Rapid informatics-driven fragment-based lead discovery for inhibitors of the histone methyltransferase NSD2

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BioBlocks
YOUR INNOVATIVE CHEMISTRY PARTNER IN DRUG DISCOVERY

REACTION BIOLOGY CORP. +PROQINASE

BioBlocks-Reaction Biology Collaboration

Ongoing multi-target FBLD collaboration

Complementary technology platforms

BioBlocks lead discovery technology broadens the scope of FBLD to more challenging targets

Reaction Biology assay repertoire offers new screening methods in difficult target classes

Our Approach: FBLD

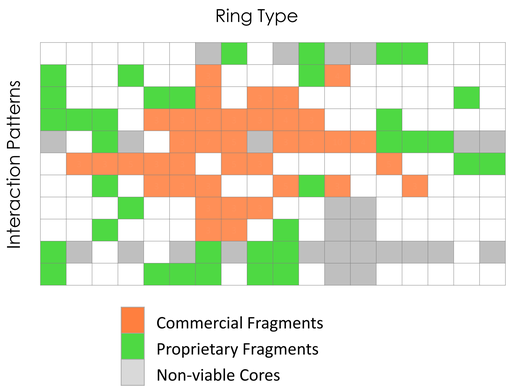
Fragment-Based Lead Discovery provides:

- Useful for targets not amenable to HTS
- Higher quality starting points for lead generation

BioBlocks' Comprehensive Fragment Library (CFL)
Designed proprietary fragments, typically:

- 11 to 13 heavy atoms
- Partially aromatic for better properties
- 1 handle for synthetic expansion
- Drug-like, novel cores

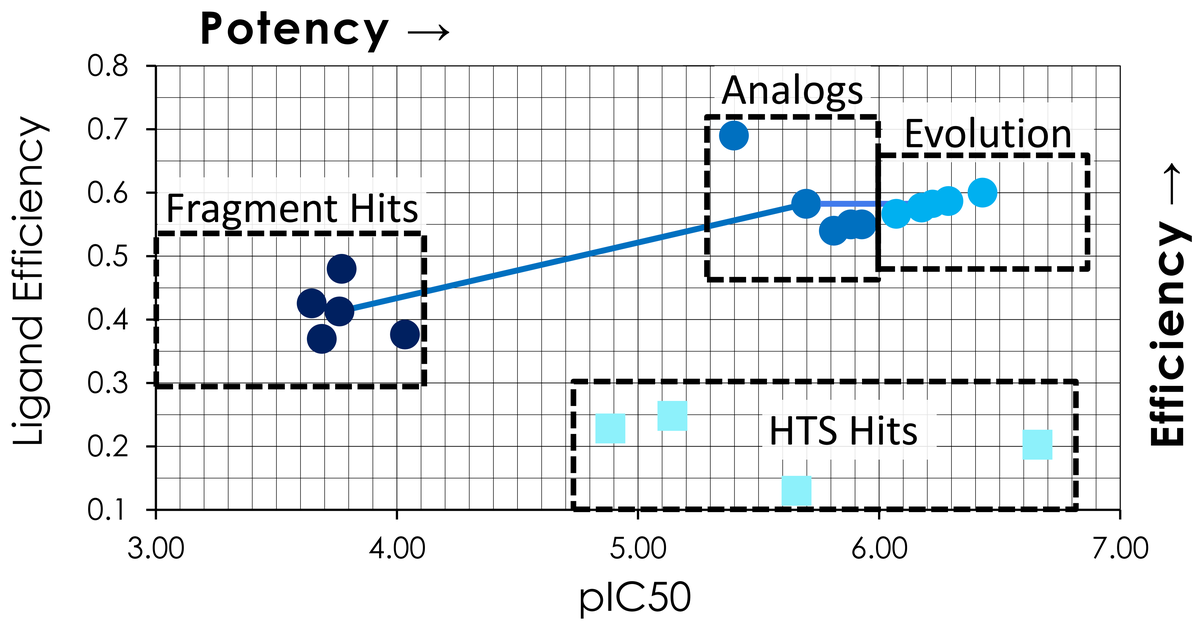
Improved Chemical Space Coverage



Improved Hit Follow up

Proprietary Leap-to-Lead™ informatics

- Rapid, low bias automated process
- Structural guidance not required
- High value analog families identified early



Our platform achieved an 86-fold potency improvement utilizing short analog cycles prior to structural biology

Biochemical Functional Screening

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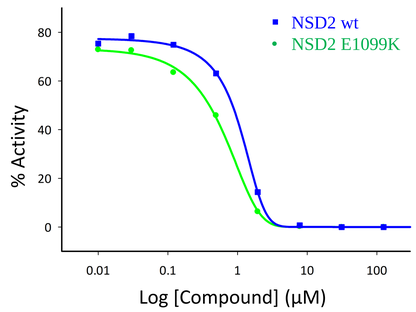
Enormous collection of kinase and epigenetic targets

Proprietary HotSpot Assays for NSD2 (wt, E1099K, others)

- ^{3}H SAM with nucleosome substrate
- Highly sensitive, direct Me transfer measurement
- No coupling enzyme, antibody or substrate label required

NSD2 Inhibition Dose Response



Emerging Oncology Target: NSD2

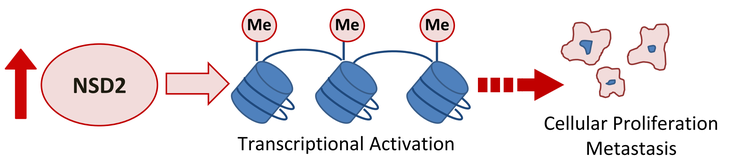
Nuclear receptor binding SET domain protein 2

Lysine methyltransferase specific for H3K36 methylations

Activating mutations frequently occur to drive pediatric leukemias

Challenging HTS target as only nucleosomes work as a substrate

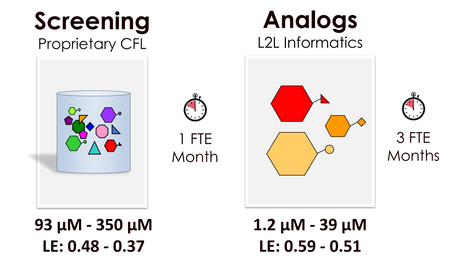
High-concentration screen of CFL delivered high quality fragment hits

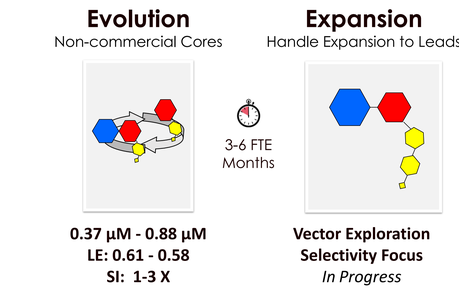


Results

Within 3 design cycles, fragment hits were elaborated to an early lead series:

- Sub-µM biochemical potency
- Selective inhibition of mutant E1099K NSD2 over wild type.





Conclusion

BioBlocks Leap-to-Lead™ (L2L) platform provides improved lead generation compared to traditional FBLD and HTS. As part of an ongoing multi-target collaboration with Reaction Biology, this informatics-driven approach efficiently delivered a potent early lead series for a challenging target.

	Leap-to-Lead™	Traditional FBLD	High Throughput Screening
Cost	$	$$	$$$$
# Compounds	~250-500	~2000	~200-500K
Set Diversity	Clustered, Unique	Redundant	Large, Complex
Chemical Space Coverage	Superior	Good	Poor
Hits	1-10 µM	~1-100 µM	~0.1-10 µM
Ligand Efficiency	Superior	Good	Poor
Follow Up	Built In	Expert Required	Standard Medicinal Chemistry