



From Research to Discovery

The Hippo pathway

Hippo-related products from Covalab

Hippo pathway

The Hippo signalling pathway has recently emerged as a fundamental regulator of organ size, stem cells function, tissue regeneration and tumour development¹⁻⁸. This pathway, highly conserved throughout the animal kingdom, has been extensively studied on *Drosophila melanogaster*, and took its name from the major kinase of the cascade, the Hippo kinase.

The core "canonical" Hippo pathway is composed of a cascade of kinases, MST1 and 2 being upstream of and activating LATS1 and 2 kinases⁹⁻¹². Upon activation, these enzymes phosphorylate the transcriptional coactivators TAZ/YAP complex which leads to its retention within the cytoplasm. Once LATS 1 and 2 are inactivated, the hypophosphorylated TAZ/YAP complex translocates into the nucleus, associates with the TEAD family of DNA binding proteins (TEAD1 to 4) and activates the transcription of a set of target genes¹³⁻¹⁴. These genes are often linked to promotion of proliferation and inhibition of apoptosis. Several regulators of the pathway have been identified over the years, such as SAV1, MOB1A and MOB1B, FRMD6, the angiomotins, RASSF1, NF2/Merlin etc, showing the complexity of the regulation of Hippo activity. Indeed, inputs coming from cell surface receptors, adhesion molecules, actin cytoskeleton and metabolic cues were shown to modulate the activity of the pathway¹⁵ for review. This results in a regulation of Hippo activity that is largely tissue-specific. For example, YAP is expressed in many tissues like liver, intestine¹⁶, heart¹⁷, and pancreas¹⁸, but YAP activity is not always linked to increased proliferation.

The role of the Hippo pathway in cancer is a rapidly growing field. Mutations of specific components of this signalling network have been identified in various cancers. For example NF2 is inactivated in a rare condition called neurofibromatosis type II, LATS mutations have been reported in mesothelioma, and RASSF1 mutations in lung cancer¹⁹⁻²⁰ for review. Their study will probably allow to identify new therapeutic targets leading to the development of better treatments.

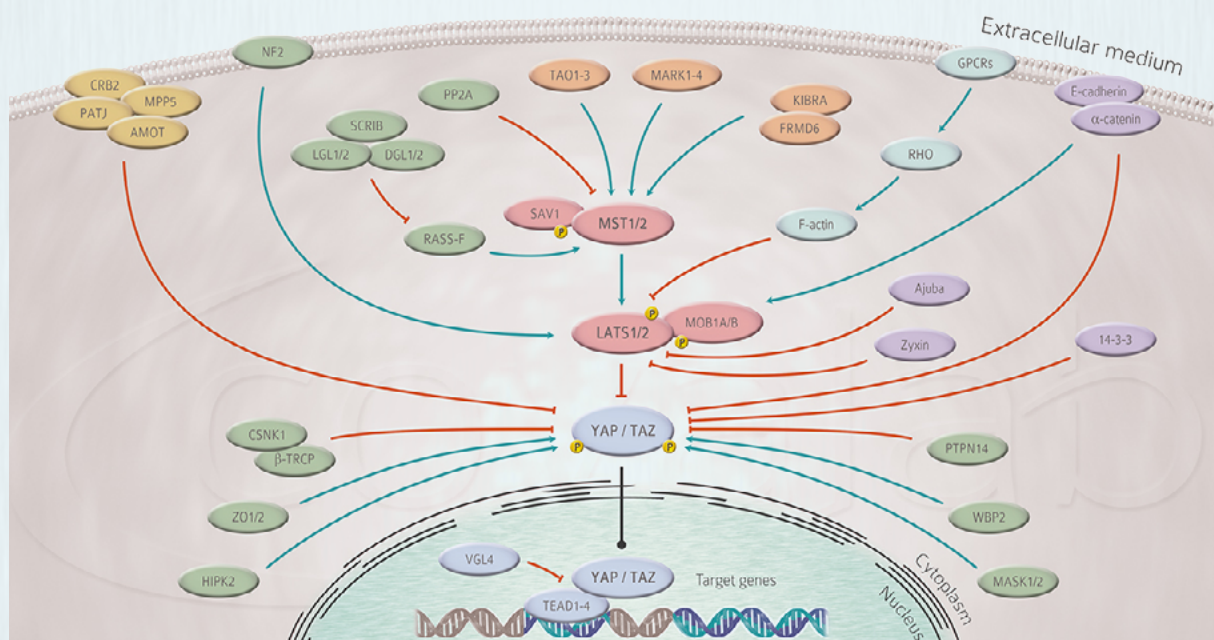


Figure 1: The Hippo pathway network

References:

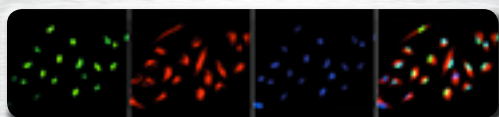
- 1 - The *Drosophila* tumor suppressor gene *warts* encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation: Justice RW. et al.; **Genes Dev.** 1995 Mar 1;9(5):534-46.
- 2 - *Shor-pe* mediates cell proliferation arrest during imaginal disc growth in *Drosophila*: Kango-Singh M. et al.; **Development.** 2002 Dec;129(24):5719-30.
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- 4 - The *Drosophila* *Mst* ortholog, *hippo*, restricts growth and cell proliferation and promotes apoptosis: Harvey KF. et al.; **Cell.** 2003 Aug 22;114(4):457-67.
- 5 - The *Drosophila* *Ste20* family kinase *dMST* functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis: Jia J. et al.; **Genes Dev.** 2003 Oct 15;17(20):2514-9.
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- 7 - *Hippo* promotes proliferation arrest and apoptosis in the *Salvador/Warts* pathway: Udan RS. et al.; **Nat Cell Biol.** 2003 Oct 5(10):914-20.
- 8 - *Hippo* encodes a *Ste-20* family protein kinase that restricts cell proliferation and promotes apoptosis in conjunction with *salvador* and *warts*: Wu S. et al.; **Cell.** 2003 Aug 22;114(4):445-56.
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- 12 - Molecular cloning of a novel human protein kinase, *kpm*, that is homologous to *warts/lats*, a *Drosophila* tumor suppressor: Hori T. et al.; **Oncogene.** 2000 Jun 22;19(27):3101-9.
- 13 - TAZ: a novel transcriptional co-activator regulated by interactions with 14-3-3 and PDZ domain proteins: Kanai F. et al.; **EMBO J.** 2000 Dec 15;19(24):6778-91.
- 14 - Akt phosphorylates the Yes-associated protein, YAP, to induce interaction with 14-3-3 and attenuation of p73-mediated apoptosis: Basu S. et al.; **Mol Cell.** 2003 Jan;11(1):11-23.
- 15 - The two faces of Hippo: targeting the Hippo pathway for regenerative medicine and cancer treatment: Johnson R., Halder G.; **Nat Rev Drug Discov.** 2014 Jan;13(1):63-79.
- 16 - *Mst1* and *Mst2* maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the *Yap1* oncogene: Zhou D. et al.; **Cancer Cell.** 2009 Nov 6;16(5):425-38.
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- 18 - Hippo signaling regulates pancreas development through inactivation of *Yap*: George NM. et al.; **Mol Cell Biol.** 2012 Dec;32(24):5116-28.
- 19 - Neurofibromatosis type 2: Asthagiri AR. et al.; **Lancet.** 2009 Jun 6;373(9679):1974-86.
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YAP1 and TAZ - Antibodies

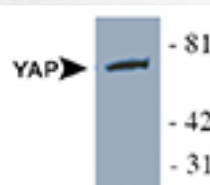
Yes-associated protein (YAP1) and Transcriptional coactivator with PDZ-binding motif (TAZ) are the main downstream mediators of the Hippo pathway. YAP1/TAZ complex plays a crucial role in organ size control and tumour suppression by restricting proliferation and promoting apoptosis. Phosphorylation of YAP1/TAZ complex by LATS1 and 2 kinases blocks its translocation in to the nucleus and thus its transcriptional co-activator function on cellular genes, important for cell death, proliferation and migration.

TARGET	HOST	SPECIES	APPLICATIONS	CAT #
TAZ (12E8)	Rat	Hu	ELISA, IF, WB	mab0129-P
TAZ	Rabbit	Hu	ELISA, IF, WB	pab0893-P
TAZ	Rabbit	Hu	WB	pab52116
TAZ	Rabbit	Hu, Ms, Rat	ICC, IF, IP, WB	pab50284
TAZ (pSer89)	Rabbit	Hu, Ms, Rat, Oth	ELISA, IF, WB	pab0949-P
TAZ [Biotin]	Rabbit	Hu, Ms, Rat	IP, WB	pab51312
TAZ [HRP]	Rabbit	Hu, Ms, Rat	IP, WB	pab51315
TAZ [DyLight 488]	Rabbit	Hu, Ms, Rat	IP, WB	pab51314
TAZ [DyLight 550]	Rabbit	Hu, Ms, Rat	IP, WB	pab51316
TAZ [DyLight 650]	Rabbit	Hu, Ms, Rat	IP, WB	pab51313
YAP1 (12b4)	Mouse	Hu	IHC, IF, WB	mab0133-P
YAP1 (1C5)	Mouse	Hu	IHC, IF, WB	mab0132-P
YAP1 (2H1)	Rabbit	Hu	IF, IHC - P, WB	mab70706
YAP1 (2F12)	Rabbit	Hu	ELISA, IF, IHC - P, WB	mab70705
YAP1	Rabbit	Hu	IHC, IF, WB	pab0848-P
YAP1	Guinea pig	Hu	IHC, IF, WB	pab0964-P
YAP1	Rabbit	Hu, Ms	IF, IHC - P, IP, WB	pab50282
YAP1 (pSer127)	Rabbit	Hu, Ms, Rat, Oth	ELISA, IHC, IF, WB	pab0950-P
YAP1 [Biotin]	Rabbit	Hu, Ms	IHC - P, IP, WB	pab51306
YAP1 [HRP]	Rabbit	Hu, Ms	IHC - P, IP, WB	pab51309
YAP1 [DyLight 488]	Rabbit	Hu, Ms	IHC - P, IP, WB	pab51308
YAP1 [DyLight 550]	Rabbit	Hu, Ms	IHC - P, IP, WB	pab51310
YAP1 [DyLight 650]	Rabbit	Hu, Ms	IHC - P, IP, WB	pab51307

Anti-YAP1 antibody IF staining of HeLa cells (green). Alpha tubulin and nuclei were counterstained using DyLight 550 (red) and DAPI (blue), respectively.



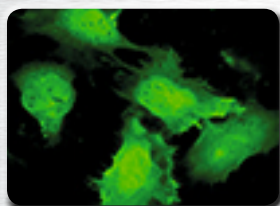
YAP1
pab50282



Anti-YAP1 antibody WB staining of whole lysate from HEK 293 cells overexpressing YAP1.

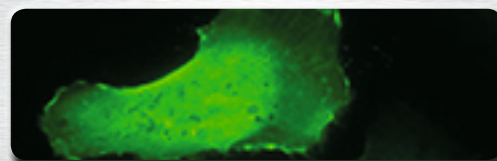
YAP1
pab50282

YAP1
pab0848-P



Anti-YAP1 antibody IF staining of HeLa cells overexpressing YAP1.

TAZ
mab0129-P



Anti-TAZ antibody IF staining of HeLa cells overexpressing TAZ protein.

Other core proteins - Antibodies

The core of the Hippo pathway also includes a kinase cascade starting by MST1 and MST2, which phosphorylate and activate LATS1 and LATS2 kinases. LATS1 and 2 phosphorylate the YAP1/TAZ complex, which maintains it within the cytoplasm. Upon dephosphorylated conditions, this complex is translocated into the nucleus and binds DNA in complex with TEAD1 to TEAD4 (TEA domain-containing-sequence-specific transcription factors).

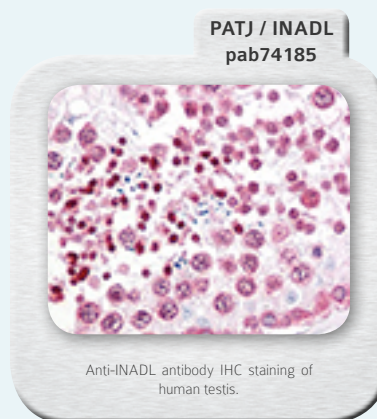
TARGET	HOST	SPECIES	APPLICATIONS	CAT #
LATS1	Rabbit	Hu	ELISA, IF, WB	pab0890-P
LATS2	Rabbit	Hu	ELISA, IF, WB	pab0891-P
MST1	Rabbit	Hu	ELISA, IF, WB	pab0940-P
MST2	Rabbit	Hu	ELISA, IF, WB	pab0892-P
TEAD-2	Rabbit	Hu	ELISA, IF, WB	pab0961-P
TEAD-4	Rabbit	Hu	ELISA, IF, WB	pab0916-P

2 Regulation of the activity of the Hippo pathway

CRB complex - Antibodies

The CRB complex, containing transmembrane CRB proteins, regulates the Hippo pathway by recruiting the members of the angiomin (AMOT) family of adaptor proteins that can directly activate LATS1 and 2 or inhibit TAZ/YAP1 complex. This negatively regulates the Hippo pathway.

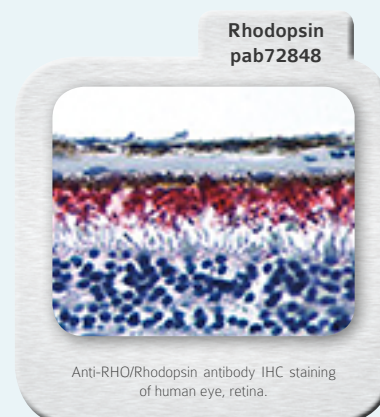
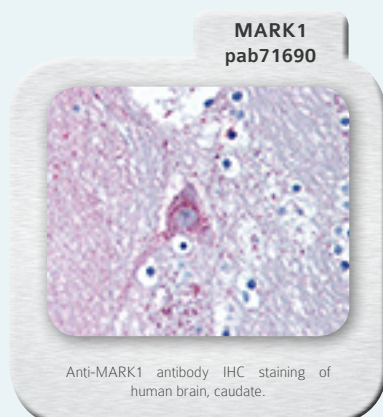
TARGET	HOST	SPECIES	APPLICATIONS	CAT #
AMOT (7D9)	Mouse	Hu	ELISA, IF, WB	mab0128-P
AMOT	Rabbit	Hu	ELISA, IF, WB	pab0915-P
AMOTL1 (10C11)	Mouse	Hu	ELISA, IF, WB	mab0135-P
AMOTL1 (2G5)	Mouse	Hu	ELISA, IF, WB	mab0136-P
AMOTL1	Rabbit	Hu	ELISA, ICC, IF, WB	pab0883-P
AMOTL1 pS262	Rabbit	Hu, Ms, Bov	ELISA, IF, WB	pab0956-P
AMOTL2	Rabbit	Hu	ELISA, IF, WB	pab0941-P
MPP5	Rabbit	Hu	IHC - P, WB	pab73334
MPP5 (N-Terminus)	Goat	Hu, Ca, Po	ELISA, IHC - P, WB	pab72329
PATJ / INADL (N-Terminus)	Goat	Hu, Mk, Bov, Rab	ELISA, IHC - P	pab74185



Kinases modulators - Antibodies

Hippo pathway is also regulated by modulation of MST1 and 2 kinases activity. This can be mediated by kinases like TAO or MARK1 that directly phosphorylate MST1 and 2 kinases but also by the adaptator protein KIBRA. Synergically with NF2, KIBRA can also induce the phosphorylation of LATS1 and 2. These pathways have a negative regulatory effect on the TAZ/YAP1 complex activity.

TARGET	HOST	SPECIES	APPLICATIONS	CAT #
KIBRA (7D11)	Mouse	Hu	ELISA, IF, WB	mab0127-P
KIBRA	Rabbit	Hu	ELISA, IF, WB	pab0889-P
MARK1 (N-Terminus)	Rabbit	Hu	IHC - P	pab71691
MARK1 (N-Terminus)	Rabbit	Hu, Mk, Ca, Bov	IHC - P	pab71690
MARK1 (Internal)	Rabbit	Hu, Mk, Rab	IHC - P	pab71689
MARK2 (N-Terminus)	Rabbit	Hu, Ms, Rat	IF, IHC - P, WB	pab74233
MARK2 (Internal)	Rabbit	Hu, Ms, Rat	ELISA, IF, IHC - P	pab74057
MARK3	Mouse	Hu, Ms	IHC - P, IP, WB	mab70394
MARK3 (N-Terminus)	Rabbit	Hu, Ms, Rat	ELISA, IHC - P, WB	pab74109
MARK4 (Internal)	Rabbit	Hu, Ms	ELISA, IF, IHC - P	pab73857
TAOK1 (Internal)	Rabbit	Hu, Ms, Rat	ELISA, IHC - P, WB	pab75768
TAOK1 (Internal)	Rabbit	Hu, Mk	IHC - P	pab73495
TAOK1 (Internal)	Rabbit	Hu, Mk, Ms, Xe...	IHC - P	pab73494
TAOK1 (C-Terminus)	Rabbit	Hu, Mk, Ms, Oth...	ELISA, IHC - P	pab73493
TAOK3 (Internal)	Goat	Hu, Mk, Bov, Ms...	ELISA, IHC - P, WB	pab72419



Cytoskeleton - Antibodies

This branch is defined by an as yet poorly understood signalling mechanism mediated by the cytoskeleton. GPCRs relay signal from soluble extracellular cues and cell matrix attachment to activate RHO GTPases. This induces a modification of the actin cytoskeleton that inhibits YAP/TAZ complex nuclear translocation, thus negatively regulating the Hippo cascade.

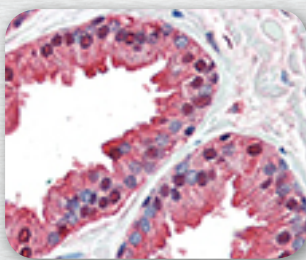
TARGET	HOST	SPECIES	APPLICATIONS	CAT #
GPR12 (Extracellular Domain)	Rabbit	Hu	IHC - P	pab71131
GPR12 (Extracellular Domain)	Rabbit	Hu, Mk, Ms, Oth...	IHC - P	pab71130
GPR12 (N-Terminus)	Rabbit	Hu	IHC - P	pab71132
GPR12 (C-Terminus)	Rabbit	Hu, Mk	IHC - P, WB	pab71129
GPR18 (Internal)	Rabbit	Hu	ELISA, IHC - P	pab75803
Rhodopsin (1D4)	Mouse	Ver	ICC, IHC, WB	mab60458
Rhodopsin (4D2)	Mouse	Hu, Ma, Fi, Chick...	IHC, IP, WB	mab60459
Rhodopsin (Extracellular Domain)	Rabbit	Hu, Ms, Rat, Po...	IHC - P	pab72848

YAP1 and TAZ - Antibodies

Hippo pathway can also be negatively regulated by adherens junction-associated proteins. E-cadherin engagement at adherens junction suppresses the nuclear location and activity of YAP by regulating MST1 and 2 activity, or via alpha-catenin by sequestering 14-3-3 protein complexes within the cytoplasm.

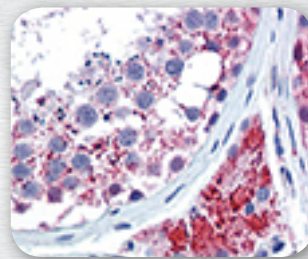
TARGET	HOST	SPECIES	APPLICATIONS	CAT #
14-3-3 (60C10)	Mouse	Hu, Ms, Rat	IHC - P, WB	mab71368
14-3-3	Rabbit	Sh, Bov, Hu, Ms...	IHC - P, IP, WB	pab74800
14-3-3 (C-Terminus)	Rabbit	Rat, Hu, Ms, Xe...	IHC - P, WB	pab70029
14-3-3 Beta (aa1-246) (J2E9)	Mouse	Hu	ELISA, IHC - P, WB	mab70291
14-3-3 Beta	Rabbit	Hu, Zfi	IF, IHC - P, WB	pab73313
14-3-3 Beta	Rabbit	Hu, Zfi	IF, IHC - P, WB	pab73314
14-3-3 Beta	Rabbit	Hu, Ms, Rat	IHC - P, WB	pab75102
14-3-3 Beta (N-Terminus)	Rabbit	Hu, Ms, Rat	IHC - P	pab72731
14-3-3 Gamma (aa1-247) (J3H10)	Mouse	Hu	ELISA, IHC - P, WB	mab70294
14-3-3 Epsilon (aa1-255) (5A5)	Mouse	Hu	ELISA, IHC - P, WB	mab70282
14-3-3 Epsilon (N-Terminus)	Rabbit	Sh, Bov, Chick, Hu...	ELISA, IHC - P, WB	pab75464
14-3-3 Eta (N-Terminus)	Rabbit	Sh, Ma, Chick, Hu...	IHC - P, WB	pab74766
14-3-3 Sigma (3C3)	Mouse	Hu	IHC - P, WB	mab70613
14-3-3 Sigma	Rabbit	Hu, Ms, Rat	ELISA, IHC, WB	pab0392
14-3-3 Sigma (aa120-170)	Rabbit	Hu, Bov, Mk, Ca...	IHC - P, WB	pab75792
14-3-3 Sigma (N-Terminus)	Rabbit	Sh, Bov, Chick, Hu...	IHC - P, WB	pab75460
14-3-3 Sigma (Internal)	Goat	Hu, Mk, Ca, Ms...	ELISA, IHC - P, WB	pab73985
14-3-3 Sigma pS248	Rabbit	Hu	ELISA, IHC, WB	pab0713
14-3-3 Tau (aa1-245) (AT1A1)	Mouse	Hu	ELISA, IHC - P, WB	mab70297
14-3-3 Zeta (aa200-245)	Rabbit	Hu, Bov, Mk, Ca...	IHC - P, WB	pab75793
14-3-3 Zeta (Internal)	Rabbit	Hu, Ms, Rat	IHC - P, WB	pab75446
14-3-3 Zeta Delta (S58)	Rabbit	Hu, Ms, Rat	IHC - P, WB	pab72083
14-3-3 Zeta Delta (Internal)	Rabbit	Hu, Ms, Rat	ELISA, IHC - P, WB	pab74404
14-3-3 Zeta Delta (C-Terminus)	Rabbit	Hu, Ms, Rat	ELISA, IF, IHC - P, WB	pab74327
14-3-3 Zeta/Delta pS184	Rabbit	Hu	ELISA, IHC, WB	pab0644
E-Cadherin (3F4)	Mouse	Hu	ELISA, IHC - P, WB...	mab70590
E-Cadherin (SHE78-7)	Mouse	Hu	FA, FC, IF, WB...	mab60121
E-Cadherin (N-Terminus)	Rabbit	Hu	IF, IHC - P, WB	pab73861
CTNNA1 (Internal)	Rabbit	Hu, Ms, Mk, Oth...	ELISA, IHC - P, WB	pab73167
CTNNA1 (C-Terminus)	Rabbit	Hu, Ms, Rat	ELISA, IHC - P, WB	pab75661

Anti-14-3-3 Beta antibody IHC staining of human prostate.



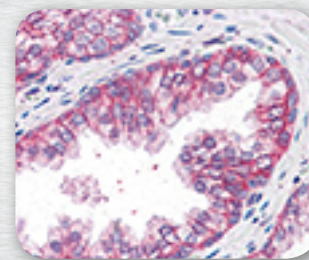
14-3-3 Beta
pab72731

E-cadherin
pab73861



Anti-E-Cadherin antibody IHC staining of human testis.

Anti-CTNNA1 antibody IHC staining of human prostate.



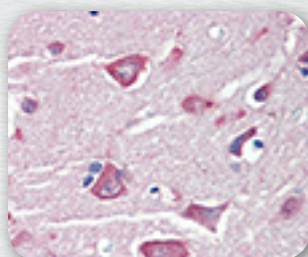
CTNNA1
pab73167

VEGF receptor 1 antibodies

Several other proteins modulate the activity of the pathway by direct interaction with YAP1/TAZ complex (e.g. MASK, ZOE or HIP2) or by interaction with the upstream kinase complex (e.g. RASSFs, PP2A, Merlin or SIK).

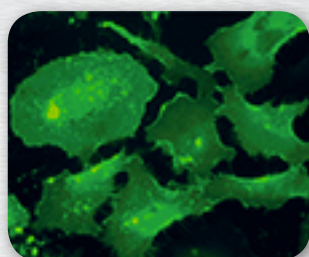
TARGET	HOST	SPECIES	APPLICATIONS	CAT #
DLG1 (S64-15)	Mouse	Hu, Ms, Rat	IHC - P, IP, WB	mab71575
HIPK2 (1F10)	Mouse	Hu, Rat	ELISA, IHC - P, WB	mab70862
Merlin / NF2	Rabbit	Hu, Ms	ELISA, WB	pab0939-P
Merlin / NF2	Rabbit	Hu, Ms	ELISA, IHC, WB	pab0845-P
Merlin / NF2 (Internal)	Goat	Zfi, Hu	ELISA, IHC - P	pab72351
Merlin / NF2 pS518	Rabbit	Hu, Ms	IHC - P, IP, WB	pab70118
Merlin / NF2 pT582	Rabbit	Hu, Ms	ELISA, IHC, WB	pab0846-P
PPP2CA (P6C7)	Mouse	Hu	ELISA, IHC - P, IP, WB	mab70258
PPP2CA	Rabbit	Hu, Ms, Rat	IHC - P, WB	pab75149
RASSF1A (Internal)	Rabbit	Hu, Bov, Po	IHC - P	pab73022
RASSF1	Rabbit	Hu	ELISA, IHC, WB	pab0960-P
SIK1 (2C12)	Mouse	Hu	ELISA, IHC - P	mab71075
SIK1 (Internal)	Rabbit	Hu	IHC - P, WB	pab73204
SIK2 (S15G10)	Mouse	Hu	IF, IHC - P, IP, WB	mab71180
SIK2 (aa100-150)	Rabbit	Hu, Bov, Mk, Ms...	IHC - P, WB	pab74535
SIK2 (Internal)	Rabbit	Hu	ICC, IF, IHC - P, WB	pab73205
ZYX / Zyxin (2D1)	Mouse	Hu, Ms	ELISA, IHC - P, WB	mab70680

RASSF1A
pab73022



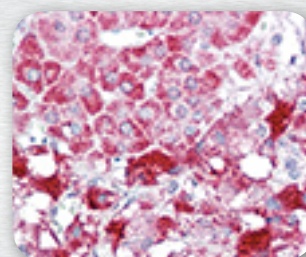
Anti-RASSF1A antibody IHC staining of human brain, cortex.

Merlin
pab0939-P



Anti-Merlin antibody IF staining of HeLa cells overexpressing NF2.

SIK2
pab73205



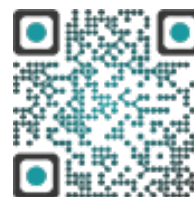
Anti-SIK2 antibody IHC staining of human adrenal gland.

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Antibody Purification

Biomolecule Labelling

Development of Immunoaffinity Supports (columns)

Functionalisation of Solid Phases (microtitration plates)

Expertise

Advice for project
design and optimisation
of R&D processes

Customised technical
troubleshooting support

Active follow-up of
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