Target: MCL1

PDB ID: 4HW3

Description of the MCL1 target

Discovery of Potent Myeloid Cell Leukemia 1 (Mcl-1) Inhibitors Using Fragment-Based Methods and Structure-Based Design

Myeloid cell leukemia 1 (MCL1) is a protein that is overexpressed in many types of cancer. MCL1 promotes the survival of tumor cells and results in these cells avoiding apoptosis. Targeting MCL1 with inhibitors could therefore lead to potential treatments for a variety of cancer types.

In recent years many MCL1 inhibitors have been developed. Some MCL1 inhibitors are in clinical trials, whereas others are already being used at the current time. Examples are: Maritoclax, VU661013, AZD5991, S63845, Motixafortide, (R)-(-)-Gossypol acetic acid, Sabutoclax, TW-37 and Gambogic acid.

The MCL1 protein is ecoded by the MCL1 gene. The protein is part of the Bcl-2 family. The Bcl-2 family is important in the regulation of apoptosis at the mitochondrion. MCL1 has two isoforms that are created through alternative splicing. Isoform 1 enhances cell survival by inhibiting apoptosis and isoform 2 promotes cell death by promoting apoptosis. MCL1 is a very important protein in the Bcl-2 family, since the loss of MCL1 gene has shown to result in embryonic death. Research has indicated that MCL1 interacts with: BAK1, BCL2L11, BID, BAD, DAD1, PMAIP1, PCNA, TCTP, and TNKS.

Isoform 1:

UNIPROT ID: Q07820

Sequence length: 350

Sequence:MFGLKRNAVIGLNLYCGGAGLGAGSGGATRPGGRLLATEKEASARREIGGGEAGAVIGGSAGASPPSTLTPDSRRVARPPPIGAEVPDVTATPARLLFFAPTRRAAPLEEMEAPAADAIMSPEEELDGYEPEPLGKRPAVLPLLELVGESGNNTSTDGSLPSTPPPAEEEEDELYRQSLEIISRYLREQATGAKDTKPMGRSGATSRKALETLRRVGDGVQRNHETAFQGMLRKLDIKNEDDVKSLSRVMIHVFSDGVTNWGRIVTLISFGAFVAKHLKTINQESCIEPLAESITDVLVRTKRDWLVKQRGWDGFVEFFHVEDLEGGIRNVLLAFAGVAGVGAGLAYLIR

Mass: 37,337 Da

Using BLAST to find identical proteins in other species:

Length: 350 AA

Identity: 22.1 - 100

Species: Human, Zebrafish, Rat, Bovine, Mouse

Main Accession: Q07820. Secondary accessions: B2R6B2, D3DV03, D3DV04, Q9HD91, Q9NRQ3

Most similar in other species are 3 proteins matching at 99.7%:

1: MCL1: A0A2R9BYH6 in Pan paniscus (Pygmy chimpanzee)(Bonobo) with 350 AA

2: CK820\_G0046961: A0A6D2X745 in Pan troglodytes (chimpanzee) with 350 AA

3: MCL1: K7D0E2 in Pan troglodytes (chimpanzee) with 350 AA

These 3 are the same entry but 3 potential isoforms. For each isoform:

Status:

unreviewed

Mass (Da):

37278 Da

Most similar in Homo Sapiens:

cDNA FLJ54274

Length:

279 AA

Accession number:

B4DU51

Mass (Da):

30205 Da

Questions (1):

- Which target is more similar compared to the original target?

MCL1 and CK820 that are found in other species are more similar to human MCL1 compared to the most similar protein in humans

- Did you expect this?

We did expect to find a more similar protein in a similar organism because the proteins between organisms are often very closely related to eachother as was also indicated by the lectures of this course

![image.png](attachment:image.png)

![image-2.png](attachment:image-2.png)

![image-3.png](attachment:image-3.png)

![image-4.png](attachment:image-4.png)

![image-5.png](attachment:image-5.png)

Q07820 is more similar to A0A2R9BYH6

In case of structure similartity: 4HW3 is most similar to 4HW2

![image-6.png](attachment:image-6.png)

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