Uniprot Activity 2

- What is the function of Src tyrosine kinases?

  As name already hints at, it is a tyrosine kinase, so it transfers Pi to tyrosine residues and thereby activating the latter protein. It is situated in the membrane of the cell and plays a crucial role in the growth signaling pathway. (Therefore also for cancer)

- Is there only one Src tyrosine kinase? What are some others?

  Only one **Src** tyrosine kinase, but a large variety of very similar tyrosine kinases. (which can even compensate for experimental src knock-out!)

- What is special about v-Src? How does it differ from c-Src?

  viral-Src is a protein that ressembles the "normal cellular-Src". The problem is, that v-Src is constitutively active and as a consequence also growth signaling, which leads to cancer formation over time…

- What is the purpose of most drug design studies against Src?
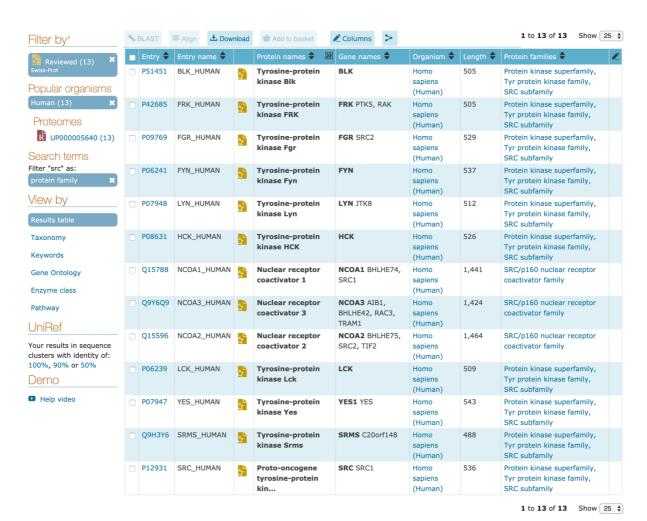
  Block constitutively form of src.

Go to the Abl kinase entry in the PDB by clicking on 1opl link in the molecule of the month page or search for the PDB ID 1OPL in PDB.

Clicking on "search on pubmed" will take you to the primary citation link for Abl kinase structure in PUBMED. What is the name of the article?

- Structural basis for the autoinhibition of c-Abl tyrosine kinase.

Now let's examine Src kinase family of proteins .Abl kinase is a Src kinase. Search for reviewed, human Src kinases with Src as the protein family filter.
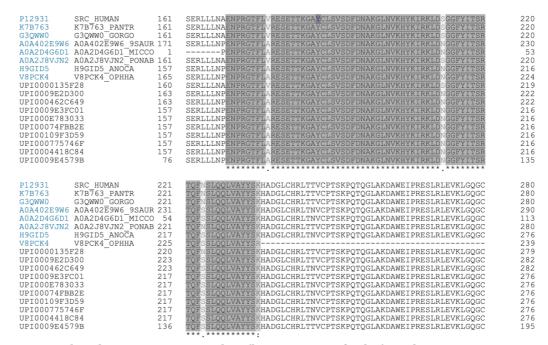
	Entry	Entry name		Protein names	Gene names	Organism	Length	Protein families
	P51451	BLK_HUMAN		Tyrosine-protein kinase Blk	BLK	Homo sapiens (Human)	505	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P42685	FRK_HUMAN		Tyrosine-protein kinase FRK	FRK PTK5, RAK	Homo sapiens (Human)	505	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P09769	FGR_HUMAN		Tyrosine-protein kinase Fgr	FGR SRC2	Homo sapiens (Human)	529	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P06241	FYN_HUMAN		Tyrosine-protein kinase Fyn	FYN	Homo sapiens (Human)	537	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P07948	LYN_HUMAN		Tyrosine-protein kinase Lyn	LYN JTK8	Homo sapiens (Human)	512	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P08631	HCK_HUMAN		Tyrosine-protein kinase HCK	HCK	Homo sapiens (Human)	526	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	Q15788	NCOA1_HUMAN		Nuclear receptor coactivator 1	NCOA1 BHLHE74, SRC1	Homo sapiens (Human)	1,441	SRC/p160 nuclear receptor coactivator family
	Q9Y6Q9	NCOA3_HUMAN		Nuclear receptor coactivator 3	NCOA3 AIB1, BHLHE42, RAC3, TRAM1	Homo sapiens (Human)	1,424	SRC/p160 nuclear receptor coactivator family
	Q15596	NCOA2_HUMAN		Nuclear receptor coactivator 2	NCOA2 BHLHE75, SRC2, TIF2	Homo sapiens (Human)	1,464	SRC/p160 nuclear receptor coactivator family
	P06239	LCK_HUMAN		Tyrosine-protein kinase Lck	LCK	Homo sapiens (Human)	509	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P07947	YES_HUMAN		Tyrosine-protein kinase Yes	YES1 YES	Homo sapiens (Human)	543	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	Q9H3Y6	SRMS_HUMAN		Tyrosine-protein kinase Srms	SRMS C20orf148	Homo sapiens (Human)	488	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily
	P12931	SRC_HUMAN		Proto-oncogene tyrosine-protein kin...	SRC SRC1	Homo sapiens (Human)	536	Protein kinase superfamily, Tyr protein kinase family, SRC subfamily

1 to 13 of 13   Show 25

- How many proteins are there?
  - How many human Src kinases? **13**
  - How many Uniref100: **4** (with SRC_Human itself) belonging to cluster with ID UniRef100_P12931
  - Uniref90? **18** (also counting SRC_Human itself) proteins belong to the **cluster with ID: UniRef90_P12931**
  - What are these? Uniref100 combines identical sequences and fragments with 11 or more residues into a single UniRef entry, while UniRef90 in

turn is built from UniRef100 sequences by clustering them so that each cluster itself then has 90% identity within its cluster.
- Select all and align.
- Can you identify any residues/regions that are highly conserved? (hint: motif) (hint: symbols underneath the alignment) (hint: look for a triplet)

In grey

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P12931        SRC_HUMAN          161  SERLLLNAENPRGTFLVRESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDSGGFYITSR  220
K7B763        K7B763_PANTR       161  SERLLLNAENPRGTFLVRESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDSGGFYITSR  220
G3QWW0        G3QWW0_GORGO       161  SERLLLNAENPRGTFLVRESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDSGGFYITSR  220
A0A402E9W6    A0A402E9W6_9SAUR   171  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  230
A0A2D4G6D1    A0A2D4G6D1_MICCO     1  -------PENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR   53
A0A2J8VJN2    A0A2J8VJN2_PONAB   161  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  220
H9GID5        H9GID5_ANOCA       157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
V8PCK4        V8PCK4_OPHHA       165  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  224
UPI0000135F28                    160  SERLLLNAENPRGTFLVRESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDSGGFYITSR  219
UPI0009E2D300                    163  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  222
UPI000462C649                    163  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  222
UPI0009E3FC01                    157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
UPI000E783033                    157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
UPI00074FBB2E                    157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
UPI00109F3D59                    157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
UPI000775746F                    157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
UPI0004418C84                    157  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  216
UPI0009E4579B                     76  SERLLLNPENPRGTFLARESETTKGAYCLSVSDFDNAKGLNVKHYKIRKLDNGGFYITSR  135
                                      ******** .*****************************************.********

P12931        SRC_HUMAN          221  TQFNSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  280
K7B763        K7B763_PANTR       221  TQFNSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  280
G3QWW0        G3QWW0_GORGO       221  TQFNSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  280
A0A402E9W6    A0A402E9W6_9SAUR   231  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  290
A0A2D4G6D1    A0A2D4G6D1_MICCO    54  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  113
A0A2J8VJN2    A0A2J8VJN2_PONAB   221  TQFNSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  280
H9GID5        H9GID5_ANOCA       217  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
V8PCK4        V8PCK4_OPHHA       225  TQFSSLQQLVAYYSR---------------------------------------------  239
UPI0000135F28                    220  TQFNSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  279
UPI0009E2D300                    223  TQFSSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  282
UPI000462C649                    223  TQFSSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  282
UPI0009E3FC01                    217  TQFSSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
UPI000E783033                    217  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
UPI00074FBB2E                    217  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
UPI00109F3D59                    217  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
UPI000775746F                    217  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
UPI0004418C84                    217  TQFSSLQQLVAYYSKHADGLCHRLTNVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  276
UPI0009E4579B                    136  TQFSSLQQLVAYYSKHADGLCHRLTTVCPTSKPQTQGLAKDAWEIPRESLRLEVKLGQGC  195
                                      ***.***********:
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- How conserved is the active site residue (how can you find it)? What is it?

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P12931        SRC_HUMAN          337  -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  395
K7B763        K7B763_PANTR       337  -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  395
G3QWW0        G3QWW0_GORGO       337  -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  395
A0A402E9W6    A0A402E9W6_9SAUR   348  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  405
A0A2D4G6D1    A0A2D4G6D1_MICCO   116  ------------------------------------------------------------  115
A0A2J8VJN2    A0A2J8VJN2_PONAB   337  -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  395
H9GID5        H9GID5_ANOCA       334  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  391
V8PCK4        V8PCK4_OPHHA       293  CEFLTTICSLVGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  352
UPI0000135F28                    336  -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  394
UPI0009E2D300                    340  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  397
UPI000462C649                    340  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  397
UPI0009E3FC01                    334  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  391
UPI000E783033                    334  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  391
UPI00074FBB2E                    334  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  391
UPI00109F3D59                    334  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  391
UPI000775746F                    320  --FLTTFYSTVGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  377
UPI0004418C84                    334  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  391
UPI0009E4579B                    253  --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI  310
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In red. It is only one amino acid (D= aspartic acid), thus negative charge. It is conserved across all other cluster-proteins

- Are there any variants around the active site residue?

The red dot at position 389 is the active site. There is a missense R > W variant right next to it (position 388) with probably damaging consequences. The change of the basic positively charged Arginine to a aromatic, neutrally charged Tryptophan could have an impact on the structure of the src kinase and due to its proximity to the active site also on that! On the whole there are other 4 variants within 4 residues.

kinase. For a Uniprot entry, there may be several PDB structures associated with it. Look under the column Positions. Pick the PDB ID with the maximum coverage (coverage refers to fraction of residues for which there is structural data with respect to the whole sequence length).

What is the PDB ID for this structure?

1A07

Visualize the structure within UniProt to obtain a view similar to that in the Abl kinase paper. Are there any red dots? What are they?