RNA: to Modify, or Not to Modify?

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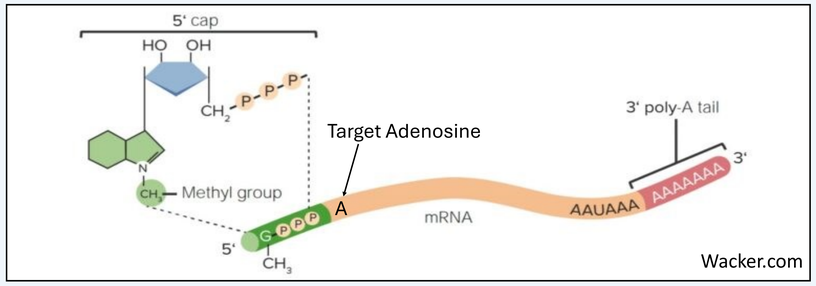
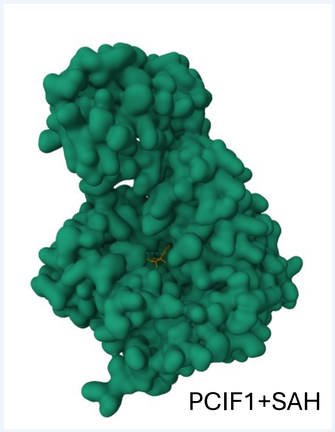
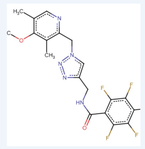
BACKGROUND

- RNA, ribonucleic acids, constitute a class of nucleic acids in charge of a number of cellular functions, from protein synthesis to gene expression.
- Most messenger RNAs are single stranded and unstable. As such, they require specific post-transcriptional modifications such as capping to avoid being digested by the cell. The methylation of nucleic acid bases or sugars is an additional RNA modification.
- PCIF1, phosphorylated CTD interacting factor 1, is a ubiquitous enzyme present in cells.
- PCIF1 transfers a methyl group from SAM (S-adenosylmethionine) to the 6-N atom of the first adenosine base after the 5'-7-methyl-guanosine cap on messenger RNAs, producing SAH (S-adenosylhomocysteine) in the process.
- FTO, an alpha-ketoglutarate-dependent dioxygenase enzyme, does the opposite RNA modifications as PCIF1.

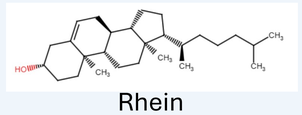




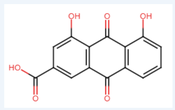
C6

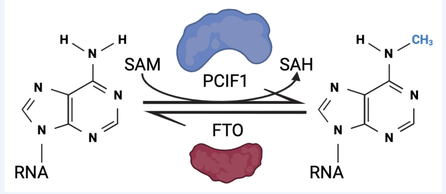


Cholesterol



Rhein





PROBLEM

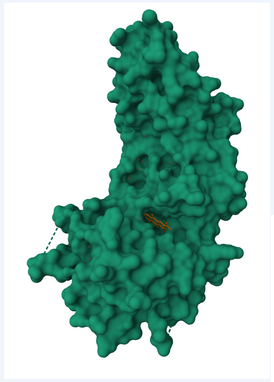
- High PCIF1 presence in cancer patients correlates to lower survival rates.
- Silencing PCIF1 can limit tumor growth and increase resistance to specific cancer therapies.

GOAL: Using in-silico modelling software, we attempt to repurpose existing FTO inhibitors and common chemicals for efficacy as SAH-competitive inhibitors against PCIF1.

METHODOLOGY

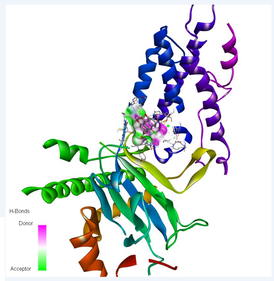
- Protein structures for PCIF1 (6IRW), FTO (3LFM), and FTO bound to specific ligands (5DAB, 4IE7, 6AK4) were pulled from the RCSD PDB database.
- Structures for preclinical FTO inhibitors (58W, Rhein, C6, meclofenamic acid, and entacapone) and common chemicals (cholesterol and caffeine) were pulled from PubChem.
- Seamdock was used to compute molecular docking binding affinities for the inhibitors to FTO and PCIF1.

RESULTS



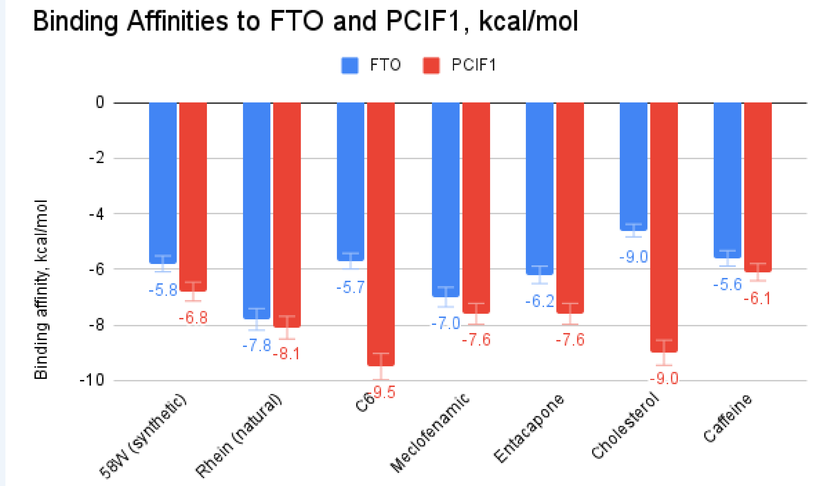
Rhein + FTO crystal

Rhein + FTO docked



Rhein + PCIF1 docked

Images generated using RCSD PDB, Biorender, and Biovia DiscoveryStudio [free edition]



DISCUSSION

- PCIF1 is an enzyme that carries out a critical post-transcriptional modification on RNAs.
- Inhibiting PCIF1 may provide new anti-cancer therapeutic avenues.
- Computer-based molecular docking showed C6, Rhein, and cholesterol as potential potent PCIF1 inhibitors.

CONCLUSION

In silico methods, including molecular docking, can save researchers and companies time and money. Instead of laboriously testing numerous compounds in the lab, molecular docking can help identify inhibitor candidates for further investigation.

FUTURE WORK

- The inhibitors tested here can be further optimized for potency.
- Molecular dynamics simulations allow us to visualize how the binding of an inhibitor to a protein structure impacts its conformation and ability to function.
- *In vitro* and *in vivo* validation of pharmacokinetic properties is always warranted for any *in silico* study.