Identification of DOT1L Inhibitors via Structure-Based Ligand Optimization

Javier J. Pineda
Summer Research Program in Genomics
Bradner Lab
Dana-Farber Cancer Institute
August 3, 2011
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)
MLL = cause of 70% of infant leukemia

Recruited by disease-linked MLL translocations

Recruitment → expression of leukemogenic genes

The only non-SET KMT (H3K79)

DOT1L STRUCTURE

**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

THE SCREENING PROCESS

Protein Prep → Protein Grid Generation
Ligand Prep → Glide HTVS Docking
Glide SP Docking → Glide XP Docking
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
ACKNOWLEDGEMENTS

- Jason Marineau, PhD. (Mentor)
- Jun Qi, PhD. (Mentor)
- James Bradner, M.D. (P.I.)
- Guille Estiu, PhD. (University of Notre Dame Associate Research Professor)
- Olaf Wiest, PhD. (University of Notre Dame Research Professor)
- Broad SRPG