



2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

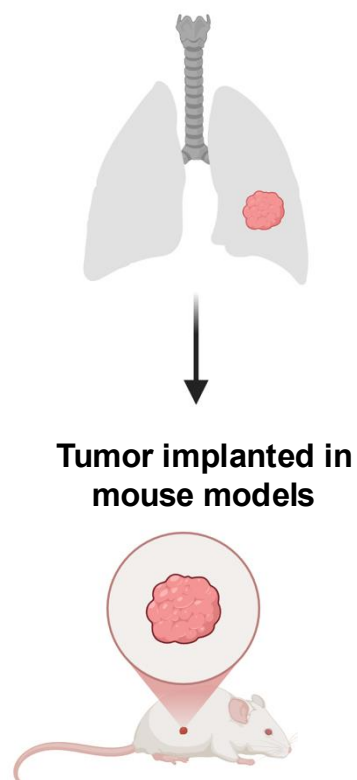
Screening NSCLC patient organoids with epigenetic compound library identifies a therapeutic vulnerability to PRMT5 Inhibition

Khadija Jafarova

*Princess Margaret Cancer Centre
Toronto, Canada*

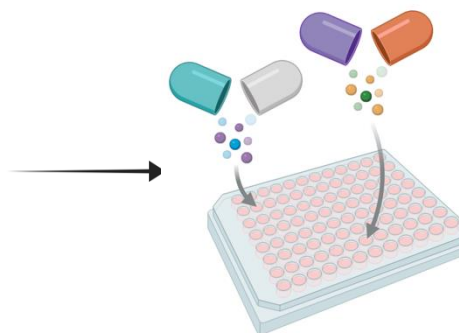
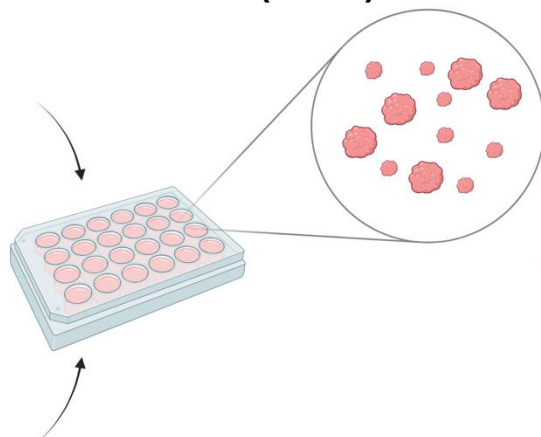
Non-small cell lung cancer (NSCLC) patient-derived models are screened for sensitivity to epigenetic inhibitors

NSCLC patient tumor sample



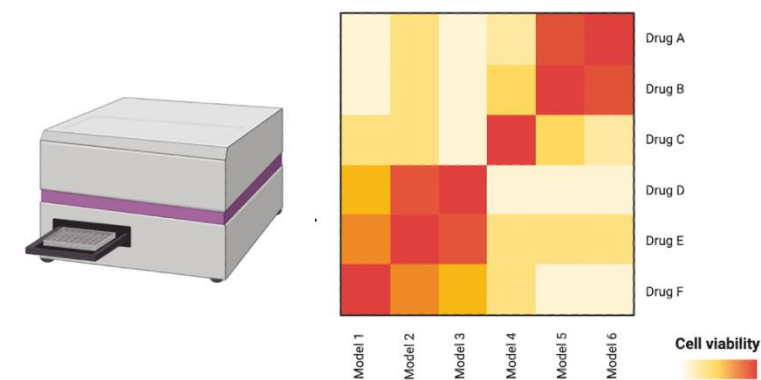
Tumor implanted in
mouse models

NSCLC patient-derived organoid (PDO)



DAY 1. PDOs screening
with epigenetic
compounds at 1uM

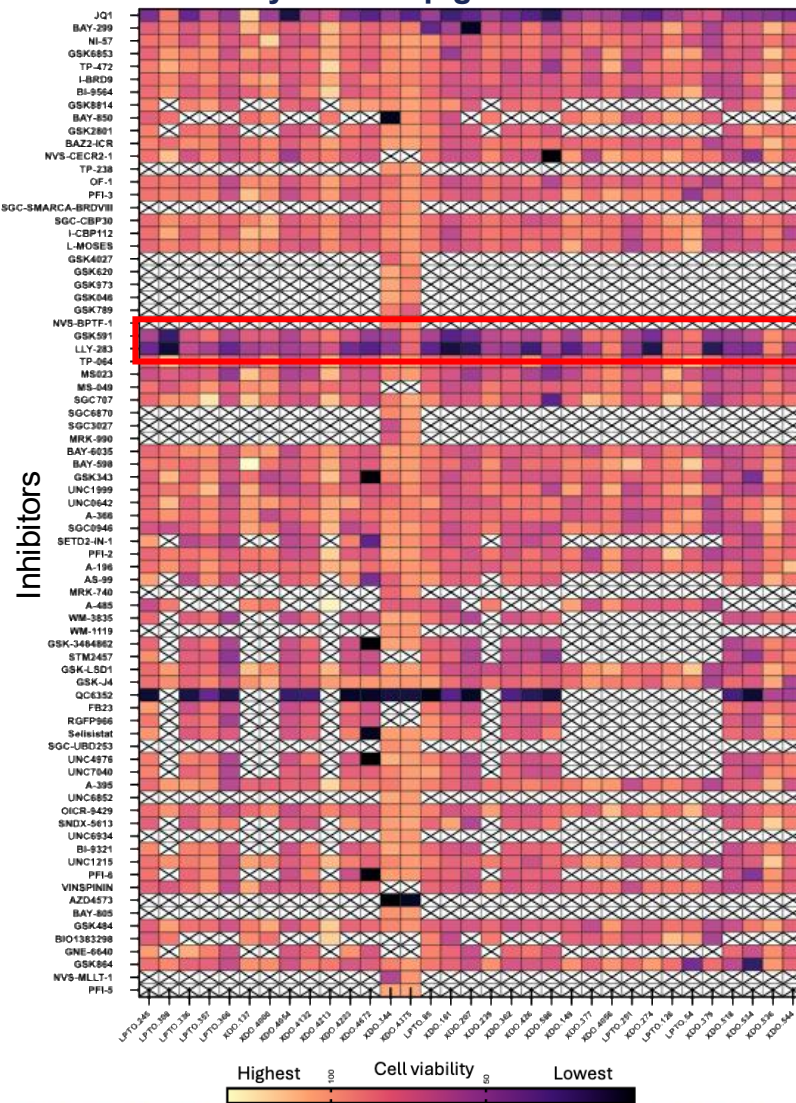
DAY 9. Cell Titre Glo reading and cell viability analysis



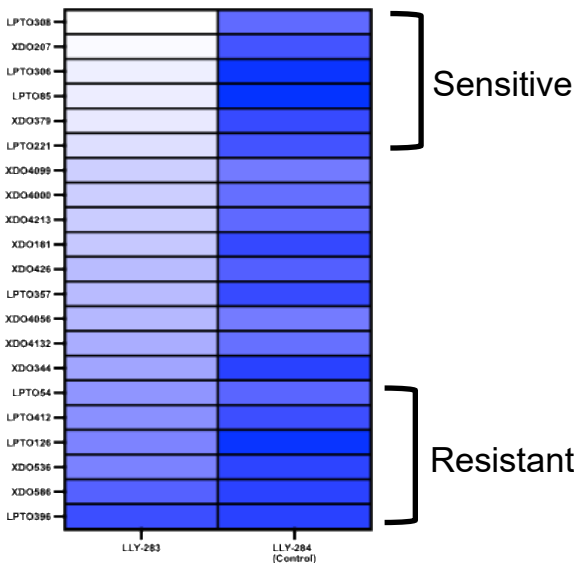
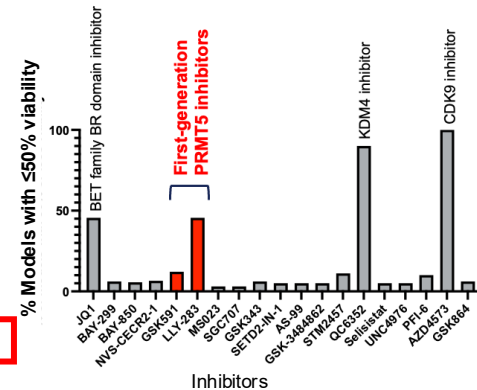
NSCLC patient-xenograft tumor sample

PRMT5 inhibition reduces cell viability in a subset of NSCLC PDOs

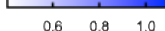
Cell viability across epigenetic inhibitor screen



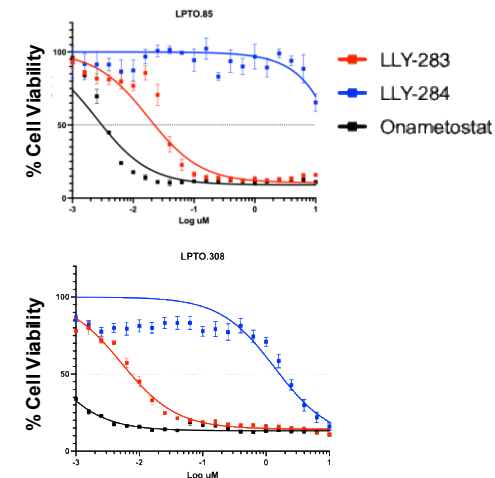
PRMT5i



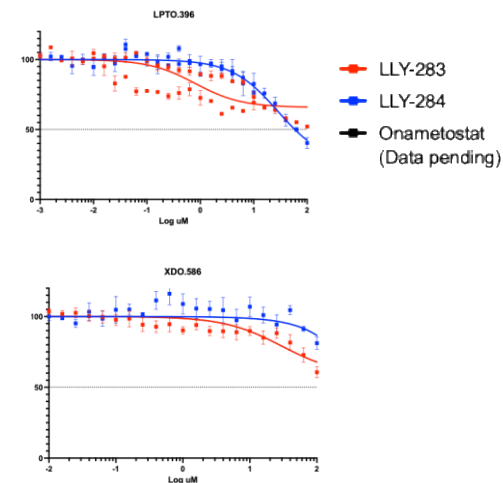
Area under the curve (AUC)



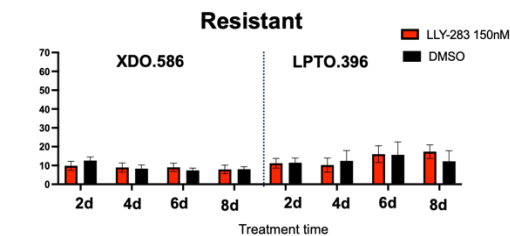
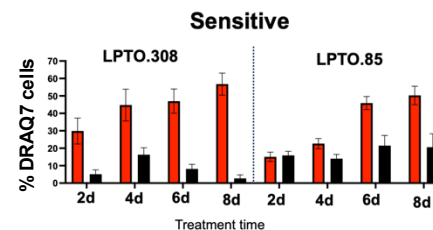
Sensitive



Resistant



LLY-283 increased DRAQ7+ dead cells over 8 days of treatment in sensitive, but not resistant PDOs



LLY-283 sensitive and resistant PDOs are associated with differential baseline splicing program

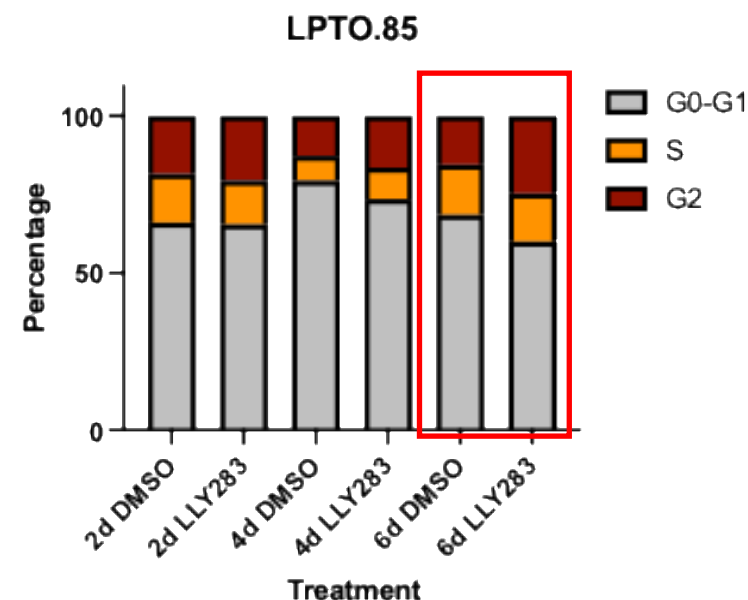
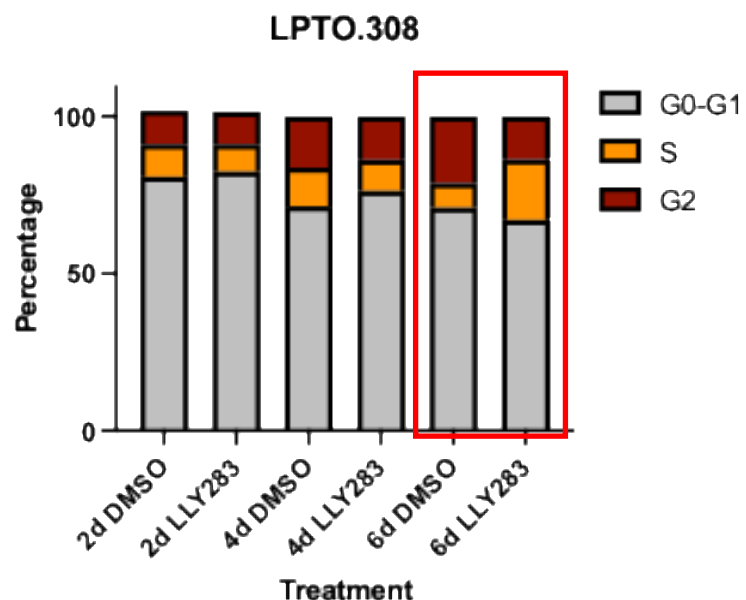
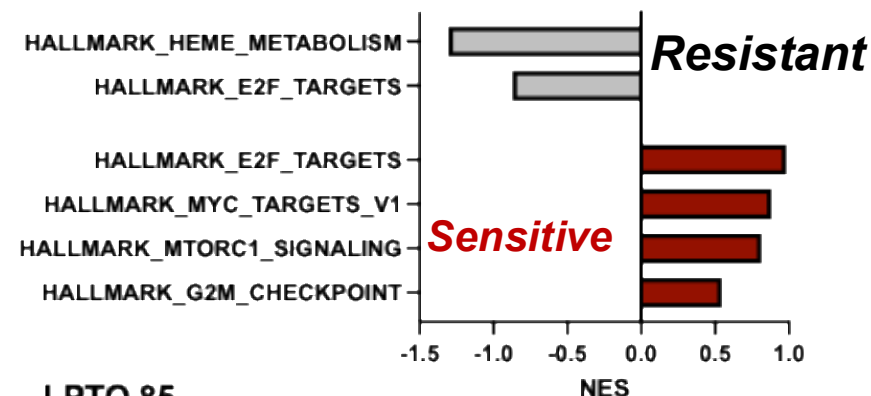
Sensitive
differential splicing events
FDR<0.05, $|\Delta\text{PSI}| > 0.1$

751 events in 640 genes

Resistant
differential splicing events
FDR<0.05, $|\Delta\text{PSI}| > 0.1$

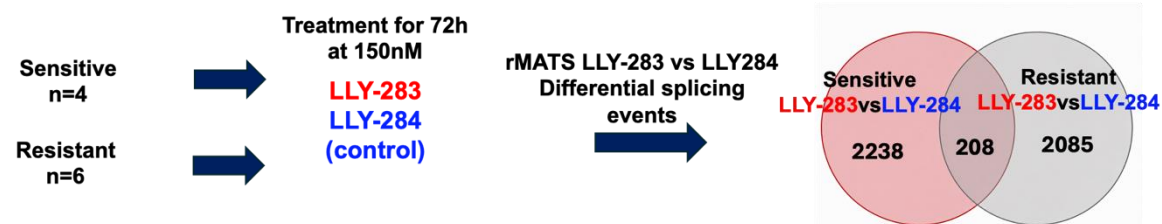
893 events in 722 genes

Gene set
enrichment analysis



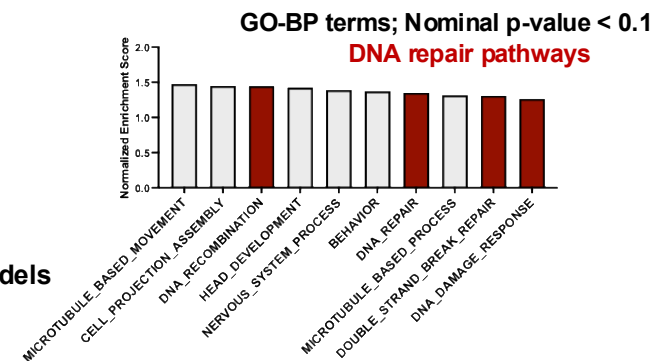
LLY-283 treatment altered cell-cycle distribution in sensitive PDOs, with increased S- and G2-phase populations by day 6

LLY-283 induced intron retention in sensitive models enriches for DNA repair related pathways



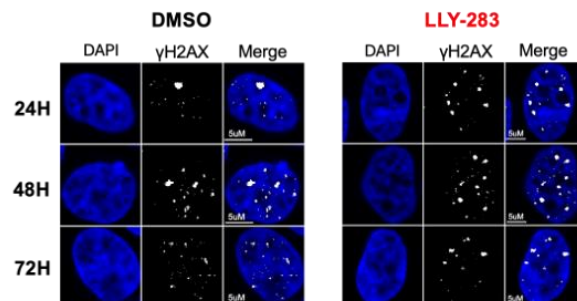
Event	Sensitive LLY283vsLLY284 differential splicing events p-value<0.05	Resistant LLY283vsLLY284 differential splicing events p-value<0.05
Intron retention	514	369
Exon skip	1100	1117
Mutually exclusive exon	118	106
Alternative 3' splice	305	275
Alternative 5' splice	201	218

514 IR events in 450 unique genes in sensitive models

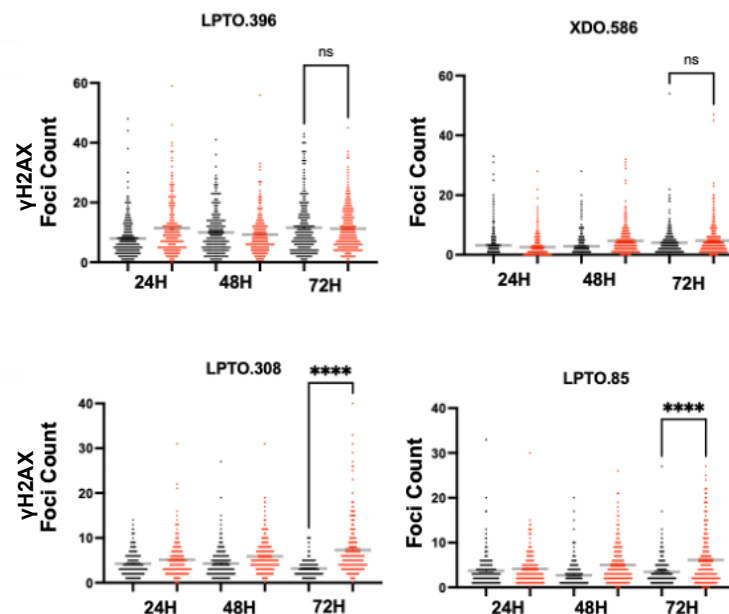
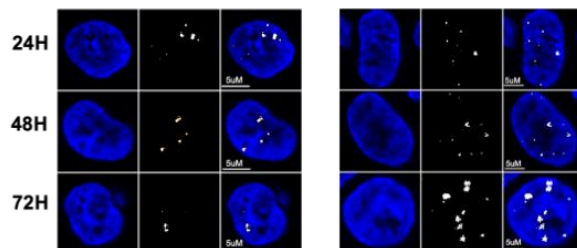


No DNA repair-related pathway enrichment is observed in the resistant models (data not shown)

Resistant



Sensitive



Mann-Whitney test p-value < 0.0001

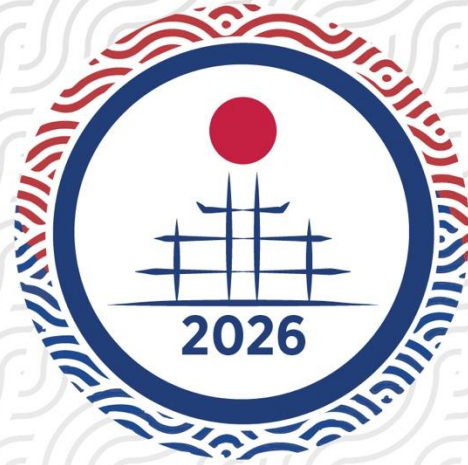
LLY-283 increases DNA damage as measured by γH2AX foci in the sensitive, but not resistant models

Summary

- NSCLC PDOs respond to inhibitors of PRMT5 - LLY-283, GSK591 and Onametostat
- Sensitive and Resistant PDOs show distinct baseline and treatment induced splicing programs
- LLY-283 induces intron retention in the sensitive PDOs including events involving genes associated with DNA repair
- Sensitive models accumulate γ H2AX foci following LLY-283 treatment linking PRMT5 inhibition with increased DNA damage

Future Directions

- Investigate upstream pathways responsible for differential γ H2AX foci accumulation in sensitive vs resistant models
- Validate LLY-283 induced intron retention events affecting DNA damage response genes in sensitive models



Thank You.