



TNG961: a selective, oral HBS1L molecular glue degrader for the treatment of FOCAD-deleted cancers

Hilary E. Nicholson, Ph.D.

Tango Therapeutics, Boston, MA




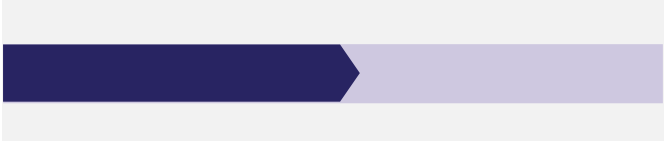
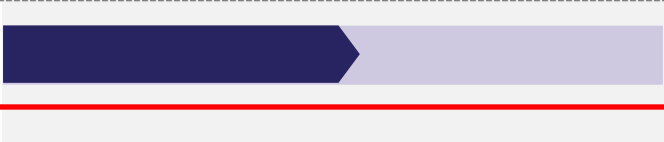


Disclosure Information

Hilary E. Nicholson, Ph.D.

I have the following relevant financial relationships to disclose:

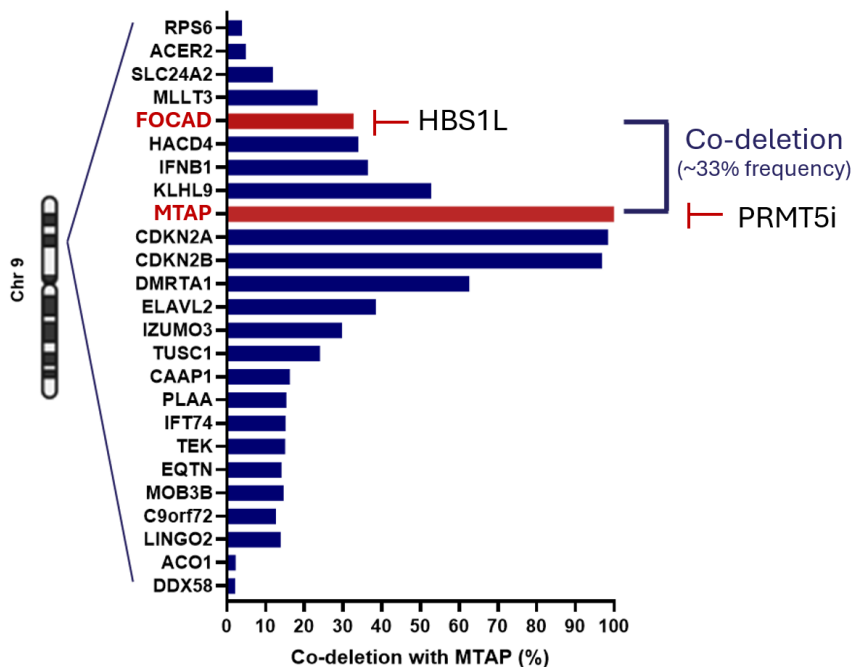
- Employee of Tango Therapeutics
- Stockholder in Tango Therapeutics

Wholly-owned pipeline targeting multiple high value indications

MOLECULE	PATIENT SELECTION	TARGET	INDICATIONS	CLINICAL TRIALS			STATUS
				PRE-CLINICAL	PHASE 1/2	PHASE 3	
Vopimetostat (TNG462)	MTAP-del cancers	PRMT5	Pancreatic, Lung, non-CNS cancer				Phase 1/2 data in 2026
	MTAP-del/RAS-mut (+RASi)	PRMT5 / RAS	Pancreatic, Lung cancer				Phase 1/2 data in 2026
TNG456	MTAP-del cancers	PRMT5	Glioblastoma				Phase 1/2 data in 2026
TNG961	MTAP/FOCAD-del cancers	HBS1L	Solid tumors				IND enabling
TNG260	STK11-mut/RAS wt	CoREST	Lung cancer				Dose expansion ongoing

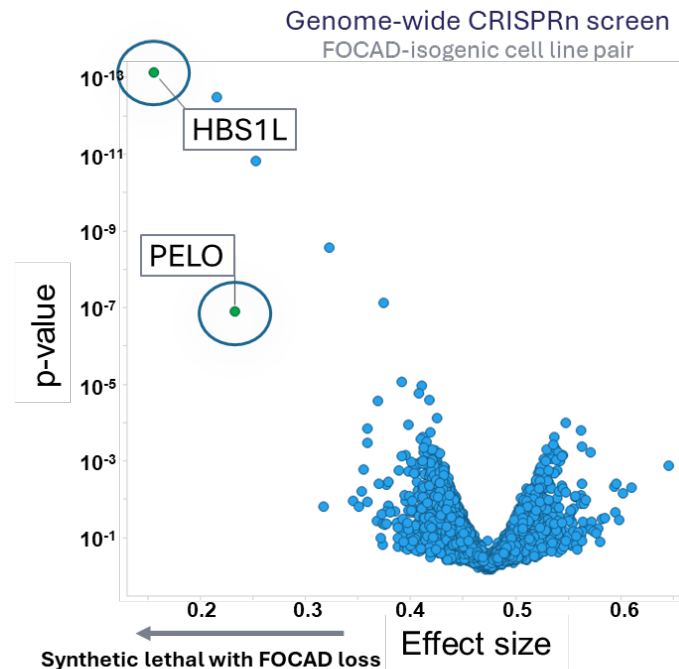
Multiple synthetic lethality opportunities created by chr9p21 loss

FOCAD deletion co-occurs with CDKN2A and MTAP loss



TCGA Pan-Cancer Atlas

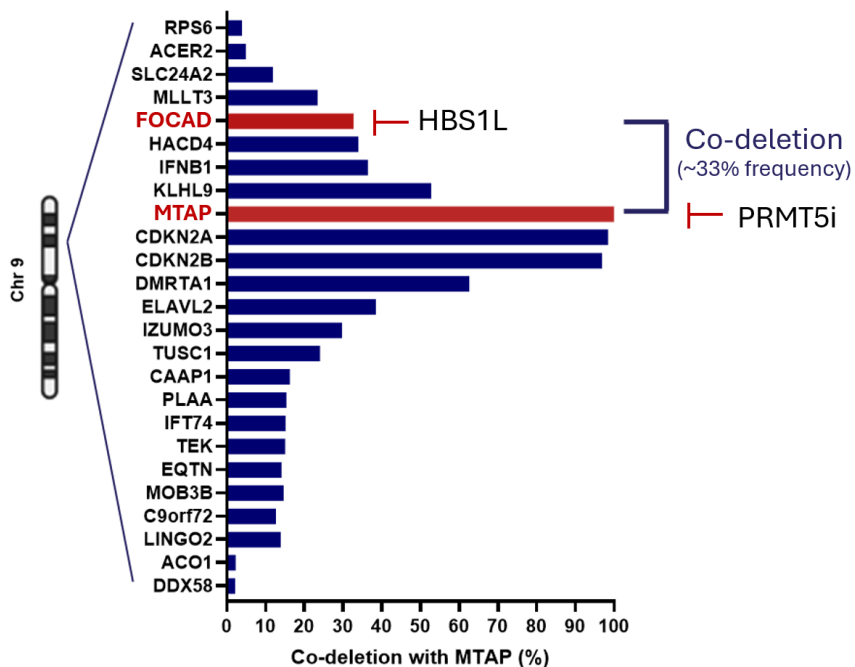
HBS1L is a top dependency in FOCAD-negative cells



Modified from Zhang et al *BBA-MCR* 2025

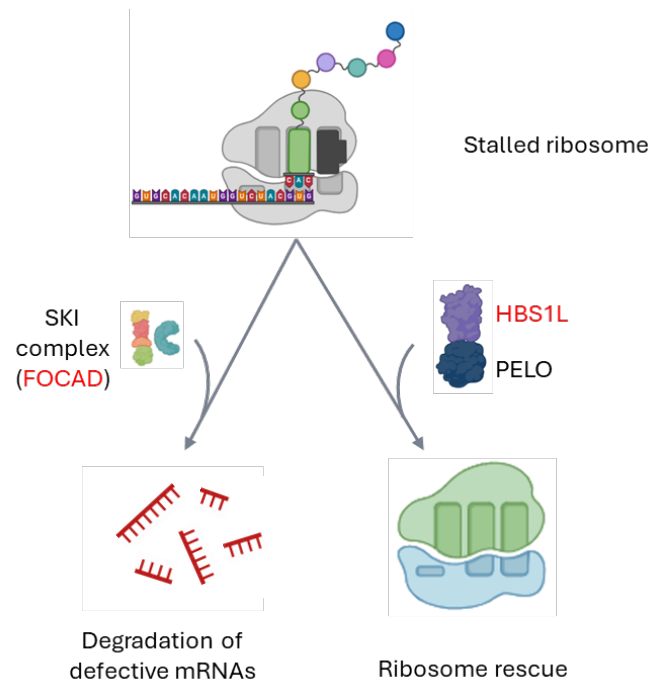
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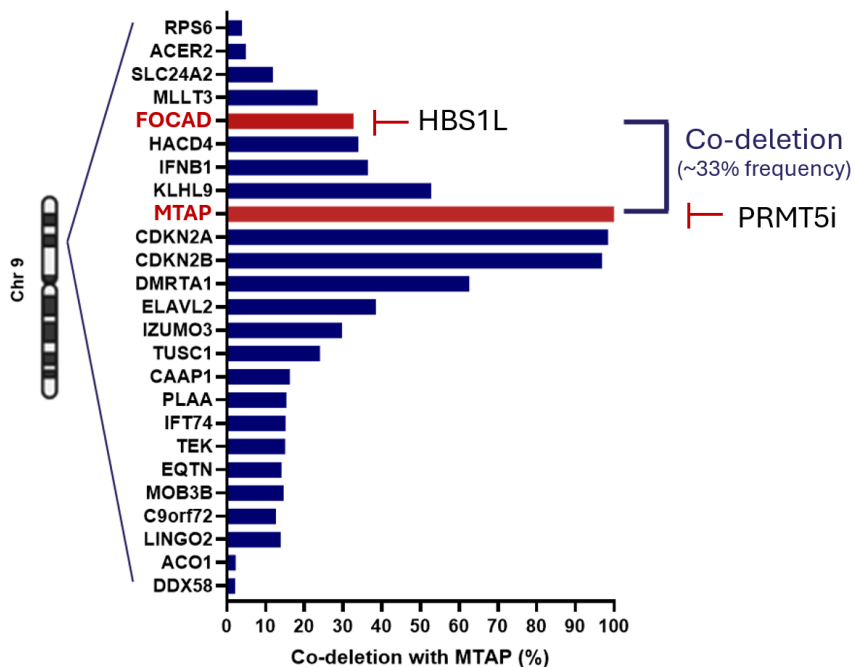
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FOCAD-negative cells require HBS1L for ribosome recycling



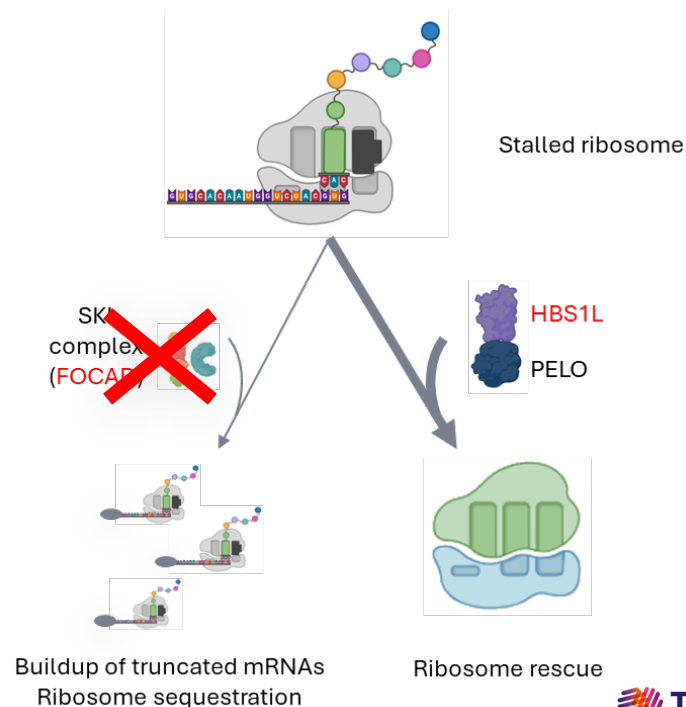
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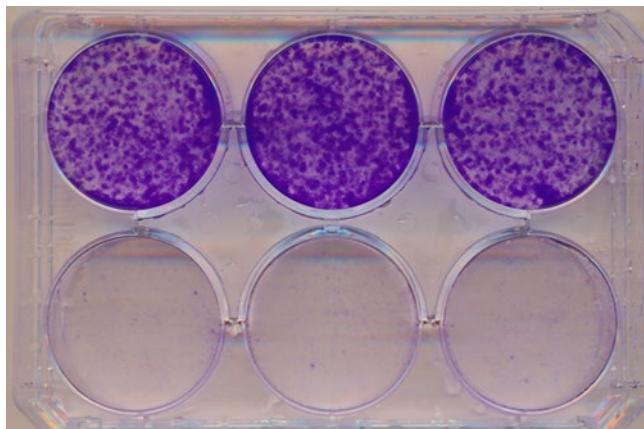
TCGA Pan-Cancer Atlas

FOCAD-negative cells require HBS1L for ribosome recycling



Multiple synthetic lethality opportunities created by chr9p21 loss

FOCAD-negative cells depend on HBS1L for ribosome recycling and survival

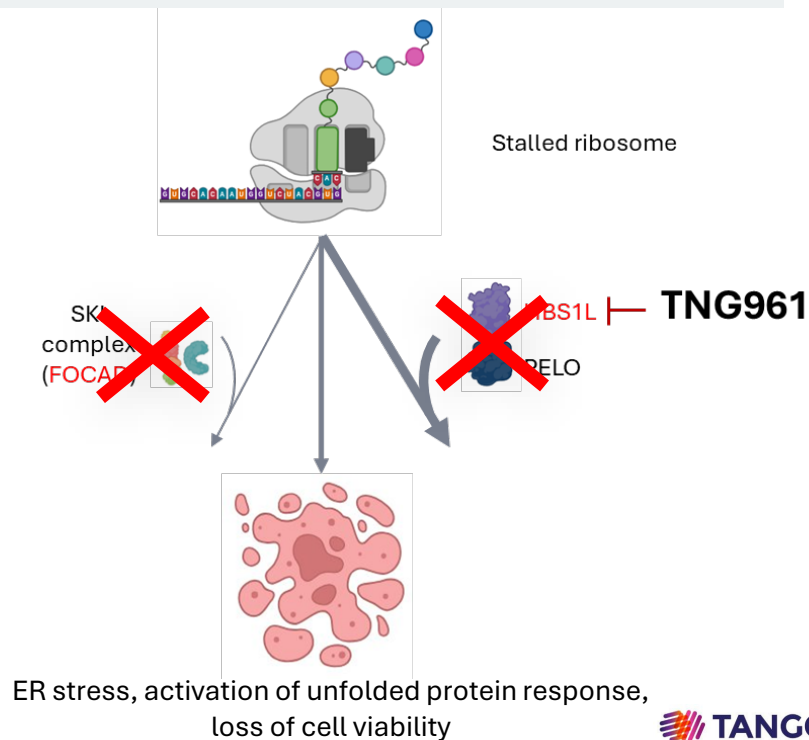


+ HBS1L cDNA

- HBS1L cDNA

HBS1L knockout in FOCAD-del
MIAPACA2 cells

Zhang et al *BBA-MCR* 2025



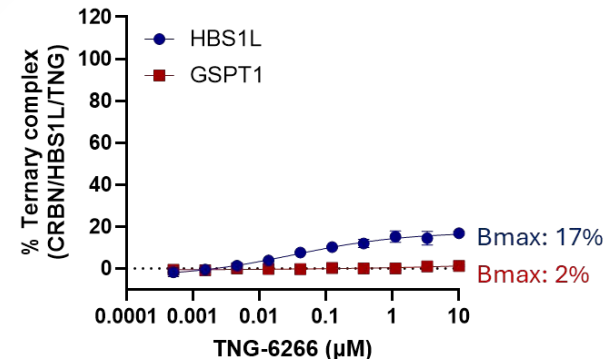
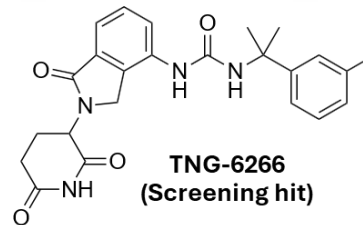
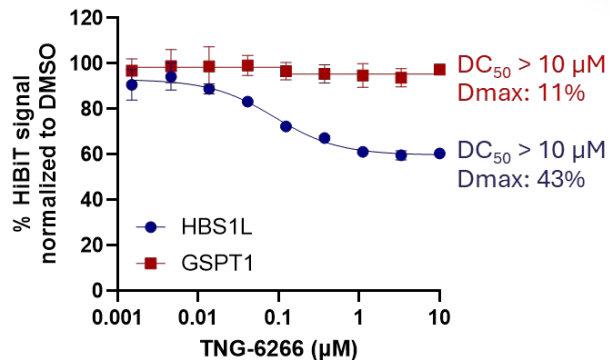
Parallel biochemical and cellular screens identified HBS1L-selective starting points

Cellular degradation
(endogenous target degradation)

Biochemical induced proximity
(ternary complex formation)

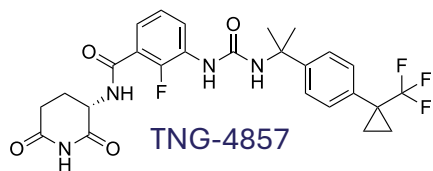
Down assay
(loss of protein)

Up assay
(protein-protein interaction)

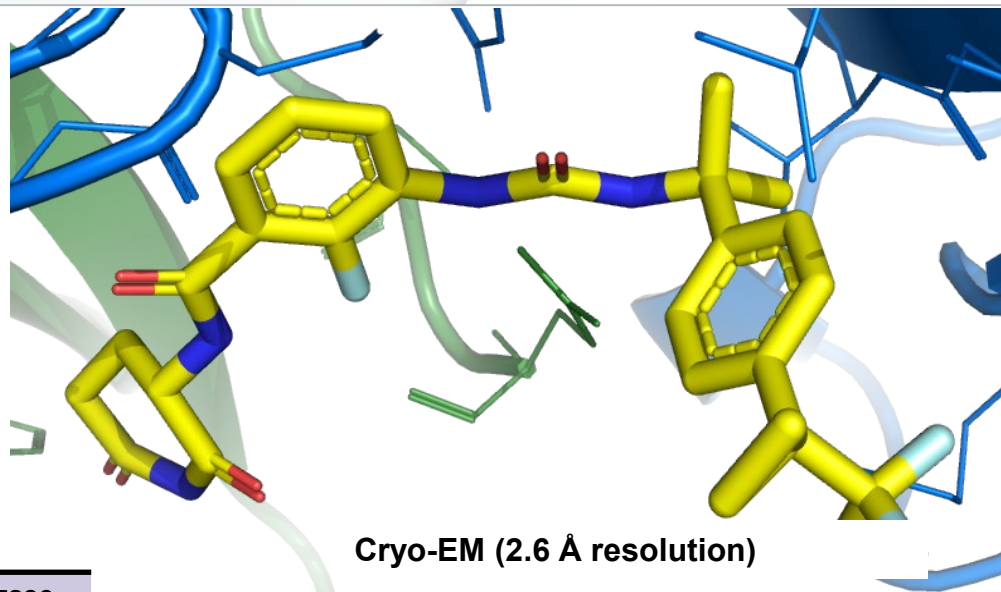
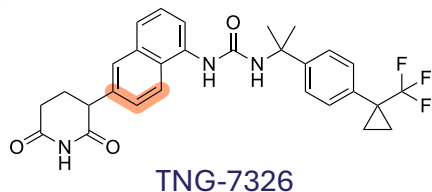
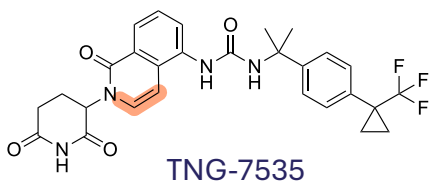


Tango molecular glue library screened in parallel against HBS1L (target) and GSPT1 (anti-target)

Structure-guided design increased HBS1L activity



↓ cyclization

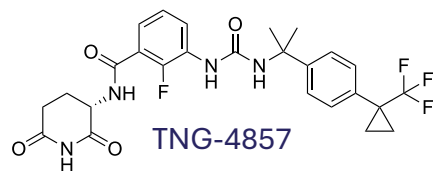


- Cyclization conferred potency benefits
- GSPT1 activity remained unpredictable
- Numerous ring systems synthesized

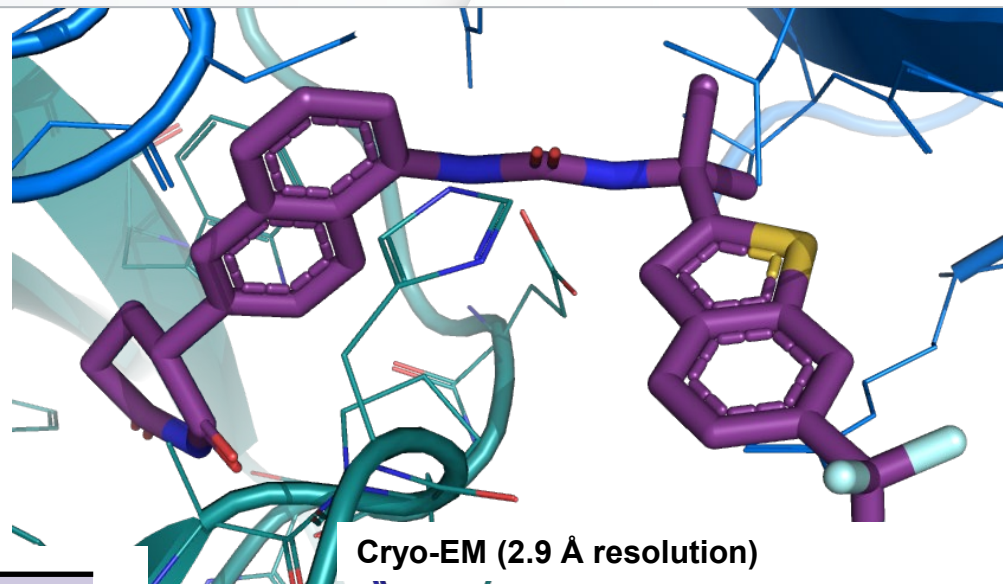
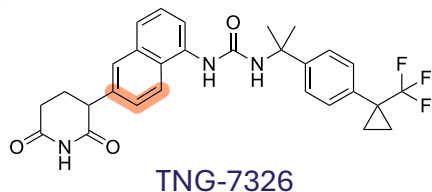
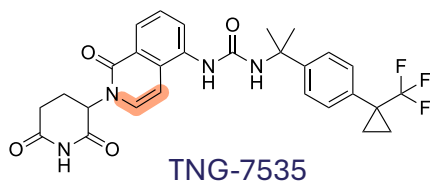
Cellular HiBit	TNG-4857	TNG-7535	TNG-7326
HBS1L DC ₅₀ (μM), Dmax (%)	0.012, 101	0.001, 69	0.0006, 92
GSPT1 DC ₅₀ (μM)	>10	0.007	> 10
Cellular viability			
AC ₅₀ (μM)	0.737	0.240	0.004

DC₅₀ and AC₅₀ corrected for media binding

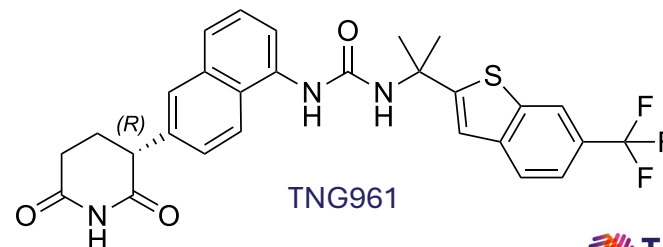
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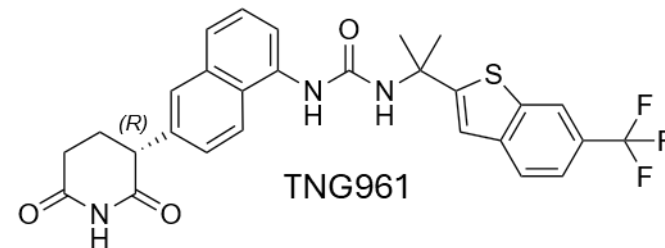
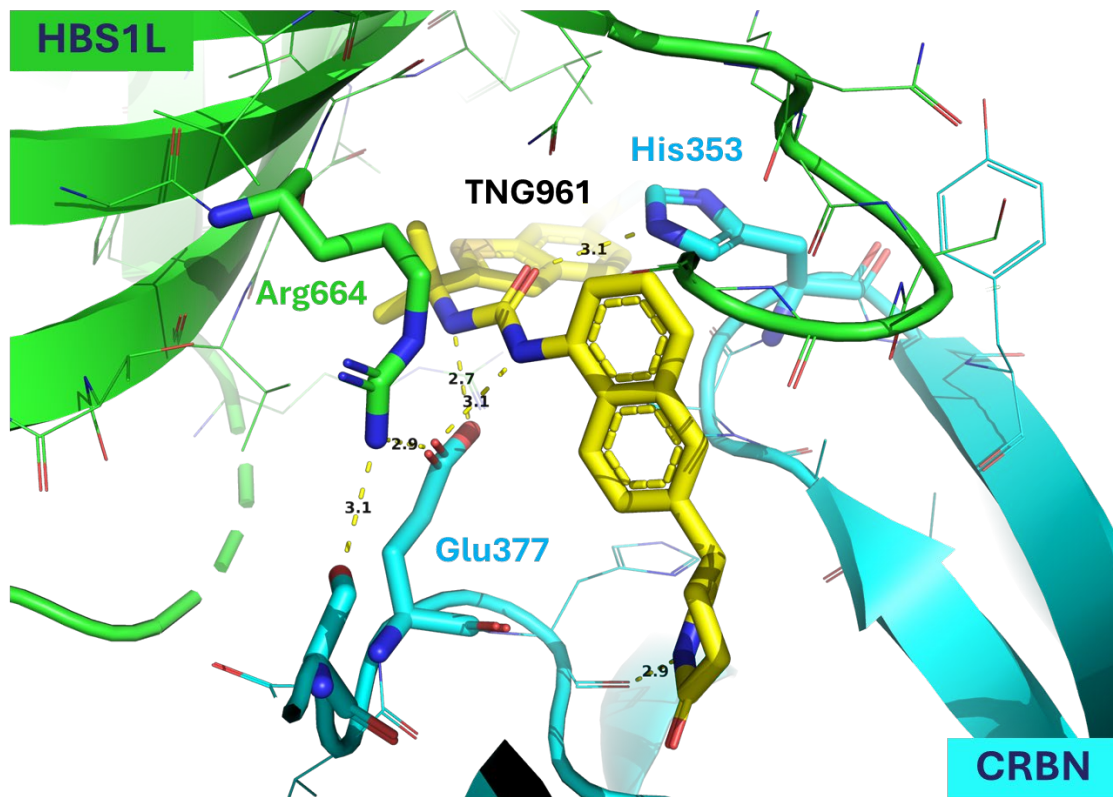


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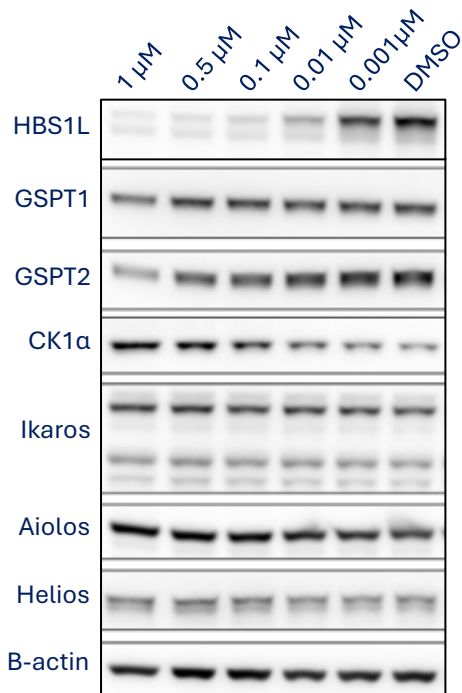
Electrostatic and hydrophobic interactions with both HBS1L and CRBN drive TNG961 potency and selectivity



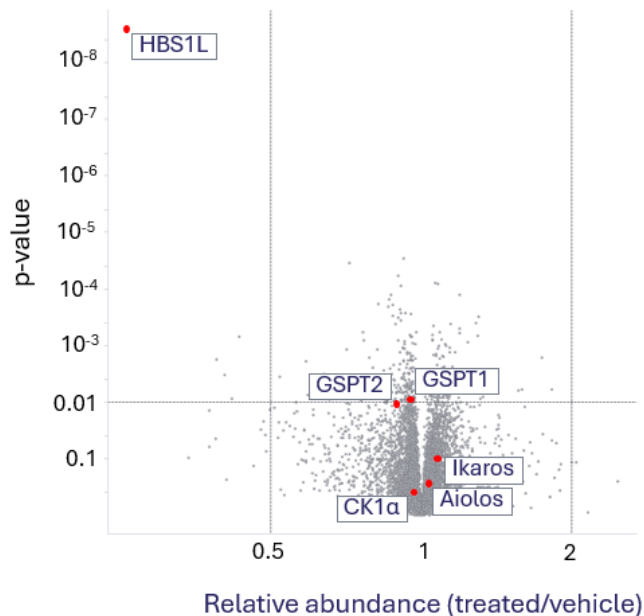
- All three urea heteroatoms interact with CRBN – key pharmacophore
- HBS1L R664 interacts with CRBN E377 forming a larger pocket than the analogous GSPT1 residues
- Pocket accommodates gem-dimethyl of TNG961

TNG961 has proteome-wide selectivity for HBS1L and only impairs viability of FOCAD-negative cells

Selective degradation of HBS1L



6 h, MM.1s



FOCAD-dependent efficacy

- TNG961 activity observed in FOCAD-negative cell lines across all lineages
- ~100-fold selectivity across five FOCAD-isogenic cell line pairs

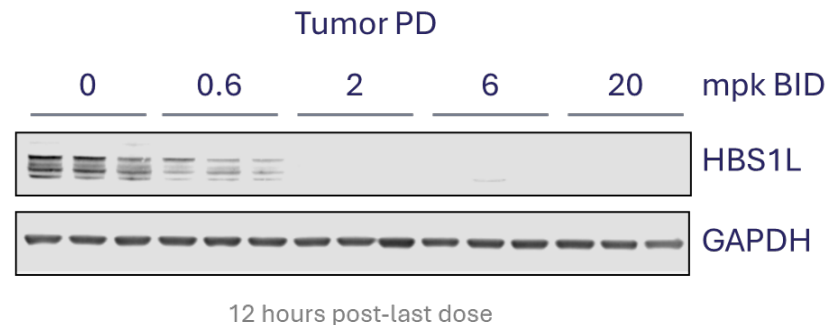
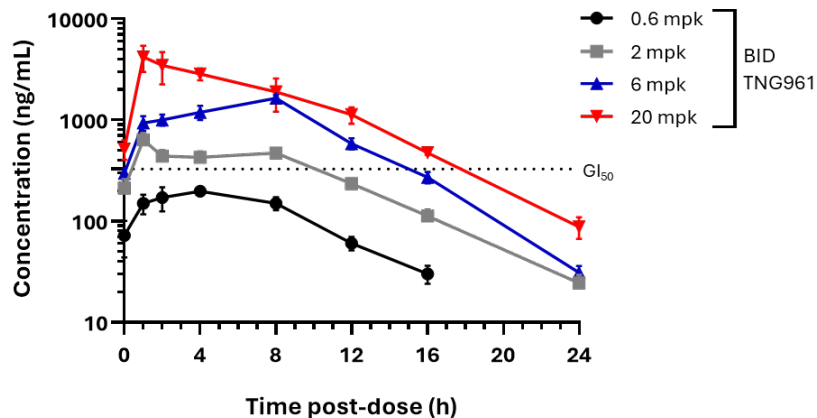
Isogenic model	Tissue	Selectivity (fold)
NCIH1755	lung	>100
MIAPACA2	pancreas	~65
HAP1	blood	>80
HeLa	cervix	>100
MDAMB231	breast	>100

Oral TNG961 induces dose-dependent HBS1L degradation in vivo

Dose-proportional PK

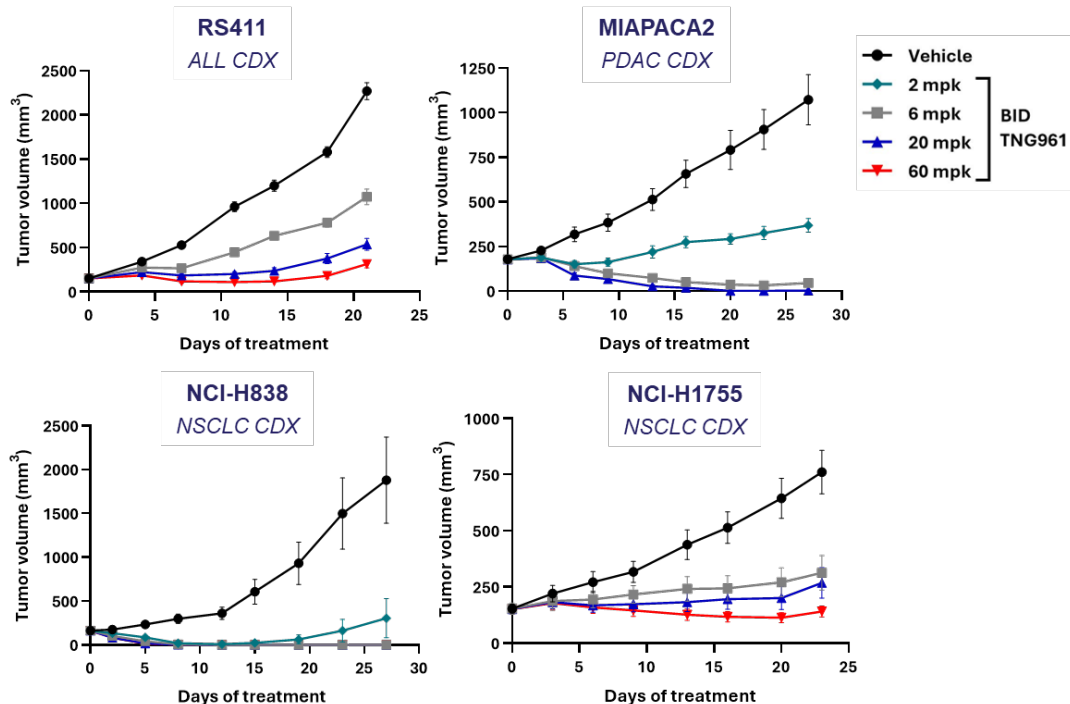
Efficient HBS1L degradation in tumors

MIAPACA2 FOCAD-negative PDAC CDX
6-day PK/PD



TNG961 demonstrates broad activity across indications

Efficacy in FOCAD-negative xenografts

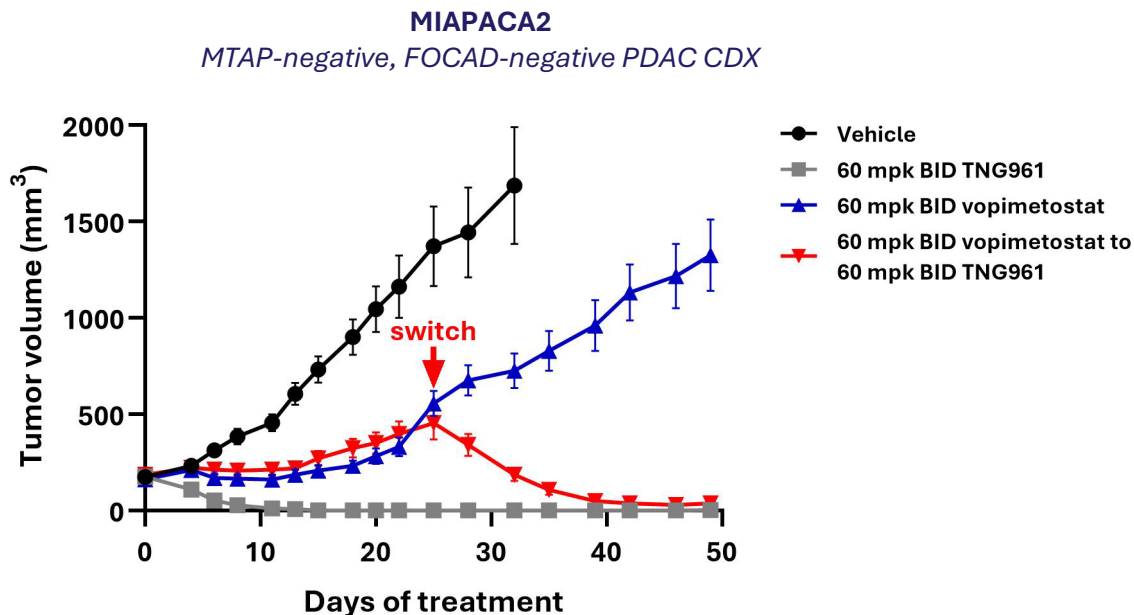


Broad development opportunity

- Efficacy observed across CDX models from different histologies
- Complete regression observed in models representing high unmet medical need (PDAC and NSCLC)

TNG961 has non-overlapping sensitivity with MTA-cooperative PRMT5 inhibitors

TNG961 regresses tumors that progress on PRMT5i treatment



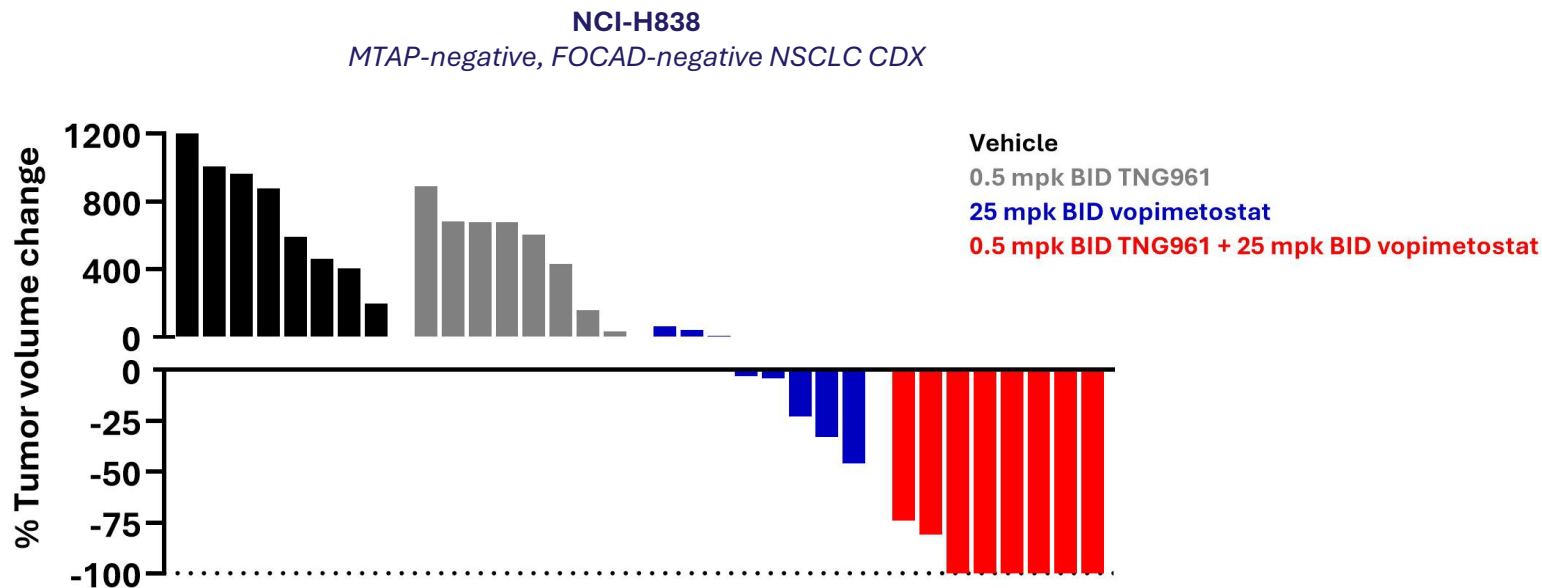
Distinct mechanism

- Data suggest patients who become refractory to PRMT5i may benefit from TNG961 monotherapy

MIAPACA2 also refractory to BMS-986504 (Drizyte-Miller et al., 2025)

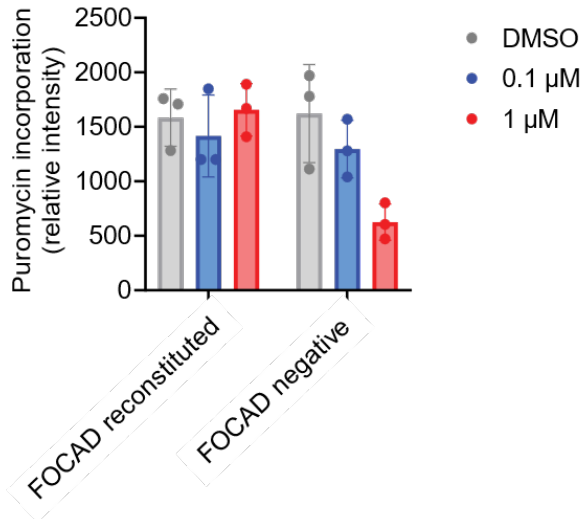
TNG961 + MTA-cooperative PRMT5 inhibitor drives strong combination benefit

Complete responses observed with TNG961 + vopimetostat combination

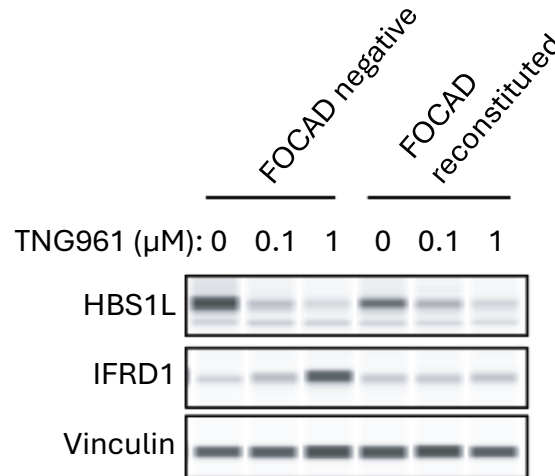


TNG961 induces translational arrest and stress response selectively in FOCAD-negative cells

Decreased protein translation

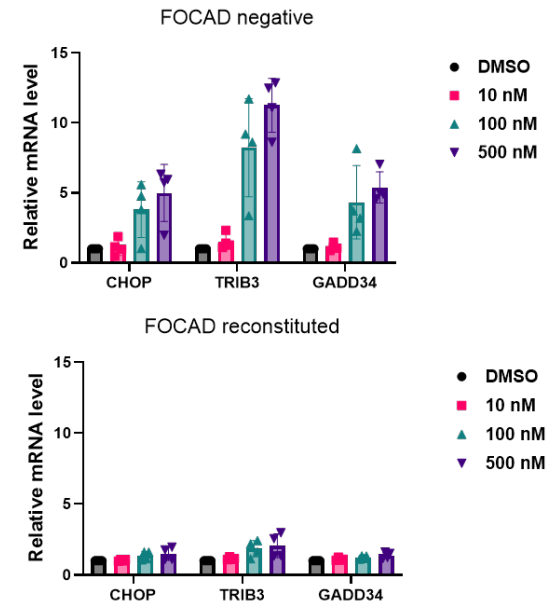


Activation of integrated stress response



Similar data observed for ATF4

Activation of unfolded protein response

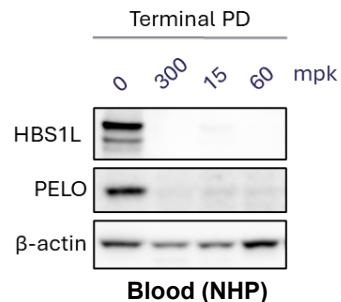


GLP studies support FIH at efficacious starting dose with ample safety margin

All nonclinical safety findings reversible and monitorable

14-Day Exploratory Studies (Rat & NHP)

- Minimal, non-adverse findings
- No cardiovascular (ECG) signals
- HBS1L degradation confirmed in NHP tissues



28-Day Pivotal GLP Studies (Rat & NHP)

- Minimal and reversible clinical pathology findings
- No CNS, cardiovascular, or respiratory safety signals
- Overall favorable safety profile at tested dose levels
- > 20X safety margin at predicted human efficacious dose

Predicted TNG961 Human PK

	Estimate
CL (ml/min/kg)	1.6
Vd (L/kg)	1.7
%F	21%
Half life (h)	~16

TNG961 attributes support selection as development candidate

Properties

MW, logP, TPSA 540, 5.0, 87

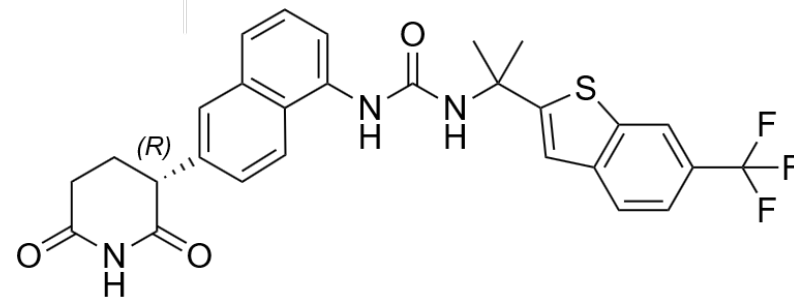
Potency and Selectivity

HBS1L Ternary Complex EC ₅₀ (nM)	14
HBS1L HiBiT DC ₅₀ (nM)*, D _{max}	0.05, 94%
Cellular viability GI ₅₀ (nM)*	2.3 nM
GSPT1 selectivity (HiBiT DC ₅₀)	~ 1500x

In vitro ADMET-PK

hCLint, hep (μL/min/10 ⁶ cells)	2.6
CYP IC ₅₀ (3A4, 2D6, 2C9) μM	> 50, > 50, 5.6
Eurofins SAFETYscan47	Acceptable
hERG IC ₅₀ (μM)	2.7

*Potency values corrected for media binding; viability from an average of 5 cell lines



In vivo PK (r, d, c)

T _{1/2} (hrs)	6.8, 7.1, 2.7
V _{dss} (L/kg)	3.4, 1.1, 1.0
%F	28, 21, 15

1 mpk IV, 3 mpk PO

Broad clinical development opportunity for TNG961 in FOCAD-deleted solid tumors

Monotherapy

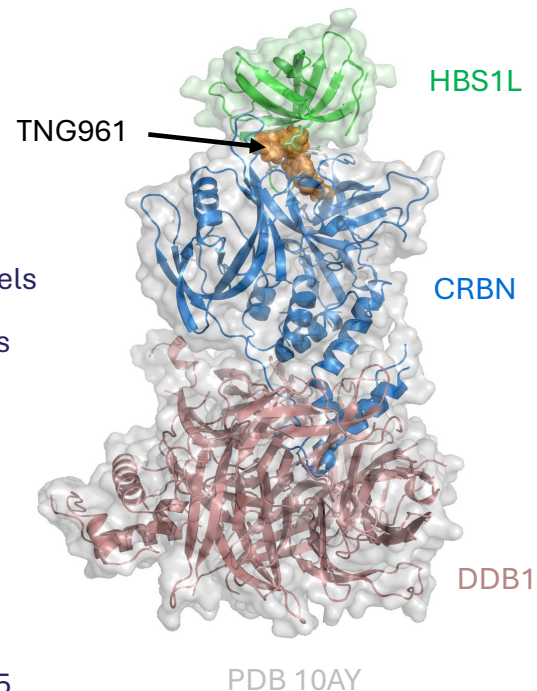
- ~4% of all human cancers are FOCAD deleted (~20,000 new metastatic cases per year in US)
 - ~5% of lung cancer is FOCAD deleted
- Patient population expansion: an additional ~2% of all tumors have SKI complex impairment
- Clinical activity anticipated as single agent

Combination

- All FOCAD-deleted tumors are also MTAP-deficient, creating opportunity for combination therapy with MTA-cooperative PRMT5 inhibitors
- Favorable safety profile predicts broad combination opportunities with standard-of-care and targeted therapies

TNG961 is an IND-ready, oral, potent, and selective HBS1L degrader for FOCAD deleted cancers

- **The HBS1L/PELO complex is a synthetic lethal target on chr9p21**
 - Approximately 1/3 of all MTAP-deleted tumors are also FOCAD-deleted
- **TNG961 is a first-in-class molecular glue degrader targeting HBS1L**
 - Anti-tumor activity across a range of chr9p21 deleted (FOCAD/MTAP-null) tumor models
 - GLP toxicology studies (NHP and rat) support advancement into first in human studies
- **Potent, selective, once-a-day oral clinical dosing**
 - Enabling formulation developed for GLP-tox and clinical studies
- **Clear clinical path**
 - Strong monotherapy activity and opportunity to combine with MTA-cooperative PRMT5 inhibitors in all FOCAD deleted tumors



Acknowledgements

Tango Therapeutics



AACR JOURNALS



Cancer Discovery: *Nicholson et al. TNG961 is a selective oral HBS1L molecular glue degrader for the treatment of FOCAD-deleted cancers*

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