# *Abstract # 445:* A next generation TEAD inhibitor with refined isoform specificity for superior safety & efficacy

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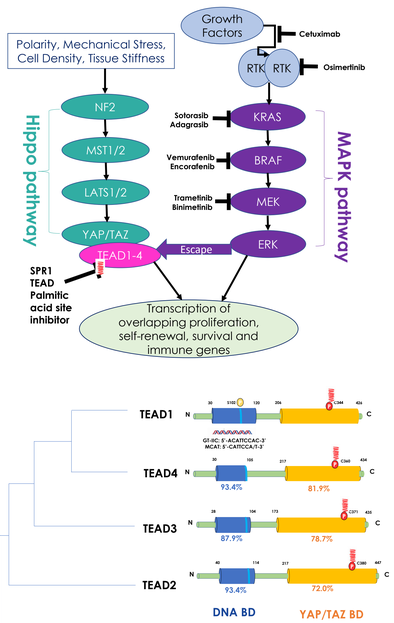
## Abstract

- The Hippo pathway is a key regulator of cell proliferation and oncogenesis not yet extensively targeted in precision oncology. It is executed by the YAP1/TAZ co-activators and the TEAD family of transcription factors, which consists of four paralogs (TEAD1-4).
- Sporos BioDiscovery has developed optimized novel inhibitors that reversibly bind to the palmitoylation site of select TEAD paralogs including TEAD1 and TEAD4, to maximize efficacy and minimize toxicity.
- Sporos's bioinformatic analyses identify TEAD2 and TEAD3 inhibition as likely undesirable due to paradoxical adverse stimulation of cell proliferation and kidney toxicity, respectively.
- SPR1-0117 (SPR1) is a TEAD1/4 preferential inhibitor that offers with: (i) low nM, single-agent activity against multiple TEAD-dependent cell lines *in vitro* including several non-mesothelioma cell lines without any obvious lesions in the upstream components of the Hippo pathway such as NF2. (ii) strong interactions with inhibitors of the MAPK pathway and its upstream activators, such as RTKs. The potency of SPR1 (TEAD1/4 inhibitor) both as monotherapy and in combination with MAPK pathway inhibitors is superior to that of the high selectivity TEAD1>TEAD2-inhibitor (VT103) (iii) activity against multiple tumor models *in vivo* with tumor regression observed in large established tumors. (iv) favorable ADME profile and safety profile including no renal findings in 7D RD rat non-GLP toxicity studies.
- In sum, SPR1 presents monotherapy opportunities in ultra-responder populations based on internal bioinformatic insights, while broader potential exists as an adjuvant for precision oncology targeted therapies, particularly within the MAPK pathway and its upstream activators.

## Background

### TEAD isoform inhibitory specificity as a key for maximizing efficacy and minimizing toxicity




- Clinical results with many high-profile oncology targets (e.g. PI3K) initially proved disappointing due pan-isoform inhibitor toxicity, which was remedied by isoform-specific inhibitors (Only PI3Ka and δ specific inhibitors FDA approved)
- 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

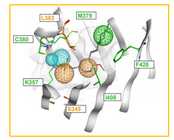
| | Mouse Knockout Phenotype | Conditional knockout | Oncfusions in TCGA | DepMap Cell Line CRISPR Dependency |
|---|---|---|---|---|
| **TEAD1** | **Lethal E12** | **Lethal** | **9** | **-0.22** |
| TEAD2 | None | ND | 2 | 0.02 |
| TEAD3 | Kidney | ND | 1 | -0.28 |
| **TEAD4** | **Lethal E3** | **None** | **9** | **-0.19** |
| YAP1 | Lethal | Lethal | 23 | -0.32 |
| WWTR1 | Lethal P21 | Lethal | 8 | -0.39 |

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

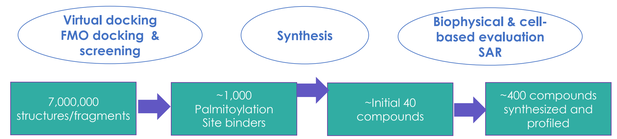
- **TEAD1:** Inhibitor binding required to block inhibition
- **TEAD2:** Inhibition associated with adverse stimulation of proliferation
- **TEAD3:** Inhibition further restricts proliferation in combination with TEAD1 but is also a potential driver of kidney toxicity
- **TEAD4:** Most similar to TEAD1;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

## Main Novel Findings

### Development of SPR1 from virtual docking to candidate selection



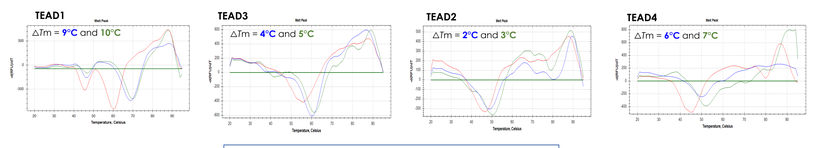
Virtual FMO structure TEAD model



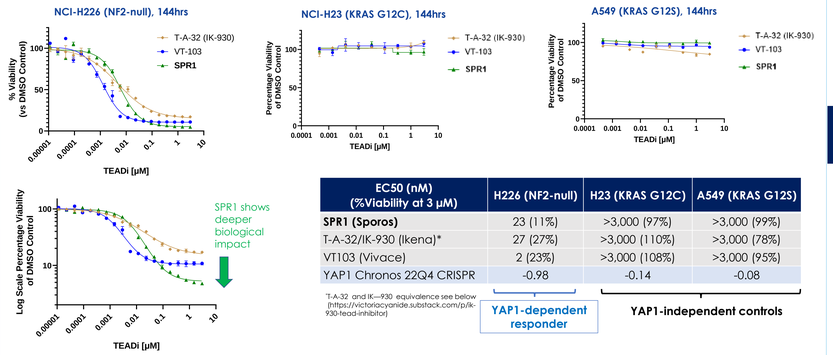

- Identified palmitoyl-binding pocket in TEAD as a suitable docking site
- Generated TEAD virtual screening Fragment Molecular Orbital (FMO) model
- Generated several proprietary series of TEAD inhibitors:
  - Two IP families of competitive TEAD palmitic-acid site inhibitors with nM activity against TEAD-dependent cancer cell lines, in vivo anti-tumor efficacy and favorable ADME properties

### SPR1 has preferential TEAD1/4 isoform specificity as shown by thermal shift assay

**SPR1 Thermal Shifts with TEAD1-4**




### TEAD1 + TEAD4 inhibition drives deeper biological impact without loosing Hippo-pathway dependent specificity




| EC50 (nM) (%Viability at 3 μM) | H226 (NF2-null) | H23 (KRAS G12C) | A549 (KRAS G12S) |
|---|---|---|---|
| **SPR1 (Sporos)** | 23 (11%) | >3,000 (97%) | >3,000 (99%) |
| T-A-32/IK-930 (Ikena)* | 27 (27%) | >3,000 (110%) | >3,000 (78%) |
| VT103 (Vivace) | 2 (23%) | >3,000 (108%) | >3,000 (95%) |
| YAP1 Chronos 22Q4 CRISPR | -0.98 | -0.14 | -0.08 |

*T-A-32 and IK—930 equivalence see below (https://victoriacyanide.substack.com/p/ik-930-tead-inhibitor)

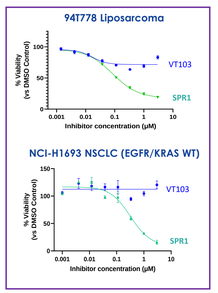
YAP1-dependent responder

YAP1-independent controls

### TEAD1 + TEAD4 inhibition extends utility beyond mesothelioma

| Cell Line | Lineage | Absolute IC50 (nM) (% viability @ 3μM) Hippo Driver Mutation | SPR1-0117 | VT103 (TEAD1>2) |
|---|---|---|---|---|
| NCI-H23 | NSCLC | NF2-WT (control) | >3,000 (83%) | >3,000 (130%) |
| Mero-14 | Mesothelioma | NF2-mutant | 16 (8%) | 17 (33%) |
| NCI-H226* | Mesothelioma | NF2-null | 30 (11%) | 4 (23%) |
| MSTO-211h* | Mesothelioma | NF2-WT (LATS1/LATS2) | 13 (11%) | 35 (43%) |
| SDM103T2 | Mesothelioma | NF2-low | 57 (18%) | 163 (45%) |
| Mero-82 | Mesothelioma | NF2-mutant | 23 (29%) | 88 (48%) |
| Mero48A | Mesothelioma | N/A – YAP hyperactive | 116 (25%) | >3,000 (52%) |
| 94T778 | Liposarcoma | N/A – YAP hyperactive | 126 (16%) | >3,000 (78%) |
| NCI-H1693* | NSCLC (Adeno) | N/A – YAP hyperactive | 118 (7%) | >3,000 (120%) |
| LOU-NH-91 | NSCLC (SCC) | NF2-mutant | 104 (32%) | >3,000 (55%) |
| Caki-1 | RCC | NF2 – homozygous deletion | 137 (36%) | >3,000 (104%) |
| BHY | Head & neck SCC | FAT1-mutant | 132 (32%) | >3,000 (70%) |
| SCC25* | Head & neck SCC | N/A – YAP hyperactive | 301 (25%) | >3,000 (82%) |

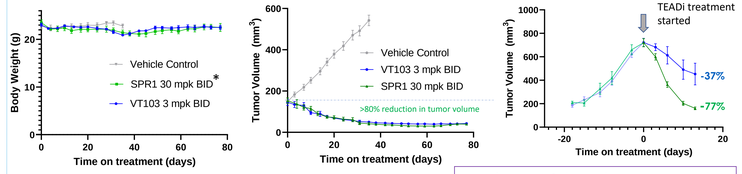
*In vivo efficacy tested and confirmed



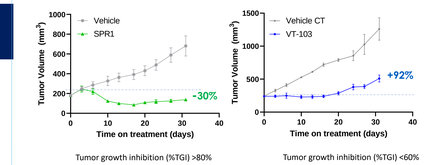

### TEAD1+4 inhibition shows exceptional *in vivo* efficacy and long-term tolerability

*SPR1 and VT103 doses selected to achieve similar exposure (AUC)

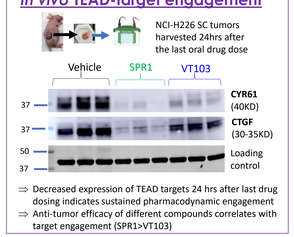
**NCI-H226 (NF2-null) mesothelioma**




**MSTO-211h (NF2-WT) mesothelioma**



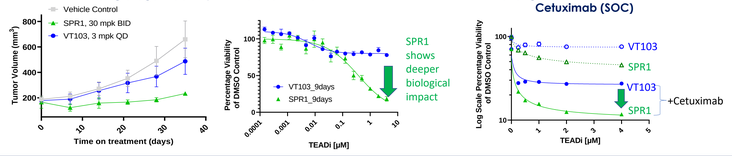

**In vivo TEAD-target engagement**




⇒ Decreased expression of TEAD targets 24 hrs after last drug dosing indicates sustained pharmacodynamic engagement
⇒ Anti-tumor efficacy of different compounds correlates with target engagement (SPR1>VT103)

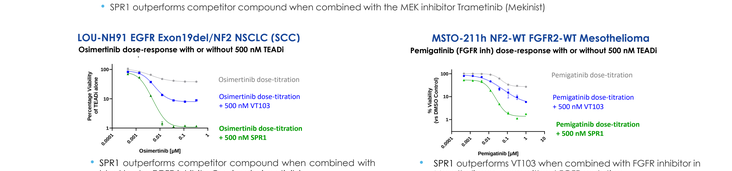
### TEAD1+4 inhibition allows *in vivo* efficacy beyond mesothelioma

**SCC25 (NF2-WT) Oral Cavity Squamous Cell Carcinoma**




### TEAD1+4 inhibition drives stronger biological response in combination treatments


* SPR1 outperforms competitor compound when combined with the MEK inhibitor Trametinib (Mekinist)




* SPR1 outperforms competitor compound when combined with blockbuster EGFR inhibitor Tagrisso (osimertinib)

* SPR1 outperforms VT103 when combined with FGFR inhibitor in Mesothelioma, even without FGFR mutation

## Concluding remarks

- SPR1 is a preferential TEAD1/4 inhibitor which provides deeper biological impact compared to TEAD1 preferential inhibitors - allowing for monotherapeutic activity beyond NF2-mutant mesothelioma and stronger interaction in combination therapy with MAPK or RTK inhibitors - yet without sacrificing safety.
- 7D RD dosing at 75 mg/kg (>10x exposure required for efficacy in mice) tolerated without adverse events including no significant findings of kidney toxicity
- Sustained pharmacodynamic target engagement observed in excised tumors from *in vivo* studies even 24 hours post last oral dose administered

## Acknowledgements

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