Abstract LB238

Expanding the TEAD Therapeutic Potential with Degraders: *In Vitro* Sensitivity, Predictive Biomarkers, and *In Vivo* Efficacy

Rajiv Sawant[1], Matthis Geitmann[1], Thomas Gossas[1], Wei Berts Emond[1], Ulf Bremberg[1], Konrad Koehler[1], Matthew G. Rees[2], Melissa M. Ronan[2], Jennifer A. Roth[2], and Peter Brandt[1]

[1]Beactica Therapeutics AB, Virdings allé 2, 754 50 Uppsala, Sweden. [2]Broad Institute of MIT and Harvard, Cambridge 02142 MA, USA.

Abstract

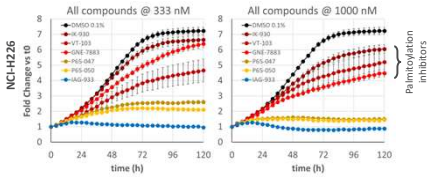
TEAD transcription factors have emerged as clinically validated targets for cancers with dysregulated Hippo signalling, such as mesothelioma driven by NF2 inactivation or deficiency. We have developed a series of novel targeted protein degraders of TEAD, designed to bind to TEAD interface 3.[1] These compounds function by inducing a ternary complex with the E3 ligase cereblon, resulting in ubiquitination and subsequent proteasomal degradation of TEAD.

P65-047, one of these degraders, was evaluated head-to-head with the palmitoylation inhibitor VT107 and the clinical candidate IAG933 using a large-scale cellular PRISM (Profiling Relative Inhibition Simultaneously in Mixtures) screen. This revealed sensitivity in cell lines beyond mesothelioma as well as a differentiation between the compounds in terms of which cell lines being sensitive. Univariate analysis of the PRISM sensitivity profile and genomic features identified VGLL3 gene expression as the strongest association for P65-047. Unlike the more well-known coactivators YAP and TAZ, which bind simultaneously to interfaces 1, 2, and 3, VGLL3 is a TEAD coactivator that binds only to interfaces 1 and 2. A multivariate gene expression biomarker analysis yielded a model that can predict cell line sensitivity to P65-047 (AUC = 0.85).

In pharmacokinetic experiments conducted in mice, intraperitoneal administration of P65-047 resulted in high exposure in both plasma and lung tissue. A dose-dependent degradation of TEAD1 was observed in lung tissue 24 hours after a single dose, with the compound being well tolerated and with no signs of toxicity.

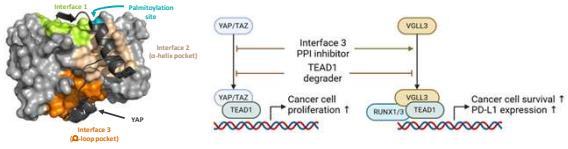
Inhibition of mesothelioma proliferation

Previous data demonstrate that Interface 3-binding TEAD degraders, such as P65-047, and the Interface 3-binding YAP–TEAD disruptor IAG933, outperform palmitoylation inhibitors in inhibiting the proliferation of mesothelioma cell lines NCI-H226 cells (NF2-deficient) and NCI-H2052 (NF-mutant) (5 days, Incucyte assay).[1]



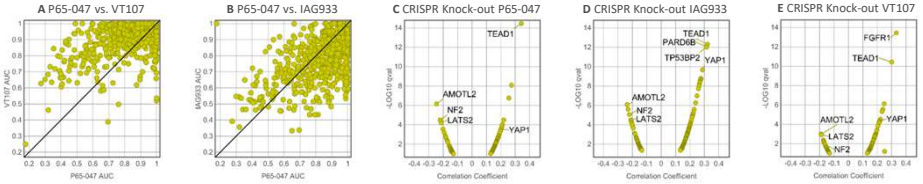
TEAD and the VGLL3 hypothesis

VGLL3 acts as a TEAD coactivator by binding exclusively to Interface 1 and 2, whereas YAP and TAZ also interact with Interface 3. TEAD degraders can bypass any VGLL3-mediated transcriptional activation of TEAD, while inhibitors targeting Interface 3 may instead enhance VGLL3 activation by displacing YAP and TAZ.



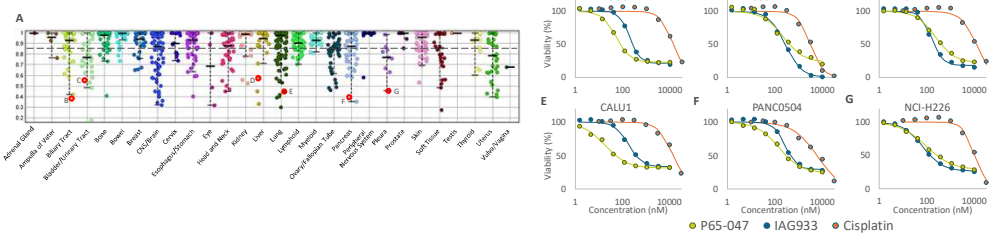
Efficacy and mechanistic landscape of P65-047, IAG933 and VT107

The three TEAD-targeting compounds were tested by the Broad Institute in a large-scale cell viability screen (PRISM). 845 cell lines were included representing over 45 major types of cancers. Comparing P65-047 with VT107 by means of AUCs reveals that the degrader in general is more efficacious (A). P65-047 compares better with IAG933 showing a strong correlation in the responses. However, it is also evident that some cell lines are selectively responsive to either of the compounds (B). We have previously demonstrated that the efficacy of P65-047 is dependent on cereblon.[1] A univariate analysis of associations between the PRISM sensitivity profiles and CRISPR knock-out data clearly confirm TEAD1 degradation as the mechanism of action for P65-047, and the negative correlation with CRISPR knock-out profiles of AMOTL2, NF2, and LATS2 further confirms the involvement of the Hippo pathway in the mechanism (C). The clean TEAD1 profile for P65-047 is not mirrored by IAG933 having additional positive correlations with PARD6B and TP53BP KO (D). Finally, the efficacy of VT107 is more correlated with FGFR1 KO than with TEAD1 KO (E).



P65-047 exhibits broad lineage coverage with selective sensitivity profiles

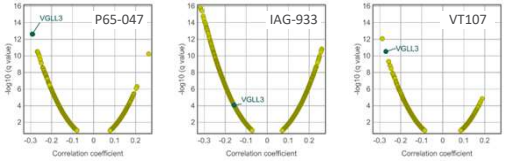
A lineage enrichment analysis of the PRISM data for P65-047 confirmed pleura cell lines (mesothelioma) as sensitive and reveals that cell lines from bladder/urinary tract and uterus are particularly sensitive. Kidney cell lines are among the least sensitive. The analysis also expose a large spread in sensitivities in most lineages, suggesting utility of P65-047 in many types of cancer. Potency against a selected set of cell lines was confirmed at an external CRO and compared to the Interface 3 inhibitor IAG933 (B–G).



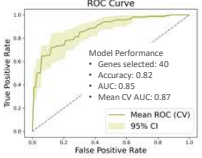
P65-047 efficacy correlates with VGLL3 expression – potential for a companion diagnostic

Gene expression correlation analysis using the PRISM AUC data revealed that out of the 19,194 genes monitored, VGLL3 was the top-ranked gene in terms of its correlation with P65-047 sensitivity (A). The corresponding ranks for IAG933 and VT107 were 1197 and 2, respectively. A further analysis using the Reactome pathway database with top correlated genes, revealed a very clean profile of P65-047 where the top correlated genes are focused on Hippo signalling, YAP/TAZ-stimulated gene expression, and extracellular matrix organization. A random forest predictive model of cell line sensitivity was developed using gene expression data from PRISM-tested cell lines (B). The model achieved an AUC of 0.85, demonstrating strong predictive power. These findings support the potential development of a companion diagnostic for patient stratification.

A Gene expression correlation analyses



B Prediction of Sensitivity



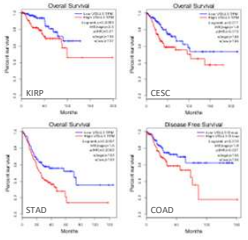
- Random Forest classifier (Python 3.12.2, Scikit-learn 1.4.2)
- Gene expression data (TPM, log-transformed) from DepMap
- Training set included only Quartile 1 (sensitive) and Quartile 4 (resistant) cell lines
- 5-fold stratified cross-validation
- 95% CI estimated from 1,000 bootstrap samples

Opportunity in cancers overexpressing VGLL3

Overexpression of TEAD co-activator VGLL3 correlates with statistically significant worse outcome for patients with the following cancer types:

- Kidney
  - Kidney renal papillary cell carcinoma (KIRP)
  - Kidney renal clear cell carcinoma (KIRC)
- Gastric
  - Stomach adenocarcinoma (STAD)
- Cervical
  - Cervical esophageal squamous cell carcinoma (CESC)
- Colon
  - Colon adenocarcinoma (COAD)

VGLL3 may drive cancer cell proliferation in these cancer types and if so, they may be resistant to TEAD interface 3 inhibitors while sensitive to degraders

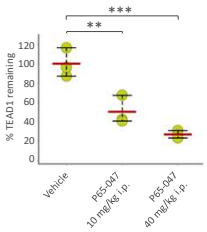


Data source: The Cancer Genome Atlas (TCGA).

In vivo TEAD1 degradation in lung

The TEAD degrader P65-047 was given as a single dose intra-peritoneally to Balb mice to investigate tolerability, pharmacokinetics and TEAD1 degradation in target tissue.

- No acute toxicity observed
- Good exposure in target tissue (lung)
- Significant and dose-dependent elimination of TEAD1 in target tissue (lung) measured 24 h after administration



Summary

- Targeted protein degraders of the TEAD transcription factors, incl. P65-047, have previously been generated and characterised in mesothelioma cell lines, exhibiting excellent stand-alone efficacy as well as synergies with several marketed drug classes.[1]
- A PRISM viability screen across 845 human cancer cell lines from 45 major cancer types revealed a clean profile of P65-047, confirming TEAD and the Hippo pathway as the mechanism of action.
- Sensitivity to P65-047 was observed across the 845 cancer cell lines, suggesting a therapeutics potential beyond mesothelioma for this compound.
- The efficacy of P65-047 exhibited a remarkable correlation with VGLL3-regulated transcription, which is noteworthy as overexpression of VGLL3 is associated with worse patient outcome in several cancers with significant unmet medical need.
- *In vivo* observations from mouse PK study with P65-047 include a lack of acute toxicity and a significant and dose-dependent elimination of TEAD1 in the target tissue.

Reference

1) Sawant, R. *et al.* Proceedings of the American Association for Cancer Research Annual Meeting 2024; Part 2 (Late-Breaking, Clinical Trial, and Invited Abstracts). Philadelphia (PA): AACR; Cancer Res 2024;84(7_Suppl): Abstract nr LB029.

Correspondence: Peter.Brandt@beactica.com