Designing potent inhibitors of human P38γ for effective breast cancer therapy

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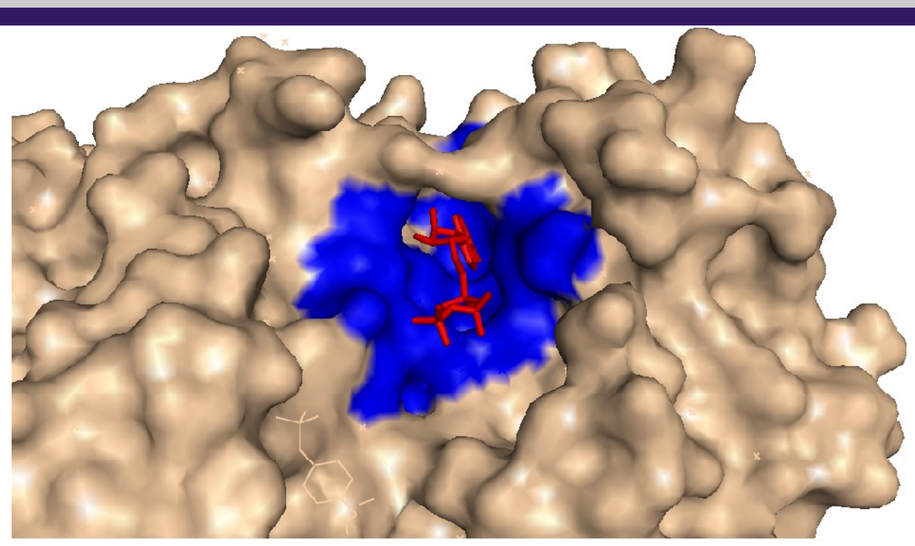
Key points:

- Oncogenic constitutive enzyme human p38γ is a serine/threonine protein kinase, activated through phosphorylation by environmental stress and pro-inflammatory cytokines responses (Lechner *et al*., 1996). Over expression of the protein leads to formation of tumerogenesis effectors.
- Human p38γ protein is highly expressed in several human malignant cell lines (Wang *et al.,* 2000; Pillaire *et al.,* 2000), indicating its possible role in tumerogenesis. Human p38γ specifically integrates their antagonistic activity to stimulate cell invasion. Human p38γ over expression increases invasion that is the spread of malignant cells to new sites of the body in ER+ and higher levels in ER^- breast cancer cells (Qi *et al.,* 2006).
- Computational method for drug designing was practiced here to explore lead molecules targeting

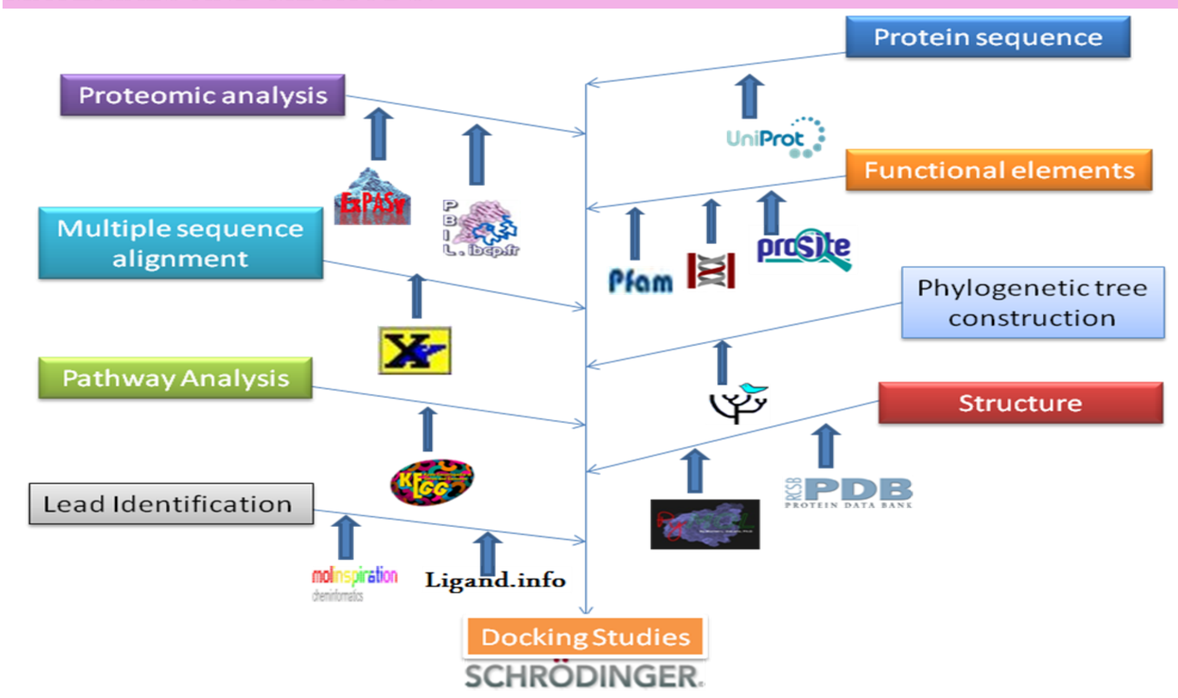


P38γ-ANP complex
Active sites : LYS56,PRO110, MET112, ASP115, GLY157, ASN158, ASP171, W2111, W2039 and W2152

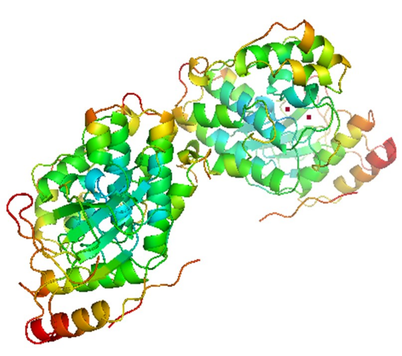
X-ray crystallography Structure visualized Through PyMol.

Figure d: X-Ray Crystallography Structure of 1CM8 (surface display, active site residues are coloured and ANP ligand stick display) visualized through pymol.

MATERIALS AND METHODS:



RESULTS AND DISCUSSION:



Symbol : MAPK12
Alt. symbol : SAPK3
Uniprot : P53778
OMIM : 602399
Structure : X-Ray diffraction
Resolution : 2.40 Å
R-Value : 0.232 (work)
R-Free : 0.283
Locus : Chr.22 q 13.33
Orientation : minus strand
Gene wt : 9536s
Length : 367 AA
MW : 41940 da
Co-factor : Two Mg ions
E.C : 2.7.11.24

```
MSSPPPARSGFYRQEVTKTAWEVRAVYRDLQPVGSGAYGAVCSAVDGRTGAKVAIKKLYRPFQSELFAKR
cccccccttceehhhccchheechhhccccccccccceeeeehhctttcchheehhhhhhhhhhhhhhhh
AYRELRLLKHMRHENVIGLLDVFTPDETLDDFTDFYLVMPFMGTDLGKLMKHEKLGEDRIQFLVYQMLKG
hhhhhhhhhhccccchheeeeeccccccccccchheeehhhhhhhhhhhhhhcccchhhhhhhhhhhhhh
LRYIHAAGIIHRDLKPGNLAVNEDCELKILDFGLARQADSEMTGYVVTRWYRAPEVILNWMRYTQTVDIW
hhhhcctheecttcttcteeeettcceeeehhccccccchhhhhhhhhhcccctheeeehccccchhhhh
SVGCIMAEMITGKTLFKGSDHLDQLKEIMKVTGTPPAEFVQRLQSDEAKNYMKGLPELEKKDFASILTNA
hhhhhhhhhhttccccccccchhhhhhhhhecccccchhhhhhhhhhhhhhhhhcccccccchhhhcccc
SPLAVNLLEKMLVLDAEQRVTAGEALAHPYFESLHDTEDEPQVQKYDDSFDDVDRTLDEWKRVTYKEVLS
ccchhhhhhhhhecctttcceehhhhhhhhhhhhcccccccccccccccchhhhhhhhhhhhhhhhhhh
FKPPRQLGARVSKETPL
hhhhhhhhhhcttcccce
```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>sp|P53778|MK12_HUMAN Mitogen-activated protein kinase 12 OS=Homo sapiens GN=MAPK12 PE=1 SV=3
MSSPPPARSGFYRQEVTKTAWEVRAVYRDLQPVGSGAYGAVCSAVDGRTGAKVAIKKLYR
PFQSELFAKRAYRELRLLKHMRHENVIGLLDVFTPDETLDDFTDFYLVMPFMGTDLGKLM
KHEKLGEDRIQFLVYQMLKGLRYIHAAGIIHRDLKPGNLAVNEDCELKILDFGLARQADS
EMTGYVVTRWYRAPEVILNWMRYTQTVDIWSVGCIMAEMITGKTLFKGSDHLDQLKEIMK
VTGTPPAEFVQRLQSDEAKNYMKGLPELEKKDFASILTNASPLAVNLLEKMLVLDAEQRV
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VSKETPL
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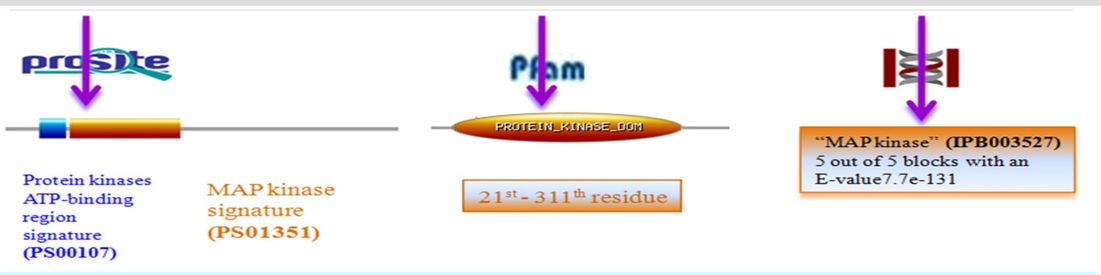
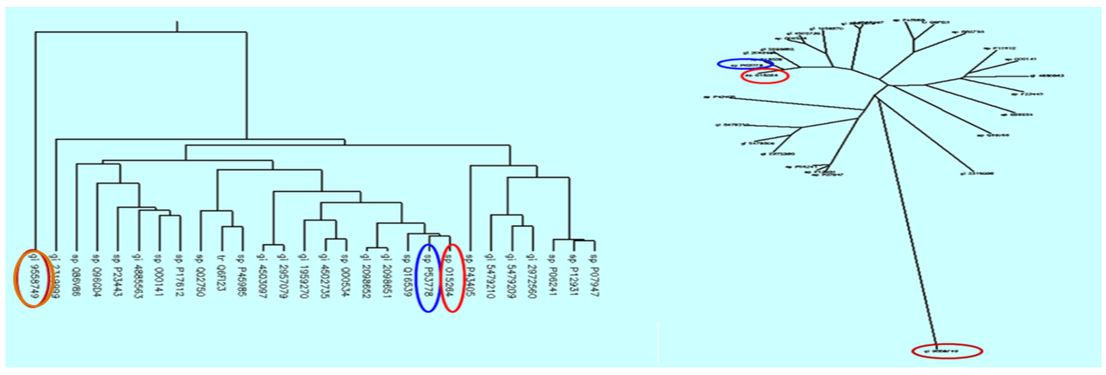




- Rooted tree and Un-rooted tree was constructed by using the UPGMA algorithm of distance based method respectively. Mitogen-activated protein kinase 13 (P38δ) is closely related and Eukaryotic elongation factor 2 kinase (EEF2K) is distantly related respectively to human p38γ protein.

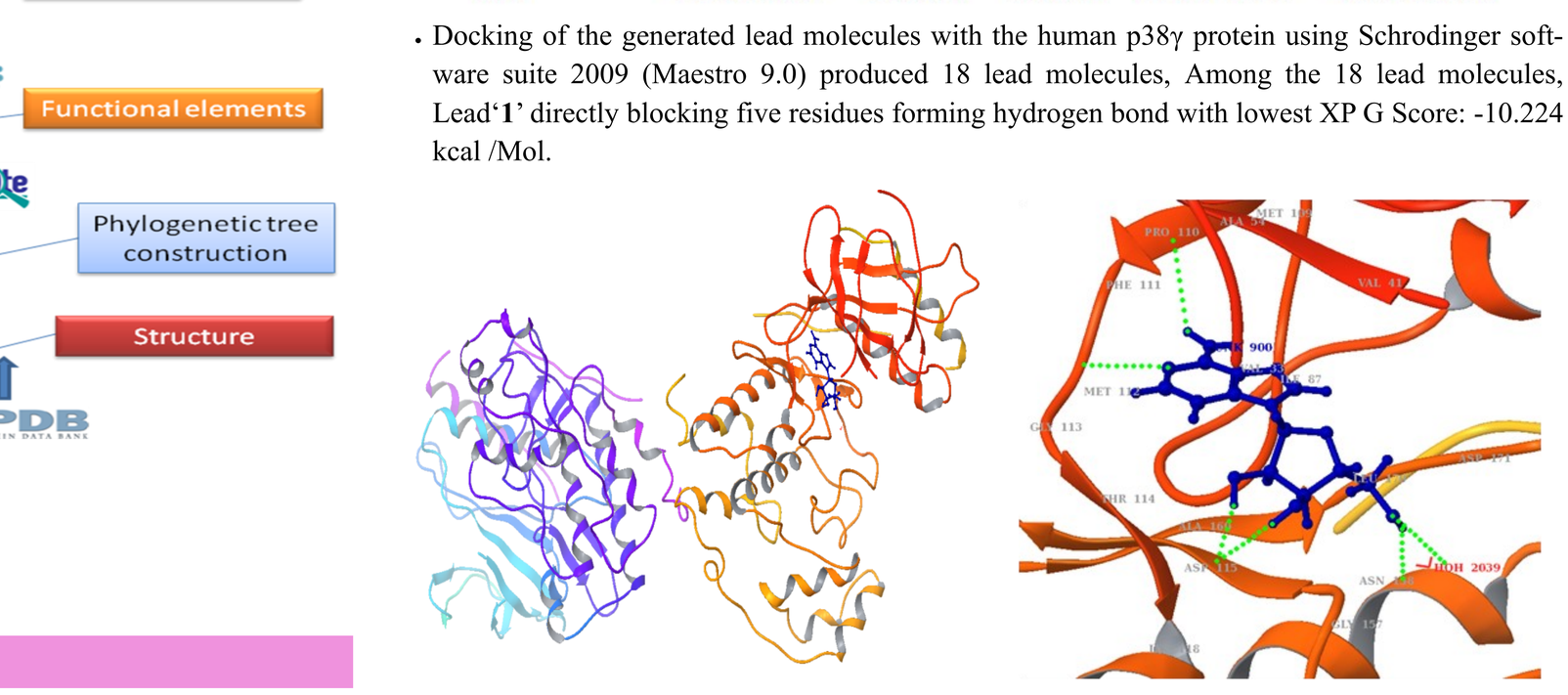
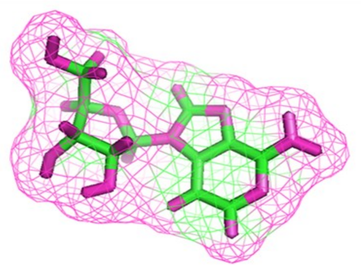


Figure e: Representing the hydrogen bonds of lead '1' with the human p38γ protein.

Analysis of binding orientations of the docking complex revealed that four amino acid residues Pro110, Met112, Asp115 (two Hydrogen bonds), Asn158 and W2039 of active site were directly involved in formation of hydrogen bond network for human p38γ protein functional activity inhibition with Lead '1' that complements well with previous crystallographic reports of human p38γ –ANP inhibitor complex.

3-DEAZA-ADENOSINE (Lead '1') was involved in good van der Waal interaction with Lys56 that is highly important for ATP binding and subsequent activation of human p38γ.



Lead '1'
MOL. WEIGHT : 266.26
Docking Score : -10.224
Docking energy : -72.683

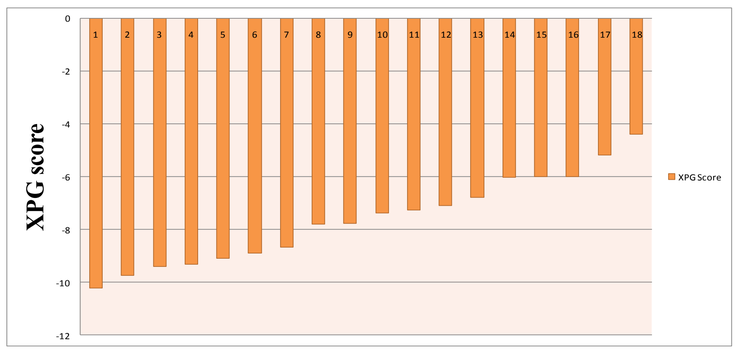


Figure f: Graphical representation of XPG scores

Conclusion:

3-DEAZA-ADENOSINE reports with good docking energy, docking score, stable conformation, orientation and exhibits functional activity inhibition. Thus it might be encouraging for new directions as a drug for human p38γ protein for the novel class treatment of breast cancer.

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