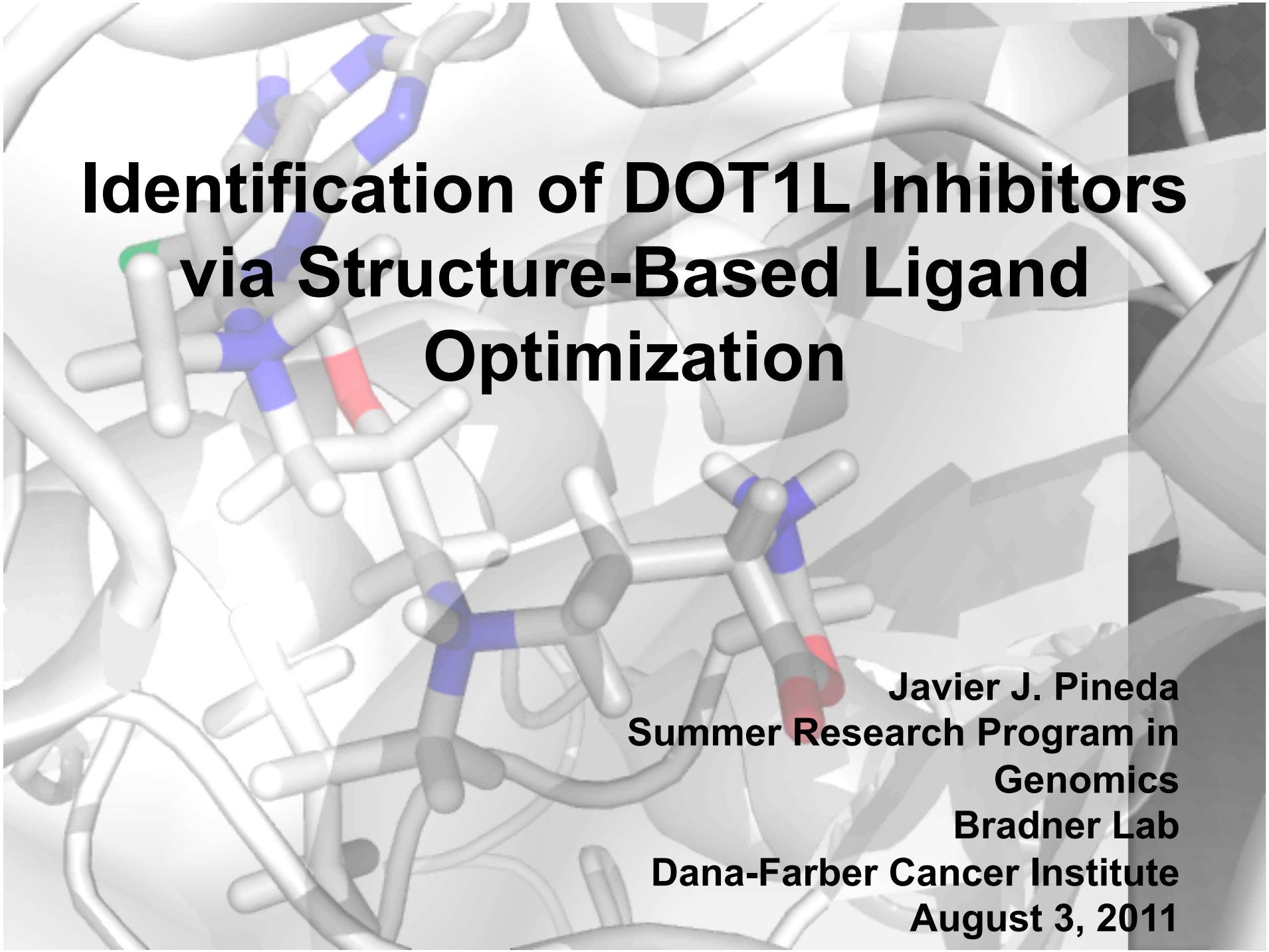

Identification of DOT1L Inhibitors via Structure-Based Ligand Optimization

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Summer Research Program in Genomics
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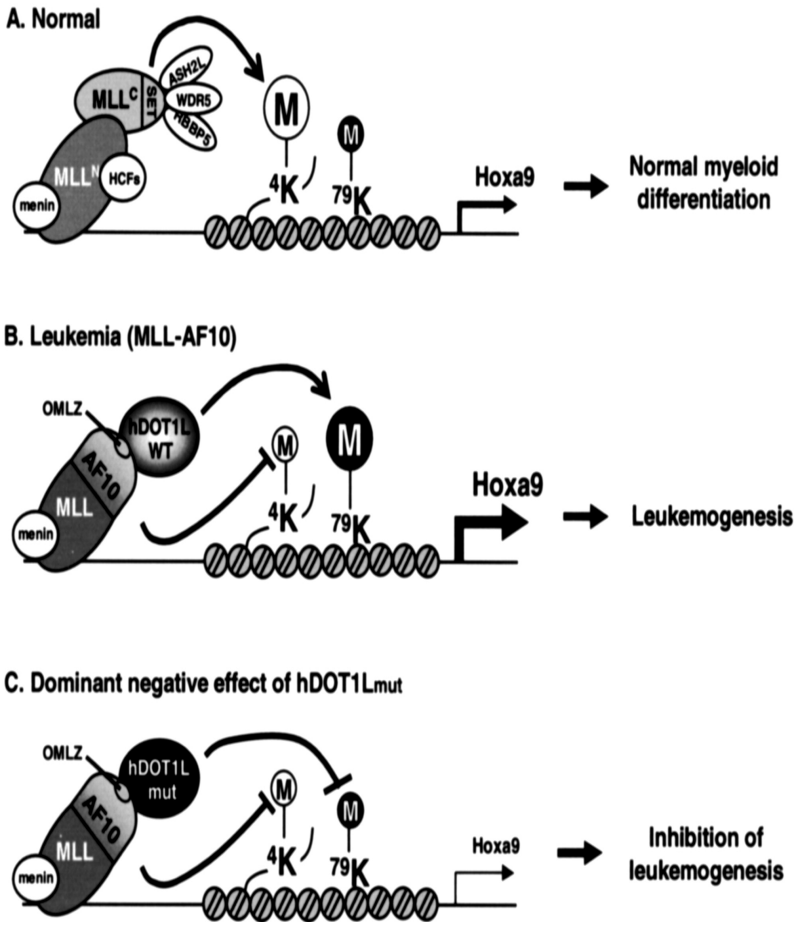
August 3, 2011

METHYLTRANSFERASES

- Enzymes that methylate Lys or Arg on histone proteins or DNA bases
- Non-genetic post-translational modification
- Alter histone structure and gene expression
- DOT1L is one of 52 known lysine methyltransferases (KMTs)

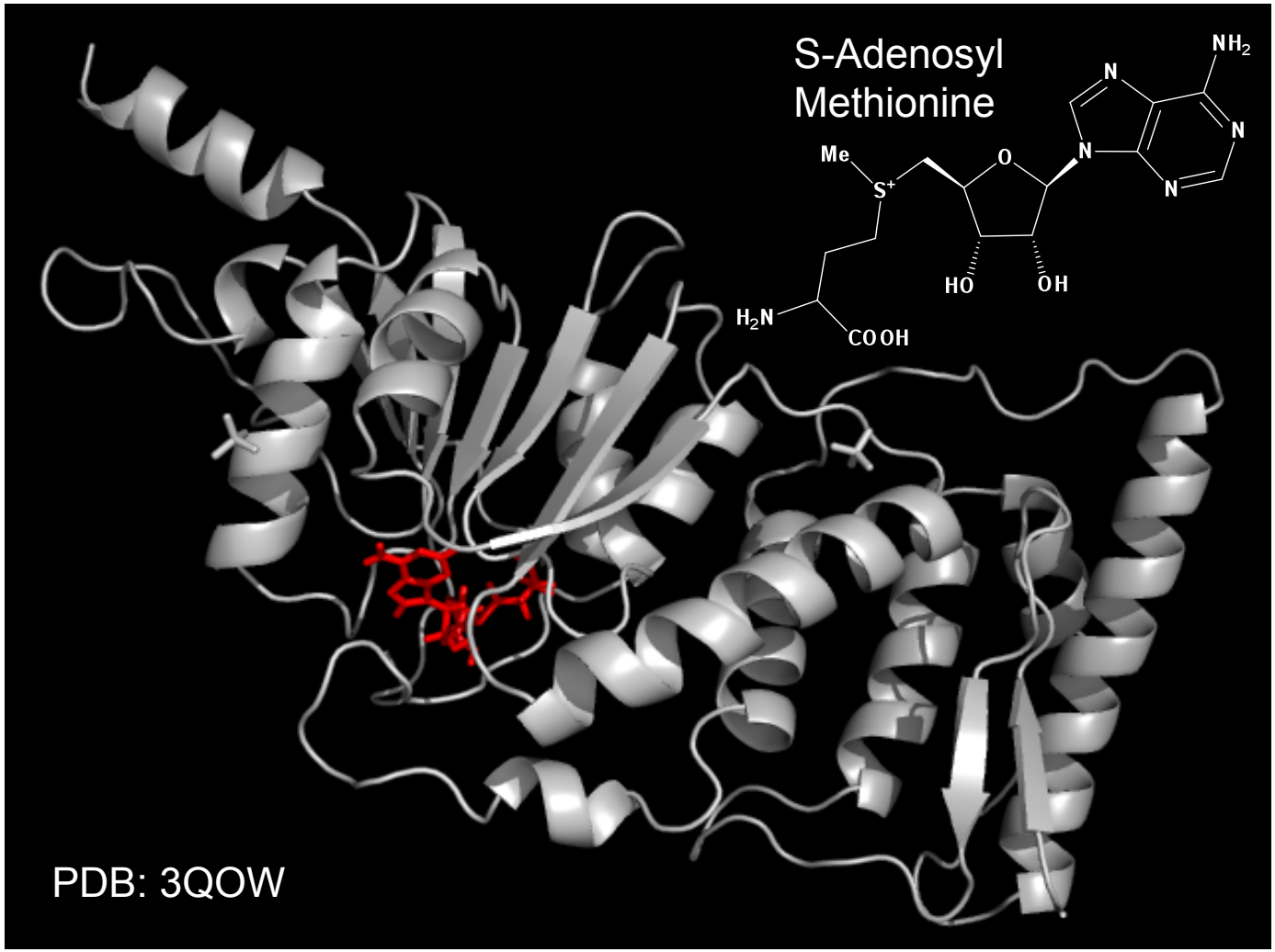
WHY DOT1L?

- MLL = cause of 70% of infant leukemia
- Recruited by disease-linked MLL translocations
- Recruitment → expression of leukemogenic genes
- The only non-SET KMT (H3K79)



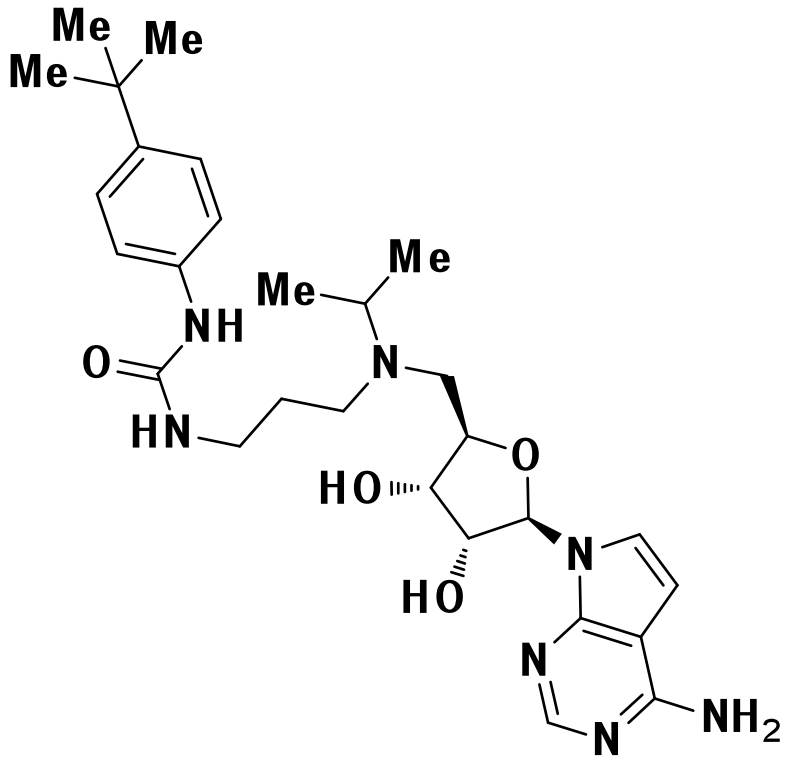
Okada Y. et al. "hDOT1L Links Histone Methylation to Leukemogenesis." *Cell* 121 (2005): 167-178.

DOT1L STRUCTURE



Richon et al. “Chemogenetic Analysis of Human Methyltransferases.” *Chem. Biol. & Drug Des. 78* (2011): 199-210.

EPIZYME COMPOUND EPZ004777



Good

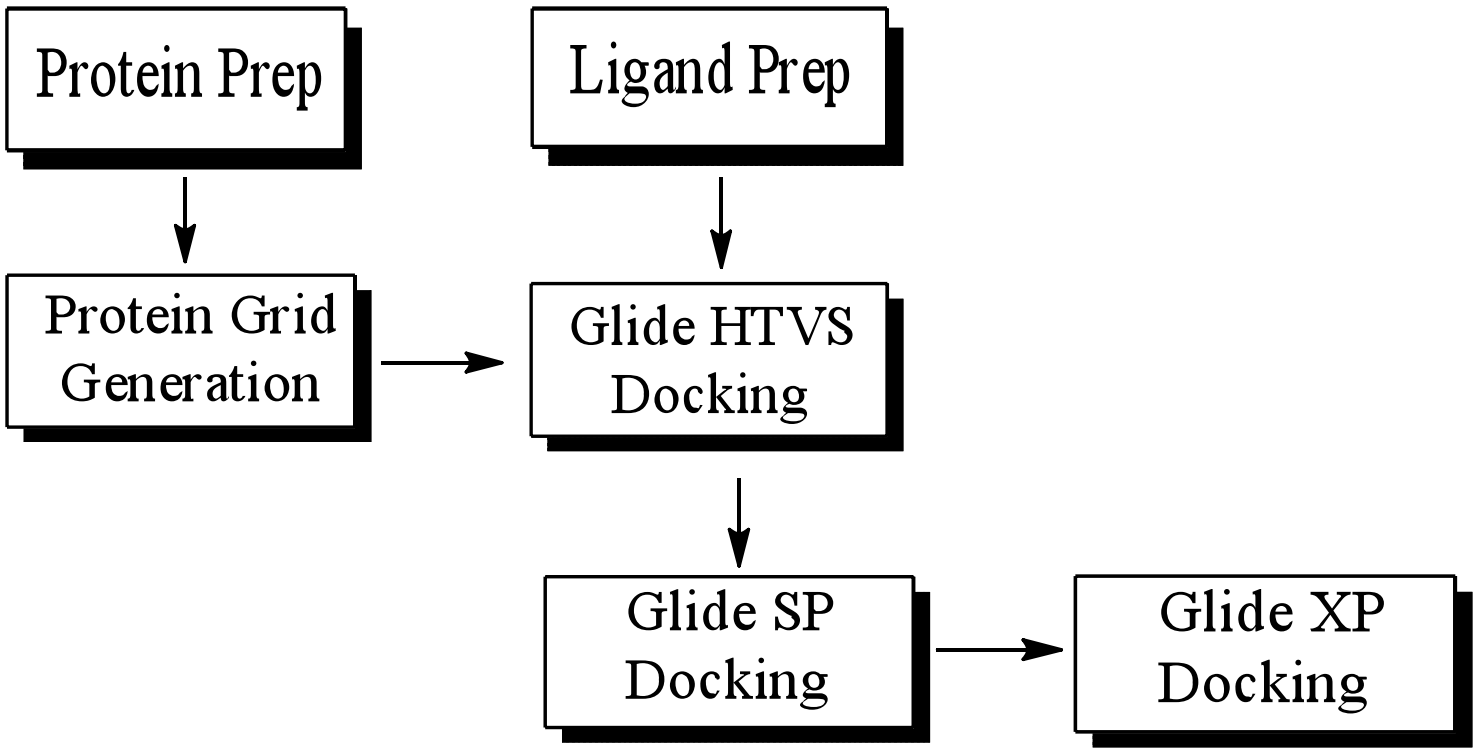
- Potent *in vitro* (IC_{50} of 400pM)
- Selective *in vitro*, but…

Bad

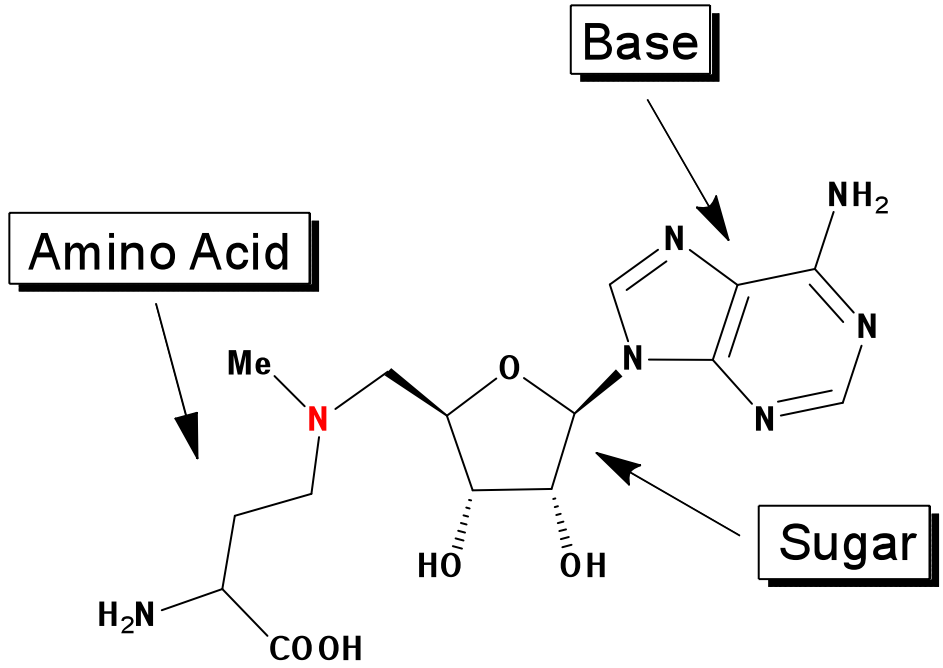
- Reduced potency *in vivo* (IC_{50} in μM range)
- Found to have poor drug-like properties

Daigle, S. et al. "Selective Killing of Mixed Lineage Leukemia Cells by a Potent Small-Molecule DOT1L Inhibitor." *Cancer Cell* 20 (2011): 53-65.

THE SCREENING PROCESS

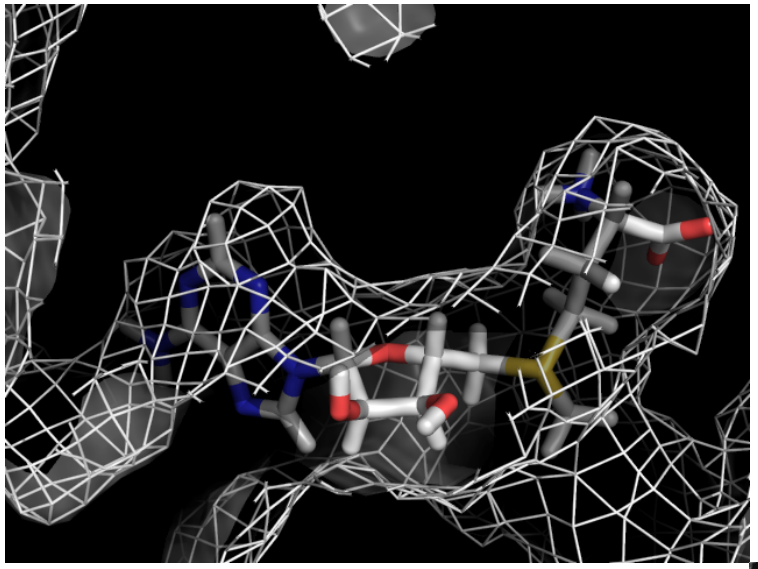


AZA-SAM: OUR STARTING POINT

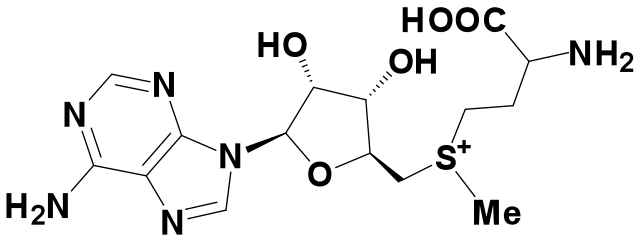


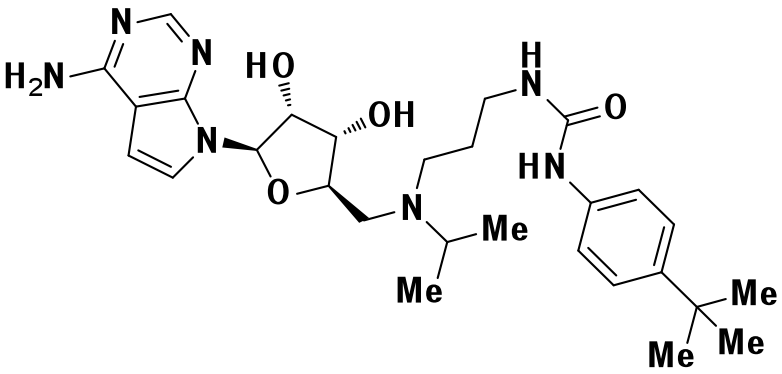
Joce C. et al. "Identification of stable S-adenosylmethionine (SAM) analogues derivatised with bioorthogonal tags: effect of ligands on the affinity of the E. coli methionine repressor, MetJ, for its operator DNA." *Org. Biomol. Chem.* 7 (2009): 635-638.

BINDING POCKET



S-Adenosyl Methionine





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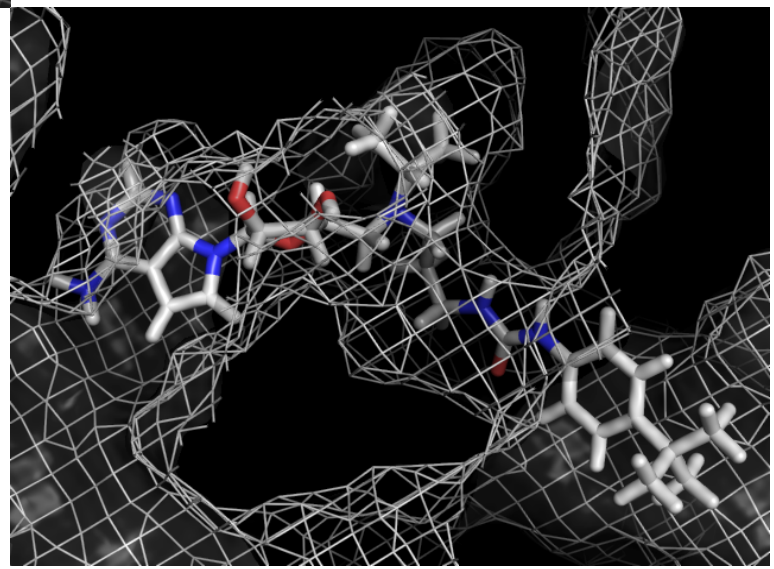

CONCLUSIONS

- *In silico* screening has proved useful for the optimization of analogues
- Analyzing protein-ligand interactions is key
- We should take advantage of the uniqueness of this non-SET binding pocket

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