Immunpathologia I.

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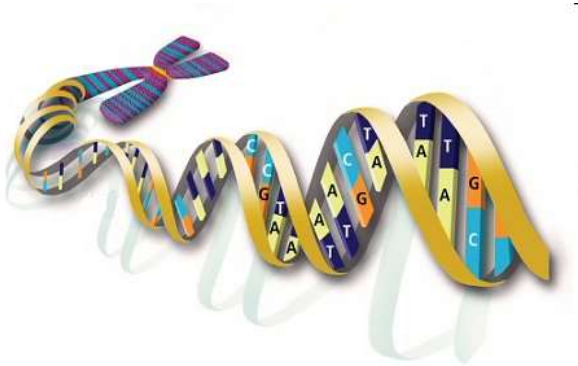
Budapest
II. Pathologiai Intézet

Őszi Szemeszter
2020 november

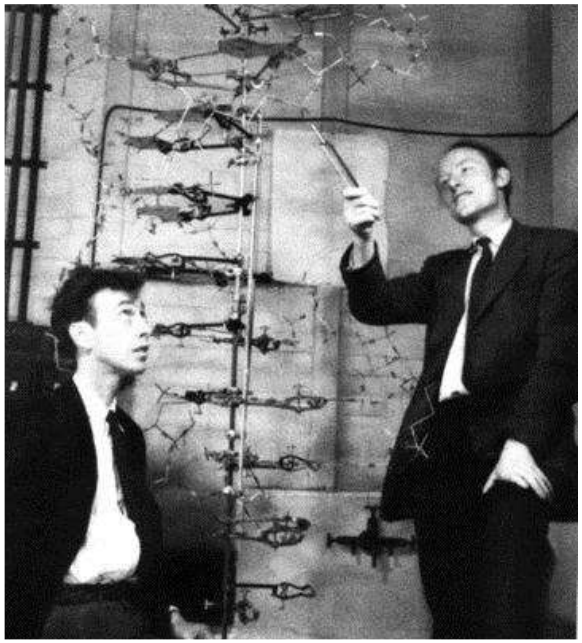


Morgagni,1761

GI betegségek

Virchow,1858

„Zellularpathologie”

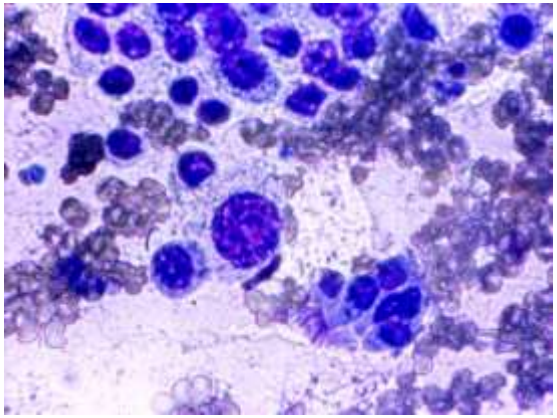
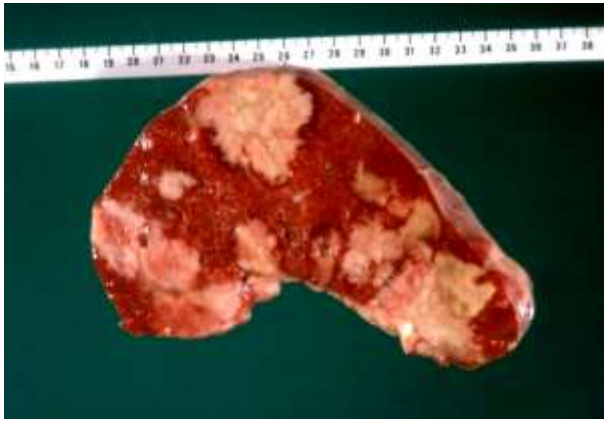
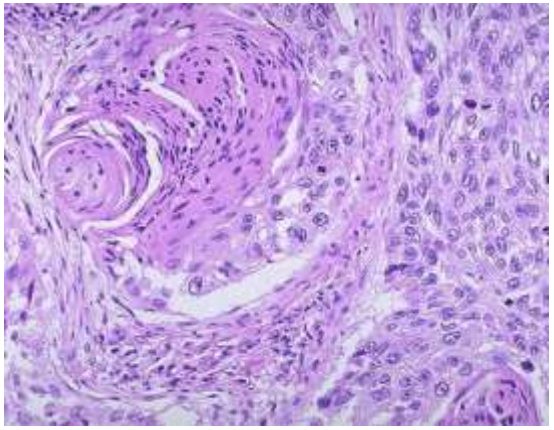
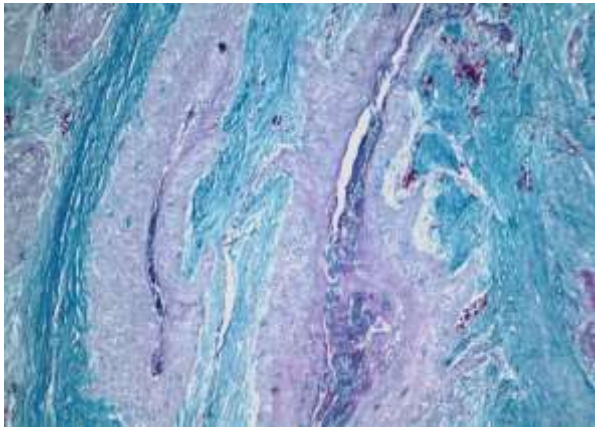
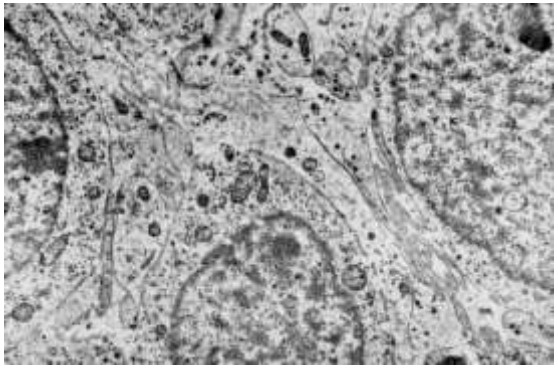
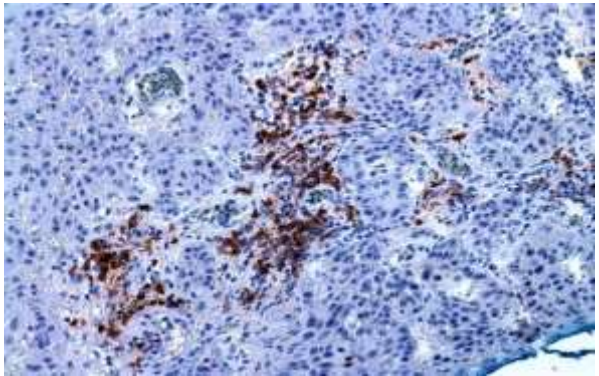


Watson & Creek, 1953

DNS szerkezete

XX. századi technologiák

- Makroszkópia (indítás)
- Citologia
- Szövettan
- Citokémia
- Immunhiszto/citokémia
- Electronmikroszkópia
- Molekuláris biológia
- Molekuláris genetika
- XXI. század.

Gyulladások klasszifikációja időbeni lefolyás alapján

HYPERAKUT (Perakut)

AKUT

SUBAKUT

KRÓNIKUS

PRIMER KRÓNIKUS (pl. PCP)

SZEKUNDER KRÓNIKUS


SZEPTIKUS LÉP

Az immunrendszer feladata

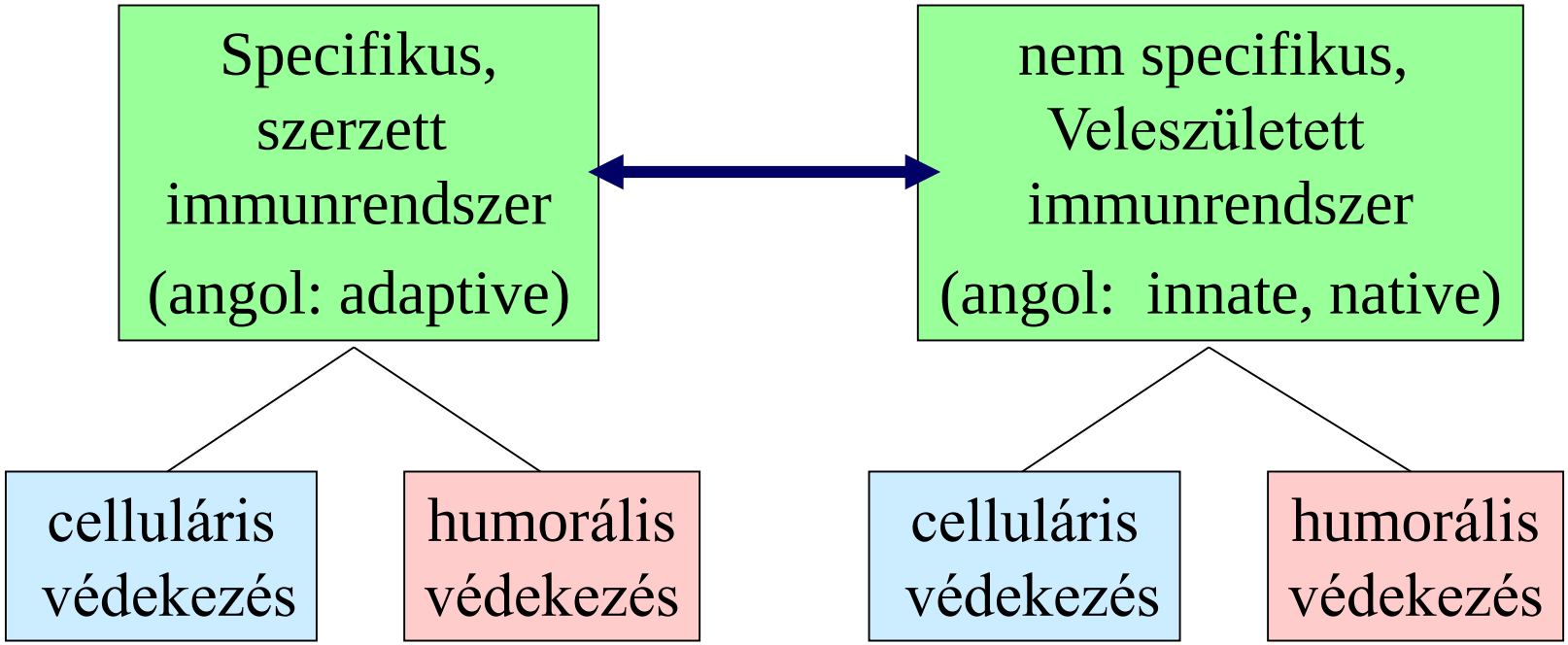
a szervezet integritásának megőrzése

az egyedi/saját struktúrák védelme

védelem a kórokozók ellen

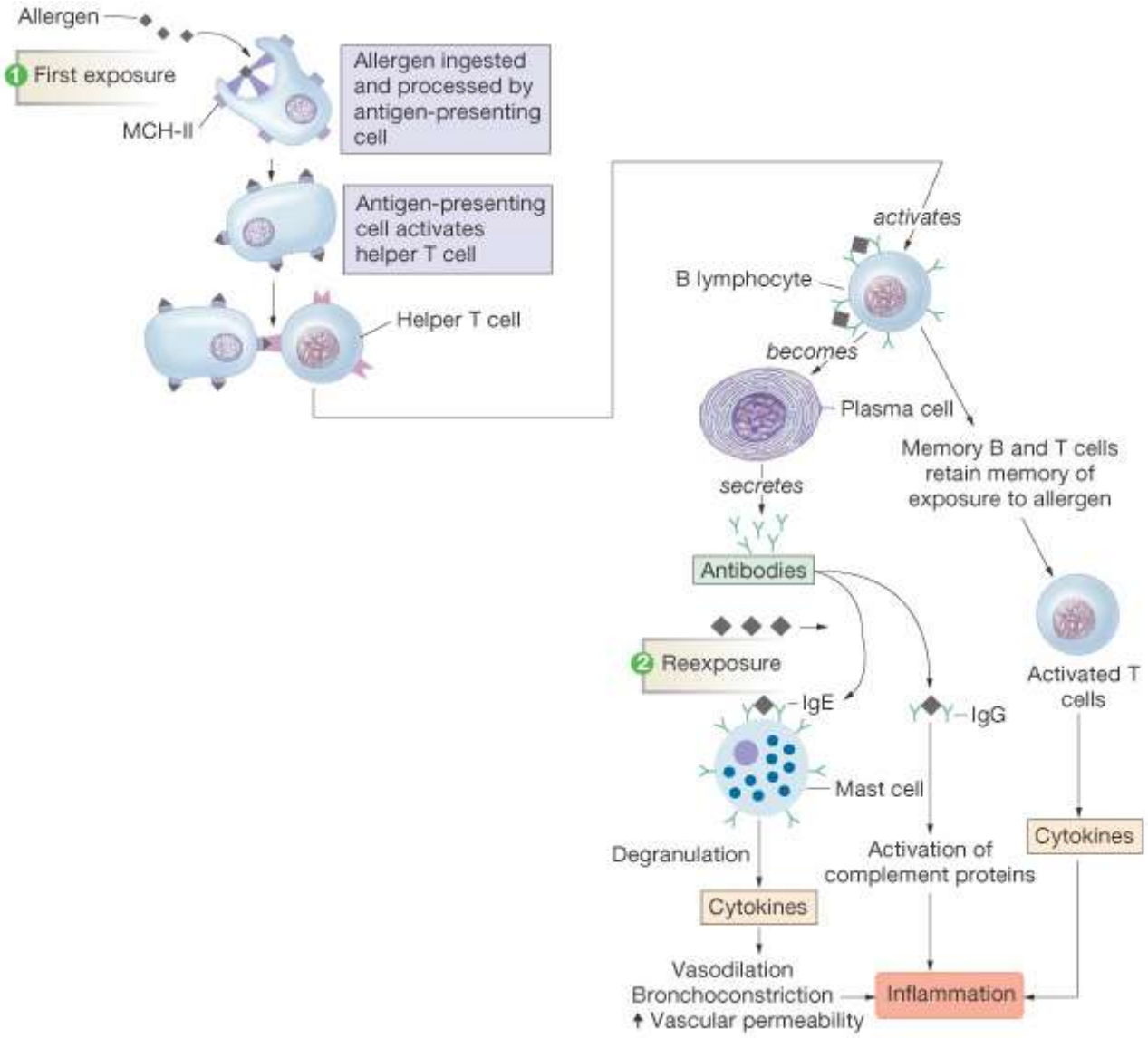
védelem a malignus tumorok ellen

Immunrendszer a kórokozók elleni védelemre

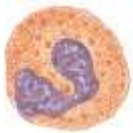
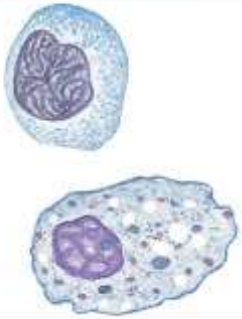
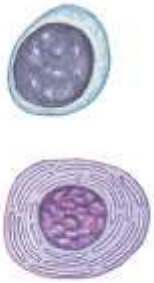


- Lymphocyta
- Antitest
- Makrophag
- Granulocyta
- NK sejtek
- hízósejtek
- dendritikus sejtek
- Komplement
- Lyzozym
- C-reaktiv protein

Allergiás gyulladás nem pathogén károsodásra

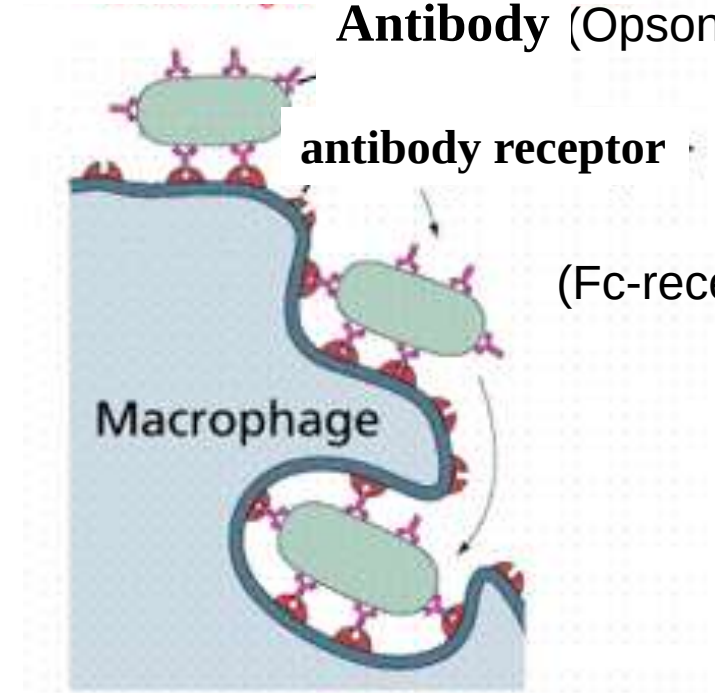


A gyulladás sejtes elemei

	Basophils and Mast Cells	*Neutrophils*	*Eosinophils*	*Monocytes and Macrophages*	*Lymphocytes and Plasma Cells*	*Dendritic Cells*
						
% of WBCs in blood	*Rare*	*50–70%*	*1–3%*	*1–6%*	*20–35%*	*NA*
Subtypes and nicknames		Called "polys" or "segs" Immature forms called "bands" or "stabs"		Called the mononuclear phagocyte system	B lymphocytes, Plasma cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells Memory cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation in lymph nodes
Classifications		*Phagocytes*				
		Granulocytes				
			Cytotoxic cells		*Cytotoxic cells (some types)*	
				Antigen-presenting cells		

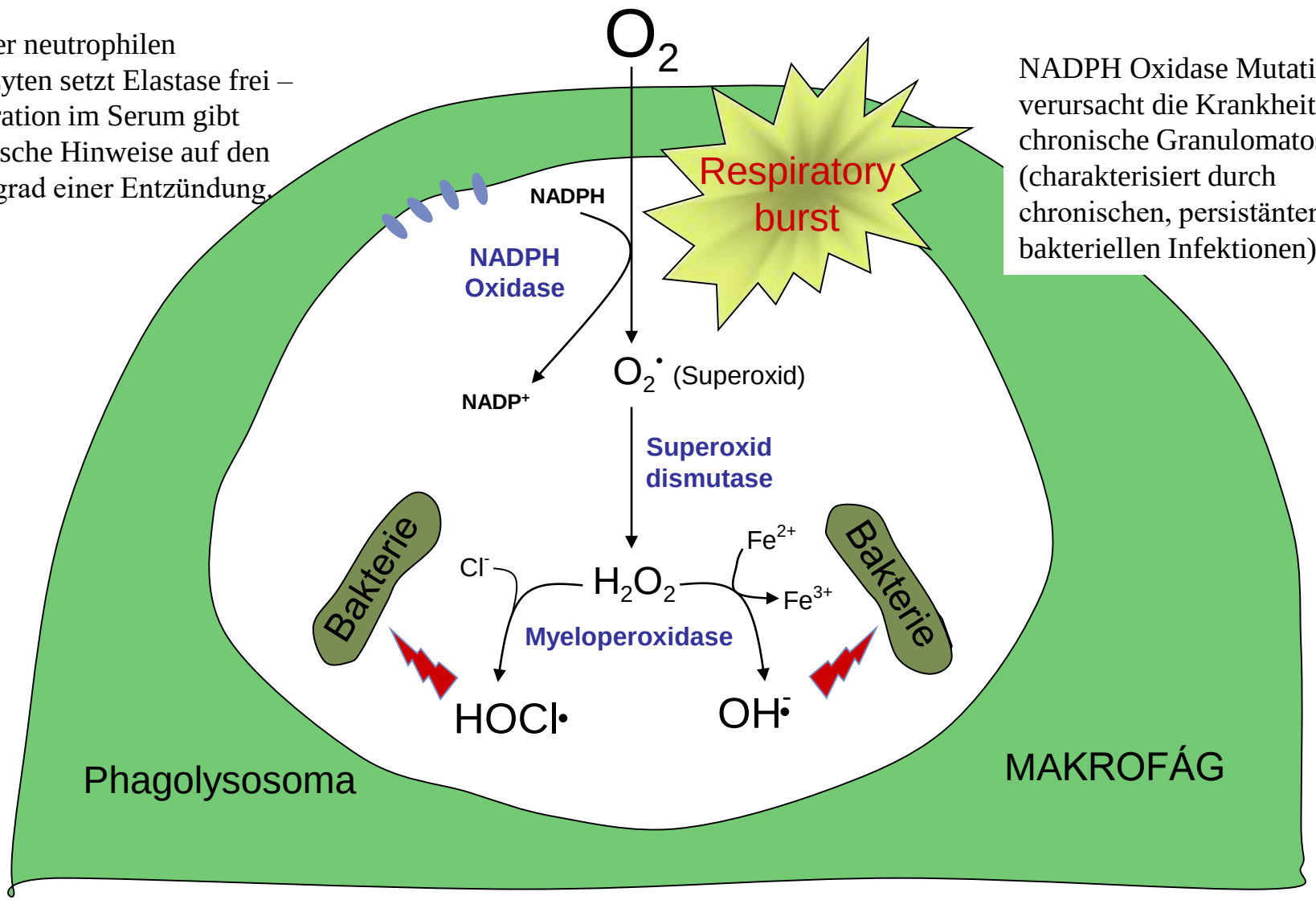
A nem specifikus immunrednszer sejtjei

makrofágok, dendritikus sejtek, granulociták, hízósejtek, NK sejtek

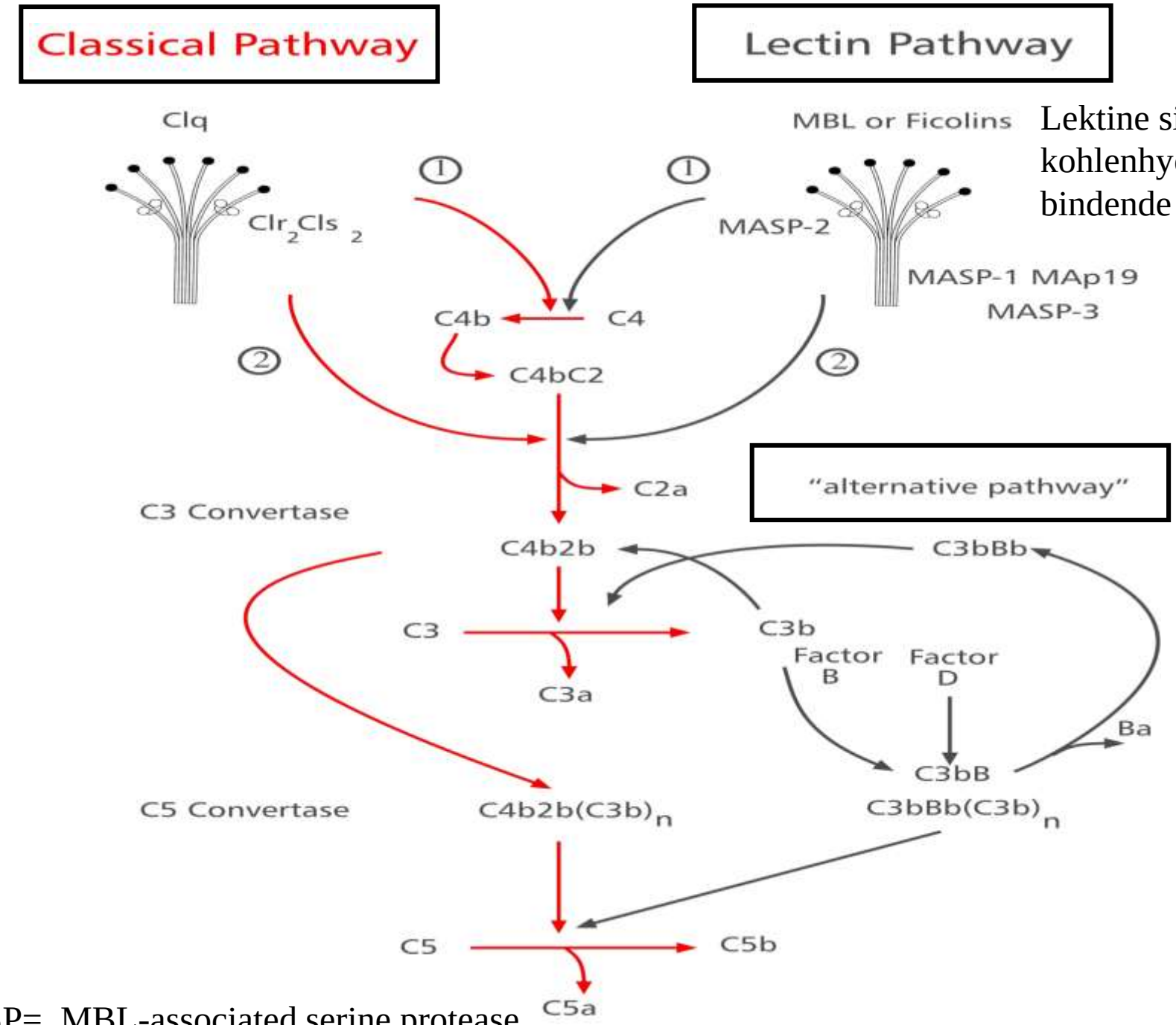


Phagocytosis makrofágokban és neutrofil granulocitákban

Zerfall der neutrophilen Granulozyten setzt Elastase frei – Konzentration im Serum gibt diagnostische Hinweise auf den Schweregrad einer Entzündung.



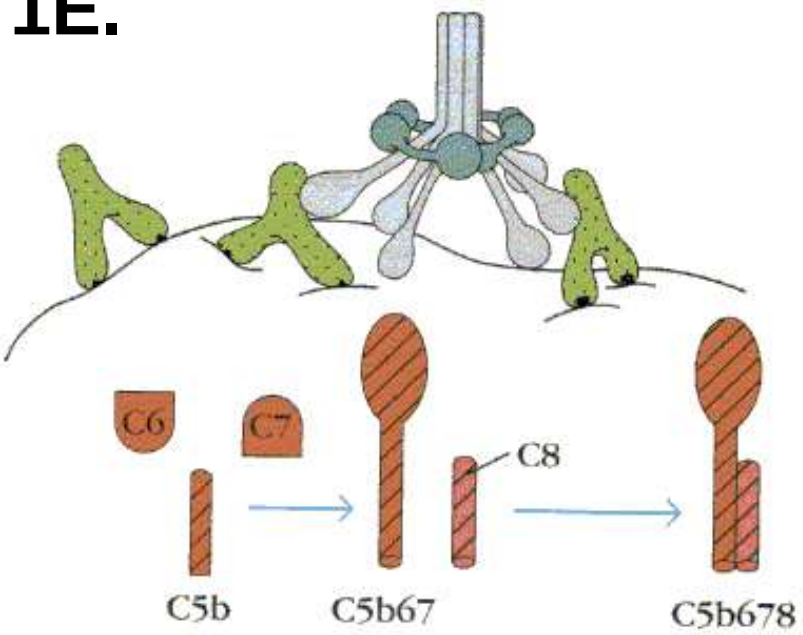
NADPH Oxidase Mutation – verursacht die Krankheit chronische Granulomatose (charakterisiert durch chronischen, persistänten bakteriellen Infektionen).



MASP= MBL-associated serine protease

Komplement aktiváció: klasszikus útvonal

1E.



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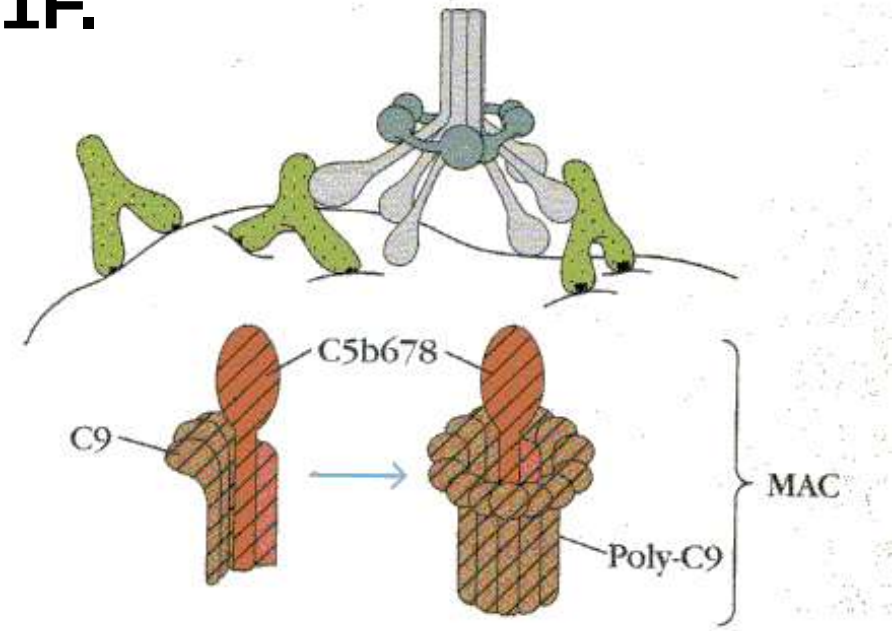
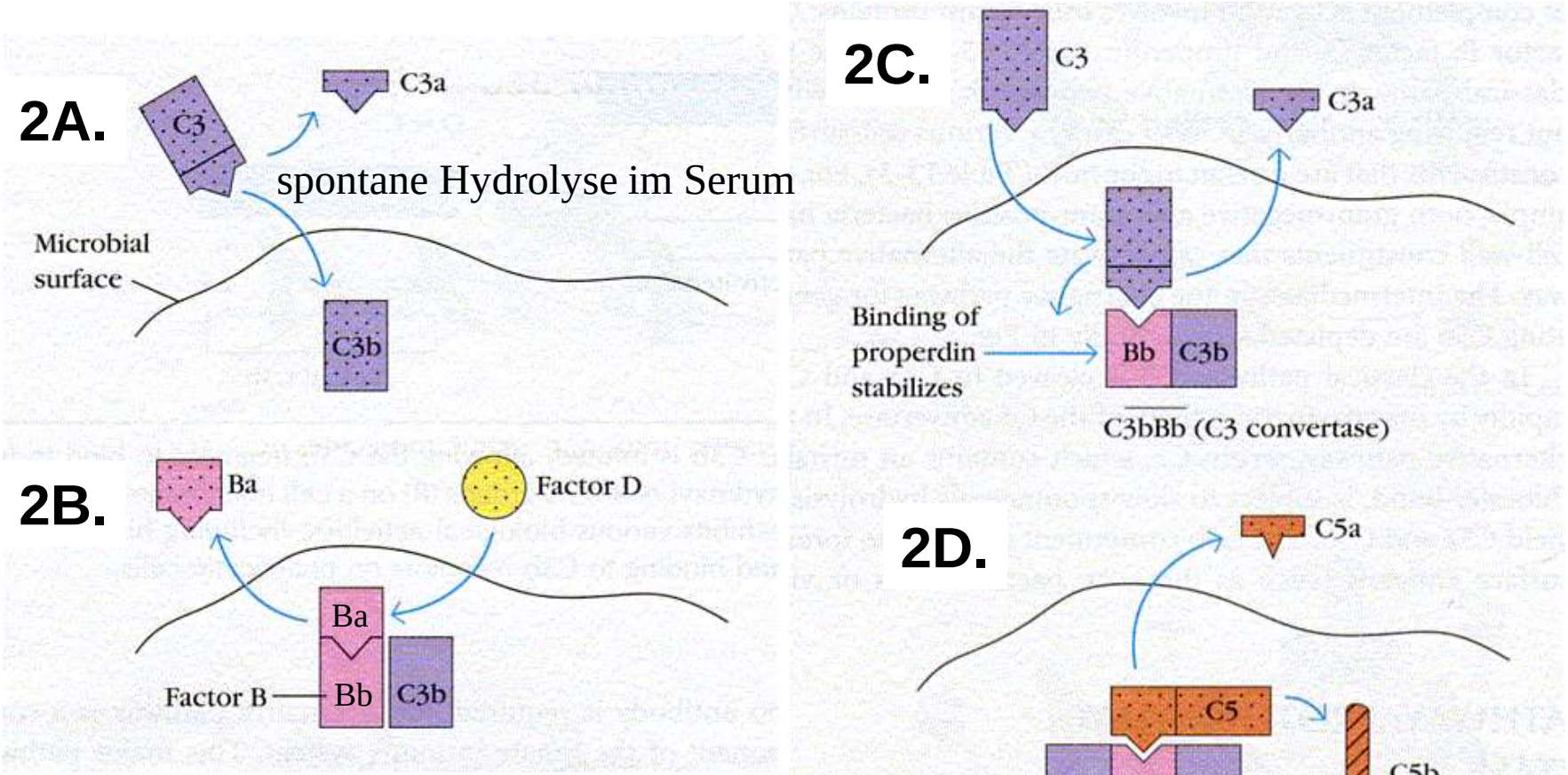


MAC-membrane-attack complex

Quelle: Kuby Immunology, W.H. Freeman and Company

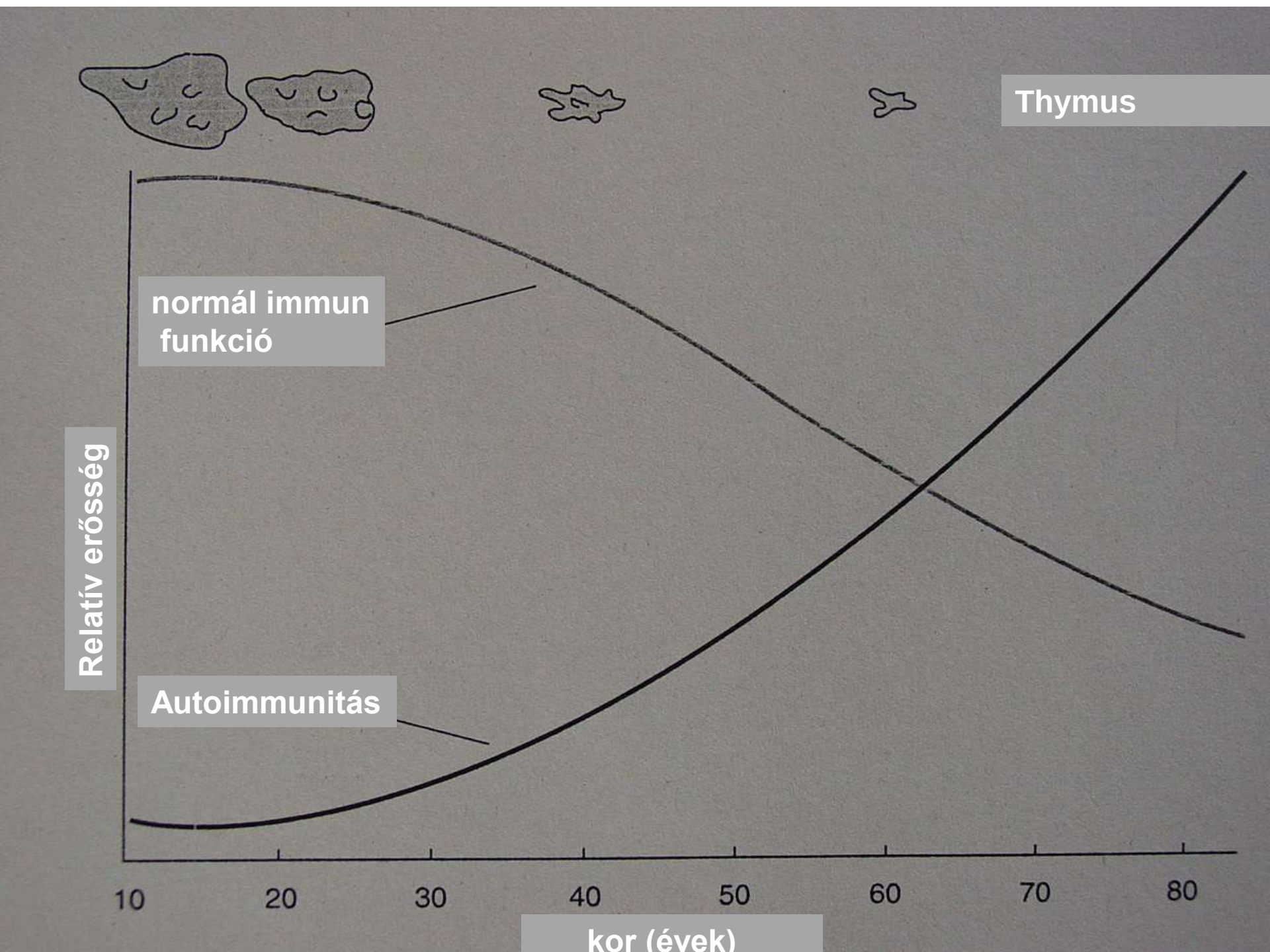
Komplement aktiváció 2.: alternatív útvonal (antitest független)

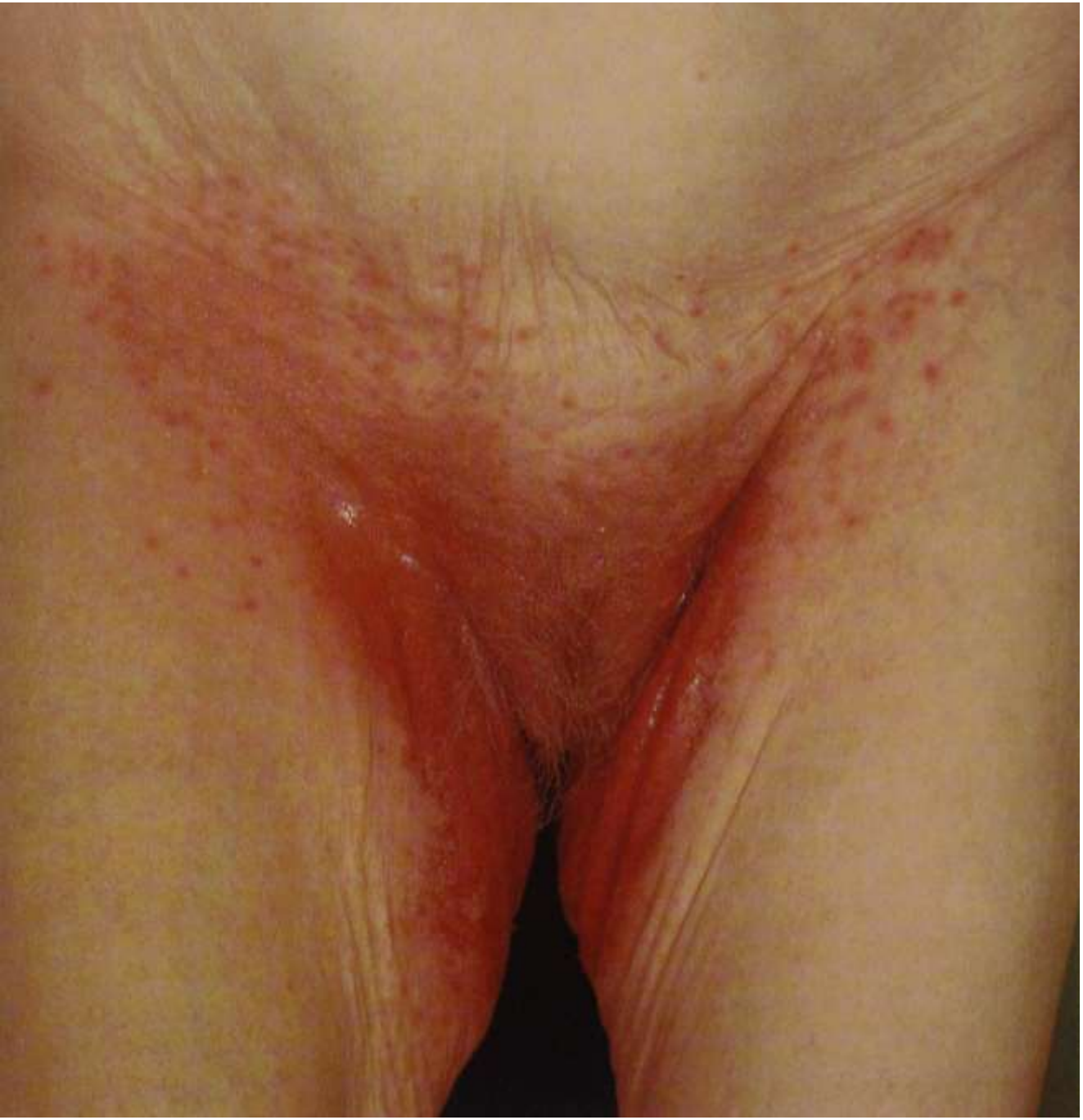


Initiiert durch körperfremde bakterielle Zelloberflächemoleküle!

Sialinsäure auf eukaryotischen Zellen inhibieren C3b!!!

Quelle: Kuby Immunology, W.H. Freeman and Company


Thymus
normál immun funkció
Autoimmunitás
Relatív erősség
10
20
30
40
50
60
70
80
kor (évek)



Candidiasis - soor mycosis

Száj nyálkahártya

Bőr hajlatok

glans penis

Női genitáliák

Inkább idős vagy obes betegek, nők

Predispositio:

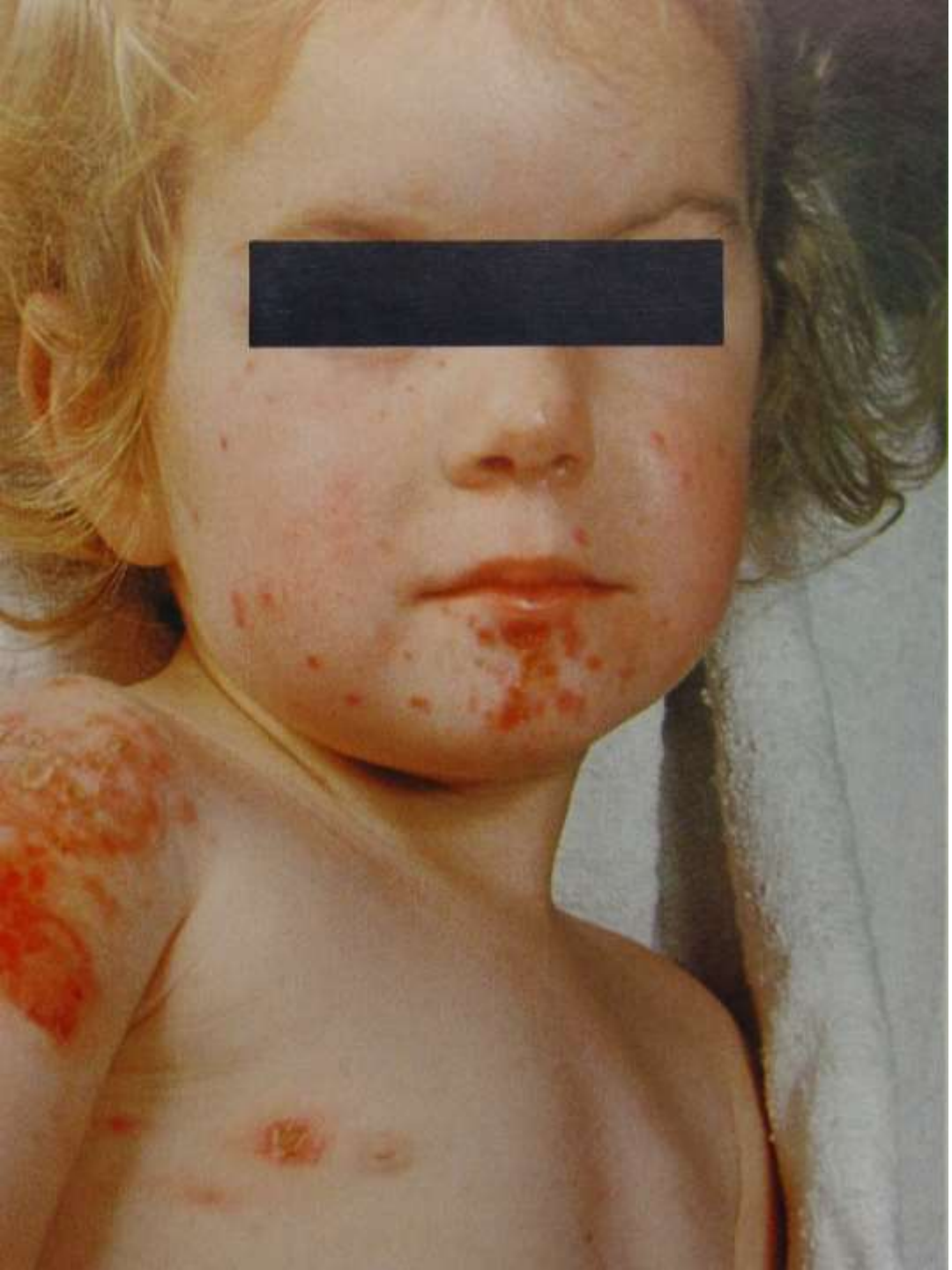
- diabetes
- nedves felületek
- B vitamin hiány
- terhesség
- atrophia

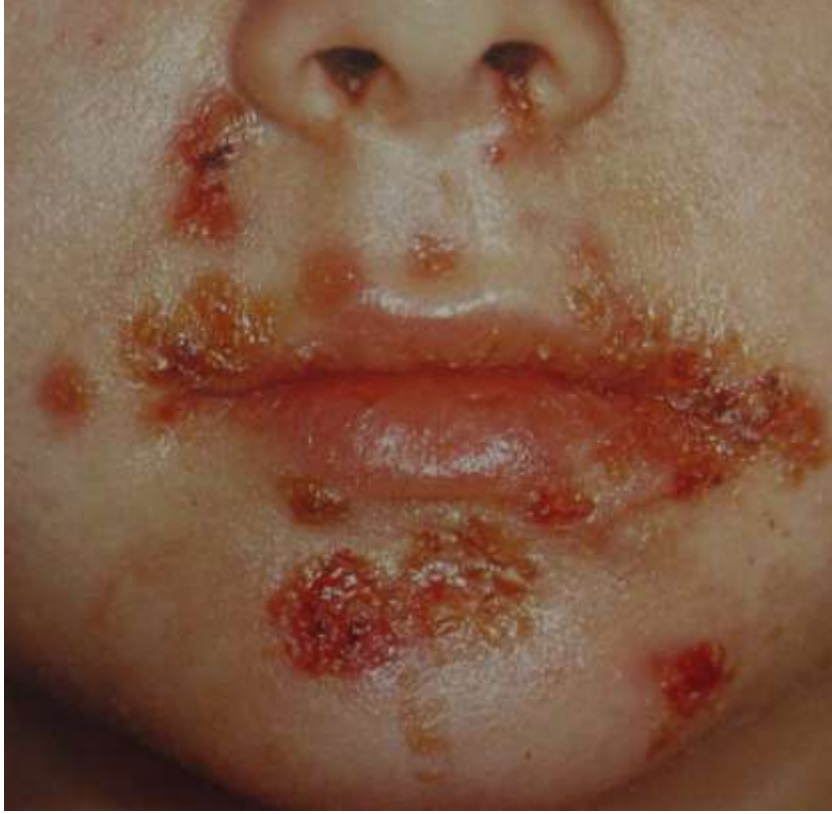
<u>Immuntolerancia</u>: elnyomott vagy hiányzó reaktivitás
BIZONYOS ANTIGÉNEKRE, míg másokra megtartott válaszreakció
Embryonalis fázisban – de nem érett immunrendszerben – antigének, mint saját struktúraként elismerve és ez az állapot fennmarad.

Megkülönböztetve: »saját « és „ idegen”/ » nem saját «
Ez elveszhet később „tolerogének ” hatására, és így autoaggresszív betegségek keletkezéséhez vezethet.
Veleszületett: saját , testazonos antigénekre (Autoantigének)

Szerzett: reciprok immuntolerancia ikrekben
(éranasztomózisok placentában)

<u>Immun deficiencia szindrómák</u>: defekt, sérült immunreakció
Általános elégtelensége a szervezetnek, hogy egy immunreakcióval válaszoljon egy egyébként elégséges antigén stimulusra
(a specifikus tolerancia ellentéte)



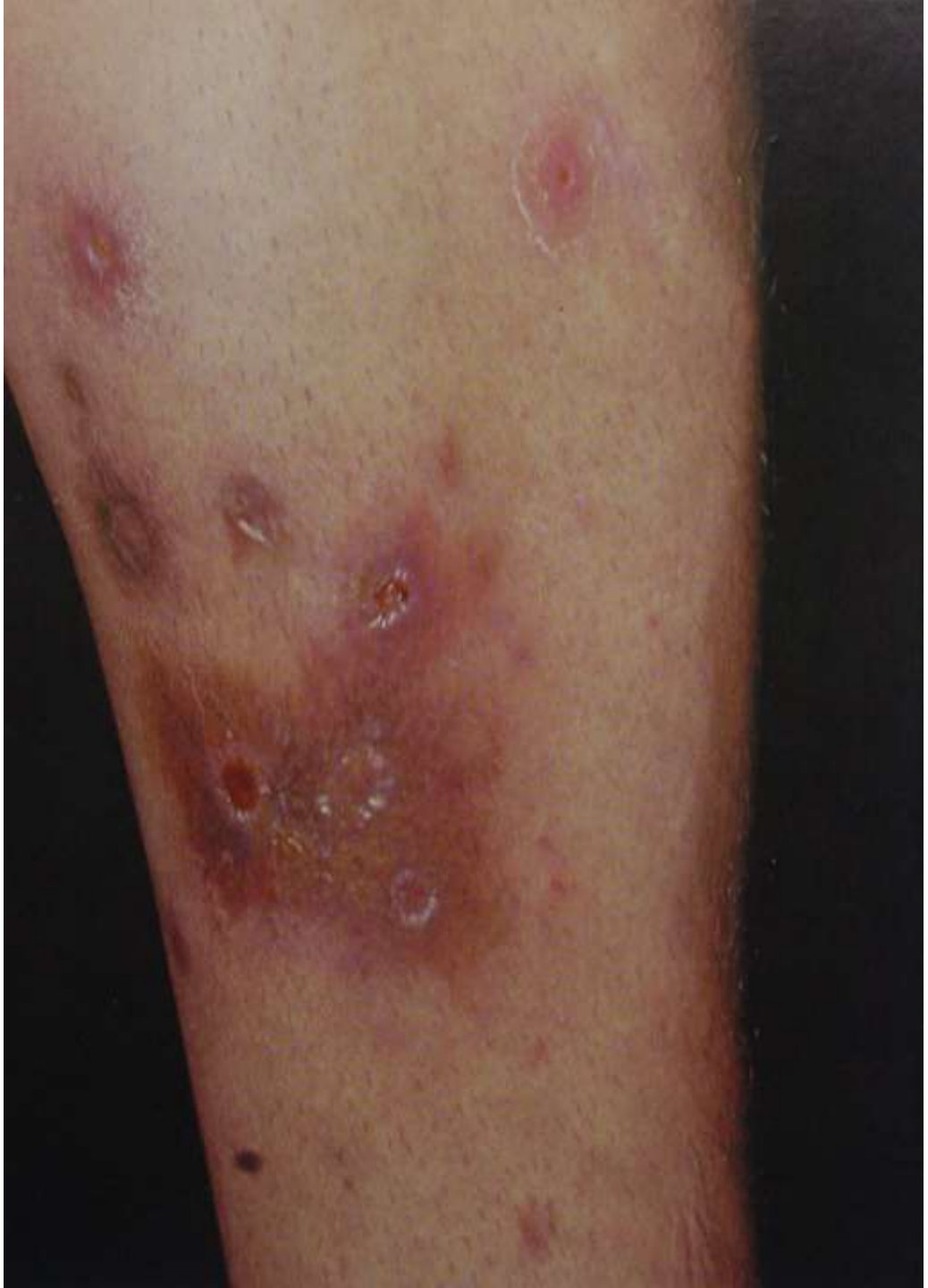


Impetigo contagiosa

Primeren gennyes bőrfertőzés.
Leginkább immundeficiens gyerekekben

Koszos/ non / higiénikus körülmények , karmolások elősegítik

Komplikáció.: Impetigo-Nephritis



Ekthyma
Kifekélyesedett pyodermia

Kompl.: Lymphangitis
Lymphadenitis,
Phlebitis

ß-hämolyth. streptococcus

Csökkent bőrvédekezés

Lokális keringési zavar

Tumorimmunitás

A malignus daganatok gyakrabban fordulnak elő legyengült immunitással rendelkező vagy immundeficiens betegeknél.

Okai: kor, chemoterápia, irradiáció, immundefektusok

A tumor sejtek az immunrendszert elkerülő mechanizmusokat fejlesztenek ki:

(neo) antigén negatív variánsok (subklónok)

a hisztokompatibilitás antigének elveszett vagy csökkent expressziója
$\Rightarrow$ a tumorsejtek elkerülik a cytotoxikus T-sejteket

hiányzó peptidantigén-ko-stimuláció

immunsuppresszió, pl. TGF-ß termelődése és szekréciója tumorokban

A cytotoxikus T-sejtek apoptosisa a FAS-Ligandok expresszója által: pl. melanoma, hepatocellular carcinoma

Az immun védelem sejtjei: lymphocyták, natural killer sejtek,

makrophágok

Onkológiai immunterápia

Specifikus, aktivált T-sejtek: lymphokin aktivált Killer sejtek (NK)

a beteg véréből izolálva

sejtkultúrában stimulálva

visszaadva a betegnek

Blokkoló antitestek terápiás alkalmazása:

epidermal growth factor receptor: EGFR ellen

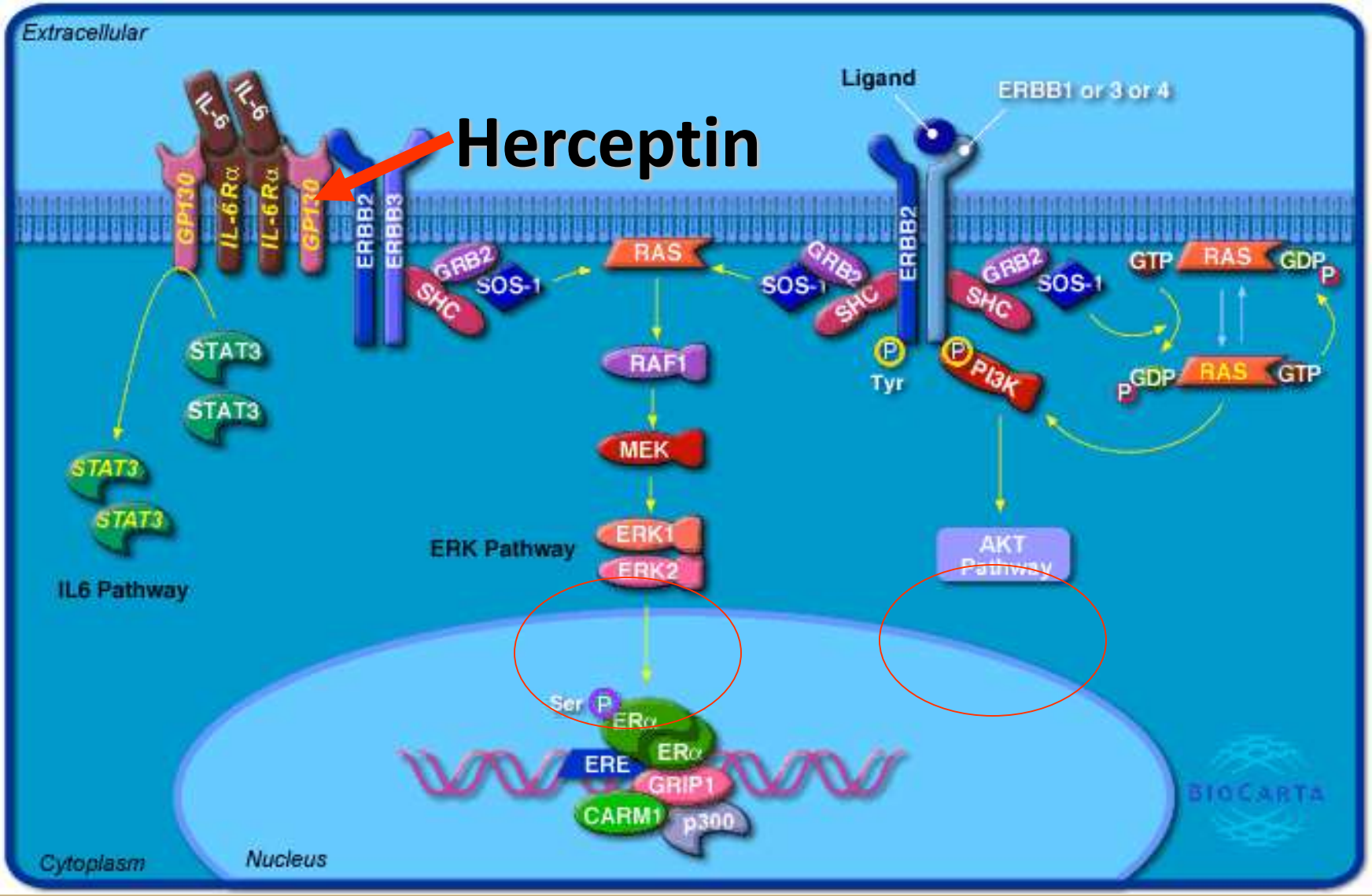
C-Kit receptor fehérje blokkolás (Thyrosin kinase function) CML, GIST

Overexpresszált receptorok blokkolása antitestel: Herceptin (Erbb2)

Tumorok antiegenitásának növelése apathogenén vírus infekcióval

Immunprofilaxis speciális esetekben: – pl. HBV-vakcina: primer hepatocellular carcinoma prevenció

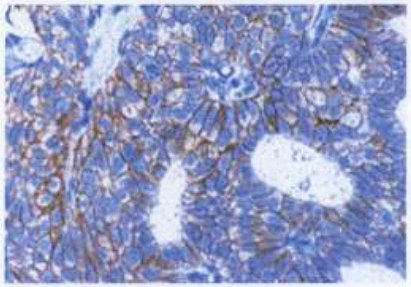
EGFR2/HER2 signal transduction (physiologic cond.)



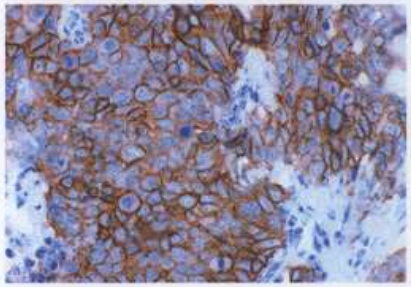
Guidelines for Scoring **HercepTest™**

DAKO

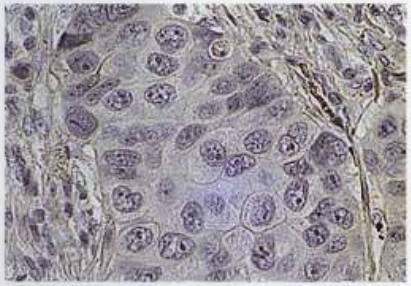
Score to report	HER2 protein overexpression assessment	Staining pattern
0	Negative	No staining is observed, or membrane staining in less than 10% of the tumour cells.
1+	Negative	A faint/barely perceptible membrane staining is detected in more than 10% of the tumour cells. The cells are only stained in part of the membrane.
2+	Positive	A weak to moderate complete membrane staining is observed in more than 10% of the tumour cells.
3+	Positive	A strong complete membrane staining is observed in more than 10% of the tumour cells.



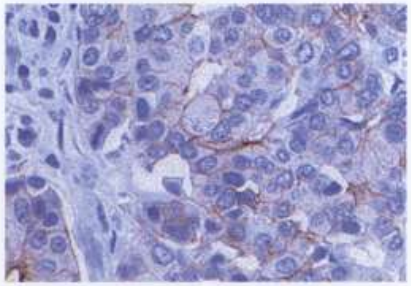
Score: 2+



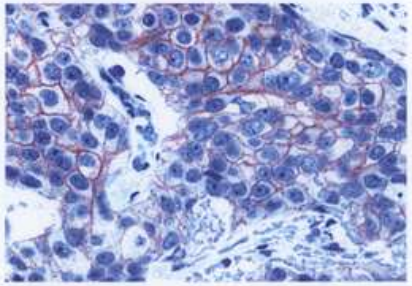
Score: 3+



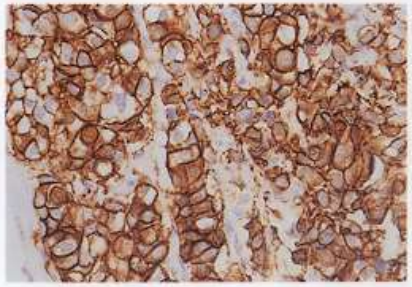
Score: 0



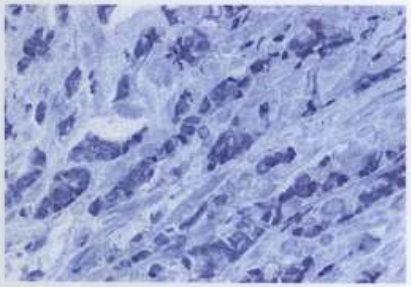
Score: 1+



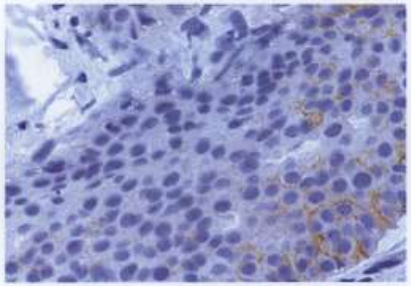
Score: 2+



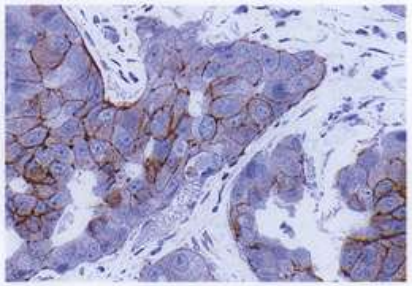
Score: 3+



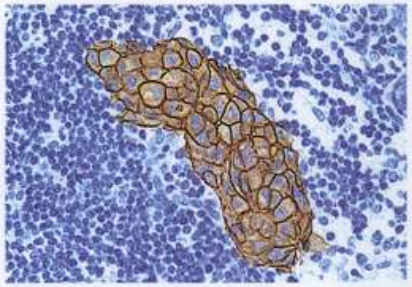
Score: 0



Score: 1+

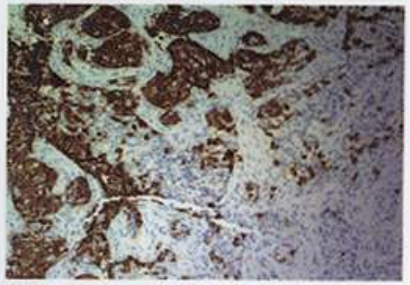


Score: 2+

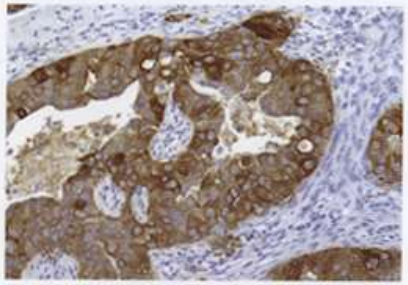


Score: 3+

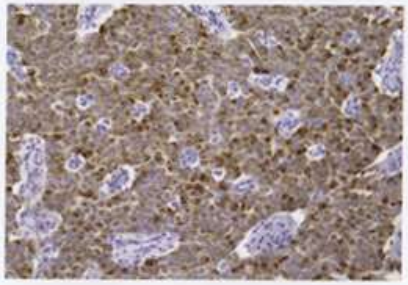
HercepTest™ Rare Staining Patterns and Artifacts



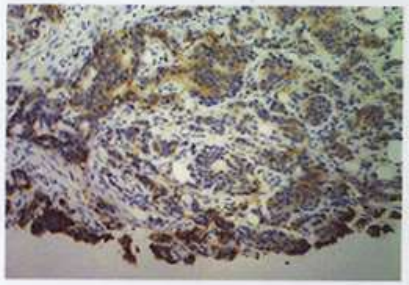
Example of heterogenous staining. Score: 3+



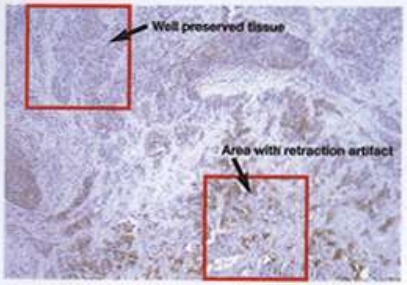
Example of cytoplasmic staining. Score: 0



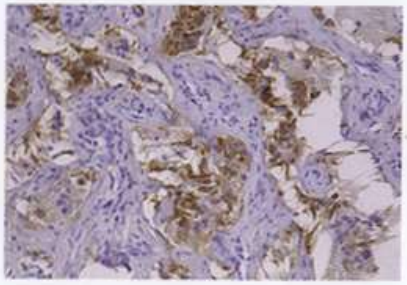
Example of dot artifact. Score: 0



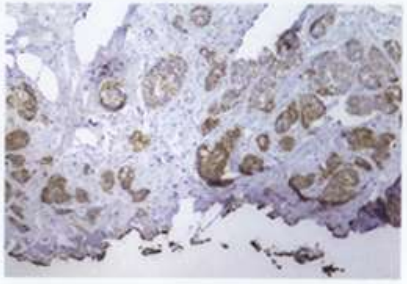
Example of edge artifact. Score: 1+



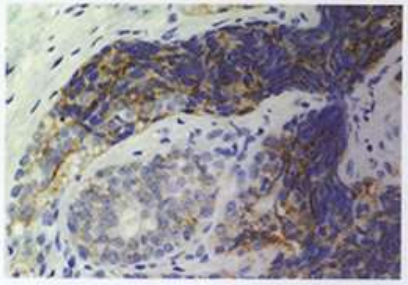
Example of retraction artifact. Score: 1+



Example of retraction artifact. Score: 1+



Example of thermal artifact. Score: 1+



Example of crushing artifact. Score: 1+

DAKO

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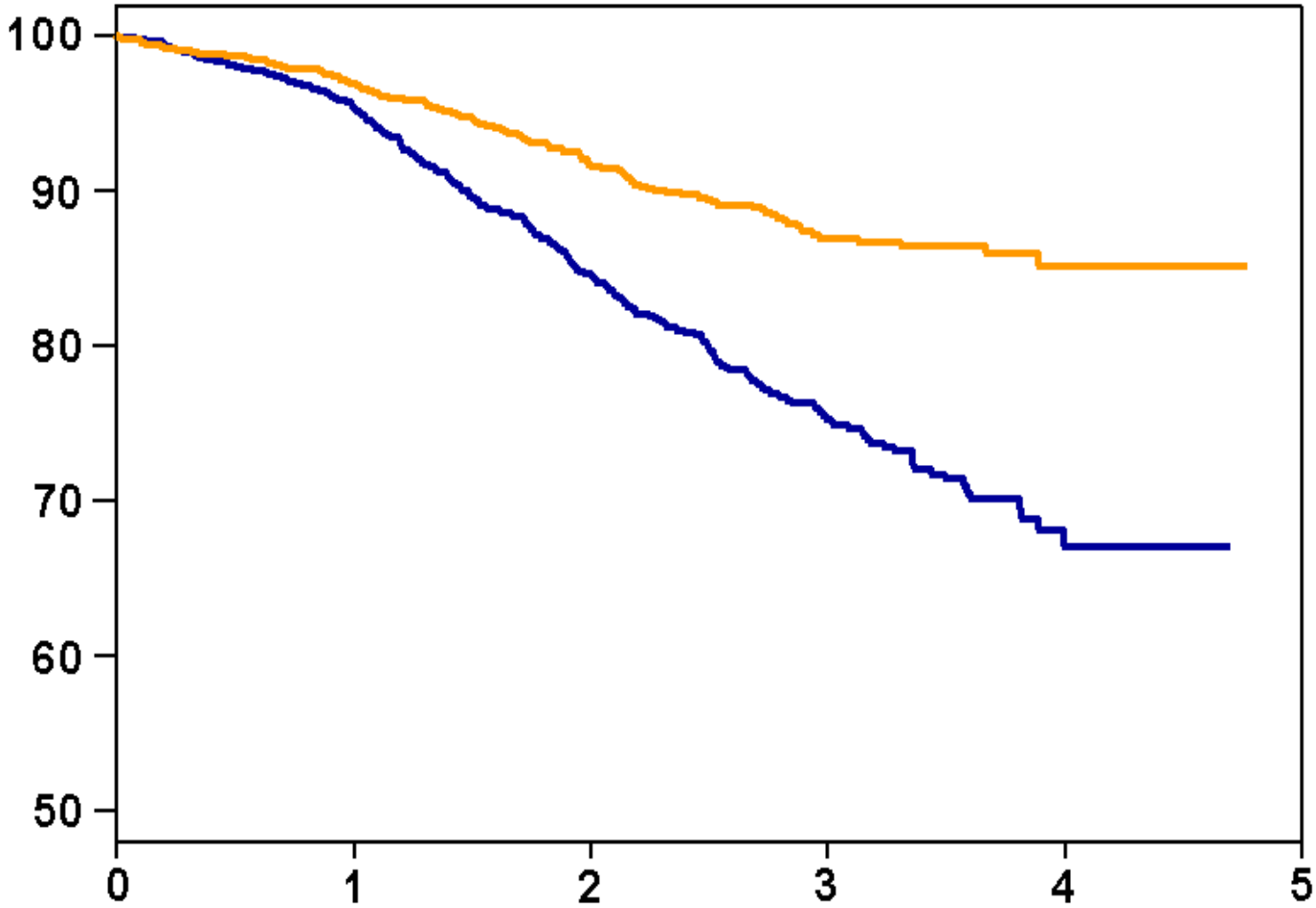
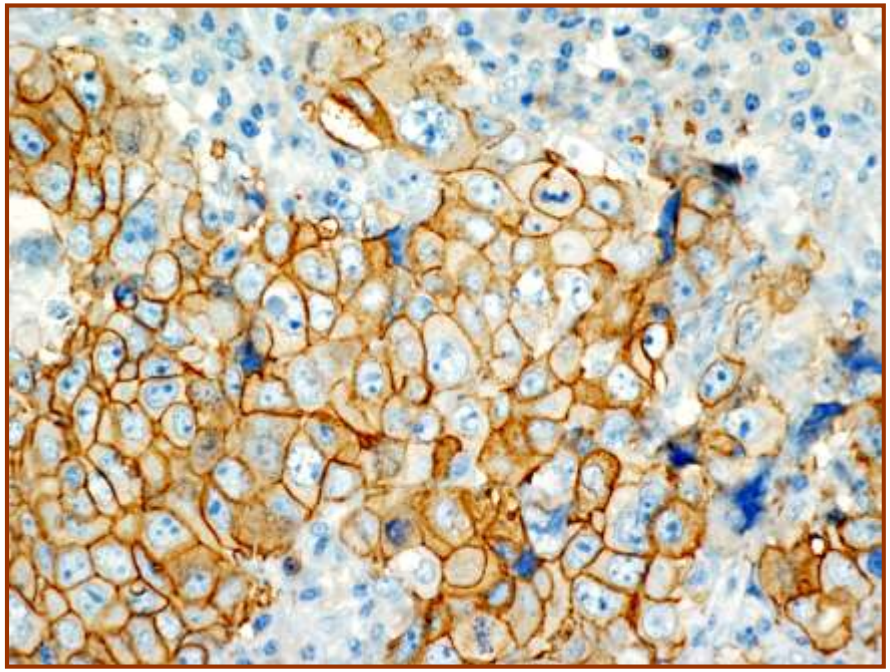
Photos by James Thompson, MD, PhD, Director of Pathology, Biopharmaceutical Services, Impath Laboratories, Frolan Espinoza, MD, Molecular Tissue Pathology, Quest Diagnostics/Nichols Institute and DAKO.

Krankheits-Frei Überleben

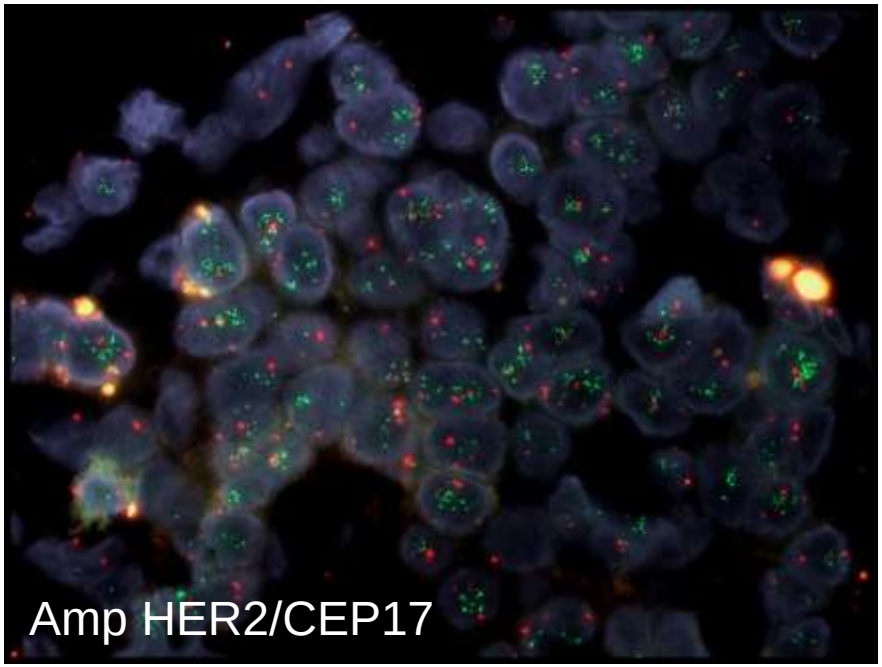
Romond H et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer NEJM 2005; 353:1673-1684



HER2 expression in breast cancer

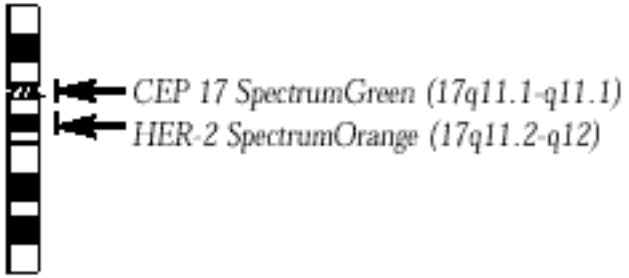


3+ CB11

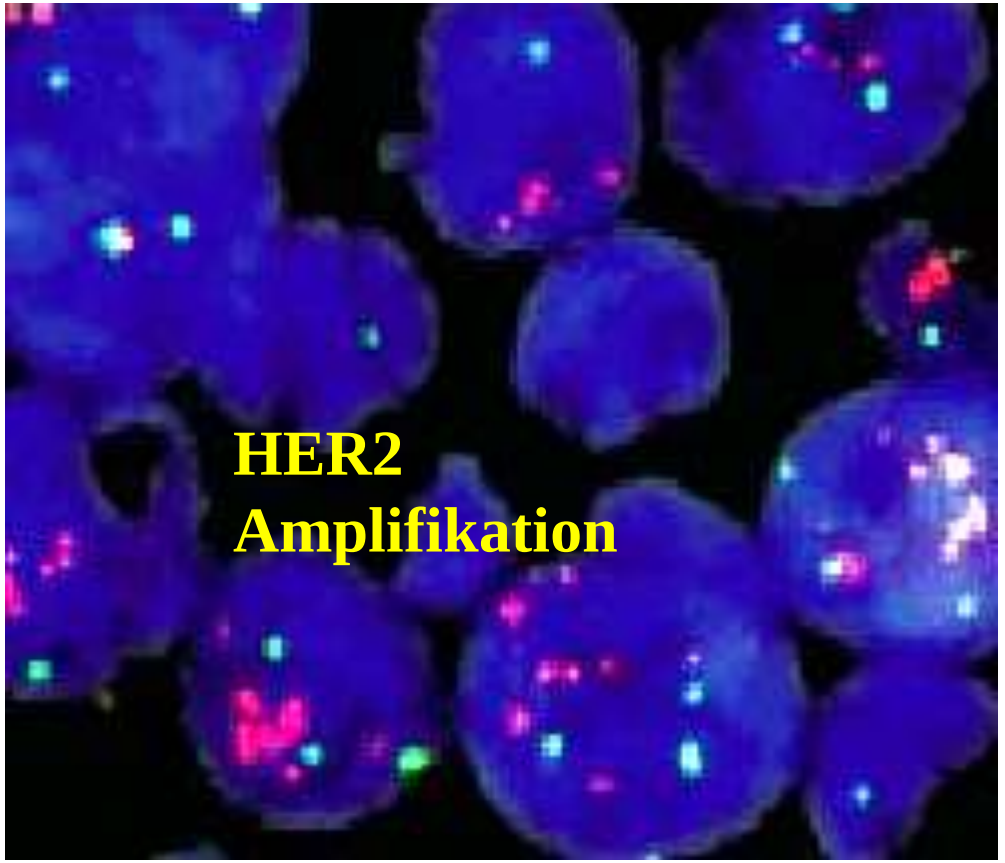


MOLEKULAR PATHOLOGIE

HER-2 - Mammakarzinom



Chromosome 17



The Founders of Modern Immunology and Immuno-Therapy

Robert Koch

Paul Ehrlich

William Coley

Emil v. Behring

Louis Pasteur

Rudolf Virchow

Ilja Iljitsch Metschnikow

ImmunoTherapy: Does it Work in Solid Tumors? Paul Ehrlich's Immunosurveillance Concept: 100+ years of progress

- Magic Bullet (Paul Ehrlich)
- Immunosurveillance (P Ehrlich (1909)
- Intratumoral application (Coley1906)

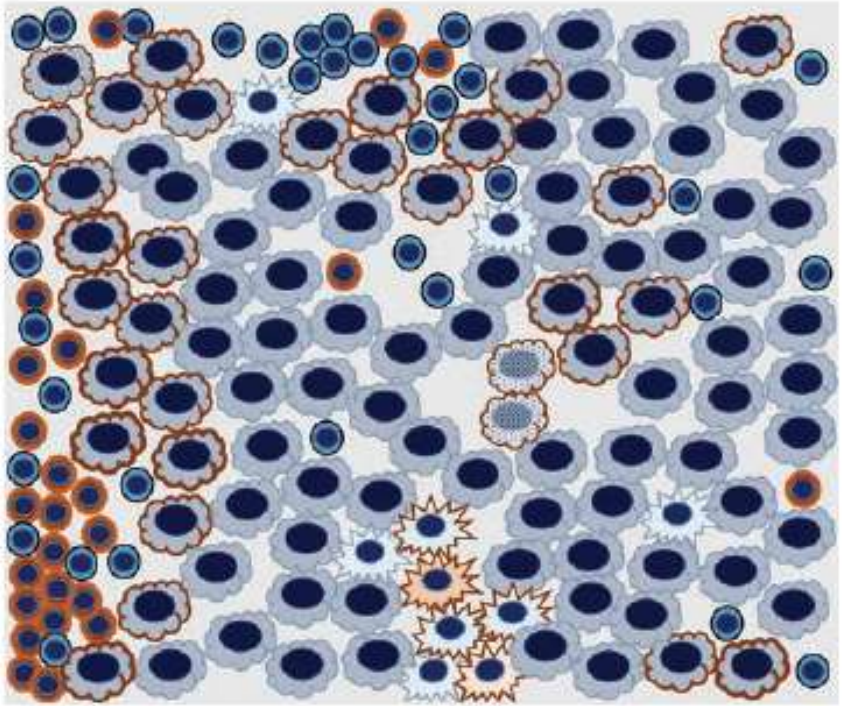
Paul Ehrlich

William Coley

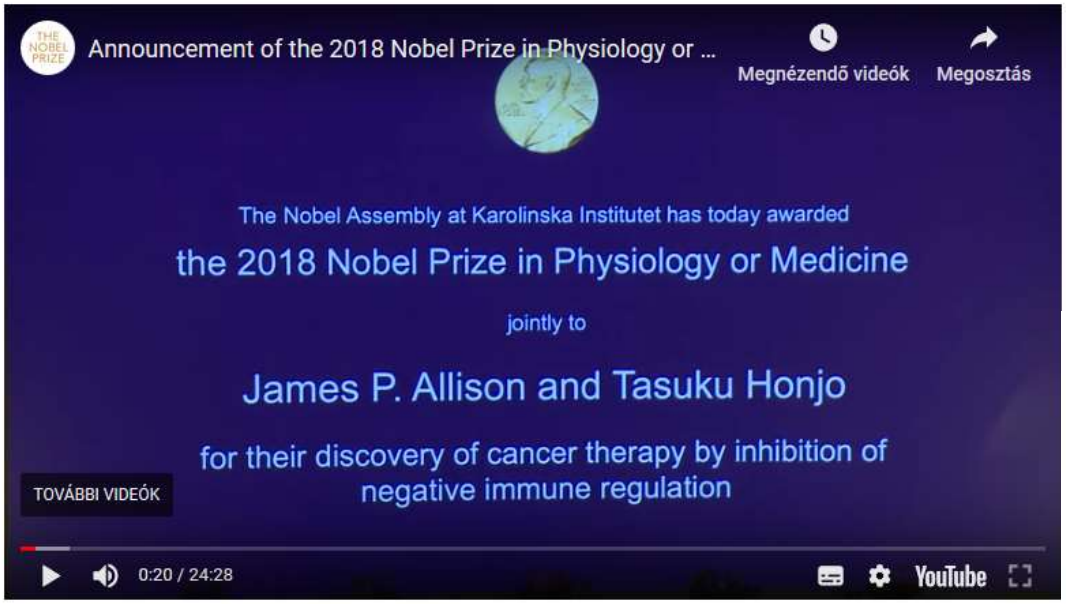
PD-L-1 és PD-1 blokkolók

	Pembrolizumab (anti-PD-1)	Nivolumab (anti-PD-1)	Atezolizumab (anti-PD-L1)	Durvalumab (anti-PD-L1)	Avelumab (anti-PD-L1)
NSCLC első vonal metasztatikus (monoterápiában)	ALK- és EGFR-negatív esetekben **Kísérő IVD: 22C3 ≥50% TPS**				
NSCLC első vonal metasztatikus nem laphám (kemoterápiával)	IHC nélkül alkalmazható ALK- és EGFR-negatív esetekben		IHC nélkül alkalmazható ALK- és EGFR-negatív esetekben		
NSCLC másodvonal	**Kísérő IVD: 22C3 ≥1% TPS**	IHC nélkül alkalmazható* Kiegészítő: 28-8 ≥1% TPS	IHC nélkül alkalmazható* Kiegészítő: SP142 ≥50% TC / ≥10% IC	**Kísérő IVD: SP263[a] ≥1% TC**	
SCLC (előrehaladott) első vonal (kemoterápiával)			IHC nélkül alkalmazható		
SCLC (előrehaladott) másodvonal		IHC nélkül alkalmazható			
Urotelialis első vonal (cisplatinkezelésre alkalmatlanoknál)	**Kísérő IVD: 22C3 ≥10 CPS**		**Kísérő IVD: SP142 ≥5% IC**		
Urotelialis másodvonal (korábban platinaalapú kezelésen átesett)	IHC nélkül alkalmazható	IHC nélkül alkalmazható* Kiegészítő: 28-8 ≥1% TPS	IHC nélkül alkalmazható	Kiegészítő: SP263 ≥25% TC vagy ≥1% ICP és ≥25% IC vagy ICP=1% és IC=100%	IHC nélkül alkalmazható
Fej-nyaki laphámrák első vonal	Kísérő: 22C3 ≥1 CPS	IHC nélkül alkalmazható Kiegészítő: 28-8 ≥1% TPS			
Fej-nyaki laphámrák másodvonal	**Kísérő IVD: 22C3 ≥50% TPS**	IHC nélkül alkalmazható			
Klasszikus Hodgkin-limfóma másodvonal	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
Melanóma	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
RCC első vonal (kombinációban)	IHC nélkül alkalmazható	IHC nélkül alkalmazható			IHC nélkül alkalmazható
RCC másodvonal		IHC nélkül alkalmazható			
Tripla-negatív emlőrák			**Kísérő IVD: SP142 ≥1% IC**		
Méhnyakrák	Kísérő: 22C3 ≥1% TPS				
Gyomorrák	Kísérő: 22C3 ≥1% TPS				
HCC	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
Merkel-sejtes karcinóma	IHC nélkül alkalmazható				IHC nélkül alkalmazható

	Pembrolizumab (anti-PD-1)	Nivolumab (anti-PD-1)	Atezolizumab (anti-PD-L1)	Durvalumab (anti-PD-L1)	Avelumab (anti-PD-L1)
dMMR/MSI-H kolorektális karcinóma	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
dMMR/MSI-H (bármely tumor)	IHC nélkül alkalmazható				



Prize announcement



Announcement of the 2018 Nobel Prize in Physiology or Medicine by Professor Thomas Perlmann, Secretary of the Nobel Committee for Physiology or Medicine, on 1 October 2018.

"We can cure cancer with it"

Klas Kärre, member of the Nobel Committee, on the life-changing possibilities of this year's Nobel Prize awarded discovery. Professor Kärre, member of the Nobel Committee for Physiology or Medicine, was interviewed by freelance journalist Lotta Fredholm following the announcement of the 2018 Nobel Prize in Physiology or Medicine.

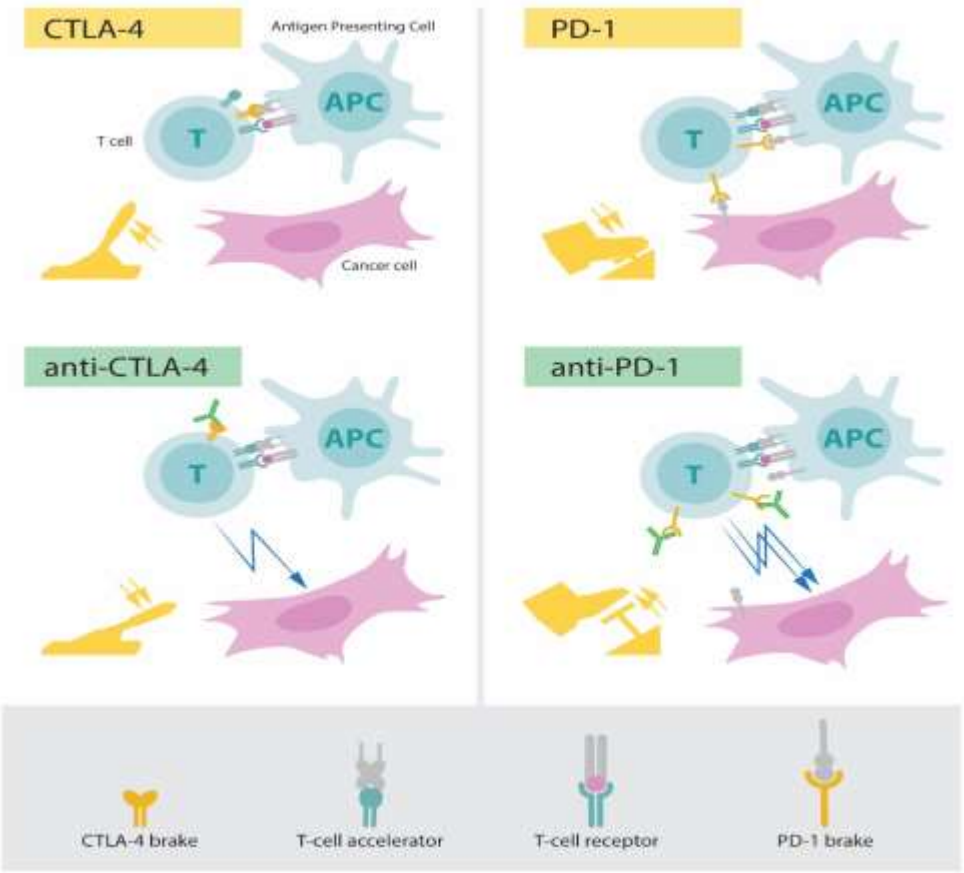


Figure: Upper left: *Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as ”non-self”. A protein functioning as a T-cell accelerator is also required for T cell activation. CTLA- 4 functions as a brake on T cells that inhibits the function of the accelerator.* ***Lower left:*** *Antibodies (green) against CTLA-4 block the function of the brake leading to activation of T cells and attack on cancer cells.****Upper right:*** *PD-1 is another T-cell brake that inhibits T-cell activation.* ***Lower right:*** *Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells.*

SUMMARY

Cancer kills millions of people every year and is one of humanity's greatest health challenges. By stimulating the inherent ability of our immune system to attack tumor cells this year's Nobel Laureates have established an entirely new principle for cancer therapy.
James P. Allison studied a known protein that functions as a brake on the immune system. He realized the potential of releasing the brake and thereby unleashing our immune cells to attack tumors. He then developed this concept into a brand new approach for treating patients.
In parallel, Tasuku Honjo discovered a protein on immune cells and, after careful exploration of its function, eventually revealed that it also operates as a brake, but with a different mechanism of action. Therapies based on his discovery proved to be strikingly effective in the fight against cancer.
Allison and Honjo showed how different strategies for inhibiting the brakes on the immune system can be used in the treatment of cancer. The seminal discoveries by the two Laureates constitute a landmark in our fight against cancer.

Can our immune defense be engaged for cancer treatment?

Cancer comprises many different diseases, all characterized by uncontrolled proliferation of abnormal cells with capacity for spread to healthy organs and tissues. A number of therapeutic approaches are available for cancer treatment, including surgery, radiation, and other strategies, some of which have been awarded previous Nobel Prizes. These include methods for hormone treatment for prostate cancer (Huggins, 1966), chemotherapy (Elion and Hitchins, 1988), and bone marrow transplantation for leukemia (Thomas 1990). However, advanced cancer remains immensely difficult to treat, and novel therapeutic strategies are desperately needed.

In the late 19th century and beginning of the 20th century the concept emerged that activation of the immune system might be a strategy for attacking tumor cells. Attempts were made to infect patients with bacteria to activate the defense. These efforts only had modest effects, but a variant of this strategy is used today in the treatment of bladder cancer. It was realized that more knowledge was needed. Many scientists engaged in intense basic research and uncovered fundamental mechanisms regulating immunity and also showed how the immune system can recognize cancer cells. Despite remarkable scientific progress, attempts to develop generalizable new strategies against cancer proved difficult.

Accelerators and brakes in our immune system

The fundamental property of our immune system is the ability to discriminate “self” from “non-self” so that invading bacteria, viruses and other dangers can be attacked and eliminated. T cells, a type of white blood cell, are key players in this defense. T cells were shown to have receptors that bind to structures recognized as non-self and such interactions trigger the immune system to engage in defense. But additional proteins acting as T-cell accelerators are also required to trigger a full-blown immune response (see Figure). Many scientists contributed to this important basic research and identified other proteins that function as brakes on the T cells, inhibiting immune activation. This intricate balance between accelerators and brakes is essential for tight control. It ensures that the immune system is sufficiently engaged in attack against foreign microorganisms while avoiding the excessive activation that can lead to autoimmune destruction of healthy cells and tissues.

A new principle for immune therapy

During the 1990s, in his laboratory at the University of California, Berkeley, James P. Allison studied the T-cell protein CTLA-4. He was one of several scientists who had made the observation that CTLA-4 functions as a brake on T cells. Other research teams exploited the mechanism as a target in the treatment of autoimmune disease. Allison, however, had an entirely different idea. He had already developed an antibody that could bind to CTLA-4 and block its function (see Figure). He now set out to investigate if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. Allison and co-workers performed a first experiment at the end of 1994, and in their excitement it was immediately repeated over the Christmas break. The results were spectacular. Mice with cancer had been cured by treatment with the antibodies that inhibit the brake and unlock antitumor T-cell activity. Despite little interest from the pharmaceutical industry, Allison continued his intense efforts to develop the strategy into a therapy for humans. Promising results soon emerged from several groups, and in 2010 an important clinical study showed striking effects in patients with advanced melanoma, a type of skin cancer. In several patients signs of remaining cancer disappeared. Such remarkable results had never been seen before in this patient group.

Discovery of PD-1 and its importance for cancer therapy

In 1992, a few years before Allison's discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. Determined to unravel its role, he meticulously explored its function in a series of elegant experiments performed over many years in his laboratory at Kyoto University. The results showed that PD-1, similar to CTLA-4, functions as a T-cell brake, but operates by a different mechanism (see Figure). In animal experiments, PD-1 blockade was also shown to be a promising strategy in the fight against cancer, as demonstrated by Honjo and other groups. This paved the way for utilizing PD-1 as a target in the treatment of patients. Clinical development ensued, and in 2012 a key study demonstrated clear efficacy in the treatment of patients with different types of cancer. Results were dramatic, leading to long-term remission and possible cure in several patients with metastatic cancer, a condition that had previously been considered essentially untreatable.

Immune checkpoint therapy for cancer today and in the future

After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been dramatic. We now know that the treatment, often referred to as "immune checkpoint therapy", has fundamentally changed the outcome for certain groups of patients with advanced cancer. Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with the aim of improving therapies and reducing side effects.

Of the two treatment strategies, checkpoint therapy against PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer, renal cancer, lymphoma and melanoma. New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma. Thus, Allison and Honjo have inspired efforts to combine different strategies to release the brakes on the immune system with the aim of eliminating tumor cells even more efficiently. A large number of checkpoint therapy trials are currently underway against most types of cancer, and new checkpoint proteins are being tested as targets.

For more than 100 years scientists attempted to engage the immune system in the fight against cancer. Until the seminal discoveries by the two laureates, progress into clinical development was modest. Checkpoint therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how cancer can be managed.

Key publications

Ishida, Y., Agata, Y., Shibahara, K., & Honjo, T. (1992). Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.*, *11*(11), 3887–3895.

Leach, D. R., Krummel, M. F., & Allison, J. P. (1996). Enhancement of antitumor immunity by CTLA-4 blockade. *Science*, *271*(5256), 1734–1736.

Kwon, E. D., Hurwitz, A. A., Foster, B. A., Madias, C., Feldhaus, A. L., Greenberg, N. M., Burg, M.B. & Allison, J.P. (1997). Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. *Proc Natl Acad Sci USA*, *94*(15), 8099–8103.

Nishimura, H., Nose, M., Hiai, H., Minato, N., & Honjo, T. (1999). Development of Lupus-like Autoimmune Diseases by Disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*, *11*, 141–151.

Freeman, G.J., Long, A.J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, L.J., Malenkovich, N., Okazaki, T., Byrne, M.C., Horton, H.F., Fouser, L., Carter, L., Ling, V., Bowman, M.R., Carreno, B.M., Collins, M., Wood, C.R. & Honjo, T. (2000). Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*, *192*(7), 1027–1034.

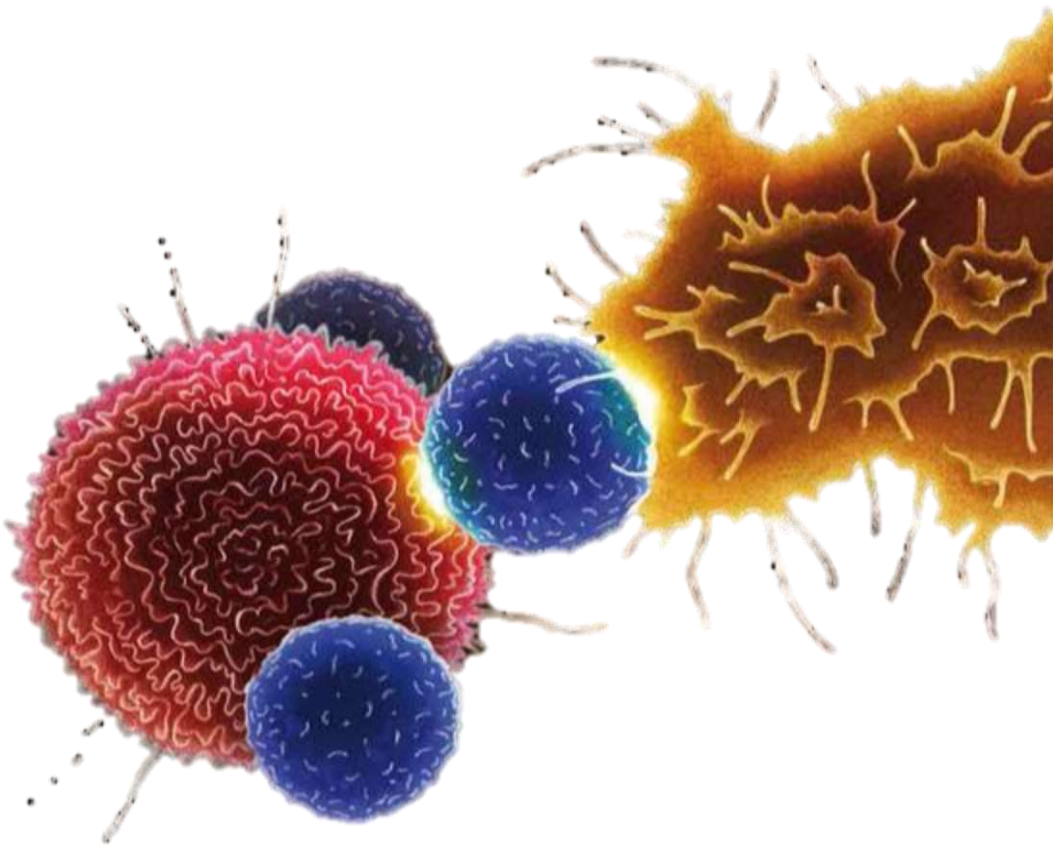
Hodi, F.S., Mihm, M.C., Soiffer, R.J., Haluska, F.G., Butler, M., Seiden, M.V., Davis, T., Henry-Spires, R., MacRae, S., Willman, A., Padera, R., Jaklitsch, M.T., Shankar, S., Chen, T.C., Korman, A., Allison, J.P. & Dranoff, G. (2003). Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Natl Acad Sci USA*, *100*(8), 4712-4717.

Iwai, Y., Terawaki, S., & Honjo, T. (2005). PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int Immunol*, *17*(2), 133–144.

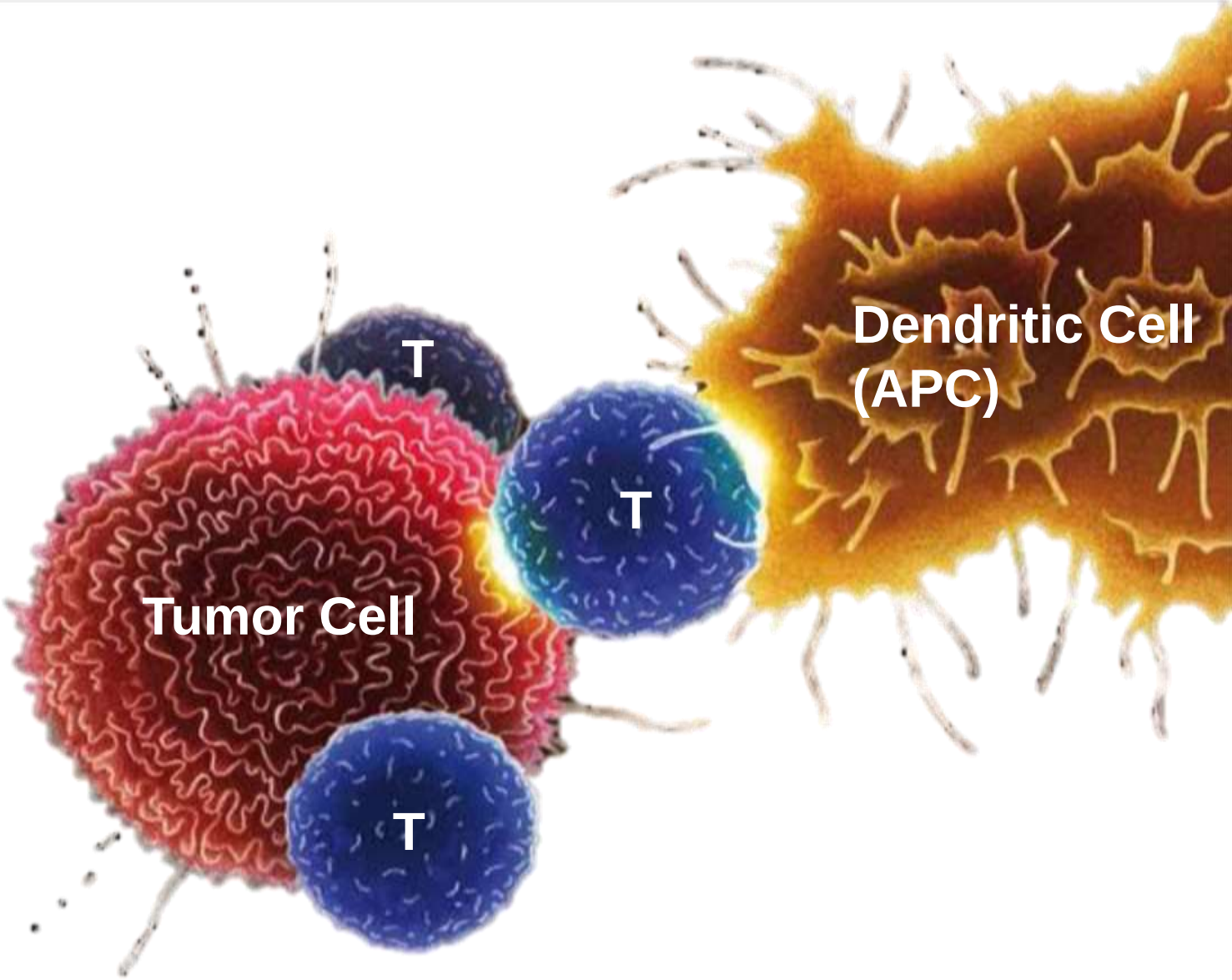
James P. Allison was born 1948 in Alice, Texas, USA. He received his PhD in 1973 at the University of Texas, Austin. From 1974-1977 he was a postdoctoral fellow at the Scripps Clinic and Research Foundation, La Jolla, California. From 1977-1984 he was a faculty member at University of Texas System Cancer Center, Smithville, Texas; from 1985-2004 at University of California, Berkeley and from 2004-2012 at Memorial Sloan-Kettering Cancer Center, New York. From 1997-2012 he was an Investigator at the Howard Hughes Medical Institute. Since 2012 he has been Professor at University of Texas MD Anderson Cancer Center, Houston, Texas and is affiliated with the Parker Institute for Cancer Immunotherapy.

Tasuku Honjo was born in 1942 in Kyoto, Japan. In 1966 he became an MD, and from 1971-1974 he was a research fellow in USA at Carnegie Institution of Washington, Baltimore and at the National Institutes of Health, Bethesda, Maryland. He received his PhD in 1975 at Kyoto University. From 1974-1979 he was a faculty member at Tokyo University and from 1979-1984 at Osaka University. Since 1984 he has been Professor at Kyoto University. He was a Faculty Dean from 1996-2000 and from 2002-2004 at Kyoto University.

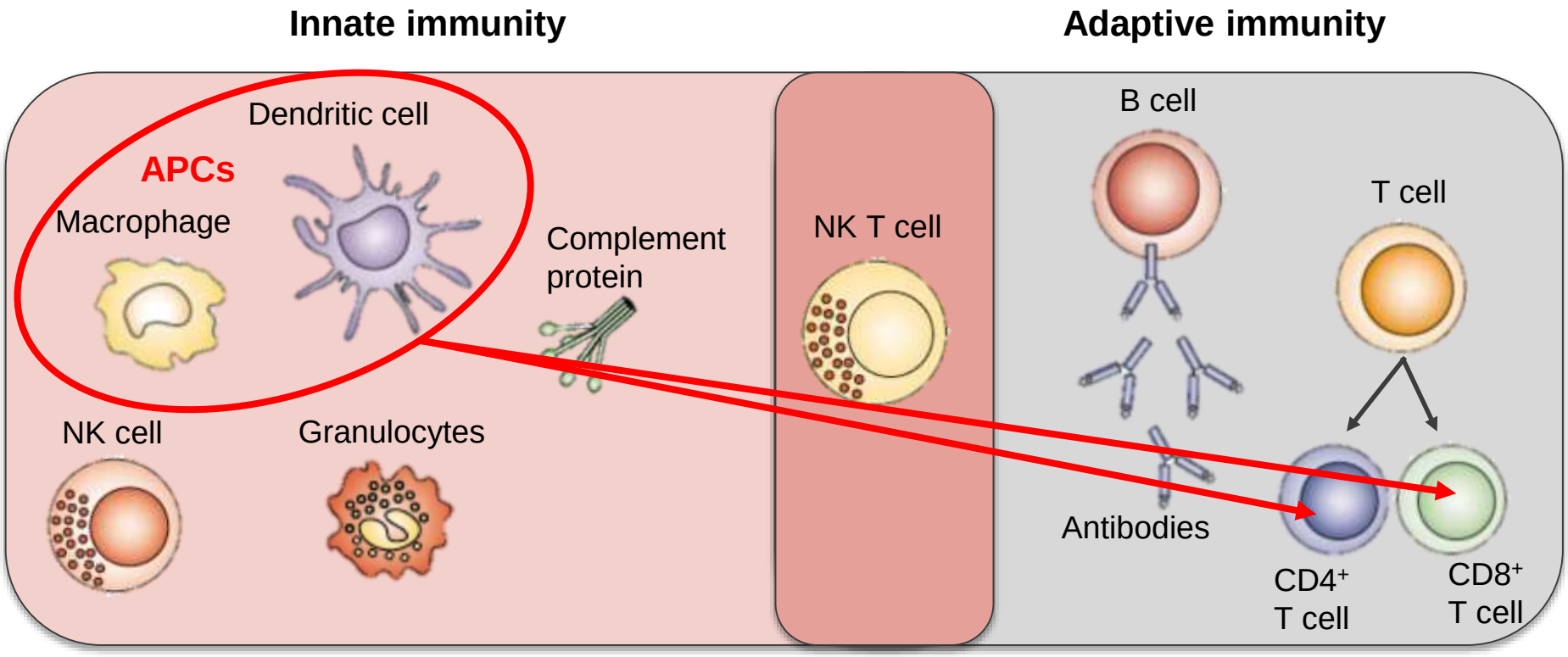
“Immune Checkpoint-Blockade In Cancer” Beginning of a New Era!



Immuno Oncology: A Graphical Abstract



The Immune System



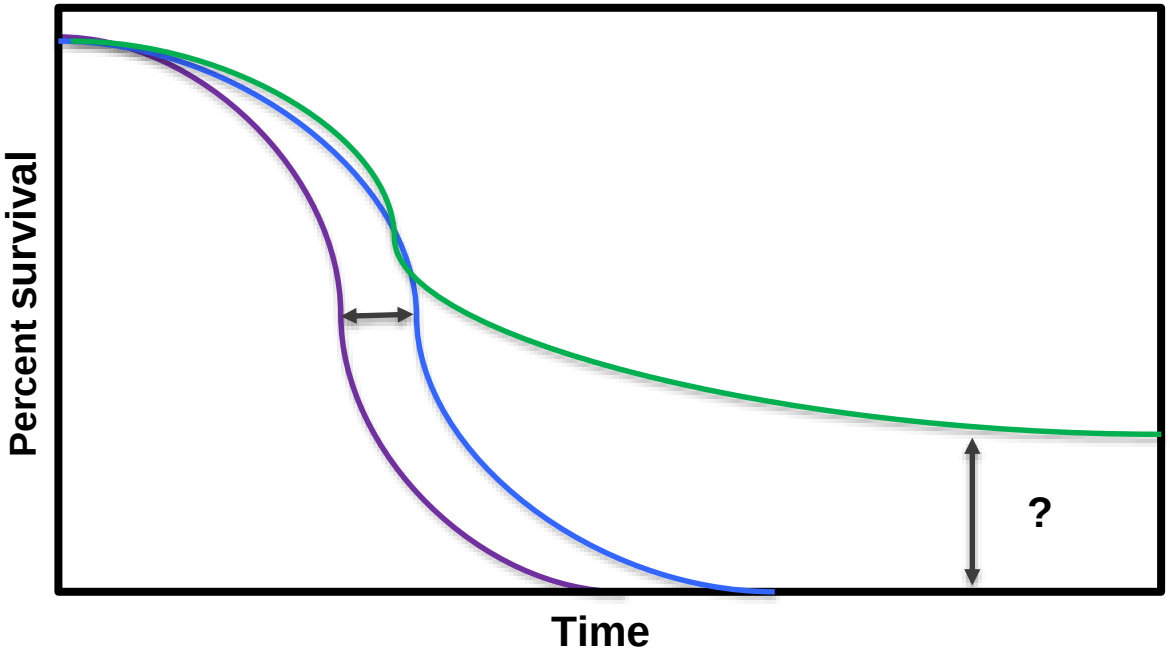
⇒ **fast response and low specificity**

- **Antibodies**
- **Cytokines**
- **Ag receptors (10^9 / individual)**

⇒ **specificity, diversity, and memory**

Dranoff, 2004

Anticancer Therapies and their Targets



Chemotherapy

Targeted therapy ⇒ **clinical responses in majority of patients**
⇒ **limited duration of responses**

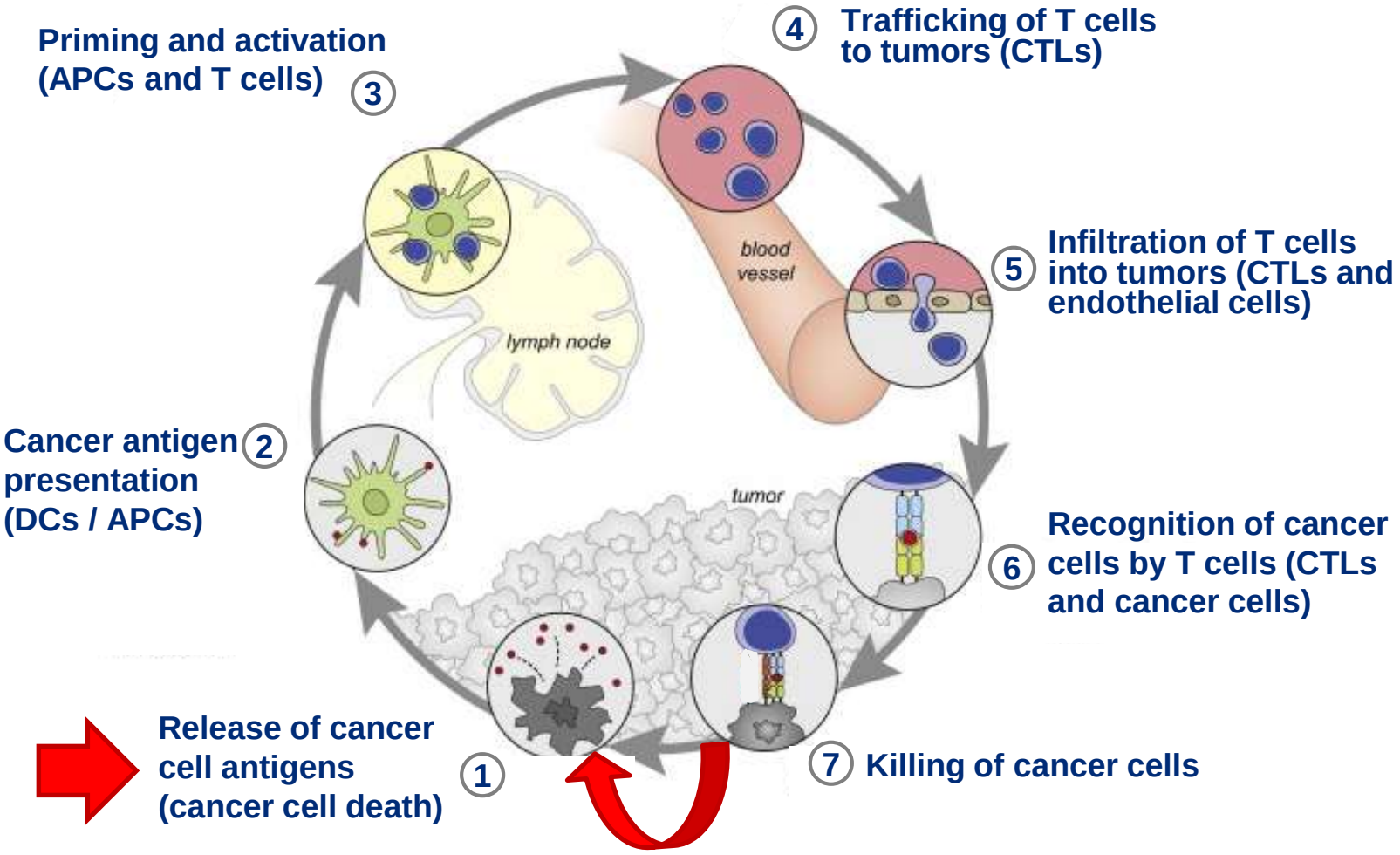
Immune therapy ⇒ **long lasting responses?**

adapted from Allison et al., 2015

ImmunoTherapy: Does it Work in Solid Tumors?
Paul Ehrlich's magic bullet concept:
100+ years of progress

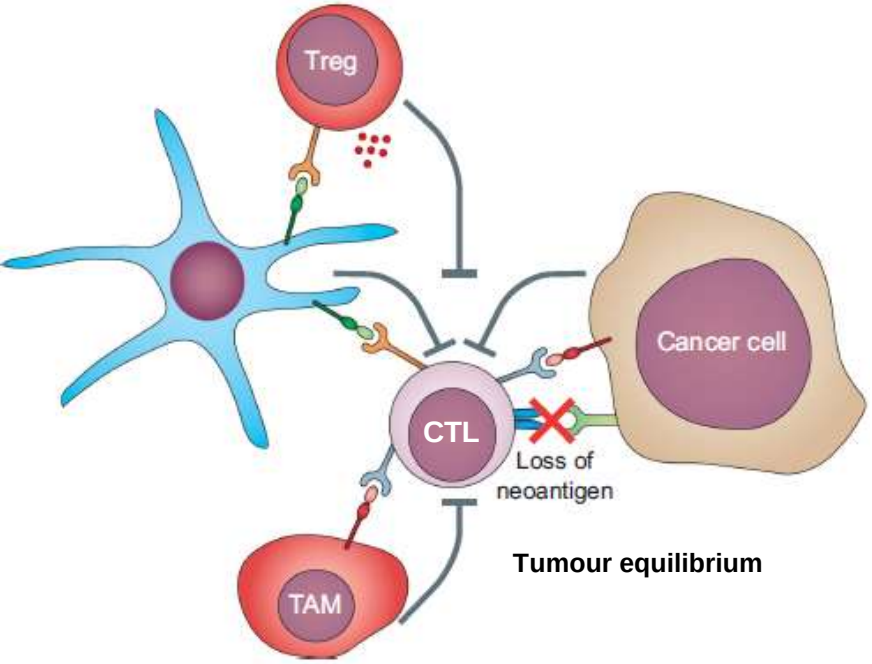
- Magic Bullet (Paul Ehrlich)
- Immunosurveillance (P Ehrlich (1909)
- Intratumoral application (Coley1906)
- ~~Cancer Vaccines ??~~
  - BCG bladder
- ~~Immunostimulants ??~~
  - Big business

The Cancer-Immunity Cycle
- Immunoediting: 1.) Elimination -

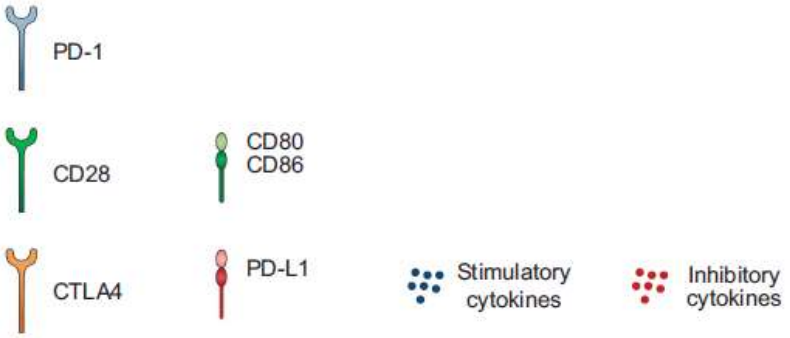


Chen and Mellman Immunity, 2013, 39:1-10

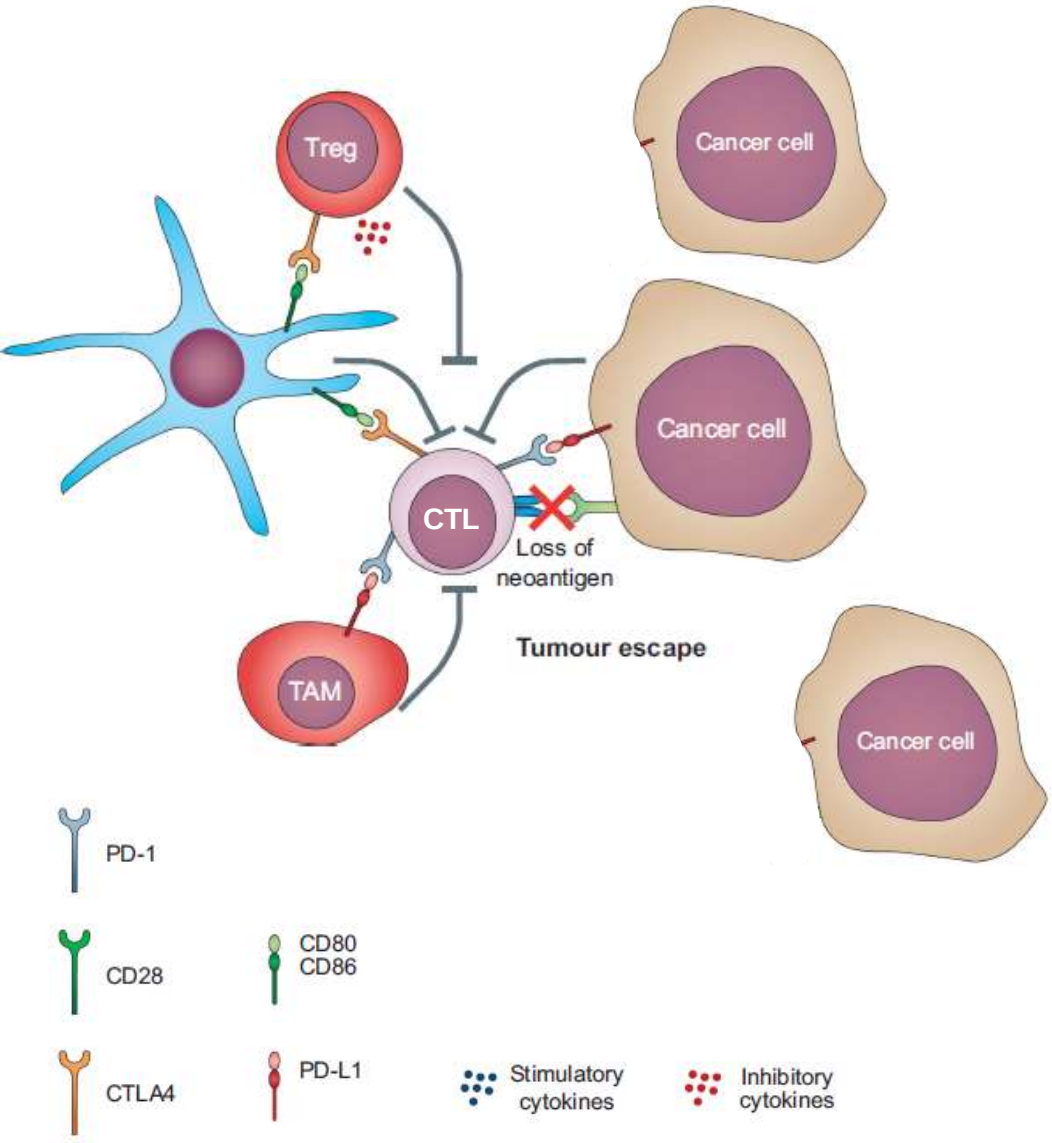
The Cancer-Immunity Cycle
- Immunoediting: 2.) Equilibrium -



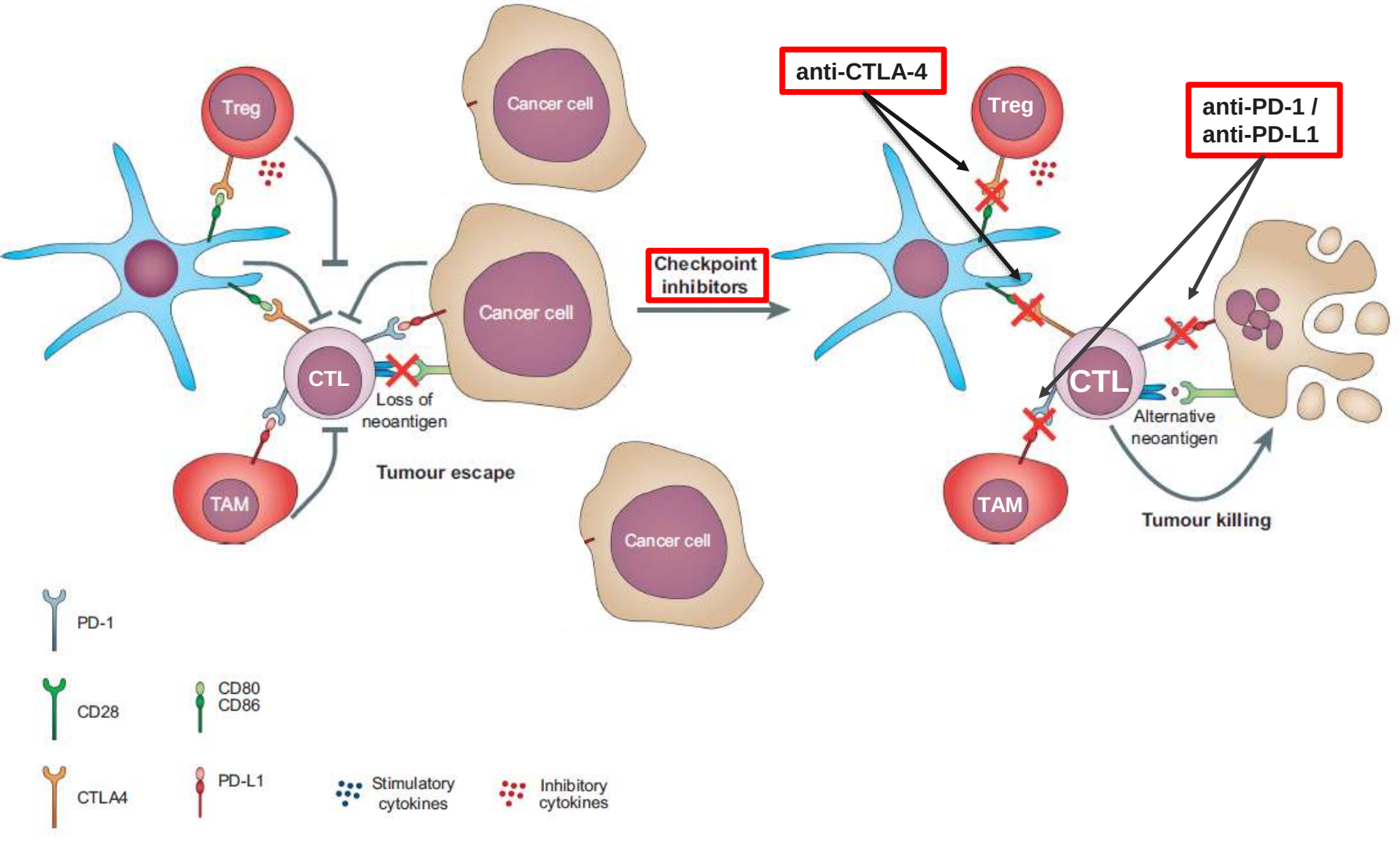
Tumour equilibrium



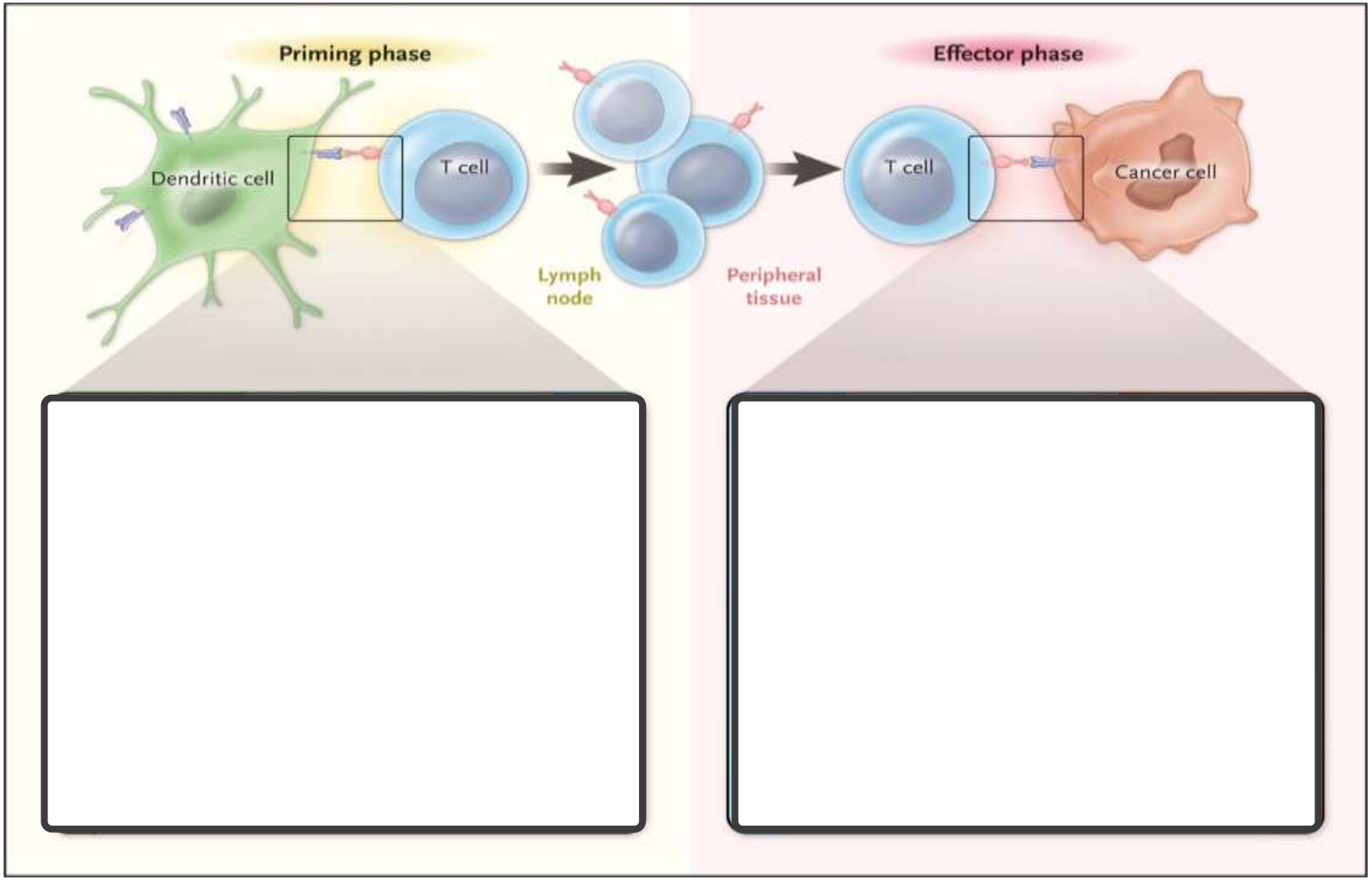
The Cancer-Immunity Cycle
- Immunoediting: 3.) Escape -



Immune Checkpoint Inhibitors



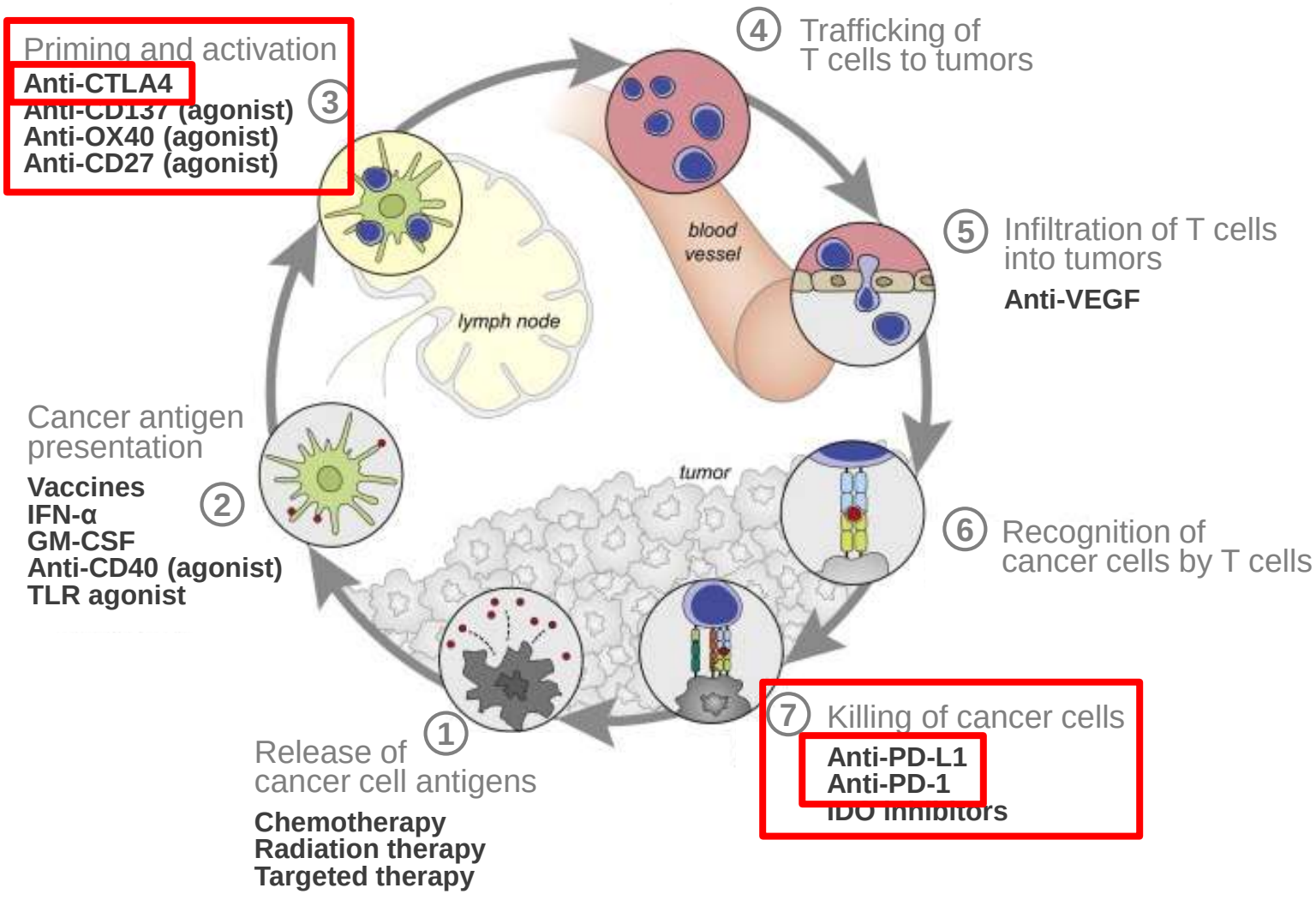
Checkpoint Pathway in Cancer Immunology



CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TCR, T cell receptor.

Ribas A. *N Engl J Med.* 2012;366:2517-2519.

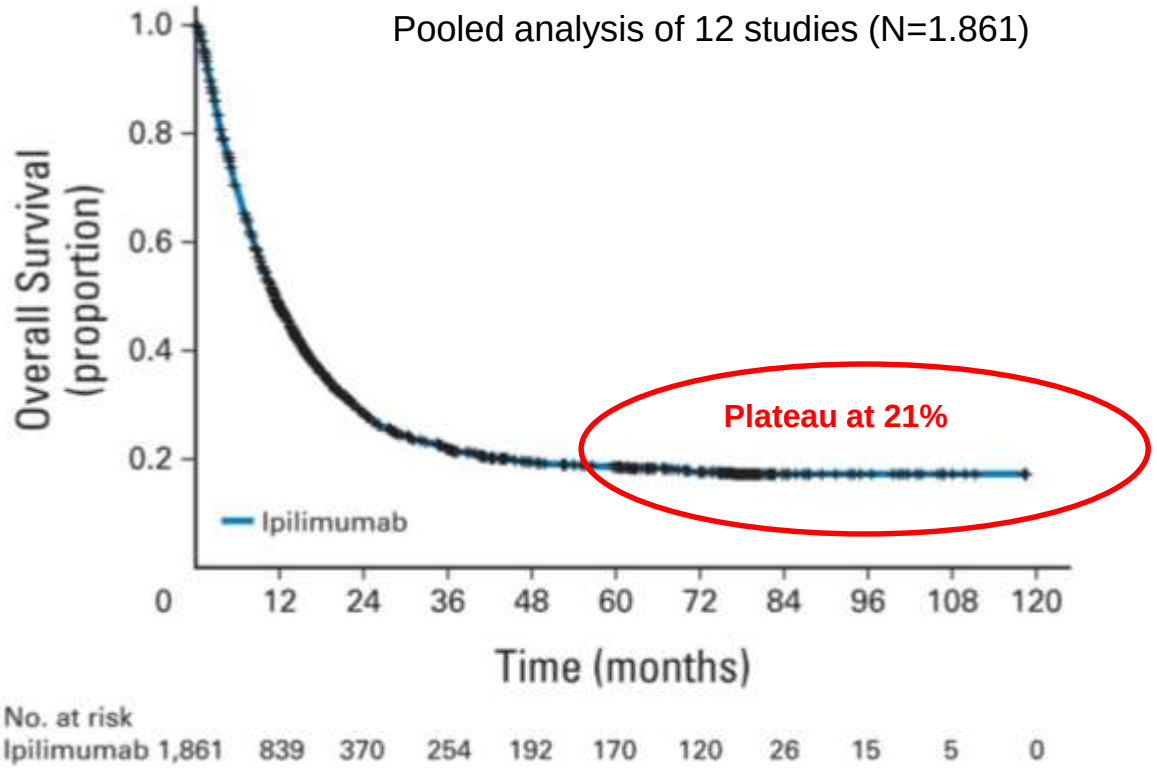
Immune Checkpoint Inhibitors



Chen and Mellman Immunity, 2013, 39:1-10

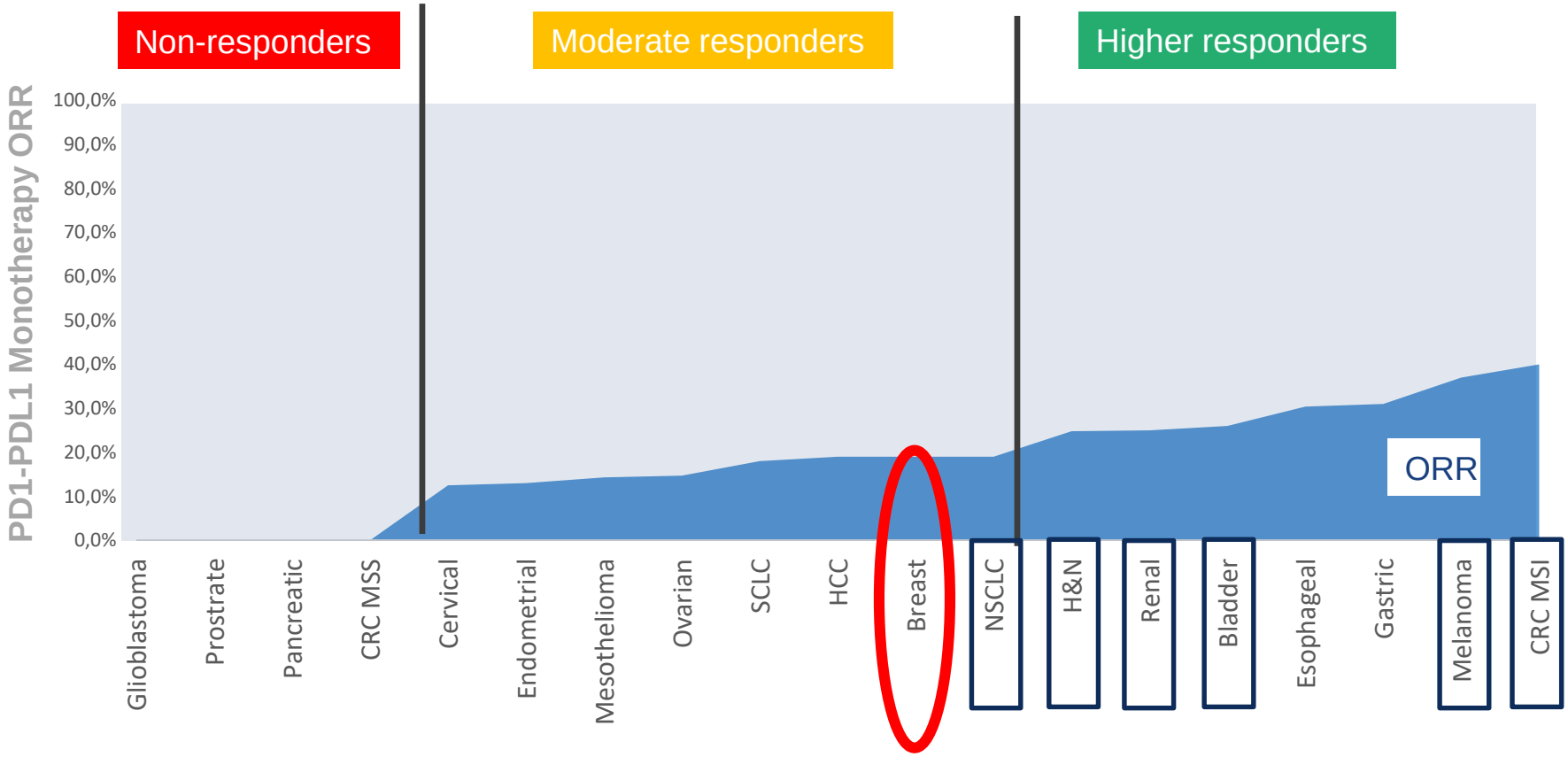
Immune Checkpoint Inhibitors: Breakthrough Therapy in Melanoma

Pooled analysis of 12 studies (N=1.861)

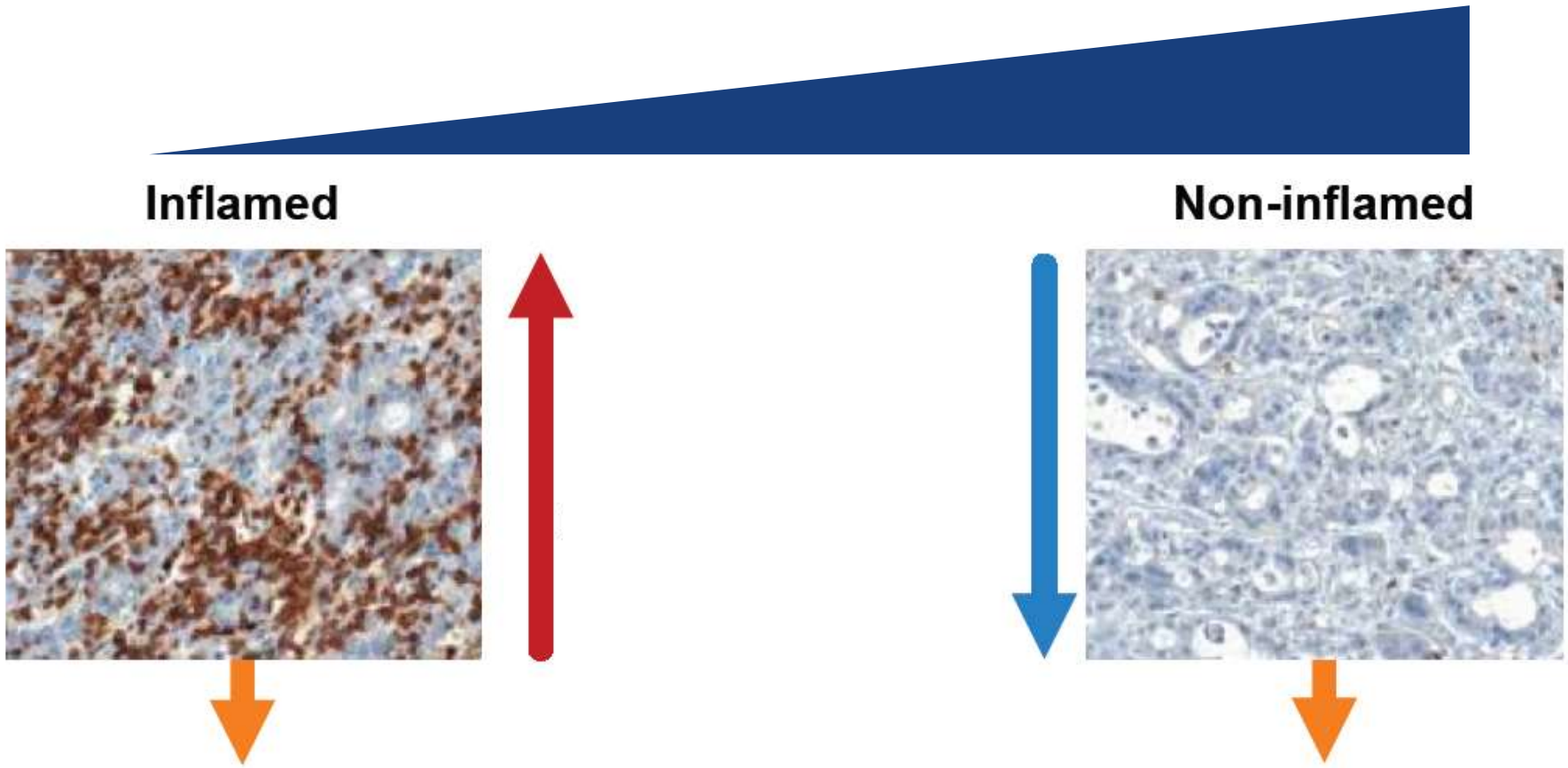


Schadendorf D, et al. J Clin Oncol 33:1889-94, 2015

Three Categories of Response to Anti-PD-1/PD-L1

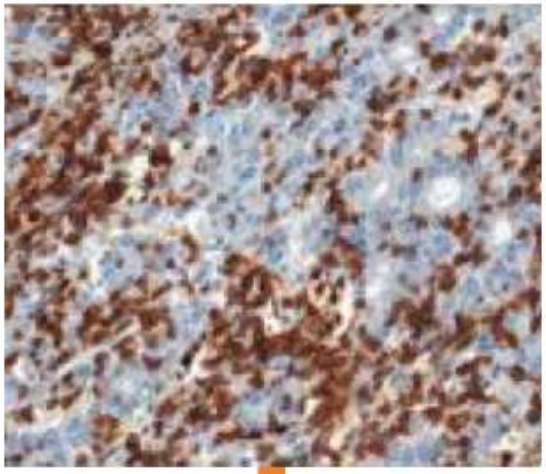


Immunogenic vs. Non-immunogenic Tumors



Immunogenic vs. Non-immunogenic Tumors

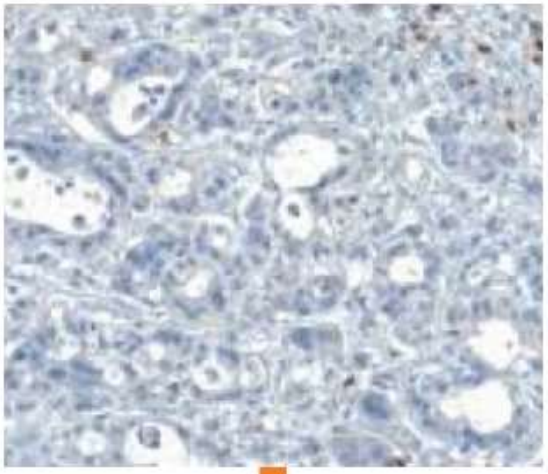
Inflamed



Respond favorably to checkpoint inhibition

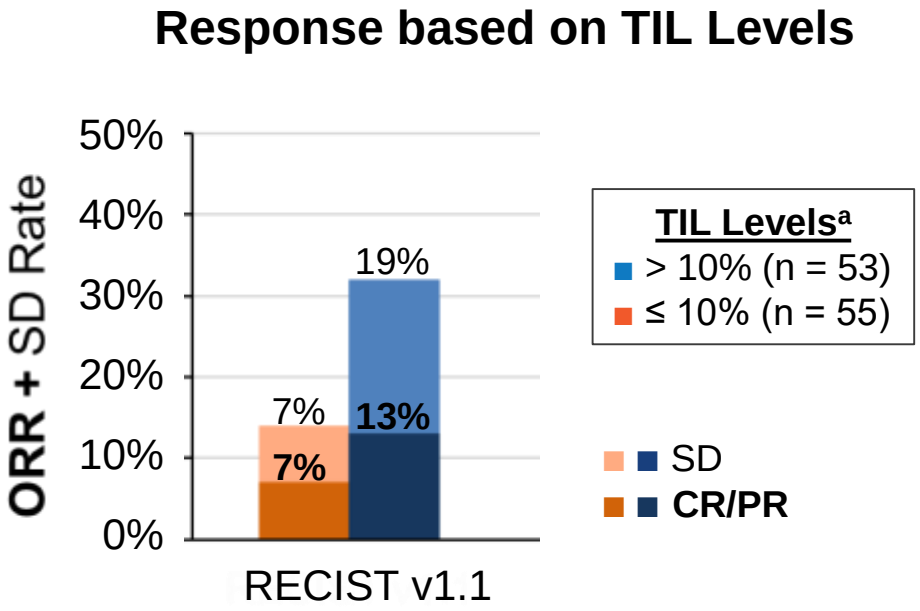
TILs
PD-L1 expression
CD8+ T cells
Genomic instability
Pre-existing immunity

Non-inflamed



How do you convert these tumors to inflamed tumor?

Biomarker Analysis: Tumor-Infiltrating Lymphocytes



Schmid P, et al. AACR 2017 Phase Ia Atezolizumab in TNBC

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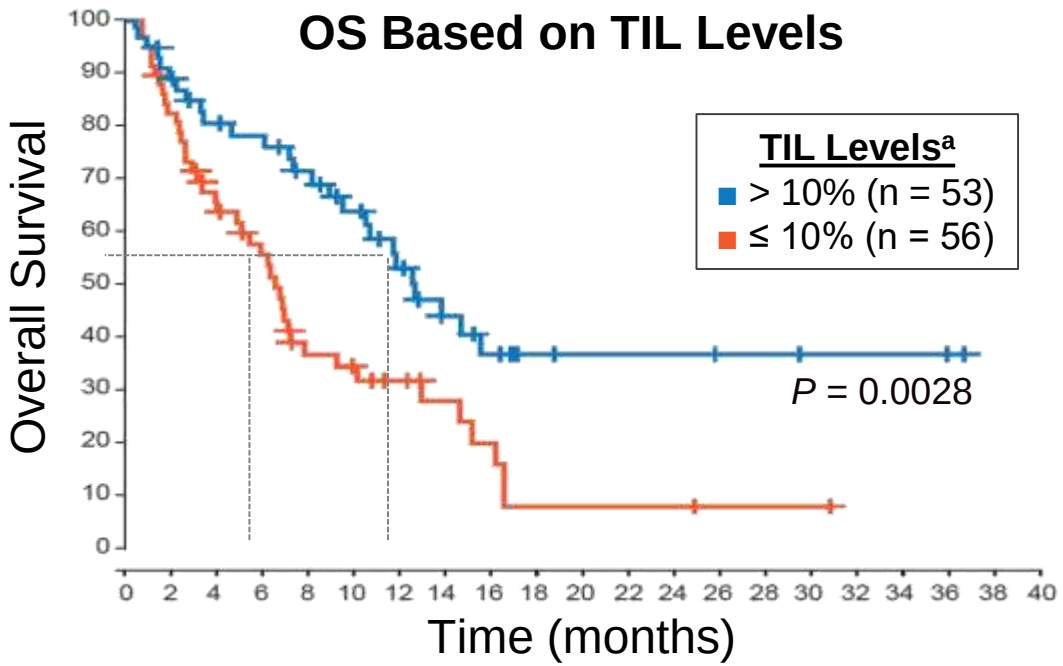


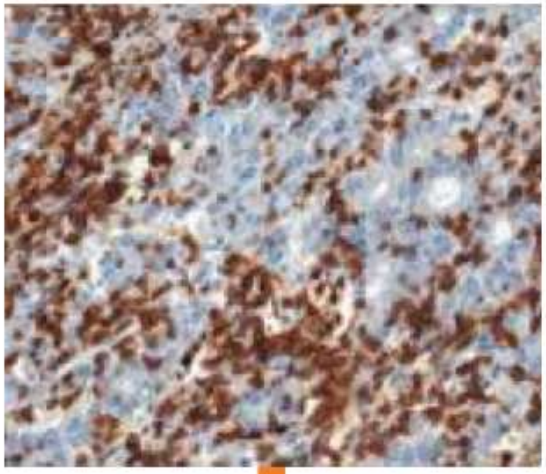
	≤ 10% TILs (n = 53)	> 10% TILs (n = 56)
mOS (95% CI)	6.6 mo (4.9, 10.2)	12.6 mo (10.5, NA)

- Higher ORR and longer OS were seen with higher baseline TIL (CD8) infiltration

Schmid P, et al. AACR 2017 Phase Ia Atezolizumab in TNBC

Immunogenic vs. Non-immunogenic Tumors

Inflamed



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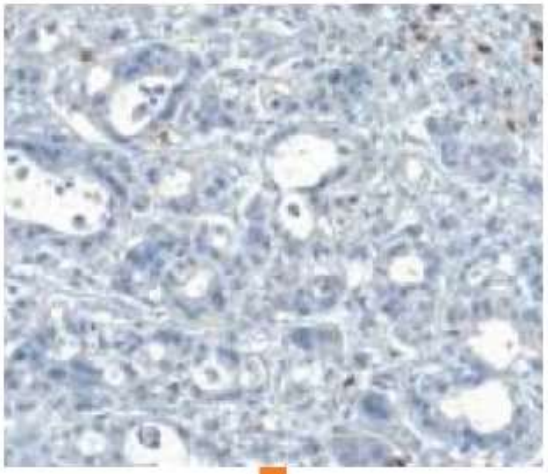

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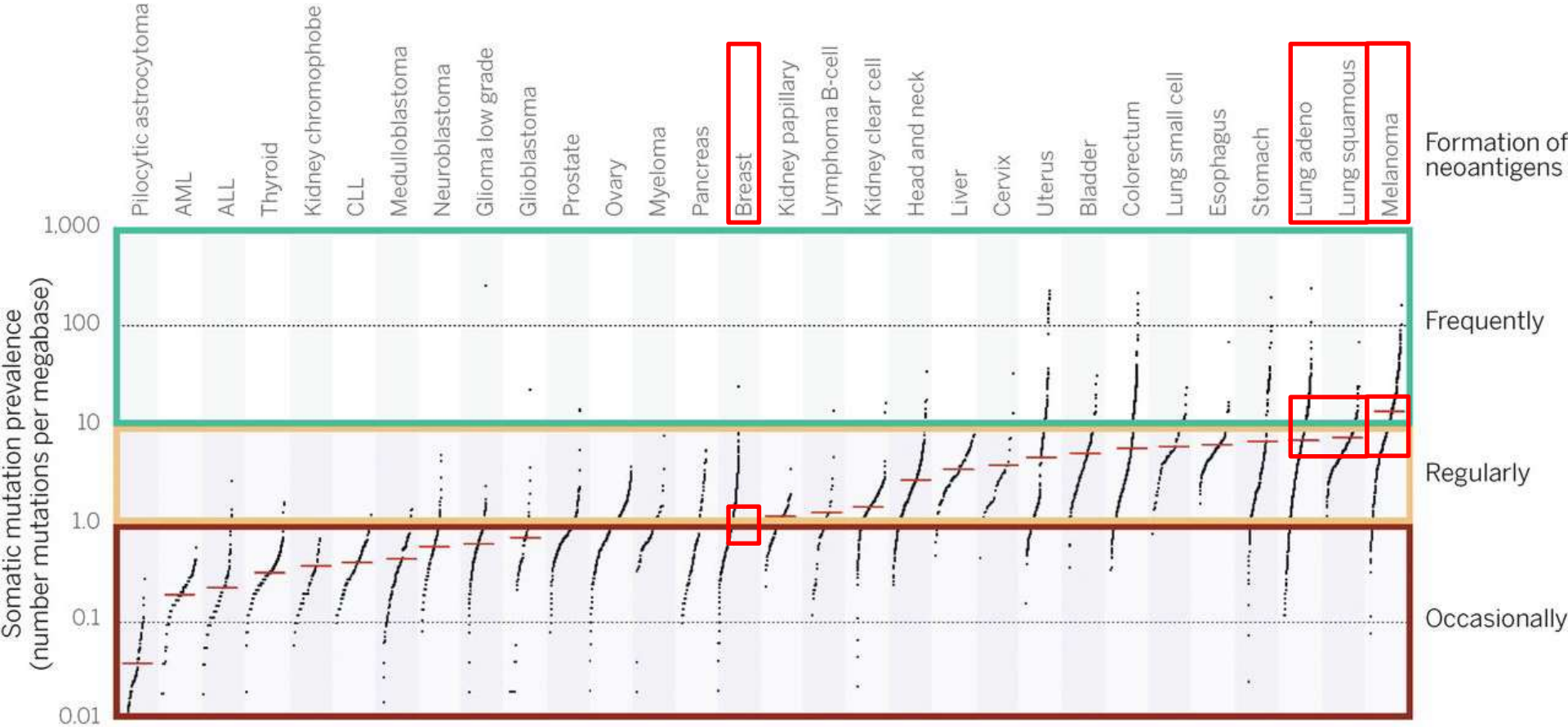
Immunogenic vs. Non-immunogenic Tumors



Alexandrov et al., 2013

Immunogenic vs. Non-immunogenic Tumors

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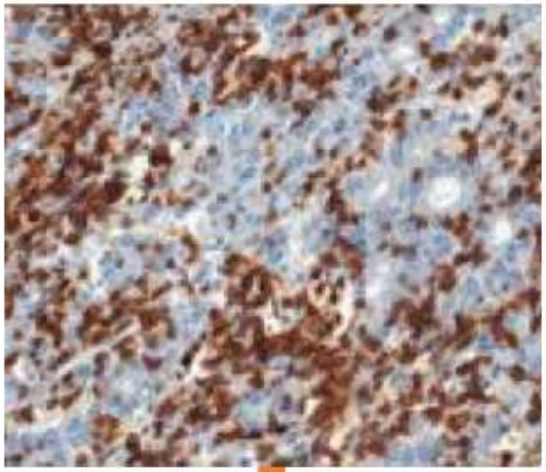

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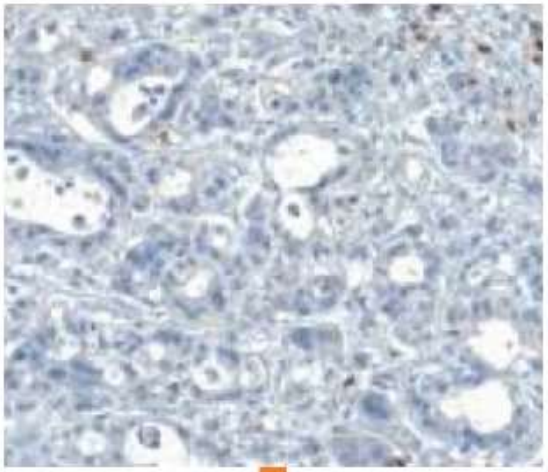
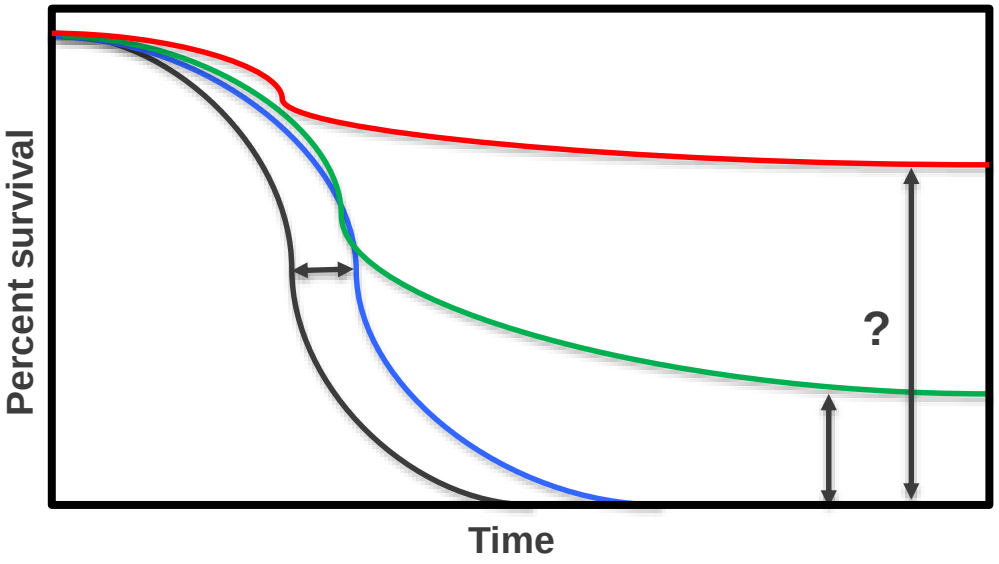


How do you convert these tumors to inflamed tumor?

Future Directions in Immuno-Oncology



Chemotherapy

Targeted therapy

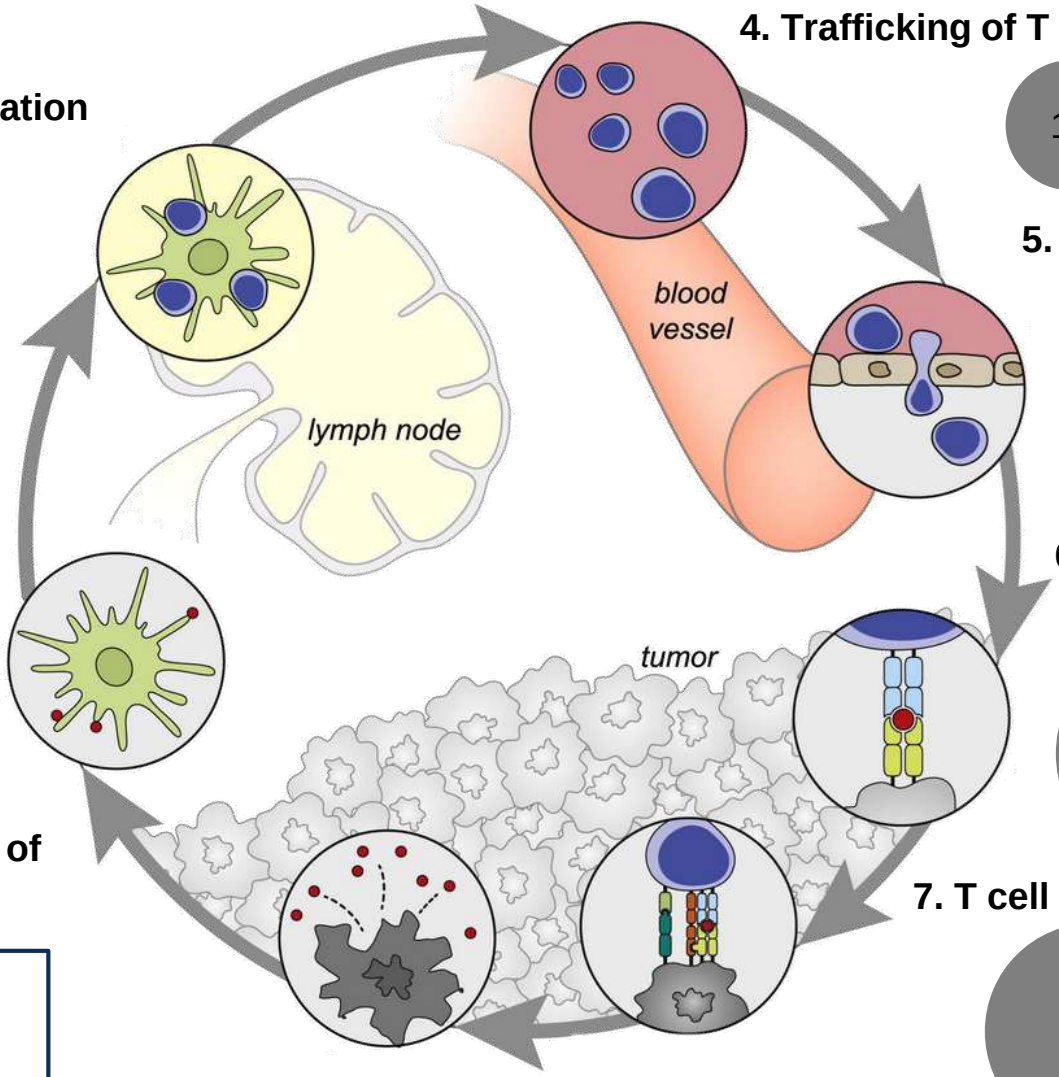
Immune checkpoint therapy

⇒ long lasting responses
⇒ applicable in various cancer types

Combination therapy

⇒ increase in response rate?
⇒ increase in efficiency?

Future Directions in Immuno-Oncology



1. Release/Exposure of cancer antigens

Chemotherapy

2. Cancer antigen presentation

3. Priming and activation

16 7

4. Trafficking of T cells to tumors

14 1

5. Effector T cell Infiltration into tumors

11 12 2

6. T cell recognition of cancer cells

29 23 4

7. T cell killing of cancer cells

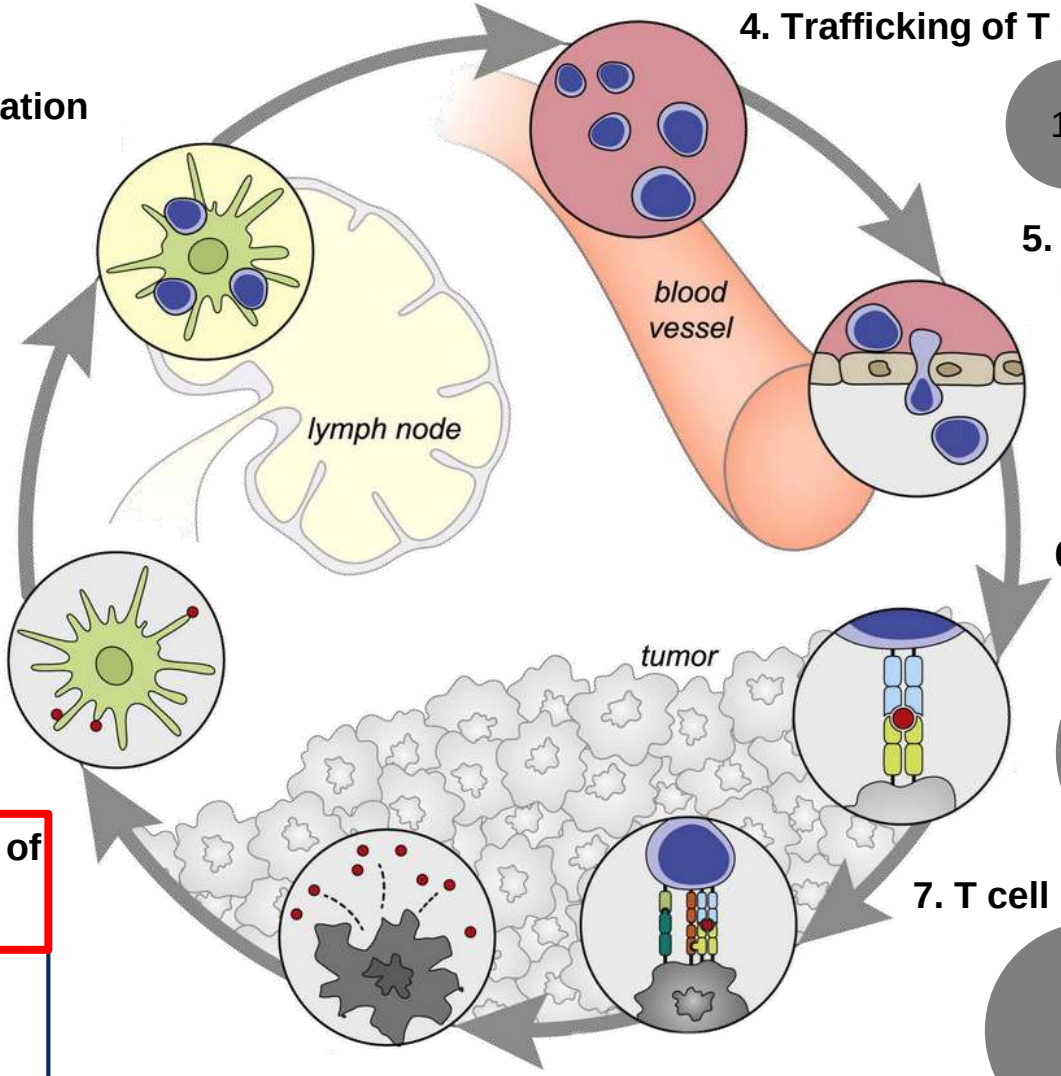
26 12

The bubble contains # of trials in -
- Phase I
- Phase II
- Phase III

Note - Trials may test more than 1 agent

Chen and Mellman Immunity, 2013, 39:1-10

Future Directions in Immuno-Oncology



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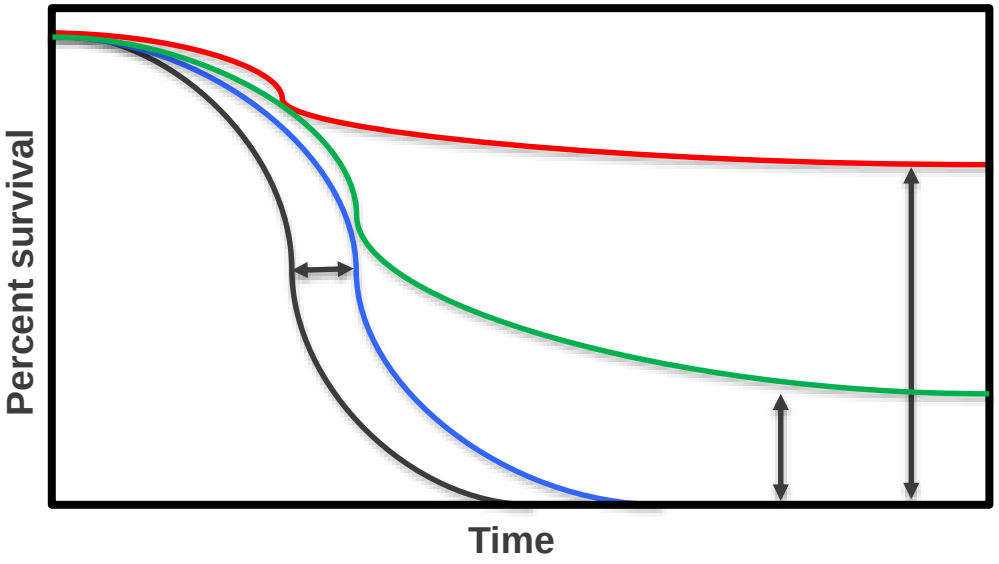
Chen and Mellman Immunity, 2013, 39:1-10

Immune response and chemotherapy

Drug	Effect on immune system
Taxanes	• Enhances T cell and NK cell function • Increases recruitment of TIL • Increase efficacy of immuno-stimulatory agents
Doxorubicin	• Induces immunogenic cell death • Increases proliferation of CD8 T cells • Stimulates antigen presentation by DCs • Stimulates MCP1 and M6PR
Cyclophosphamide	• Induces immunogenic cell death • Suppresses Treg inhibitory functions and restores the proliferative capacity of effector T cells and NK cell cytotoxicity
Gemcitabine	• Reduces the number of myeloid suppressor cells • Increases the antitumor activity of CD8(+) T cells and activated NK cells
Oxaliplatin	• Induces immunogenic cell death • Increases MHC I complex • Inhibits PD-L2

Kono et al. Cell Death and Disease 2013

Summary and Future Directions



Chemotherapy

Targeted therapy

Immune checkpoint therapy

⇒ long lasting responses
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Combination therapy

⇒ increase in response rate
⇒ increase in efficiency

Immunhistochemistry

- Deparaffinization

- Antigen Retrieval / Microwave treatment (proteases, pressure cooker, etc,)

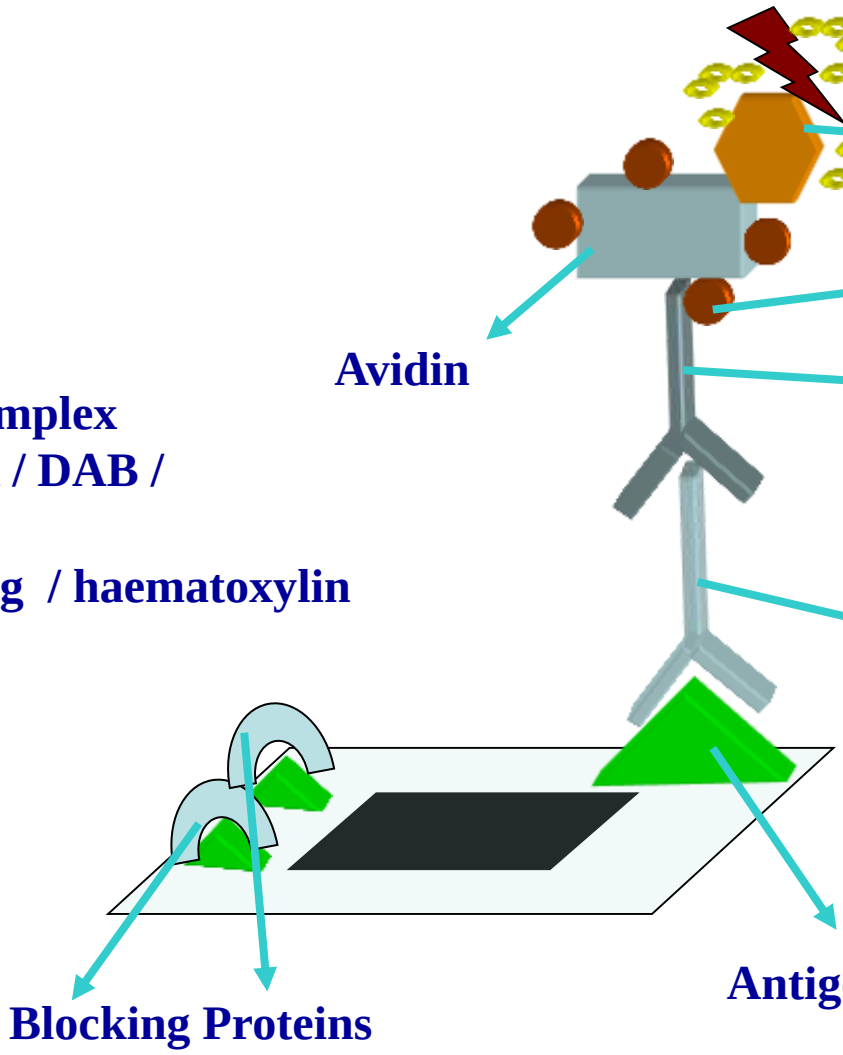
- Blocking Serum

- Primayr AB

- Secondary AB

- Avidin - Biotin - Complex
-Peroxidase Reaction / DAB /

- Backgorund staining / haematoxylin
(Nuclei are blue)



The Nobel Prize in Physiology or Medicine 1984

Niels K. Jerne

Georges J.F. Köhler

César Milstein

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein *"for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"*.

50,297 80 éves férfi

Anamnézis:

Strumektomia, Diabetes Mellitus II. típus

Parkinson bet. Katarakta (opus)

Stroke

Agyi atrophia, Demencia

Ösophagusfekély

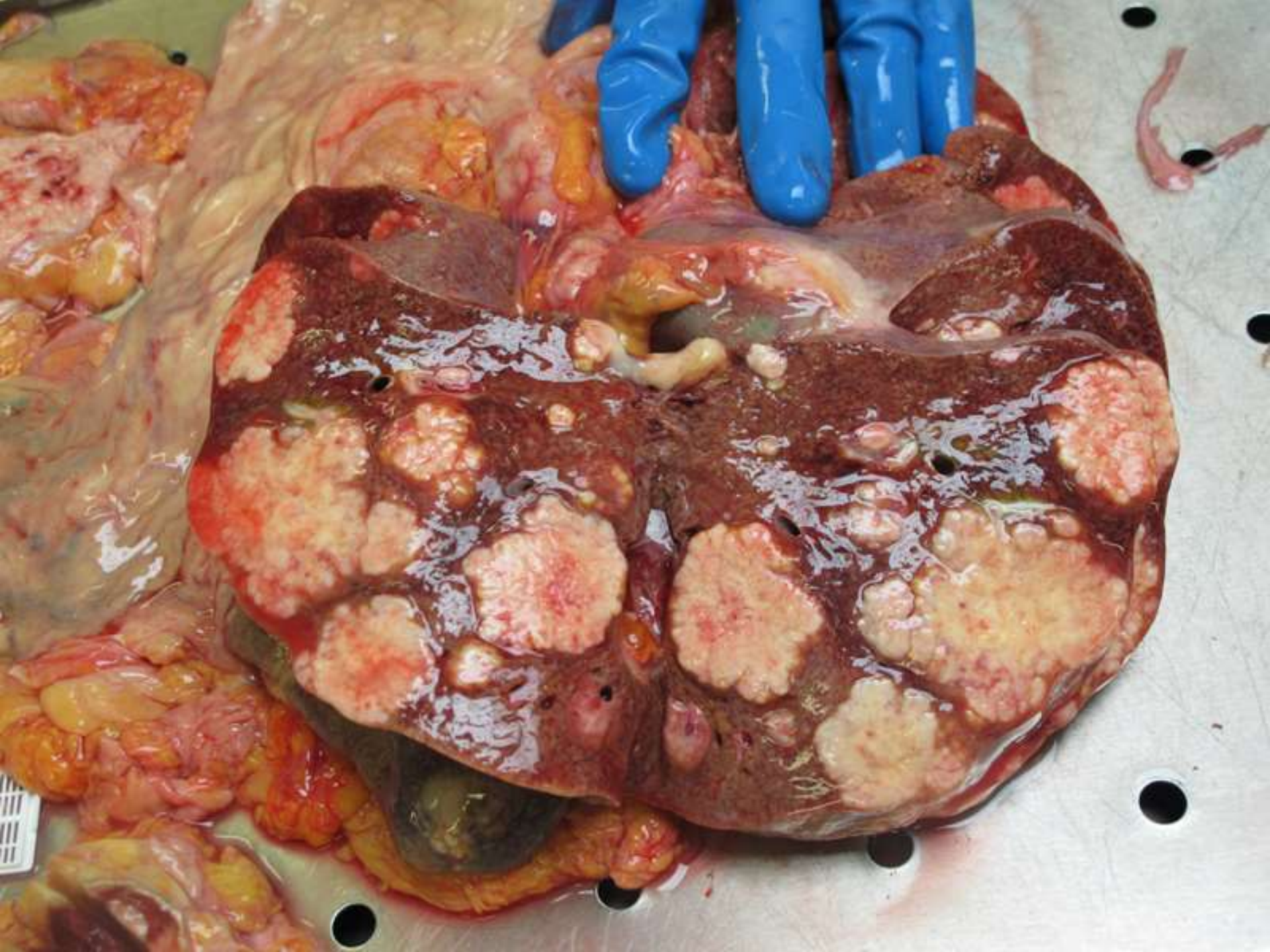
Hospitalizáció bronchitis miatt

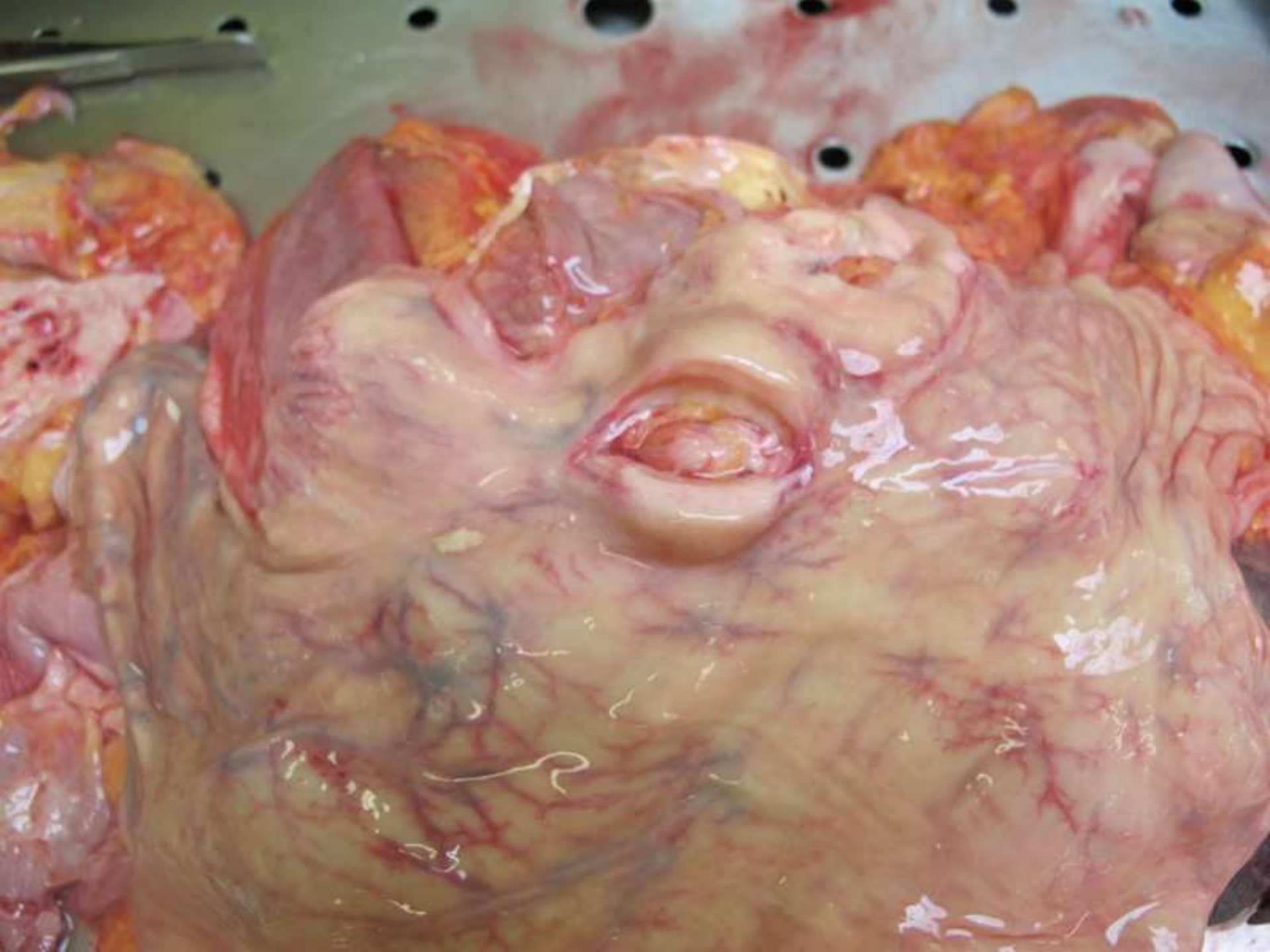
Felvételkor: Hypoglikémia, Exsiccatio

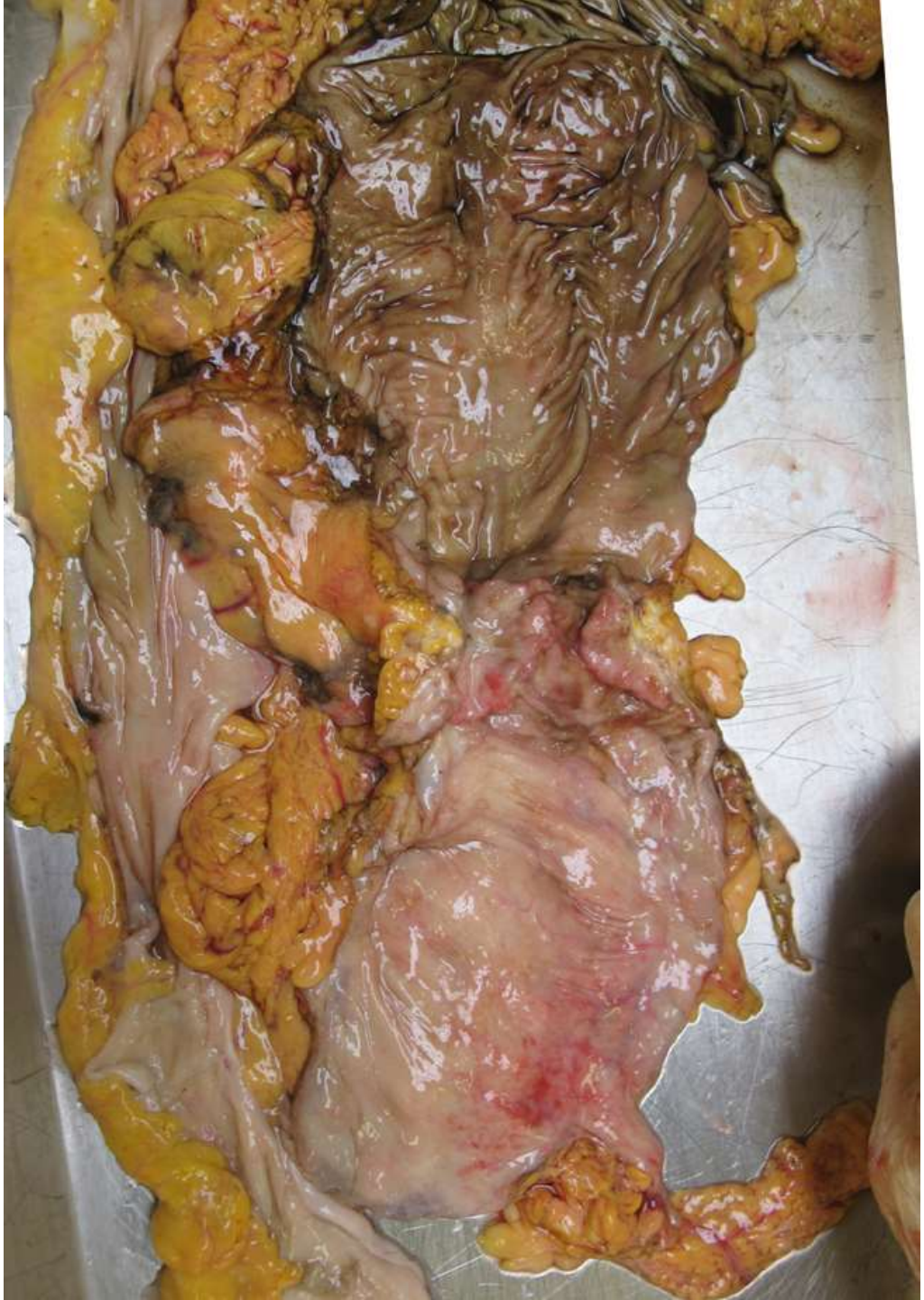
Gastroskopia: szövettan: **gyomorrák**

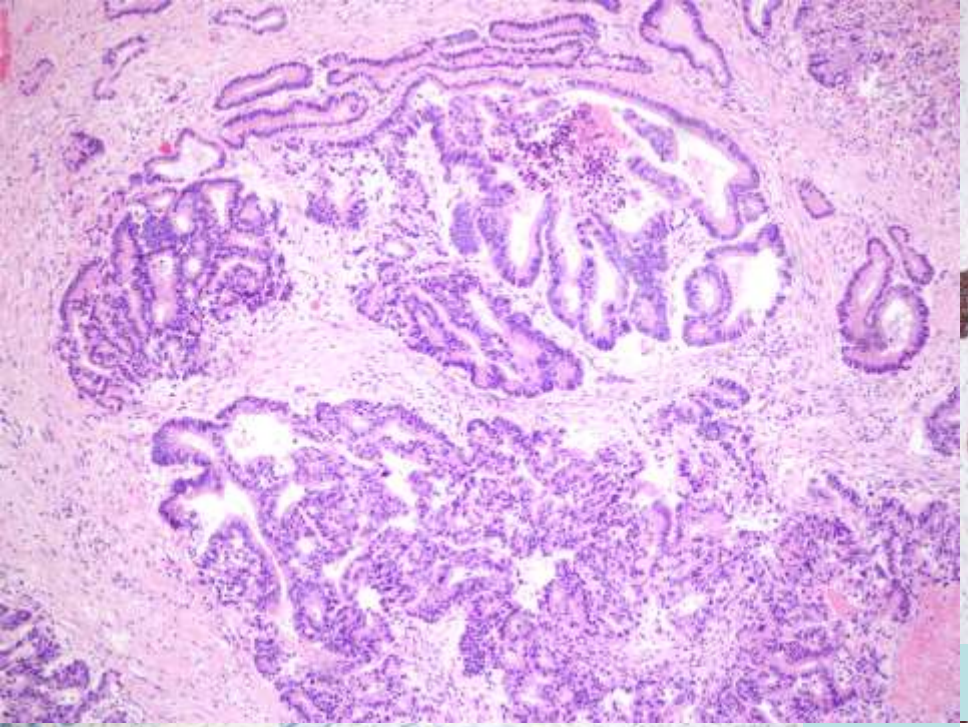
UH: májmet. asp. Citologia, FNAB : kolorektalis cc. Met. ??? Primer Tumor ???

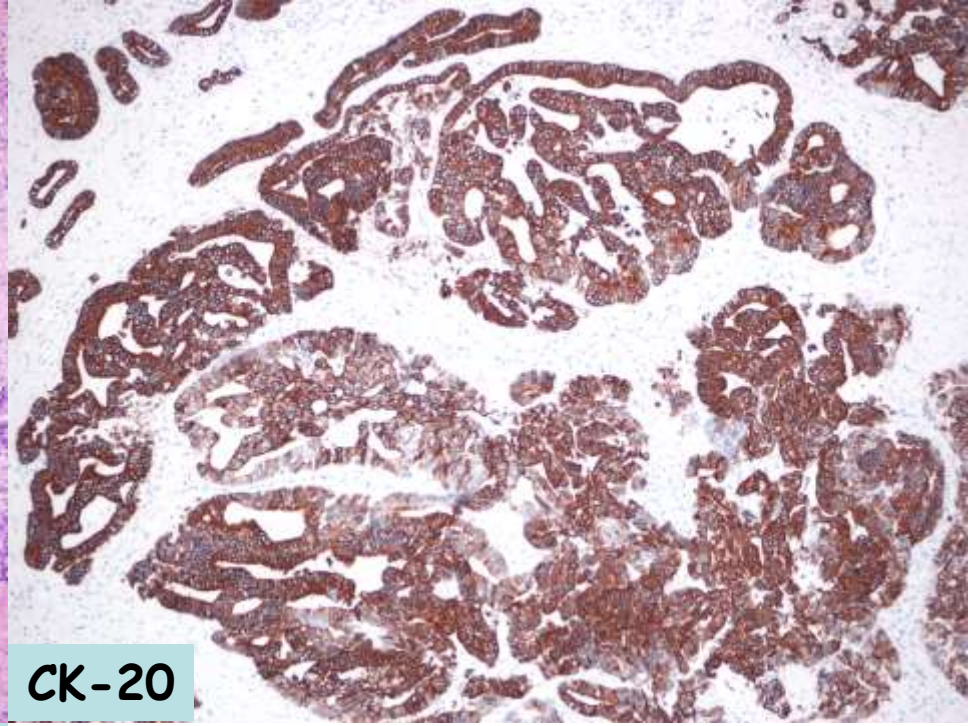
Gravis Anémia - Transfusiók - ext: tumoros kachexia

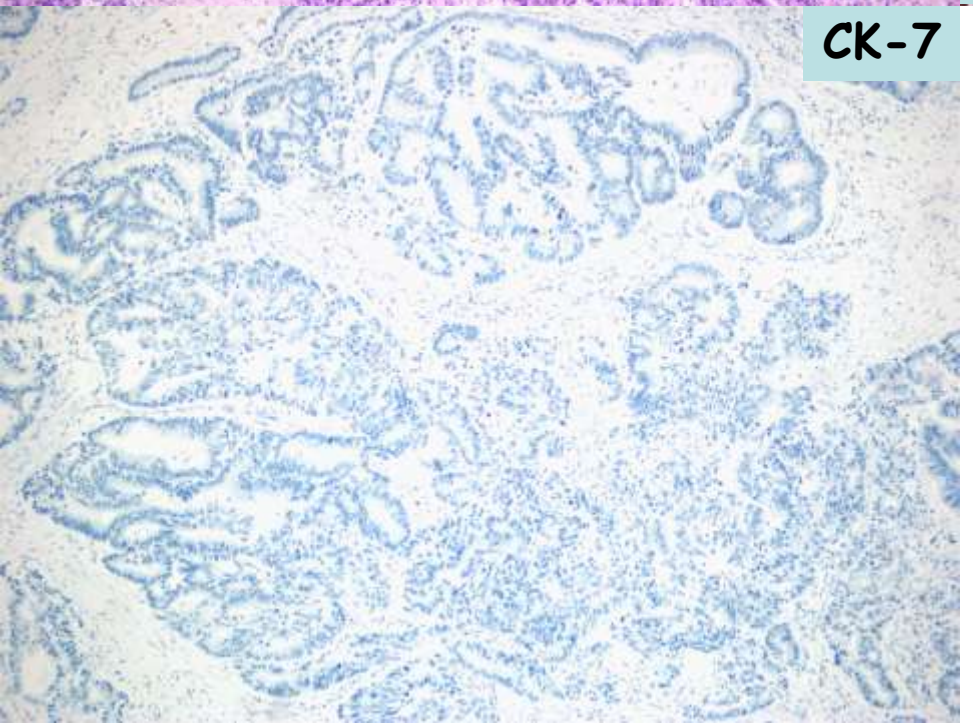




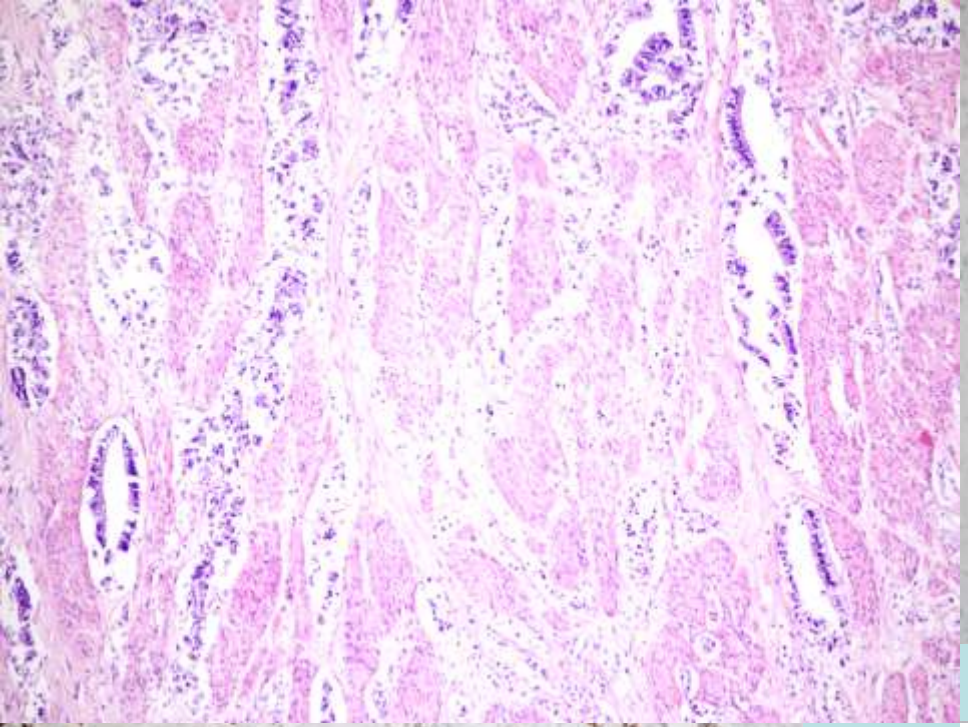


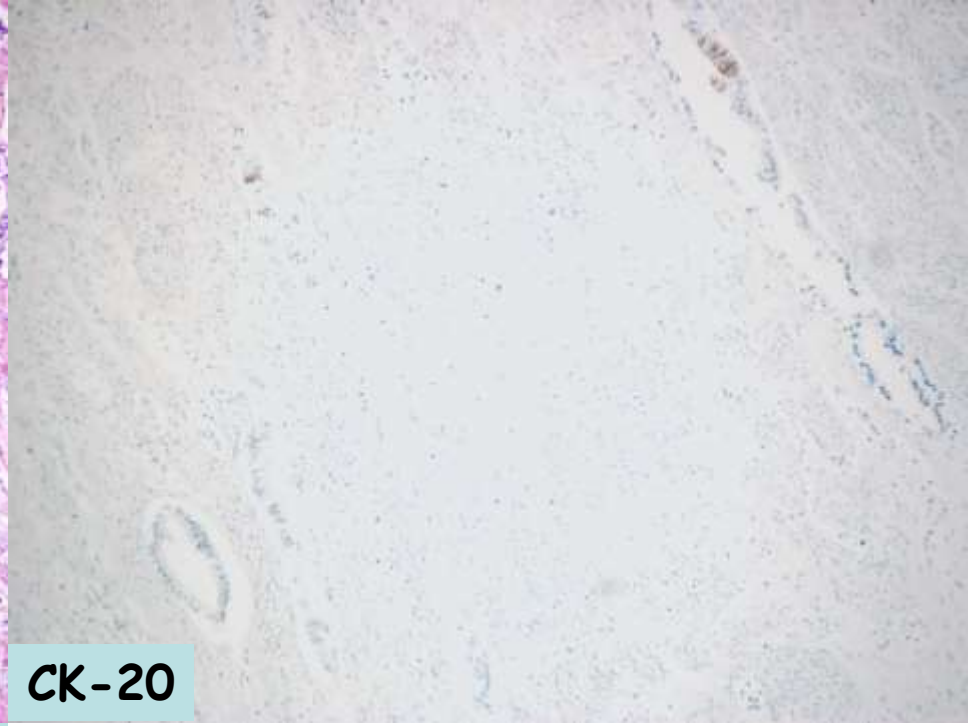






Sigma cc.

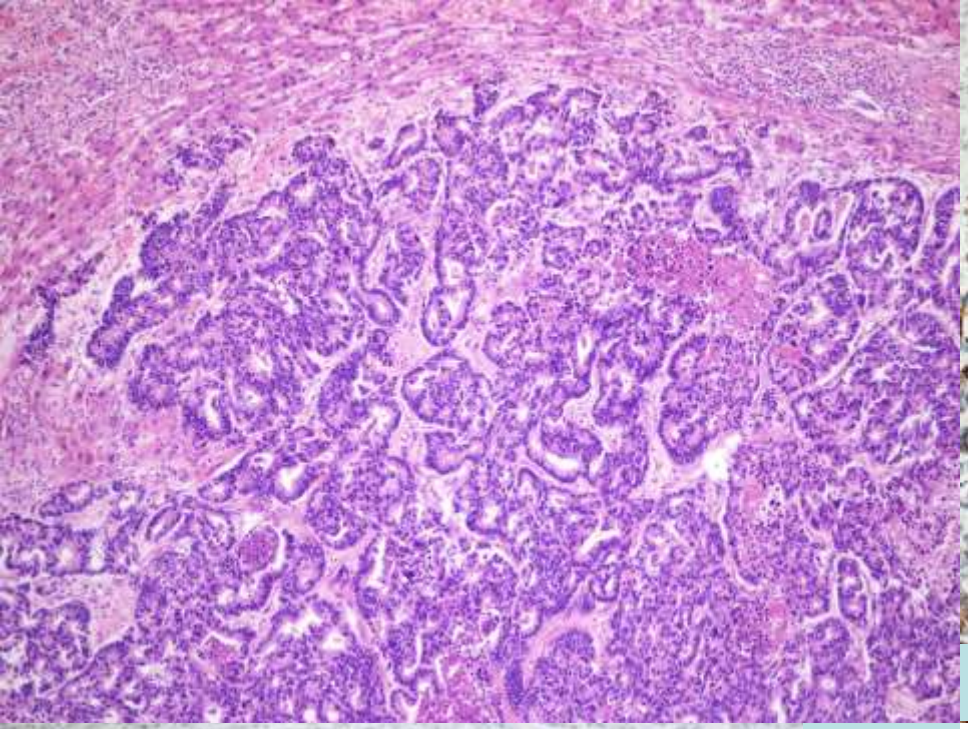


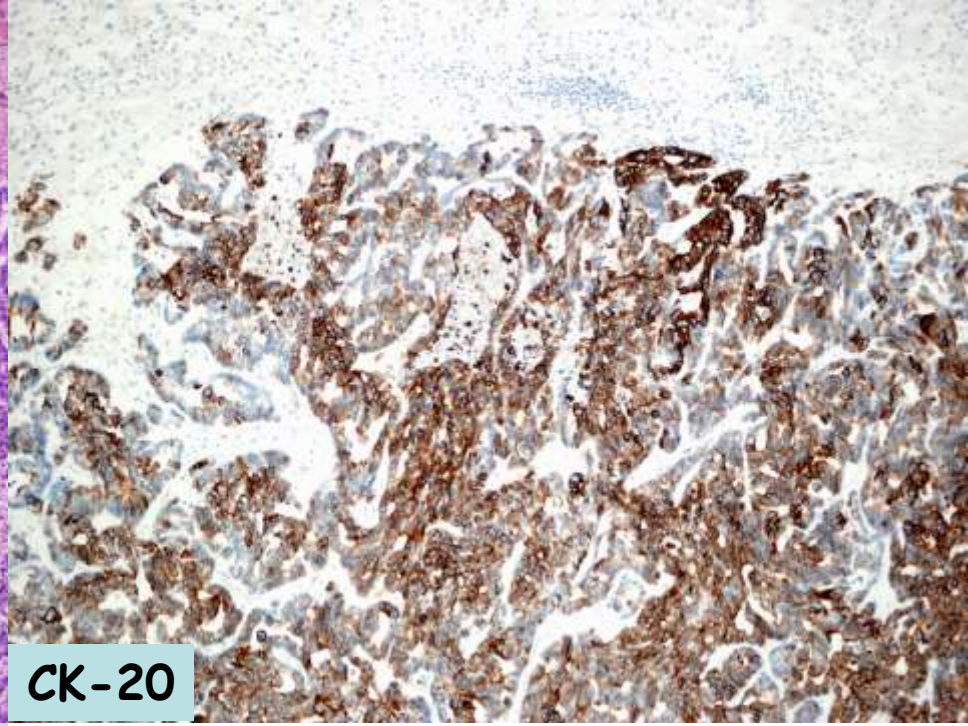


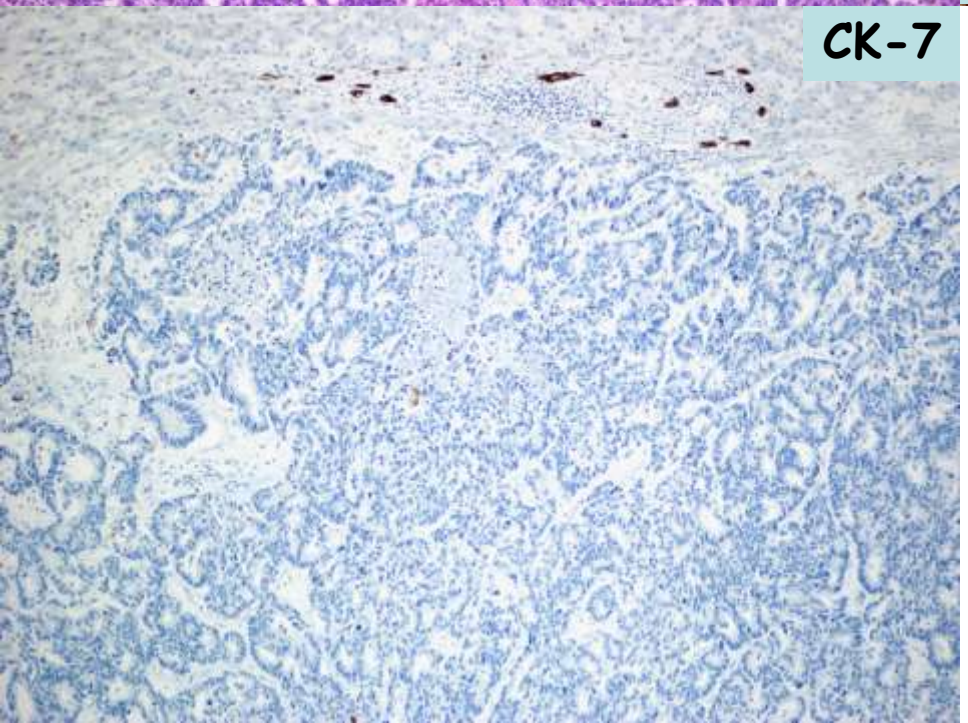
CK-20

CK-7

gyomor cc.







MÁJ MET.

IHC vizsgálatból következik:
A májmetastasist a vastagbélrák adta.

I. Típusú túlérzékenységi reakció

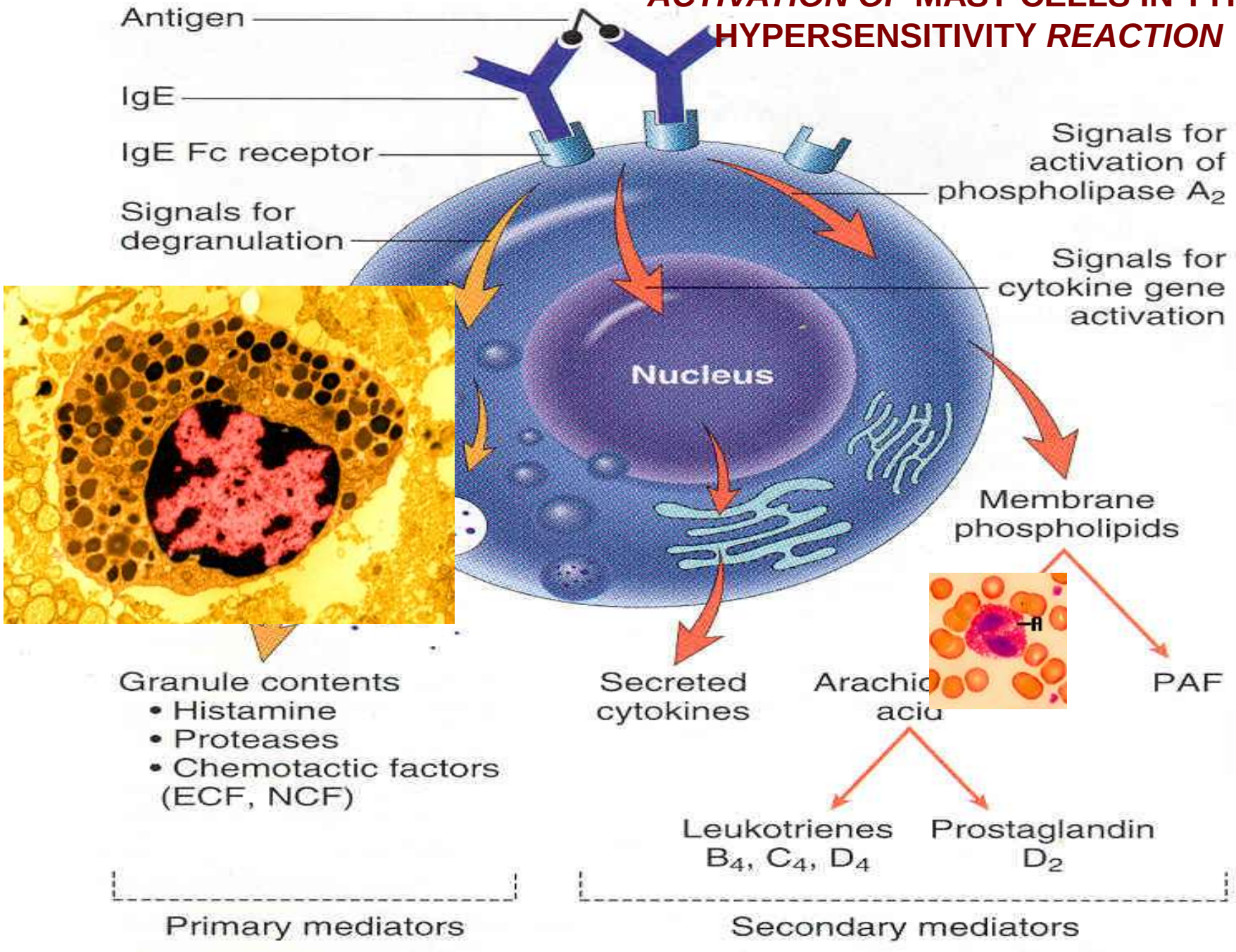
első antigén expozíció

(hízósejt, bazofil leukocita FcεR)

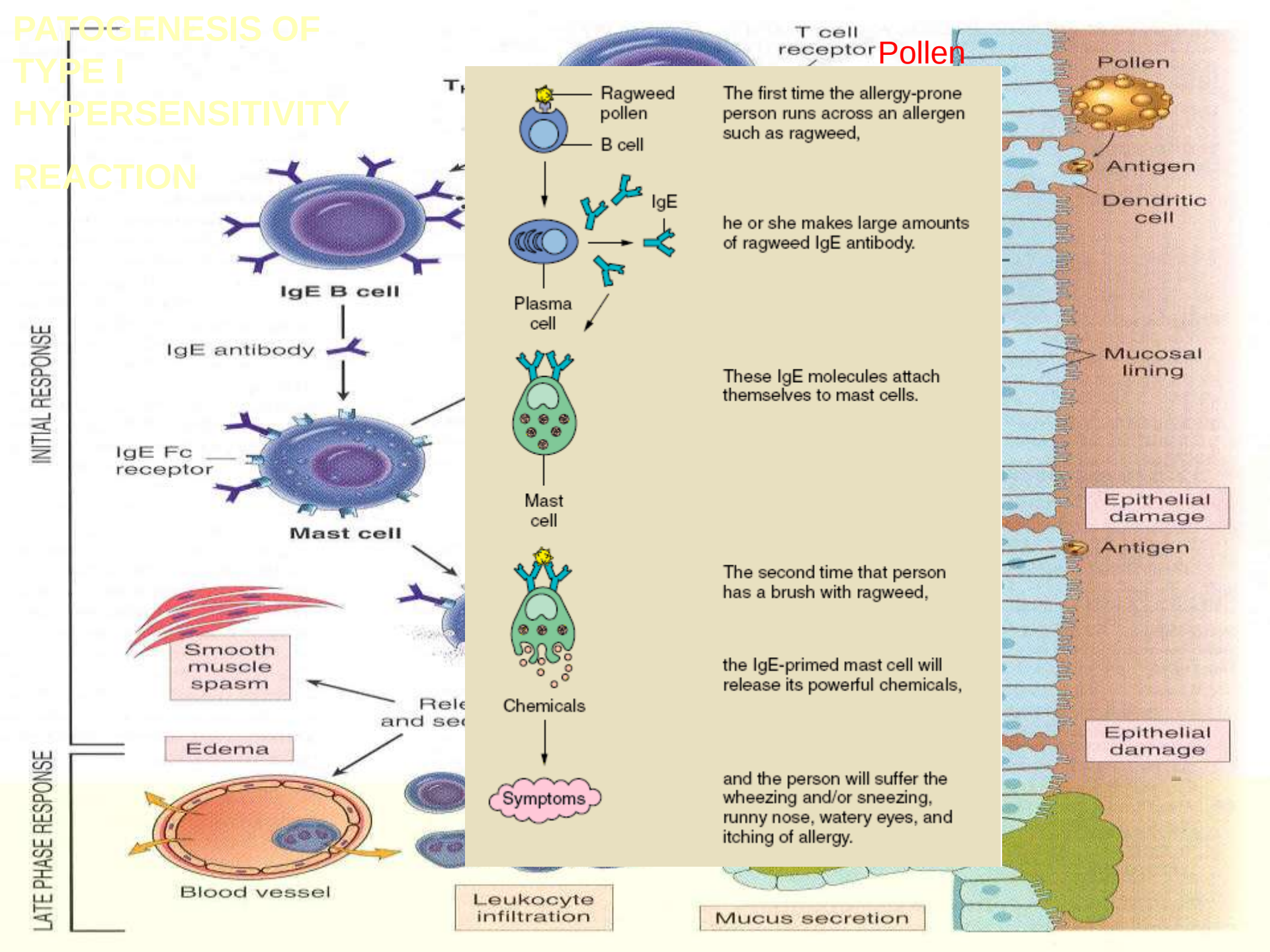
DEGRANULÁCIÓ

LTB4	histamin	hisztamin
Kemotaktikus faktorok	PAF	LTD4
Cytokinek	PGE_2	PE
	LTD4E4	PAF
Kemotaxis/exsudatio	vasodilatatio érpermeabilitás nő	simaizom-spazmus

ACTIVATION OF MAST CELLS IN TYPE I HYPERSENSITIVITY *REACTION*

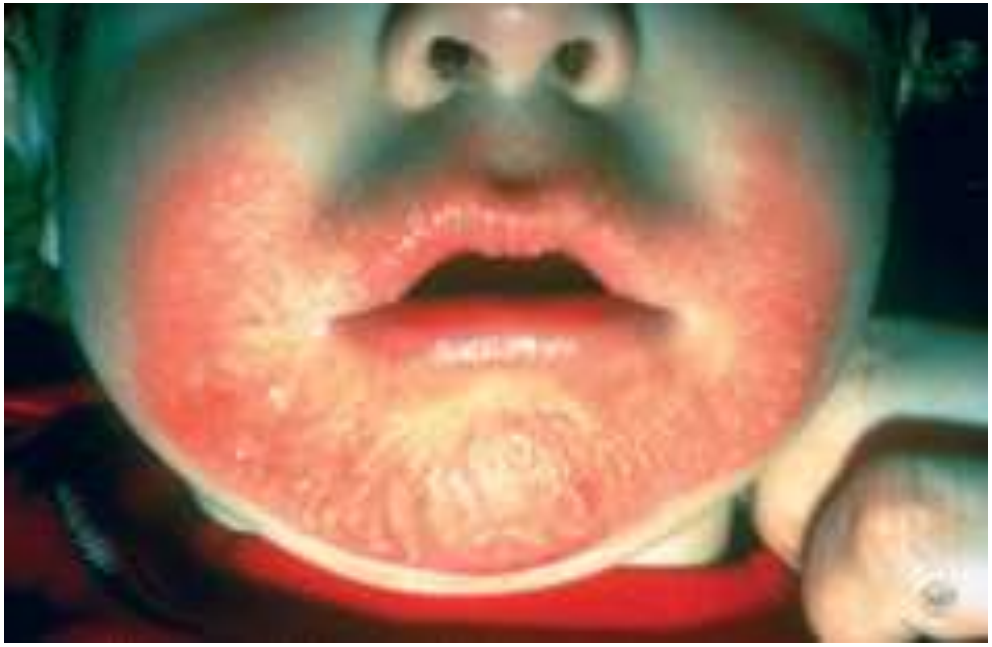


PATOGENESIS OF TYPE I HYPERSENSITIVITY REACTION

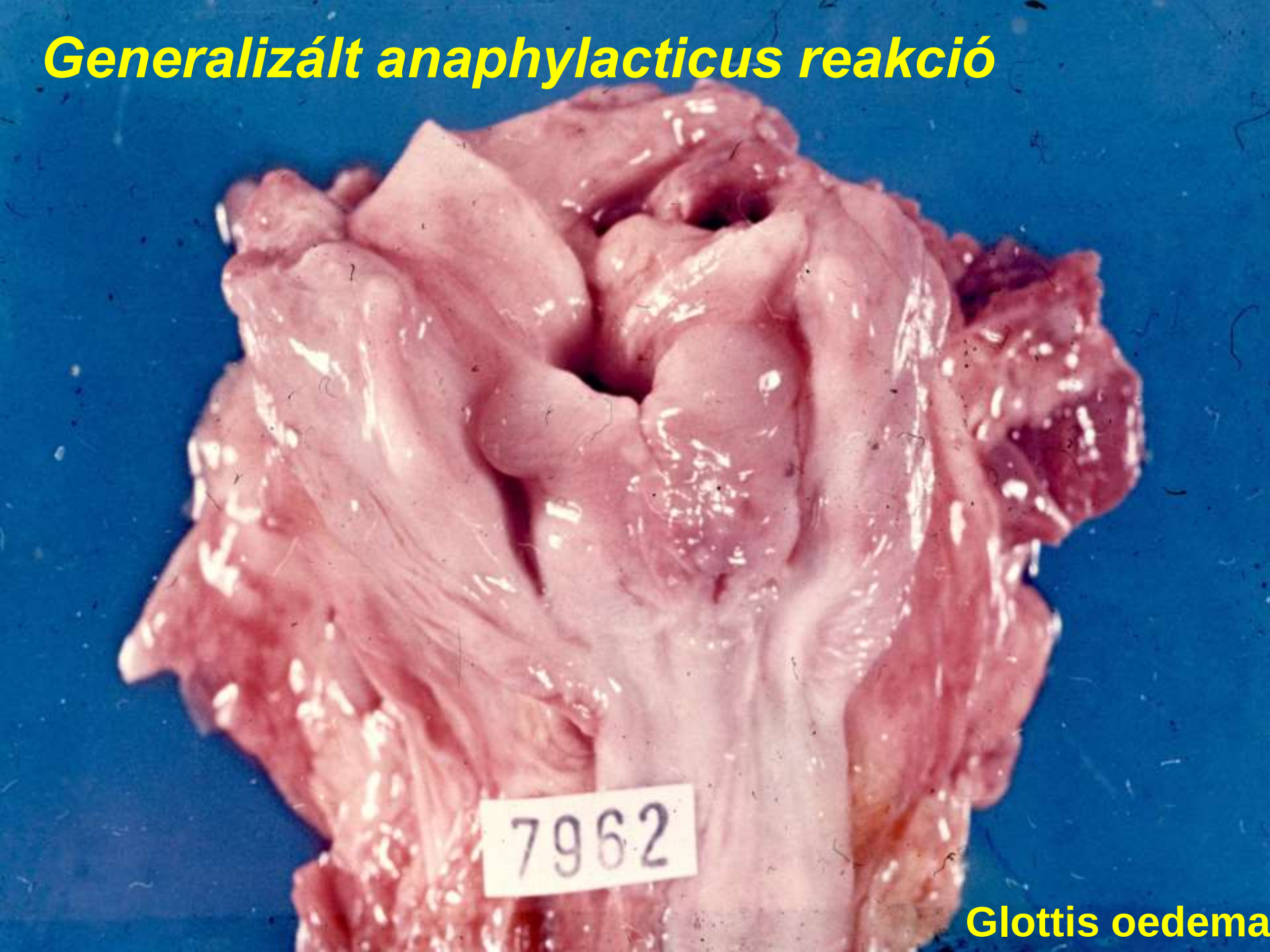


Allergia

- Lokális: rhinitis, asthma, conjunctivitis
  - bőr: urticaria, ekzema, angioneurotikus oedema,
- Szisztémás: anaphylaxias shock
- (adrenalin: simaizom relax, nincs vasospazmus)



Generalizált anaphylacticus reakció



Glottis oedema

"You are allergic to strawberries, caffeine and bad air. You must avoid these substances and find another planet to live on."

II. Típusú túlérzékenységi reakció

A. Komplement-függő reakció

Célsejt antitest-kötése

C5-9 C1423

Komplement-függő sejtpusztulás

B. Antitest-függő celluláris citotoxicitás

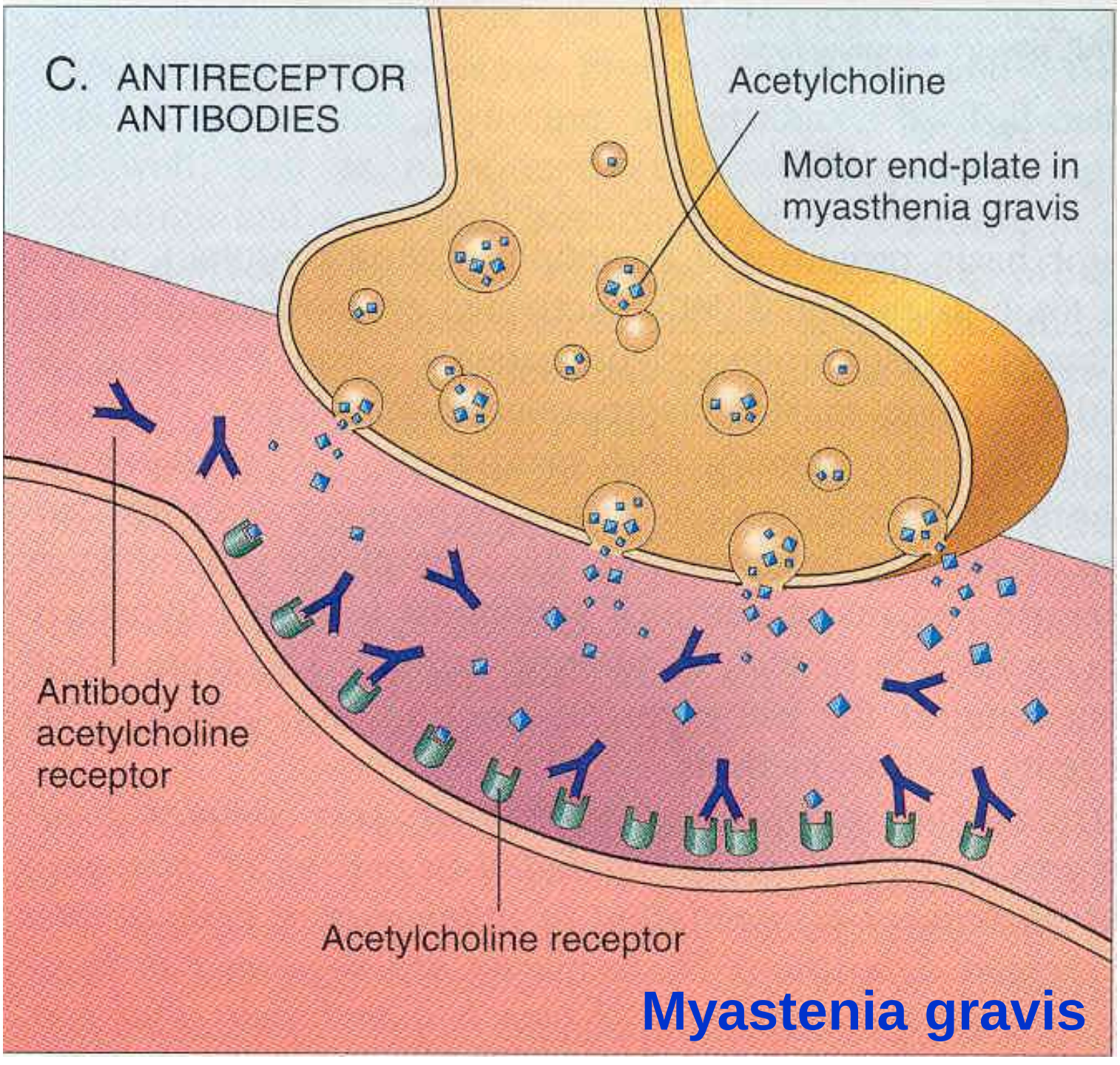
Célsejt antitest-kötése (Fc expozíció)

FcR+ effektorsejt-kapcsolat (NK sejt, makrofág)

Célsejt pusztulás

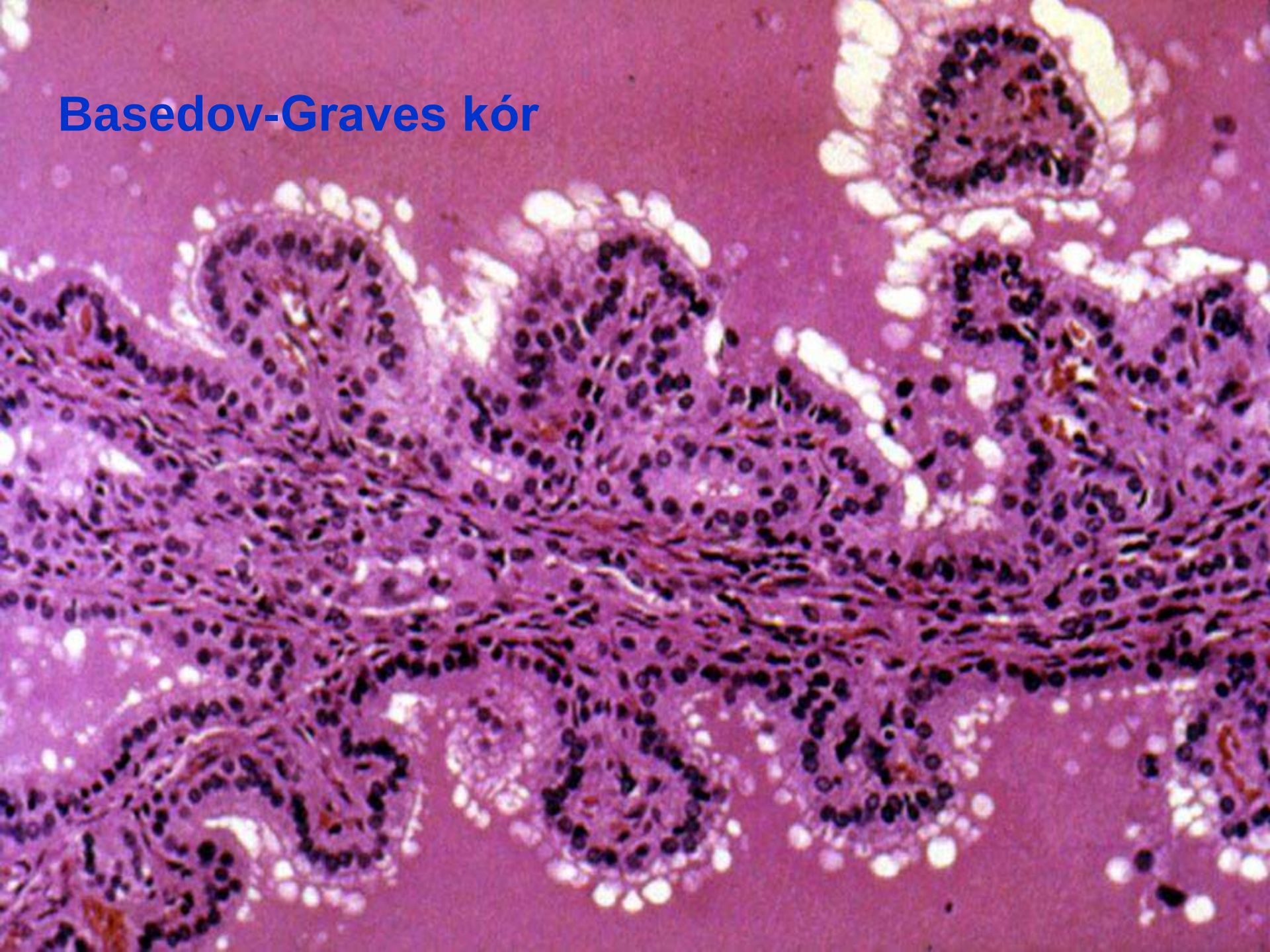
C. Receptor-ellenes antitestek által mediált folyamatok

Anti-receptor-antitest termelődés

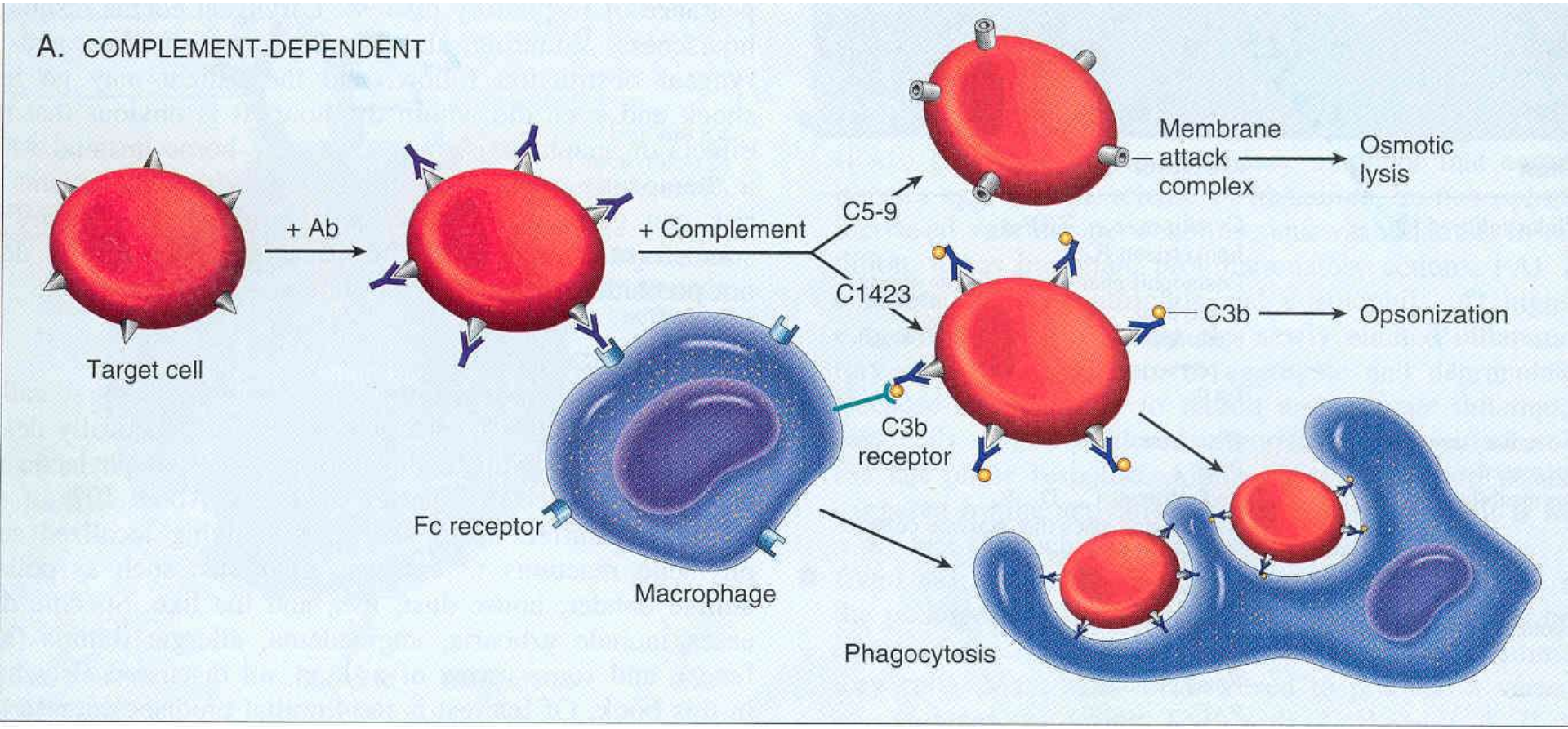


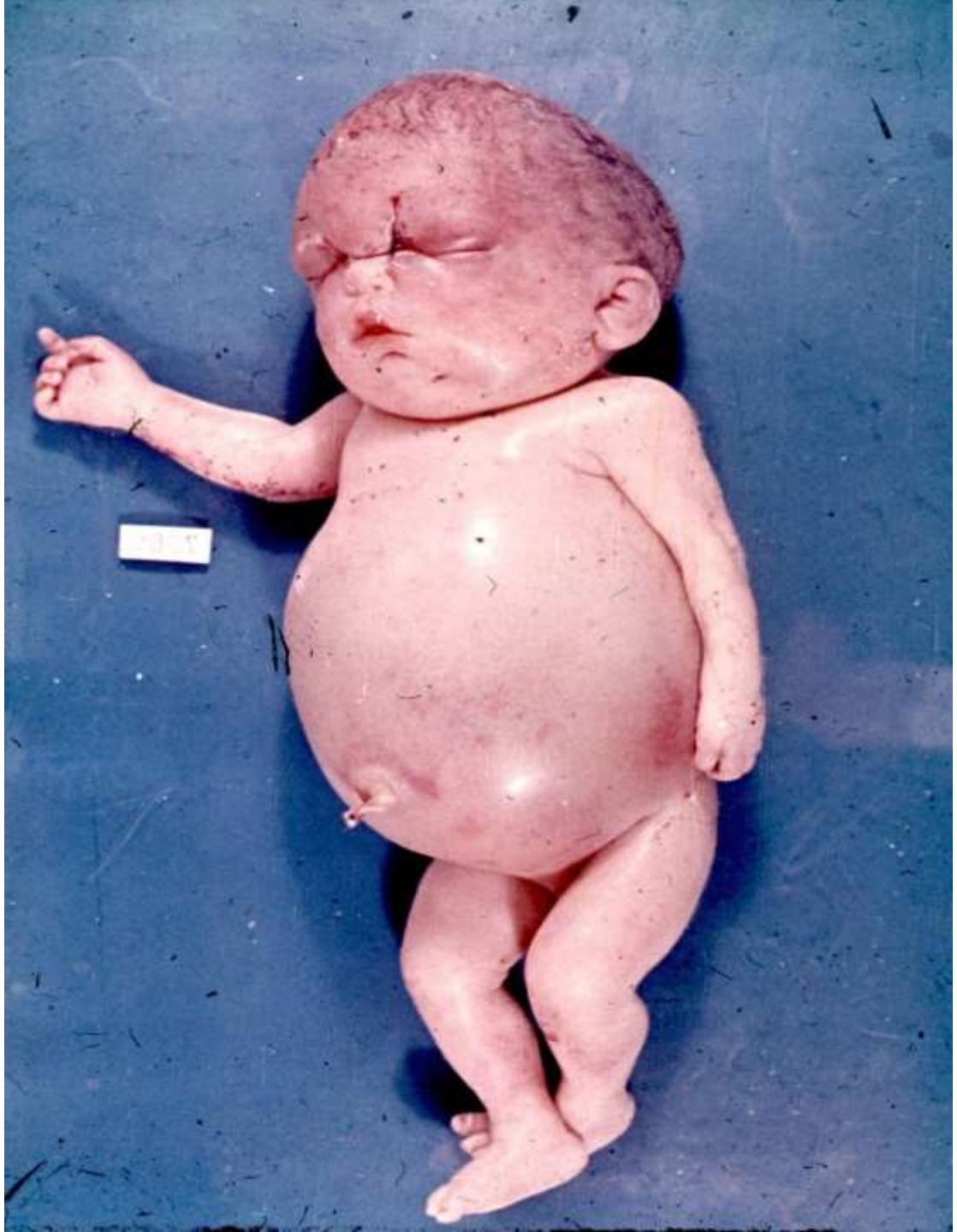
Myastenia gravis

Basedov-Graves kór



II-es típusú hypersensitivitási reakció (cytotoxicus)

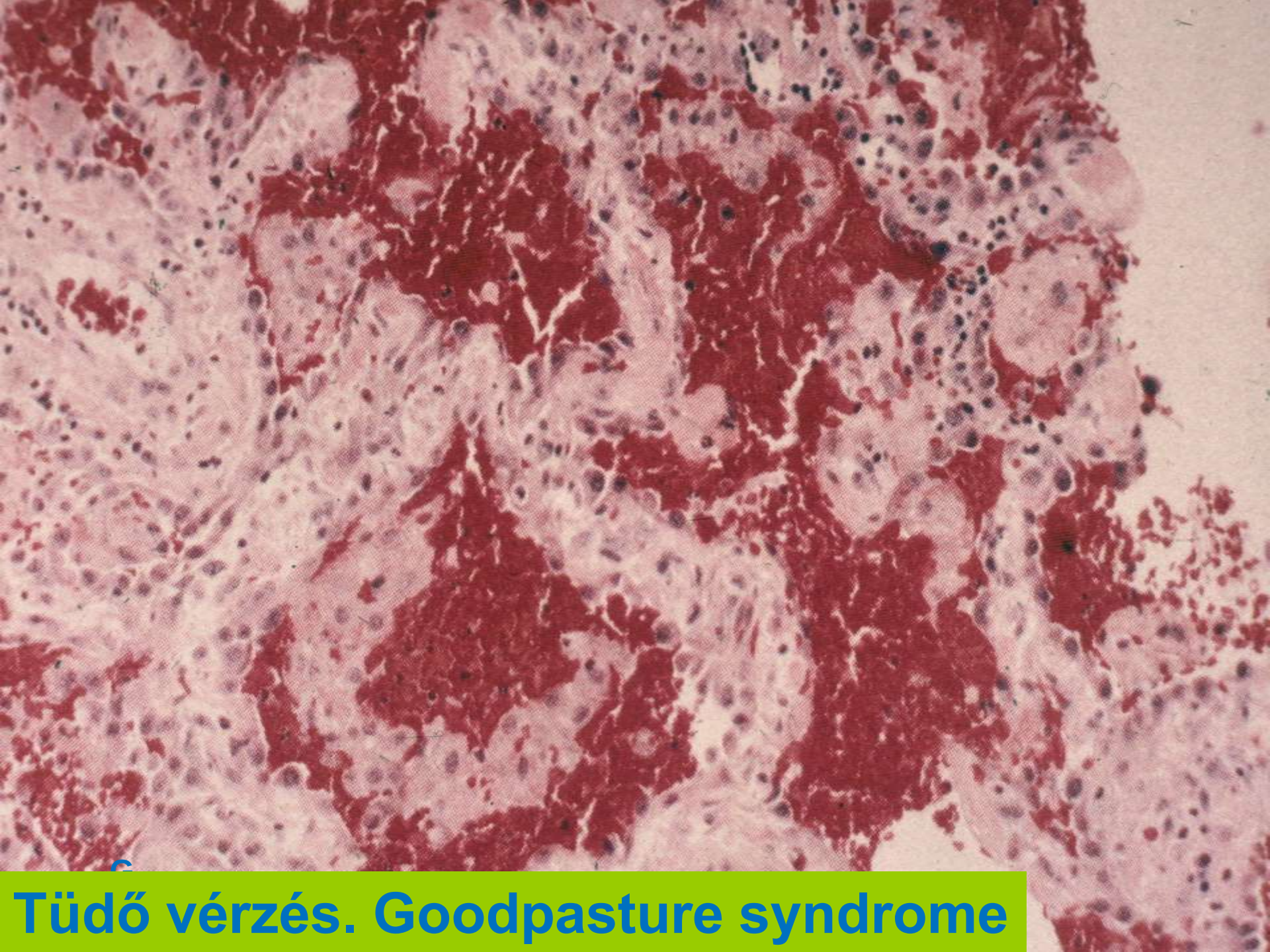




Hydrops foetus universalis

Rh incompatibilitás

(Parvovirus B 19 infectio)



Tüdő vérzés. Goodpasture syndrome

III. Típusú túlérzékenységi reakció

2. antigén-expozíció — antigén/antitest komplex keletkezés (keringés)

immunkomplex lerakódás
(vese, bár, savós hártyák, érfal)

vazodilatáció
oedema

neutrofil migráció
degranuláció

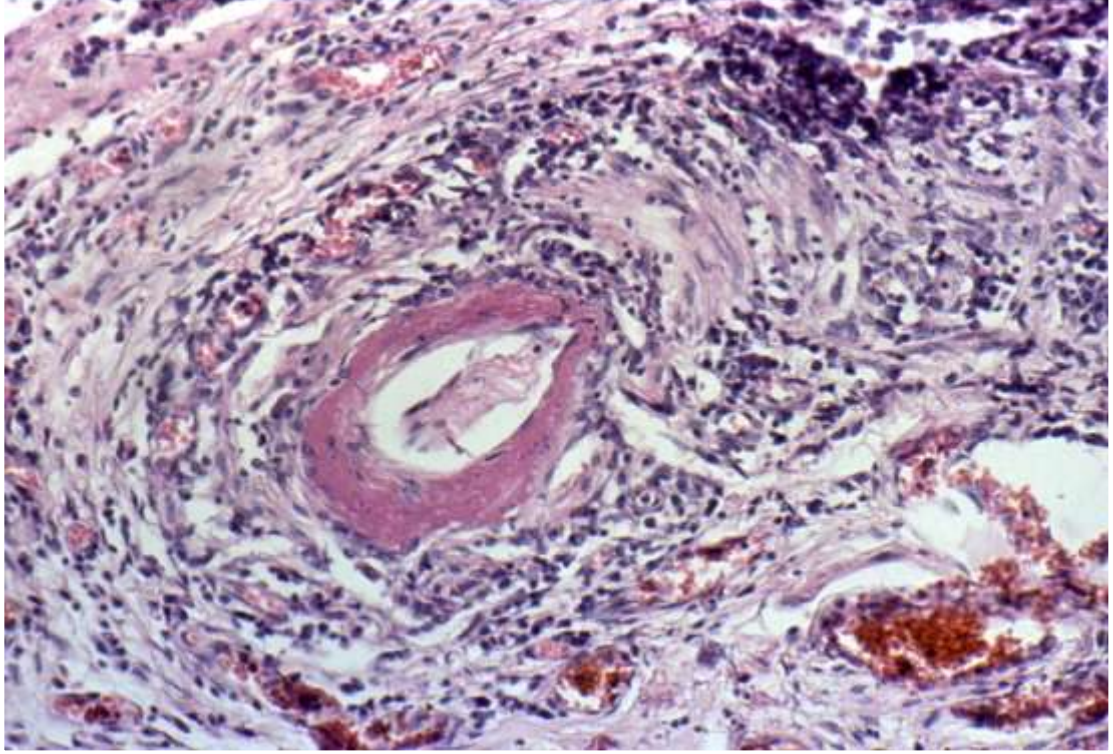
thrombocyta aggregáció
microthrombus
ischemia

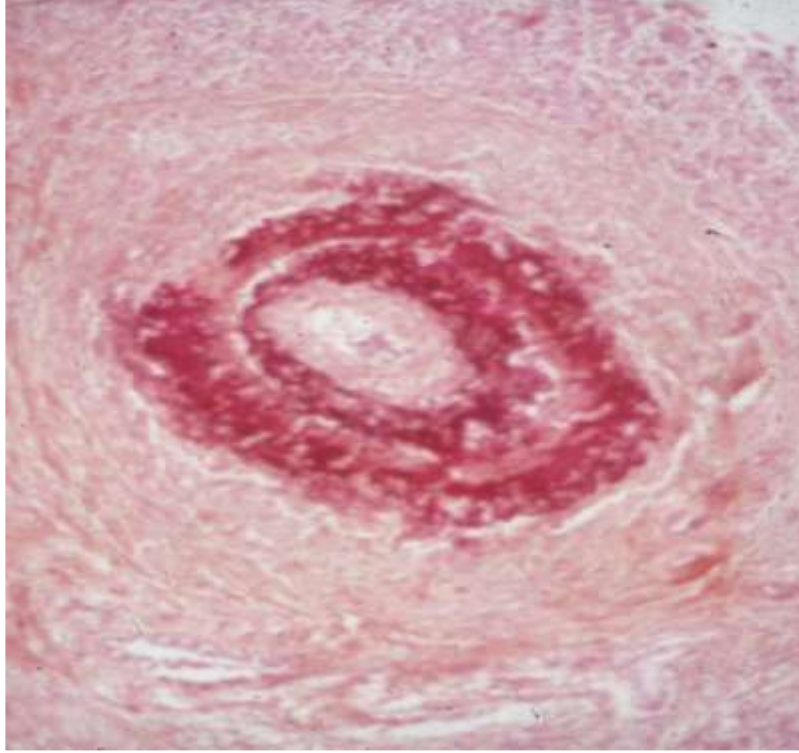
szövet-nekrózis

patomechanizmus

- Acut:
- AG/AT komplex (Se), lerakódás, gyulladás…..C3b (fagocitózis)C5b,6/7: kemotaxis, (gyulladás), C5-9membránattak komplex…sejtpusztulás

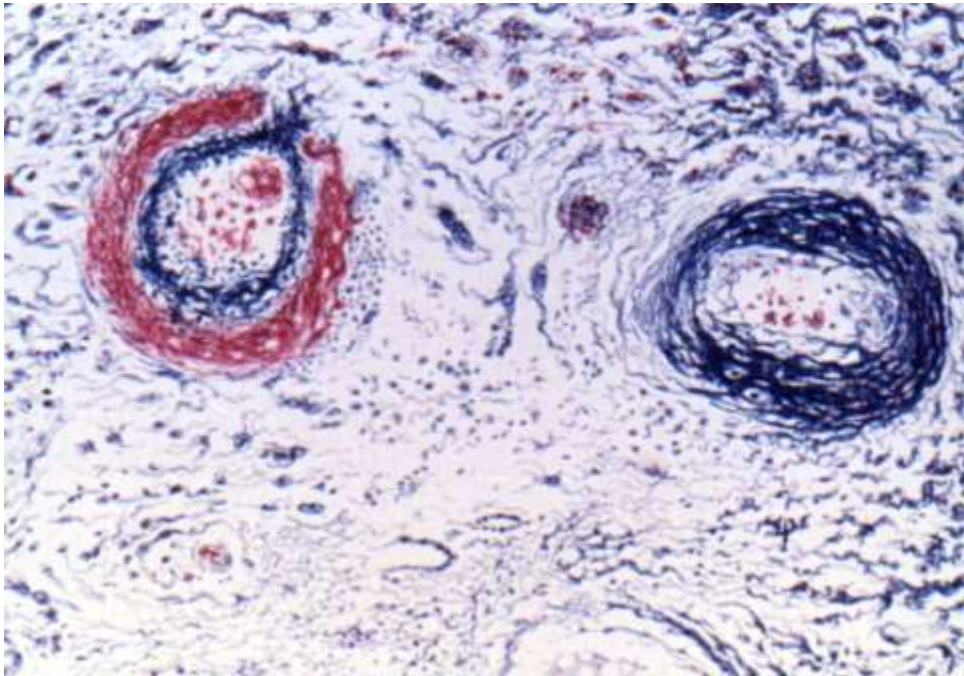
- Fibronoid érfal necrosis, vasculitis (neu)





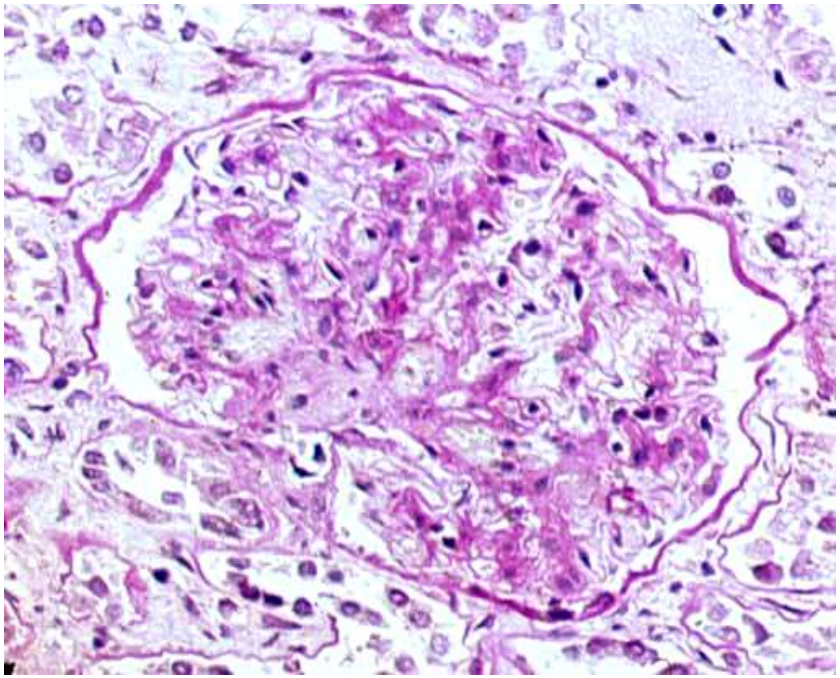
Az alapvető szövettani jelenség a:

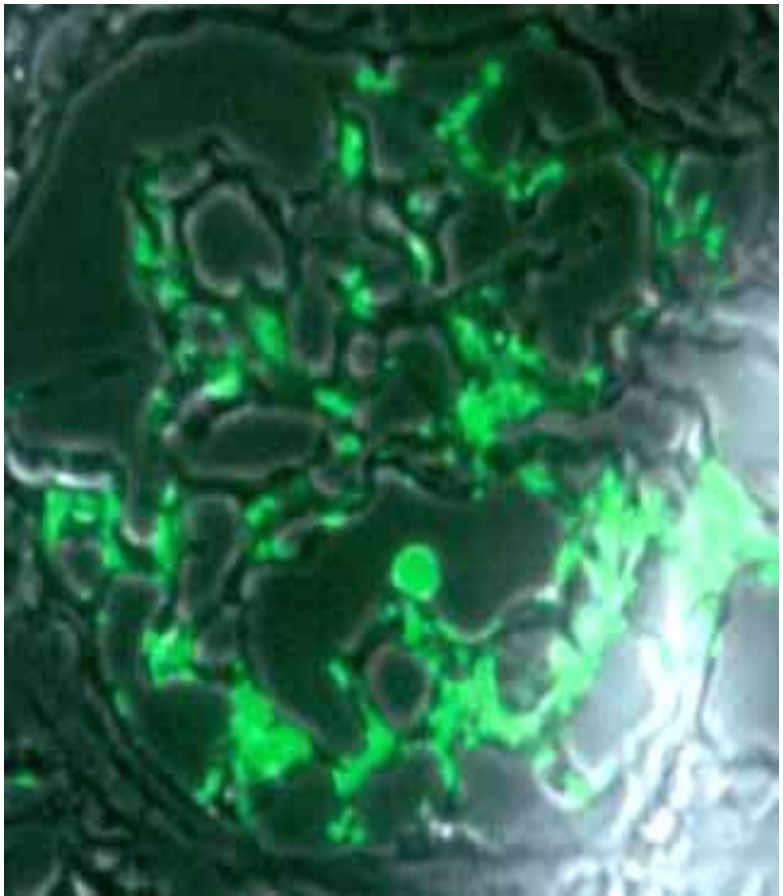
***necrotisáló* vasculitis**



II. patomechanizmus

- Chronicus: perzisztens antigén
- Okok: „autoimmun betegség”
- kigyóméreg elleni szérumok, egér anti-humán T sejt szérum, bakteriális streptokináz, iv. penicillin





IV. Típusú túlérzékenységi reakció

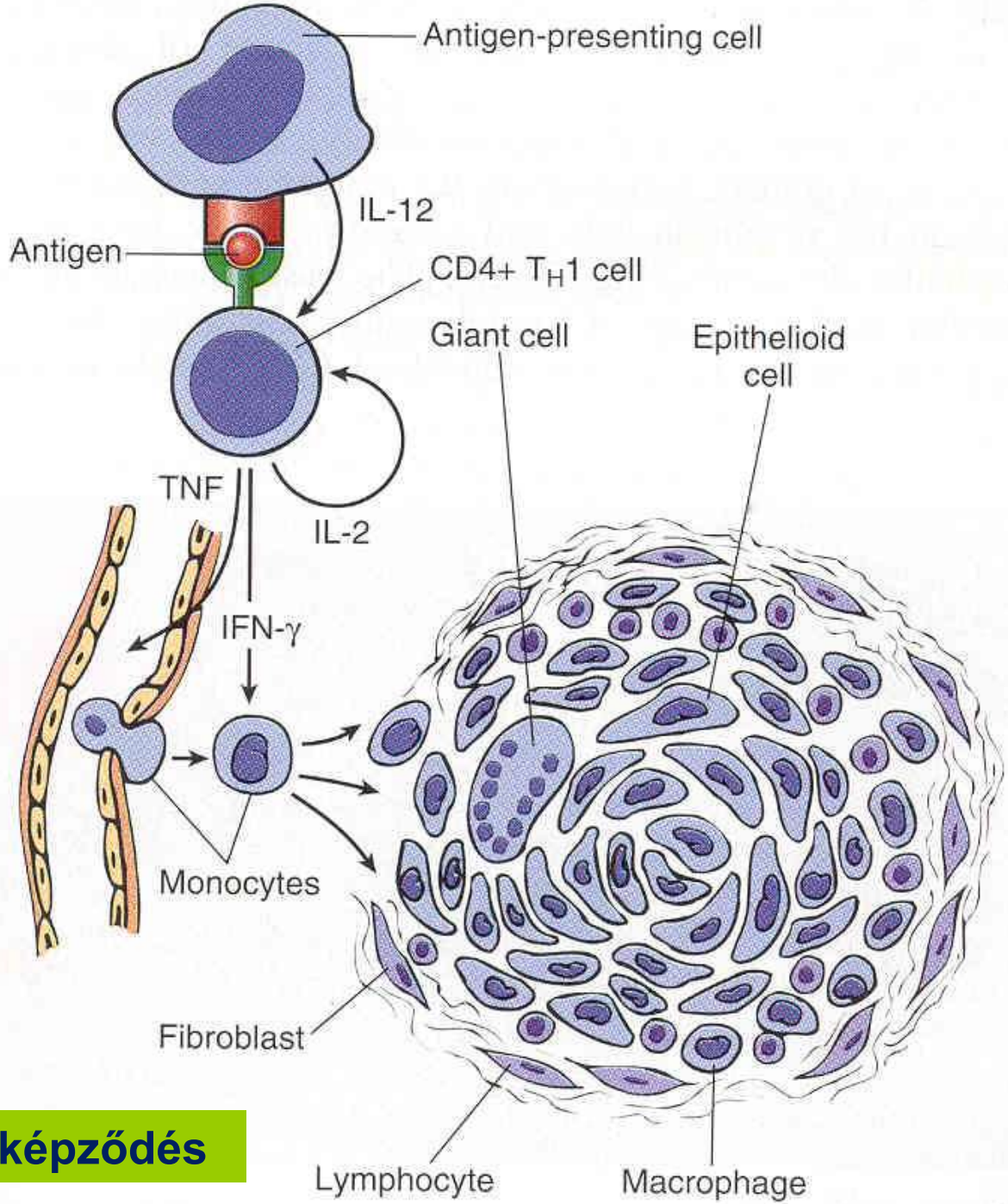
A. Késői típusú hypersensitivitás

2. antigén-expozíció — dendritikus sejt – T sejt kapcsolódás (IL-2, TNFα, IFNγ)

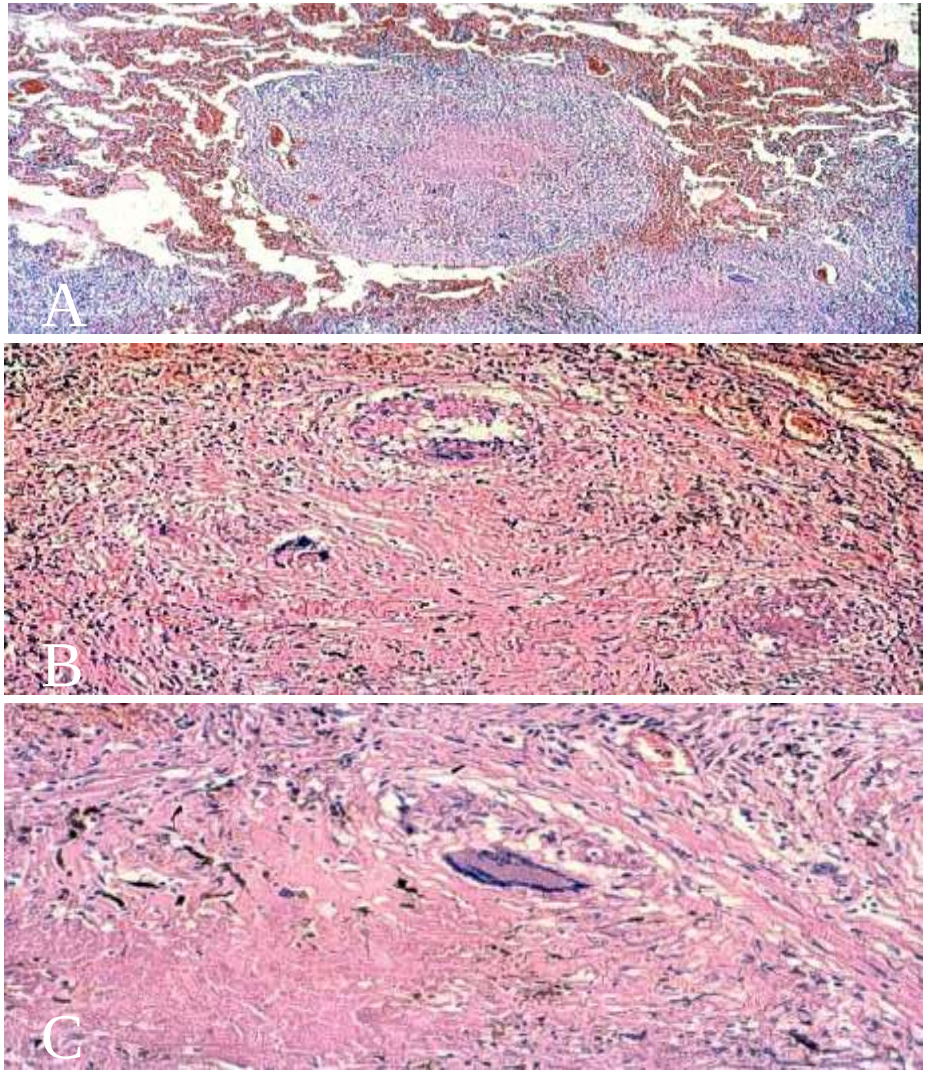
lymphocyta accumulatio — fibroblast-proliferáció érújdonképződés — makrofág-aktiválódás

B. T-sejt mediált celluláris cytotoxicitás

Idegen antigén-hordozó célsejt (vírus-fertőzött sejt, allograft)



Granuloma képződés

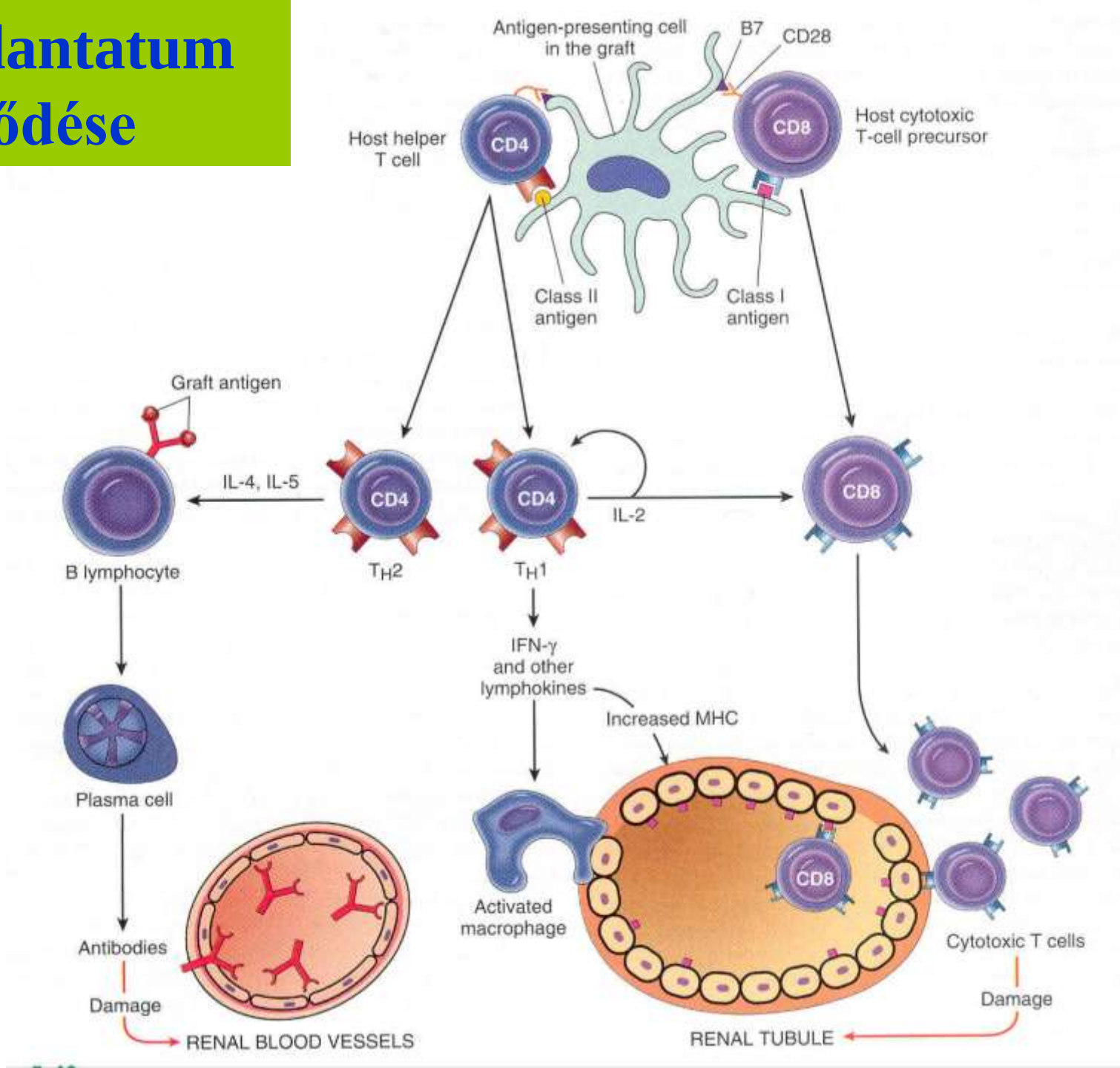


TBC-tüdő

Transplantatios patologia

- Host-versus graft: szervtranspl
- Graft-versus host (csontvelő trpl)

A transplantatum kilökődése



A TRANSPLANTÁTUM KILÖKŐDÉSE (REJECTIO, VESE)

HYPERACUT

perceken belül

(a recipiensben performált AT-ek

ACUT

hetek-hónapok hirtelen veseelégtelenség

therápia!!!

therápia resistens!!!

CHRONICUS

hónapok-évek

azotaemia

oliguria

hypertonia

ARTHUS-REACTIO

fibrinoid necrosis az érfalban

./ Cellularis

interstit. nephr. **II.-IV. h.r.**

(mononucl. oedema)

a tubularis epith. focalis necrosisa

Cyclosporin A toxicitás!!!

./ Vascularis

necrotisalo vasculitis

glomerulus necrosis

III. h.r. **a cortex a. thrombosisa**

subacut vasculitis (intima prolifer.)

érelváltozások

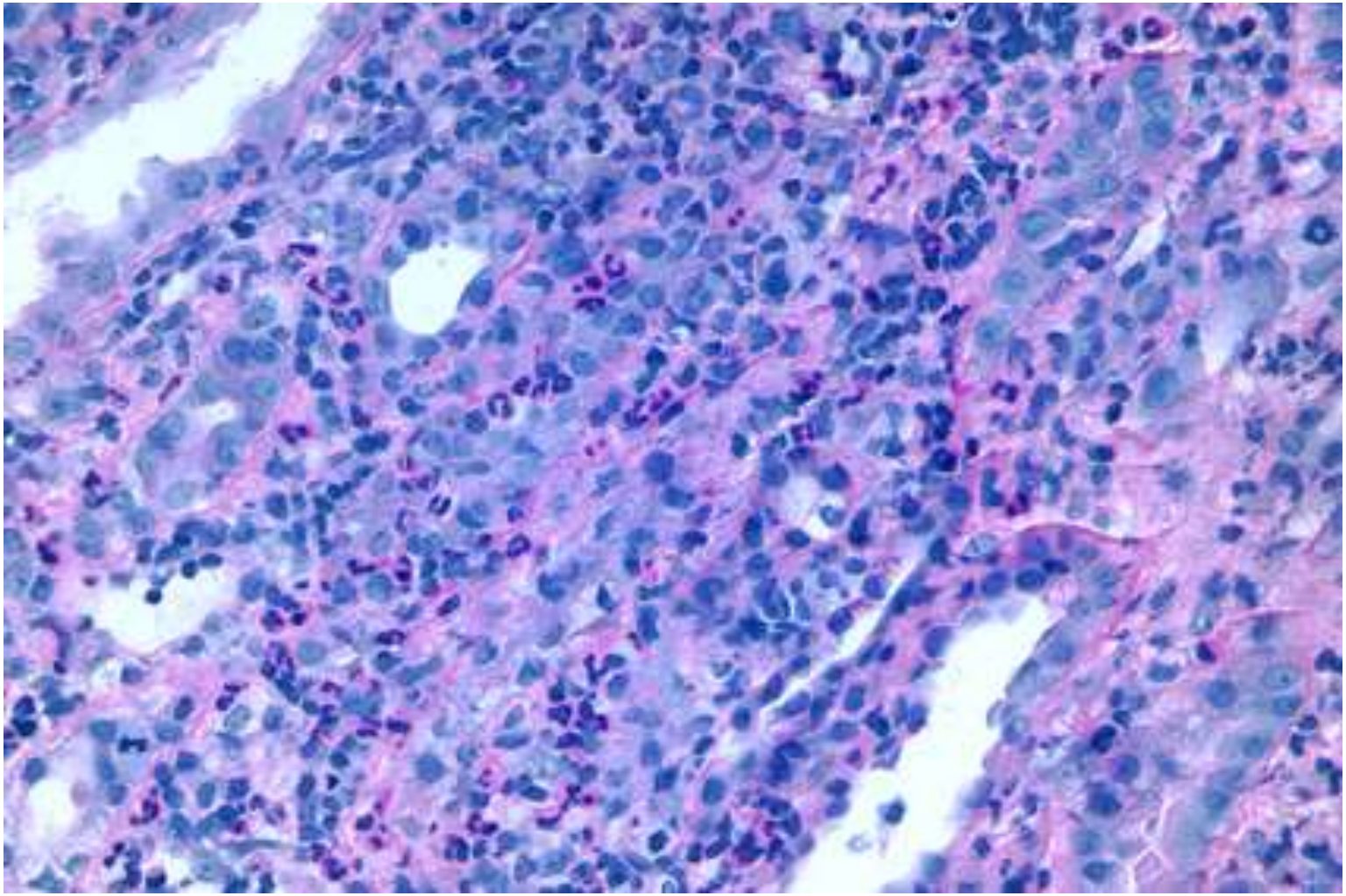
intimafibrosis **sec. ishaemia** →

↓

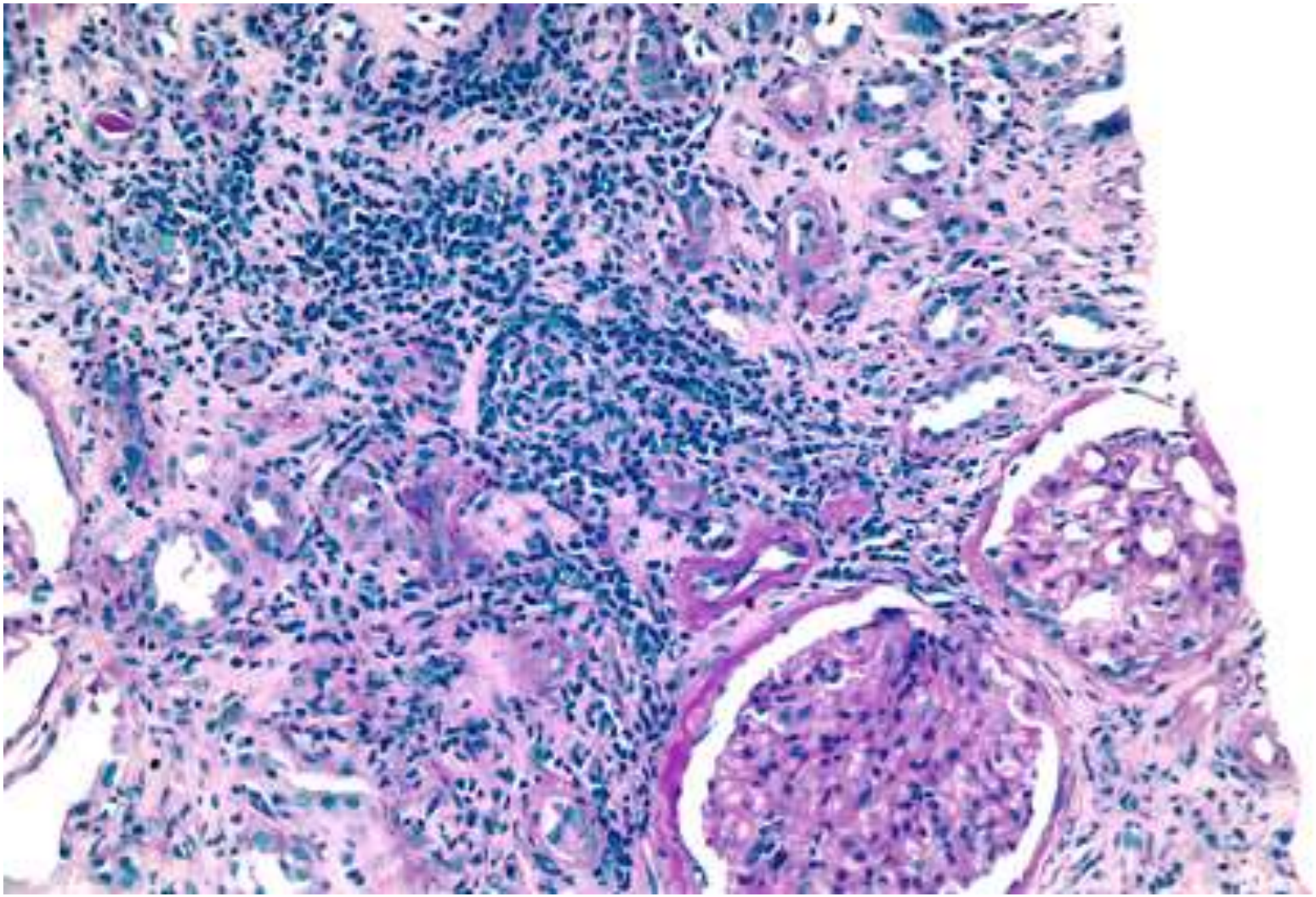
tubularis atrophia

interstit. fibrosis- vese zsugorodás

Acut rejectio



Chronicus rejectio



Örökletes immunhiányos állapotok, humorális

- X-kötött hypogammaglobulinaemia (Bruton), BTK hiány, propreB van csak,

Enterális fertőzések (vírus, Giardia, Mycopl)

- Átmeneti hypogammaglobulinaemia (T helper)
- Hyper-IgM (CD40L hiány)

Izotípus váltás nincsen, ok CD4+T sejt funkciózavar (IgA, IgE IgG hiány), kóros IgM, nincsen csíracentrum…..

- Variábilis hypogammaglobulinaemia (B és T zavar)
- **Szelektív IgA hiány (leggyakoribb)**

C4A-del, CD8+T zavar, izotípusváltási zavar: bél, bőr fertőzések…

- 5'-nukleotidáz hiány: perB van csak……

Örökletes immunhiányos állapotok, celluláris

- Di-George (thymus aplasia, 22q11del)

Szívfejlődési rendell+ hypoparathyr), fejlődési rendellenesség (3/4 garatív), preT van csak

- Chr mucocutan candidiasis

Örökletes immunhiányos állapotok, kevert

- SCID: CYKR g-lánc mutáció

Főleg T probléma (X kötött, fiúkban)

- Adenozin deamináz hiány (au-rec)

dATP toxikus a T sejtekre….DNS lézió!!!

- Purinnukleotid foszforiláz-hiány (dGTP toxikus, T, DNS!!!)
- Wiskott-Adrich szindroma (X-kötött, fiúk)

Xp1123 gén hiány

Fertőzések, thrombocytopenia, ekzema

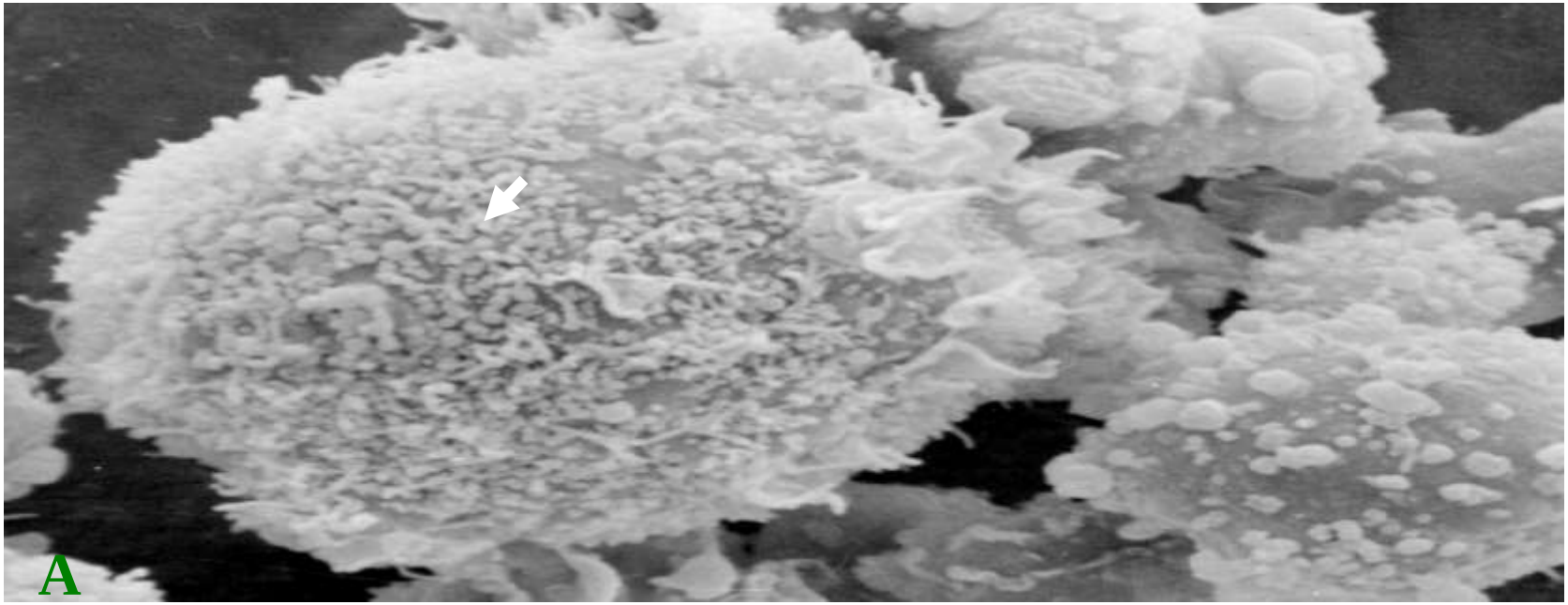
- Ataxia teleangiectasia .

Thymus hyopolasia, nycs atrophia, T+IgG/IgA hiány (DNS hibajavító gén)

- Retikuláris dysgenesis (myel, ly őssejt zavar)
- Csupasz ly szindroma (HLA-II hiány), CD4T probléma: CIITA, RFX transzkripciós faktorok zavara
- Alacsony HLA-I expresszió (peptidtranszporter zavar) CD8 zavar…..

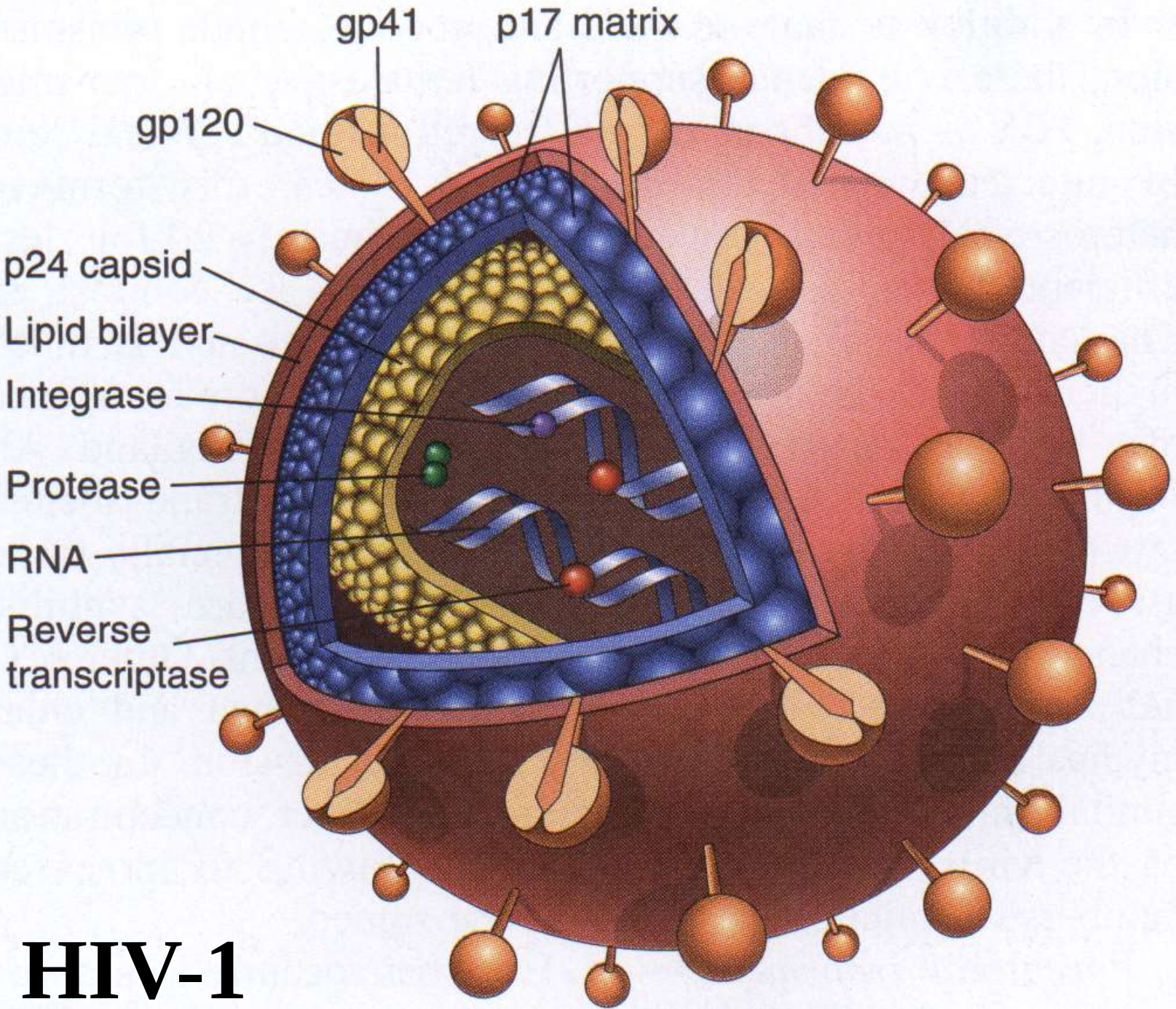
Szerzett immunhiányos állapot, AIDS

- HIV1/2 fertőzés okozta szelektív CD4 hiány
- Szex, vér, transzplacentáris behatolás
- Célsejt: CD4+T (gp120HIV), citotoxikus
- Célsejt: makrofág (nem toxikus, rezervoár)….endotél?
- Szolubilis gp120+CD4T/anti-gp120 ADCC



CD4/CD8 arány: 2-4/1

HIV fertőzéskor: lecsökken/megfordul

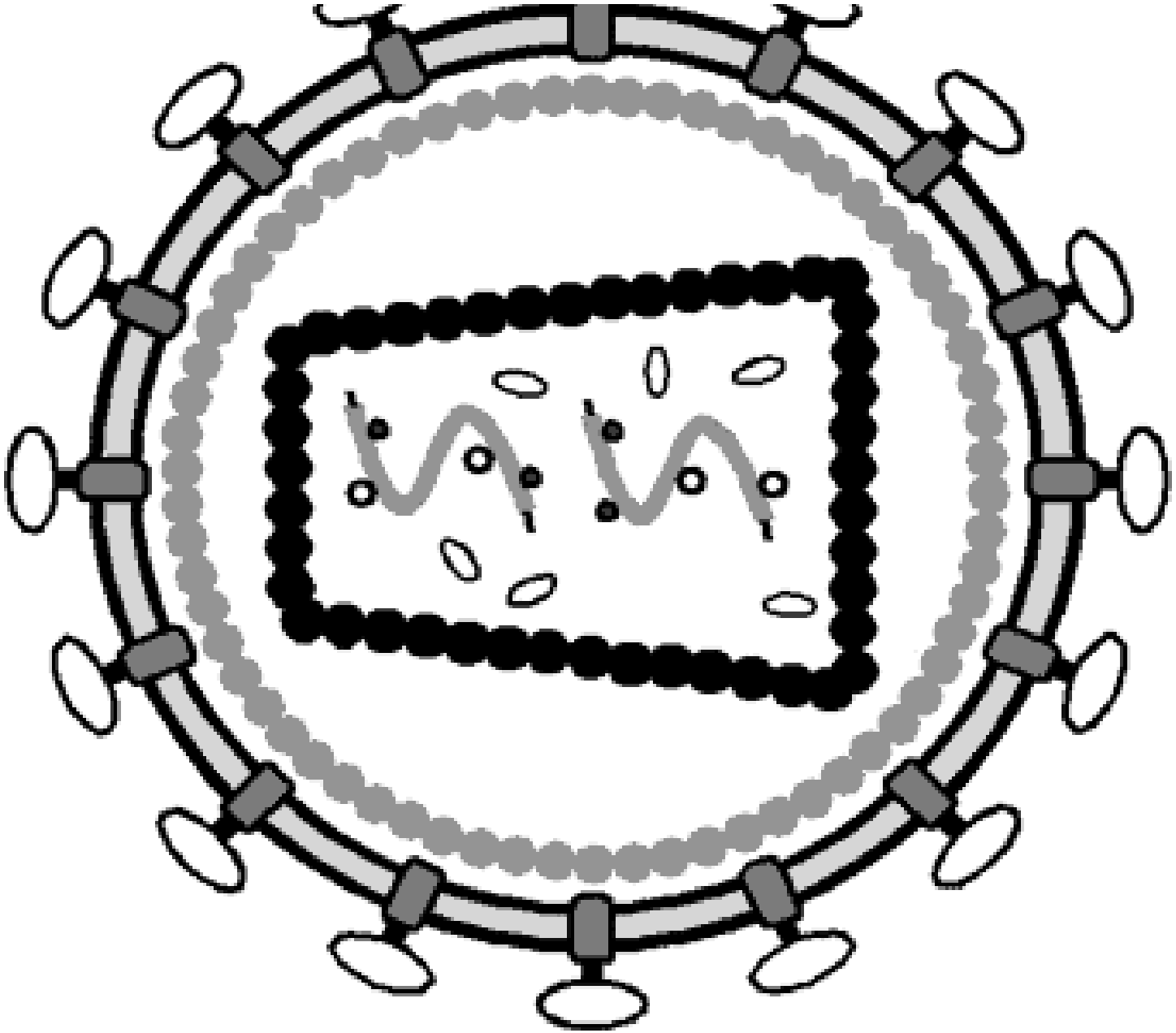

gp41
p17 matrix
gp120
p24 capsid
Lipid bilayer
Integrase
Protease
RNA
Reverse transcriptase

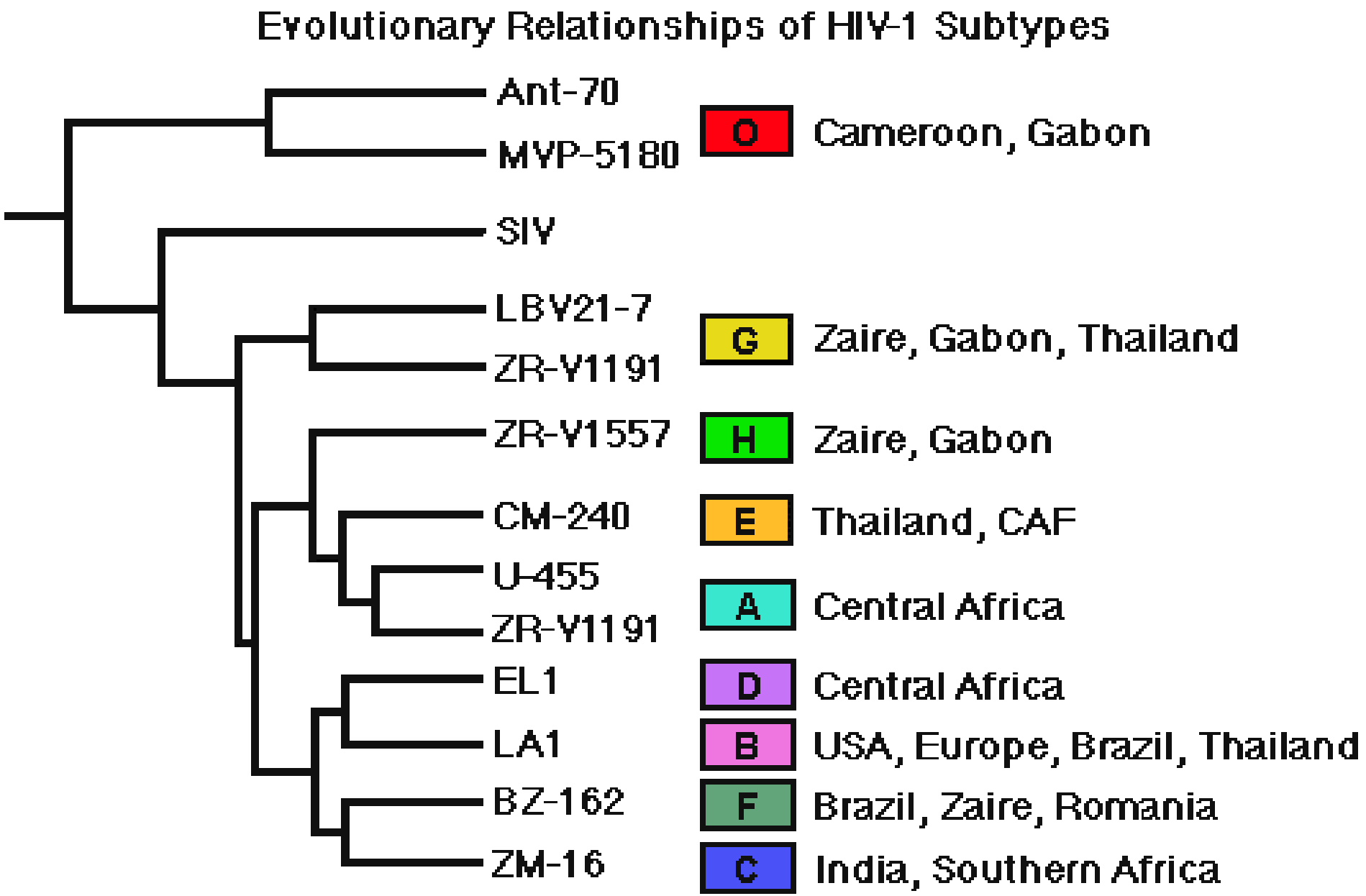
HIV-1

AIDS-Tote in Kenia - apokalyptischer Zustand

in Afrika verheert das Virus Völker und Volkswirtschaften

structural components of human immunodeficiency virus, the key antigenic components are diagrammed here





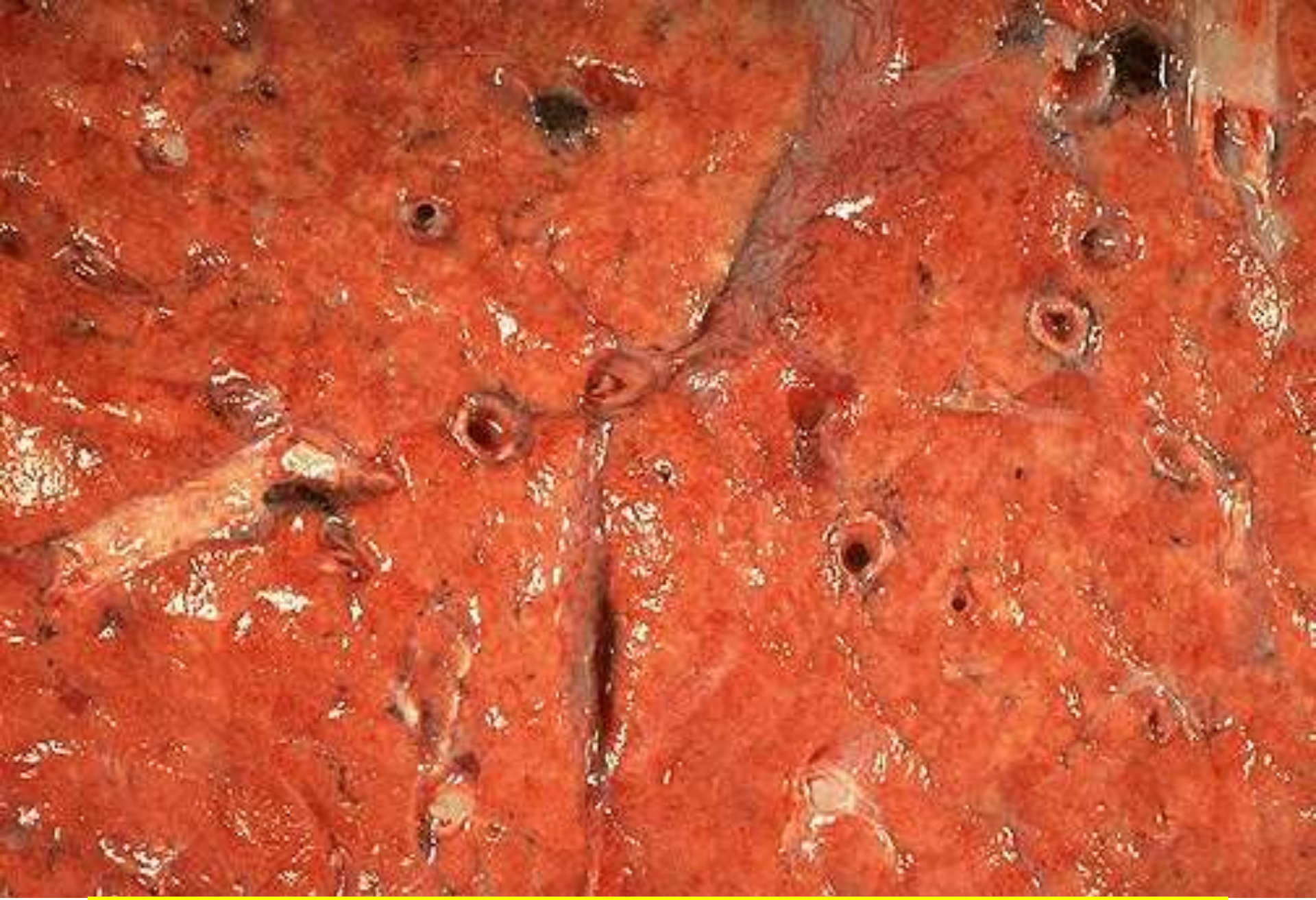
the phylogeny of human immunodeficiency virus (HIV) subtypes and simian immunodeficiency virus (SIV)

AIDS lefolyása

- LND: follikuláris hyperplasia (B), HIV+T zóna, CD4->5OO/ul,, p24+
- Follikuláris involutio (dendritikus sejtes zavar), latens AIDS:CD4T csökken, lappang a vírus
- Opportunista fertőzések: krízis, viraemia, CD4T<2OO/ul
- Lép, thymus sorvadás, dementia (microglia)
- Kaposi sarcoma (HHV8-angiosarcoma), B-NHL (agyi), méhnyakrák-HPV

Opportunista fertőzések AIDS-ben

Helminthiasis		
	Strongyloides	gastroenteritis, sepsis
Protozoonok		
	Pneumocystis carinii	pneumonia
	Toxoplasma gondii	encephalitis, disseminalt forma
	Cryptosporidium	enteritis
	Isospora belli	enteritis
Gombák		
	Candida albicans	oesophagitis
	Cryptococcus	meningitis
	Histoplasmosis	disseminalt forma
	Coccidiomycosis	disseminalt forma
Baktériumok		
	Mycobacterium avium	disseminalt forma
	Mycobacterium kansasii	
	Mycobacterium bovis	extrapulmonáris tuberculosis
	Salmonella	septicaemia
	Bacterialis pneumonia	recidivans
Vírusok		
	Herpes simplex	mucocutan
		Bronchialis
		Oesophagealis
	CMV	disseminalt
Prion	vCJ betegség	leucoencephalopathia

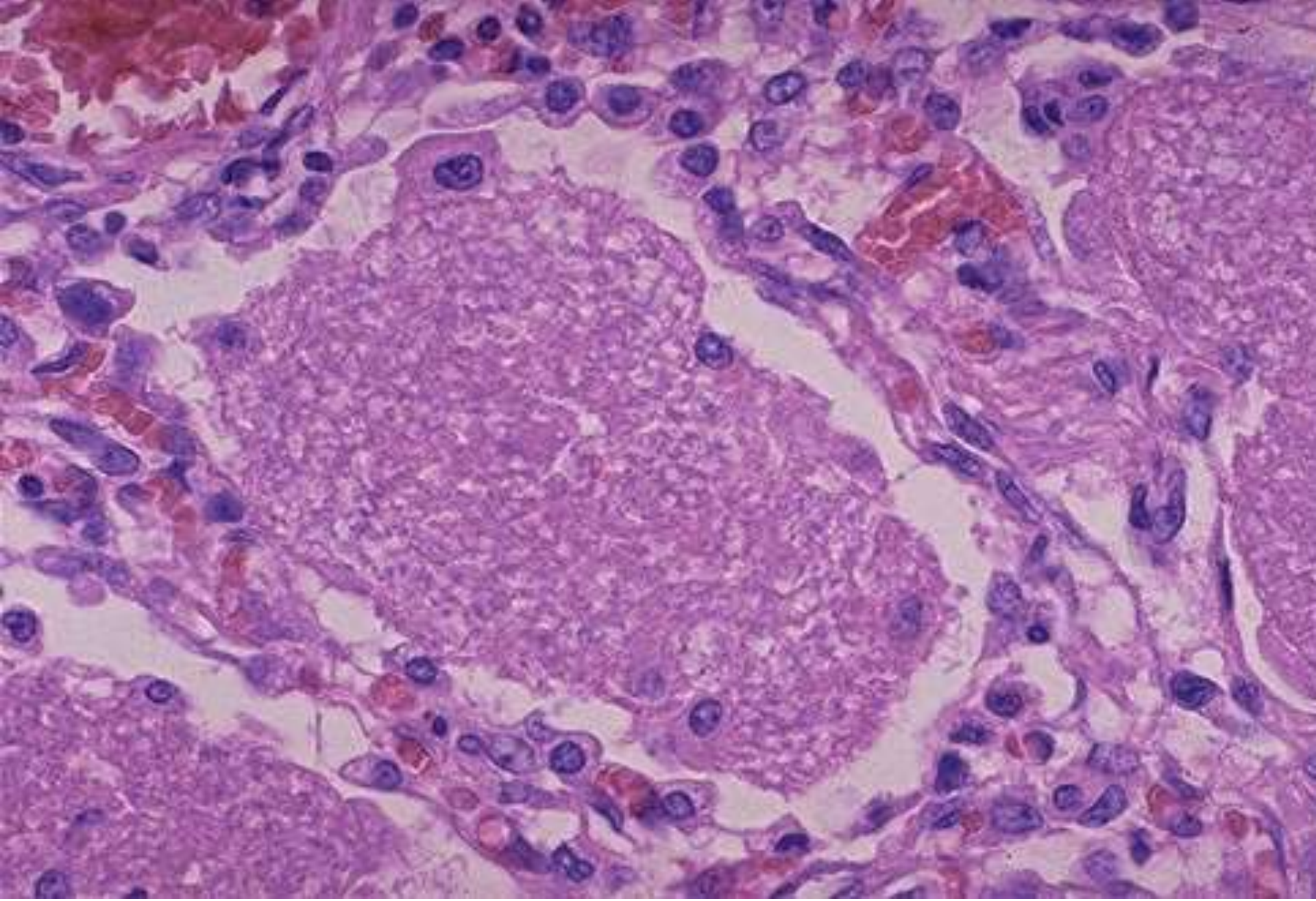


the appearance of Pneumocystis carinii caused extensive pneumonia

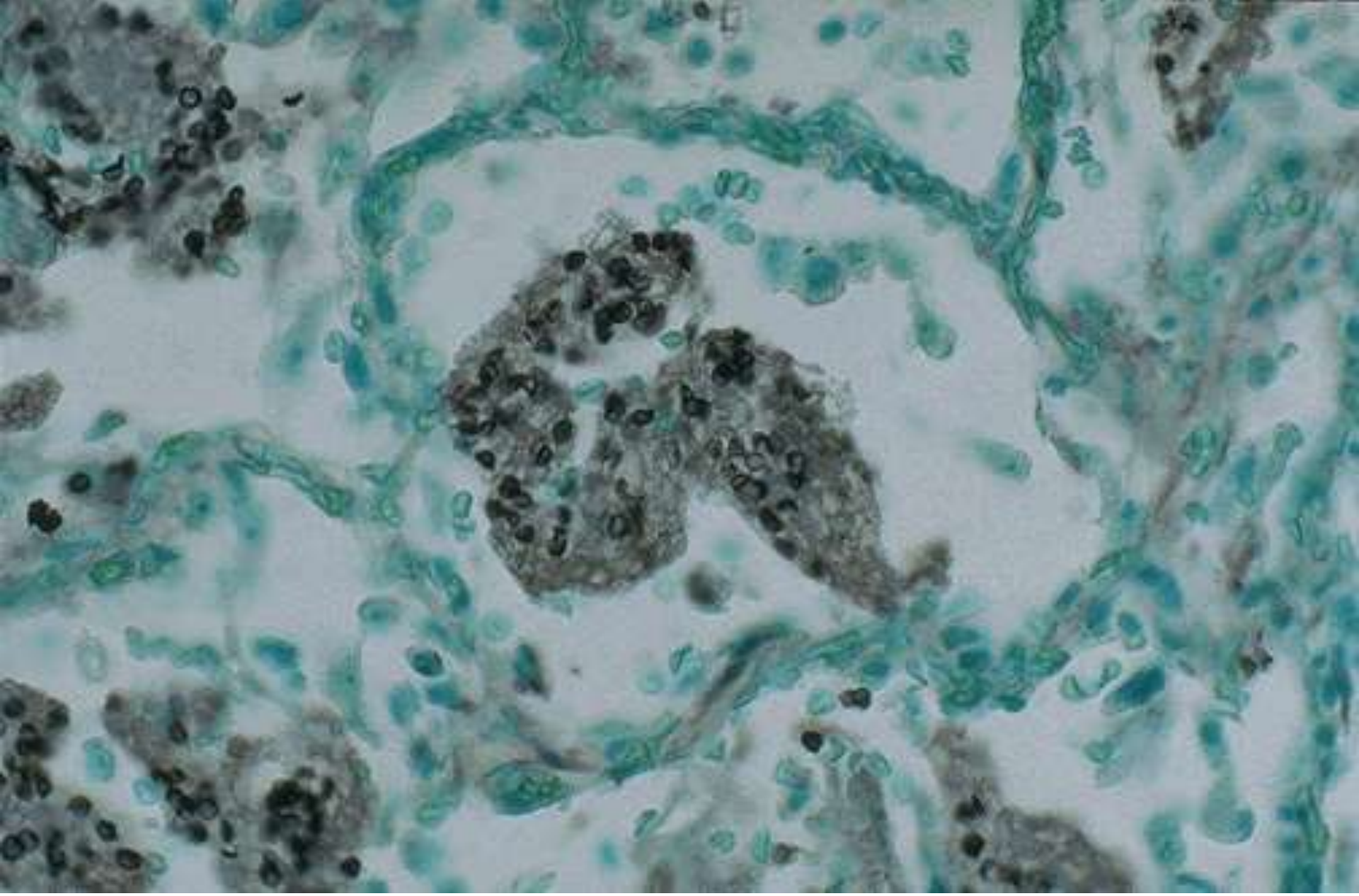
Pneumocystis carinii pneumonia

may produce cavitary change

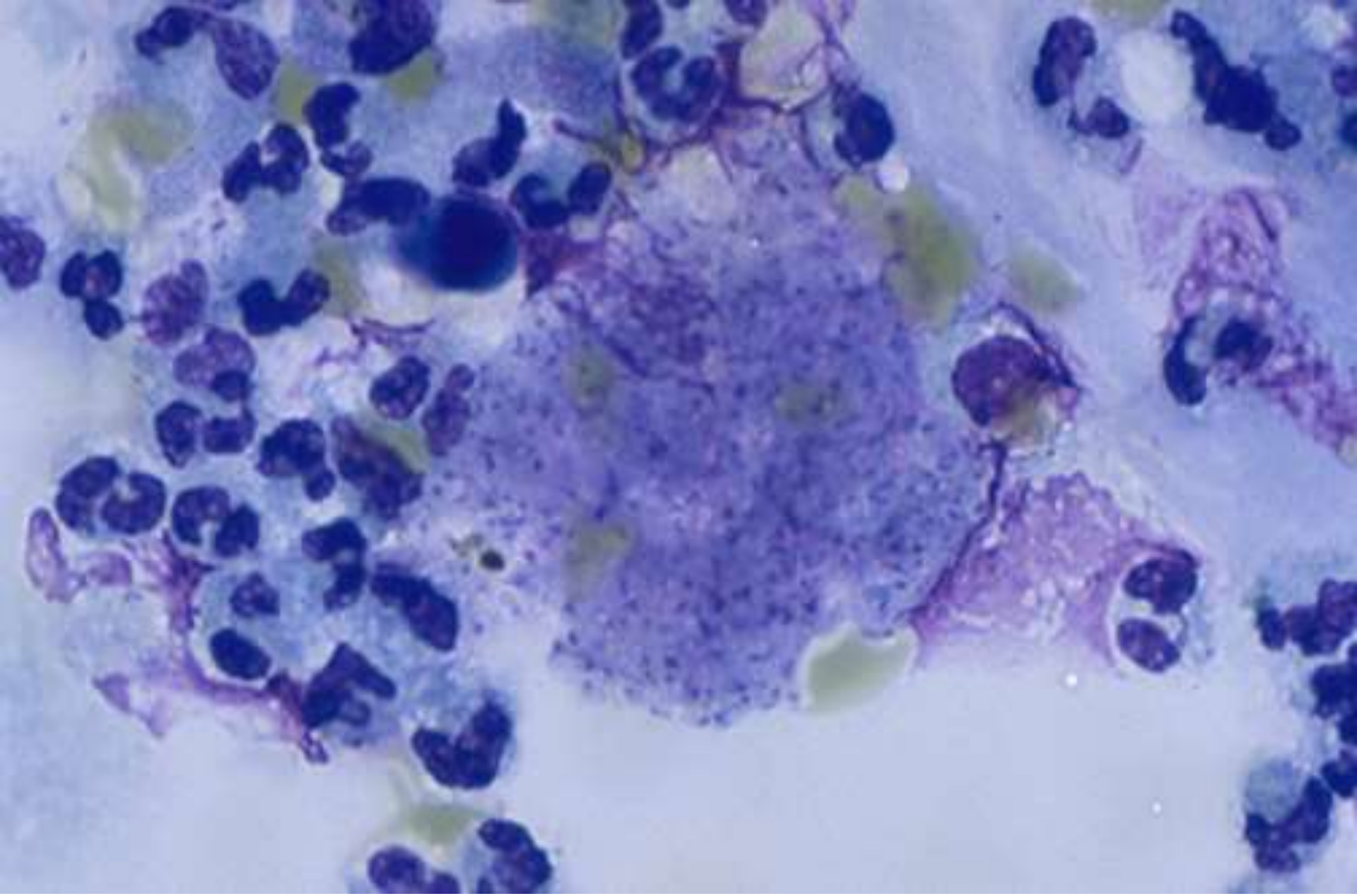
in rare cases



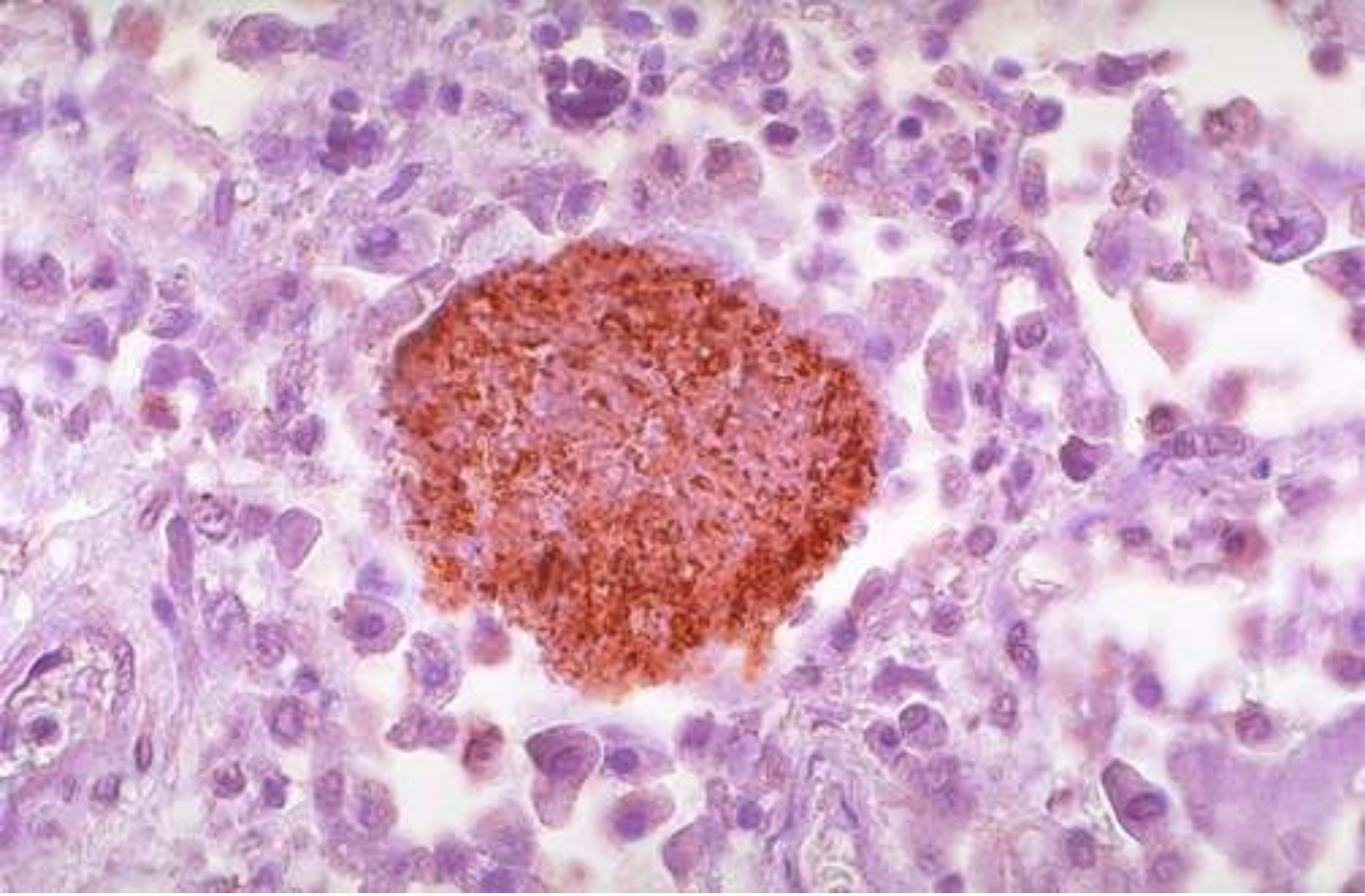
the appearance of Pneumocystis carinii in lung with exudate in nearly every alveolus



Pneumocystis carinii in lung is demonstrated by the appearance of brown to black cysts in the alveolar exudate - Gömöri stain

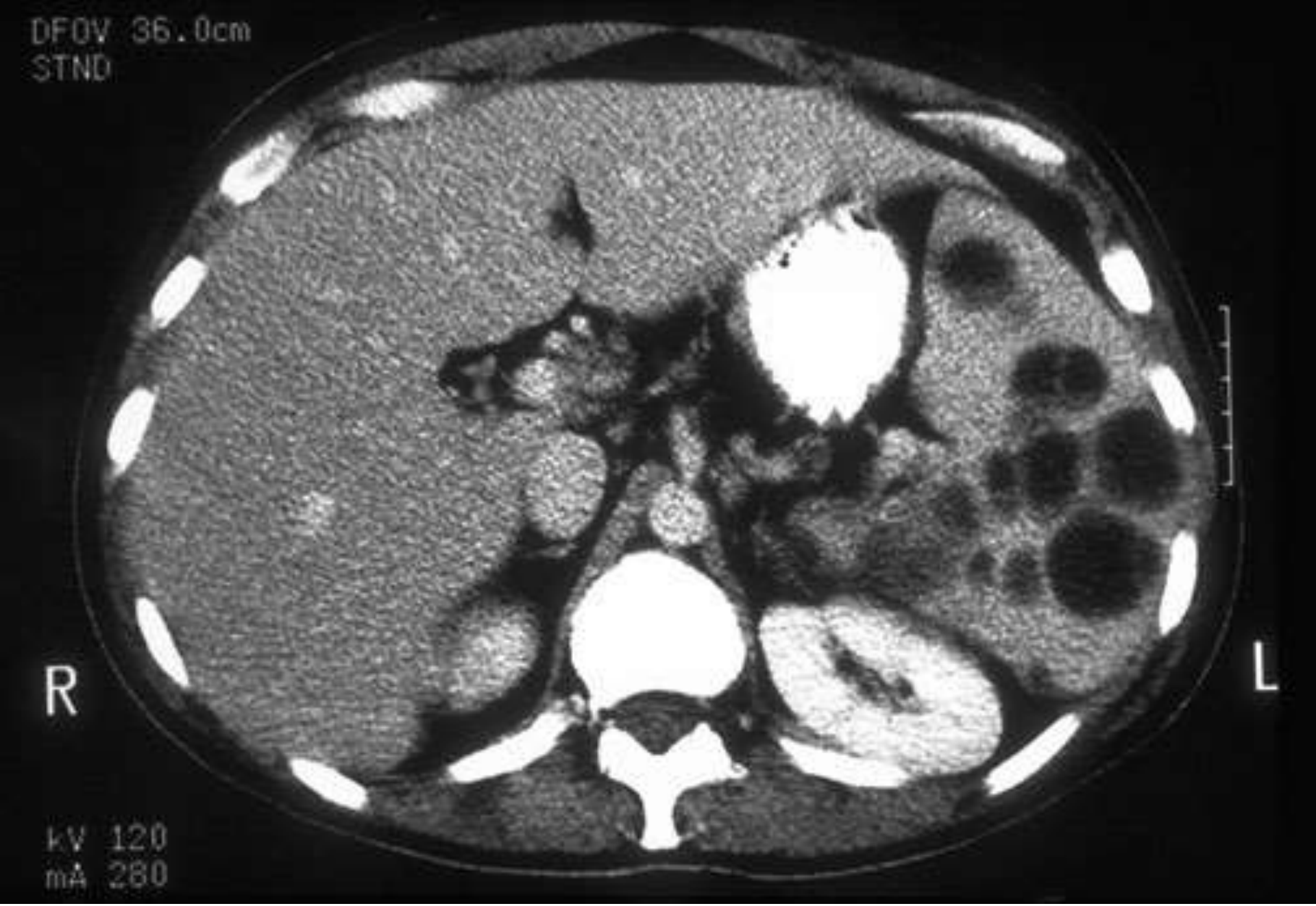


faint bluish dot-like intracystic bodies of Pneumocystis carinii in lung in this cytologic preparation from a BAL - Giemsa stain

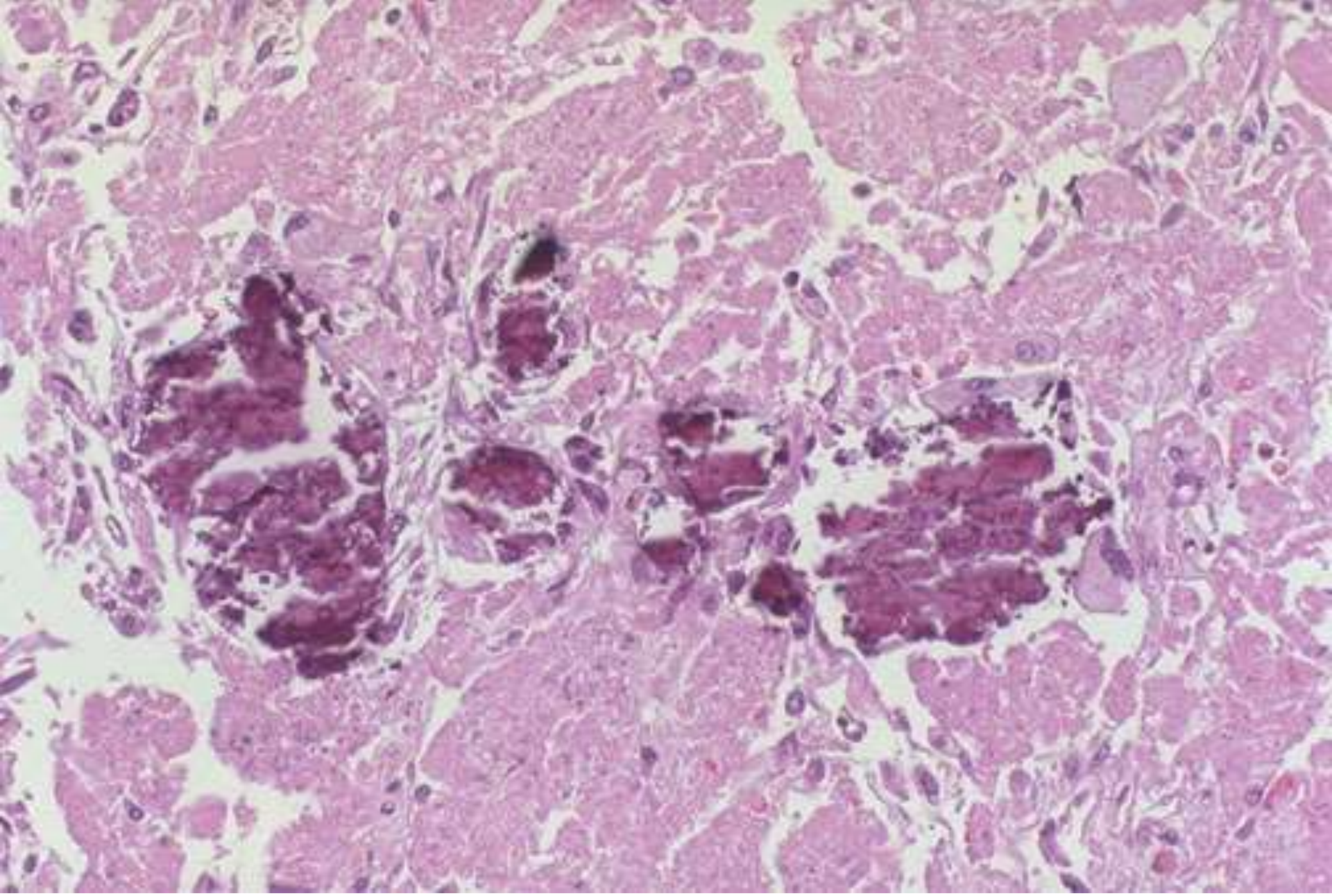


immunoperoxidase stain with antibody to Pneumocystis carinii: the brown-red reaction produce is seen highlighting the exudates

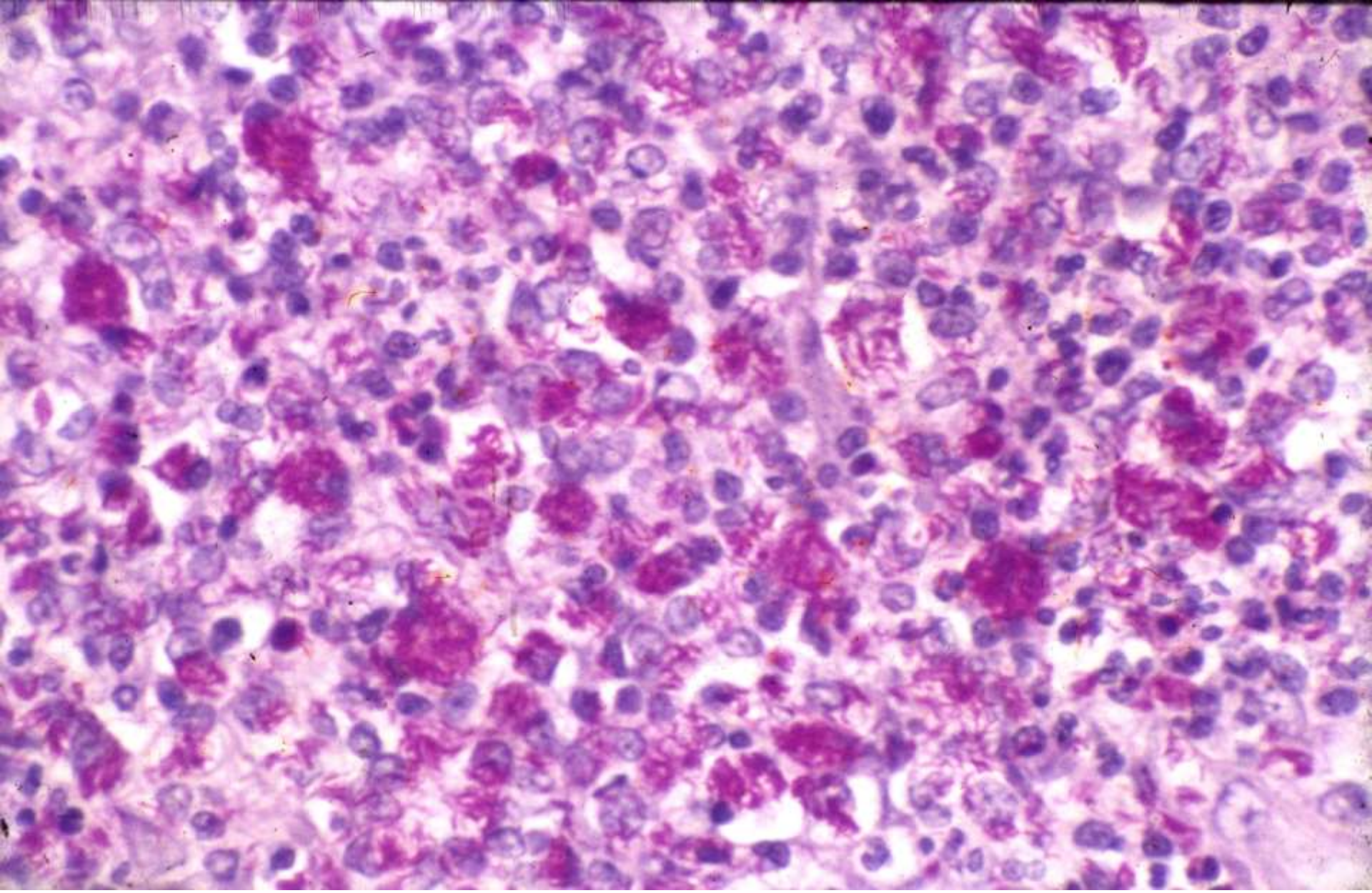
dissemination to extrapulmonary sites: Pneumocystis carinii tends to produce foci with prominent calcification

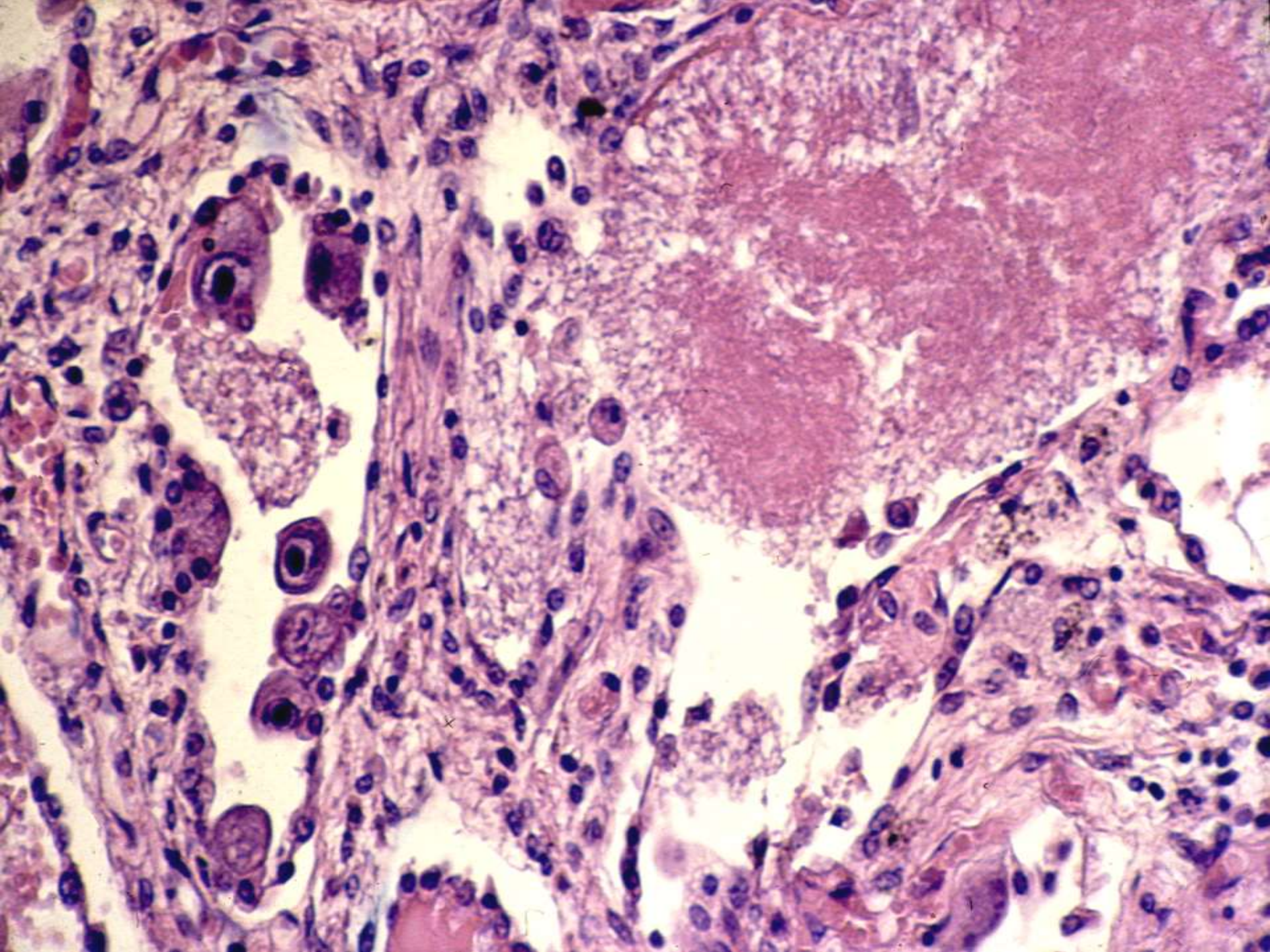


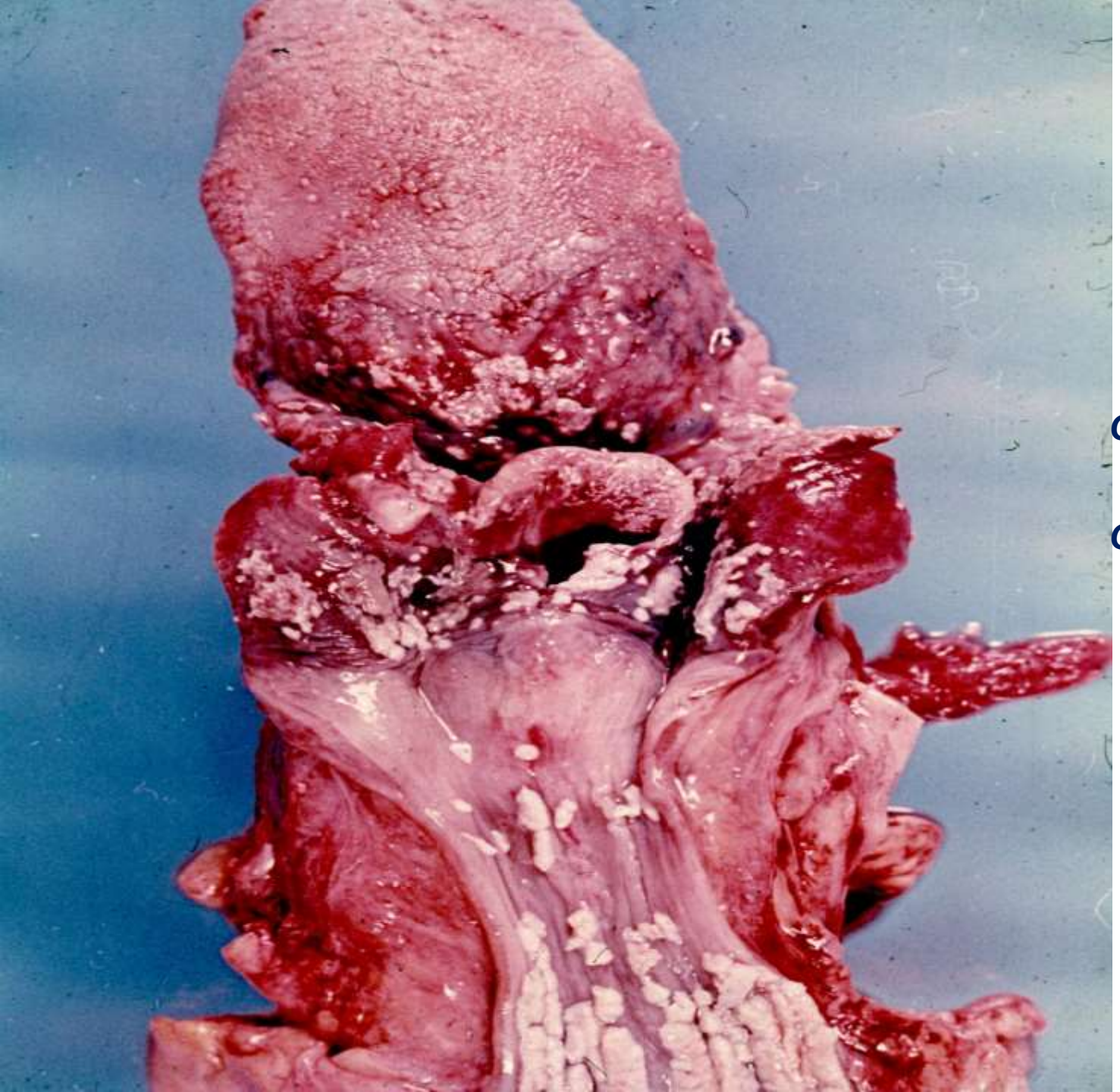
disseminated of Pneumocystis carinii has led to splenomegaly, and the masses of exudate produce the lucent areas in spleen - CT scan



Pneumocystis carinii can produce large areas of the foamy pink exudate that can calcify in the lung

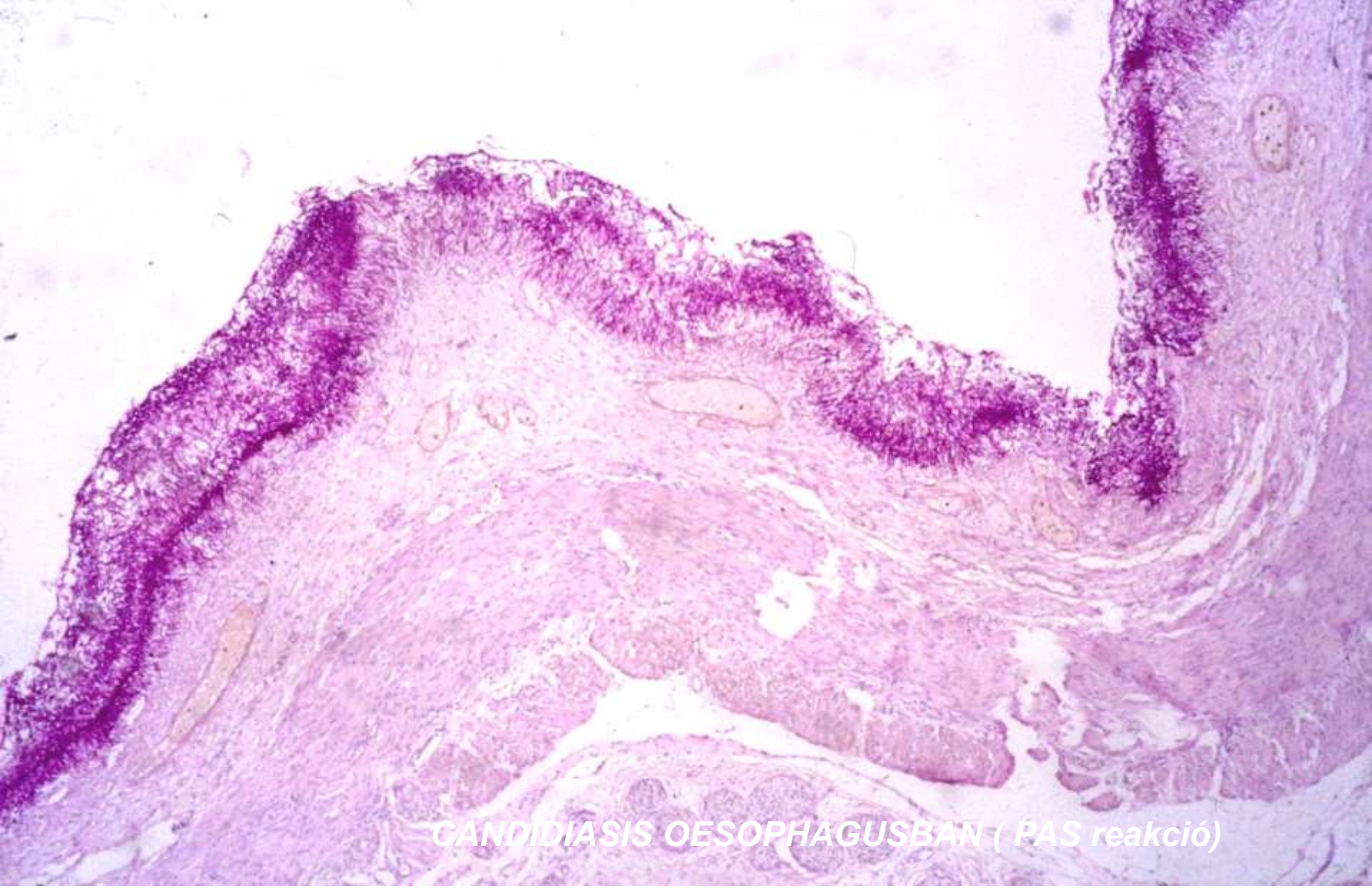






CANDIDIASIS az

OESOPHAGUSBAN



CANDIDIASIS OESOPHAGUSBAN (PAS reakció)