

International Symposium on Immunohistochemistry

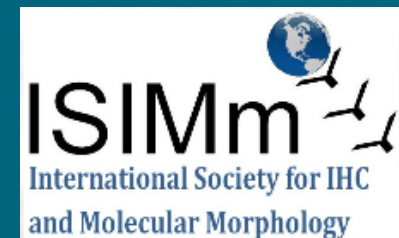
January 4th - 7th, 2018

Hosted by Dept. of Histopathology, Tata Medical Center, Kolkata, India

In collaboration with NordiQC, Alborg, Denmark and ISIMM, California, USA

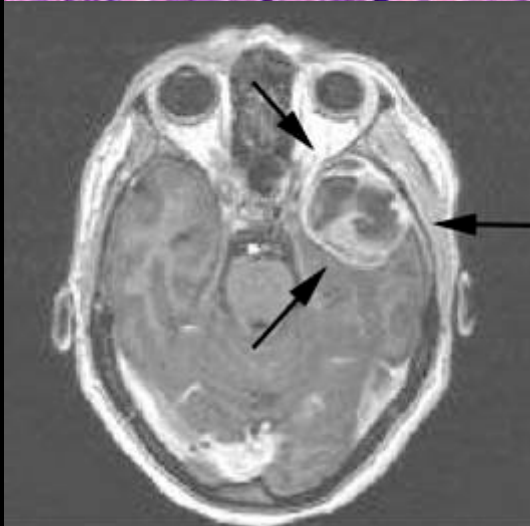
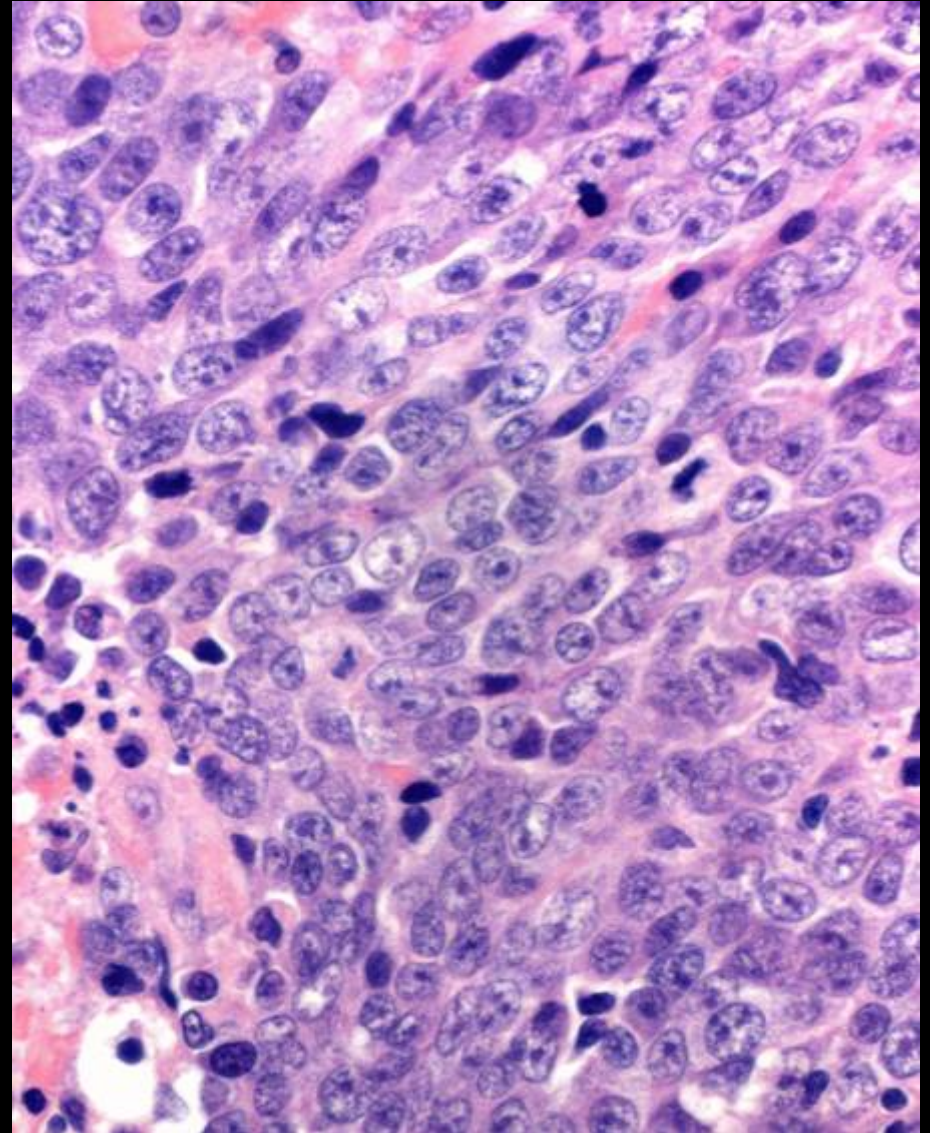
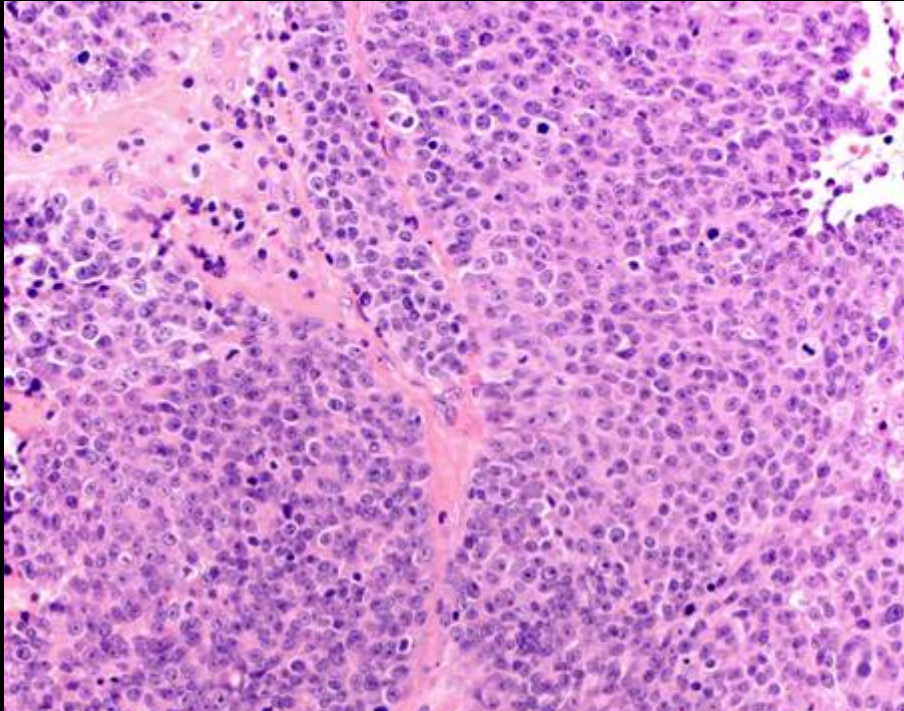


IHC Classification of undifferentiated tumors – the primary panel



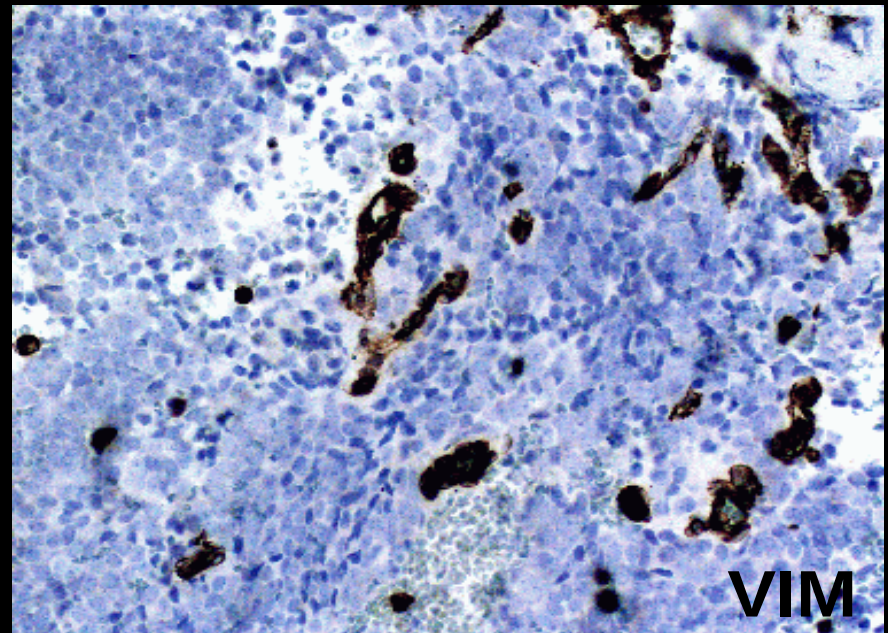
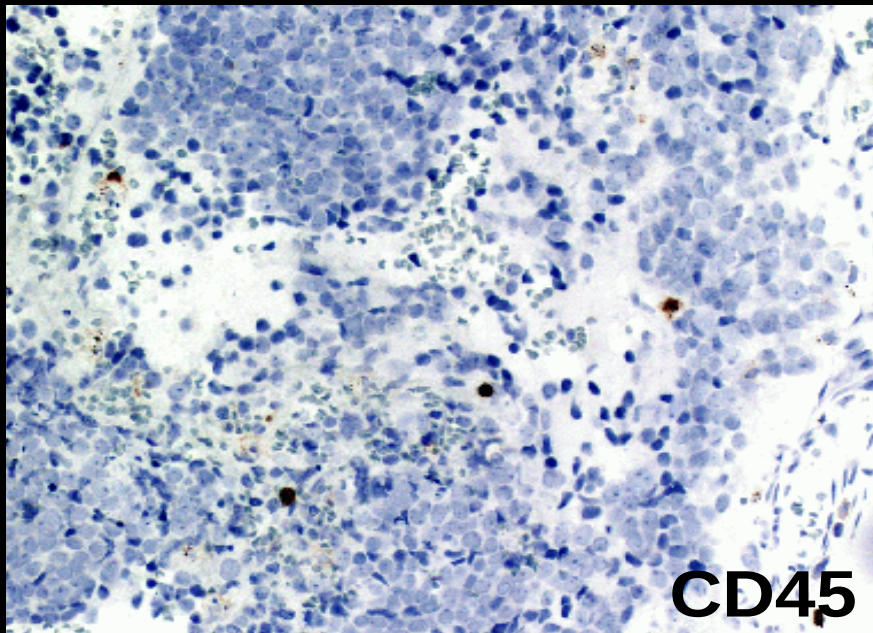
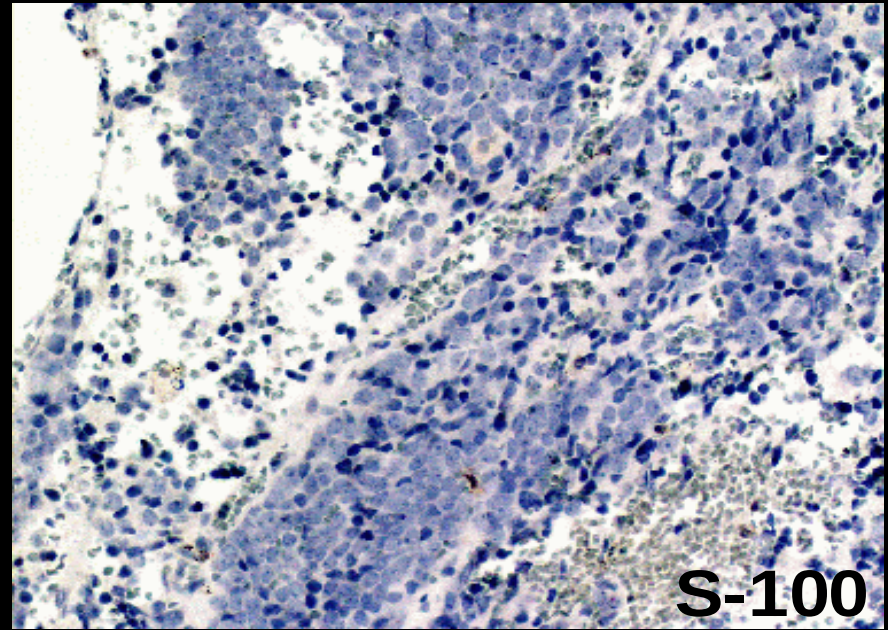
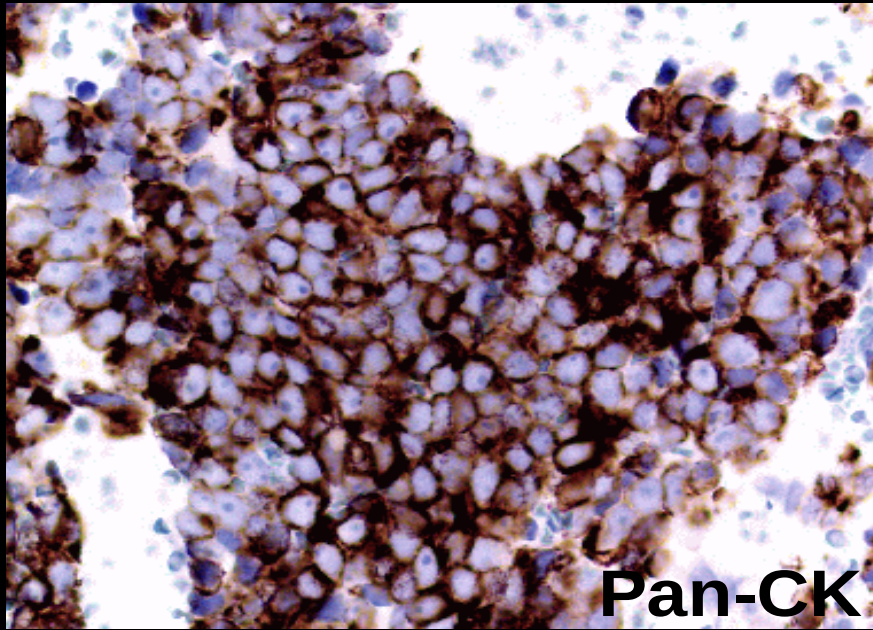
Mogens Vyberg
Professor of Clinical Pathology
Director of NordiQC
Aalborg University Hospital,
Aalborg, Denmark

Tumours of unknown origin: Histology



Brain tumour - biopsy

Tumours of unknown origin: Immunohistochemistry



■ IHC classification of the Unknown Primary Tumour

UPT: A tumour appearing in metastatic setting without a histologically proven primary tumour.

UPT pose an increasing challenge for the pathologist - due to the progress in surgical and oncological treatment possibilities.

■ IHC classification of the Unknown Primary Tumour

New, relatively specific antibodies give the pathologist more and better diagnostic tools.

But the diagnostic work also become more complex in terms of planning, optimization of protocols, interpretation of reaction patterns and error trapping.

■ IHC classification of the Unknown Primary Tumour

10 - 15% of cancers remained UPTs

+ ??% uncertain if primary or metastatic

- liver, lung, bone, lymph nodes, brain, peritoneum . . .

‘Undifferentiated’ neoplasms (5-10%)

- carcinomas, sarcomas, melanomas, germ cell tumours
- malignant lymphomas

● Adenocarcinomas (80-90%)

- lung, breast, prostate, colorectum, ovary, pancreas ...

● Squamous cell carcinomas (5-10%)

- lung, esophagus, uterine cervix ...

■ IHC classification of the Unknown Primary Tumour

Differences in prognosis

Differences in treatment regimes

- malignant lymphomas

- carcinomas (breast, prostate, ovary . . .)

- sarcomas (GIST, synovial sarcoma . . .)

- germ cell tumours

Pathology tests cost effective

Pathology tests save patient discomfort

The patient's 'right to know'

The risk of hereditary cancer

■ IHC classification of the Unknown Primary Tumour

- Most likely diagnoses
- Relevant differential diagnoses



- Optimal selection of antibodies for a **diagnostic algorithm**
 - Primary and secondary antibody panels
 - Turn-around-time
 - Laboratory expenses

■ IHC classification of the Unknown Primary Tumour

Pathologist

- knowledge, acceptance, skill

Tumour material

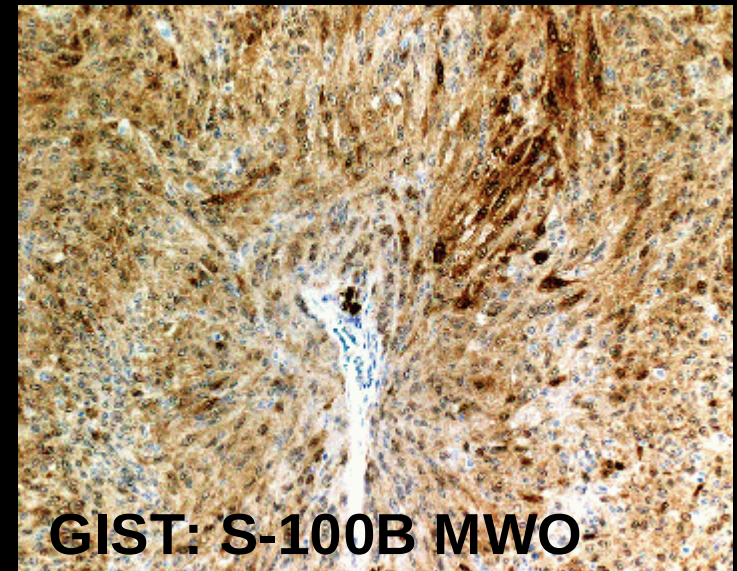
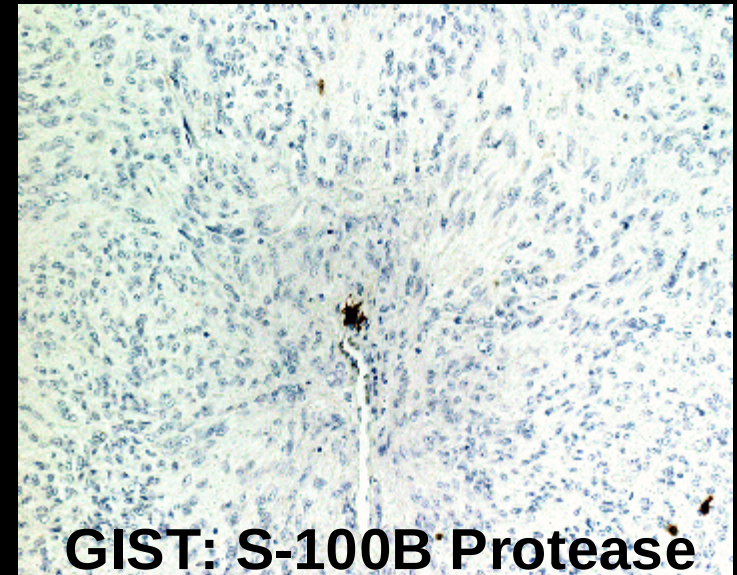
- diagnostic markers

Antibodies available

- applic. in diagnostic algorithms

Methods

- protocol:
 - sensitivity, specificity, reliability
- interpretation:
 - cut-off level for positivity
 - clinical relevance



■ IHC classification of the Unknown Primary Tumour

Pathologist

- knowledge, acceptance, skill

Tumour material

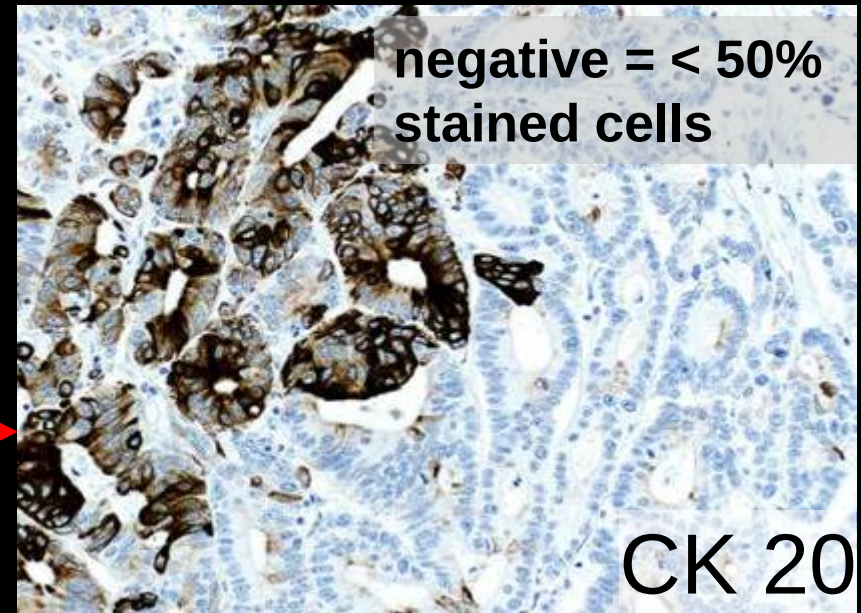
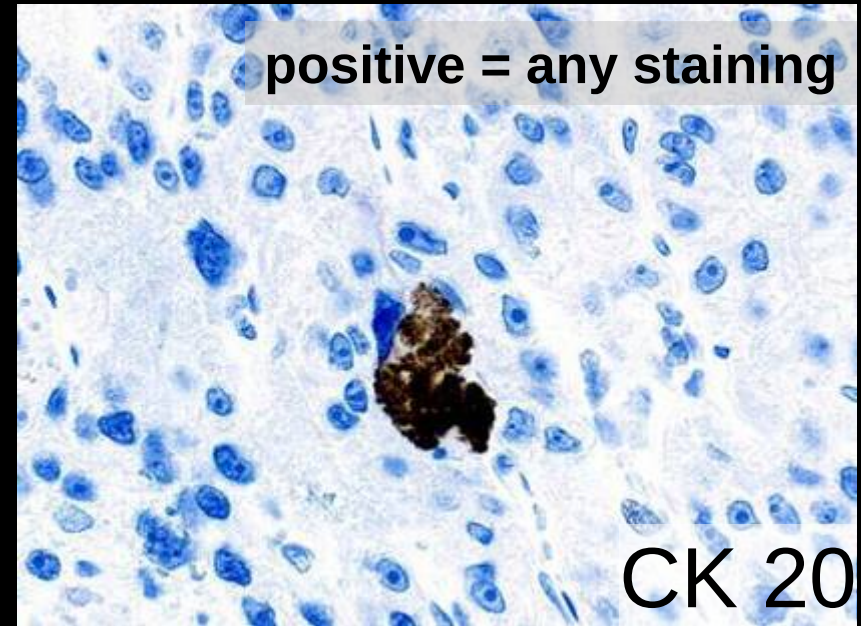
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- applic. in diagnostic algorithms

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- protocol:
 - sensitivity, specificity, reliability
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 - cut-off level for positivity →
 - clinical relevance



MPP
19

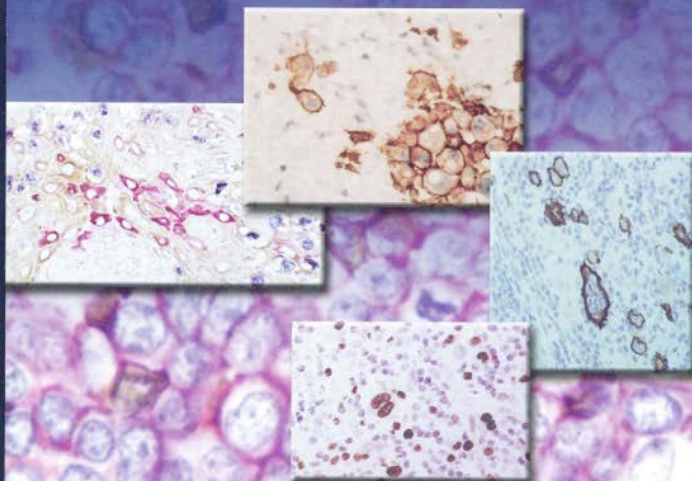
Clive R. Taylor
Richard J. Cote

Immunomicroscopy

*A Diagnostic Tool
for the Surgical
Pathologist*

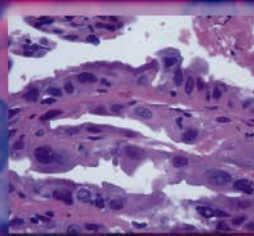
MAJOR PROBLEMS IN PATHOLOGY

THIRD EDITION

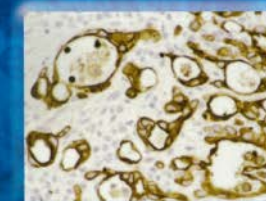
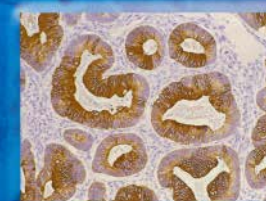


SAUNDERS
ELSEVIER

Diagnostic Immunohistochemistry



DAVID DABBS



SECOND EDITION

HURCHILL
BRINGSTONE
ELSEVIER

Emilia

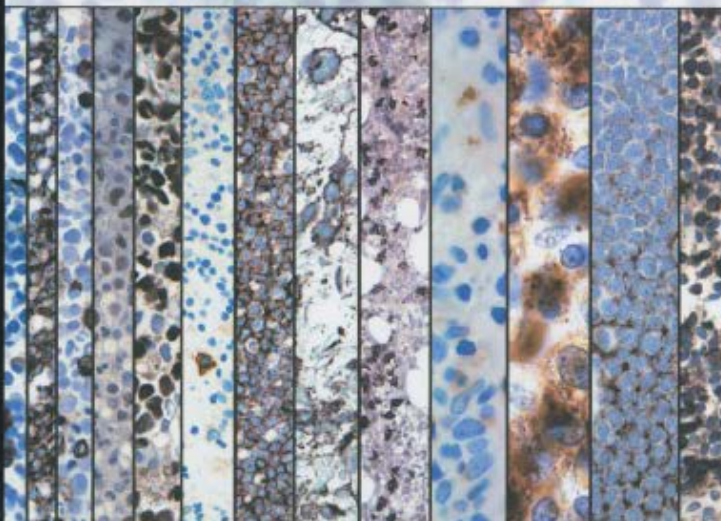
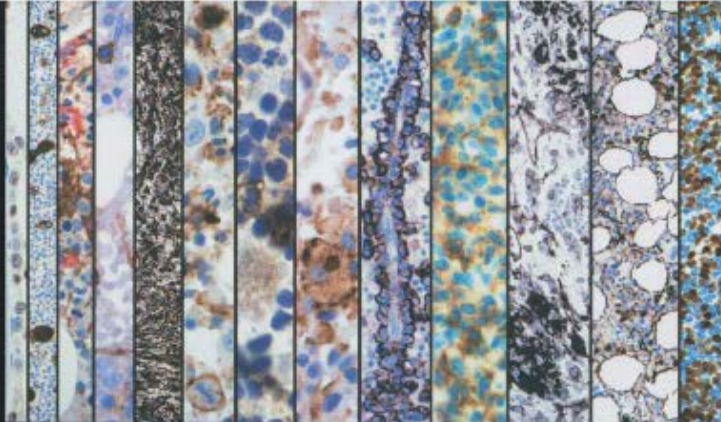
Torlakovic

Kikkeri N

Naresh

Richard D

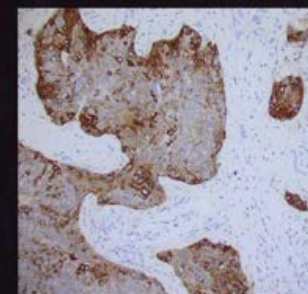
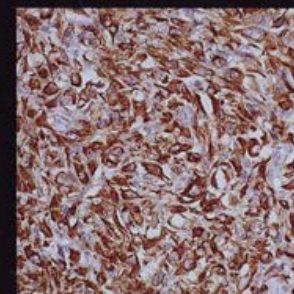
Brunning



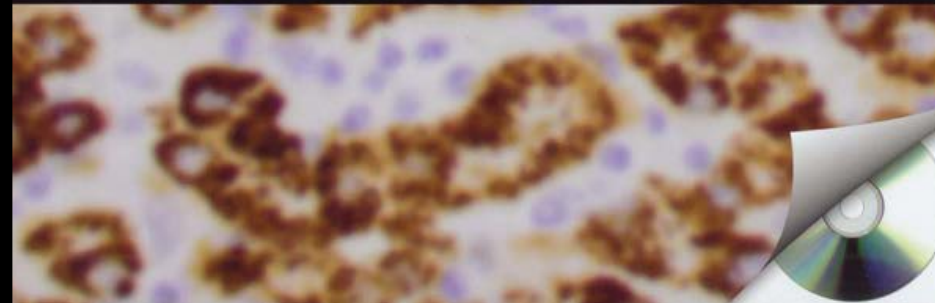
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Medicine

Illustrated Surgical Pathology
SERIES EDITOR: LAWRENCE WEISS

MODERN IMMUNOHISTOCHEMISTRY



Peiguo Chu • Lawrence Weiss



Planning diagnostic immunohistochemistry

An immunohistochemical vade mecum

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version date October 2012

Planning diagnostic immunohistochemistry

Vade mecum

Tilbage

Fremad

Udskriv

Indstillinger

Indhold

Indeks

Søg

Foretrukne

Indtast søgeord:

CD45

Vis emner

Vis

Vælg emne:

Fundet: 31

Titel	Placering	Niveau
CD 45	Vade me...	1
Diffuse large B cell ly...	Vade me...	2
Anaplastic large cell ...	Vade me...	3
mediastinal large B-c...	Vade me...	4
gastrointestinal glom...	Vade me...	5
Plasmacytoma / plas...	Vade me...	6
Subcutaneous pann...	Vade me...	7
Primary effusion lymph...	Vade me...	8
Intravascular large B...	Vade me...	9
CHL differential	Vade me...	10
T-cell rich B-cell lym...	Vade me...	11
pleural thymic epithel...	Vade me...	12
Diffuse large B-cell ly...	Vade me...	13
Merkel cell carcinoma	Vade me...	14
Follicular dendritic c...	Vade me...	15
Systemic mastocytosis	Vade me...	16
Gastrointestinal stro...	Vade me...	17
Glomus tumour	Vade me...	18
T and B cell markers	Vade me...	19
Small round cell tum...	Vade me...	20
Histiocytic sarcoma	Vade me...	21
CD 38	Vade me...	22
Pyothorax-associate...	Vade me...	23
Nodular lymphocyte ...	Vade me...	24
Classical Hodgkin's ...	Vade me...	25
Precursors B lymphob...	Vade me...	26
CD 45RA	Vade me...	27
Langerhans cell sarc...	Vade me...	28
CD 10	Vade me...	29
Langerhans cell histi...	Vade me...	30
Interdigitating dendrit...	Vade me...	31

☐ Søg i tidligere resultater
☒ Medtag lignende ord
☐ Søg kun i overskrifter

☐ Søg kun i overskrifter

Histopathology

Small to medium-sized blast cells with scanty cytoplasm. Nucleoli are inconspicuous.

- Bone marrow: the blasts are relatively uniform with round/oval indented, sometimes convoluted, nuclei. Nucleoli are variable but usually inconspicuous. Mitotic figures are less common than in T-ALL>
- Lymph nodes in B-LBL; there is usually diffuse involvement but sometimes paracortical infiltration. Cytology as for the bone marrow. Mitoses usually frequent. There may focally be "starry sky" pattern.

Immunohistochemistry 80%-90% of cases show an immature B cell immunophenotype:

TdT	+	nuclear positivity is unique to LBL
CD10	most cases, except for t(4;11) (q21;q23) ALL which is usually negative	
CD13	may be positive	
CD19 †	almost always	
CD20	variable	
CD22	variable	cytoplasmic staining is considered lineage-specific
CD24	most cases, except for t(4;11) (q21;q23) ALL which is frequently negative	
CD33	may be positive	
CD45	variable	
CD79a	almost always	
HLA-DR	+	
Surface Ig	rarely positive	
Surface Ig	rarely positive	

Planning diagnostic immunohistochemistry



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CD Markers

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Bold and underlined topics are hypertext links

Navigational links to CD markers

	1	2	3	4	5	6	7	8	9
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[CD 100-247](#)

Primary references

[top](#)

[American Journal of Surgical Pathology](#) (AJSP), Jan 2001-Feb 2003

[Archives of Pathology and Lab Medicine](#) (Archives), Jan 2002-Feb 2003

[Human Pathology](#) (Hum Path), Jan 2002-Dec 2002



CD45

[top](#)

Also called leukocyte common antigen (LCA),

An essential regulator of T and B cell antigen re

The target of immunosuppressive antibody treat

Major component of glycocalyx

Negative regulator of IgE class switch recombination ([J Biol Chem 2002;277:28830](#))

Mutations with loss of CD45 cause severe combined immunodeficiency - autosomal recessive, T cell negative, B cell positive, NK cell positive ([OMIM 608971](#)); patients have a defect in function or B and T cell development, lymphopenia, and deficiency in humoral and cell-mediated immunity.

77C to G mutation may increase intensity of T cell receptor signaling ([J Immunol 2006;176:931](#)), and cause some cases of systemic sclerosis ([Genes Immun 2003;4:168](#)), multiple sclerosis (controversial, [Nat Genet 2000;26:495](#)) and autoimmune hepatitis ([Genes Immun 2003;4:79](#))

Loss of CD45 activity in lymphocytes of elderly may cause T cell dysfunction in elderly ([Mech Ageing Dev 2003;124:191](#))

Necrotic lymphomas are still CD45+, but necrotic carcinomas may also be CD45+ ([AJCP 1998;110:641](#))

Different subsets of hematopoietic cells express different CD45 isoforms due to variable exon splicing, which can change in response to cytokines:

CD45RA - naive/resting T cells, medullary thymocytes

CD45RO - memory/activated T cells, cortical thymocytes

Uses: confirm presence of inflammatory cells, including intestinal intraepithelial lymphocytes ([Archives 2002;126:897](#)); confirm hematopoietic nature of tumors; classify lymphomas and leukemias ([AJCP 1998;110:797](#))

Micro images: *normal* - [liver with CD45+ Kupffer cells and lymphocytes](#); [small intestine with CD45+ intraepithelial lymphocytes](#); [splenic lymphocytes](#); [thymus](#); [tonsil](#)

lymphoma - [B cell lymphoma-unusual CD45 negative case \(figure 6\)](#); [CLL: #2 - urine cytology: Hodakin's-Reed-Sternbera cells are CD45 neg \(figure 3C\)](#)

intravascular (figure 4); primary bone lymphoma (figure 1b)

other - [lymphoepithelioma-like carcinoma #1 of stomach \(CD45+ lymphocytes\)](#); [#2 of esophagus](#)

Flow cytometry images: [transient myeloproliferative disorder with erythroid differentiation](#)

Virtual slides: [diffuse large B cell lymphoma](#)

Positive staining (normal): hematopoietic cells (including monocytes, macrophages / histiocytes, platelets and megakaryocytes; dendritic cells, fibrocytes ([J Immunol 1998;160:419](#)), thymus (me

Positive staining (disease): AML ([AJCP 1998;109:211](#)), anaplastic large cell lymphoma ([AJCP](#)

(+) lineage-negative malignancies ([AJSP 2005;29:1274](#)), dendrocytoma ([AJSP 1990;14:867](#)), giant

[1993;17:1011](#)), histiocytic sarcoma ([AJSP 1998;22:1386](#)), inflammatory pseudotumors (some, [A](#)

lymphocyte predominant Hodgkin's lymphoma ([AJSP 1994;18:526](#)), osteoclasts in osteoclast gi

(variable, [Blood Cells Mol Dis 2004;32:293](#)), post-transplant lymphoproliferative disorders ([AJCP 20](#)

effusion lymphoma ([AJCP 1996;105:221](#), [AJSP 2004;28:1401](#)), reticulohistiocytoma (variable, [AJS](#)

Candida albicans yeast forms ([AJCP 2000;113:59](#)); rarely carcinomas (undifferentiated / neuroen

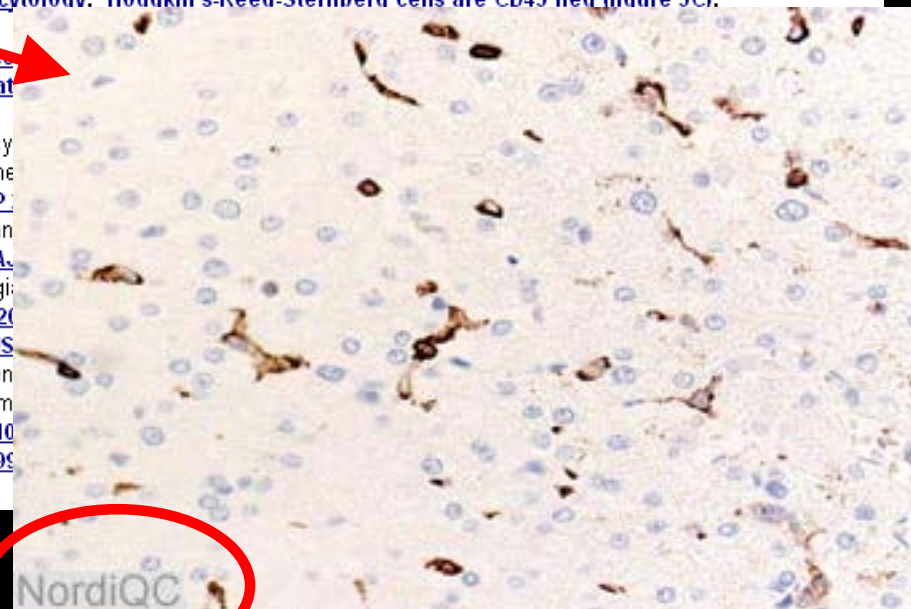
Negative staining (although infiltrating leukocytes are CD45+): red blood cells and their im

carcinomas may be CD45+, [AJCP 1998;110:641](#)), follicular dendritic cell sarcoma ([AJCP 1995;10](#)

9%, [AJCP 2004;121:482](#)), Reed-Sternberg cells in classic Hodgkin's lymphoma ([Am J Pathol 199](#)

References: [OMIM 151460](#)

CD Markers CD1 to CD49





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Build Dx Panel

Build Ab Panel

Analyze Results

Enter a search phrase to select a Diagnosis Group (and repeat for a 2 or 3 Dx Group search), set Sensitivity and Minimum Refs, then click Build Panel button.

| [View All](#)

- + **Adenoca CK07 positive CK20 Negative**
[Mesothelioma, NOS](#)
- + **Mesothelioma, All**
[Mesothelioma, Biphasic; Proliferation, Mesothelial, NOS;](#)
[Mesothelioma, Sarcomatoid; Mesothelioma, NOS;](#)
[Mesothelioma, Epithelioid](#)
- + **Mesothelioma, benign proliferations**
[Proliferation, Mesothelial, NOS](#)
- + **Mesothelioma, lymphohistiocytoid**

Selected Dxs:

none selected

Set Sensitivity: [?](#)

☒ 1 ☐ 2 ☐ 3

Set Minimum Refs: [?](#)

☐ All ☒ > 1 ☐ > 5

[▶ Build Panel](#)

Open Cases

Start date

Case Description

[▶ View Panel](#) [▶ Analyze Results](#) [▶ Delete](#)

Diagnosis Group and Antibody Education

Enter a Diagnosis Group or Antibody search phrase and select the desired item.

Learn About a Diagnosis Group:

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Dx Panel for Mesoth

References For CALRETININ:

Close

Articles Sorted by relevance: 31

Year Published: 2008

Author(s): Lyons-Boudreaux V, Mody DR, Zhai J, Coffey D

Article: [Cytologic malignancy versus benignancy: how useful are the "newer" markers in body fluid cytology?](#)

Publication: ARCH PATHOL LAB MED. 132:23-28

Year Published: 2006

Author(s): BARNETSON,R.J. , BURNETT,R.A. , DOWNIE,I. , HARPER,C.M. , ROBERTS,F.

Article: [IMMUNOHSTIOCHEMICAL ANALYSIS OF PERITONEAL MESOTHELIOMA AND PRIMARY AND SECONDARY SEROUS CARCINOMA OF THE PERITONEUM. ANTIBODIES TO ESTROGEN AND PROGESTERONE RECEPTORS ARE USEFUL.](#)

Publication: AM J CLIN PATHOL. 125 :67-76

Year Published: 2006

Author(s): WINSTANLEY,A.M. , LANDON,G. , BERNEY,D. , MINHAS,S. , FISHER,C. , PARKINSON,M.C.

Article: [THE IMMUNOHISTOCHEMICAL PROFILE OF MALIGNANT MESOTHELIOMAS OF THE TUNICA VAGINALIS. A STUDY OF 20 CASES.](#)

Publication: AM J SURG PATHOL. 30 :1-6

Year Published: 2003

Author(s): LUGLI,A. , FORSTER,Y. , HAAS,P. , NOCITO,A. , BUCHER,C. , BISSIG,H. , MIRLACHER,M. , STORZ,M. , MIHATSCH,M.J. , SAUTER,G.

Article: [CALRETININ EXPRESSION IN HUMAN NORMAL AND NEOPLASTIC TISSUES: A TISSUE MICROARRAY ANALYSIS ON 5233 TISSUE SAMPLES.](#)

Publication: HUM PATHOL. 34 :994-1000

Antibody

[G-GCS-H](#)

[EPO](#)

[CK 19](#)

[CK 18](#)

[C-MET](#)

[AMAD-2](#)

[AE1](#)

[PKK1](#)

[CAM 5.2](#)

[35BH11](#)

[H-CALDESMON](#)

[AE1 AE3](#)

[KERATIN-PAN](#)

[CK 05](#)

[CD44H](#)

[MESOTHELIN](#)

[CA 15-3](#)

[PODOPLANIN](#)

[CALRETININ](#)

[CK 05 06](#)

[34BE12](#)

[N-CADHERIN](#)

89%

19

76 - 100

[1](#)

85%

503

82 - 100

[6](#)

85%

1,345

83 - 87

[31](#)

83%

646

80 - 86

[33](#)

82%

82

73 - 90

[1](#)

81%

242

76 - 86

[6](#)



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Build Dx Panel

Build Ab Panel

Analyze Results

Enter a search phrase to select a Diagnosis Group (and repeat for a 2 or 3 Dx Group search), set Sensitivity and Minimum Refs, then click Build Panel button.

[View All](#)

- + Endomet, Clear, Serous**
Adenocarcinoma, Papillary, [Serous](#), Uterine; Carcinoma, Clear Cell or [Serous](#), Endometrial
- + Ovarian serous tumors**
[Serous](#) Carcinoma, Low Grade, Ovarian; Cystadenocarcinoma, [Serous](#), Ovarian, Metastatic; Adenocarcinoma, [Serous](#), Low Grade, Ovary; [Serous](#) Carcinoma, High Grade, Ovarian; Cystadenocarcinoma, [Serous](#), Ovarian, NOS
- + Ovarian tumors, nonmucinous**

Selected Dxs:

- ☒ Mesothelioma, All 
- ☒ Ovarian serous tumors 

Set Sensitivity: 

☒ 1 ☐ 2 ☐ 3

Set Minimum Refs: 

☐ All ☒ > 1 ☐ > 5

[▶ Build Panel](#)

Open Cases

Start date

Case Description

▶ [View Panel](#) ▶ [Analyze Results](#) ▶ [Delete](#)

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ERP

NUCLEAR

H-CALDESMON

MOC-31

BER-EP4

S-100

CYTOPLASMIC/NUCLEAR

TAG-72

LEWIS-Y

E-CADHERIN

MEMBRANE/CYTOPLASMIC

CALRETININ

Nucleus/Cytoplasm

CA 19-9

CYTOPLASMIC

PRP

NUCLEAR

THROMBOMOD

CYTOPLASMIC

PODOPLANIN

MEMBRANE/CYTOPLASMIC

Mesothelioma, All



Positive	Cases	vs2	
0%	71		
97%	70		
8%	404		
10%	1,421		
5%	208		
5%	1,545		
8%	266		
35%	265		
85%	1,345		
1%	152		
0%	22		
65%	1,039		
85%	503		

Ovarian Serous Tumors



Positive	Cases	vs1	
95%	63		
5%	40		
98%	62		
97%	99		
73%	52		
73%	85		
73%	45		
100%	20		
22%	232		
64%	85		
62%	63		
5%	108		
28%	111		



Mesothelioma, All

Positive Cases vs2

Ovarian Serous Tumors

Positive Cases vs1

CK 05 CYTOPLASMIC	92%	48			57%	14	
RCC	21%	193			0%	22	
HBME-1 CYTOPLASMIC/MEMBRANE	79%	687			100%	16	
N-CADHERIN	81%	242			100%	20	
MESOTHELIN CYTOPLASMIC/MEMBRANE	89%	253			99%	70	
CK 20 CYTOPLASMIC	3%	90			11%	98	
KERATIN-PAN CYTOPLASMIC	94%	1,071			100%	3	
MELAN-A103 CYTOPLASMIC	0%	4			6%	16	
INHIBIN cytoplasm	0%	1			4%	23	
AE1 AE3	96%	197			100%	20	
CEA-P	3%	1,066			1%	142	
CEA-M CYTOPLASMIC	2%	1,125			0%	64	
CDX-2 NUCLEAR	0%	65			1%	228	



Build Dx Panel

Build Ab Panel

Analyze Results

Enter a search phrase to select an Antibody (and repeat for a 2 or 3 Antibody search), then click Build Panel button.

| [View All](#)

+ **KERATIN-HMW**
KERATIN-HMW

+ **KERATIN-LMW**
KERATIN-LMW

+ **KERATIN-PAN**
KERATIN-PAN

Selected Abs:

- VIMENTIN



- KERATIN-PAN



► Build Panel



Discrete Diagnosis (15)

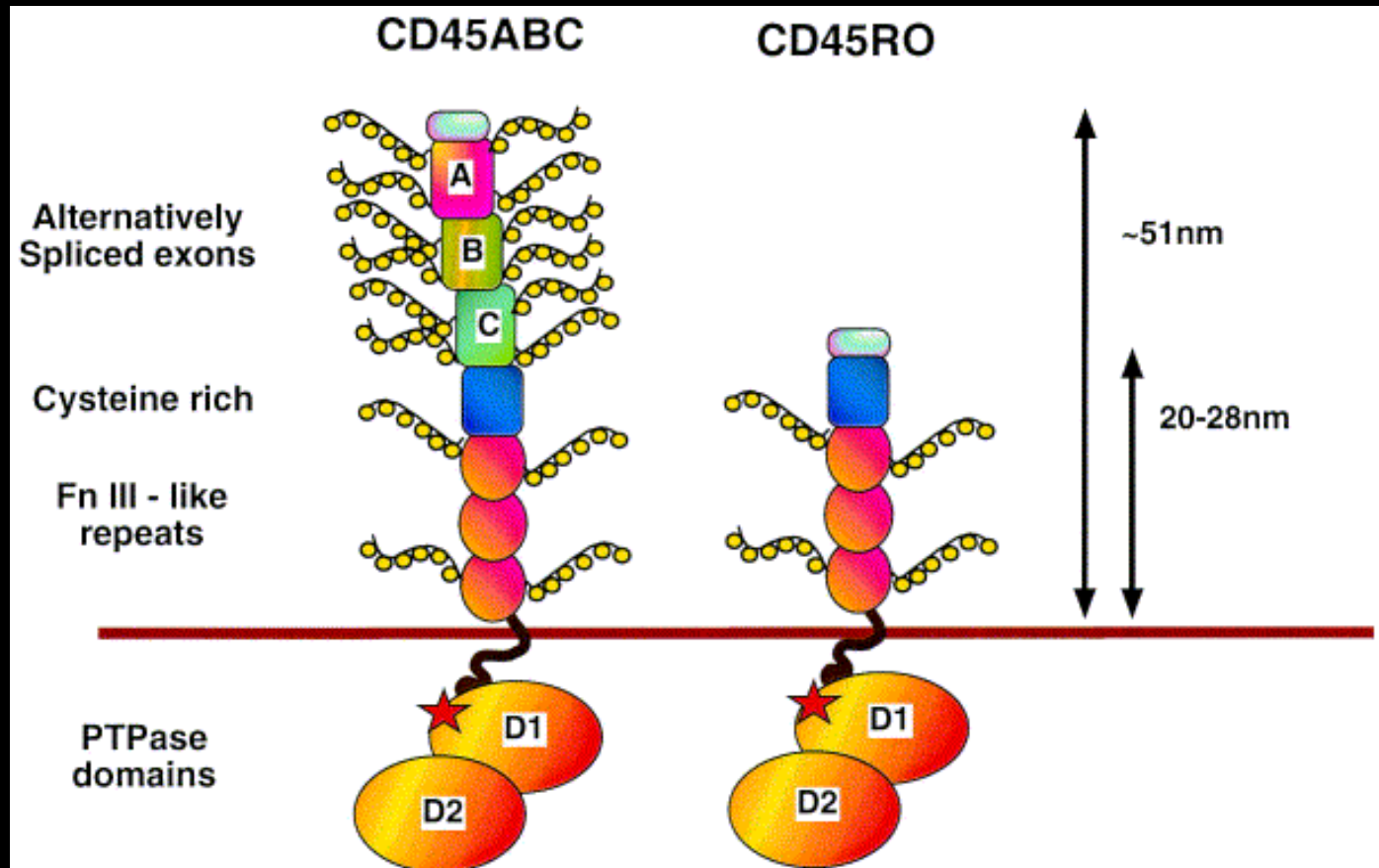
	VIMENTIN			KERATIN-PAN			# of Refs
	Pos	Positive	Cases	Pos	Positive	Cases	
Ewing's Sarcoma, Atypical		44%	9		0%	5	<u>2</u>
Carcinoma, Small Cell, Breast		44%	9		0%	2	<u>2</u>
Medulloblastoma, NOS		42%	57		0%	53	<u>2</u>
Pheochromocytoma, NOS		40%	63		16%	116	<u>4</u>
Stromal Sarcoma, Low Grade		38%	8		0%	6	<u>2</u>
Askin Tumor		37%	19		0%	14	<u>2</u>
Seminoma, Testes		30%	96		21%	170	<u>6</u>
Clear Cell Tumor Of Lung		29%	17		0%	32	<u>5</u>
Alveolar Soft Part Sarcoma		25%	4		0%	3	<u>4</u>
Leiomyoma, Epithelioid		20%	5		15%	13	<u>2</u>
Neuroblastoma, Olfactory		8%	13		8%	38	<u>4</u>
Thymic Carcinoma, Spindle Cell		0%	10		0%	10	<u>1</u>
Solitary Fibrous Tumor, Malignant		0%	1		0%	1	<u>1</u>
Seminoma, Spermatocytic		0%	7		0%	3	<u>2</u>
Sarcoma, Perivascular Epithelioid Cell		0%	4		0%	4	<u>1</u>

Primary panel for the unknown primary tumour

"Real"	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

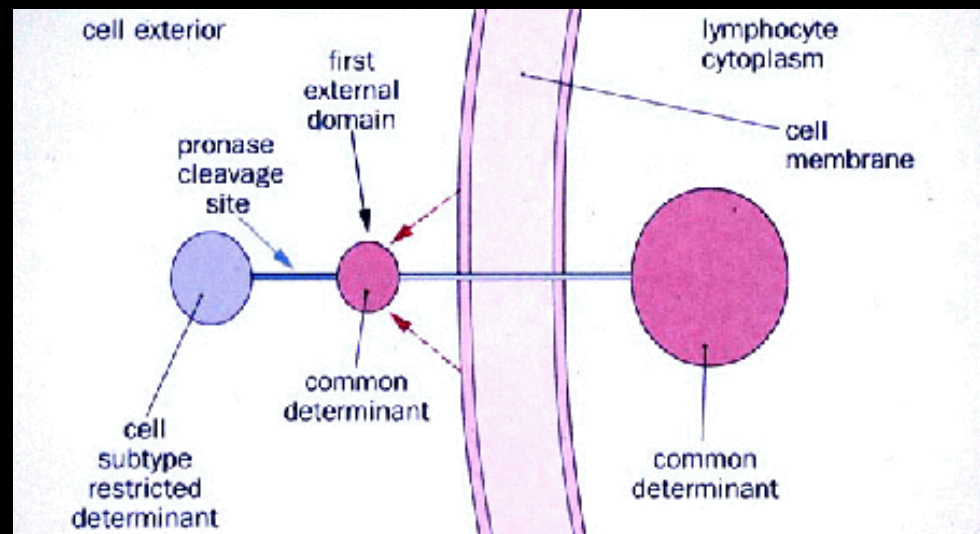
CD45 - Leucocyte common antigen (LCA)

- Transmembrane protein tyrosin phosphatase essential for haematopoietic signal transduction and cell activation
- Membrane associated component: 5 isotypes
- Intracellular component: one common type

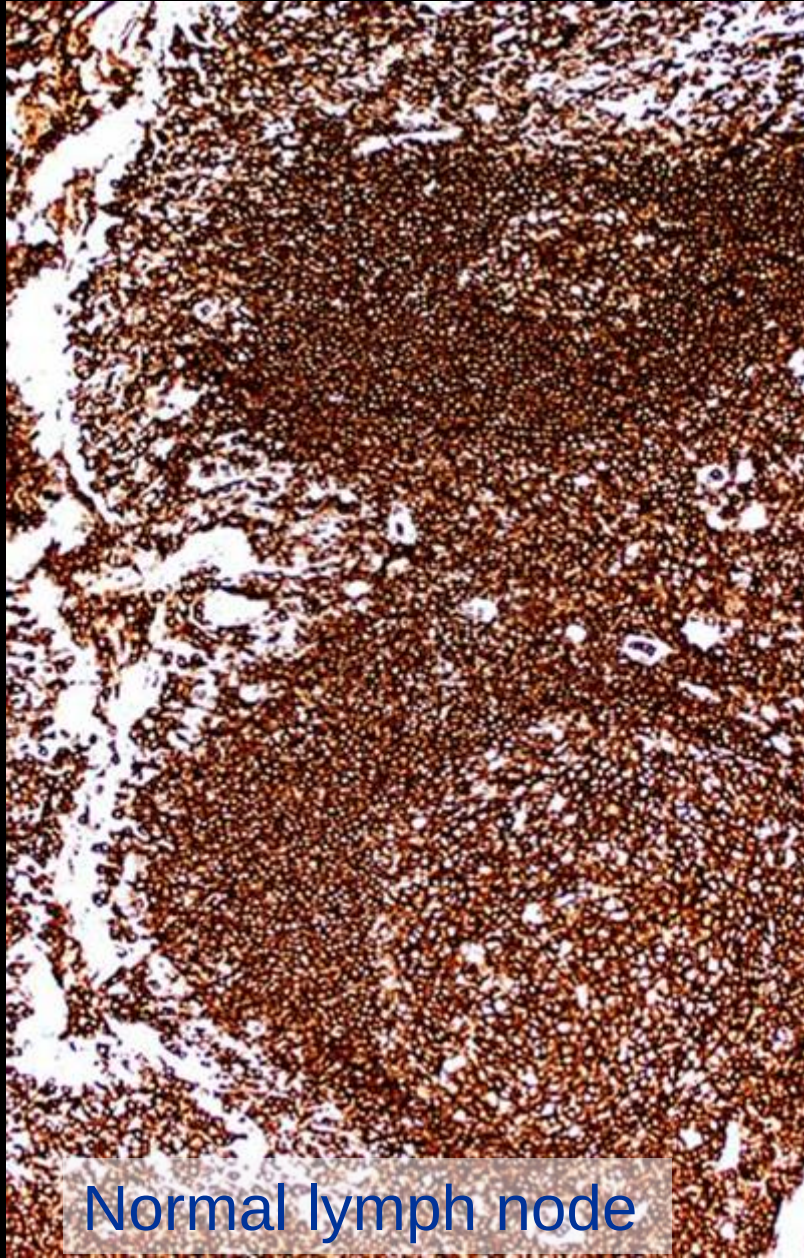


CD45 - Leucocyte common antigen (LCA)

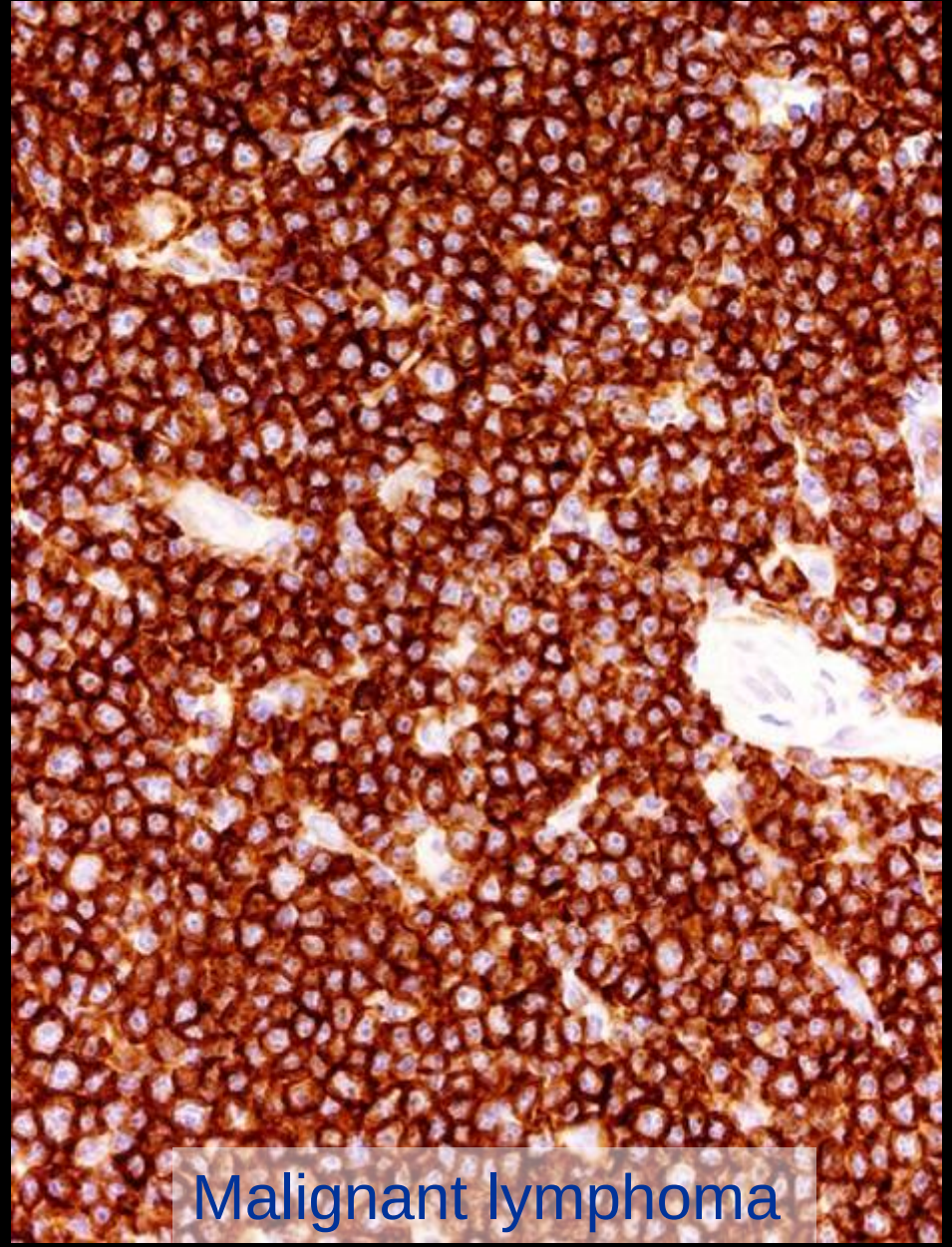
- Transmembrane protein tyrosin phosphatase essential for haematopoietic signal transduction and cell activation
- Membrane associated component: 5 isotypes
- Intracellular component: one common type
- Large majority of haematolymphoid cells
- Lost in maturing erythrocytes, megakaryocytes and plasmacells
- "Never" found in non-haematolymphoid cells



CD45 - Leucocyte common antigen (LCA)



Normal lymph node



Malignant lymphoma

CD45 - Leucocyte common antigen (LCA)

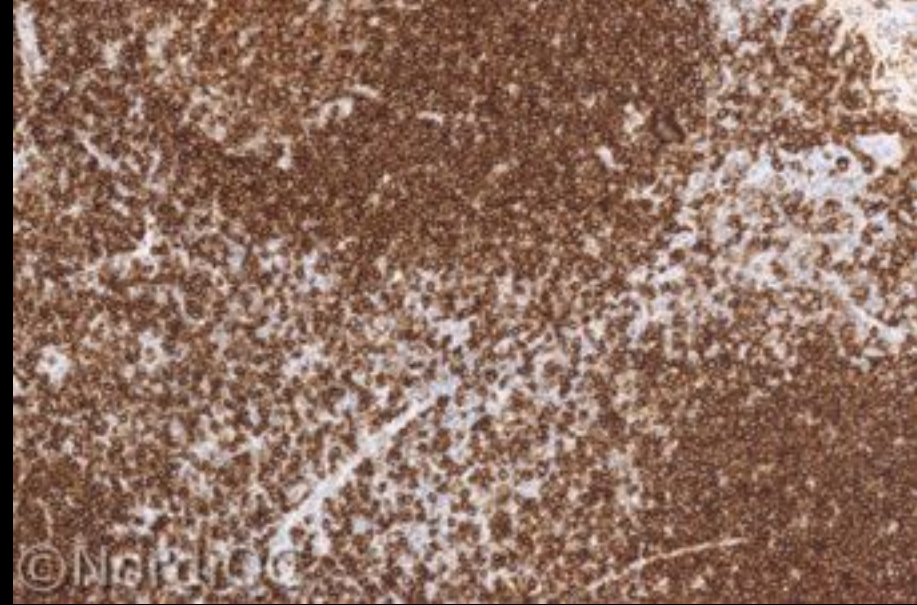
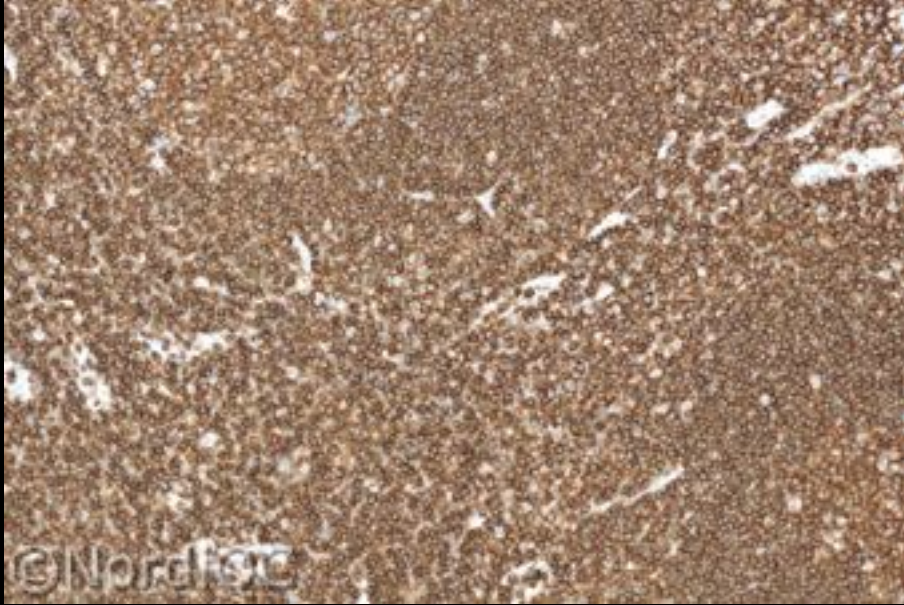
Liver

Brain



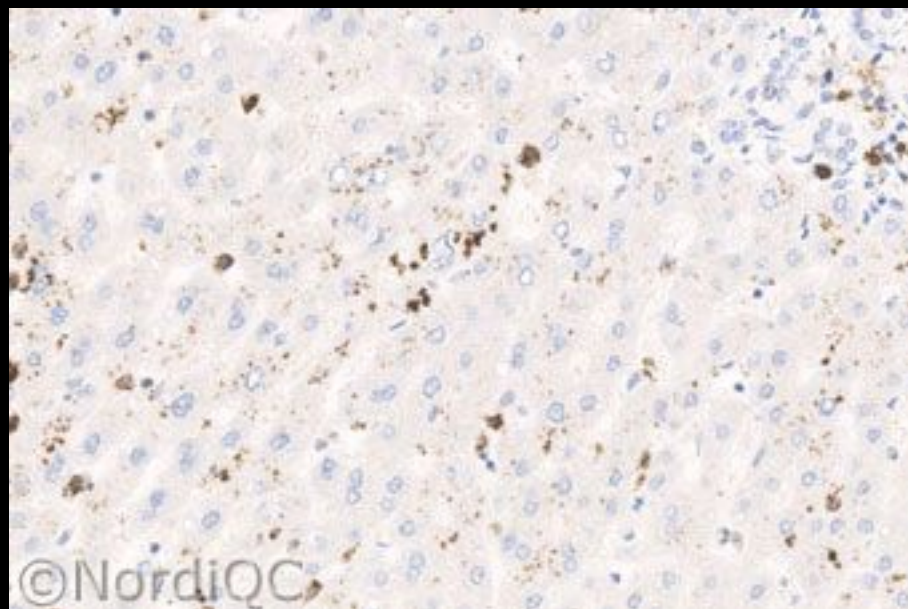
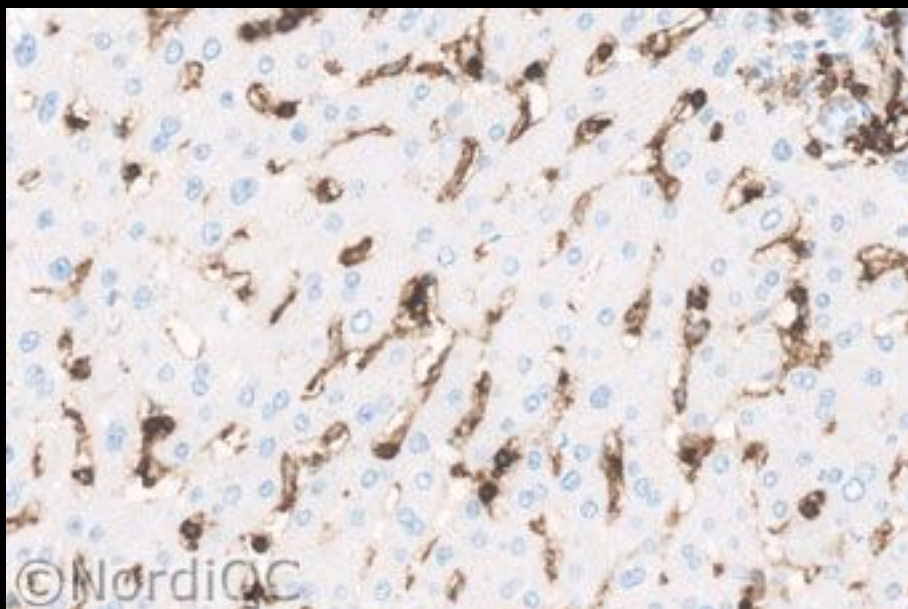
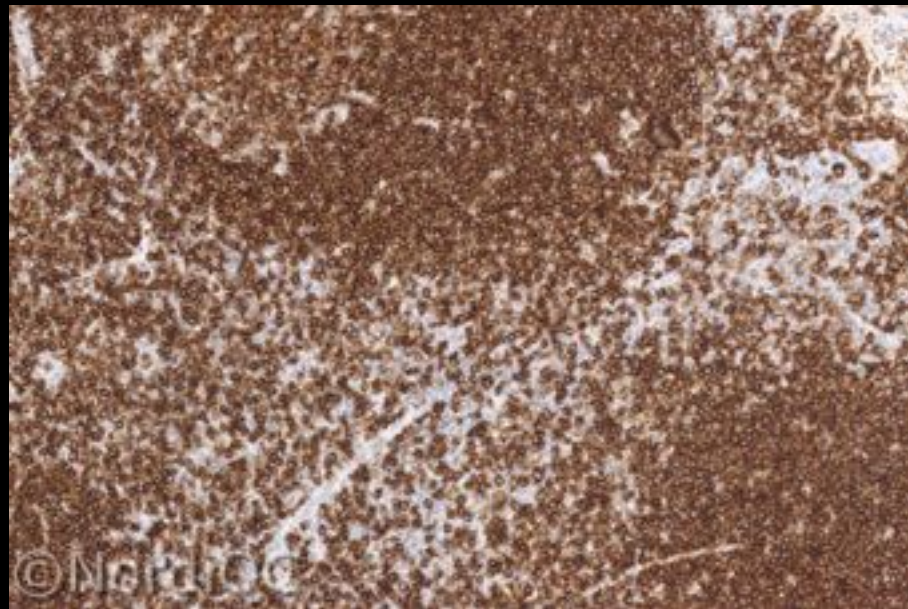
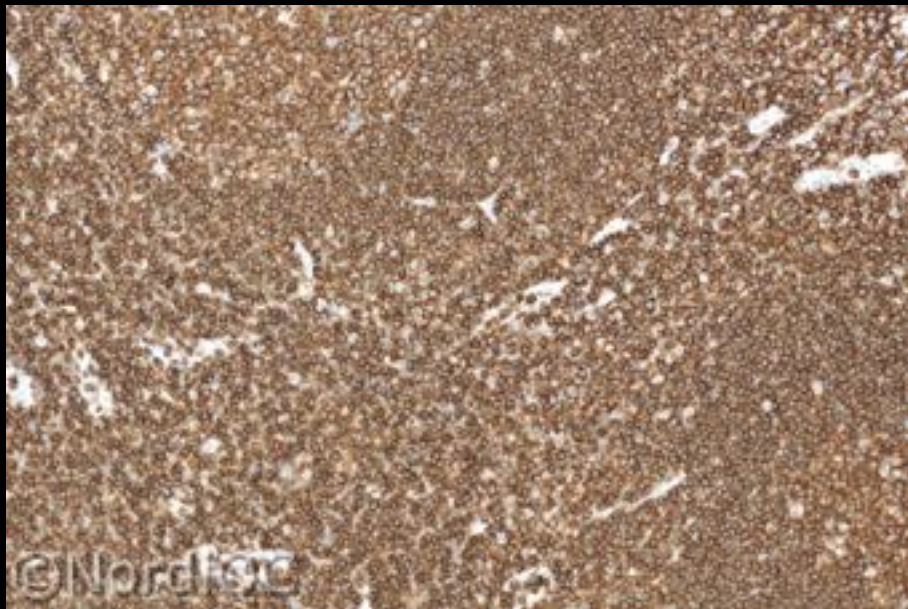
Critical assay performance control

CD45 – NordiQC run 37 2013



Which is best?

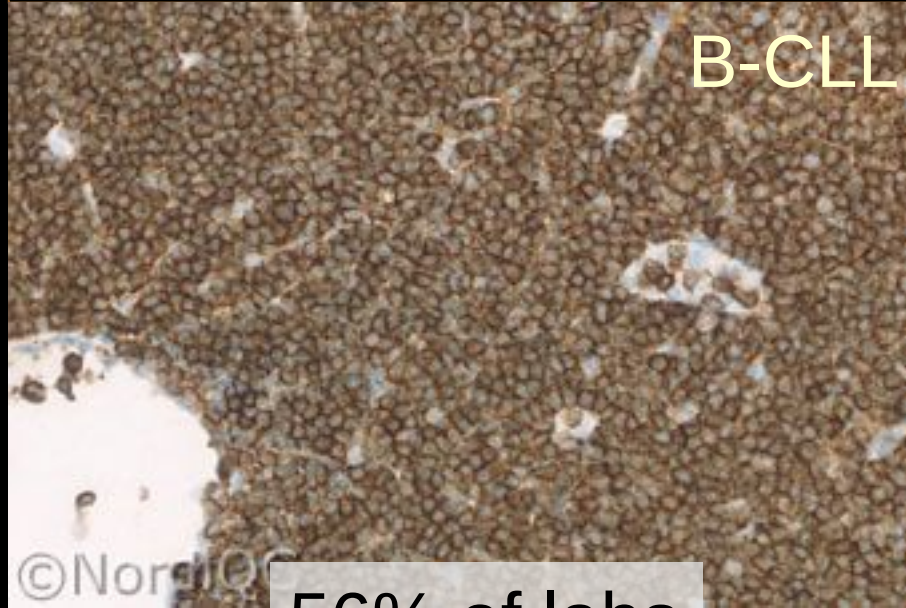
CD45 – NordiQC run 37 2013



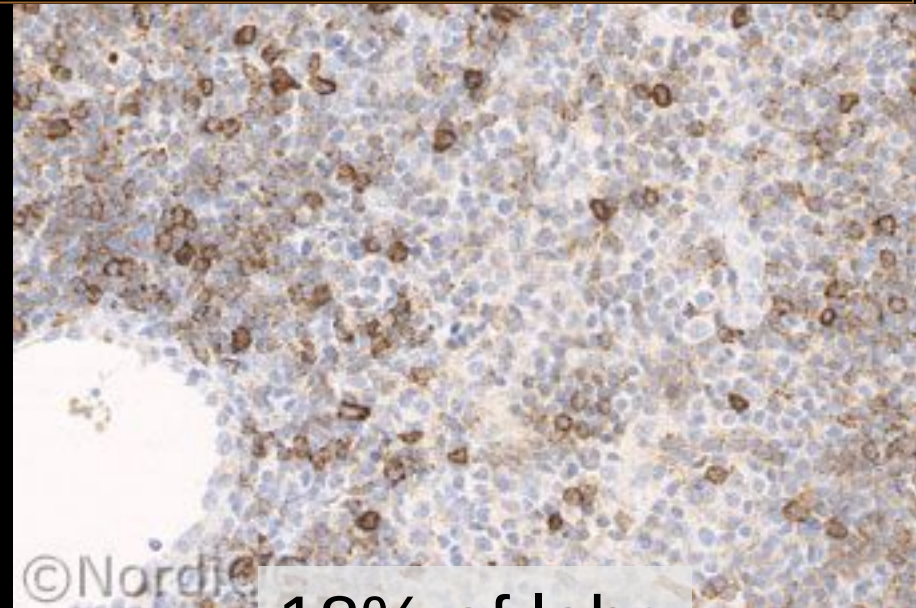
Optimal

Insufficient

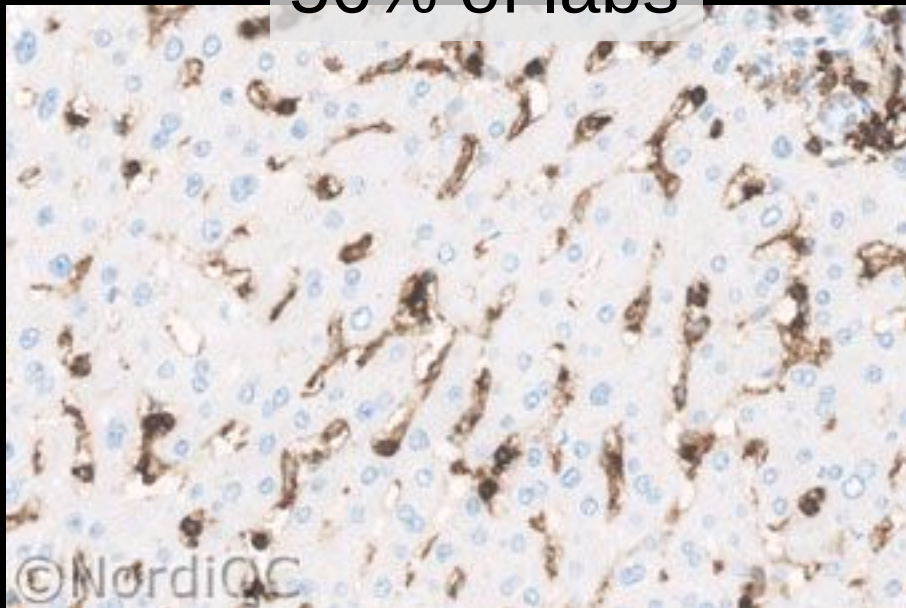
CD45 – NordiQC run 37 2013



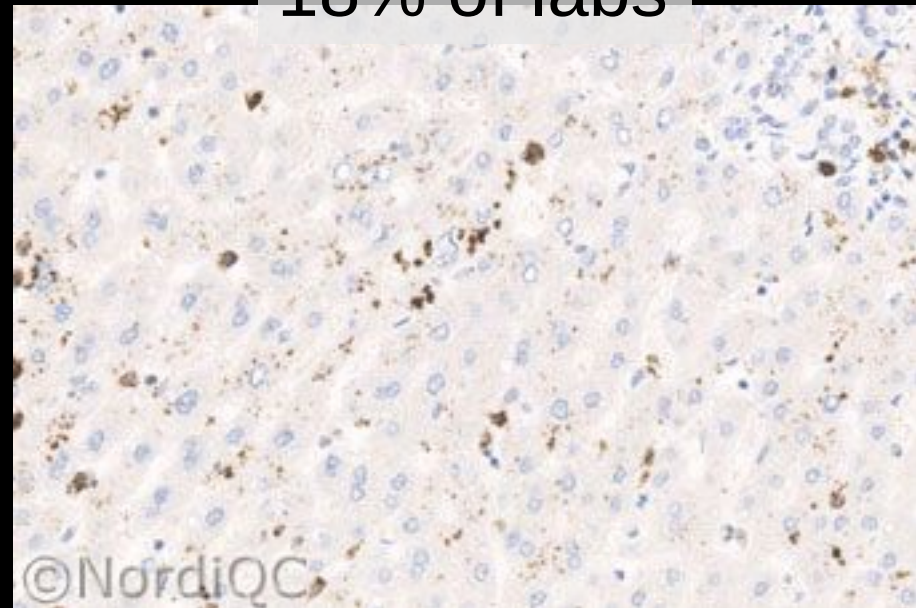
56% of labs



18% of labs



Optimal

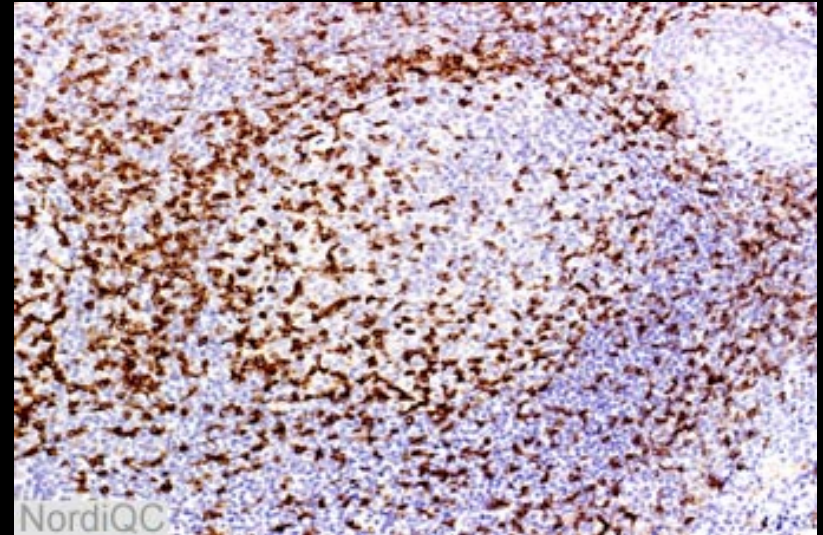


Insufficient

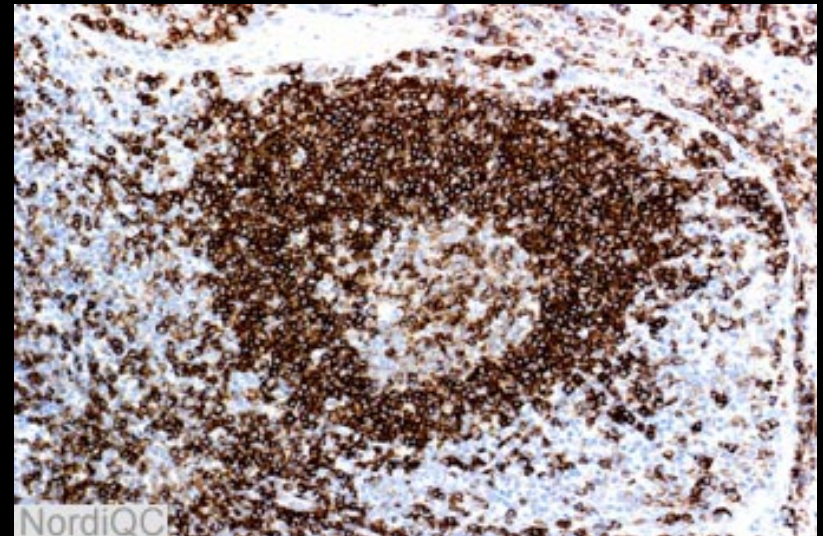
CD45 - Leucocyte common antigen (LCA)



Lymph node/Tonsil



■ CD45 RO ~ T-cells



■ CD45 RA ~ B-cells

Cytokeratin-Positive, CD45-Negative Primary Centroblastic Lymphoma of the Adrenal Gland

A Potential for a Diagnostic Pitfall

Ludvik R. Donner, MD, PhD; Frank E. Mott, MD; Isaac Tafur, MD

● We report a case of cytokeratin-positive, CD45-negative primary polymorphic centroblastic lymphoma of the adrenal gland. Additional immunostaining, which demonstrated positivity for CD20 and κ light chain, as well as detection of the monoclonal rearrangement of the immunoglobulin heavy chain gene, helped to establish the diagnosis of lymphoma and to rule out an initially favored diagnosis of poorly differentiated carcinoma.

(*Arch Pathol Lab Med.* 2001;125:1104–1106)

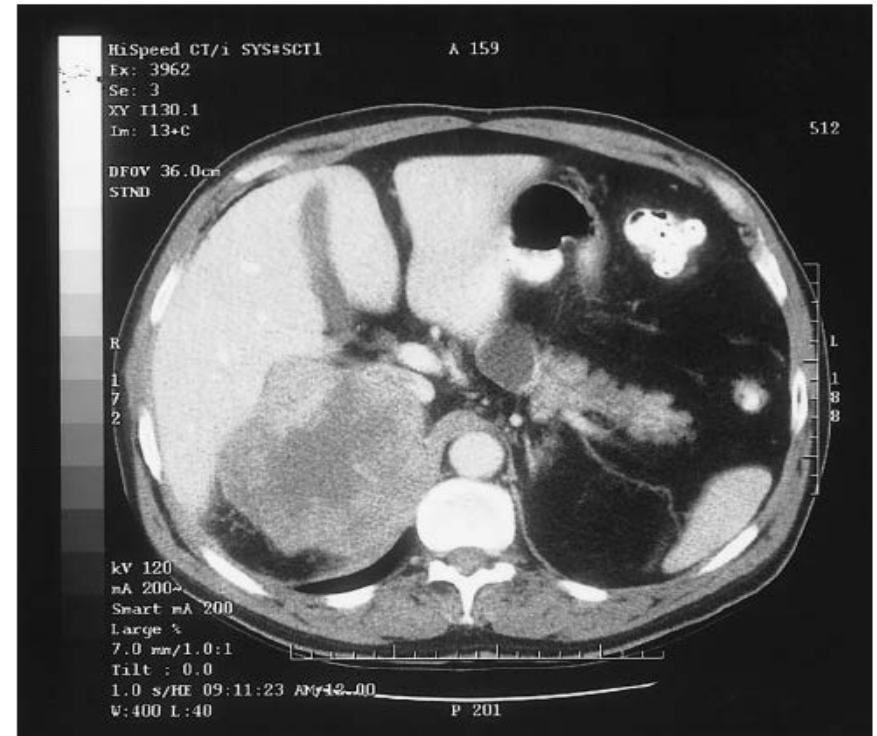
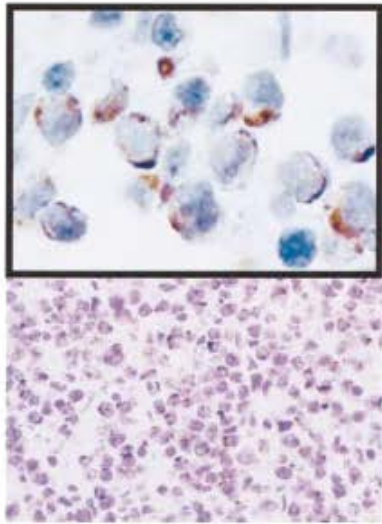
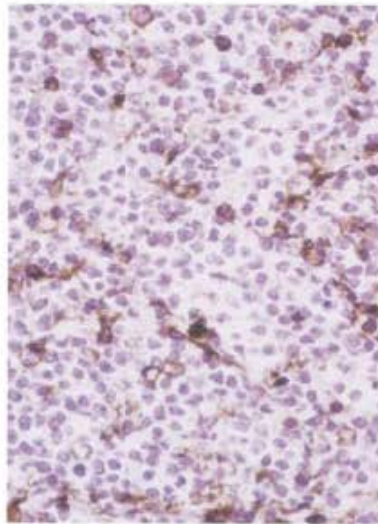


Figure 1. Computed tomography of a large right suprarenal mass involving the liver.

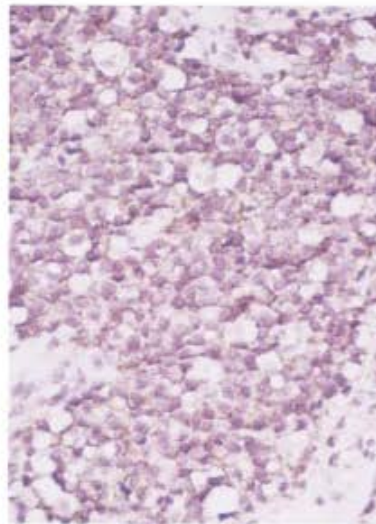
CD45 - Leucocyte common antigen (LCA)



A



B



C

Figure 3. Note immunoreactivity of the lymphoma cells for cytokeratin (A) and CD20 (C) but not CD45 (B) (original magnification $\times 100$, inset $\times 250$).

Molecular Biologic Findings

Monoclonal rearrangement of the immunoglobulin heavy chain gene was identified by polymerase chain reaction (data not shown).

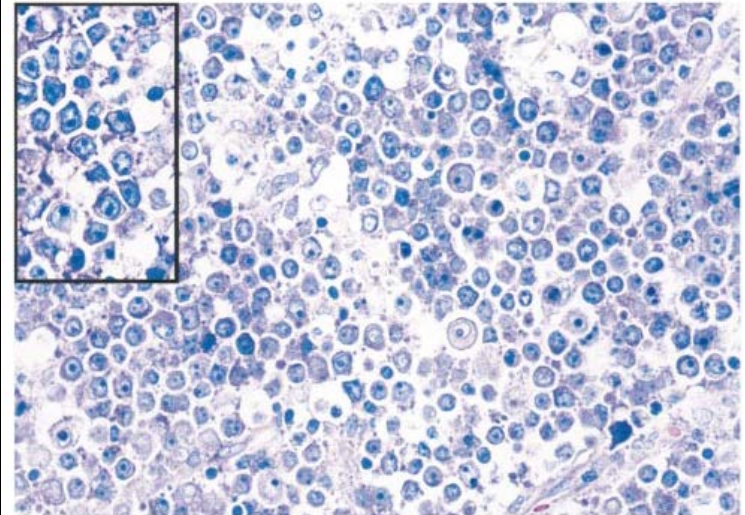


Figure 2. Light microscopic appearance of the tumor (Giemsa stain, original magnification $\times 100$, inset $\times 250$).

CD45 - Leucocyte common antigen (LCA)

MATERIALS AND METHODS

We performed immunohistochemical stains for cytokeratin (AE1 / AE3, Cell Marque, Austin, Tex; CAM5.2, Becton Dickinson, San Jose, Calif; cytokeratins 5/6, Zymed, San Francisco, Calif; cytokeratin 7, Dako Corporation, Carpinteria, Calif; cytokeratin 20, Dako; 34 β E12, Enzo, New York, NY), CD3, CD20, CD30, CD45RO, CD68, κ light chain, λ light chain, myeloperoxidase, epithelial membrane antigen, neuron-specific enolase, synaptophysin, S100 protein, HMB-45 (Dako), and chromogranin A (Cell Marque) on a TechMate 500 with a ChemMate Secondary Detection Kit-Peroxidase/DAB (Ventana Medical Systems, Tucson, Ariz). The histologic sections were pretreated by steaming in citrate buffer solution (Target Retrieval Solution, Dako) for 30 minutes at 99°C.

The monoclonal antibodies AE1/AE3 (working concentration, 0.4 μ g of protein/mL) were applied for 25 minutes at room temperature. The immunostaining was repeated twice, each time with identical results.

Primary panel for the unknown primary tumour

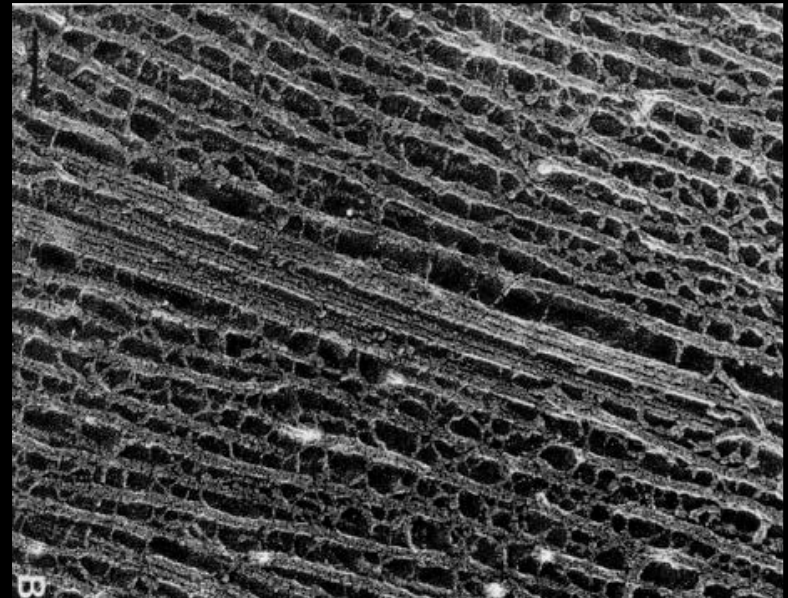
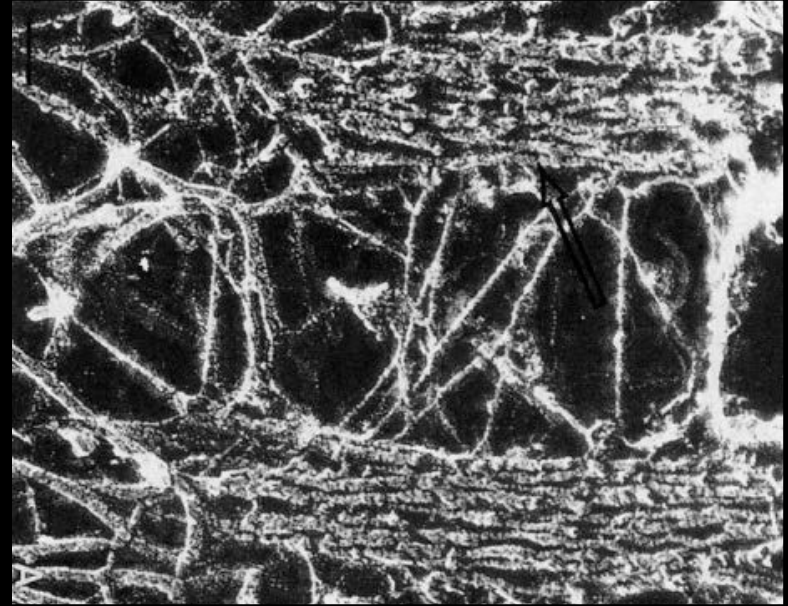
	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

Cellular filaments

Microfilaments: (6 nm)

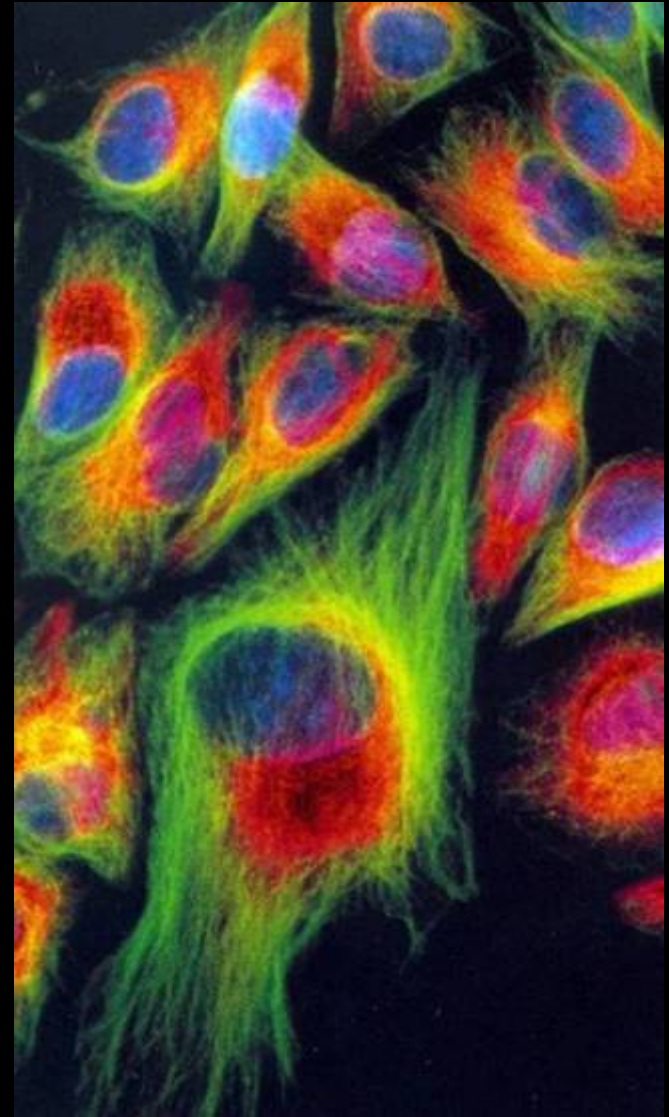
Intermediate filaments
(7- 11 nm)

Microtubuli (23 nm)

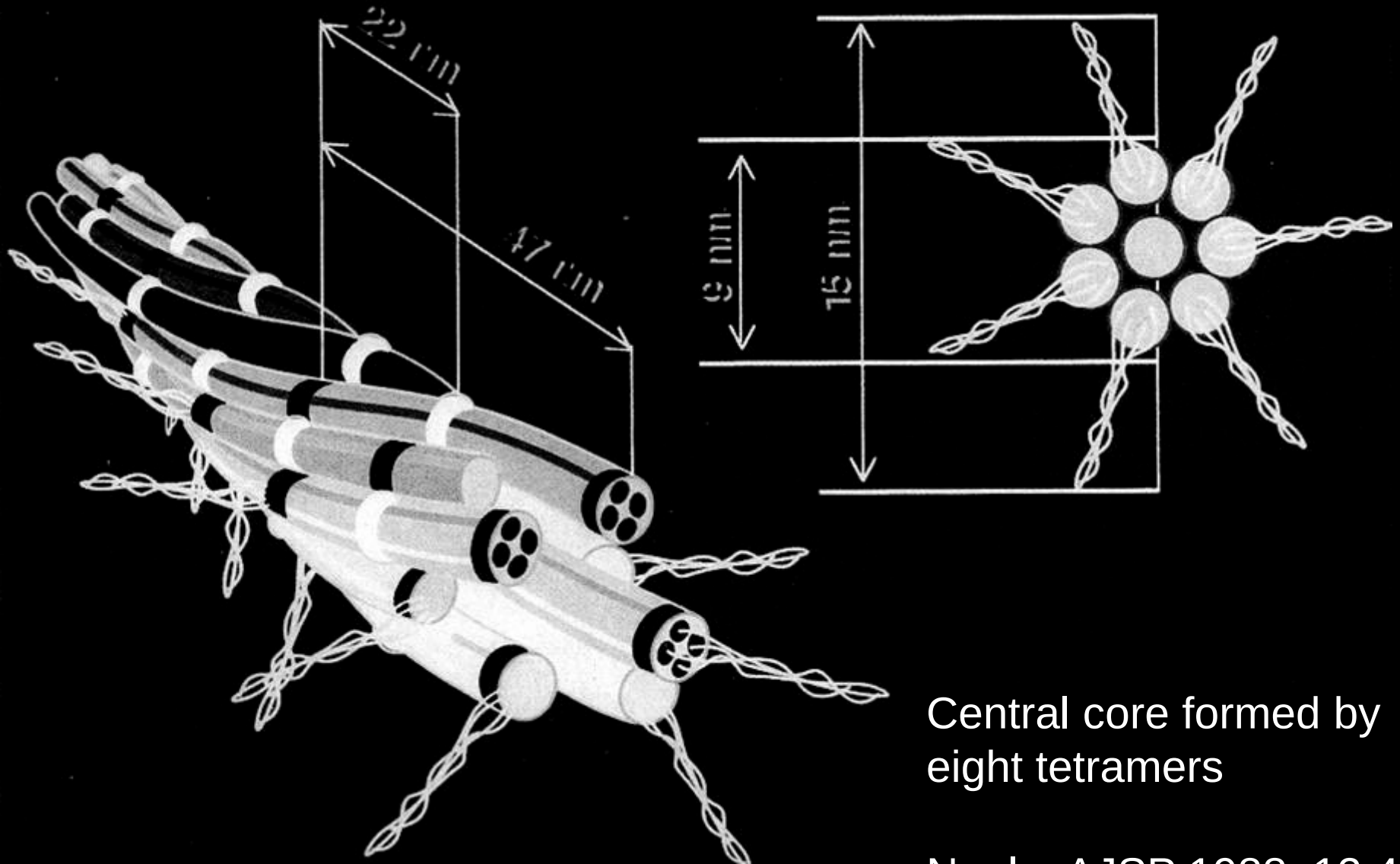


Intermediate filaments

- Group of mainly cytoplasmic filaments 7 – 11 nm in diameter
- Part of the cytoskeleton in virtually all cells, creating a meshwork and connecting nuclear membrane with cell membrane
- Often associated with microfilaments (6 nm) and microtubules (23 nm)
- Important for mechanical strength and cellular functions



Intermediate filaments – tetrameric units

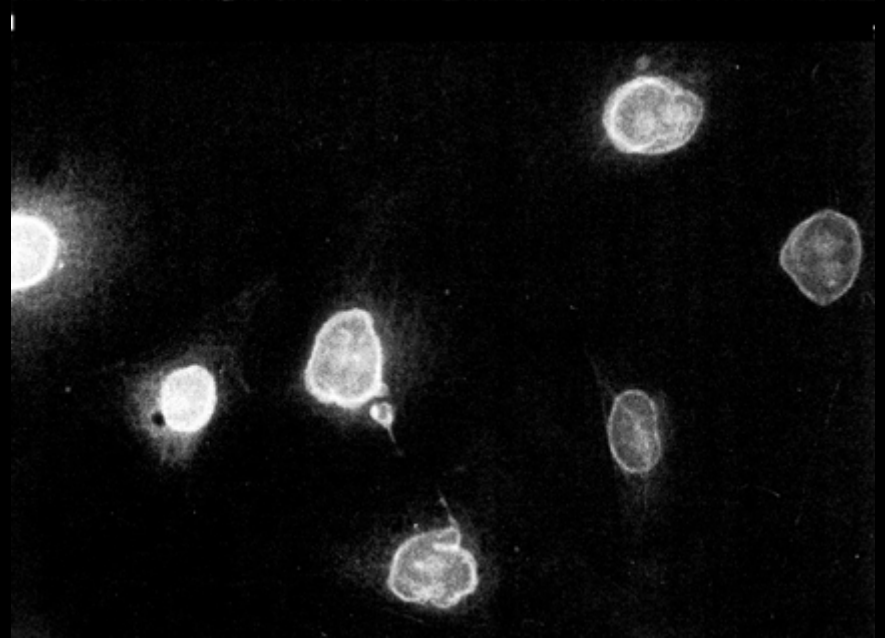
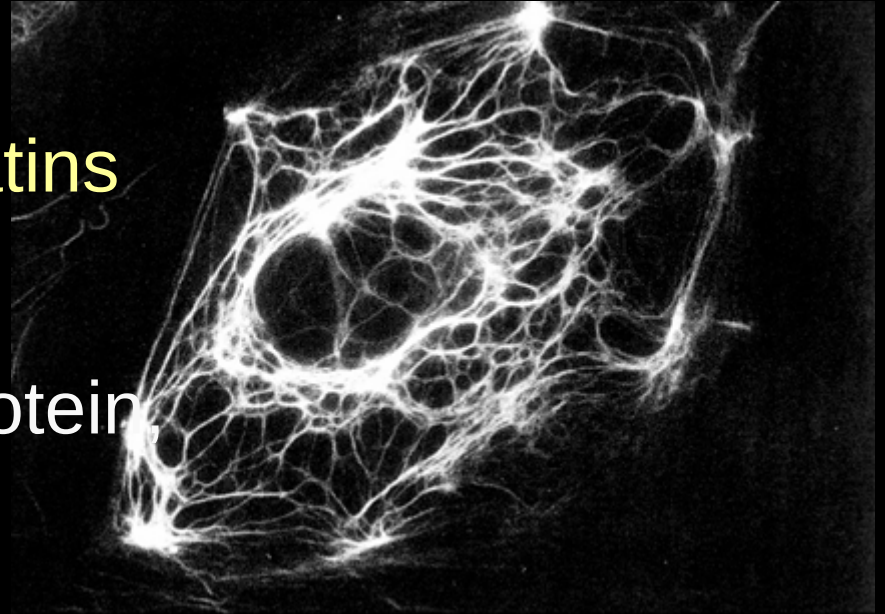


Central core formed by
eight tetramers

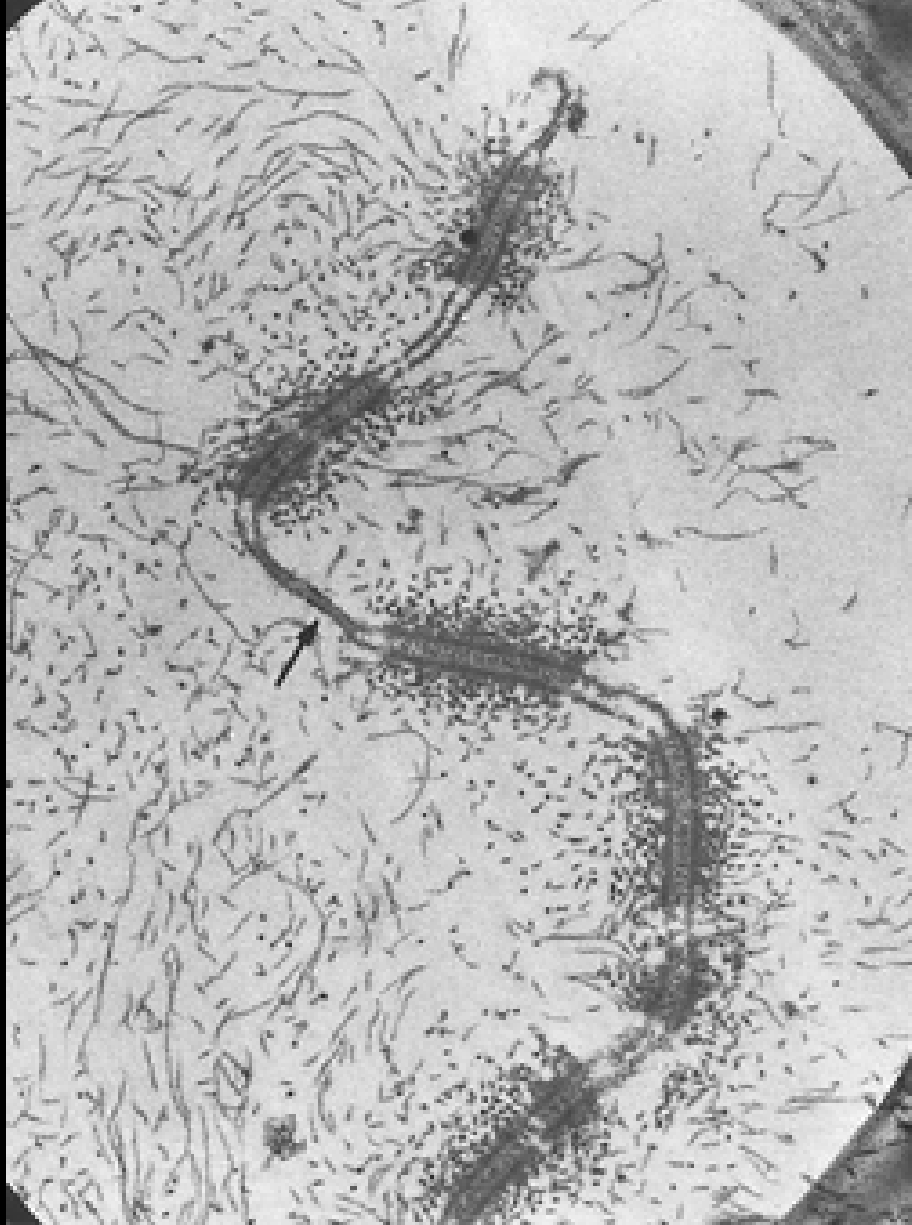
Nagle, AJSP 1988, 12:4

Intermediate filaments - 5 classes

- I acidic cytokeratins
- II basic-neutral cytokeratins
- III vimentin, desmin,
glial fibrillary acidic protein,
peripherin
- IV neurofilament protein,
 α -internexin, nestin
- V lamins



Cytokeratins as tonofilaments



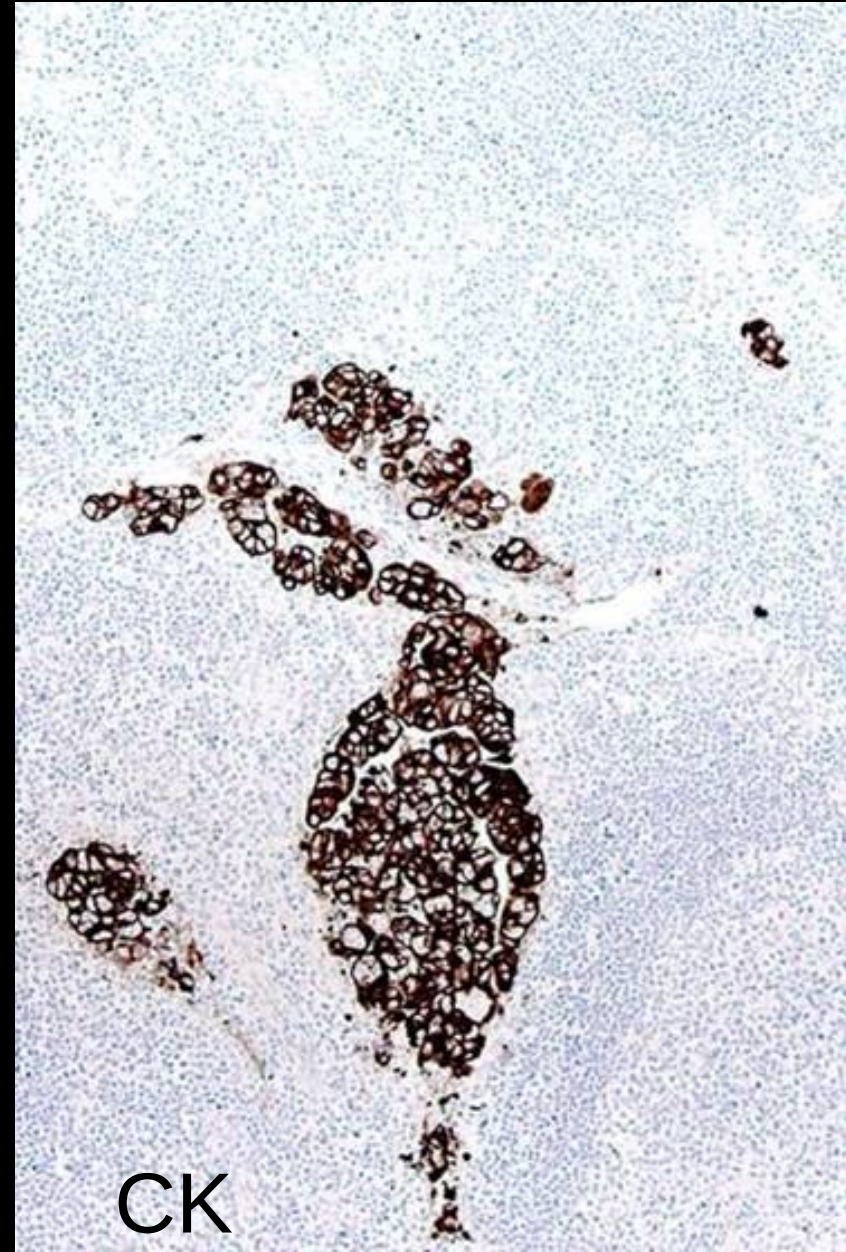
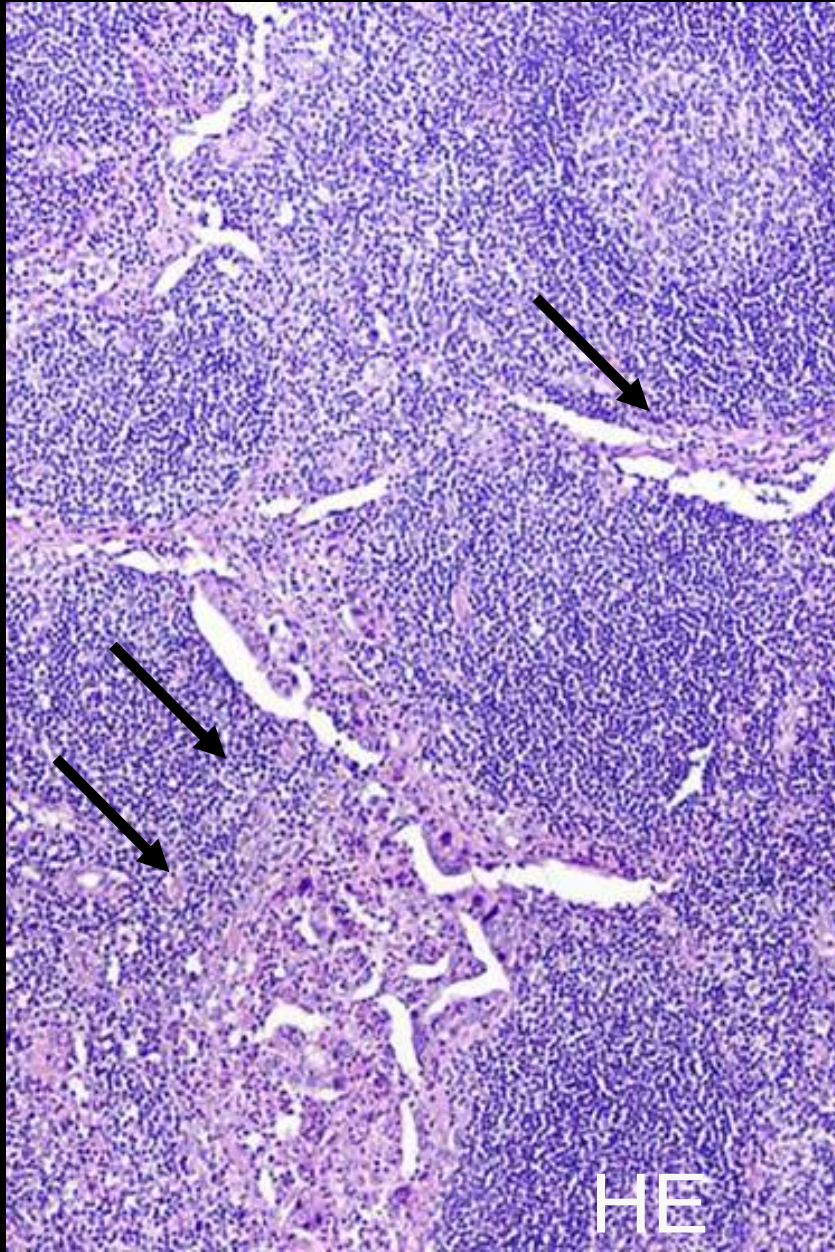
Cytokeratin intermediate filaments attached to desmosomes

Drochmans et al.
J Cell Biol. 1978, 79:427

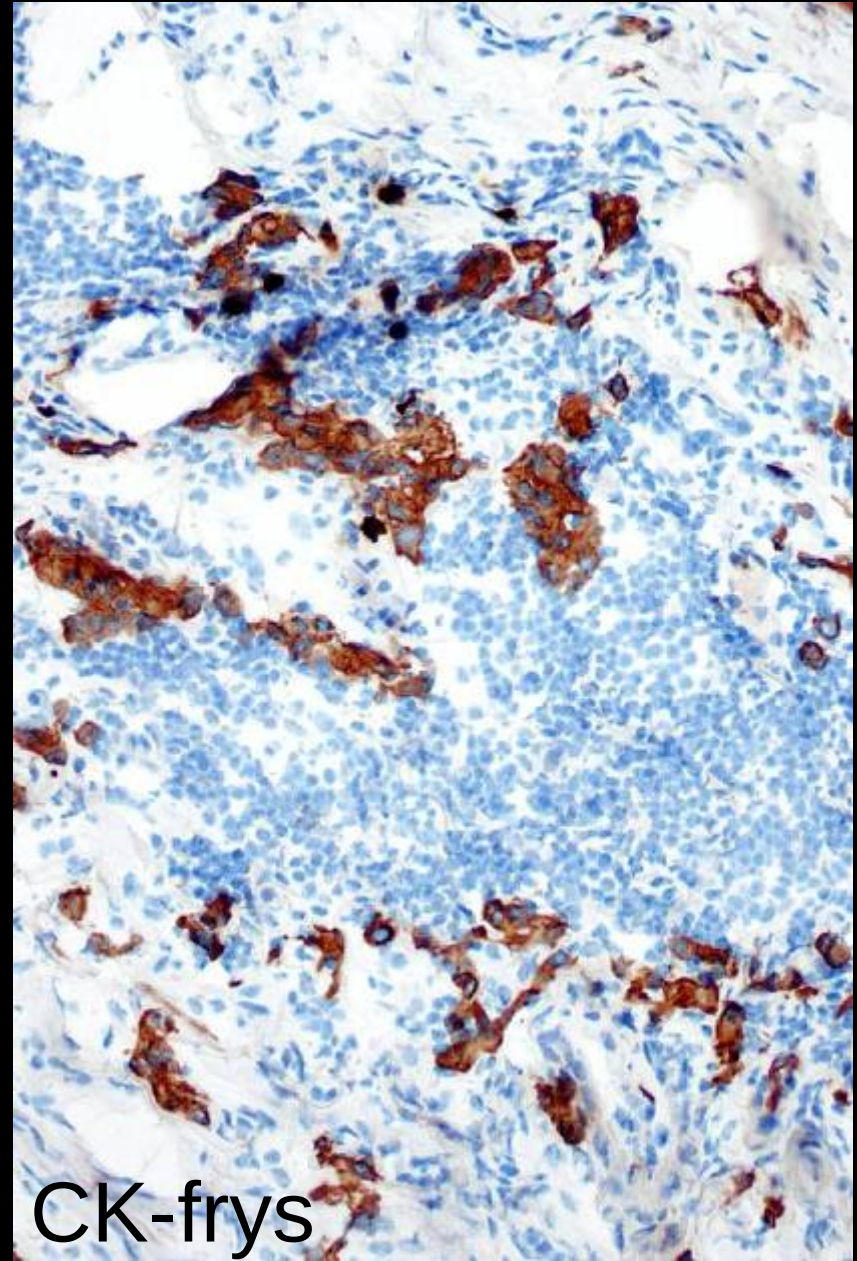
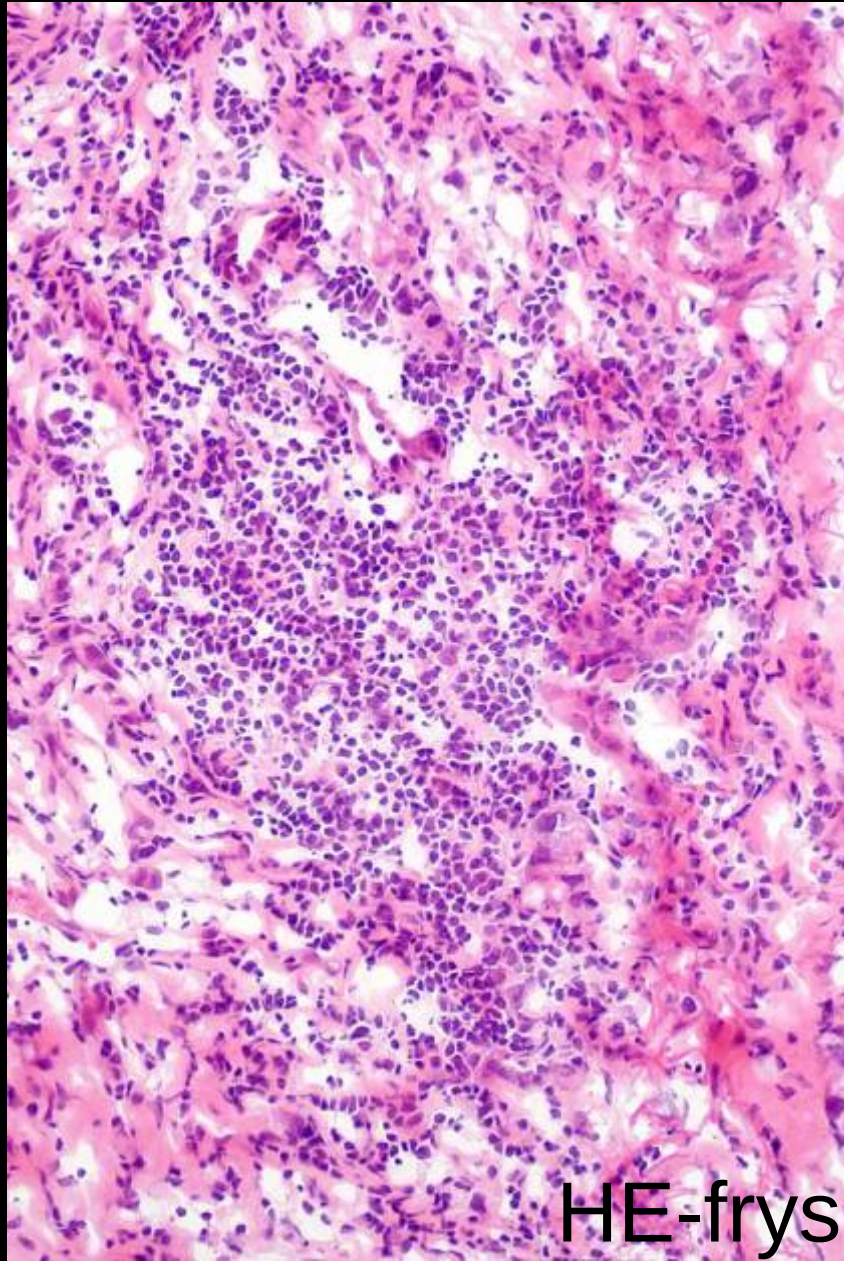
Cytokeratins in diagnostic pathology

- Cytokeratins (CKs) belong to the most fundamental markers of epithelial differentiation
- CKs comprise a large family of subtypes. Different cell types express different patterns of CK subtypes
- Cancers generally express CK patterns that at least in part represent the pattern of the putative cell of origin
- Metastases express CK patterns fairly concordant with those of the primary tumours

Micrometastases identified by cytokeratin

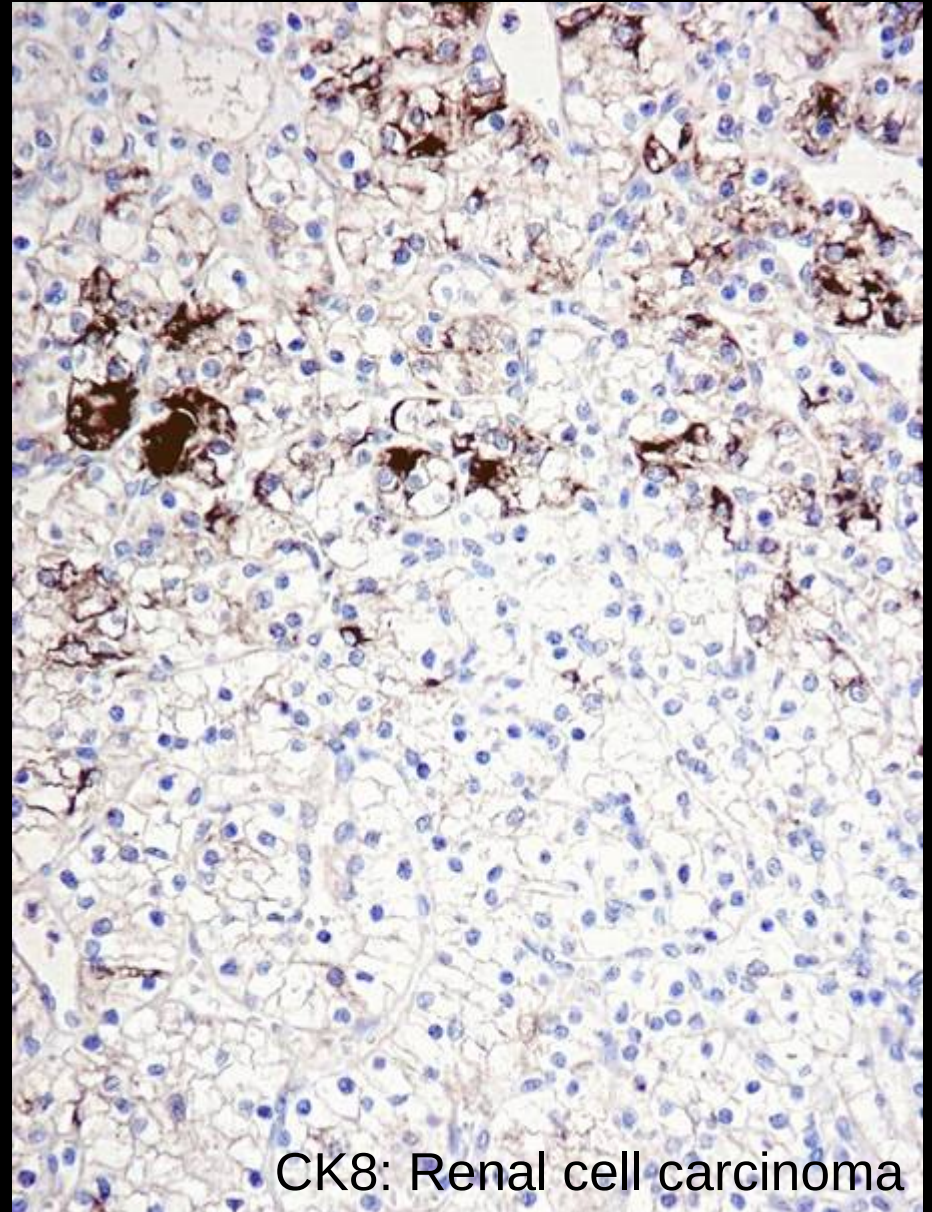
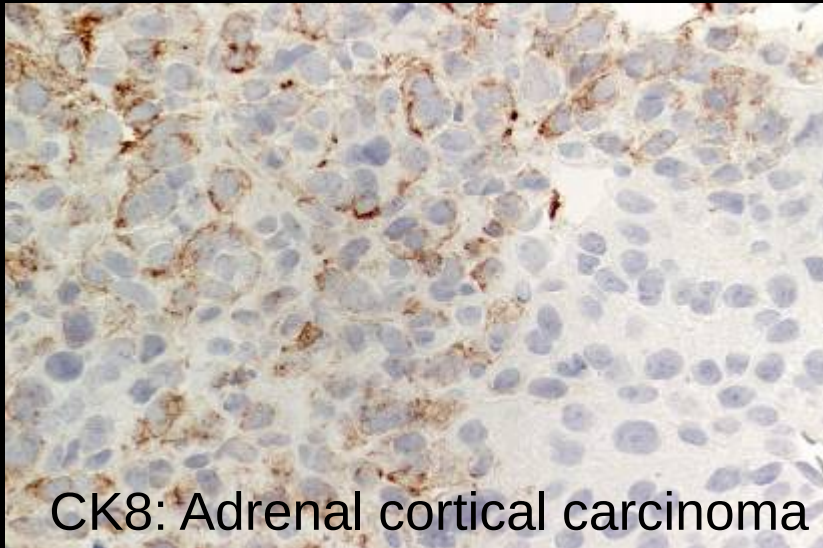


Carcinoma in frozen section identified by cytokeratin



Low molecular weight cytokeratins in carcinomas

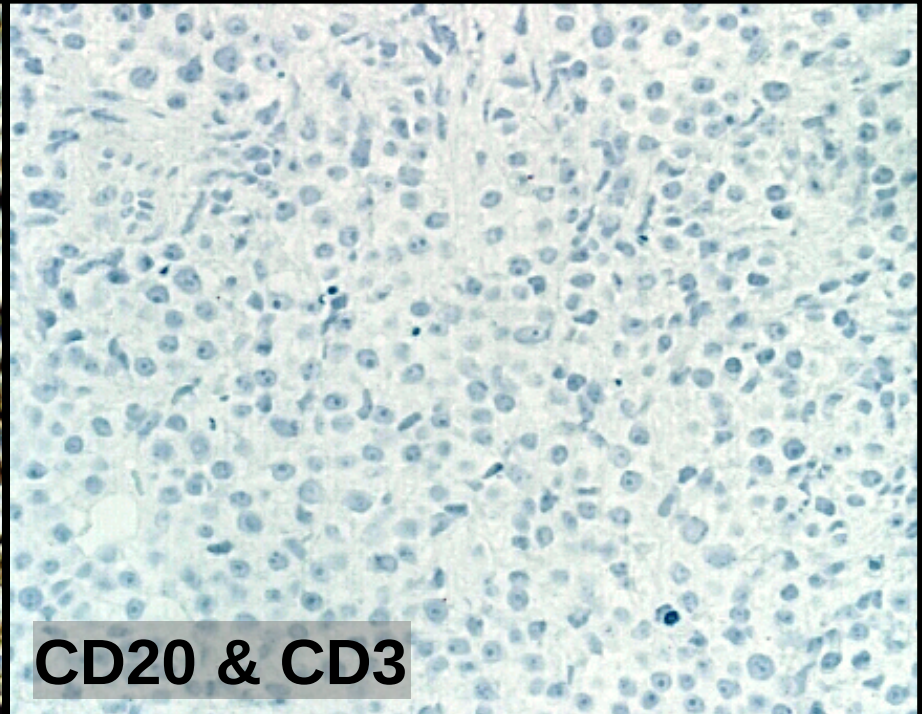
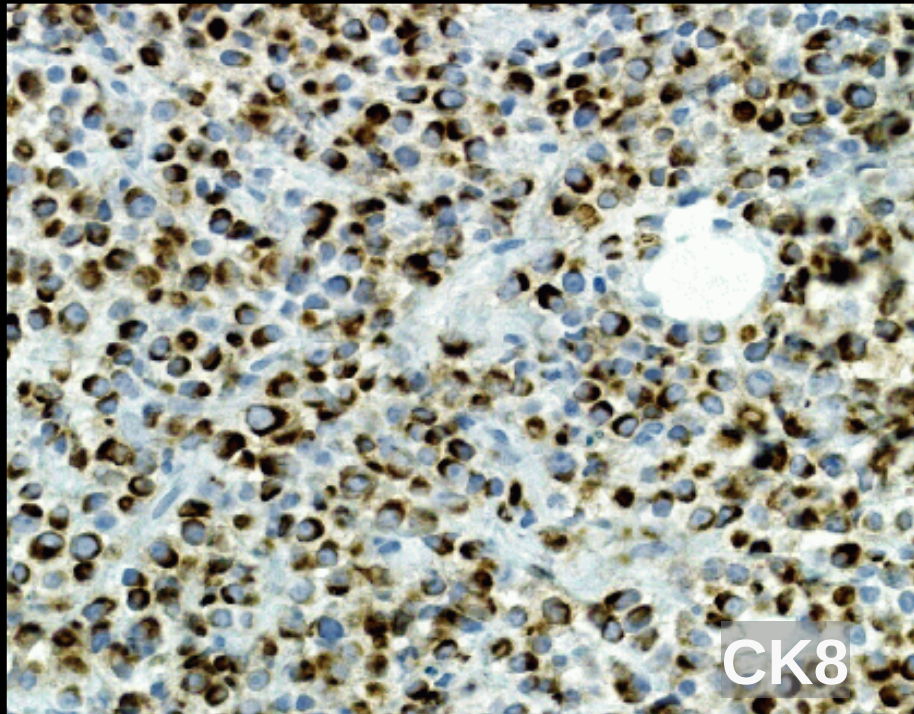
- Carcinomas “always” LMW-CK-positive, except some cases of
 - Renal cell carcinoma
 - Adrenal cortical carcinoma
 - Small cell carcinoma



Primary panel for the unknown primary tumour

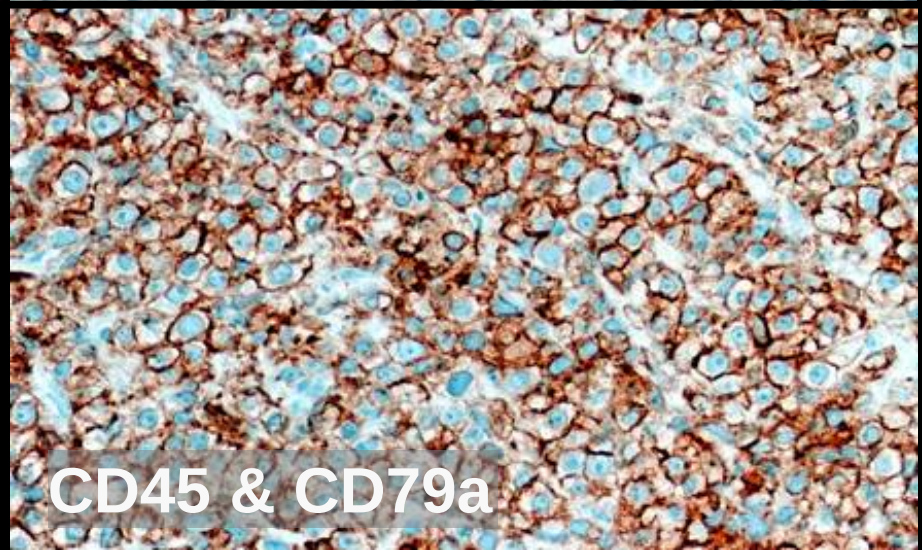
	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

Cytokeratins in non-epithelial tumours



♀ 42 y, tumour infiltrating
retroperitoneum

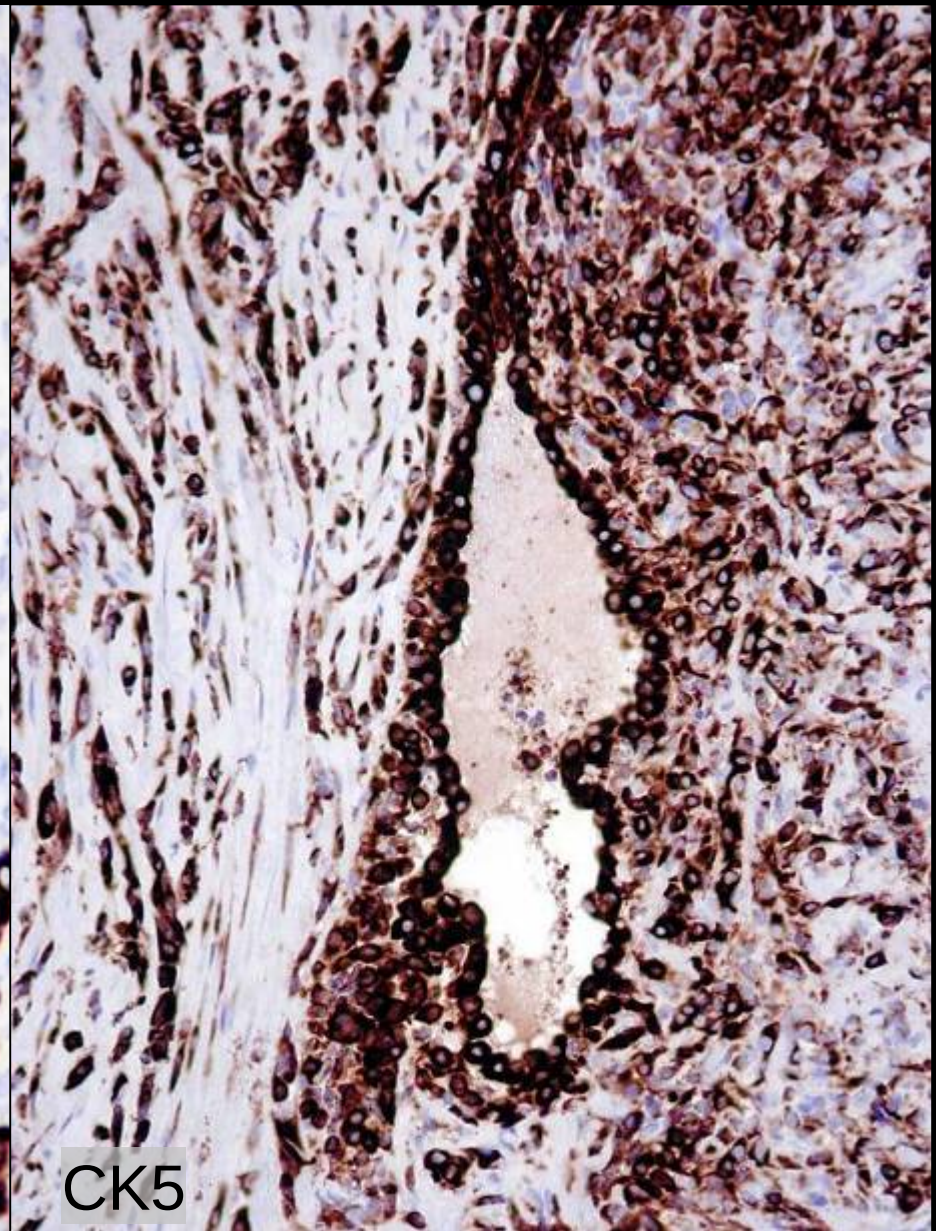
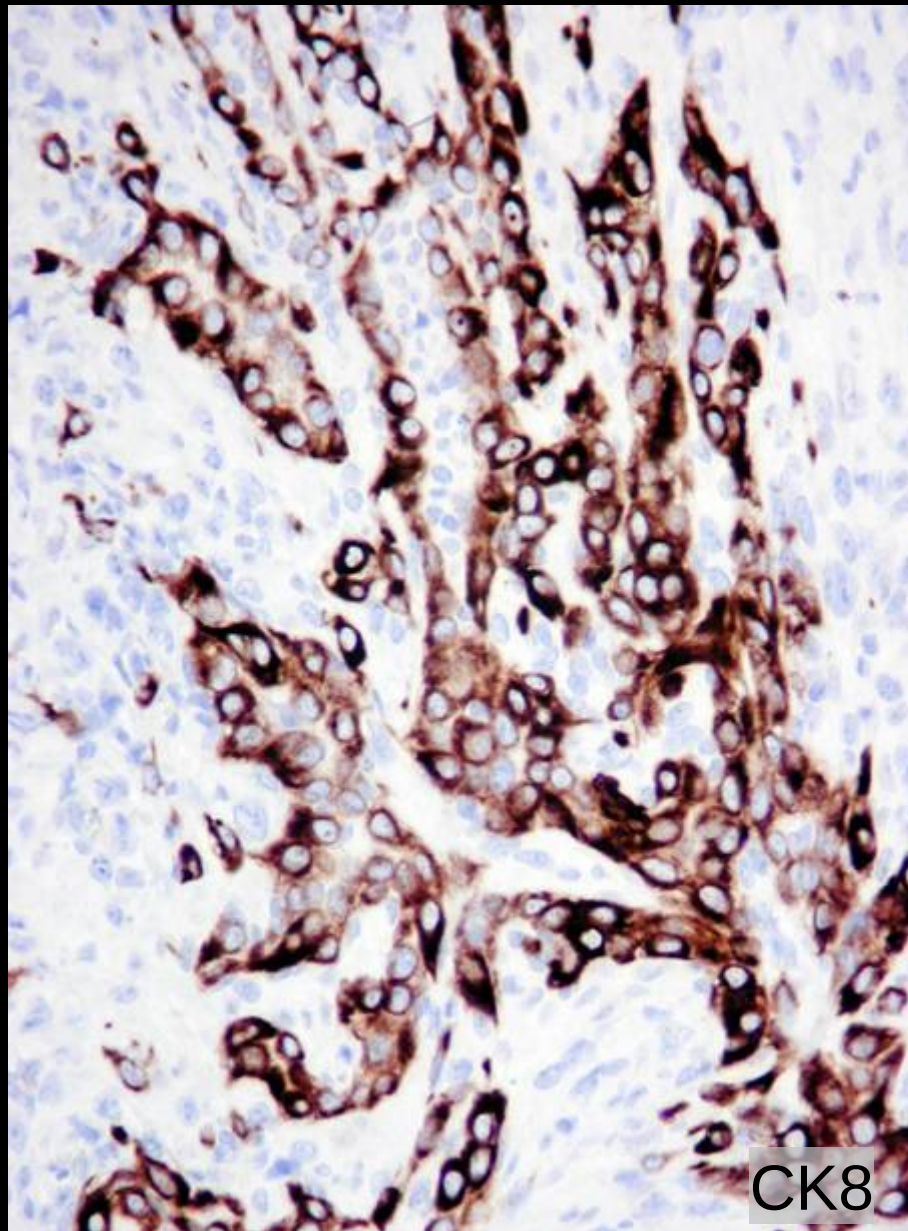
Malignant lymphoma !



Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

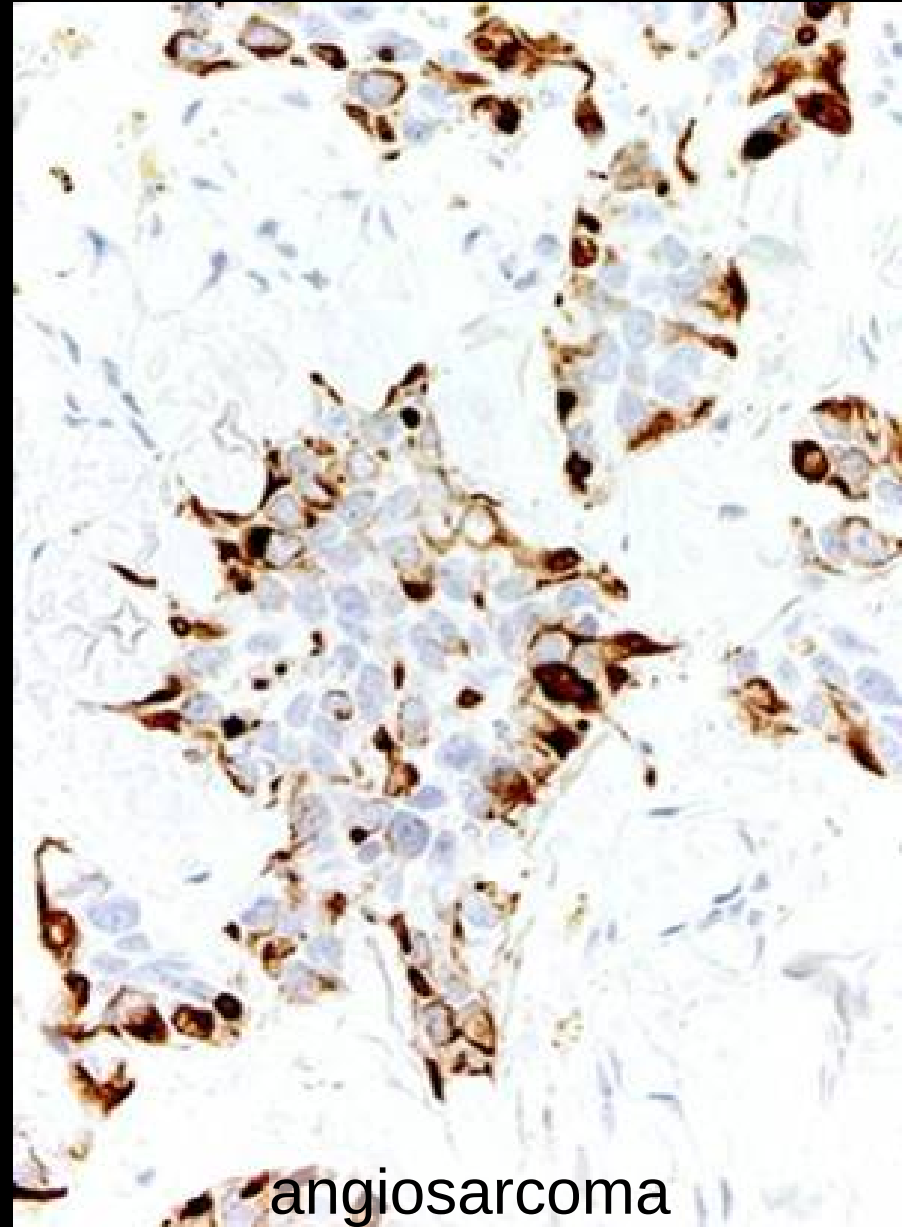
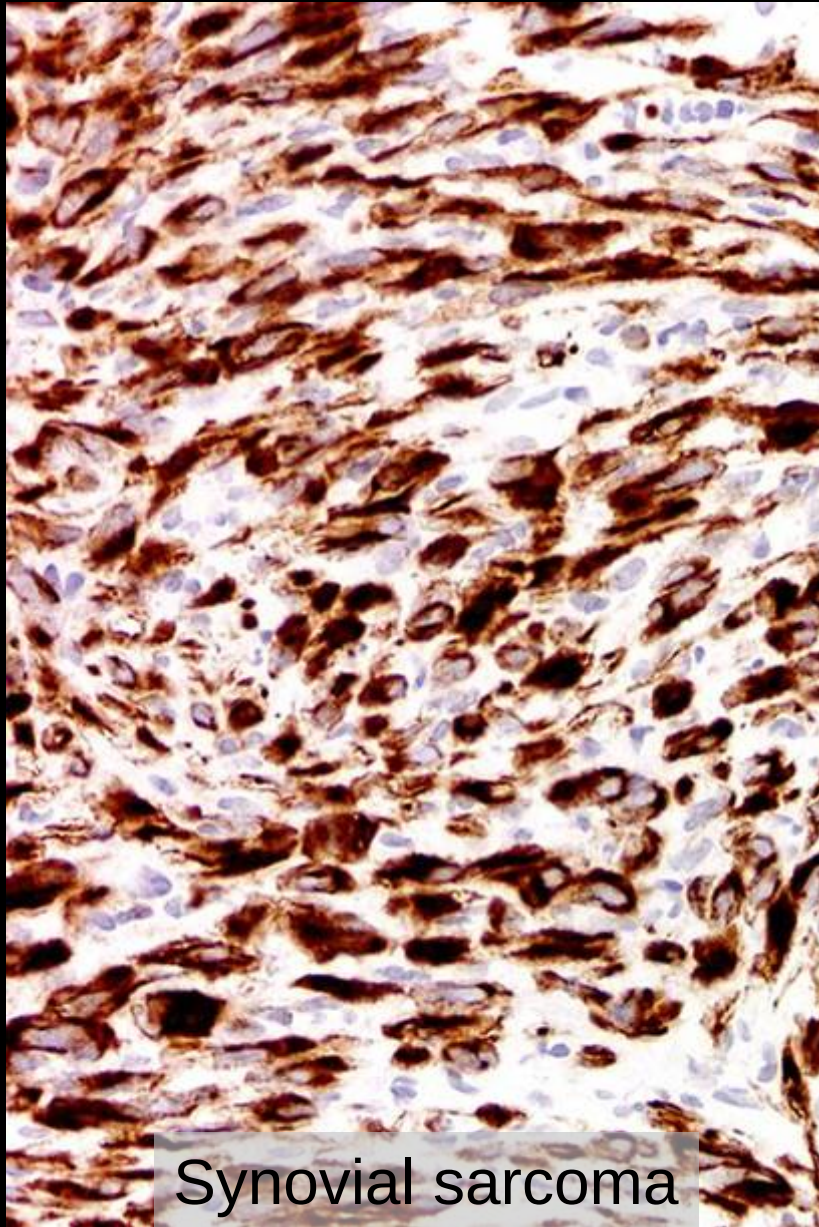
Cytokeratins in malignant mesothelioma



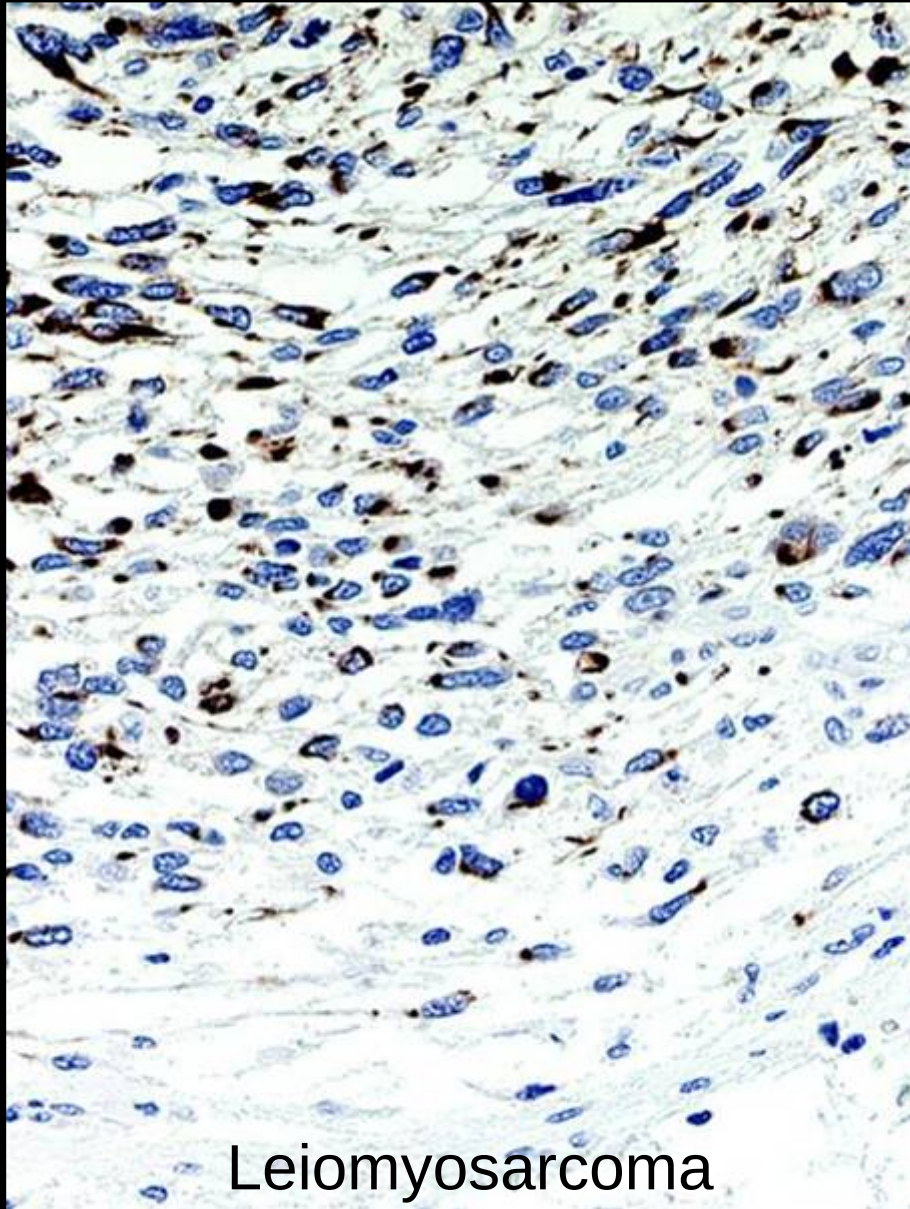
Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

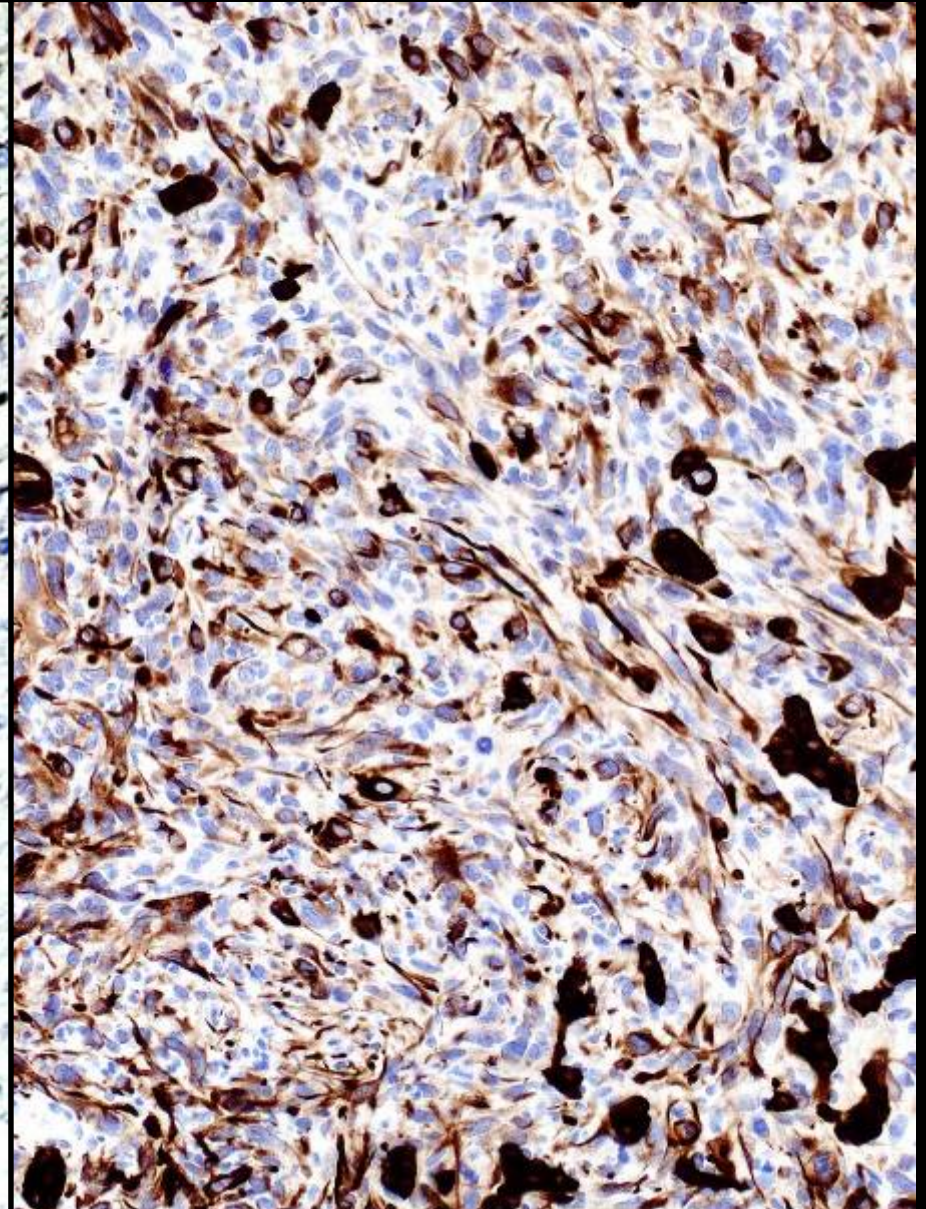
Cytokeratins in sarcomas



Cytokeratins in non-epithelial tumours



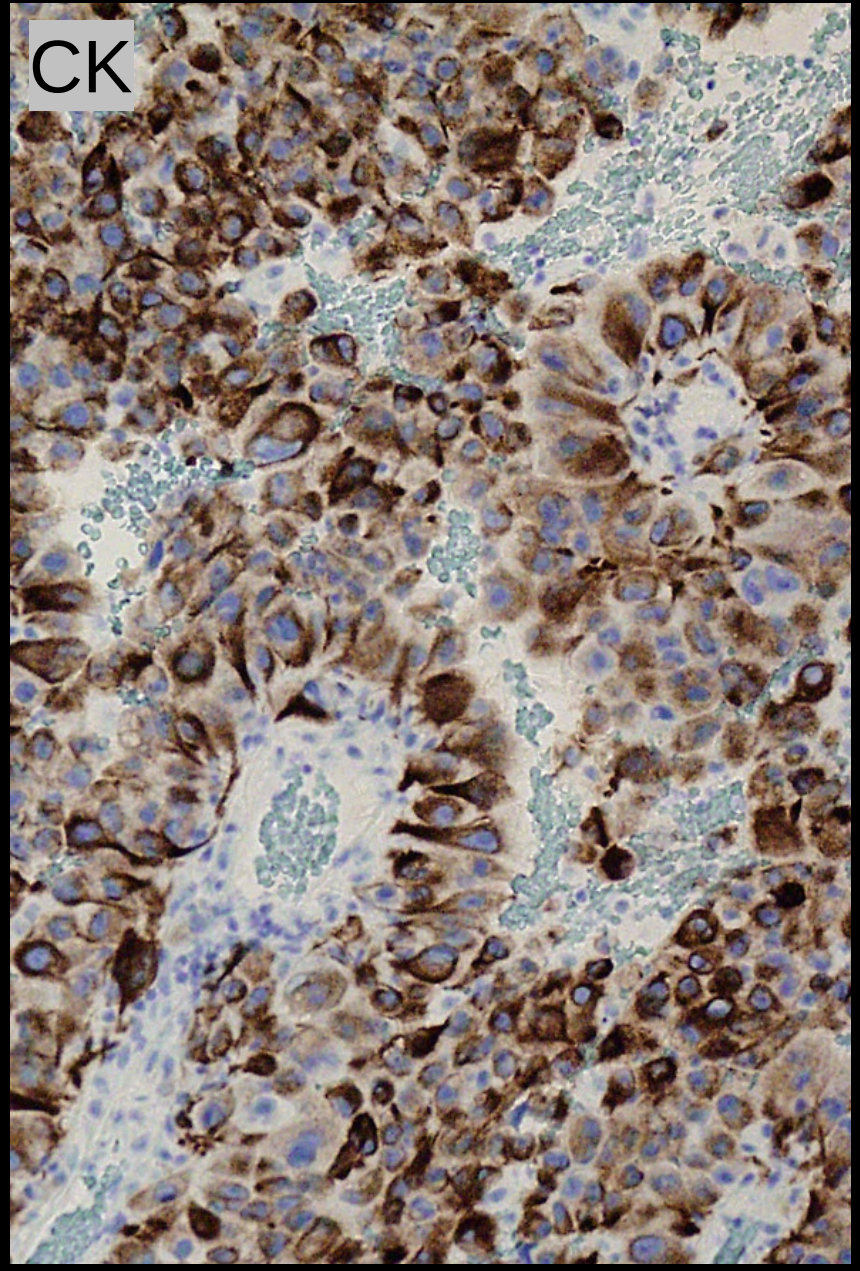
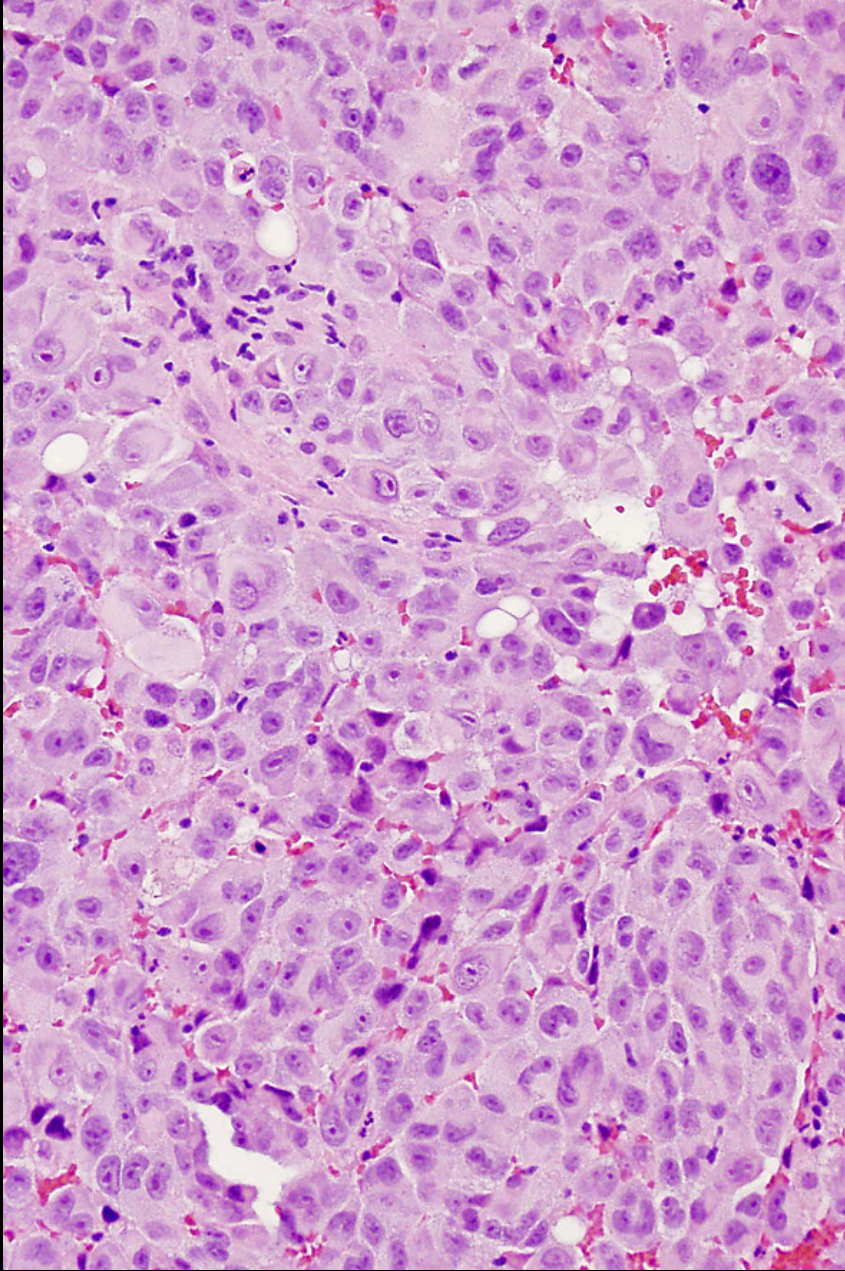
Leiomyosarcoma



Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

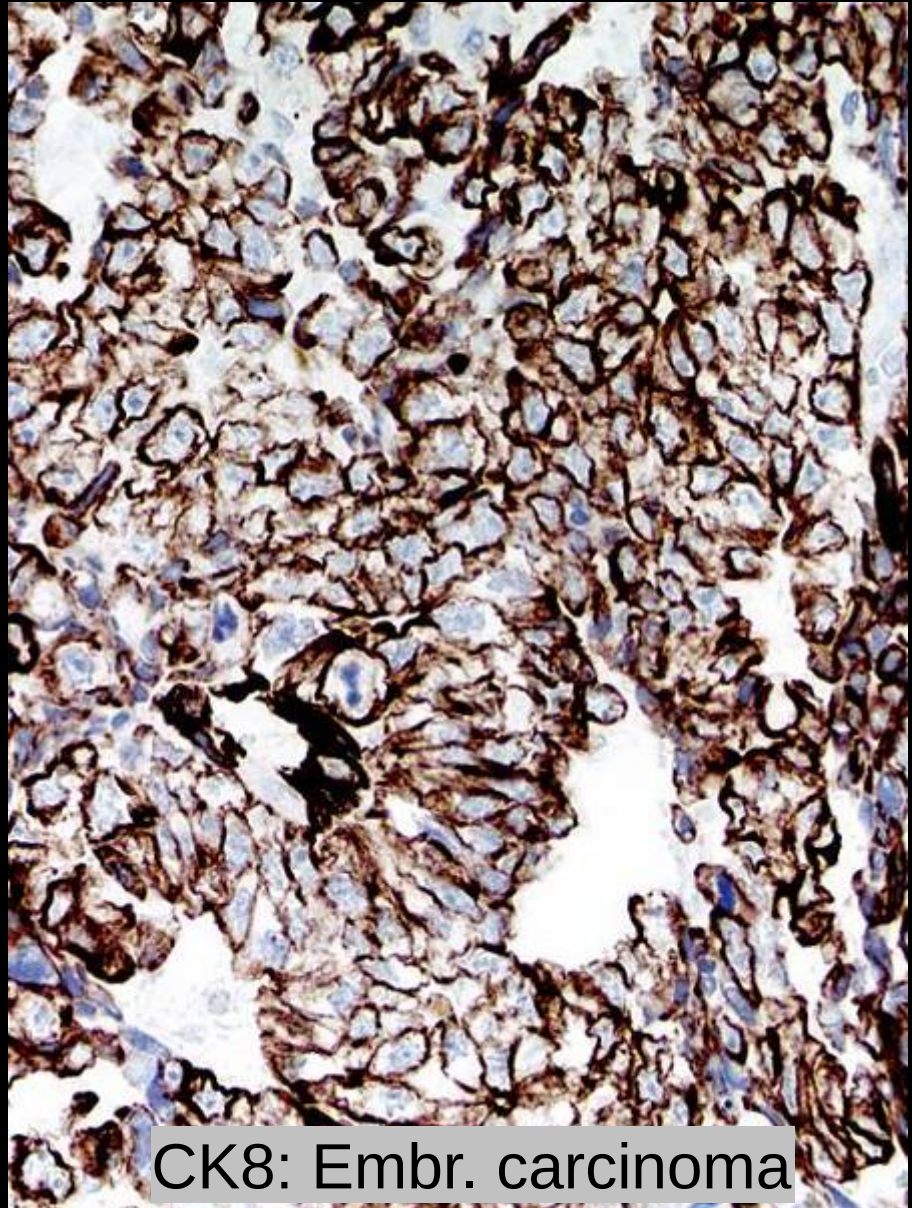
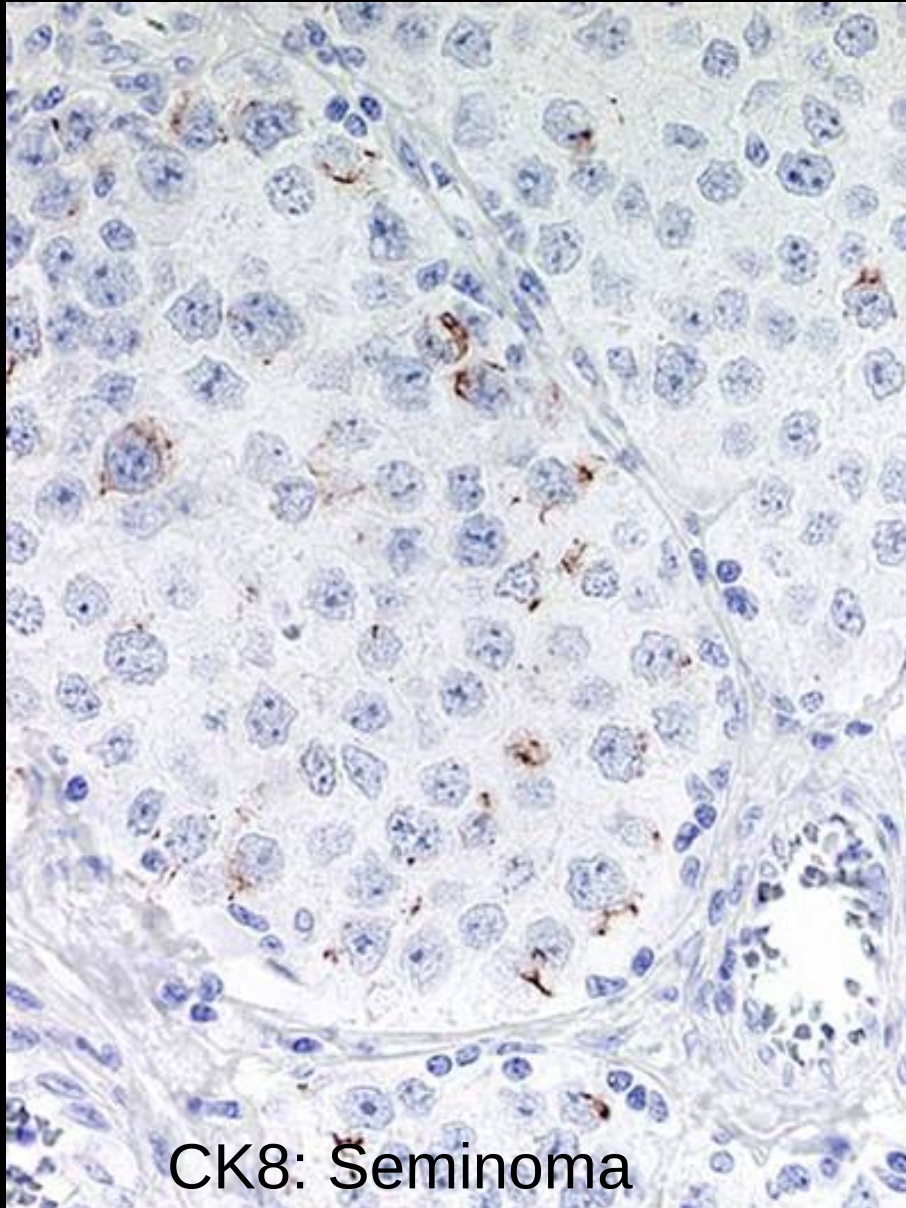
Cytokeratins in malignant melanoma



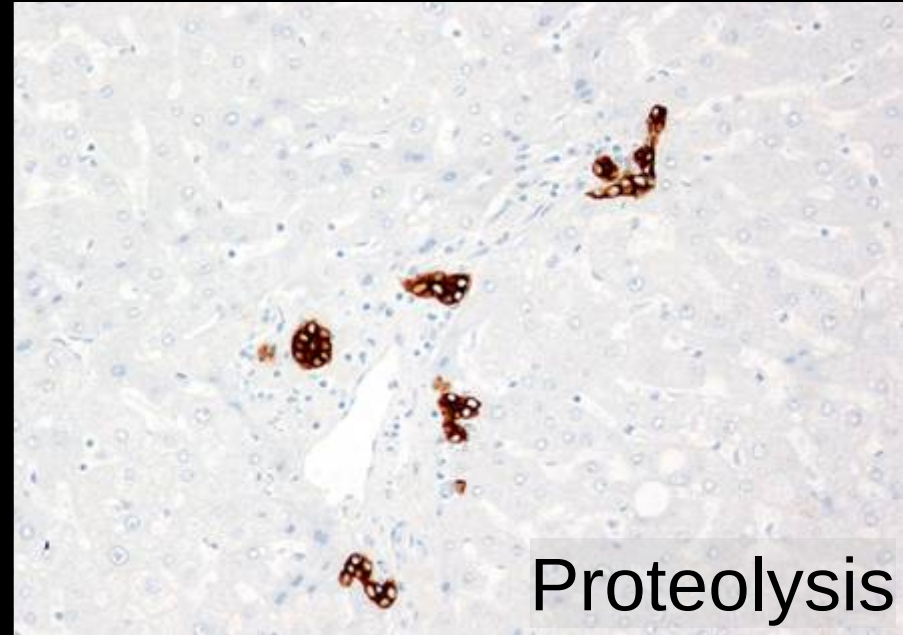
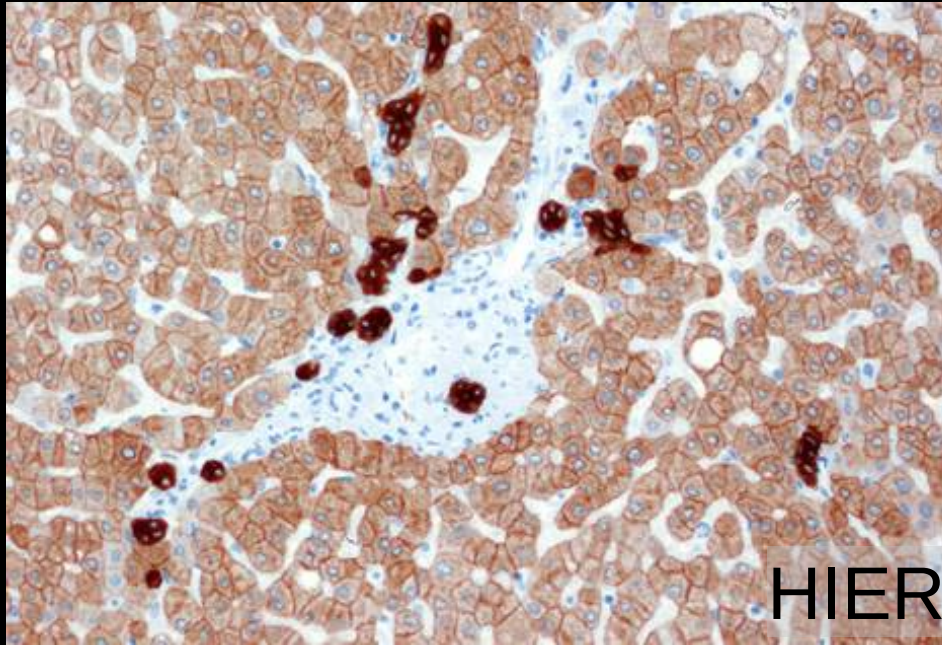
Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

Cytokeratins in germ cell tumours

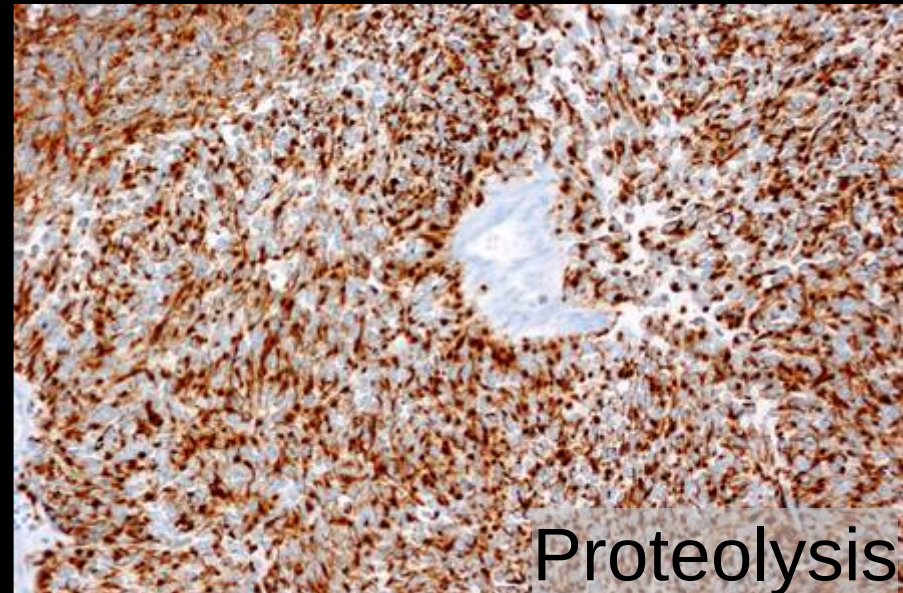


Cytokeratins: retrieval causing false negativity

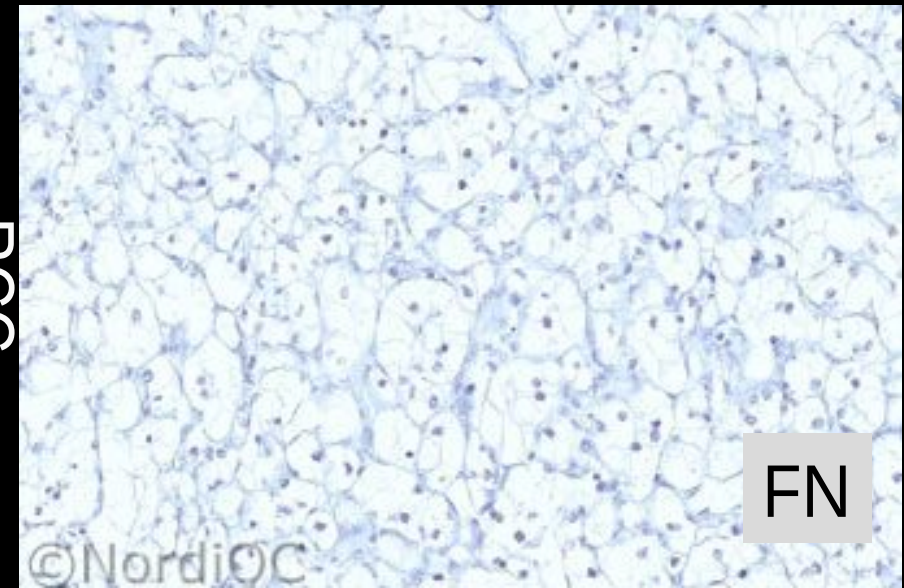
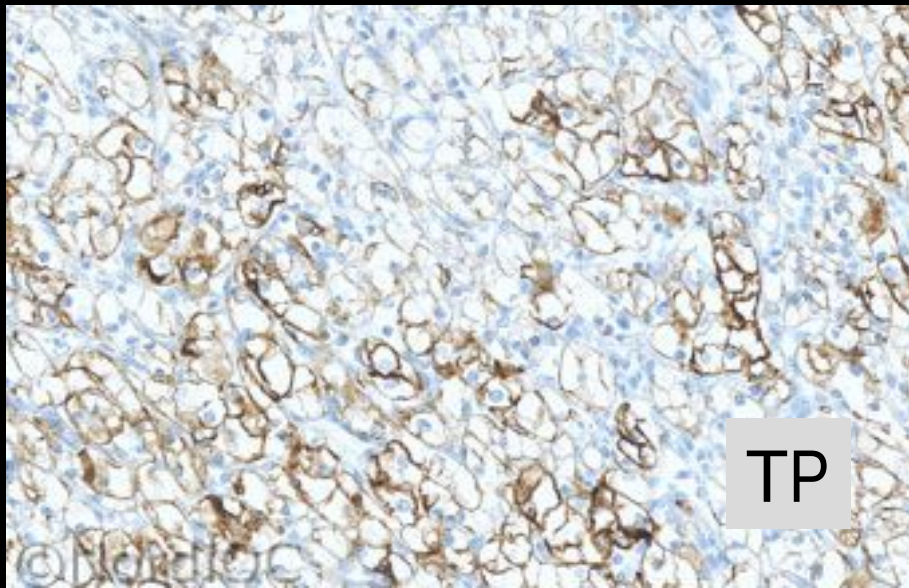
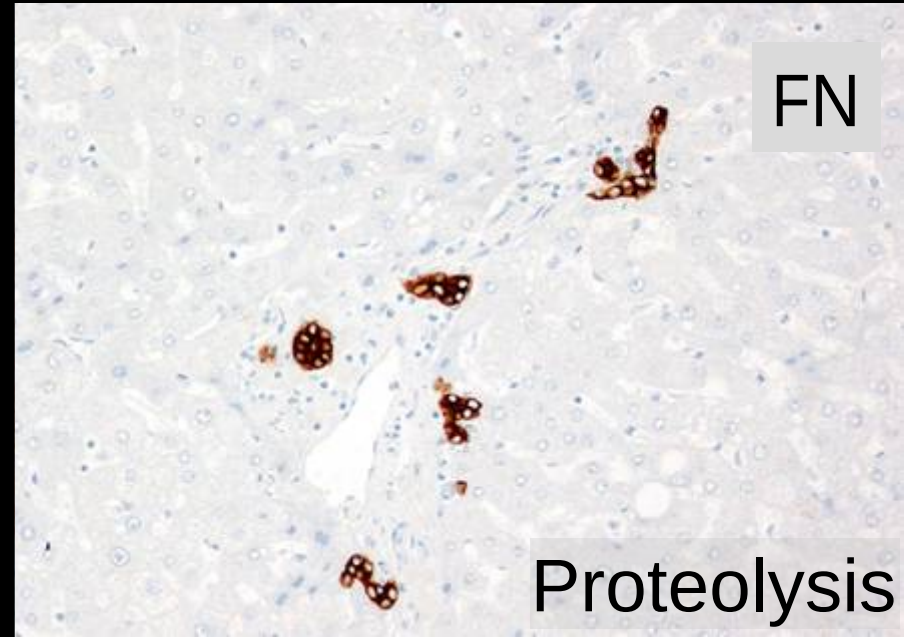
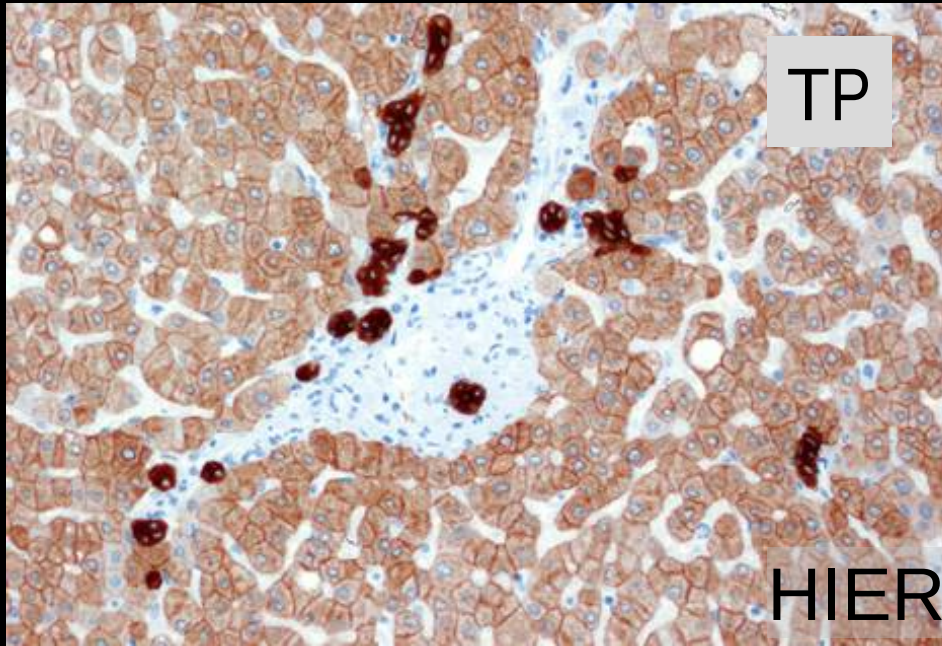


- AE1 detects CK8 after HIER only
- AE1 does not detect CK18
- AE3 does not detect CK8/CK18

SCLC



Cytokeratins: retrieval causing false negativity



RCC

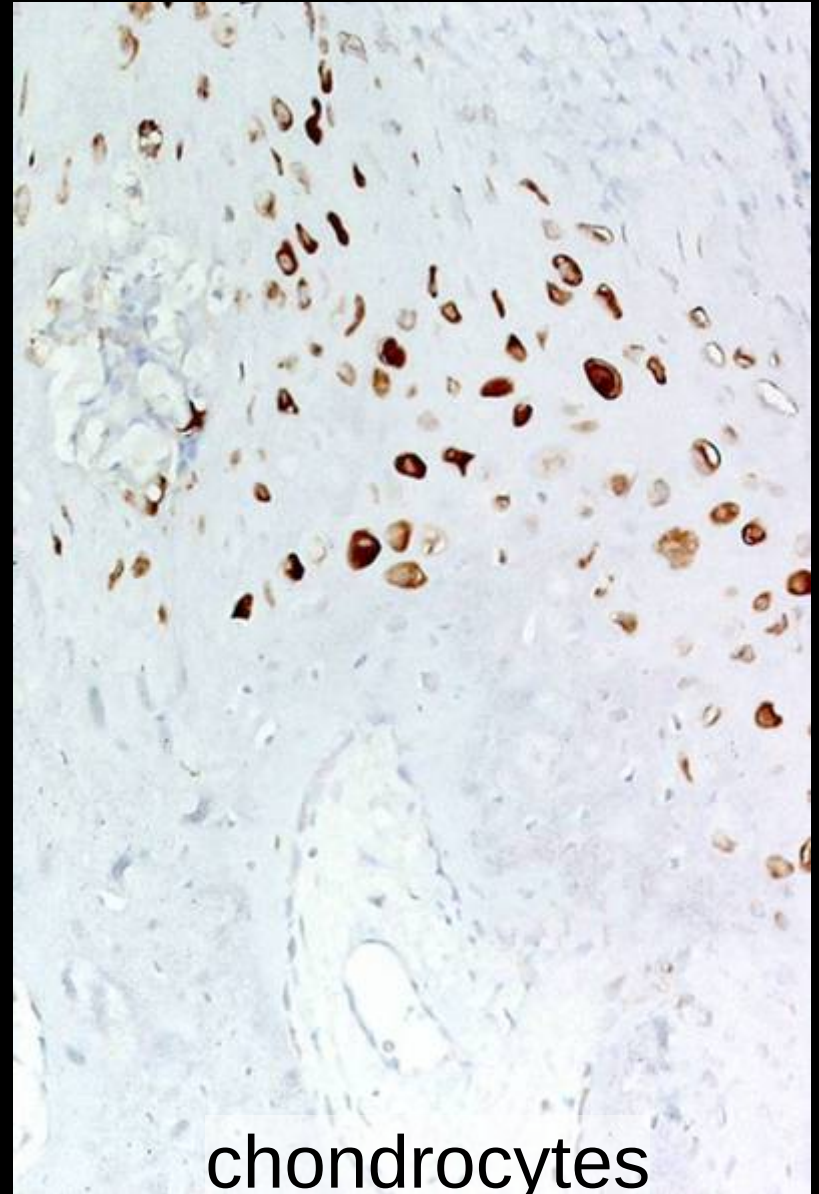
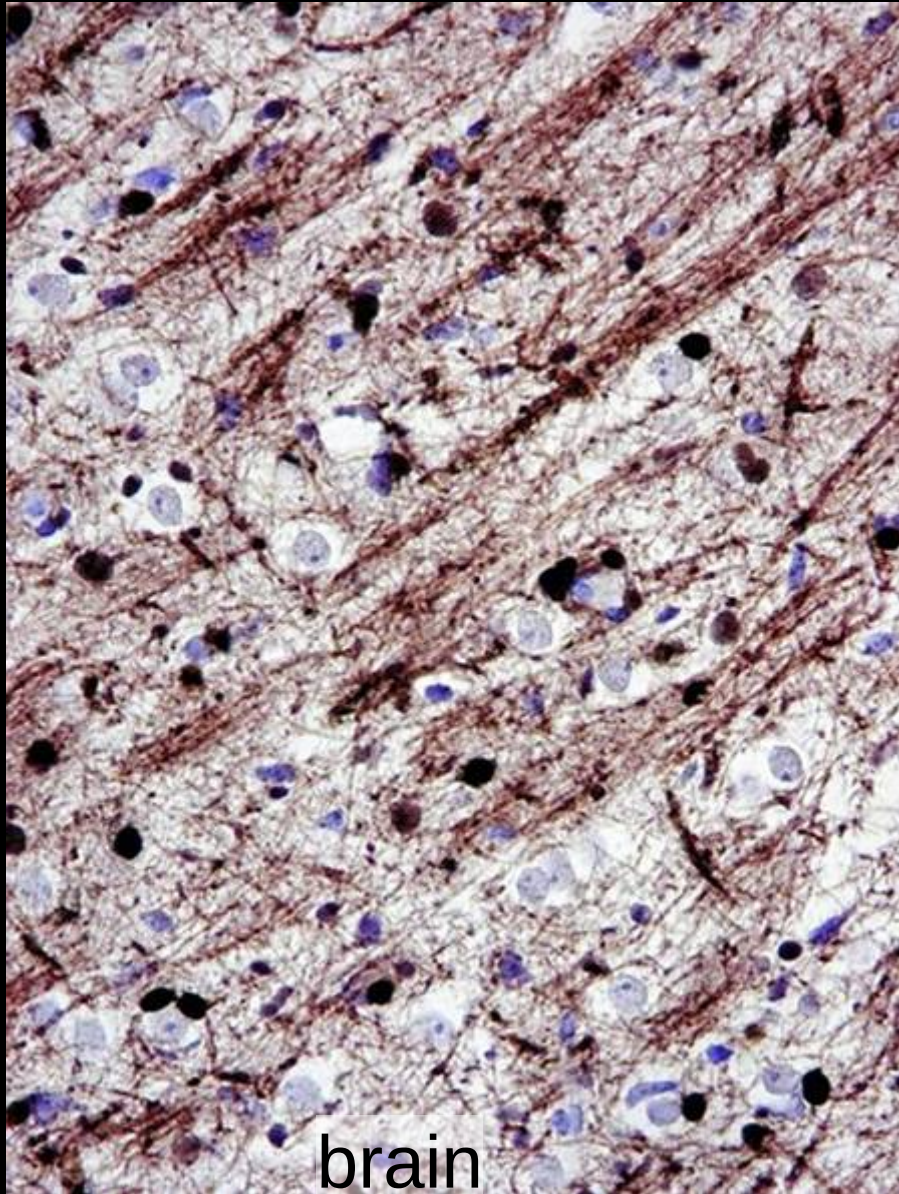
Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

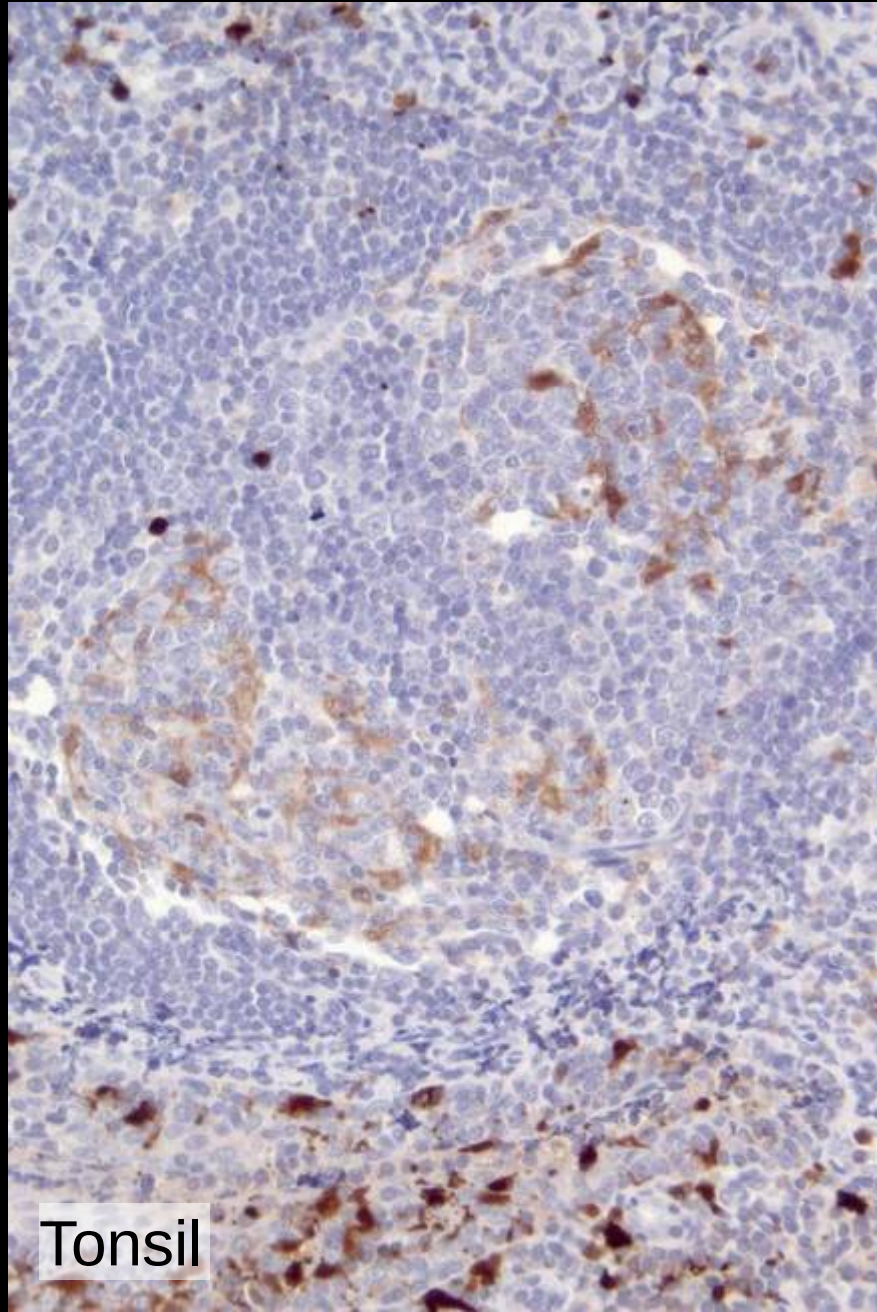
S-100 protein

- Family of acid calcium binding proteins 9/13 kDa
- Located in nuclei, cytoplasm and cell membranes
- at least 10 α -chains and one β -chain creating homo- and heterodimers
- S-100 β -chain mainly found in
 - Melanocytes
 - Glial cells
 - Langerhans' cells / interdigitating reticulum cells
 - Fat cells
 - Myoepithelial cells
- Polyclonal antibodies primarily detects the β -chain

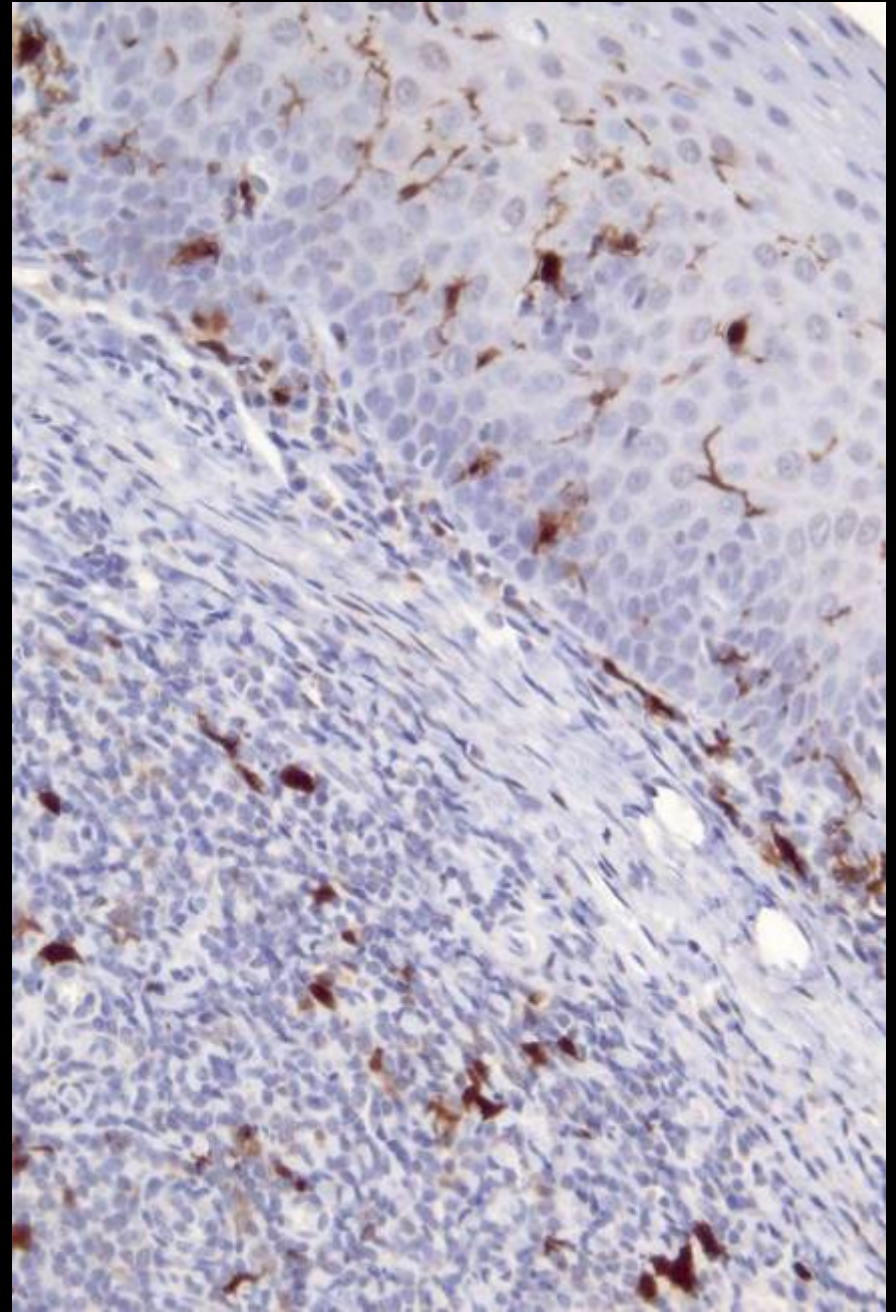
S-100 protein



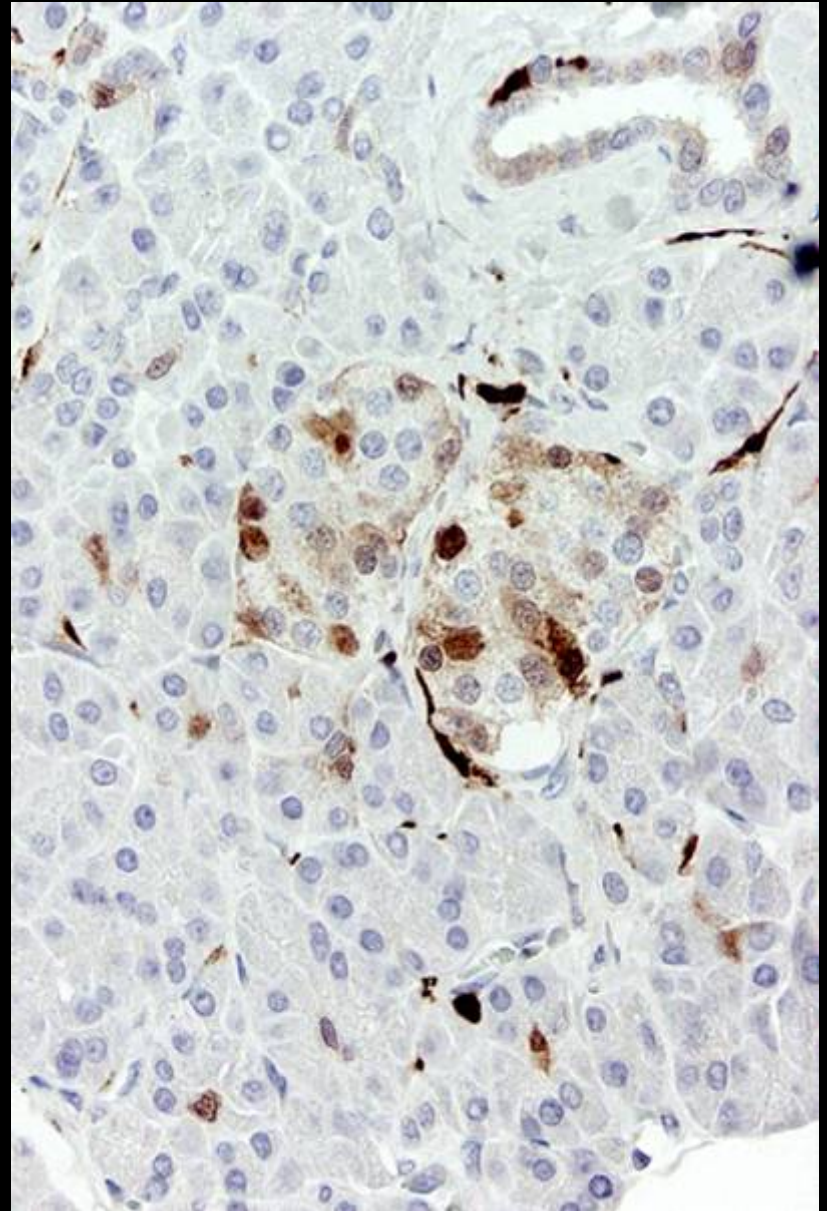
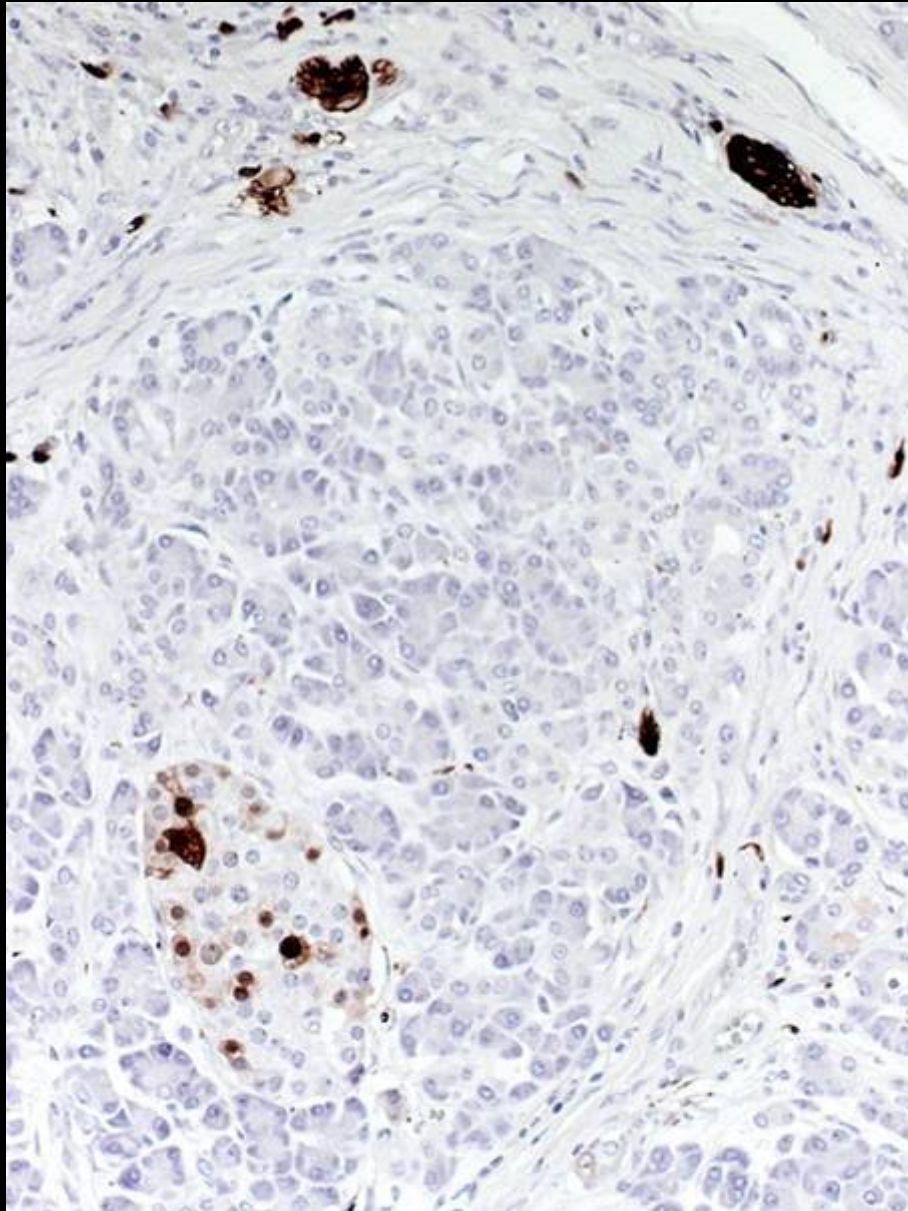
S-100 protein



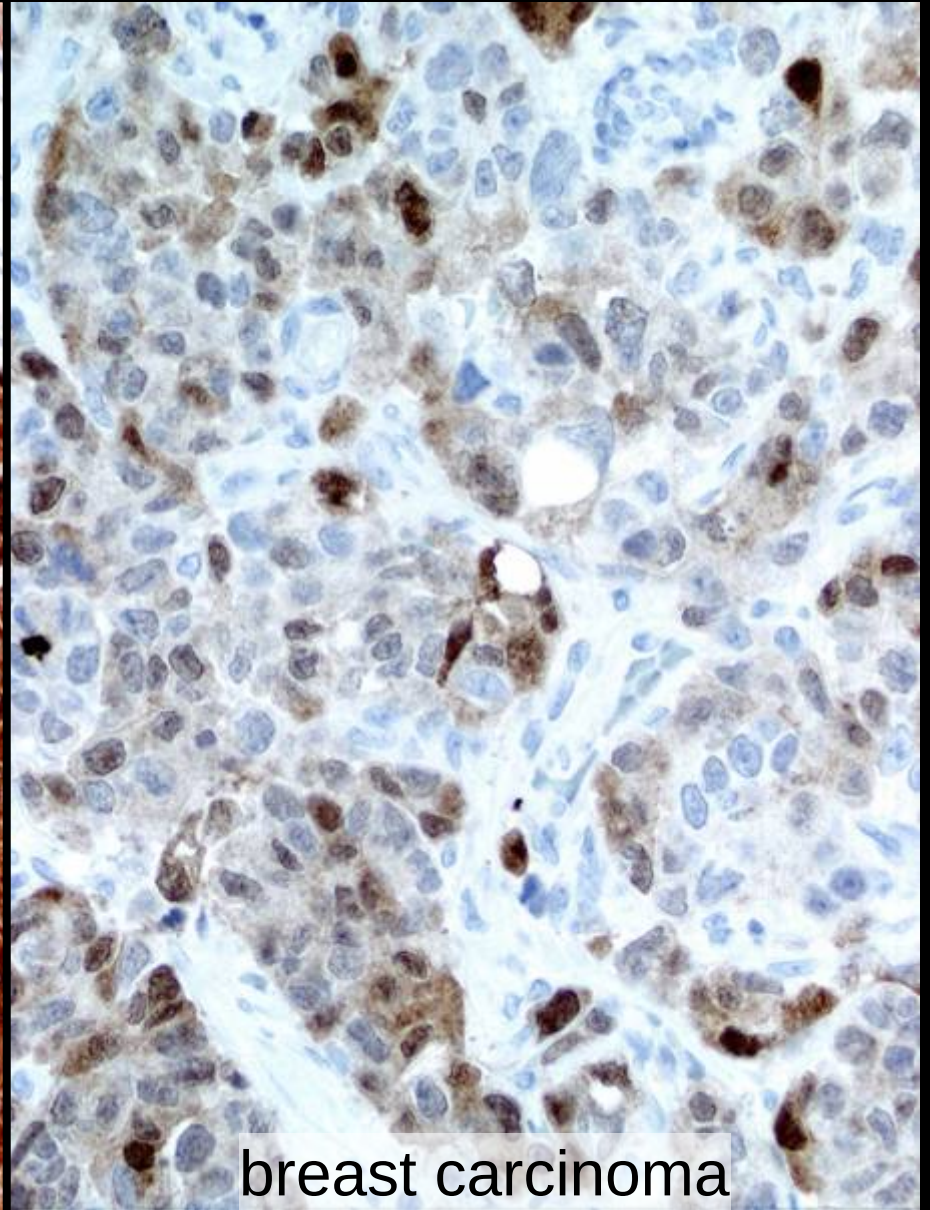
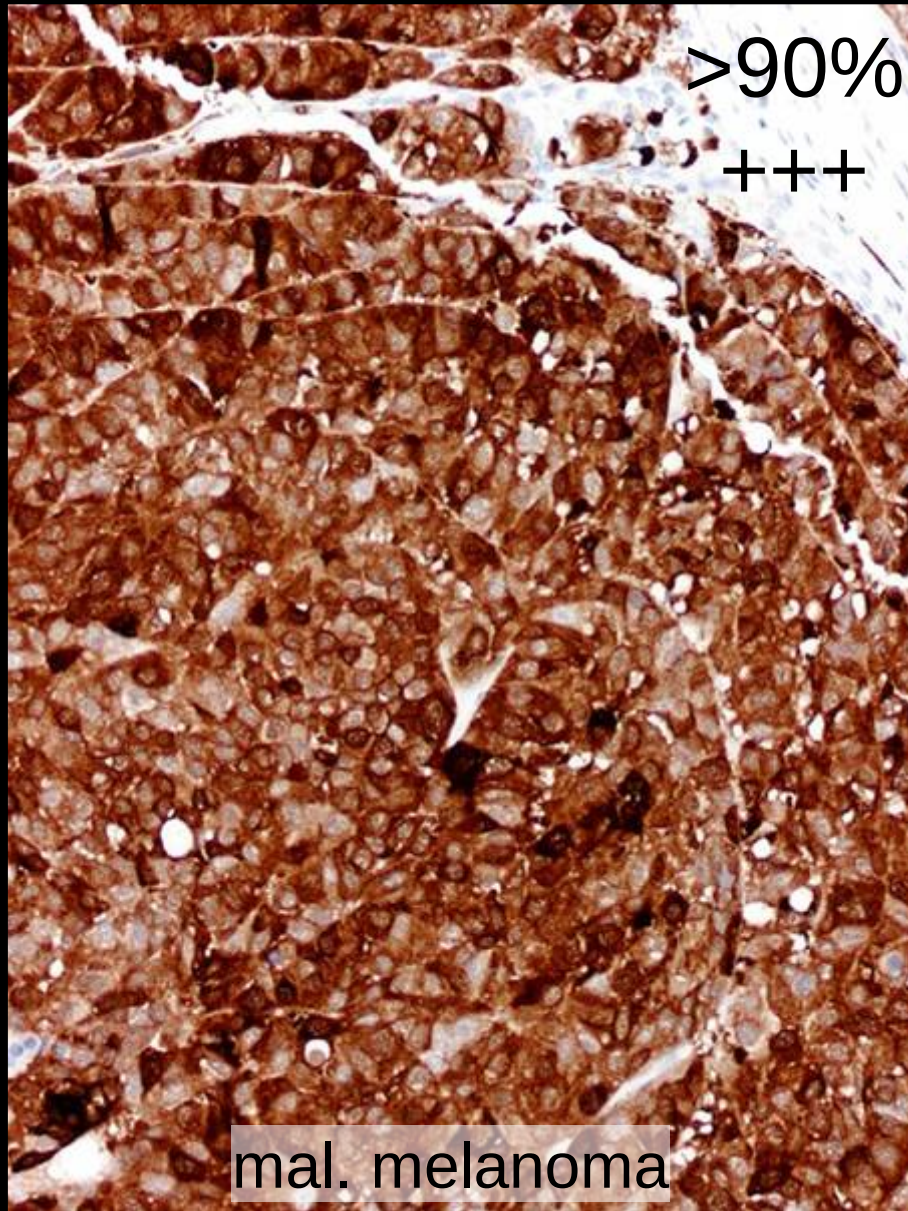
Tonsil



S-100 protein – pancreas

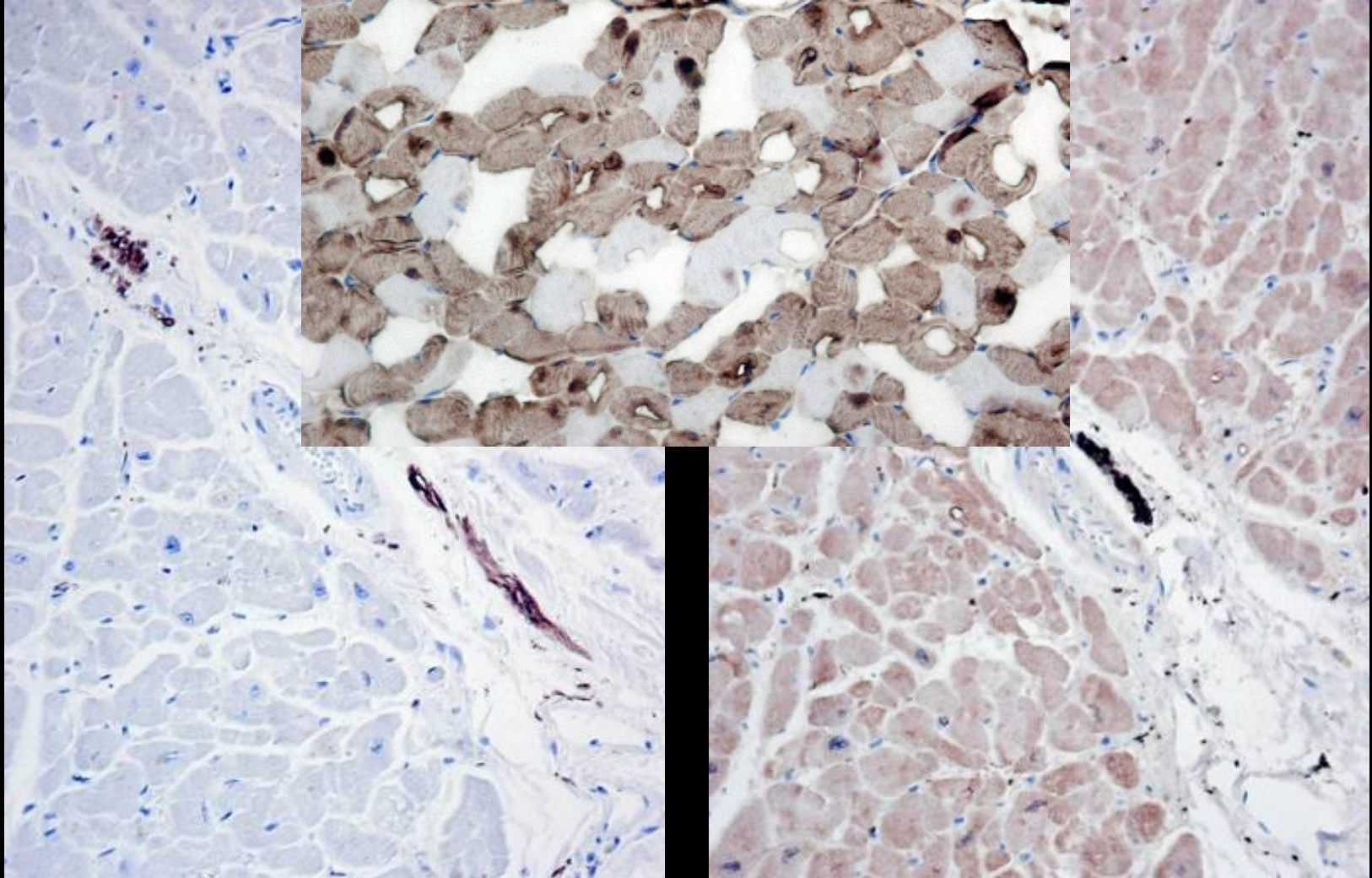


S-100 in malignant tumours



S-100 protein

To HIER or not..



Proteolytic

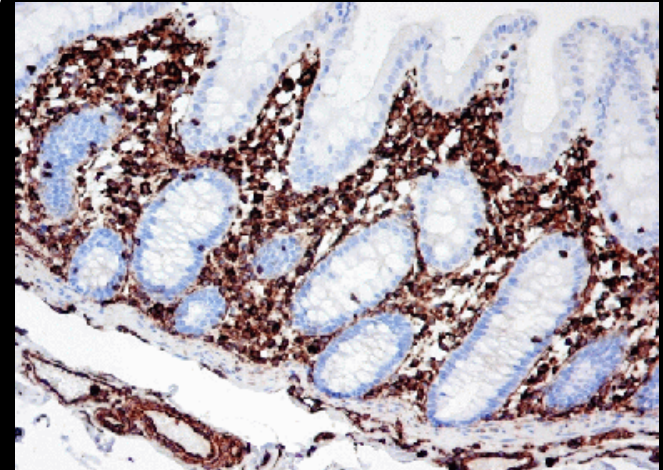
HIER

Primary panel for the unknown primary tumour

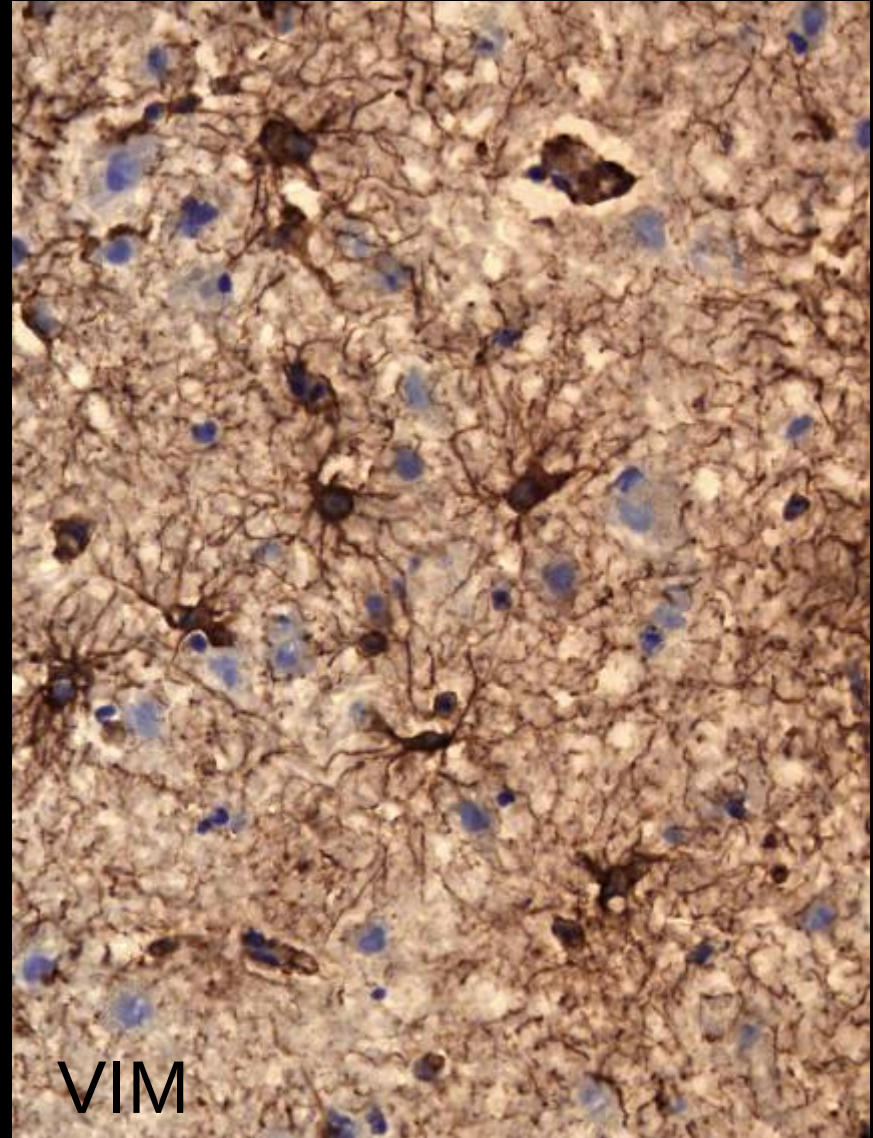
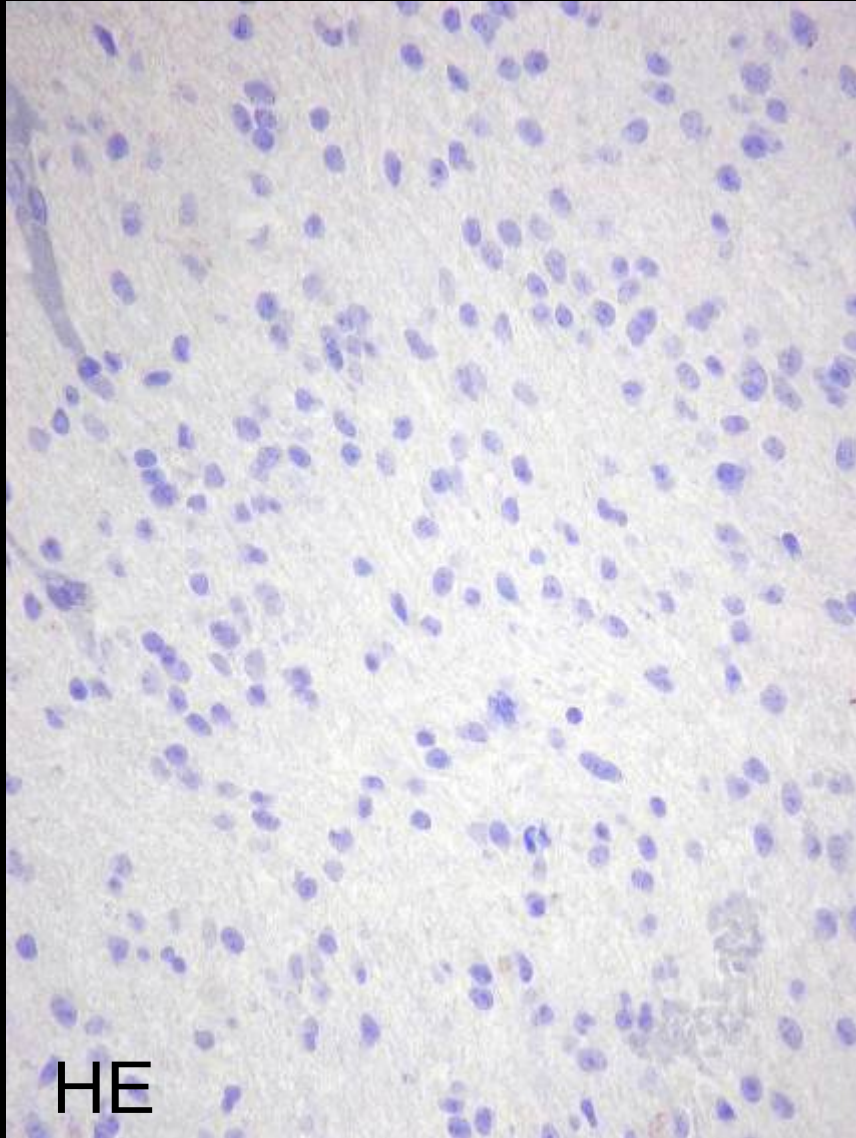
"Real"	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+ / (-)	- / (+)	- / (+)	+ / (-)
Epithelial neoplasms	-	+ / (-)	- / +	- / +
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	- / (+)	- / +	+
Non-neuronal neuroepithelial neoplasms	-	- / (+)	+	+
Germ cell neoplasms	-	- / +	- / +	+

Vimentin

- Cytoplasmic intermediate filament, 57 kDa
- Present in all mesenchymal cells
- Present in early stages of all cells, replaced by other intermediate filaments in most non-mesenchymal cells
- Coexpressed with cytokeratin in some epithelia
 - Endometrium, renal tubules, thyroid gland ...
- Coexpressed with cytokeratin in some non-epithelial cells
 - Mesothelium

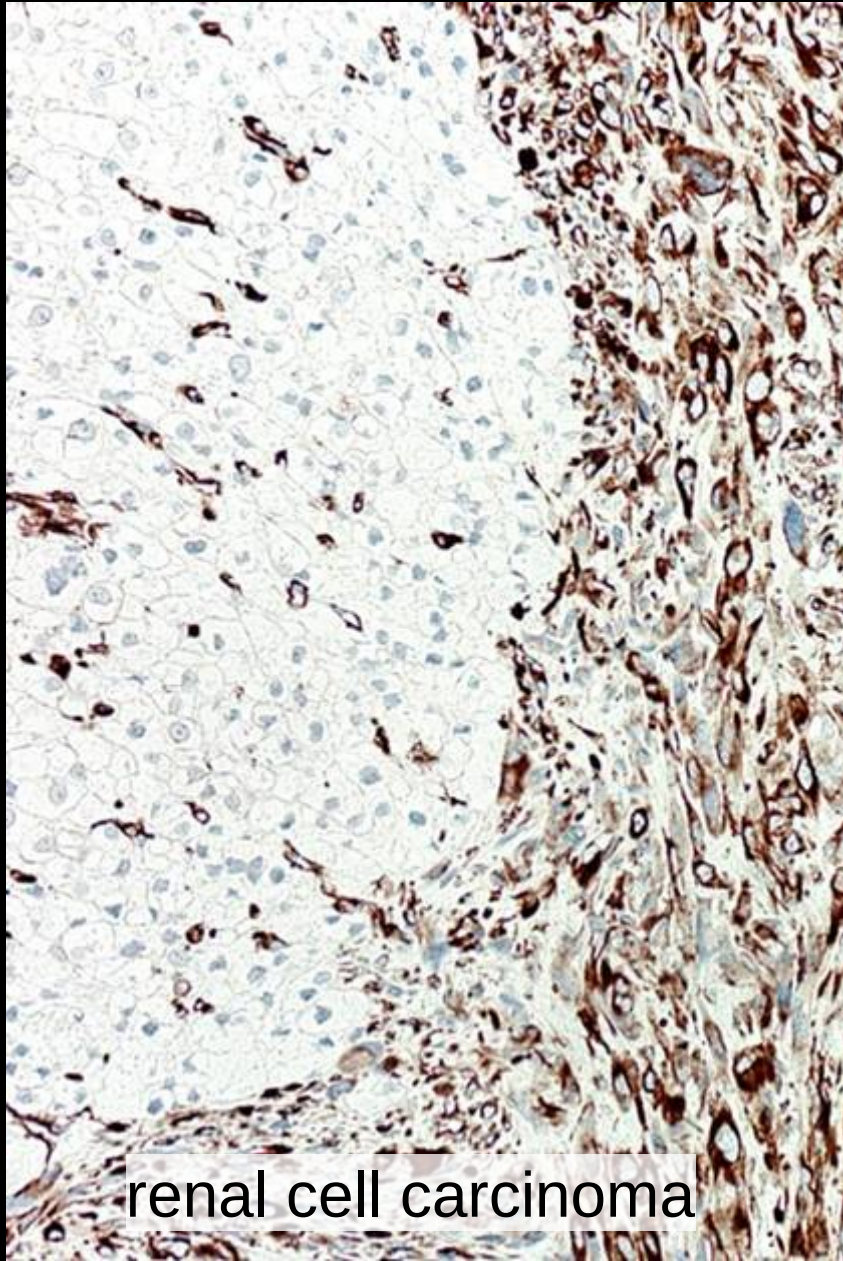


Vimentin in normal tissue

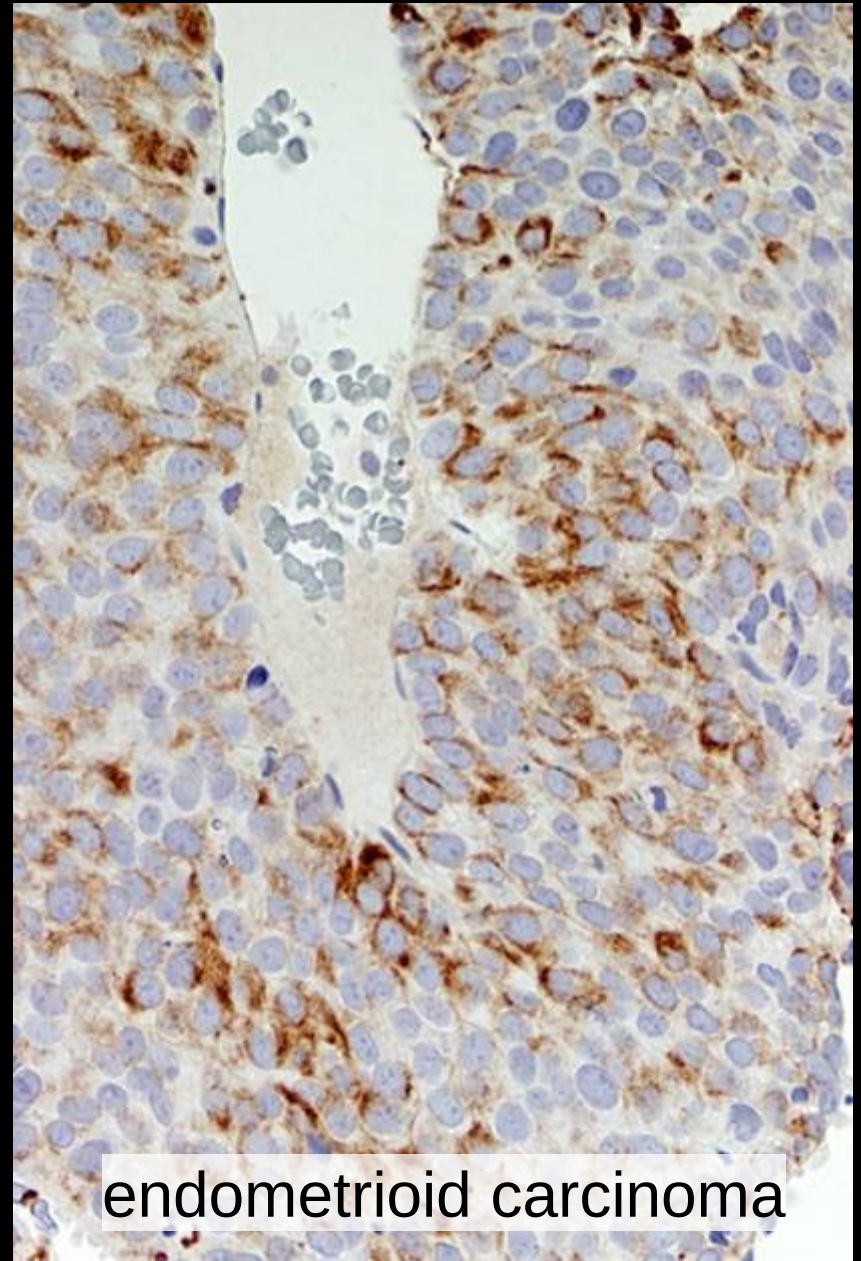


Normal brain

Vimentin in carcinomas

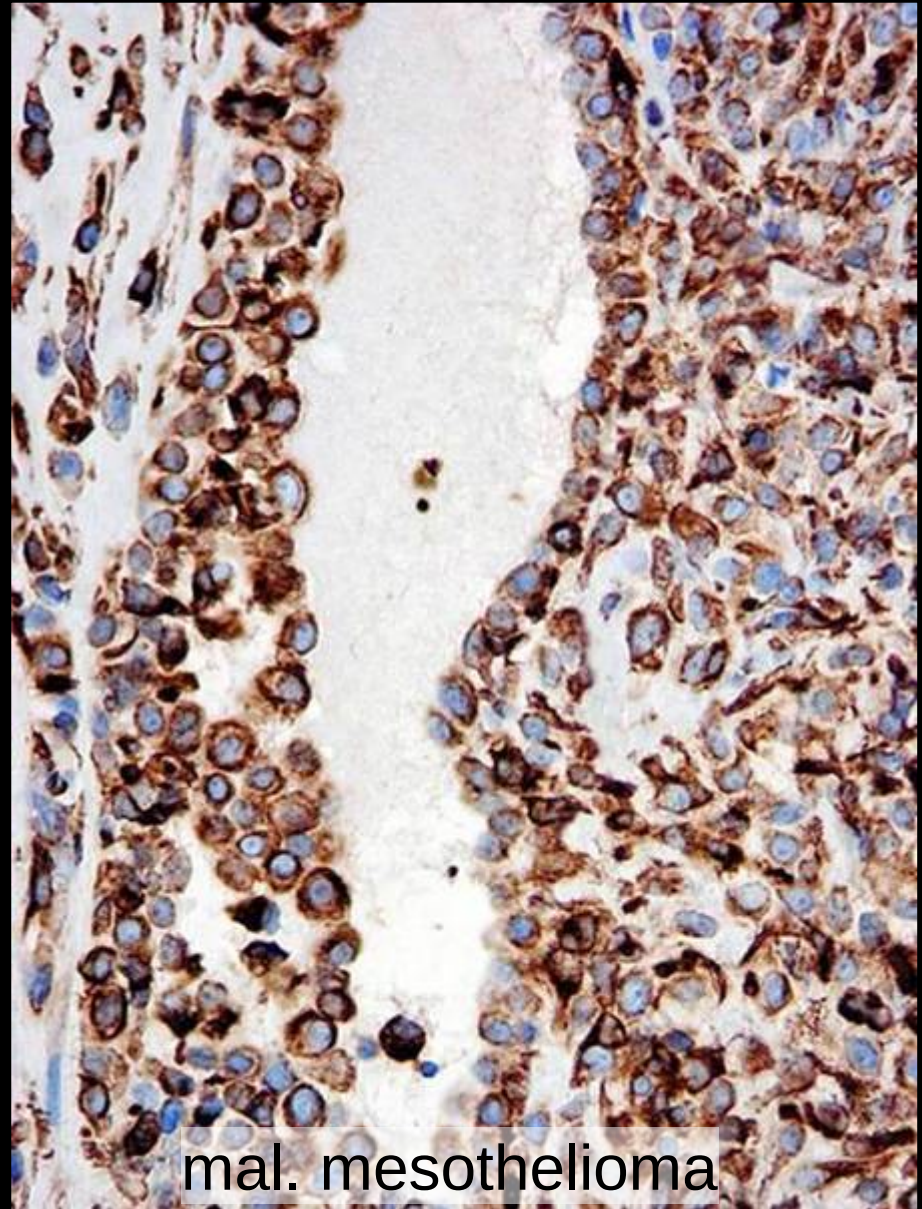
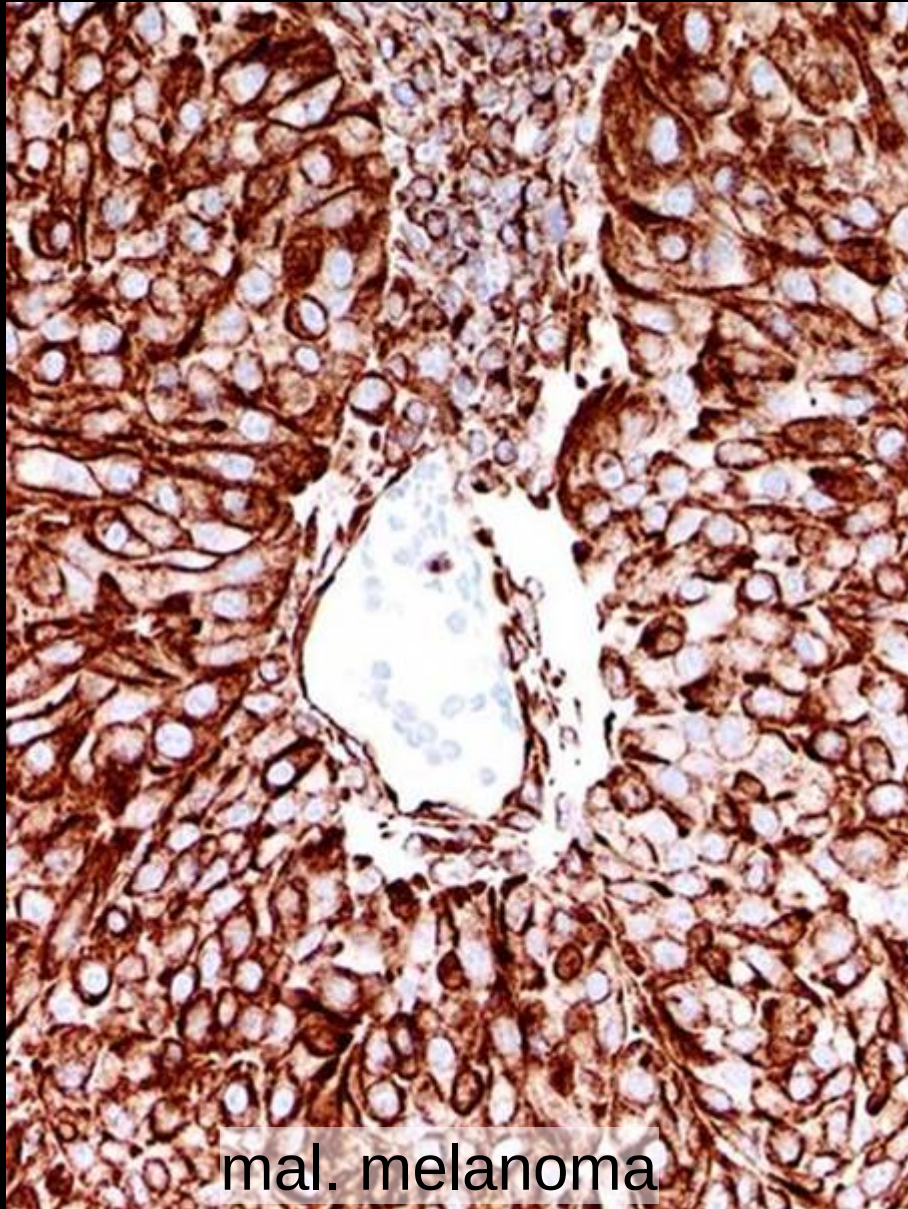


renal cell carcinoma



endometrioid carcinoma

Vimentin in non-epithelial tumours



International Symposium on Immunohistochemistry

January 4th - 7th, 2018

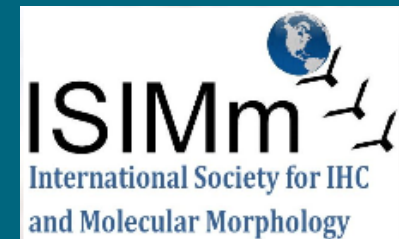
Hosted by Dept. of Histopathology, Tata Medical Center, Kolkata, India

In collaboration with NordiQC, Alborg, Denmark and ISIMM, California, USA



IHC Classification of undifferentiated tumors – the primary panel

Thank you
for your attention



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