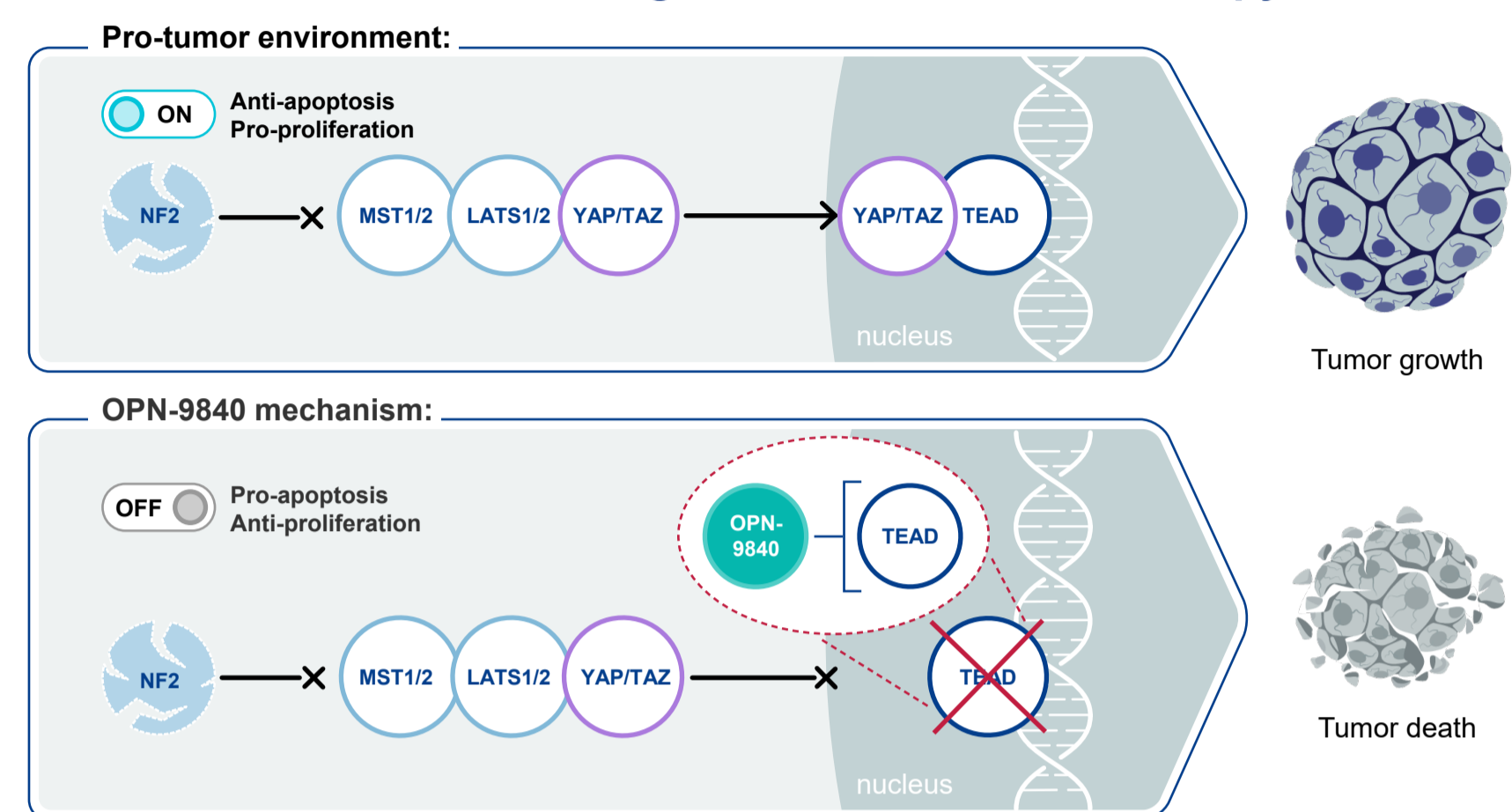


OPN-9840, a non-covalent potent pan-TEAD inhibitor, exhibits single agent efficacy in preclinical malignant mesothelioma models

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TEAD inhibitors block tumor growth and overcome therapy resistance



The Hippo pathway regulates critical cellular processes during development. In ~10% of human cancers, Hippo pathway dysregulation results in YAP/TAZ overactivation and increased TEAD-dependent transcription that promotes tumor growth and therapy resistance - often by supporting drug-tolerant persister survival. In 40% of malignant mesotheliomas (MM), neurofibromatosis (*NF2*) gene mutations inactivate the Merlin protein, an upstream negative regulator of TEAD. Preclinical studies indicate high TEAD dependency in *NF2*-mutant MM. We have discovered an array of potent covalent and non-covalent small molecule inhibitors that occupy the palmitate-binding pocket of TEAD proteins, with varying paralog selectivity profiles.

OPN-9840 is an orally active, non-covalent pan-TEAD inhibitor displaying dose-dependent and on-target *in vitro* and *in vivo* efficacy for NCI-H226, an *NF2*-mutant MM cell line. Additionally, OPN-9652 is an orally active covalent compound from a separate chemical series to OPN-9840. We present data here to demonstrate monotherapy and combination efficacies of both compounds in preclinical MM models.

OPN-9840 and OPN-9652 are potent pan-TEAD small molecule inhibitors

Compound	Protein Thermal Shift dTm (°C)				Cellular		
	TEAD1	TEAD2	TEAD3	TEAD4	Reporter (µM)	Proliferation (µM)	
OPN-9840	10	10	10	10	0.244	0.24	1.02
OPN-9652	10	20	20	6	0.014	3.40	2.74

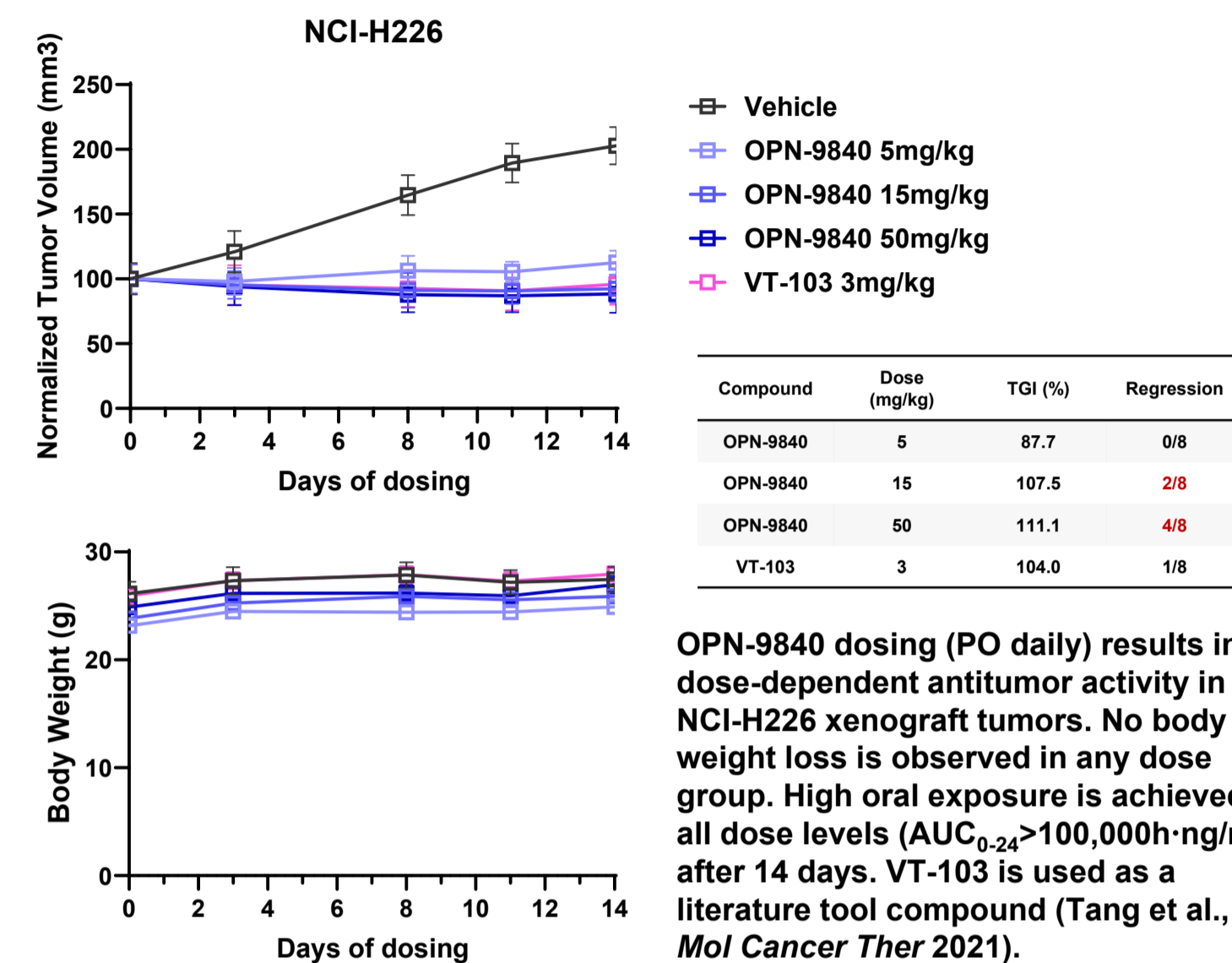
Both OPN-9840 and OPN-9652 are pan-TEAD inhibitors based on protein thermal shift assay data. In MSTO-211H cells, both compounds inhibit a TEAD-dependent luciferase reporter with sub-micromolar activities. In 5-day cell proliferation assays, cell viability is measured with CellTiter-Glo. While both compounds impair proliferation of the *NF2*-deficient mesothelioma cell lines, NCI-H226 and NCI-H2050, OPN-9840 displays improved pharmaceutical properties.

OPN-9840 is safe and has brain penetration potential

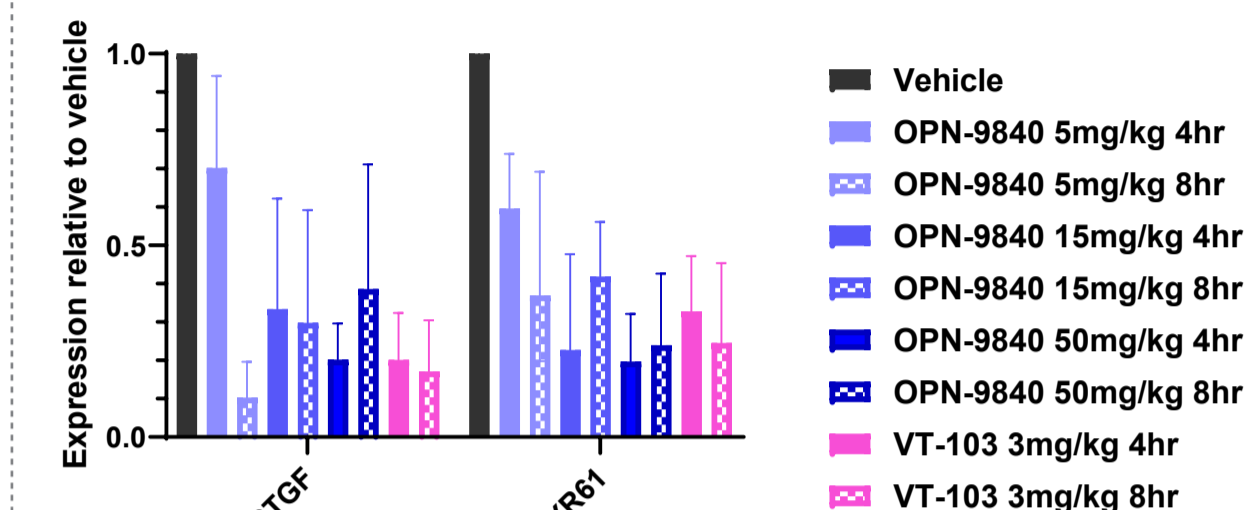
Parameter	Cytotoxicity (µM)		Phototoxicity (PIF ratio)	BBB PAMPA (-Log P _o)
	HEK293T	Hep G2		
OPN-9840	>50	>50	1.02	4.73

OPN-9840 shows no *in vitro* cytotoxicity in HEK293T or Hep G2 cells after 1 or 3 day(s) of incubation. Photo-irritancy factor (PIF) of 1.02 indicates no phototoxicity. Blood-brain barrier (BBB) specific parallel artificial membrane permeability assay (PAMPA) reveals high BBB penetration potential. Overall, OPN-9840 has a favorable safety profile and is likely brain penetrant.

OPN-9840 exhibits dose-dependent and on-target antitumor activity in NCI-H226 xenograft tumors

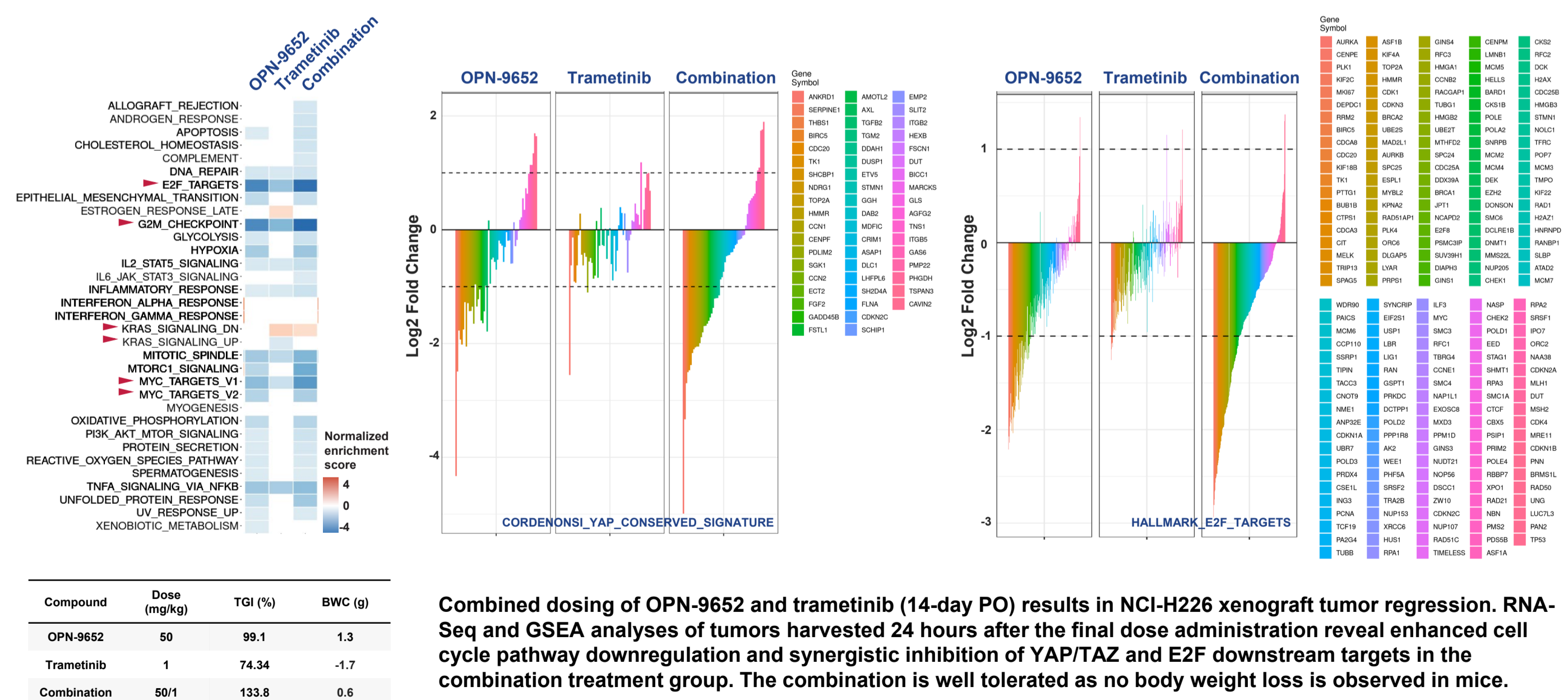


RESULTS

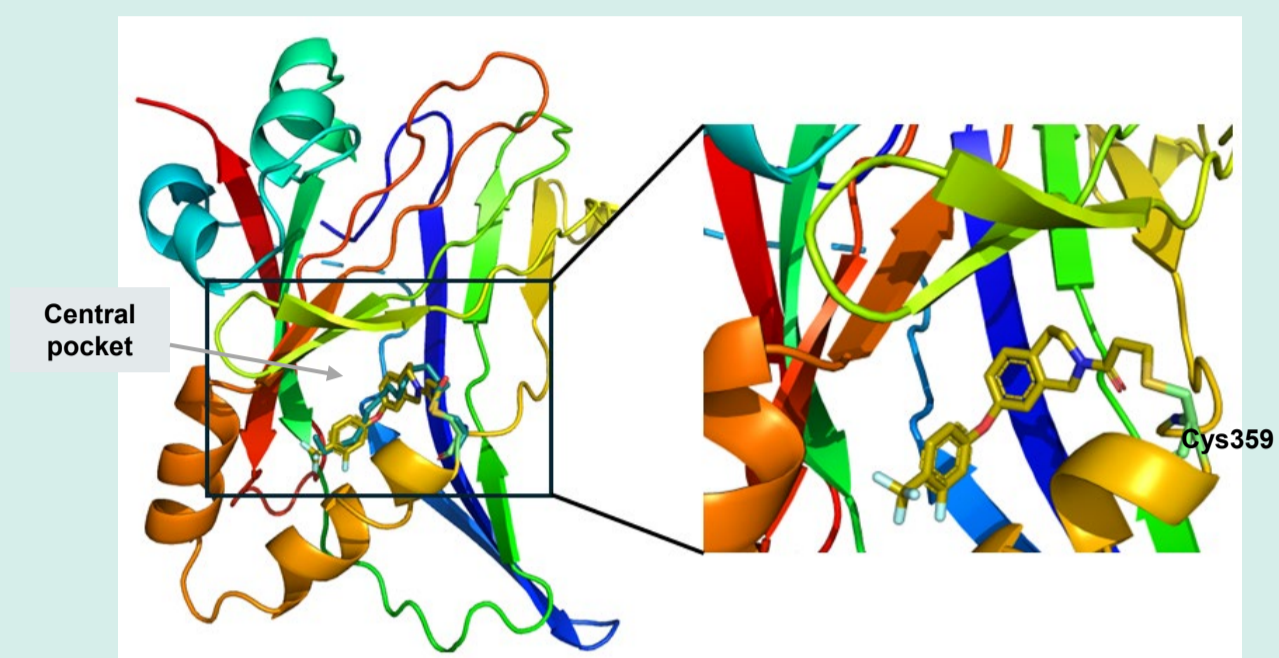


Pharmacodynamic analysis of tumors harvested 4 or 8 hours after the final compound administration shows significantly decreased expression of TEAD target genes, *CTGF* and *CYR61*, in OPN-9840- and VT-103-treated NCI-H226 xenograft tumors. 15 or 50mg/kg of OPN-9840 results in >50% of target gene expression reduction.

Combined TEAD and MAPK inhibition synergistically suppresses YAP/TAZ and E2F targets in NCI-H226 tumors



Co-crystal structure of OPN-9652 bound to TEAD1



Co-crystal structure of OPN-9652 bound to TEAD1 (residues 209-426) was solved to 2.03Å resolution (PDB ID: 8S6Y). OPN-9652 occupies the central palmitate-binding pocket and covalently modifies Cys359 on TEAD1 protein. Figure on the left shows an overlay of OPN-9652 (gold) and palmitate (green) in the central pocket of TEAD1. Zoomed in figure on the right shows covalent modification of Cys359 (mint) by OPN-9652 (gold).

CONCLUSIONS:

- ✓ OPN-9840 and OPN-9652 are orally active, potent pan-TEAD small molecule inhibitors.
- ✓ OPN-9840 non-covalently and OPN-9652 covalently bind to the central palmitate-binding pocket of TEAD proteins.
- ✓ OPN-9840 is safe and has brain penetration potential.
- ✓ OPN-9840 as monotherapy shows on-target and dose-dependent *in vivo* efficacy for MM, achieving high exposure and tumor regression with oral daily dosing in mice.
- ✓ Gene expression profiling of OPN-9652 and trametinib combination-treated tumors reveals synergistic inhibition of YAP/TAZ and E2F targets.
- ✓ Further development of OPN-9840 as monotherapy and in combination with other agents in MM as well as additional oncology indications is planned.

