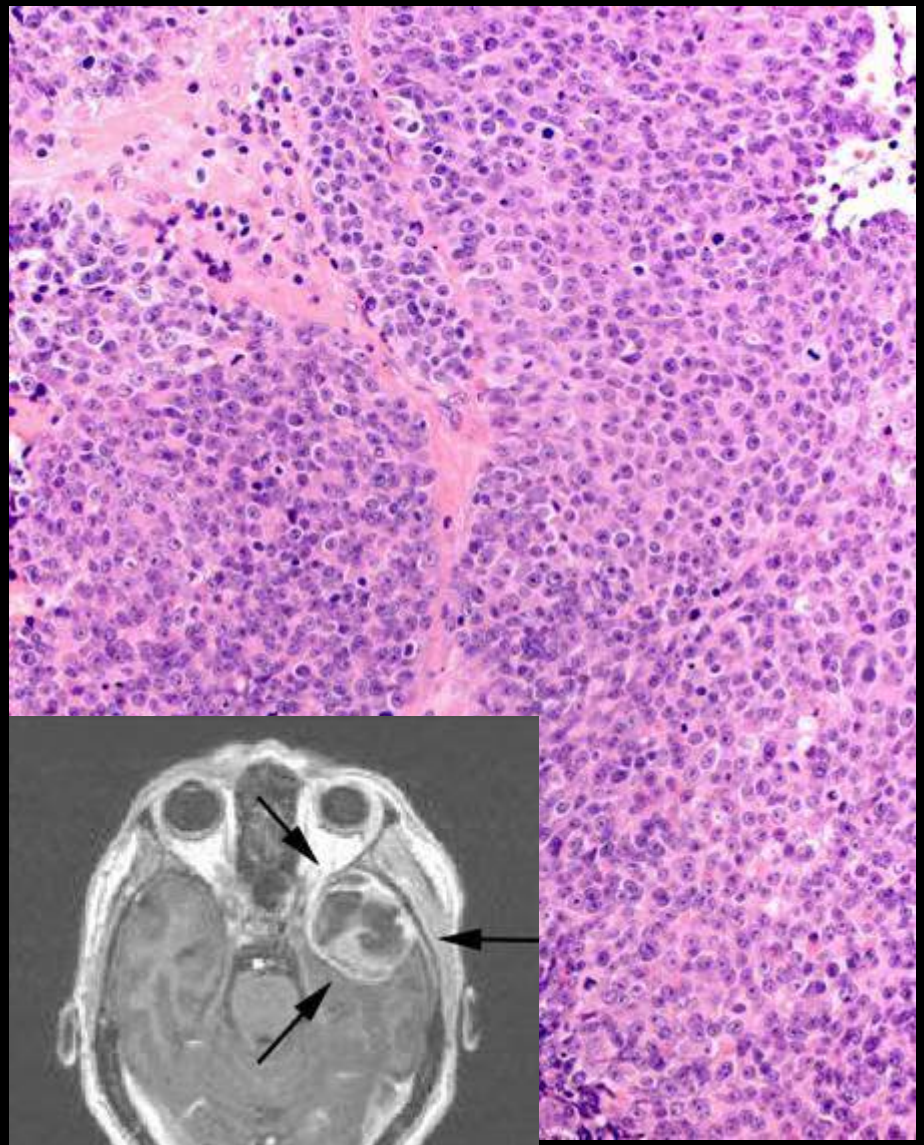
The Fifth International Workshop in Diagnostic Immunohistochemistry

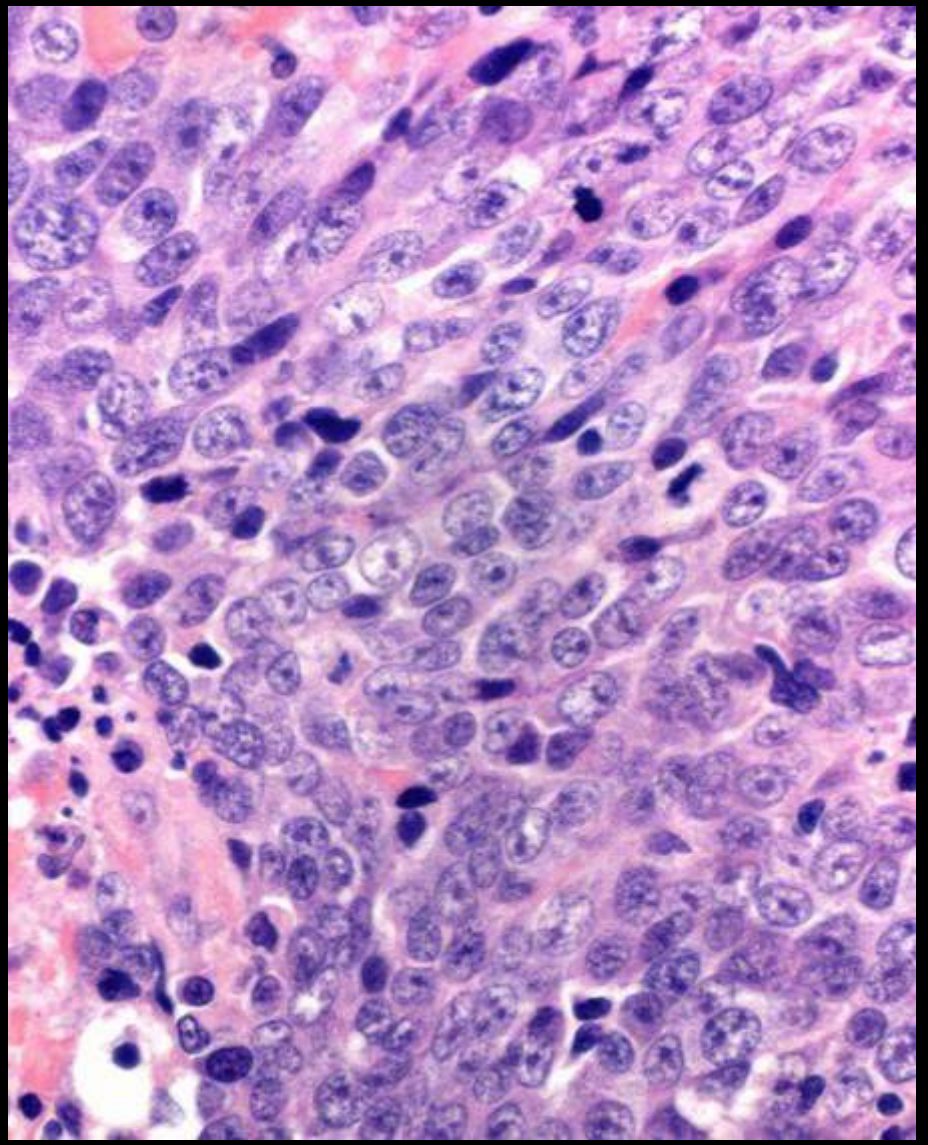
NordiQC

# Immunohistochemical classification of the unknown primary, undifferentiated tumor

Prof. Mogens Vyberg
NordiQC
Institute of Pathology
Aalborg, Denmark

# Tumours of unknown origin: Histology

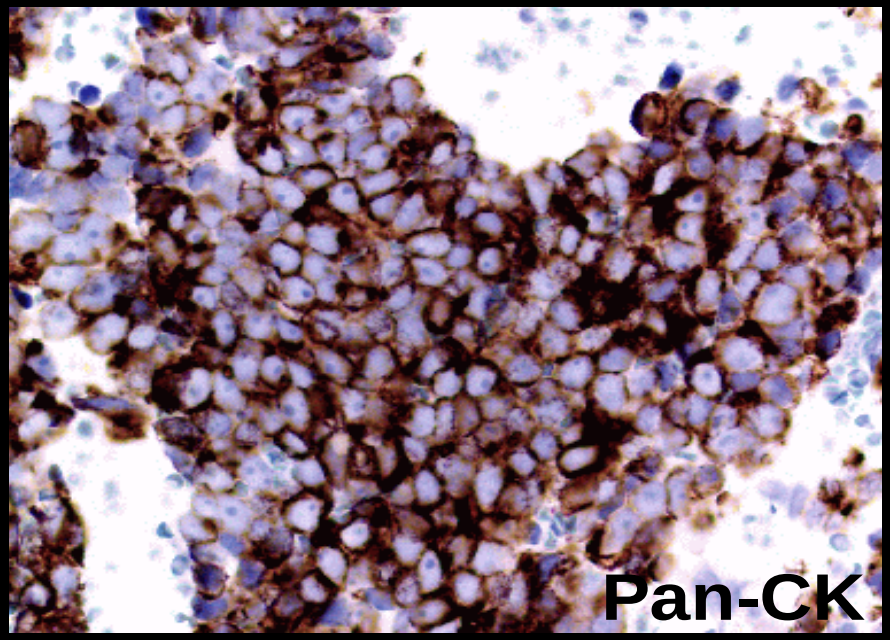


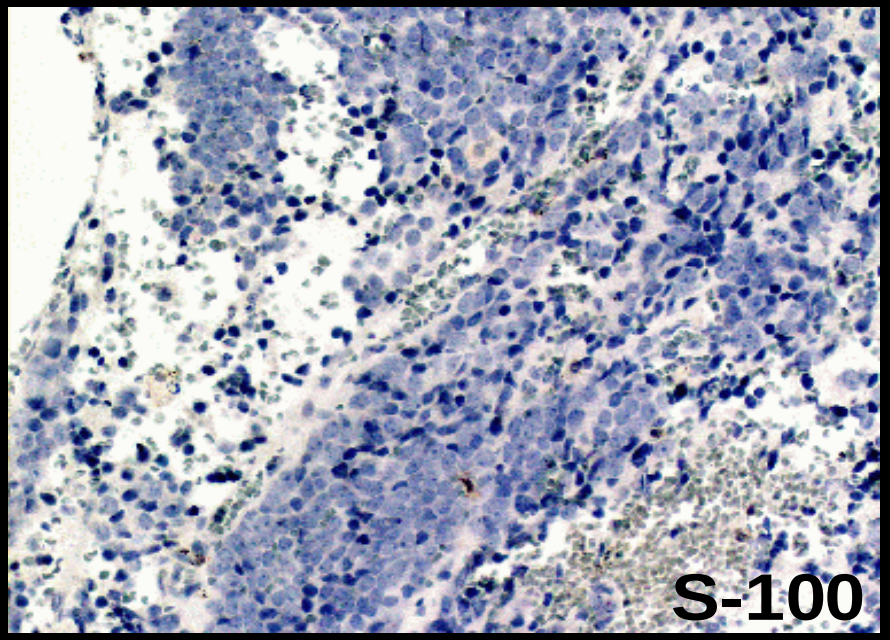


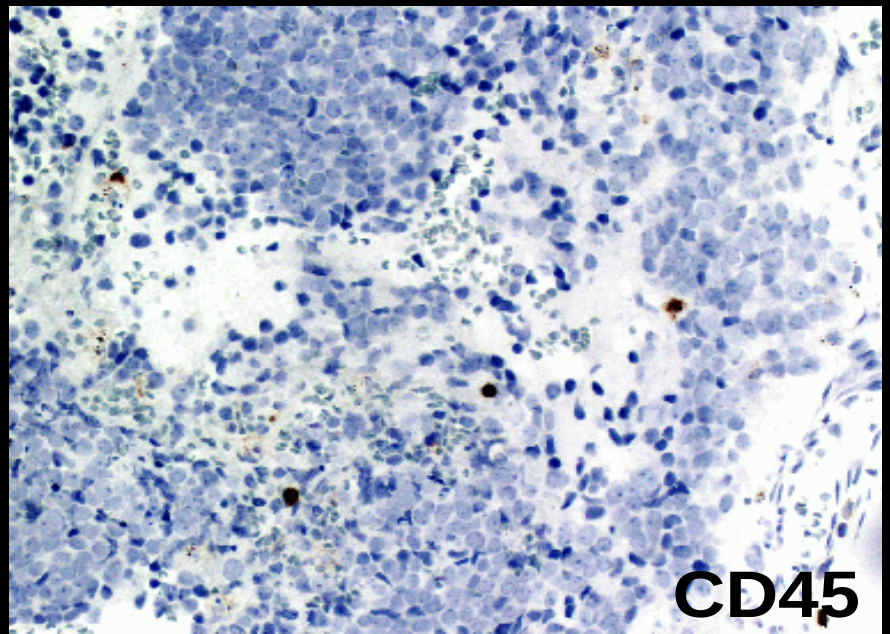


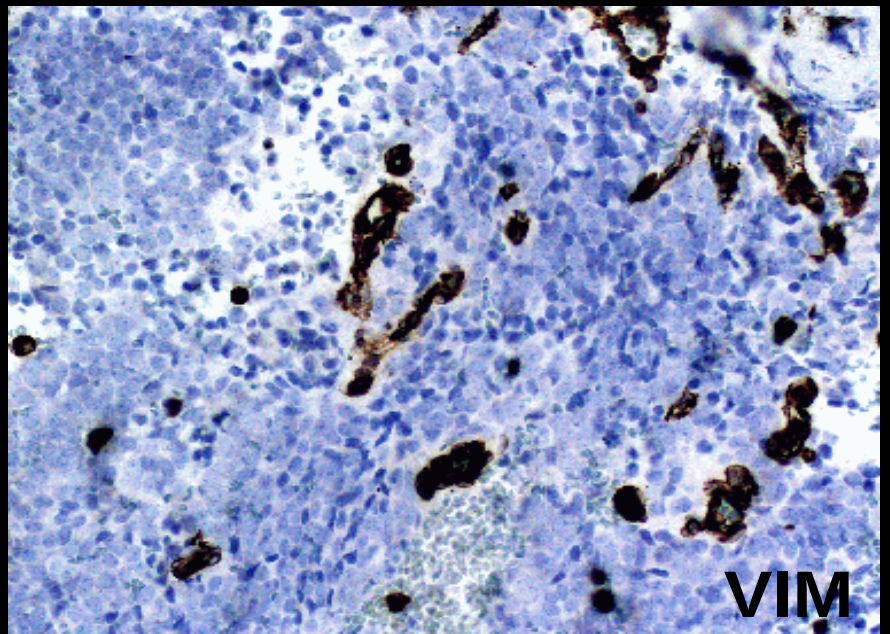
Brain tumour - biopsy

# 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 remain 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

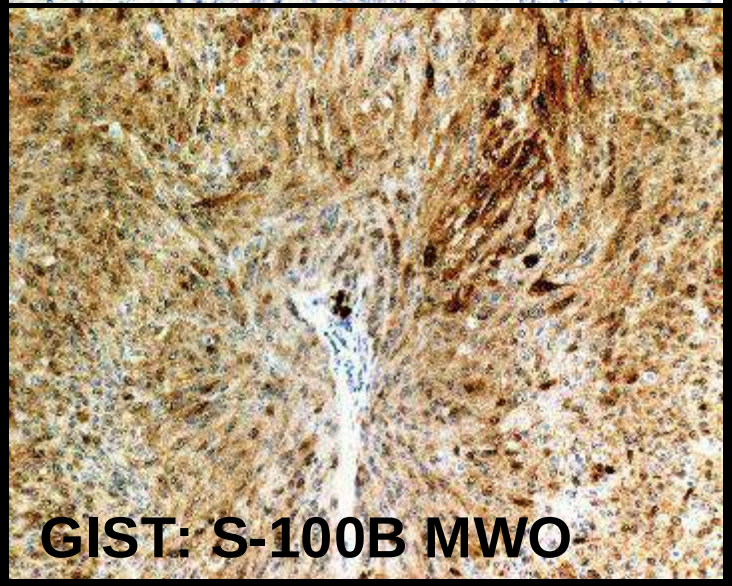
- diagnostic markers

## Antibodies available

- applic. in diagnostic algorithms

## Methods

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

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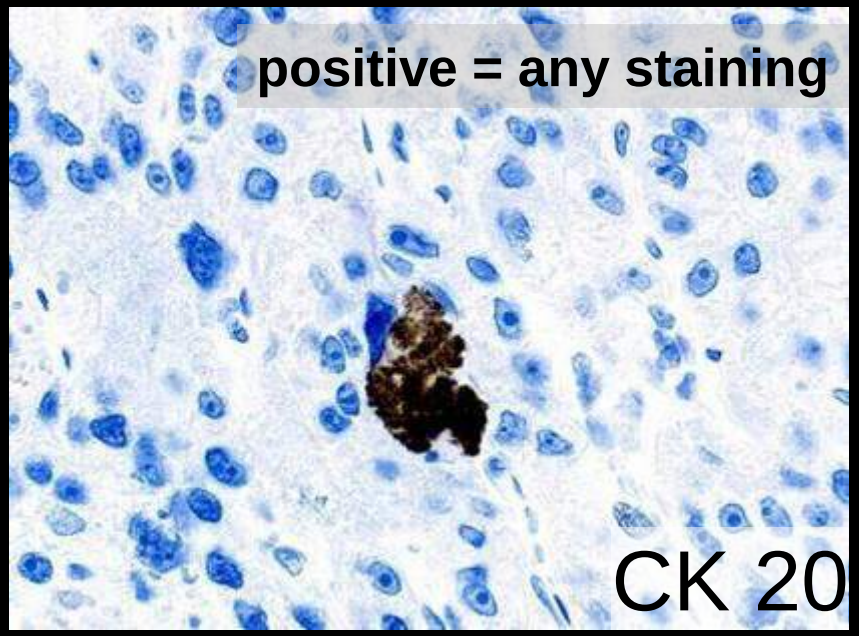
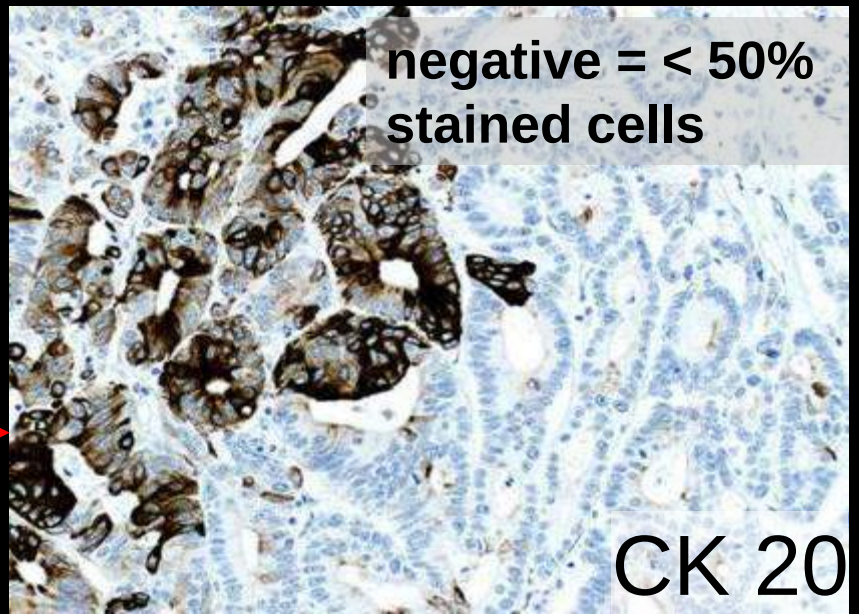
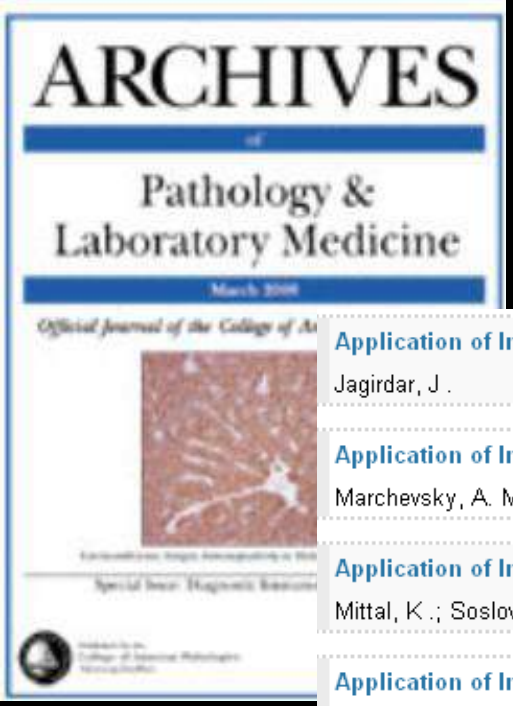


# IHC classification of the Unknown Primary Tumour

- Likelihood of a given diagnosis
- Relevant differential diagnoses

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




# March 2008

**Application of Immunohistochemistry to the Diagnosis of Primary and Metastatic Carcinoma to the Lung**

Jagirdar, J .

**Application of Immunohistochemistry to the Diagnosis of Malignant Mesothelioma**

Marchevsky, A. M .

**Application of Immunohistochemistry to Gynecologic Pathology**

Mittal, K .; Soslow, R .; McCluggage, W. G .

**Application of Immunohistochemistry to Infections**

Eyzaguirre, E .; Haque, A. K .

**Application of Immunohistochemistry to the Genitourinary System (Prostate, Urinary Bladder, Testis, and Kidney)**

Hammerich, K. H .; Ayala, G. A .; Wheeler, T. M .

**Application of Immunohistochemistry in the Diagnosis of Non-Hodgkin and Hodgkin Lymphoma**

Higgins, R. A .; Blankenship, J. E .; Kinney, M. C .

**Acute Leukemia Immunohistochemistry: A Systemic Diagnostic Approach**

Olsen, R. J .; Chang, C.-C .; Herrick, J. L .; Zu, Y .; Ehsan, A .

**Application of Immunohistochemistry to Soft Tissue Neoplasms**

Heim-Hall, J .; Yohe, S. L .

**Application of Immunohistochemistry to Liver and Gastrointestinal Neoplasms: Liver, Stomach, Colon, and Pancreas**

Geller, S. A .; Dhall, D .; Alsabeh, R .

**The Differential Diagnosis of Central Nervous System Tumors: A Critical Examination of Some Recent Immunohistochemical Applications**

Edgar, M. A .; Rosenblum, M. K .

MPP 19

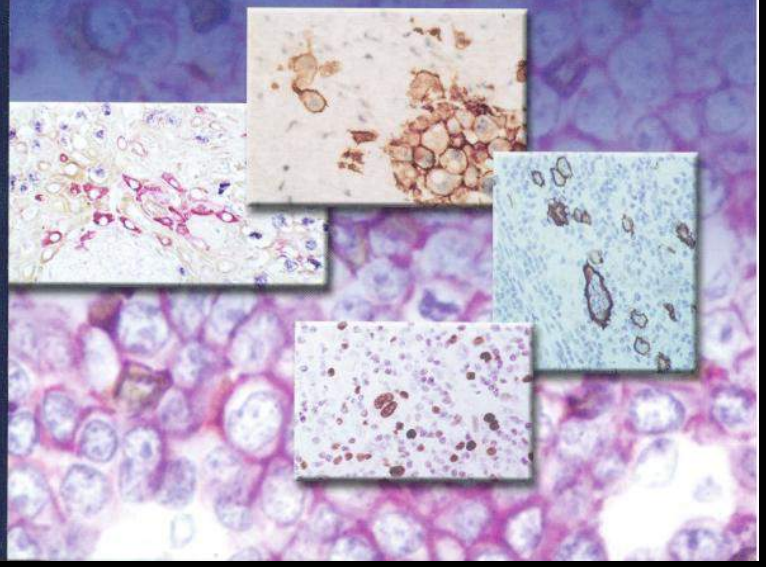
Clive R. Taylor
Richard J. Cote

# Immunomicroscopy

## A Diagnostic Tool for the Surgical Pathologist

MAJOR PROBLEMS IN PATHOLOGY

THIRD EDITION



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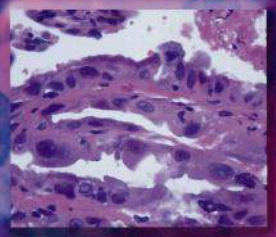
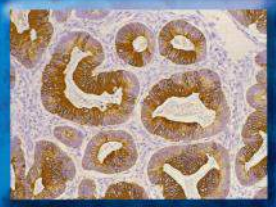
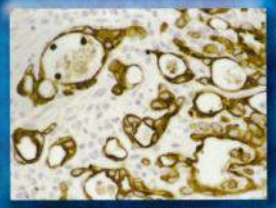


# Diagnostic Immunohistochemistry

DAVID DABBS





SECOND EDITION

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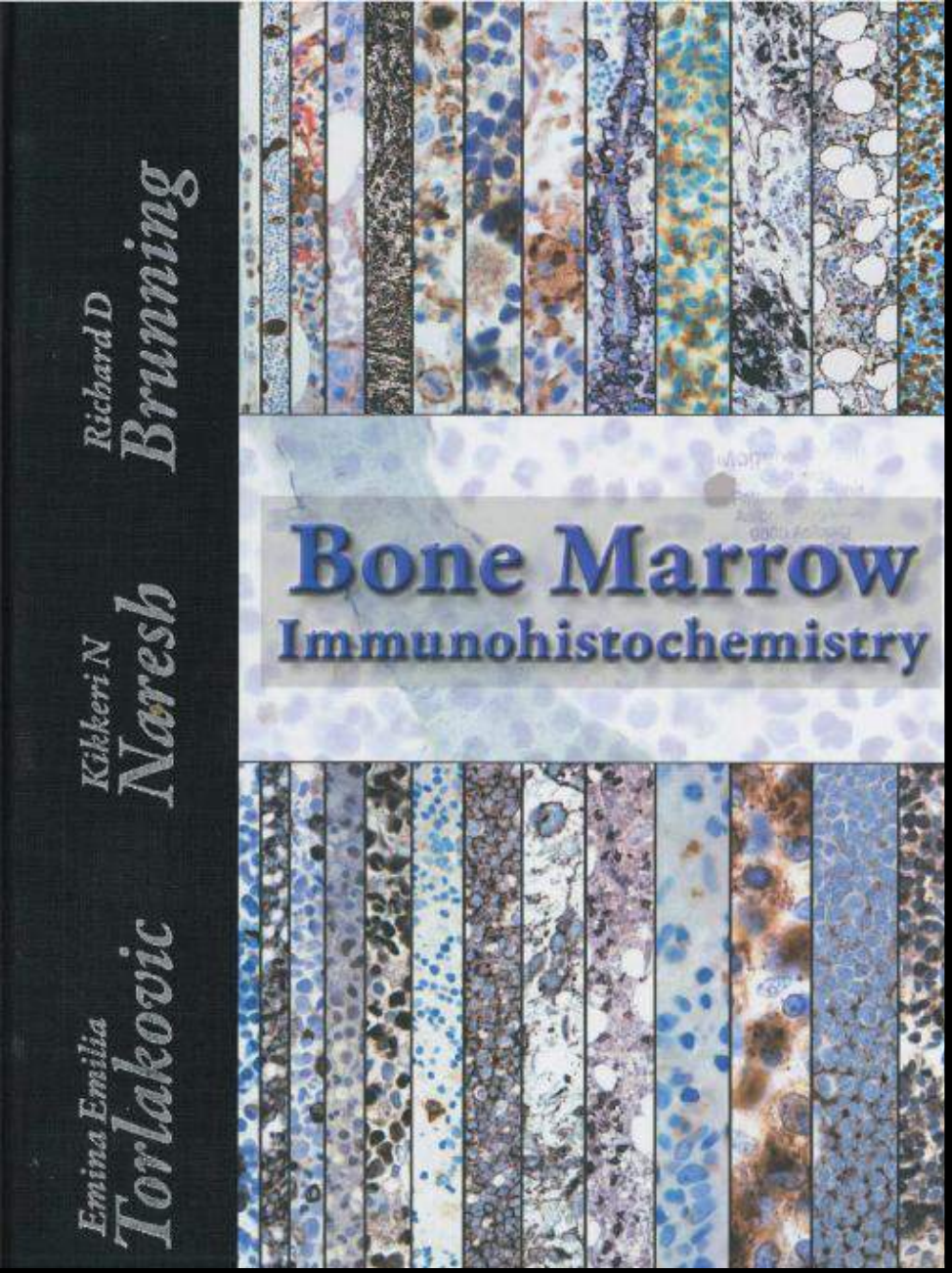
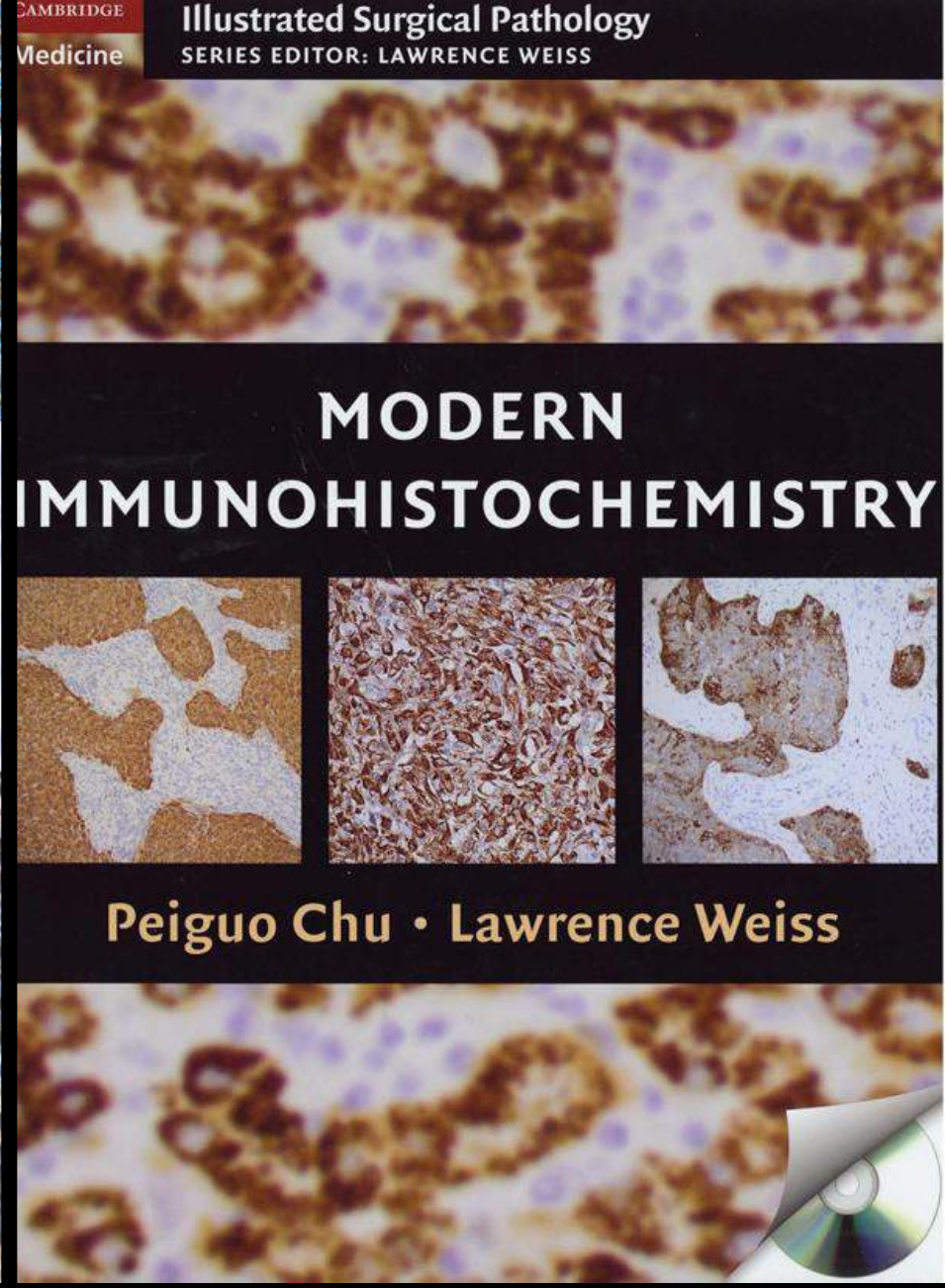

Emina Emilia Torlakovic
Kikkeri N Naresh
Richard D Brunning
Bone Marrow
Immunohistochemistry


CAMBRIDGE
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SERIES EDITOR: LAWRENCE WEISS
MODERN
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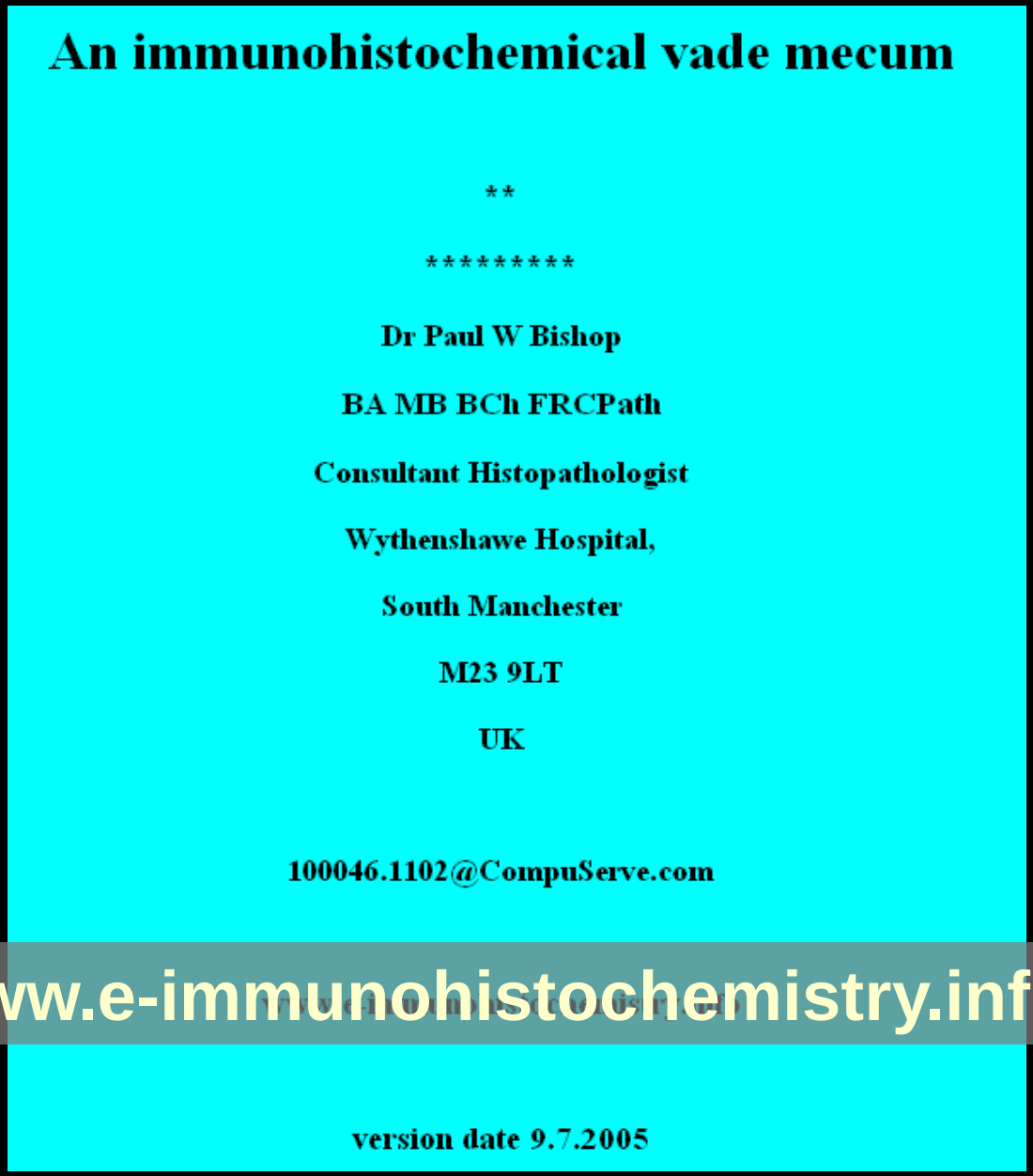
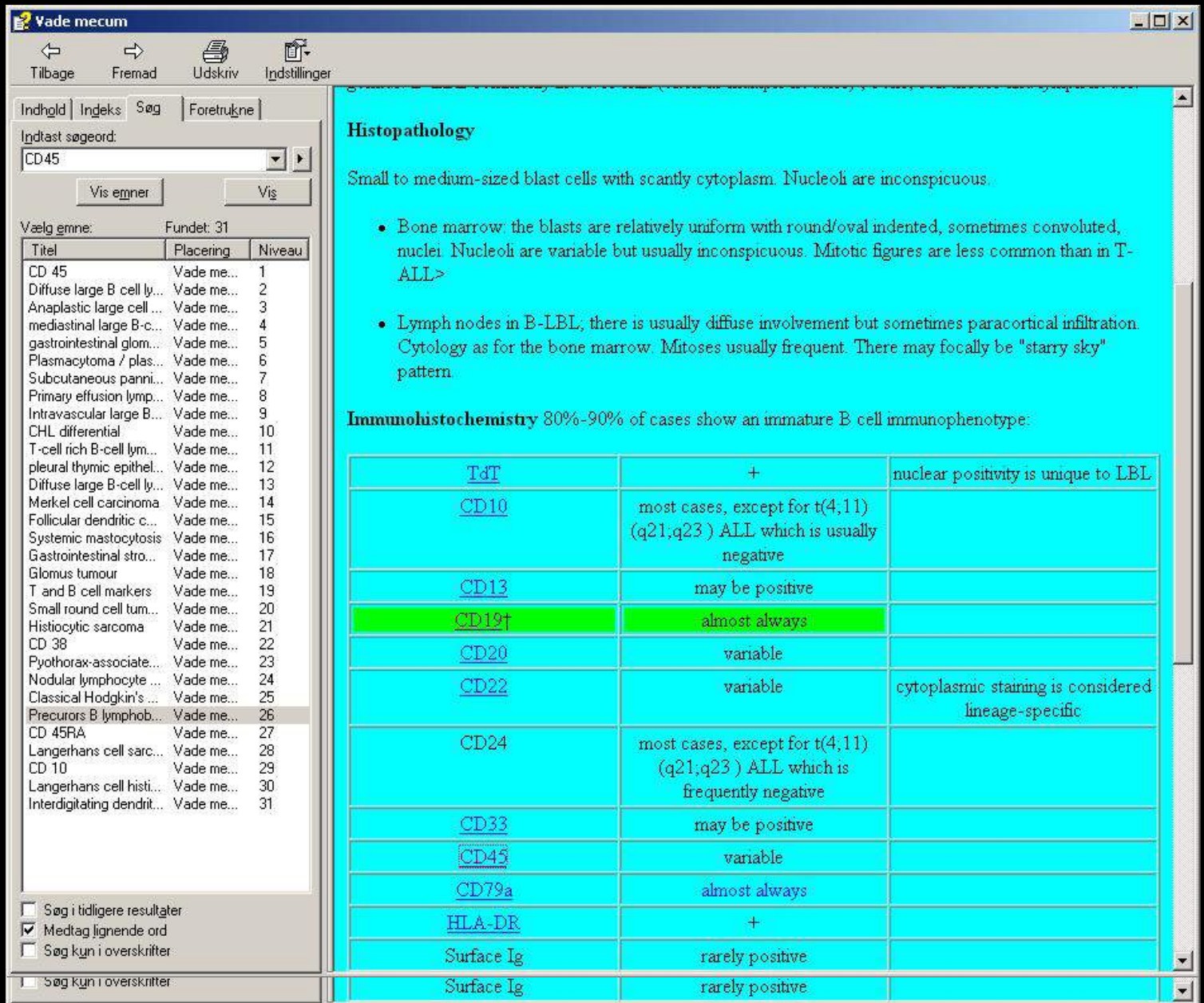
# Planning diagnostic immunohistochemistry




www.e-immunohistochemistry.info

# Planning diagnostic immunohistochemistry



# Planning diagnostic immunohistochemistry

www.PathologyOutlines.com

## CD Markers



Home Page
PRINTER FRIENDLY VERSION
Bold and underlined topics are hypertext links

### Navigational links to CD markers

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 |
| 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 |
| 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 |
| 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 |
| 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 |
| 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 |
| 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 |

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

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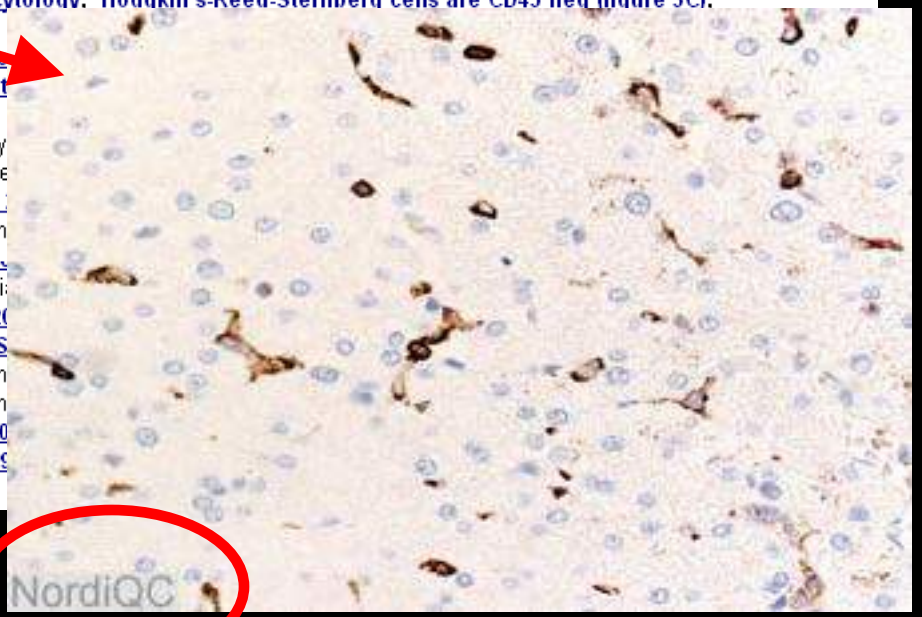
# CD Markers CD1 to CD49

## 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 B); CLL; #2 - urine cytology; Hodgkin's-Reed-Sternberg 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
**Flow cytometry images:** transient myeloproliferative disorder with erythroid differentiat
**Virtual slides:** diffuse large B cell lymphoma
**Positive staining (normal):** hematopoietic cells (including monocytes, macrophages / histiocy
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), gian
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 2
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



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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.

meso | 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) 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.

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Learn About an Antibody:

News:

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Ask an Expert | Meta-analysis

Dx Panel for Mesoth...

| 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 | 89% | 19 | 76 - 100 | 1 |
| PODOPLANIN | 85% | 503 | | 6 |
| CALRETININ | 85% | 1,345 | 83 - 87 | 31 |
| CK 05_06 | 83% | 646 | 80 - 86 | 18 |
| 34BE12 | 82% | 82 | 73 - 90 | 3 |
| N-CADHERIN | 81% | 242 | 76 - 86 | 6 |

**References For CALRETININ:** Close X

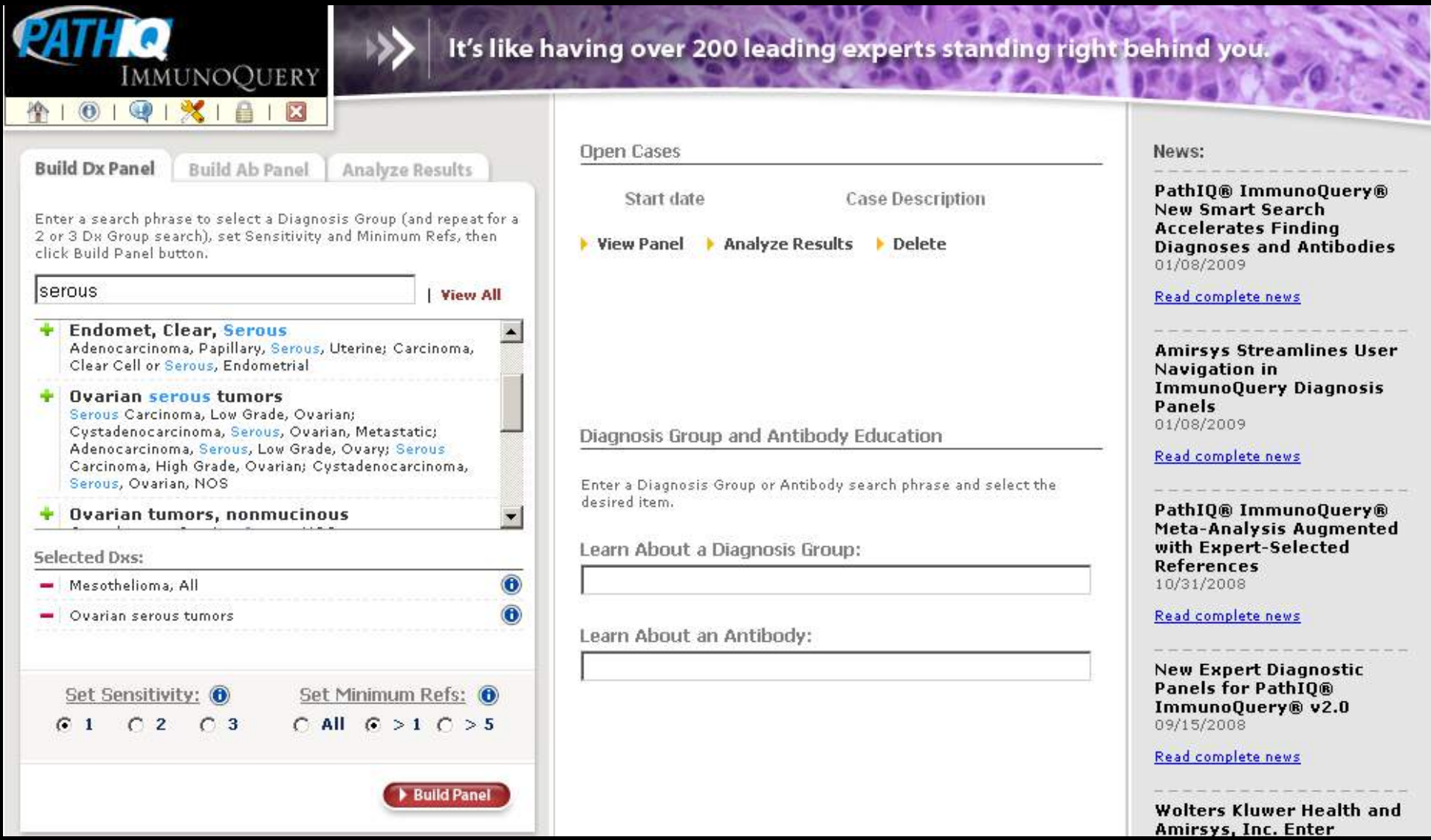
Articles Sorted by relevance: 31

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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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.
serous
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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| | Mesothelioma, All | | | Ovarian Serous Tumors | | |
|---|---|---|---|---|---|---|
| | Positive | Cases | vs2 | Positive | Cases | vs1 |
| ERP NUCLEAR | 0% | 71 | | 95% | 63 | |
| H-CALDESMON | 97% | 70 | | 5% | 40 | |
| MOC-31 | 8% | 404 | | 98% | 62 | |
| BER-EP4 | 10% | 1,421 | | 97% | 99 | |
| S-100 CYTOPLASMIC/NUCLEAR | 5% | 208 | | 73% | 52 | |
| TAG-72 | 5% | 1,545 | | 73% | 85 | |
| LEWIS-Y | 8% | 266 | | 73% | 45 | |
| E-CADHERIN MEMBRANE/CYTOPLASMIC | 35% | 265 | | 100% | 20 | |
| CALRETININ Nucleus/Cytoplasm | 85% | 1,345 | | 22% | 232 | |
| CA 19-9 CYTOPLASMIC | 1% | 152 | | 64% | 85 | |
| PRP NUCLEAR | 0% | 22 | | 62% | 63 | |
| THROMBOMOD CYTOPLASMIC | 65% | 1,039 | | 5% | 108 | |
| PODOPLANIN MEMBRANE/CYTOPLASMIC | 85% | 503 | | 28% | 111 | |


| | Mesothelioma, All | | | Ovarian Serous Tumors | | |
|---|---|---|---|---|---|---|
| | Positive | Cases | vs2 | Positive | Cases | vs1 |
| CK 05<br>CYTOPLASMIC | 92% | 48 | | 57% | 14 | |
| RCC | 21% | 193 | | 0% | 22 | |
| HBME-1<br>CYTOPLASMIC/MEMBRANE | 79% | 687 | | 100% | 16 | |
| N-CADHERIN | 81% | 242 | | 100% | 20 | |
| MESOTHELIN<br>CYTOPLASMIC/MEMBRANE | 89% | 253 | | 99% | 70 | |
| CK 20<br>CYTOPLASMIC | 3% | 90 | | 11% | 98 | |
| KERATIN-PAN<br>CYTOPLASMIC | 94% | 1,071 | | 100% | 3 | |
| MELAN-A103<br>CYTOPLASMIC | 0% | 4 | | 6% | 16 | |
| INHIBIN<br>cytoplasm | 0% | 1 | | 4% | 23 | |
| AE1 AE3 | 96% | 197 | | 100% | 20 | |
| CEA-P | 3% | 1,066 | | 1% | 142 | |
| CEA-M<br>CYTOPLASMIC | 2% | 1,125 | | 0% | 64 | |
| CDX-2<br>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.

kera | 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 | 2 |
| Carcinoma, Small Cell, Breast | | 44% | 9 | | 0% | 2 | 2 |
| Medulloblastoma, NOS | | 42% | 57 | | 0% | 53 | 2 |
| Pheochromocytoma, NOS | | 40% | 63 | | 16% | 116 | 4 |
| Stromal Sarcoma, Low Grade | | 38% | 8 | | 0% | 6 | 2 |
| Askin Tumor | | 37% | 19 | | 0% | 14 | 2 |
| Seminoma, Testes | | 30% | 96 | | 21% | 170 | 6 |
| Clear Cell Tumor Of Lung | | 29% | 17 | | 0% | 32 | 5 |
| Alveolar Soft Part Sarcoma | | 25% | 4 | | 0% | 3 | 4 |
| Leiomyoma, Epithelioid | | 20% | 5 | | 15% | 13 | 2 |
| Neuroblastoma, Olfactory | | 8% | 13 | | 8% | 38 | 4 |
| Thymic Carcinoma, Spindle Cell | | 0% | 10 | | 0% | 10 | 1 |
| Solitary Fibrous Tumor, Malignant | | 0% | 1 | | 0% | 1 | 1 |
| Seminoma, Spermatocytic | | 0% | 7 | | 0% | 3 | 2 |
| Sarcoma, Perivascular Epithelioid Cell | | 0% | 4 | | 0% | 4 | 1 |

# HUMAN PROTEIN ATLAS

The human protein atlas shows expression and localization of proteins in a large variety of normal human tissues, cancer cells and cell lines with the aid of immunohistochemistry (IHC) images.

Enter search: search

Advanced search

Or choose a chromosome:

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y

OTHER

Version: **3.1** Atlas updated: **2008-02-15** (release history)
Atlas content: **3014** antibodies and **2,940,744** images.

Knut och Alice Wallenbergs Stiftelse

The HPR project is funded by the Knut & Alice Wallenberg foundation. The atlas is part of the HUPO Human Antibody Initiative (HAI).

**2008-02-15**
An update to the Human Protein Atlas has been released. The new version (3.1) displays more tissue information, more cell images has been added, some celltypes has got corrected names. See release history for full details.

**2007-10-09**
A new feature with immunofluorescent (IF) images generated with confocal microscopy has been added. At present, the subcellular localization for 769 antibodies in three human cell lines are shown.

**2007-10-09**
A new feature has been added to allow the possibility to search for proteins with specific expression patterns in normal and/or cancer tissues.

KTH

UPPSALA UNIVERSITET



## Advanced Search

Search for proteins expressed in

cytokeratin

Add free search | Add tissue search | Clear search

search

## Search Results

Search results for advanced query : **20 hits** (genes)

Choose, if available:
- an Antibody ID to view the annotation data
- a link button to open a new window with Ensembl/NCBI/Uniprot info

| # | Gene name | Description | Chr | Links | Antibody ID | Validation |
|---|---|---|---|---|---|---|
| 1 | Cytokeratin (HMW) | No description | | | CAB000033 | N/A |
| 2 | Cytokeratin AE1/AE3 | No description | | | CAB000025 | N/A |
| 3 | Cytokeratin MNF116 | No description | | | CAB000026 | N/A |
| 4 | KRT1 | Keratin, type II cytoskeletal 1 (Cytokeratin-1) (CK-1) (Keratin-1) (K1) (67 kDa cytokeratin) (Hair alpha protein). | 12:q13.13 | U N E | CAB002153 | N/A |
| 5 | KRT10 | Keratin, type I cytoskeletal 10 (Cytokeratin-10) (CK-10) (Keratin-10) (K10). | 17:q21.2 | U N E | CAB000132 | N/A |
| 6 | KRT13 | Keratin, type I cytoskeletal 13 (Cytokeratin-13) (CK-13) (Keratin-13) (K13). | 17:q21.2 | U E | CAB000133 | N/A |
| 7 | KRT14 | Keratin, type I cytoskeletal 14 (Cytokeratin-14) (CK-14) (Keratin-14) (K14). | 17:q21.2 | U N E | CAB000134 | N/A |
| 8 | KRT15 | Keratin, type I cytoskeletal 15 (Cytokeratin-15) (CK-15) (Keratin-15) (K15). | 17:q21.2 | U N E | CAB000135 | N/A |
| 9 | KRT16 | Keratin, type I cytoskeletal 16 (Cytokeratin-16) (CK-16) (Keratin-16) (K16). | 17:q21.2 | U N E | CAB000136 | N/A |
| 10 | KRT17 | Keratin, type I cytoskeletal 17 (Cytokeratin-17) (CK-17) (Keratin-17) (K17) (39.1). | 17:q21.2 | U N E | CAB000029<br>HPA000452<br>HPA000453<br>HPA000539 | N/A<br>High<br>High<br>High |
| 11 | KRT18 | Keratin, type I cytoskeletal 18 (Cytokeratin-18) (CK-18) (Keratin-18) (K18). | 12:q13.13 | U N E | CAB000008<br>CAB000030<br>HPA001605 | N/A<br>N/A<br>Medium |
| 12 | KRT19 | Keratin, type I cytoskeletal 19 (Cytokeratin-19) (CK-19) (Keratin-19) (K19). | 17:q21.2 | U N E | CAB000031<br>HPA002465 | N/A<br>High |
| 13 | KRT2 | Keratin, type II cytoskeletal 2 epidermal | 12:q13.13 | U N E | HPA006200 | Medium |

**Search**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y OTHER

search

Show search results:

1 to 20

help for this page

# CAB000025 expression profiles. Validation score: N/A

## Gene data

Description: N/A
Chromosome: N/A
EnsEMBL ID: N/A

## Normal Tissues - IHC

alph. sort order

| | | | |
|---|---|---|---|
| Adrenal gland | cortical cells | Lymph node | lymphoid cells outside reaction centra |
| Appendix | glandular cells | | reaction center cells |
| | lymphoid cells | Nasopharynx | respiratory epithelial cells |
| Bone marrow | bone marrow poietic cells | Oral mucosa | squamous epithelial cells |
| Breast | glandular cells | Ovary | follicle cells |
| Bronchus | respiratory epithelial cells | | ovarian stromal cells |
| Cerebellum | cells in granular layer | Pancreas | exocrine glandular cells |
| | cells in molecular layer | | islet cells |
| | purkinje cells | Parathyroid gland | glandular cells |
| Cerebral cortex | glial cells | Placenta | decidual cells |
| | neuronal cells | | trophoblastic cells |
| Cervix, uterine | glandular cells | Prostate | glandular cells |
| | squamous epithelial cells | Rectum | glandular cells |
| Colon | glandular cells | Salivary gland | glandular cells |
| Corpus, uterine 1 | cells in endometrial stroma | Seminal vesicle | glandular cells |
| | glandular cells | Skeletal muscle | myocytes |
| Corpus, uterine 2 | cells in endometrial stroma | Skin | adnexal cells |
| | glandular cells | | epidermal cells |
| Duodenum | glandular cells | Small intestine | glandular cells |
| Epididymis | glandular cells | Smooth muscle | smooth muscle cells |
| Esophagus | squamous epithelial cells | Soft tissue 1 | mesenchymal cells |
| Fallopian tube | glandular cells | Soft tissue 2 | mesenchymal cells |
| Gall bladder | glandular cells | Spleen | cells in red pulp |
| Heart muscle | myocytes | | cells in white pulp |
| Hippocampus | glial cells | Stomach 1 | glandular cells |
| | neuronal cells | Stomach 2 | glandular cells |
| Kidney | cells in glomeruli | Testis | cells in seminiferus ducts |
| | cells in tubules | | leydig cells |
| Lateral ventricle | glial cells | Thyroid gland | glandular cells |
| | neuronal cells | Tonsil | lymphoid cells outside reaction centra |
| Liver | bile duct cells | | reaction center cells |
| | hepatocytes | | squamous epithelial cells |
| Lung | alveolar cells | Urinary bladder | urothelial cells |
| | macrophages | Vagina | squamous epithelial cells |
| | | Vulva/anal skin | squamous epithelial cells |

## Navigation

Home
Search result
CAB000025
Expression profiles
Normal tissues
Cancer tissues
Cells IHC
Antibody info

## Search

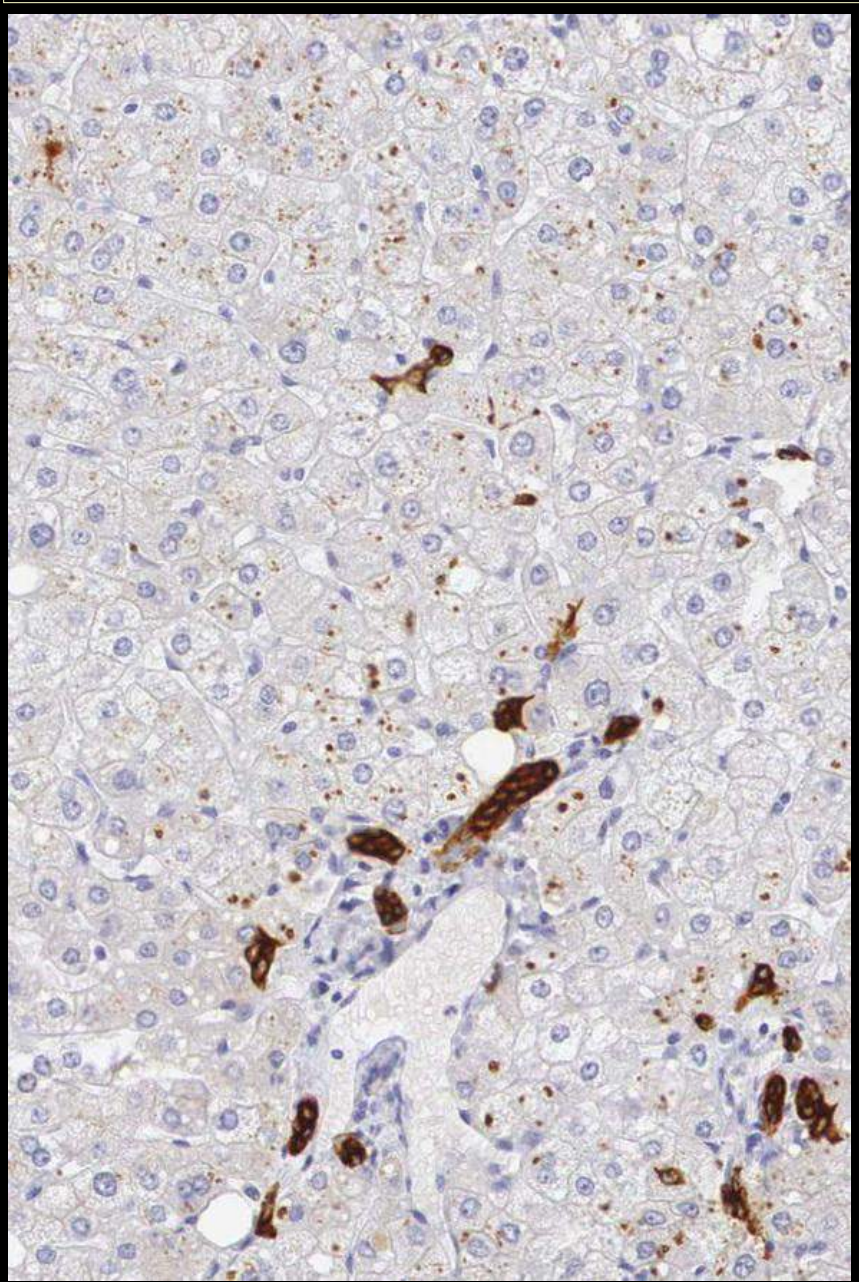
search

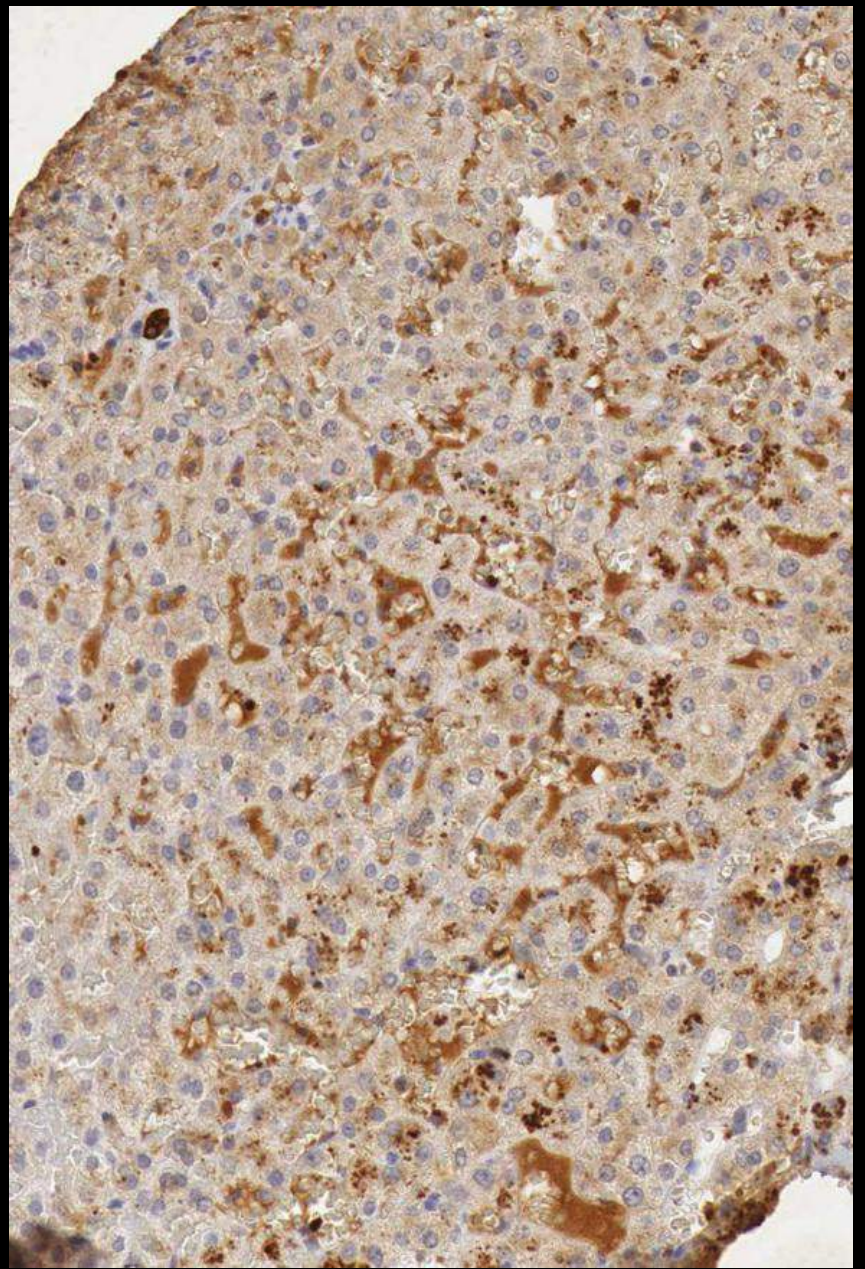
## Protein expression

Strong
Moderate
Weak
Negative
Not representative

help for this page

# Human protein Atlas – AE1/AE3

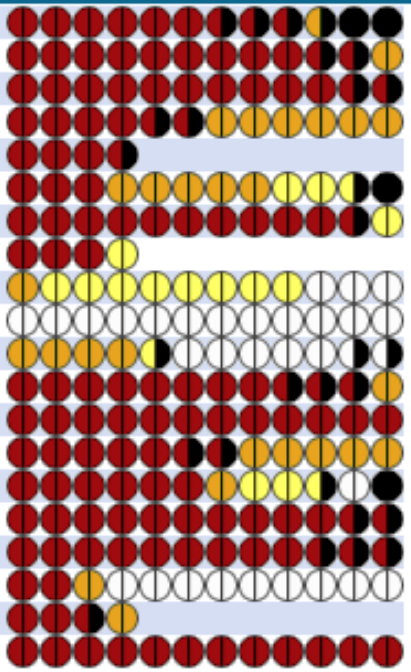




alph. sort order

## Cancer Tissues - IHC

- Breast cancer
- Cervical cancer
- Colorectal cancer
- Endometrial cancer
- Head & neck cancer
- Liver cancer
- Lung cancer
- Malignant carcinoid
- Malignant glioma
- Malignant lymphoma
- Malignant melanoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Renal cancer
- Skin cancer
- Stomach cancer
- Testis cancer
- Thyroid cancer
- Urothelial cancer



## Cell lines - IHC

### Myeloid

- HEL
- HL-60
- HMC-1
- K-562
- NB-4
- THP-1
- U-937

### Lymphoid

- Daudi
- HDLM-2
- Karpas-707
- KM3
- LP-1
- MOLT-4
- RPMI-8226
- U-266/70
- U-266/84
- U-698

### Abdominal

- CACO-2
- CAPAN-2
- Hep-G2

### Breast, female reproductive system

- AN3-CA
- EFO-21
- HeLa
- MCF-7
- SiHa
- SK-BR-3

### Urinary, male reproductive system

- NTERA-2
- PC-3
- RT-4

### Skin

- A-431
- HaCaT
- SK-MEL-30

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# Poorly differentiated cancer from an unknown primary site

**Authors**
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F Anthony Greco, MD

**Section Editor**
George P Canellos, MD

**Deputy Editor**
Michael E Ross, MD

**Disclosures**

All topics are updated as new evidence becomes available and our peer review process is complete.
**Literature review current through:** Jul 2013. | **This topic last updated:** jan 3, 2013.

**INTRODUCTION** — Cancer of unknown primary site (CUP) is a relatively common clinical entity, with about 4 to 5 percent having an apparent primary at presentation [1]. Within this category, tumors from many primary sites with varying biology a of unknown primary site are adenocarcinomas, and can be recognized by routine histologic examination. However, 20 to 25 differentiated, and cannot be precisely characterized by histologic examination. About 80 percent of these poorly differentiat carcinoma, and are termed "poorly differentiated carcinoma" after initial pathologic examination. In the remainder, histologic diagnosis of "poorly differentiated neoplasm", signifying the inability to distinguish between carcinoma, melanoma, lymphom tumor.

As accurate a diagnosis as possible is essential since the therapy for various tumors can be quite different and may be cur diagnostic approach to poorly differentiated cancers of unknown primary site will be reviewed here, along with the prognostic

Other relevant topics include:

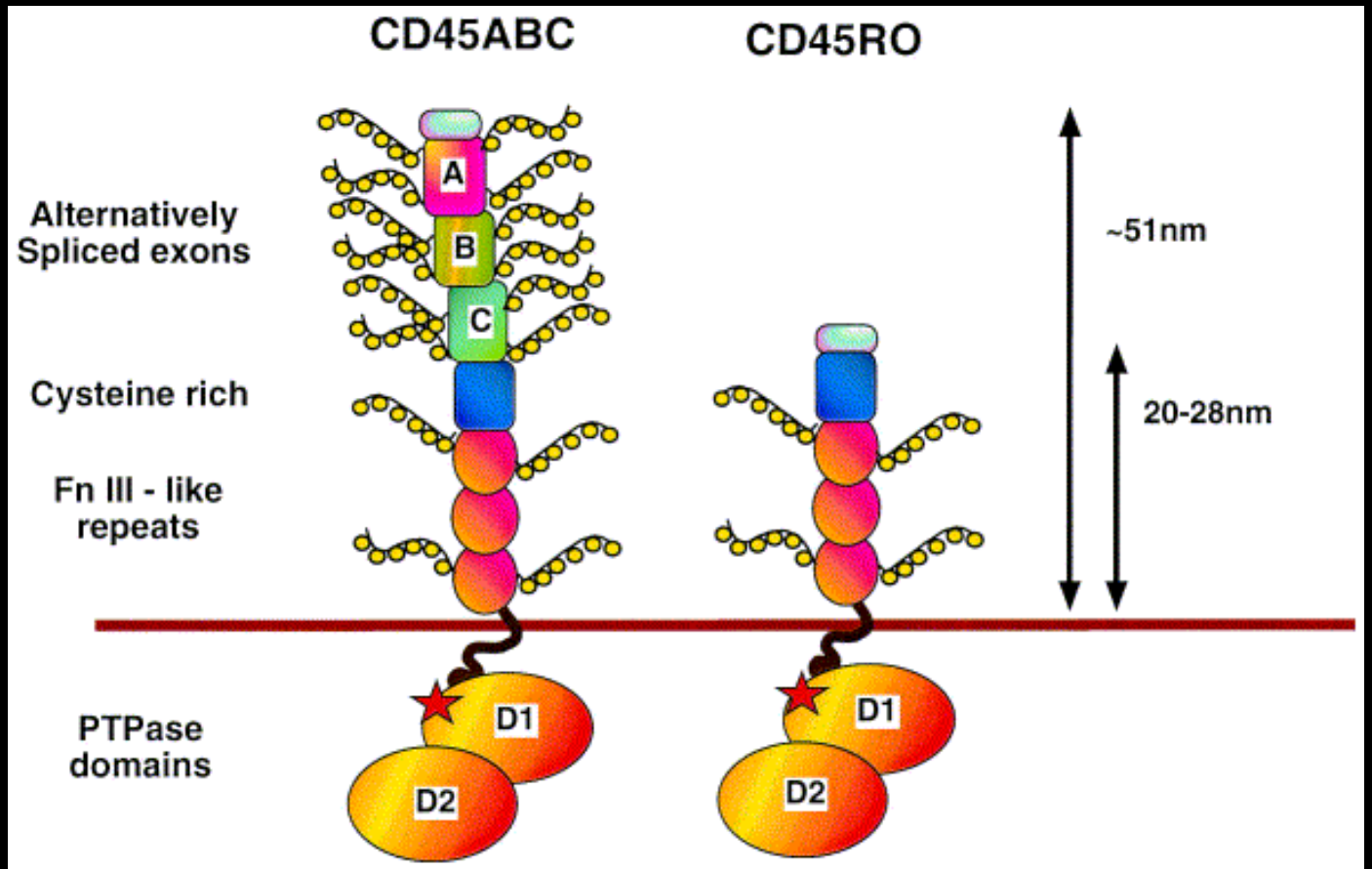
- (See "Overview of the classification and management of cancers of unknown primary site".)
- (See "Adenocarcinoma of unknown primary site".)
- (See "Squamous cell carcinoma of unknown primary site".)
- (See "Head and neck squamous cell carcinoma of unknown primary".)
- (See "Neuroendocrine cancer of unknown primary site".)
- (See "Axillary node metastases with occult primary breast cancer".)

# 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)

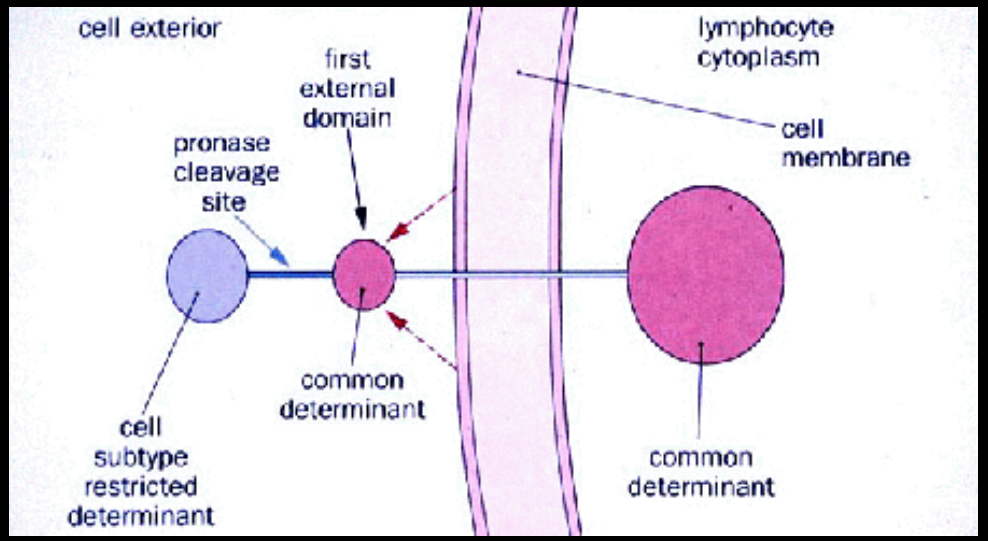
- Transmembrane protein tyrosin phospatase essential for haematopoietic signal transduction and cell activation
- Membrane associated component: 5 isotypes
- Intracellular component: one common type



# CD45 - Leucocyte common antigen (LCA)

- Transmembrane protein tyrosin phospatase 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 erythocytes, megakaryocytes and plasmacells
- ”Never” found in non-haematolymphoid cells

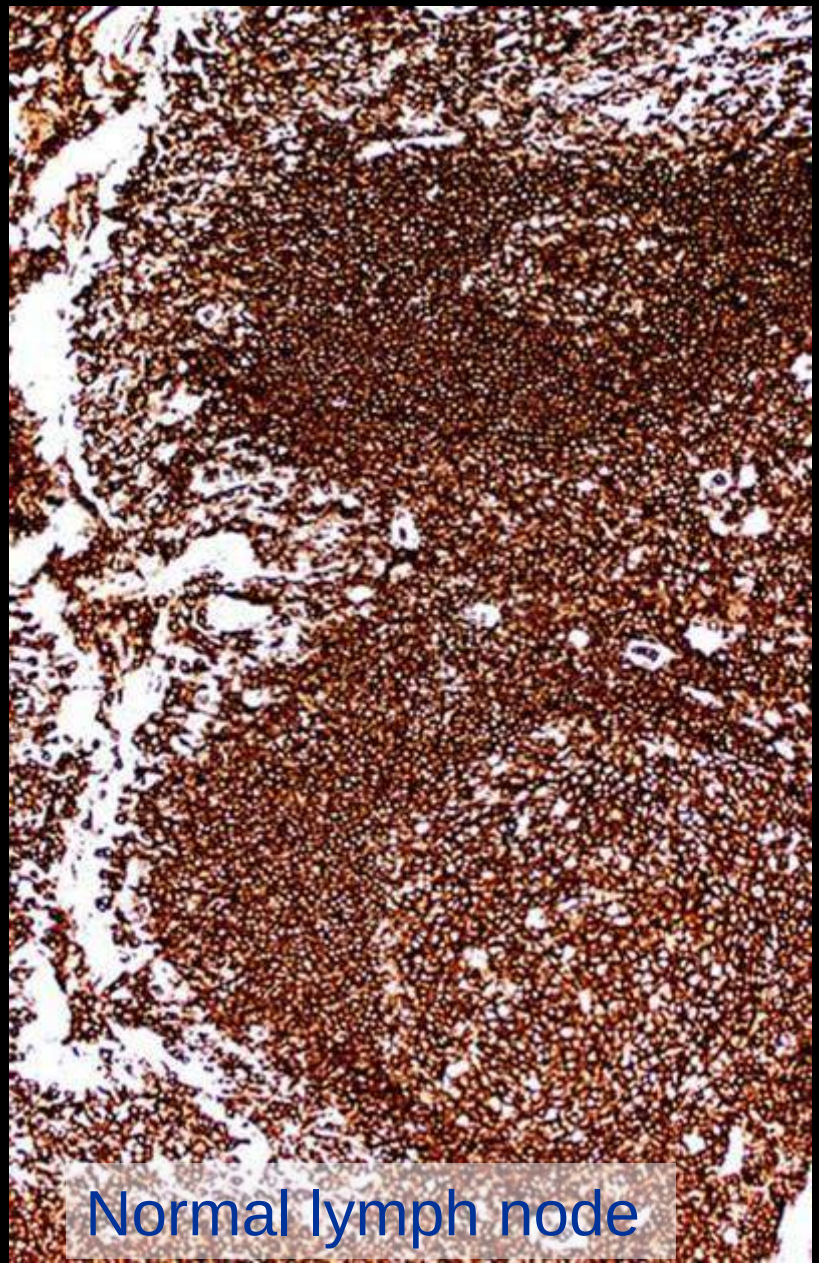


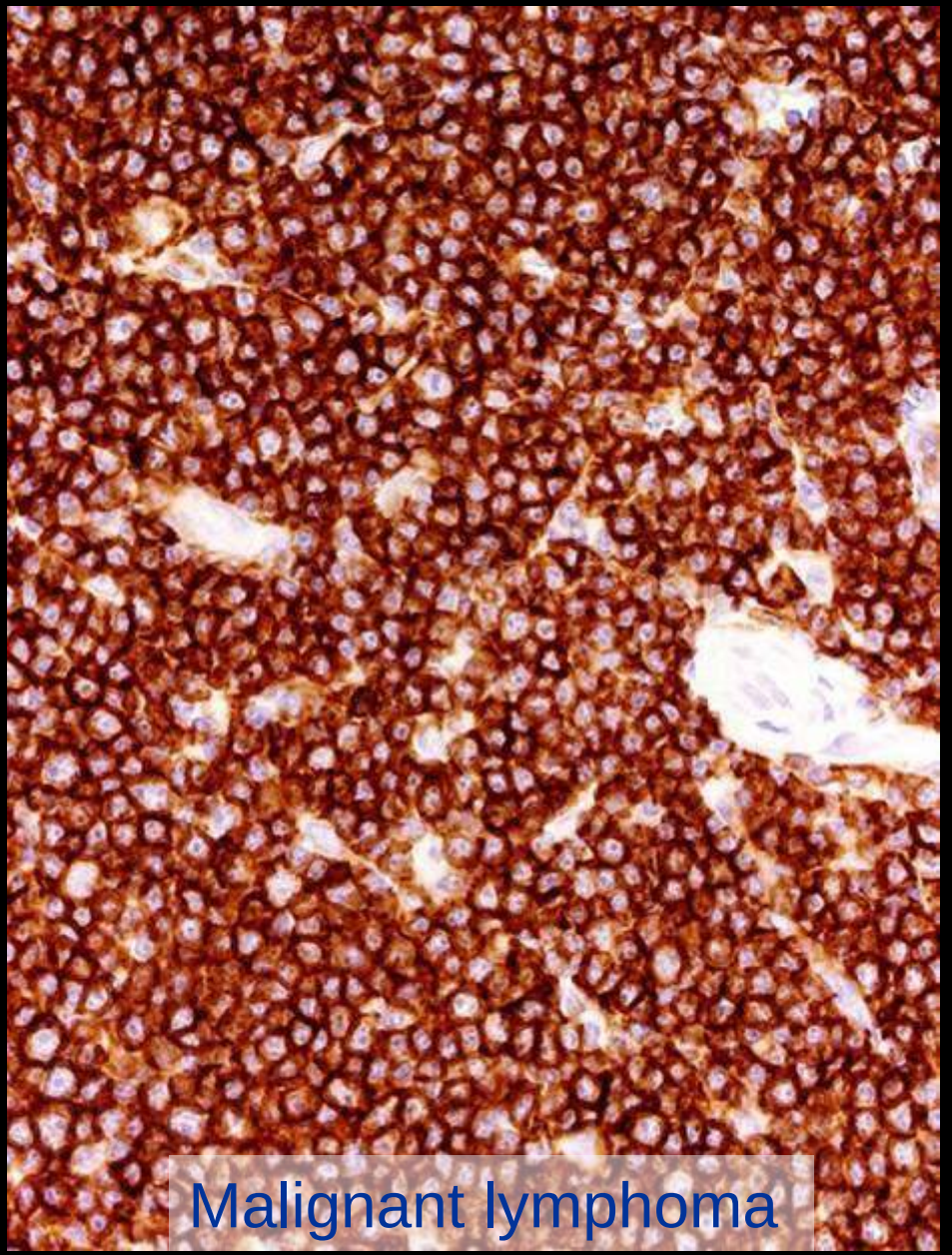
# CD45 - Leucocyte common antigen (LCA)

- **More than 90% of lymphomas are positive**
- PEL is positive in addition to CD138/CD38
- Weak positivity found also on dendritic cells and histiocytes

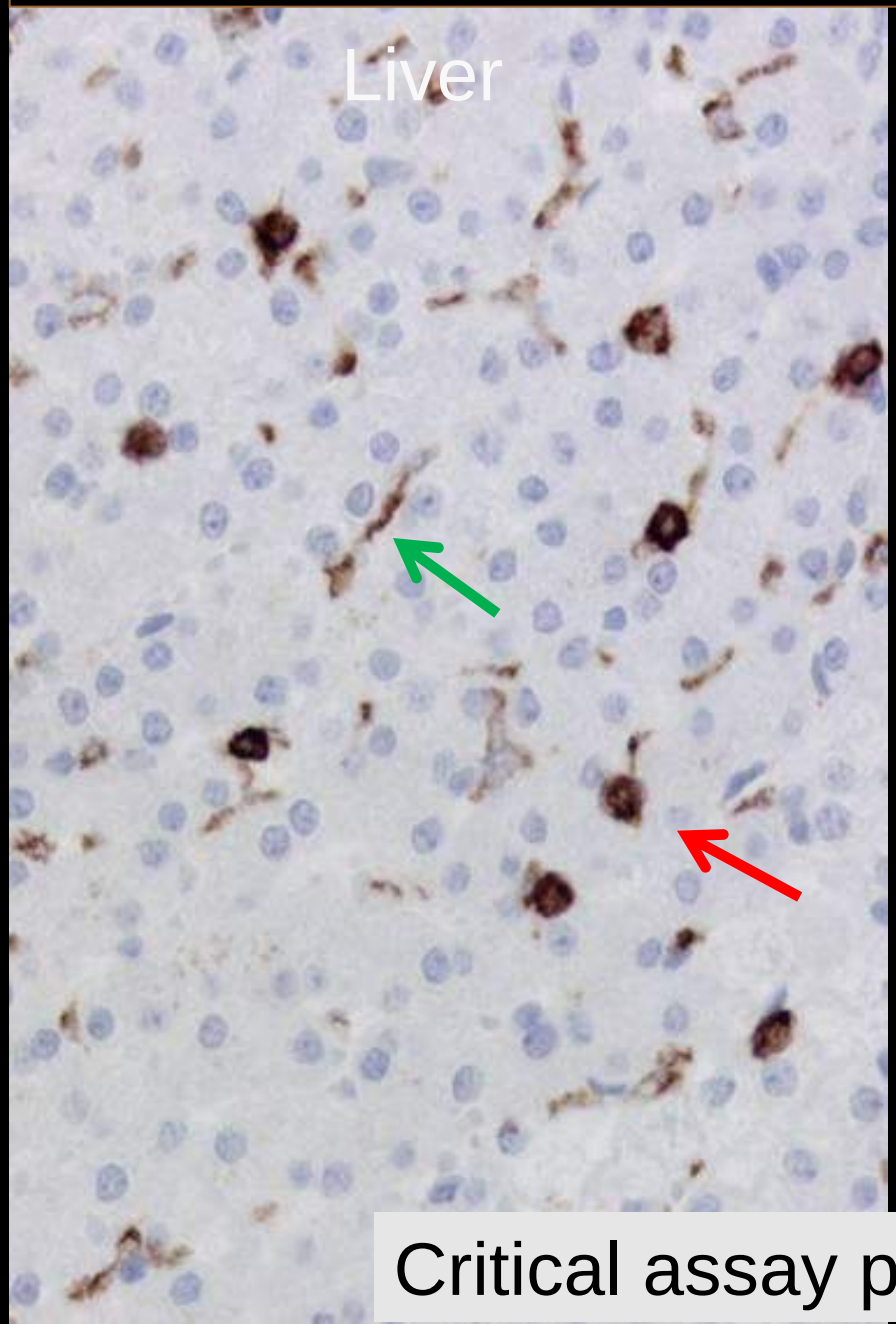
- Negative on:
  - some Acute Lymphoblastic Leukaemia/LBL
  - plasma cell malignancies
  - HR-S cells in classic Hodgkin Lymphoma
  - some Anaplastic Large Cell Lymphoma (ALCL)
  - ALK+ Large B-Cell Lymphoma
- Exceptionally positive in non haematol. Tumours ?

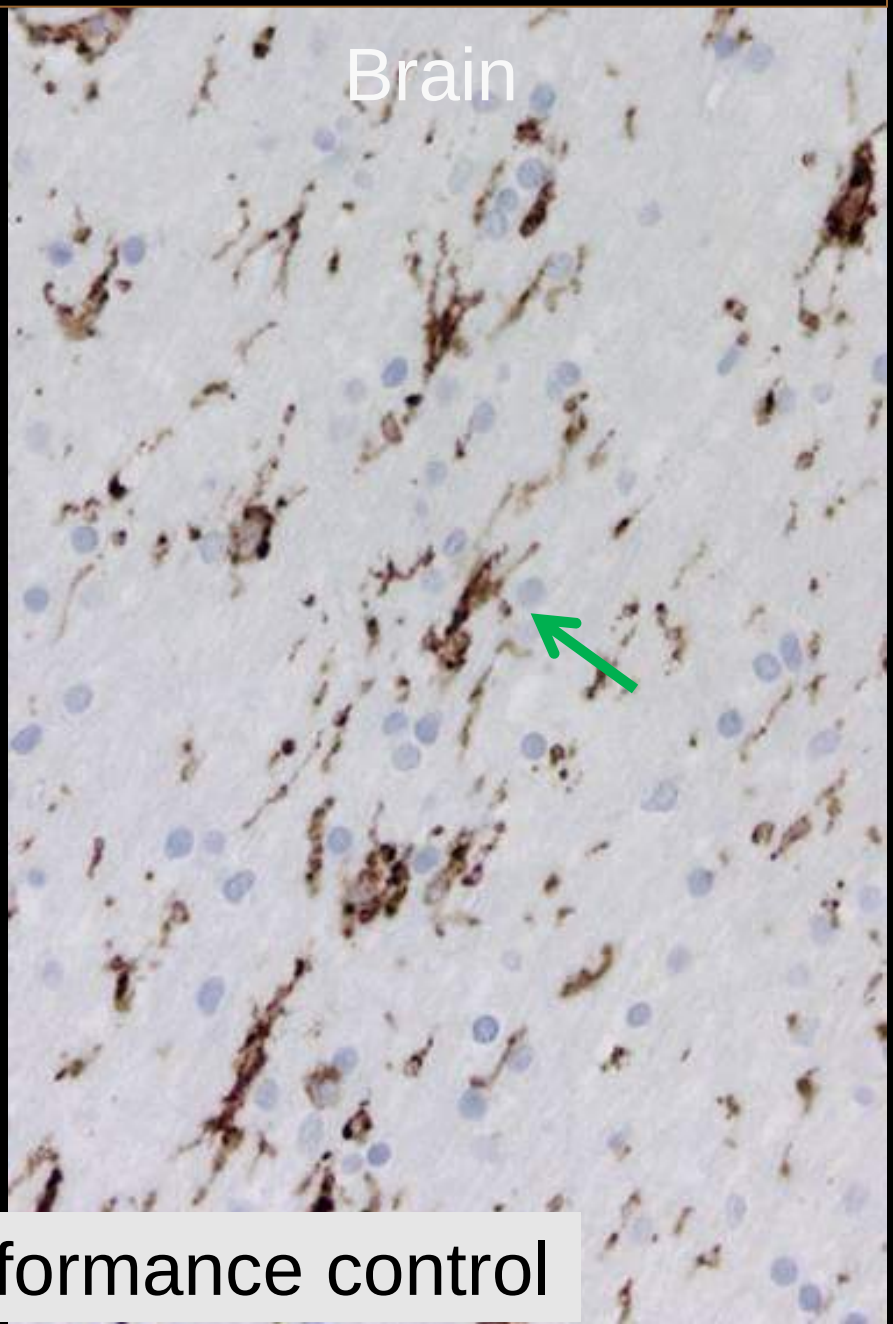
# CD45 - Leucocyte common antigen (LCA)



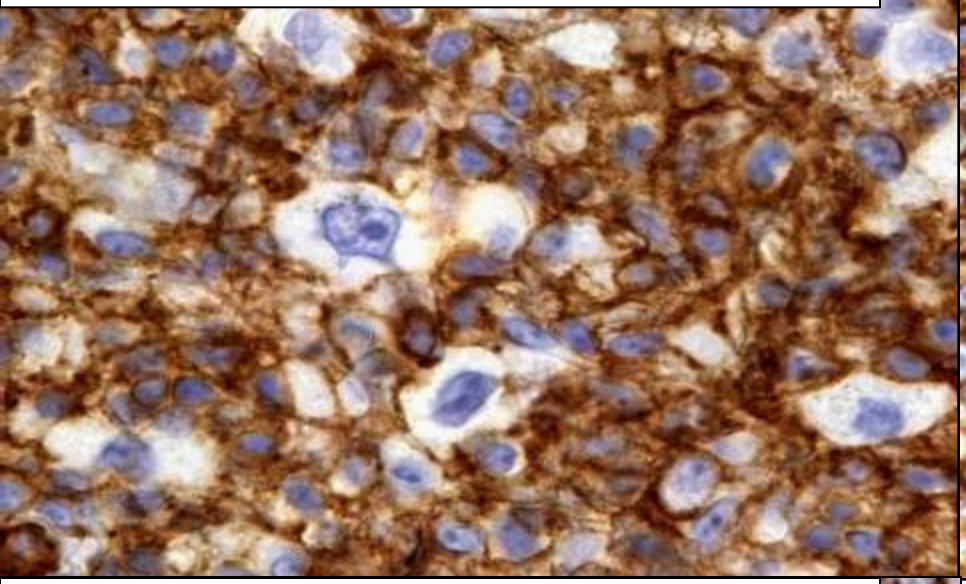
# CD45 - Leucocyte common antigen (LCA)



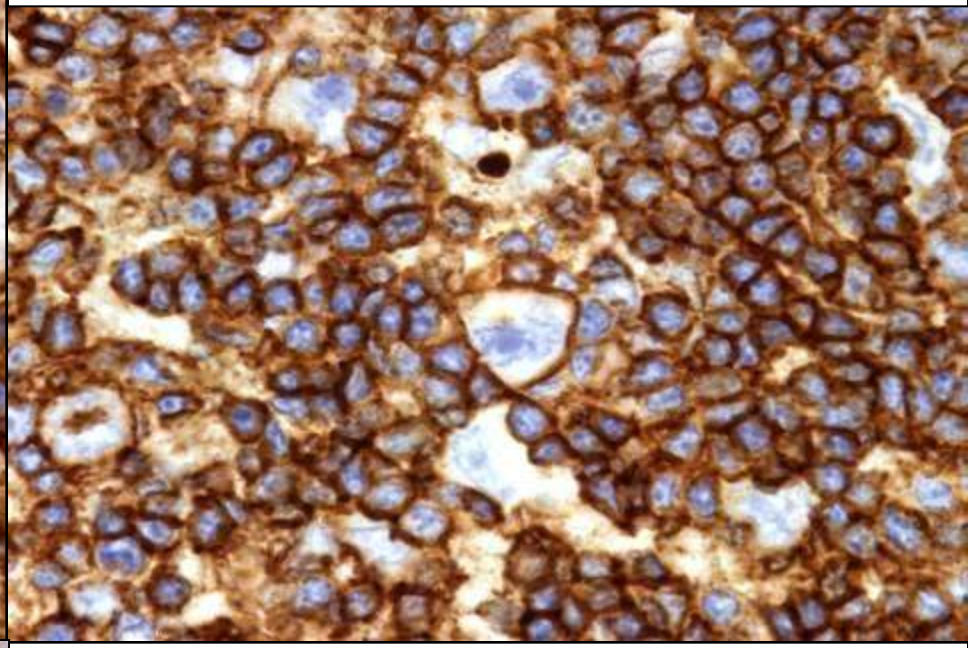




Critical assay performance control

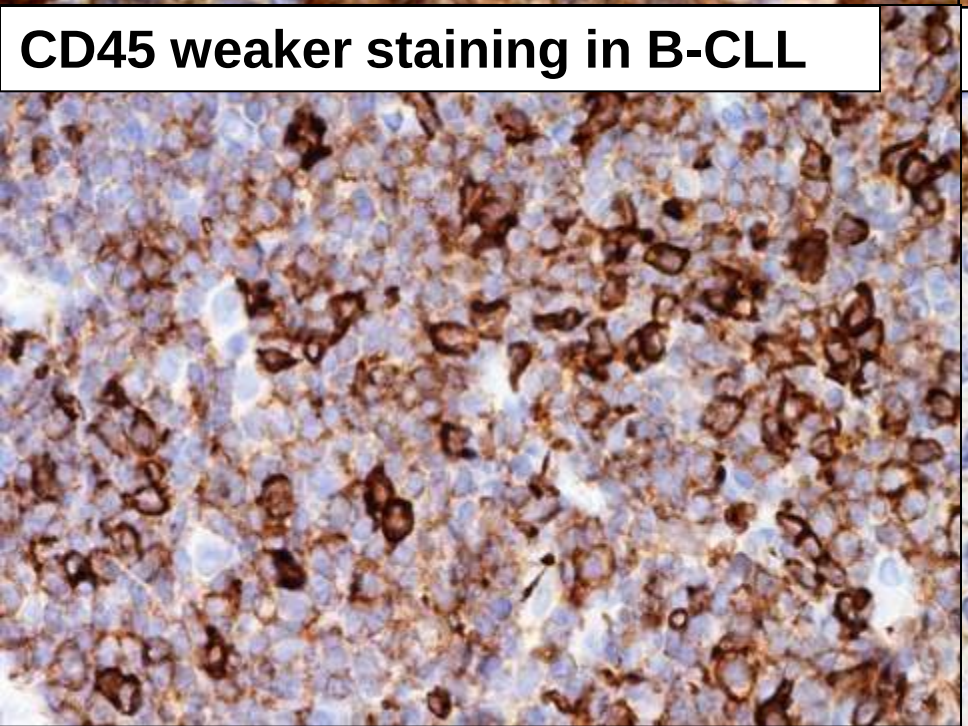
CD45 negative HRS cells in classic Hodgkin Lymphoma



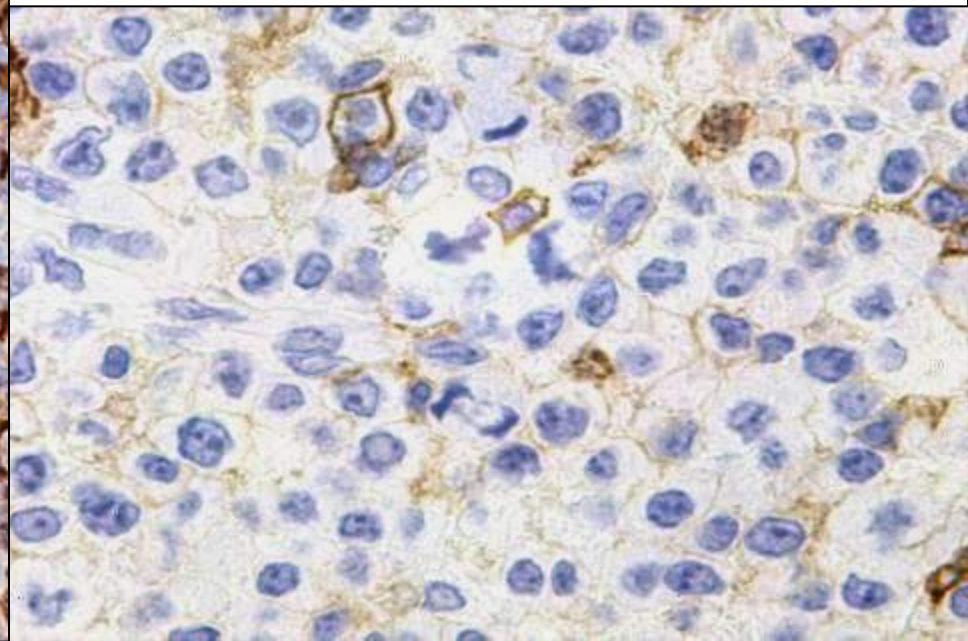
CD45 positive LH cells in NLPHL



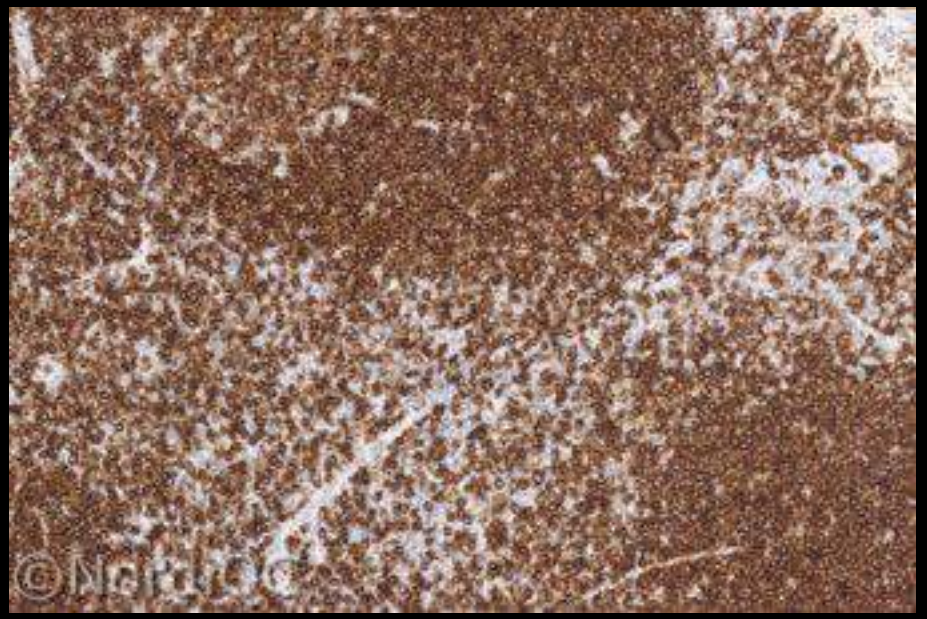
CD45 weaker staining in B-CLL



CD45 weak reactivity in ALCL

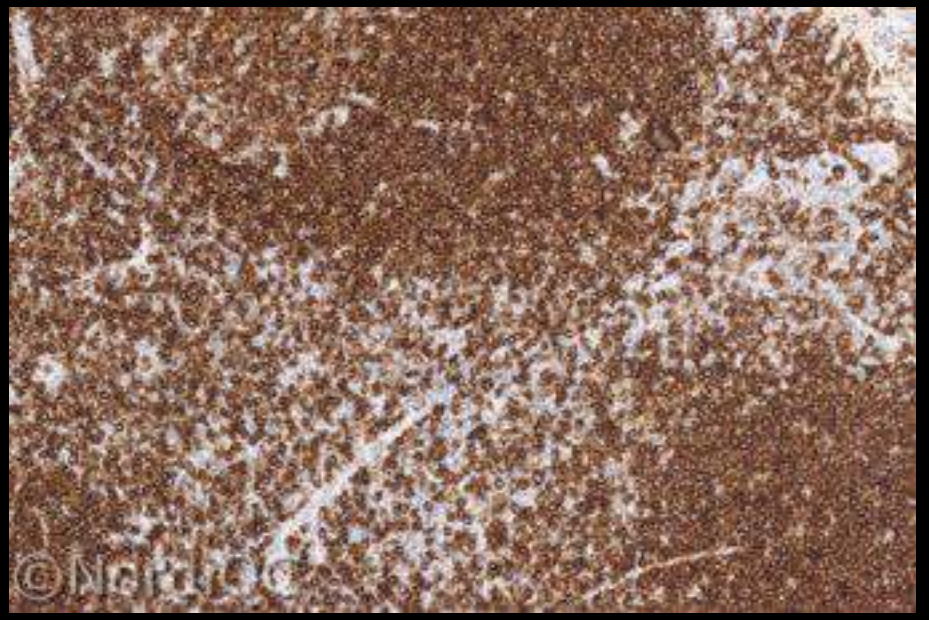


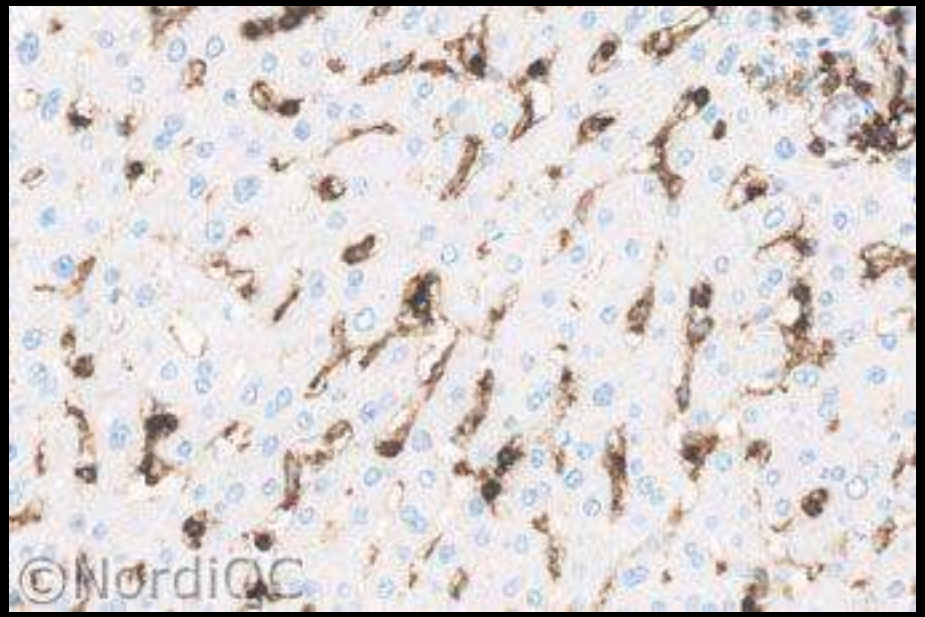
# CD45 – NordiQC run 37 2013

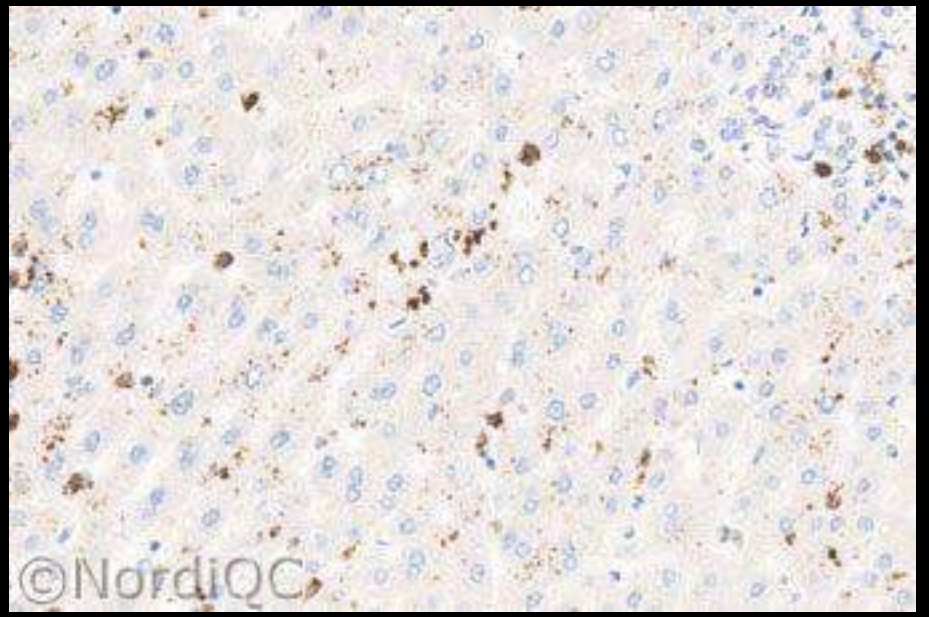




Which is best?

# CD45 – NordiQC run 37 2013

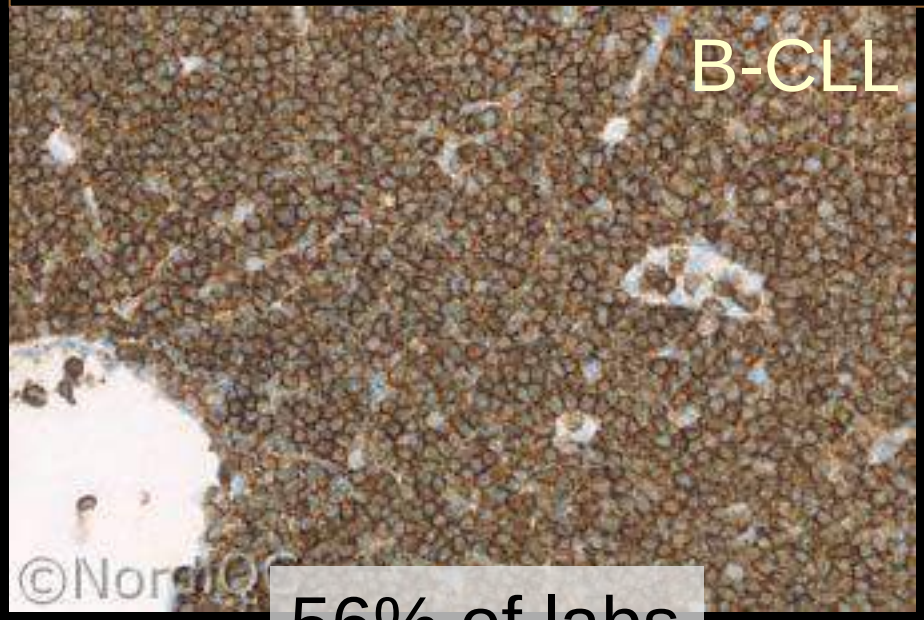



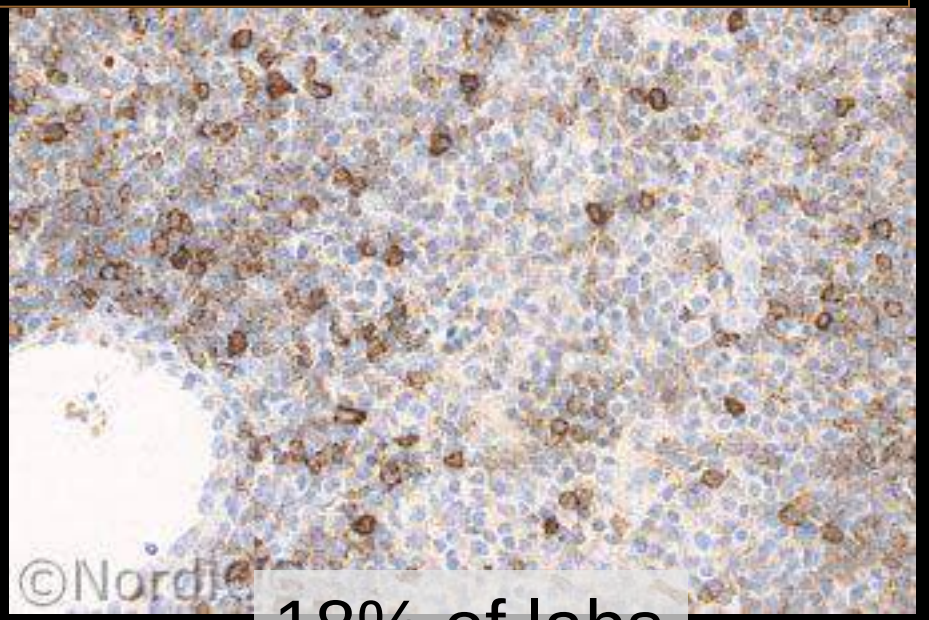




Optimal

Insufficient

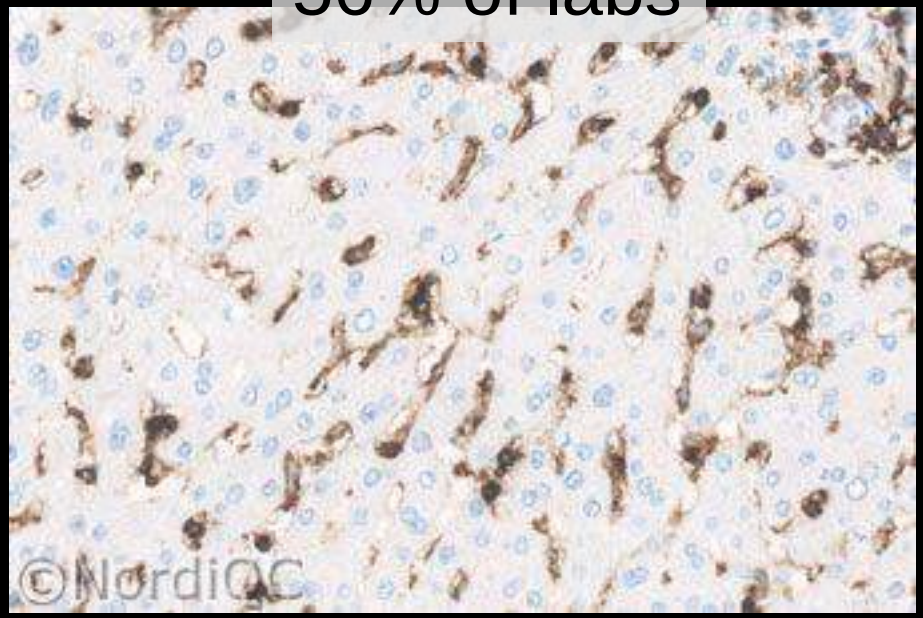
# CD45 – NordiQC run 37 2013

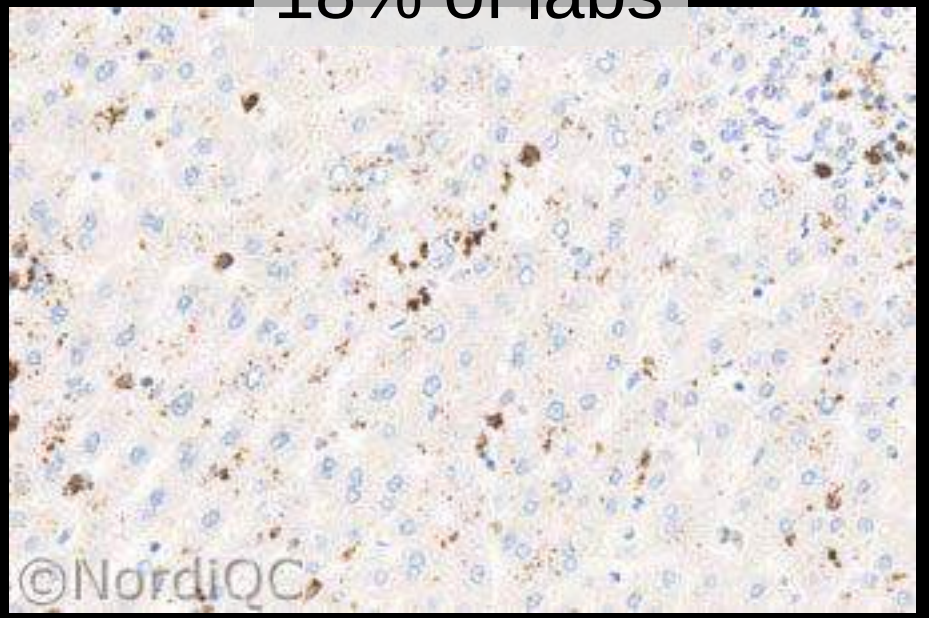



56% of labs

18% of labs



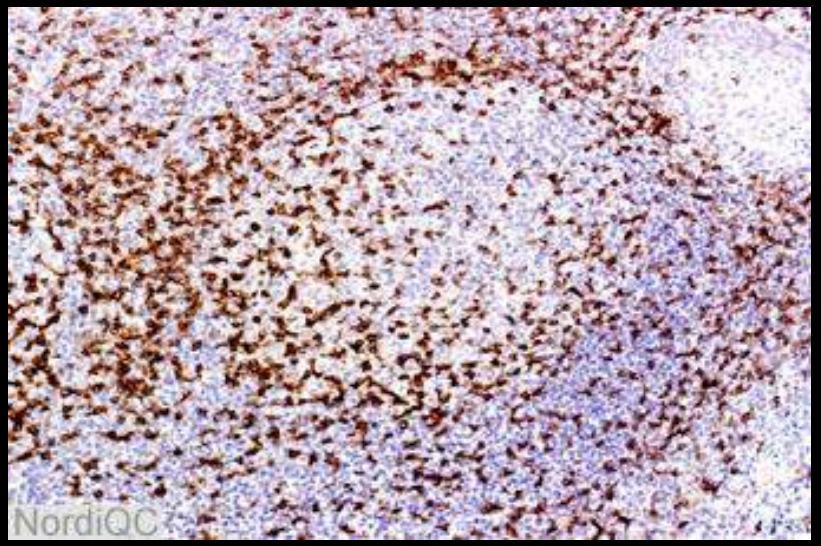




Optimal

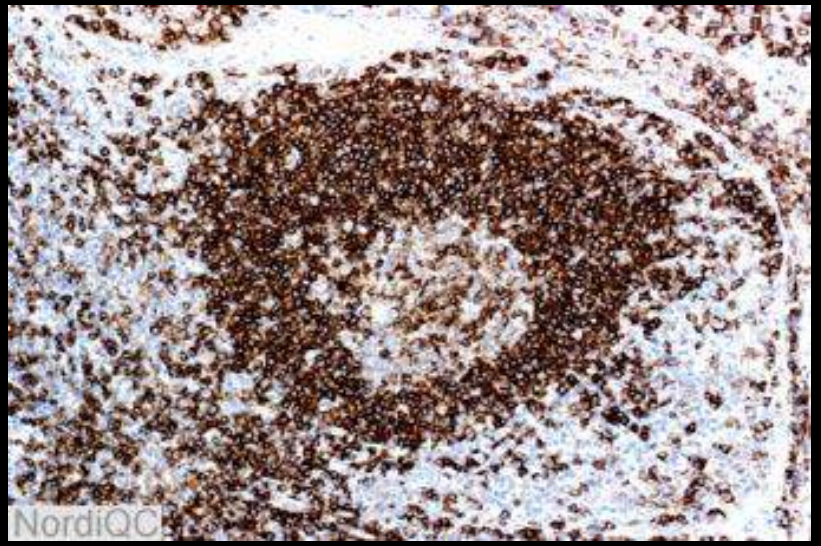
Insufficient

# CD45 - Leucocyte common antigen (LCA)

Lymph node/Tonsil




- CD45 RO ~ T-cells




- CD45 RA ~ B-cells

# CD45 - Leucocyte common antigen (LCA)

## 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)

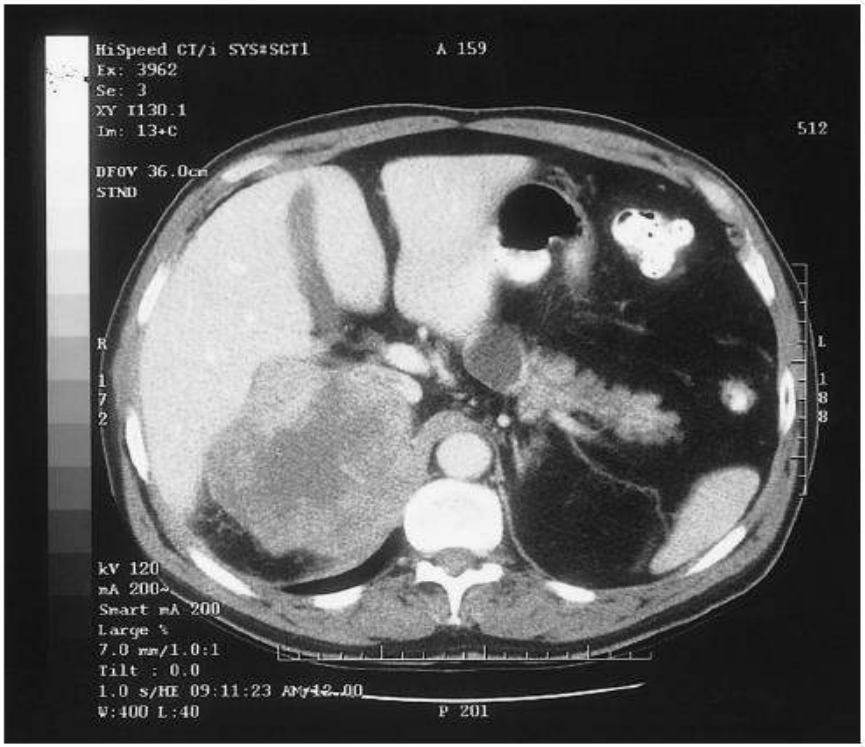



**Figure 1.** *Computed tomography of a large right suprarenal mass involving the liver.*

# CD45 - Leucocyte common antigen (LCA)

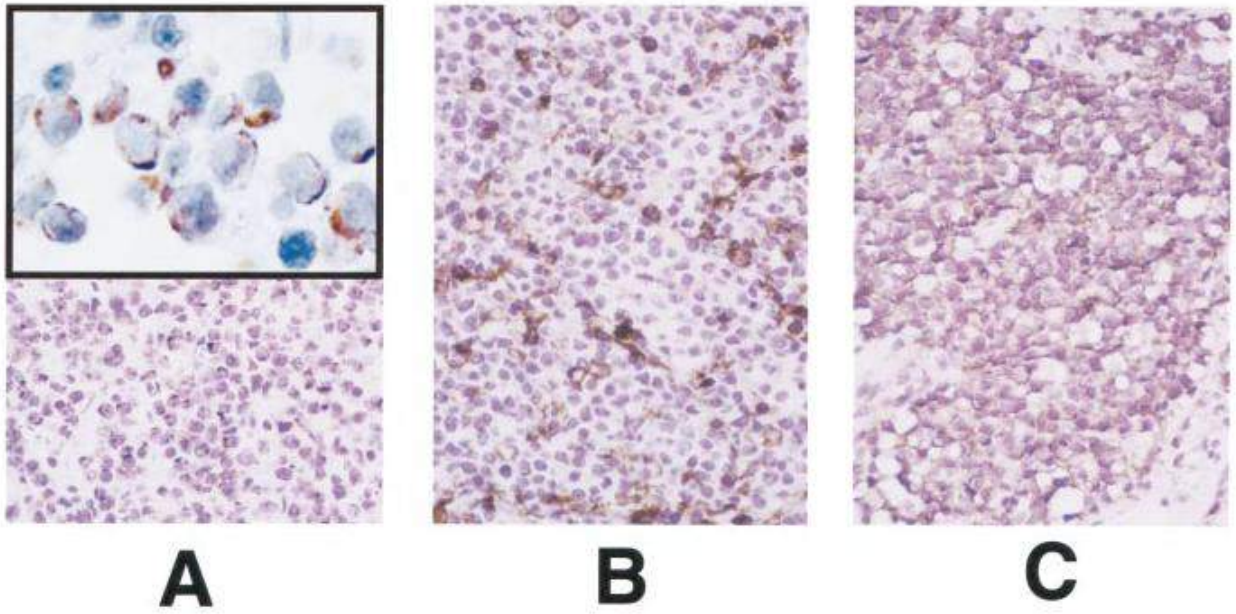



**Figure 3.** *Note immunoreactivity of the lymphoma cells for cytokeratin (A) and CD20 (C) but not CD45 (B) (original magnification ×100, inset ×250).*

### Molecular Biologic Findings

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

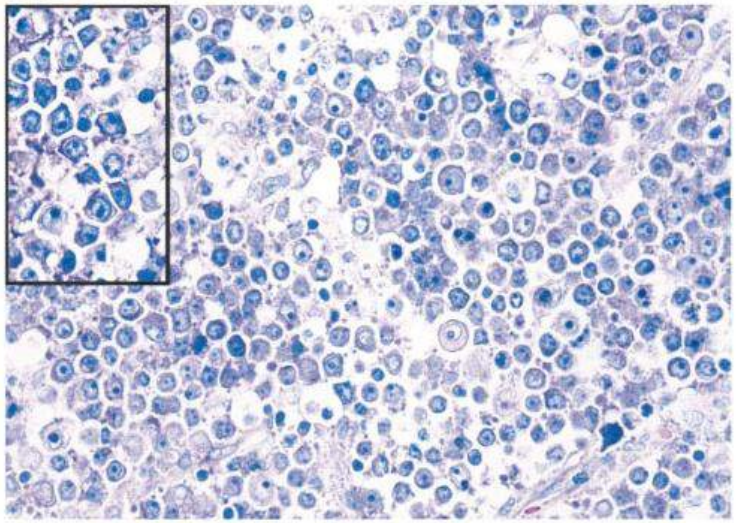


**Figure 2.** *Light microscopic appearance of the tumor (Giemsa stain, original magnification ×100, inset ×250).*

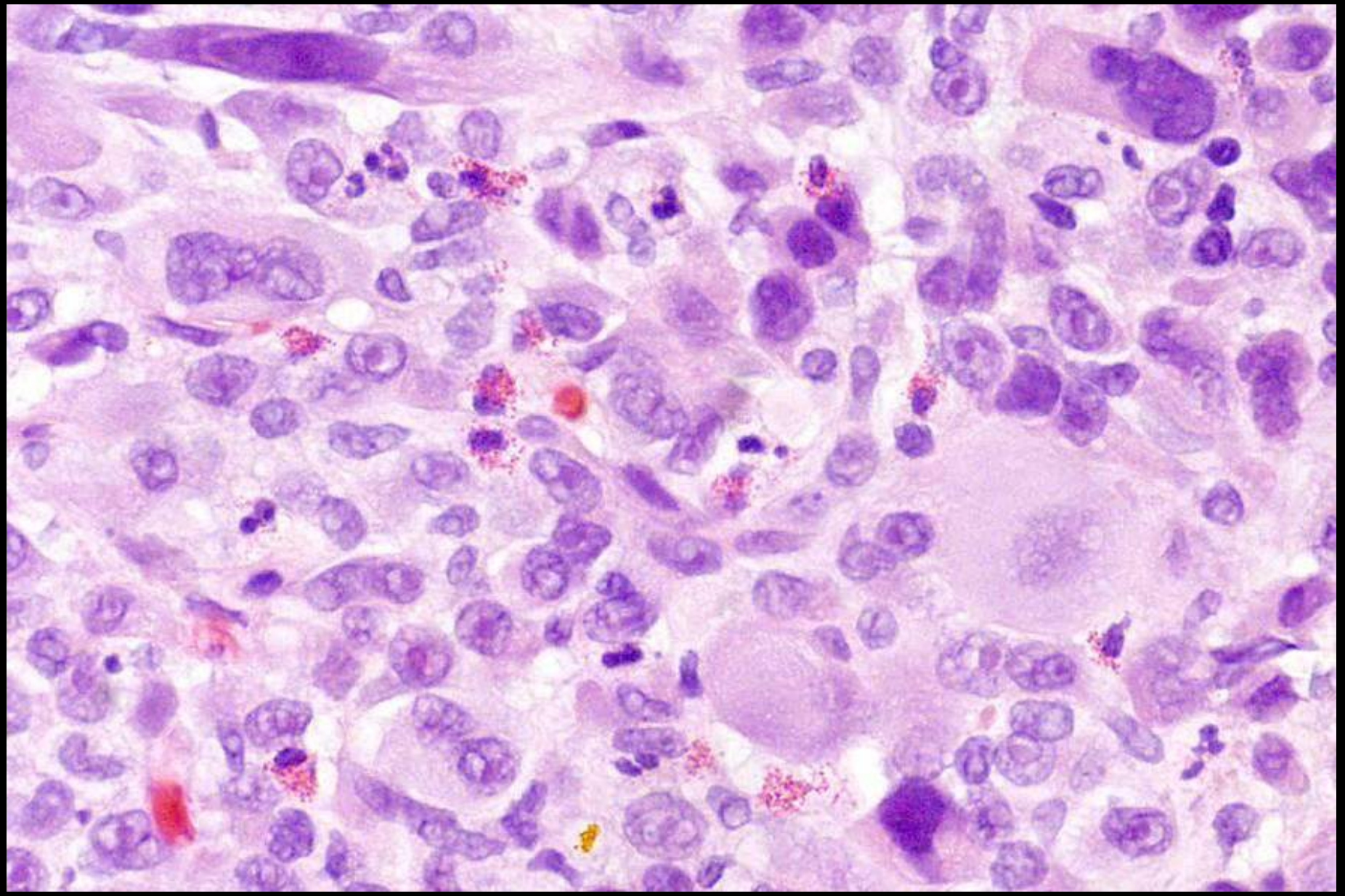
# CD45 - Leucocyte common antigen (LCA)

## MATERIALS AND METHODS

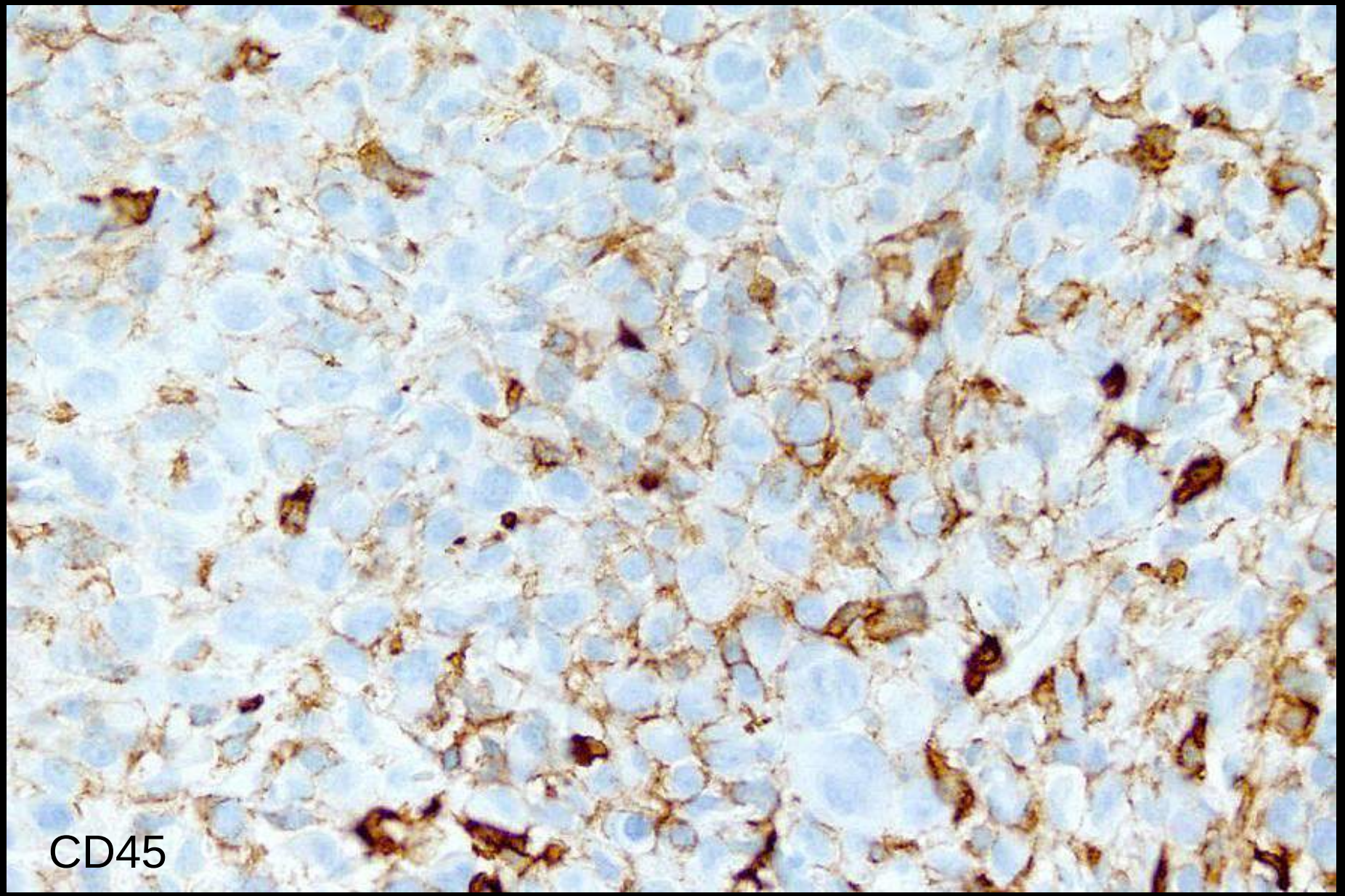
We performed immunohistochemical stains for cytokeratin (AE1/AE3. Cell Marque. Austin. Tex: CAM5.2. Becton Dickinson. San Jose, Calif; cytokeratins 5/6, Zymed, San Francisco, Calif; cytokeratin 7, Dako Corporation, Carpinteria, Calif; cytokeratin 20, Dako; 34βE12, Enzo, New York, NY), CD3, CD20, CD30, 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 μg of protein/mL) were applied for 25 minutes at room temperature. The immunostaining was repeated twice, each time with identical results.

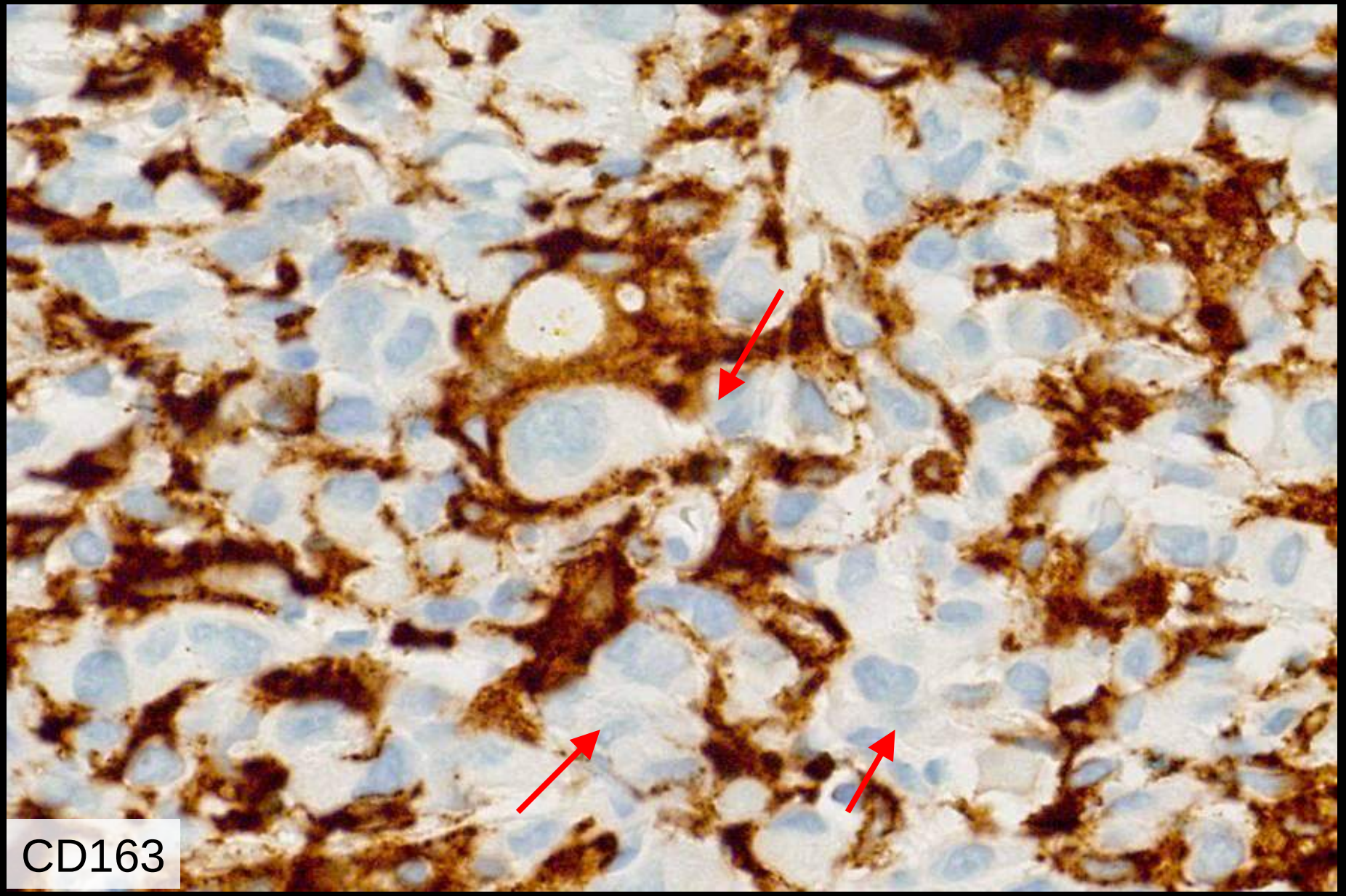
# Pancreas tumour



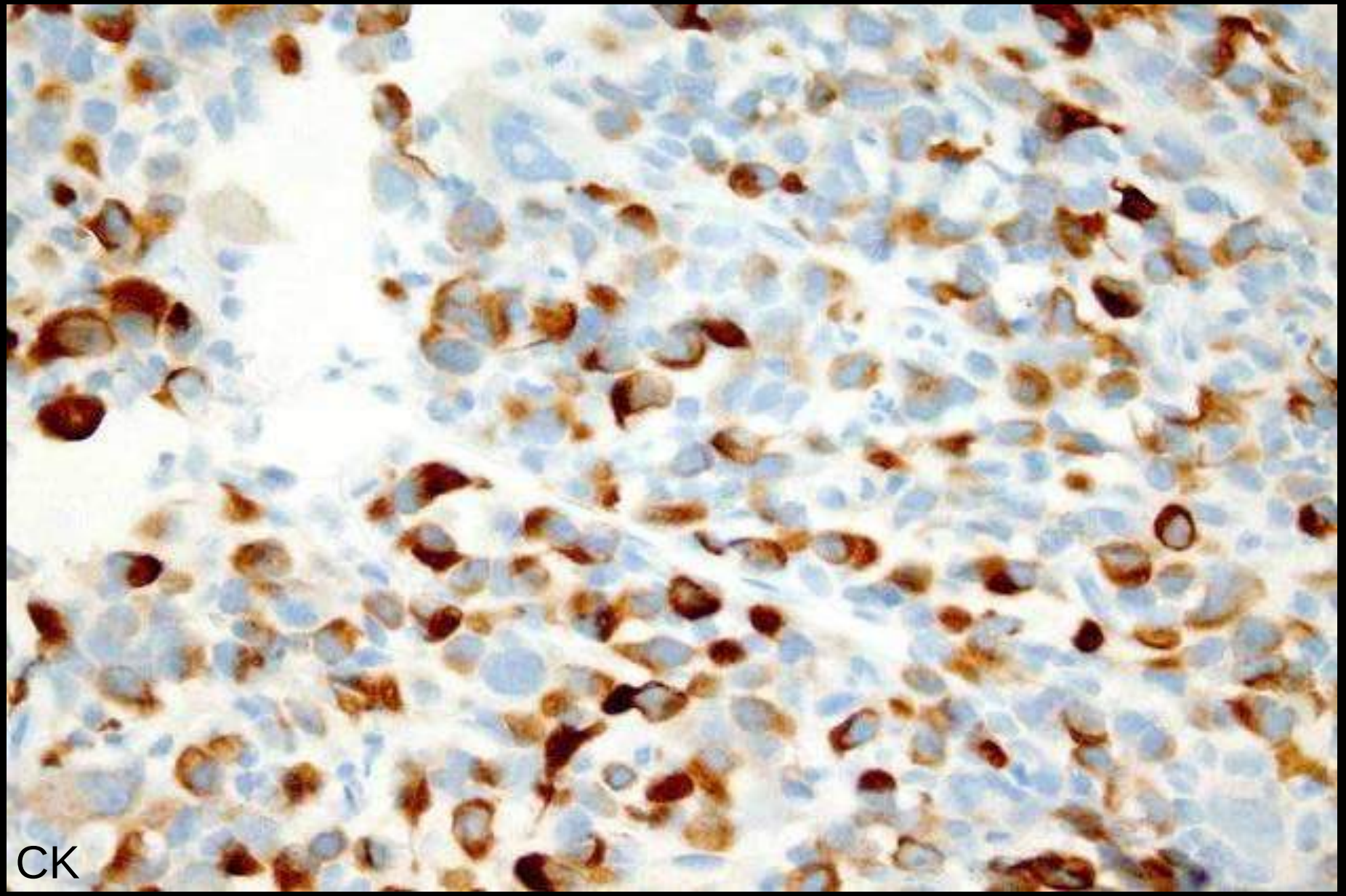
# Pancreas tumour



# Pancreas tumour



# Pancreas tumour: undifferentiated carcinoma

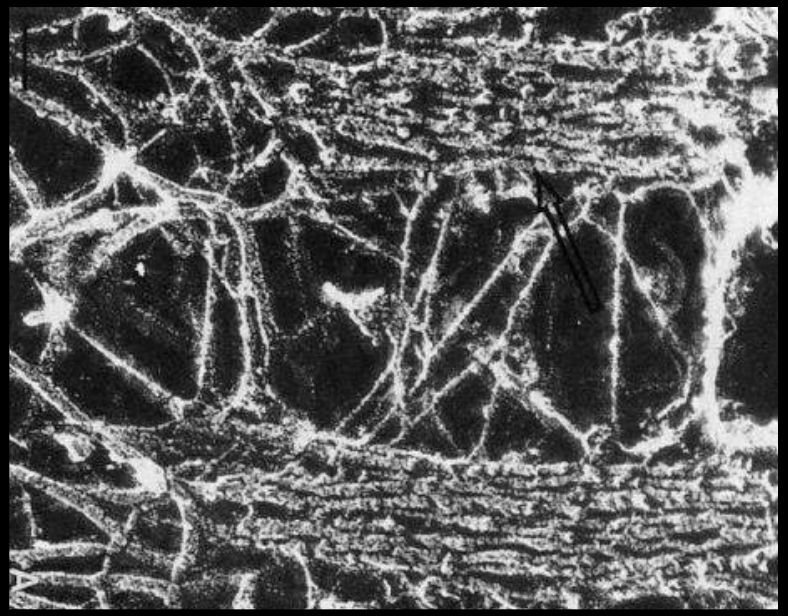


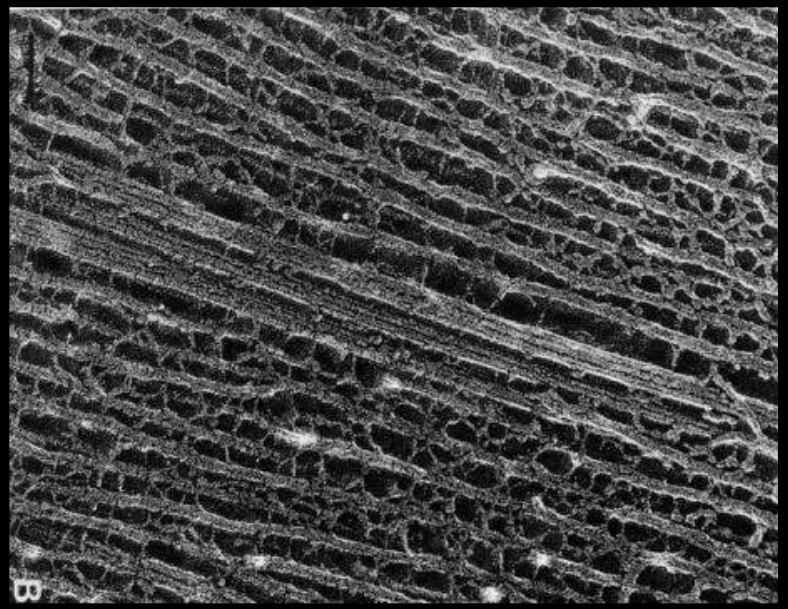
# Primary panel for the unknown primary tumour

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

# Cellular filaments

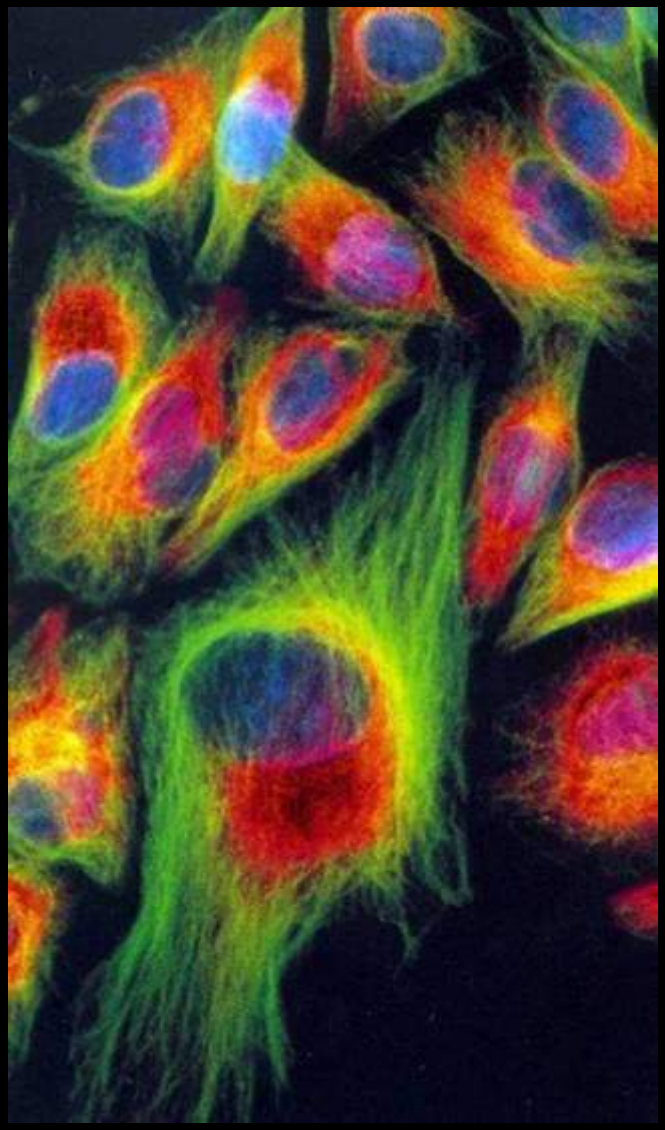
- Microfilaments: (6 nm)
- Intermediate filaments (7- 11 nm)
- Microtubuli (23 nm)



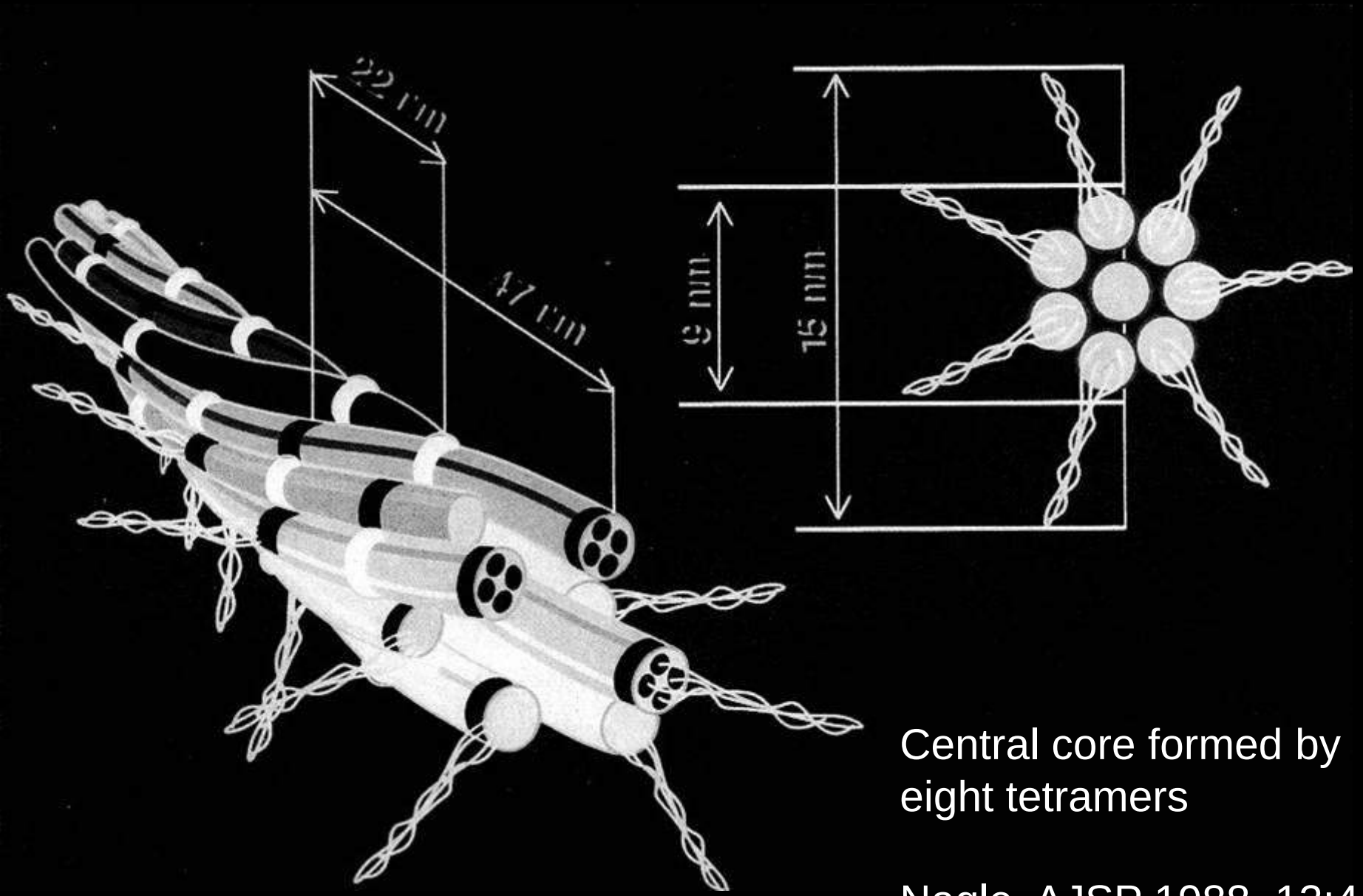



# Intermediate filaments

- Group of mainly cytoplasmic filaments 7 – 11 nm in diameter
- Part of the cytoskeleton in virtually all cells, creating as 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

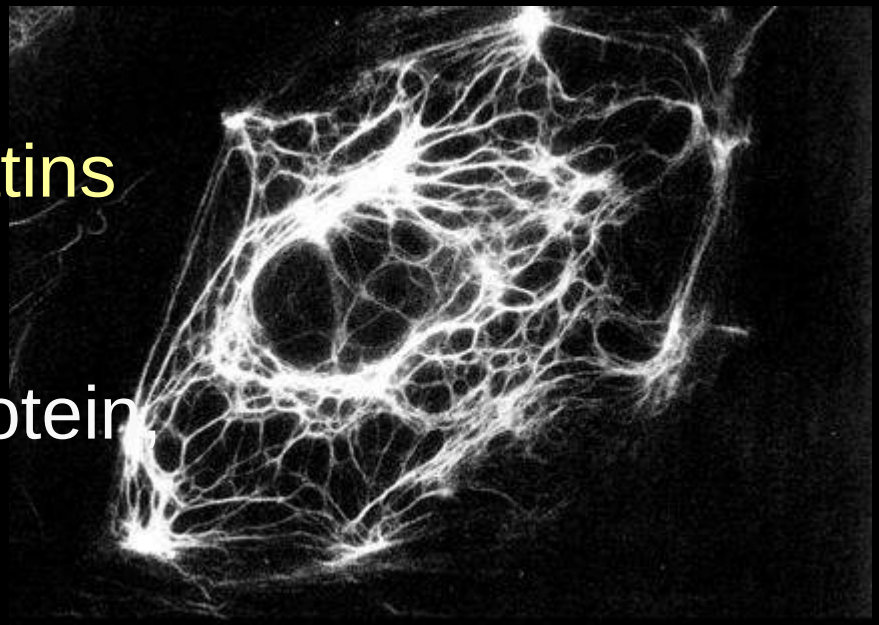


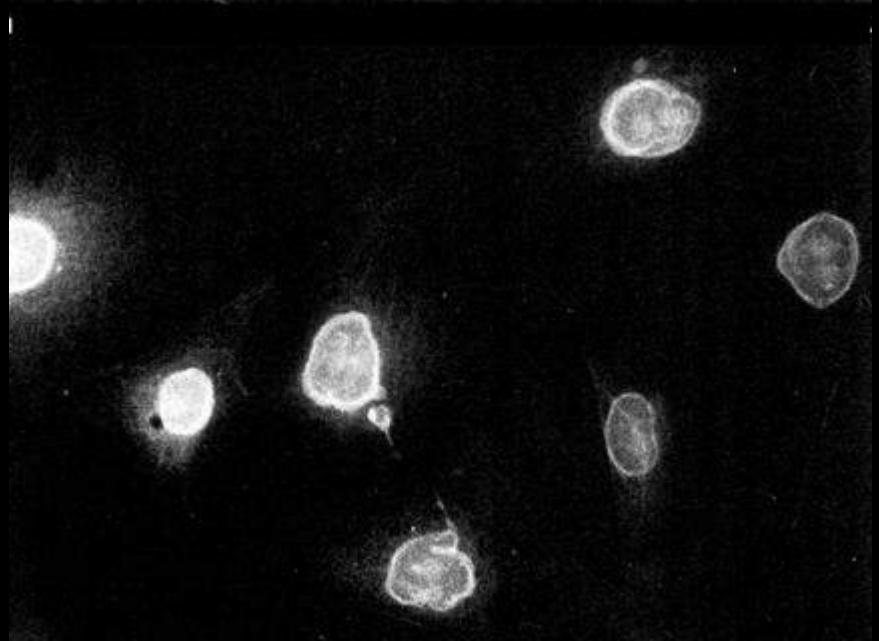

Central core formed by eight tetramers

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

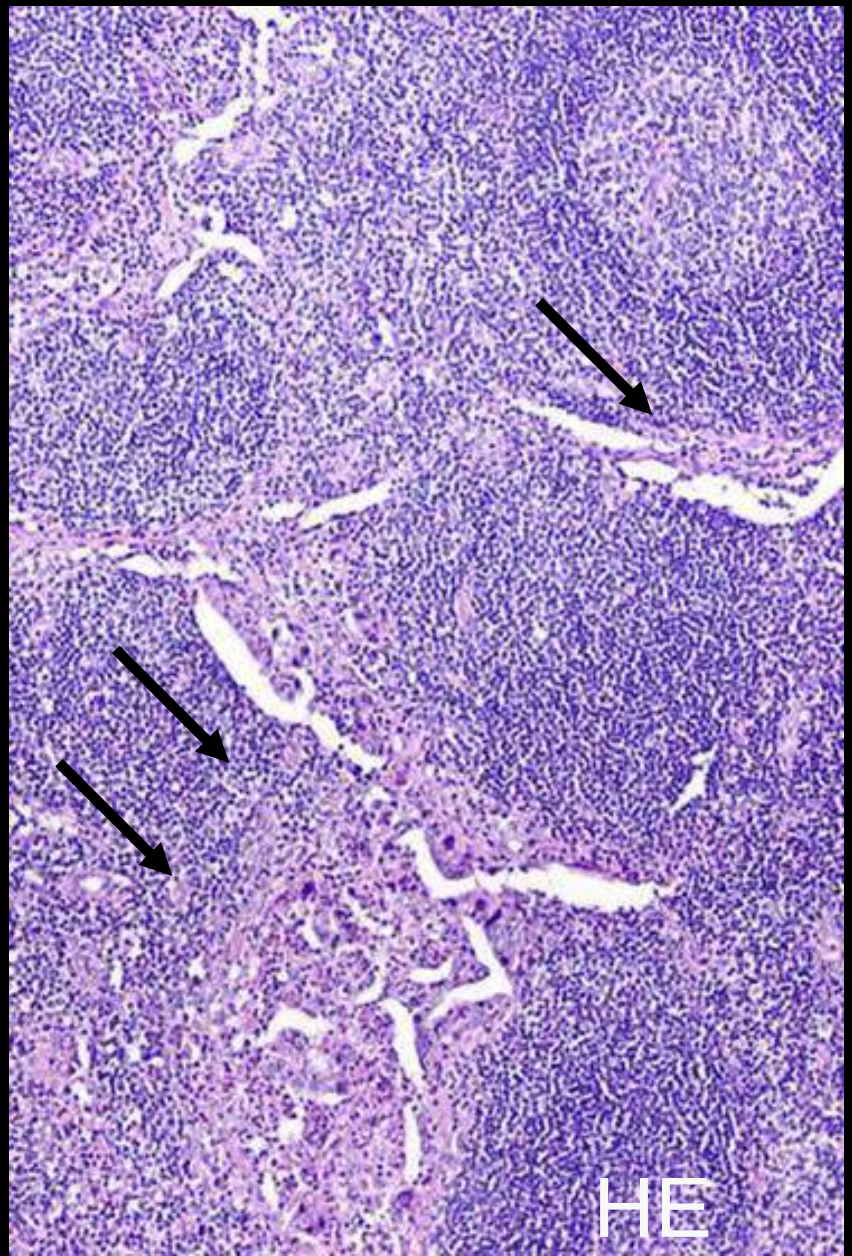
Cytokeratin intermediate filaments attached to desmosomes

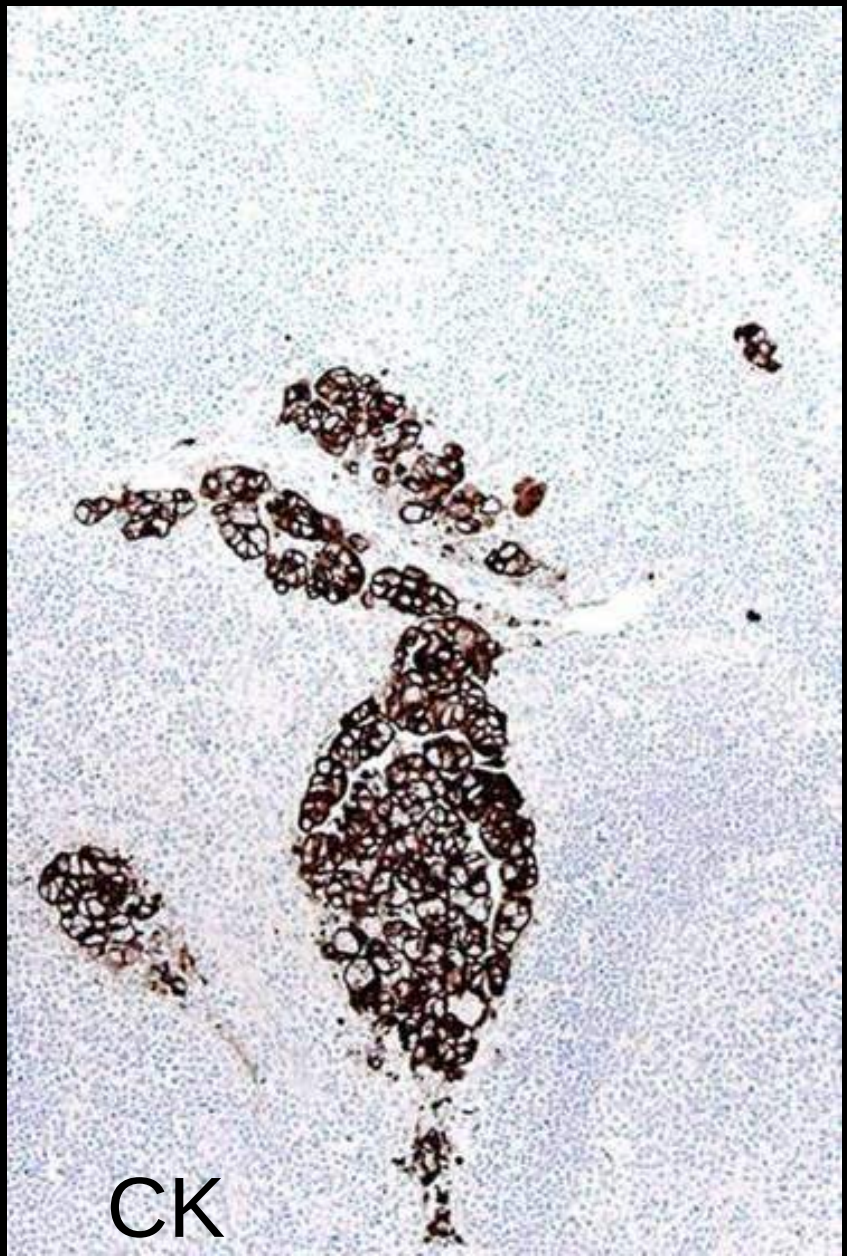
**Drochmans et al.**
**J Cell Biol. 1978, 79:427**

# Cytokeratins in diagnostic pathology

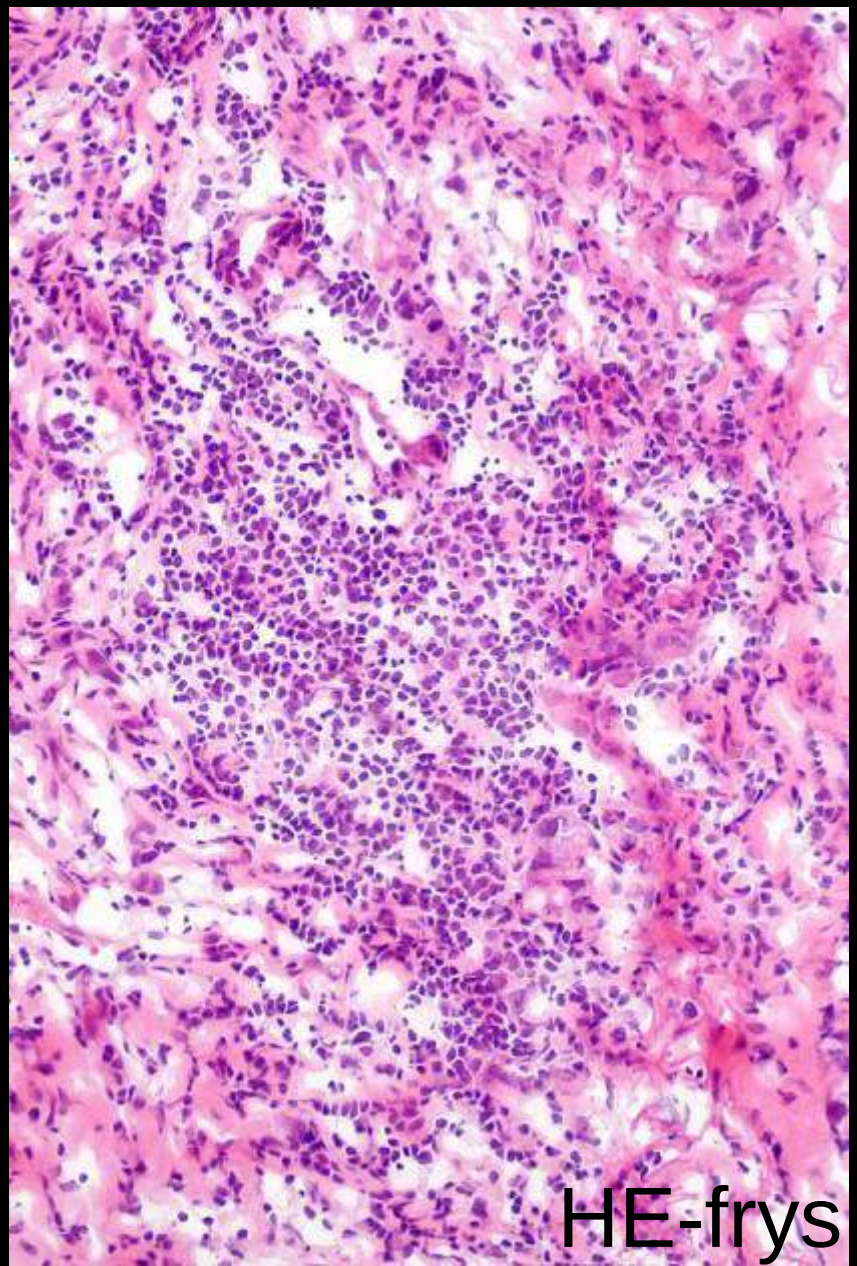
- Cytokeratins (CKs) belong to the most fundamental markers of epithelial differentiation
- CKs comprise a large family of subtypes. Different cell types express different patterns of CK subtypes
- Cancers generally express CK patterns that at least in part represent the pattern of the putative cell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

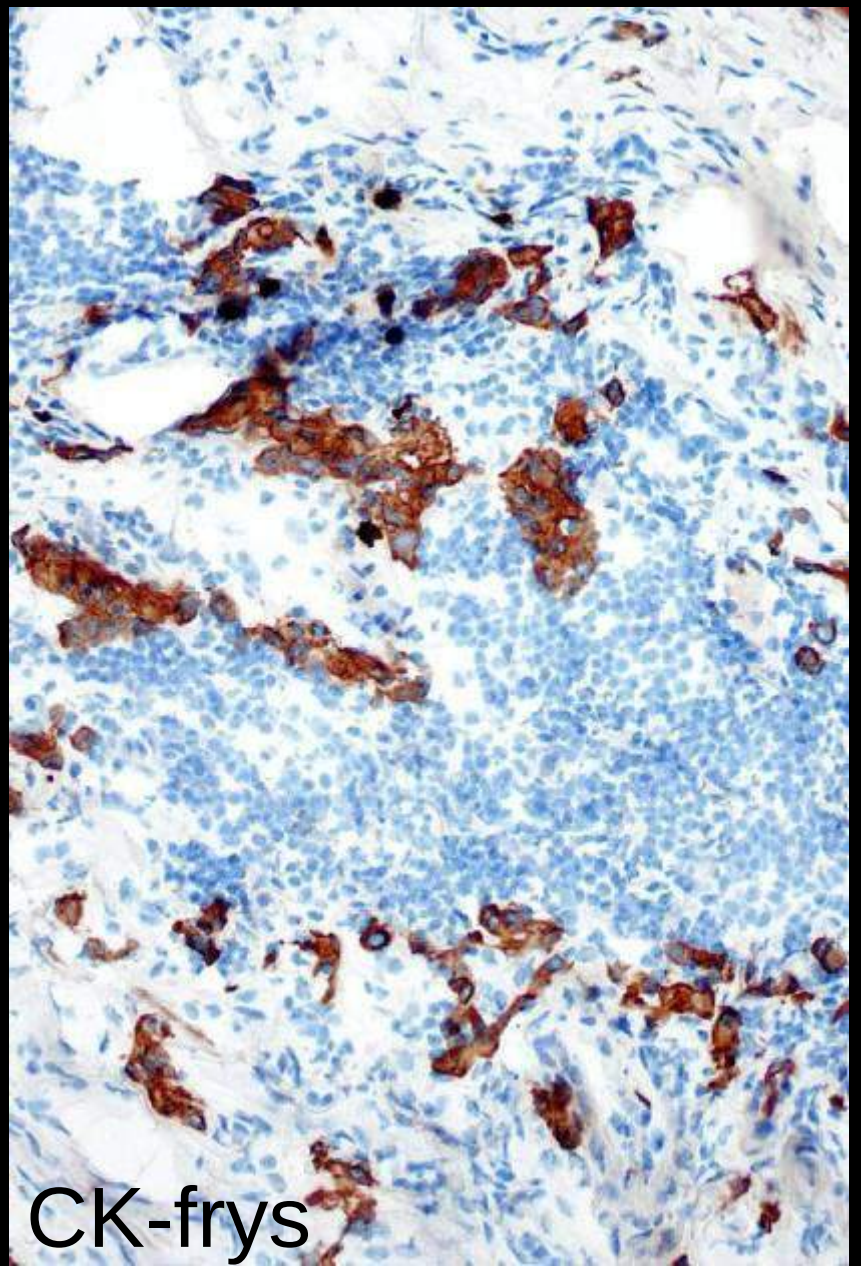
# Micrometastases identified by cytokeratin



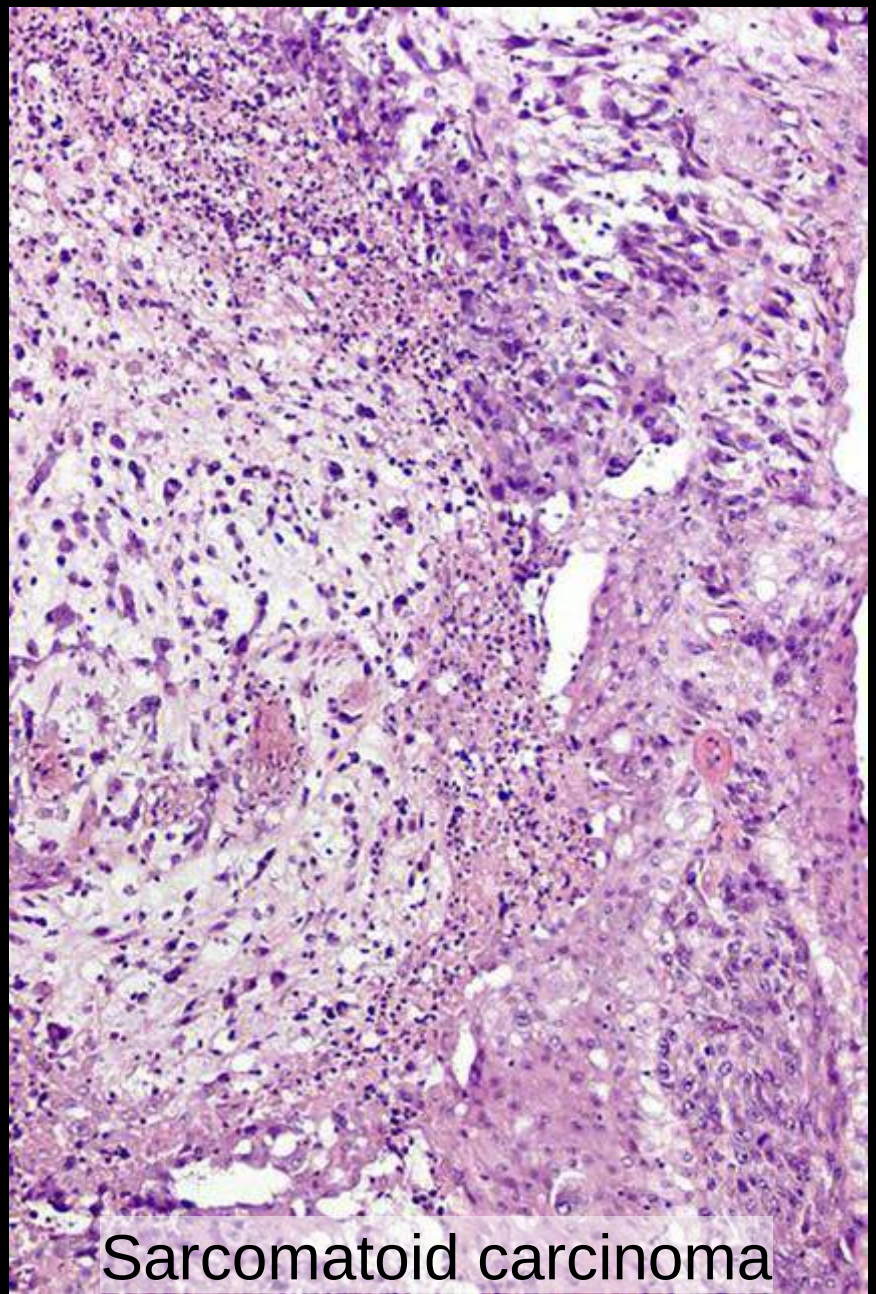



# Carcinoma in frosen section identified by cytokeratin

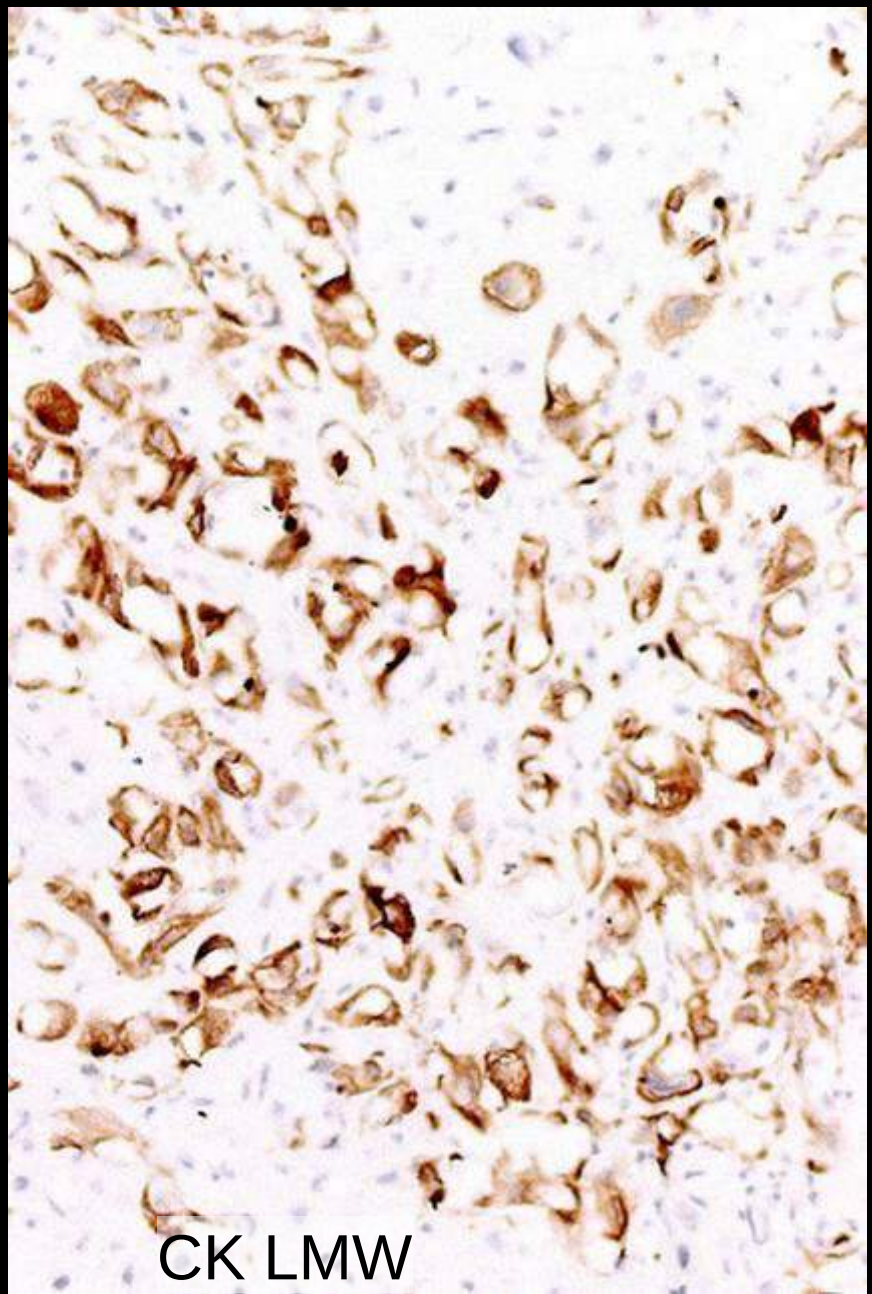


# Cytokeratins in carcinomas with aberrant growth patterns



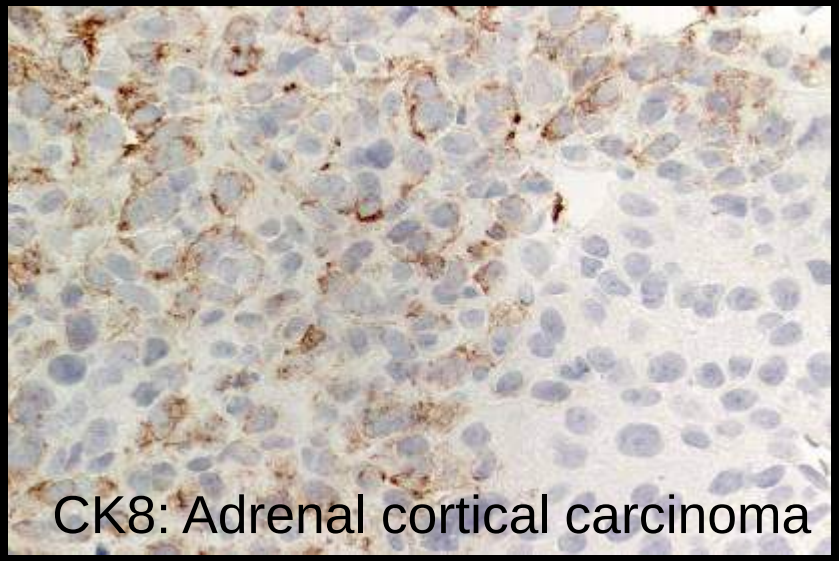
Sarcomatoid carcinoma



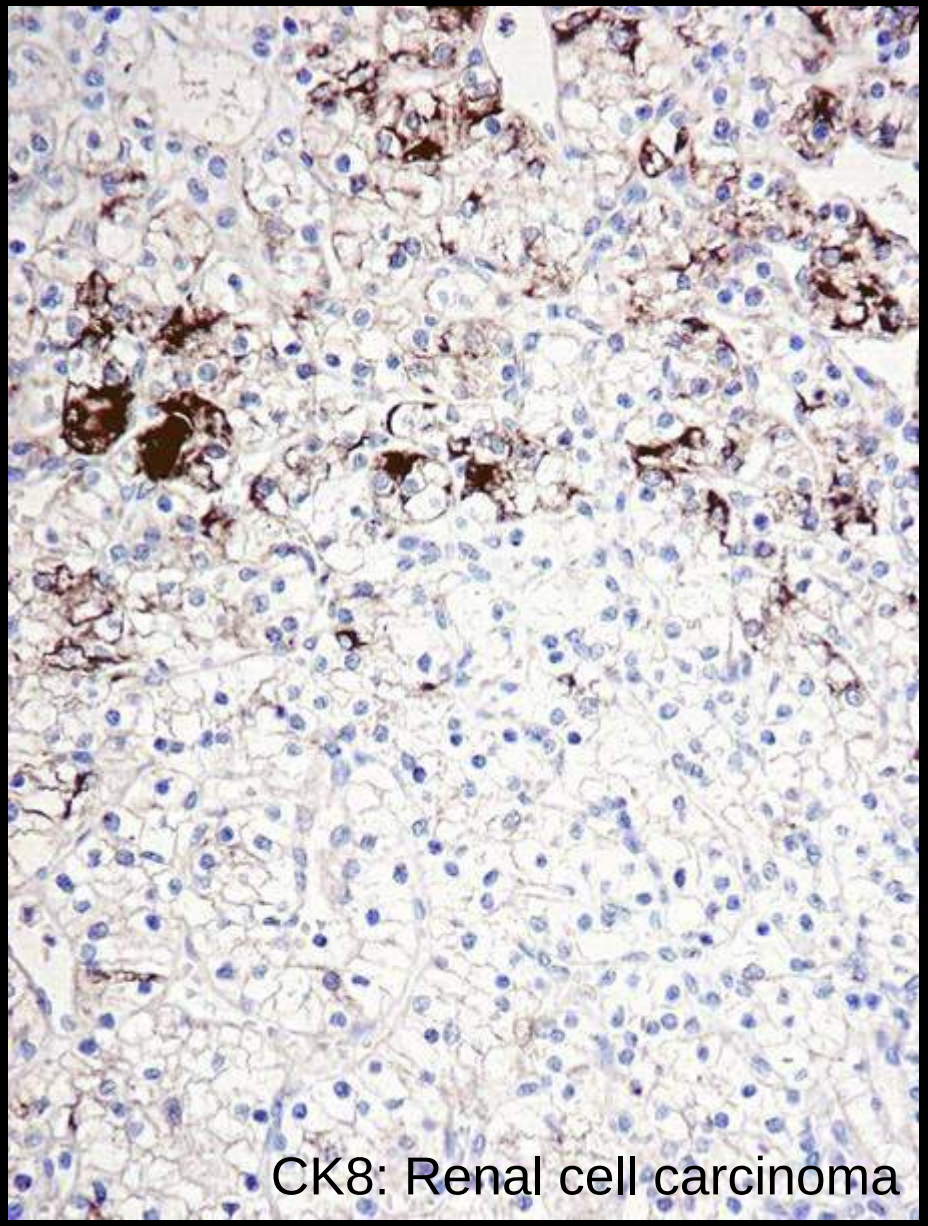
CK LMW

# Low molecular weight cytokeratins in carcinomas

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



CK8: Adrenal cortical carcinoma

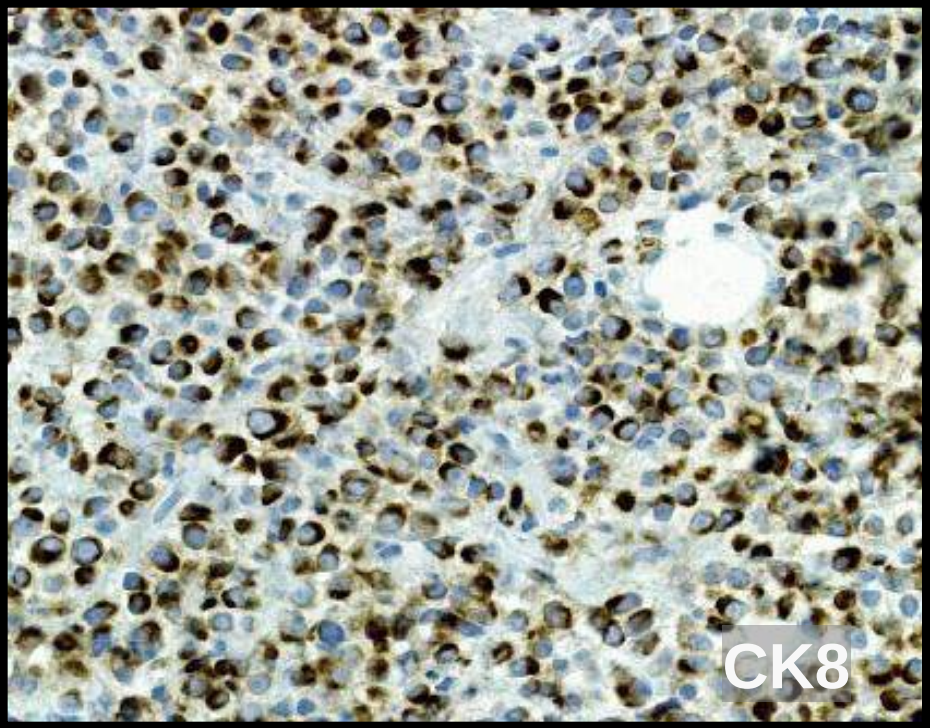


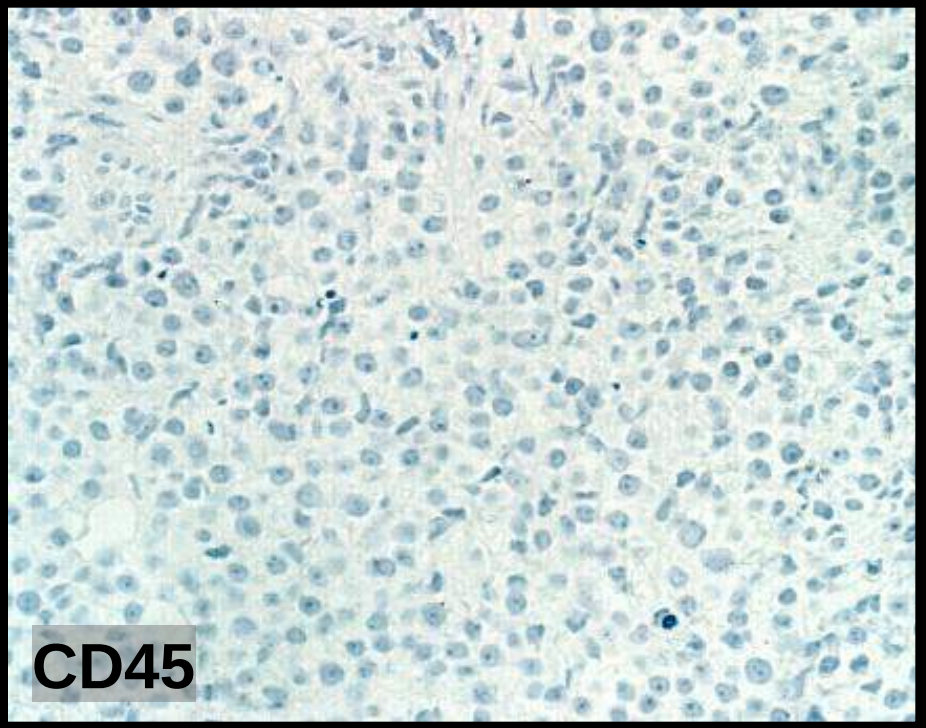
CK8: Renal cell carcinoma

# 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 | - | -/+ | -/+ | + |

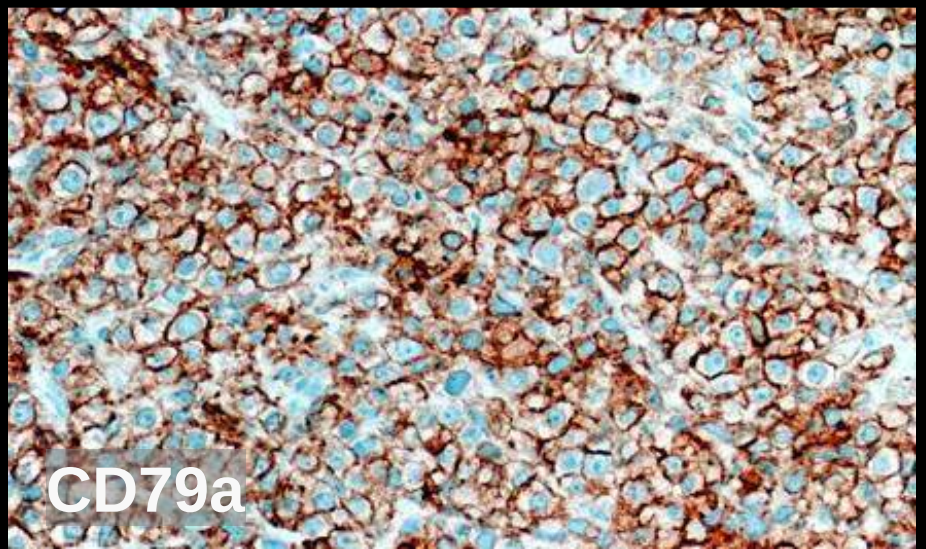
# Cytokeratins in non-epithelial tumours




42 y, tumour infiltrating retroperitoneum

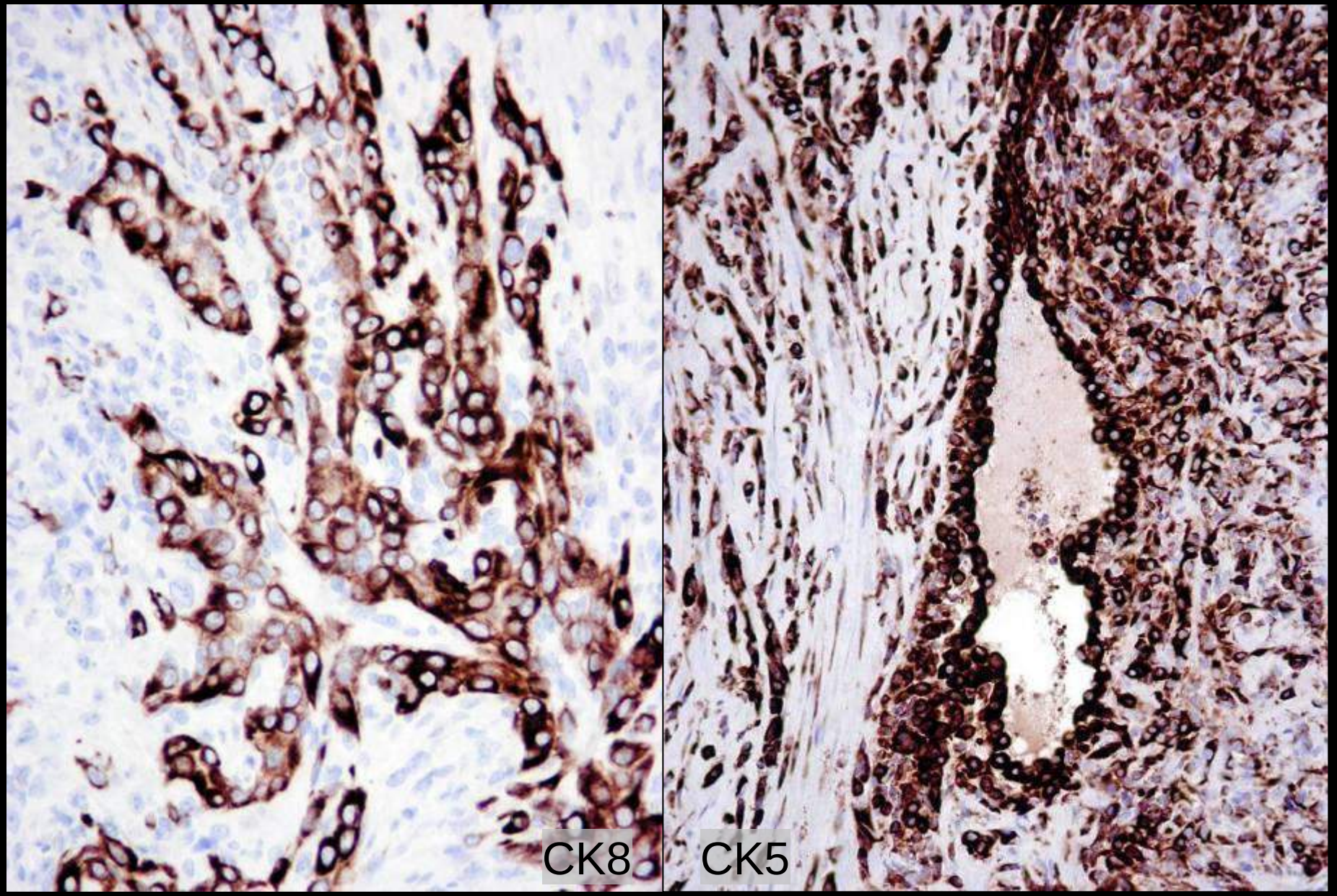
Malignant lymphoma !



# 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 | - | -/+ | -/+ | + |

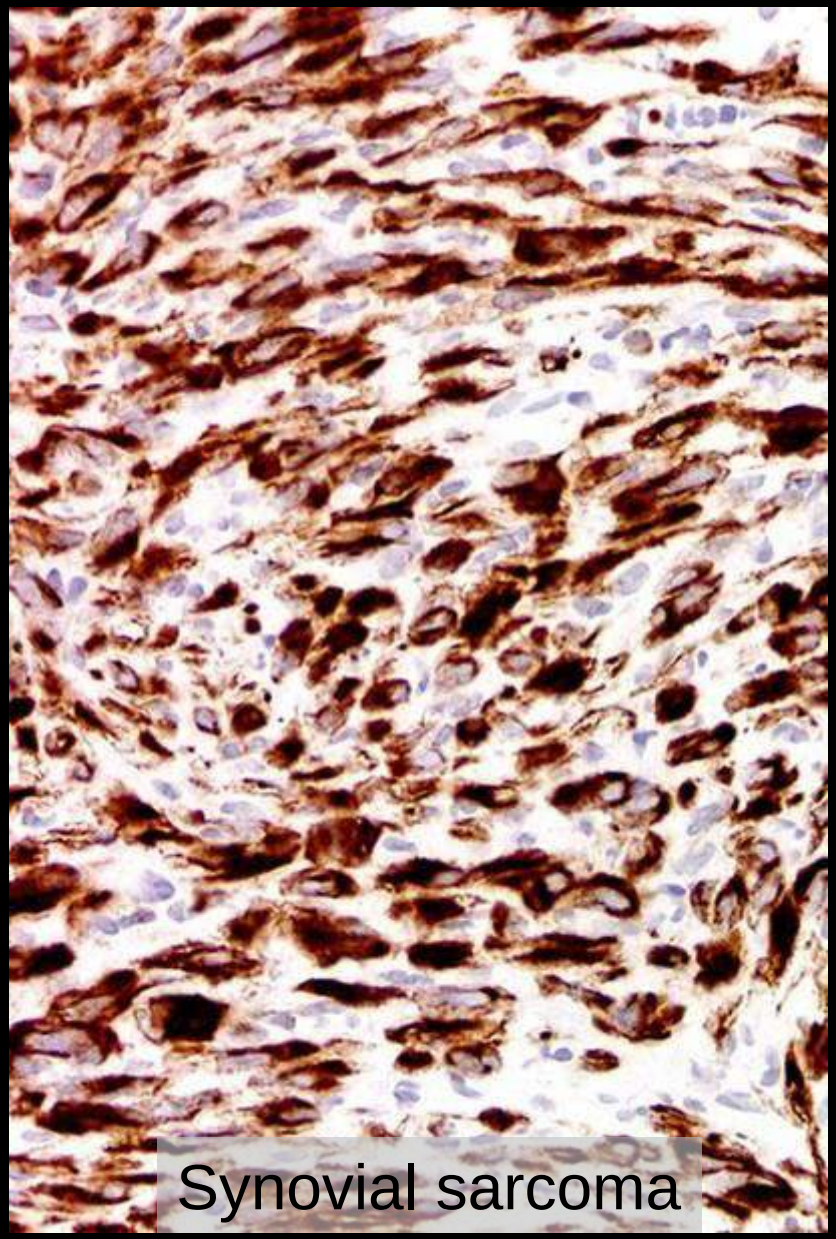
# Cytokeratins in malignant mesothelioma



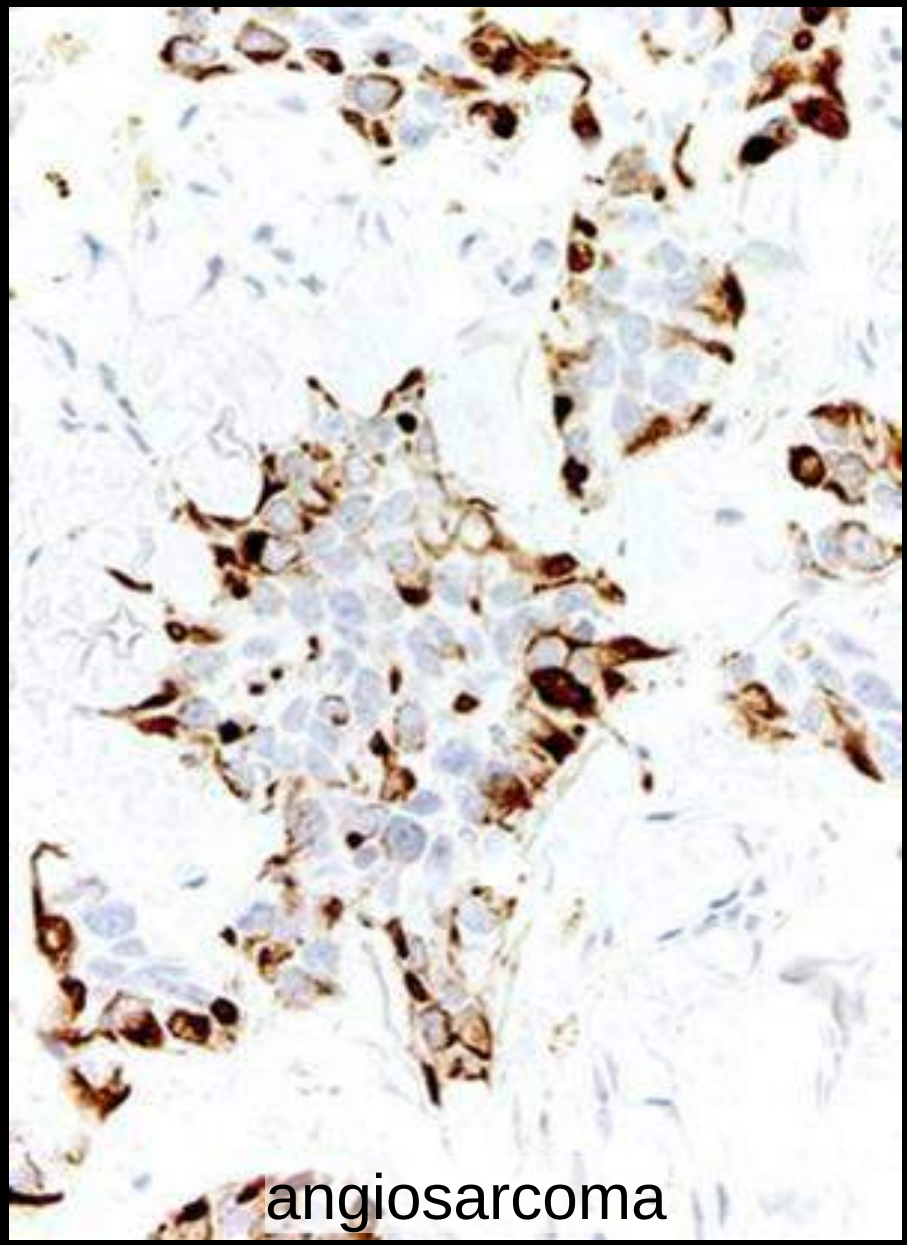
# Primary panel for the unknown primary tumour

| | 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

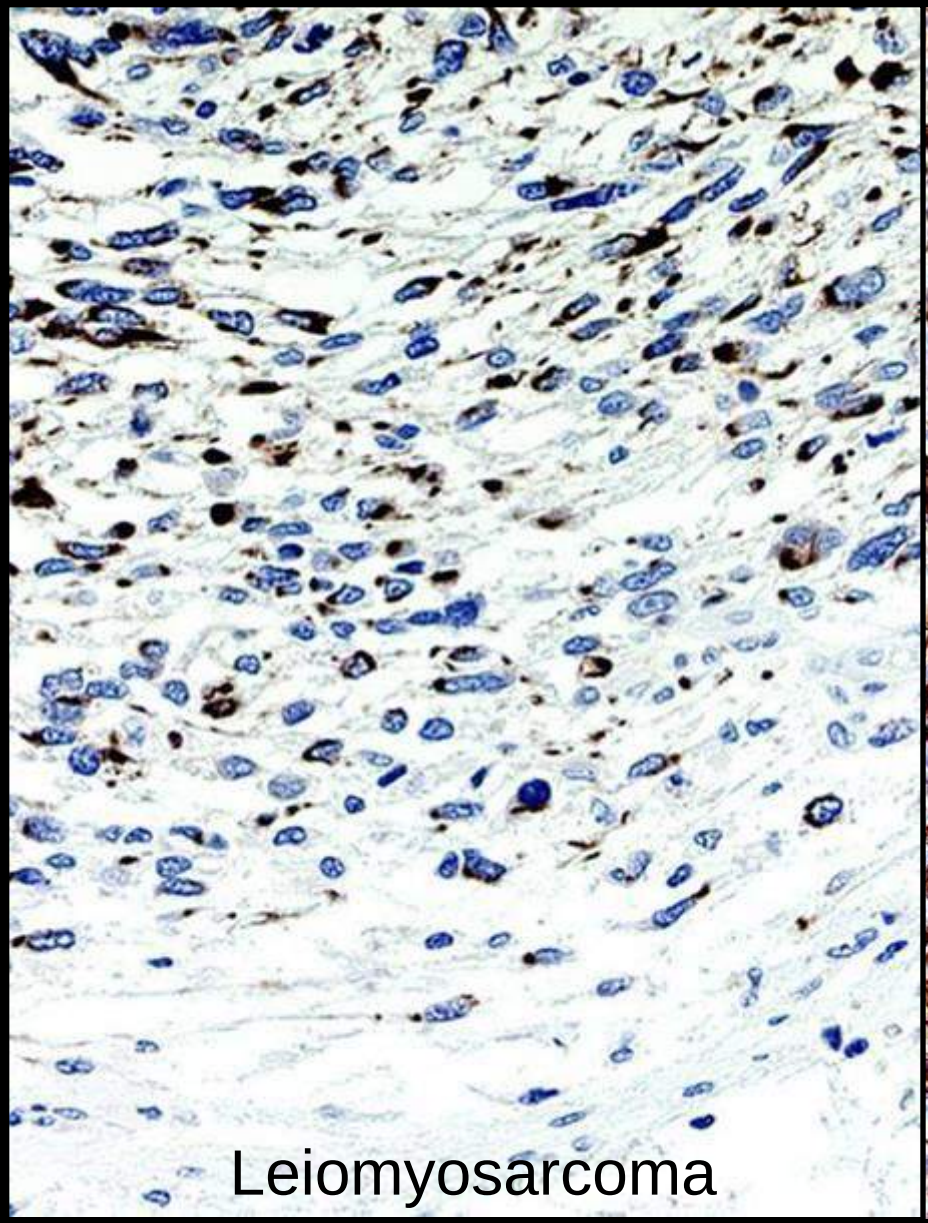


Synovial sarcoma

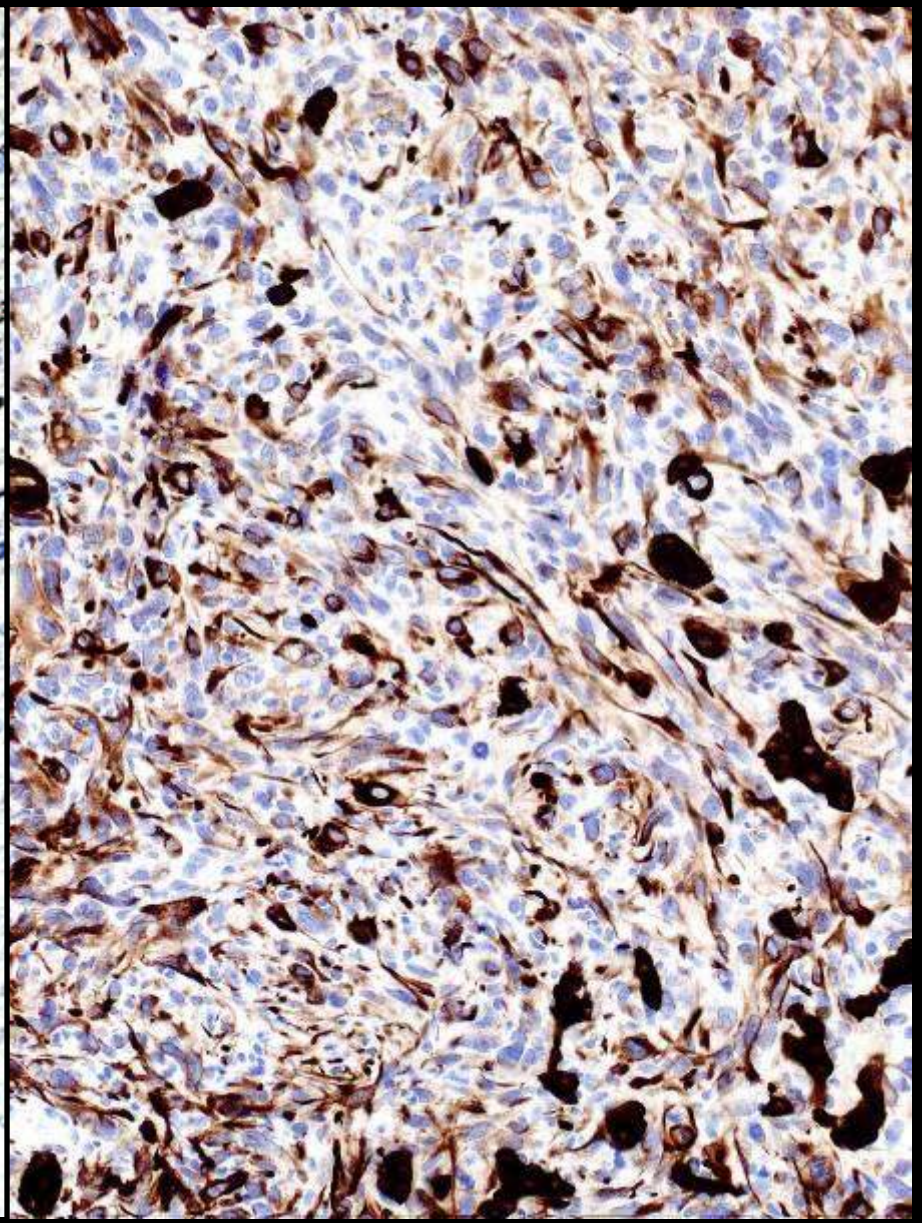


angiosarcoma

# Cytokeratins in non-epithelial tumours



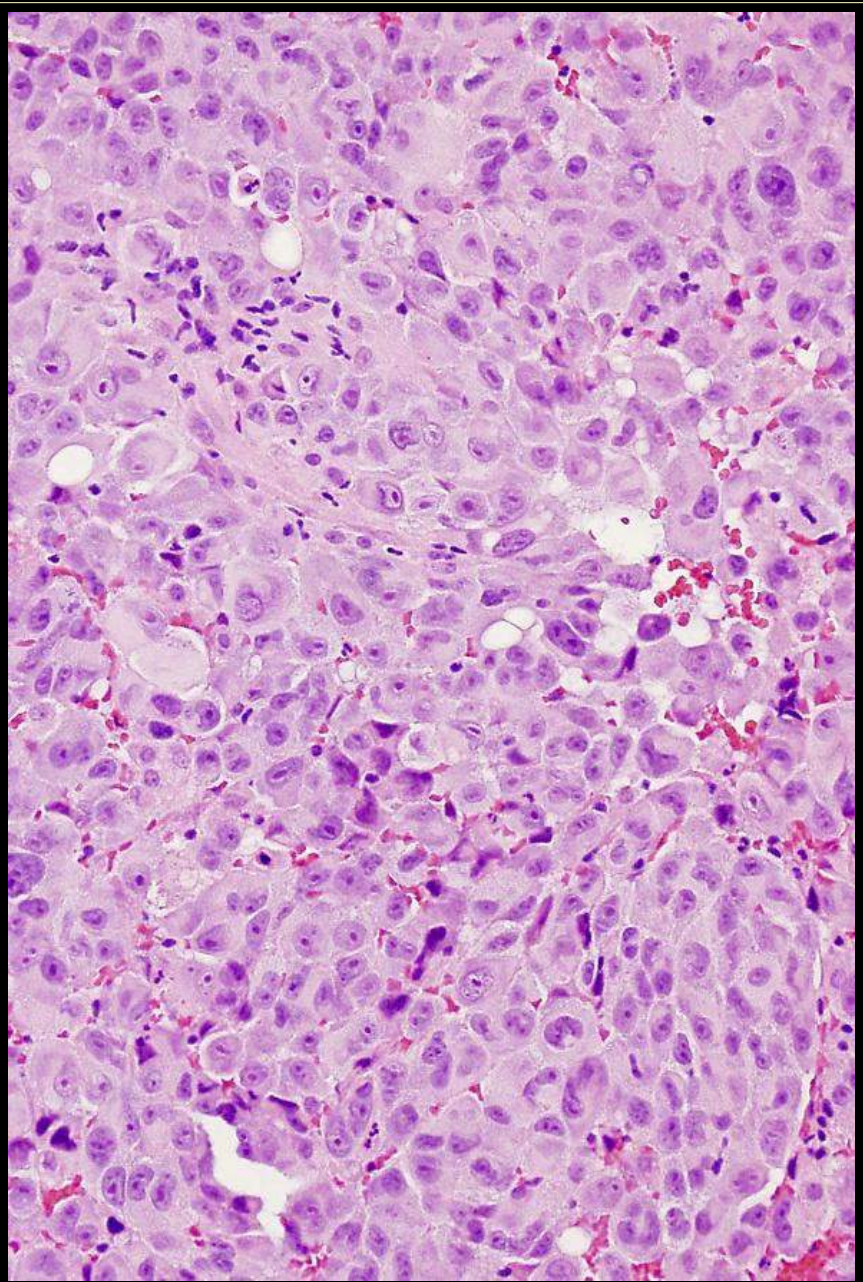
Leiomyosarcoma

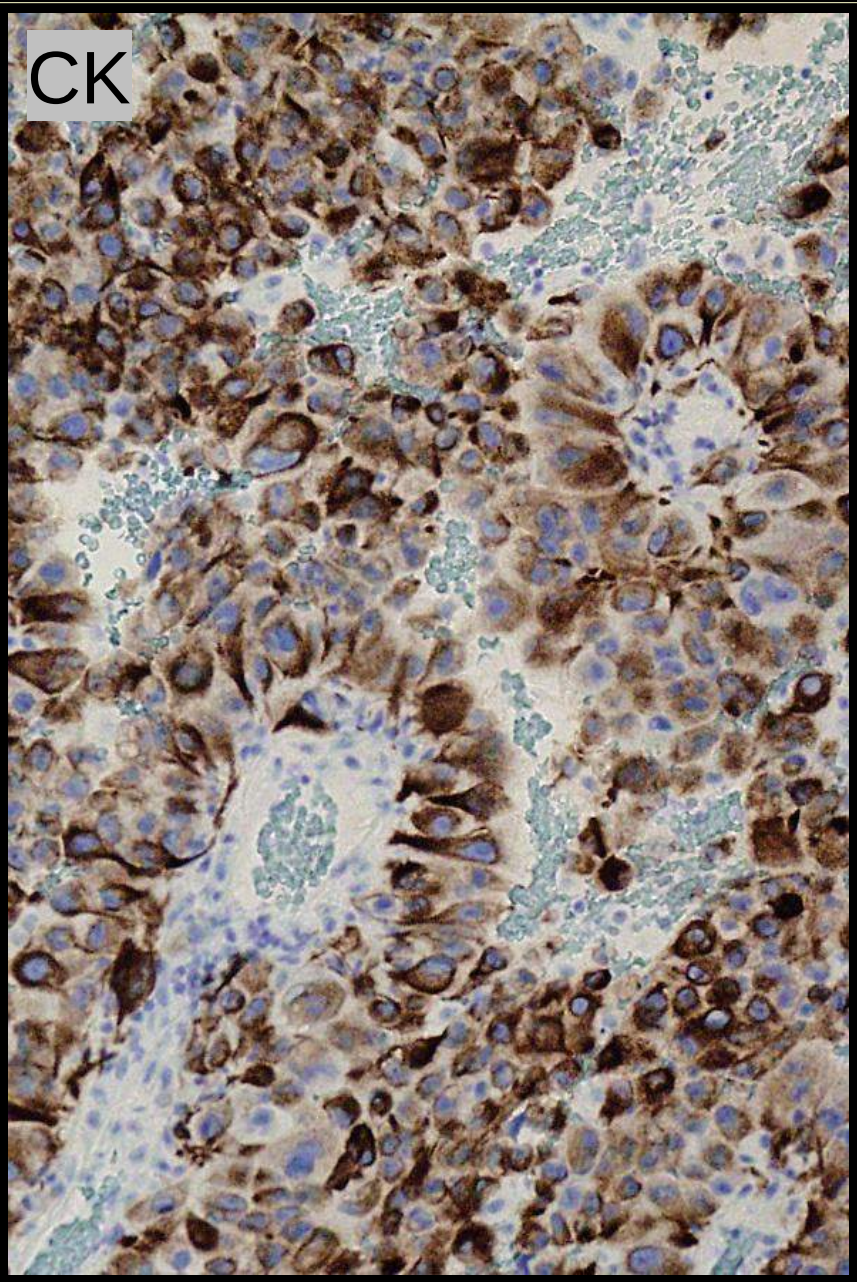


# Primary panel for the unknown primary tumour

| | 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

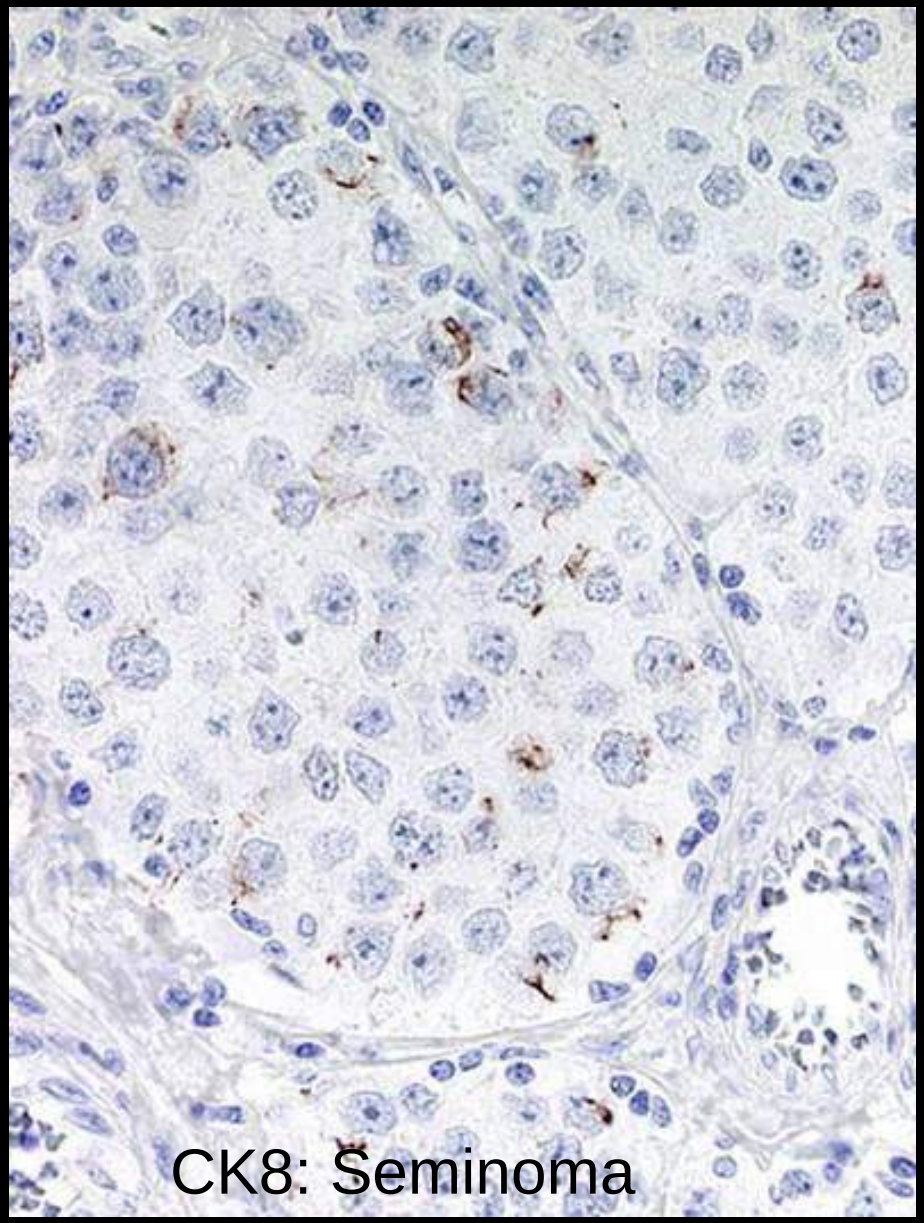




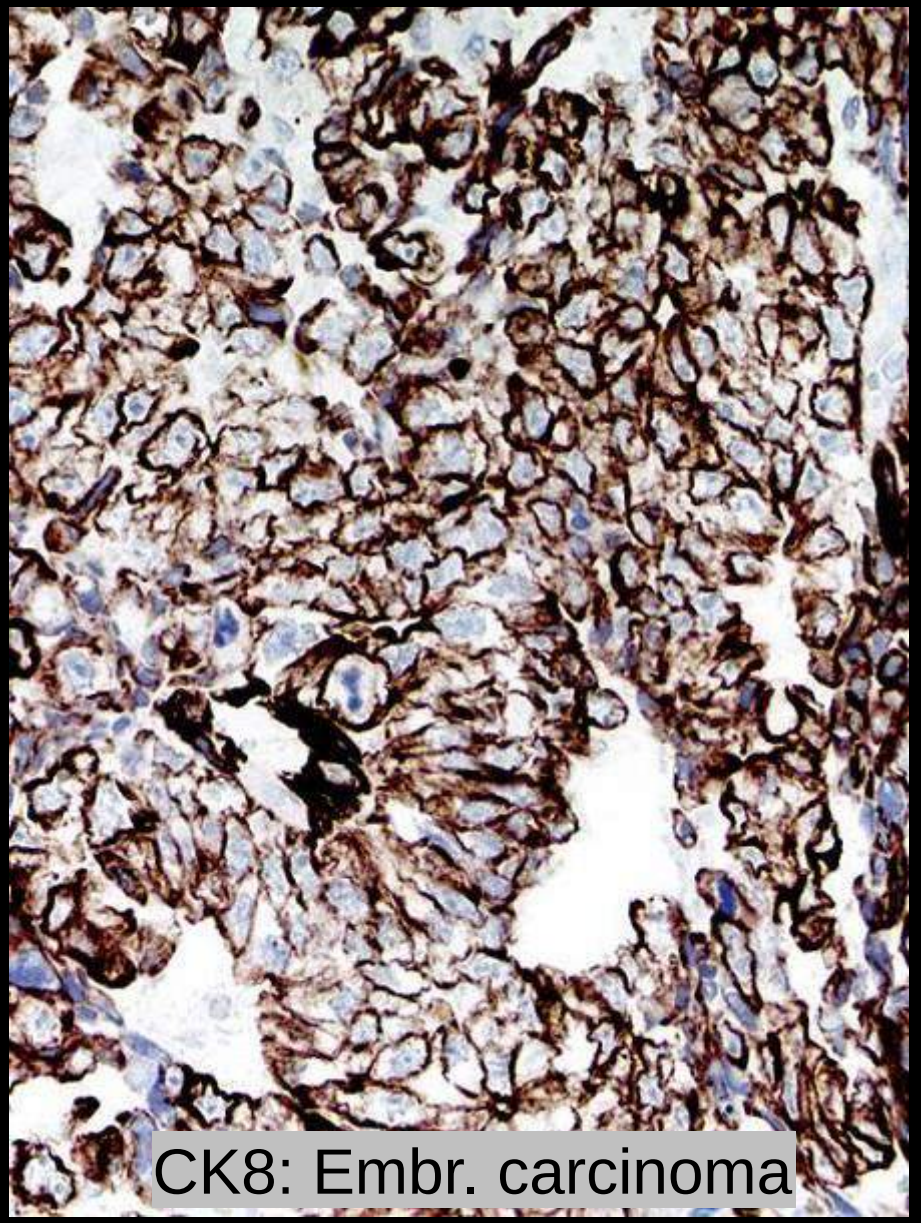
# Primary panel for the unknown primary tumour

| | 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

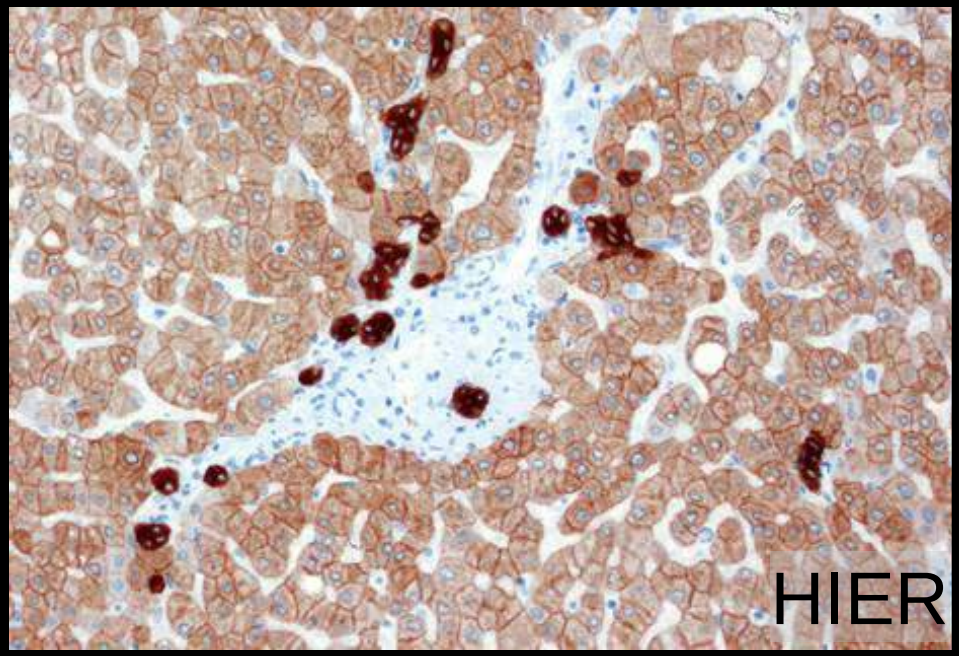


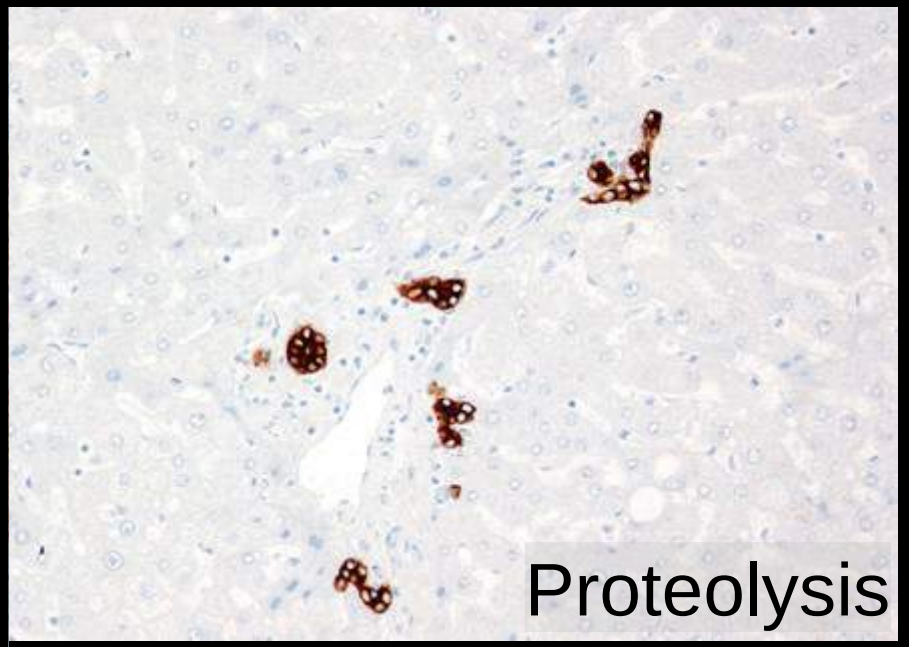
CK8: Seminoma



CK8: Embr. carcinoma

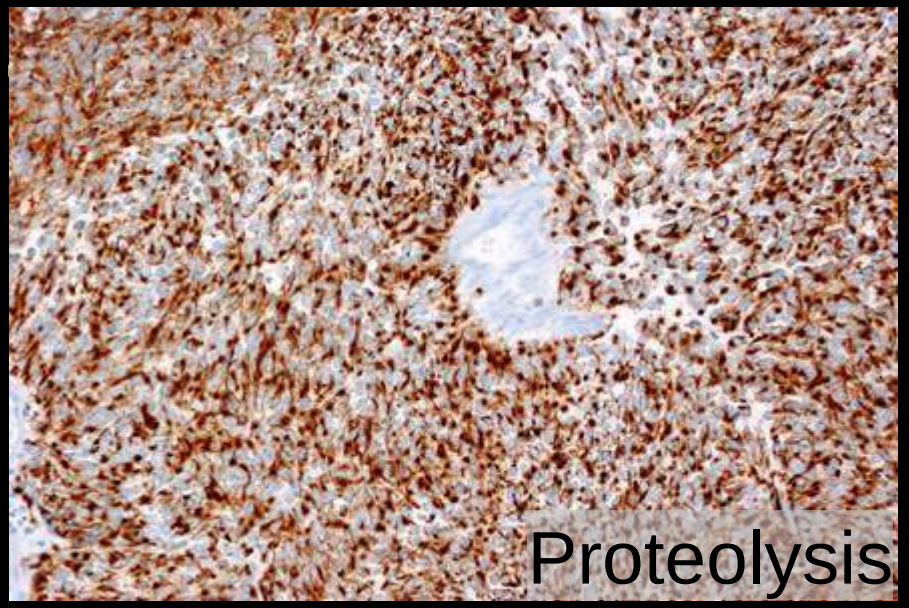
# Cytokeratins: retrieval causing false negativity



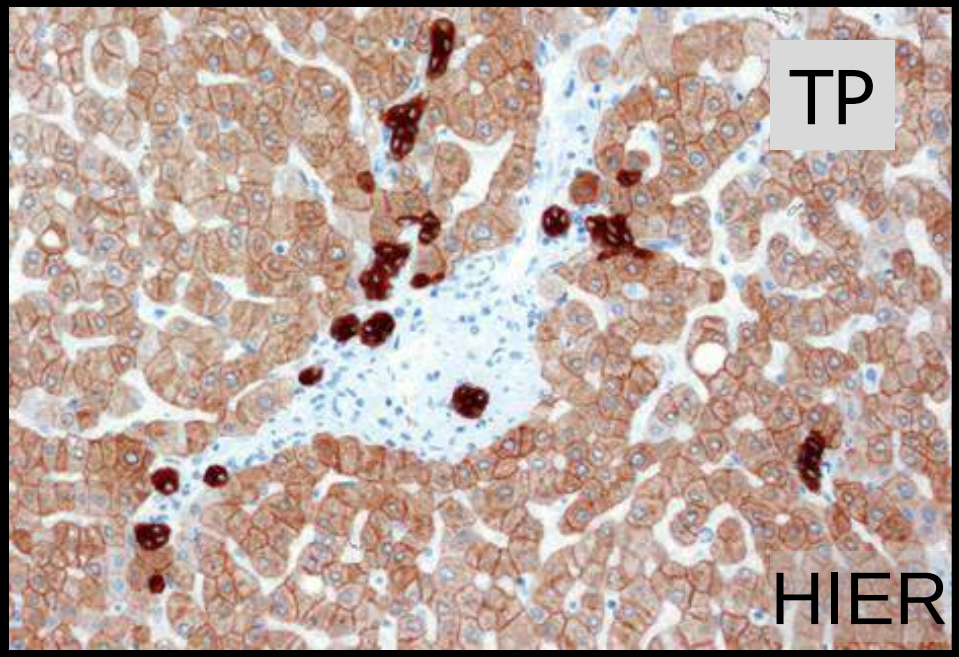



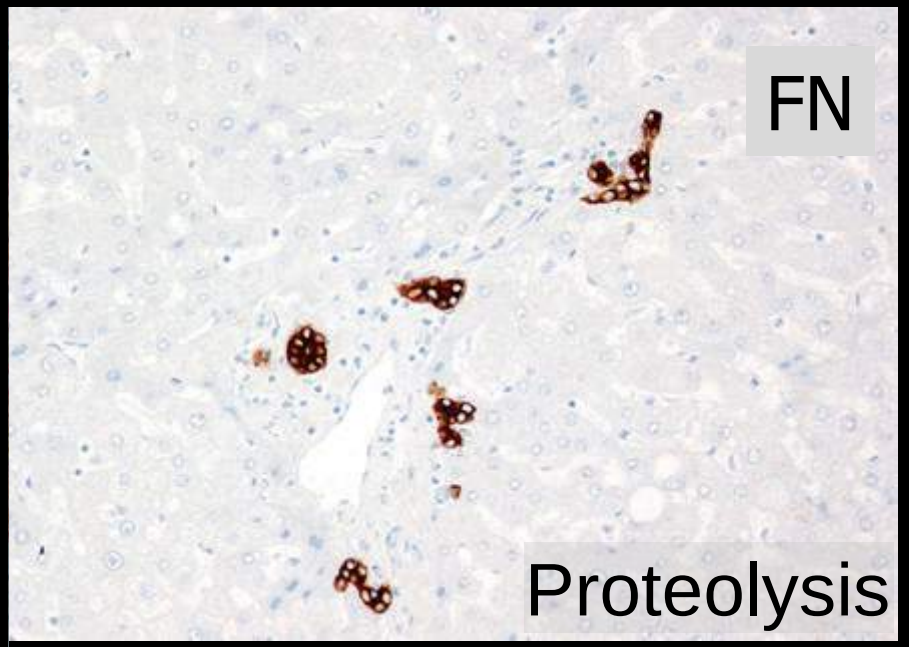

- AE1 detects CK8 after HIER onl
- AE1 does not detect CK18
- AE3 does not detect CK8/CK18

SCLC

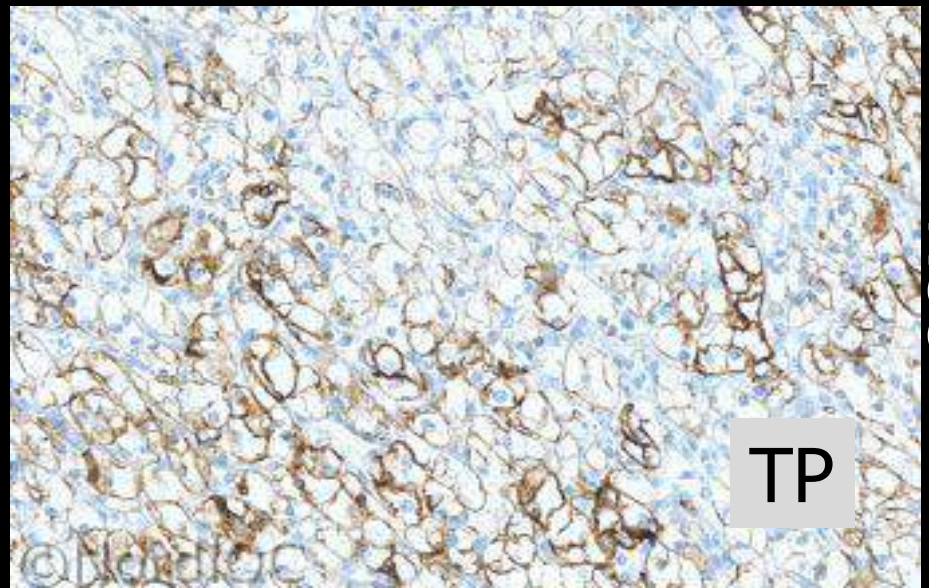


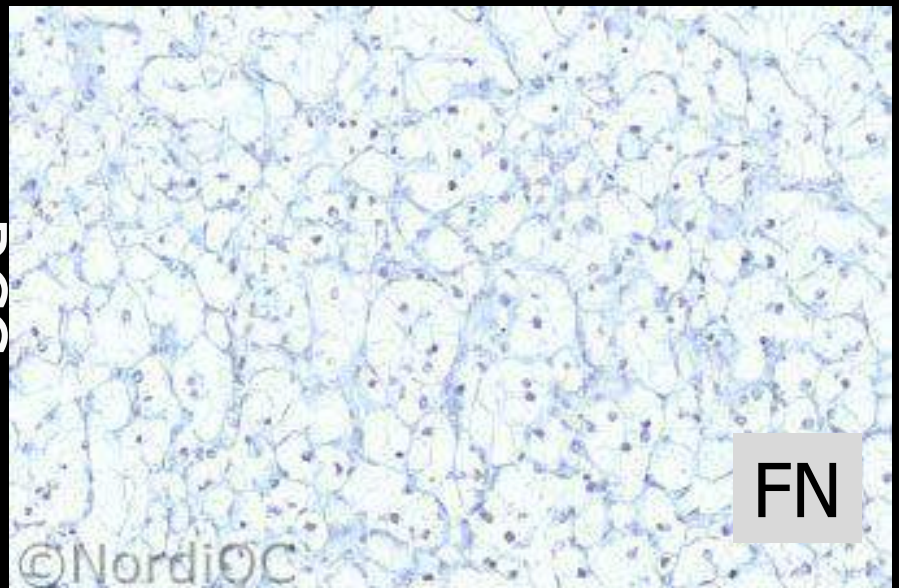
# Cytokeratins: retrieval causing false negativity




RCC



# Primary panel for the unknown primary tumour

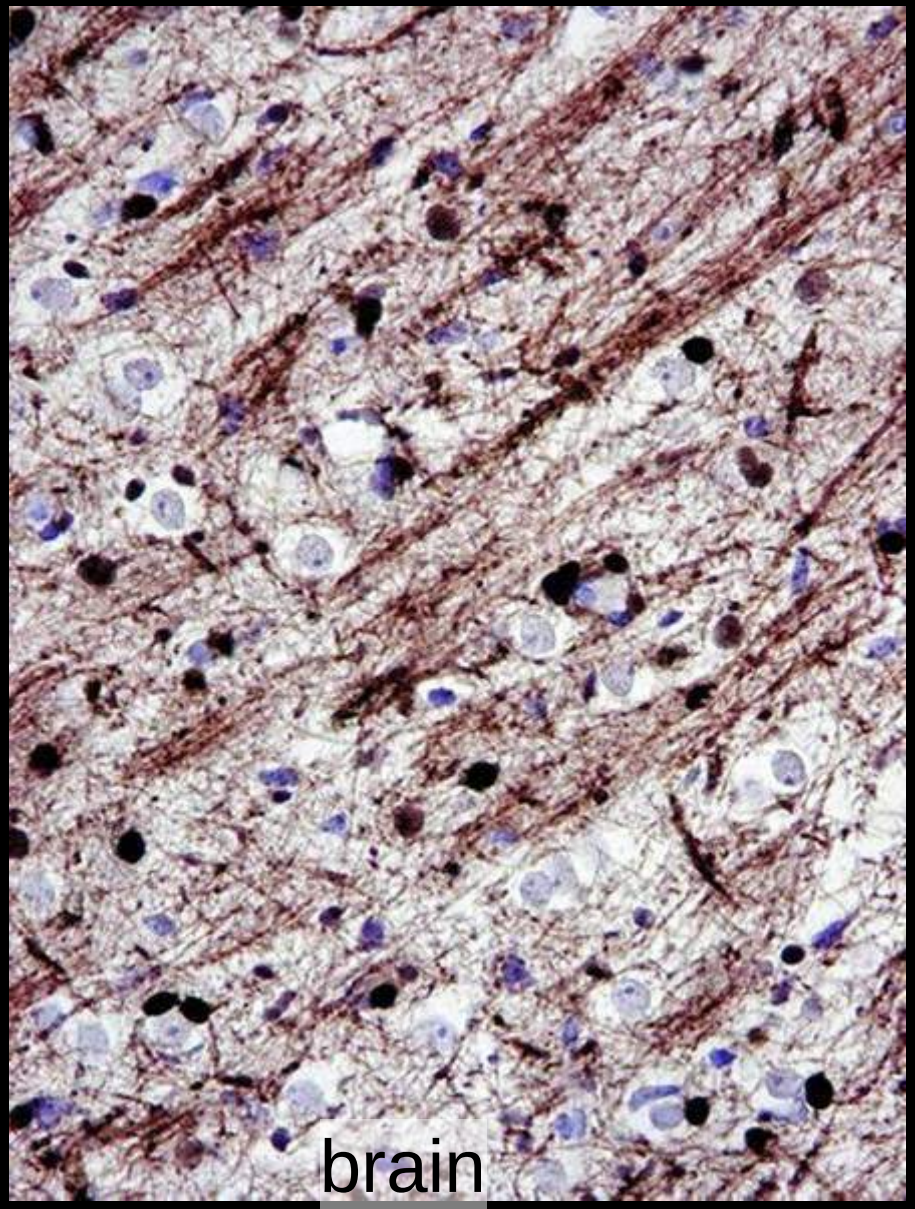
| | CD45 | CK | S-100 | VIM |
|---|---|---|---|---|
| Haemato-lymphoid neoplasms | +/(-) | -/(+) | -/(+) | +/(-) |
| Epithelial neoplasms | - | +/(-) | -/+ | -/+ |
| Mesothelial neoplasms | - | + | - | + |
| Mesenchymal and neuronal neoplasms | - | -/(+) | -/+ | + |
| Non-neuronal neuroepithelial neoplasms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

# S-100 protein

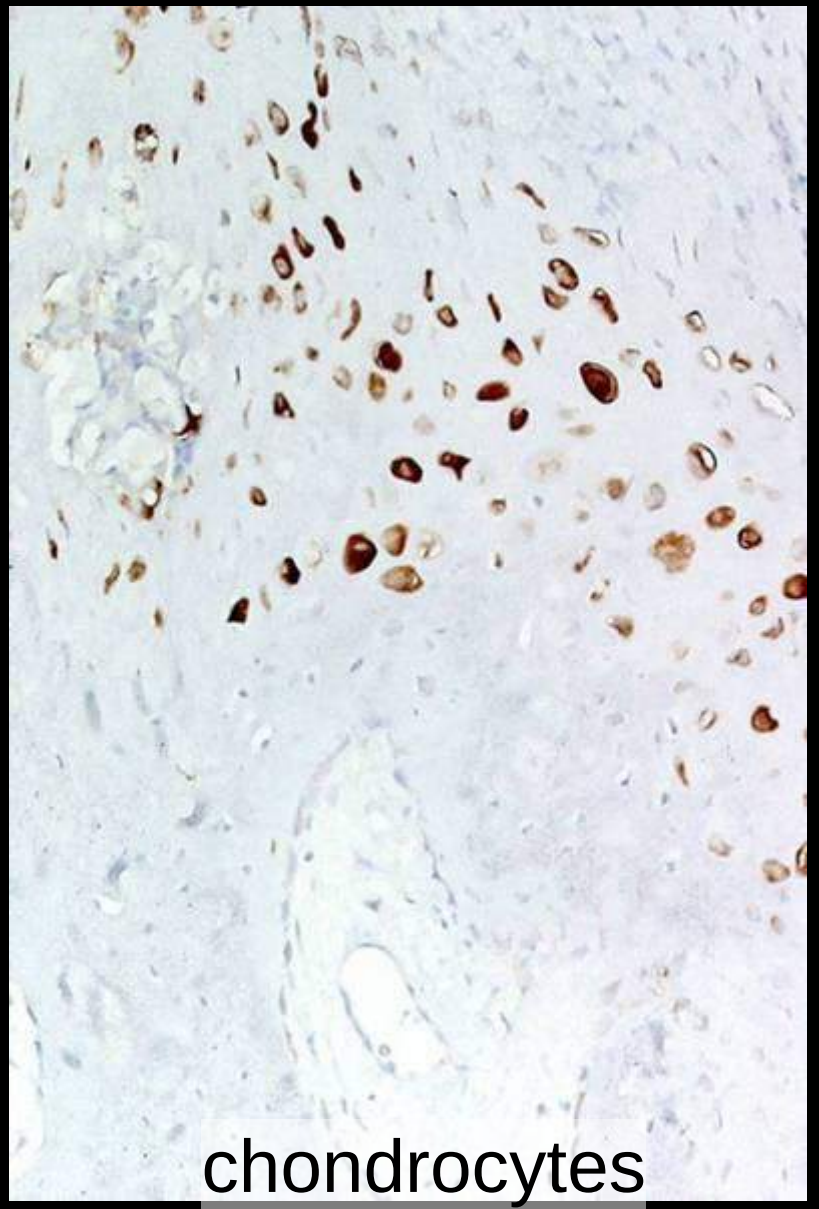
- Family of acid calcium binding proteins 9/13 kDa
- Located in nuclei, cytoplasm and cell membranes
- at least 10 α-chains and one β-chain creating homo- and heterodimers

- 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

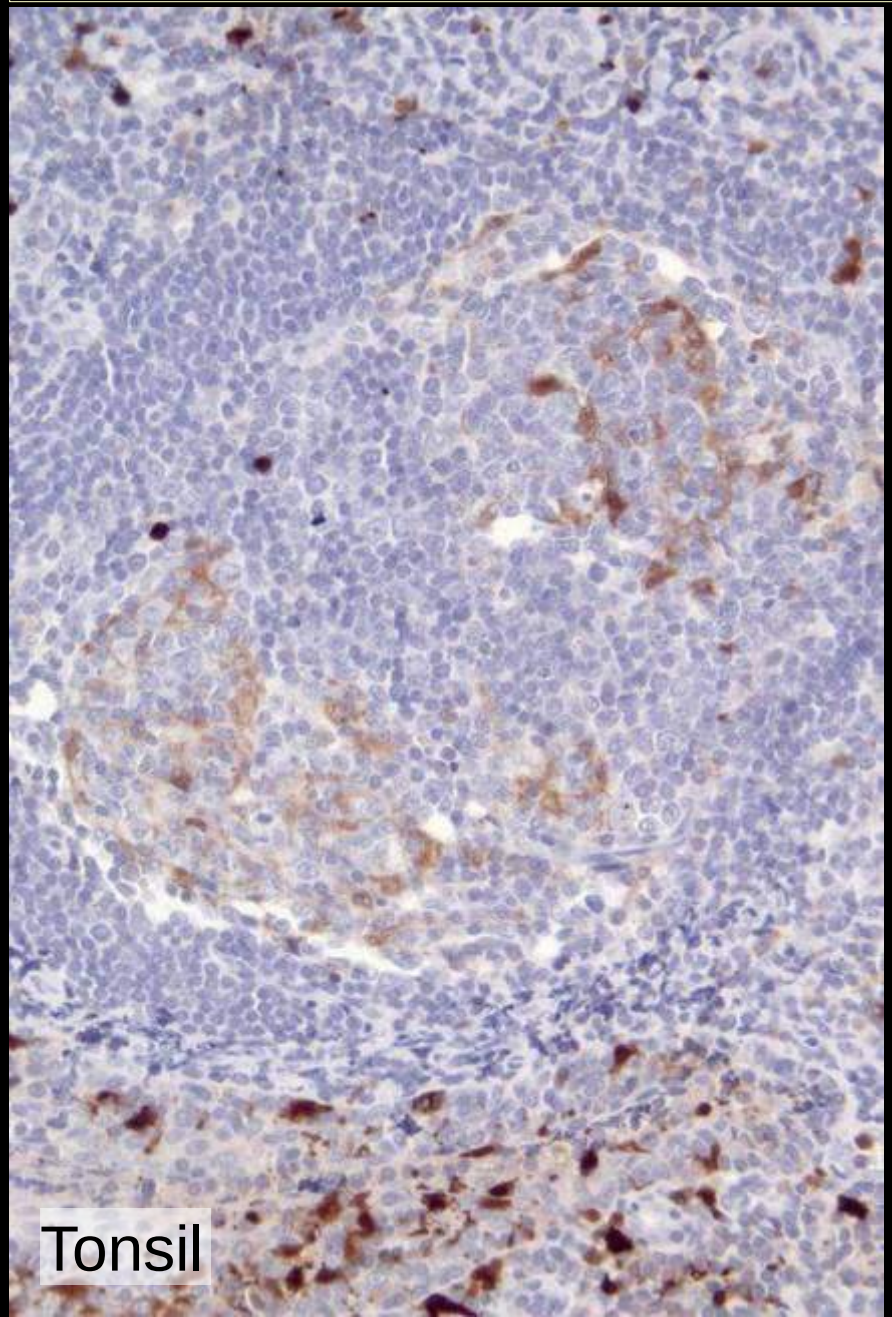


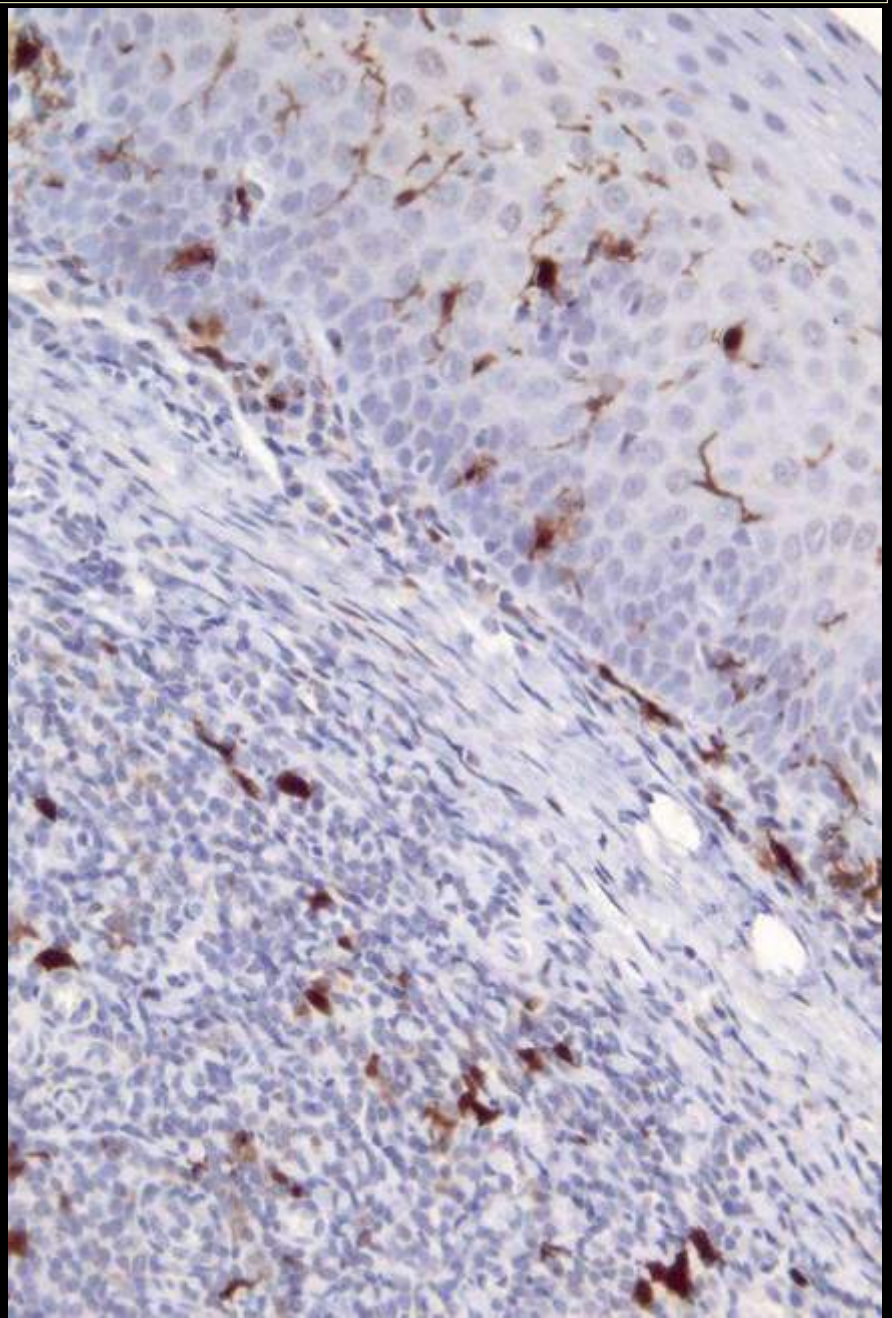
brain



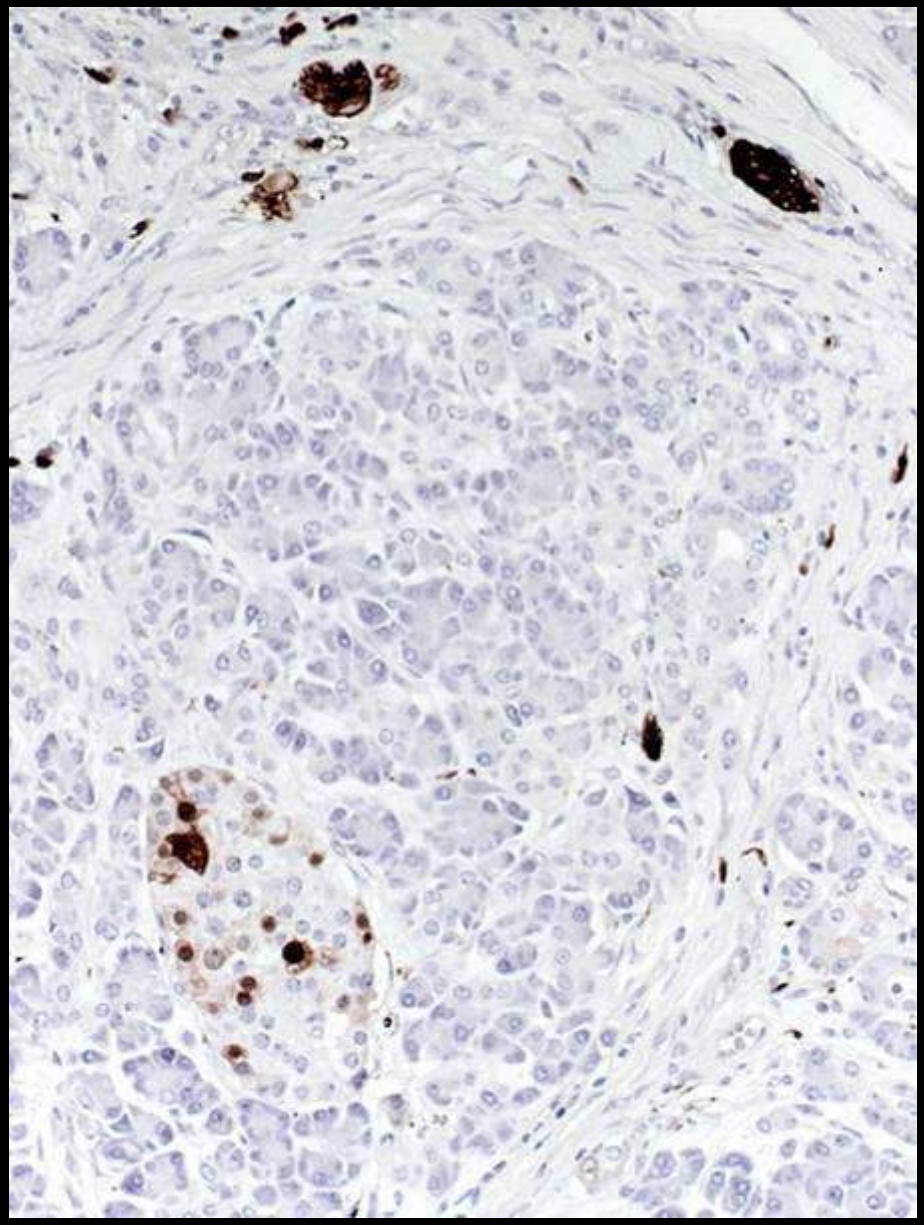
chondrocytes

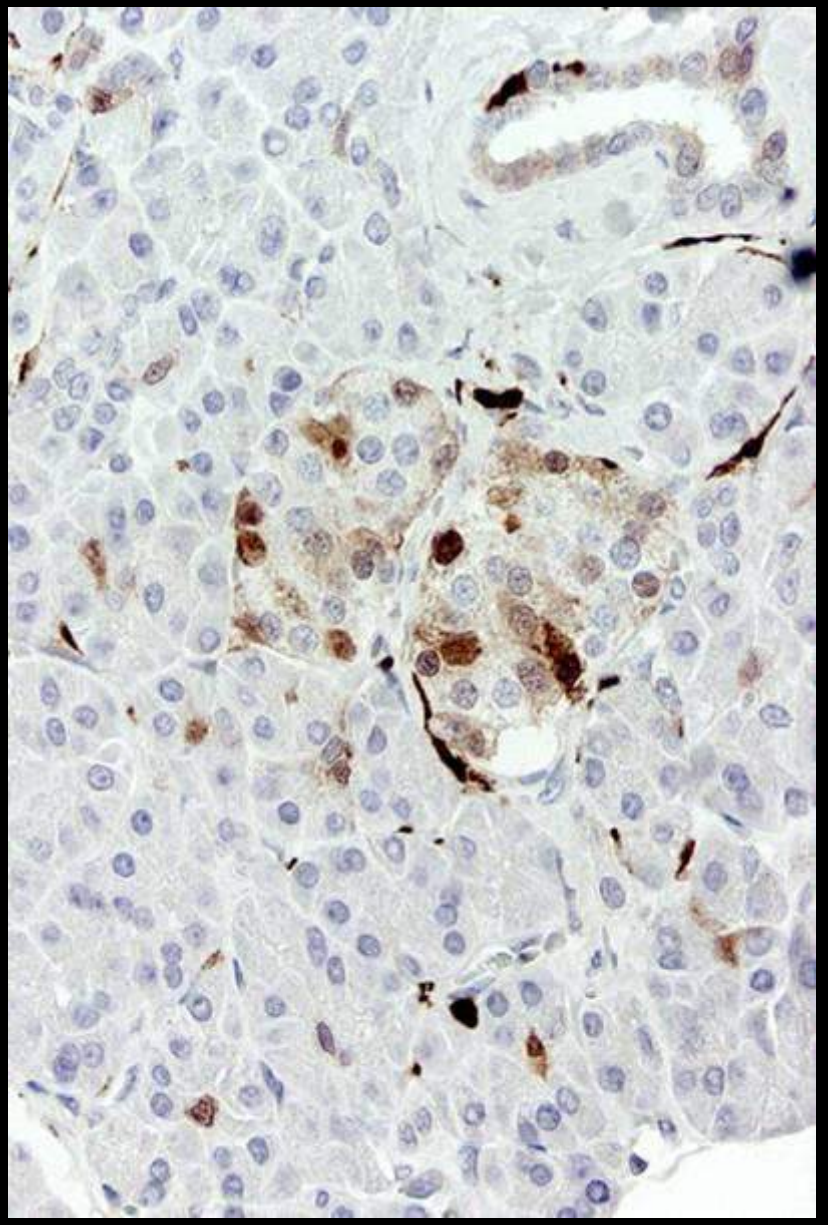
# S-100 protein



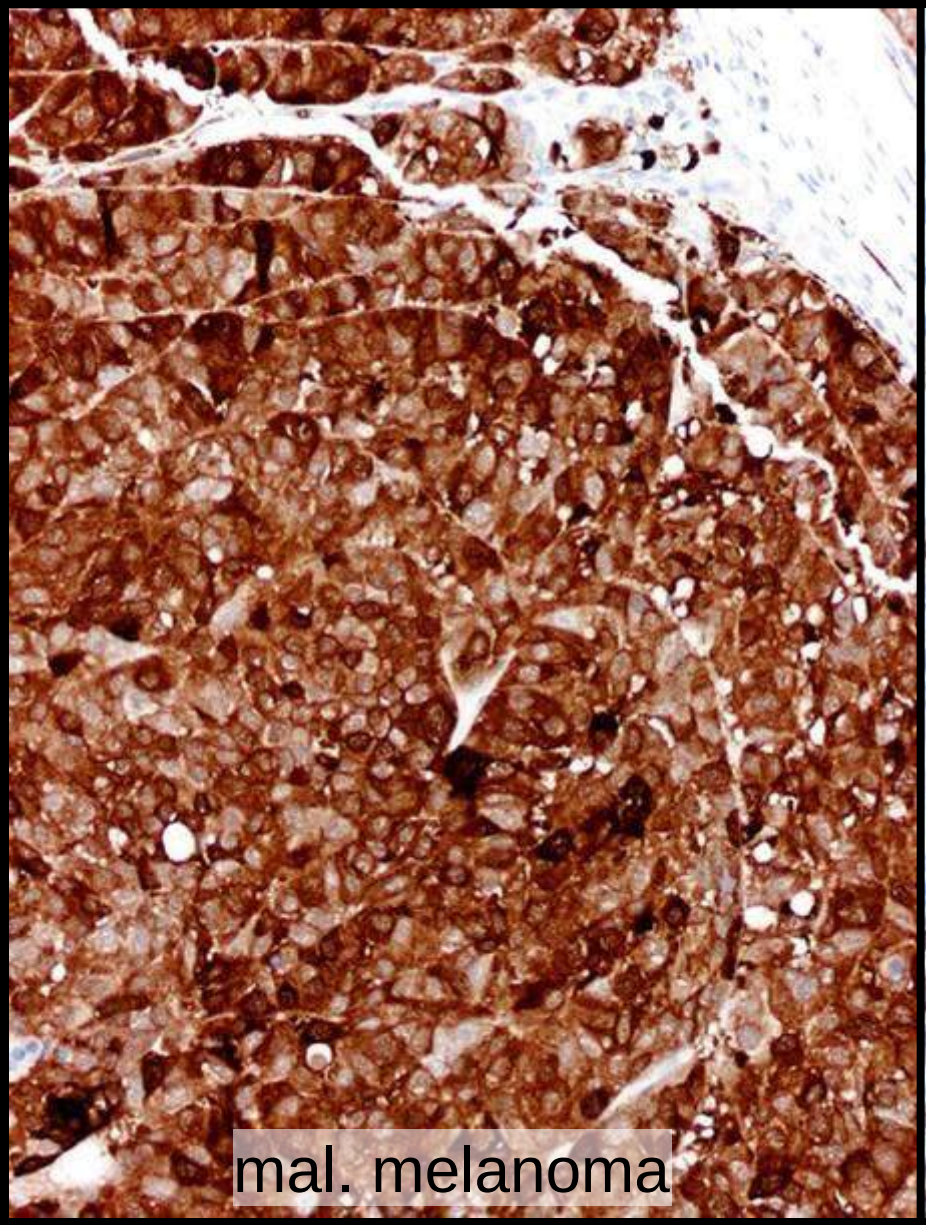



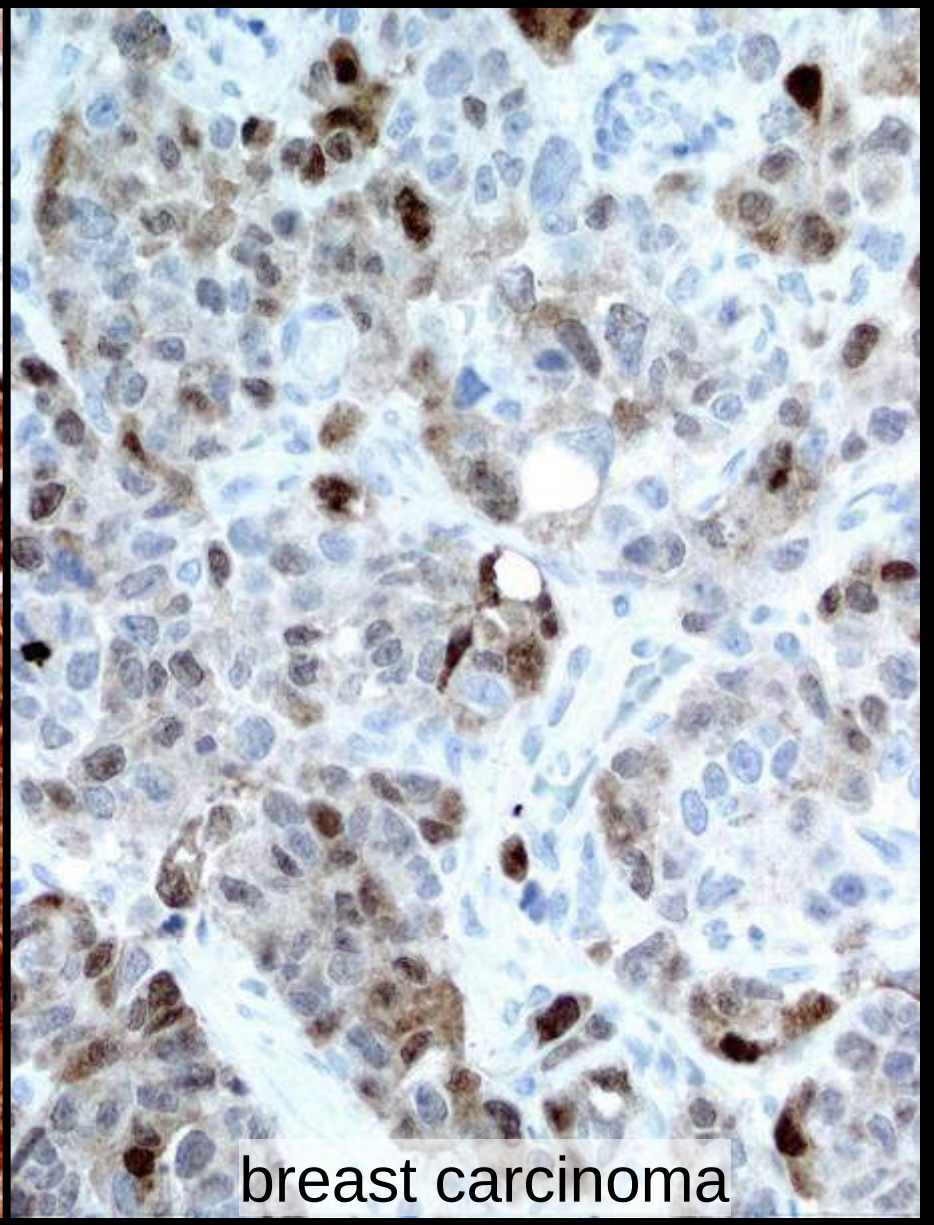
# S-100 protein – pancreas





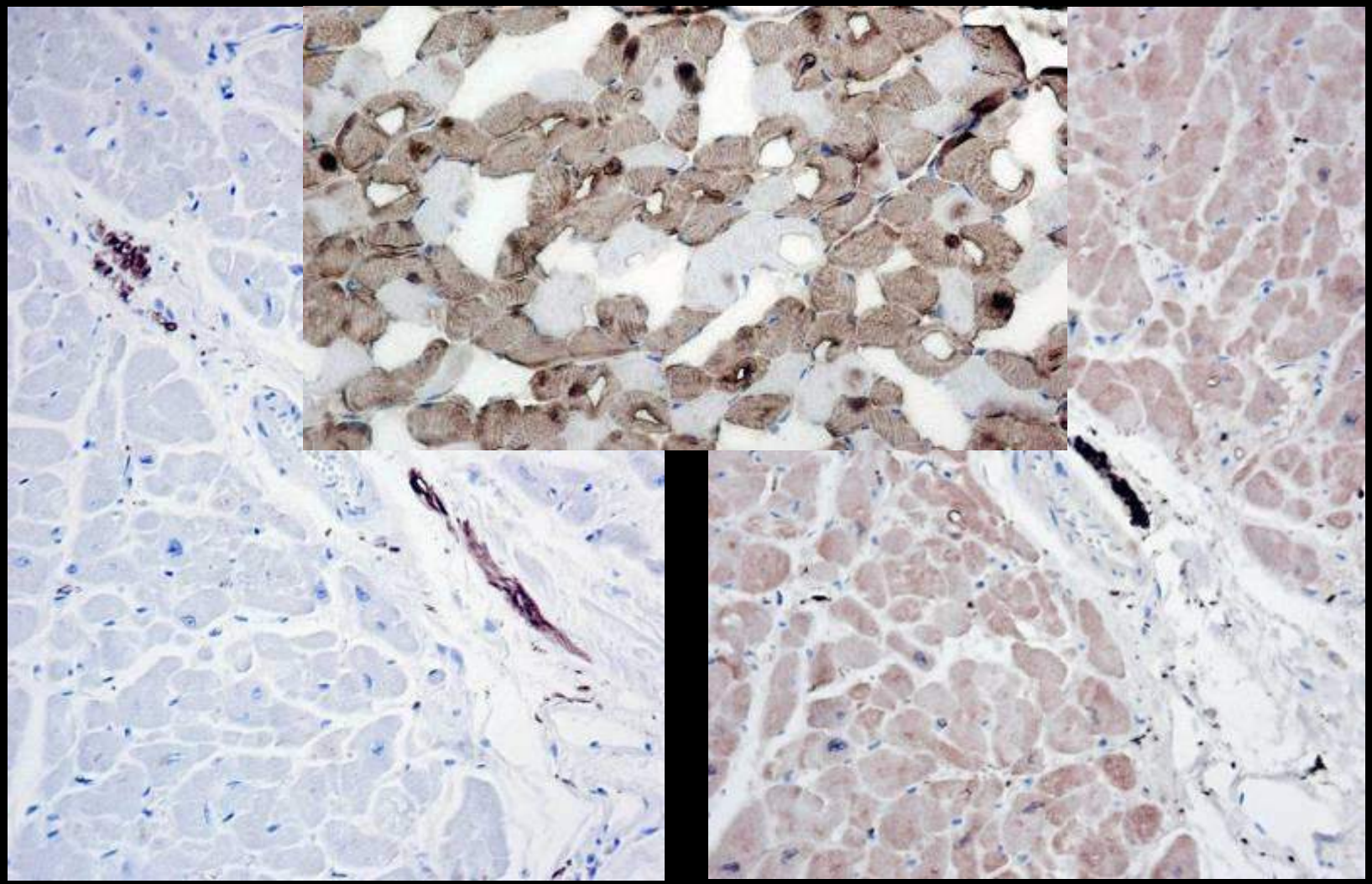
# S-100 in malignant tumours



# S-100 protein

**To HIER or not..**



Proteolytic

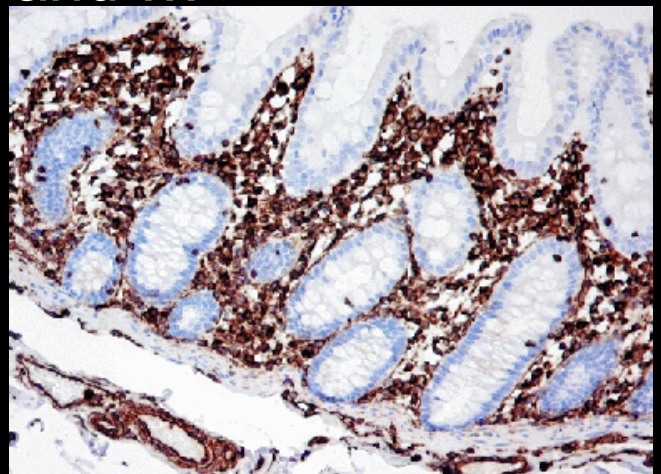
HIER

# Primary panel for the unknown primary tumour

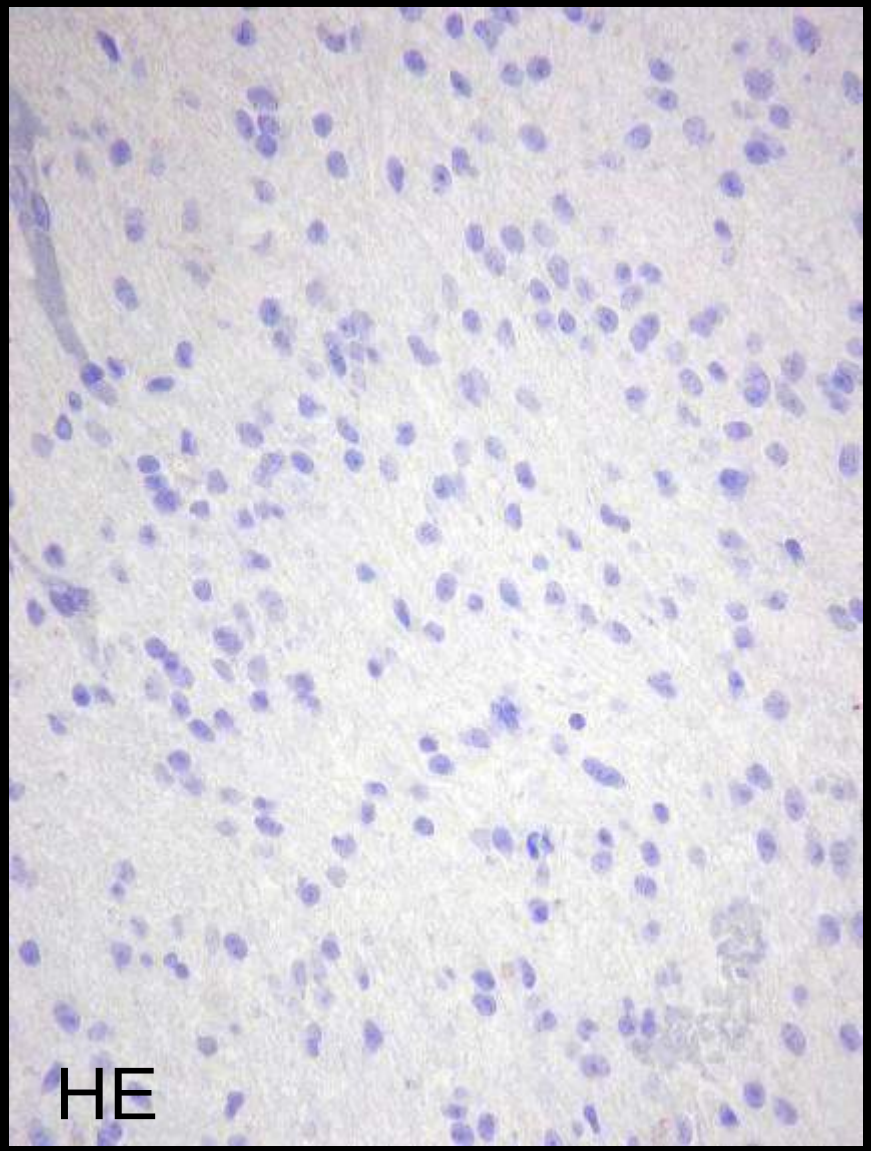
| ”Real” | CD45 | CK | S-100 | VIM |
|---|---|---|---|---|
| Haemato-lymphoid neoplasms | +/(-) | -/(+) | -/(+) | +/(-) |
| Epithelial neoplasms | - | +/(-) | -/+ | -/+ |
| Mesothelial neoplasms | - | + | - | + |
| Mesenchymal and neuronal neoplasms | - | -/(+) | -/+ | + |
| Non-neuronal neuroepithelial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

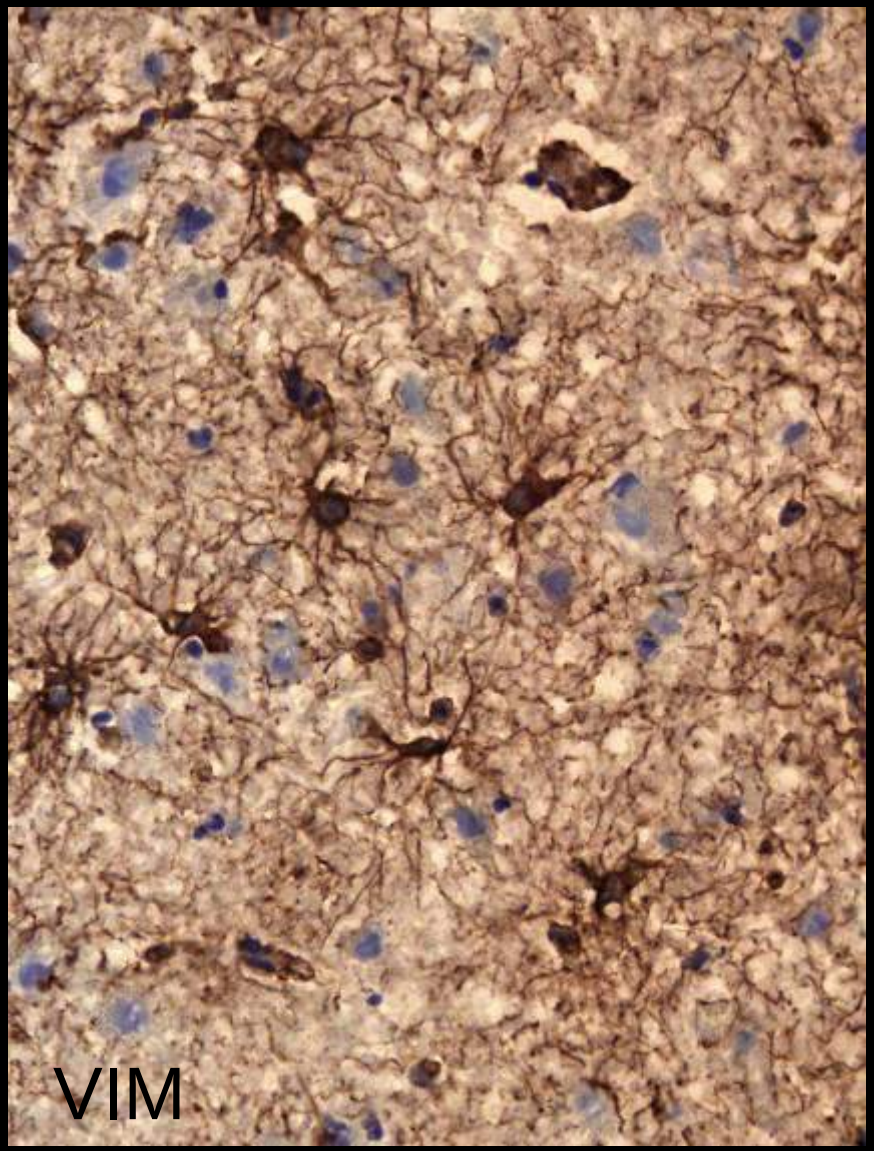
# Vimentin

- 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



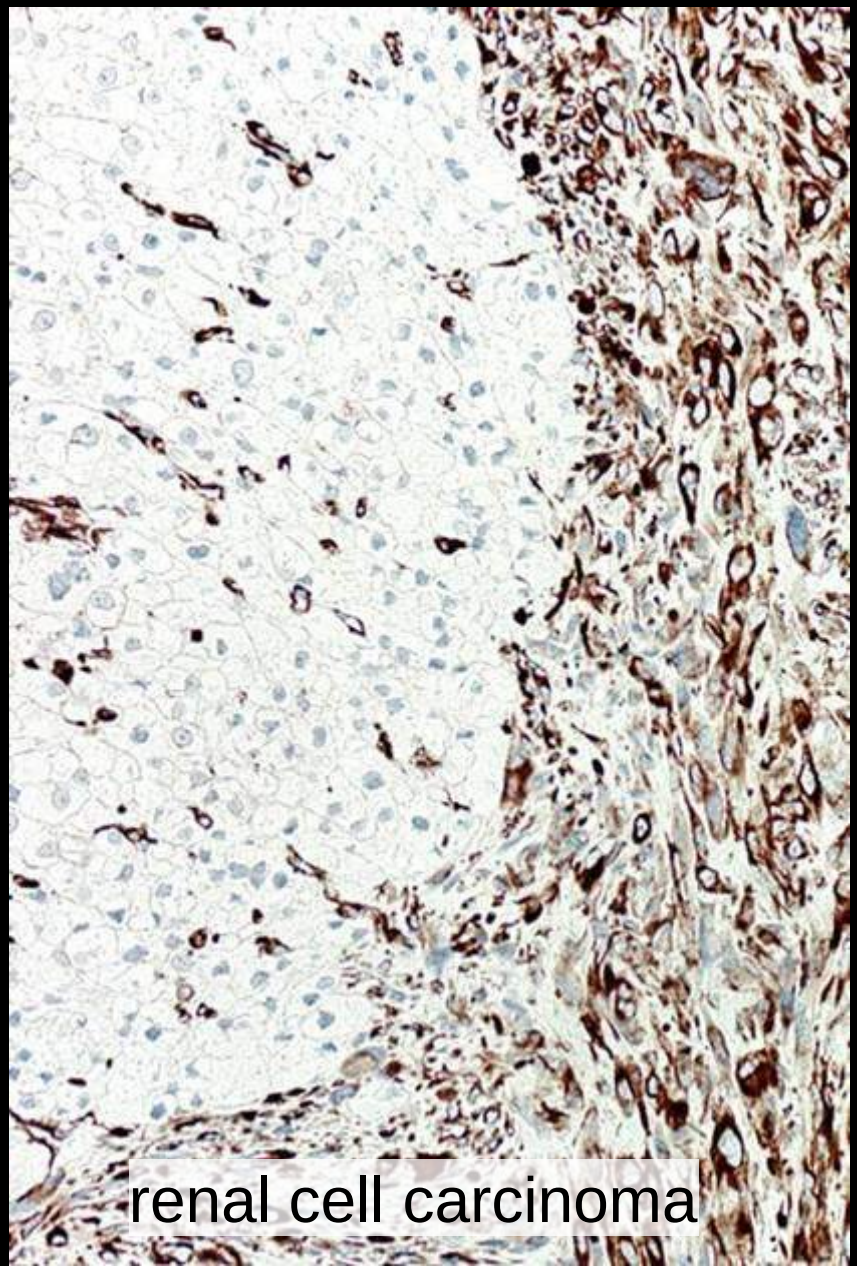
# Vimentin in normal tissue



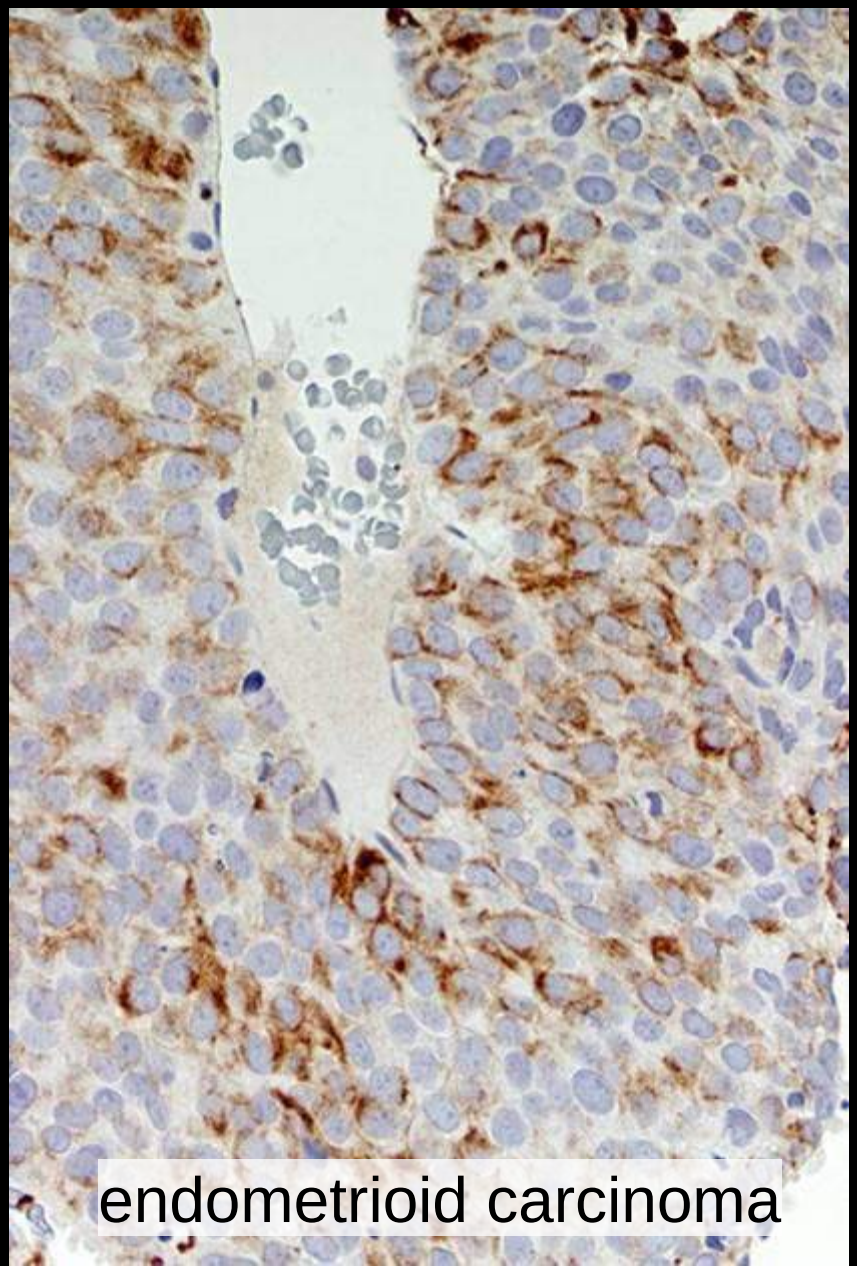




Normal brain

# Vimentin in carcinomas

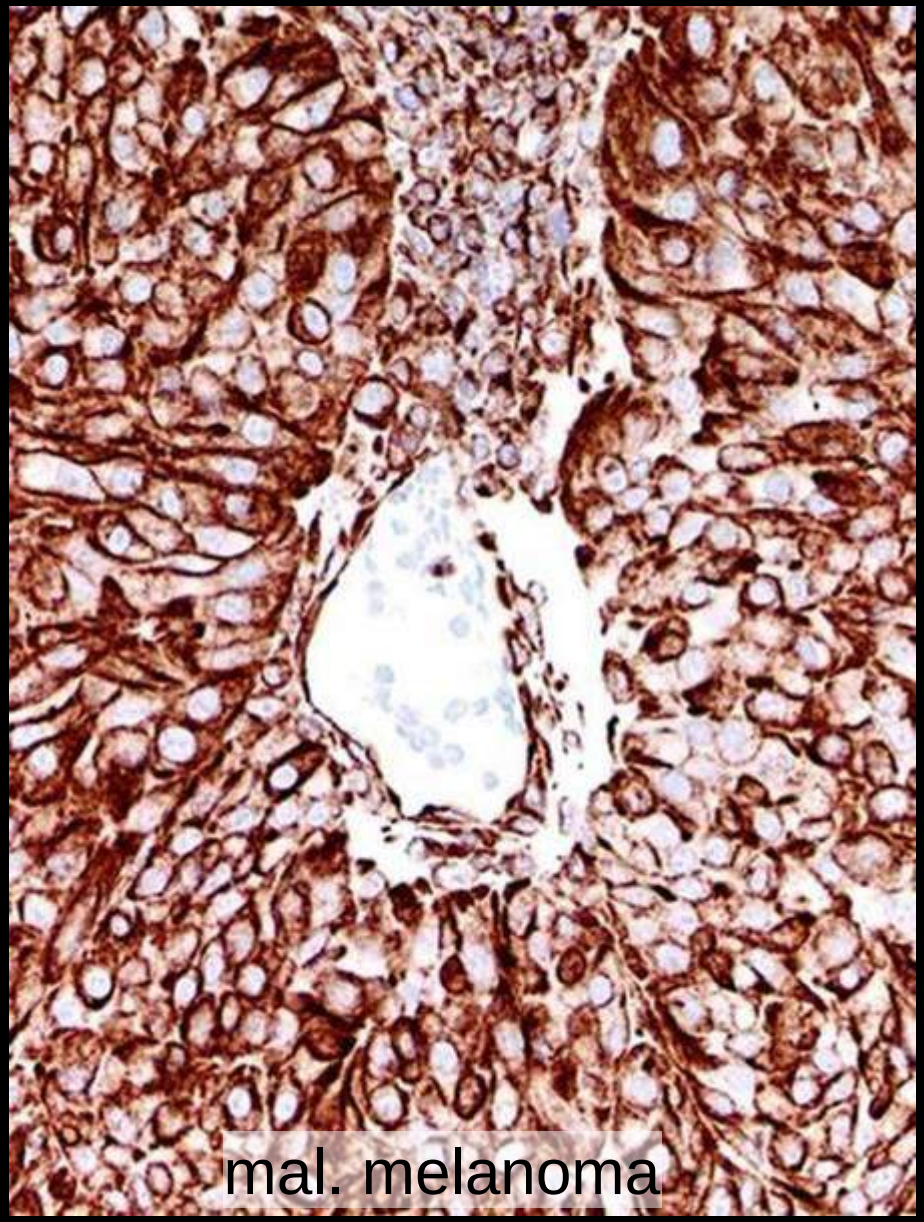


renal cell carcinoma

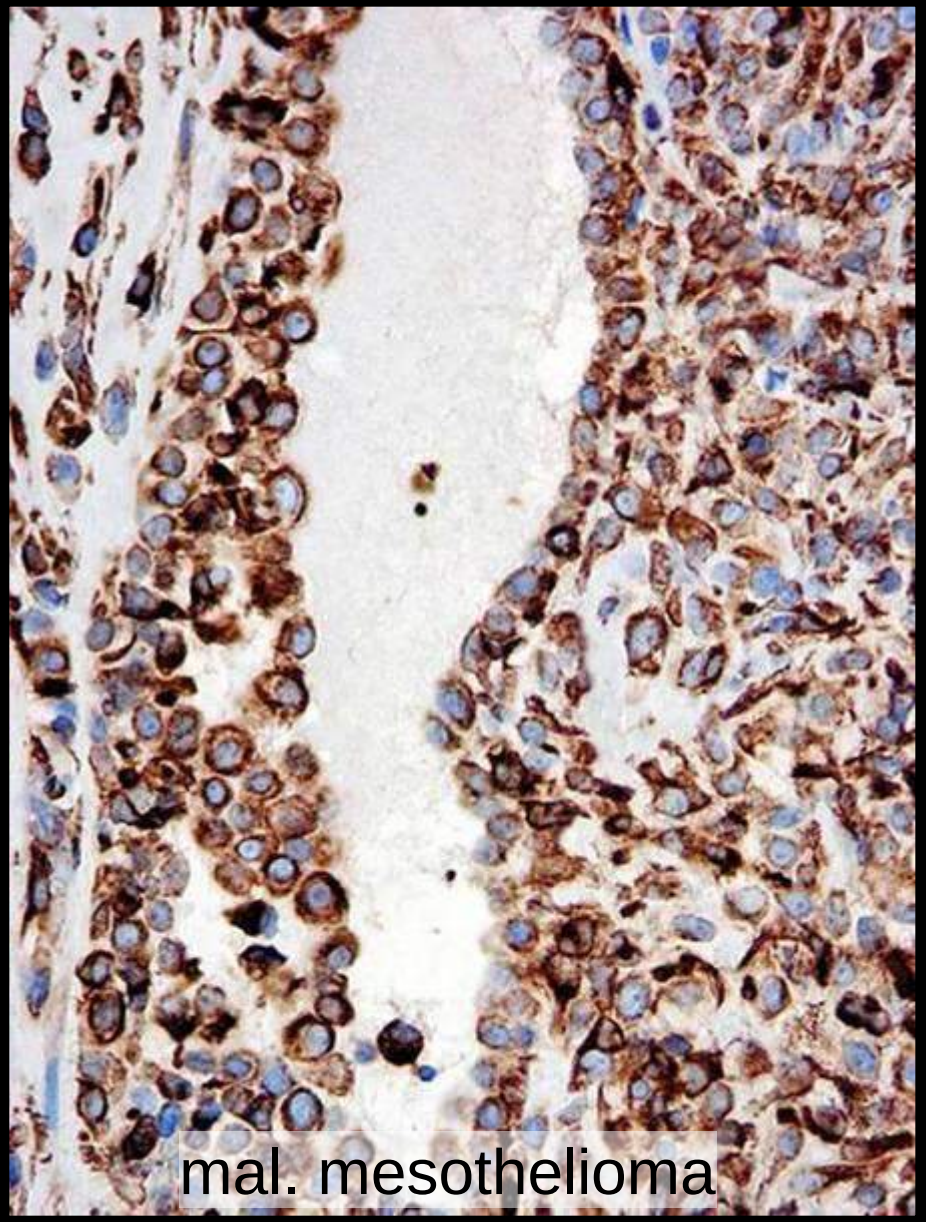


endometrioid carcinoma

# Vimentin in non-epithelial tumours



mal. melanoma



mal. mesothelioma

# Secondary panels for **carcinoma** identification/subclassification

- **Cytokeratin subtypes**
- Oncofetal proteins
- Transcription factors
- Neuroendocrine proteins
- Hormone receptors
- Secretory proteins
- Cell adhesion molecules
- . . .

- ”Breast markers”
- ”Lung markers”
- ”GI-markers”
- ”Fem.gen.tract markers”
- ”Urinary tract markers”
- Prostate markers
- Squamous cell markers
- ”Mesothelial markers”
- NE cell markers
- ”Liver markers”
- ”Adrenal cortical markers”
- Germinal cell markers