Abstract #5913: TEAD1/4 inhibitors exhibit deeper biological impact and broader activity compared to TEAD1-only inhibitors in both monotherapy and combination without additional kidney toxicity

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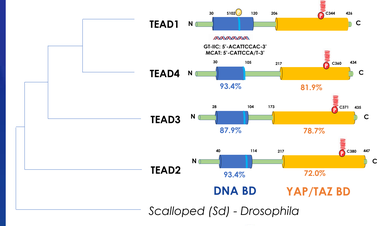
Poster #3

SPOROS BIODISCOVERY

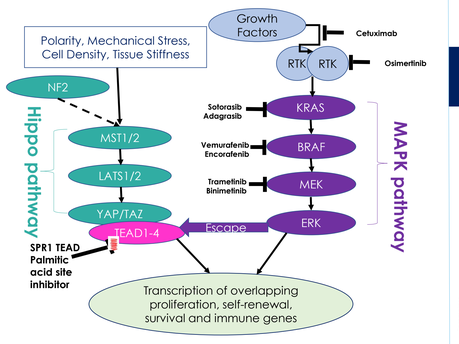
Abstract

- The TEAD transcription factors in association with the YAP/TAZ co-activators drive the expression of pro-proliferative and pro-oncogenic genes that underly the transformed phenotype of many carcinomas.
- YAP-TEAD transcriptional activity is emerging as a major resistance mechanism for diverse precision oncology drugs, with the most extensive data for resistance to drugs targeting the MAPK pathway.
- Clinical activity with confirmed RECIST objective responses reported with the TEAD1/2/3 inhibitor VT3989 but no RECIST objective responses with the TEAD1-preferential inhibitor IK930
- IK930 (TEAD1-preferential) showed a more favorable safety profile compared to VT3989 (TEAD1/2/3) with respect to proteinuria.
- Here, we provide novel, corroborating data supporting the TEAD-paralog inhibitor profile of SPR1 for TEAD1 and TEAD4 and the exclusion of TEAD2 and TEAD3
- We show that 1) SPR1 displays broader and deeper cell-based activity and extends the utility of TEAD inhibitors outside of mesothelioma and NF2 mutants 2) SPR1 shows stronger activity than TEAD1-only inhibitors in combination with MAPK and EGFR inhibitors in vitro and in vivo 3) SPR1 does not cause proteinuria in mice; dogs or rats even above therapeutic doses 4) SPR1 does not show the context-specific stimulation of tumor growth in Lung PDX previously observed with VT3989 and other inhibitors that include TEAD2 in their profile.
- Taken together – the data suggests SPR1 is positioned to become a best-in-class TEAD palmitic acid site inhibitor with broad utility in both monotherapy and combination setting.

The TEAD transcription factors are key oncogenic drivers and mediate resistance to MAPK pathway inhibition



- Four TEAD family members with redundant and unique functions
- Genetic and pharmacological data strongly indicate that inhibition of specific TEAD family members will likely be deleterious in the clinic and limit dosing
- Sporos wet-lab and bioinformatic analysis has identified which TEAD paralogs are most critical to inhibit for anti-tumor activity and which to avoid for minimizing toxicity



Target profile: TEAD1/TEAD4>TEAD3>>>TEAD2

- **TEAD1: Inhibitor binding required to block inhibition**
- **TEAD2: Inhibition associated with adverse stimulation of proliferation**
- **TEAD3: Inhibition further restricts proliferation in combination with TEAD1 but is also a driver of kidney toxicity**
- **TEAD4: Inhibition increases proliferation inhibition in combination with TEAD1 not associated with deleterious effects**

Summary of key onocgenoic data of the YAP and TEAD paralogues

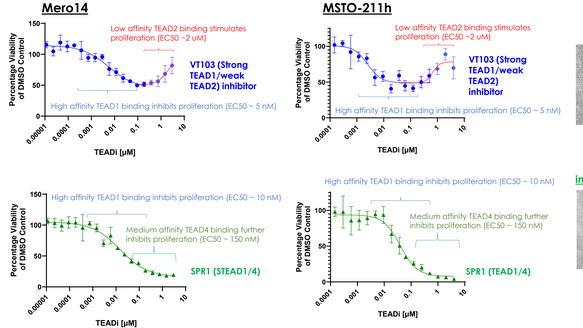
	Germline Knockout Phenotype	Adult knockout	Oncofusions (TCGA)	Focal Amplifications (TCGA)	DepMapr Cell Line Median mRNA Expression (log2 TPM)	DepMap Cell Line CRISPR Dependency	Dependent Cell lines (CRISPR, out of 1093) Cheonos 22Q2	Dependent Cell lines (RNAi, out of 710) DEMETER2	Copy-number/Dependency correlation P-value
TEAD1	Lethal E12	Lethal	9	4	4.07	-0.22	201	76	NS
TEAD2	Viable	ND	2	0	3.03	0.02	1	0	NS
TEAD3	Kidney	ND	1	4	3.13	-0.28	105	1	NS
TEAD4	Lethal E3	Viable	9	18*	3.84	-0.19	40	4	1.85e-11
YAP1	Lethal	Kidney	23	61*	4.50	-0.32	298	47	1.88e-13
WWTR1 (TAZ)	Lethal P21	Kidney	8	10*	3.95	-0.39	349	29	NS

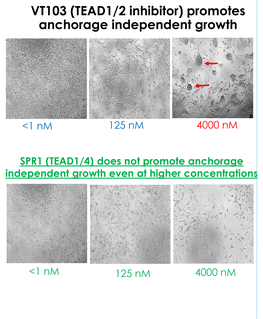
SPR1 has a unique isoform TEAD1/4 specificity as compared leading TEAD inhibitors

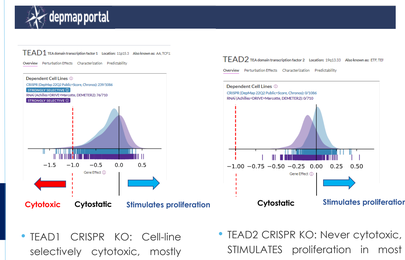
Company	Asset	Isoform Profile	Notes
Sporos BioDiscovery	**SPR1**	**TEAD1/4**	• **First-in-class TEAD1/4 inhibitor with potential best-in-class profile** • **No significant findings of kidney toxicity in preclinical models** • **Submission of IND application expected in Q1:24**
Ikena Oncology	IK930	TEAD1*	• Preliminary Phase 1 data expected in H2:2023 • Planned combination study with AstraZeneca's EGFR inhibitor Tagrisso (osimertinib)
Vivace Therapeutics	VT103	TEAD1#	• Preclinical development only • Highly active against TEAD1 with weak TEAD2 binding
Vivace Therapeutics	VT3989	TEAD1/2/3#	• Initial Phase 1 data reported at AACR 2023 with seven patients achieving PRs (six with mesothelioma, one sarcoma) • No DLTs reported, but increases in albuminuria observed
Novartis	IAG933	Pan-TEAD^	• Phase 1 started in late 2021; data expected in 2023
SpringWorks Therapeutics	SW-682	Pan-TEAD*	• Submission of IND application expected in 2023
Betta Pharmaceuticals	BPI-460372	TEAD1/3/4*	• Phase 1 to start in China in 2023 • Proteinuria observed at higher dose levels in preclinical animal model (species not disclosed)

* Updated at AACR 2023
* From published literature

Stimulation of cell proliferation *in vitro* and tumor growth *in vivo* by palmitic acid site inhibitors with TEAD2 activity







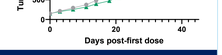
- TEAD1 CRISPR KO: Cell-line selectively cytotoxic, mostly cytostatic
- TEAD2 CRISPR KO: Never cytotoxic, STIMULATES proliferation in most cell lines

Compounds that include TEAD2 in their isoform inhibitory profile may paradoxically promote tumor growth

Drug	Model	%TGI*	Treatment Length for TGI calculation	Source
SPR1-326	LU-01-1291 Lung Adeno PDX	12.7	15 days	This study
IK930 (TEAD1)	LU-01-1291 Lung Adeno PDX	-0.8	~15 days	Hidalgo et al 2023 AACR Poster #3852; Figure 6
"panTEAD" (TEAD1/3/2)	LU-01-1291 Lung Adeno PDX	-47.6	~15 days	Hidalgo et al 2023 AACR Poster #3852; Figure 6
Osimertinib (mEGFR)	LU-01-1291 Lung Adeno PDX	+89.0	~15 days	Hidalgo et al 2023 AACR Poster #3852; Figure 6
VT3989 (TEAD1/2/3)	LU-01-1291 Lung Adeno PDX	-37.5	~17 days	Tang and Post 2022 AACR Poster #5364
Osimertinib (mEGFR)	LU-01-1291 Lung Adeno PDX	+98.1	~17 days	Tang and Post 2022 AACR Poster #5364
VT3989 (TEAD1/2/3)	LU-01-1291 Lung Adeno PDX	-40.6	~17 days	Tang and Post 2023 NCI-AACR-EORTC Poster #B088
VT3989 (TEAD1/2/3)	HT-29 COAD CDX	-56.5	23 days	Tang and Post 2023 NCI-AACR-EORTC Poster #B088
VT3989 (TEAD1/2/3)	CR-6243 COAD PDX	-64.0	28 days	Tang and Post 2023 NCI-AACR-EORTC Poster #B088
VT3989 (TEAD1/2/3)	LU-01-1137 Lung NSCLC PDX	-22.9	34 days	Tang and Post 2023 NCI-AACR-EORTC Poster #B088
VT3989 (TEAD1/2/3)	EBC1 Lung NSCLC CDX	-57.7	21 days	Tang and Post 2023 NCI-AACR-EORTC Poster #B088

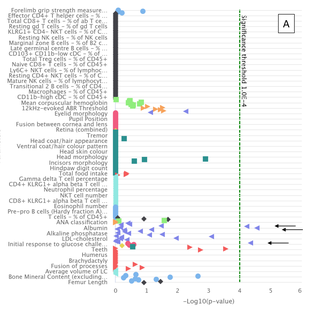
*%TGI was calculated as 100% x (1 - [Tumor volume Treated]/[Tumor volume Vehicle]) between 15 and 21 days. Negative TGI numbers indicate drug treatments that resulted in larger tumors than vehicle.

SPR1 (TEAD1/4) does not show paradoxical stimulation of tumor growth

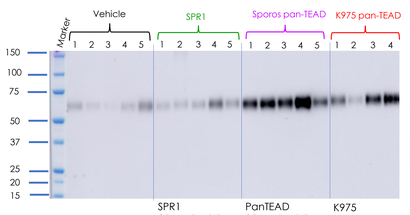


TEAD3 inhibition and kidney toxicity

***Tead3*$^{-/-}$ mice show plasma Creatinine elevation and Albumin reduction – consistent with a podocyte effacement/proteinuria phenotype previously reported in Podocyte-specific YAP1/TAZ knockout mice**



Mouse Phenotype Database (IMPC) features (969 measured metrics) of *Tead3*$^{-/-}$ (MGI: 109241) were downloaded from the IMPC consortium page with a summary shown in **Panel A** with select blood chemistry alterations reaching statistical significance (corrected for multiple comparison testing) indicated by arrows. Detailed view of the blood chemistry features are shown in **Panel B** with elevation of plasma creatinine and Magnesium as well as decrease in plasma Albumin reaching significance. **Panel C** shows quantification of creatinine levels in plasma with a statistically significant increase that reached statistical significance for both sexes (Mean +/- S.D. N = 7 for Tead3 homozygotes (blue bars) and N = 2048 for reference controls (orange)]. Male P< 0.0254; female P<0.000693; combined genotype P<5.92×10^{-5}.



No Albuminuria/proteinuria after 28 days of dosing SPR1 in mice but readily observed as early as 14-days with the Pan-TEAD inhibitor K975

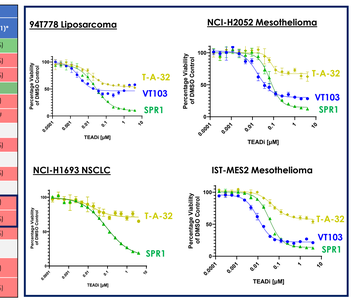
IB: Albumin antibody Cell signaling #4929

Mouse urine - Albumin IB - Day 28 samples

TEAD1-specific inhibition is necessary but not sufficient for impactful response

TEAD1/4 Inhibition Outperforms TEAD1 in Mesothelioma and Extends Utility Beyond NF2 Mutant Mesothelioma

Cell Line	Lineage	Absolute IC50 (nM) (% viability @ 3μM)		
		Hippo Driver Mutation	SPR1 (TEAD1/4)	VT103 (TEAD1>2)	T-A-32 (TEAD1)*
NCI-H23	NSCLC	NF2-WT (control)	>3,000 (83%)	>3,000 (130%)	>3,000 (83%)
NCI-H2452	Mesothelioma	No Hippo driver mutations	398 (37%)	>3,000 (58%)	>3,000 (62%)
IST-MES2	Mesothelioma	No Hippo driver mutations	263 (27%)	764 (43%)	>3,000 (74%)
NCI-H226*	Mesothelioma	NF2-null	30 (11%)	4 (23%)	70 (22%)
NCI-H2052	Mesothelioma	NF2-mutant/LATS2-del	54 (13%)	24 (21%)	2,954 (54%)
Mero-14	Mesothelioma	NF2-mutant	16 (8%)	17 (33%)	Insensitive#
MSTO-211h*#	Mesothelioma	NF2-WT (LATS1/LATS2)	13 (11%)	35 (43%)	No Data
MSTO-211h (Jabs)	Mesothelioma	NF2-WT (LATS1/LATS2)	110 (9%)	>3,000 (67%)	>3,000 (64%)
SDM103T2	Mesothelioma	NF2-low	57 (18%)	163 (45%)	No Data
Mero-82*	Mesothelioma	NF2-mutant	94 (19%)	1,037 (60%)	>3,000 (80%)
Mero48A	Mesothelioma	N/A – YAP hyperactive	116 (25%)	>3,000 (52%)	No Data
947778	Liposarcoma	N/A – YAP hyperactive	31 (10%)	>3,000 (78%)	1,386 (52%)
NCI-H1693*	NSCLC (Adeno)	N/A – YAP hyperactive	118 (18%)	>3,000 (120%)	>3,000 (65%)
LOU-NH-91	NSCLC (SCC)	NF2/LATS1-mutant	104 (32%)	>3,000 (55%)	>3,000 (81%)
Caki-1	RCC	NF2 – homozygous deletion	137 (36%)	>3,000 (104%)	No Data
BHY	Head & neck SCC	FAT1-mutant	164 (32%)	>3,000 (70%)	1,241 (26%)
SCC25*	Head & neck SCC	N/A – YAP hyperactive	301 (25%)	>3,000 (82%)	>3,000 (63%)

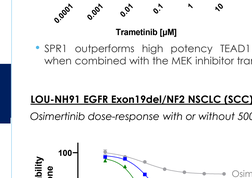


* T-A-32 identified as IK-930 (https://victoriacayonde.substack.com/p/ik-930-tead-inhibitor)
# Insensitive to VT3989 (Competitor's TEAD1/2/3 inhibitor in fIH trial) with IC50 values greater than 150nM as presented by Vivace Therapeutics at AACR2023
# Insensitive to IK930 (Competitor's TEAD1 inhibitor in trials) as reported by IKENA Therapeutics at AACR2023;
* Cell lines validated for their sensitivity to SPR1 in vivo CDX.

TEAD1/4 inhibition achieves a deeper anti-neoplastic response in combination

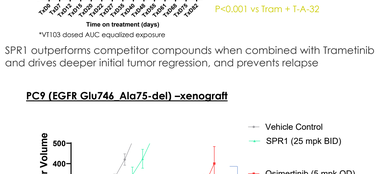
MDA-MB-231 KRAS G13D/NF2

Trametinib dose-response with or without 500 nM TEADi



- SPR1 outperforms high potency TEAD1 inhibitor when combined with the MEK inhibitor trametinib

MDA-MB-231 KRAS G13D/NF2 – Orthotopic xenograft

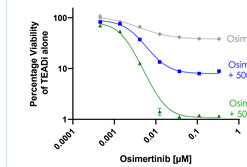


*VT103 dosed AUC equalized exposure

- SPR1 outperforms competitor compounds when combined with Trametinib and drives deeper initial tumor regression, and prevents relapse

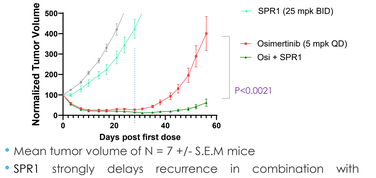
LOU-NH91 EGFR Exon19del/NF2 NSCLC (SCC)

Osimertinib dose-response with or without 500 nM TEADi



- SPR1 outperforms competitor compound when combined with blockbuster EGFR inhibitor osimertinib

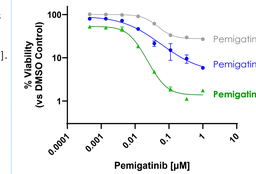
PC9 (EGFR Glu746_Ala75-del) –xenograft



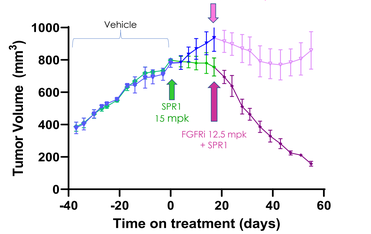
- Mean tumor volume of N = 7 +/- S.E.M mice
- SPR1 strongly delays recurrence in combination with blockbuster EGFR inhibitor Osimertinib (treatment discontinued at Day 28 indicated by dashed line)

MSTO-211h NF2-WT FGFR2-WT Mesothelioma

Pemigatinib (FGFR inh) dose-response with or without 500 nM TEADi



- SPR17 outperforms VT103 when combined with FGFR inhibitor in FGFR-WT Mesothelioma



- Exceptionally strong Interaction between SPR1 and FGFRi in vivo

Conclusions: TEAD1/4 paralog specificity offers an optimal balance between anti-tumor efficacy as well as toxicity and portends SPR1 as a best-in-class TEAD inhibitor

Acknowledgements

We thank Xing Hai (WuXi) for excellent technical support with CDX experiments and Lauren Hopfer for preparation of the poster.