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EP CLONES

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Catalog Supplement
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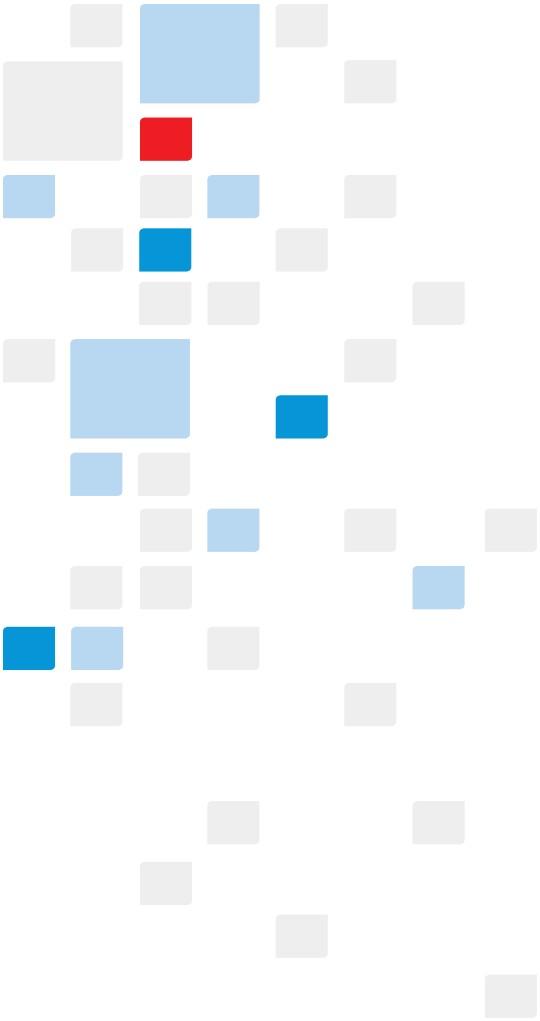

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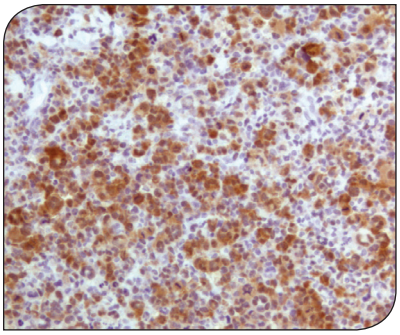


Anaplastic large cell lymphoma stained with anti-ALK

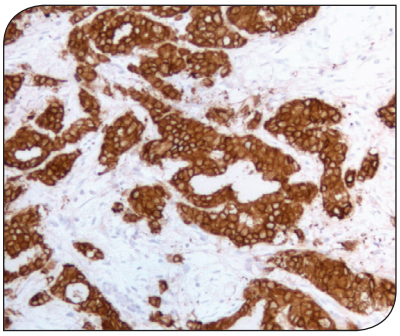
ALK (EP302)

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase of the insulin receptor superfamily. ALK is typically expressed at low levels in regions of the developing central and peripheral nervous system.

ALK may be activated in cancer through multiple mechanisms. The most common mechanism is through formation of a fusion protein from chromosomal translocations, as in the case of anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumors. ALK may also be amplified through mutation, as in neuroblastomas. Various solid tumors, such as non-small cell lung carcinoma (NSCLC) and brain cancers were also found to aberrantly express ALK.

ALK staining is present within both the nucleus and cytoplasm, and are positive in about 60% of ALCL. ALK protein expression by tumor cells is an independent prognostic factor that predicts a favorable outcome.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0285A 1 ml . . . . . #AC-0285	ALK+ anaplastic large cell lymphoma	cytoplasmic, nuclear



Breast carcinoma stained with anti-AGR2

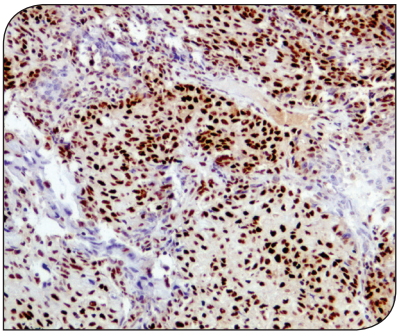
Anterior Gradient 2 (AGR2) (EP329)

Anterior Gradient 2 (AGR2), also known as HAG-2 or Gob-4, is the human orthologue of the Xenopus laevis AGR protein XAG-2. In the frog embryo, XAG-2 is involved in cement gland differentiation and neural marker expression. However, the function of AGR2 in humans is unclear. AGR2 was first identified in studies focused on differentiating genes in estrogen receptor (ER)-positive breast cancers and is predominately expressed in tissues that contain mucus-secreting cells and/or function as endocrine organs. Strong AGR2 mRNA expression was found in normal human colon, stomach, rectum, prostate and breast.

AGR2 has been shown to be co-expressed with ER in breast cancer cell lines and overexpression was found to attenuate p53 activation in UV-damaged cells. Immunohistochemical studies demonstrated cytoplasmic AGR2 staining in 65-83% of breast cancers. Positive staining for AGR2 in ER-positive breast cancers was significantly associated with poorer patient survival.

Subsequent studies have also shown elevated AGR2 expression in adenocarcinomas of the esophagus, pancreas, and prostate. ARG2 expression was also highly expressed in Barrett's esophagus, a premalignant lesion characterized by intestinal metaplasia compared with normal esophageal epithelium.

Product Availability:	Control:	Visualization:
0.1 ml . . . . # AC-0286RUOA 1 ml . . . . . #AC-0286RUO	breast, estrogen receptor (ER) positive-breast carcinoma	cytoplasmic



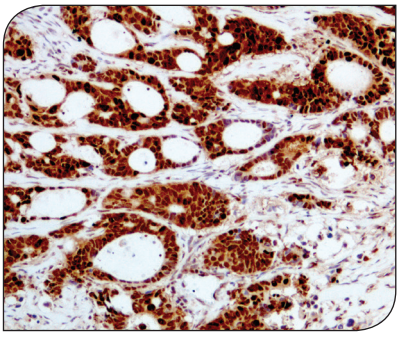
Endometrial carcinoma stained with anti-ARID1A

ARID1A (BAF250a) (EP303)

ARID1A (AT-rich interactive domain-containing protein 1A), also known as BAF250a, is a recently identified tumor suppressor that is a component of the SWI/SNF chromatin remodeling complex. ARID1A functions by binding AT-rich DNA sequences to regulate gene expression of nucleosome mobilization and chromatin processes. While ARID1A is typically expressed in most normal tissues, it is frequently mutated in a multitude of tumors, including breast, lung, gastric, renal and ovarian cancers.

Genomic sequencing revealed that most ARID1A mutations are truncating mutations, and the presence of mutations is highly correlative with loss of ARID1A protein expression by immunohistochemistry. Deficient ARID1A expression was observed in approximately 70% of renal cell carcinomas, 50% of gastric cancers, 40% of clear cell ovarian carcinomas, and 40% of endometrioid carcinomas. Furthermore, loss of ARID1A expression was determined as an independent marker for poor prognosis; tumors were correlated with higher stage and grade, are more likely to be chemoresistant, and associated with shorter progression-free and overall survival rates. ARID1A antibody may be used for identifying ARID1A defect tumors.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0275A 1 ml . . . . . #AC-0275	colon	nuclear



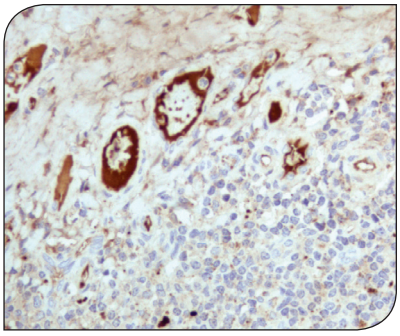
Colon carcinoma stained with anti-Beclin-1

Beclin-1 (EP304)

Beclin-1 is an essential protein for the initiation of autophagy, the type II programmed cell death pathway. This 60 kDa protein is induced during autophagy, binds with additional autophagic proteins to regulate the formation of the autophagosome. While Beclin-1 is broadly expressed in most normal tissues, its expression was found to be weak in the normal gastric and colonic mucosa. In contrast, Beclin-1 was monoallelically deleted in approximately 40-75% of human breast, cervical, ovarian, and prostate cancers. Further, lower Beclin-1 mRNA levels were detected in glioblastoma compared to normal brain tissue from the same subject.

Beclin-1 expression is correlative with protein immunoreactivity, and variable loss of beclin-1 expression was observed in cancer cells when compared with adjacent normal tissue, with notable exceptions in gastric and colorectal cancers. In 68% of hepatocellular carcinomas and 33% of esophageal squamous cell carcinomas, beclin-1 immunoreactivity was lost. Multiple studies have determined beclin-1 as an independent prognostic marker, where high expression of beclin-1 is associated with positive prognosis including higher disease-free and overall survival rates. In contrast, loss of beclin-1 was associated with increased depth of invasion, lymph node metastasis and higher tumor grade.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0276RUOA 1 ml . . . . . #AC-0276RUO	breast	nuclear, cytoplasmic



Tonsil stained with anti-C4d

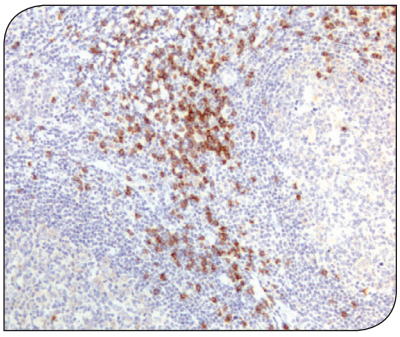
C4d (EP272)

C4d is the degradation product of the activated complement factor C4. Following activation and degradation of the C4 molecule, thioester groups are exposed which allow transient, covalent binding of the degradation product C4d to endothelial cell surfaces and extracellular matrix components of vascular basement membranes near the sites of C4 activation. C4d is also found in intracytoplasmic vacuoles of endothelial cells. Covalent binding renders C4d a stable molecule that can easily be detected by immunohistochemistry.

Feucht et al. were the first to demonstrate the occurrence of capillary C4d staining in kidney allografts and its association with inferior graft outcomes, and later confirmed by other studies. It was demonstrated that patients with suspected antibody-mediated injury in the renal graft had a linear C4d staining pattern in peritubular capillaries and that the presence of C4d was associated with impaired graft function. Except kidney allografts, little is known currently about C4d accumulation in other solid organ allografts. Preliminary data suggest that heart allografts are comparable with kidney transplants. C4d was found in early posttransplant endomyocardial biopsies and was associated with poor graft survival. In dysfunctioning lung transplants, C4d could be detected in septal capillaries. C4d has also been found in liver allografts carrying a diagnosis of antibody-mediated rejection.

In 2003, C4d was incorporated in the Banff classification, the accumulation of C4d along peritubular capillaries is generally regarded as a marker for an antibody-mediated alloresponse and is associated with poor graft survival.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0260A 1 ml . . . . . #AC-0260	tonsil, renal biopsy of antibody-mediated rejection	cytoplasmic



Tonsil stained with anti-CD8

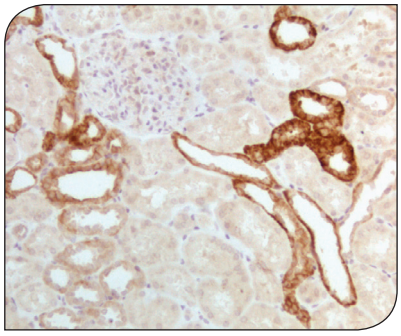
CD8 (EP334)

CD8 (cluster of differentiation 8) is a transmembrane glycoprotein that functions as a co-receptor with the T-cell receptor (TCR). The CD8 molecule consists of a heterodimer of α and β chains covalently linked by a disulfide bond, and is predominantly expressed on the surface of cytotoxic T-cells. CD8 expression can also be detected on natural killer cells, cortical thymocytes, and dendritic cells.

Cytotoxic CD8+ T lymphocytes are crucial components of the adaptive immune system that execute immunosurveillance to eliminate nascent tumor cells. Upon simultaneous binding to the major histocompatibility complex (MHC) class I molecule with the TCR, cytotoxic T-cell sensitivity is increased 100-fold. CD8 is commonly expressed in T-cell large granular lymphocyte leukemia and is also co-expressed with CD4 in some T-lymphoblastic lymphoma.

Recently, detection of tumor infiltrating CD8+ lymphocytes have been correlated with favorable prognosis and improved survival in patients with colorectal, ovarian, esophageal, renal, lung and pancreatic tumors. A high CD8+/CD4+ T-cell ratio is also associated with improved survival in colon and ovarian cancer patients.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . # AC-0301A 1 ml . . . . . # AC-0301	tonsil	membrane



Kidney stained with anti-Claudin-8

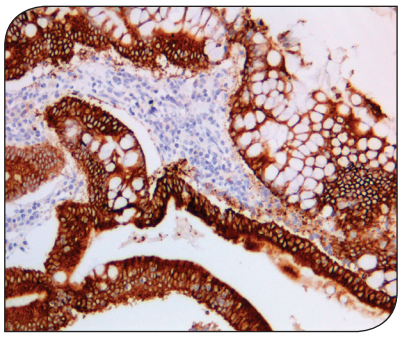
Claudin 8 (EP305)

Claudins are a large family of tight junction proteins that regulate cellular adhesion, polarity and glandular differentiation. Claudin-8 is one of the 24 member family known to exist in humans, with each having its tissue specific expression. Claudin-8 expression has been demonstrated in multiple organs, presenting a membranous and cytoplasmic staining pattern in the distal convoluted tubules and collecting ducts of the kidney, and apicolateral staining of luminal cells in the breast.

Disruption of tight junctions is believed to be one of the processes that occur in carcinogenesis that allows for the loss of cellular cohesion, aggressive growth, and de-differentiation of cancer cells. Studies have shown down regulation in Claudin-8 expression in intra- and extrahepatic bile duct cancer, gallbladder carcinoma, colorectal carcinoma and invasive ductal carcinoma. A study measuring expression levels of multiple claudins revealed that claudin-low breast cancer patients had significantly worse recurrent-free survival than other patients.

Additionally, Claudin-8 has been suggested as a sensitive marker for oncocytomas. In one study, the majority of oncocytomas (92%) had moderate to strong staining, which differentiated it from papillary (14%), clear cell (12%) and chromophobe (0%) renal cell carcinomas.

Product Availability:	Control:	Visualization:
0.1 ml. . . . #AC-0289RUOA 1 ml . . . . . #AC-0289RUO	kidney, oncocytoma	membrane, cytoplasm



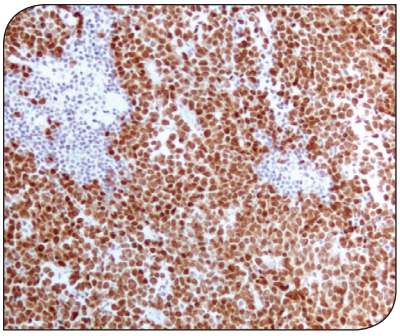
Colon adenocarcinoma stained with anti-COX-2

COX-2 (EP293)

COX-2, also known as prostaglandin-endoperoxidase synthase 2 (PTGS2), is an immediate-early gene that encodes a critical enzyme for the conversion of arachidonic acids to prostaglandins. Functionally, COX-2 exists as a homodimer, consisting of two 70kDa subunits. COX-2 derived prostanoids have been shown to increase resistance to apoptosis, promote angiogenesis, induce metastasis and invasion, and impair immune surveillance.

Immunohistochemical expression of COX-2 has been described in multiple tissue types. While COX-2 expression is limited in most normal tissues, it is induced by various stimuli and elevated during inflammatory responses. Reports have associated COX-2 expression with cancers from multiple tissues. Lung, colon, gastric, prostate, and breast carcinomas were described to have elevated levels of COX-2. Further, elevated COX-2 levels has been associated with poor prognosis and decreased survival in patients with breast cancer.

Product Availability:	Control:	Visualization:
0.1 ml. . . . . # AC-0273A 1 ml . . . . . .# AC-0273	colon carcinoma	cytoplasmic



Retinoblastoma stained with anti-CRX

CRX (CORD2) (EP323)

The cone-rod homeobox protein CRX, encoded by CORD2 is a transcription factor proposed as a regulator of photoreceptor differentiation, normal retina development, and pineal function. CRX is expressed in uncommitted proliferating cells and cells committed to the bipolar lineage in as early as 10.5 weeks gestation in the developing human eye. Mutations in CORD2 are associated with retinal degenerative diseases including cone-rod dystrophies and Leber congenital amaurosis, a disorder of the retina resulting in severe visual impairment. In the mature eye, CRX is highly expressed in photoreceptor cells while moderately in bipolar cells.

Elevated and extensive nuclear CRX expression was observed in all retinoblastoma cell lines and >95% of retinoblastoma cells. CRX was identified in undifferentiated regions as well as rosettes and flerettes, which are features of tumor differentiation. Additionally, nuclear CRX staining was also observed in >90% pineal parenchymal tumors. CRX was reported as a sensitive and specific marker for retinoblastoma and pineal parenchymal tumors when used as part of a panel comprising of Synaptophysin and GFAP.

Product Availability:	Control:	Visualization:
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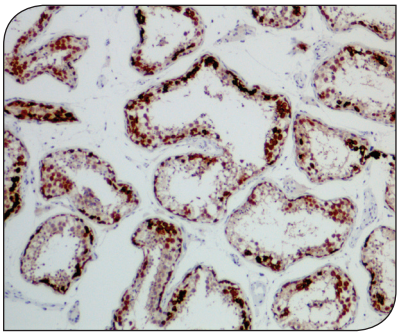

Testis stained with anti-CTAG1B

CTAG1B (NY-ESO-1) (EP311)

CTAG1B (cancer/testis antigen 1), also known as NY-ESO-1 (Autoimmunogenic cancer/testis antigen) is an 18 kDa protein with putative roles in germ cell self-renewal and/or differentiation. Of cancer/testis (CT) antigens, CTAG1B is the most immunogenic CT antigen known to date. CTAG1B staining is predominantly cytoplasmic with focal nuclear expression. Tissue distribution is highly restricted in the normal adult; it is only detected in spermatogonia and primary spermatocytes within the testis. Surrounding non-gametogenic cells, including Sertoli cells and spermatids are negative. CTAG1B is also undetected in the ovaries. However, expression is observed in germ cells of the fetal testis and ovaries.

In cancer, genome wide demethylation was shown to induce CTAG1B expression. Immunohistochemical expression has been demonstrated commonly in myxoid and round cell liposarcoma (89-100%), neuroblastoma (82%), synovial sarcoma (80%), melanoma (46%) and epithelial ovarian cancer (43%). Staining in lung, esophageal, liver, gastric, and bladder cancers has also been noted with lower prevalence. Immunoreactivity was only observed in tumor cells; no staining was present in adjacent cells. Furthermore, previous studies have correlated CTAG1B antigen expression with advance stage of disease and indicated a subset of more aggressive tumors that may be less susceptible to known treatments. CTAG1B antibody has been used for identification of myxoid and round cell liposarcoma.

Product Availability:	Control:	Visualization:
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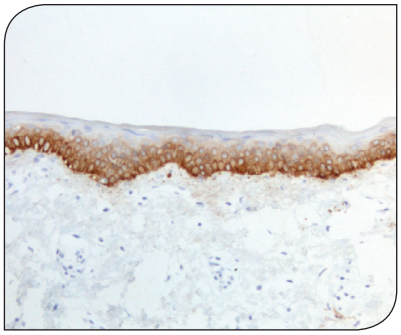


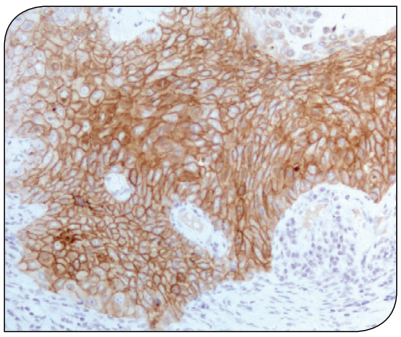
Skin stained with anti-Cytokeratin 16

Cytokeratin 16 (EP297)

Cytokeratin 16 (CK16), also known as keratin 16, is a member of the large intermediate filament protein family that form the cytoskeleton. This family is subdivided into acidic (type I) and basic (type II) cytokeratins, but are obligatory heteropolymers, where expression of at least one member of each subfamily is required for filament formation. CK16 is classified as type I, pairing with type II cytokeratin 6. In normal tissues, CK16 is constitutively expressed at low levels in the palmar and plantar epidermis, tongue, oral mucosa, and hair follicles.

Studies have proposed a modulatory role of CK16 in cell proliferation, suggesting its utility as a marker for proliferation. Rapid induction of CK16 expression near the edge of wounds, up regulation in response to epidermal growth factor stimulus, and overexpression in hyperproliferative disorders, including psoriasis and chronic contact dermatitis, support this assertion. In psoriasis, the severity of disease is correlated with the amount of CK16. Additionally, CK16 expression has been described in neoplasms of multiple tissues. Progressive CK16 abundance and intensity were observed with increased grade of severity of cervical intraepithelial neoplasia lesions. Furthermore, 10% of invasive carcinomas were diffusely or focally positive. In keratocystic odontogenic tumors, CK16 was observed in 79% of cases. These observations support CK16 as a marker of hyperproliferation.

Product Availability:	Control:	Visualization:
0.1 ml. . . . . #AC-0290A 1 ml . . . . . #AC-0290	skin, squamous cell carcinoma	cytoplasmic



Squamous cell carcinoma stained with anti-Desmoglein 3

Desmoglein 3 (EP306)

Desmogleins (DSGs) are a family of cadherins of four known subfamily members, DSG1-4. DSG3 functions as a cell-cell adhesion receptor in desmosome junctions, responsible for mediating cell adhesion and desmosome formation. It was initially described in Pemphigus Vulgaris, an autoimmune skin blistering disorder caused by binding of auto-antibodies against the extracellular domain of DSG3. Studies have reported impaired cell-cell adhesive function following DSG3 depletion from desmosomes.

In normal tissues, DSG3 staining is membrane localized on epithelial cells in skin, kidney, and esophagus. Recently, DSG3 was described as a positive biomarker of squamous cell carcinoma (SqCC), discriminating lymph node metastasis in head and neck SqCC between positive and benign nodes with ~100% accuracy. Additionally, DSG3 staining had a sensitivity of 99% and specificity of 87% for SqCC in primary tumors from multiple organ sites. DSG3 was also shown as a marker in differentiating lung SqCC from other non-small cell lung cancer subtypes, staining positively in 98% of SqCC and negatively in 99% of non-SqCC cases. Positive DSG3 staining was also significantly correlated with a favorable prognosis, while down-regulation is associated with a loss of differentiation and enhanced metastasis.

Product Availability:	Control:	Visualization:
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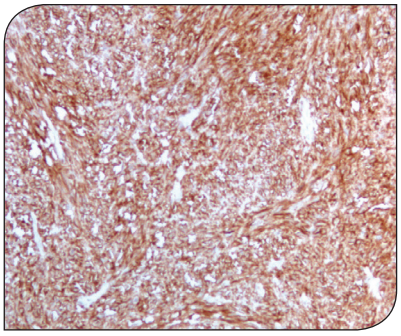


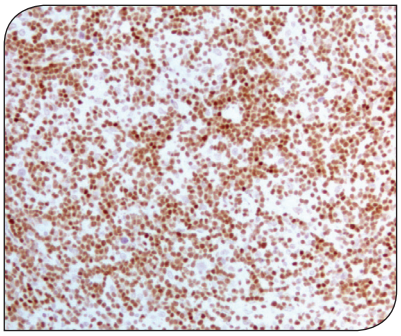
GIST stained with anti-DOG1

DOG1 (EP332)

DOG1, "discovered on GIST 1" encodes for a protein of unknown function that is highly sensitive and specific for gastrointestinal stromal tumors (GIST). GISTs occur in bowel walls and are proposed to originate from the interstitial cells of Cajal. The majority of GISTs harbor activating mutations in KIT but approximately 5-15% of GIST are negative for c-Kit by immunohistochemistry, mainly associated with mutations in the PDGFRA gene.

Antibodies against DOG1 have been shown to be highly sensitive and specific, demonstrating 98-100% reactivity to GIST. DOG1 staining pattern is cytoplasmic and membranous, staining tumor cells and interstitial cells of Cajal. Its sensitivity was deemed superior to c-Kit in that many cases with PDGFRA mutations that failed to show c-kit reactivity were DOG-1 positive.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0303A 1 ml . . . . . #AC-0303	gastrointestinal stromal tumor (GIST)	cytoplasm



Tonsil stained with anti-FOXP3

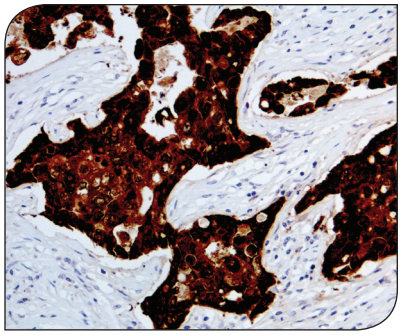
FOXP3 (EP340)

FOXP3 is a member of the forkhead box (FOX) transcription factors, found to be a regulator in the development and function of regulatory T-cells (Treg). While FOXP3 has been widely accepted as the best marker for Treg identification, it can also be transiently expressed on non-regulatory CD4+ T-cells upon T-cell antigen receptor activation, and in nonlymphocytic normal or cancer cells.

Tregs are defined as immunosuppressive T-cells that can mediate local suppression of antitumor immunity and also inhibit functions of dendritic cells, natural killer cells, and B-cells. Recruitment of Tregs into tumors has been suggested as one of the mechanisms by which malignant cells evade host immunity. Treg tumor infiltration, an enlarged pool of Treg in the peripheral blood, and draining lymph nodes have been observed in multi cancer types.

Intratumoral FOXP3-positive T-cells were associated with a higher risk of recurrence and poor overall survival of patients with a variety of solid neoplasms. Significant tissue infiltration of Treg were also observed in cases of malignant transformation.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0304RUOA 1 ml . . . . . #AC-0304RUO	Hodgkin's lymphoma	nuclear



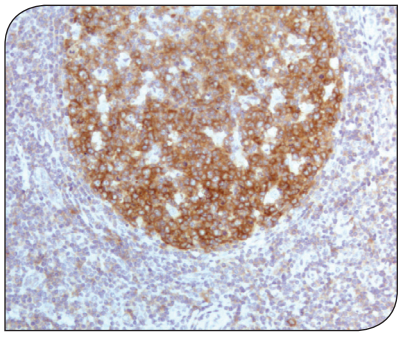
Breast carcinoma stained with anti-GRB7

GRB7 (EP308)

Growth factor receptor-bound protein-7 (Grb7) is a member of a family of adaptor molecules that regulates signal transduction pathways related to cell motility and tumorigenesis. In particular, Grb7 plays a role in cell migration by its interaction with focal adhesion kinase. In normal tissues, Grb7 is constitutively expressed in multiple tissues including the pancreas, kidney, placenta, prostate, intestine, colon, liver, lung and gonads.

The Grb7 gene is located in the chromosomal region at 17q12-q21 in the HER-2/ErbB2 amplicon. In breast cancer, Grb7 has been shown to be co-amplified with HER-2 to synergistically enhance tumor formation in cases with 17q11-21 amplification. Furthermore, high Grb7 protein expression was determined as an independent prognostic factor for decreased survival. Grb7 overexpression was also associated with poor outcomes in triple-negative breast cancers, and correlative with severity of disease in chronic lymphocytic leukemia. Grb7 was observed in 67% of patients with pancreatic cancer with lymph node metastasis and 31% of esophageal carcinomas.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0279RUOA 1 ml . . . . . #AC-0279RUO	breast, breast carcinoma	nuclear, cytoplasmic



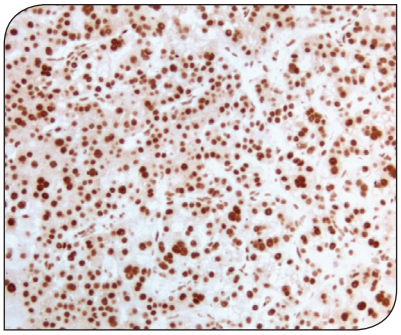
Tonsil stained with anti-hGAL (GCET2)

hGAL (GCET2) (EP316)

The human germinal center-associate lymphoma (hGAL) protein, also known as the germinal center expressed transcript-2 (GCET2) gene, is located on chromosome 3q13.3, encoding for a 178 amino acid protein. GCET2 is an ortholog to a mouse germinal center (GC)-expressed transcript, M17. GCET2 is highly expressed in the normal GC with moderate expression in the thymus and spleen. HGAL protein is localized in the cytoplasm, and expressed in GC in normal lymphoid tissue and in GC-derived lymphomas. Expression of GCET2 mRNA was one of the top 10 candidate molecules that predicted improved survival and an independent positive prognostic factor in patients with diffuse large B-cell lymphoma (DLBCL).

HGAL staining is also present in 100% of Burkitt lymphomas, 97.6% of follicular lymphomas, 87.5% of mediastinal large B-cell lymphomas and 68% of DLBCLs. HGAL was demonstrated to be more frequently positive in follicular lymphomas, superior to Bcl-6 and CD10 staining. Through gene expression profiling, DLBCL are classified further into two additional subgroups: GC B-cell like and activate B-cell like DLBCL that cannot be reliably distinguished by morphology. Addition of hGAL to the Hans, Choi, and Tally immunohistological algorithms has been shown to improve the detection of the GC B-cell like subgroup.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0292A 1 ml . . . . . #AC-0292	tonsil, germinal center B-cell type diffuse large B-cell lymphoma	cytoplasmic



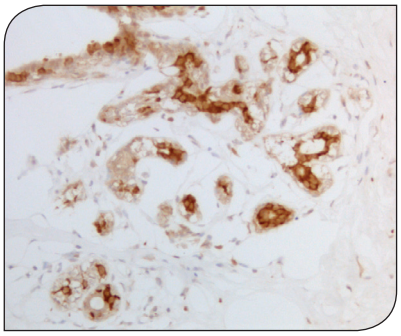
Hepatocellular carcinoma stained with anti-hnRNP K

hnRNP K (EP330)

Heterogeneous nucleus ribonucleoprotein (hnRNP) K is a component of the hnRNP complex, encoding for a 464 amino acid protein that mediates DNA and RNA binding. It is involved in the transcription, splicing and translation processes and recently implicated in tumorigenesis. Several oncogenes, such as c-Src, eIF4E and c-myc are regulated by hnRNP K. Correlation between elevated expression of hnRNP K and tumor development and progression are well documented. It has also been found to enhance cell proliferation and neoplastic transformation.

In normal tissues, hnRNP K is present primarily in the nucleus. Nuclear and aberrant cytoplasmic overexpression have been described in colorectal, prostate, hepatic, esophageal, and breast cancers that have been significantly associated with poor prognosis.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0305A 1 ml . . . . . #AC-0305	hepatocellular carcinoma	nuclear, cytoplasmic



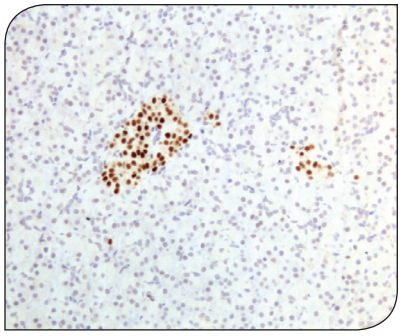
Breast stained with anti-INPP4B

INPP4B (EP328)

The type II inositol 3,4-bisphosphate 4-phosphatase (INPP4B) is a recently identified tumor suppressor modulating the PI3K/Akt signaling pathway. Mechanistically, INPP4B hydrolyzes phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) to regulate phosphorylation and cytoplasmic activation of Akt. Loss or silenced INPP4B expression was associated with increased activated Akt and anchorage-independent growth.

INPP4B expression has been evaluated in breast, ovarian and prostate cancers. Immunohistochemical studies using tumor tissues and tissue microarrays demonstrated significantly reduced expression in cancer cells compared with benign tissue. In gene expression studies, INPP4B RNA levels were decreased in 8% of clinically localized, and 47% of metastatic disease. In breast cancer, loss of INPP4B occurs most frequently in aggressive hormone receptor-negative basal-like breast carcinomas, with higher tumor grade and size. Diminished INPP4B levels are correlated with poor outcomes and reduced recurrence-free survival.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0306RUOA 1 ml . . . . . #AC-0306RUO	breast	cytoplasmic



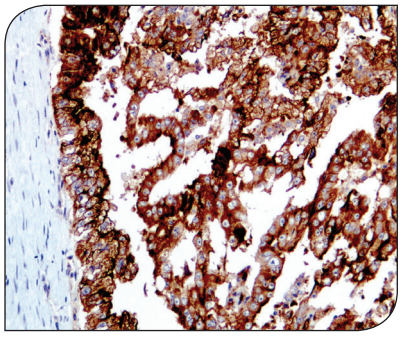
Pancreas stained with anti-Islet 1

Islet 1 (EP283)

Islet 1 is a transcription factor encoded by ISL-1 gene in the LIM-homeodomain subfamily. It is involved in the embryogenesis and differentiation of beta cells within the islets of Langerhans and crucial for pancreatic and motor neuron development. Islet 1 represents a differentiation marker expressed in the pancreas within normal islet cells and has been proposed as a marker for pancreatic neuroendocrine tumors.

Islet 1 is a sensitive lineage-specific marker for pancreatic neuroendocrine neoplasms and their metastases. Sensitivity ranges from 69-90% for primary pancreatic neoplasms, and 67-76% for metastatic neoplasms. Islet 1 has also been reported in duodenal, colonic and rectal neuroendocrine neoplasms. Due to the difficulty in distinguishing the primary site from metastatic neuroendocrine tumors with histological features, addition of Islet 1 staining to a panel of immunohistochemistry markers (PAX8, TTF1, and CDX2) identified the correct primary site in 75% of metastatic cases, demonstrating significant improvement over the three antibody panel (67%). Addition of Islet 1 to an immunohistochemical panel would be a useful adjunct to determine the site of origin in metastatic neuroendocrine tumor of unknown primary.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0293A 1 ml . . . . . #AC-0293	pancreas, pancreatic neuroendocrine tumor	nuclear, cytoplasmic



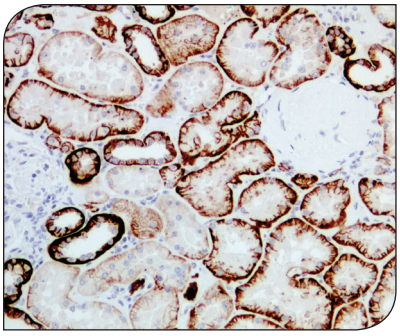
Renal cell carcinoma stained with anti-KIM-1 (HAVcr-1)

KIM-1 (HAVcr-1) (EP309)

KIM-1 (kidney injury molecule 1), also known as HAVcr-1 (Hepatitis A virus cellular receptor 1), is a transmembrane glycoprotein that contributes to immune modulation, allergic response and viral disease susceptibility. KIM-1 has wide tissue distribution, and is localized on the apical membrane. While KIM-1 protein expression is generally undetectable in the normal kidney, high levels were observed in the proximal tubules in the post-ischaemic kidney, suggesting its utility as a dedifferentiation marker for early indication of epithelial response to injury. A considerable number of studies demonstrated KIM-1 mRNA and protein regulation following acute nephrotoxicity. Consequently, this biomarker was qualified by the FDA as an acceptable biomarker in detecting acute drug-induced nephrotoxicity in rats during preclinical drug development.

KIM-1 has also been extensively evaluated in renal cell carcinoma (RCC) tissues. Overexpression of KIM-1 was observed in over 90% of clear cell RCC and 82% of primary RCC. Compared to normal kidney, expression is reduced in benign oncocytomas. Additionally, KIM-1 was also detected in lymph nodes to which tumors have metastasized. These observations are consistent with the interpretation that clear cell and papillary RCC are derived from proximal tubular cells while oncocytomas are of the distal nephron. Recently, KIM-1was also found overexpressed in ovarian clear cell carcinoma and colorectal cancer.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0280RUOA 1 ml . . . . . #AC-0280RUO	kidney, renal clear cell carcinoma	cytoplasmic



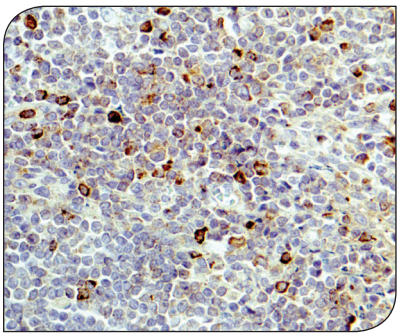
Kidney stained with anti-Cadherin-16

Ksp-cadherin (EP296)

Kidney-specific cadherin, also known as Cadherin-16, is a member of the calcium dependent family of adhesion molecules that play important roles during embryonic development, maintenance of tissue architecture and growth control during tumorigenesis. In the kidney, Ksp-cadherin expression is uniquely localized predominantly in the distal portion of the nephron.

There are four major subtypes of renal neoplasms; clear cell and papillary renal cell carcinoma are thought to be of proximal tubular origin, while oncocytoma and chromophobe renal cell carcinoma (RCC) are derived from cells of the distal nephron. Studies have shown high sensitivity and specificity of Ksp-cadherin to chromophobe RCC (86-100%) and oncocytoma (76-95%). Conversely, low reactivity was observed with clear cell RCC (14-30%) and papillary RCC (0-13%), supporting the use of Ksp-cadherin as a marker for the distal portion of the nephron, and for its use as an adjunct for the diagnosis of chromophobe RCC and oncocytoma.

Product Availability:	Control:	Visualization:
0.1 ml..... #AC-0277A 1 ml .....#AC-0277	kidney, chromophobe renal cell carcinoma	cytoplasmic, membranous



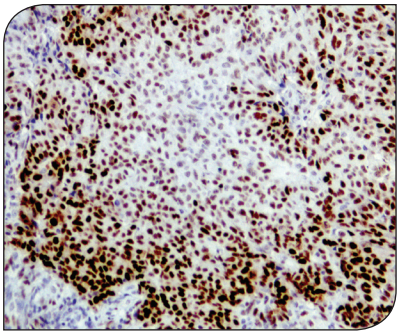
Tonsil stained with anti-LAG-3 (CD223)

LAG-3 (CD223) (EP294)

Lymphocyte activation gene-3 (LAG-3), also known as CD223, is a protein expressed by activated CD4+ and CD8+ T-cells. This protein binds to major histocompatibility complex (MHC) class II molecules with significantly higher affinity than CD4, and is associated with the T-cell receptor complex at the cell surface. It is hypothesized that LAG-3 might act as an important negative competitor of CD4, to modulate T cell proliferation, function and homeostasis.

Both MHC class II and LAG-3 are strongly upregulated in inflammatory responses. In tumor tissues, LAG-3 has been detected in tumor infiltrating lymphocytes. Immunohistochemical analysis revealed LAG-3 expression was distributed on lymphocytes scattered in renal cell carcinoma, melanoma and lymphomas. They were also detected in the tumor stroma as well as in the peritumoral tissue. In melanoma, expression of MHC II has been associated with poor prognosis. Recently, a study demonstrated that LAG-3 can prevent MHC II-positive melanoma cells from undergoing Fas-mediated apoptosis and also activate MAPK/Erk and PI3K/Akt survival pathways, conferring melanoma resistance to apoptosis and progression. Proper molecular regulation of T-cell activation is critical for control of T-cell homeostasis.

Product Availability:	Control:	Visualization:
0.1 ml..... #AC-0294A 1 ml .....#AC-0294	tonsil	membranous, cytoplasmic



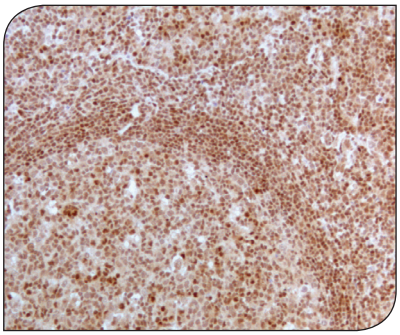
Endometrial carcinoma stained with anti-LEF-1

LEF-1 (EP310)

Lymphoid enhancer-binding factor 1 (LEF-1) is a crucial transcription factor that functions as a key nuclear mediator of WNT/β-catenin signaling, responsible for regulating cell proliferation and survival. LEF-1 has an important role in lymphopoiesis, and is typically expressed in T-cells and B cell precursors. Differentiation into mature B and plasma cells downregulates LEF-1 expression. In normal lymphoid tissues, LEF-1 is nuclear localized and observed predominantly in T cells of the paracortical regions; staining was undetected in B cells.

LEF-1 expression has been reported in a variety of cases of leukemia and lymphoma. Gene expression profiling revealed overexpression of LEF-1 in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). In one study, LEF-1 immunostaining was detected in all neoplastic cells of 92 CLL/SLL cases. LEF-1 was identified in 50% of high grade follicular lymphoma and 38% of diffuse large B-cell lymphoma, but not in mantle cell lymphoma or marginal zone lymphoma. Recently, high LEF-1 was demonstrated as a favorable prognostic marker in cytogenetically normal acute myeloid leukemia. Due to its high sensitivity, LEF-1 has been proposed to be a suitable immunohistochemical marker for diagnosis and differential diagnosis for CLL/SLL. Recent studies have expanded upon the role of LEF-1. Alternately spliced isoforms may play additional roles in regulating cell growth in colon carcinoma, and nuclear LEF-1 immunostaining was detected in 36% of adenocarcinoma brain metastases.

Product Availability:	Control:	Visualization:
0.1 ml. . . . . #AC-0281A 1 ml . . . . . #AC-0281	tonsil, lymphocytic lymphoma	nuclear



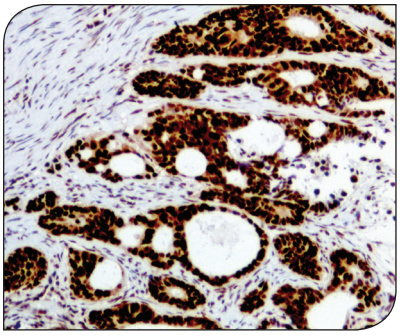
Tonsil stained with anti-MGMT

MGMT (EP337)

The DNA lesion repair enzyme, O6-methylguanine-DNA methyltransferase (MGMT) is essential for reverting mispaired lesions to maintain genomic stability. While MGMT expression is present in all normal tissues, its expression is heterogeneous in tumors. MGMT promoter hypermethylation and reduced MGMT protein appear to be early events in tumorigenesis and are associated with poor tumor differentiation. Epigenetic silencing may lead to transition mutations in p53, K-ras, and PIK3CA.

The independent prognostic value of MGMT varies in different tumors. Reduced or loss of MGMT expression was correlated with poor outcomes in breast ductal adenocarcinoma, gastric cancers, hepatocellular carcinoma, and lung carcinoma. Approximately 31% of endometrial and 25-37% of lung carcinomas demonstrated loss of MGMT expression. Conversely, MGMT deficiency predicted favorable treatment and survival in glioblastoma and melanoma, while positive MGMT expression associated with poor survival in basal-like breast cancer patients.

Product Availability:	Control:	Visualization:
0.1 ml. . . . #AC-0307RUOA 1 ml . . . . . #AC-0307RUO	tonsil	nuclear, cytoplasmic



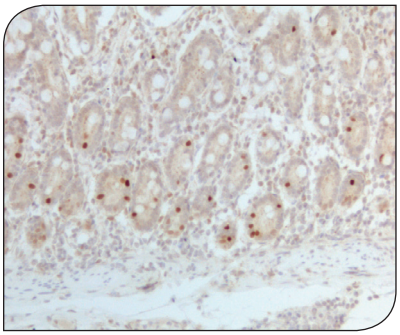
Colon stained with anti-MRE11

MRE11 (EP318)

Double-strand break repair protein MRE11 is a multifunctional protein that forms a MRE11-NBS1-RAD50 (M-N-R) complex in response to DNA damage. MRE11 is required for the correct assembly of the M-N-R complex, which plays a crucial role in activating cell cycle checkpoints and localizes at sites which DNA is undergoing repair. Mutations in MRE11 is linked with the Ataxisa-Telangiectasia-like disorder (AT-LD), and recently implicated to predispose to cancer via inactivation of the M-N-R complex.

While nuclear MRE11 staining is nearly ubiquitous in normal tissues, MRE11 mutations have been frequently identified in microsatellite instability (MSI) tumors, characteristic of mutations in the defective mismatch repair (MMR) system. MMR-defective cells progressively accumulate replication errors which may cause inactivation of potential tumor suppressor gene, leading to cancer progression. Several immunohistochemistry studies have reported the loss of MRE11 expression ranging from 50-83% in MSI and MMR-deficient colorectal, gastric, bladder, and endometrial cancers. Reduced or loss of MRE11 protein expression is an independent factor associated with worse cancer survival.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0295RUOA 1 ml . . . . . #AC-0295RUO	colon	nuclear



Small intestine stained with anti-NKX2.2

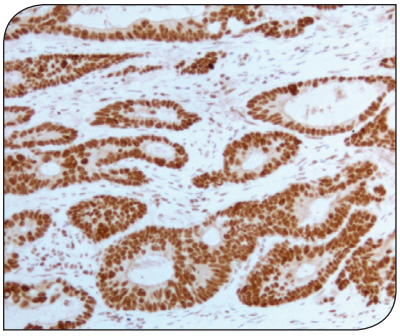
NKX2.2 (EP336)

NKX2.2, a homeodomain-containing transcription factor containing DNA-binding, transcriptional activation and repression domains, is a member of the NK2 family of homeobox genes. NKX2.2 is expressed in the developing forebrain and spinal cord. Functionally, the transcription factor is thought to be involved with neuronal developing, patterning, and fate specification of neurons and oligodendrocytes.

NKX2.2 was recently reported as a valuable marker for Ewing's sarcoma. The vast majority of Ewing's sarcomas (85%) harbor a chromosomal translocation, most commonly t(11;22)(q24;q12) encoding an aberrant EWS-FLI transcription factor. NKX2.2 expression is tightly correlated with EWS-FLI expression, a critical downstream target that is required for the cancerous behavior of Ewing's sarcoma.

While CD99 is the classical marker for Ewing's sarcoma diagnosis, it is relatively nonspecific. In addition to Ewing's sarcoma, CD99 is also expressed on lymphocytes, hematopoietic cells, endothelial cells and a variety of tumors. In contrast, NKX2.2 labels 93% of Ewing's sarcoma and only a small subset (14/130) of non-Ewing tumors, demonstrating a sensitivity of 93% and specificity of 89%. Staining with NKX2.2 can aid in the differential diagnosis of small round cell tumors.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0308A 1 ml . . . . . #AC-0308	Ewing's sarcoma	nuclear



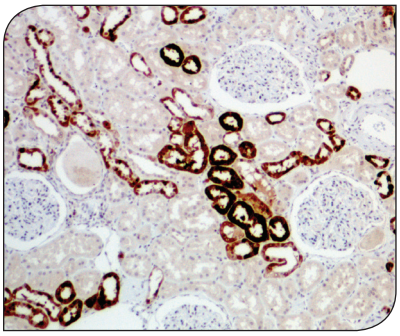
Colon carcinoma stained with anti-p84

p84 (THOC1) (EP320)

p84, a nuclear matrix protein, also known as THO complex subunit 1 (THOC1) is involved in regulation of gene transcription.

p84 is ubiquitously expressed in normal and tumor cells with increased expression level in tumor cells. Overexpression of p84 triggers p53-independent apoptosis and is associated with tumor progression in a variety of cancers including carcinomas of the breast, prostate, colon and non-small cell lung cancer (NSCLC).

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0309RUOA 1 ml . . . . . #AC-0309RUO	colon, colon carcinoma	nuclear



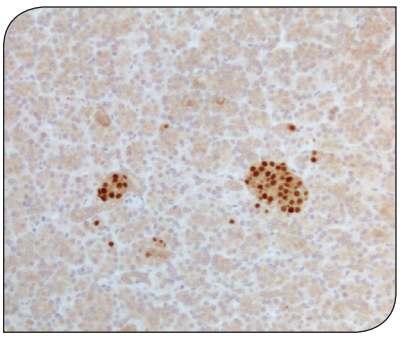
Kidney stained with anti-parvalbumin

Parvalbumin (EP300)

Parvalbumin is a 12 kDa calcium-binding protein that modulates intracellular calcium dynamics. Capable of binding two calcium ions, parvalbumin functions as a relaxing factor that shuttles calcium ions from other calcium-binding proteins to buffer intracellular calcium. First detected in glycolytic skeletal muscle fibers, it is also expressed in the axons and terminals of cerebellar interneurons of the cerebellum, horizontal and ganglion cells of the retina, and distal convoluted tubules and connecting tubules in the kidney.

In cancer, parvalbumin has been suggested as a useful marker for distinguishing primary and metastatic chromophobe renal cell carcinoma and renal oncocytoma from papillary renal cell and clear cell carcinomas. It stains 80-100% of chromophobe carcinomas and 69-82% of oncocytomas, compared to 0-8% clear cell and 0-31% papillary renal cell carcinomas. Sensitivity and specificity was determined as 80% and 89%, respectively. Although parvalbumin was evaluated in retinoblastoma, it was deemed to be a poor marker of tumor cells, labeling 0 of 52 cases.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0282A 1 ml . . . . . #AC-0282	kidney, chromophobe carcinoma	nuclear, cytoplasmic



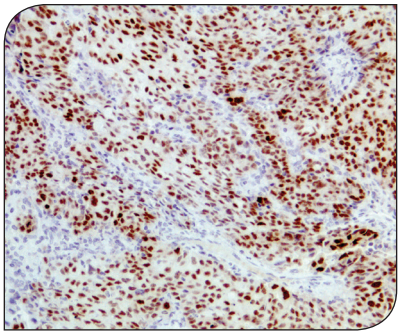
Pancreas stained with anti-PAX6

PAX6 (EP341)

PAX6 is a member of the paired box family of transcription factors expressed in the developing sensory organs (including eye, nasal and olfactory tissues), central nervous and endocrine system. The expression of PAX6 is sustained in the neuroendocrine system of adults.

PAX6 labels neuroendocrine cells and derived tumor cells. A recent study showed that PAX6 is positive in the majority of neuroendocrine tumors originated from pancreas, duodenum, and colon. PAX6 might be helpful in identification of neuroendocrine tumors.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0310A 1 ml . . . . . #AC-0310	pancreas, neuroendocrine tumor	nuclear



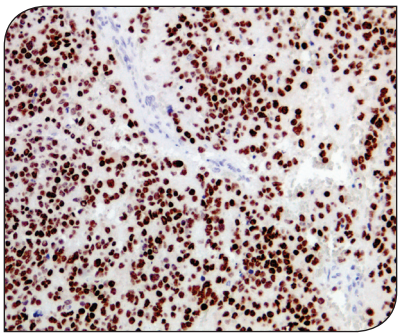
Endometrial carcinoma stained with anti-PAX8

PAX8 (EP298)

Paired box protein Pax-8 (PAX8) is a member of the PAX family of transcription factors. It is essential for organogenesis during embryonic development of the kidney, thyroid and paramesonephric ducts, giving rise to the urogenital organs including the seminal vesicles, vas deferens, ureter, uterus, and fallopian tubes. Although PAX8 is crucial for organogenesis, sustained expression in the normal kidney, thyroid, breast, seminal vesicles, ovarian, cervical, and endometrial epithelia suggests a role for homeostatic control of mature tissues. Immunohistochemical staining revealed almost exclusive nuclear localization, with low or negligible cytoplasmic expression.

Due to the restrictive expression in normal tissues, PAX8 has been suggested to be a sensitive and specific marker for both primary and metastatic tumors derived from the above mentioned organs and tissues. PAX8 is expressed in renal cell carcinoma of clear cell, papillary and chromophobe subtypes. It is also found in endometrioid carcinoma, serous carcinoma, and thyroid carcinomas. However, PAX8 expression in lymphoid tissue has been controversial. The N-terminal polyclonal PAX8 antibody was found to cross-react with PAX5; previous data suggesting the use of PAX8 for diagnosis of malignant lymphomas should be re-evaluated. The cause may be due to a substantial sequence homology in the N-terminus of PAX8 and PAX5 (70%). PAX8, Clone EP298, is targeted to the central region of PAX8, no lymphocyte reactivity has been found with this antibody.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0296A 1 ml . . . . . #AC-0296	kidney, renal cell carcinoma	nuclear



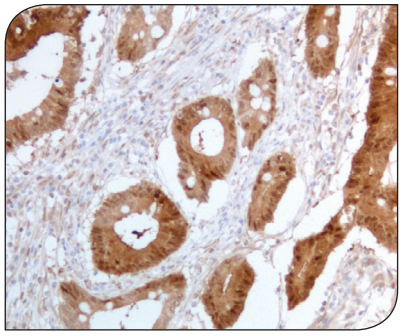
Neuroblastoma stained with anti-PHOX2B

PHOX2B (EP312)

PHOX2B (Paired mesoderm homeobox protein 2B) is an essential transcription factor determinant of neuronal fate from neural crest precursors. Neural crest progenitors are a transient, migratory population of multipotent stem cells that develops into neurons of the sympathetic chain, neuroglia and chromaffin cells of the adrenal medulla during embryonic development. Mutations in PHOX2B have been associated with the development of disease such as congenital central hypoventilation syndrome, Hirschsprung disease and neuroblastoma.

Neuroblastoma is the most common malignant pediatric extra-cranial tumor of the sympathetic nervous system. It is a heterogenous group of tumors histologically ranging from undifferentiated or poorly differentiated neuroblasts to predominantly full differentiated neurons. Compared to normal tissues, PHOX2B was found overexpressed in neuroblastoma and cell lines. Often in undifferentiated and poorly differentiated neuroblastomas, immunohistochemistry is required to confirm neuroblastic lineage. IHC studies have demonstrated PHOX2B expression in all neuroblastoma, and have suggested that PHOX2B is a potential marker for diagnosing undifferentiated neuroblastoma. Supplemental studies containing a panel of antibodies can differentiate neuroblastoma from other small-blue-round cell tumors such as Ewing's sarcoma and Wilms' tumor.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0283A 1 ml . . . . . #AC-0283	neuroblastoma	nuclear



Endometrial carcinoma stained with anti-S100A6

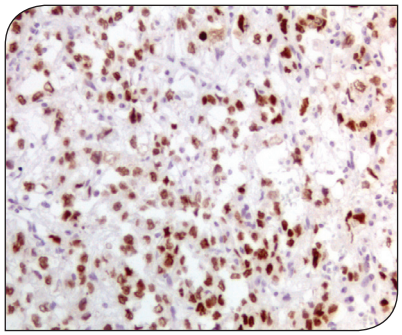
S100A6 (EP313)

S100A6, also known as Calcyclin, is a low molecular weight calcium binding protein encoded near the cluster of S100 family genes on chromosome 1. The S100 family of proteins are structurally related and share Ca2+ binding domains. Monomers of S100A6 can bind 2 Ca2+, but can form homodimers in a Ca2+-independent manner.

S100A6 is a cytoplasmic and nuclear protein, associating with the plasma membrane and the nuclear envelope in the presence of Ca2+. It is abundantly expressed in fibroblasts and epithelial cells. It is also detected in some neurons, glial cells, smooth muscle, myocytes, and lymphocytes.

S100A6 has been studied in many human tumors, including pancreatic, melanocytic, gastric, and colorectal cancers. In pancreatic cancer, elevation of S100A6 RNA and protein was observed in malignant cells. Nuclear S100A6 expression is associated with reduced survival time in pancreatic cancer patients. S100A6 expression was also significantly correlated with melanoma metastases and survival times. It was upregulated in 50% of gastric cancers, and highly expressed at the invasive margins of colorectal carcinoma.

Product Availability:	Control:	Visualization:
0.1 ml. . . . #AC-0297RUOA 1 ml . . . . . #AC-0297RUO	colon, colon carcinoma	nuclear, cytoplasmic



Yolk sac tumor stained with anti-SALL4

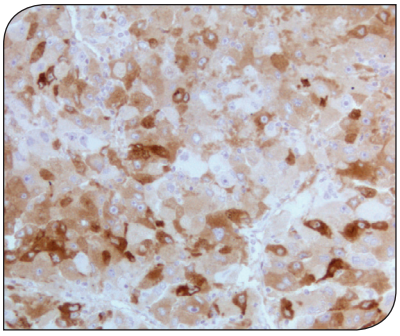
SALL4 (EP299)

The Sal-like protein 4, SALL4 is a zinc finger transcription factor located on chromosome 20q13.13-13.2. It is essential during development by maintaining embryonic stem cell pluripotency and self-renewal. Mutations in SALL4 lead to acro-renal-ocular and Okihiro syndromes, a disorder of the eyes and abnormalities of bones in the arms and hands.

Recently, SALL4 has been identified as a novel sensitive diagnostic marker for germ cell tumors. Strong SALL4 staining was observed in all seminoma/dysgerminoma/germinomas, embryonal carcinomas, and yolk sac tumors, yielding 100% sensitivity for these malignancies. Compared with α-fetoprotein and glypican-3, SALL4 demonstrated superior sensitivity in detecting yolk sac tumors. Focal SALL4 staining was also observed in choriocarcinomas (66-71%) and teratomas (50-64%).

In non-germ cell tumors, SALL4 is expressed in all cases of acute myeloid leukemia, and majority of precursor B-cell acute lymphoblastic lymphomas (79%). In a large immunohistochemical study of >3200 cases, SALL4 was also detected in ~20% of cases of ovarian, urothelial and gastric adenocarcinomas, and <5% in mammary, colorectal, prostatic and squamous cell carcinomas.

Product Availability:	Control:	Visualization:
0.1 ml. . . . . #AC-0298A 1 ml . . . . . #AC-0298	yolk sac tumor	nuclear



Hepatocellular carcinoma stained with anti-SAA

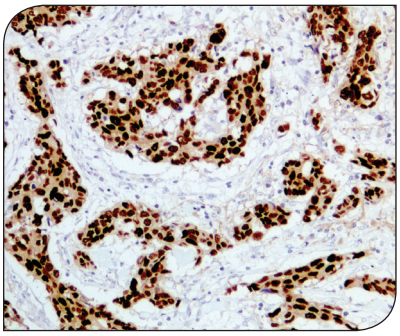
Serum Amyloid A (EP335)

Serum Amyloid A (SAA) is an acute-phase protein primarily synthesized in the liver. While it is typically found at low concentrations in healthy individuals, pro-inflammatory cytokines upregulate SAA production to encourage recruitment of immune cells to inflammatory sites.

Amyloidosis is a disease characterized by the abnormal build-up of amyloid, abnormal non-branching fibrillary β-pleated sheet proteins that are insoluble and highly resistant to proteolytic degradation that result in localized or systemic organ dysfunction. Amyloidoses are grouped as AL (primary), AA (secondary), and hereditary forms. Proper classification is important since treatment and prognoses of the disorders are vastly different. AA amyloidosis is associated with a variety of chronic inflammatory conditions and infections, derived from SAA. Immunohistochemical staining using a panel of antibodies including κ and λ Ig light chains, amyloid A, and transthyretin can aid in recognizing most forms of amyloid.

Recently, SAA has also been investigated as a potential marker for neoplastic activity. SAA concentrations have been reported to be a marker of poor prognosis, elevated in patients with advanced stages of cancer and those with malignant disease.

Product Availability:	Control:	Visualization:
0.1 ml . . . . . #AC-0311A 1 ml . . . . . #AC-0311	kidney, amyloidosis	extracellular, cytoplasmic



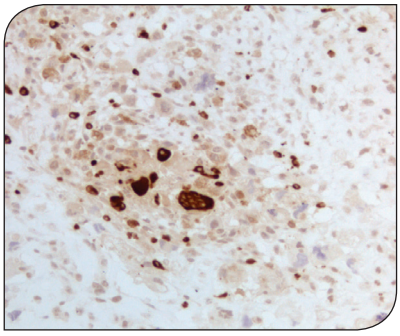
Breast carcinoma stained with anti-SOX9

SOX9 (EP317)

SOX9, known as sex determining region Y (SRY)-related high mobility group (HMG)-box 9, is an important transcription factor required for development. As a transcriptional regulator, SOX9 is an important downstream gene of β-Catenin. It is expressed during embryogenesis, in the cartilage, neural crest, kidney, and pancreas. SOX9 is also involved in the regulation of sex determination and progenitor cell pool maintenance, required for committed differentiation. In normal colorectal mucosa, SOX9 expression is found predominantly to the lower part of crypts, the proliferative compartment and putative site of stem cells, suggesting SOX9 as a putative stem or progenitor cell biomarker.

Recent studies have indicated the overexpression of SOX9 in solid tumors. Compared to normal tissues, immunohistochemical analysis revealed staining that is more intense and widespread staining in many cancer types, including but not limited to, gastric carcinoma, non-small cell lung cancer (NSCLC), lung adenocarcinoma, prostate cancer, breast carcinoma, pancreatic ductal adenocarcinoma, glioma, colorectal cancer, hepatocellular carcinoma (HCC) and ovarian cancer. Amplification of 17q24.3, the chromosomal region of SOX9 has been found in prostate, neuroblastoma, medulloblastoma, breast and ovarian cancer, which all exhibit high SOX9 expression. Although staining is predominantly nuclear, cytoplasmic SOX9 may serve as a valuable prognostic marker for invasive ductal carcinomas and metastatic breast cancer. Further, SOX9 upregulation has been associated with higher tumor stage and grade, and overexpression have been recognized as an independent prognostic marker for decreased survival in NSCLC and HCC patients.

Product Availability:	Control:	Visualization:
0.1 ml . . . . #AC-0284RUOA 1 ml . . . . . #AC-0284RUO	colon, colon carcinoma	nuclear



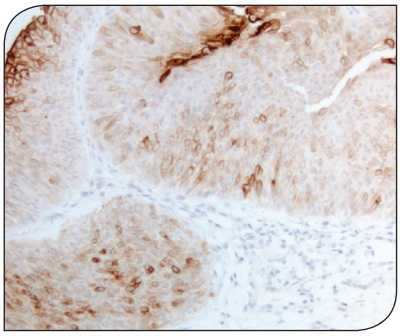
Osteosarcoma stained with anti-TRAcP

TRAcP (EP338)

Tartrate-resistant acid phosphatase (TRAcP), also known as type-5 acid phosphatase and purple acid phosphatase, is a metallophosphoesterase participating in osteoclast-mediated bone turnover.

The TRAcP enzyme is highly expressed by bone-resorbing cells, osteoclasts, and a subpopulations of monocytes/macrophages and dendritic cells. TRAcP has been an important diagnostic marker for hairy cell leukemia (HCL).

Product Availability:	Control:	Visualization:
0.1 ml. . . . . # AC-0312A 1 ml . . . . . #AC-0312	Hairy cell leukemia	cytoplasmic



Bladder carcinoma stained with anti-Uroplakin III

Uroplakin III (EP321)

Uroplakin III (UP III) is one of the four transmembrane proteins (UPIa, UPIb, UPII, and UPIII) that are specifically expressed in terminally differentiated urothelial cells.

Studies have shown that UPIII is highly specific for identification of primary and metastatic urothelial carcinomas. However, the sensitivity of UPIII in detection of urothelial carcinoma is moderate. Combined use of a panel of antibodies is important in the diagnosis of urothelial tumors.

Product Availability:	Control:	Visualization:
0.1 ml. . . . . #AC-0313A 1 ml . . . . . #AC-0313	bladder, urothelial carcinoma	membrane, cytoplasm

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