMLELDRGLT			
<i>H. sapiens</i> STK10	WEIVGELGDGAFGVYKAQNKE-TGALAAAAKVIETKS-EEELEDYIIVEIEILATCD-HPYIVKLGG-AYYYDGKLWMIIEFCPGGAVDAIMLELDRGLT			
	Nematodes			
<i>C. elegans</i> GCK-4	EDQIAYIGYVYCDALKWLHSQNIIRDLKAGNILLTQDGQVRЛАDFGVSAKLISEKRDFTFIGTPYWMAPEVMACETFK	*		
<i>C. briggsae</i>	EDQIAYIGYVYCDALKWLHSQNIIRDLKAGNILLTQDGQVRЛАDFGVSAKLISEKRDFTFIGTPYWMAPEVMACETFK			
<i>P. pacificus</i>	EPQIAYIARTCEALAYLHEQNIIIRDLKAGNILLTSDAIVKLADFGVSAKLDRDQAERKDTFIGTPYWMAPEVMACETFK			
<i>H. contortus</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>N. americanus</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>A. duodenale</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>D. viviparus</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>A. ceylanicum</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>S. ratti</i>	EQQISYVTHTCVGLNLHKKNNIIIRDMKAGNILLTGDGVVKLADFGVSAKLDCNEKRDTFIGTPYWVYV1KPNAPERKTA			
<i>B. malayi</i>	EQQIQYIMKEILKALDFLHGKNNIIIRDLKAGNILLTSDARVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>O. ochengi</i>	EGHIAVILREILKGLEYLHSERKIIIRDIAKANVLLSERGDVVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>L. loa</i>	EQQIQYIMKEILKALDFLHGKNNIIIRDLKAGNILLTSDARVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>T. trichiura</i>	EQQIQYIMKEILKALDFLHGKNNIIIRDLKAGNILLTSDARVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>D. rerio</i>	EPQIVRKICKQMLEALQYHLHSMKIIIRDLKAGNILLTLDGDIKLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVMCETMK			
<i>G. gallus</i>	EPQIVRKICKQMLEALQYHLHSMKIIIRDLKAGNILLTLDGDIKLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVMCETMK			
<i>M. musculus</i>	EPQIVVCRQMLEALNFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVLCETMK			
<i>R. norvegicus</i>	EPQIVVCRQMLEALNFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>C. familiaris</i>	EPQIVVCRQMLEALNFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>O. aries</i>	EPQIVVCRQMLEALTFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>B. taurus</i>	EPQIVVCRQMLEALTFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>H. sapiens</i> STK10	EPQIVVCRQMLEALNFHLHSMKIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
	Vertebrates			
<i>C. elegans</i> GCK-4	EDQIAYIGYVYCDALKWLHSQNIIRDLKAGNILLTQDGQVRЛАDFGVSAKLISEKRDFTFIGTPYWMAPEVMACETFK	*		
<i>C. briggsae</i>	EDQIAYIGYVYCDALKWLHSQNIIRDLKAGNILLTQDGQVRЛАDFGVSAKLISEKRDFTFIGTPYWMAPEVMACETFK			
<i>P. pacificus</i>	EPQIAYIARTCEALAYLHEQNIIIRDLKAGNILLTSDAIVKLADFGVSAKLDRDQAERKDTFIGTPYWMAPEVMACETFK			
<i>H. contortus</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>N. americanus</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>A. duodenale</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>D. viviparus</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>A. ceylanicum</i>	EQQIAYVARYTCCEAVFLHDNNIIIRDLKAGNILLTSDGVVKLADFGVSAKLDRNEKRDTFIGTPYWMAPEVMCETFK			
<i>S. ratti</i>	EQQISYVTHTCVGLNLHKKNNIIIRDMKAGNILLTGDGVVKLADFGVSAKLDCNEKRDTFIGTPYWVYV1KPNAPERKTA			
<i>B. malayi</i>	EQQIQYIMKEILKALDFLHGKNNIIIRDLKAGNILLTSDARVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>O. ochengi</i>	EGHIAVILREILKGLEYLHSERKIIIRDIAKANVLLSERGDVVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>L. loa</i>	EQQIQYIMKEILKALDFLHGKNNIIIRDLKAGNILLTSDARVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>T. trichiura</i>	EQQIQYIMKEILKALDFLHGKNNIIIRDLKAGNILLTSDARVKLADFGVSAKLDCNEKRDTFIGTPYWMAPEV1CETFK			
<i>D. rerio</i>	EPQIVRKICKQMLEALQYHLHSMKIIIRDLKAGNILLTLDGDIKLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVMCETMK			
<i>G. gallus</i>	EPQIVRKICKQMLEALQYHLHSMKIIIRDLKAGNILLTLDGDIKLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVMCETMK			
<i>M. musculus</i>	EPQIVVCRQMLEALNFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVLCETMK			
<i>R. norvegicus</i>	EPQIVVCRQMLEALNFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>C. familiaris</i>	EPQIVVCRQMLEALNFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>O. aries</i>	EPQIVVCRQMLEALTFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>B. taurus</i>	EPQIVVCRQMLEALTFHLGKRIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			
<i>H. sapiens</i> STK10	EPQIVVCRQMLEALNFHLHSMKIIIRDLKAGNVLMTLEGDIRLADFGVSAKLNKTLQRDRDSFIGTPYWMAPEVVMCETMK			

(K) Structure and alignment of STK10 and GCK-4. Structure of PDB: 6EIM (Human STK10) in green with GW683134A bound (in yellow), aligned to *C. elegans* GCK-4 homology model in blue. The human and *C. elegans* kinase domains share 56% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 6EIM, 4EQU and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).

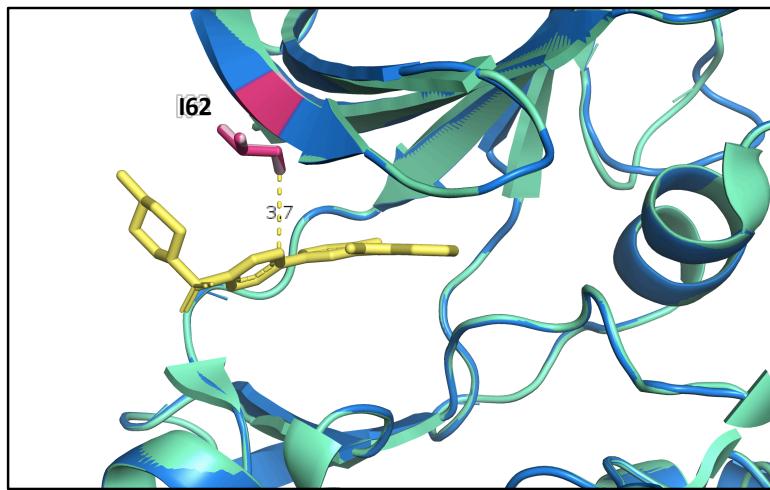


Human CSNK1D crystal structure **Human residue**
C. elegans KIN-20 homology model **C. elegans residue**

		88	*
Nematodes	<i>C. elegans</i> KIN-20	FRLGRKIGSSGSGFDIYLQGNIQTNEEVAVKLECVKSHPQLHIESRLYRIMLGGIPEIRWCQEGDYNVVMELLGPSLEDLFNFQCRKFSLKTVLLADQM	
	<i>C. briggsae</i>	FRLGRKIGSSGSGFDIYLQGNIQTNEEVAVKLECVKSHPQLHIESRLYRIMLGGIPEIRWCQEGDYNVVMELLGPSLEDLFNFQCRKFSLKTVLLADQM	
	<i>P. pacificus</i>	-----SEL[P]QVH[R]KA[GQN]HHNNEEVAVKLECFKTKHPQLHIEVRLYKIMNGGIGIP[V]KWCYGEHEYNVVMELLGPSLEDLFNFQCRRFSLKTVLLADQM	
	<i>H. contortus</i>	YKLIRKIGSSGSGFDIYT[V]SINVNTGEEVAKLCECSNRARHPOLLYESKVRILQGGVGIP[H]IRWYTEREYN[V]LMDLLGPsLEDLFNFCSRFTMKTVLMLADQM	
	<i>N. americanus</i>	FRLGRKIGSSGSGFDIYLGLNVQTNEEVAVKLECVKSHPQLHIEGLRIVRMSGGVGIPDV[K]WCLEGEYNVVMELLGPSLEDLFNFQCRKFSLKTVLLADQM	
	<i>A. duodenale</i>	FRLGRKIGSSGSGFDIYTGLNVQTNEEVAVKLECVKSHPQLHIEGLRIVRMSGGVGIPDV[K]WCLEGEYNVVMELLGPSLEDLFNFQCRKFSLKTVLLADQM	
	<i>D. viviparus</i>	YKLIRKIGSSGSGFDIYTGLNVQTNEEVAVKLECVKSHPQLHIEGLRIVRMSGGVGIPDV[K]WCLEGEYNVVMELLGPSLEDLFNFQCRKFSLKTVLLADQM	
	<i>A. ceylanicum</i>	FRLGRKIGSSGSGFDIYTGLNVQTNEEVAVKLECVKSHPQLHIEGLRIVRMSGGVGIPDV[K]WCLEGEYNVVMELLGPSLEDLFNFQCRKFSLKTVLLADQM	
	<i>S. ratti</i>	YRVKRKIG[G]GSFHDIFLGINITNGEEVAKIMESSKARHPQLMVEYKVRIILNGGVGIP[H]IRFVGVEREYN[C]LMDLLGPsLEDLFFCGRRTFMKTVLMLADQM	
	<i>B. malayi</i>	FRLGRKIGSSGSGFDIYTGLQNIQTQEEVAKLCEVKTKHPQLHIEARLYKIMSSGGGIGIP[Q]VKWCYGEHEYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>O. oehnogi</i>	FRLGRKIGSSGSGFDIYTGLQNIQTQEEVAKLCEVKTKHPQLHIEARLYKIMSSGGGIGIP[Q]VKWCYGEHEYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>L. loa</i>	FRLGRKIGSSGSGFDIYTGLQNIQTQEEVAKLCEVKTKHPQLHIEARLYKIMSSGGGIGIP[Q]VKWCYGEHEYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>T. trichiura</i>	YL1VRKIGSSGSGFDIYLAINKSNGEEEVAKVSEISKRHPQLQEVESKVRILLQGGIGIVPHIKWKGGEYGCN[I]LMDLLGPsLEDLFNFCSRFTMKTVLMLADQM	
Vertebrates	<i>D. rerio</i>	YRLGRKIGSSGSGFDIYLGTGTDISVGEEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>G. gallus</i>	YRLGRKIGSSGSGFDIYLGTGTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>M. musculus</i>	YRLGRKIGSSGSGFDIYLGTGTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>R. norvegicus</i>	YRLGRKIGSSGSGFDIYLGTGTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>C. familiaris</i>	WFWI[QAHQK]PCTSW[H]LGTGTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>O. aries</i>	-----GTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>B. taurus</i>	YRLGRKIGSSGSGFDIYLGTGTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>H. sapiens</i> CSNK1D	YRLGRKIGSSGSGFDIYLGTGTDIAGEEVAKLCEVKTKHPQLHIESKIKYKMMQGGVGIP[T]KWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	
	<i>H. sapiens</i> CSNK1E	YRLGRKIGSSGSGFDIYLGANIASGEEEVAKLCEVKTKHPQLHIESKFKYKMMQGGVGIP[S]TKWCAGEGDYNVVMELLGPSLEDLFNFCSRFTLKTVLLADQM	

Nematodes	<i>C. elegans</i> KIN-20	LSRVEFIHCRDYIHRDIKPDNFLMGLG--KRGNLVYIIDFGLAKYRDS	
	<i>C. briggsae</i>	LSRVEFIHLDYIHRDIKPDNFLMGLG--KRGNLVYIIDFGLAKYRDS	
	<i>P. pacificus</i>	LSRVEFIHMMHYIHRDIKPDNFLMGLG--KKGNLVYIIDFGLAKRFRDQ	
	<i>H. contortus</i>	IGRIEVHVKNFIRDIKPDNFLMGLG--RHCNKLFLIDFGLAKKFRDS	
	<i>N. americanus</i>	ITRIEYIHHERDYIHRDIKPDNFLMGLG--KRGNLVYIIDFGLAKKYRDS	
	<i>A. duodenale</i>	ITRIEYIHHERDYIHRDIKPDNFLMGLG--KRGNLVYIIDFGLAKKYRDS	
	<i>D. viviparus</i>	IGRIEVHVKNFIRDIKPDNFLMGLG--RHCNKLFLIDFGLAKKYRDS	
	<i>A. ceylanicum</i>	ITRIEYIHHERDYIHRDIKPDNFLMGLG--KRGNLVYIIDFGLAKKYRDS	
	<i>S. ratti</i>	IGRIEVHVKNFIRDIKPDNFLMGLG--RHCNKLFLIDFGLAKKYRET	
	<i>B. malayi</i>	LSRIEYIHSDRFIHRDIKPDNFLMGLG--KKGNLVYIIDFGLAKKYRCs	
	<i>O. oehnogi</i>	LSRIEYIHSDRFIHRDIKPDNFLMGLG--KKGNLVYIIDFGLAKKYRCs	
	<i>L. loa</i>	LSRIEYIHSDRFIHRDIKPDNFLMGLG--KKGNLVYIIDFGLAKKYRCs	
	<i>T. trichiura</i>	IGRIEFLHVKGFIHRDIKPDNFLMGLG--RHCNRLFLIDFGLAKKYRDS	
Vertebrates	<i>D. rerio</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>G. gallus</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>M. musculus</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>R. norvegicus</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>C. familiaris</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>O. aries</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>B. taurus</i>	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>H. sapiens</i> CSNK1D	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	
	<i>H. sapiens</i> CSNK1E	ISRIEYIHSKNFIRDKPDNFIMLGIG--KKGNLVYIIDFGLAKKYRDA	

(L) Structure and alignment of CSNK1D and KIN-20. Structure of PDB: 5MQV (Human CSNK1D) in green with inhibitor bound (in yellow), aligned to *C. elegans* KIN-20 homology model in blue. The human and *C. elegans* kinase domains share 80% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 5MQV, 5OKT and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).

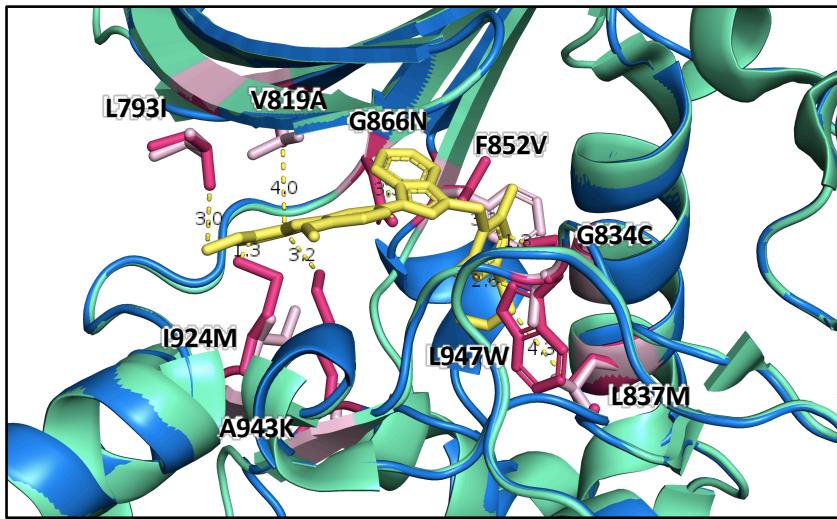


**Human GSK3B crystal structure Human residue
C. elegans GSK-3 homology model *C. elegans* residue**

		62	
	Nematodes	*	
<i>C. elegans</i> GSK-3	YYDQKVIIGNGSFGVVFIAKLSTT-----NEMVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>C. briggsae</i>	YYDQKVIIGNGSFGVVFIAKLSTT-----NEMVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>P. pacificus</i>	YYDQKVIIGNGSFGVVFIAKLSTT-----NEMVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>H. contortus</i>	YSDLKVYNGSFGVVFLAQLRALTDGKSTDPGEQIAIKVKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>N. americanus</i>	YSDLKVYNGSFGVVFLAQLRALTDGKSTDPGEQIAIKVKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>D. viviparus</i>	YSDLKVYNGSFGVVFLAQLRALTDGKSTDPGEQIAIKVKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>A. ceylanicum</i>	YCDQKVVGNGSFGVVFIAKLQEN-----NEPVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>S. ratti</i>	YCDQKVVGNGSFGVVFIAKLQEN-----NEPVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>B. malayi</i>	YCDQKVVGNGSFGVVFIAKLQEN-----NEPVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>O. ochenigi</i>	YCDQKVVGNGSFGVVFIAKLQEN-----NEPVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>L. loa</i>	YCDQKVVGNGSFGVVFIAKLQEN-----NEPVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>T. trichiura</i>	YCDQKVVGNGSFGVVFIAKLQEN-----NEPVAIKVLQDKRFKNRELQIMRKLNHNPNIVKLKYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSQ
<i>D. rerio</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYNKT
<i>G. gallus</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>M. musculus</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>R. norvegicus</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>C. familiaris</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>O. aries</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>B. taurus</i>	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>H. sapiens</i> GSK3B	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA
<i>H. sapiens</i> GSK3A	YTDTKVIGNGSFGVVIQAKLCD-----GELVAIKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDELYNLNILEYVPE		TYRVARHYSRA

		62	
	Nematodes	*	
<i>C. elegans</i> GSK-3	RQQIPMIYVKLYMQLLRSLAYIHSIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRNPEVNSYICSRRYRAPELIF		
<i>C. briggsae</i>	RQSIPMIYVKLYMQLLRSLAYIHSIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRNPEVNSYICSRRYRAPELIF		
<i>P. pacificus</i>	RQOIPIIYVKLYMQLFRALDYIHIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRGEPNVSYICSRRYRAPELIF		
<i>H. contortus</i>	RQSIPLIYVKLYMQLFRALAYIHIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRGEPNVSYICSRRYRAPELIF		
<i>N. americanus</i>	RQSIPLIYVKLYMQLFRALAYIHIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRGEPNVSYICSRRYRAPELIF		
<i>D. viviparus</i>	RQAIPLIYVKLYMQLFRALAYIHIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRGEPNVSYICSRRYRAPELIF		
<i>A. ceylanicum</i>	RQSIPLIYVKLYMQLFRALAYIHIGICHRDIKPQNLLIDPESGVLKLCDFGSAKYLVRGEPNVSYICSRRYRAPELIF		
<i>S. ratti</i>	DQQIPIIATKVFTYQIFRALGYIHNLGICHCRDIKPQNLLIDWETGVILKLCDFGSAKKLVEGEPEVNSYICSRRYRAPELIF		
<i>B. malayi</i>	RQIIPALYIKLYMQLFRALAYIHSLGVCVRDICKPQNLLIDPDSAVLKLCDFGSAKHLVRGEPNVSYICSRRYRAPELIF		
<i>O. ochenigi</i>	RQIIPALYIKLYMQLFRALAYIHSLGVCVRDICKPQNLLIDPDSAVLKLCDFGSAKHLVRGEPNVSYICSRRYRAPELIF		
<i>L. loa</i>	RQIIPALYIKLYMQLFRALAYIHSLGVCVRDICKPQNLLIDPDSAVLKLCDFGSAKHLVRGEPNVSYICSRRYRAPELIF		
<i>T. trichiura</i>	KQIIPMMYVKLEMQLFRALAYIHSLGVCVRDICKPQNLLIDPDSAVLKLCDFGSAKHLVRGEPNVSYICSRRYRAPELIF		
<i>D. rerio</i>	KQTLPMVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>G. gallus</i>	KQTLPMVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>M. musculus</i>	KQTLPIVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>R. norvegicus</i>	KQTLPIVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>C. familiaris</i>	KQTLPIVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>O. aries</i>	KQTLPIVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>B. taurus</i>	KQTLPIVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>H. sapiens</i> GSK3B	KQTLPIVYVKLYMQLFRSLAYIHSFGICHRDIKPQNLLIDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		
<i>H. sapiens</i> GSK3A	KLTIPILYVKVYMYQLFRSLAYIHSQGVCHRDICKPQNLLVDPTDAVLKLCDFGSAKQLVRGEPNVSYICSRRYRAPELIF		

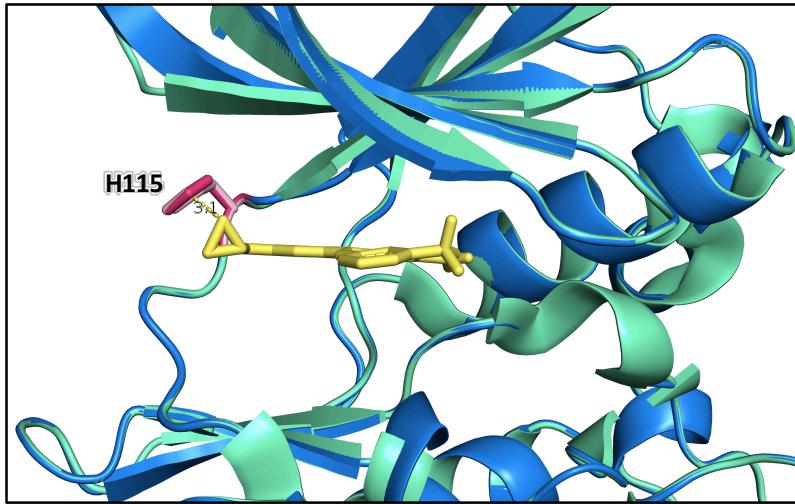
(M) Structure and alignment of GSK3B and GSK-3. Structure of PDB: 6HK3 (Human GSK3B) in green with inhibitor bound (in yellow), aligned to *C. elegans* GSK-3 homology model in blue. The human and *C. elegans* kinase domains share 82% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 6HK3, 5HNL and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



Human BUB1 crystal structure Human residue
C. elegans BUB-1 homology model *C. elegans* residue

		793	819	834	837	852	866
Nematodes	<i>C. elegans</i> BUB-1	LHIQTLGQGGYAKVYRAVTDD-----QRTVAVKYEVPSCSWEVYICDQMNRNLKDGRG-----LELMAKCCIME-----VMDAYVYSTASLLVIVQHEYHGTLLF	*	*	*	*	*
	<i>C. briggsae</i>	FHIQTLGQGGYAKVYKVANNE-----KKVVAVKYEVPSCSWEVYICDQMNRNLKDREDRVKMADWCIMK-----VMDAYVFTSTASLLVIVEYHEYHGTLLF					
	<i>D. viviparus</i>	YKIVALGQGGFAKVKYKVSVNEE-----GKVLALKHETPSCAWEVHICSELRRMRIGKEKRF-----LDSVMEVIAFDDVTEAYVFCNASVLNFNEYYPHGTLLD					
	<i>A. ceylanicum</i>	FNILELVGQGGFAKVKYCTNEE-----GKTLALKYEIPSCWEIYICSEVKMRIDRSKQFV-----LDSVMEVTEAYVFTTNASVLNFNEYYPHGTLLD					
	<i>B. malayi</i>	FDIECLGEGGFAKVKYKSSED-----GNFYIHKFEMPCKWEIYACETLIRIPKAM-----LGGMVN-----IRDAYLFSNNSAIIVVEYHKHGNLLD					
	<i>O. ochengi</i>	FDIECLGEGGFAKVKYKGKSED-----GNFYIWKLOMPCKWEIYACETLIRIMPKIM-----LGGMN-----IRDAYLFSNNSAIIVVEYHKHGNLLD					
	<i>L. loa</i>	FDIECLGEGGFAKVKYKGKSED-----GNFYIWKLOMPCKWEIYACETLIRIMPKAM-----LGGMN-----IRDAYLFPNNSAIIVVEYHKHGNLLD					
Vertebrates	<i>D. rerio</i>	LRVDFLGQGAFATVYQATN-----LMTTQKLFLKVQKPANPWEFYIDCQLNKRLLQPSPERHL-----YNS-----IHS AHLFNNNGSVLVQLHNCGTLIN					
	<i>G. gallus</i>	VCVDSLVGQGGFAQVYQASVLNASDPRSNQKVFKVQKPANPWEFYIATQQLVERLDPSP1HHL-----YI-----LYSAHFFQNGSILIGELYNYGTLLN					
	<i>M. musculus</i>	VVYNHLLGEGGAAQVFEAIHGDVRNAKSEQKCILKVKVQKPANPWEFYIIGMQLMERLKPEVHHM-----FIK-----FYS AHLFKNGSILVGELEYSYGTLLN					
	<i>R. norvegicus</i>	VVYNHLLGEGGAAQVFEAIHGD-----KSKQKCLILKVKVQKPANPWEFYIIGMQLMERLKPEVHHM-----FIK-----FYS AHLFQNGSILVGELEYSYGTLLN					
	<i>C. familiaris</i>	VVVDHLLGEGGAAQVYEVTHGEVNDTCKNQKQFVFLKVQKPANPWEFYIGTQQLMERLKPSMRHM-----FIK-----FYS AHLFQNGSVLVGDLYSYGTLLN					
	<i>O. aries</i>	VVVDHFTGEGGAAQVYEVTHGDVNNSKNKEFLVKVQKPANPWEFYIGTQQLMERLNPGAQHM-----FIR-----FYS AHLFQNGSVLVGDLYSYGTLLN					
	<i>B. taurus</i>	VVVDHFTGEGGAAQVYEVTHGDVNNSKNKEFLVKVQKPANPWEFYIGTQQLMERLKPSMQHM-----FIK-----FYS AHLFQNGSVLVGDLYSYGTLLN					
	<i>H. sapiens</i> BUB1	VVYHHL LGEGGAAQVYEVATQGDLNDAKNCQKFVFLKVQKPANPWEFYIGTQQLMERLKPSMQHM-----FMK-----FYS AHLFQNGSVLVGDLYSYGTLLN					
Nematodes	<i>C. elegans</i> BUB-1	YANNMKDPNW-H----ITCFLITQMARVVKEVHASKIIHGDIKPDPNFVITRKIDDKWGKDALMSNDSFVIIIDNG	*	*	*	*	*
	<i>C. briggsae</i>	YANSMKDPNW-H----ISCFLITQMARILKEVHACNIIHGDIKPDPNFVITRKIDPNWWDKDALMSNDFVIIIDNG					
	<i>D. viviparus</i>	ISNKMHDPSW-Y----ILLIAIQMAVKLVRDIHSVEIIHGDKVPKDNFVIVNKLNAHNDVKEI-INTPLILIDNG					
	<i>A. ceylanicum</i>	LSNKVDPSPW-Y----IALLIGQIAKVLRELHAAKIIHGDIKPDPNFMLGKLSCDRNDEI-LSTPILRLIDNG					
	<i>B. malayi</i>	MMNKLQAKNM-SCSGLLTQVYLAQWQISRILEAVHNQVIHGDIKPDPNFMLHRLNEDAALEQITLEKKSFTLILIDNG					
	<i>O. ochengi</i>	MVNKLQARNM-SCSGLLTQVYLAWEIGRILRAVHNQVIHGDIKPDPNFMLHRLNEDATELQEQLIDRKSFTLILIDNG					
	<i>L. loa</i>	MINNLQAKNM-SCSGLLTQVYLAWEIGRILRAVHNQVIHGDIKPDPNFMLNRLNEDATELQEQLIDRKSFTLILIDNG					
Vertebrates	<i>D. rerio</i>	AINLYKRRSEKLMQPQPLVLYFSVCILKMWELLHAAHHIHADIKPDPNFIGLGERFLENDCFDQ--ENLQHGLALIDNG					
	<i>G. gallus</i>	AINIYKLLPEKVMQPAFVLYFAVKILHMHVEELHSCKIIHGDIKPDPNFILGGERFLNDTCI--DLSHGLTLIDNG					
	<i>M. musculus</i>	VINLYKNTSEKVMQPAVLTVLTAIRMLYMVQVHSCEIIHGDIKPDPNFILGHRFLEQDD---EDLATGTLALIDNG					
	<i>R. norvegicus</i>	VINLYKNTSEKVMQPAVLVSFAIRMLCMIEQVHDCEIIHGDIKPDPNFILGSRFLEQDGEE-D-DISAGLAALIDNG					
	<i>C. familiaris</i>	AINLYKNTPEKVMQPAVLAFARMLCMICQQVHDCEIIHGDIKPDPNFILGNRFLEQDNK-D-DDLSAGLVLIIDNG					
	<i>O. aries</i>	AINLYKNTPEKVMQPAVLAFARMLCMICQQVHDCEIIHGDIKPDPNFILGNRFLEQDNK-D-DDLSAGLVLIIDNG					
	<i>B. taurus</i>	AINLYKNTPEKVMQPAVLAFARMLCMICQQVHDCEIIHGDIKPDPNFILGNRFLEQDNK-D-DDLSAGLVLIIDNG					
	<i>H. sapiens</i> BUB1	AINLYKNTPEKVMQPAQGLVISFAMRMLYMIEQVHDCEIIHGDIKPDPNFILGNGFLEQDDE---DDLSAGLVLIIDNG					

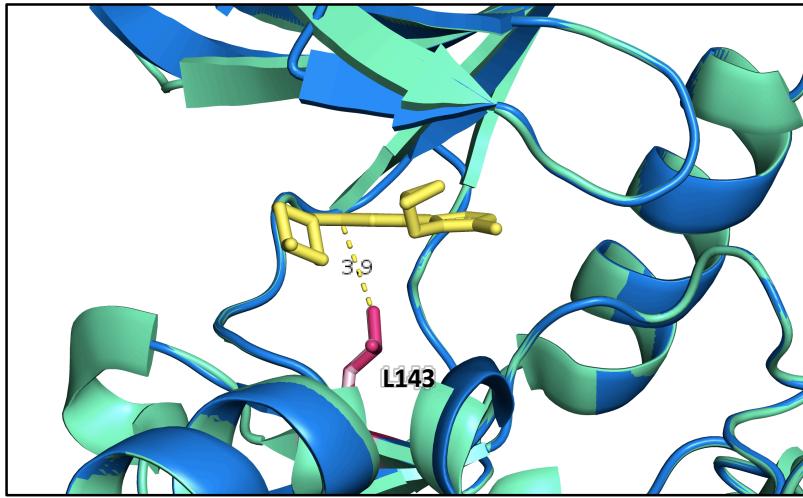
(N) Structure and alignment of BUB1 and BUB-1. Structure of PDB: 6F7B (Human BUB1) in green with BAY-1816032 bound (in yellow), aligned to *C. elegans* BUB-1 homology model in blue. The human and *C. elegans* kinase domains share 30% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 6F7B, 4QPM and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



**Human CSNK2A1 crystal structure Human residue
C. elegans KIN-3 homology model *C. elegans* residue**

		*115
Nematodes	<i>C. elegans</i> KIN-3	YQLVRKLGGRKYSEVFEGFKMSTDEKVVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEHVNNSDFKQLYQTLSDYDIRYYLY
	<i>C. briggsae</i>	YQLVRKLGGRKYSEVFEGVKMSTDEKVVKLCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEHVNNSDFKQLYQTLSDFDIRYYLY
	<i>P. pacificus</i>	YQLVRKLGGRKYSEVFEGVNLKADSKCVCVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEYVNNNTDFKQLYQTLTMDIRYYLF
	<i>H. contortus</i>	YQLVRKLGGRKYSEVFEGVKITTEDEKVVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEYVNNNSDFKQLYGTLSLDLDIRYYLY
	<i>A. duodenale</i>	YQLVRKLGGRKYSEVFEGVKITTEEKVVVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEYVNNNSDFKQLYGTLSDFDIRYYLY
	<i>D. viviparus</i>	YQLVRKLGGRKYSEVFEGVKITTEDEKVVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEYVNNNSDFKQLYGTLSLDLDIRYYLY
	<i>A. ceylanicum</i>	YQLVRKLGGRKYSEVFEGVKITTEEVVVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEYVNNNSDFKQLYGTLSDFDIRYYLY
	<i>S. ratti</i>	YQLVRKLGGRKYSEVFEGVKITTEEVVVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEYVNNNSDFKQLYGTLSDFDIRYYLY
	<i>B. malayi</i>	YELTRKLGGRKYSEVFGLDTEKNERIVIKLCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIFEHVNQDFKTLYQTLTEYDIRYYLF
	<i>O. ochengi</i>	YOLTRKLGGRKYSEVFEGVKSPLDEKCVCVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIVEYVNNNTDFKQLYQTLTDYDIRYYLY
	<i>L. loa</i>	YQLIRKLGGRKYSEVFEGVRSLLDEKCVCVKILCPVKKKKIREIKILENLRGGTNITLLDVVKDPISRTPALIVEYVNNNTDFKQLYQTLTDYDIRYYLY
	<i>T. trichiura</i>	YNLTRKLGGRKYSEVFEGVIDVNTDEHVVVKILCPVKKKKIREIKILENLRGGNVITLNKVVVKDPISRTPALIVEYVNNNADEFKVLYQTLSDYIEIRYYLY
	<i>D. rerio</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLSDYDIRFYMY
Vertebrates	<i>G. gallus</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>M. musculus</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>R. norvegicus</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>C. familiaris</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>O. aries</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>B. taurus</i>	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>H. sapiens</i> CSNK2A1	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
	<i>H. sapiens</i> CSNK2A2	YQLVRKLGGRKYSEVFEAINITNEKEVVKILCPVKKKKIREIKILENLRGGPNITLLDIIKDPVSRTPALVFEHVNNNTDFKQLYQTLTDYDIRFYMY
Nematodes	<i>C. elegans</i> KIN-3	ELLKALDFCHSQGIMHRDVKPKNVMDAEKRELRLIDWGLAEFYHPRQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>C. briggsae</i>	ELLKALDFCHSQGIMHRDVKPKNVMDAEKRELRLIDWGLAEFYHPRQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>P. pacificus</i>	ELLRALDYCHSM-----
	<i>H. contortus</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>A. duodenale</i>	ELLK-----RLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>D. viviparus</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>A. ceylanicum</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>S. ratti</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>B. malayi</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>O. ochengi</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>L. loa</i>	ELLKALDYCHSQGIMHRDVKPKNVMDHEKKQLRLIDWGLAEFYHPKQDYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>T. trichiura</i>	ELLKALDFCHSQGIMHRDVKPKNVMDHEEGKRLRLIDWGLAEFYHPGDEYNVRVASRYFKGPELLVDYQCYDYSLSDMWSL
	<i>D. rerio</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
Vertebrates	<i>G. gallus</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>M. musculus</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>R. norvegicus</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>C. familiaris</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>O. aries</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>B. taurus</i>	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>H. sapiens</i> CSNK2A1	EILKALDYCHSMGIMHRDVKPKNVMDHEHKKRLRLIDWGLAEFYHPGQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL
	<i>H. sapiens</i> CSNK2A2	EILKALDYCHSKGIMHRDVKPKNVMDHQKKRLRLIDWGLAEFYHPAQEYNVRVASRYFKGPELLVDYQMDYSLSDMWSL

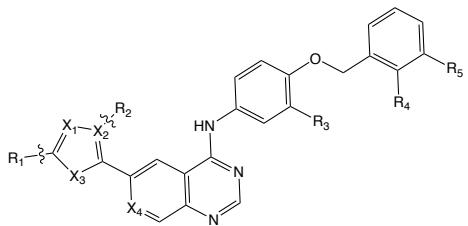
(O) Structure and alignment of CSNK2A1 and KIN-3. Structure of PDB: 3R0T (Human CSNK2A1) in green with inhibitor bound (in yellow), aligned to *C. elegans* KIN-3 homology model in blue. The human and *C. elegans* kinase domains share 86% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structures 3R0T, 3NSZ and associated *C. elegans* homology models). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).



**Human CSNK1A1 crystal structure Human residue
C. elegans KIN-19 homology model *C. elegans* residue**

	Nematodes	Vertebrates
<i>C. elegans</i> KIN-19	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>C. briggsae</i>	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>P. pacificus</i>	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>H. contortus</i>	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>N. americanus</i>	-----QARHPQHESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	-----QARHPQHESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>D. viviparus</i>	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYVSINVNGEEVAIKLESNRARHPQLLYESKVKYRILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>A. ceylanicum</i>	RK-IGCGSFQDFIPLGINITNGEEVAIKMESSKARHPOLMEYKVKYRILQGGVGIPHIRFVGVEREYNLVMDLILGPSPLEDLFFCGRRFTMKTVLMLVDQ	RK-IGCGSFQDFIPLGINITNGEEVAIKMESSKARHPOLMEYKVKYRILQGGVGIPHIRFVGVEREYNLVMDLILGPSPLEDLFFCGRRFTMKTVLMLVDQ
<i>S. ratti</i>	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>B. malayi</i>	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>O. ochengi</i>	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>L. loa</i>	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	IRKIGSGSFGDIYLAINITNGEEVAVKMESSKARHPQLLYESKVKYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>T. trichiura</i>	VRKIGSGSFGDIYLAINKSNGEEAVAKVESIKSRHPOLYESKVKYRILQLOGGIVGPHIKWYGGEGYGCNLVMDLILGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINKSNGEEAVAKVESIKSRHPOLYESKVKYRILQLOGGIVGPHIKWYGGEGYGCNLVMDLILGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>D. rerio</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>G. gallus</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>M. musculus</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>R. norvegicus</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>C. familiaris</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>O. aries</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>B. taurus</i>	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
<i>H. sapiens</i> CSNK1A1	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ	VRKIGSGSFGDIYLAINITNGEEVAVKLESQSKARHPQLLYESKLYKILQGGVGIPHIRWYGTREYNVLVMIDLGPSPLEDLFNFCSSRRFTMKTVLMLADQ
	*13	
	Nematodes	Vertebrates
<i>C. elegans</i> KIN-19	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>C. briggsae</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>P. pacificus</i>	MIAREVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIAREVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>H. contortus</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>N. americanus</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>D. viviparus</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>A. ceylanicum</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>S. ratti</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>B. malayi</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>O. ochengi</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>L. loa</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>T. trichiura</i>	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN	MIGRIEVYHVKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDSRTTRHPIPYREDKNLTGTARYASIN
<i>D. rerio</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>G. gallus</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>M. musculus</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>R. norvegicus</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>C. familiaris</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>O. aries</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>B. taurus</i>	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN
<i>H. sapiens</i> CSNK1A1	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN	MISRIEVYVHTKNFIHRD1KPDNFIMGIGRHCNKLFLIDFGGLAKKYRDNRTRQHPIPYREDKNLTGTARYASIN

(P) Structure and alignment of CSNK1A1 and KIN-19. Structure of PDB: 6GZD (Human CSNK1A1) in green with inhibitor bound (in yellow), aligned to *C. elegans* KIN-19 homology model in blue. The human and *C. elegans* kinase domains share 90% identity. All residues that are proximal to the inhibitor binding site with side-chains facing inwards are highlighted on the alignment (identified from PDB structure 6GZD and associated *C. elegans* homology model). Residues of interest are indicated on the structure above in dark pink (*C. elegans* residue) and light pink (human residue).

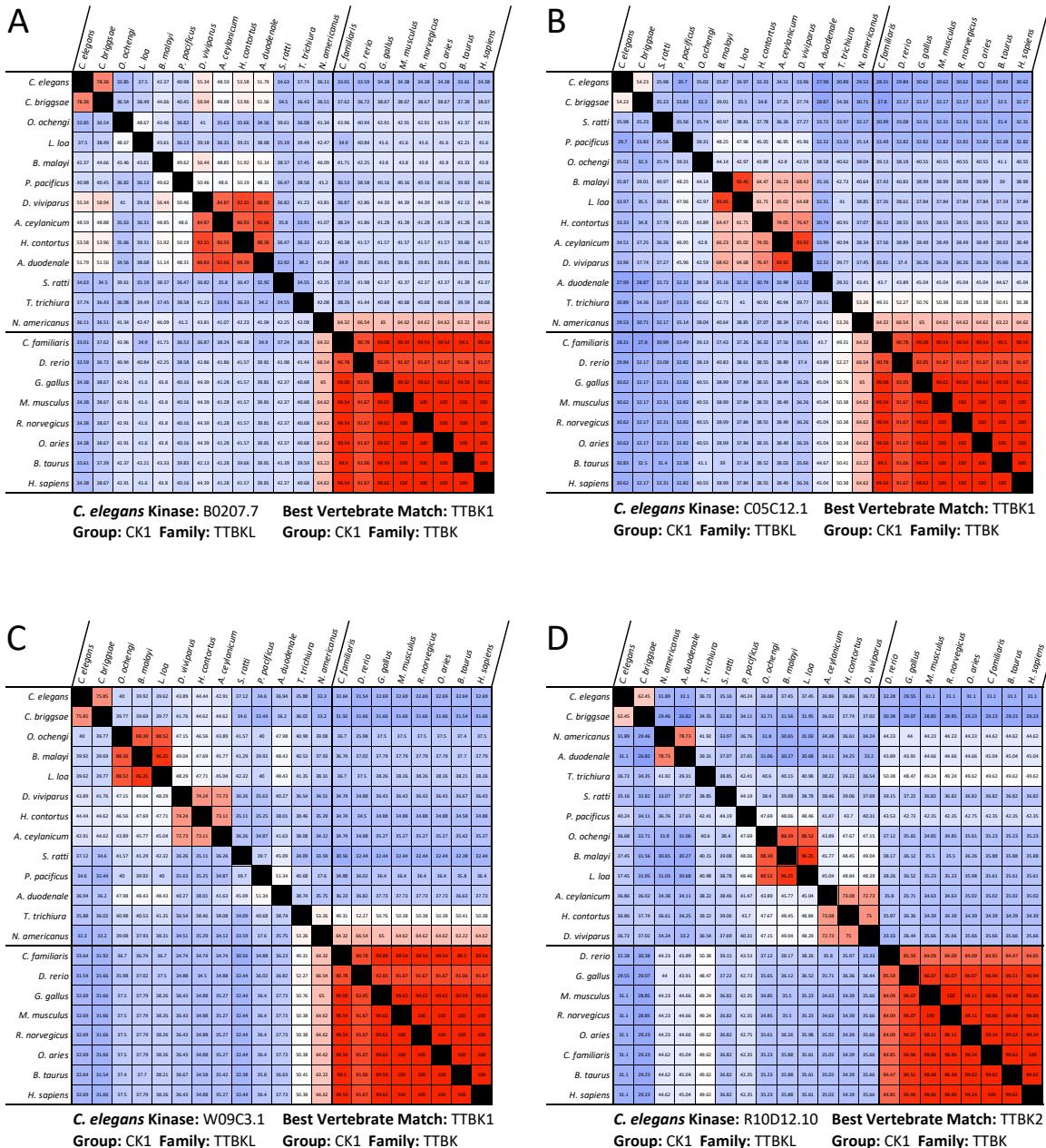


Compound ID	R ₁	R ₂	R ₃	R ₄	R ₅	Cel Activity				pH=7	pH=4.5
						X ₁	X ₂	X ₃	X ₄		
GW576609B		H	Cl	H	F	C	C	O	C	Let	Let
GW576924A		H	F	H	H	C	C	O	C	Emb	Let
GW583373A		H	Cl	H	H	C	C	O	C	Emb	Let
GW574783B		H	Cl	H	H	C	C	O	C	Lva	
GW580496A		H	Br	H	H	C	C	O	C	Lva	
GW576484X		H	CF ₃	H	F	C	C	O	C	Lva	
GW458787B		H	H	H	H	C	C	O	C	Ste	
GW566221B			H	H	H	C	O	C	C	Ste	
GW568377B	H		H	H	H	C	C	O	C	Ste	
GW320571X	H		H	H	H	N	C	N-CH ₃	C	Ste	
GW284372X	H		H	H	H	H	C	C	O	C	Ste
GW582764A		H	Cl	H	H	S	C	N	C		Emb
GW569530A		H	H	H	CF ₃	S	C	N	C		Lva
GW583340C		H	Cl	H	F	S	C	N	C		Lva
GW633459A		H	Cl	H	F	C	C	O	C		Lva
GW281179X	H		H	H	H	N	C	N-CH ₃	N		Lva
GW567808A		H	H	H	CF ₃	C	C	O	C		Ste
GW574782A		H	CF ₃	H	H	C	C	O	C		Ste
GW615311X		H	Cl	H	F	C	C	O	C		Ste
GW616030X		H	Cl	H	F	C	C	O	C		Ste
GW621823A		H	Cl	H	F	C	C	O	C		Ste
GW424170A	CF ₃		Cl	F	H	N	N	O	C		

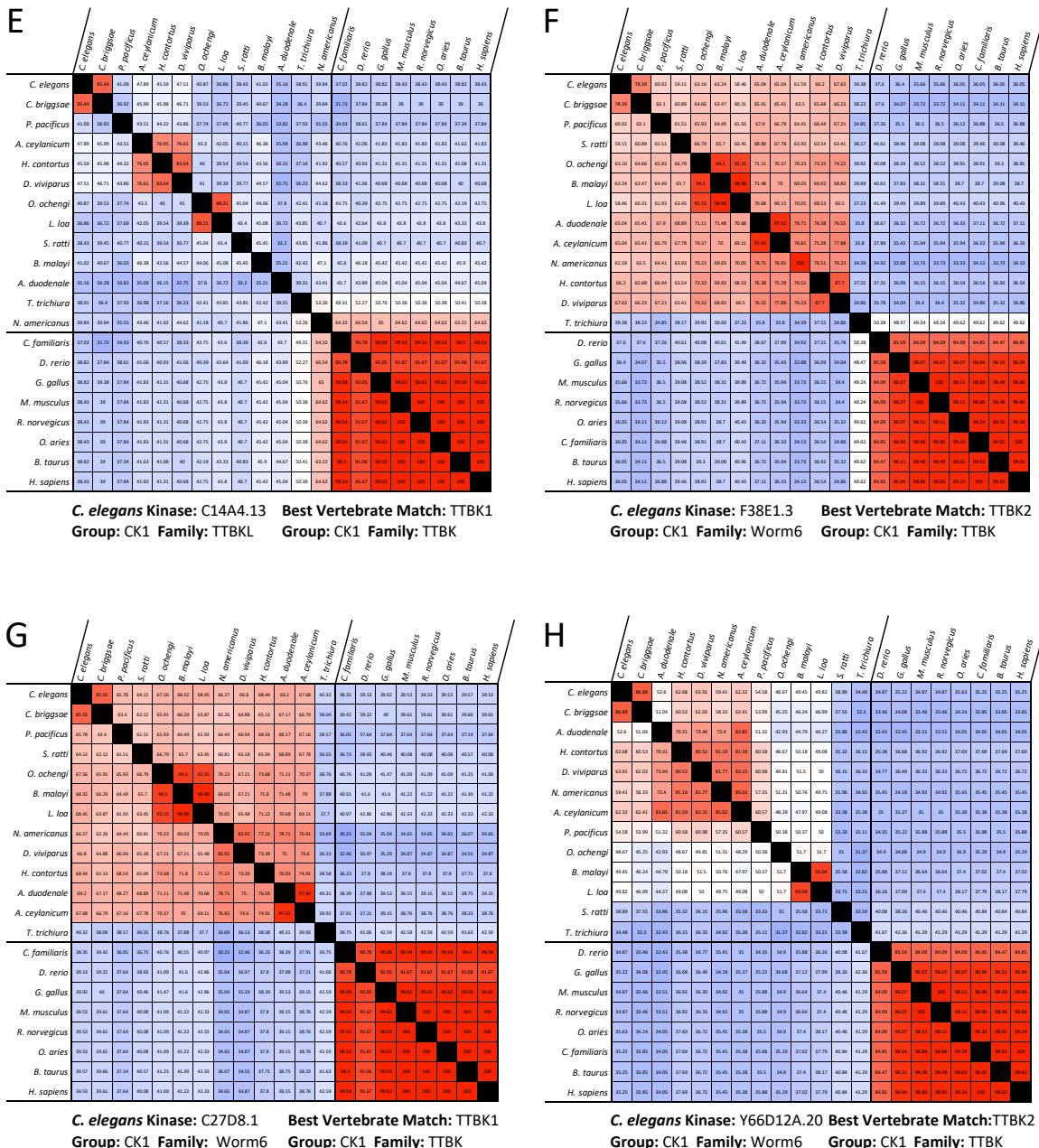
>>50 nb >50 26-50 11-25 0-10

living worms per well

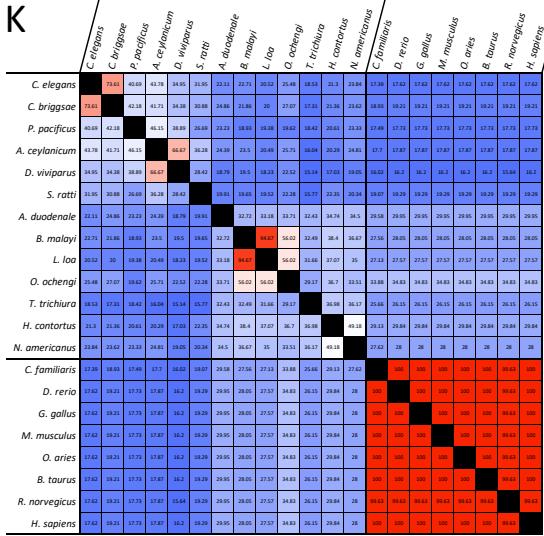
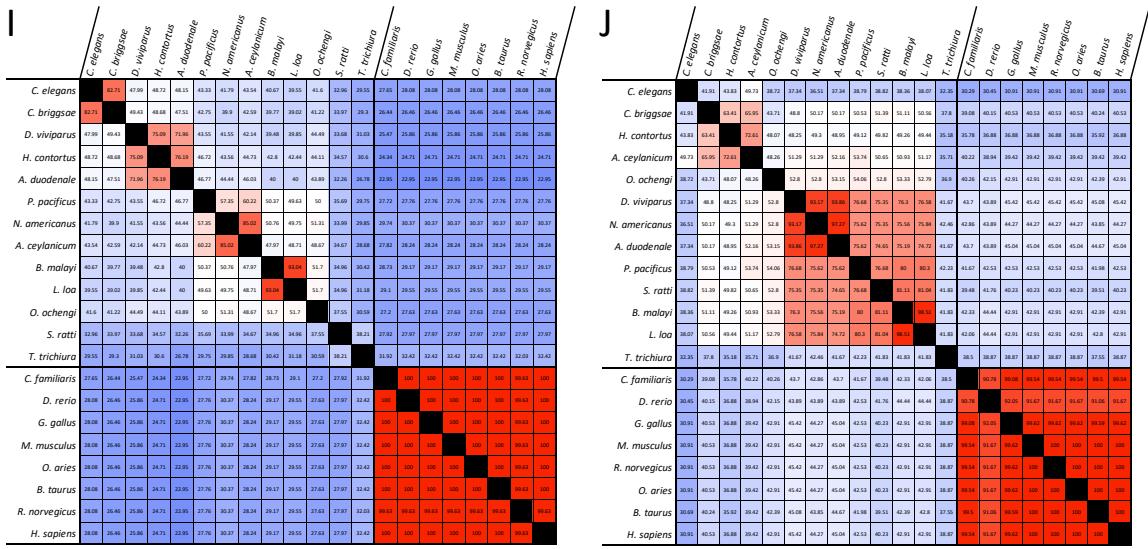
Supplementary Figure 3. 4AQ SAR highlighting favorable structural features for nematode activity *in vivo*. Screen phenotypes induced by inhibitor exposure including lethality (Let), embryonic lethality (Emb), larval arrest (Lva) and sterility (Ste) are shown. The resulting population growth defects are indicated by the colour coded scale (nb, no bacteria remaining in the well).



Supplementary Figure 4. Conservation of essential nematode-specific kinases across species. Matrices show the percent sequence identity between the kinase domain of the *C. elegans* essential nematode-specific kinase and that of the most similar kinase found across nematode species along with the kinase domain sequence of the best human kinase match and its ortholog across vertebrate species. *C. elegans* kinases from nematode-specific families (A-P) and nematode-expanded families (Q-Z) are shown. Sequence identity matrices for the kinase domain of the well-conserved kinases MEK1/MEK-2, PLK1/PLK-1 and EGFR/LET-23 are included for comparison (AA-AC). Kinase sequences were identified using NCBI BLASTP. Percent identity matrices were generated using Clustal Omega.



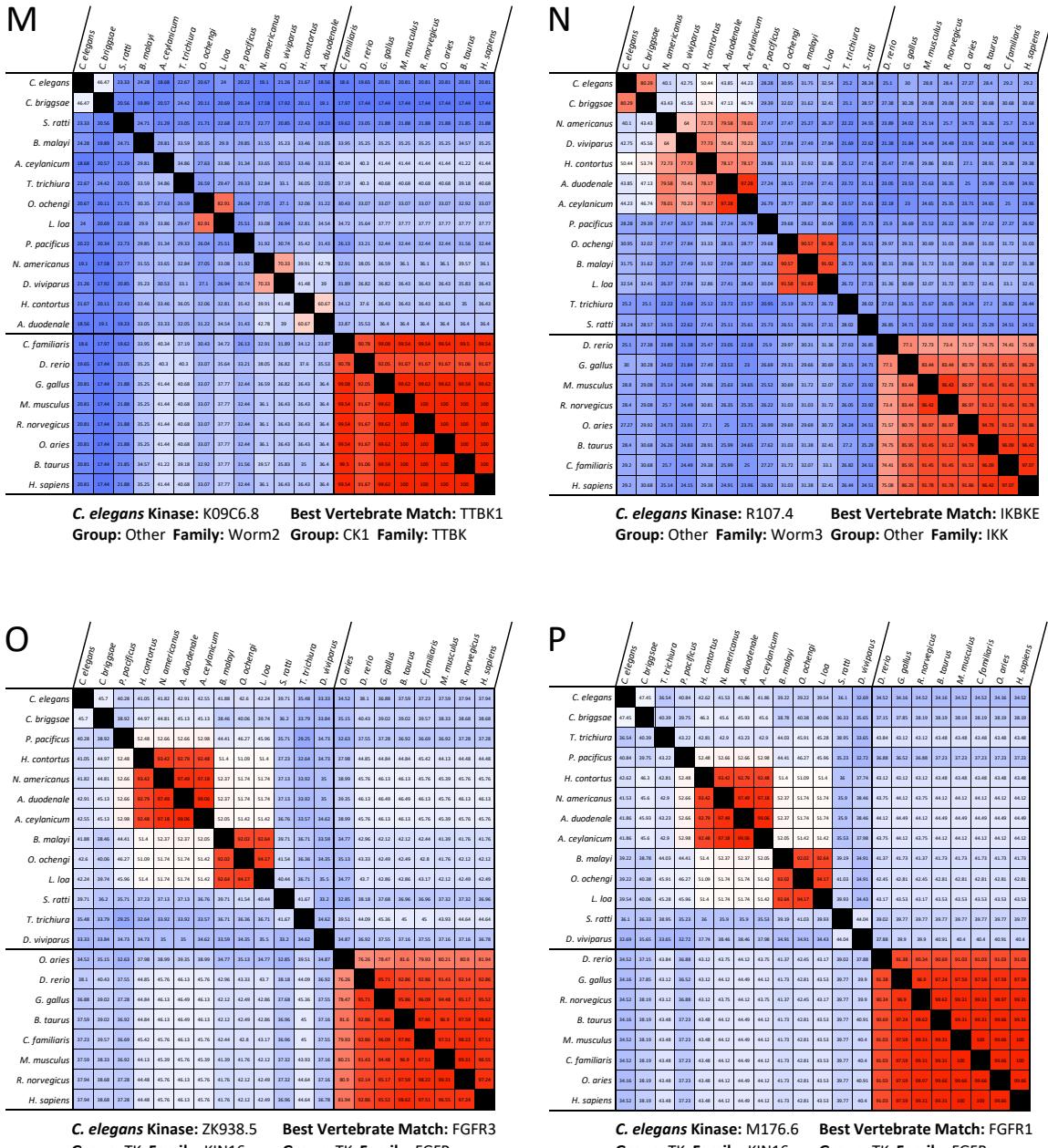
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C. elegans Kinase: K09E4.1 Best Vertebrate Match: CSNK1A1
Group: CK1 Family: Unique Group: CK1 Family: CK1
Subfamily: CK1-A



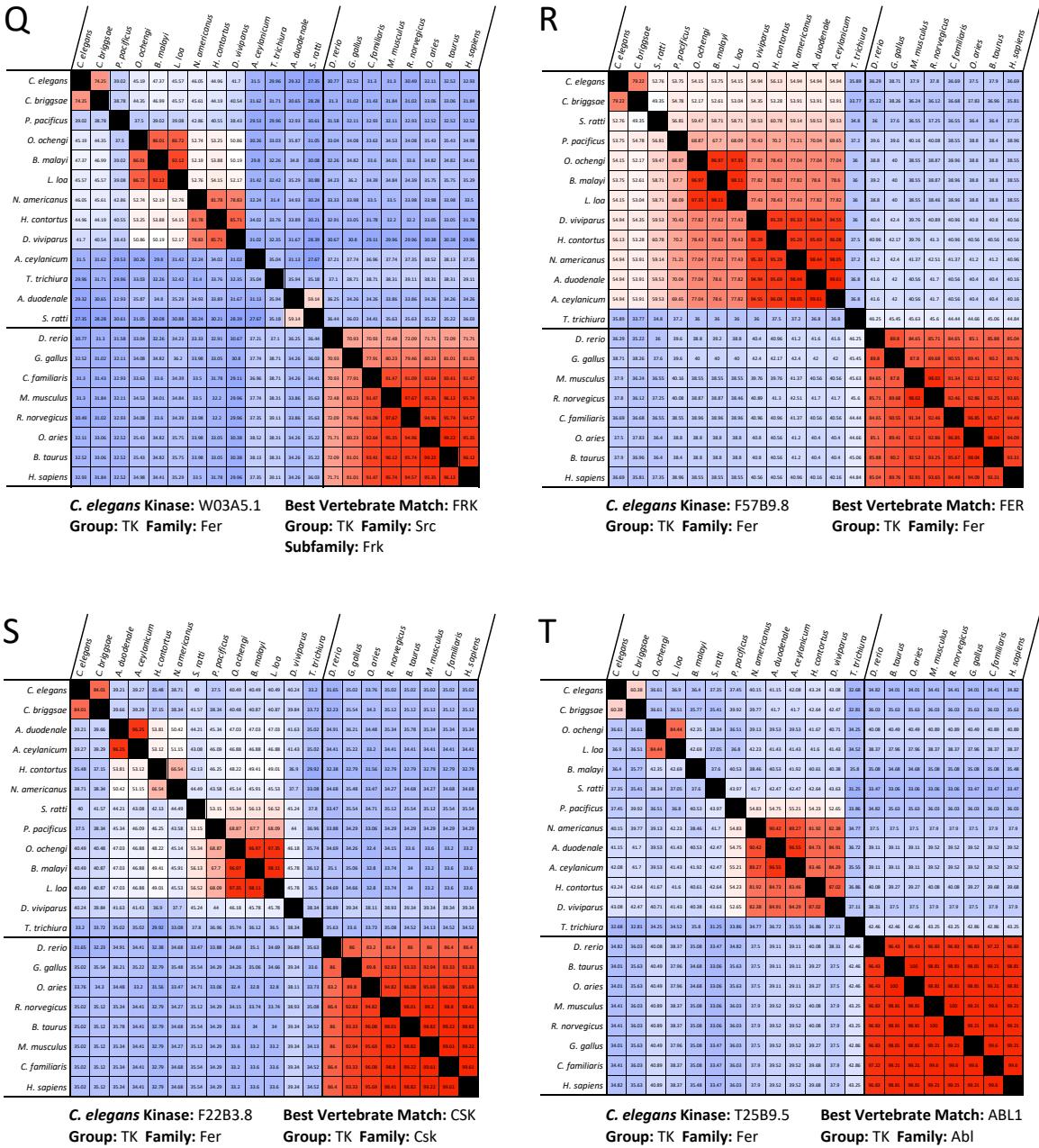
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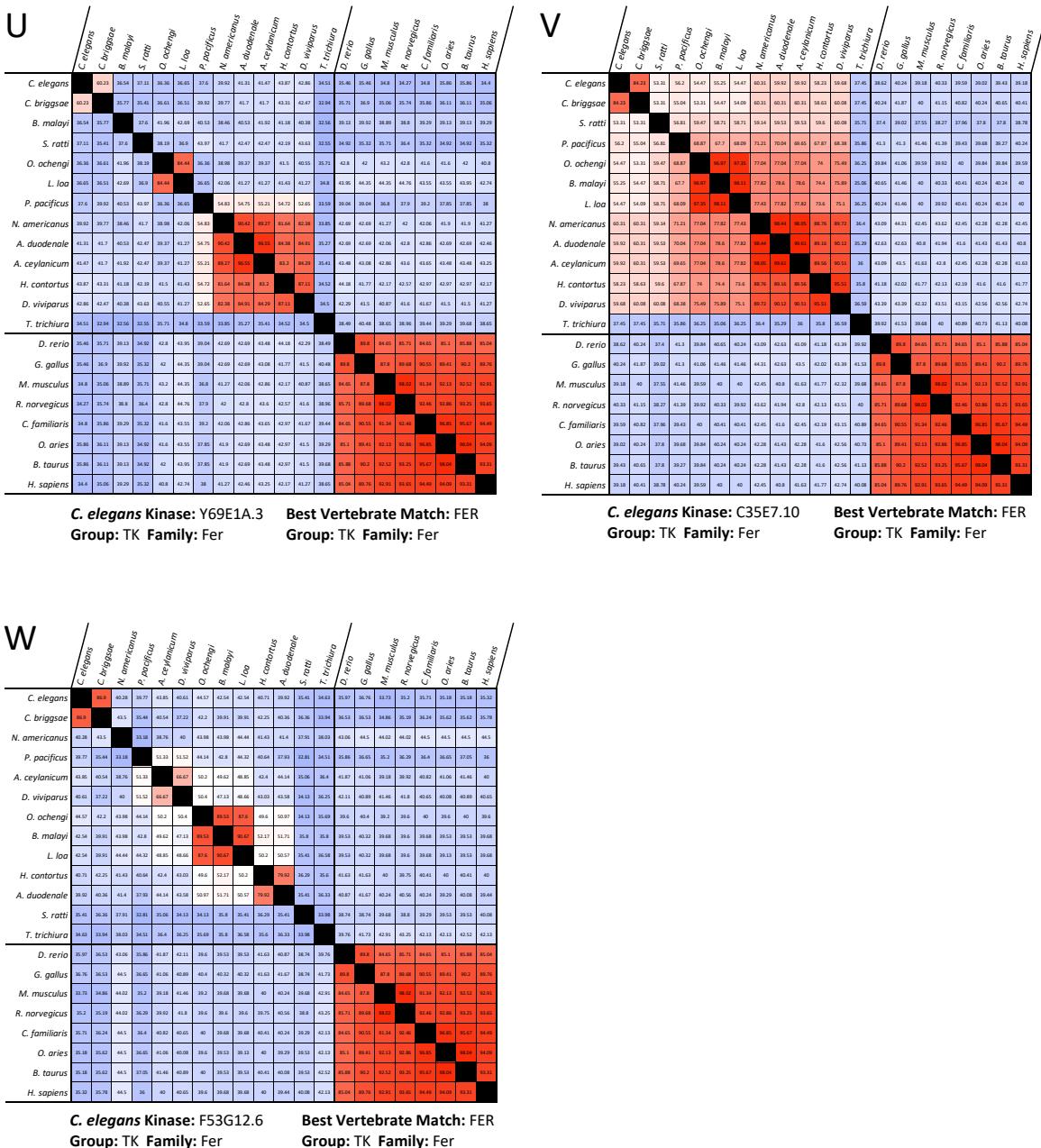
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Sequence % Identity

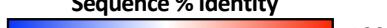
100



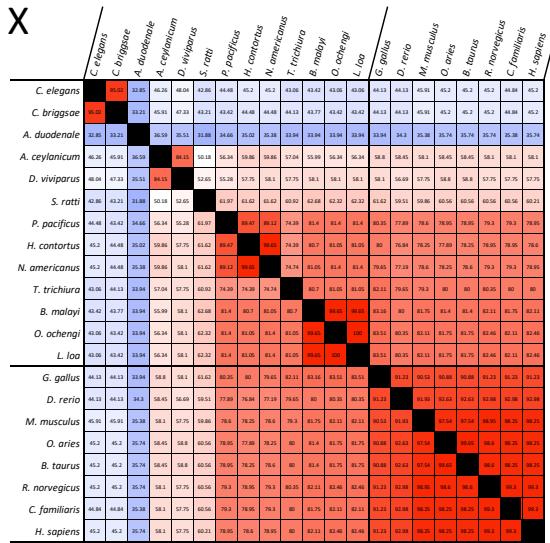
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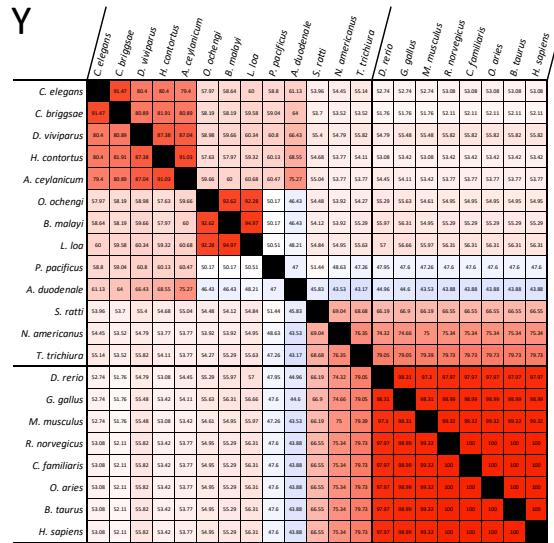
Sequence % Identity

0  100

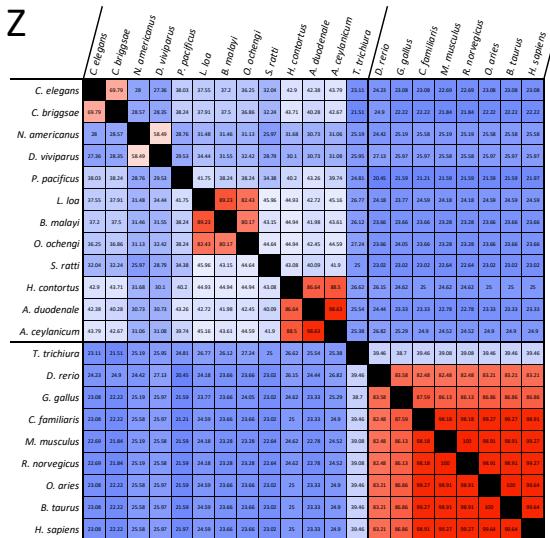
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**C. elegans Kinase: C44H4.6 Best Vertebrate Match: GSK3A
Group: CMGC Family: GSK Group: CMGC Family: GSK**



**C. elegans Kinase: T07A9.3 Best Vertebrate Match: MAPK10
Group: CMGC Family: MAPK Group: CMGC Family: MAPK
Subfamily: JNK Subfamily: JNK**



**C. elegans Kinase: B0240.3 Best Vertebrate Match: NPR2
Group: RGC Family: RGC Group: RGC Family: RGC**

Sequence % Identity



100

Supplementary Figure 4. Conservation of essential nematode-specific kinases across species. Matrices show the percent sequence identity between the kinase domain of the *C. elegans* essential nematode-specific kinase and that of the most similar kinase found across nematode species along with the kinase domain sequence of the best human kinase match and its ortholog across vertebrate species. *C. elegans* kinases from nematode-specific families (A-P) and nematode-expanded families (Q-Z) are shown. Sequence identity matrices for the kinase domain of the well-conserved kinases MEK1/MEK-2, PLK1/PLK-1 and EGFR/LET-23 are included for comparison (AA-AC). Kinase sequences were identified using NCBI BLASTP. Percent identity matrices were generated using Clustal Omega.

