Virtual Screening and Modeling of Phosphoglycerate Mutase 1

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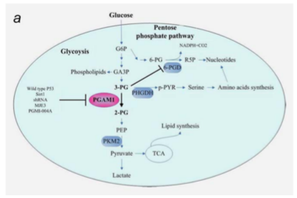
Abstract

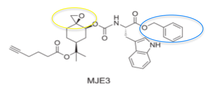
Phosphoglycerate Mutase 1 (PGAM1) is a glycolytic protein upregulated in many types of cancer cells. In a phenomenon called the Warburg Effect, cancer cells have a higher rate of glycolysis than healthy cells. Altering PGAM1 activity can change cancer cell proliferation and thus is an important pharmacological target for cancer suppression. A small molecule, MJE3, inhibits PGAM1 activity and decreases cancer cell proliferation. A binding model of MJE3 to PGAM1 was created using molecular dynamic simulations and protein-ligand dockings. Key interactions were used to create pharmacophore models and perform virtual screenings of purchasable compounds for potential new drug targets of PGAM1 inhibition.

Introduction/Background

PGAM1 converts 3PG to 2PG during glycolysis. 3PG and 2PG are important substrates for metabolic and biosynthetic pathways. Inhibition of PGAM1 increases levels of 3PG and decreases levels of 2PG resulting in inhibition of 6PGD (pentose phosphate pathway). Decreased activity in this metabolic pathway decreases levels of biosynthetic materials important for cancer cells to be able to rapidly divide.

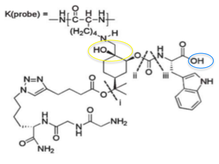


Role of PGAM1 in metabolic pathways (Li and Ren)



MJE3

Unbound State of MJE3 (Sorensen and Cravatt)



Covalently Bound State of MJE3 to Lysine 100 (Sorensen and Cravatt)

MJE3 inhibits PGAM1 by covalently binding to lysine 100 on PGAM1 (circled in yellow). The epoxide bond on MJE3 is broken open by the nitrogen on lysine 100. MJE3 is hydrolyzed in situ of its benzyl ester substituent before binding (circled in blue). Currently there are no crystallized structures of MJE3 bound to PGAM1. A complete model will give us more insight to MJE3's action and lead us to find other drug alternatives. Sorensen and Cravatt have created a docking model, but have not used it to search for other binding agents. We aim to create a model of our own to compare to the Sorensen and Cravatt model while also finding drugs that dock similarly.

We docked MJE3 to PGAM1 to sample conformations and poses that will produce models of binding. Docking software holds the receptor rigid, so molecular dynamics simulations are useful to move the receptor and ligand into more energy efficient and realistic poses. Given a structural model, we performed a virtual screen of available compounds using pharmacophore models. A pharmacophore is a group of features of a compound that show the interactions between other molecules such as hydrogen binding and hydrophobes.

Analogues of MJE3 with alterations in the indole side chain do not effectively label PGAM1. Our docking and pharmacophore models will focus around the epoxide and indole groups, for we know that those are important groups for binding.

Acknowledgements

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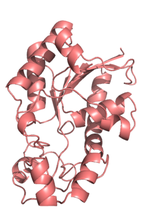
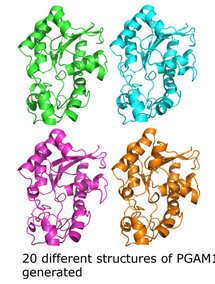
Methods



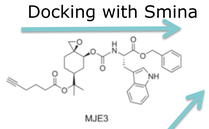
PGAM1 Crystallized Structure – 4GPZ

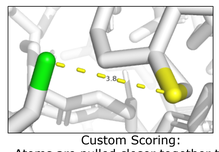
Molecular Dynamics Simulation



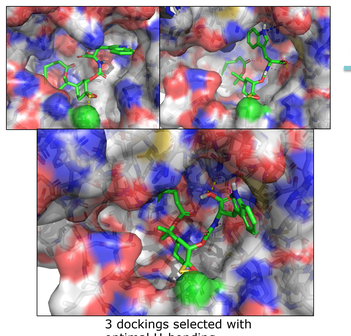
20 different structures of PGAM1 generated

Docking with Smina



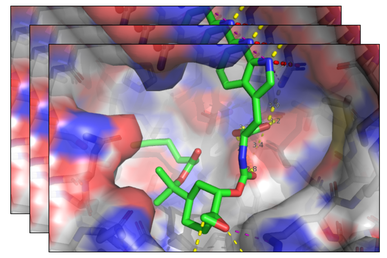


Custom Scoring: Atoms are pulled closer together to simulate covalent binding

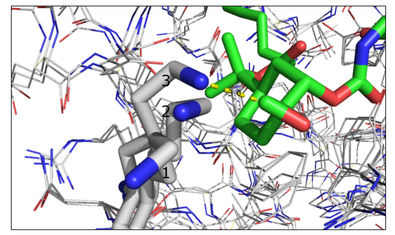


3 dockings selected with optimal H-bonding

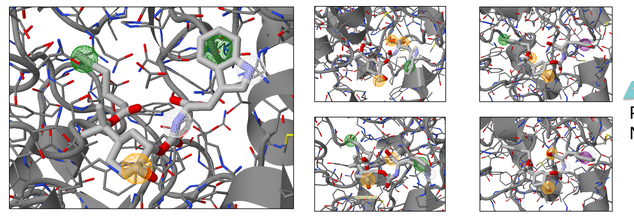
MD



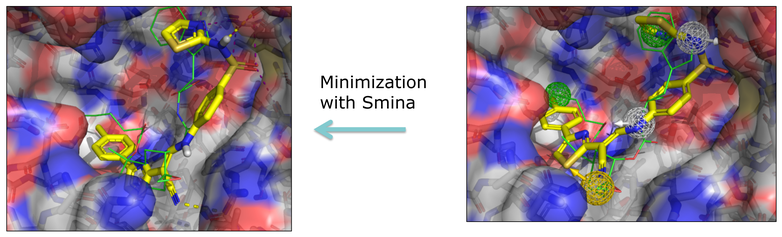
Steered MD



Pharmacophore Models



ZincPharmer Search



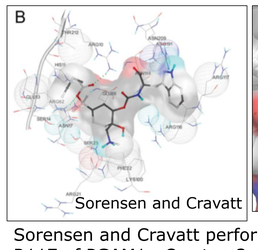
Minimization with Smina

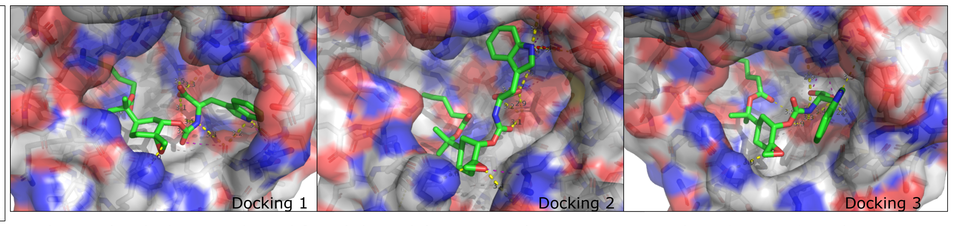
Filtered for minimized affinity < -6 and minimized RMSD < 2

Filtering of Compounds

Seven Compounds Selected for Further Study

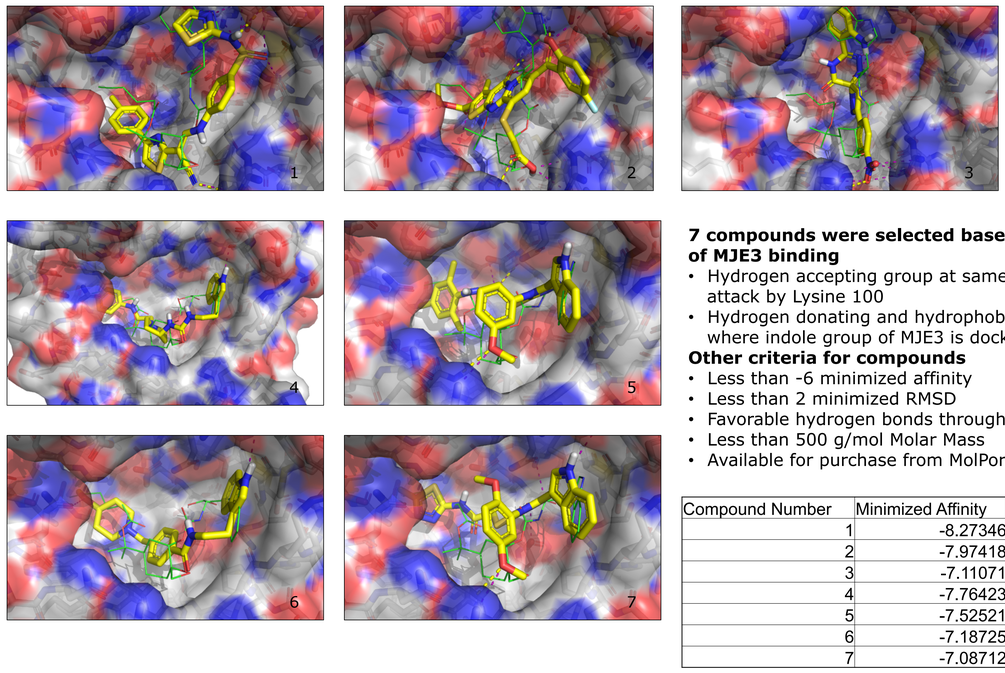
Results - Docking





Sorensen and Cravatt performed a similar docking study and found the indole group to lie near amino acids R191, R116, and R117 of PGAM1. Our top 3 dockings also had the indole group docked near those amino acids, but flipped to different orientations. In our models, the hydrogen on the nitrogen of the indole group made hydrogen bonds with double bonded oxygen on the backbone.

Results – Selected Compounds



7 compounds were selected based on our hypothesis of MJE3 binding

- Hydrogen accepting group at same location as site of attack by Lysine 100
- Hydrogen donating and hydrophobic or aromatic region where indole group of MJE3 is docked

Other criteria for compounds

- Less than -6 minimized affinity
- Less than 2 minimized RMSD
- Favorable hydrogen bonds throughout the compound
- Less than 500 g/mol Molar Mass
- Available for purchase from MolPort

Compound Number	Minimized Affinity	Minimized RMSD
1	-8.27346	1.92313
2	-7.97418	1.77765
3	-7.11071	1.54039
4	-7.76423	1.59627
5	-7.52521	1.35302
6	-7.18725	1.39386
7	-7.08712	1.01424

Conclusions

Using structural and molecular dyamics modeling techniques, we created a model of how MJE3 binds to PGAM1 as well as multiple pharmacophore models to screen for available compounds. We developed a similar docking model as Sorensen and Cravatt, but we were able to add to that model with multiple pharmacophore models. From our models, we selected 7 compounds that we predict to have similar binding characteristics as MJE3 to PGAM1.

Future Directions

The selected compounds will be purchased from MolPort and tested for PGAM1 inhibition.

References

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