Abstract #112: A Family of Novel TEAD Palmitoylation Site Inhibitors with Exceptional Pre-clinical Anti-neoplastic Activity as a Monotherapy and in Combination with MAPK Inhibitors

Florian Muller, Dora Warshaviak, Jeno Gyuris, Erkan Baloglu, Andrew Morley, Deepavali Chakravarti, Sharon Shacham
Sporos Bioventures, @JLABS Suite 201, 2450 Holcombe Blvd, Houston, TX 77021

Abstract

- The Hippo pathway (effected by the YAP/TAZ-TEAD transcriptional complex) is a major regulator of cell density and organ size, and is a major pro-growth, pro-survival pathway yet to be targeted in precision oncology.
- YAP/TAZ-TEAD transcription is hyperactivated by specific genetic events (e.g. YAP/TAZ oncofusions, NF2 mutations) and has been demonstrated as a key mechanism of resistance to MAPK pathway inhibition, as well as inhibition of its upstream inputs, such as EGFR and other receptor tyrosine kinases.
- SPOROS Biodiscovery has developed a series of next-generation small molecule inhibitors (SPR1) of the TEAD transcription factors, with improved efficacy and safety, through fine-tuning of TEAD isoform specificity
- We show that SPR1 TEAD inhibitors have exceptional anti-tumor activity *in vivo*, achieving regression even with large tumors

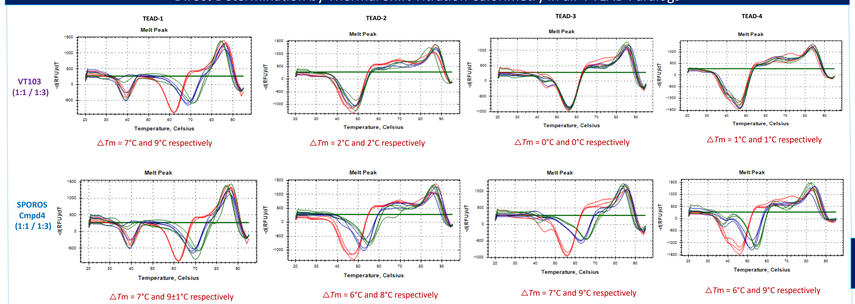
Background

- The Hippo pathway is executed by the YAP1/WWTR1 co-activators and TEAD1-4 transcription factors
- Palmitoylation of TEADs is required for transcriptional activity and constitutes a druggable pocket
- SPOROS generated two families of next-generation TEAD palmitoylation site inhibitors with optimized TEAD isoform specificity maximizing anti-proliferative activity and minimizing toxicity

Main Novel Findings

TEAD Isoform Inhibitory Specificity Quantification

Direct Determination by Thermal Shift Titration Calorimetry in all 4 TEAD Paralogs



Compounds	TEAD1	TEAD2	TEAD3	TEAD4
	ΔTm(°C)			
	10 µM TEAD Protein			
VT103 (1:1 / 1:3)	△7° / △9°	△2° / △2°	△0° / △0°	△1° / △1°
SPOROS Cmpd4 (1:1 / 1:3)	△7° / △9±1°	△6° / △8°	△7° / △9°	△6° / △9°

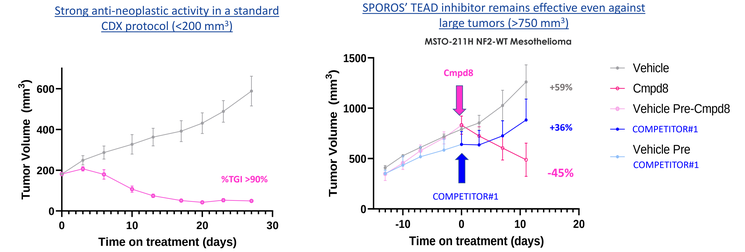
Broad and Potent Cell-Based Activity of SPOROS TEAD inhibitors

TEAD inhibitor (nM)	H226 (NF2-null)	H2052 (NF2-mutant)	Mero-14 (NF2-mutant)	Mero-82 (NF2-mutant)	H23 (NF2-WT)	MeT-5A (normal epithelial cells)
SPOROS Cmpd4	12	5	ND	ND	>10,000	>10,000
SPOROS Cmpd5	14	51	8	11	>10,000	>10,000
SPOROS Cmpd3	17*	4	6	7	>10,000	>10,000
SPOROS Cmpd8	3	ND	2	13	>10,000	ND
COMPETITOR #3	20	49	5	23	2,710	ND
COMPETITOR #2	87	1000	35	240	>10,000	ND
COMPETITOR #1	2	1	>10,000	>10,000	>10,000	>10,000

- Low-nM potency, combined with broad activity in TEAD-dependent cell lines
- Minimal toxicity to non-transformed cells

SPOROS TEAD Inhibitors Drive Regression Even in Very Large Tumors

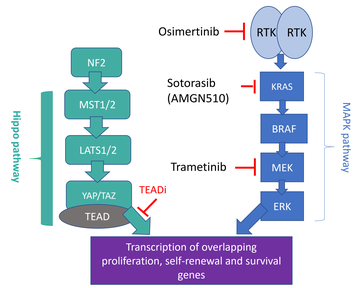
Unique to SPOROS With No Comparable Data from other TEAD inhibitors to Date

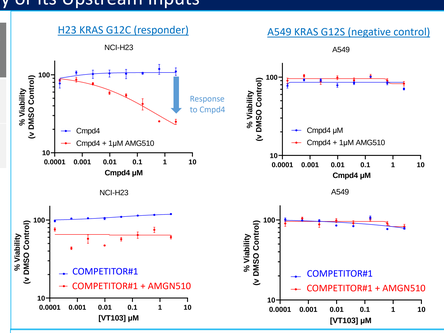


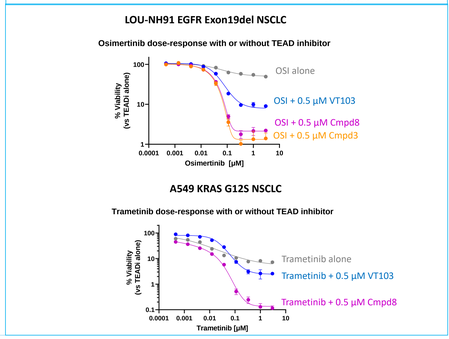
SPOROS TEAD Inhibitors Synergize with Precision Oncology Drugs Targeting the MAPK Pathway or its Upstream Inputs

TEAD Inhibitor (nM)	H23 (KRAS G12C) EC50	H23 (KRAS G12C) + AMGN-510	A549 (KRAS G12D) EC50	A549 (KRAS G12D) + AMGN-510
SPOROS Cmpd4	>2,500	27	>2,500	>2,500
COMPETITOR#1	>2,500	>2,500	>2,500	>2,500

- Highly specific interaction with KRAS inhibitor in G12C, but not in G12S mutant cell line
- No obvious interaction of KRAS inhibitor with competitor's TEAD inhibitor [COMPETITOR#1]







Conclusion

- TEAD inhibitors show exceptional anti-tumor effects in pre-clinical models in vivo, with rapid regression in large tumors
- As molecular pathways predict, TEAD inhibitors strongly interact with direct inhibitors of the MAPK pathway or inhibitors of upstream activators of the MAPK pathway
- SPOROS TEAD inhibitors lead to regression even in large tumors, most likely because of favorable TEAD isoform inhibitory specificity.

Acknowledgements

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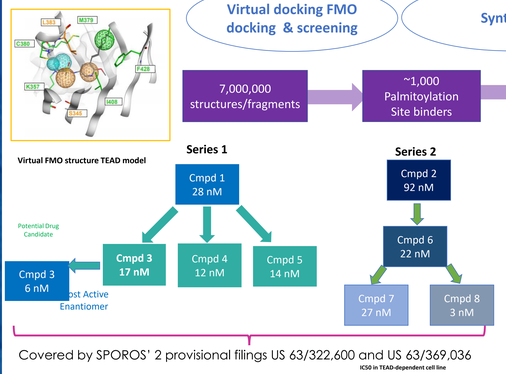
SPOROS' TEAD Inhibitors

From VD Model & SAR to Single-digit nM Activity in Cell-based Systems



- Identified palmitoyl-binding pocket in TEAD as a suitable docking site
- Generated TEAD virtual screening Fragment Molecular Orbital (FMO) model
- Generated several proprietary series of TEAD inhibitors with a diverse spectrum of TEAD isoform inhibitory profiles

SPOROS' Lead Compound Shows Favorable PK & Safety Profiles

- Highly selective over a broad panel of safety-associated receptors, enzymes and ion channels (>100X IC50 in H226)
- Minimal hERG binding (>10 µM, 500-fold over H226 IC50)
- No Cyp inhibition (>10 µM against 5 major CYP tested)
- Exceptionally low toxicity (MTD >300 mg/kg, >20X efficacious dose)
- Not a substrate for P-gp or other multidrug resistance pumps
- Good oral bioavailability in mouse, rat, dog and monkey
- Moderate brain penetration

Pre-clinical PK Summary		
Mouse	T1/2	4.3 h
	Vd	4.5 L/Kg
	Oral bio	41%
Rat	T1/2	5.5 h
	Vd	3.7
	Oral bio	36%
NHP	T1/2	1.7 h
	Vd	2.9 L/Kg
	Oral bio	60%
Dog	T1/2	7.6 h
	Vd	4.2 L/Kg
	Oral bio	87%