TARGET VALIDATION

Covalent Inhibitor Selectivity Profiling

IQ PROTEOMICS

Covalent small molecule inhibitors offer unique advantages over traditional drugs, including increased potency and prolonged efficacy. Notable irreversible inhibitors include Afatinib (EGFR), Ibrutinib (BtK), Neratinib (ErbB), and ARS-853 (RASK G12C). IQ Proteomics provides an LC-MS based, unbiased assay for screening the targets of cysteine-directed covalent inhibitors.

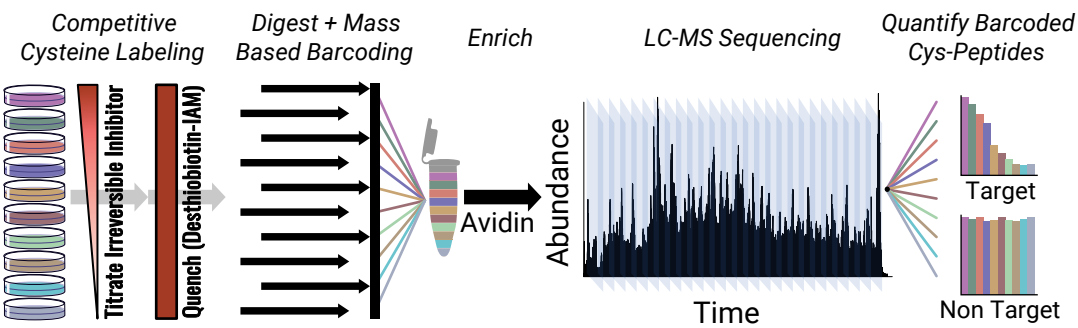
Features

- >8000 Quantified Cys-Peptides
- High efficiency streptavidin-based enrichment
- High Throughput Proteomics
  - TMT™ 11-Plex Technology
  - Orbitrap Lumos (SPS-MS3)

Applications

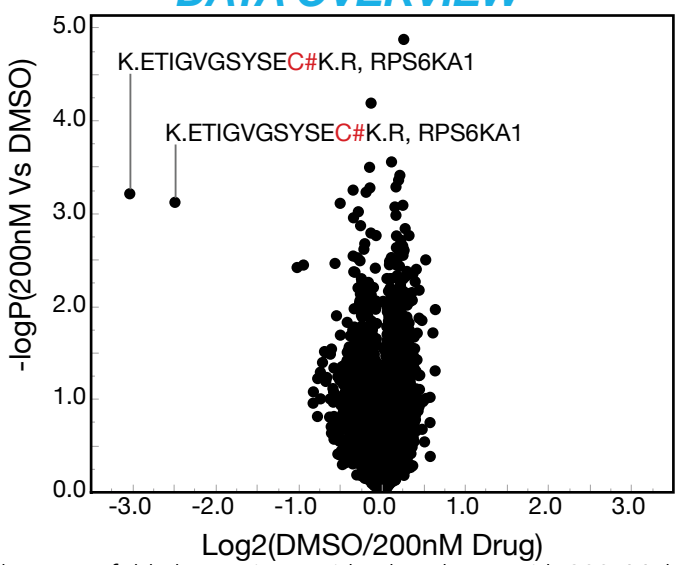
- Target Identification
- Selectivity Profiling
- High Throughput Screening

ASSAY OVERVIEW



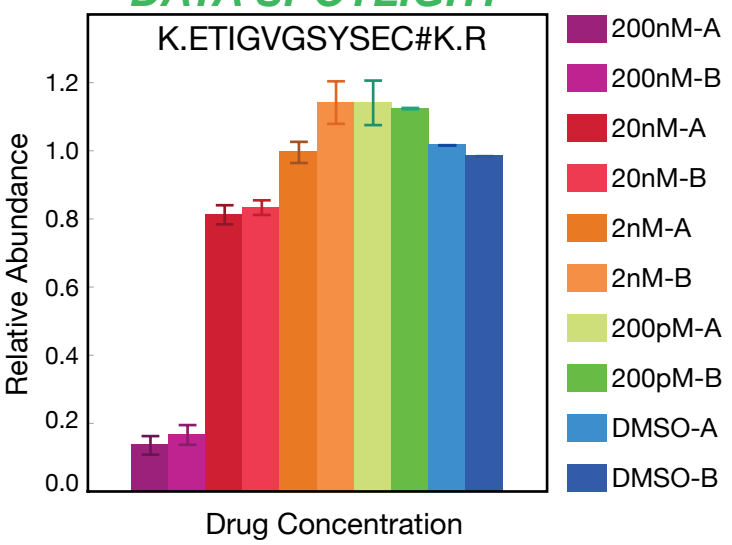
Whole cell lysates are treated with a titration series of a cysteine-specific covalent inhibitor (FMK). All unreacted cysteine residues are quenched with desthiobiotin iodoacetamide (IAM). Proteomes are proteolytically digested, labeled with isobaric reagents, mixed, and reactive cysteine-containing peptides are enriched with streptavidin and quantified via LC-MS. Drug targets exhibit a characteristic quantitative profile marked by a reduction in intensity with increasing drug concentration.

DATA OVERVIEW



The mean fold change in peptide abundance with 200nM drug compared to DMSO vs the statistical significance highlights the specificity of FMK for a peptide within the active site of its known target RPS6KA1, against a background of >8000 quantified peptides (# : desthiobiotion modification)

DATA SPOTLIGHT



The mean relative abundance (error bars: standard deviation) of the peptide within RPS6KA1 active site containing the targeted cysteine across the entire FMK titration series (n=2) shows excellent agreement between replicate concentrations and repeat measurements. '#' indicates desthiobiotin modification

IQ PROTEOMICS

840 Memorial Drive - Cambridge, MA 02139 www.iqproteomics.com info@iqproteomics.com