TNG961: A selective oral molecular glue degrader of HBS1L inducing tumor regression in naïve and PRMT5i-refractory FOCAD-deleted models

Abstract B027

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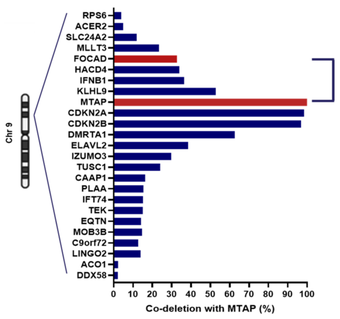
ABSTRACT

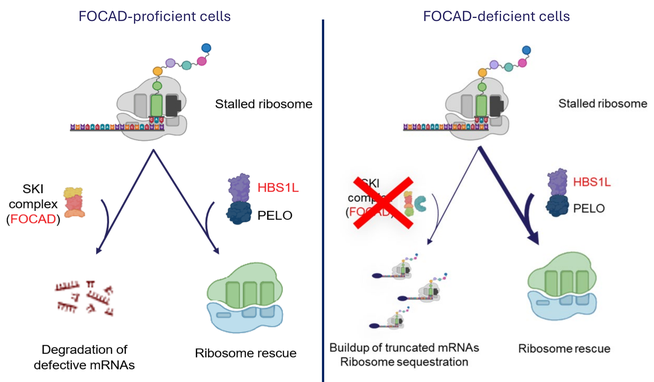
Chromosomal deletion of tumor suppressor genes can lead to collateral loss of nearby genes, creating therapeutic opportunities for synthetic lethal targeting. One example is the frequent co-deletion of MTAP with CDKN2A/B on chromosome 9p, which creates a dependency on PRMT5 for cell survival. Located telomeric to CDKN2A and MTAP is FOCAD, a gene encoding a protein essential for stabilizing the SKI complex. The SKI complex is responsible for degrading aberrant mRNAs, thereby maintaining mRNA homeostasis. Loss of FOCAD disrupts SKI complex function, resulting in ribosome stalling on aberrant mRNA transcripts. These stalled ribosomes are dependent on the HBS1L/PELO complex for rescue and recycling, establishing a synthetic lethal interaction between HBS1L/PELO and FOCAD loss.

TNG961 is a first-in-class molecular glue that targets HBS1L for degradation, representing a novel therapeutic strategy for FOCAD-deleted tumors. In vitro, TNG961 treatment leads to a dose-dependent decrease in HBS1L protein levels, which in turn destabilizes the portion of PELO involved in ribosome rescue. TNG961 displays proteome-wide selectivity for HBS1L, with no change in SALL4 protein level as determined by western blot. TNG961-induced HBS1L degradation and PELO destabilization can both be rescued by inactivation of CRBN confirming mechanism, which is further supported by cryoEM data. In engineered HiBiT knock-in cells, treatment with TNG961 induces maximal HBS1L degradation within 4 hours, without affecting GSPT1 protein levels. This selective degradation translates to potent growth inhibition in FOCAD-deleted cells, with ~100-fold selectivity compared to FOCAD-proficient cells across 5 isogenic pairs. This selective vulnerability is preserved in a large cell line panel of over 90 models. Finally, oral administration of TNG961 induces dose-dependent degradation of HBS1L and subsequent destabilization of PELO protein in FOCAD-deleted xenograft models, resulting in tumor stasis or regression across multiple lineages. Notably, TNG961 remains effective in a pancreatic model that has become refractory to PRMT5 inhibitor treatment, supporting its potential utility in PRMT5i-resistant settings. TNG961 has been nominated as a development candidate and is currently in IND-enabling studies.



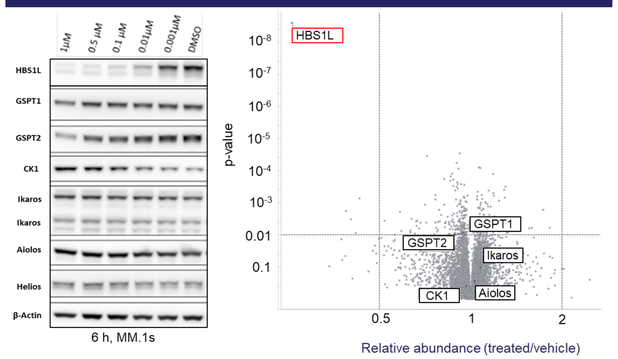
20-40% of MTAP-deleted cancers are also FOCAD-deleted

1. THERAPEUTIC HYPOTHESIS



FOCAD stabilizes the SKI complex; in the absence of FOCAD, the SKI complex is destabilized and aberrant mRNAs are not properly degraded. This results in increased ribosome stalling and disrupted mRNA homeostasis.

2. TNG961 IS A FIRST-IN-CLASS HBS1L SELECTIVE MOLECULAR GLUE DEGRADER



Western blotting and global proteomics (500 nM (>50X DC_{50}), 6 h) revealed TNG961 has proteome-wide selectivity for HBS1L and does not degrade common IMiD neosubstrates.

Kinetic monitoring of endogenous HBS1L by HiBiT knock-in demonstrates rapid and durable HBS1L degradation upon TNG961 treatment, without comparable impact to GSPT1.

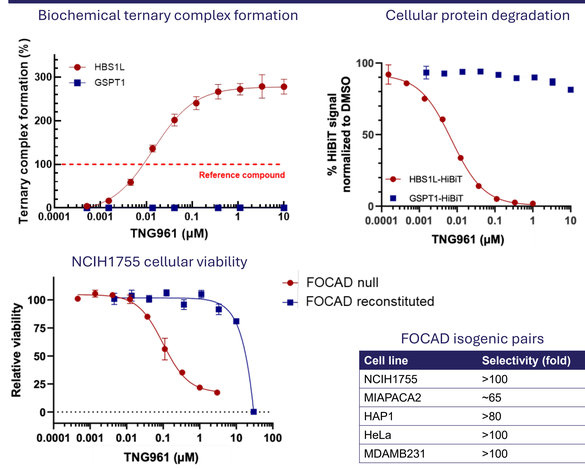
3. TNG961 INDUCES HBS1L DEGRADATION IN A CRBN-DEPENDENT MANNER

CRBN knockout (top) or inhibition of NEDDylation with MLN4924 (bottom) rescue TNG961-induced HBS1L degradation.

4. CRYO-EM STRUCTURE SHOWS TNG961 FACILITATES DIRECT CONTACT BETWEEN HBS1L AND CRBN

Specificity is driven by a combination of hydrogen bonds and hydrophobic interactions. Structure provides rationale for selectivity over GSPT1 through steric clash.

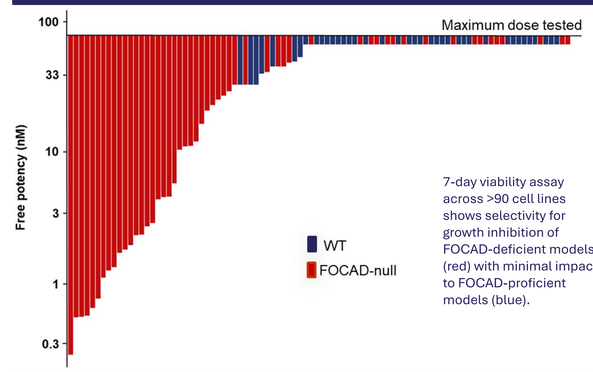
5. TNG961 DRIVES FORMATION OF A TERNARY COMPLEX WITH HBS1L AND CRBN AND LEADS TO HBS1L DEGRADATION AND FOCAD-DEPENDENT LOSS OF VIABILITY



FOCAD isogenic pairs

Cell line	Selectivity (fold)
NCIH1755	>100
MIAPACA2	~65
HAP1	>80
HeLa	>100
MDAMB231	>100

6. CELL LINE PANEL SHOWS EXCELLENT SELECTIVITY FOR FOCAD-DELETED VIABILITY IMPAIRMENT

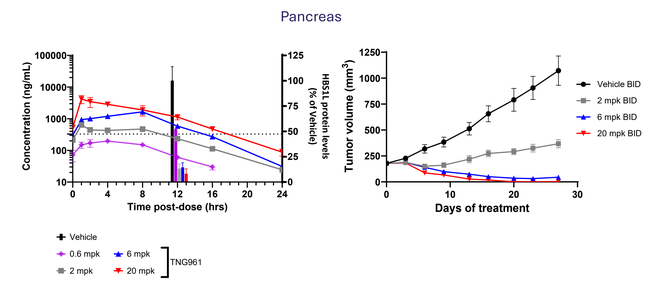


7-day viability assay across >90 cell lines shows selectivity for growth inhibition of FOCAD-deficient models (red) with minimal impact to FOCAD-proficient models (blue).

7. PRISM SCREEN OF >900 CELL LINES CONFIRMS CHR9P21 DELETION AS TOP CONTEXT FOR TNG961 AND HBS1L/PELO AS TOP GENE EXPRESSION CORRELATE

Left: Loss of Chr9p21 genes FOCAD and KLHL9 are top correlates for sensitivity to TNG961, confirming the synthetic lethal context.
Right: Knockout of HBS1L or its binding partner PELO most closely phenocopy the sensitivity profile of TNG961 across >900 cell lines, further supporting the on-target nature of its activity.

8. ORAL DOSING OF TNG961 DRIVES ON-TARGET AND DOSE-DEPENDENT ANTITUMOR ACTIVITY ACROSS MULTIPLE HISTOLOGIES



Dashed line reflects G50 value adjusted for mouse plasma protein and media binding.

TNG961 treatment causes tumor regressions in diverse in vivo models and is well tolerated at all doses tested.

9. PRECLINICAL DATA SUPPORTS POTENTIAL EFFICACY OF TNG961 IN PATIENTS WHO PROGRESS ON PRMT5i

TNG961 regresses tumors that progress after PRMT5i treatment.

SUMMARY

- TNG961 is a first-in-class HBS1L molecular glue degrader for the treatment of FOCAD-deficient cancers.
- TNG961 has excellent biochemical and cellular potency.
- TNG961 has proteome-wide selectivity for HBS1L.
- In a cell line panel of >90 models, TNG961 showed excellent selectivity for inhibiting growth of FOCAD-deficient models over FOCAD-proficient models.
- Oral dosing of TNG961 led to tumor growth inhibition or regression in multiple FOCAD-deficient xenograft models representing diverse histologies.
- TNG961 is currently in IND-enabling studies.

Acknowledgements

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