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Review article

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Targeting the Hippo pathway in cancer

Kieran F. Harvey [1,2,3] ✉ & Tracy T. Tang [4]

Abstract

The Hippo pathway is a highly conserved signalling network that controls tissue growth and cell fate, responding to physical properties of the tissue microenvironment and cell biological features such as adhesion and polarity. Hippo signalling perturbation is associated with several human diseases, particularly various solid cancers. Hippo pathway-targeted therapies are beginning to emerge for the treatment of cancer, most of which are focused on disrupting the ability of the YAP and TAZ transcription co-activator proteins to promote transcription of genes with their cognate TEAD1–4 DNA binding proteins. Recently, TEAD inhibitors have shown promise in a phase I clinical trial in cancers that are enriched for Hippo pathway mutations, such as mesothelioma. Moreover, Hippo pathway-targeted therapies have great potential to be combined with RAS–MAPK pathway inhibitors, given the close functional relationship that these signalling pathways share in development and disease.

Sections

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia. [2]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria, Australia. [3]Department of Anatomy and Developmental Biology, Monash University, Clayton, Victoria, Australia. [4]Vivace Therapeutics, Inc., San Mateo, CA, USA. ✉e-mail: kieran.harvey@petermac.org

Introduction

Founding members of what is now referred to as the Hippo pathway were originally identified in *Drosophila* genetic screens and cloned in the mid-1990s and early 2000s[1–9]. Mutations in the *warts*, *salvador* and *hippo* genes were uncovered because they triggered striking overgrowth of *Drosophila* epithelial tissues[1–9]. These discoveries led to the conclusion that the Hippo pathway was important for epithelial tissue growth control, and the discovery that the human *salvador* orthologue *SAV1* was deleted in kidney cancer cell lines provided initial evidence of a role for this pathway in human cancer[1].

After these discoveries, Hippo pathway research surged, enabling significant insight into how this pathway mediates signal transduction and its biological functions in various cell types, tissues, species and human diseases[10–16]. More than 40 Hippo pathway proteins have been discovered, the vast majority of which are conserved throughout evolution, for example, between *Drosophila* and mammals (see Table 1 for conserved Hippo pathway proteins and Fig. 1 for a simplified pathway depiction)[10–16]. Key steps in pathway regulation were identified, such as the phosphorylation of the key oncoproteins Yes-associated protein (YAP) and transcriptional co-activator with PDZ binding motif (TAZ) (*Drosophila* Yorkie (Yki)), which controls their nucleocytoplasmic distribution and ability to regulate transcription[17–20]. The Hippo pathway was found to be evolutionarily ancient, with the discovery that several central pathway proteins pre-date the existence of metazoans[21,22], and the pathway was shown to regulate cell fate as well as tissue growth[23,24]. An appreciation of the role of the Hippo pathway in various human cancers was further revealed though large-scale cancer genome sequencing studies, which identified roles in many solid cancers, in particular mesothelioma and meningioma[25,26]. This rich knowledge base laid a platform for therapeutic targeting of the Hippo pathway, which holds great promise for both cancer and regenerative medicine.

A multitude of Hippo-targeted therapies are currently in active development, with several already undergoing clinical trials. Interestingly, most of these therapies target the TEA domain transcription factor 1 (TEAD1)–TEAD4 DNA binding proteins, which are highly homologous and sit at the very base of the Hippo pathway. TEAD inhibitory compounds have been developed with a view to them being deployed as novel anticancer therapies. In the context of tissue regeneration and repair, efforts have been made to target central Hippo pathway kinases such as the serine/threonine protein kinases LATS1 and LATS2 and mammalian sterile-20-like kinase 1 (MST1; also known as STK4) and MST2 (also known as STK3) (hereafter LATS1/2 and MST1/2, respectively), as well as proteins that promote the activity of these kinases, such as Salvador.

This Review first provides an overview of the Hippo pathway, its regulation, signalling and biological functions. The latest developments in the field of Hippo pathway-targeted therapies are discussed, with a focus on TEAD inhibitors, primarily in the context of cancers, given that disease-focused human genome sequencing efforts have revealed a prominent role for Hippo signalling in cancers compared with other human diseases. The potential for TEAD inhibitors to be used both as anticancer monotherapies and as combination therapies is assessed, given the important functional relationships that exist between the Hippo pathway and the RAS–MAPK pathway, another developmental signalling pathway of major importance for human cancer. Finally, TEAD inhibitors that have progressed to phase I human clinical trials are highlighted.

Discovery and biological functions of the Hippo pathway

The Hippo pathway was initially discovered through genetic studies in *Drosophila*, in which mutations in pathway genes were found to cause strong epithelial tissue overgrowth[1–9]. Upon further investigation, mutation of founding Hippo pathway members was shown to be important for control of both cell proliferation and apoptosis. Specifically, Hippo pathway-defective cells in *Drosophila* larval imaginal discs — epithelial tissues that give rise to adult organs such as the eye and wing — proliferated more rapidly than their normal counterparts and failed to enter quiescence at the appropriate developmental stage. In addition, eye cells with compromised Hippo pathway activity were impervious to the programmed cell death that normally sculpts this organ during pupal development[1–9]. The net result was spectacular tumour-like growths caused by an excess of cells, which were subsequently shown to be driven by Yorkie/YAP hyperactivation[17]. Similarly, subsequent studies in vertebrates revealed that when Hippo signalling was disrupted, epithelial organs such as the skin, liver and gastrointestinal tract also dramatically overgrew[18,27–29]. Hippo signalling has also been linked to the growth and development of vertebrate heart and skeletal muscle, neuronal tissues and vascular networks and therefore was concluded to be a key regulator of organ growth[30–33].

Subsequently, the Hippo pathway was found to regulate cell fate decisions at various stages of organismal development. The first of these was the fate choice of a specific class of photoreceptor cells (R8 cells) in the *Drosophila* eye[23]. The Hippo pathway defines whether these cells adopt the ability to sense blue light or green light — a decision that involves most, but not all, of the pathway from upstream components to transcriptional regulators[23,34–37]. Additionally, the Hippo pathway has a crucial role in the first cell fate decision during mammalian embryonic development, determining whether a cell will become inner cell mass or trophectoderm[24]. The role of the Hippo pathway as a regulator of epithelial organ size was challenged recently, based on the observation that many cells (particularly columnar epithelial cells) have low YAP–TEAD activity and YAP or TEADs are sometimes dispensable for their normal growth[38]. This study proposed that YAP and TEAD are important for cells with 'flat' morphology (for example, endothelial cells, squamous epithelial cells and so forth) and only drive proliferation of columnar epithelia when they are ectopically hyperactivated[38]. As such, the 'normal' role of the Hippo pathway in development is still an open question, and this is important for consideration of how we can therapeutically target the pathway and manage on-target toxicity.

Regulation of Hippo pathway activity

Unlike most signalling pathways, which are regulated by transmembrane receptors and their cognate ligands, the Hippo pathway is predominantly controlled by properties of the tissue microenvironment. These properties include mechanical forces such as tension, compression and shear forces, which differ depending on the tissue and its local environment[10,39,40]. These discoveries were of major importance and revealed that mechanical forces can influence both YAP and TAZ nuclear localization directly[41], as well as upstream Hippo signalling events, which then act on YAP and TAZ[42,43]. Hippo signalling is also sensitive to perturbations in core cell biological properties, such as cell polarity and adhesion of cells to other cells and the extracellular matrix[10,39,40]. Further, Hippo signalling can be influenced by G protein-coupled receptors (GPCRs) and stresses associated with fluctuations in energy, heat and osmolarity, although these require further investigation in animals to

understand their full significance[12]. For detailed reviews of the regulation of Hippo pathway activity, the reader is referred elsewhere[10–16].

Organization of the Hippo pathway

A major challenge following the discovery of Warts, Salvador and Hippo as a three-member signalling complex comprised of two cytoplasmic kinases and an adaptor protein, was the identification of upstream and downstream Hippo pathway components. Answers to this question were largely revealed by unbiased screens — both in vivo *Drosophila* genetic screens, and *Drosophila* and human cell-based signalling activity and protein–protein interaction screens. Collectively, these efforts revealed that the Hippo pathway is a complex network of more than 40 proteins, which can be broadly organized into three groups — transcription regulators, the core kinase cassette and upstream signalling[10–16]. Table 1 lists high-confidence Hippo pathway proteins, that is, those that have convincingly been proved to be Hippo pathway proteins in multiple studies, and most of which are functionally conserved between *Drosophila* and humans. Many other proteins have been implicated in Hippo signalling but for simplicity they are not discussed in detail here. For more information on this topic the reader is referred elsewhere[10–16].

Hippo pathway transcription regulators

YAP and TAZ are transcription co-activator proteins that are the central downstream effectors of the Hippo pathway[17]. YAP, TAZ and their *Drosophila* orthologue Yorkie do not directly bind to DNA, but bridge DNA binding proteins and transcription-promoting proteins, such as the Mediator complex, Trithorax-related complex and SWI/SNF complex, to promote gene expression[44–48]. TEAD1–TEAD4 (Scalloped in *Drosophila*) are the major DNA binding proteins of the Hippo pathway and possess a TEA DNA binding domain and a YAP/TAZ binding domain[49–53]. Vestigial-like family member 4 (VGLL4; Tgi in *Drosophila*) is a transcription co-repressor protein that antagonizes YAP/TAZ by competing for an overlapping binding surface on TEAD1–TEAD4 (refs. 54,55). INSM1 (Nerfin-1 in *Drosophila*) is another TEAD-binding transcription co-repressor that binds to the TEAD DNA binding domain and therefore, unlike VGLL4, does not compete with YAP/TAZ for TEAD binding[56,57].

The biochemical mechanism by which VGLL4 and INSM1 repress transcription is not well defined, but studies in *Drosophila* and human cells have identified connections between both proteins and the CtBP transcription co-repressor complex[57–59]. Further, recent live microscopy studies revealed that *Drosophila* Scalloped binds to DNA on a range of timescales from milliseconds to minutes and that its residence time on DNA is extended by the Yki co-activator but reduced by the Tgi and Nerfin-1 co-repressors[60]. These findings, mirrored by similar observations in human cells[61], suggest that productive transcription-inducing events are mediated by Scalloped/TEADs when they bind to DNA for extended periods of time. YAP/TAZ and INSM1, and their *Drosophila* orthologues Yki and Nerfin-1 are expressed predominantly in a mutually exclusive manner (for example, YAP, TAZ and Yki are expressed in most epithelial cells whereas INSM1 and Nerfin-1 are expressed in neuroendocrine cells and neuronal subsets)[56,62], suggesting that some cell types cannot tolerate the co-expression of these proteins, as they exert competing influences on TEAD-regulated transcription. Before the discovery of the Hippo pathway, Vestigial, another transcription coregulator, was discovered as a partner of Scalloped/TEAD in *Drosophila*[63–65]. Vestigial has three human orthologues (VGLL1–VGLL3), which have been studied far less than YAP and TAZ but have also been implicated in human diseases such as cancer[66]. In *Drosophila*, the Vestigial–Scalloped complex promotes wing cell fate during development and functions largely independently of Hippo signalling in this context[67].

Hippo pathway core kinase cassette and its direct regulators

The Hippo pathway core kinase cassette comprises two serine threonine kinases and two adaptor proteins. MST1 and MST2 (Hippo in *Drosophila*) are STE20-like protein kinases that bind to the adaptor protein SAV1 (Salvador in *Drosophila*) which promotes MST1/2 activation. Activated MST1/2 phosphorylates both the adaptor proteins MOB

Table 1 | High-confidence Hippo pathway proteins

	Drosophila protein	Human orthologues
Transcription	Scalloped	TEAD1, TEAD2, TEAD3, TEAD4
	Yorkie	YAP, TAZ
	Tgi	VGLL4
	Nerfin-1	INSM1A, INSM1B
Core kinase cassette	Warts	LATS1, LATS2
	Mats	MOB1A, MOB1B
	Salvador	SAV1
	Hippo	MST1, MST2
	Happyhour	MAP4K1, MAP4K2, MAP4K3, MAP4K5
	Misshapen	MAP4K4, MAP4K6, MAP4K7
Upstream signalling	Tao	TAOK1, TAOK2, TAOK3
	STRIPAK complex	STRIPAK complex
	Merlin	NF2
	Kibra	WWC1, WWC2, WWC3
	Expanded	FRMD6?
	?	AMOT, AMOTL1, AMOTL2
	Crumbs	CRB3
	Par-1	MARK2, MARK3, MARK4
	Ajuba	AJUBA, LIMD1, WTIP
	Scribble	SCRIB
	Lethal giant larvae	LGL1, LGL2?
	Kirre?	KIRREL1
	Zyxin	ZYXIN, LPP, TRIP6
	Pez	PTPN14
	PI4KIIIα	PI4KA?
	Fat	FAT1, FAT2, FAT3, FAT4?
	α-Spectrin	SPTAN1
	β-Spectrin	SPTBN1
	β-Heavy spectrin	SPTBN5

Proteins are organized into three groups based on their known functions: transcription, core kinase cassette and upstream signalling. For simplicity, only the highest-confidence Hippo pathway proteins have been listed, with this classification based on proteins being proved in multiple independent studies and/or functional conservation between *Drosophila* and humans. Both *Drosophila* and human orthologues are listed. For some proteins, queries about functional conservation are indicated by a '?'. Note, the STRIPAK complex is comprised of multiple proteins. KIRREL1, Kirre-like nephrin family adhesion molecule; MAP4K1, mitogen-activated protein kinase kinase kinase kinase 1; MOB1A, MOB kinase activator 1A; MST1, mammalian sterile-20-like kinase 1; STRIPAK, striatin-interacting phosphatase and kinase; TAOK1, thousand and one amino acid protein kinase 1; TAZ, transcriptional co-activator with PDZ binding motif; TEAD1, TEA domain transcription factor 1; VGLL4, Vestigial-like family member 4; WWC1, WW and C2 domain-containing 1; YAP, Yes-associated protein.

kinase activator 1A (MOB1A) and MOB1B (hereafter MOB1A/B (Mats in *Drosophila*)) and the LATS1/2 kinases (Warts in *Drosophila*) to activate LATS1/2 kinase activity[1–8,68]. The MAP4K and thousand and one amino acid protein kinases 1–3 (TAOK family) kinases, which are also STE20-like protein kinases, can likewise phosphorylate the hydrophobic motif of LATS1 and LATS2 and activate them[69,70]. In addition, TAOK kinases can phosphorylate the activation loop of MST1/2 and thus activate the Hippo pathway at two points[71,72]. MST1/2 activity is antagonized by the multi-protein striatin-interacting phosphatase and kinase (STRIPAK) phosphatase complex, which reverses MST1/2 activation loop phosphorylation[73]. The central substrates of the LATS1/2 kinases are the YAP and TAZ transcription co-activators (Yorkie in *Drosophila*), which they phosphorylate on multiple serine residues, thereby limiting their nuclear access and half-life[17–20].

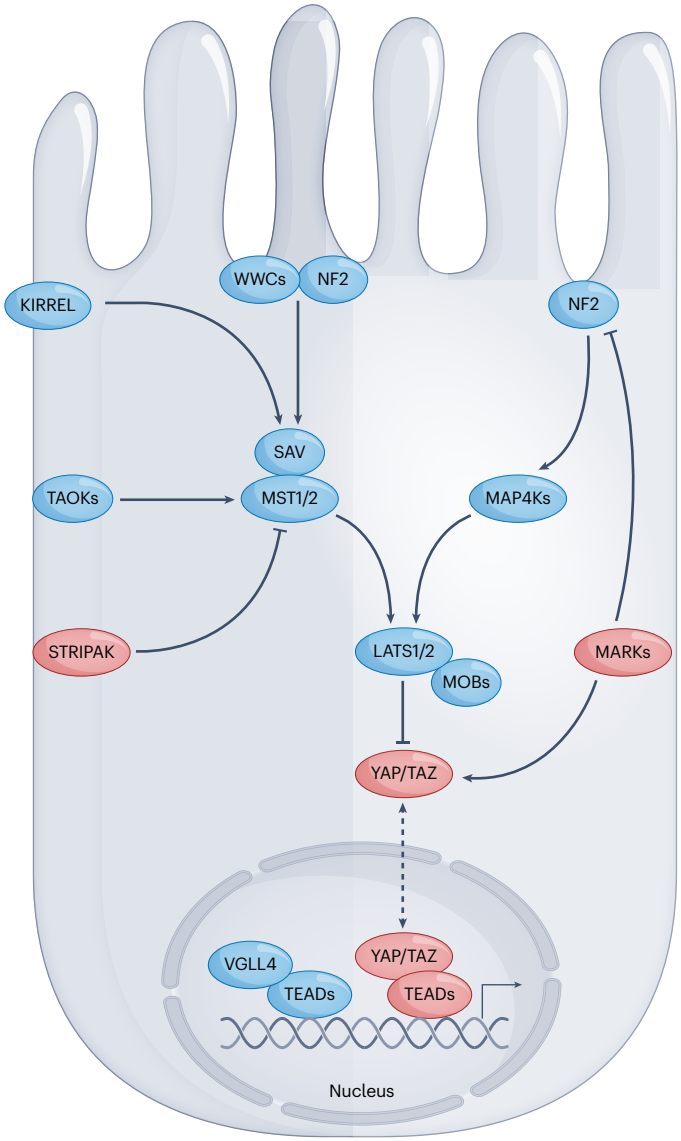


Fig. 1 | Simplified depiction of the human Hippo pathway. Proteins that promote Hippo signalling and repress Yes-associated protein/transcriptional co-activator with PDZ binding motif–TEA domain transcription factor (YAP/TAZ–TEAD) transcription are in blue and proteins that promote YAP/TAZ–TEAD transcription are in red. For detailed reviews of the Hippo pathway, the reader is referred elsewhere[10–16]. KIRREL, Kirre-like nephrin family adhesion molecule; LATS1/2, serine/threonine protein kinases; MAP4Ks, mitogen-activated protein kinase kinase kinase kinase 1–7; MARKs, microtubule affinity-regulating kinase 2–4; MOBs, MOB kinase activator 1A and 1B; MST1/2, mammalian sterile-20-like kinase 1 and 2; NF2, neurofibromin 2; SAV, salvador; STRIPAK, striatin-interacting phosphatase and kinase complex; TAOKs, thousand and one amino acid protein kinases 1–3; TEADs, TEAD1–TEAD4; VGLL4, Vestigial-like family member 4; WWCs, WW and C2 domain-containing 1–3.

Upstream Hippo signalling

Upstream Hippo signalling is complex, and consists of multiple independent branches that also engage in some degree of regulatory crosstalk[74]. Most upstream Hippo pathway proteins are conserved between *Drosophila* and humans, although some uncertainty on this remains. Additionally, upstream Hippo signalling has currently been more thoroughly characterized in *Drosophila* than in mammals, in terms of the proteins involved and their spatial organization within cells and signalling modes.

Core kinase cassette activators. The neurofibromin 2 (NF2; Merlin in *Drosophila*) and WW and C2 domain-containing 1–3 (WWC1–3; Kibra in *Drosophila*) proteins serve similar Hippo signalling functions, despite lacking obvious homology. In *Drosophila* epithelial tissues, both proteins accumulate at the apical plasma membrane and serve as scaffolds to facilitate phosphorylation and activation of the Warts/LATS kinases by Hippo/MST and Hippo-like kinases[75]. *Drosophila* Expanded likely operates in a similar manner given the genetic redundancy it exhibits with both Merlin and Kibra, although it is not obviously conserved in humans[76]. Expanded does have some sequence conservation with FRMD6 and this protein can influence YAP activity, but it is unclear whether FRMD6 is a true functional equivalent of Expanded[77]. Recent studies indicate that Merlin is recruited to epithelial apical plasma membranes via phospholipids, which also mediate assembly into condensates with altered physical properties. In *Drosophila*, the lipid kinase PI4KIII (PI4KA in humans) works together with the Pez phosphatase (PTPN14 in humans) to promote Merlin recruitment to the medial apical domain of epithelial cells[78]. Both the PIP2 and PI4P phospholipids mediate Merlin association with the plasma membrane and, somewhat paradoxically, PI4P promotes Hippo pathway activity in *Drosophila* epithelial tissues but has the opposite effect in human cultured cells[79]. Thus, further studies are warranted to clarify this important feature of Hippo signalling, perhaps via in vivo mammalian studies.

Multiple apicobasal cell polarity proteins regulate Hippo pathway activity in both *Drosophila* and mammals. In *Drosophila*, the Scribble–Lgl–Dlg basolateral cell polarity complex promotes Hippo pathway activity in the context of both organ growth and cell fate[37,80], and SCRIB performs a similar function in human cells[81]. *Drosophila* Crumbs acts via Expanded to promote Hippo pathway activity[80,82–84], whereas in humans the CRB3–PATJ–PALS complex binds to many proteins such as angiomotin family proteins (AMOT, AMOTL1 and AMOTL2) and YAP at human cell–cell adhesions to repress YAP activity and activate LATS1/2 kinase activity[85,86]. The transmembrane protein Kirre-like nephrin family adhesion molecule 1 (KIRREL1) was recently discovered to promote Hippo signalling; KIRREL1 recruits SAV1 to cell membranes, causing LATS1/2 activation and YAP repression[87,88].

The Hippo pathway couples mechanical forces to changes in cell behaviour, including proliferation and cell fate specification[41,42]. Such forces modulate actomyosin contractility and, as such, many proteins that regulate the actin cytoskeleton and the cellular sites it anchors to (for example, adherens junctions, basal spot junctions and focal adhesions)

have been linked to Hippo signalling. Among these proteins are spectrins, which are large spring-like molecules that bind to F-actin and stabilize the plasma membrane. In various *Drosophila* epithelial tissues, α-spectrin regulates Hippo signalling and does so by forming heterotetramers with either β-spectrin or β-heavy spectrin[89–91]. Various mechanisms have been ascribed to how spectrins influence Hippo signalling, from binding to Expanded and modulating the concentration of Hippo signalling complexes in the apical plasma membrane[90], to indirectly influencing Hippo signalling by controlling cortical actomyosin contractility[89]. A more recent study indicated that β-heavy spectrin influences Ajuba and Hippo signalling by competing with non-muscle myosin for F-actin binding[92].

The *Drosophila* Fat/Dachsous cadherins were the first defined Hippo pathway transmembrane proteins and are important regulators of epithelial tissue growth, as well as planar cell polarity[93–97]. A suite of proteins operate downstream of Fat/Dachsous to relay signals to the core kinase cassette, including kinases, ubiquitin ligases and mechanosensitive proteins, and together they represent a major signalling arm in the *Drosophila* Hippo pathway[98]. However, whether these proteins also regulate the human Hippo pathway is still unclear. The *FAT1–FAT4* cadherin genes are frequently mutated in many cancers and have been implicated in tumorigenesis and Hippo signalling[99,100]. However, clear and detailed biochemical signalling mechanisms that link FAT cadherins to the core Hippo pathway in mammals have not yet been defined. Further studies are required to determine whether and how the FAT1–FAT4 cadherins regulate the Hippo pathway in mammals and the contexts in which this may happen.

Core kinase cassette repressors. A well-defined upstream signalling complex that limits Hippo signalling in *Drosophila* is mediated by the LIM domain protein Ajuba[101]. Ajuba binds primarily to E-cadherin-rich complexes at adherens junctions and basal spot junctions of *Drosophila* epithelial cells in response to increased actomyosin contractility[43,102]. Here, Ajuba binds to Warts and limits its ability to be activated by Hippo, which does not accumulate at these cell junctions[43,102]. In this way, Hippo signalling is linked to mechanical forces such as stretch and compression, which offers an explanation for how this pathway regulates tissue growth in response to physical forces[43]. Ajuba has three human orthologues (AJUBA, LIMD1 and WTIP); cell culture-based studies have indicated that these proteins also bind to adherens junctions and repress LATS1/2 activity in a manner that is sensitive to actomyosin contractility[103].

Microtubule affinity-regulating kinase (MARK) family kinases have also been identified as important Hippo pathway regulators, possibly by multiple mechanisms. In *Drosophila*, Par-1 was shown to influence Hippo-regulated tissue growth both by regulating the Hippo kinase[104] and by influencing Kibra stability[105]. Independently, three human Par-1 homologues (MARK2, MARK3 and MARK4) were identified as regulators of Hippo signalling in cell-based screens[106,107]. In addition to regulating the Hippo orthologues MST1 and MST2, a recent study found that MARK2 and MARK3 phosphorylate NF2 and YAP, with both events serving to stimulate YAP activity[108]. From a cancer therapy perspective, these discoveries were important because: first, they identify a way to perturb YAP–TEAD activity that is independent of direct YAP–TEAD inhibitors; second, being kinases, the MARKs are readily druggable; and third, MARK2, MARK3 and MARK4 activate YAP and therefore are predicted to be oncogenic, whereas most Hippo pathway kinases (for example, LATS1/2 and MST1/2) are tumour suppressors and are therefore likely to be unsuitable targets for cancer therapies (see below and Figs. 1 and 2).

Interconnected upstream branches. A consistent theme in upstream Hippo signalling over many years has been regulatory crosstalk between different upstream branches of the pathway, which illustrates the complex interactions that occur in this pathway. In *Drosophila*, for instance, the Fat and Expanded branches of Hippo signalling influence the core kinase cassette via different mechanisms[109], but Fat also influences the abundance and apical membrane localization of Expanded[94,95,97]. More recently, upstream Hippo signalling was proposed to operate in two major arms, one involving NF2 and MAP4Ks and the other involving WWC1–3, SAV1 and MST1/2, which independently activate LATS1/2 (ref. 110). Although this model has merit, many other studies argue against a strict division of labour between upstream Hippo signalling complexes. For example, although NF2 and WWC1–3 could function independently of each other to some degree in the so-called HIPPO1 and HIPPO2 branches of Hippo signalling, these proteins can form physical complexes in both humans and *Drosophila* and recruit each other to sites of Hippo pathway activation, suggesting that they also function together[75,111–113]. Similarly, in *Drosophila*, Merlin/NF2 can also form a physical complex with Expanded[111–113], although these proteins probably operate largely independently of each other[75].

The role of the Hippo pathway in human diseases

Hippo pathway perturbation has been linked to select human diseases, most notably cancer and heart disease, as reviewed elsewhere[13,14,114,115]. A potential role for the Hippo pathway in human disease was first recognized in model organism studies. Specifically, mutations in Hippo pathway genes were found to disrupt multiple biological processes that are important for animal development and human disease, including cell proliferation, apoptosis, differentiation and tissue growth[10–16]. Model organism studies also revealed potential roles for the Hippo pathway in other conditions such as heart disease, in which deletion of the murine *Yap* orthologue impaired neonatal cardiac regeneration, whereas YAP hyperactivation promoted heart repair and function[115]. Subsequently, mutations in select Hippo pathway genes (*NF2* and *TEAD1*) were identified in familial human diseases. *NF2* mutations cause the cancer syndrome type 2 neurofibromatosis[116], and loss-of-function *TEAD1* mutations underpin an autosomal dominant eye disorder called Sveinsson's chorioretinal atrophy[117]. This section primarily focuses on cancer given the prevalence of Hippo pathway gene mutations in this disease compared with other human conditions. Deregulation of Hippo signalling and YAP/TAZ–TEADs have been implicated in a broad range of common solid cancers such as colorectal, lung, breast, prostate and ovarian cancer[14,25,26]. However, most of these cancers have no obvious Hippo pathway mutations and their transcriptional signatures often do not suggest dependency on YAP/TAZ–TEAD[14,25,26]. Accordingly, the discussion concentrates on solid cancers that have obvious mutations in Hippo pathway genes.

Solid cancers

Large-scale cancer genome sequencing efforts identified Hippo pathway mutations to occur across a broad range of solid cancers, leading to its classification as one of the ten most important signalling pathways in cancer[118]. Genetic disruption of the Hippo pathway occurs via various mechanisms (for example, point mutations, deletions, chromosomal translocations, amplification and overexpression)[14,25]. Typically, these perturbations reduce activity of Hippo pathway kinases (for example, LATS1/2) and cause the transcription-promoting activity of YAP/TAZ–TEADs to be elevated. Hippo pathway gene mutations are concentrated in select cancers, that is, mesothelioma, meningioma and Schwannoma. Hippo pathway gene mutations and elevated YAP and TEAD activity are also enriched in squamous epithelial cancers, which is intriguing, especially given the recent evidence that Hippo

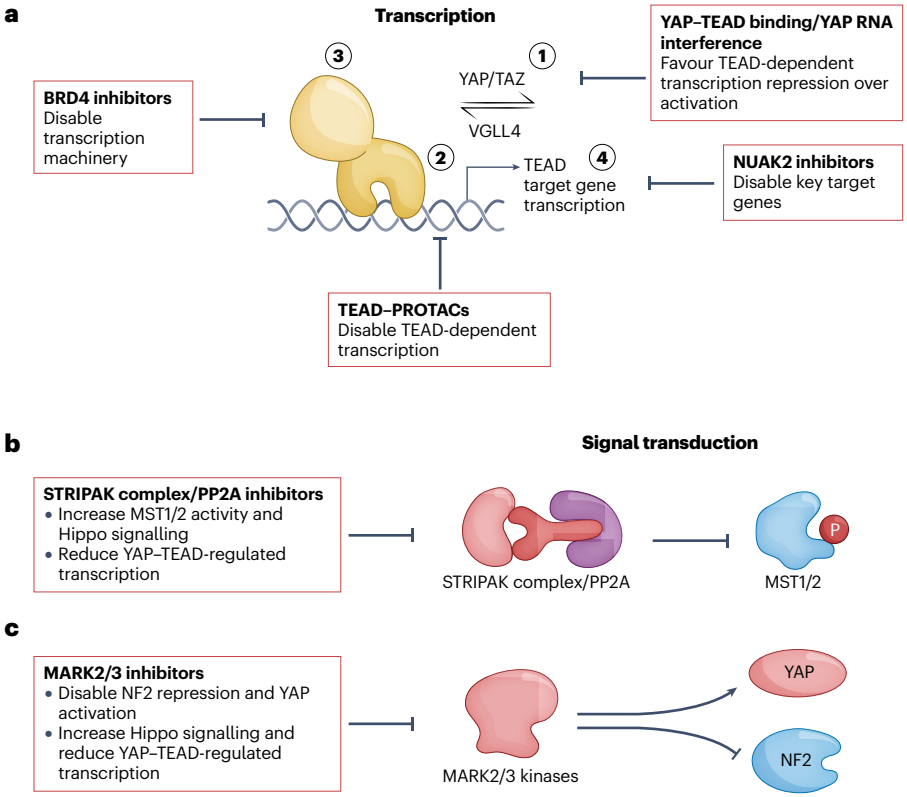


Fig. 2 | How can the Hippo pathway be therapeutically targeted? Three Hippo signalling nodes that are potential therapeutic targets in the context of cancer are depicted, as well as intervention strategies and therapy examples. **a**, Hyperactivation of Yes-associated protein (YAP)–TEA domain transcription factor (TEAD)-regulated transcription is a key event in tumorigenesis and cancer therapy resistance and theoretically could be targeted in four ways: (1) shifting the balance from YAP-mediated transcription activation to Vestigial-like family member 4 (VGLL4)-mediated transcription repression; (2) inhibiting TEAD-regulated transcription completely; (3) targeting general transcription machinery; and (4) inhibiting key YAP–TEAD target genes (note that NUAK2 can also influence YAP/transcriptional co-activator with PDZ binding motif (TAZ) activity). At least two points of Hippo signal transduction could theoretically be targeted to promote Hippo signalling and reduce YAP–TEAD-regulated transcription: **b**, inhibition of the striatin-interacting phosphatase and kinase (STRIPAK)–PP2A phosphatase complex, which normally suppresses phosphorylation and activation of mammalian STE20-like protein kinase 1 (MST1) and MST2 (MST1/2); and **c**, inhibition of the microtubule affinity-regulating kinase (MARK) kinases, which phosphorylate multiple Hippo pathway proteins that serve to activate YAP–TEAD-regulated transcription. NF2, neurofibromin 2.

signalling is especially important for the biology of 'flat' cells[25,38]. In the TCGA PanCan 2018 Combined Study, which included 87 patients with mesothelioma out of 10,953 total patients across 32 cancer types, 32.18% of patients with mesothelioma harboured *NF2* mutations. Mutation frequencies for *LATS1* and *LATS2* in mesothelioma were 2.3% and 10.3%, respectively[119,120]. Other mesothelioma studies have reported a higher mutation frequency of *LATS2* (22%[121]) and *NF2* alterations ranging from 20% to 53%[122–125]. Given that the Hippo pathway is exquisitely sensitive to changes in the tissue microenvironment, activity of this pathway is also likely to be altered by non-genetic mechanisms such as a change in tissue rigidity.

An increasing number of oncogenic fusion proteins have been defined in human cancers involving key Hippo pathway proteins, predominantly the YAP, TAZ and TEAD transcription regulators. For example, the disease-defining mutations in the sarcoma epithelioid haemangioendothelioma (EHE) are gene fusions of *TAZ* with *CAMTA1* or *YAP* with *TFE3* (refs. 126–129). *YAP* also becomes fused with various different transcription factors in other malignancies. In almost all cases, these gene fusions encode oncoproteins in which the amino terminus of YAP or TAZ is intact and fused to transcription regulatory protein, while most of the Hippo regulatory regions of YAP/TAZ are deleted[130]. As such, these fusion proteins retain their ability to both bind to TEADs and recruit transcription apparatus and drive cancer primarily by hyperactivating TEAD target genes. In addition to YAP or TAZ fusion proteins, recurrent VGLL family fusion proteins have also been documented in sarcomas such as spindle cell rhabdomyosarcoma[131,132]. Finally, in contrast to solid cancers, most of which display robust YAP/TAZ activity, haematological and neuroendocrine cancers have low YAP/TAZ activity[133]. As such, targeting YAP/TAZ–TEAD activity in these cancers is unlikely to prove beneficial.

Cancer therapy resistance. A major barrier to the effective treatment of many cancers is resistance to therapy, which can be either intrinsic or acquired[134]. In the latter scenario, therapy resistance can arise owing to de novo mutations, or by non-genetic mechanisms that invoke changes in the epigenome and gene expression[134]. Hippo pathway deregulation is recognized as a driver not only of tumorigenesis but also of cancer therapy resistance, via three main lines of evidence. Initially, targeted studies identified that manipulations such as overexpression of the YAP oncoprotein could drive resistance to common chemotherapies such as taxanes and platinum-based drugs, although the precise mechanism was not defined[135]. Subsequently, unbiased genetic studies revealed *YAP* as a gene that can supplant the oncogenic activity of *KRAS*[136,137], and that YAP hyperactivation can drive resistance to RAS–MAPK pathway-targeted therapies, such as inhibitors specific for BRAF, MEK and KRAS[138–140]. More recently, several studies focused predominantly on gastrointestinal cancers identified YAP–TEAD-regulated transcription as driving the resistance of a rare subset of tumour cells to various therapies. Based on their transcriptomic profiles, these cells are thought to resemble stem cells and their emergence in response to cancer therapies has been termed oncofetal reprogramming[141–144]. These cells resemble those that arise in the gastrointestinal tract after severe damage that may be part of a normal regenerative response[145].

Therapeutic targeting of the Hippo pathway

The Hippo pathway has long been considered a potential therapeutic target for human diseases such as cancer and heart disease. In the context of cancer, it would be ideal to inhibit YAP/TAZ–TEAD transcription activity by inactivating one or more of these proteins and/or by activating the upstream kinases such as LATS1/2 (Fig. 2). The powerful

growth-promoting properties of YAP and TAZ also offer a potential method to promote regeneration and repair of damaged organs such as the heart and ear. However, targeting the Hippo pathway for therapeutic benefit presents several challenges. When the Hippo pathway first emerged as a novel therapeutic target, the MST1/2 and LATS1/2 kinases were the most druggable components based on existing pharmacological knowledge. From a cancer treatment perspective, however, inhibiting these kinases would be inappropriate, as they are tumour suppressors that limit the activity of the YAP and TAZ oncoproteins. On the other hand, MST1/2 and LATS1/2 inhibitors have potential as regenerative therapies because of the ability of YAP and TAZ to promote tissue repair and regeneration[114,115]. Indeed, a reversible and selective MST1/2 kinase inhibitor, XMU-MP-1, can induce tissue repair and regeneration in mouse models of chemical-induced colitis and acute and chronic liver injury, and in a rat model of intracerebral haemorrhage brain injury[146,147]. Chemical modification of XMU-MP-1 led to the development of a potent and selective MST1/2 inhibitor, IHMT-MST1-58, which protected pancreatic islet β-cells from inflammatory cytokine-induced damage in vitro and demonstrated antidiabetes efficacy in rat models of type 1 diabetes and type 2 diabetes in vivo[148]. In addition to MST1/2 kinase inhibitors, significant progress has been made in the identification and development of LATS1/2 inhibitors. These compounds promoted in vitro proliferation of inner-ear sensory supporting cells and primary cardiomyocytes, ex vivo growth of organoids derived from various human tissues, cell fate transitions in the lung and regeneration of multiple organs in mice[149–155].

Although small molecule inhibitors of MST and LATS kinases show promise as regenerative therapeutics, several challenges remain in translating preclinical findings into human treatments. These include: first, ensuring the specificity and selectivity of MST1/2 or LATS1/2 targeting without affecting other kinases in crucial pathways; second, achieving tissue-specific delivery and action while avoiding unwanted systemic effects; and third, addressing potential long-term effects, such as an increased risk of cancer. Adeno-associated virus 9 (AAV9)-based gene therapy has been explored as a potential solution to some of these challenges. Specifically, local knockdown of SAV1 using AAV9 is one approach that helps to overcome limitations associated with small molecule kinase inhibitors. In a pig model of ischaemia–reperfusion-induced myocardial infarction, local delivery of AAV9–*SAV1* short hairpin RNA (shRNA) to repress LATS activity in border zone cardiomyocytes resulted in heart tissue renewal and improved heart function[156]. In an exciting recent development, this *SAV1* gene therapy (termed YAP101) recently progressed to a phase I human clinical trial for patients with ischaemic heart failure and reduced ejection fraction[157].

Beyond the founding Hippo pathway kinases MST1/2 and LATS1/2, other potential druggable targets have been identified, including specific GPCRs, ROCK, FAK, MARK2–4, NUAK1 and NUAK2 (refs. 104–108,158–165). Further, inhibitors of geranylgeranyltransferase type 1 subunit-β (PGGT1β) have been identified that inactivate YAP/TAZ activity by blocking Rho-GTPase signalling[166]. Although there are many potential upstream druggable targets to develop therapeutics to ameliorate dysfunction of the Hippo pathway and hyperactivation of YAP/TAZ in human diseases such as cancer, fibrosis and heart disease, inhibition of an upstream target that regulates multiple signalling pathways poses a challenge owing to the risk of reduced selectivity and increased toxicity. Furthermore, the upstream Hippo pathway is complex, branched and interconnected and, as such, targeting upstream pathway proteins would likely be highly susceptible to bypass signalling and therapy resistance.

An obvious way to overcome such bypass signalling is to target YAP, TAZ and TEADs, which sit at the base of the Hippo pathway (Fig. 1 and Box 1). However, these proteins are transcription regulators, which are traditionally difficult to target therapeutically. YAP and TAZ, which are transcription co-activators with no known catalytic activity, are still considered poor candidates for direct inhibition with small molecules. With this in mind, efforts have been made to target YAP expression directly via either RNA interference (for example, YAP1 antisense oligonucleotides (ASOs))[167] or targeted protein degradation strategies with YAP PROTACs[168]. In preclinical models of YAP-activated hepatocellular carcinoma (HCC) and head and neck squamous cell carcinoma (HNSCC), YAP1 ASO ION537 reduced YAP1 protein abundance and induced significant tumour regression[167] and has progressed to a phase I clinical trial in humans (NCT04659096). It remains to be seen whether direct YAP targeting is clinically efficacious in cancers, especially given that the YAP paralogue TAZ could potentially compensate for YAP loss. YAP-specific therapeutics may also have different safety profiles compared with TEAD inhibitors (see below) as YAP interacts with and regulates the activity of other transcription factors besides TEADs[169].

TEADs: the leading therapeutic target

Most signalling pathway-based therapies target cell surface receptors or signalling proteins. By contrast, Hippo pathway-targeted therapies

Box 1 | Different classes of TEAD inhibitor

Over the past 20 or so years of research, the TEA domain transcription factors (TEADs) have emerged as the dominant therapeutic target in the Hippo pathway, which is an interesting counterpoint to most other signalling pathway therapeutics, which are enriched for agents that target transmembrane receptors and signalling kinases. This phenomenon reflects Hippo signalling logistics; there is a preponderance of tumour suppressor kinases in the pathway, multiple upstream branches and no easily targetable transmembrane receptors. Traditionally, transcription machinery is difficult to therapeutically target, with currently no transcription factor-targeted therapies approved for clinical use. TEAD inhibitors have the potential to be the first, with several compounds now in phase I clinical trials. Three different types of TEAD inhibitor have been developed to date: palmitate binding pocket (PBP) inhibitors, protein–protein interaction (PPI) inhibitors and degraders (PROTACs). TEAD degraders are still in preclinical development, whereas both TEAD PBP and PPI inhibitors have entered phase I clinical trials. TEAD PBP inhibitors are by far the most common class of TEAD inhibitor, with seven now in clinical trials, and many more in late-stage preclinical evaluation. These were largely isolated from unbiased compound library screens for Hippo–Yes-associated protein (YAP)–TEAD transcription, which in itself offers powerful reinforcement that TEADs are the ideal drug targets among Hippo pathway proteins. By contrast, TEAD PPI inhibitors have been developed based on careful structural biology studies focused on the YAP–TEAD binding interfaces. Despite their differences, potent TEAD PBP inhibitors and PPI inhibitors have both been developed and have similar efficacy in preclinical cancer models. This leaves human clinical trials as the likely arbiter of whether one or both TEAD inhibitor classes prevails to become the first Hippo pathway-targeted therapy in oncology.

Table 2 | Select TEAD palmitate binding pocket inhibitors

Compound	Mode of action	Reported TEAD selectivity	Comments	Year (ref.)
DC-TEADin02	Covalent	TEAD4	Highly selective Inhibits YAP–TEAD-regulated transcription	2019 (ref. 178)
TED-347	Covalent	TEAD2/4	Inhibits YAP–TEAD binding, blocks YAP-TEAD-regulated transcription Inhibits cell viability of patient-derived glioblastoma spheroids	2019 (ref. 195)
MGH-CP-1	Non-covalent	TEAD2/4	Inhibits TEAD autopalmitoylation, directly occupying the PBP Inhibits TEAD-mediated transcription in mice	2020 (ref. 179)
K-975	Covalent	Pan-TEAD	Covalently binds to a conserved cysteine in the TEAD PBP Inhibits the YAP/TAZ–TEAD interaction and YAP–TEAD-regulated transcription Inhibits growth of mesothelioma cells/tumours in vitro and in vivo Synergistically suppresses mesothelioma tumour xenografts in combination with CDK4/6 inhibitor (palbociclib)	2020 (ref. 180)
Compound 2	Non-covalent	Pan-TEAD	Binds to TEAD PBP, blocks TEAD palmitoylation and stabilizes TEAD protein in the absence of *S*-palmitoylation Reduces *CTGF* and *CYR61* transcription Does not block TEAD binding to DNA Causes tumour stasis in a mouse xenograft model	2020 (ref. 222)
MYF-01-037	Covalent	TEAD2	Binds TEAD PBP and blocks YAP–TEAD interaction Suppresses osimertinib+trametinib (OT)-induced YAP activity in vitro Decreases dormant cell viability and growth in combination with OT	2020 (ref. 194)
VT103	Non-covalent	TEAD1	Selectively binds TEAD1, blocks TEAD1 palmitoylation and disrupts YAP/TAZ–TEAD1 interaction Inhibits TEAD transcription activity Inhibits proliferation of NF2-deficient mesothelioma cell lines in vitro and tumour growth in vivo	2021 (ref. 177)
VT107	Non-covalent	Pan-TEAD	Binds to and blocks palmitoylation of all four TEADs Disrupts YAP/TAZ–TEAD interaction and transcription activity Inhibits proliferation of NF2-deficient/Merlin-negative mesothelioma cell lines in vitro Has broad efficacy in mesothelioma cell lines	2021 (ref. 177)
MSC-4106	Non-covalent	TEAD1/3	Inhibits TEAD1 and TEAD3 palmitoylation Crystallized in the P-site of TEAD1 Shows favourable PhysChem, ADME and pharmacokinetic profile Reduces mesothelioma cell viability in vitro and tumour growth in vivo Downregulates *CYR61* expression in tumours	2022 (ref. 181)
TM2	Non-covalent	Pan-TEAD	Binds to TEAD PBP and inhibits TEAD palmitoylation Inhibits YAP–TEAD interaction and transcription Blocks YAP-dependent organoid growth and cancer cell proliferation	2022 (ref. 263)
MYF-03-176	Covalent	Pan-TEAD	Binds to TEAD PBP Inhibits YAP–TEAD-regulated transcription and proliferation of mesothelioma and liposarcoma cell lines	2023 (ref. 182)
GNE-7883	Non-covalent	Pan-TEAD	Binds TEAD PBP and disrupts YAP/TAZ–TEAD interaction Decreases chromatin accessibility at TEAD motifs and expression of YAP/TAZ–TEAD target genes Inhibits growth of YAP/TAZ-dependent cancer cell lines and mesothelioma tumour growth Overcomes resistance to KRAS(G12C) inhibitors	2023 (ref. 139)
SWTX-143	Covalent	Pan-TEAD	Irreversible and selective Binds to PBP of all four TEADs Inhibits proliferation of *hippo*-mutated cancer cell lines and mesothelioma tumours in vivo Inhibits YAP/TAZ–TEAD transcription in tumours	2024 (ref. 183)
AZ4331	Covalent	Pan-TEAD	Identified by structure-guided drug design for favourable DMPK, safety and CMC properties Inhibits TEAD1–4 palmitoylation Suppresses TEAD-dependent transcription and proliferation in mesothelioma and HNSCC Shows combination effect with osimertinib in EGFR-mutant NSCLC CDX model	2024 (ref. 185)

Table 2 (continued) | Select TEAD palmitate binding pocket inhibitors

Compound	Mode of action	Reported TEAD selectivity	Comments	Year (ref.)
MRK-A	Non-covalent	TEAD1	Selectively binds TEAD1 PBP and blocks the YAP–TEAD1 interaction Blocks YAP–TEAD-regulated transcription Reduces viability of Hippo pathway-altered mesothelioma cell lines in vitro and tumour growth in vivo Resistance mediated by HGF–Met signalling	2024 (ref. 192)
M3686	Non-covalent	TEAD1	Interacts strongly with TEAD1, weakly with TEAD3, but not TEAD2 or TEAD4 Inhibits TEAD palmitoylation and mesothelioma cell viability and tumour growth	2024 (ref. 193)
Compound 3	Covalent	Pan-TEAD	Inhibits palmitoylation of TEAD1,2,3,4 and YAP–TEAD-regulated transcription Shows antitumour efficacy in mesothelioma model	2024 (ref. 191)
BPI-460372	Covalent	TEAD1/3/4	Binds to TEAD1,3,4 Mainly metabolized by CYP2D6, CYP3A4 and CYP1A2	2025 (ref. 264)

TEA domain transcription factor (TEAD) palmitate binding pocket (PBP) inhibitors with known chemical structures are listed in chronological order based on their publication dates. The selected compounds represent various scaffolds, TEAD selectivity and modes of action. CDX, cell line-derived xenograft; DMPK, drug metabolism and pharmacokinetics; HNSCC, head and neck squamous cell carcinoma; NF2, neurofibromin 2 (Merlin); NSCLC, non-small-cell lung cancer; TAZ, transcriptional co-activator with PDZ binding motif; YAP, Yes-associated protein.

are dominated by agents that target the TEAD DNA binding proteins and their interaction with the YAP/TAZ transcription co-activators. The reasons for this are several fold: first, the Hippo pathway lacks readily targetable transmembrane receptors; second, most Hippo signalling proteins are tumour suppressors, not oncoproteins; third, both unbiased and directed drug discovery efforts identified agents that target the TEADs, as described below.

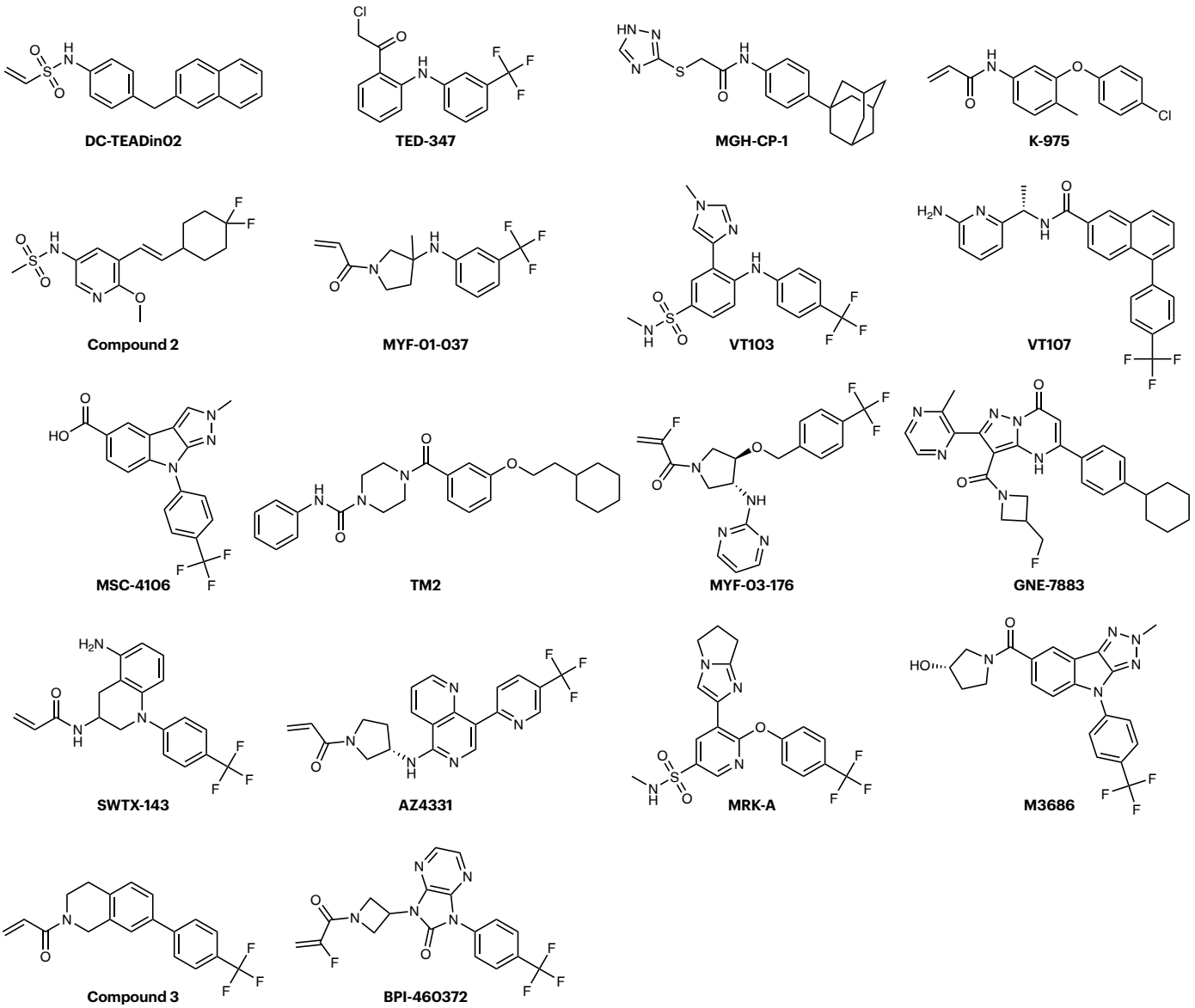
TEAD palmitate binding pocket inhibitors. A significant breakthrough in targeting the Hippo pathway was the discovery of a conserved hydrophobic palmitate binding pocket (PBP) in TEAD proteins[170–172]. All four mammalian TEAD family members contain a conserved cysteine residue that undergoes autopalmitoylation, along with a highly conserved hydrophobic pocket where the palmitate is embedded, providing an ideal binding site for drug-like small molecules. Furthermore, autopalmitoylation influences the interaction of TEADs with the YAP and TAZ transcription co-activators and is required for TEADs to promote target gene transcription[170–172]. Thus, binding of a small molecule in this central lipid pocket was theorized to displace palmitate and prevent autopalmitoylation of TEADs, resulting in a disruption of that ability of YAP/TAZ to bind to TEADs. Via both phenotypic screens (for example, cellular assays such as TEAD transcription reporter assays and TEAD palmitoylation assays) and structure-based design, many covalent and non-covalent TEAD autopalmitoylation inhibitors that bind to the central PBP have been reported ([173–175] and references within; Table 2 and Fig. 3a). The four mammalian TEAD proteins are highly homologous. Thus far, the field has attempted to infer the relevance of the TEADs in cancer by examining their expression in cell lines and patient samples and via large-scale genetic screens performed as part of the Cancer Dependency Map[176]. However, because homologous genes can compensate for each other, genetic studies in which single genes are targeted have obvious challenges. As such, in the context of cancer therapy, it is still unclear whether one or more TEADs have greater functional relevance.

To date, more than 30 biotechnology and pharmaceutical companies and academic laboratories have developed TEAD PBP inhibitors ([139,177–191]). Table 2 and Fig. 3 present select examples of TEAD PBP inhibitors for which the chemical structures and biological activities have been published in peer-reviewed journals and/or conference presentations. In general, both covalent and non-covalent TEAD inhibitors that display similar potency in TEAD transcription assays exhibit comparable in vitro anti-proliferation activity and in vivo antitumour efficacy in preclinical mesothelioma models[177,183,191]. However, it remains to be determined whether the different modes of action of TEAD PBP inhibitors (that is, irreversible inhibition of TEADs by a covalent cysteine PBP binder versus reversible inhibition of TEAD autopalmitoylation by a non-covalent binder) will influence the therapeutic index and durability of response in clinical settings. In addition to their mode of action, Table 2 highlights that not all TEAD PBP inhibitors target all four TEAD family members. For instance, certain inhibitors are selective for TEAD 1, 2 or 4 (refs. 177,178,192–194), whereas others are selective for pairs of TEADs, such as TEAD2 and TEAD4 (refs. 179,195) or TEAD1 and TEAD3 (ref. 181). As described in more detail below, some TEAD PBP inhibitors have advanced into clinical trials, with the first-in-class VT3989 (Vivace Therapeutics) showing clinical responses (see below, NCT04665206 and refs. 196,197).

TEAD protein–protein interaction inhibitors. Before the discoveries of the central TEAD PBP and TEAD autopalmitoylation itself, efforts were made to identify small molecules or peptides that prevent YAP/TAZ interaction with TEADs (Fig. 3b). Verteporfin was the first reported YAP–TEAD PPI inhibitor[198] and is commonly used as a tool compound in Hippo pathway research. However, owing to its mechanism of action as a photosensitizer, verteporfin activity is not specific. Detailed characterization of the molecular interactions in the interface between YAP/TAZ and TEAD proteins[199–201] and structure-based design paved the way for the discovery of specific YAP/TAZ–TEAD PPI inhibitors that work by binding to the α-helix or Ω-loop pockets on the surface of TEADs ([173,174] and references within; for example,[200,202–207]). Select examples of non-peptide TEAD PPI inhibitors that have been published in peer-reviewed journals are presented in Table 3 and Fig. 3b. Currently, the most advanced YAP/TAZ–TEAD PPI inhibitor is IAG933 (Novartis).

Although both TEAD PBP inhibitors and YAP/TAZ–TEAD PPI inhibitors suppress TEAD transcription activity by attenuating YAP/TAZ binding to TEAD, their mechanisms of action differ significantly. YAP/TAZ–TEAD PPI inhibitors, such as IAG933, directly bind to the TEAD Ω-loop pocket and competitively displace YAP/TAZ[206]. This action occurs regardless of the palmitoylation status of TEAD proteins.

a **TEAD palmitate binding pocket inhibitors**



b **YAP–TEAD protein–protein interaction inhibitors**

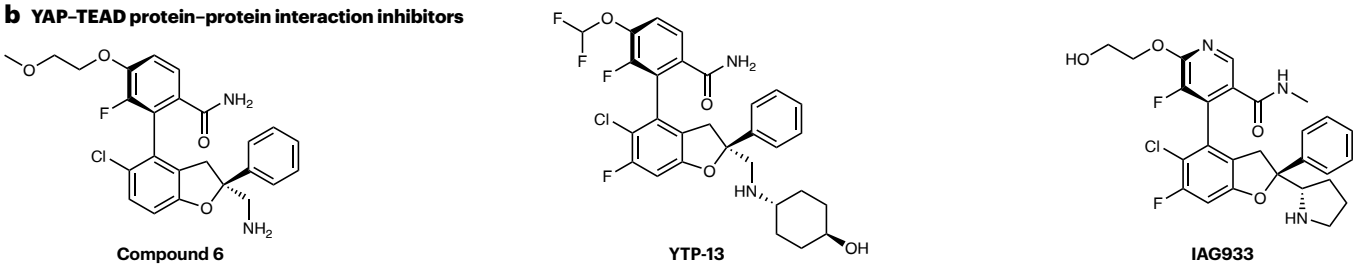


Fig. 3 | Structures of select TEAD palmitate binding pocket and YAP–TEAD protein–protein interaction inhibitors. TEA domain transcription factor (TEAD) palmitate binding pocket (PBP) inhibitors (part **a**) and Yes-associated protein (YAP)–TEAD protein–protein interaction (PPI) inhibitors (part **b**) with known chemical structures.

In contrast, TEAD PBP inhibitors (both covalent and non-covalent) indirectly disrupt the YAP/TAZ–TEAD interaction by allosterically modulating TEADs[177,208]. These inhibitors can bind to the central pocket of TEADs only when these proteins are not autopalmitoylated. When a TEAD inhibitor is first introduced to cells, there is almost certainly a pool of pre-existing autopalmitoylated TEAD proteins, which would be impervious to TEAD PBP inhibitors. As a result, YAP/TAZ–TEAD PPI inhibitors are likely to exert a faster and more profound initial inhibitory effect than TEAD PBP inhibitors. This concept has been substantiated by comparing IAG933 (ref. 206), VT104 (ref. 177) and K-975 (ref. 180) head to head in preclinical studies[206]. These contrasting mechanisms may influence both the clinical efficacy of different classes of TEAD inhibitor and their degree of on-target toxicity.

TEAD degraders. TEAD degraders (PROTACs) are another class of TEAD inhibitors that have been developed ([174] and references within), and consist of a TEAD-binding moiety, a chemical linker and a ligand for the substrate recognition component of an E3 protein ligase complex (for example, cereblon). To date, they have been designed based on either TEAD Ω-loop pocket binders[209,210] or TEAD PBP binders[211,212] and recruit the ubiquitin–proteasome machinery to induce selective degradation of TEAD proteins. The development of this class of TEAD inhibitors remains challenging, but it will be of interest to see how TEAD degraders compare with TEAD PBP and PPI inhibitors, particularly in terms of both antitumour efficacy and toxicity.

Another important consideration in relation to the relative impact of TEAD degraders and TEAD small molecule inhibitors is the role of the VGLL4 transcription co-repressor (Tgi in *Drosophila*)[213–215]. VGLL4 was originally identified in *Drosophila* as mediating a default repressor function of Scalloped/TEADs and competes with YAP for overlapping binding sites on TEADs[54,55]. Specifically, while YAP interacts with TEADs at three distinct sites – interface 1 (a β-strand), interface 2 (an α-helix) and interface 3 (an Ω-loop pocket) – VGLL4 binds only to interfaces 1 and 2, but not to the Ω-loop pocket[139,215,216]. As such, IAG933, an Ω-loop pocket binder, both prevents the YAP–TEAD PPI and promotes the VGLL4–TEAD PPI, as suggested by the finding that IAG933-treated mesothelioma cells exhibit an enrichment of VGLL4 on TEAD genome binding sites at the expense of YAP[206]. This suggests that VGLL4–TEAD-mediated transcription repression may contribute significantly to the antitumour effects of IAG933. VGLL4 might also be important for TEAD PBP inhibitor efficacy; in support of this, an unbiased genome-wide genetic screen identified *VGLL4* as a gene conferring resistance to VT107, a pan-TEAD PBP inhibitor[217]. Interestingly, a group of sulfonamide-containing TEAD PBP inhibitors (namely, Compound 2, VT103 and IK-930) strongly promote TEAD–VGLL4 complex formation, whereas they only weakly impact the YAP–TEAD PPI (T.T.T., Mingyue Ma, Jian Li, and Fa-Xing Yu, unpublished data;[184,218]). In both in vitro and animal studies, these sulfonamide-containing TEAD PBP inhibitors exhibited greater reliance on VGLL4 for cell killing and tumour reduction than non-sulfonamide-containing TEAD PBP inhibitors[218]. Given these findings, differential VGLL4 engagement by different classes of TEAD inhibitor may well impact their therapeutic index and toxicity. Further, TEAD PBP and PPI inhibitors might have superior antitumour properties to TEAD degraders because the latter group of molecules will not be able to induce TEAD–VGLL4-mediated transcription repression, although this remains to be assessed.

A further predicted point of difference between TEAD PBP and PPI inhibitors, and TEAD degraders relates to the Hippo-independent transcription cofactors, VGLL1–3 and INSM1A/B. VGLL1–3, which are the orthologues of *Drosophila* Vestigial, and share homology with VGLL4, are co-activators of TEADs/Scalloped[63–65], but are not regulated by the Hippo pathway. INSM1A/B, which are the orthologues of *Drosophila* Nerfin-1, repress transcription in partnership with TEADs/Scalloped[56,57]. Theoretically, TEAD degraders would abolish not only YAP-mediated transcription, but transcription regulated by these additional TEAD cofactors. Whether TEAD PBP and PPI inhibitors also influence TEAD-regulated transcription by VGLL1–3 and/or INSM1A/B awaits investigation, but it is likely that degradation-induced loss of TEAD occupancy will impact transcription differently from TEAD PBP and PPI inhibitors.

Hippo pathway mutations are driver events in several human cancers, and it is in these cancers that TEAD inhibitors are most likely to prove efficacious as monotherapies (for example, refer to cancers discussed in refs. 26,114). In preclinical studies, TEAD inhibitors have demonstrated the most promising antitumour efficacy as a monotherapy in mesothelioma, highlighting the dependence of these tumours on YAP/TAZ–TEAD hyperactivity[177,180,181,183,193,206]. TEAD inhibitors have also displayed single-agent antitumour activity in preclinical models of EHE[206,219], diffuse gastric cancer[220], HCC[221], HNSCC[222,223], pancreatic ductal adenocarcinoma[224], glioblastoma[225], Schwannoma and meningioma[226]. Moreover, as discussed below, in a phase I clinical trial (clinicaltrials.gov ID: NCT04665206), the TEAD PBP inhibitor VT3989 demonstrated not only safety and tolerability but durable antitumour activity in patients with advanced mesothelioma[196], and both VT3989 and IK-930 showed promising results, with patients with EHE experiencing stable disease on treatment[196,227].

Table 3 | Select non-peptide YAP–TEAD protein–protein interaction inhibitors

PPI inhibitor	Mode of action	Comments	Year (ref.)
Compound 6	PPI — Ω-loop pocket of TEAD	Disrupts YAP–TEAD interaction in vitro Inhibits YAP–TEAD-dependent transcription and cell proliferation	2022 (ref. 203)
YTP-13	PPI — Ω-loop pocket of TEAD	Complexes with TEAD4 Suppresses YAP–TEAD-regulated transcription and mesothelioma tumours in mice	2023 (ref. 205)
IAG933	PPI — Ω-loop pocket of TEAD	Binds to the Ω-loop binding region (one of three YAP-binding interfaces) of all four TEADs Disrupts the YAP/TAZ–TEAD interaction More rapid and deeper inhibition of TEAD-dependent transcription and cell viability Induces loss of YAP and gain of VGLL4 from TEAD genomic motifs Shows rapid PD and antitumour efficacy in NF2-deficient and *TAZ* gene fusion cancer models Improves antitumour efficacy of RTK, KRAS and RAF inhibitors in tumour models	2024 (ref. 206)

Yes-associated protein (YAP)–TEA domain transcription factor (TEAD) protein–protein interaction (PPI) inhibitors that have been published in peer-reviewed journals. These compounds have similar chemical scaffolds to each other and bind to the Ω-loop pocket of TEADs. NF2, neurofibromin 2 (Merlin); PD, pharmacodynamics; TAZ, transcriptional co-activator with PDZ binding motif; VGLL4, Vestigial-like family member 4.

Table 4 | YAP–TEAD-targeting drugs in cancer clinical trials

Drug	Sponsor	Mode of action	TEAD selectivity	Clinical trial
ION537[a]	Ionis Pharmaceuticals	YAP1 antisense oligonucleotides	NA	NCT04659096 Phase I, study start 5 Jan 2021
VT3989	Vivace Therapeutics	Non-covalent Autopalmitoylation inhibitor	TEAD1,(2),3,(4)	NCT04665206 Phase I and phase II, study start 24 Mar 2021
IAG933	Novartis Pharmaceuticals	YAP/TAZ–TEAD PPI inhibitor	Pan-TEAD	NCT04857372 Phase I, study start 21 Oct 2021
IK-930[b]	Ikena Oncology	Non-covalent Autopalmitoylation inhibitor	TEAD1	NCT05228015 Phase I, study start 7 Jan 2022
BPI-460372	Betta Pharmaceuticals	Covalent Autopalmitoylation inhibitor	TEAD1,3,4	NCT05789602 Phase I, study start 24 Apr 2023
ODM-212[c]	Orion Pharma	Non-covalent Autopalmitoylation inhibitor	Unknown	ISRCTN99739590 Phase I/2, study start 25 Oct 2023
BGC515	BridGene Biosciences	Covalent Autopalmitoylation inhibitor	Pan-TEAD	NCT06452160 Phase I, study start 27 Jun 2024
SW-682	SpringWorks Therapeutics	Autopalmitoylation inhibitor	Pan-TEAD	NCT06251310 Phase I, study start 30 Jul 2024
ISM6331	Insilico Medicine	Non-covalent Autopalmitoylation inhibitor	Pan-TEAD	NCT06566079 Phase I, study start 27 Dec 2024

Drugs targeting Yes-associated protein (YAP) or TEA domain transcription factor (TEAD) in cancer clinical trials are listed in chronological order based on the start dates of their phase I studies. More detailed information on the trials can be found on ClinicalTrials.gov or the UK's Clinical Study Registry (ISRCTN) using the trial IDs shown in the last column. [a]The study was completed on 19 Oct 2022. [b]Ikena Oncology announced discontinuation of the clinical IK-930 programme (press release 28 May 2024)[228]. [c]First posted on ClinicalTrials.gov on 10 Dec 2024 (NCT06725758). NA, not applicable; TAZ, transcriptional co-activator with PDZ binding motif.

Clinical trials in cancer. In exciting developments over the past few years, nine Hippo pathway-targeted therapies have entered human cancer clinical trials (Table 4). These trials have centred on cancers with a high incidence of genetic disruptions in the Hippo pathway (for example, *NF2* mutations, oncogenic *YAP/TAZ* gene fusions, or *YAP* amplification). These cancers include mesothelioma, EHE, HCC, HNSCC and other advanced solid cancers. Seven of these therapies are TEAD PBP inhibitors, one is a YAP/TAZ–TEAD PPI inhibitor and one is RNA interference-based therapy (YAP ASO) (Table 4).

VT3989, a multi-TEAD PBP inhibitor, was the first-in-class and first-in-human TEAD inhibitor in clinical trials, and has shown compelling clinical activity (NCT04665206)[196]. In a phase I, multi-centre, open-label, dose-escalation and expansion study, VT3989 was evaluated in patients with refractory, locally advanced or metastatic solid tumours, particularly those with *NF2* gene mutations or *YAP* or *TAZ* gene fusions. Data from an interim analysis were presented at the 2023 American Association for Cancer Research Annual Meeting. Among 69 enrolled patients, 43 had mesothelioma, nine had meningioma (four with germline *NF2* mutations (*gNF2m*), four with somatic NF2 mutations (*sNF2m*) and one without detectable *NF2* mutations), four had *sNF2m* sarcoma, two had EHE and 11 had other solid tumours with or without *sNF2m*. VT3989 showed durable antitumour activity; six patients with mesothelioma achieved partial responses with target lesion changes ranging from −30% to −81% and treatment durations of 6.5+ to 21+ months, and one patient with *sNF2m* sarcoma achieved a partial response (−35%; treatment duration of 8 months). Additionally, among those with measurable disease and at least one post-treatment tumour assessment, 34 patients achieved stable disease, with notable cases including a patient with *sNF2m* nasopharyngeal cancer (−24% change, 7.4 months) and a patient with EHE (−22%, 9.5+ months). Treatment was ongoing at the time of data cut-off for the interim analysis. Importantly, VT3989 is safe and well tolerated, with no dose-limiting toxicities observed. The most common treatment-related adverse events were albuminuria and proteinuria, which were reversible at all doses and schedules[197]. Excitingly, the clinical activity of VT3989 not only demonstrates the druggability of the Hippo pathway but also validates it as a viable target for cancer therapy and underscores its potential for continued drug development.

The second TEAD inhibitor to enter clinical trials was IAG933 (Novartis). It is the only TEAD PPI inhibitor in clinical trials to date and is being evaluated in a phase I study for advanced mesothelioma and other solid tumours (NCT04857372; Table 4). Clinical data for IAG933 have yet to be disclosed, but it will be fascinating to compare its clinical impact with that of the TEAD PBP inhibitors. The phase I study of IK-930, a TEAD1-selective PBP inhibitor, was terminated for strategic reasons by the sponsor[228] (Table 4). Before discontinuation, IK-930 showed early signs of clinical benefit in EHE, with seven of seven patients achieving stable disease. However, contrary to preclinical data that suggested the TEAD1-selective PBP inhibitor would have a superior safety profile, with no evidence of renal changes compared with pan-TEAD PBP inhibitors[184], proteinuria was observed in the initial dose-escalation cohort of IK-930 (ref. 227). Interestingly, VT103, a TEAD1-selective PBP inhibitor that is tenfold and 75-fold more potent than IK-930 in YAP reporter assays in vitro and in NCI-H226 tumour xenograft studies in vivo, respectively, exhibited renal toxicity in 28-day rat studies[177,229]. These findings indicate that TEAD1 has an important role in podocyte function (see below). ION537 is the only YAP-specific targeted therapy using ASOs that has been evaluated in clinical trials to date. Although the trial was completed, clinical response and safety data have not yet been reported. As we await further updates from ongoing clinical trials

(Table 4), additional TEAD inhibitors including SPR1 (a non-covalent TEAD1/TEAD4 PBP inhibitor; Sporos Biodiscovery) and OPN-9840 (a non-covalent pan-TEAD PBP inhibitor; Opna Bio) are being developed and are currently in the IND-enabling stages, meaning that further trials are imminent.

Potential limitations of TEAD inhibitors. Given that TEAD transcription factors are broadly expressed and essential for both animal development and homeostasis, the deployment of agents that inhibit their functions could theoretically pose substantial risks. YAP and TEADs are essential for murine embryonic development; they regulate the very first cell fate choice in pre-implantation embryos, that is, trophectoderm versus inner cell mass[24], and subsequently control cell competition in the epiblast[230]. Accordingly, targeted disruption of various TEAD genes in mice causes embryonic lethality[231,232]. This occurs at different stages of embryonic development and, coupled with the fact that expression of the four TEAD genes is to some degree non-overlapping, suggests that they have both overlapping and tissue-specific roles[231–235]. As TEAD transcription factors and the Hippo signalling pathway are highly evolutionarily conserved, inhibition of TEADs would be predicted to have similar deleterious consequences for human embryonic development. Thus, one may anticipate TEAD inhibitors to affect fertility, embryo–fetal development, and pre- and postnatal development. However, it is important to note that gene mutations and small molecule inhibitors perturb biological systems in very different ways, and to date the possibility of reproductive toxicity is theoretical with no evidence.

Genetically engineered inducible mouse models have enabled the investigation of *YAP*, *TAZ* and the TEAD genes beyond embryonic development. These have revealed that while *YAP* and *TAZ* are largely dispensable in many tissues (for example, epithelial cells in the intestinal epithelium and hepatocytes in the liver) they are essential for epithelial tissue regeneration after injury, and in certain cell types (for example, the skin and biliary ducts of the liver) ([236] and references within). Of note, several reports revealed that *YAP* and *TAZ* have an essential role in kidney development and podocyte homeostasis[237–239]. Podocytes are specialized epithelial cells that have long foot processes that wrap around the capillaries of the glomerulus in the kidney, and are crucial to filter blood plasma and maintain the structural integrity of the glomerulus[240]. Glomerular diseases including Diabetic Nephropathy and Focal Segmental Glomerulosclerosis (FSGS) are characterized by podocyte loss, which results in proteinuria and significant loss of albumin in the urine. It is important to note that mouse models of FSGS, in which *YAP* or *TAZ* was deleted specifically in the podocytes congenitally with a non-inducible podocin promoter-driven Cre, is different from inhibition of TEAD in adults with systemic exposure of TEAD inhibitors. Bypassing the requirement of *YAP/TAZ* during podocyte development, inducible podocyte-specific deletion of YAP or TAZ in adult mice enables normal kidney function with no sign of proteinuria[241,242]. Podocyte-specific deletion of *YAP/TAZ* in adult mice resulted in exacerbated kidney function only when mice were also administered with podocyte-damaging agents[241–244].

Concerns about kidney toxicity emerged when preclinical safety studies in rats and monkeys revealed pathological findings at high TEAD inhibitor doses suggestive of renal toxicity[245,246]. Despite preclinical evidence indicating that podocytes depend on YAP/TAZ signalling in response to damage, early clinical trials of the Vivace TEAD inhibitor VT3989 showed that it is well tolerated and safe. In addition, several cancer patients experienced durable partial responses or stable disease (see Clinical trials above)[196]. Although some patients developed proteinuria during treatment with VT3989, it was reversible upon treatment interruption. Importantly, this proteinuria has not been associated with clinically meaningful renal insufficiency or hypoalbuminaemia. Similarly, nephrotoxicity induced by the covalent TEAD inhibitor K-975 in rats was reversible and monitorable[247]. Although the proteinuric effect of TEAD inhibitors raises concerns about potential glomerular injury and scarring with long-term use – especially in patients with pre-existing proteinuria – strategies to mitigate this risk, such as intermittent dosing schedules, could allow for effective treatment while minimizing proteinuria-related toxicity. In summary, the only toxicity seen so far is proteinuria, consistent with what has been seen in preclinical species and the literature about the role of TEADs in

Box 2 | Hippo and RAS–MAPK: a relationship to be leveraged

The Hippo and RAS–MAPK pathways are both core signal transduction cascades that are implicated in tissue growth, cell differentiation and cancer. The RAS–MAPK pathway was pieced together using biochemistry and genetics in the 1980s and 1990s[265]. The discovery and characterization of the Hippo pathway happened much later, with most of the pathway assembled in the 2000s and 2010s, with *Drosophila* genetics taking the lead[1–9]. Fascinatingly, close functional relationships between these pathways have been identified time and again, predominantly in unbiased genetic screens in human cultured cells, but also in vivo. In 2014, Yes-associated protein (YAP) was found to possess the ability to supplant the oncogenic function of KRAS in both human cultured cells and mice[136,137]. At a similar time, again in unbiased genetic screens, YAP conferred resistance to the RAS–MAPK-targeted therapies BRAF inhibitor and MEK inhibitor in different cancer cell lines[138]. Subsequently, this role for YAP was extended to additional RAS–MAPK pathway-targeted therapies[138,139,194,226,252–255,257,266], and, more recently, elevated RAS–MAPK pathway activity was identified as conferring resistance to TEA domain transcription factor (TEAD) inhibitors in mesothelioma[217,250]. Consistently, combining TEAD inhibitors with RAS–MAPK-targeted therapies has proved beneficial in multiple preclinical tumour models of both Hippo-driven and RAS-driven cancers[139,140,206,217,250,256–262]. The precise mechanisms by which these pathways crosstalk are still being elucidated but multiple studies have revealed links between each pathway's transcription factors, that is, YAP–TEAD and the AP-1 family proteins. These proteins coregulate many genes in both cancer cell lines and in vivo in *Drosophila* and regulate cancer cell survival and tissue growth[47,267–271]. Protein–protein interactions between these transcription factors have also been reported, as well as the ability to impact each other's abundance[47,270]. This wealth of evidence indicates great potential to combine Hippo pathway and RAS–MAPK pathway inhibitors as cancer therapies.

glomeruli. Ultimately, identification of TEAD inhibitors with the most favourable therapeutic index and durable responses remains crucial.

In addition to on-target toxicity, most cancer therapies are also limited by acquired or intrinsic resistance. In preclinical studies, several resistance mechanisms to TEAD inhibitors have already been identified, including activation of the RAS–MAPK, JAK–STAT and PI3K–AKT pathways, as well as MYC signalling[192,217,248–250]. Further, a recent study reported that elevation of cellular acyl-CoA levels (including palmitoyl-CoA) could confer some degree of resistance to multiple TEAD PBPs[251]. As more TEAD inhibitors continue to undergo evaluation in clinical trials, it will be important to monitor the emergence of resistance in patients. Gaining insight into the mechanisms of resistance will be essential to develop strategies to overcome it.

Combination therapies. Many studies have revealed a special relationship between the Hippo and RAS–MAPK signalling pathways in both development and disease (Box 2). For example, YAP/TAZ–TEAD activation can drive resistance to multiple RAS–MAPK pathway-targeted cancer therapies, including EGFR, BRAF, ALK and RAS inhibitors[138,194,252–255]. Preclinical studies have revealed that TEAD inhibitors enhance the efficacy and durability of the response to many of these targeted therapies, including clinically approved EGFR inhibitors (osimertinib, lazertinib), MET inhibitors (savolitinib, capmatinib), EGFR–MET bispecific antibody (amivantamab), KRAS(G12C) inhibitors (sotorasib, adagrasib), BRAF inhibitors (encorafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib) and mTOR inhibitor (everolimus)[139,140,206,217,256–262]. Furthermore, various RAS–MAPK pathway inhibitors such as trametinib and cobimetinib were recently found to enhance the antitumour properties of TEAD inhibitors such as VT107 and IAG933 in both mesothelioma and non-small-cell lung cancer[206,217]. Although preclinical evidence strongly supports combination of TEAD inhibitors with other targeted therapies, the translation of this into clinical outcomes remains to be seen, pending clinical trial data. It is still early days for TEAD inhibitors in the clinic but combining them with RAS–MAPK pathway therapies could significantly expand the application of TEAD inhibitors in cancer treatment, particularly as Hippo pathway-driven cancers are far rarer than RAS–MAPK pathway-driven cancers.

Outlook

Just under 20 years elapsed between the discovery of the Hippo pathway in *Drosophila* as a new growth-control signalling network and the entry of Hippo-targeted therapies into cancer clinical trials. This stands as yet another powerful example of how discovery research can reveal truly novel potential ways to treat human diseases. Interestingly, most drug discovery efforts from dozens of academic and industry groups have landed on the same targets, the TEAD transcription factors. Compounds that disrupt the ability of these proteins to form stable complexes with the YAP and TAZ transcription co-activators have shown great potential as anticancer therapies in preclinical studies and more recently in a phase I clinical trial. Further clinical trial results are eagerly awaited and will ultimately determine the efficacy of TEAD inhibitors both when administered as monotherapies in Hippo-driven cancers such as mesothelioma, and in combination with agents that target the RAS–MAPK pathway in cancers driven by this pathway. If successful, TEAD inhibitors will give added impetus to transcription factor targeting in medicine, as well as pursuit of compounds that target additional Hippo pathway proteins such as the MARK and NUAK kinases.

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References

1. Tapon, N. et al. Salvador promotes both cell cycle exit and apoptosis in *Drosophila* and is mutated in human cancer cell lines. *Cell* **110**, 467–478 (2002).
2. Pantalacci, S., Tapon, N. & Leopold, P. The Salvador partner Hippo promotes apoptosis and cell-cycle exit in *Drosophila*. *Nat. Cell Biol.* **5**, 921–927 (2003).
3. Justice, R. W., Zilian, O., Woods, D. F., Noll, M. & Bryant, P. J. The *Drosophila* tumor suppressor gene *warts* encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. *Genes Dev.* **9**, 534–546 (1995).
4. Xu, T., Wang, W., Zhang, S., Stewart, R. A. & Yu, W. Identifying tumor suppressors in genetic mosaics: the *Drosophila lats* gene encodes a putative protein kinase. *Development* **121**, 1053–1063 (1995).
5. Wu, S., Huang, J., Dong, J. & Pan, D. Hippo encodes a Ste-20 family protein kinase that restricts cell proliferation and promotes apoptosis in conjunction with Salvador and Warts. *Cell* **114**, 445–456 (2003).
6. Jia, J., Zhang, W., Wang, B., Trinko, R. & Jiang, J. The *Drosophila* Ste20 family kinase dMST functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis. *Genes Dev.* **17**, 2514–2519 (2003).
7. Kango-Singh, M. et al. Shar-pei mediates cell proliferation arrest during imaginal disc growth in *Drosophila*. *Development* **129**, 5719–5730 (2002).
8. Udan, R. S., Kango-Singh, M., Nolo, R., Tao, C. & Halder, G. Hippo promotes proliferation arrest and apoptosis in the Salvador/Warts pathway. *Nat. Cell Biol.* **5**, 914–920 (2003).
9. Harvey, K. F., Pfleger, C. M. & Hariharan, I. K. The *Drosophila* MST ortholog, Hippo, restricts growth and cell proliferation and promotes apoptosis. *Cell* **114**, 457–467 (2003).
10. Gaspar, P. & Tapon, N. Sensing the local environment: actin architecture and Hippo signalling. *Curr. Opin. Cell Biol.* **31C**, 74–83 (2014).
11. Zheng, Y. & Pan, D. The Hippo signaling pathway in development and disease. *Dev. Cell* **50**, 264–282 (2019).
12. Meng, Z., Moroishi, T. & Guan, K. L. Mechanisms of Hippo pathway regulation. *Genes Dev.* **30**, 1–17 (2016).
13. Moya, I. M. & Halder, G. Hippo-YAP/TAZ signalling in organ regeneration and regenerative medicine. *Nat. Rev. Mol. Cell Biol.* **20**, 211–226 (2019).
14. Harvey, K. F., Zhang, X. & Thomas, D. M. The Hippo pathway and human cancer. *Nat. Rev. Cancer* **13**, 246–257 (2013).
15. Staley, B. K. & Irvine, K. D. Hippo signaling in *Drosophila*: recent advances and insights. *Dev. Dyn.* **241**, 3–15 (2012).
16. Enderle, L. & McNeill, H. Hippo gains weight: added insights and complexity to pathway control. *Sci. Signal.* **6**, re7 (2013).
17. Huang, J., Wu, S., Barrera, J., Matthews, K. & Pan, D. The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the *Drosophila* homolog of YAP. *Cell* **122**, 421–434 (2005).
18. Dong, J. et al. Elucidation of a universal size-control mechanism in *Drosophila* and mammals. *Cell* **130**, 1120–1133 (2007).
19. Zhao, B. et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev.* **21**, 2747–2761 (2007).
20. Oka, T., Mazack, V. & Sudol, M. Mst2 and Lats kinases regulate apoptotic function of Yes kinase-associated protein (YAP). *J. Biol. Chem.* **283**, 27534–27546 (2008).
21. Sebé-Pedrós, A., Zheng, Y., Ruiz-Trillo, I. & Pan, D. Premetazoan origin of the Hippo signaling pathway. *Cell Rep.* **1**, 13–20 (2012).
22. Ikmi, A. et al. Molecular evolution of the Yap/Yorkie proto-oncogene and elucidation of its core transcriptional program. *Mol. Biol. Evol.* **31**, 1375–1390 (2014).
23. Mikeladze-Dvali, T. et al. The growth regulators warts/lats and melted interact in a bistable loop to specify opposite fates in *Drosophila* R8 photoreceptors. *Cell* **122**, 775–787 (2005).
24. Nishioka, N. et al. The Hippo signaling pathway components Lats and Yap pattern Tead4 activity to distinguish mouse trophectoderm from inner cell mass. *Dev. Cell* **16**, 398–410 (2009).
25. Wang, Y. et al. Comprehensive molecular characterization of the Hippo signaling pathway in cancer. *Cell Rep.* **25**, 1304–1317.e1305 (2018).
26. Kulkarni, A., Chang, M. T., Vissers, J. H. A., Dey, A. & Harvey, K. F. The Hippo pathway as a driver of select human cancers. *Trends Cancer* **6**, 781–796 (2020).
27. Zhou, D. et al. MST1 and MST2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the YAP1 oncogene. *Cancer Cell* **16**, 425–438 (2009).
28. Camargo, F. D. et al. YAP1 increases organ size and expands undifferentiated progenitor cells. *Curr. Biol.* **17**, 2054–2060 (2007).
29. Lee, J. H. et al. A crucial role of WW45 in developing epithelial tissues in the mouse. *EMBO J.* **27**, 1231–1242 (2008).
30. Kobayashi, S., Cox, A. G., Harvey, K. F. & Hogan, B. M. Vasculature is getting Hip(po): Hippo signaling in vascular development and disease. *Dev. Cell* **58**, 2627–2640 (2023).
31. Heallen, T. et al. Hippo pathway inhibits WNT signaling to restrain cardiomyocyte proliferation and heart size. *Science* **332**, 458–461 (2011).
32. Watt, K. I. et al. The Hippo pathway effector YAP is a critical regulator of skeletal muscle fibre size. *Nat. Commun.* **6**, 6048 (2015).
33. Cao, X., Pfaff, S. L. & Gage, F. H. YAP regulates neural progenitor cell number via the TEA domain transcription factor. *Genes Dev.* **22**, 3320–3334 (2008).
34. Jukam, D. et al. Opposite feedbacks in the Hippo pathway for growth control and neural fate. *Science* **342**, 1238016 (2013).
35. Pojer, J. M., Manning, S. A., Kroeger, B., Kondo, S. & Harvey, K. F. The Hippo pathway uses different machinery to control cell fate and organ size. *iScience* **24**, 102830 (2021).

36. Pojer, J. M., Saiful Hilmi, A. J., Kondo, S. & Harvey, K. F. Crumbs and the apical spectrin cytoskeleton regulate R8 cell fate in the *Drosophila* eye. *PLoS Genet.* **17**, e1009146 (2021).
37. Jukam, D. & Desplan, C. Binary regulation of Hippo pathway by Merlin/NF2, Kibra, Lgl, and Melted specifies and maintains postmitotic neuronal fate. *Dev. Cell* **21**, 874–887 (2011).
38. Kowalczyk, W. et al. Hippo signaling instructs ectopic but not normal organ growth. *Science* **378**, eabg3679 (2022).
39. Halder, G., Dupont, S. & Piccolo, S. Transduction of mechanical and cytoskeletal cues by YAP and TAZ. *Nat. Rev. Mol. Cell Biol.* **13**, 591–600 (2012).
40. Sun, S. & Irvine, K. D. Cellular organization and cytoskeletal regulation of the Hippo signaling network. *Trends Cell Biol.* **26**, 694–704 (2016).
41. Dupont, S. et al. Role of YAP/TAZ in mechanotransduction. *Nature* **474**, 179–183 (2011).
42. Wada, K., Itoga, K., Okano, T., Yonemura, S. & Sasaki, H. Hippo pathway regulation by cell morphology and stress fibers. *Development* **138**, 3907–3914 (2011).
43. Rauskolb, C., Sun, S., Sun, G., Pan, Y. & Irvine, K. D. Cytoskeletal tension inhibits Hippo signaling through an Ajuba-Warts complex. *Cell* **158**, 143–156 (2014).
44. Oh, H. et al. Genome-wide association of Yorkie with chromatin and chromatin-remodeling complexes. *Cell Rep.* **3**, 309–318 (2013).
45. Oh, H. et al. Yorkie promotes transcription by recruiting a histone methyltransferase complex. *Cell Rep.* **8**, 449–459 (2014).
46. Qing, Y. et al. The Hippo effector Yorkie activates transcription by interacting with a histone methyltransferase complex through Ncoa6. *eLife* **3**, e02564 (2014).
47. Zanconato, F. et al. Genome-wide association between YAP/TAZ/TEAD and AP-1 at enhancers drives oncogenic growth. *Nat. Cell Biol.* **17**, 1218–1227 (2015).
48. Galli, G. G. et al. YAP drives growth by controlling transcriptional pause release from dynamic enhancers. *Mol. Cell* **60**, 328–337 (2015).
49. Goulev, Y. et al. Scalloped interacts with Yorkie, the nuclear effector of the hippo tumor-suppressor pathway in *Drosophila*. *Curr. Biol.* **18**, 435–441 (2008).
50. Ota, M. & Sasaki, H. Mammalian tead proteins regulate cell proliferation and contact inhibition as transcriptional mediators of Hippo signaling. *Development* **135**, 4059–4069 (2008).
51. Wu, S., Liu, Y., Zheng, Y., Dong, J. & Pan, D. The TEAD/TEF family protein Scalloped mediates transcriptional output of the Hippo growth-regulatory pathway. *Dev. Cell* **14**, 388–398 (2008).
52. Zhang, L. et al. The TEAD/TEF family of transcription factor Scalloped mediates Hippo signaling in organ size control. *Dev. Cell* **14**, 377–387 (2008).
53. Zhao, B. et al. TEAD mediates YAP-dependent gene induction and growth control. *Genes Dev.* **22**, 1962–1971 (2008).
54. Koontz, L. M. et al. The Hippo effector Yorkie controls normal tissue growth by antagonizing Scalloped-mediated default repression. *Dev. Cell* **25**, 388–401 (2013).
55. Guo, T. et al. A novel partner of Scalloped regulates Hippo signaling via antagonizing Scalloped-Yorkie activity. *Cell Res.* **23**, 1201–1214 (2013).
56. Vissers, J. H. A. et al. The Scalloped and Nerfin-1 transcription factors cooperate to maintain neuronal cell fate. *Cell Rep.* **25**, 1561–1576.e1567 (2018).
57. Guo, P. et al. Nerfin-1 represses transcriptional output of Hippo signaling in cell competition. *eLife* **8**, e38843 (2019).
58. Vissers, J. H. A., Dent, L. G., House, C. M., Kondo, S. & Harvey, K. F. Pits and CtBP control tissue growth in *Drosophila melanogaster* with the Hippo pathway transcription repressor Tgi. *Genetics* **215**, 117–128 (2020).
59. Zhang, W. et al. The TEA domain family transcription factor TEAD4 represses murine adipogenesis by recruiting the cofactors VGLL4 and CtBP2 into a transcriptional complex. *J. Biol. Chem.* **293**, 17119–17134 (2018).
60. Manning, S. A. et al. The *Drosophila* Hippo pathway transcription factor Scalloped and its co-factors alter each other's chromatin binding dynamics and transcription in vivo. *Dev. Cell* **59**, 1640–1654.e1645 (2024).
61. Kroeger, B. et al. Hippo signalling regulates the nuclear behaviour and DNA dwell times of YAP and TEAD to control transcription. Preprint at https://doi.org/10.1101/2025.03.11.642705 (2025).
62. Asrani, K. et al. Reciprocal YAP1 loss and INSM1 expression in neuroendocrine prostate cancer. *J. Pathol.* **255**, 425–437 (2021).
63. Halder, G. et al. The Vestigial and Scalloped proteins act together to directly regulate wing-specific gene expression in *Drosophila*. *Genes Dev.* **12**, 3900–3909 (1998).
64. Paumard-Rigal, S., Zider, A., Vaudin, P. & Silber, J. Specific interactions between Vestigial and Scalloped are required to promote wing tissue proliferation in *Drosophila melanogaster*. *Dev. Genes Evol.* **208**, 440–446 (1998).
65. Zider, A., Paumard-Rigal, S., Frouin, I. & Silber, J. The vestigial gene of *Drosophila melanogaster* is involved in the formation of the peripheral nervous system: genetic interactions with the *scute* gene. *J. Neurogenet.* **12**, 87–99 (1998).
66. Sonnemann, H. M., Pazdrak, B., Antunes, D. A., Roszik, J. & Lizee, G. Vestigial-like 1 (VGLL1): an ancient co-transcriptional activator linking wing, placenta, and tumor development. *Biochim. Biophys. Acta Rev. Cancer* **1878**, 188892 (2023).
67. Simmonds, A. J. et al. Molecular interactions between Vestigial and Scalloped promote wing formation in *Drosophila*. *Genes Dev.* **12**, 3815–3820 (1998).
68. Lai, Z. C. et al. Control of cell proliferation and apoptosis by Mob as tumor suppressor, Mats. *Cell* **120**, 675–685 (2005).
69. Meng, Z. et al. MAP4K family kinases act in parallel to MST1/2 to activate LATS1/2 in the Hippo pathway. *Nat. Commun.* **6**, 8357 (2015).
70. Zheng, Y. et al. Identification of Happyhour/MAP4K as alternative Hpo/Mst-like kinases in the Hippo kinase cascade. *Dev. Cell* **34**, 642–655 (2015).
71. Boggiano, J. C., Vanderzalm, P. J. & Fehon, R. G. Tao-1 phosphorylates Hippo/MST kinases to regulate the Hippo-Salvador-Warts tumor suppressor pathway. *Dev. Cell* **21**, 888–895 (2011).
72. Poon, C. L., Lin, J. I., Zhang, X. & Harvey, K. F. The sterile 20-like kinase Tao-1 controls tissue growth by regulating the Salvador-Warts-Hippo pathway. *Dev. Cell* **21**, 896–906 (2011).
73. Ribeiro, P. S. et al. Combined functional genomic and proteomic approaches identify a PP2A complex as a negative regulator of Hippo signaling. *Mol. Cell* **39**, 521–534 (2010).
74. Grusche, F. A., Richardson, H. E. & Harvey, K. F. Upstream regulation of the Hippo size control pathway. *Curr. Biol.* **20**, R574–R582 (2010).
75. Su, T., Ludwig, M. Z., Xu, J. & Fehon, R. G. Kibra and Merlin activate the Hippo pathway spatially distinct from and independent of Expanded. *Dev. Cell* **40**, 478–490.e473 (2017).
76. Sun, S., Reddy, B. V. & Irvine, K. D. Localization of Hippo signalling complexes and Warts activation in vivo. *Nat. Commun.* **6**, 8402 (2015).
77. Angus, L. et al. Willin/FRMD6 expression activates the Hippo signaling pathway kinases in mammals and antagonizes oncogenic YAP. *Oncogene* **31**, 238–250 (2012).
78. Guo, P. et al. PI4P-mediated solid-like Merlin condensates orchestrate Hippo pathway regulation. *Science* **385**, eadf4478 (2024).
79. Li, F. L. et al. Hippo pathway regulation by phosphatidylinositol transfer protein and phosphoinositides. *Nat. Chem. Biol.* **18**, 1076–1086 (2022).
80. Grzeschik, N. A., Parsons, L. M., Allott, M. L., Harvey, K. F. & Richardson, H. E. Lgl, aPKC, and Crumbs regulate the Salvador/Warts/Hippo pathway through two distinct mechanisms. *Curr. Biol.* **20**, 573–581 (2010).
81. Cordenonsi, M. et al. The Hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. *Cell* **147**, 759–772 (2011).
82. Robinson, B. S., Huang, J., Hong, Y. & Moberg, K. H. Crumbs regulates Salvador/Warts/Hippo signaling in *Drosophila* via the FERM-domain protein expanded. *Curr. Biol.* **20**, 582–590 (2010).
83. Ling, C. et al. The apical transmembrane protein Crumbs functions as a tumor suppressor that regulates Hippo signaling by binding to Expanded. *Proc. Natl Acad. Sci. USA* **107**, 10532–10537 (2010).
84. Chen, C. L. et al. The apical-basal cell polarity determinant Crumbs regulates Hippo signaling in *Drosophila*. *Proc. Natl Acad. Sci. USA* **107**, 15810–15815 (2010).
85. Varelas, X. et al. The Crumbs complex couples cell density sensing to Hippo-dependent control of the TGF-beta-SMAD pathway. *Dev. Cell* **19**, 831–844 (2010).
86. Bossuyt, W. et al. An evolutionary shift in the regulation of the Hippo pathway between mice and flies. *Oncogene* **33**, 1218–1228 (2014).
87. Wang, C. et al. Integrated screens uncover a cell surface tumor suppressor gene KIRREL involved in Hippo pathway. *Proc. Natl Acad. Sci. USA* **119**, e2121779119 (2022).
88. Gu, Y. et al. Transmembrane protein KIRREL1 regulates Hippo signaling via a feedback loop and represents a therapeutic target in YAP/TAZ-active cancers. *Cell Rep.* **40**, 111296 (2022).
89. Deng, H. et al. Spectrin regulates Hippo signaling by modulating cortical actomyosin activity. *eLife* **4**, e06567 (2015).
90. Fletcher, G. C. et al. The spectrin cytoskeleton regulates the Hippo signalling pathway. *EMBO J.* **34**, 940–954 (2015).
91. Wong, K. K. et al. β-Spectrin regulates the hippo signaling pathway and modulates the basal actin network. *J. Biol. Chem.* **290**, 6397–6407 (2015).
92. Ibar, C., Chinthalapudi, K., Heissler, S. M. & Irvine, K. D. Competition between myosin II and beta(H)-spectrin regulates cytoskeletal tension. *eLife* **12**, RP84918 (2023).
93. Tyler, D. M. & Baker, N. E. Expanded and Fat regulate growth and differentiation in the *Drosophila* eye through multiple signaling pathways. *Dev. Biol.* **305**, 187–201 (2007).
94. Willecke, M. et al. The Fat cadherin acts through the hippo tumor-suppressor pathway to regulate tissue size. *Curr. Biol.* **16**, 2090–2100 (2006).
95. Silva, E., Tsatskis, Y., Gardano, L., Tapon, N. & McNeill, H. The tumor-suppressor gene Fat controls tissue growth upstream of expanded in the Hippo signaling pathway. *Curr. Biol.* **16**, 2081–2089 (2006).
96. Cho, E. et al. Delineation of a Fat tumor suppressor pathway. *Nat. Genet.* **38**, 1142–1150 (2006).
97. Bennett, F. C. & Harvey, K. F. Fat cadherin modulates organ size in *Drosophila* via the Salvador/Warts/Hippo signaling pathway. *Curr. Biol.* **16**, 2101–2110 (2006).
98. Gridnev, A. & Misra, J. R. Emerging mechanisms of growth and patterning regulation by Dachsous and Fat protocadherins. *Front. Cell Dev. Biol.* **10**, 842593 (2022).
99. Martin, D. et al. Assembly and activation of the Hippo signalome by FAT1 tumor suppressor. *Nat. Commun.* **9**, 2372 (2018).
100. Lu, W. T. et al. TRACERx analysis identifies a role for FAT1 in regulating chromosomal instability and whole-genome doubling via Hippo signalling. *Nat. Cell Biol.* **27**, 154–168 (2025).
101. Das Thakur, M. et al. Ajuba LIM proteins are negative regulators of the Hippo signaling pathway. *Curr. Biol.* **20**, 657–662 (2010).
102. Kroeger, B. et al. Basal spot junctions of *Drosophila* epithelial tissues respond to morphogenetic forces and regulate Hippo signaling. *Dev. Cell* **59**, 262–279.e266 (2024).
103. Ibar, C. et al. Tension-dependent regulation of mammalian Hippo signaling through LIMD1. *J. Cell Sci.* **131**, jcs214700 (2018).
104. Huang, H. L. et al. Par-1 regulates tissue growth by influencing Hippo phosphorylation status and Hippo-Salvador association. *PLoS Biol.* **11**, e1001620 (2013).
105. Tokamov, S. A. et al. Cortical tension promotes Kibra degradation via Par-1. *Mol. Biol. Cell* **35**, ar2 (2024).

106. Heidary Arash, E., Shiban, A., Song, S. & Attisano, L. MARK4 inhibits Hippo signaling to promote proliferation and migration of breast cancer cells. *EMBO Rep.* **18**, 420–436 (2017).
107. Kwan, J. et al. DLG5 connects cell polarity and Hippo signaling protein networks by linking PAR-1 with MST1/2. *Genes Dev.* **30**, 2696–2709 (2016).
108. Klingbeil, O. et al. MARK2/MARK3 kinases are catalytic codependencies of YAP/TAZ in human cancer. *Cancer Discov.* **14**, 2471–2488 (2024).
109. Feng, Y. & Irvine, K. D. Fat and Expanded act in parallel to regulate growth through Warts. *Proc. Natl Acad. Sci. USA* **104**, 20362–20367 (2007).
110. Qi, S. et al. Two Hippo signaling modules orchestrate liver size and tumorigenesis. *EMBO J.* **42**, e115749 (2023).
111. Yu, J. et al. Kibra functions as a tumor suppressor protein that regulates Hippo signaling in conjunction with Merlin and Expanded. *Dev. Cell* **18**, 288–299 (2010).
112. Genevet, A., Wehr, M. C., Brain, R., Thompson, B. J. & Tapon, N. Kibra is a regulator of the Salvador/Warts/Hippo signaling network. *Dev. Cell* **18**, 300–308 (2010).
113. Baumgartner, R., Poernbacher, I., Buser, N., Hafen, E. & Stocker, H. The WW domain protein Kibra acts upstream of Hippo in *Drosophila*. *Dev. Cell* **18**, 309–316 (2010).
114. Dey, A., Varelas, X. & Guan, K. L. Targeting the Hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. *Nat. Rev. Drug Discov.* **19**, 480–494 (2020).
115. Wang, J., Liu, S., Heallen, T. & Martin, J. F. The Hippo pathway in the heart: pivotal roles in development, disease, and regeneration. *Nat. Rev. Cardiol.* **15**, 672–684 (2018).
116. Petrilli, A. M. & Fernández-Valle, C. Role of Merlin/NF2 inactivation in tumor biology. *Oncogene* **35**, 537–548 (2016).
117. Fossdal, R. et al. A novel TEAD1 mutation is the causative allele in Sveinsson's chorioretinal atrophy (helicoid peripapillary chorioretinal degeneration). *Hum. Mol. Genet.* **13**, 975–981 (2004).
118. Sanchez-Vega, F. et al. Oncogenic signaling pathways in the Cancer Genome Atlas. *Cell* **173**, 321–337.e310 (2018).
119. Cerami, E. et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* **2**, 401–404 (2012).
120. Gao, J. et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* **6**, pl1 (2013).
121. Murakami, H. et al. *LATS2* is a tumor suppressor gene of malignant mesothelioma. *Cancer Res.* **71**, 873–883 (2011).
122. Sekido, Y. Inactivation of Merlin in malignant mesothelioma cells and the Hippo signaling cascade dysregulation. *Pathol. Int.* **61**, 331–344 (2011).
123. Bueno, R. et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat. Genet.* **48**, 407–416 (2016).
124. Markowitz, P. et al. Genomic characterization of malignant pleural mesothelioma and associated clinical outcomes. *Cancer Treat. Res. Commun.* **25**, 100232 (2020).
125. Sekido, Y. & Sato, T. NF2 alteration in mesothelioma. *Front. Toxicol.* **5**, 1161995 (2023).
126. Tanas, M. R. et al. Identification of a disease-defining gene fusion in epithelioid hemangioendothelioma. *Sci. Transl. Med.* **3**, 98ra82 (2011).
127. Errani, C. et al. A novel *WWTR1-CAMTA1* gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer* **50**, 644–653 (2011).
128. Merritt, N. et al. TAZ-CAMTA1 and YAP-TFE3 alter the TAZ/YAP transcriptome by recruiting the ATAC histone acetyltransferase complex. *eLife* **10**, e62857 (2021).
129. Seavey, C. N., Pobbati, A. V. & Rubin, B. P. Unraveling the biology of epithelioid hemangioendothelioma, a *TAZ-CAMTA1* fusion driven sarcoma. *Cancers* **14**, 2980 (2022).
130. Garcia, K., Gingras, A. C., Harvey, K. F. & Tanas, M. R. TAZ/YAP fusion proteins: mechanistic insights and therapeutic opportunities. *Trends Cancer* **8**, 1033–1045 (2022).
131. Agaimy, A. et al. Recurrent *VGLL3* fusions define a distinctive subset of spindle cell rhabdomyosarcoma with an indolent clinical course and striking predilection for the head and neck. *Genes Chromosomes Cancer* **61**, 701–709 (2022).
132. Guo, S. et al. VGLL2 and TEAD1 fusion proteins identified in human sarcoma drive YAP/TAZ-independent tumorigenesis by engaging EP300. *eLife* **13**, 98386 (2025).
133. Pearson, J. D. et al. Binary pan-cancer classes with distinct vulnerabilities defined by pro- or anti-cancer YAP/TEAD activity. *Cancer Cell* **39**, 1115–1134.e1112 (2021).
134. Marine, J. C., Dawson, S. J. & Dawson, M. A. Non-genetic mechanisms of therapeutic resistance in cancer. *Nat. Rev. Cancer* **20**, 743–756 (2020).
135. Nguyen, C. D. K. & Yi, C. YAP/TAZ signaling and resistance to cancer therapy. *Trends Cancer* **5**, 283–296 (2019).
136. Kapoor, A. et al. Yap1 activation enables bypass of oncogenic Kras addiction in pancreatic cancer. *Cell* **158**, 185–197 (2014).
137. Shao, D. D. et al. KRAS and YAP1 converge to regulate EMT and tumor survival. *Cell* **158**, 171–184 (2014).
138. Lin, L. et al. The Hippo effector YAP promotes resistance to RAF- and MEK-targeted cancer therapies. *Nat. Genet.* **47**, 250–256 (2015).
139. Hagenbeek, T. J. et al. An allosteric pan-TEAD inhibitor blocks oncogenic YAP/TAZ signaling and overcomes KRAS G12C inhibitor resistance. *Nat. Cancer* **4**, 812–828 (2023).
140. Mukhopadhyay, S. et al. Genome-wide CRISPR screens identify multiple synthetic lethal targets that enhance KRASG12C inhibitor efficacy. *Cancer Res.* **83**, 4095–4111 (2023).
141. Tape, C. J. Plastic persisters: revival stem cells in colorectal cancer. *Trends Cancer* **10**, 185–195 (2024).
142. Han, T. et al. Lineage reversion drives WNT independence in intestinal cancer. *Cancer Discov.* **10**, 1590–1609 (2020).
143. Qin, X. et al. An oncogenic phenoscape of colonic stem cell polarization. *Cell* **186**, 5554–5568.e5518 (2023).
144. Rebekah, M. et al. Patient-derived colorectal cancer organoids upregulate revival stem cell marker genes following chemotherapeutic treatment. *J. Clin. Med.* **9**, 128 (2020).
145. Ayyaz, A. et al. Single-cell transcriptomes of the regenerating intestine reveal a revival stem cell. *Nature* **569**, 121–125 (2019).
146. Fan, F. et al. Pharmacological targeting of kinases MST1 and MST2 augments tissue repair and regeneration. *Sci. Transl. Med.* **8**, 352ra108 (2016).
147. Zhang, P. et al. Exploration of MST1-mediated secondary brain injury induced by intracerebral hemorrhage in Rats via Hippo signaling pathway. *Transl. Stroke Res.* **10**, 729–743 (2019).
148. Wu, Y. et al. Discovery of IHMT-MST1-58 as a novel, potent, and selective MST1 inhibitor for the treatment of type 1/2 diabetes. *J. Med. Chem.* **65**, 11818–11839 (2022).
149. Kastan, N. et al. Small-molecule inhibition of Lats kinases may promote Yap-dependent proliferation in postmitotic mammalian tissues. *Nat. Commun.* **12**, 3100 (2021).
150. Kastan, N. R. et al. Development of an improved inhibitor of Lats kinases to promote regeneration of mammalian organs. *Proc. Natl Acad. Sci.* **119**, e2206113119 (2022).
151. Aihara, A. et al. Small molecule LATS kinase inhibitors block the Hippo signaling pathway and promote cell growth under 3D culture conditions. *J. Biol. Chem.* **298**, 101779 (2022).
152. Issabayeva, G. et al. Discovery of selective LATS inhibitors via scaffold hopping: enhancing drug-likeness and kinase selectivity for potential applications in regenerative medicine. *RSC Med. Chem.* **15**, 4080–4089 (2024).
153. Namoto, K. et al. NIBR-LTSi is a selective LATS kinase inhibitor activating YAP signaling and expanding tissue stem cells in vitro and in vivo. *Cell Stem Cell* **31**, 554–569.e517 (2024).
154. Burgess, C. L. et al. Generation of human alveolar epithelial type I cells from pluripotent stem cells. *Cell Stem Cell* **31**, 657–675.e658 (2024).
155. Dost, A. F. M. et al. A human organoid model of alveolar regeneration reveals distinct epithelial responses to interferon-gamma. Preprint at https://doi.org/10.1101/2025.01.30.635624 (2025).
156. Liu, S. et al. Gene therapy knockdown of Hippo signaling induces cardiomyocyte renewal in pigs after myocardial infarction. *Sci. Transl. Med.* **13**, eabd6892 (2021).
157. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/search?term=NCT06831825 (2025).
158. Yu, F. X. et al. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell* **150**, 780–791 (2012).
159. Kim, N. G. & Gumbiner, B. M. Adhesion to fibronectin regulates Hippo signaling via the FAK-Src-PI3K pathway. *J. Cell Biol.* **210**, 503–515 (2015).
160. Woodard, G. A., Yang, Y. L., You, L. & Jablons, D. M. Drug development against the Hippo pathway in mesothelioma. *Transl. Lung Cancer Res.* **6**, 335–342 (2017).
161. Dhanaraman, T. et al. RASSF effectors couple diverse RAS subfamily GTPases to the Hippo pathway. *Sci. Signal.* **13**, eabb4778 (2020).
162. Gill, M. K. et al. A feed forward loop enforces YAP/TAZ signaling during tumorigenesis. *Nat. Commun.* **9**, 3510 (2018).
163. Yuan, W. C. et al. NUAK2 is a critical YAP target in liver cancer. *Nat. Commun.* **9**, 4834 (2018).
164. Port, J. et al. Colorectal tumors require NUAK1 for protection from oxidative stress. *Cancer Discov.* **8**, 632–647 (2018).
165. Skalka, G. L., Whyte, D., Lubawska, D. & Murphy, D. J. NUAK: never underestimate a kinase. *Essays Biochem.* **68**, 295–307 (2024).
166. Graham, K. et al. Discovery of YAP1/TAZ pathway inhibitors through phenotypic screening with potent anti-tumor activity via blockade of Rho-GTPase signaling. *Cell Chem. Biol.* **31**, 1247–1263.e1216 (2024).
167. Macleod, A. R. The discovery and characterization of ION-537: a next generation antisense oligonucleotide inhibitor of YAP1 in preclinical cancer models. *Cancer Res.* **81** (Suppl. 13), Abstr. ND11 (2021).
168. Zhou, C. et al. Exploring degradation of intrinsically disordered protein Yes-associated protein induced by proteolysis targeting chimeras. *J. Med. Chem.* **67**, 15168–15198 (2024).
169. Barbosa, I. A. M. et al. Cancer lineage-specific regulation of YAP responsive elements revealed through large-scale functional epigenomic screens. *Nat. Commun.* **14**, 3907 (2023).
170. Pobbati, A. V. et al. Targeting the central pocket in human transcription factor TEAD as a potential cancer therapeutic strategy. *Structure* **23**, 2076–2086 (2015).
171. Chan, P. et al. Autopalmitoylation of TEAD proteins regulates transcriptional output of the Hippo pathway. *Nat. Chem. Biol.* **12**, 282–289 (2016).
172. Noland, C. L. et al. Palmitoylation of TEAD transcription factors is required for their stability and function in Hippo pathway signaling. *Structure* **24**, 179–186 (2016).
173. Baroja, I., Kyriakidis, N. C., Halder, G. & Moya, I. M. Expected and unexpected effects after systemic inhibition of Hippo transcriptional output in cancer. *Nat. Commun.* **15**, 2700 (2024).
174. Brennan, D., Liang, Y., Mlynarski, S. & Zhu, B.-Y. in *2024 Medicinal Chemistry Reviews* (vol. 59) Ch. 9, 175-201 (ACS, 2024).
175. Pobbati, A. V., Kumar, R., Rubin, B. P. & Hong, W. Therapeutic targeting of TEAD transcription factors in cancer. *Trends Biochem. Sci.* **48**, 450–462 (2023).
176. Tsherniak, A. et al. Defining a cancer dependency map. *Cell* **170**, 564–576.e516 (2017).
177. Tang, T. T. et al. Small molecule inhibitors of TEAD auto-palmitoylation selectively inhibit proliferation and tumor growth of NF2-deficient mesothelioma. *Mol. Cancer Ther.* **20**, 986–998 (2021).

178. Lu, W. et al. Discovery and biological evaluation of vinylsulfonamide derivatives as highly potent, covalent TEAD autopalmitoylation inhibitors. *Eur. J. Med. Chem.* **184**, 111767 (2019).
179. Li, Q. et al. Lats1/2 sustain intestinal stem cells and Wnt activation through TEAD-dependent and independent transcription. *Cell Stem Cell* **26**, 675–692.e678 (2020).
180. Kaneda, A. et al. The novel potent TEAD inhibitor, K-975, inhibits YAP1/TAZ-TEAD protein-protein interactions and exerts an anti-tumor effect on malignant pleural mesothelioma. *Am. J. Cancer Res.* **10**, 4399–4415 (2020).
181. Heinrich, T. et al. Optimization of TEAD P-site binding fragment hit into in vivo active lead MSC-4106. *J. Med. Chem.* **65**, 9206–9229 (2022).
182. Lu, W. et al. Structure-based design of Y-shaped covalent TEAD inhibitors. *J. Med. Chem.* **66**, 4617–4632 (2023).
183. Hillen, H. et al. A novel irreversible TEAD inhibitor, SWTX-143, blocks Hippo pathway transcriptional output and causes tumor regression in preclinical mesothelioma models. *Mol. Cancer Ther.* **23**, 3–13 (2024).
184. Young, N. et al. Abstract 1646: IK-930, a paralog-selective TEAD inhibitor for treating YAP/TAZ-TEAD dependent cancers. *Cancer Res.* **83** (Suppl. 7), 1646 (2023).
185. Gordon, J. A. et al. Abstract 6589: Discovery of potent and selective pan-TEAD autopalmitoylation inhibitors for the treatment of Hippo-pathway altered cancers. *Cancer Res.* **84** (Suppl. 6), 6589 (2024).
186. Guo, S. et al. Abstract 4976: Preclinical characterization of BGI-9004, a covalent TEAD inhibitor with exceptional anti-cancer activity and combination potential. *Cancer Res.* **83** (Suppl. 7), 4976 (2023).
187. Han, X. et al. Abstract 7575: BPI-460372, a covalent, irreversible TEAD inhibitor in phase I clinical development. *Cancer Res.* **84** (Suppl. 6), 7575 (2024).
188. Chen, P.-Y. et al. Abstract 7264: OPN-9840, a non-covalent potent pan-TEAD inhibitor, exhibits single agent efficacy in preclinical malignant mesothelioma models. *Cancer Res.* **84** (Suppl. 6), 7264 (2024).
189. Lu, J. et al. Abstract 7265: ETS-005, a highly selective TEAD4 palmitoylation inhibitor with potent anti-tumor activity and brain penetrating capability. *Cancer Res.* **84** (Suppl. 6), 7265 (2024).
190. Muller, F., Kunnimalaiyaan, S., Mangrolia, P. & Olson, J. 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. *Cancer Res.* **84** (Suppl. 6), 5913 (2024).
191. Kim, J. et al. Pan-transcriptional enhanced associated domain palmitoylation pocket covalent inhibitor. *J. Med. Chem.* **67**, 18957–18968 (2024).
192. Moure, C. J. et al. Activation of hepatocyte growth factor/MET signaling as a mechanism of acquired resistance to a novel YAP1/TEAD small molecule inhibitor. *Mol. Cancer Ther.* **23**, 1095–1108 (2024).
193. Heinrich, T. et al. MoA studies of the TEAD P-site binding ligand MSC-4106 and its optimization to TEAD1-selective amide M3686. *J. Med. Chem.* **68**, 6149–6164 (2025).
194. Kurppa, K. J. et al. Treatment-induced tumor dormancy through YAP-mediated transcriptional reprogramming of the apoptotic pathway. *Cancer Cell* **37**, 104–122.e112 (2020).
195. Bum-Erdene, K. et al. Small-molecule covalent modification of conserved cysteine leads to allosteric inhibition of the TEAD·Yap protein-protein interaction. *Cell Chem. Biol.* **26**, 378–389.e313 (2019).
196. Yap, T. A. et al. Abstract CT006: First-in-class, first-in-human phase 1 trial of VT3989, an inhibitor of Yes-associated protein (YAP)/transcriptional enhancer activator domain (TEAD), in patients (pts) with advanced solid tumors enriched for malignant mesothelioma and other tumors with neurofibromatosis 2 (NF2) mutations. *Cancer Res.* **83** (Suppl. 8), CT006 (2023).
197. Yap, T. A. et al. First-in-class, first-in-human phase 1 trial of VT3989, an inhibitor of Yes-Associated Protein (YAP)/Transcriptional EnhancerActivator Domain (TEAD), in patients with advanced solid tumors enriched for malignant mesothelioma and other tumors with neurofibromatosis 2 (NF2) mutations. *AACR Annual Meeting 2023* https://vivacetherapeutics.com/wp-content/uploads/Vivace-Therapeutics-2023-AACR-Presentation.pdf (2023).
198. Liu-Chittenden, Y. et al. Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. *Genes Dev.* **26**, 1300–1305 (2012).
199. Hau, J. C. et al. The TEAD4-YAP/TAZ protein-protein interaction: expected similarities and unexpected differences. *Chembiochem* **14**, 1218–1225 (2013).
200. Zhang, Z. et al. Structure-based design and synthesis of potent cyclic peptides inhibiting the YAP-TEAD protein-protein interaction. *ACS Med. Chem. Lett.* **5**, 993–998 (2014).
201. Mesrouze, Y. et al. Dissection of the interaction between the intrinsically disordered YAP protein and the transcription factor TEAD. *eLife* **6**, e25068 (2017).
202. Furet, P. et al. Structure-based design of potent linear peptide inhibitors of the YAP-TEAD protein-protein interaction derived from the YAP omega-loop sequence. *Bioorg. Med. Chem. Lett.* **29**, 2316–2319 (2019).
203. Furet, P. et al. The first class of small molecules potently disrupting the YAP-TEAD interaction by direct competition. *ChemMedChem* **17**, e202200303 (2022).
204. Mesrouze, Y. et al. Biochemical and structural characterization of a peptidic inhibitor of the YAP:TEAD interaction that binds to the α-Helix pocket on TEAD. *ACS Chem. Biol.* **18**, 643–651 (2023).
205. Sellner, H. et al. Optimization of a class of dihydrobenzofurane analogs toward orally efficacious YAP-TEAD protein-protein interaction inhibitors. *ChemMedChem* **18**, e202300051 (2023).
206. Chapeau, E. A. et al. Direct and selective pharmacological disruption of the YAP–TEAD interface by IAG933 inhibits Hippo-dependent and RAS–MAPK-altered cancers. *Nat. Cancer* **5**, 1102–1120 (2024).
207. Lu, J. et al. Abstract 4585: discovery of ETS-006, a highly potent YAP/TEADs PPI inhibitor with broad anti-tumor activity as a single agent. *Cancer Res.* **84**, 4585(2024).
208. Karatas, H. et al. Discovery of covalent inhibitors targeting the transcriptional enhanced associate domain central pocket. *J. Med. Chem.* **63**, 11972–11989 (2020).
209. Sawant, R. et al. Abstract LB029: Degraders of TEAD transcription factors based on interface 3 binders. *Cancer Res.* **84** (Suppl. 7), LB029 (2024).
210. Lu, Y. et al. Selective degradation of TEADs by a PROTAC molecule exhibited robust anticancer efficacy in vitro and in vivo. *J. Med. Chem.* **68**, 5616–5640 (2025).
211. Chen, H. et al. Targeted degradation of specific TEAD paralogs by small molecule degraders. *Heliyon* **10**, e37829 (2024).
212. Li, H. et al. Design, synthesis, and bioevaluation of transcriptional enhanced assocciated domain (TEAD) PROTAC degraders. *ACS Med. Chem. Lett.* **15**, 631–639 (2024).
213. Deng, X. & Fang, L. VGLL4 is a transcriptional cofactor acting as a novel tumor suppressor via interacting with TEADs. *Am. J. Cancer Res.* **8**, 932–943 (2018).
214. Cai, J. et al. YAP-VGLL4 antagonism defines the major physiological function of the Hippo signaling effector YAP. *Genes Dev.* **36**, 1119–1128 (2022).
215. Zhao, B., Pobbati, A. V., Rubin, B. P. & Stauffer, S. Leveraging hot spots of TEAD-coregulator interactions in the design of direct small molecule protein-protein interaction disruptors targeting Hippo pathway signaling. *Pharmaceuticals* **16**, 583 (2023).
216. Jiao, S. et al. A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. *Cancer Cell* **25**, 166–180 (2014).
217. Kulkarni, A. et al. Identification of resistance mechanisms to small-molecule inhibition of TEAD-regulated transcription. *EMBO Rep.* **25**, 3944–3969 (2024).
218. Guarnaccia, A. D. et al. TEAD-targeting small molecules induce a cofactor switch to regulate the Hippo pathway. Preprint at https://doi.org/10.1101/2024.11.15.623512 (2024).
219. Seavey, C. N. et al. Loss of CDKN2A cooperates with WWTR1(TAZ)-CAMTA1 gene fusion to promote tumor progression in epithelioid hemangioendothelioma. *Clin. Cancer Res.* **29**, 2480–2493 (2023).
220. Zhang, F. et al. Recurrent RhoGAP gene fusion CLDN18-ARHGAP26 promotes RHOA activation and focal adhesion kinase and YAP-TEAD signalling in diffuse gastric cancer. *Gut* **73**, 1280–1291 (2024).
221. Saito, Y. et al. A therapeutically targetable TAZ-TEAD2 pathway drives the growth of hepatocellular carcinoma via ANLN and KIF23. *Gastroenterology* **164**, 1279–1292 (2023).
222. Holden, J. K. et al. Small molecule dysregulation of TEAD lipidation induces a dominant-negative inhibition of Hippo pathway signaling. *Cell Rep.* **31**, 107809 (2020).
223. Sato, K. et al. Targeting YAP/TAZ-TEAD signaling as a therapeutic approach in head and neck squamous cell carcinoma. *Cancer Lett.* **612**, 217467 (2025).
224. Murakami, S., White, S. M., McIntosh, A. T., Nguyen, C. D. K. & Yi, C. Spontaneously evolved progenitor niches escape Yap oncogene addiction in advanced pancreatic ductal adenocarcinomas. *Nat. Commun.* **14**, 1443 (2023).
225. Barrette, A. M. et al. Anti-invasive efficacy and survival benefit of the YAP-TEAD inhibitor verteporfin in preclinical glioblastoma models. *Neuro Oncol.* **24**, 694–707 (2022).
226. Laraba, L. et al. Inhibition of YAP/TAZ-driven TEAD activity prevents growth of NF2-null schwannoma and meningioma. *Brain* **146**, 1697–1713 (2023).
227. Press release: Ikena Oncology shares initial positive and differentiated dose escalation data from IK-930 phase I trial and reports third quarter 2023 financial results. *Ikena Oncology* https://ir.ikenaoncology.com/node/7936/pdf (2023).
228. Press Release: Ikena Oncology announes strategic update. *Ikena Oncology* https://ir.ikenaoncology.com/node/8131/pdf (2024).
229. Tang, T. T. & Post, L. Abstract 7282: Comparing TEAD palmitoylation inhibitors with differential TEAD selectivity in combination efficacy with targeted therapies and in renal safety. *Cancer Res.* **84** (Suppl. 6), 7282 (2024).
230. Hashimoto, M. & Sasaki, H. Epiblast formation by TEAD-YAP-dependent expression of pluripotency factors and competitive elimination of unspecified cells. *Dev. Cell* **50**, 139–154.e135 (2019).
231. Nishioka, N. et al. Tead4 is required for specification of trophectoderm in pre-implantation mouse embryos. *Mech. Dev.* **125**, 270–283 (2008).
232. Sawada, A. et al. Redundant roles of Tead1 and Tead2 in notochord development and the regulation of cell proliferation and survival. *Mol. Cell Biol.* **28**, 3177–3189 (2008).
233. Chen, Z., Friedrich, G. A. & Soriano, P. Transcriptional enhancer factor 1 disruption by a retroviral gene trap leads to heart defects and embryonic lethality in mice. *Genes Dev.* **8**, 2293–2301 (1994).
234. Kaneko, K. J., Kohn, M. J., Liu, C. & DePamphilis, M. L. Transcription factor TEAD2 is involved in neural tube closure. *Genesis* **45**, 577–587 (2007).
235. Yagi, R. et al. Transcription factor TEAD4 specifies the trophectoderm lineage at the beginning of mammalian development. *Development* **134**, 3827–3836 (2007).
236. Kakiuchi-Kiyota, S., Schutten, M. M., Zhong, Y., Crawford, J. J. & Dey, A. Safety considerations in the development of Hippo pathway inhibitors in cancers. *Front. Cell Dev. Biol.* **7**, 156 (2019).
237. Wong, J. S., Meliambro, K., Ray, J. & Campbell, K. N. Hippo signaling in the kidney: the good and the bad. *Am. J. Physiol. Ren. Physiol.* **311**, F241–F248 (2016).
238. Schwartzman, M. et al. Podocyte-specific deletion of Yes-associated protein causes FSGS and progressive renal failure. *J. Am. Soc. Nephrol.* **27**, 216–226 (2016).
239. Chen, J., Wang, X., He, Q. & Harris, R. C. TAZ is important for maintenance of the integrity of podocytes. *Am. J. Physiol. Ren. Physiol.* **322**, F419–F428 (2022).

240. Pavenstädt, H., Kriz, W. & Kretzler, M. Cell biology of the glomerular podocyte. *Physiol. Rev.* **83**, 253–307 (2003).
241. Chung, J. J. et al. Single-cell transcriptome profiling of the kidney glomerulus identifies key cell types and reactions to injury. *J. Am. Soc. Nephrol.* **31**, 2341–2354 (2020).
242. Chen, J. et al. Inhibition of transcriptional coactivator YAP impairs the expression and function of transcription factor WT1 in diabetic podocyte injury. *Kidney Int.* **105**, 1200–1211 (2024).
243. Rinschen, M. M. et al. YAP-mediated mechanotransduction determines the podocyte's response to damage. *Sci. Signal.* **10**, eaaf8165 (2017).
244. Haley, K. E. et al. YAP translocation precedes cytoskeletal rearrangement in podocyte stress response: a podometric investigation of diabetic nephropathy. *Front. Physiol.* **12**, 625762 (2021).
245. Kaneda, A. et al. Abstract 3086: discovery of a first-in-class TEAD inhibitor which directly inhibits YAP/TAZ-TEAD protein-protein interaction and shows a potent anti-tumor effect in malignant pleural mesothelioma. *Cancer Res.* **79**, 3086 (2019).
246. Paul, S., Sims, J., Pham, T. & Dey, A. Targeting the Hippo pathway in cancer: kidney toxicity as a class effect of TEAD inhibitors? *Trends Cancer* **11**, 25–36 (2024).
247. Otsuki, H. et al. Reversible and monitorable nephrotoxicity in rats by the novel potent transcriptional enhanced associate domain (TEAD) inhibitor, K-975. *J. Toxicol. Sci.* **49**, 175–191 (2024).
248. Sun, Y. et al. Pharmacological blockade of TEAD-YAP reveals its therapeutic limitation in cancer cells. *Nat. Commun.* **13**, 6744 (2022).
249. Akao, K. et al. TEAD-independent cell growth of Hippo-inactive mesothelioma cells: unveiling resistance to TEAD inhibitor K-975 through MYC signaling activation. *Mol. Cancer Ther.* **24**, 709–719 (2025).
250. Paul, S. et al. Cooperation between the Hippo and MAPK pathway activation drives acquired resistance to TEAD inhibition. *Nat. Commun.* **16**, 1743 (2025).
251. Nutsch, K. et al. Augmented acyl-CoA biosynthesis promotes resistance to TEAD palmitoylation site inhibition. *ACS Chem. Biol.* **20**, 967–975 (2025).
252. White, S. M. et al. YAP/TAZ inhibition induces metabolic and signaling rewiring resulting in targetable vulnerabilities in NF2-deficient tumor cells. *Dev. Cell* **49**, 425–443.e429 (2019).
253. Coggins, G. E. et al. YAP1 mediates resistance to MEK1/2 inhibition in neuroblastomas with hyperactivated RAS signaling. *Cancer Res.* **79**, 6204–6214 (2019).
254. Nilsson, M. B. et al. A YAP/FOXM1 axis mediates EMT-associated EGFR inhibitor resistance and increased expression of spindle assembly checkpoint components. *Sci. Transl. Med.* **12**, eaaz4589 (2020).
255. Tsuji, T. et al. YAP1 mediates survival of ALK-rearranged lung cancer cells treated with alectinib via pro-apoptotic protein regulation. *Nat. Commun.* **11**, 74 (2020).
256. Tang, T. T. & Post, L. Abstract B088: VT3989, the first-in-class and first-in-human TEAD auto-palmitoylation inhibitor, enhances the efficacy and durability of multiple targeted therapies of the MAPK and P13K/AKT/mTOR pathways. *Mol. Cancer Ther.* **22** (Suppl. 12), B088 (2023).
257. Edwards, A. C. et al. TEAD inhibition overcomes YAP1/TAZ-driven primary and acquired resistance to KRASG12C inhibitors. *Cancer Res.* **83**, 4112–4129 (2023).
258. Ogimoto, T. et al. Combination therapy with EGFR tyrosine kinase inhibitors and TEAD inhibitor increases tumor suppression effects in EGFR mutation–positive lung cancer. *Mol. Cancer Ther.* **23**, 564–576 (2024).
259. Haderk, F. et al. Focal adhesion kinase-YAP signaling axis drives drug-tolerant persister cells and residual disease in lung cancer. *Nat. Commun.* **15**, 3741 (2024).
260. Wasko, U. N. et al. Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer. *Nature* **629**, 927–936 (2024).
261. Schirmer, A. et al. 234 (PB222): Rational combination of pan-TEAD inhibitor SW-682 and MEK inhibitor mirdametinib in head and neck squamous cell carcinomas leads to synergistic response. *Eur. J. Cancer* **211**, 114752 (2024).
262. Chen, L. et al. 39 (PB027): TEAD inhibition by SW-682 potentiates activity of targeted therapies in NSCLC models. *Eur. J. Cancer* **211**, 114567 (2024).
263. Hu, L. et al. Discovery of a new class of reversible TEA domain transcription factor inhibitors with a novel binding mode. *eLife* **11**, e80210 (2022).
264. Liu, X. et al. In vitro and in vivo drug metabolism analysis of BPI-460372 - a covalent TEAD1/3/4 inhibitor. *Curr. Drug Metab.* **25**, 754–768 (2025).
265. Marshall, C. J. Ras effectors. *Curr. Opin. Cell Biol.* **8**, 197 (1996).
266. Adachi, Y. et al. Scribble mis-localization induces adaptive resistance to KRAS G12C inhibitors through feedback activation of MAPK signaling mediated by YAP-induced MRAS. *Nat. Cancer* **4**, 829–843 (2023).
267. Pascual, J. et al. Hippo reprograms the transcriptional response to Ras signaling. *Dev. Cell* **42**, 667–680.e664 (2017).
268. Mitchell, K. A. et al. The JNK and Hippo pathways control epithelial integrity and prevent tumor initiation by regulating an overlapping transcriptome. *Curr. Biol.* **34**, 3966–3982.e3967 (2024).
269. Stein, C. et al. YAP1 exerts its transcriptional control via TEAD-mediated activation of enhancers. *PLoS Genet.* **11**, e1005465 (2015).
270. Pham, T. H. et al. Machine-learning and chemicogenomics approach defines and predicts cross-talk of Hippo and MAPK pathways. *Cancer Discov.* **11**, 778–793 (2021).
271. Park, J. et al. YAP and AP-1 cooperate to initiate pancreatic cancer development from ductal cells in mice. *Cancer Res.* **80**, 4768–4779 (2020).

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Competing interests
T.T.T. reports employment with Vivace Therapeutics and has equity interest in Vivace Therapeutics. K.F.H. declares no competing interests.

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