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?

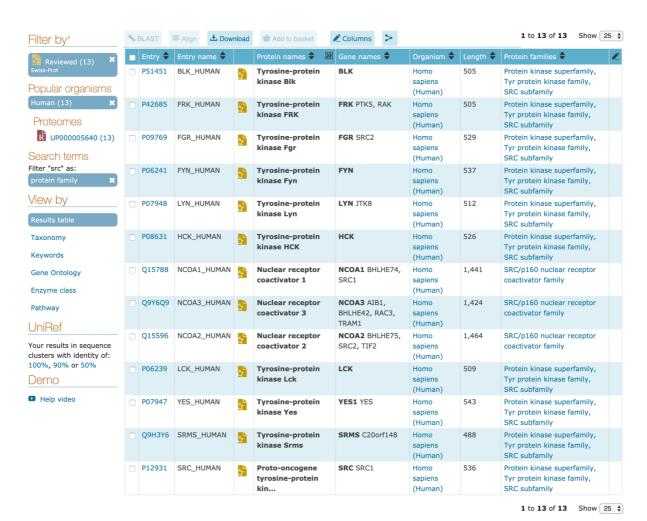
Block constitutively form of src.

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 10PL 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.

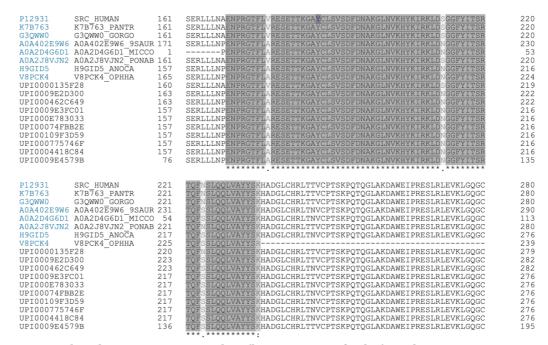


- How many proteins are there?
 - How many human Src kinases? 13
 - How many Uniref100: 4 (with SRC_Human itself) belonging to cluster with ID UniRef100_P12931
 - Uniref90? 18 (also counting SRC_Human itself) proteins belong to the cluster with ID: UniRef90_P12931
 - What are these? Uniref100 combines 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



How conserved is the active site residue (how can you find it)? What is it?

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SRC_HUMAN
K7B763_PANTR
G3QWW0_GORGO
                                                                 ·IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHR<mark>D</mark>LRAANI
K7B763
                                                    337
                                                               -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
                                                                                                                                                                                                395
G30WW0
                                                     337
                                                               -IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
--YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
                                                                                                                                                                                                395
G3QWW0 G3AG0

A0A402E9W6 A0A402E9W6 9SAUR 348

A0A2D4G6D1 A0A2D4G6D1 MICCO 116

A0A2J8VJN2 A0A2J8VJN2 PONAB 337
                                                                -IYIVTEYMSKGSLLDFLKGETGKYLRLPOLVDMAAOIASGMAYVERMNYVHRDLRAANI
                                                                                                                                                                                                395
                    H9GID5_ANOCA
V8PCK4_OPHHA
                                                               --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAQIASGMAYVERNNYVHRDLRANI
CEFLTTICSLVGSLLDFLKGEMGKYLRLPQLVDMAQIASGMAYVERNNYVHRDLRANI
-IYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAQIASGMAYVERMNYVHRDLRANI
                                                     334
                                                                                                                                                                                                391
V8PCK4 V8
UPI0000135F28
                                                                                                                                                                                                352
394
UPI0009E2D300
                                                    340
                                                               --YIVTEYMCKGSLLDFLKGEMGKYLRLPOLVDMAAOIASGMAYVERMNYVHRDLRAANI
                                                                                                                                                                                                397
                                                               --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAQIASGMAYVERNNYVHRDLRANI
--YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAQIASGMAYVERNNYVHRDLRANI
--YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAQIASGMAYVERMNYVHRDLRANI
UPI000462C649
UPI0009E3FC01
                                                                                                                                                                                                397
UPI000E783033
                                                     334
                                                                                                                                                                                                391
                                                               --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
--YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
--FLTTFYSTVGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
UPI00074FBB2E
                                                     334
                                                                                                                                                                                                391
UPI00109F3D59
UPI000775746F
                                                               --YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
--YIVTEYMCKGSLLDFLKGEMGKYLRLPQLVDMAAQIASGMAYVERMNYVHRDLRAANI
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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



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. $\underline{\text{https://www.sciencedirect.com/science/article/pii/S0092867403001946?via\%3Dihub}}$

Are there any red dots? What are they? Phosphate Groups

