Introduction to Immunotherapy & Novel treatment strategies: temperature modulated immunotherapy

ESHO School

Arlene L. Oei

September 12, 2022

Amsterdam UMC

What type of researcher are you?

Physicist

Biologist

MD

Amsterdam UMC

Oei-group Amsterdam

Radiobiology
Amsterdam UMC

Gregor van Bochove

Glioblastoma

Breast cancer

Yasmin Civil

Yihe Zhao

Bella Bokan

Roxan Helderman

Colorectal cancer

Hans Rodermond

Karin Nuijens

Prostate cancer

Cervix cancer

Marloes IJff

Xionge Mei

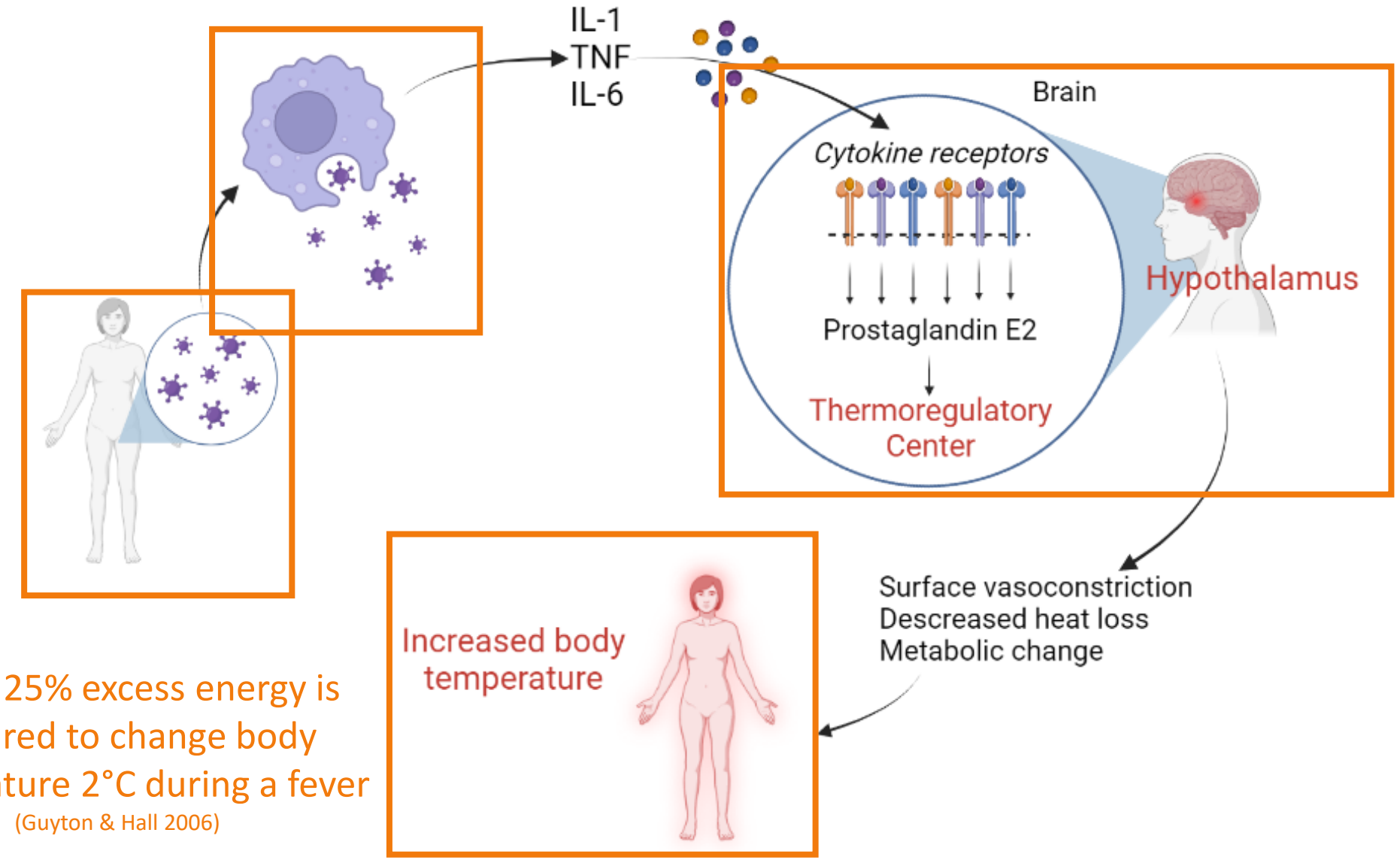
Barbara Snoek

Seth Fobian

Wenjing Gou
(starts in Oct 2022)

Fan Yang
(starts in Nov 2022)

What happens after an infection?



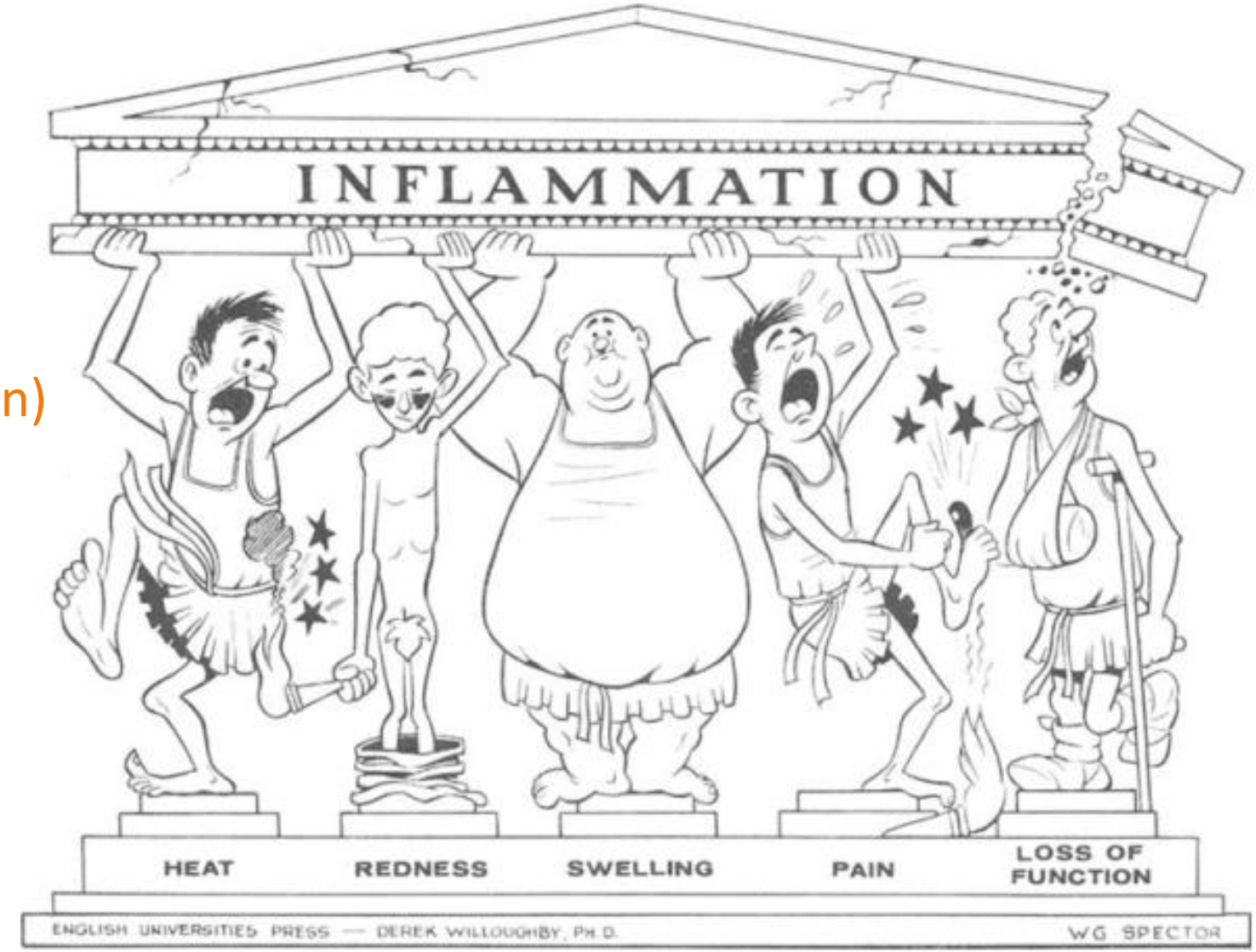
About 25% excess energy is required to change body temperature 2°C during a fever
(Guyton & Hall 2006)

(Adapted from Dinarello et al 2004)

Amsterdam UMC

Inflammation response

Inflammation:
Flamma = fire (Latin)

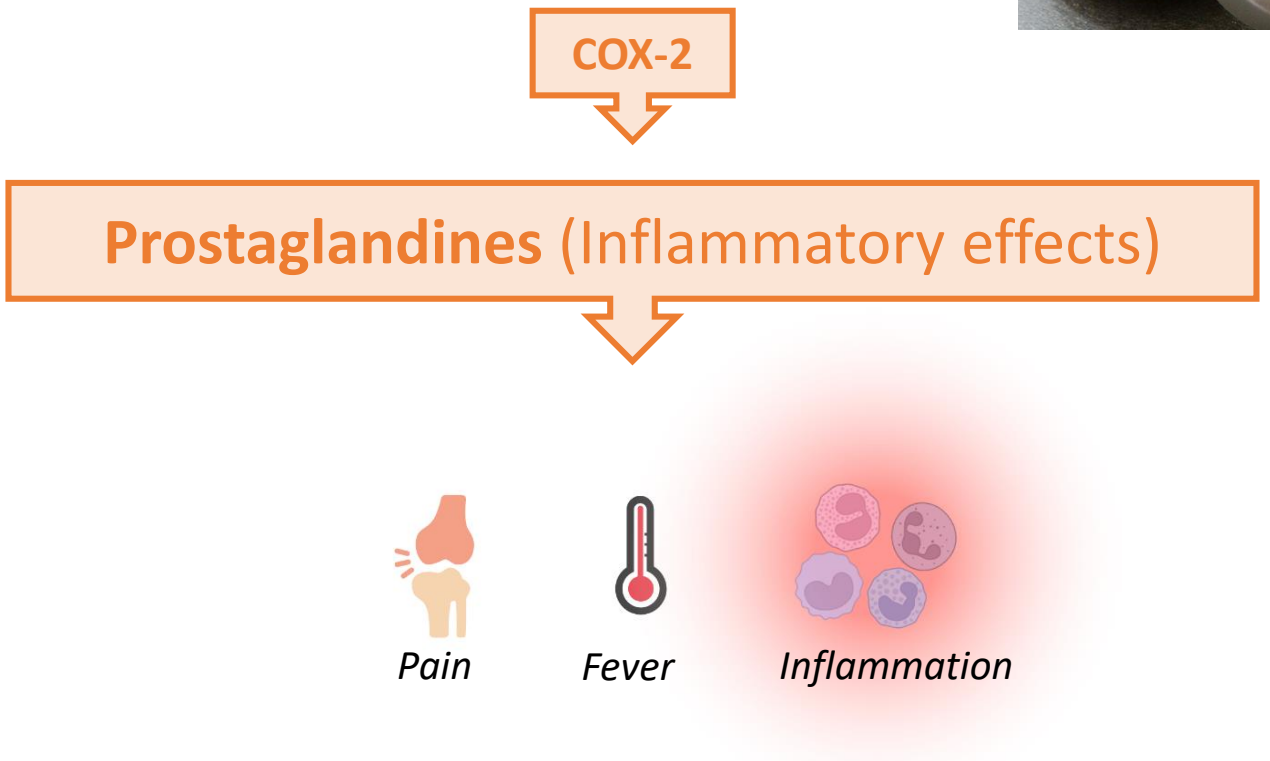


CALOR RUBOR TUMOR DOLOR Functio laesa

Amsterdam UMC

COX2-inhibitor

- NSAID (nonsteroidal anti-inflammatory drug)
- Targets COX-2 (cyclooxygenase-2)
- Thereby reducing inflammation, pain and fever



Amsterdam UMC

Fever: To treat or not to treat?

Go to www.menti.com and use the code 4872 2756

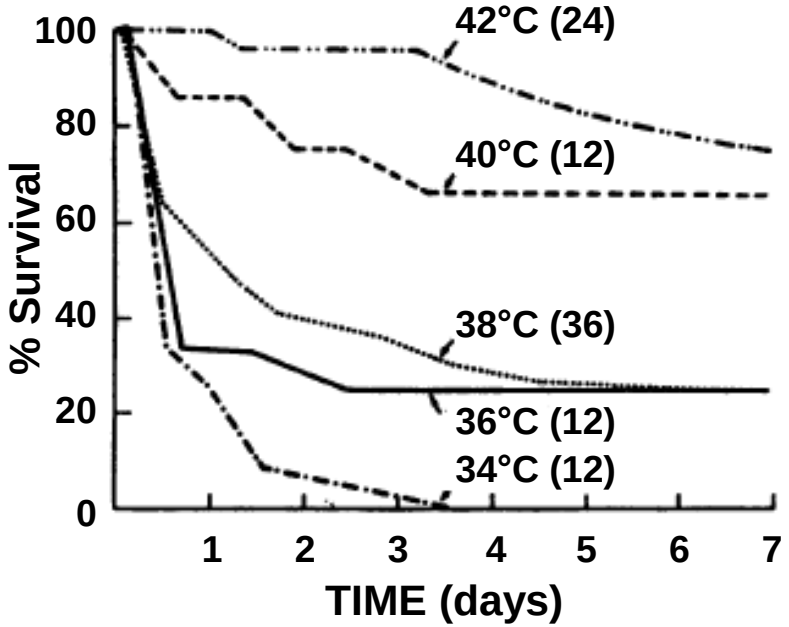
A. <u>Treat:</u> Fever is noxious. Suppression of fever will reduce its noxious effect.

B. <u>Don't treat:</u> Fever is a natural response with important biological responses.

Amsterdam UMC

After bacterial infection: increased host survival (Ectotherms)

Dipsosaurus dorsalis
"Northern Desert Iguana"



By monitoring the thermoregulatory behavior of the desert lizard after bacterial infection (*A. hydrophila*) animals that raised their core temperature by 4°C over normal had better survival than those who did not.

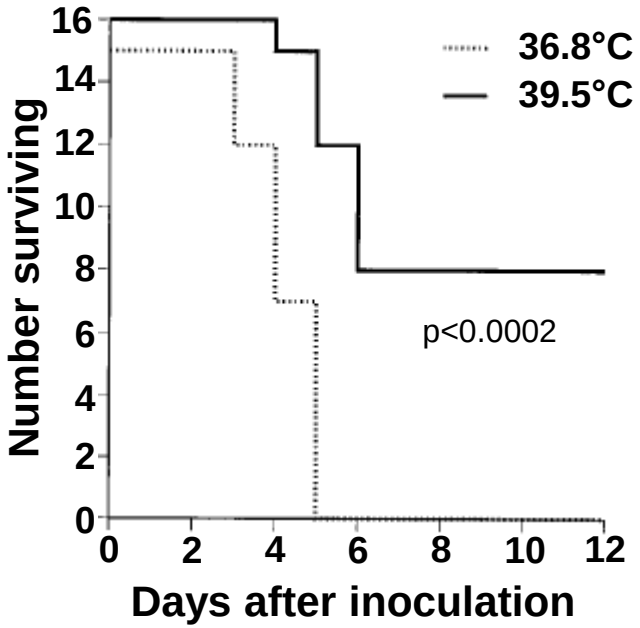
(Kluger et al. Science, 1975)

Amsterdam UMC

After bacterial infection: increased host survival (Endotherms)

CD-1 mouse

Infected with *K. pneumoniae*



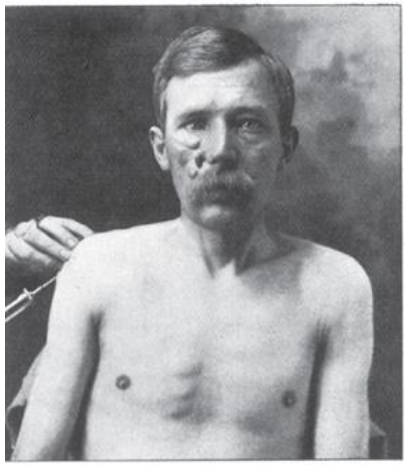
Increasing core body temperature from 37°C to 39.5°C:

- **Increase in host defense**
- Improved survival
- Altered cytokine production/expression
- Reduced bacterial load

(Jiang et al. Infection and Immunity, 2000)

Amsterdam UMC

William Coley – “The Father of Immunotherapy”



Investigating the death of a patient
Coley’s research: *evidence of the relationship between infection and cancer regression*

Coley’s therapy (utilized in his initial studies for patients with inoperable sarcoma) consists of the injection of by-products of two common bacteria: *Streptococcus pyogenes* and *Serratia marcescens*

Later analysis showed that the sickest, judged by those who got the highest fevers, did the best and often had “spontaneous remissions” of the tumor

(Wiemann and Starnes, Pharmacology & Therapeutics, 1994)

Amsterdam UMC

Fever: Good or bad?

"…whether to treat an elevated temperature that occurs with an infectious disease is the subject of an ongoing debate.

Experimental evidence suggests that host defense mechanisms are enhanced by elevated temperature; thus, fever is potentially beneficial and should not be routinely suppressed."

(Merck Manual, 2009)

Amsterdam UMC

Fever at critically ill patients ICU: To treat or not to treat?

Patients in the ICU who have probable infection are treated with Acetaminophen.

Amsterdam UMC

Fever at critically ill patients ICU: To treat or not to treat?

Go to www.menti.com and use the code 4872 2756

A. **Treat:** These patients are critically ill, they need all their energy to recover.

B. **Don't treat:** Fever helps is a natural response with important biological responses.

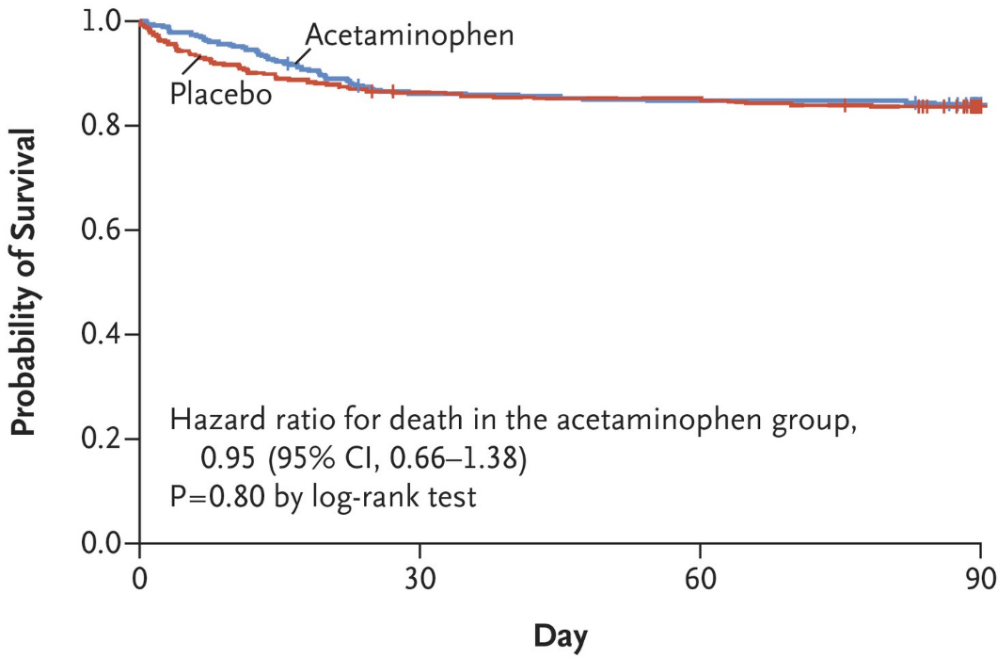
Amsterdam UMC

Fever at critically ill patients ICU: To treat or not to treat?

700 ICU patients with fever of known or suspected infectious etiology
Randomly assigned: 1 g i.v. acetaminophen or placebo, every 6 hours until discharge, resolution of fever, cessation of antimicrobial therapy or death.

Treated patients had a -0.28°C lower temp (P<0.001)

ICU free days to day 28: 23 vs 22 days
Deaths by day 90: 15.9% vs 16.6%



No. at Risk				
Acetaminophen	346	296	291	225
Placebo	343	294	290	214

(Young et al. NEJM, 2015)

Amsterdam UMC

Fever at critically ill patients ICU: To treat or not to treat?

Outcome	Acetaminophen (N = 346)	Placebo (N = 344)	Absolute Difference†	P Value
			days (95% CI)	
Primary outcome: ICU-free days — median (IQR)	23 (13–25)	22 (12–25)	0 (0–1)‡	0.07
Key secondary outcomes				
Hospital-free days — median (IQR)	12 (0–19)	10 (0–18)	0 (0–0)	0.27
Days free from mechanical ventilation — median (IQR)	27 (19–28)	26 (17–28)	0 (0–0)	0.14
Days free from inotropes or vasopressors — median (IQR)	27 (25–28)	27 (24–28)	0 (0–0)	0.36
Days free from renal-replacement therapy — median (IQR)	28 (28–28)	28 (28–28)	0 (0–0)	0.53
Days free from ICU support — median (IQR)	26 (16–27)	25 (15–27)	0 (0–1)	0.14
			Relative Risk (95% CI)	**P Value**
			Unadjusted / Adjusted§	Unadjusted / Adjusted§
Death by day 28 — no. (%)	48 (13.9)	47 (13.7)	1.02 (0.68–1.52) / 1.00 (0.67–1.50)	0.94 / 0.99
Death by day 90 — no. (%)¶	55 (15.9)	57 (16.6)	0.96 (0.66–1.39) / 0.94 (0.65–1.35)	0.84 / 0.73

(Young et al. NEJM, 2015)

Amsterdam UMC

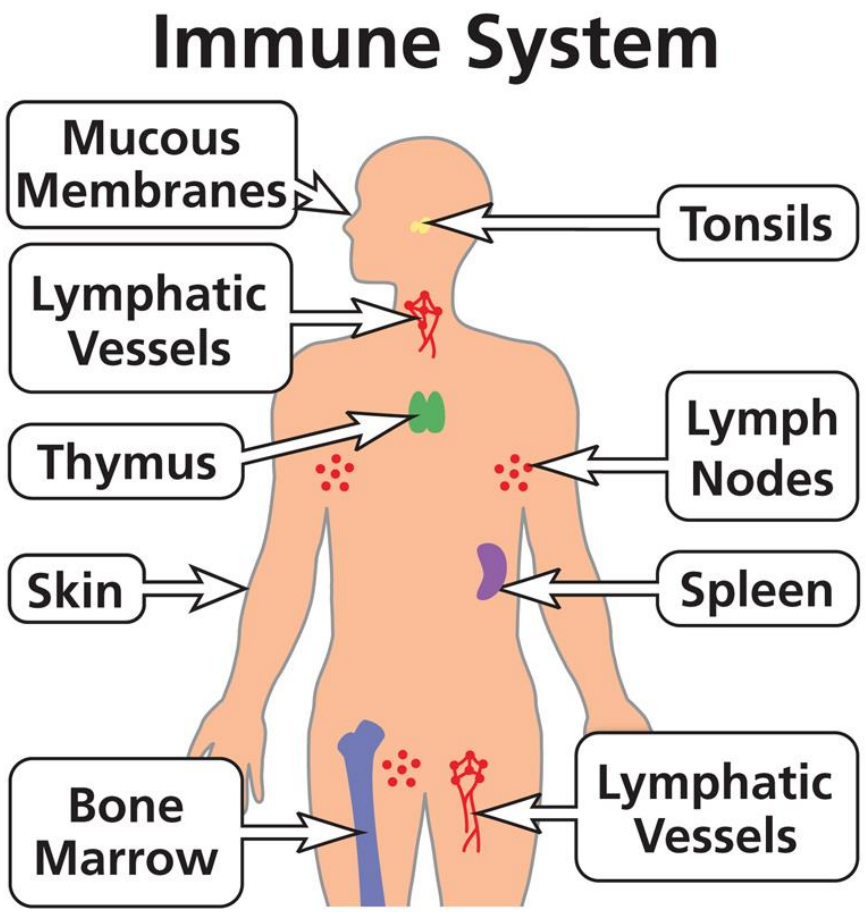
Fever

Fever is the body's host defense mechanism.

"An army of soldiers are fighting the enemy"

Amsterdam UMC

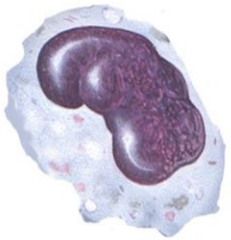
What does that army look like?



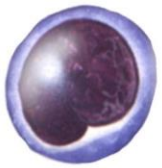
- **Cells**
  - Innate response - several cell types
  - Adaptive (specific) response - lymphocytes
- **Organs**
  - Primary: where lymphocytes develop/mature
  - Secondary where mature lymphocytes get activated
- **Circulatory system** (blood)
- **Lymphatic system** (lymph)

Amsterdam UMC

Blood cells

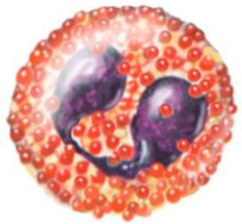


Monocyte

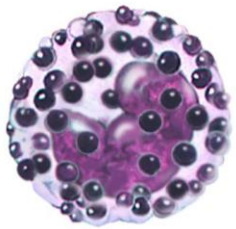


Lymphocyte

Neutrophil

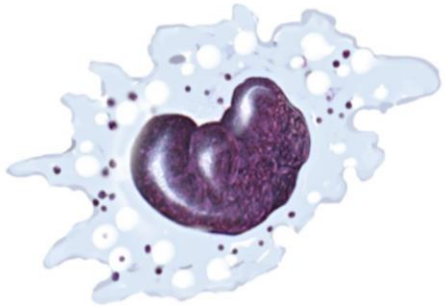


Eosinophil



Basophil

Dendritic Cell



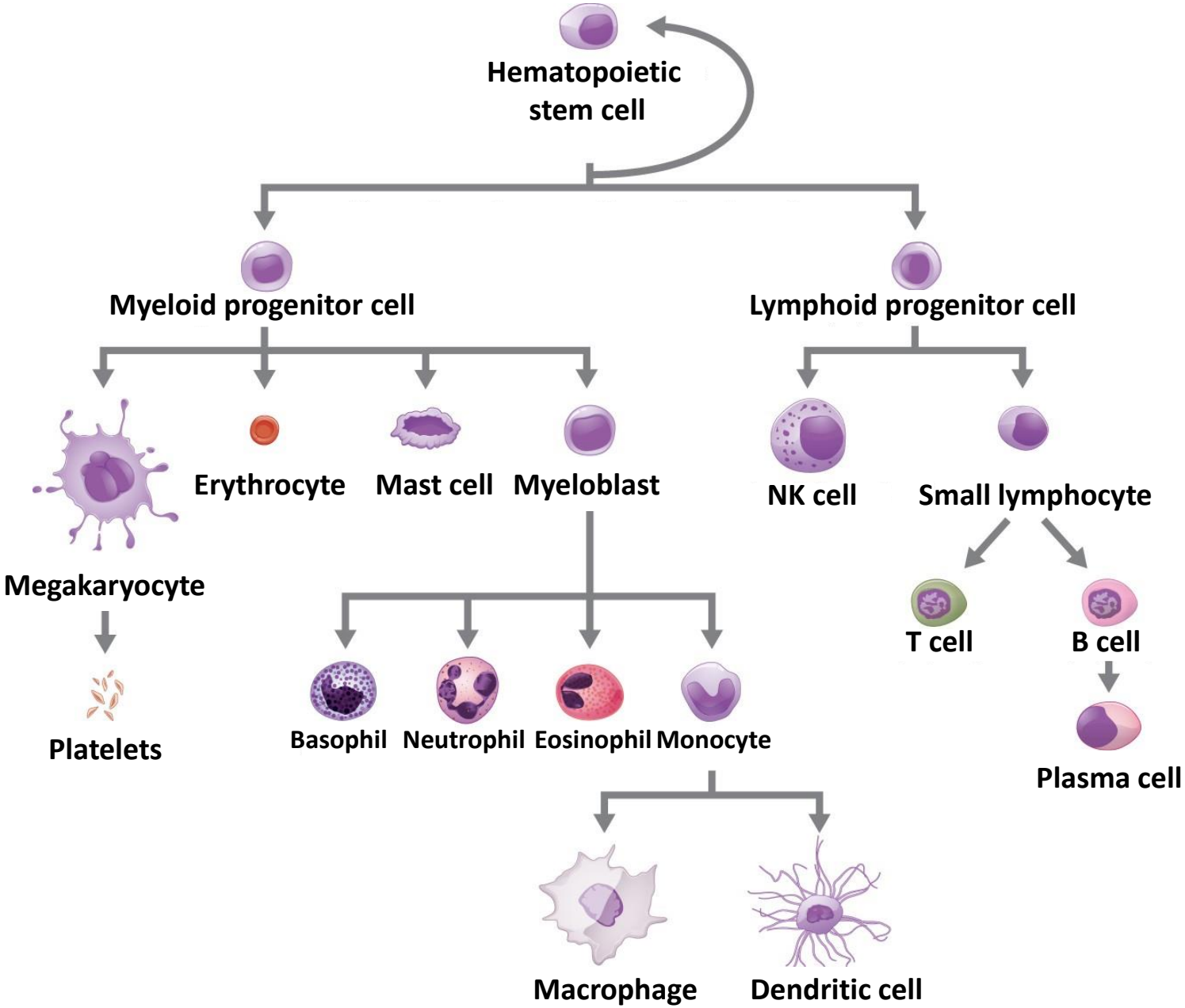
Macrophage

Erythrocyte

Platelets

Amsterdam UMC

Blood cells

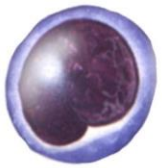


Amsterdam UMC

Blood cells

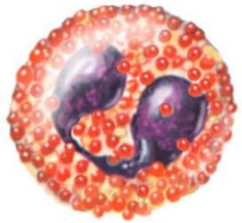
“FIRST RESPONDERS”

Monocyte

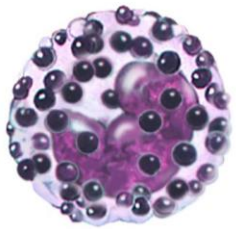


Lymphocyte

Neutrophil

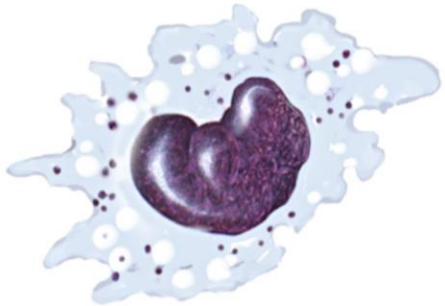


Eosinophil



Basophil

Dendritic Cell



Macrophage

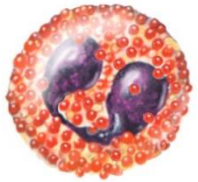
Erythrocyte

Platelets

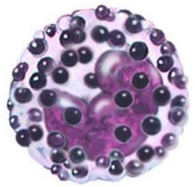
Amsterdam UMC

Granulocytes

Neutrophil



Eosinophil



Basophil

- Characterized by granules in their cytoplasm
- Polymorphnuclear leukocytes
- Produced in the bone marrow
- Front line of attack during immune response
  - Once neutrophils receive appropriate signals: approx. 30 min to leave the blood and reach the site of an infection

Neutrophils

- Most abundant: neutrophils (50-70% of WBC)
- One of the main effector cells in the innate immune system
- Released from bone marrow, circulate 7-10 hrs, enter tissues, live only a few days
- Numbers & recruitment increases during infections "*leukocytosis*" diagnostic
- Shown to kill microorganisms by phagocytosis 100 years ago
- Main cellular component of pus

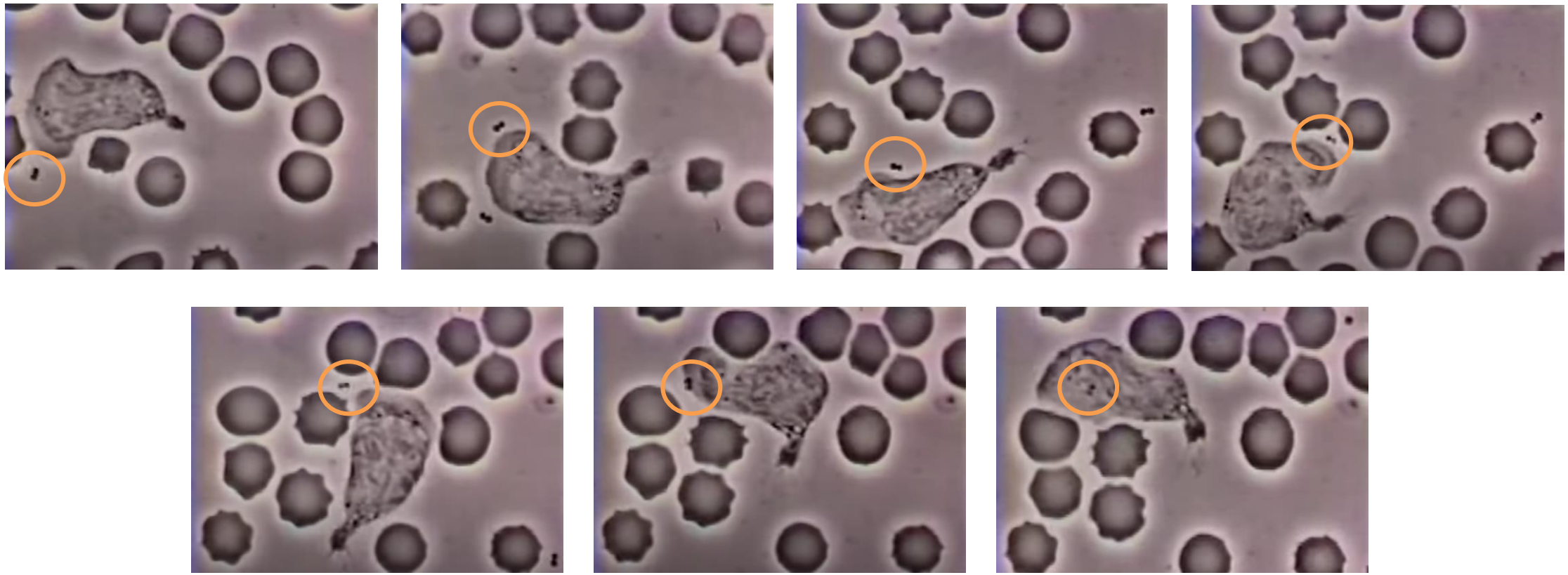
Neutrophil chasing bacteria

Amsterdam UMC

Neutrophil chasing bacteria

https://youtu.be/I_xh-bkiv_c

(Just in case, if the link does not work)



Amsterdam UMC

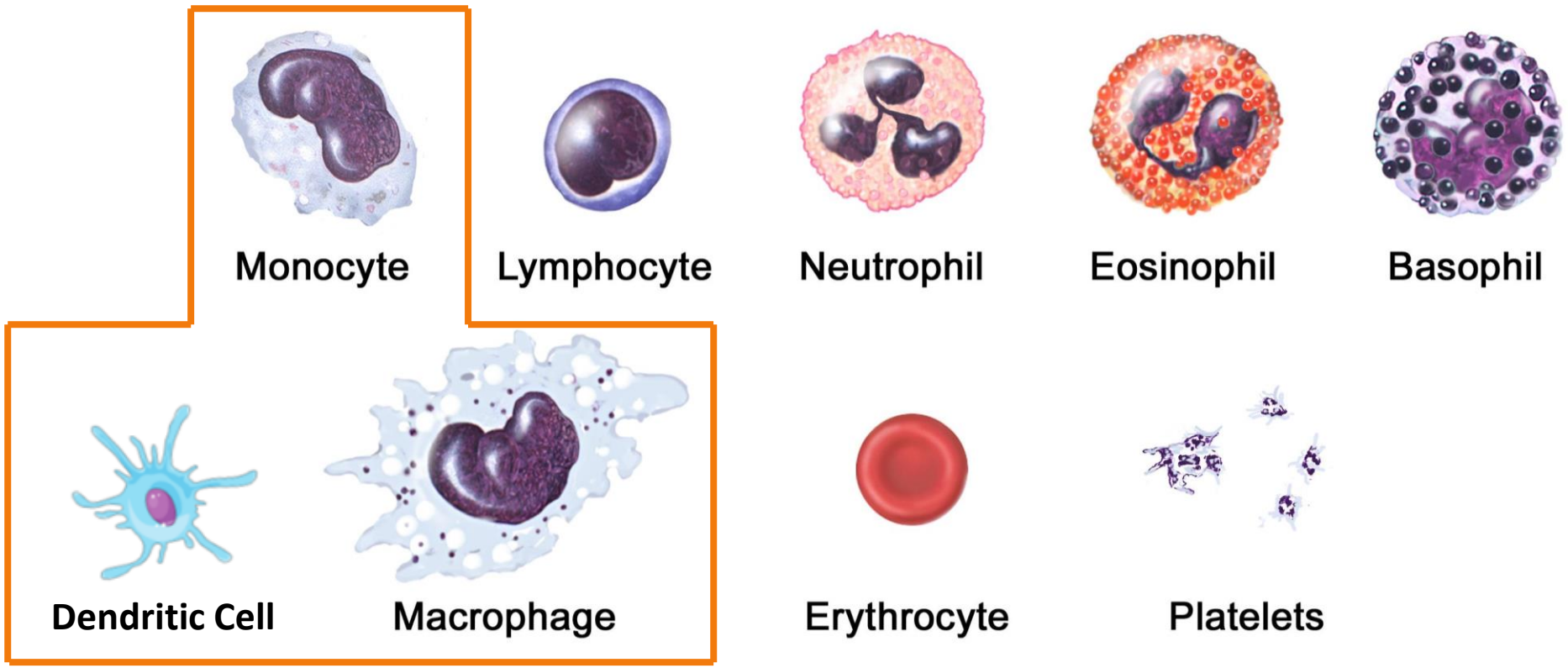
Eosinophil

- Bilobed nuclei (2-4 lobes)
- Motile, phagocytic
- Crucial part in killing of parasites, worms
- Their granules contain unique and toxic protein receptors that bind to IgG and IgA
- They are antigen-presenting cells: regulate other immune cell functions (e.g. CD4+ T cells, DCs, B cells, mast cells, neutrophils, basophils)

Basophil

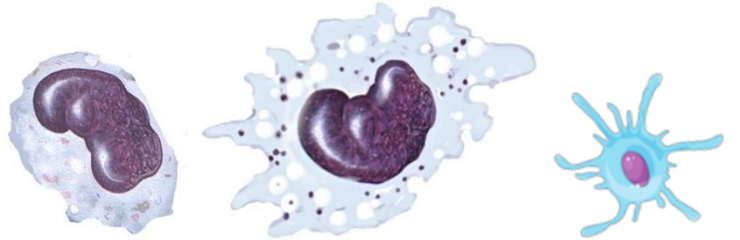
- One of the least abundant of all leukocytes (<1%)
- Bilobed
- Non-phagocytic
- Important in some allergic responses
- Critical to response to parasites
- Have receptors that can bind IgE, IgG, complement and histamine
- Bind circulating Abs and release histamine-increasing permeability of blood vessels

Blood cells

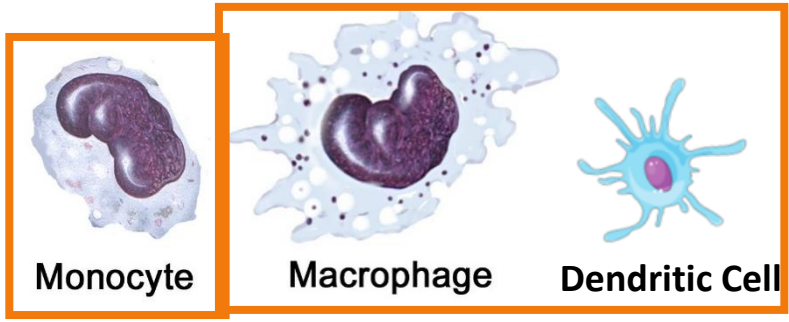

Monocyte
Lymphocyte
Neutrophil
Eosinophil
Basophil
Dendritic Cell
Macrophage
Erythrocyte
Platelets

Myeloid antigen presenting cells

- Phagocytic
- Ingest, digest into peptides, present on cell surface
- Bridge between innate and adaptive immune responses
- Make contact with antigens in periphery and then interact with lymphocytes in lymph node
- Secrete proteins that attract and activate other immune cells

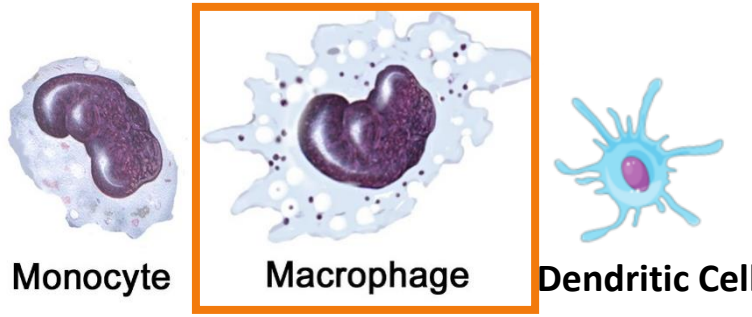


Monocyte



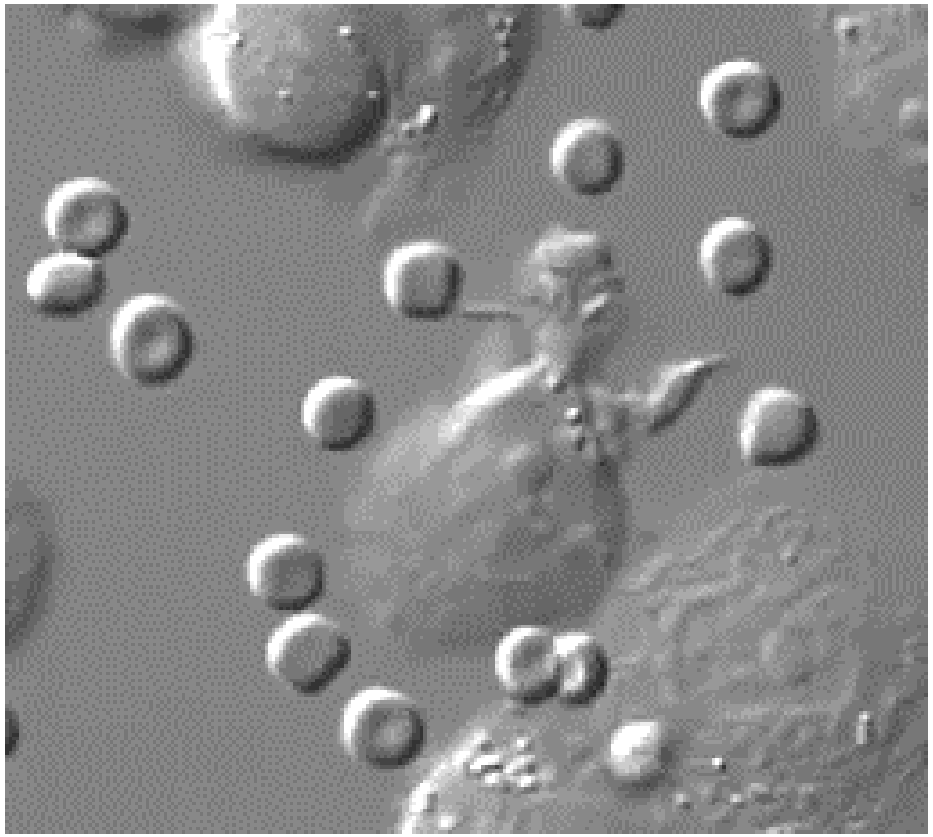
- Largest type of leukocyte (15-22 µm)
- Mononuclear, bean-shaped or kidney-shaped
- Circulate in blood for approx. 8 hrs
- Enter tissues and become fully mature macrophages and Dendritic cells
  - Enlarge
  - Become phagocytic

Macrophages



- Engulf and digest pathogens, such as cancer cells, microbes, cellular debris, foreign substances
- Phagocyte
- Play an critical role in nonspecific defense (innate immunity), and help to initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells, such as lymphocytes

Macrophage engulfs foreign cells

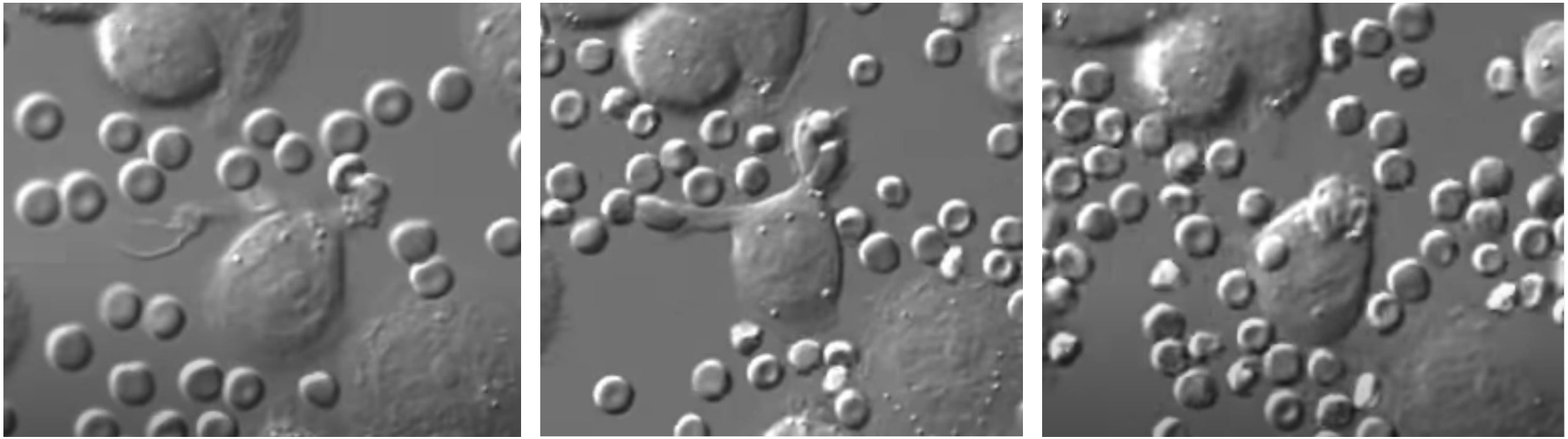


Amsterdam UMC

Macrophages

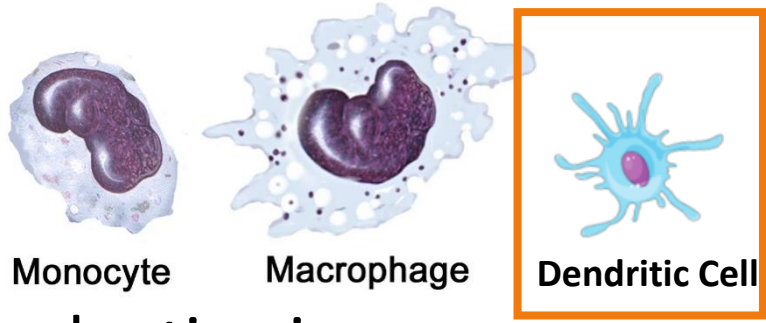
https://youtu.be/w0-0Bqoge2E

(Just in case, if the link does not work)



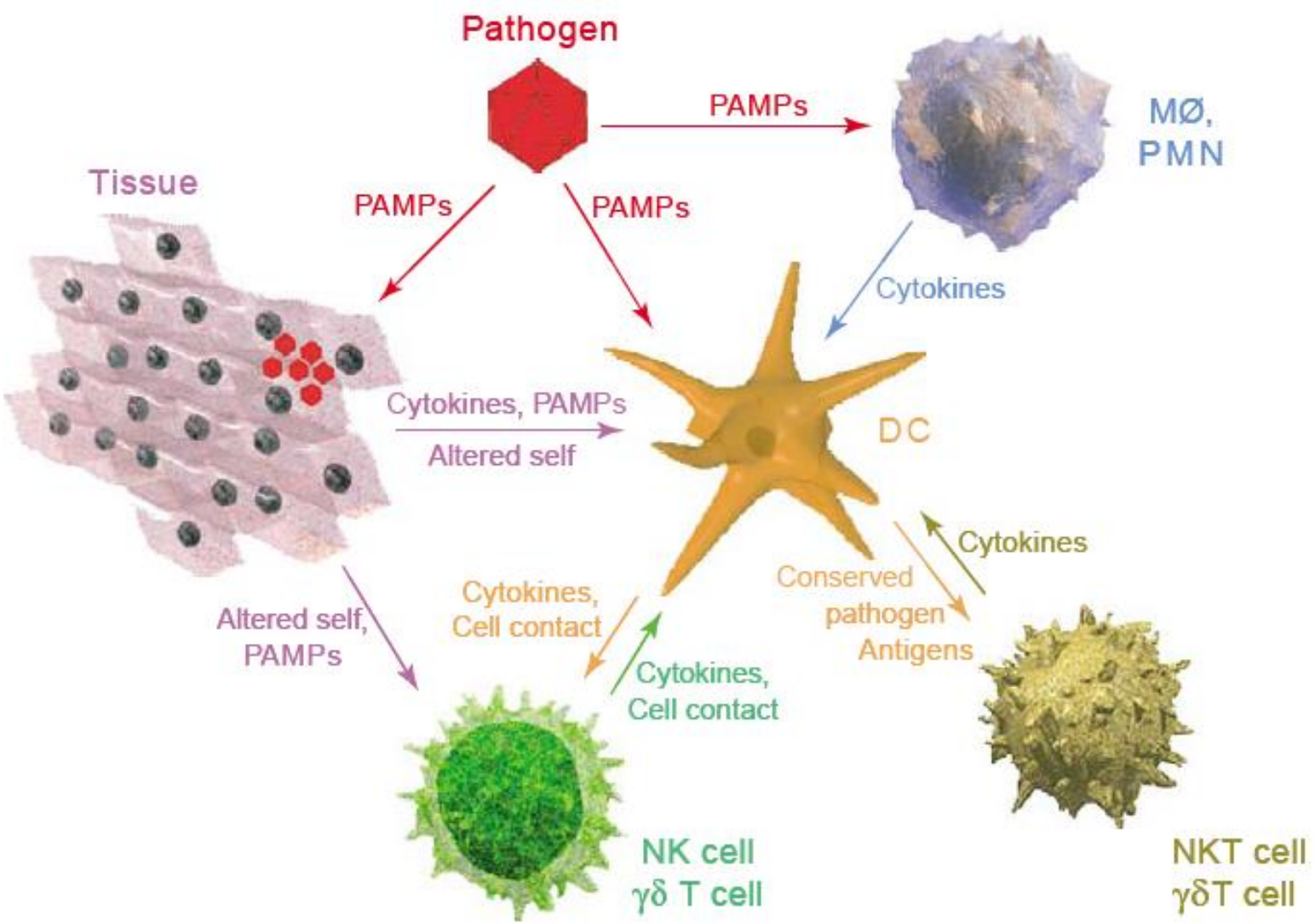
Amsterdam UMC

Dendritic cells



- Main function: to process antigen material and present it to the cell surface to the T-cells
- They act as messengers between the innate and the adaptive immune system
- Are present in tissue that are in cntact with the external environment such as skin (there a specialized DC is called Langerhans cells), inner lining of the nose, lungs, stomach and intestines
- Once activated, they migrated to the lymph nodes
- Interact with T cells and B cells and shape the adaptive immune response

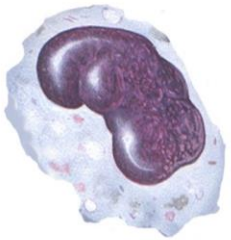
DC Activation



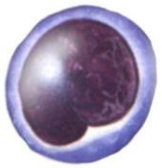
Reise e Sousa, Current Opionions in Immunology (2004)

Amsterdam UMC

Blood cells

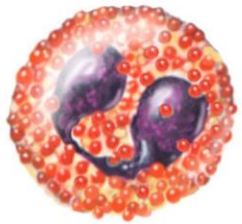


Monocyte

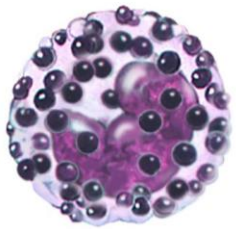


Lymphocyte

Neutrophil

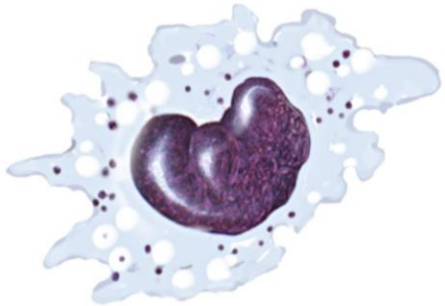


Eosinophil



Basophil

Dendritic Cell



Macrophage

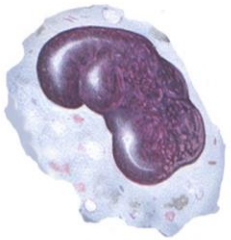
Erythrocyte

Platelets

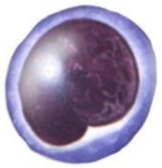
- Thrombocytes (2-3µm)
  "Clot" + "cell" (greek)
- Initiating blood clot
- No nucleus
- Fragments of cytoplasm of megakaryocyte

Amsterdam UMC

Blood cells

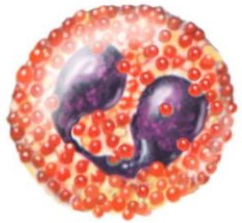


Monocyte

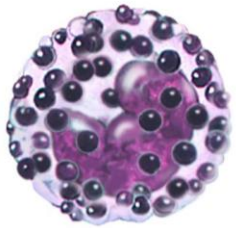


Lymphocyte

Neutrophil

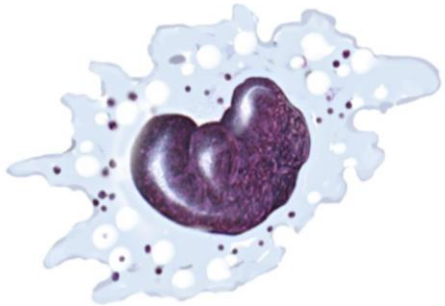


Eosinophil



Basophil

Dendritic Cell



Macrophage

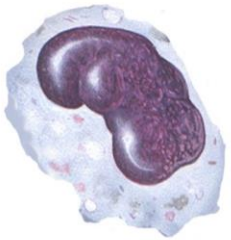
Erythrocyte

Platelets

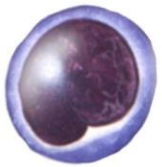
- Erythrocytes (6-8 µm)
  "Red" + "cell" (greek)
- Delivering oxygen
- No nucleus
- Hemoglobin binds O2
- Circulate 100-120d

Blood cells

Adaptive Immune Response

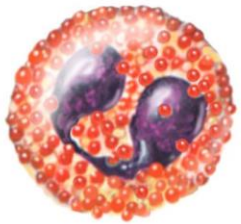


Monocyte

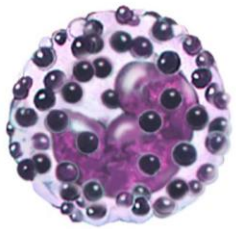


Lymphocyte

Neutrophil

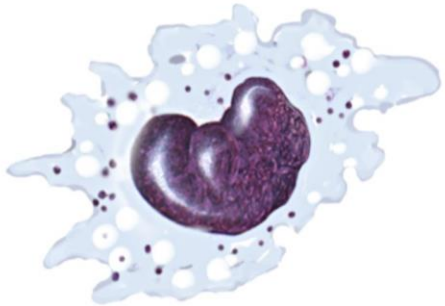


Eosinophil



Basophil

Dendritic Cell



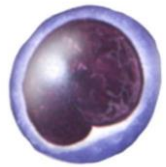
Macrophage

Erythrocyte

Platelets

Amsterdam UMC

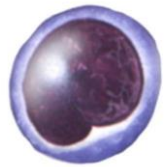
Lymphocytes



Lymphocyte

- 20-40% of WBC
- Large nucleus with dense heterochromatin
- Thin rim of cytoplasm
- Recognize specific antigenic determinants. Thus are responsible for specificity and memory of adaptive immune response

Lymphocytes

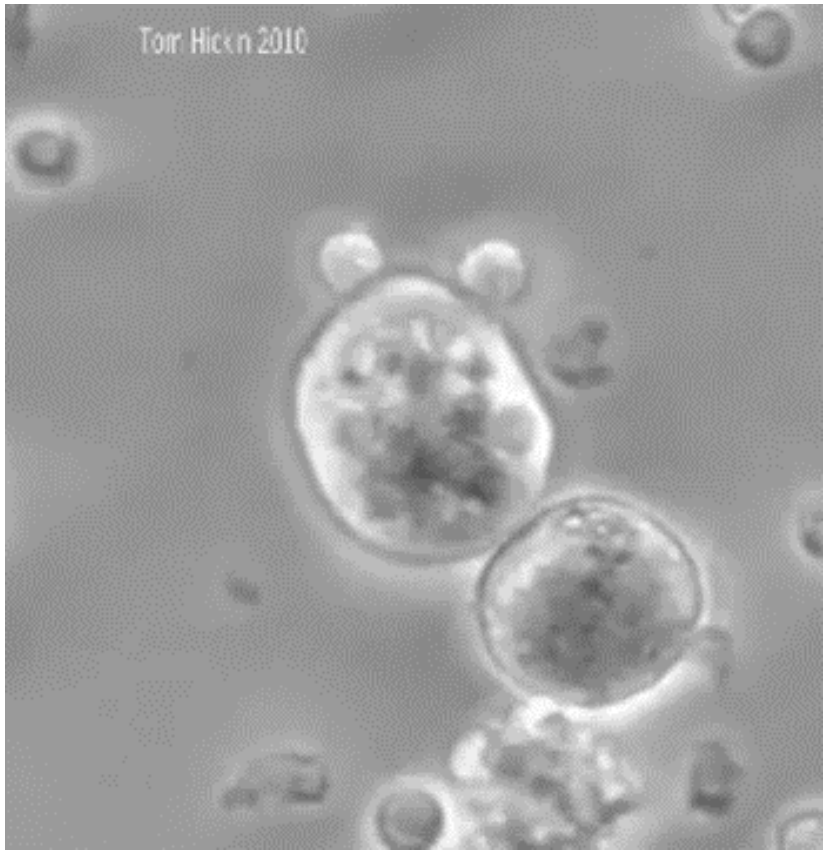


Lymphocyte

Three types: cannot be distinguished morphologically

- T-cells
  - helper CD4+ recognize Ag in context of MHCII
  - cytotoxic CD8+ recognize Ag in MHCI
- B-cells
  - become antibody producing plasma cells
- NK cells
  - part of the innate immune response

T-cells can kill tumor cells!

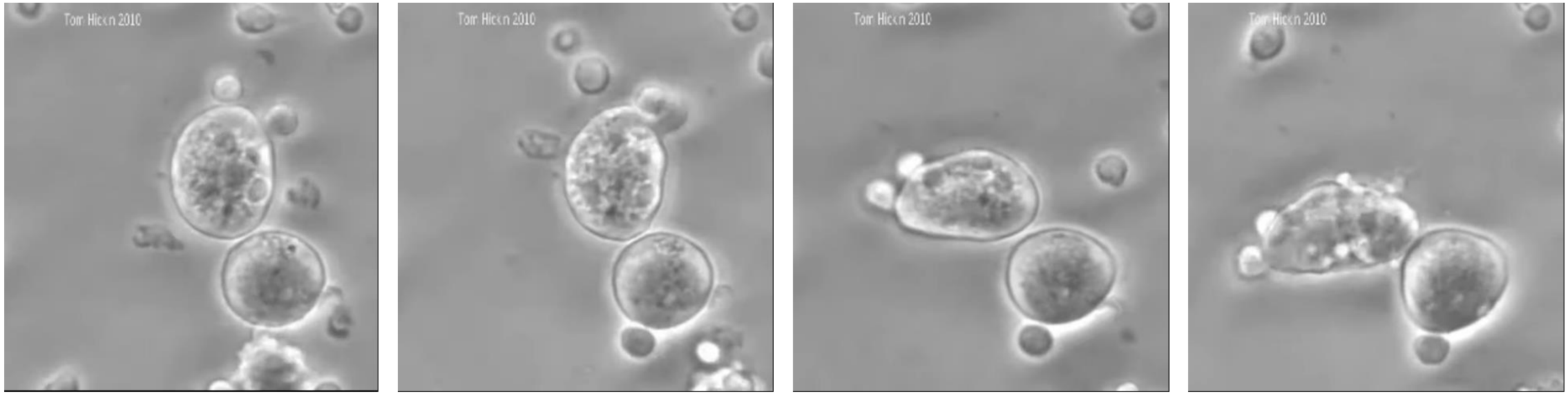


Amsterdam UMC

T-cells can kill tumor cells!

https://youtube.com/shorts/IDvUBz_zQsc?feature=share

(Just in case, if the link does not work)



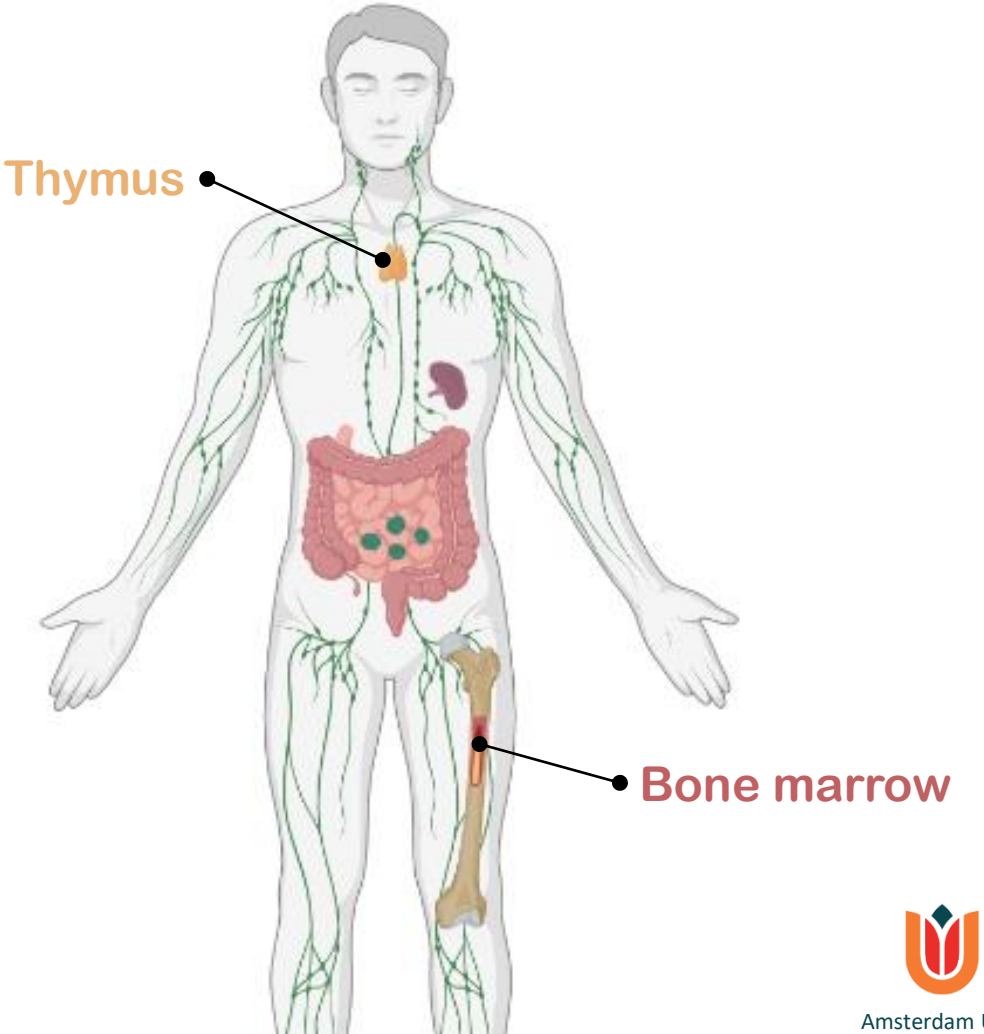
Amsterdam UMC

Lymphatic system

Primary lymphoid organ: Where lymphocytes are formed + mature

- Bone marrow
  - production of T-cells and B-cells
  - maturation of B-cells

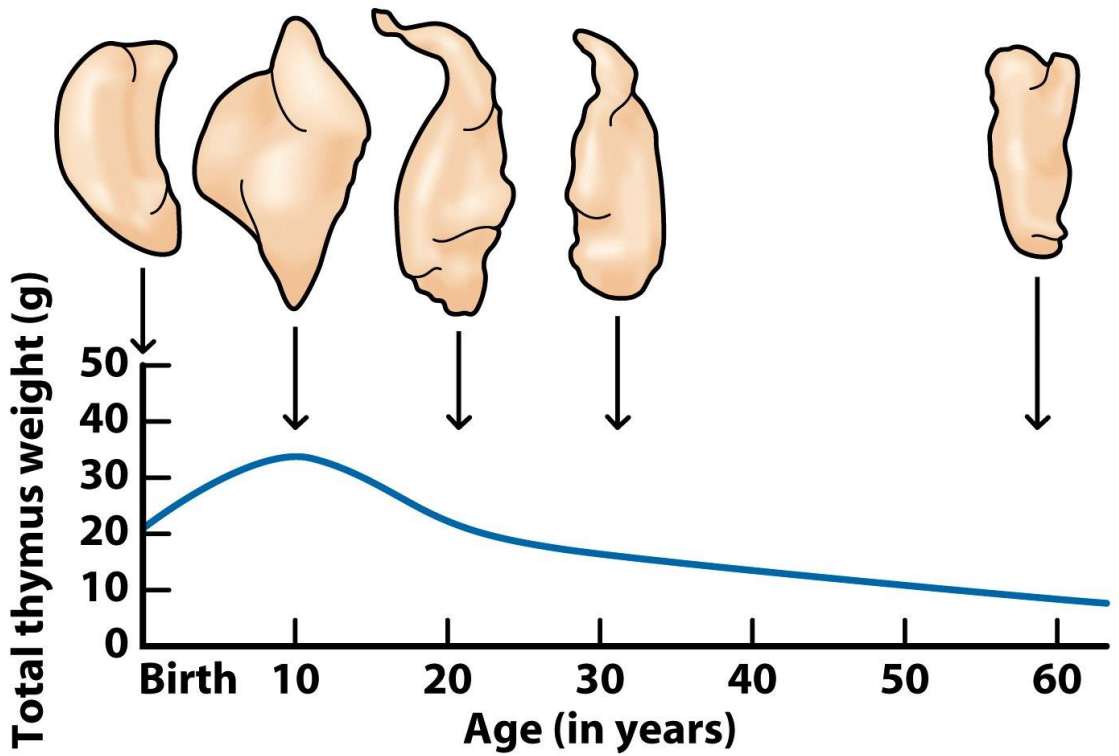
- Thymus
  - maturation of T-cells



Amsterdam UMC

Adult thymus

- Rate of T-cell production peaks prior to puberty
- Greatly reduced but continuous through adulthood
- Thymus undergoes Involution
  - Fatty infiltration
  - Lymphocyte depletion

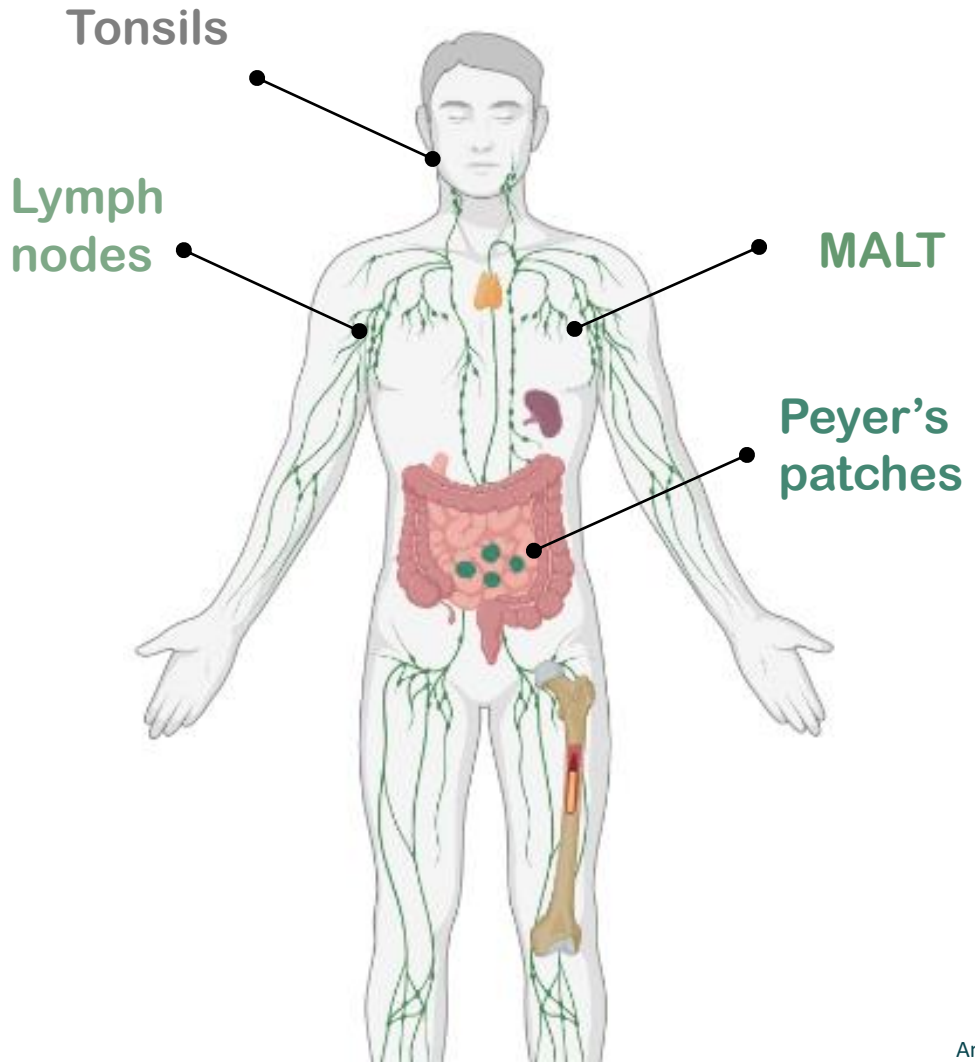


Amsterdam UMC

Lymphatic system

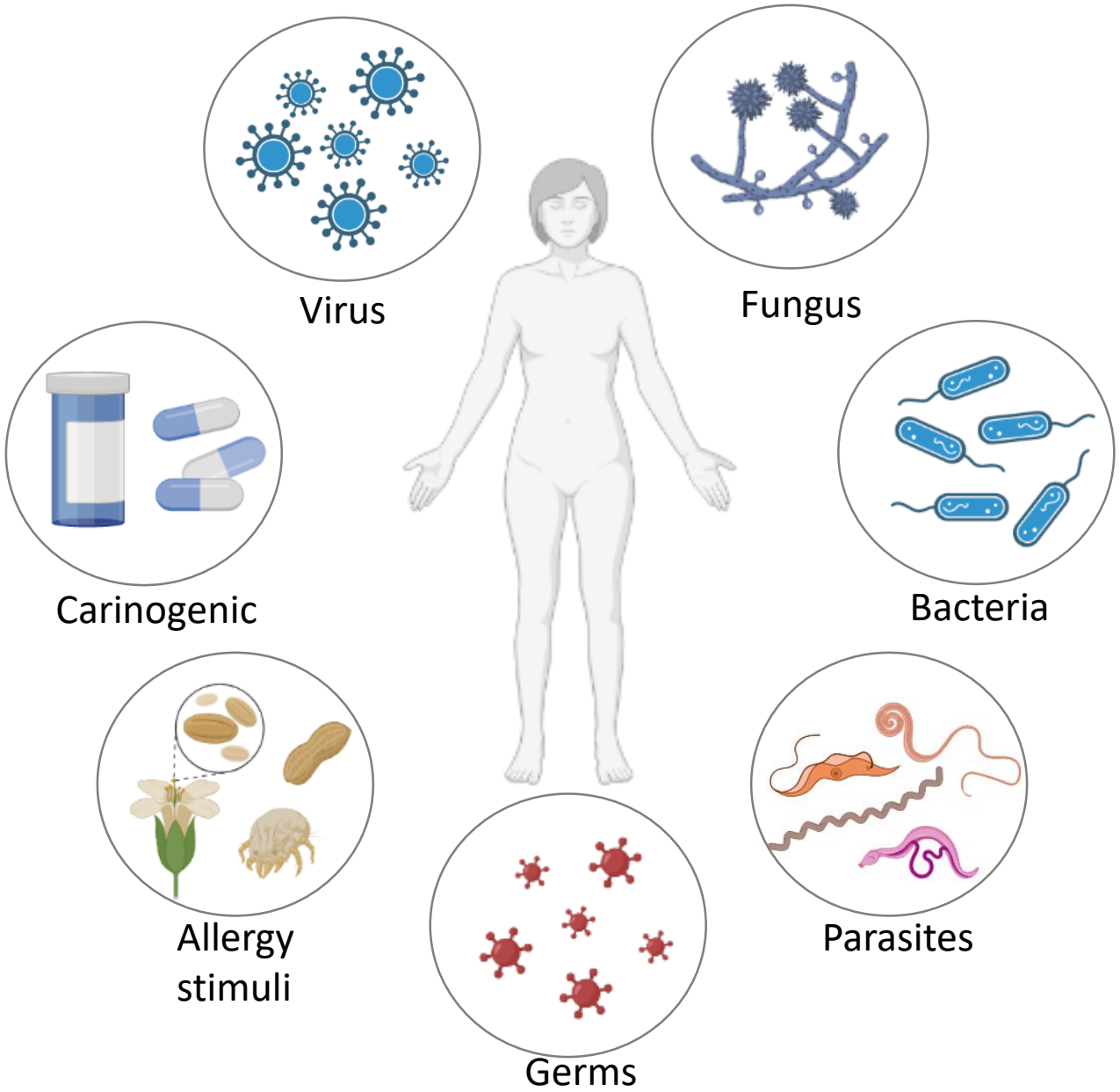
Secondary lymphoid organ: Where lymphocytes are activated

- Lymph nodes (adults ~450 LN)
- Tonsils
- Peyer's patches
- Mucosa associated lymphoid tissue (MALT)



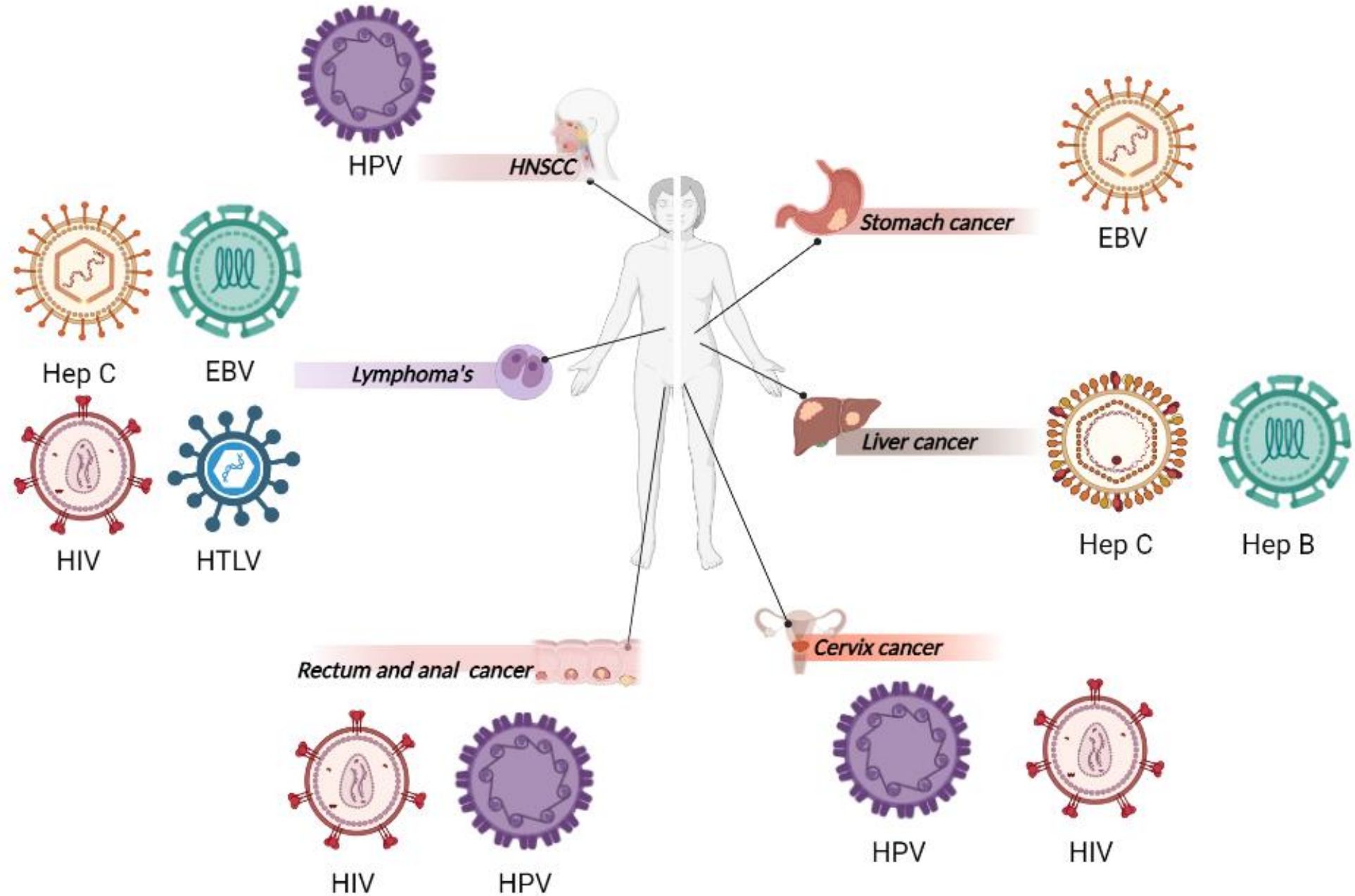
Amsterdam UMC

Our immune response is very powerful



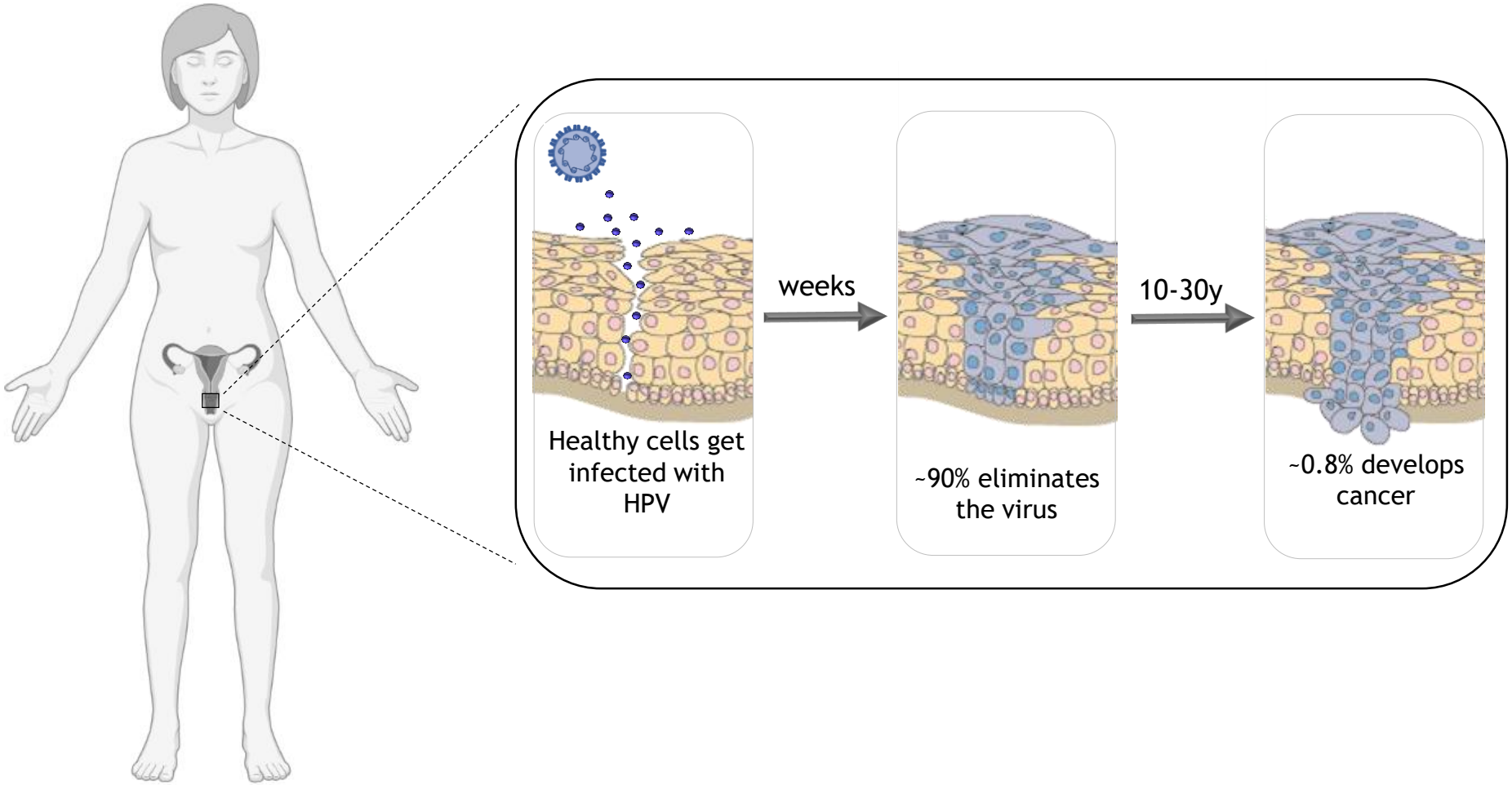
Amsterdam UMC

Virus-related cancer



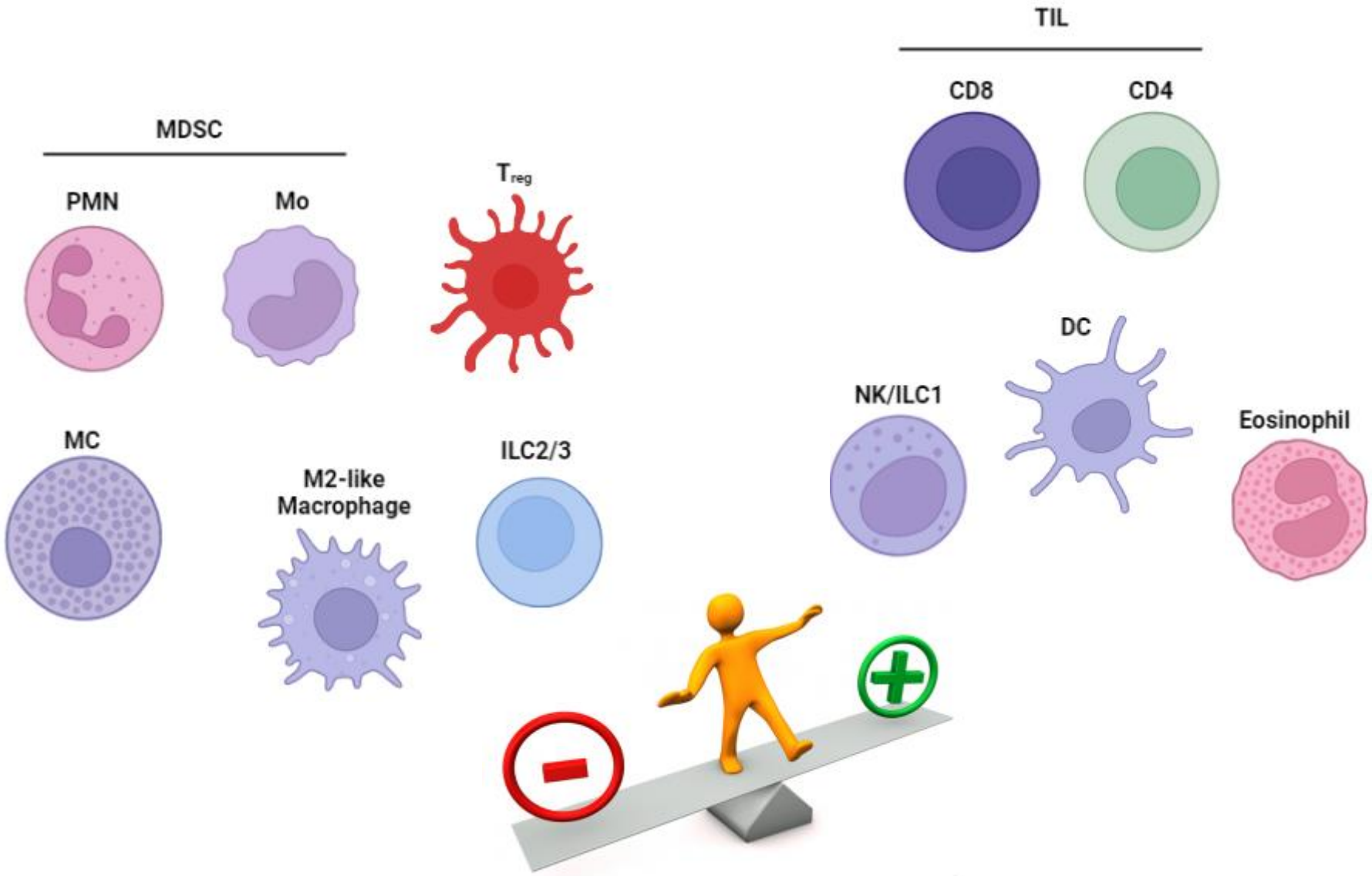
Amsterdam UMC

Human Papillomavirus causes cervical cancer



Amsterdam UMC

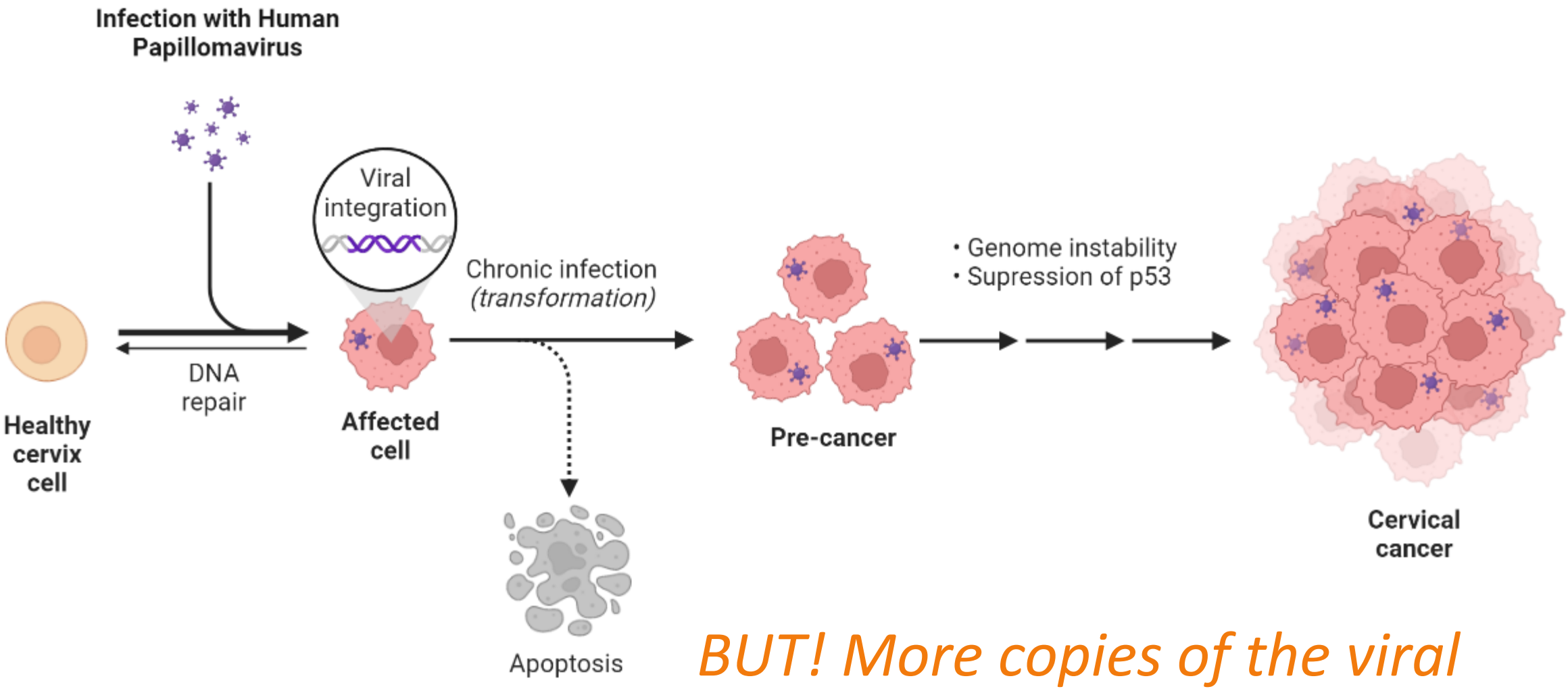
Why do some people develop cancer while others don’t?



(Adapted from Salemme et al, Front Oncol, 2021)

Amsterdam UMC

HPV integrates to the human DNA



BUT! More copies of the viral DNA can get integrated

HPV in cell lines

Cervical cancer is mainly caused by HPV16 and HPV18

SiHa cells	1 copy of viral DNA/cell 1 copy gets transcribed
Caski cells	500 copies of viral DNA/cell 499 copies are silenced

What does this mean?

Amsterdam UMC

What do you think…?

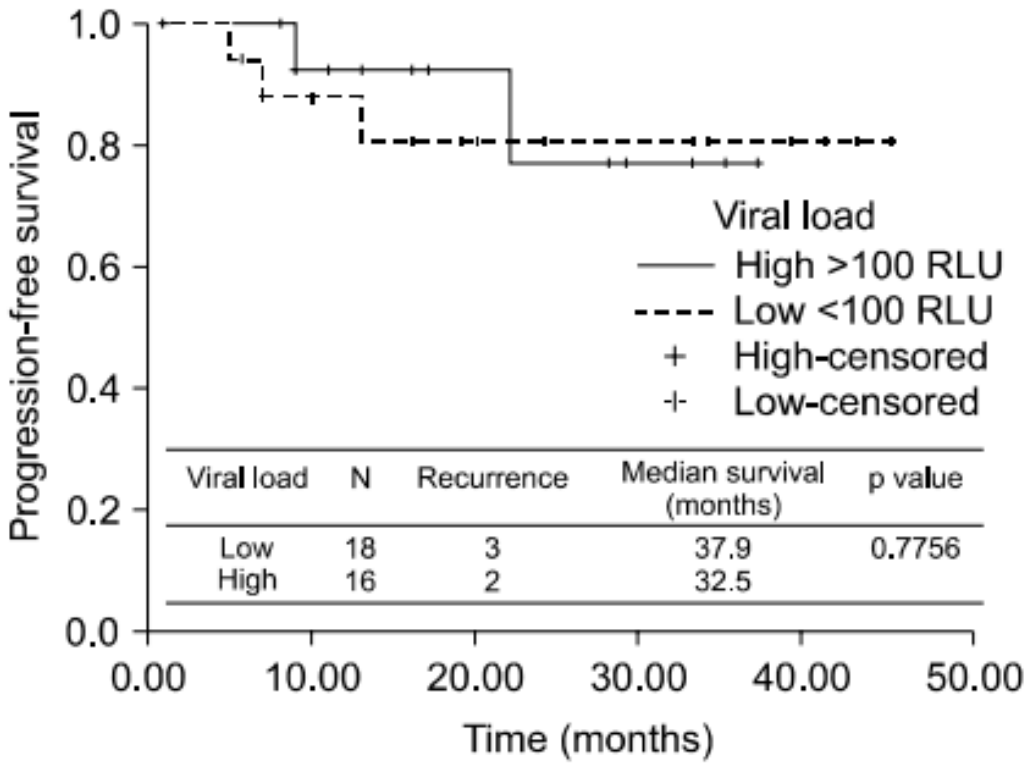
Go to www.menti.com and use the code 4872 2756

Is the viral load correlated to treatment response?

A. Definitely! More viral DNA will cause more viral proteins, thus more suppression of your immune system
B. No, of course not: a person is just positive or not for HPV, the amount of virus doesn’t matter

Amsterdam UMC

No sign. Correlation of HPV load and PFS

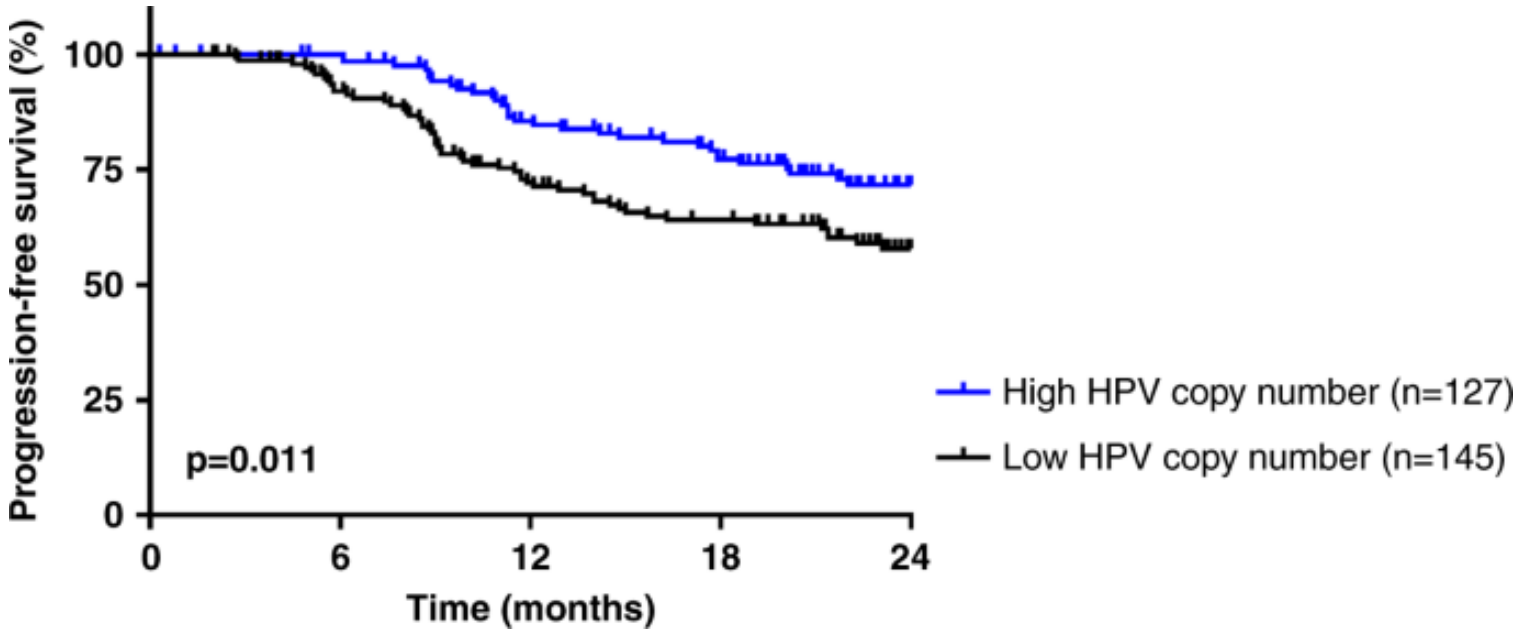


Viral load	N	Recurrence	Median survival (months)	p value
Low	18	3	37.9	0.7756
High	16	2	32.5	

Kim et al, J Gynecol Oncol (2008)

Amsterdam UMC

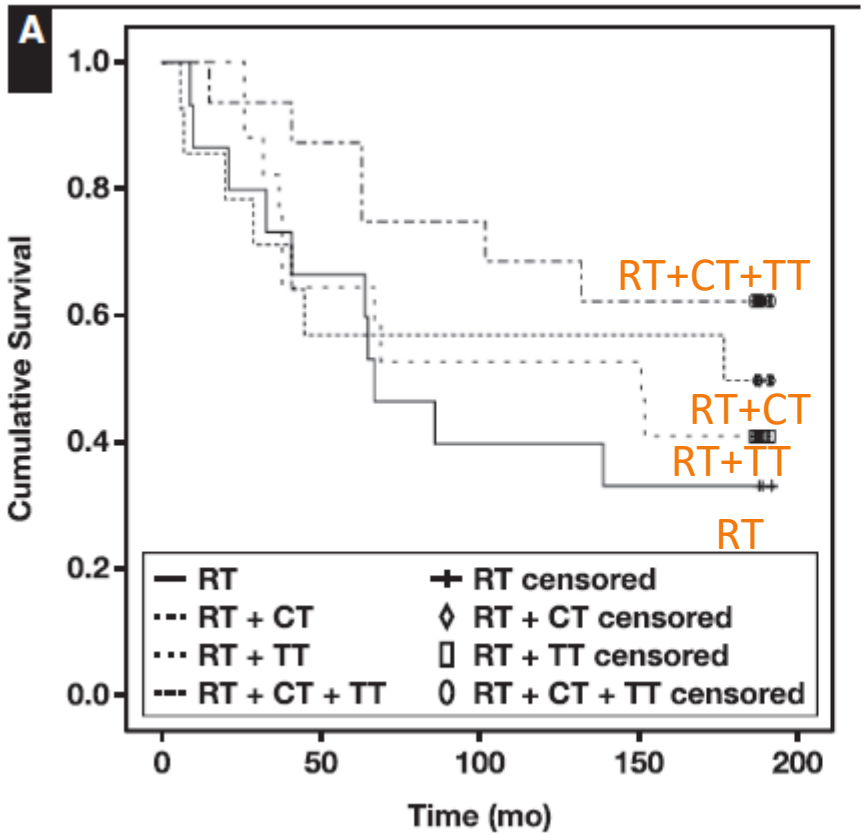
High HPV copy number is associated with longer PFS

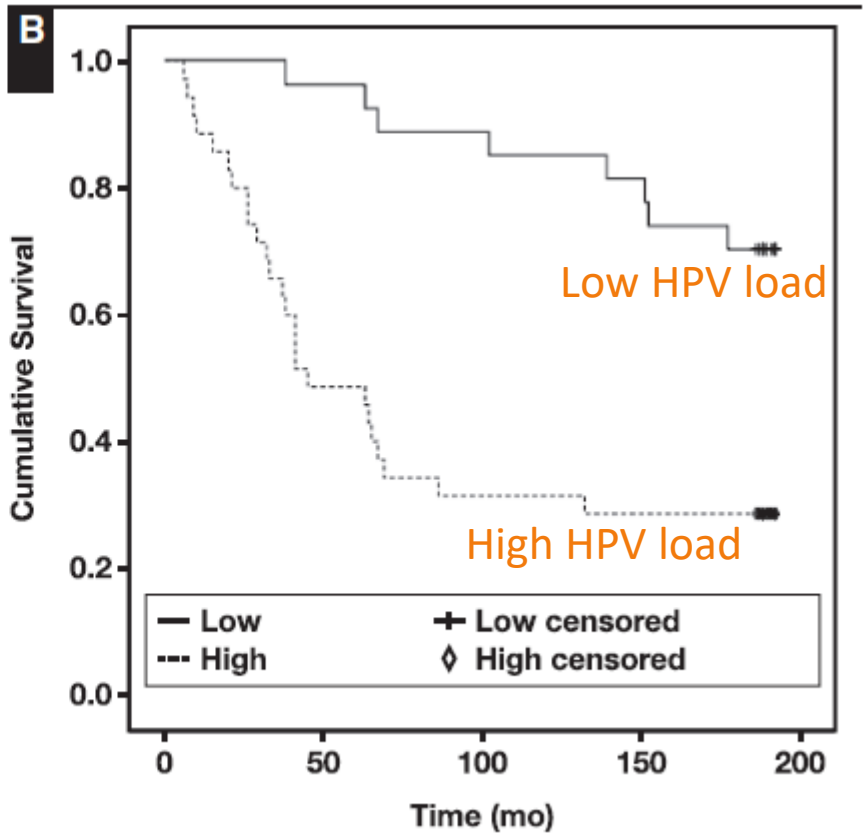


Maud et al, BJC (2020)

Amsterdam UMC

High HPV load is correlated with poor survival





Cao et al, Am J Clin Pathol (2020)

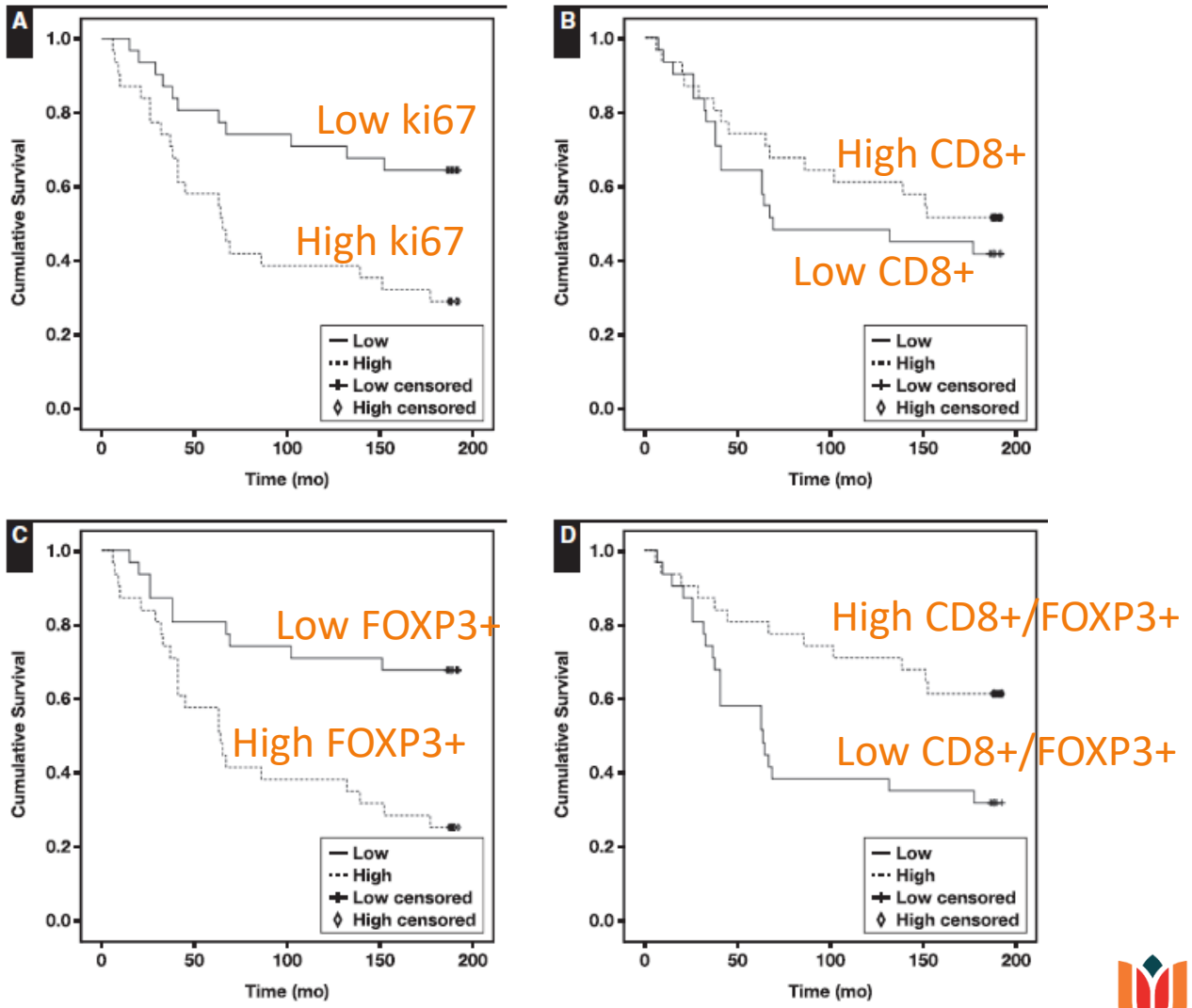
Amsterdam UMC

Increased HPV viral load is associated with Immunosuppr. TME and predicts worse long-term survival

Overall Survival of the Patients Under Various Treatment Approaches

Group	Survival, No./ Total No. (%)	χ^2 Value	*P* Value
RT	5/15 (33.3)	2.950	.399
RT + CT	7/14 (50.0)		
RT + TT	7/17 (41.2)		
RT + CT + TT	10/16 (62.5)		
Total	29/62 (46.8)		

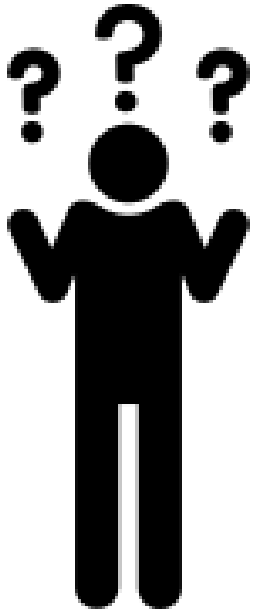
CT, chemotherapy; RT, radiotherapy; TT, thermotherapy.



Cao et al, Am J Clin Pathol (2020)

Amsterdam UMC

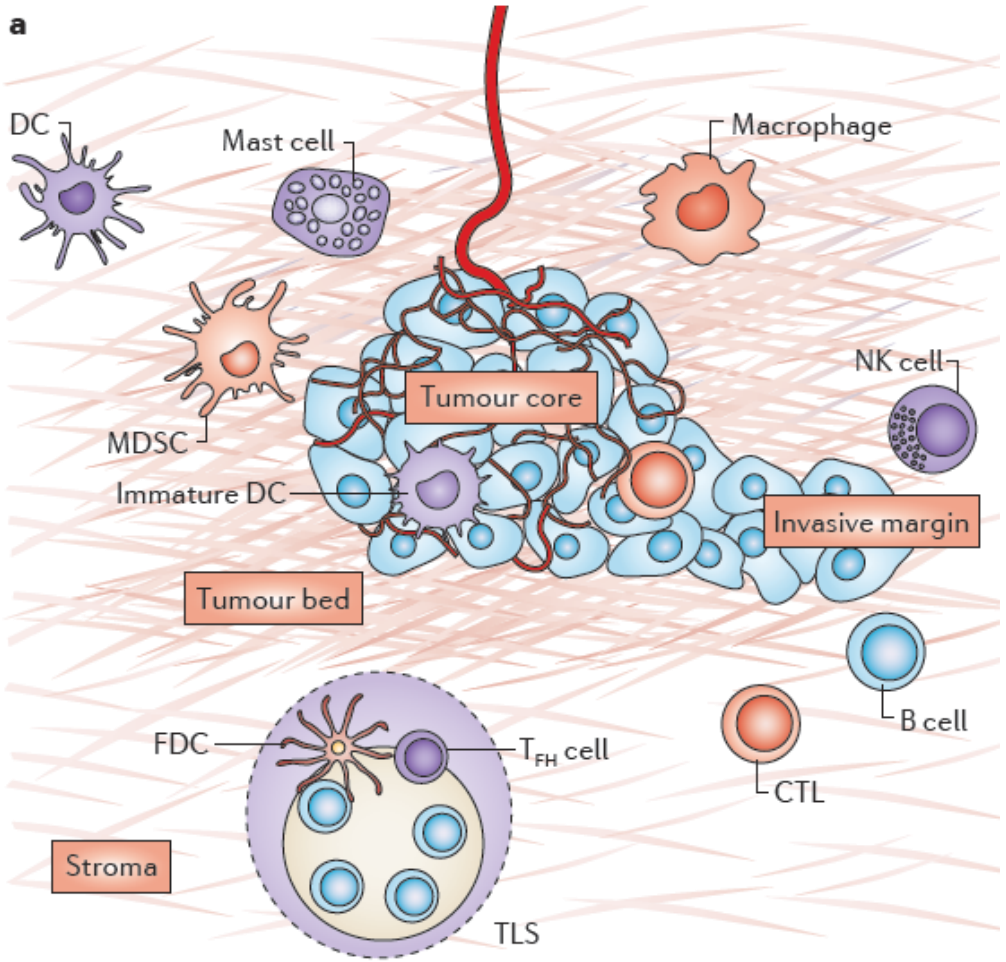
Some think they know the answer



Looking at all the data:
we actually don't have an answer yet

Amsterdam UMC

The Immune contexture

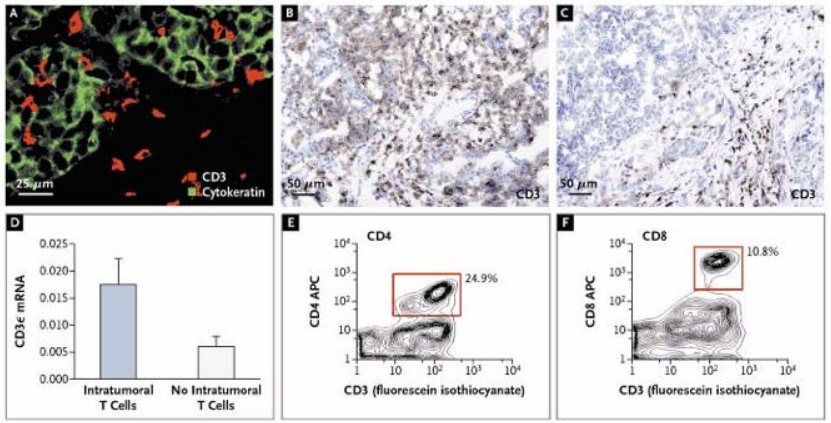


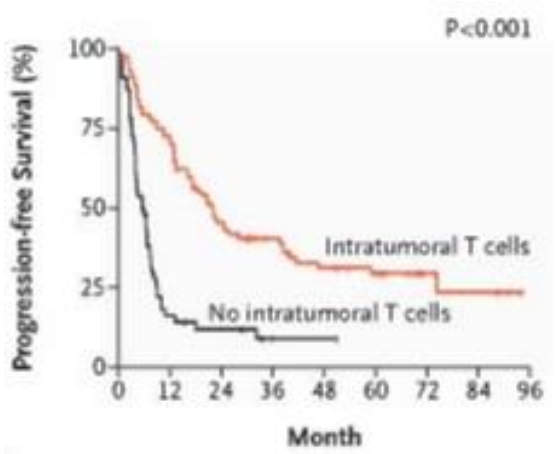
Many types of immune cells can be found in the TME

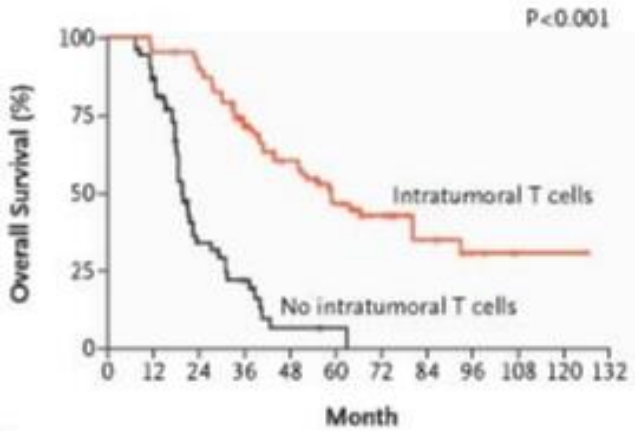
Fridman/Galon Nat Rev Cancer (2012)

Amsterdam UMC

TIL correlate with survival in ovarian cancer patients







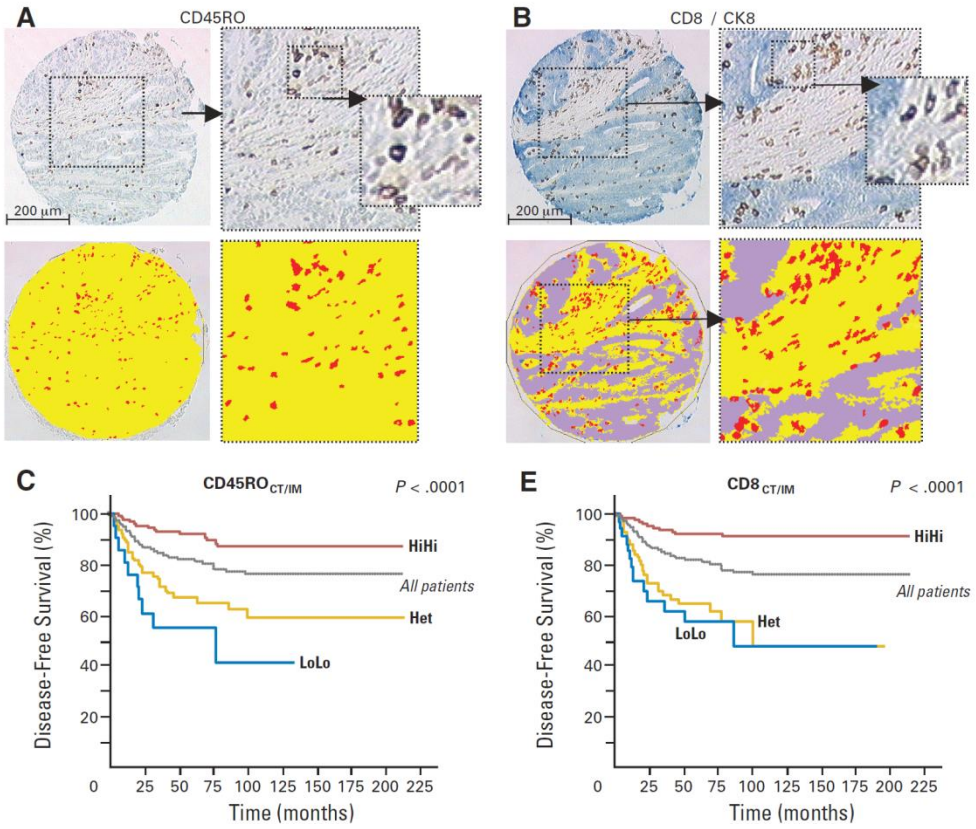
Zhang et al, NEJM, 2003

Amsterdam UMC

Patients: TIL correlated with 5y outcome

IHC

Image analysis



Immune contexture

- **Location**
- **Density**
- **Functional orientation**

Center vrs. invasive margin

Pager/Galon, J Clin Oncol (2009)

Amsterdam UMC

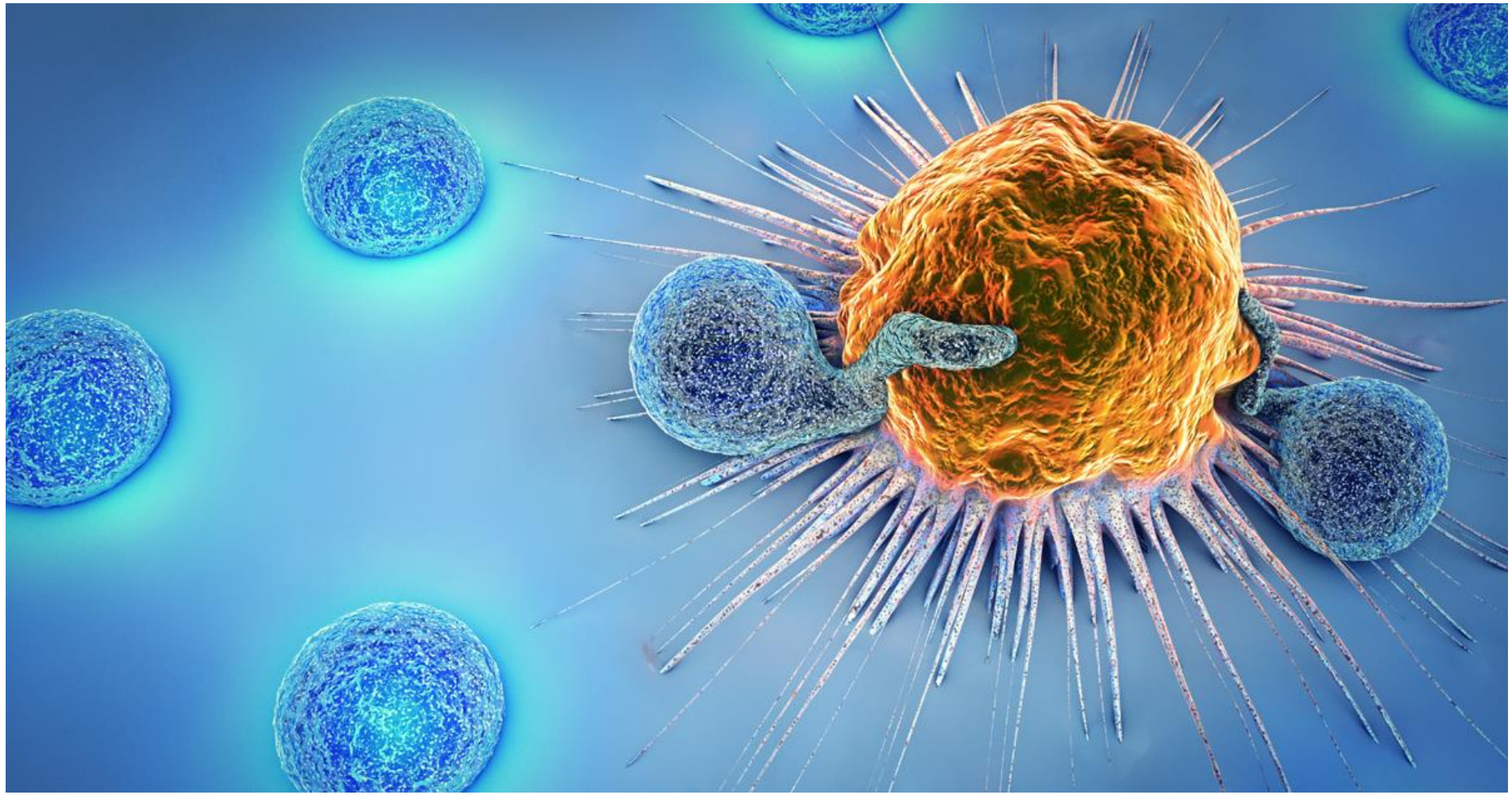
Cancer classification using the “Immunoscore”: a worldwide task force

- Currently histopathological stage scoring is based on TNM (Tumor, Node, Metastasis) - characteristics of the **tumor**
- Little value in predicting response to therapy
- Proposed “**Immunoscore**”- first **immune based** classification

Galon et al, J Trans Med (2012)

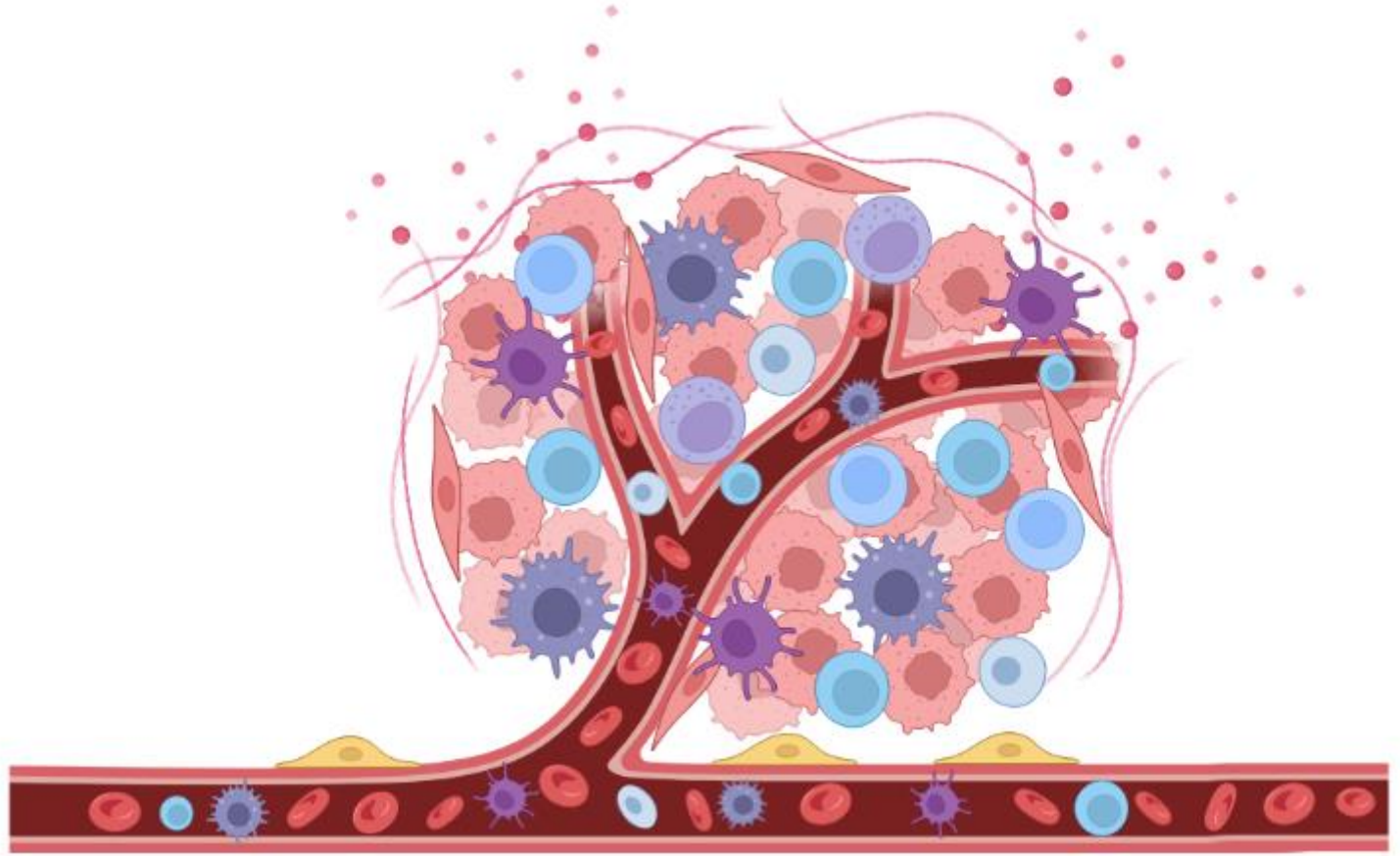
Amsterdam UMC

Using our immune system to fight cancer



Amsterdam UMC

Mild hyperthermia has many effects on the immune system



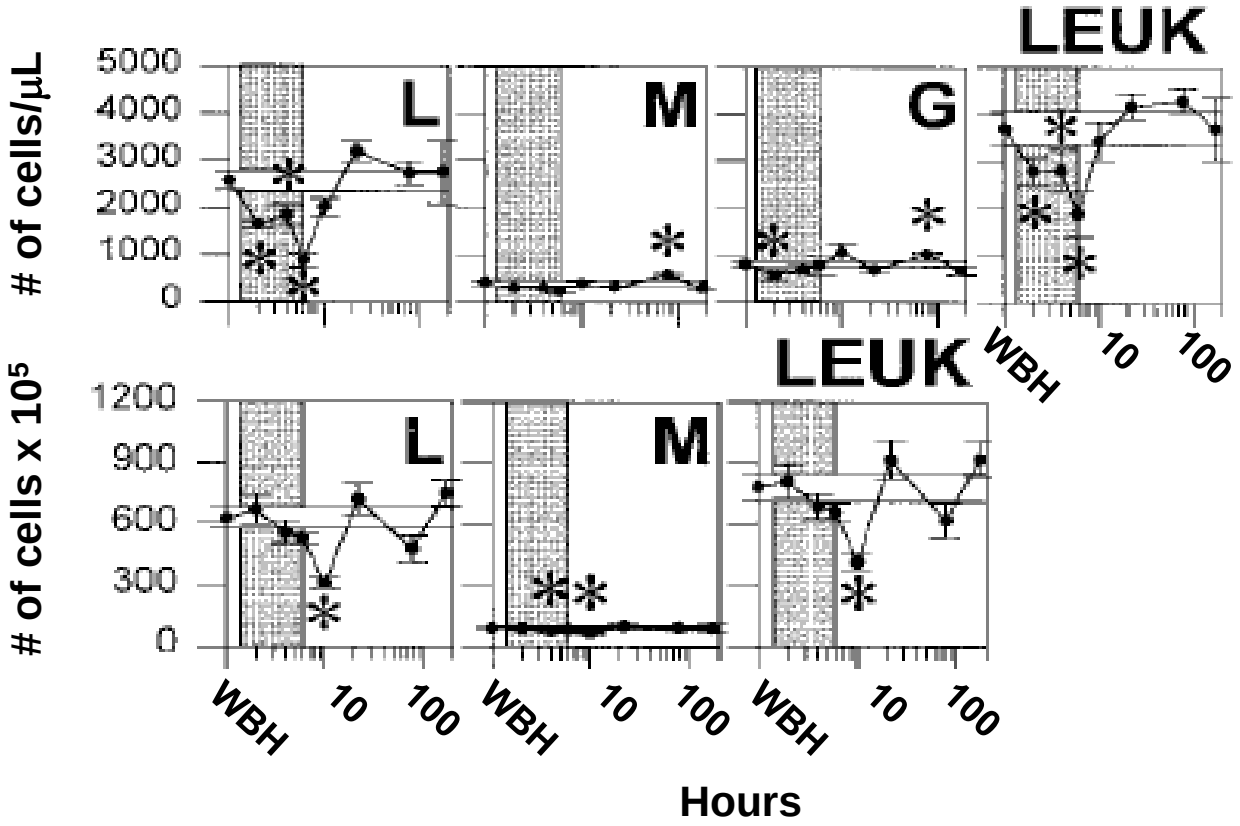
- Migration of immune effector cells to target site
- Regulation of effecte molecules and release of soluble factors
- Proliferation of effector cells
- Killing of target cells

Amsterdam UMC

Fever-range hyperthermia alters leukocyte distribution

BLOOD

SPLEEN



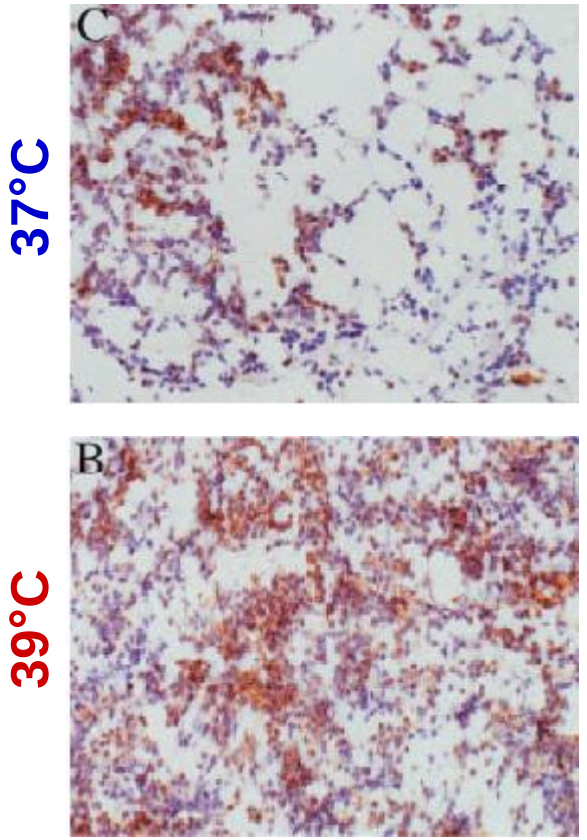
Hyperthermia treatment alone can alter lymphocyte, monocyte, and granulocyte numbers in mice.

Ostberg and Repasky, IJH (2000)

Amsterdam UMC

Fever-range HT increases neutrophil accumulation

Lung After Infection

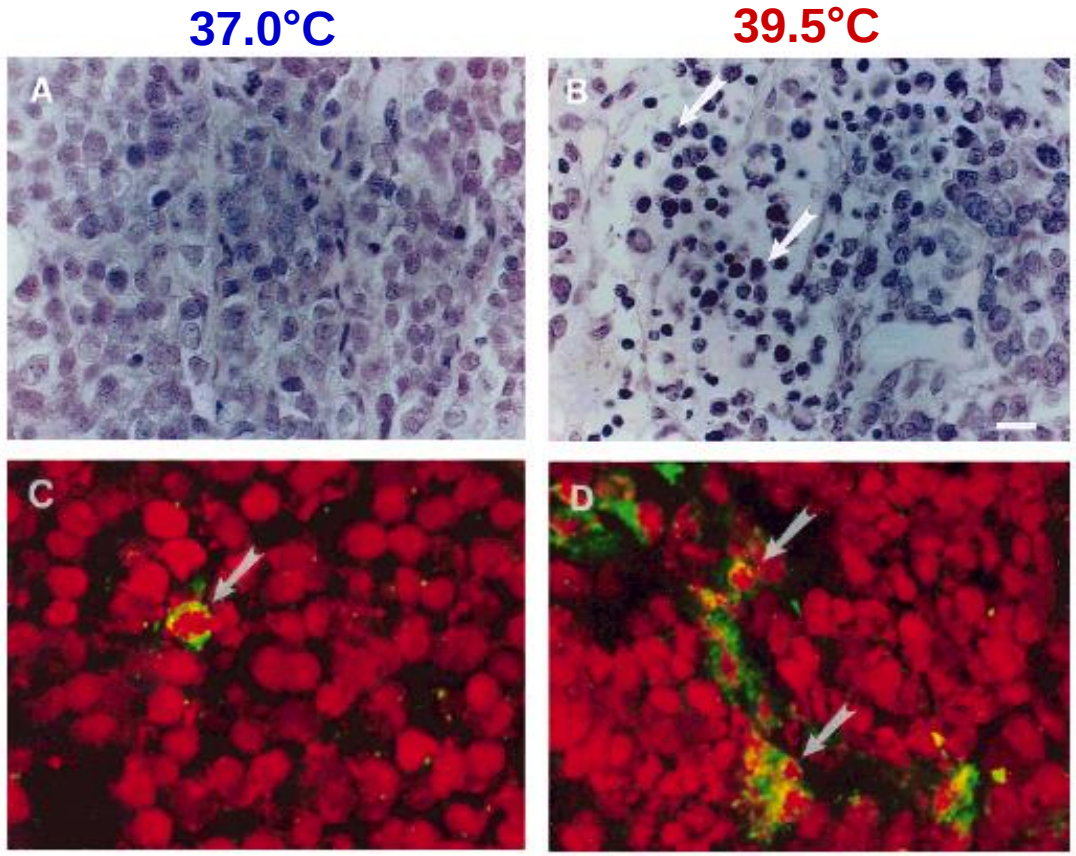


- Elevating murine body temperature to 39°C after i.t. injection of *K. pneumoniae* or LPS leads to:
  - enhanced PMN infiltration into the lung
  - decreased bacterial burden due to host related immunity
  - decreased survival due to extensive lung damage caused by the heightened immune response
- Increasing core body temperature to 39.7°C after i.p. injection of *K. pneumoniae* or LPS lead to:
  - enhanced PMN numbers in the peritoneum
  - decreased bacterial burden
  - increased survival (from 0%-50%)

Rice et al, Journal of Immunology (2005)
Jiang et al, Infection and Immunity (2000)

Amsterdam UMC

Fever-range HT recruits NK cells into tumor tissue

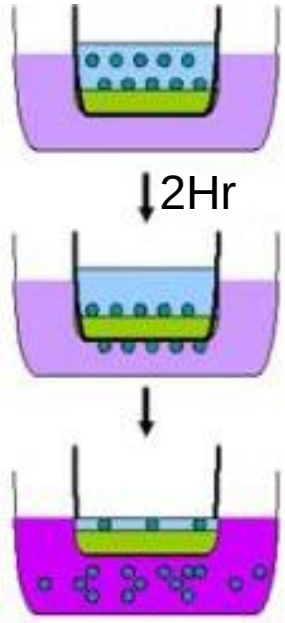


SCID mice with patient breast cancer xenografts

Burd et al., Journal of Cellular Physiology (1996)

Amsterdam UMC

Moderate HT increases Mo-derived DC migration toward chemokine signaling



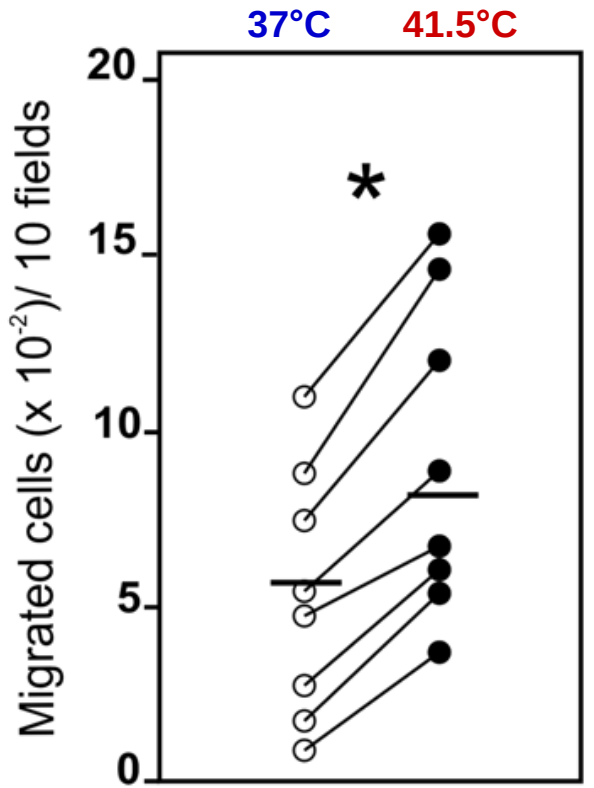
moDCs placed in upper chamber

2Hr

Migratory cells pass through membrane and cling to the bottom side

Migratory cells are detached and counted

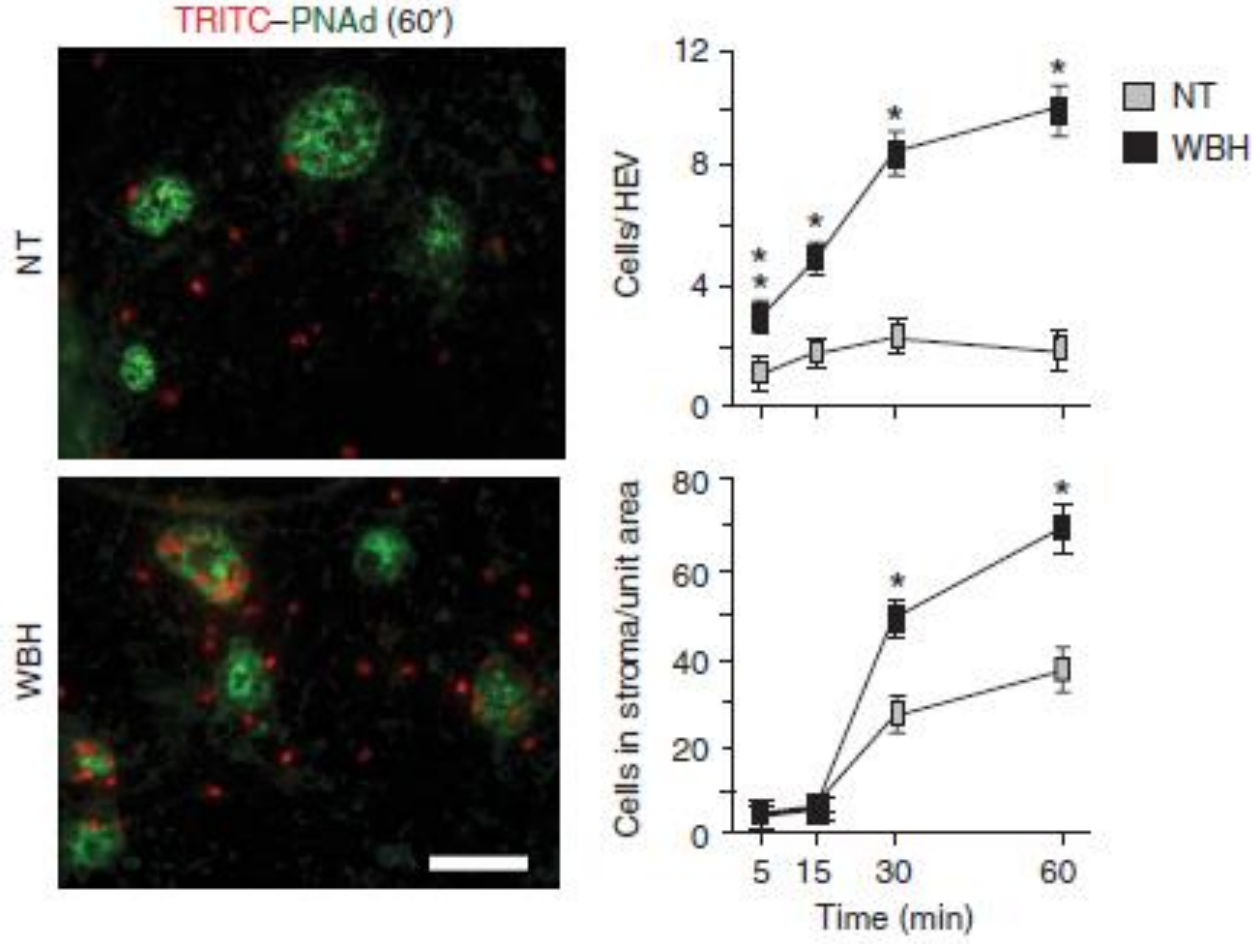
Serum-free media
LPS & MIP-3β media
Membrane
Cell detachment buffer



Hatzfeld-Charbonnier, Journal of Leukocyte Biology, 2007; 81(5): 1179--87

Amsterdam UMC

Fever-range HT promotes lymphocyte trafficking into Lymph nodes

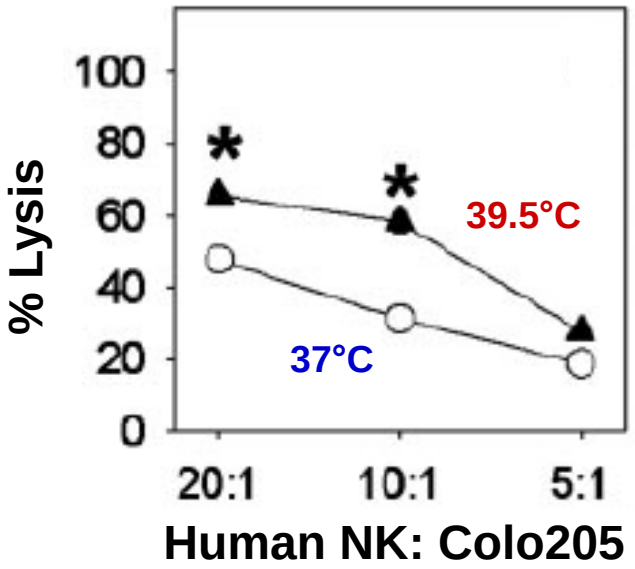


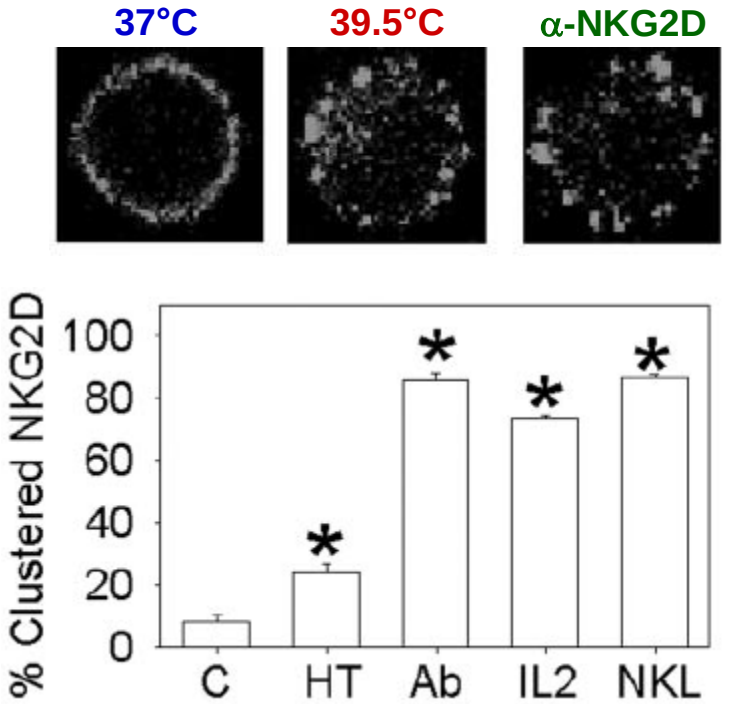
Hyperthermia's effect is dependent on an IL-6-mediated up-regulation of ICAM-1.

Chen et al., Nature Immunology (2006)

Amsterdam UMC

Fever-range HT enhances NKG2D-mediated NK cell cytotoxicity



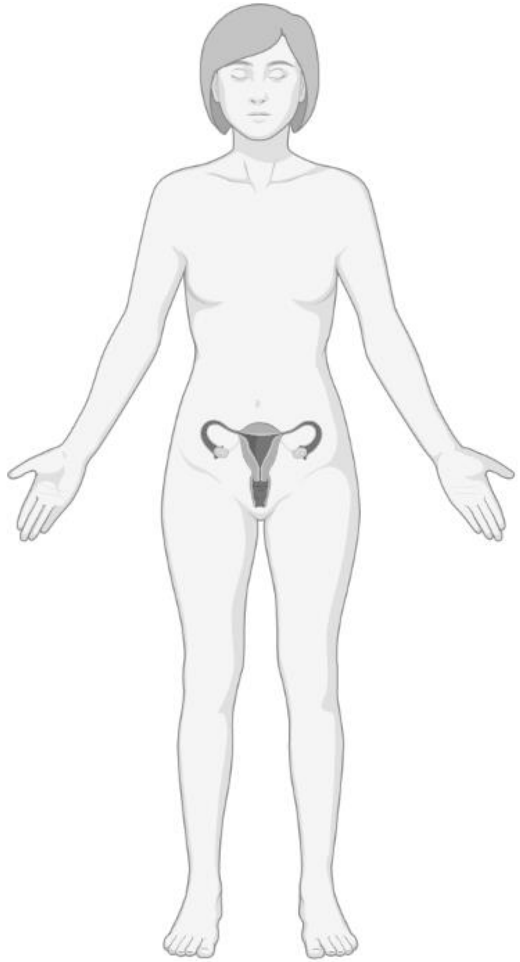


Hyperthermia's enhancement of NK cell cytotoxicity is also associated with an increase of the NKG2D ligand, MICA, on the target cell surface.

Ostberg et al., Journal of Leukocyte Biology (2005)

Amsterdam UMC

Treatment for cervical cancer



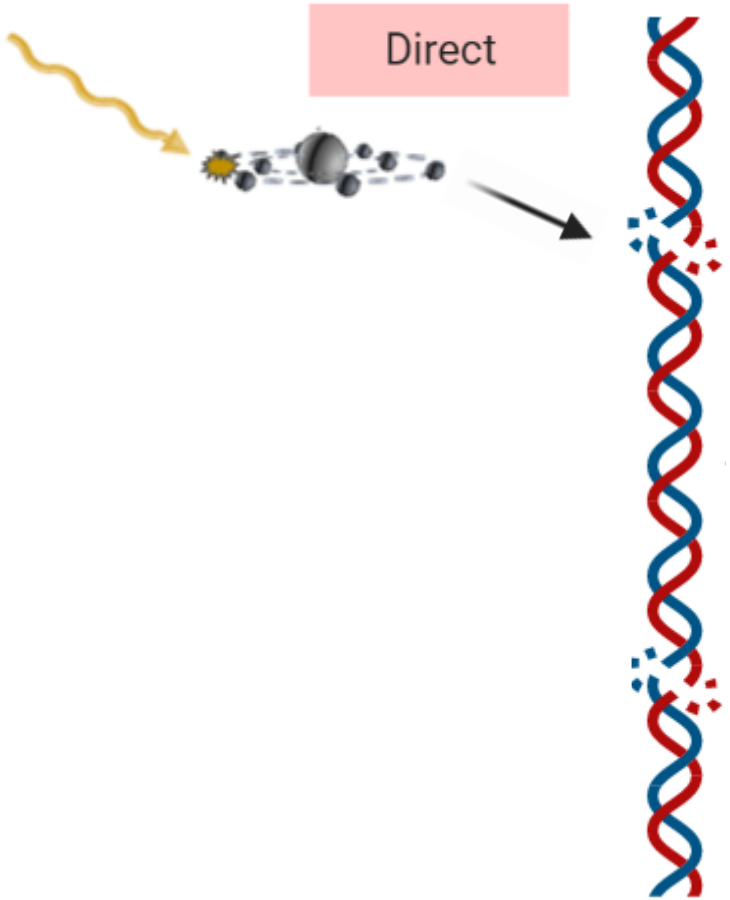
Standard-of-care = chemoradiation

In case of contra-indications

Thermoradiation

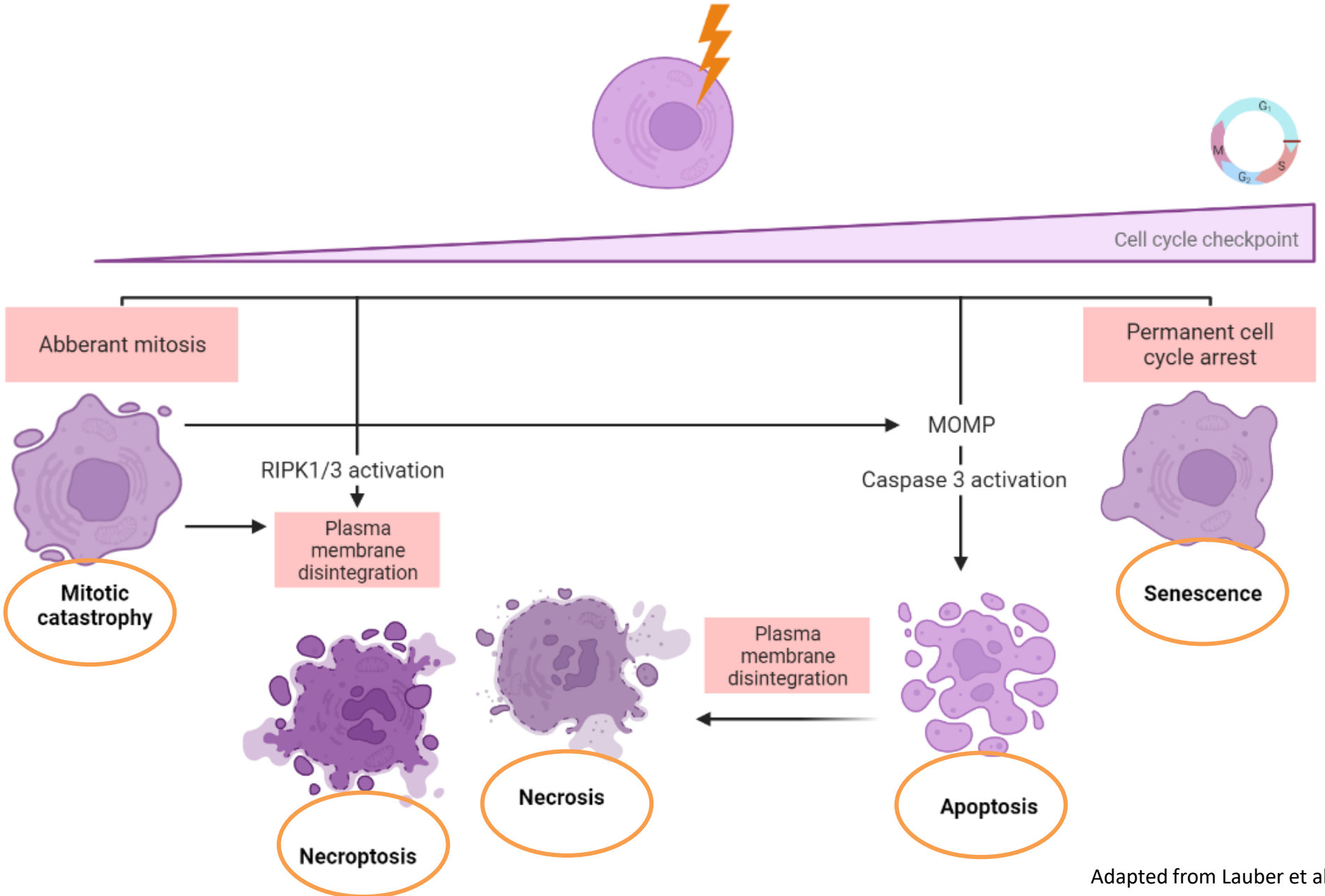
Amsterdam UMC

Target of ionizing radiation



Amsterdam UMC

Different types of cell death



Adapted from Lauber et al, Front. Oncol. 2012

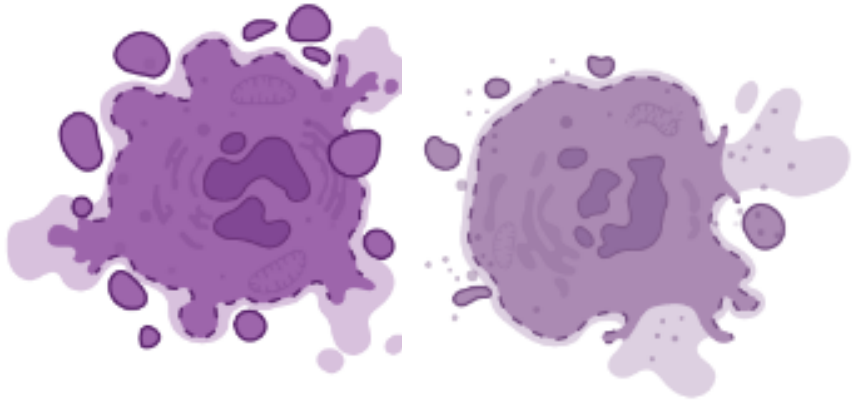
Different types of cell death

Quiet cell death

Apoptosis

- No danger signal
- Phagocytosis by macrophage
- Antigen presented without co-stimulation
- Immunosuppressive cytokines
- T-cell death

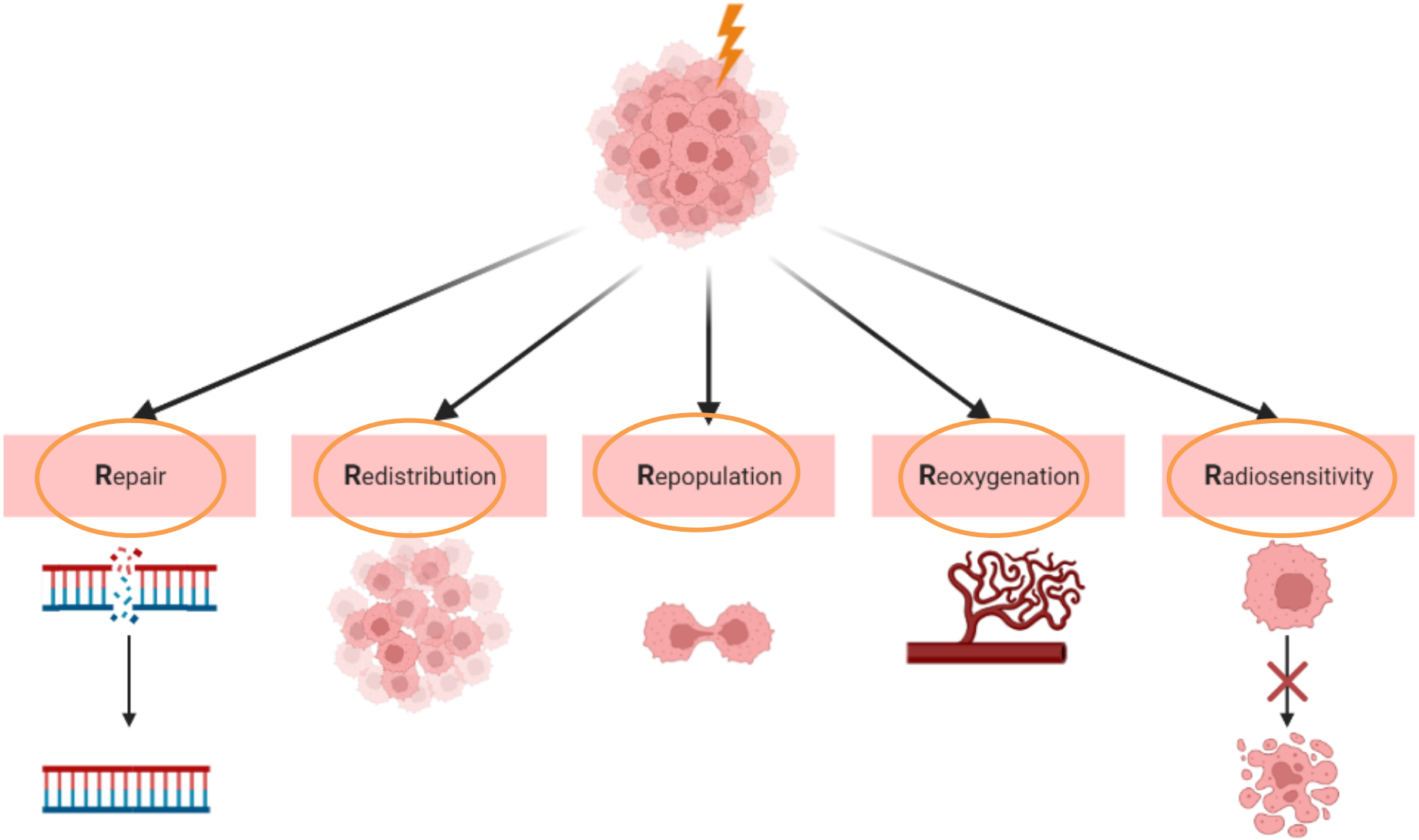
Danger-signalling cell death



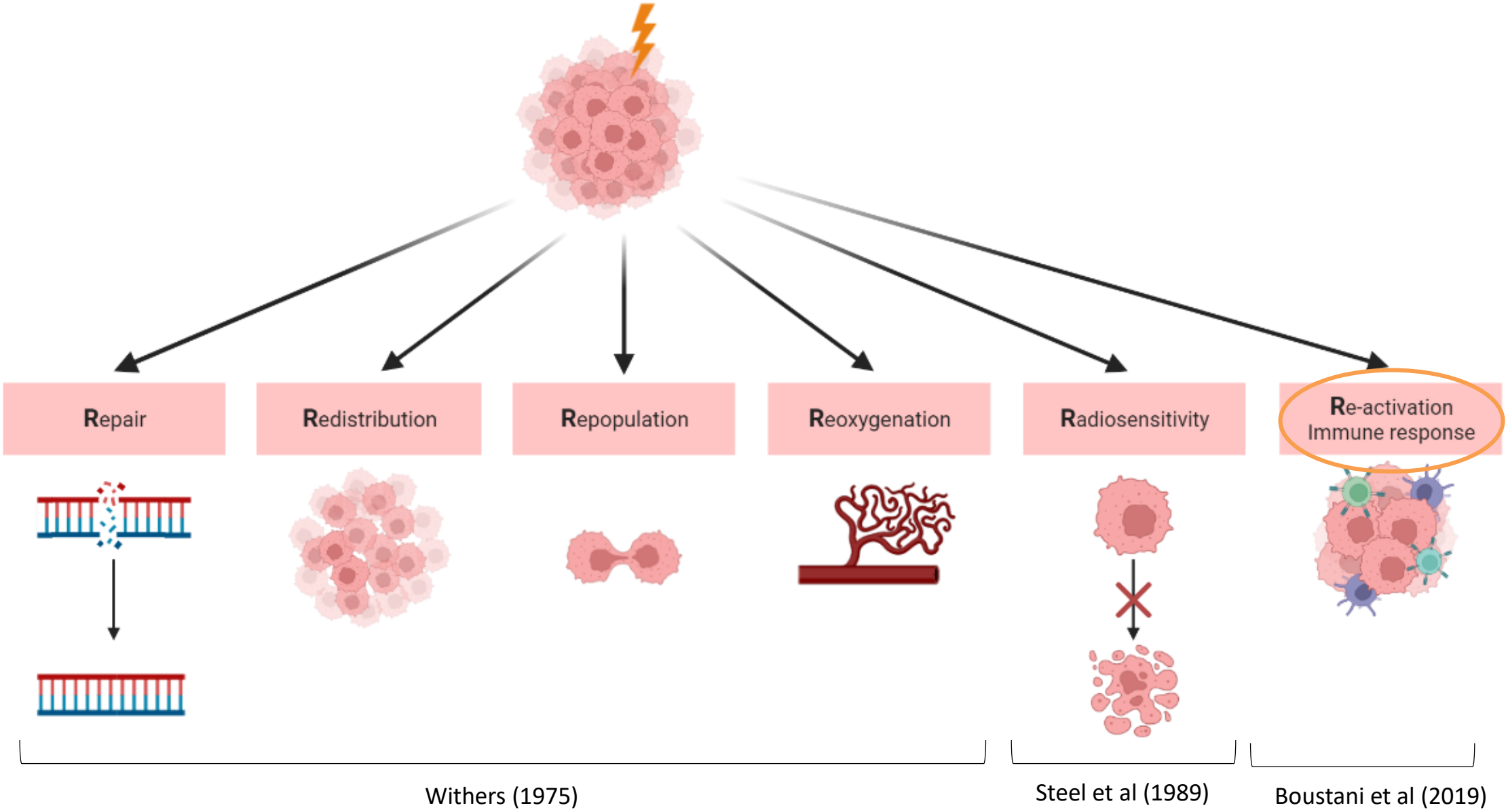
Necroptosis Necrosis

- Release of danger signals
- Antigens taken up by dendritic cells
- DC mature and migrate to lymph nodes
- Antigen presented + co-stimulation
- Proinflammatory response
- T-cell activation

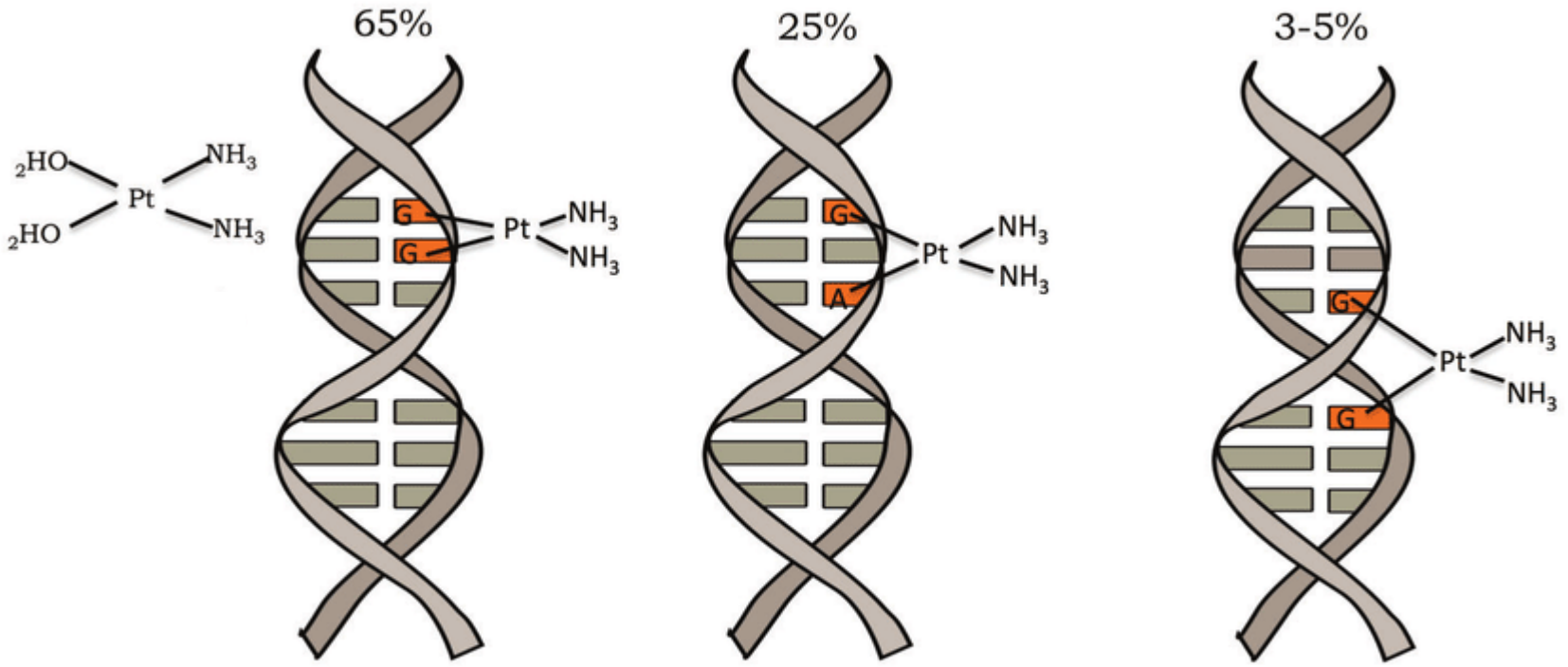
Factors influencing local tumor control: 5 R's



Factors influencing local tumor control: 6 R's



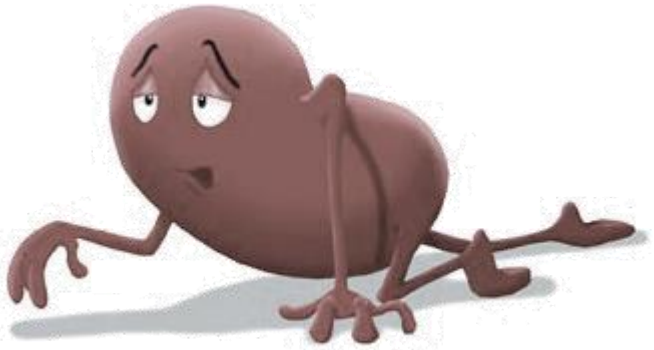
Cisplatin-based chemotherapy



Intrastrand adduct

Interstrand crosslink

Reducing side effects

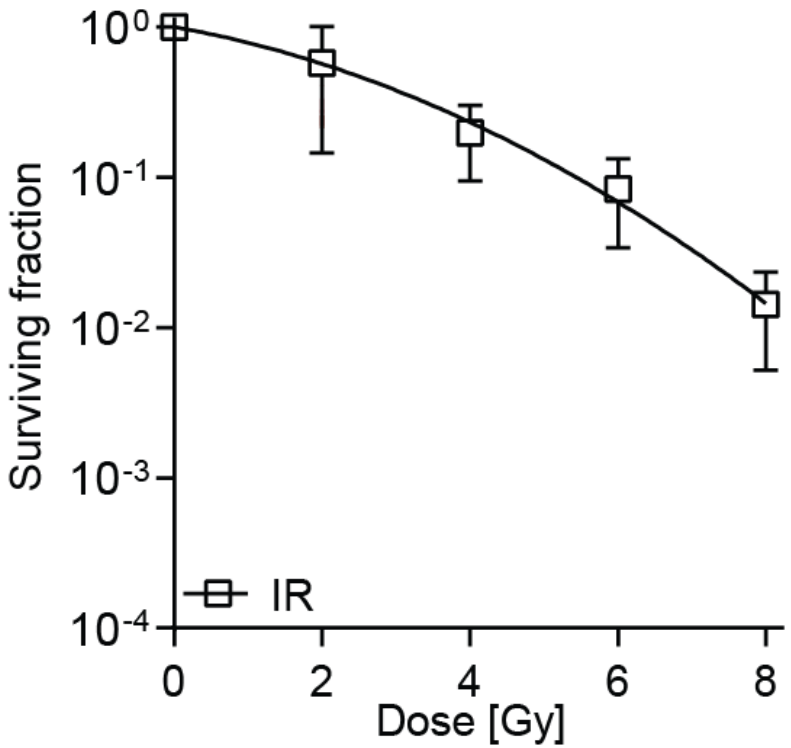


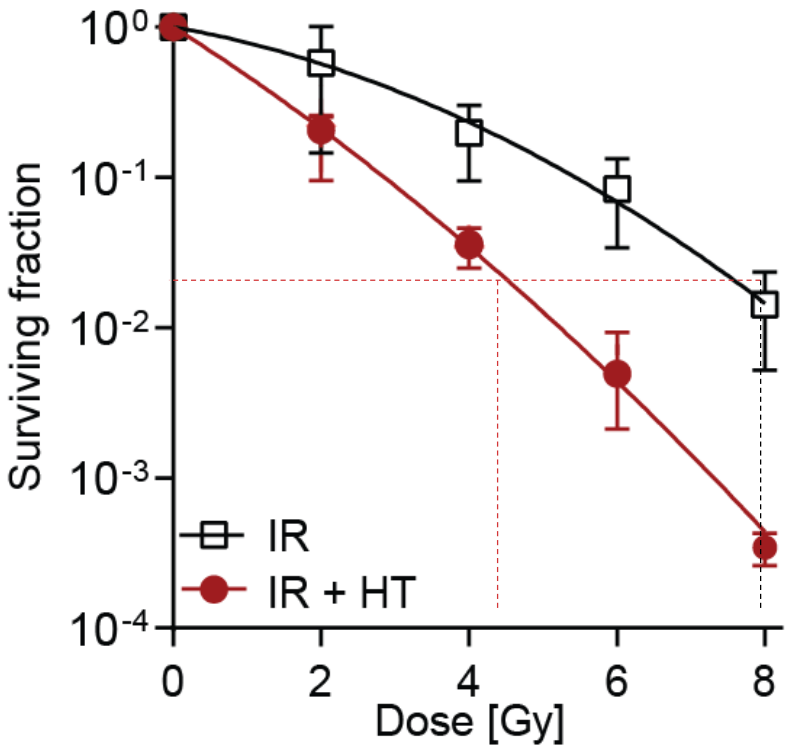
Renal dysfunction

Hearing loss

Radiosensitizer: Hyperthermia

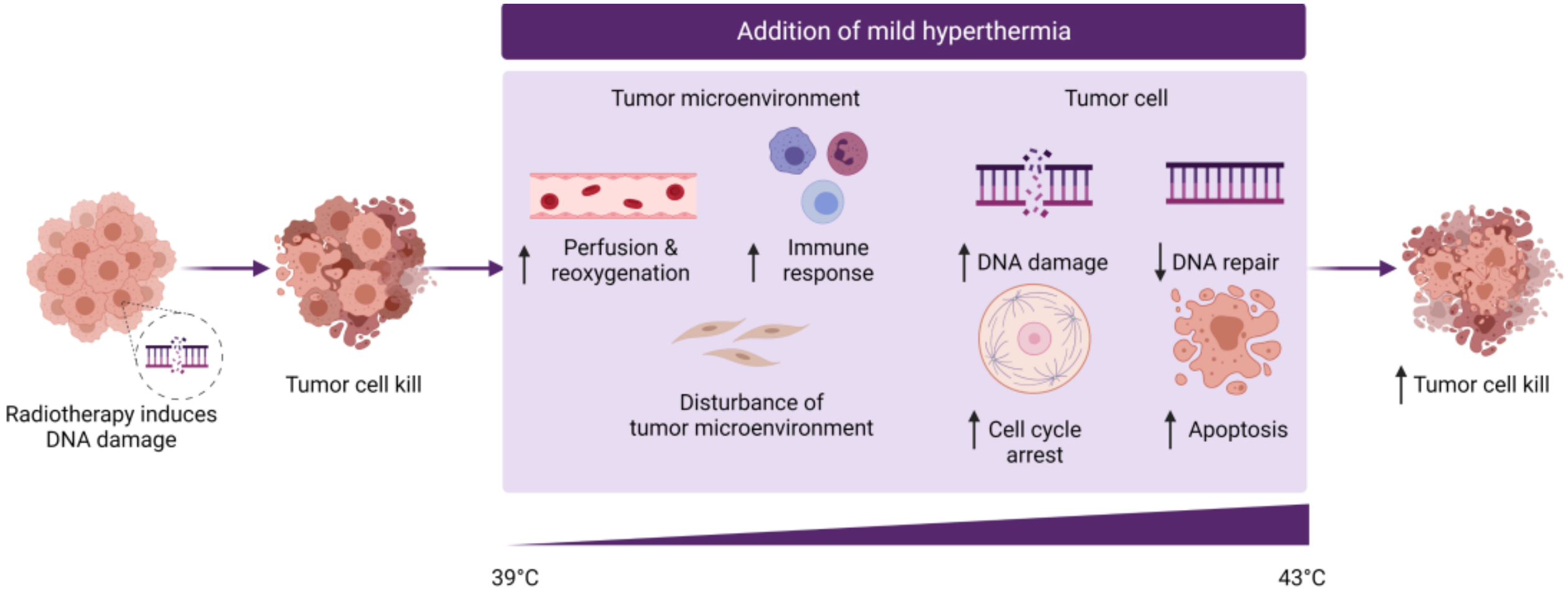
Cervical cancer patients, in case of contraindication for cisplatin: Thermoradiation





Amsterdam UMC

Hyperthermia



Clinical trials prove: hyperthermia is effective

Figure in Internationl Radiobiology book; Chapter 6 – Radiosensitizers – Figure by A.L. Oei

The abscopal effect

Go to www.menti.com and use the code 4872 2756

Do you know what the abscopal effect is?

A. YES

B. NO

Amsterdam UMC

The abscopal effect is immune mediated

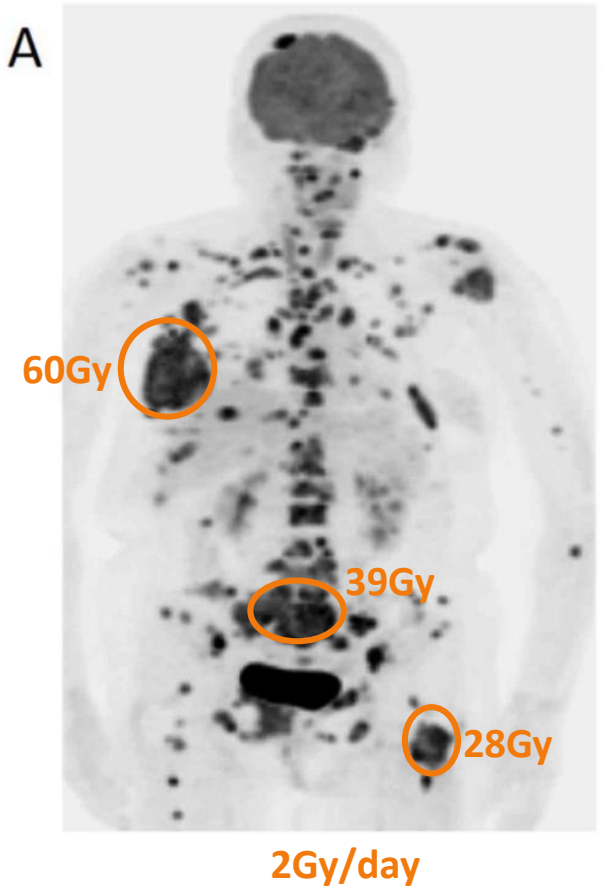
RH Mole, British journal of Radiology, 1953
‘Very rare antitumor immune response’

Observed in:

- Malignant melanoma (2014, 2015)
- Lymphoma (2017)
- Renal cell carcinoma (2012)
- Hepatocellular carcinoma (2008, 1998)
- Lung cancer (2017, 2013)
- Uterine cervical carcinoma (2007)

Azami et al, Spandidos, 2018

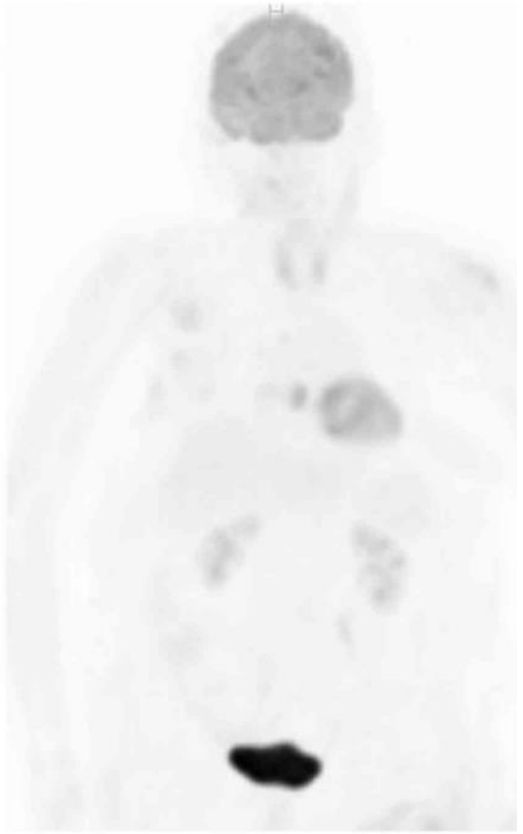
The abscopal effect



64y old woman, breast cancer
Breast mass + pain in hip:
breast cancer + mets in bone, lung and lymp nodes

Local radiotherapy to breast tumor + some bone metastases
ER+/HER2-
No chemotherapy

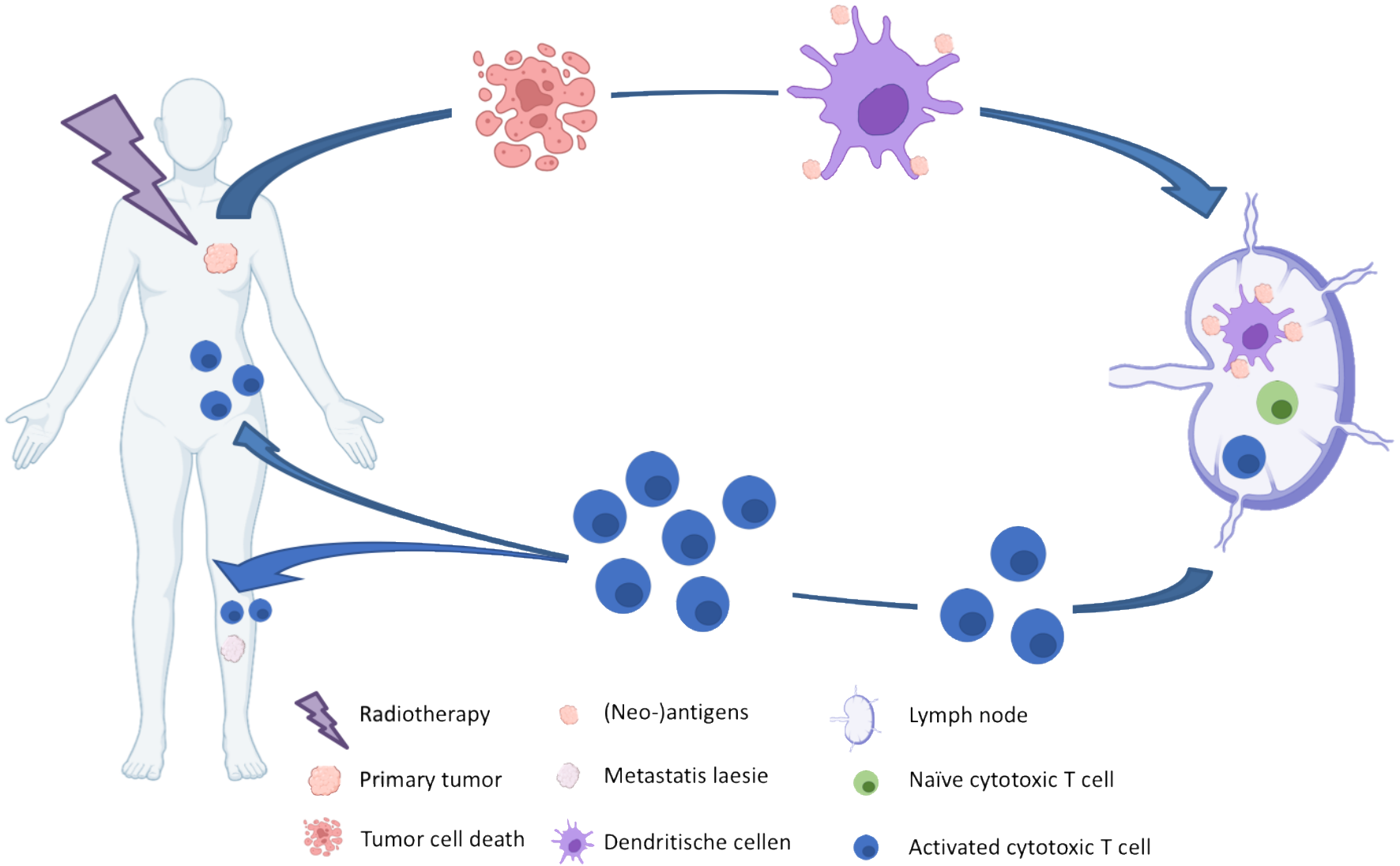
At 10 months after radiotherapy:
Spontaneaous regression



Azami et al, Spandidos, 2018

Amsterdam UMC

The abscopal effect is immune mediated



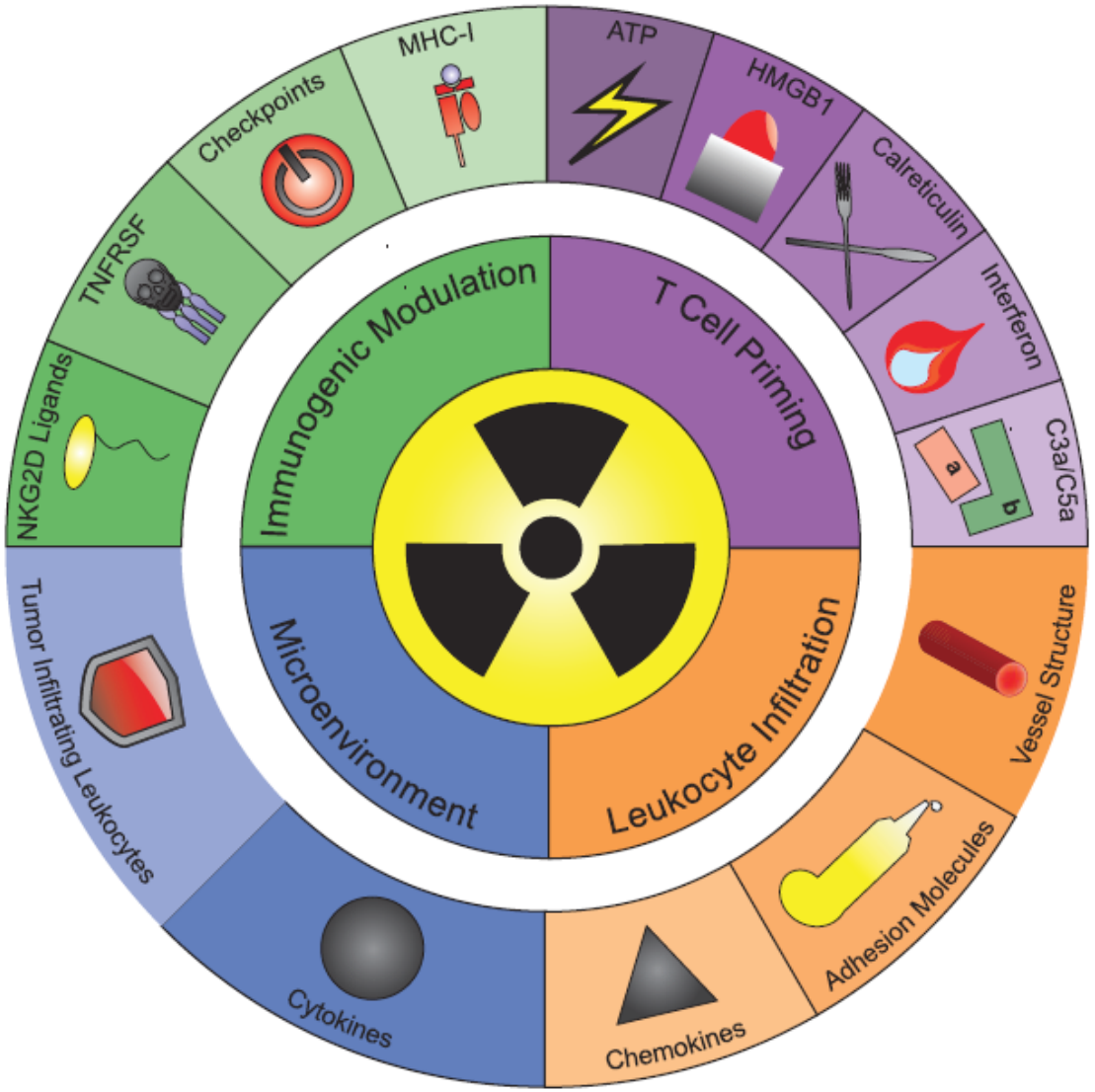
Ansems & Verheij, NtvO, 2022

Amsterdam UMC

Principles of the radiation-induced immune response

Changes to immunogenicity of *tumor* cells

T Cell Priming
Ag uptake & DC maturation



Immune cell infiltration into tissue/ cytokines & changes to suppressive cells

Immune cell infiltration into tissue

Walle et al, Ther Adv in Med Oncol, 2018

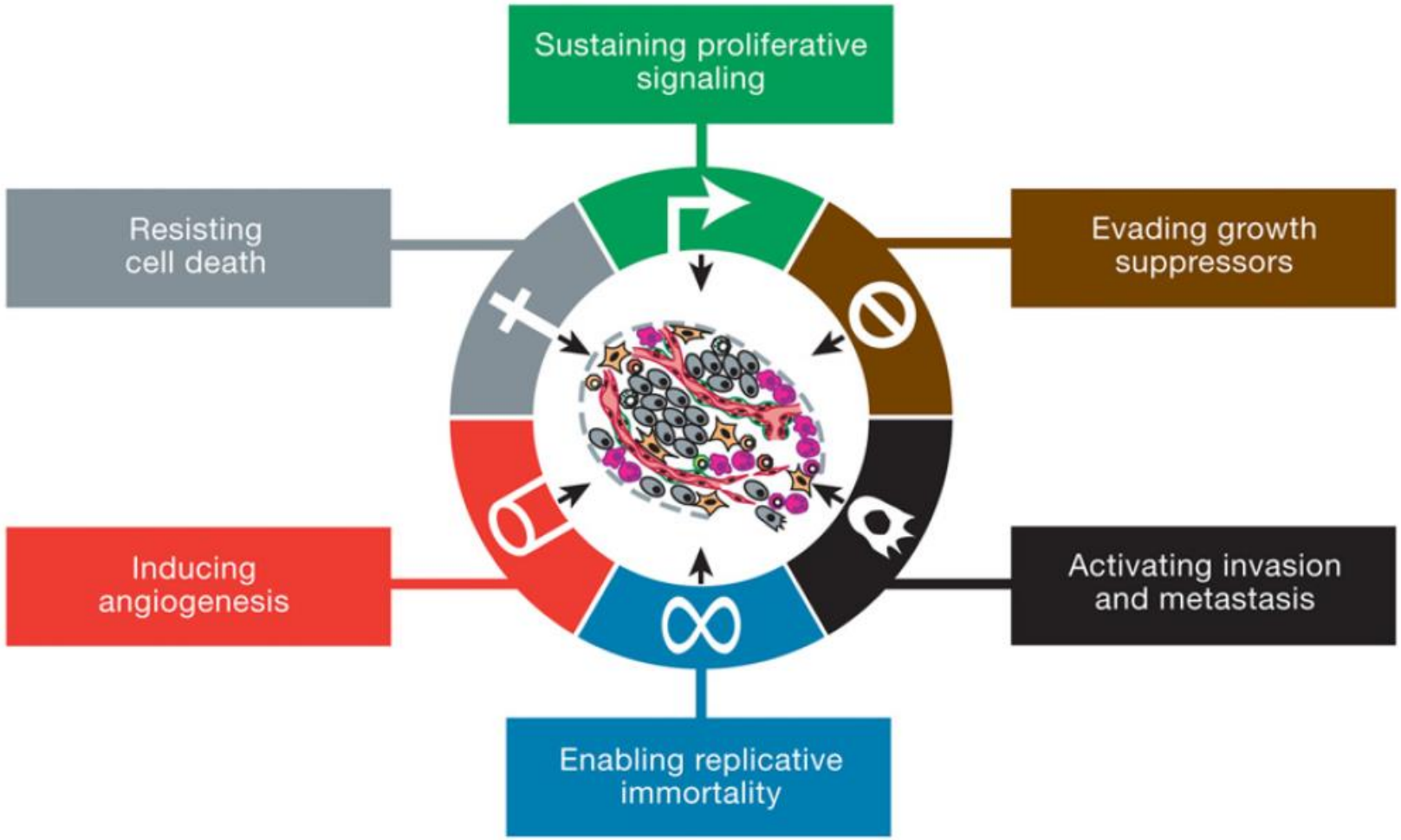
Cancer immunotherapy in the news

2013- Breakthrough of the Year!

"This year marks a turning point in cancer".

Amsterdam UMC

Original 6 “Hallmarks of Cancer”

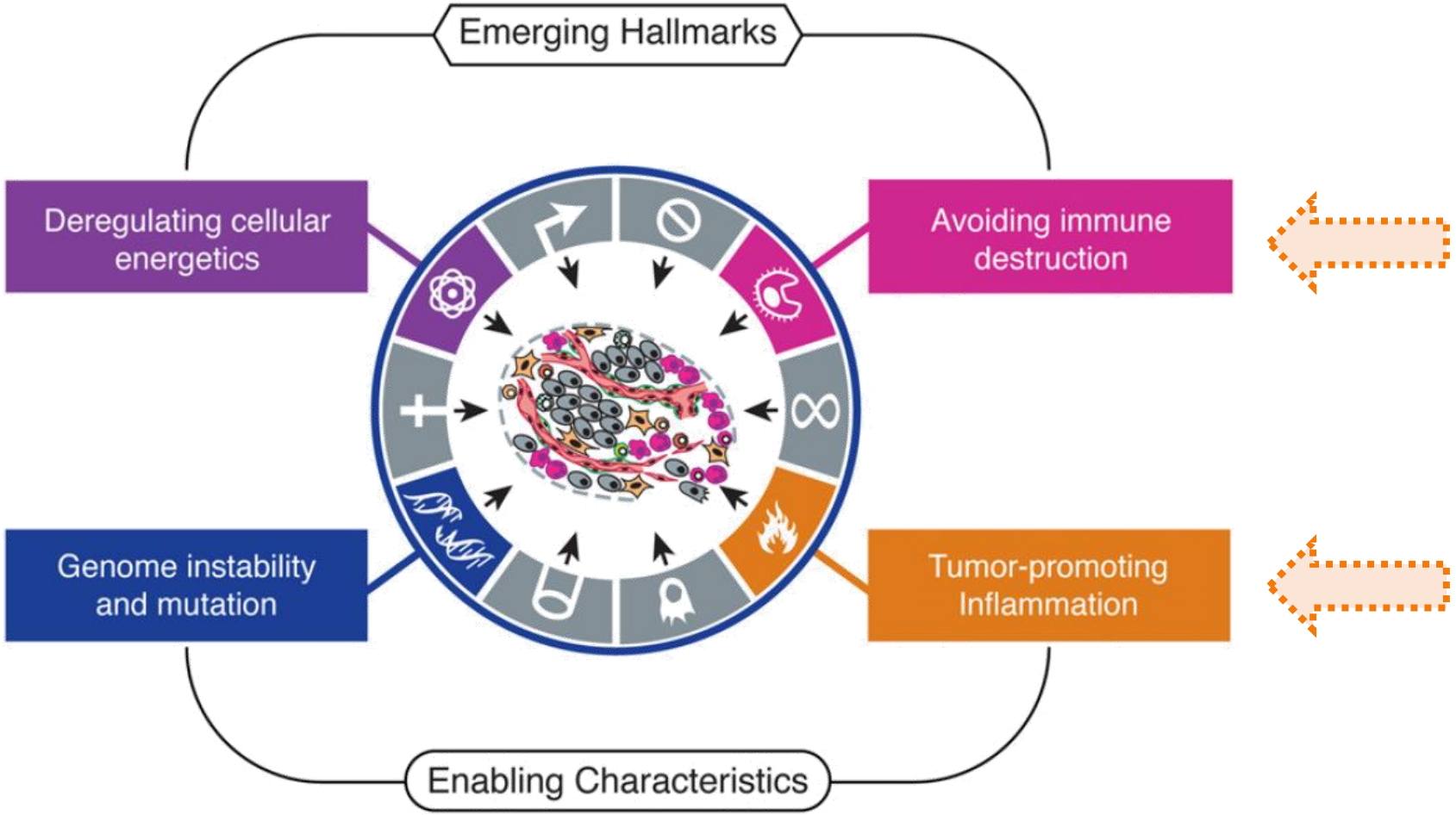


Hanahan & Weinberg Cell (**2000)**

Amsterdam UMC

Hallmarks of Cancer – The next generation

A decade later

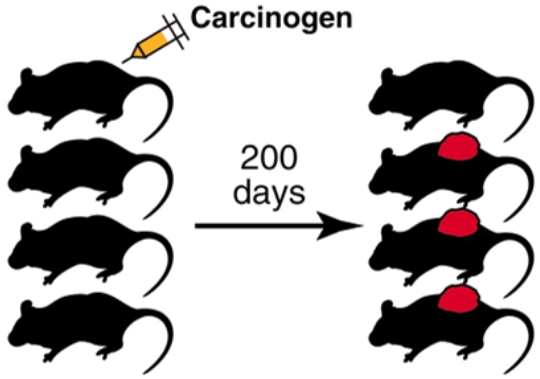


Hanahan & Weinberg Cell (**2011**)

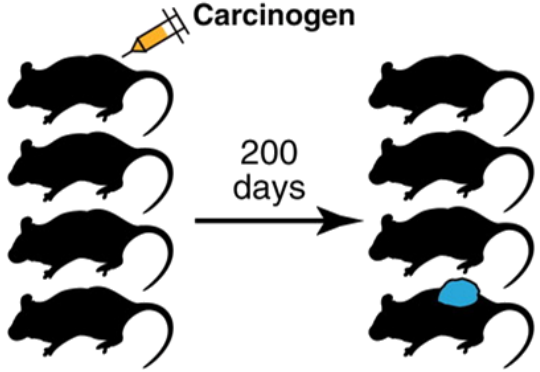
Amsterdam UMC

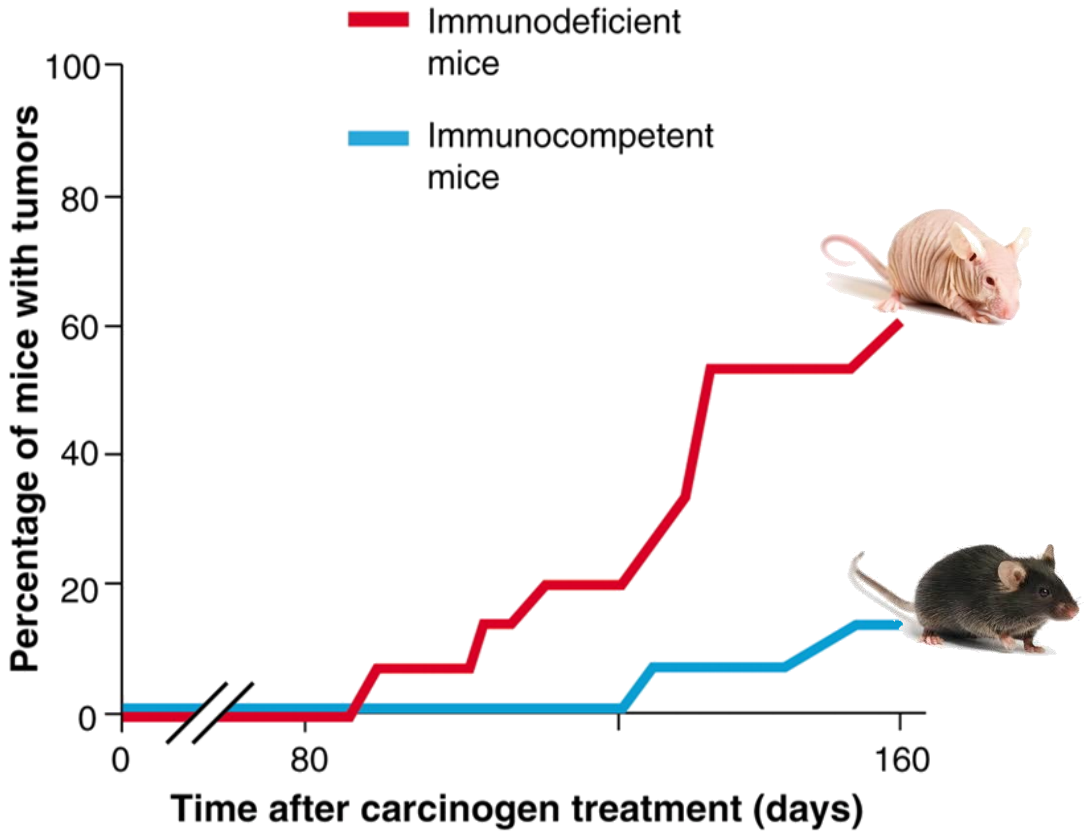
Immune status of mice determines susceptibility to carcinogens = role for immune cells

Immunodeficient



Immunocompetent



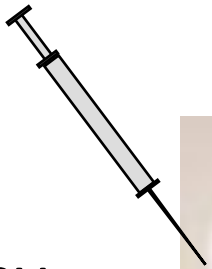


RD Schreiber et al. Science (2011)

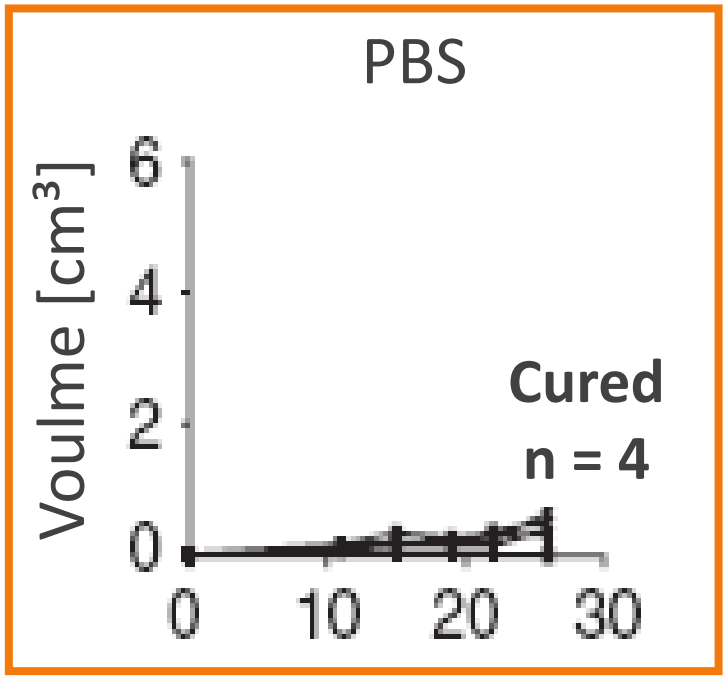
Amsterdam UMC

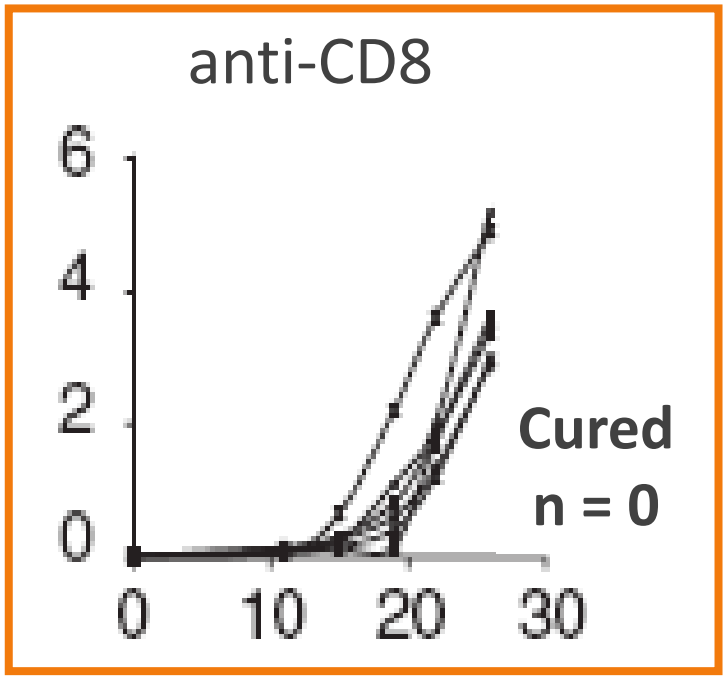
The adaptive immune response increases efficacy of chemo

CT26 tumor



Intratumoral chemotherapy

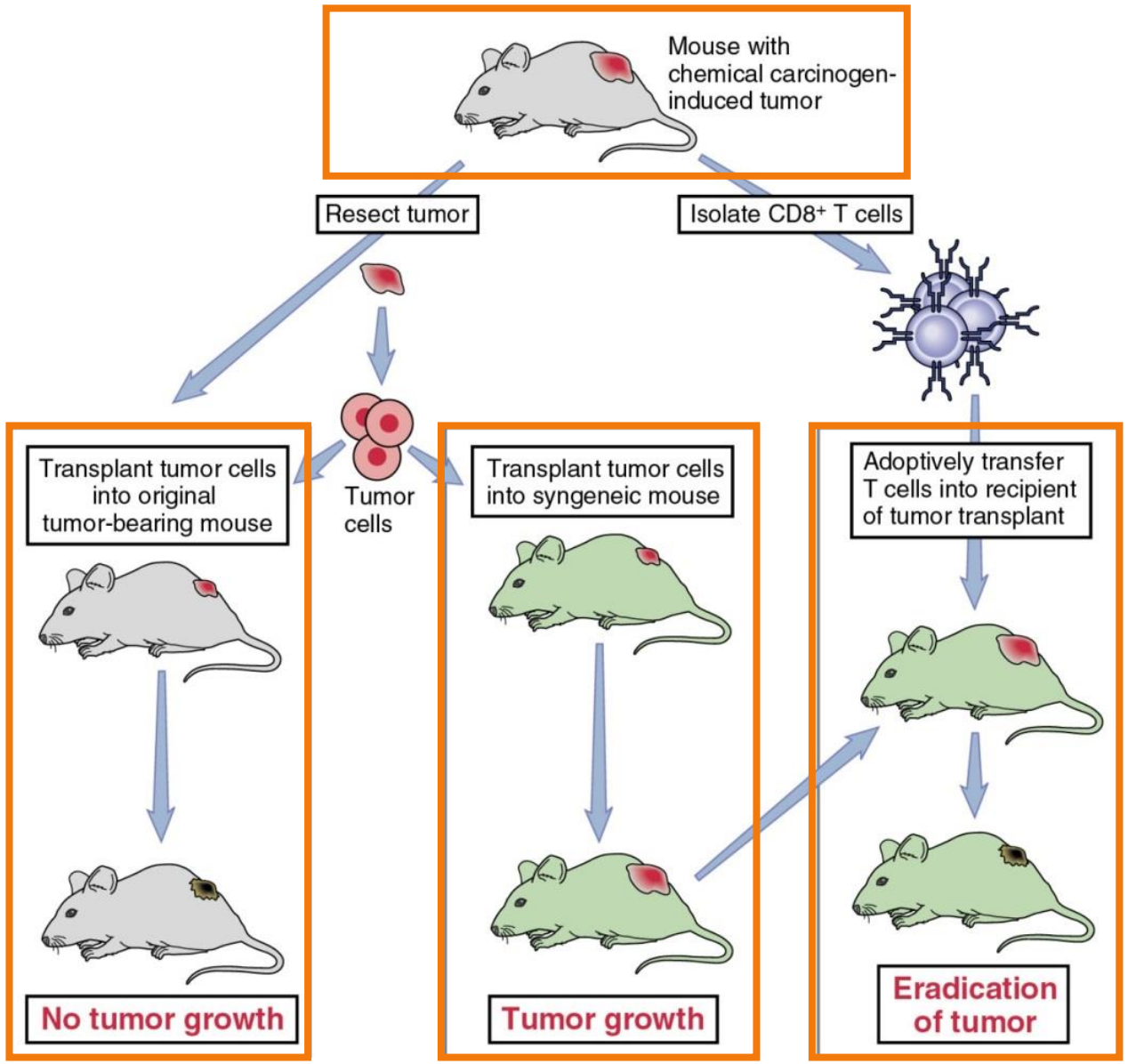




Obeid et al, Nature Medicine, 2007

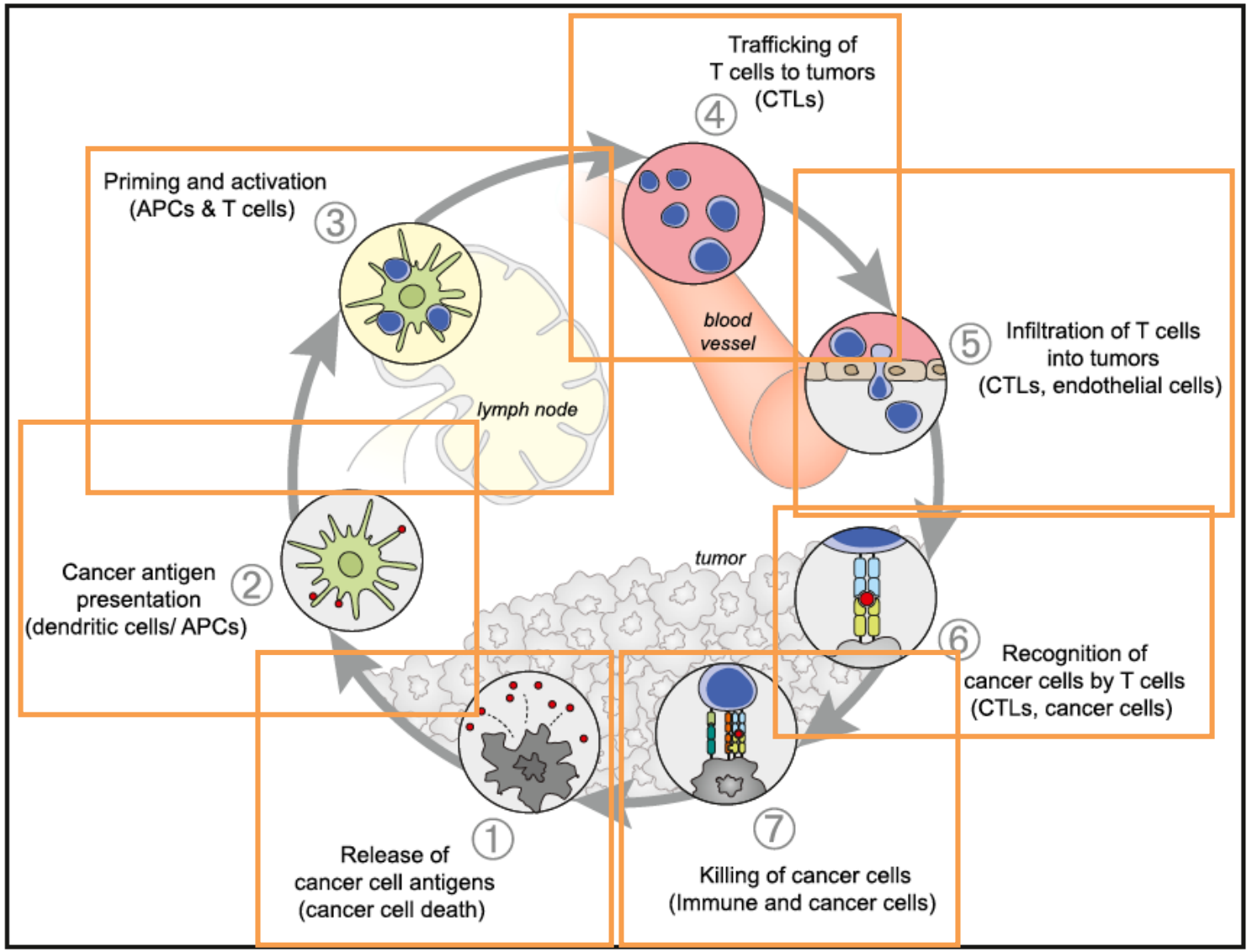
Amsterdam UMC

The immune system CAN control tumors



A proof of principle experiment

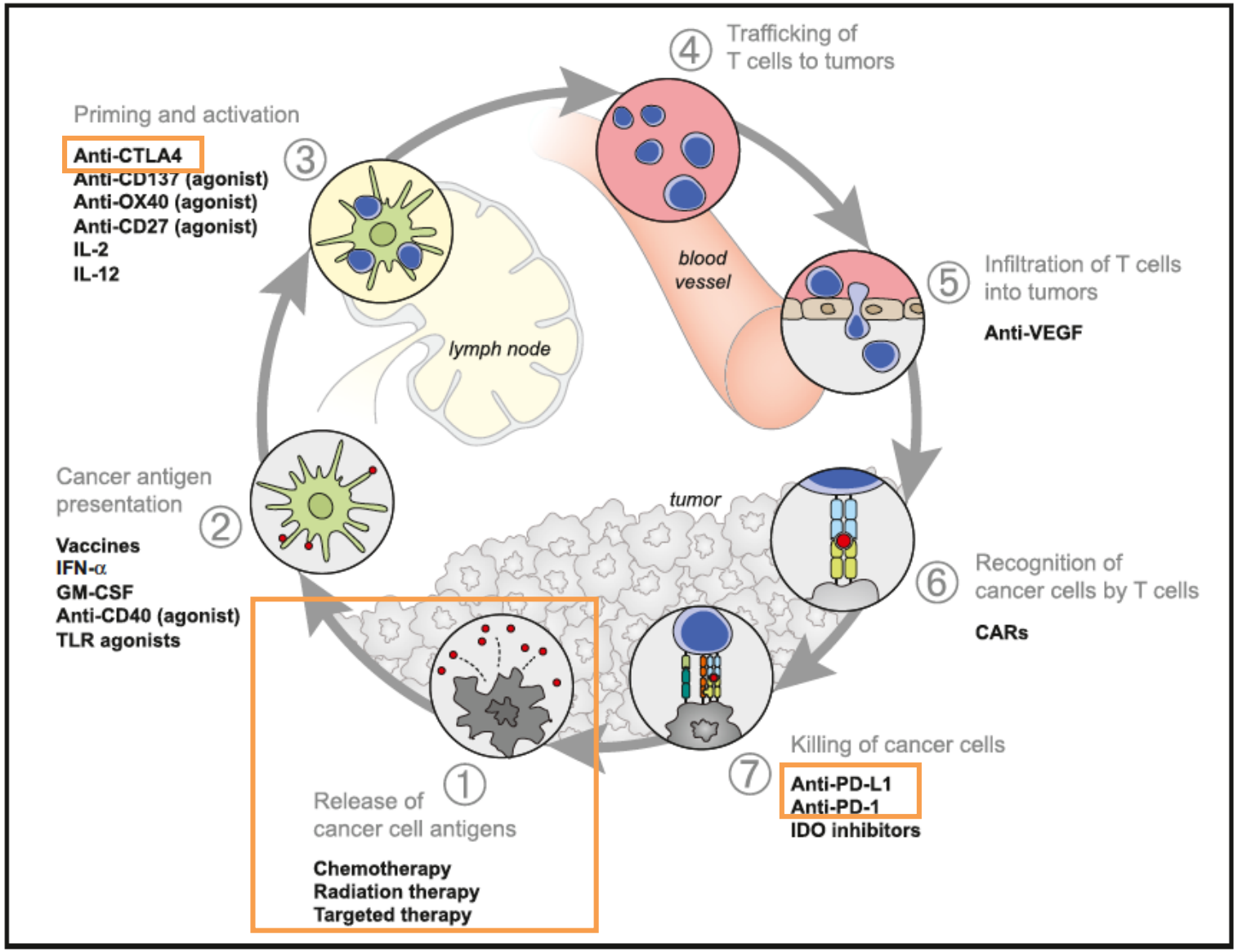
The Cancer-Immunity Cycle



Chen and Mellman, Immunity, 2013

Amsterdam UMC

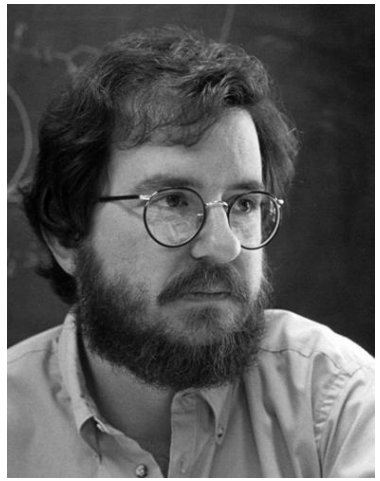
Therapies that might affect the Cancer-Immunity Cycle



Chen and Mellman, Immunity, 2013

Amsterdam UMC

Nobel Prizes 2018



James P. Allison and Tasuku Honjo

"for their discovery of cancer therapy by inhibition of negative immune regulation."

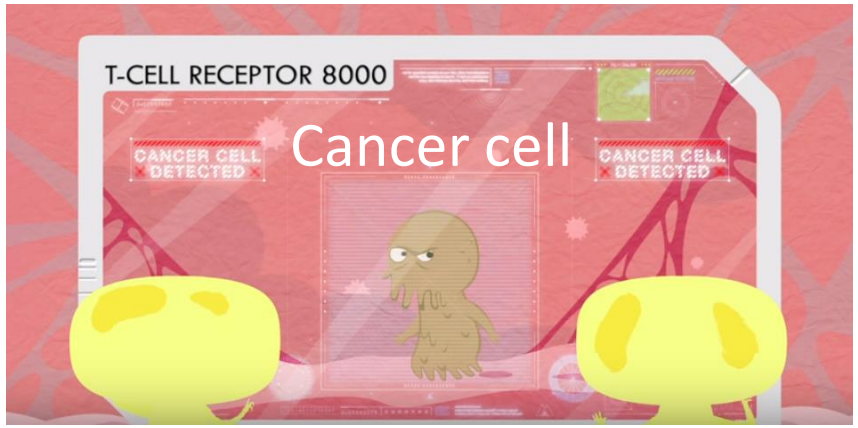
- 1982- discovered CTLA-4
- 1996- showed that malignant tumors could be successfully treated in animals by blocking CTLA-4
- Currently MD Anderson

- 1992- discovered PD-1
- Showed that malignant tumors could be successfully treated in animals by blocking PD-1/PD-L1 interaction
- Currently- Kyoto University

Amsterdam UMC

”Checkpoints” constrain the immune response

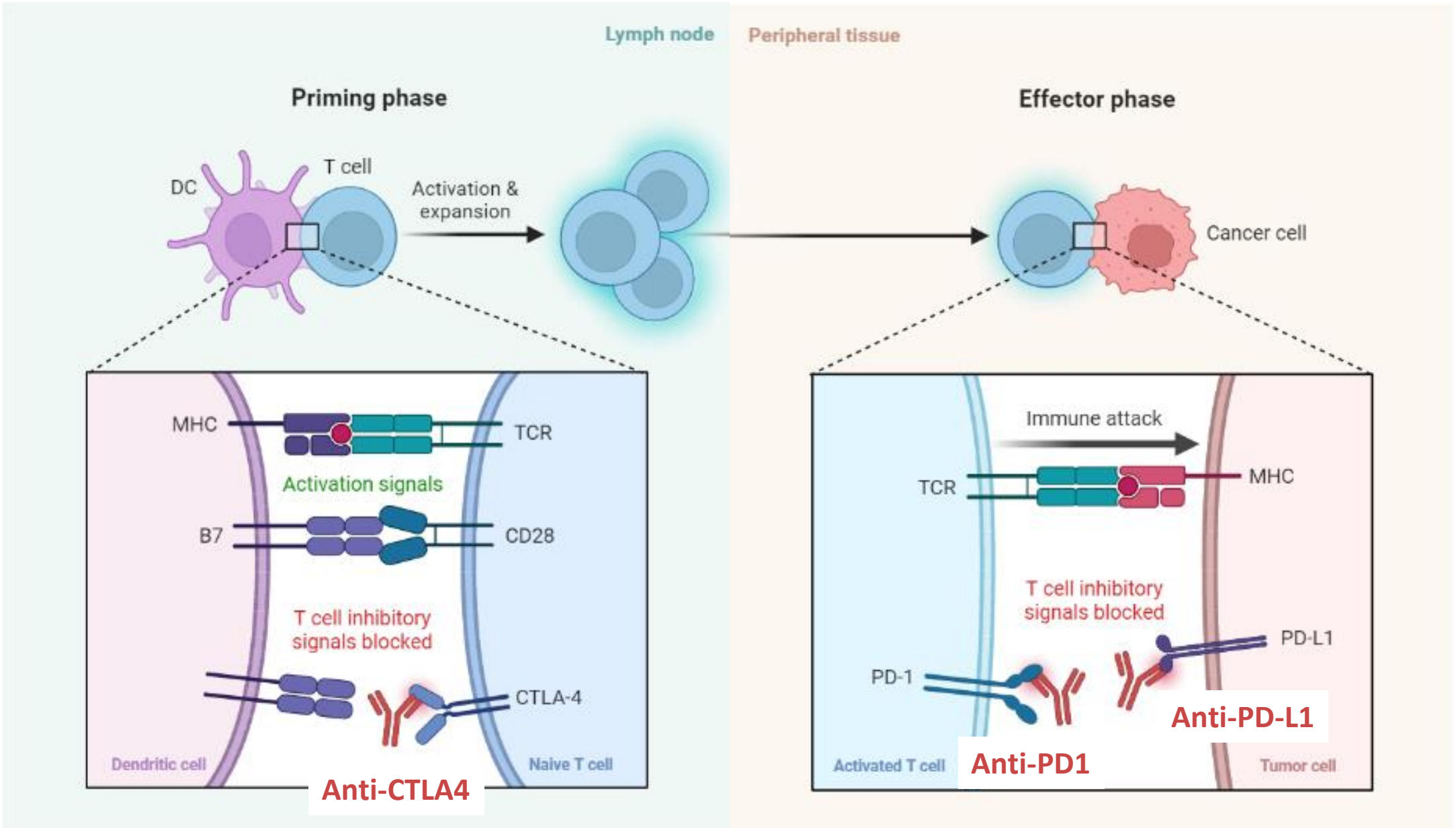
Immune system detecting



Cancer cells escape from immune system by PD1

Amsterdam UMC

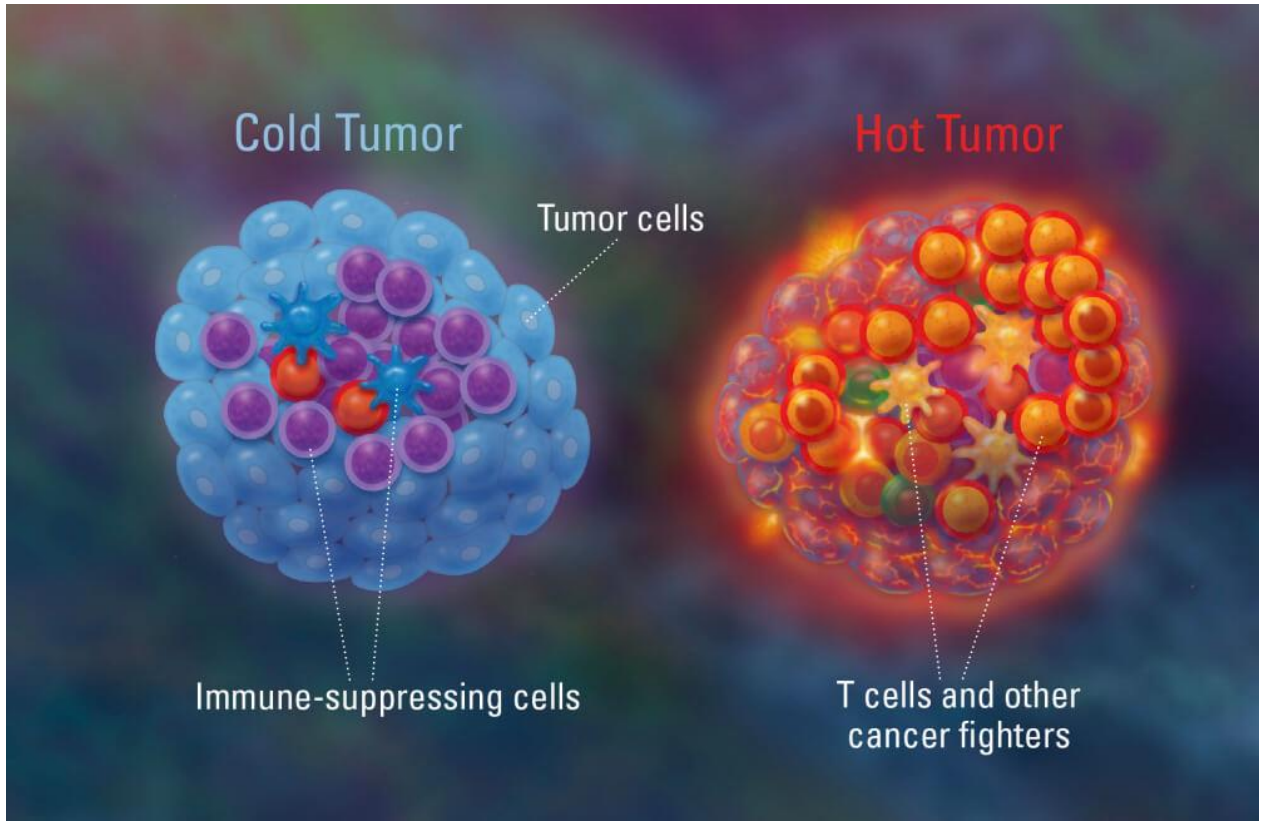
”Checkpoints” constrain the immune response



Amsterdam UMC

“Cold” vs. “Hot tumors”

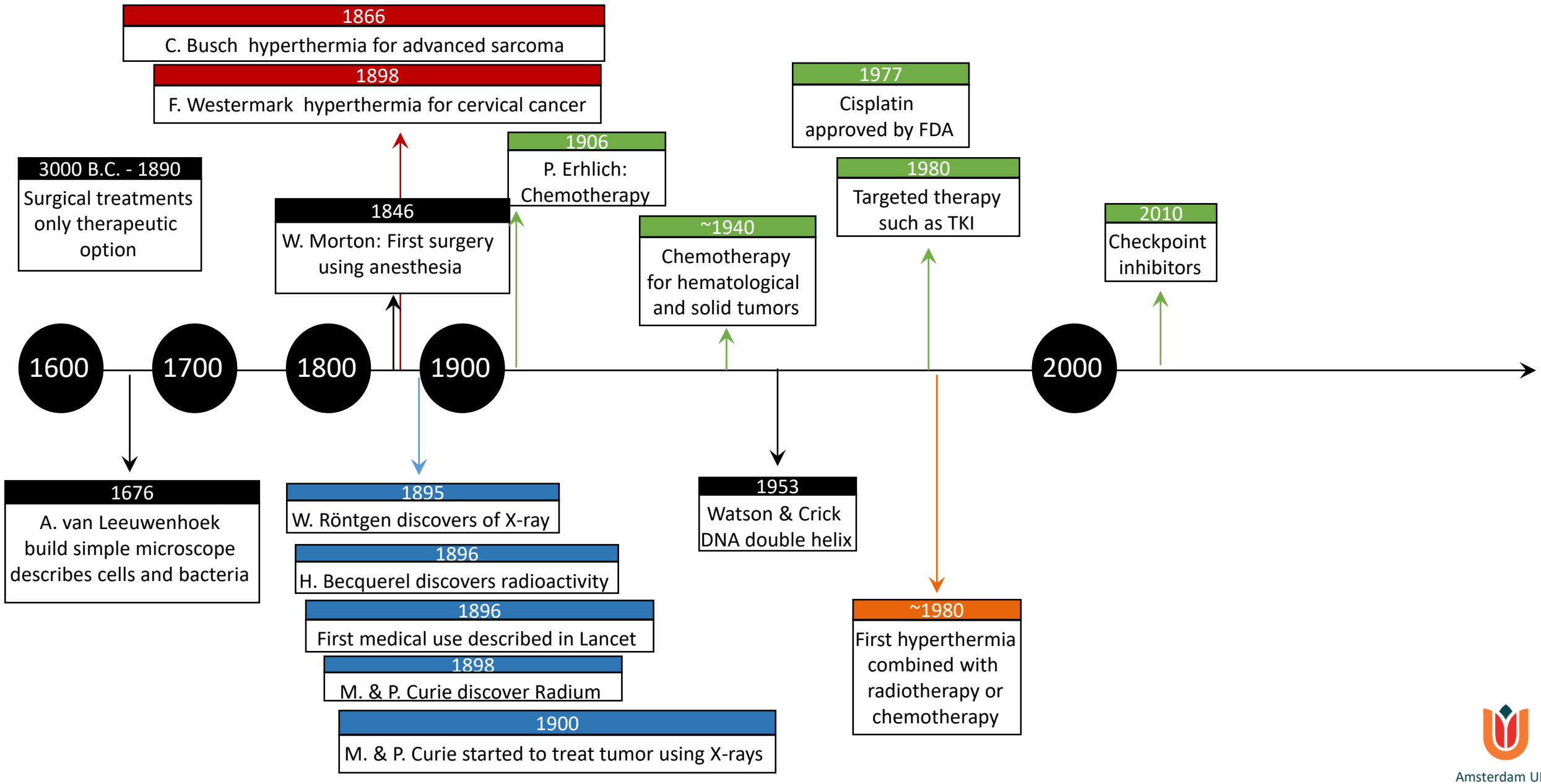
Immune desert



Dana Farber

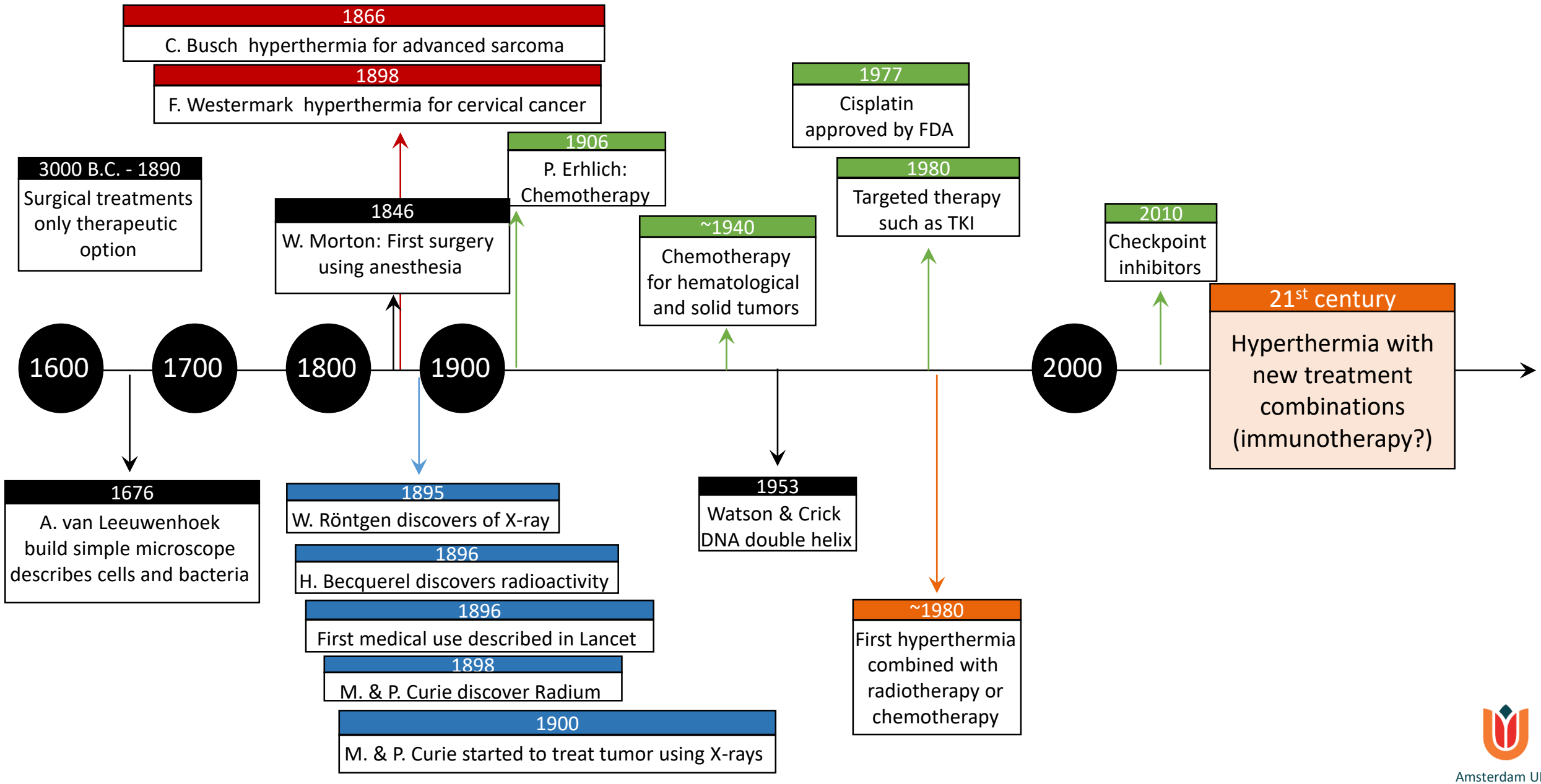
Amsterdam UMC

Timeline of anti-cancer treatments



Amsterdam UMC

Timeline of anti-cancer treatments



Amsterdam UMC

Thank you for your attention

Amsterdam UMC

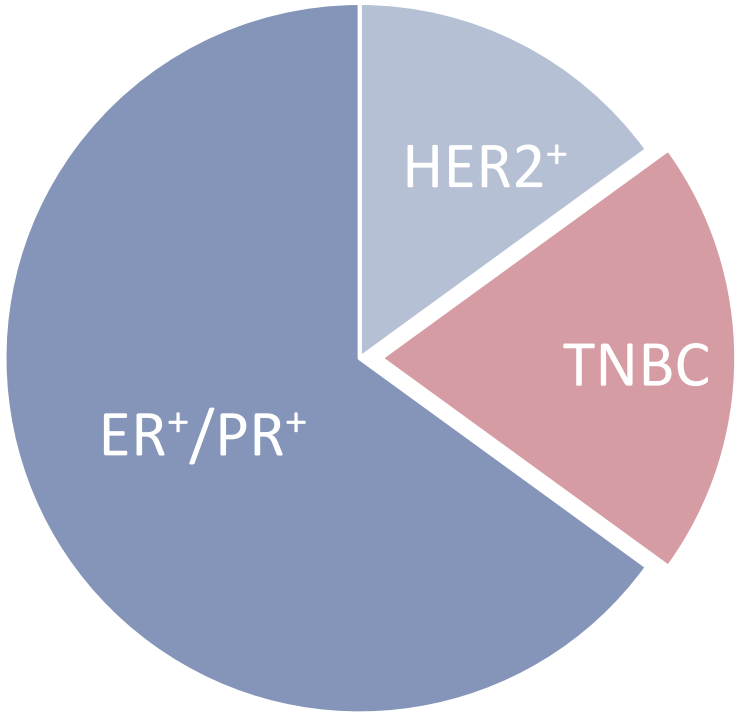
Some extra slides below

Incidence of Breast Cancer

- 1.7 million new cases/ year
- 12% of all cancers
- 25% of all cancers in women

5-year survival:

- 80-90% at early stage
- 24% at more advanced stage

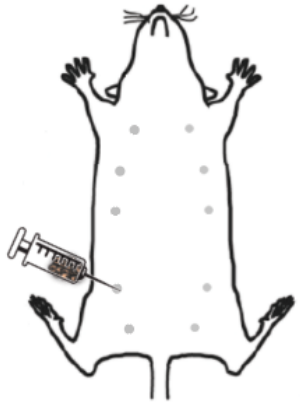


- 10-20% are TNBC
- 5-year survival 77%

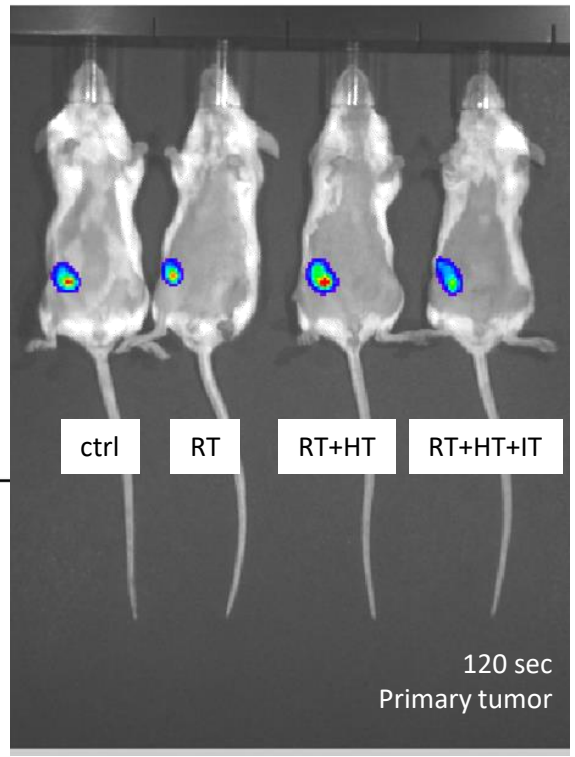
Amsterdam UMC

4T1 highly metastatic breast cancer muring model

Injection of tumour cells in mammary fat pad

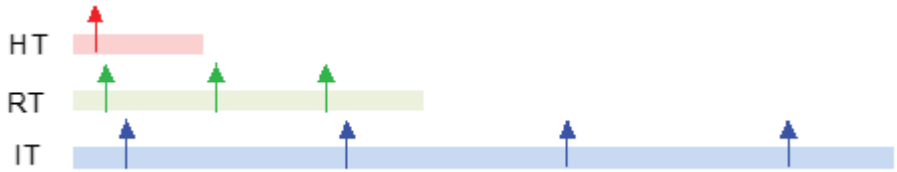


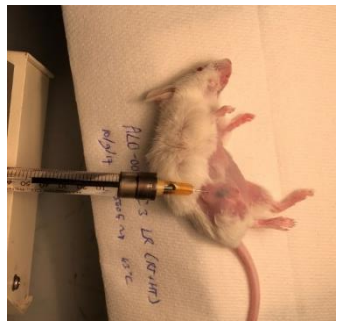
Days -7

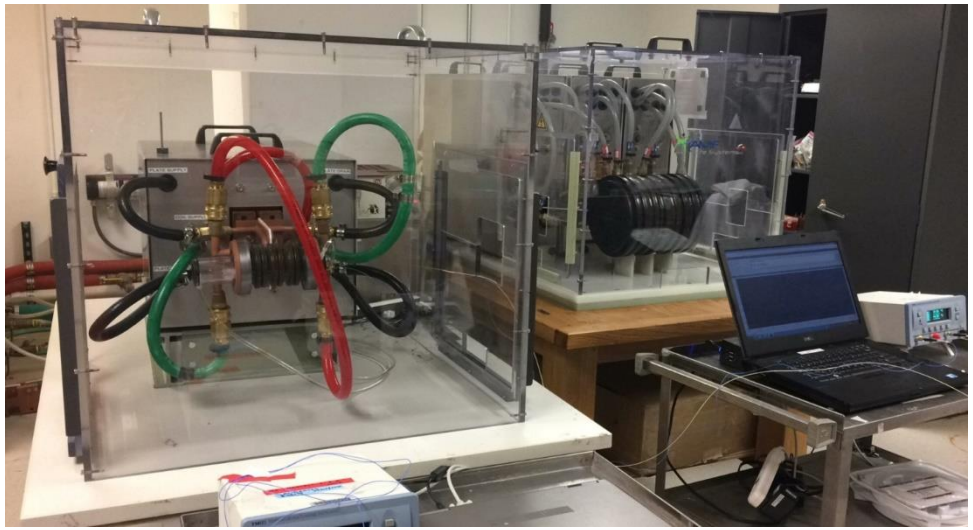


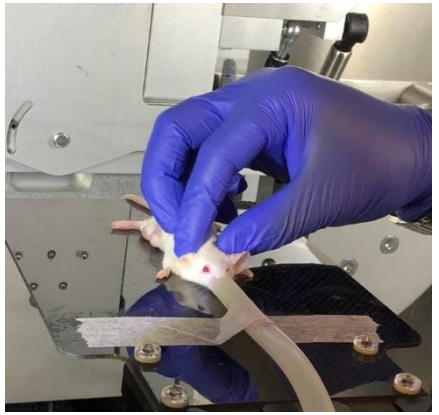
Amsterdam UMC

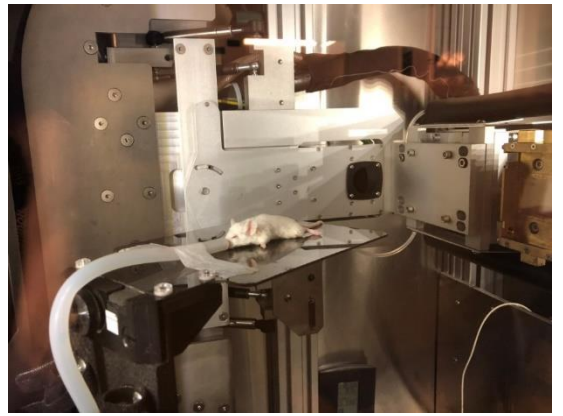
Primary tumor growth after various treatments

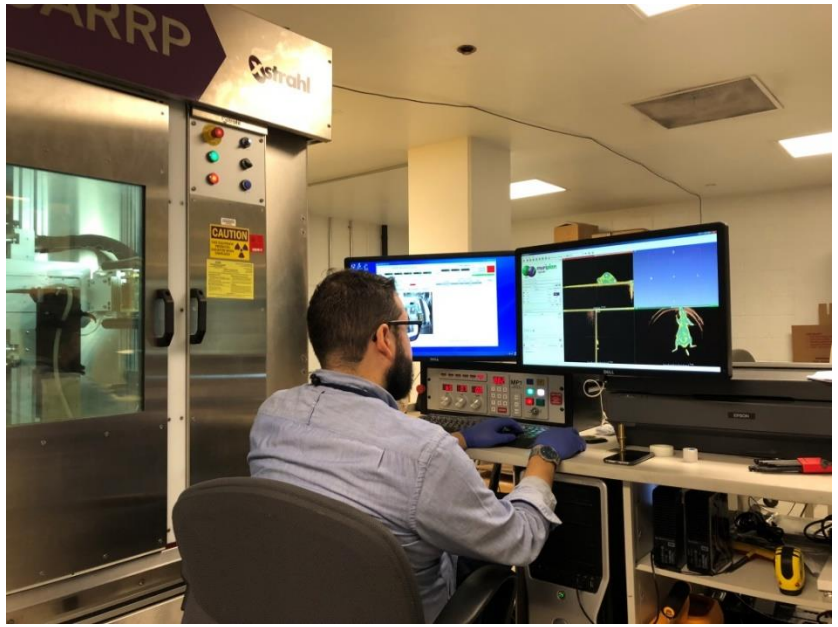






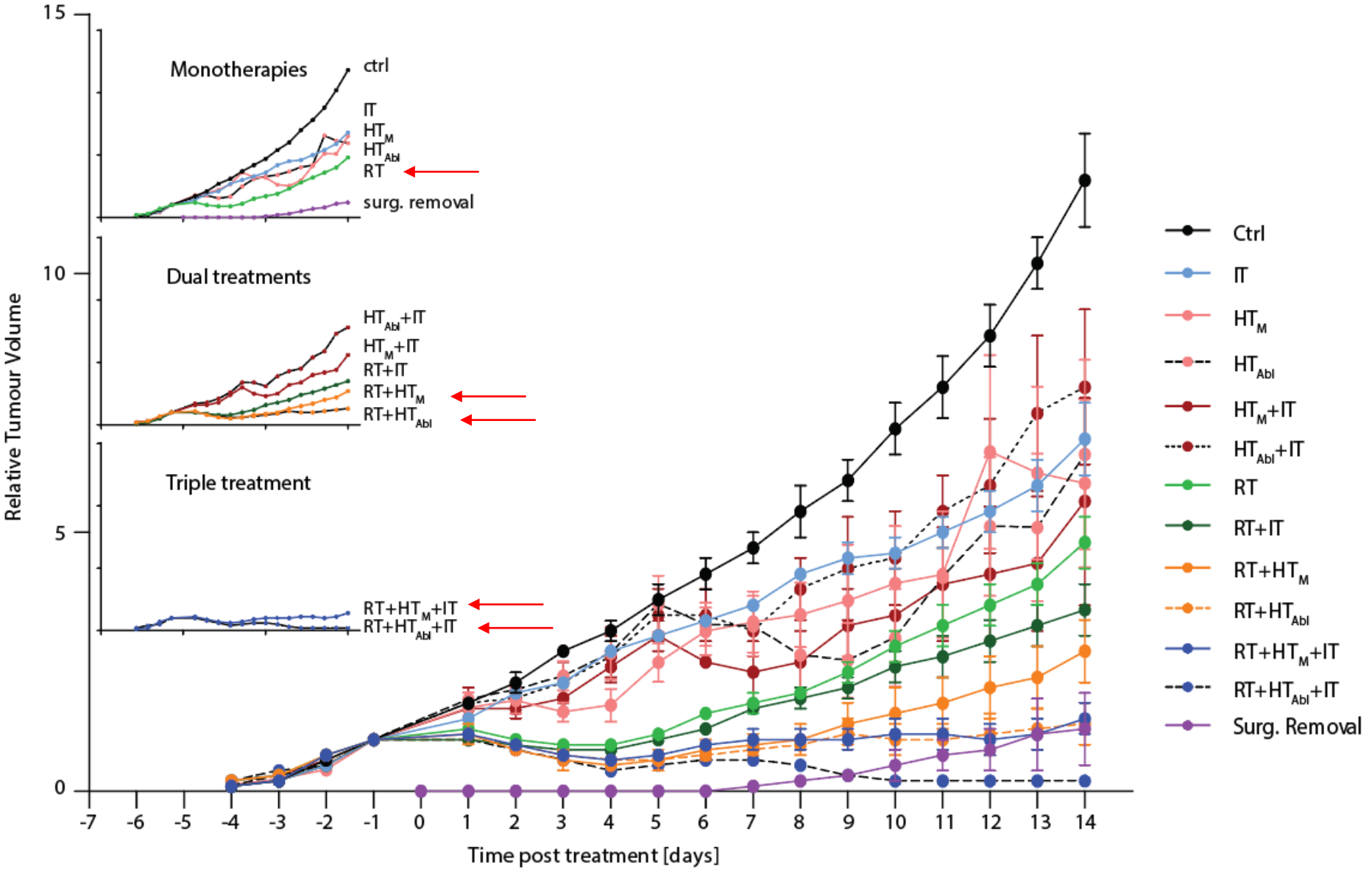






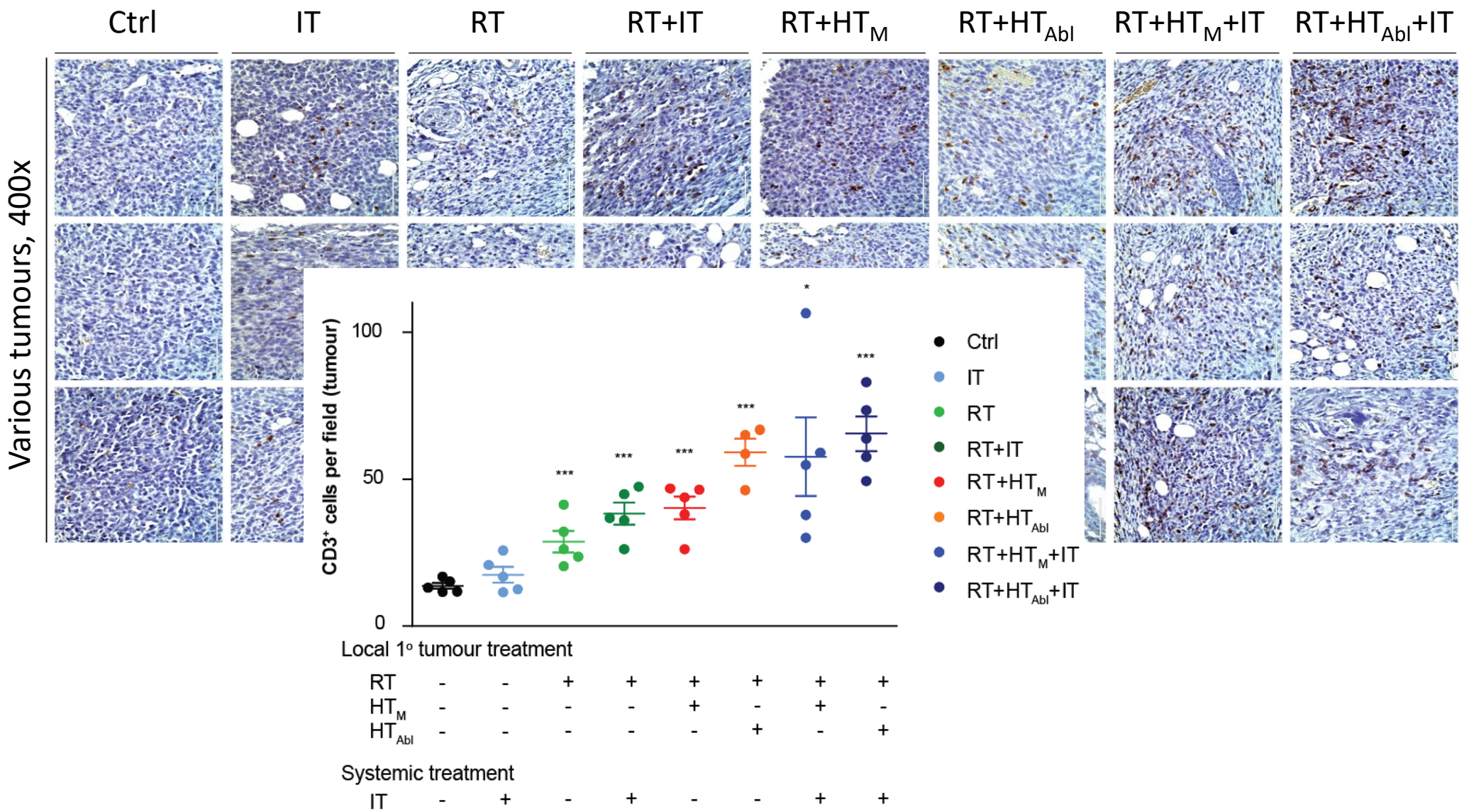
Amsterdam UMC

Primary tumor growth after various treatments



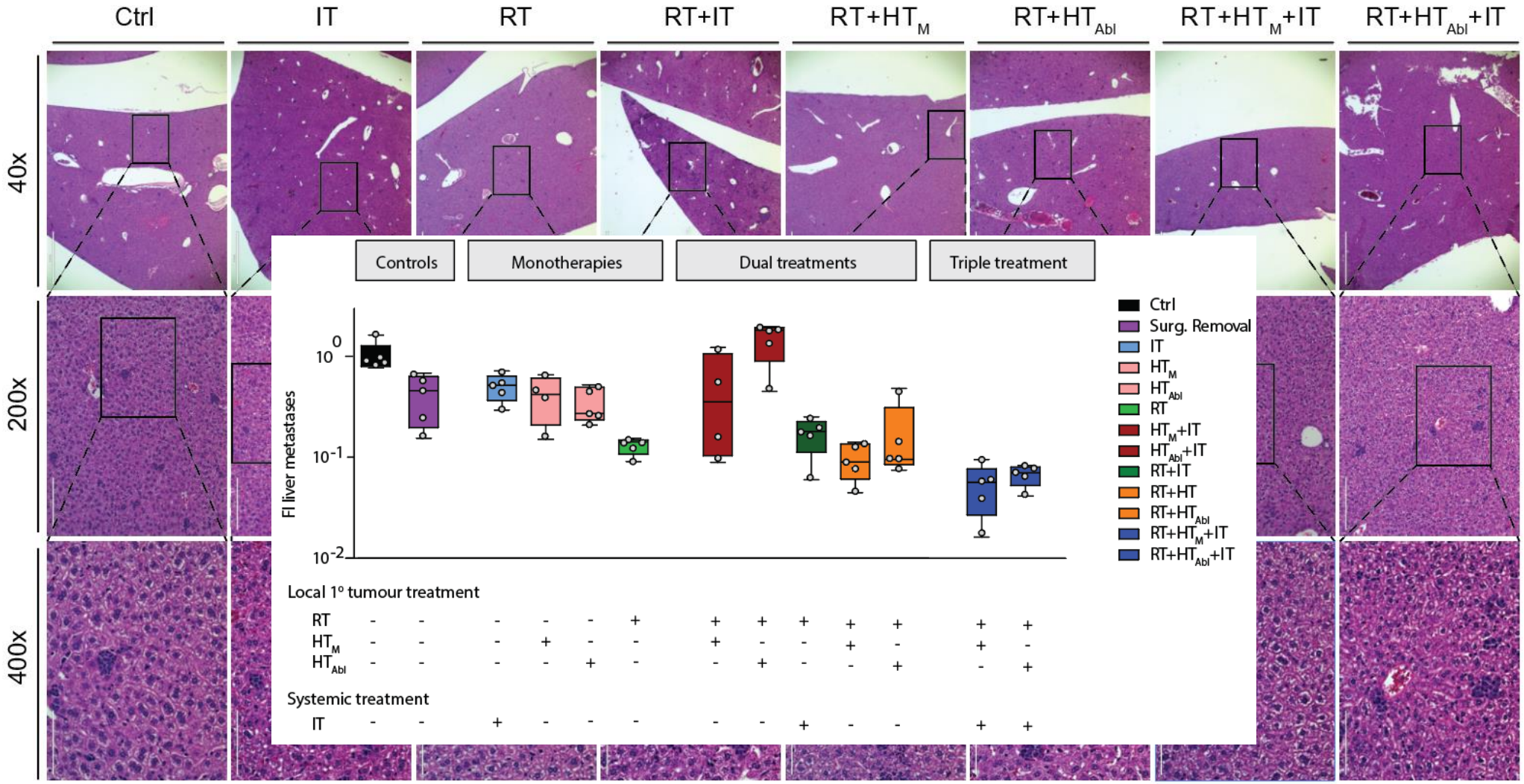
Amsterdam UMC

Addition of IT → T-cell infiltration



Amsterdam UMC

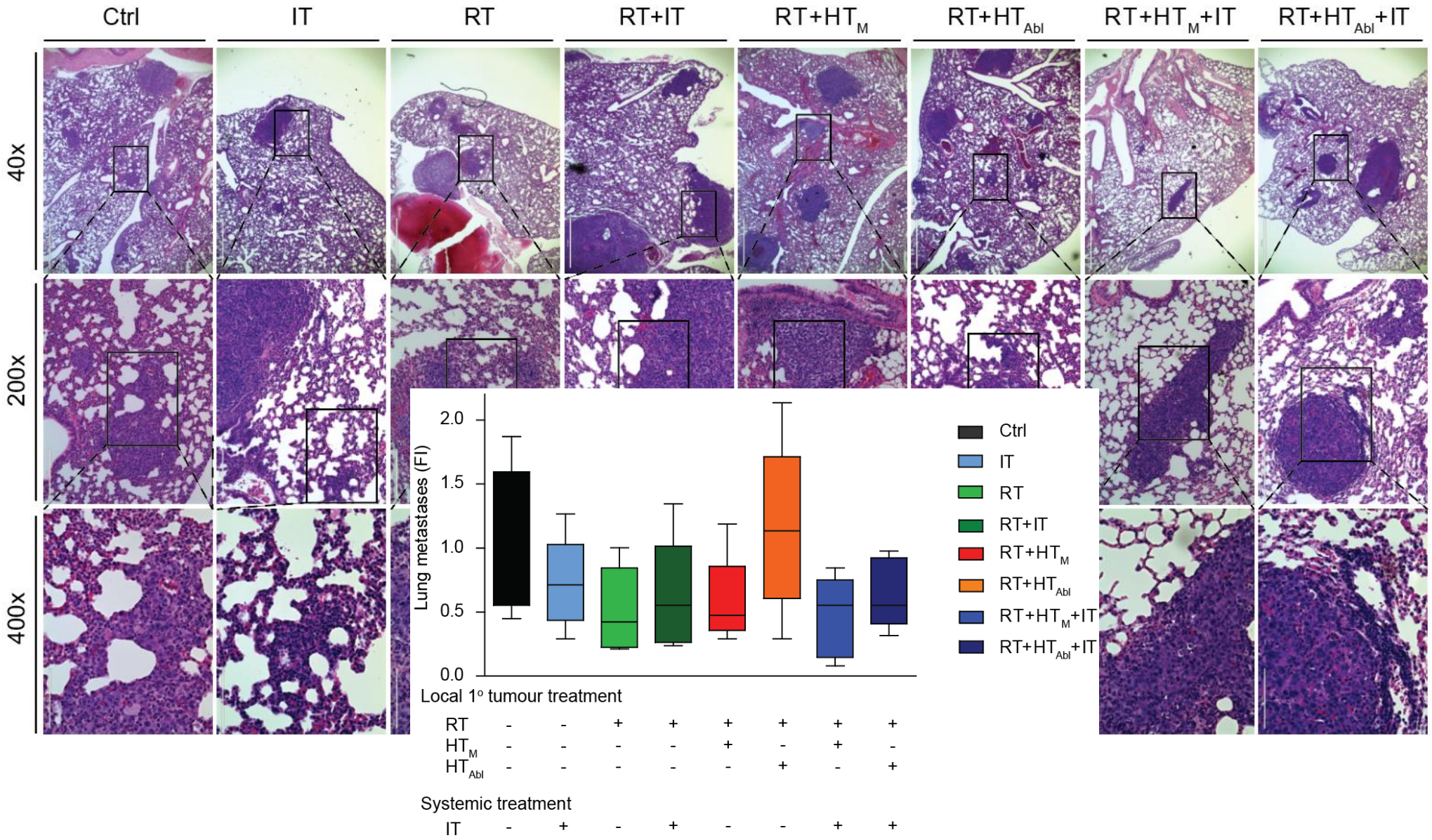
Reduction in No of liver metastases



Amsterdam UMC

Minor reduction in No of lung metastases

H&E



Amsterdam UMC