

Voordracht

Maandag 16 april om 19u.

ZoWe Hogeschool
Barrièrestraat 2d, 8200 BRUGGE

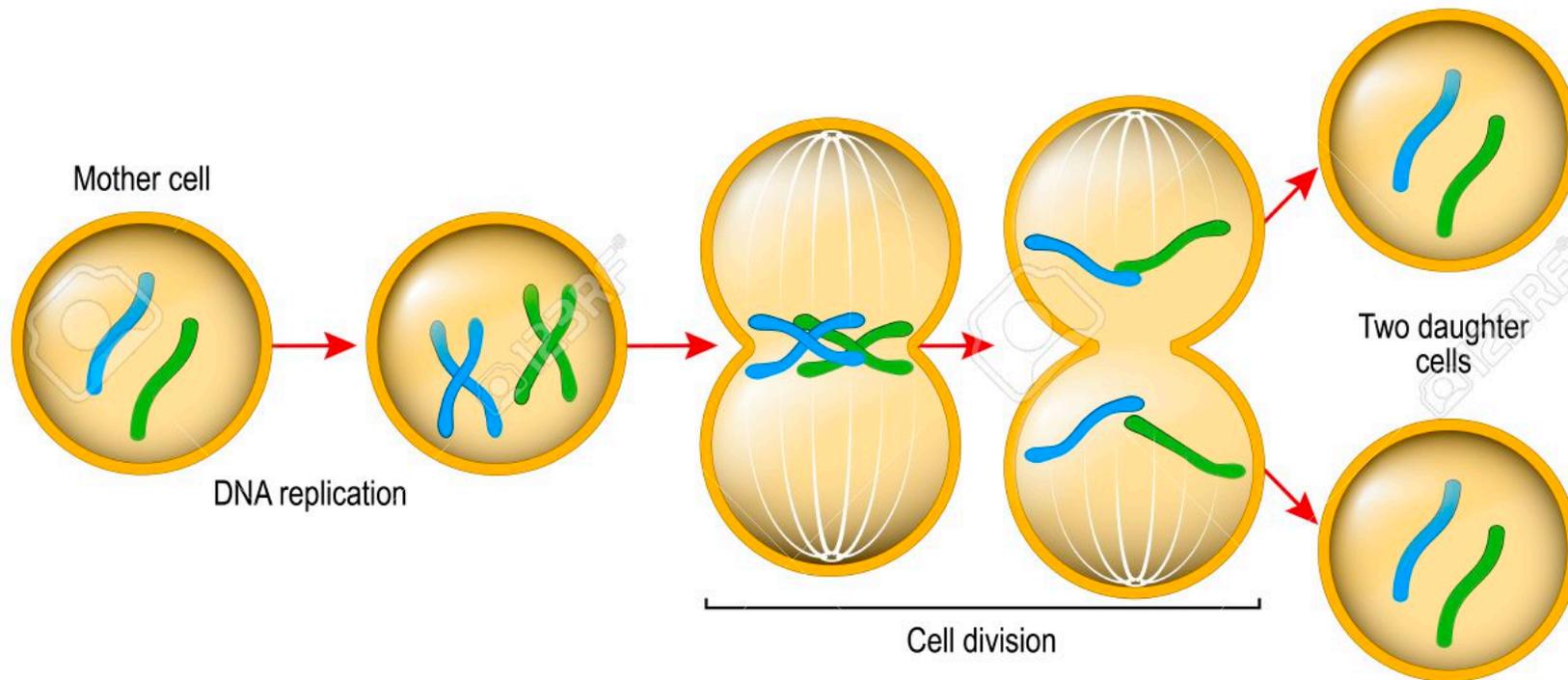


Immunotherapie en darmkanker

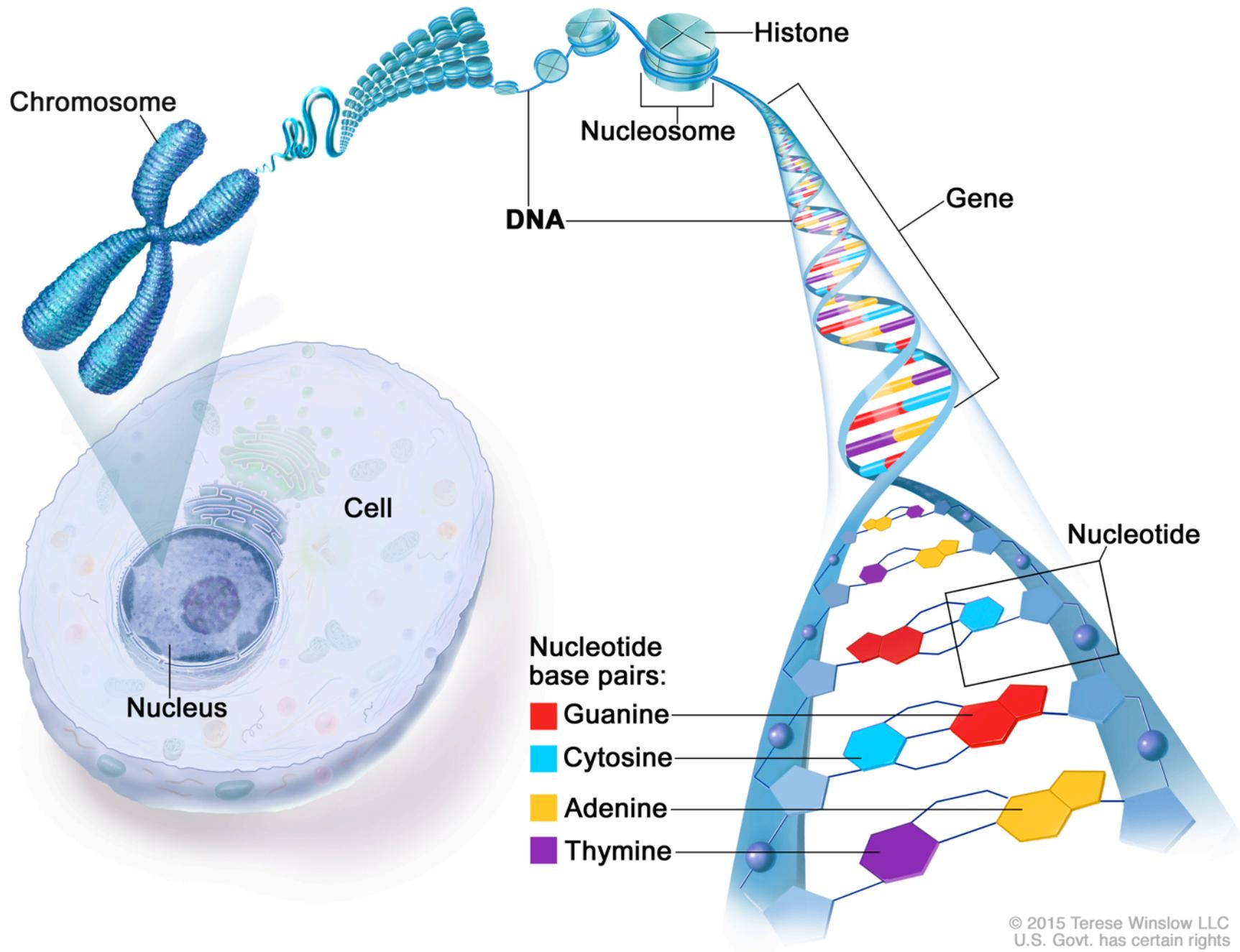
Dr. Alain Bols MD

Coördinator Oncologisch Zorgprogramma
Diensthoofd Medische Oncologie
Departement Oncologisch Centrum
AZ St Jan AV Brugge-Oostende Campus Brugge

MITOSIS



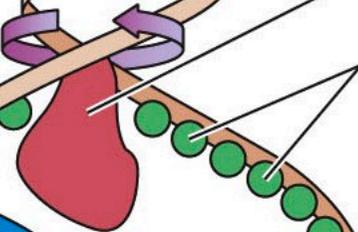
DNA Structure



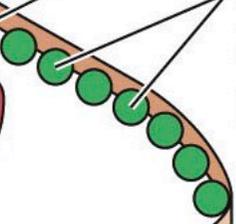
Replication
fork movement



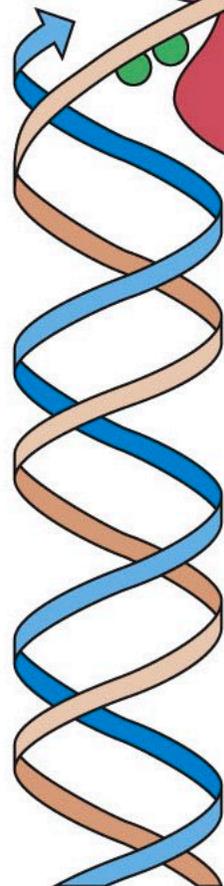
Helicase



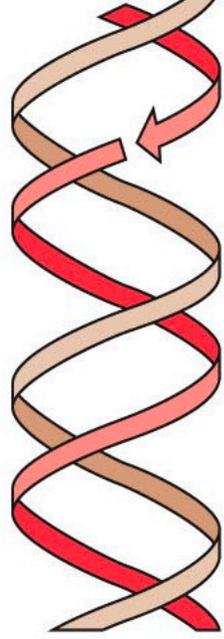
Single-stranded
DNA binding
proteins

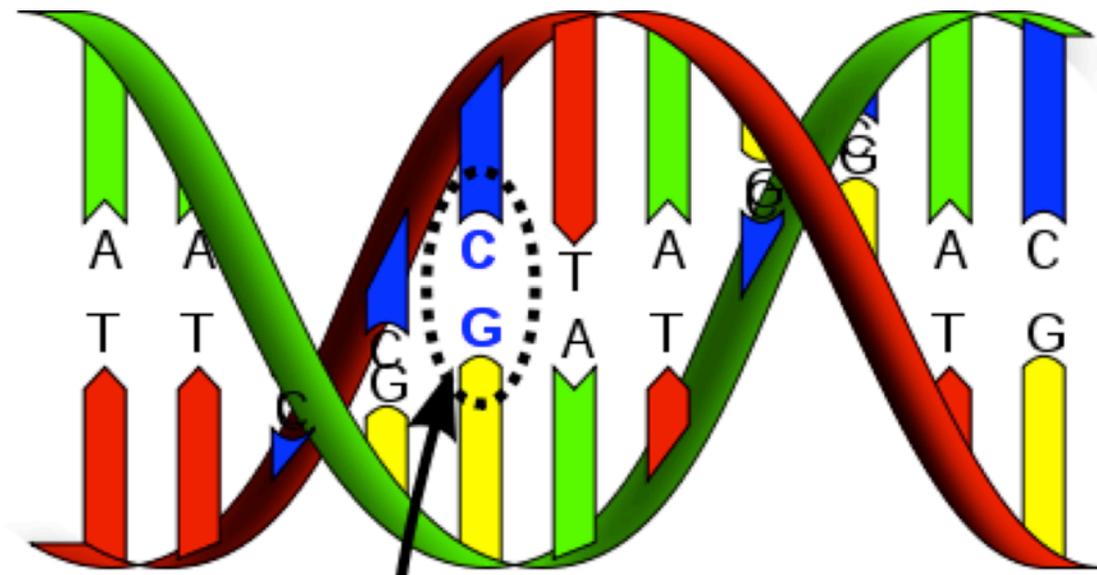


Leading
strand



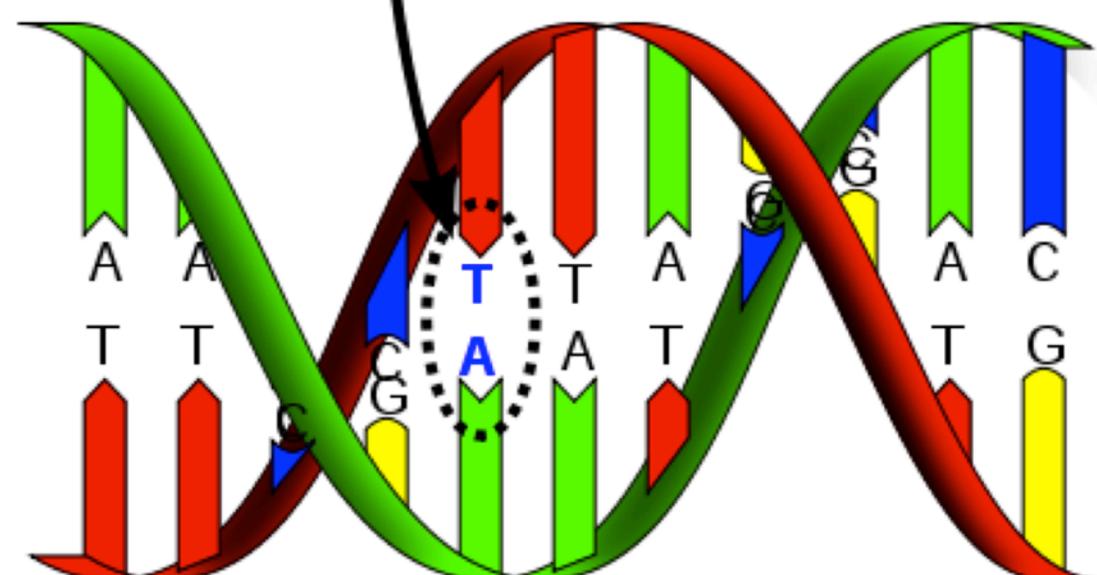
Lagging
strand





1

Point
Mutation



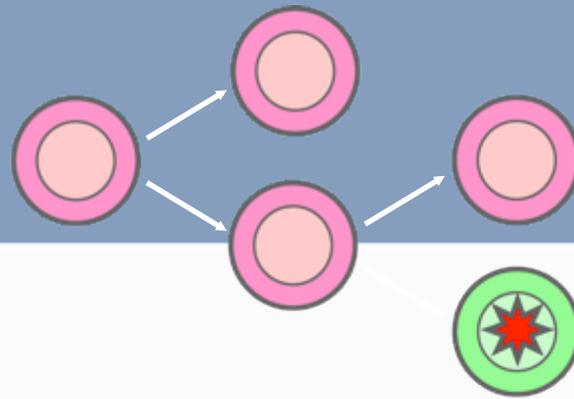
2

How are Normal and Cancer Cell Division Different?



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Normal
cell division



Cell damage—
no repair



Cell Suicide or Apoptosis

Cancer
cell division



First
mutation



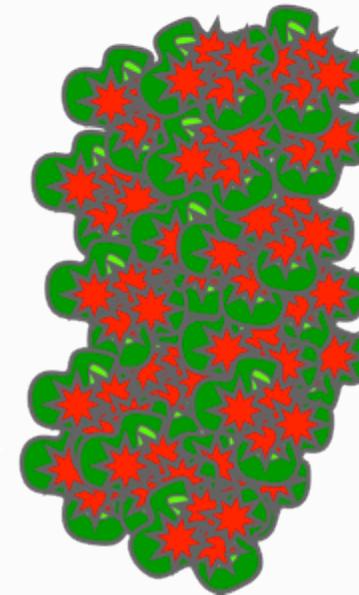
Second
mutation



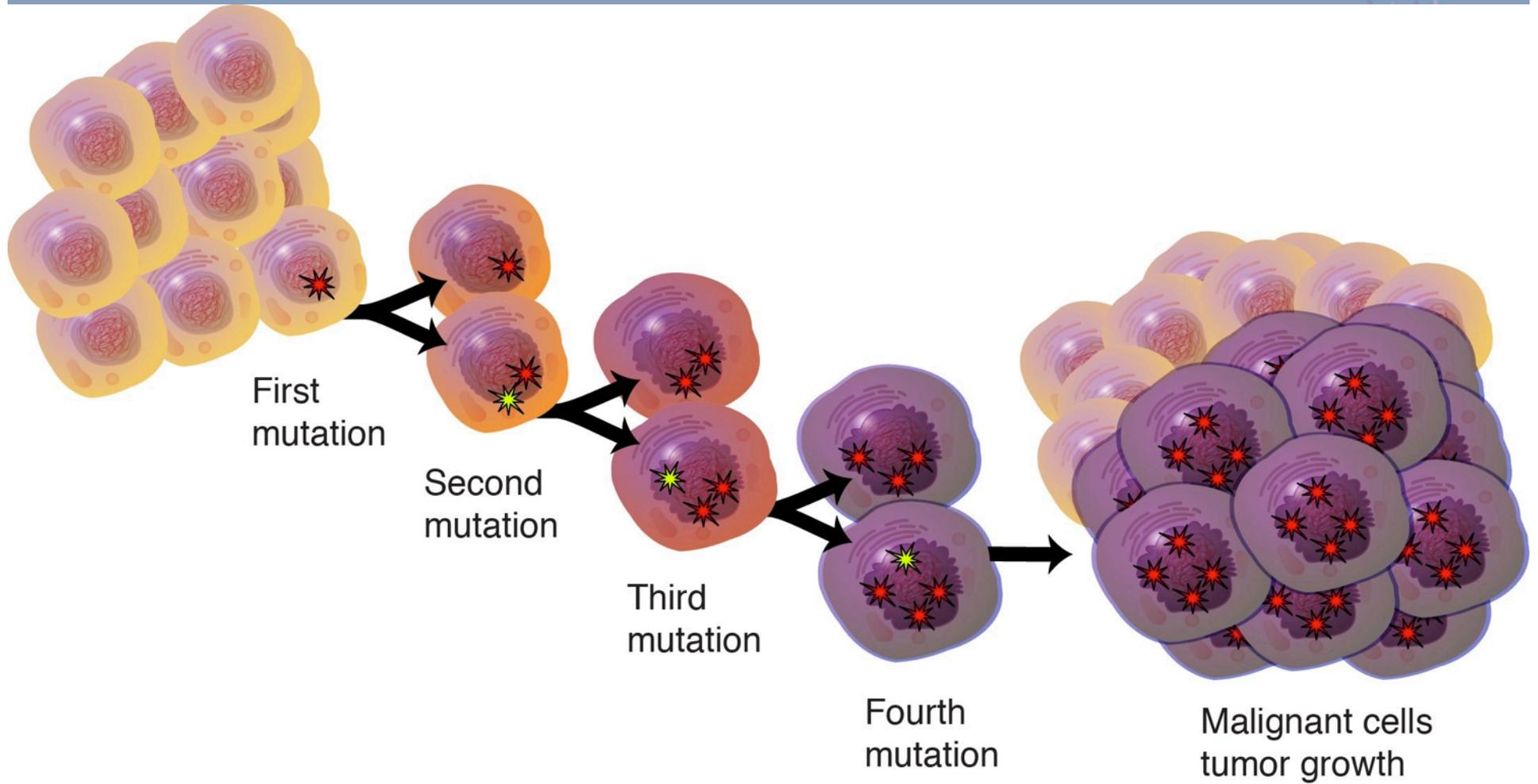
Third
mutation

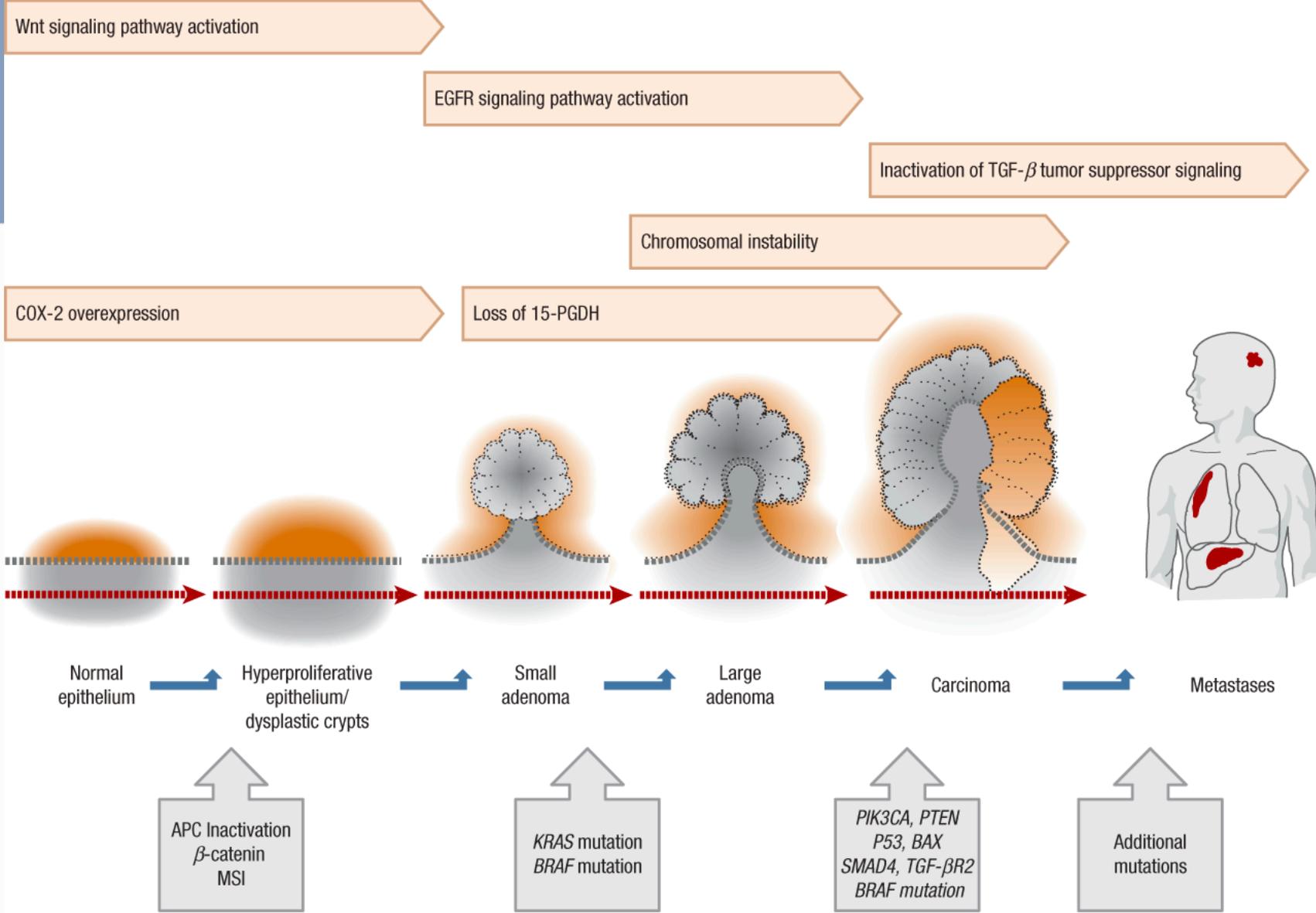


Fourth or
later mutation



Uncontrolled growth

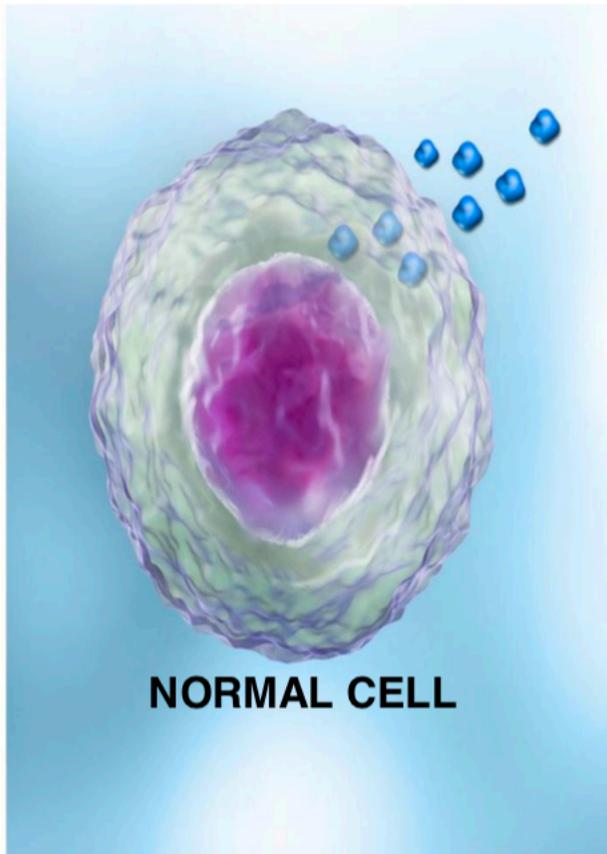




Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM:
Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:
www.accesspharmacy.com
 Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

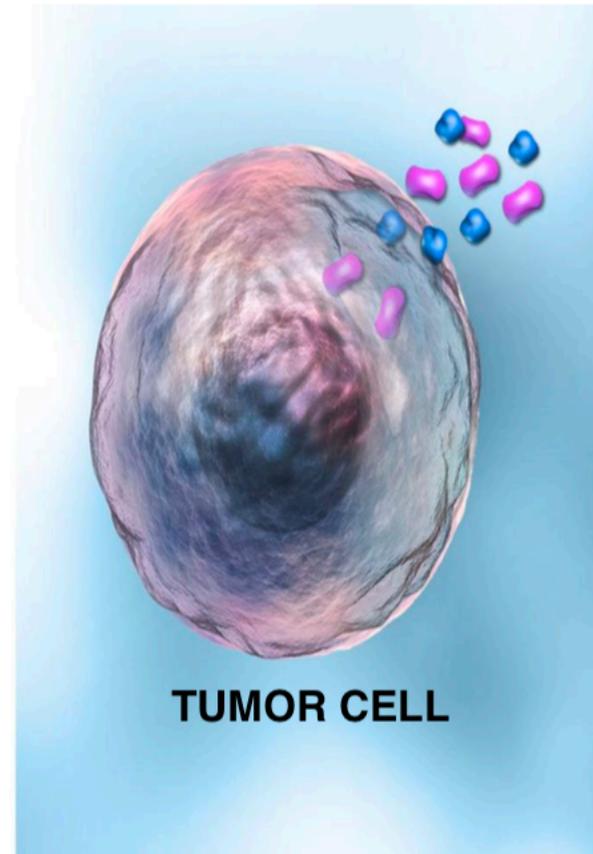
Normal Cells

Express antigens that do not elicit an immune response



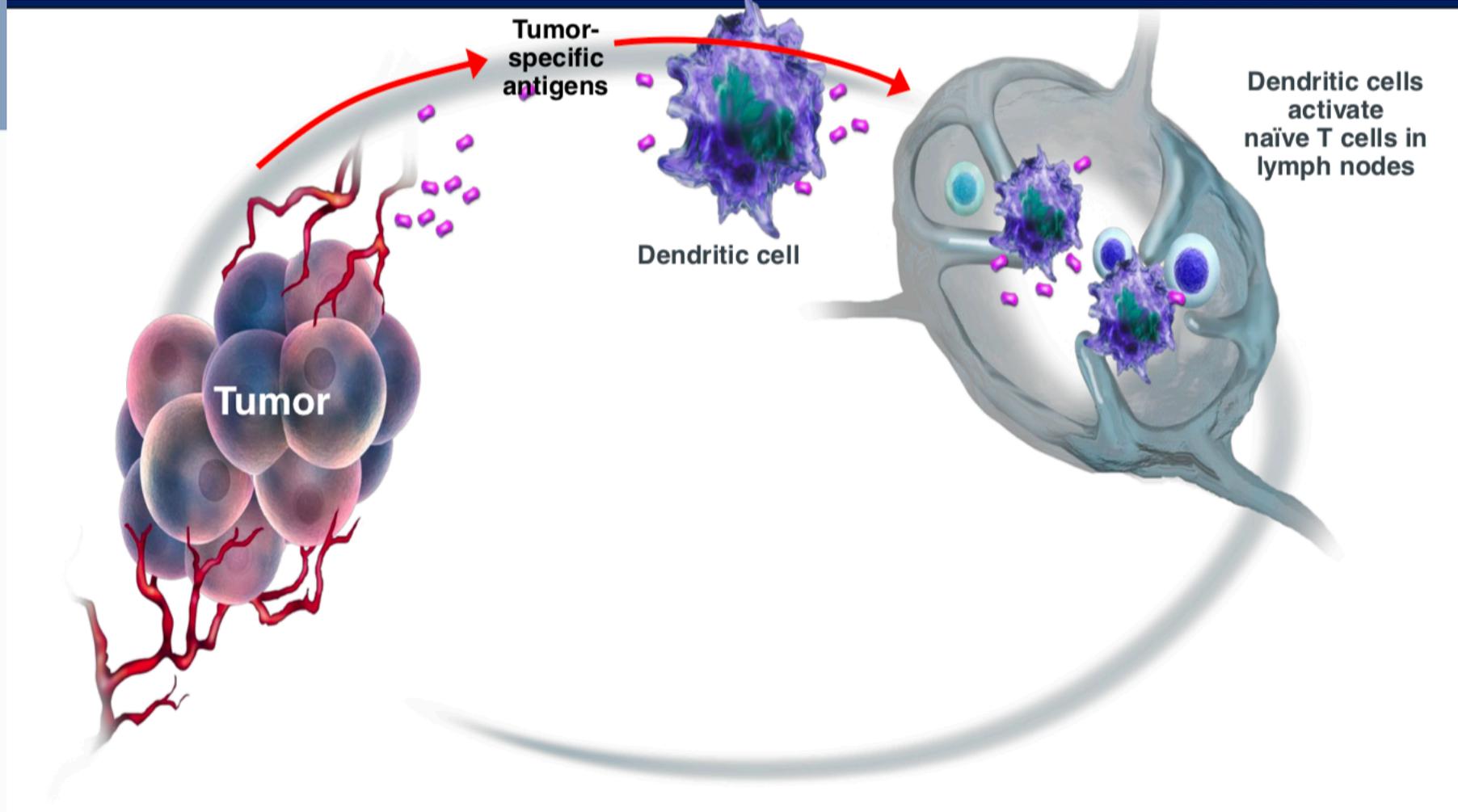
Tumor Cells

Express both normal antigens and tumor antigens



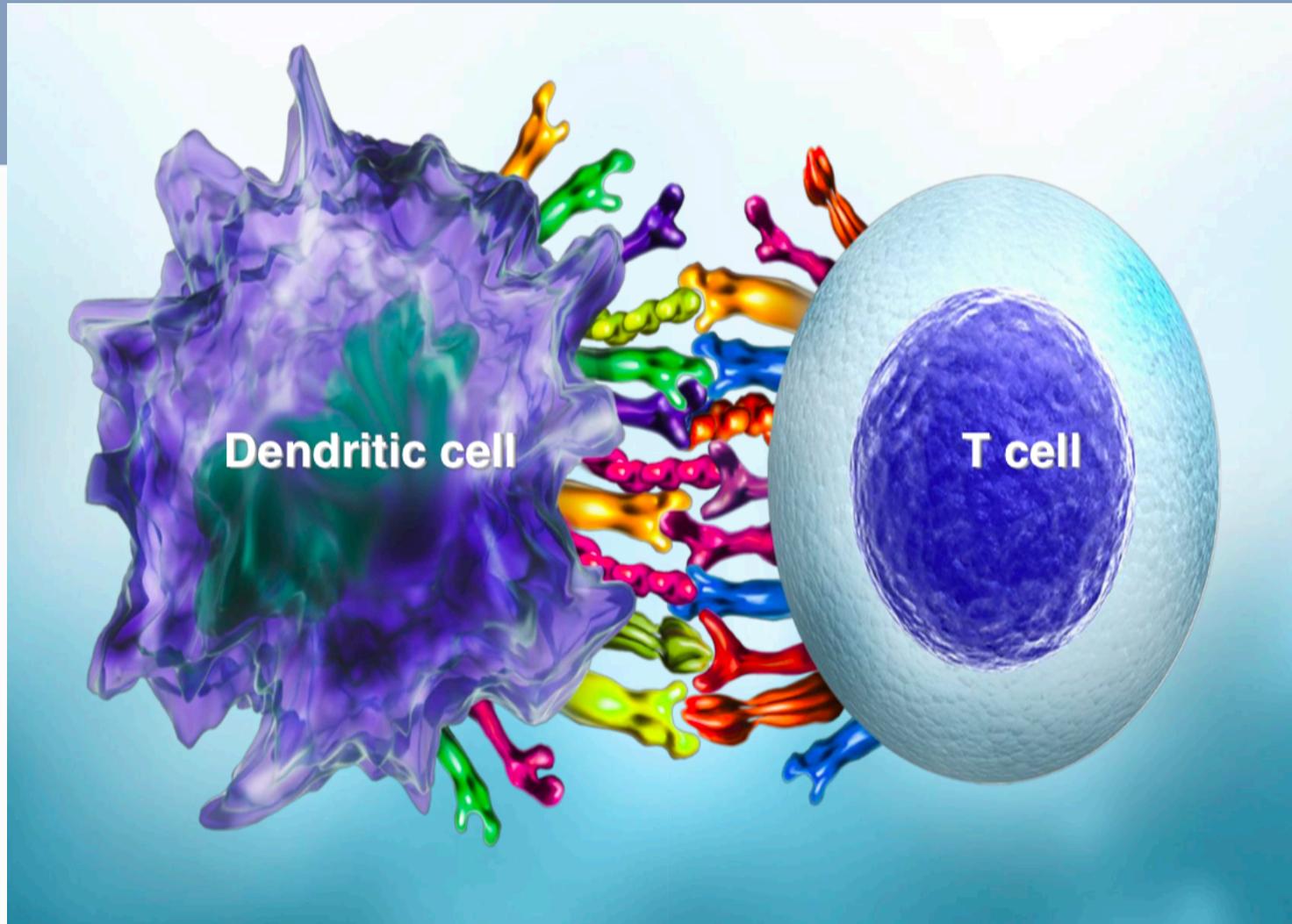


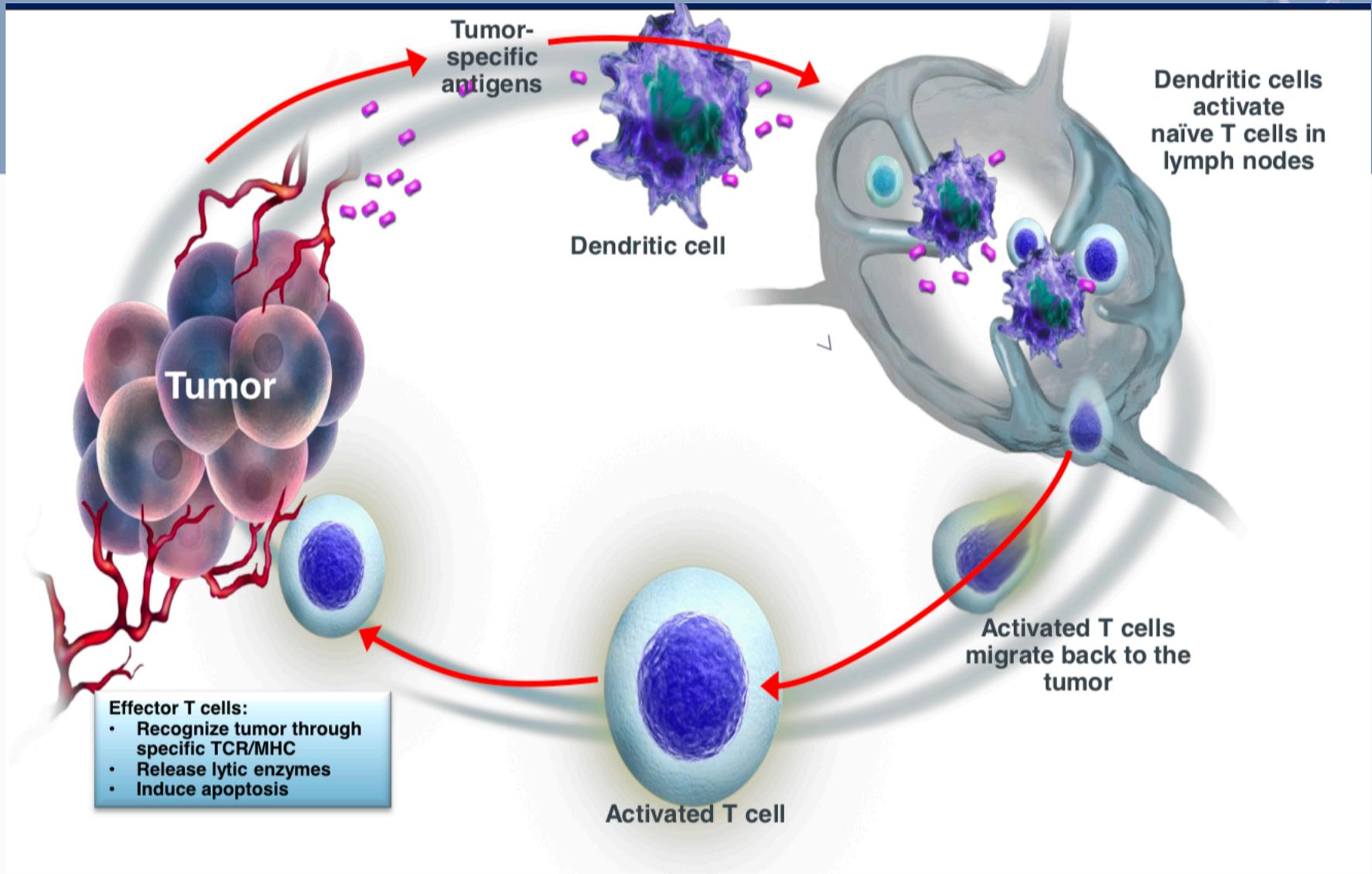
antigen

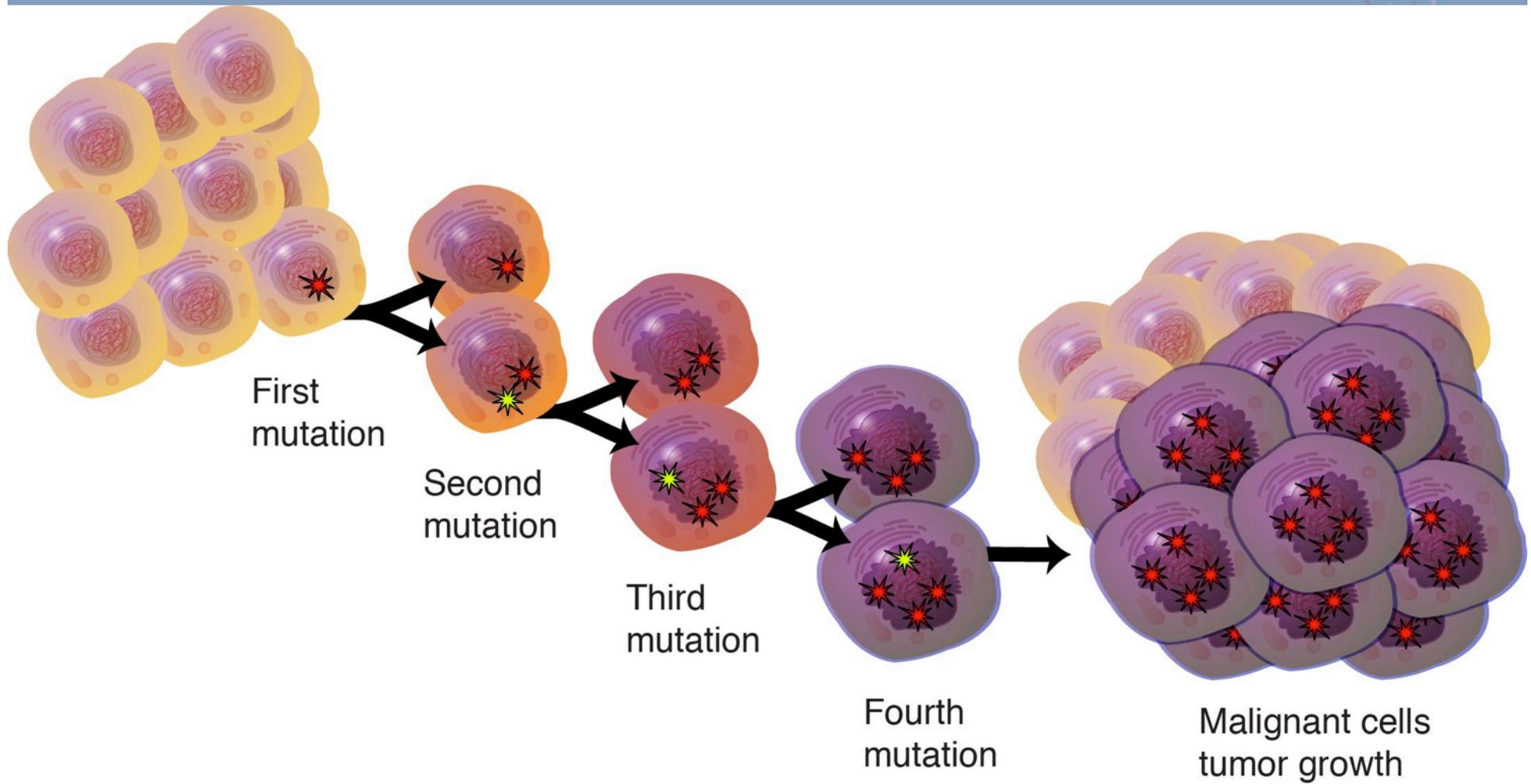




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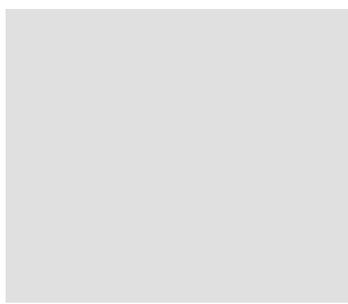
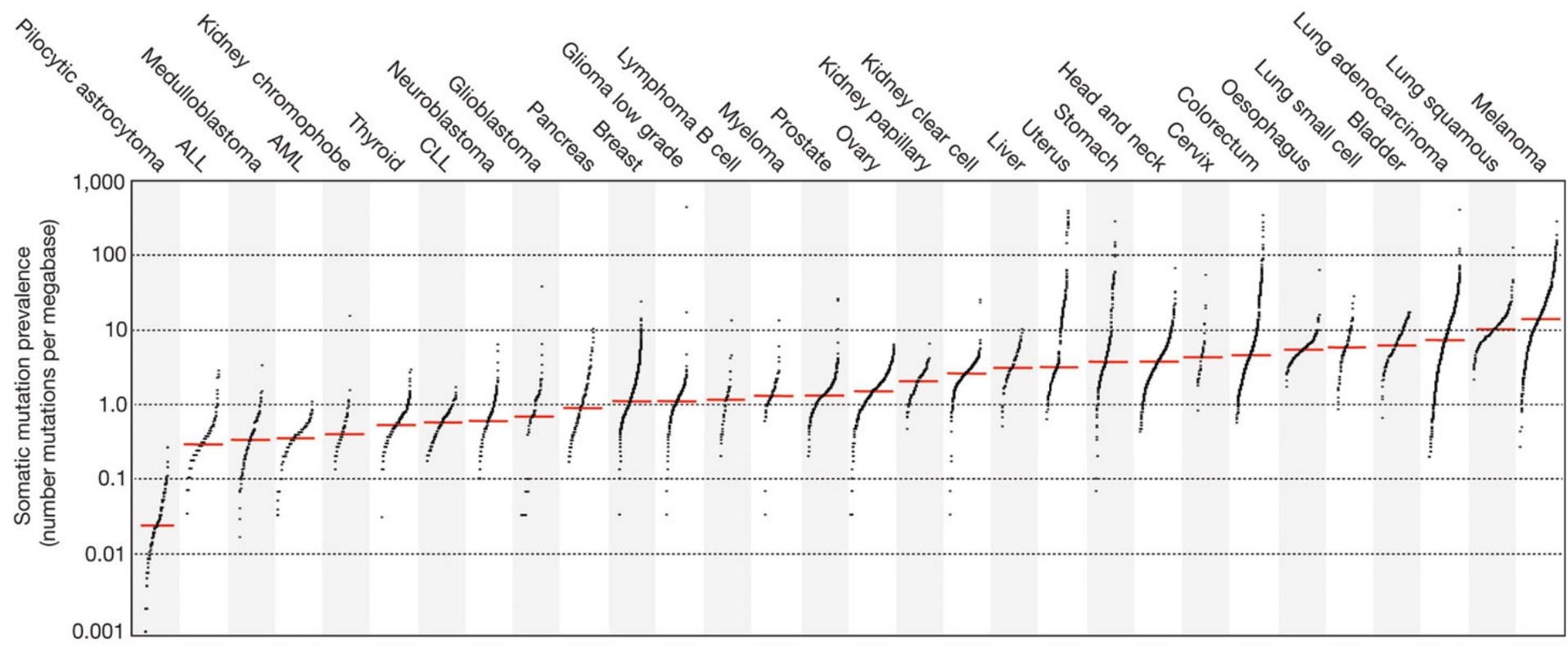




**Des te meer mutaties in een tumor
des te meer ontstekingsreactie**



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Handwritten text in an ancient script, likely Coptic, on a yellowed parchment page. The text is arranged in approximately 20 horizontal lines. The script is a mix of black and red ink, with red ink used for certain characters or words, possibly indicating a specific part of the text like a title or a section. The parchment shows signs of age, including some staining and uneven coloring. The text is written in a dense, cursive style characteristic of early medieval manuscripts.



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St. Peregrine
Laziosi



Patron Saint of Cancer/Running Sores
May 1



Prayer to Saint Peregrine

O great St. Peregrine, you have been called "The Mighty," "The Wonder-Worker," because of the numerous miracles which you have obtained from God for those who have had recourse to you. For so many years you bore in your own flesh this cancerous disease that destroys the very fiber of our being, and who had recourse to the source of all grace when the power of man could do no more. You were favored with the vision of Jesus coming down from His Cross to heal your affliction. Ask of God and Our Lady, the cure of the sick whom we entrust to you.

(Pause here and silently recall the names of the sick for whom you are praying)

Aided in this way by your powerful intercession, we shall sing to God, now and for all eternity, a song of gratitude for His great goodness and mercy.

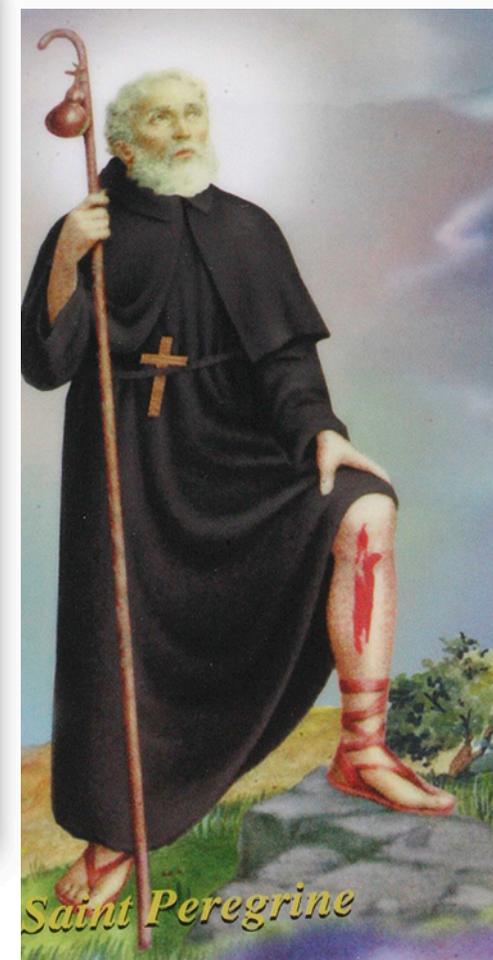
Amen



HC9-145E

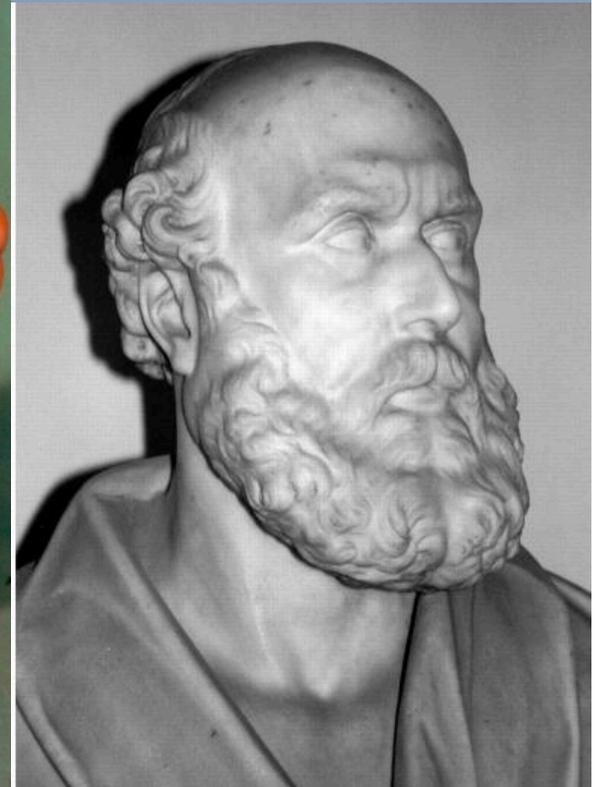



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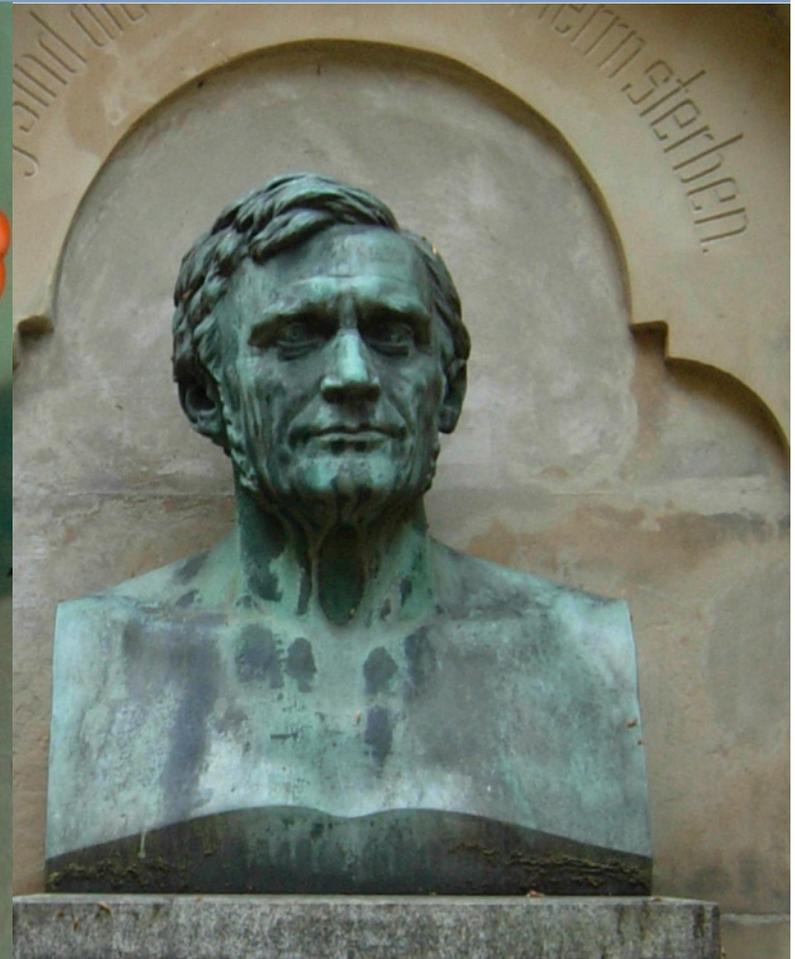


1875 Campbell de Morgan


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W. Busch



New York Times - July 29, 1908

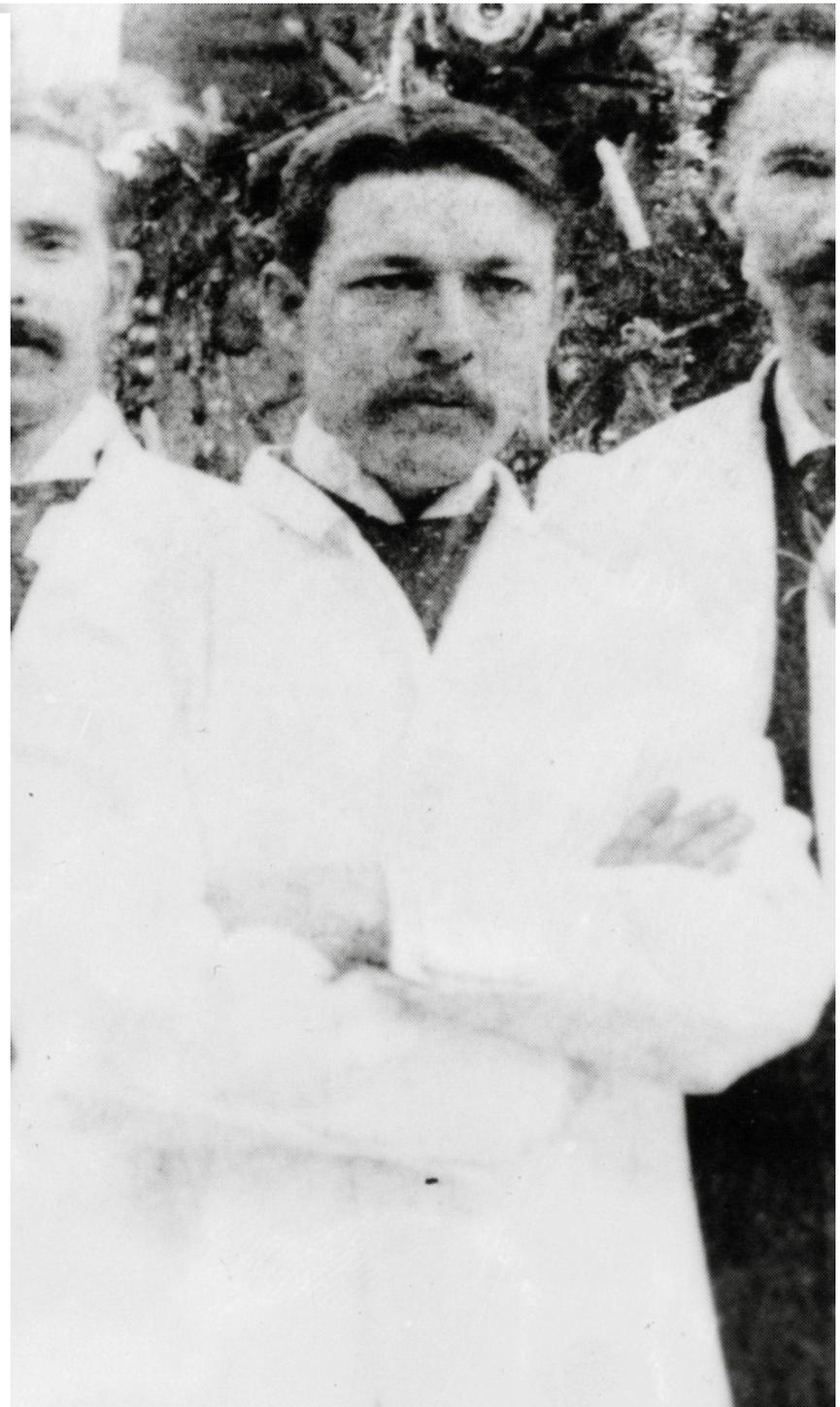
ERYSIPELAS GERMS AS CURE FOR CANCER

**Dr. Coley's Remedy of Mixed
Toxins Makes One Disease
Cast Out the Other.**

MANY CASES CURED HERE

**Physician Has Used the Cure for 15
Years and Treated 430 Cases—
Probably 150 Sure Cures.**

Following news from St. Lou's that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York it came out yester-

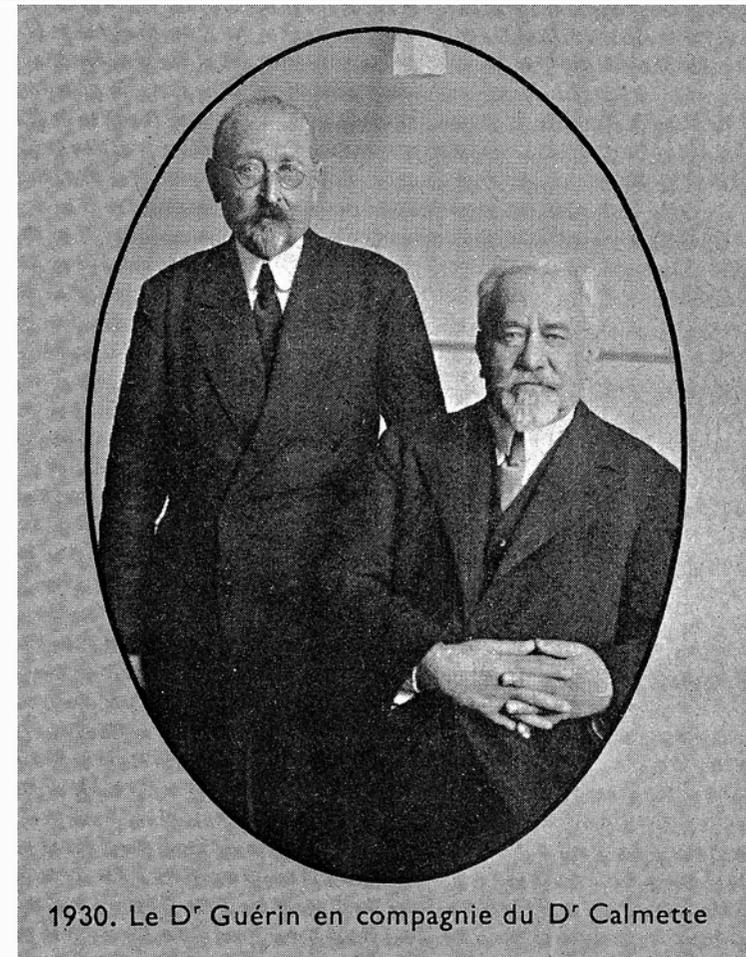




BCG VACCINE

Bacillus Calmette–Guérin (historically Vaccin Bilié de Calmette et Guérin commonly referred to as Bacille de Calmette et Guérin or BCG) is a vaccine against tuberculosis that is prepared from a strain of the

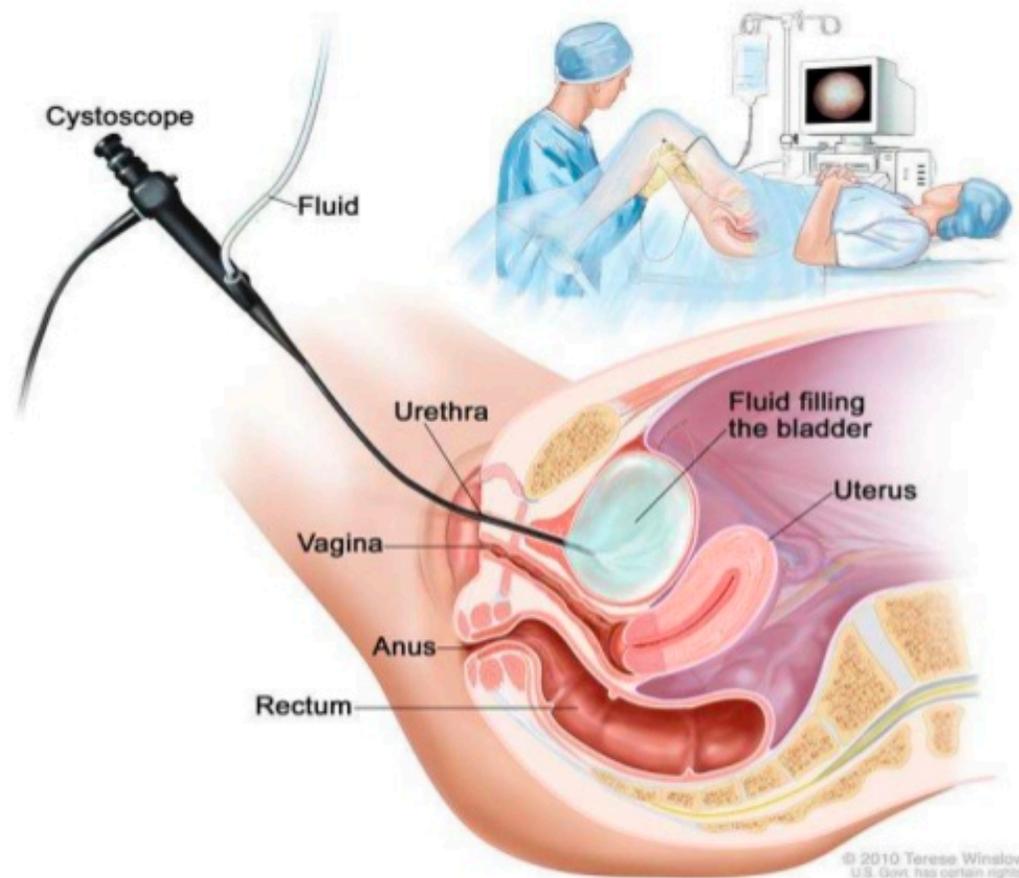
attenuated (virulence-reduced) live bovine tuberculosis bacillus, *Mycobacterium bovis*, that has lost its virulence in humans by being specially subcultured in a culture medium, usually Middlebrook 7H9.



1930. Le D^r Guérin en compagnie du D^r Calmette



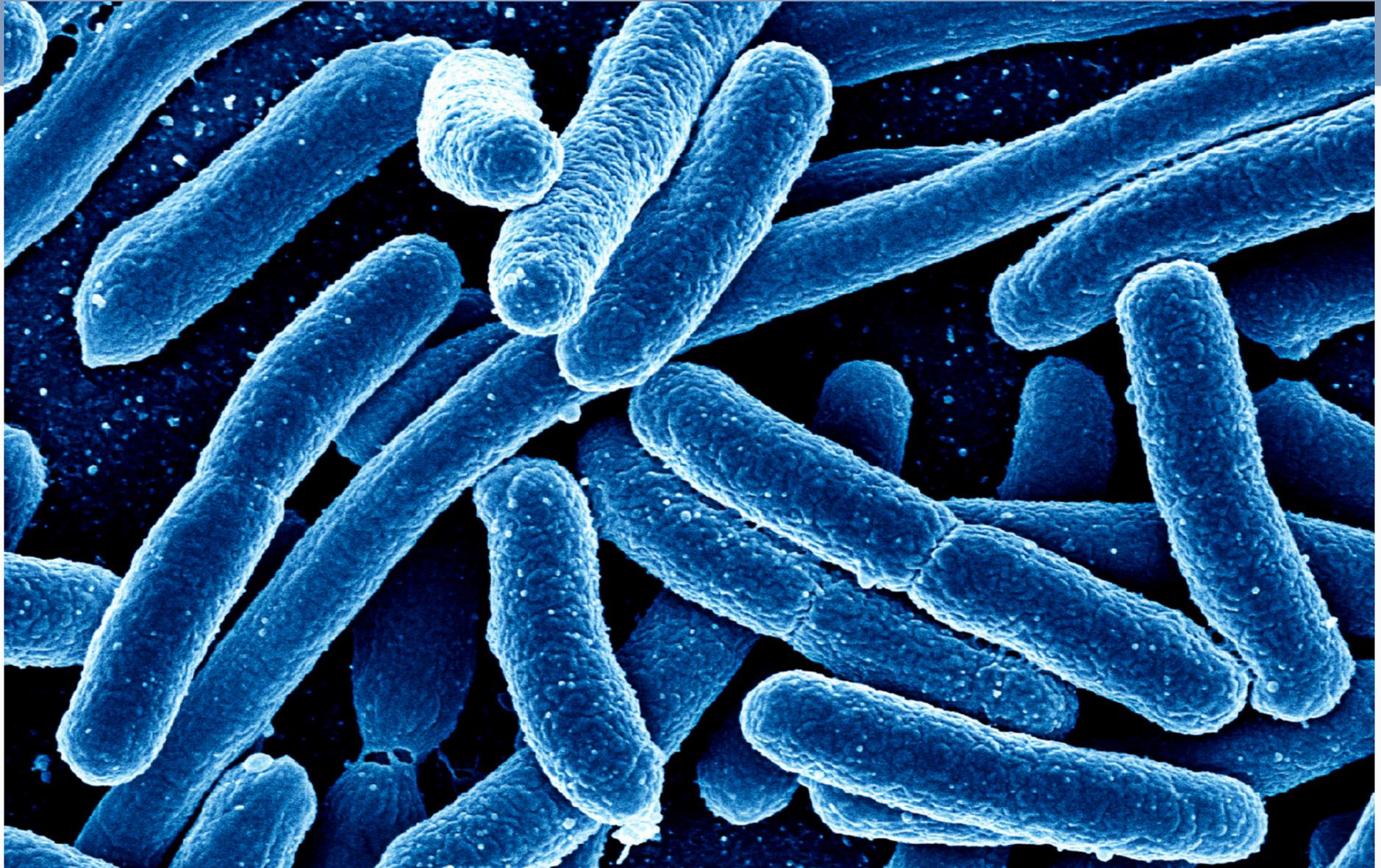
Cystoscopy





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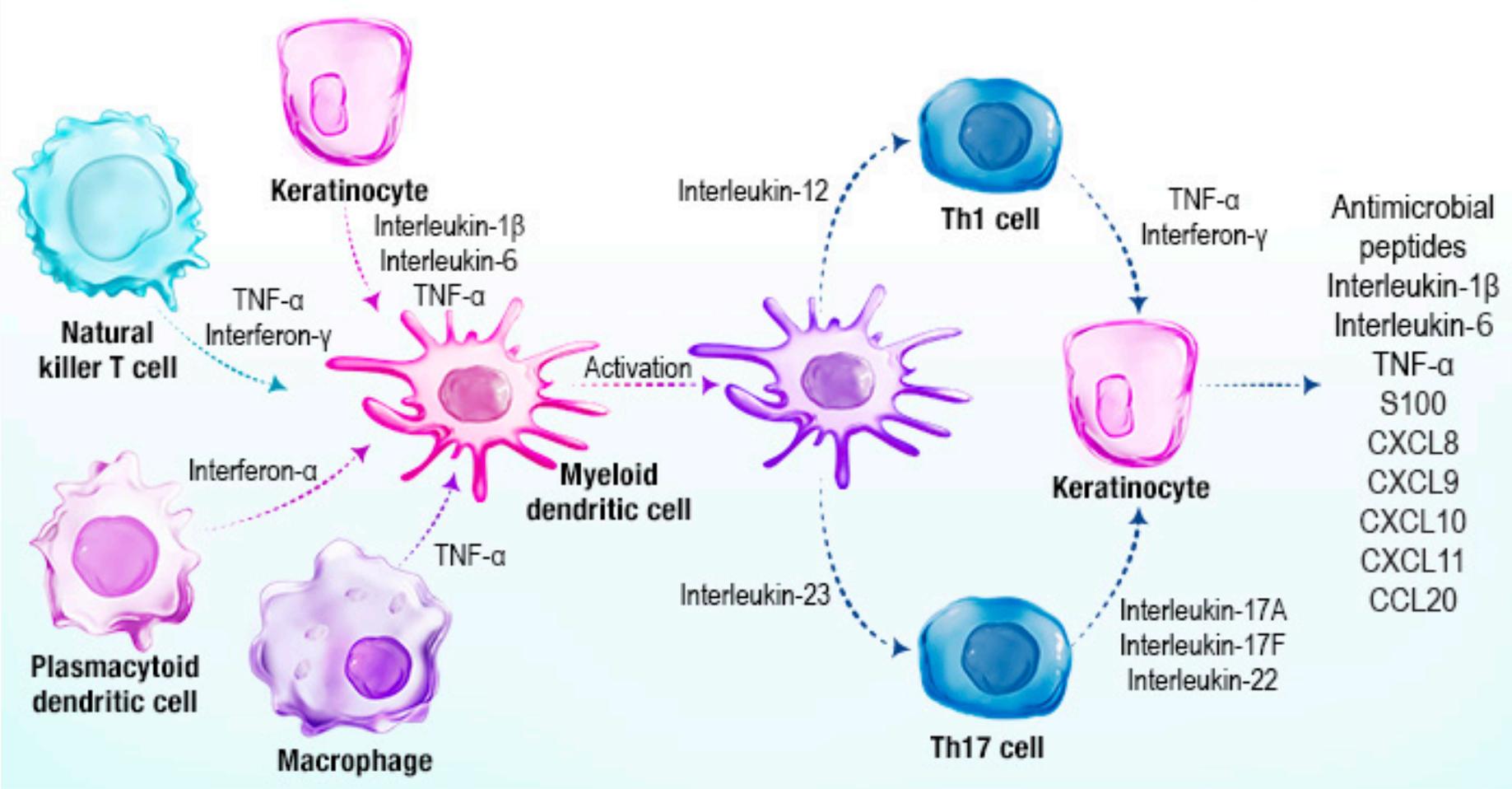






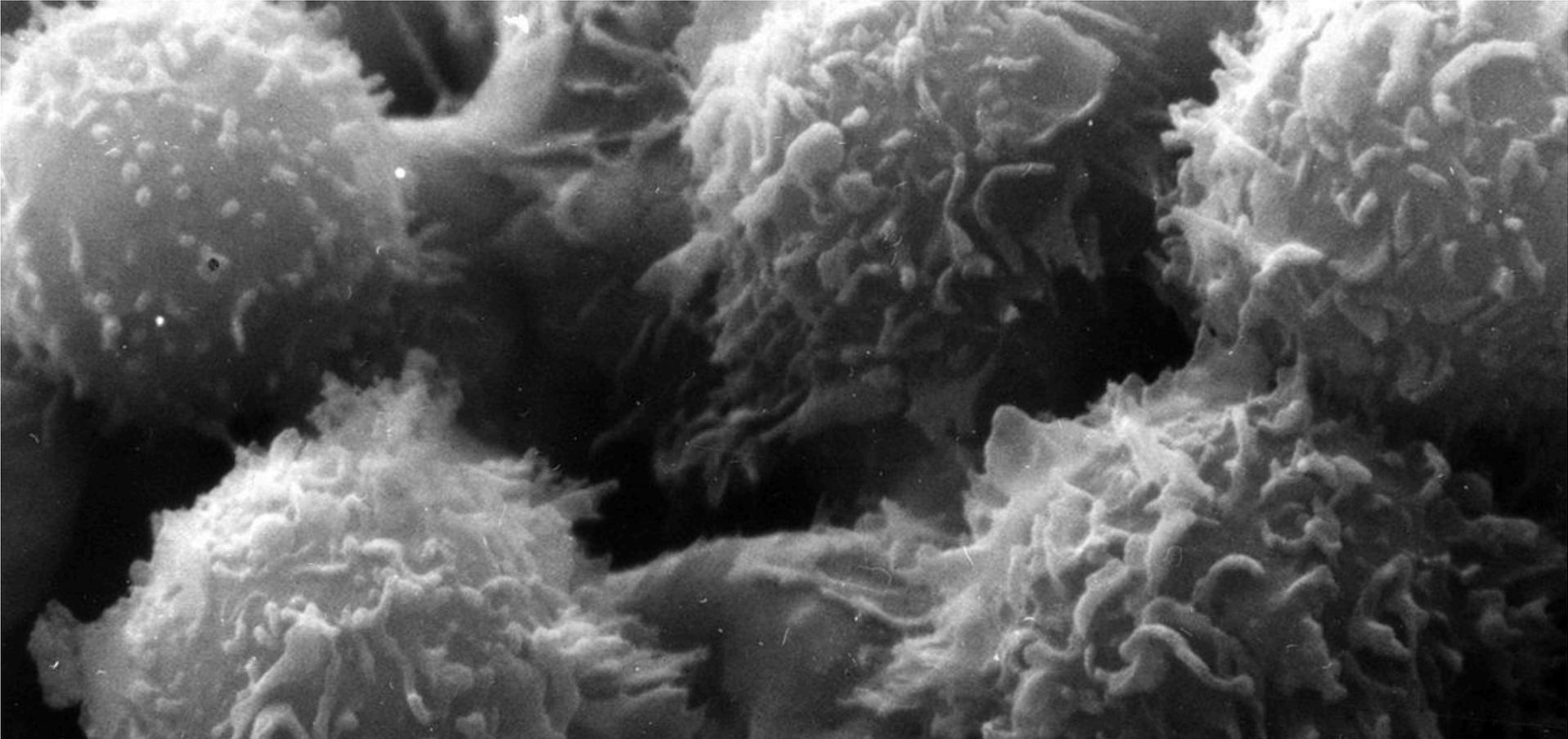
Initiation

Perpetuation



Modified from: Nestle FO, et al. *N Engl J Med.* 2009;361:496-509.

Visual representation based on preclinical evidence

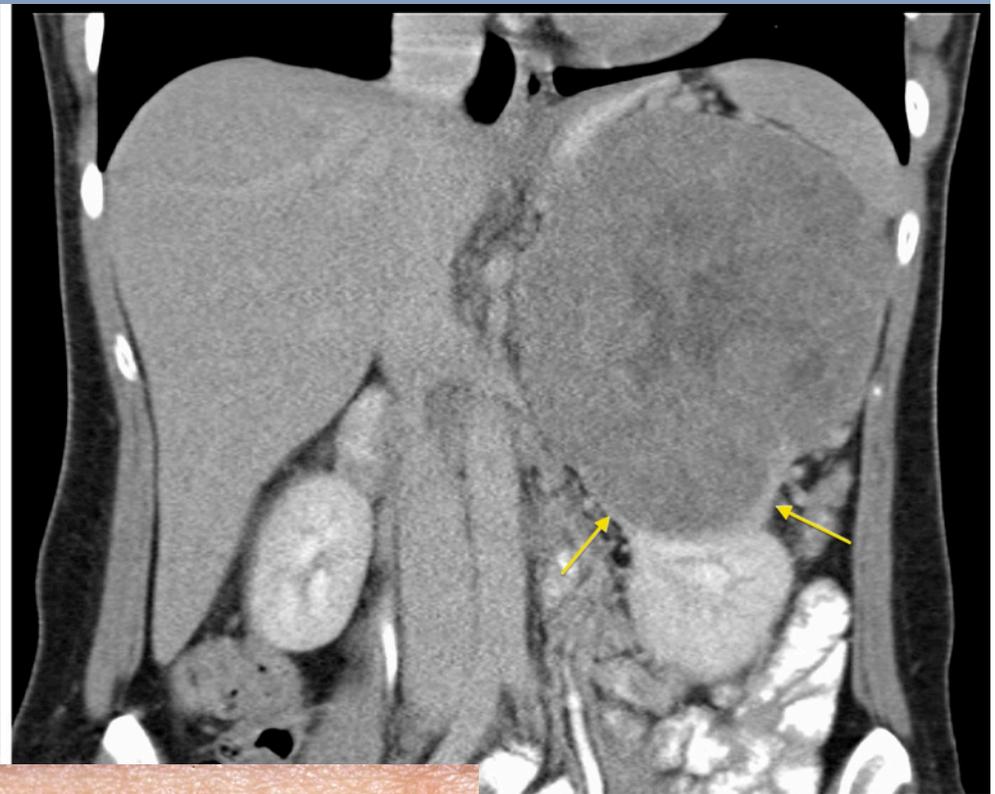
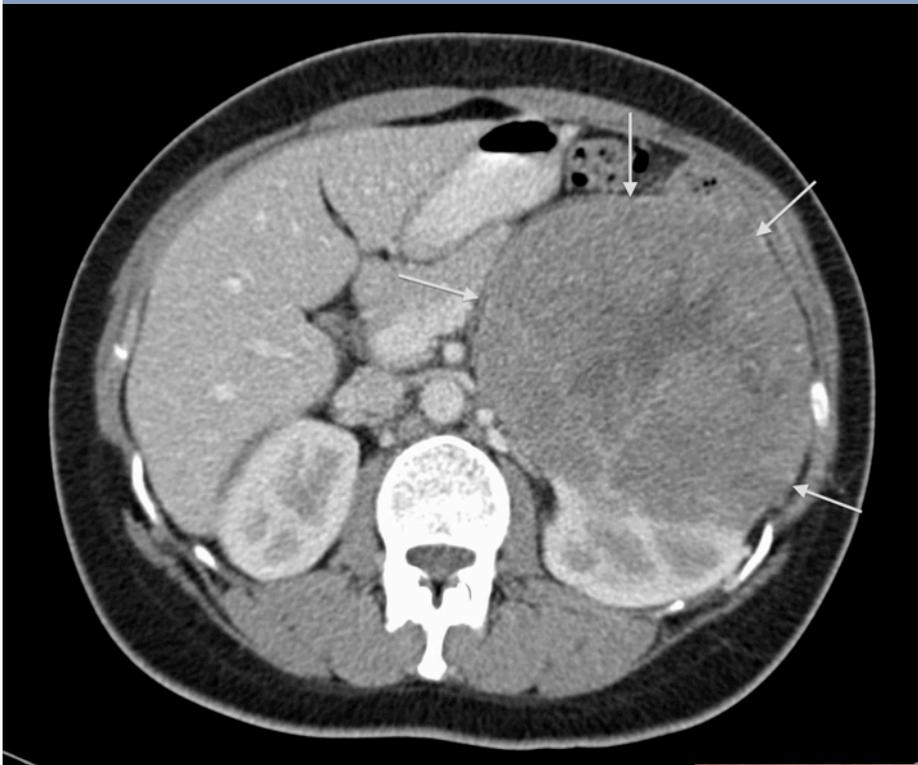


Treatment of Hairy Cell Leukemia With Alpha Interferons

JORGE R. QUESADA, MD, JORDAN U. GUTTERMAN, MD, AND EVAN M. HERSH, MD

Cancer 57:1678-1680, 1986.





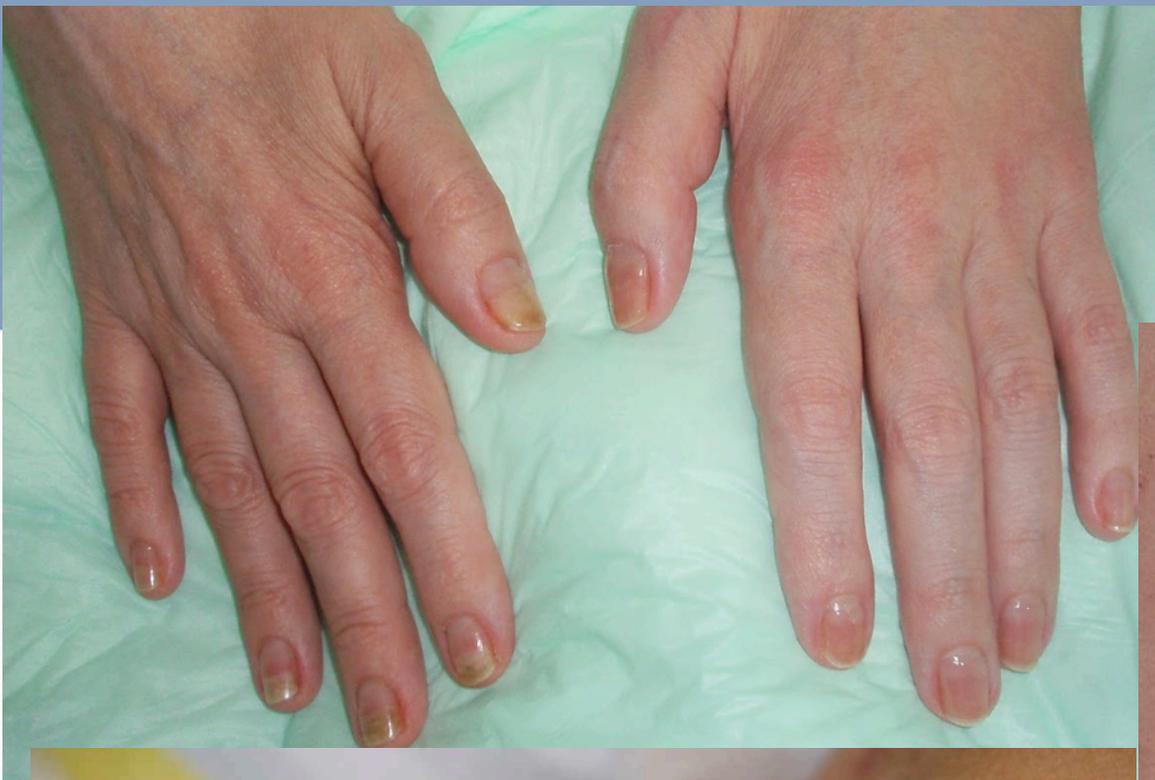
Interleukine

www.emmasaying.com





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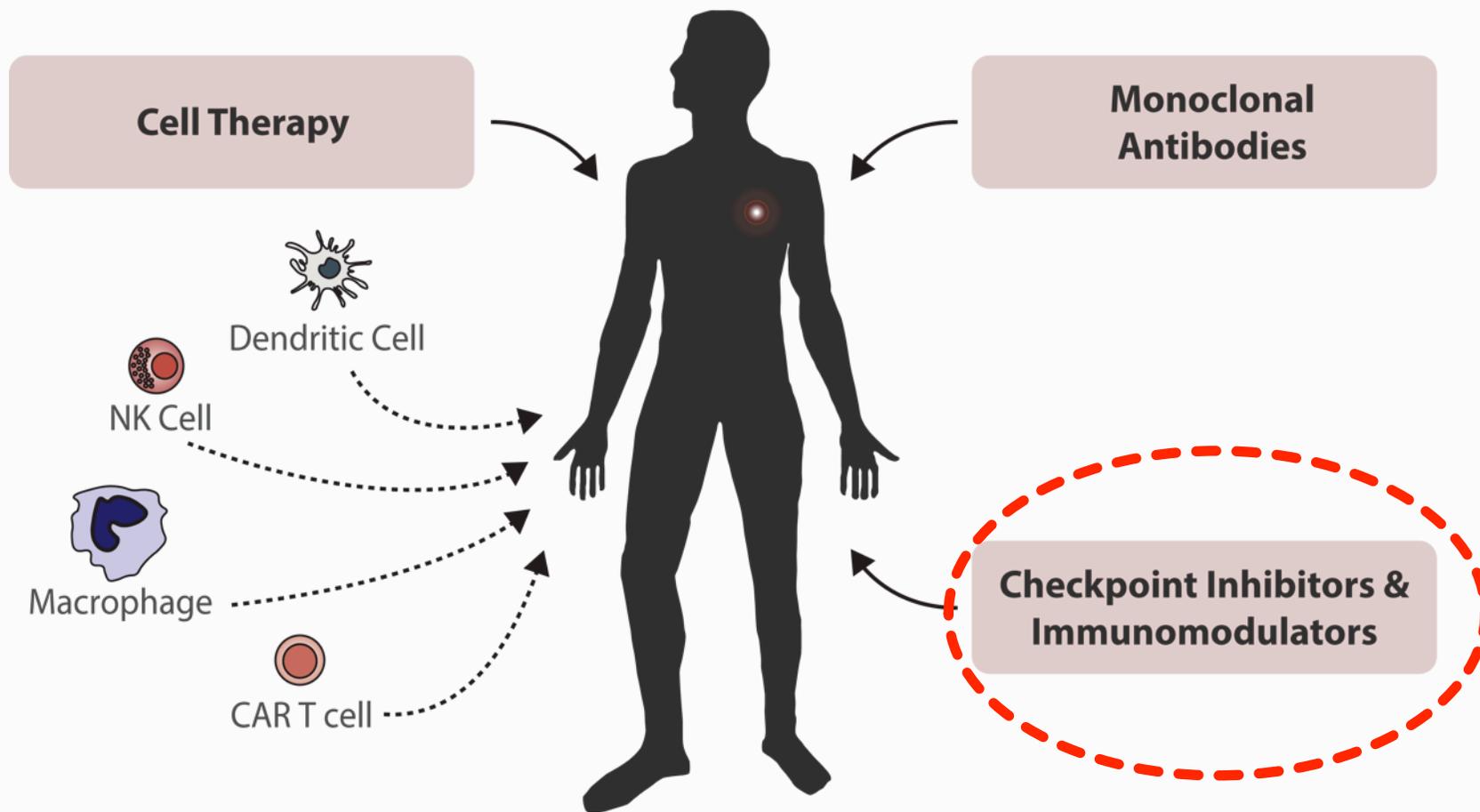


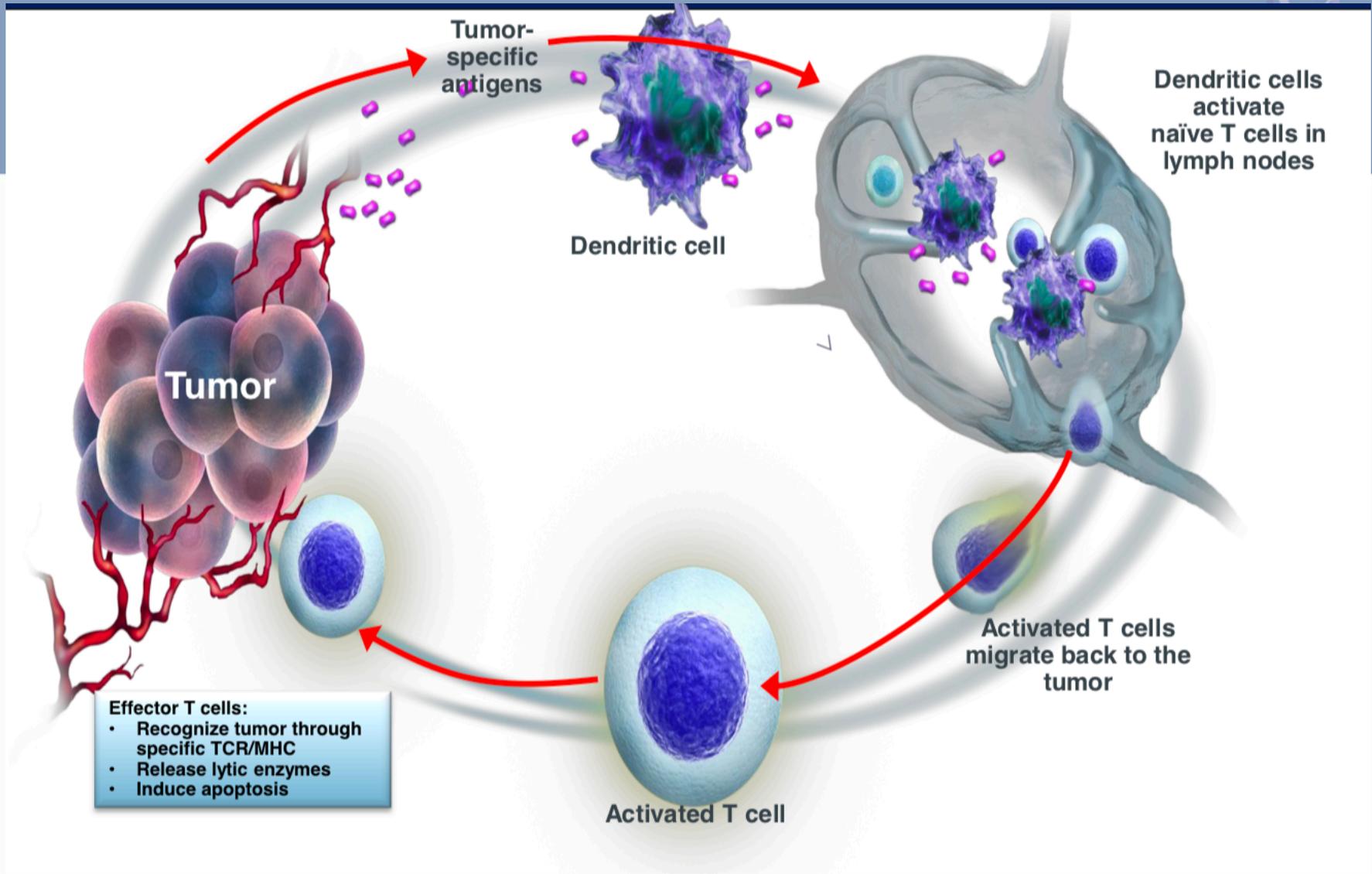
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ziekenhuis



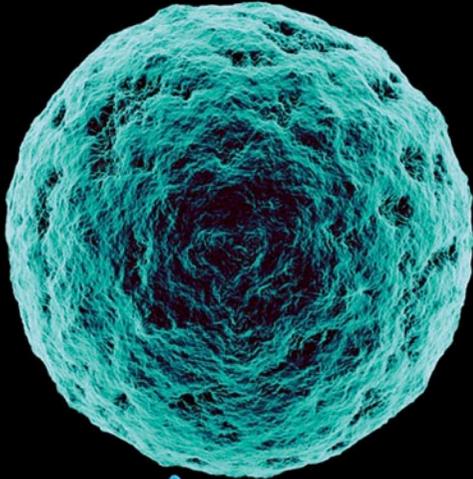
Interleukine

Cancer Immunotherapy

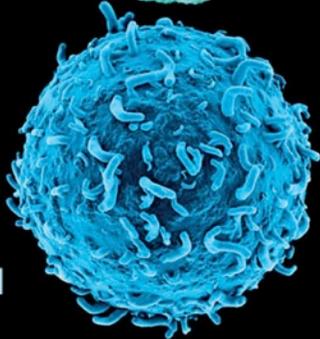




Cancer cell



T cell



T cell approaches cancer cell.



T cell attacks cancer cell.

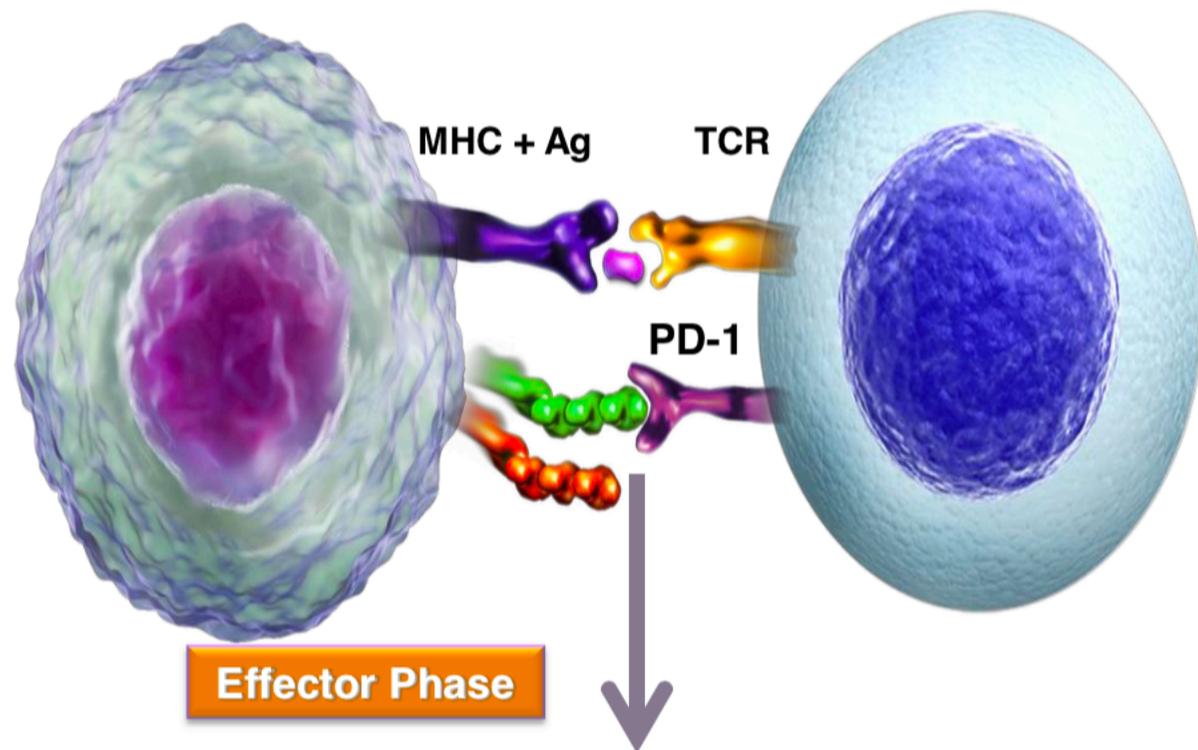


Cancer cell destroyed.



Normal Cell

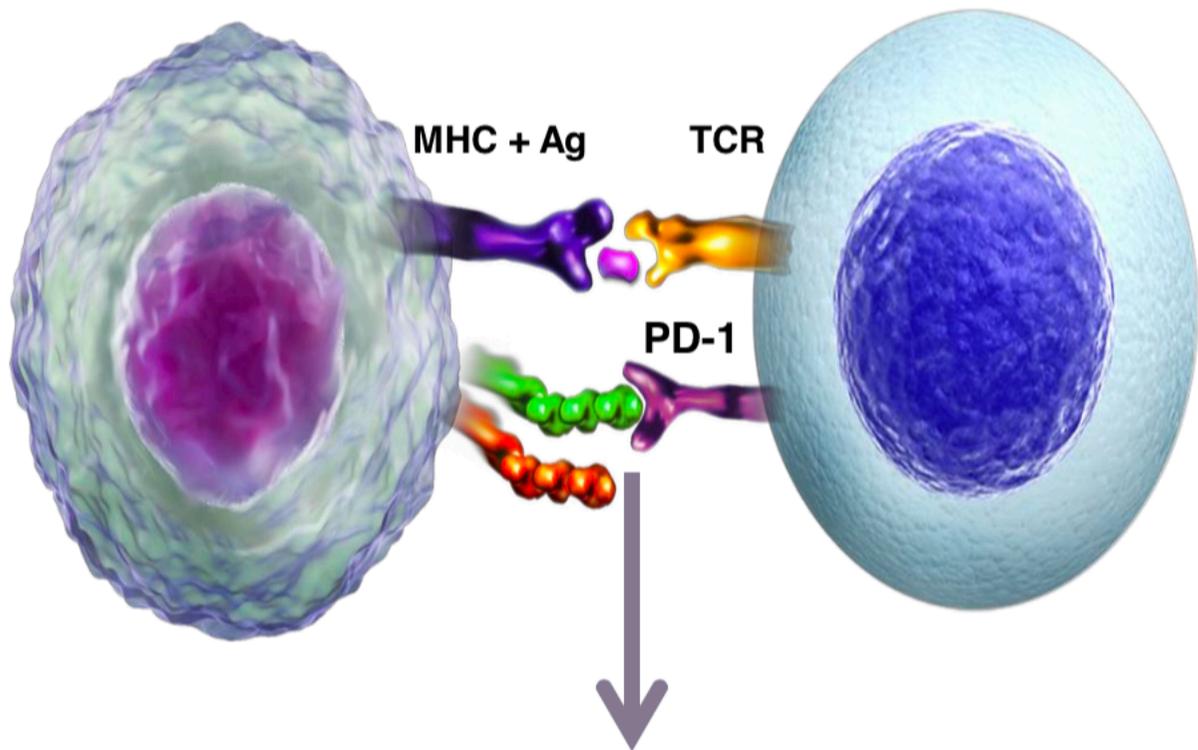
Effector T cell

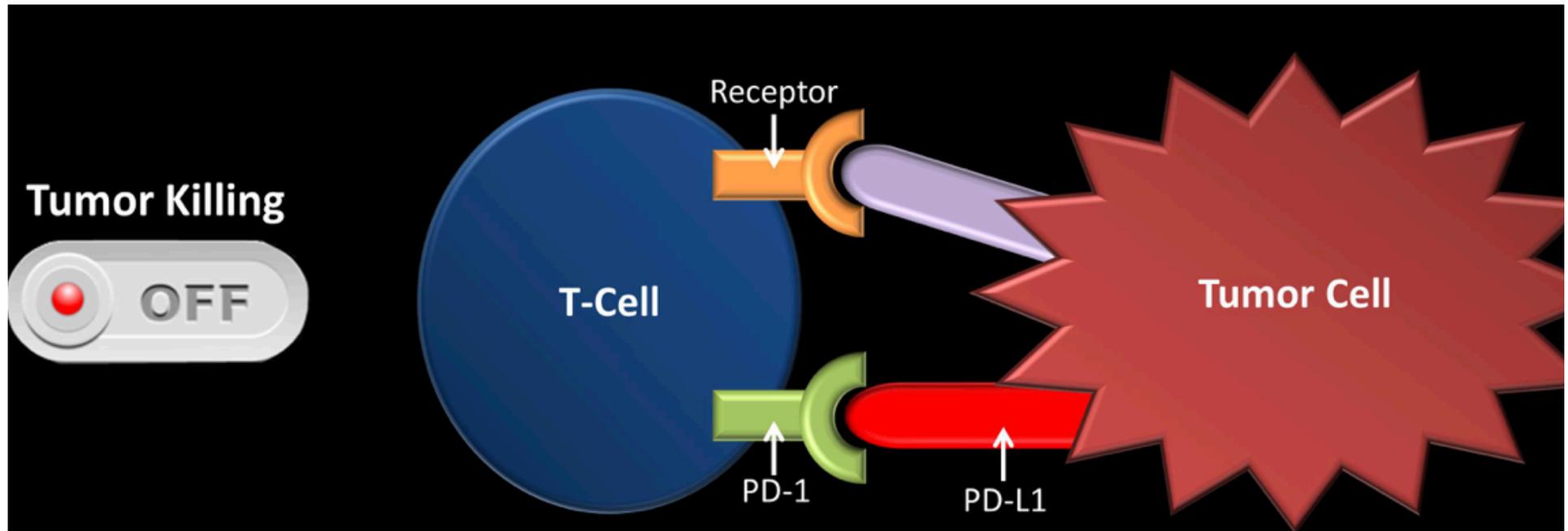




Tumor Cell

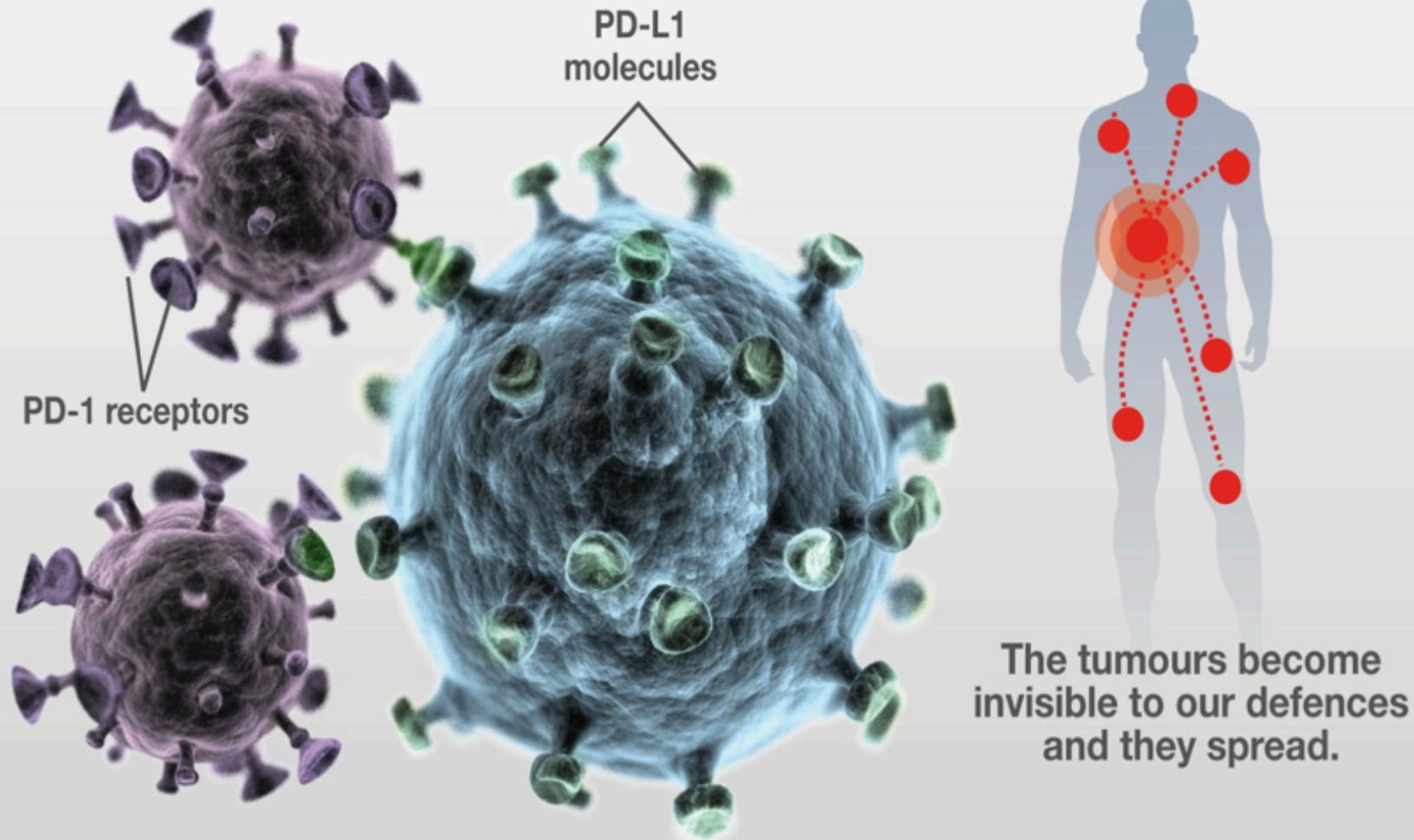
Effector T cell





2. Camouflage of tumour cells

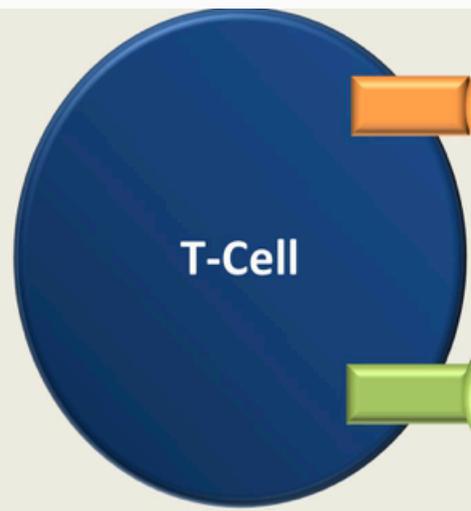
Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.





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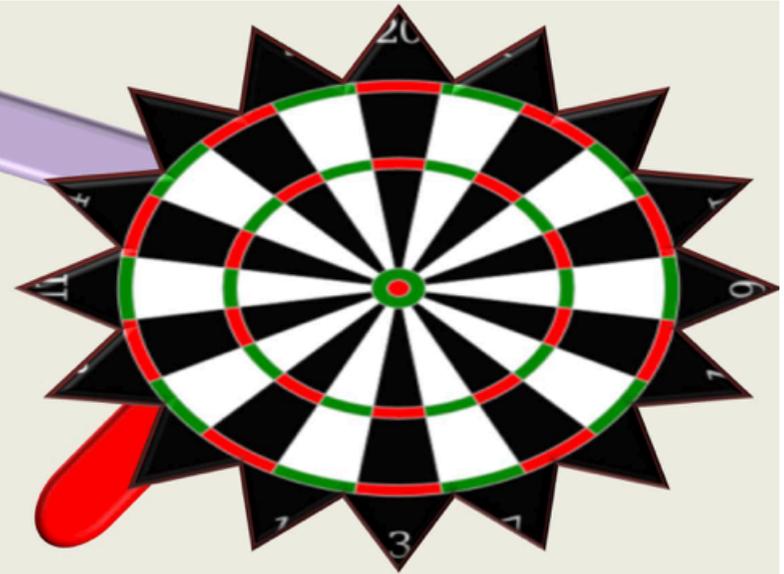
Tumor Killing



T-Cell

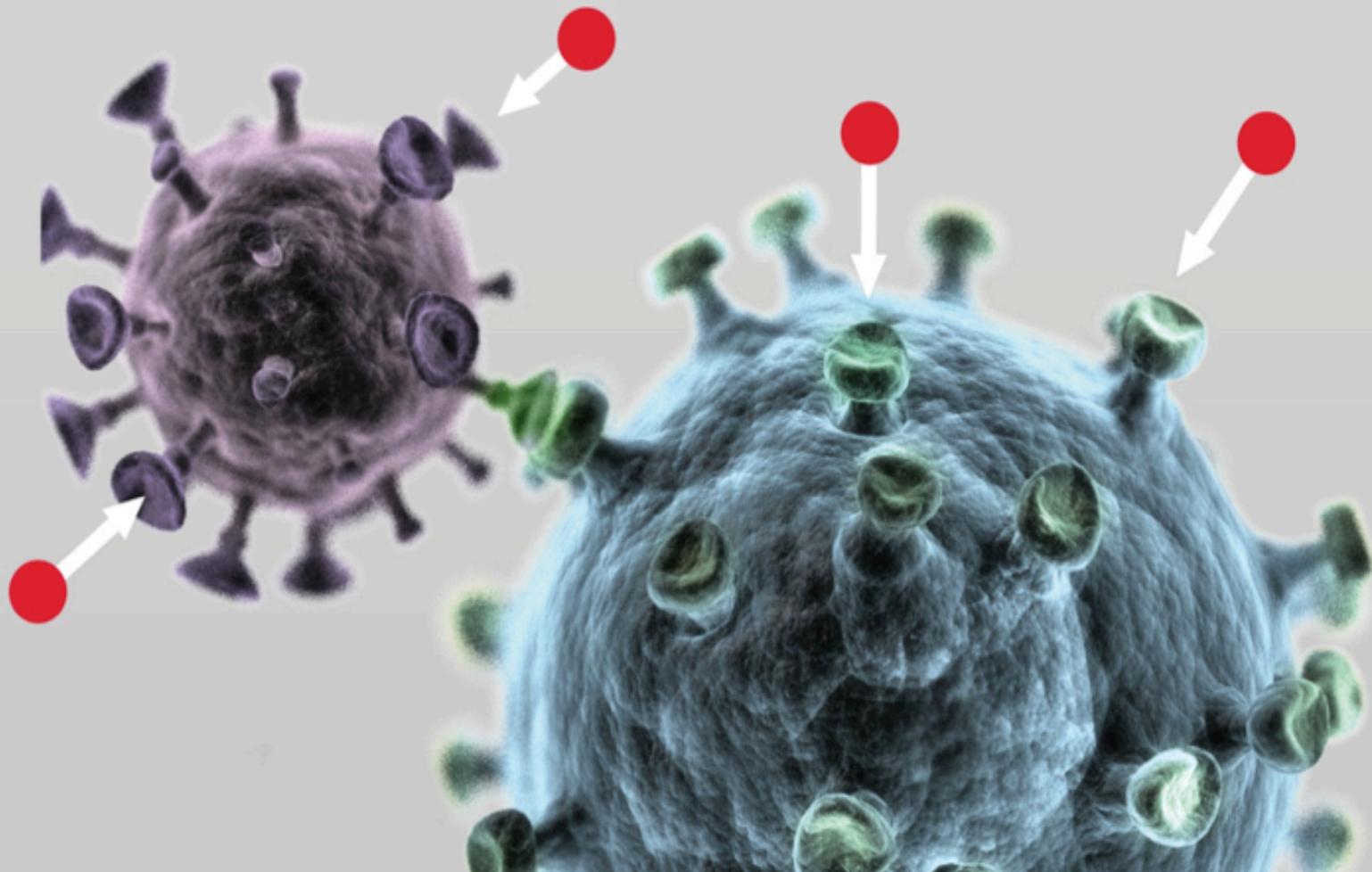


Anti PD-1



3. Action of the new inhibitor drugs

The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.



1. Normal work of the immune system

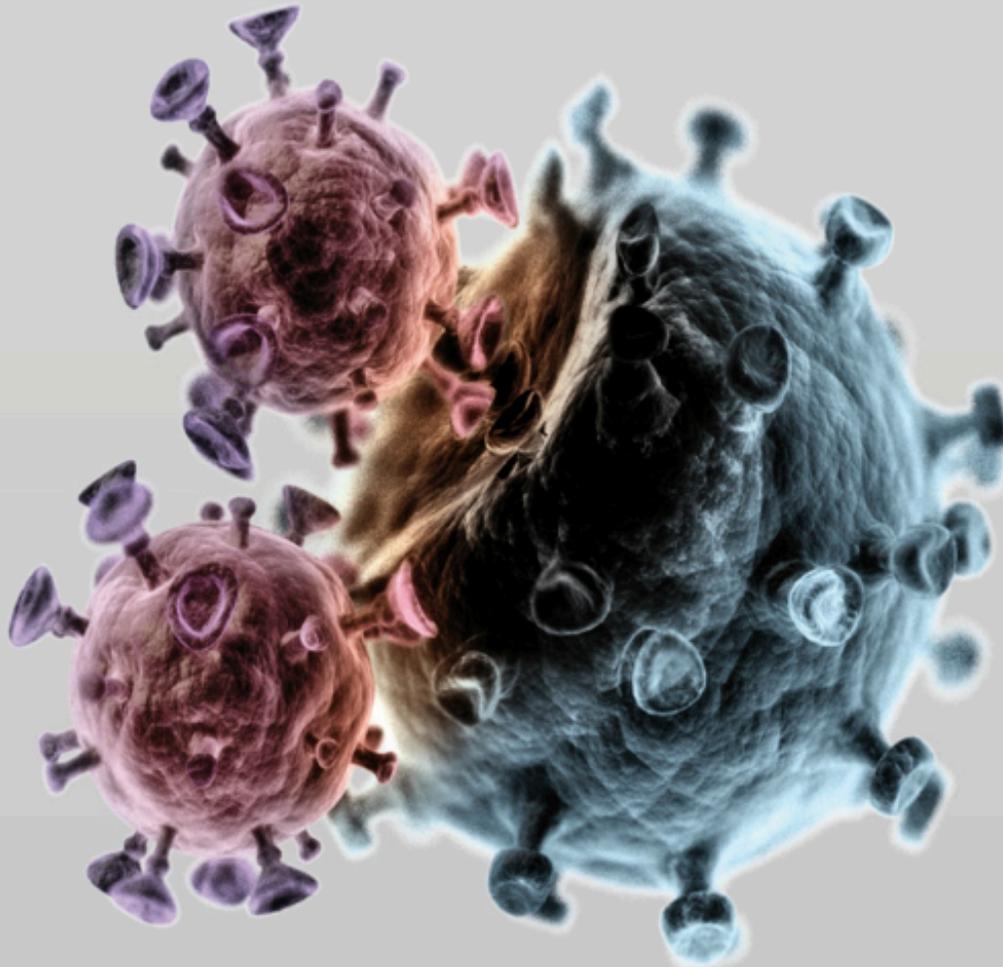
2. Camouflage of tumour cells

T lymphocytes

4. Result of immunotherapy

Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.

lymphocytes

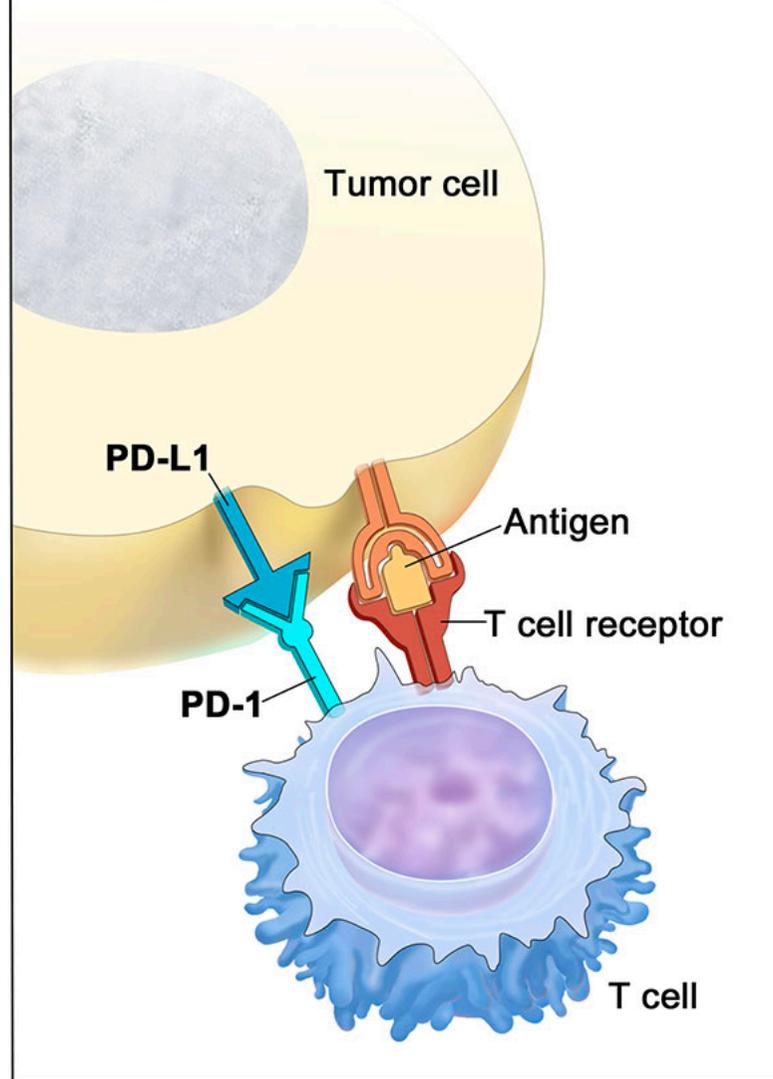


3. Active immunity

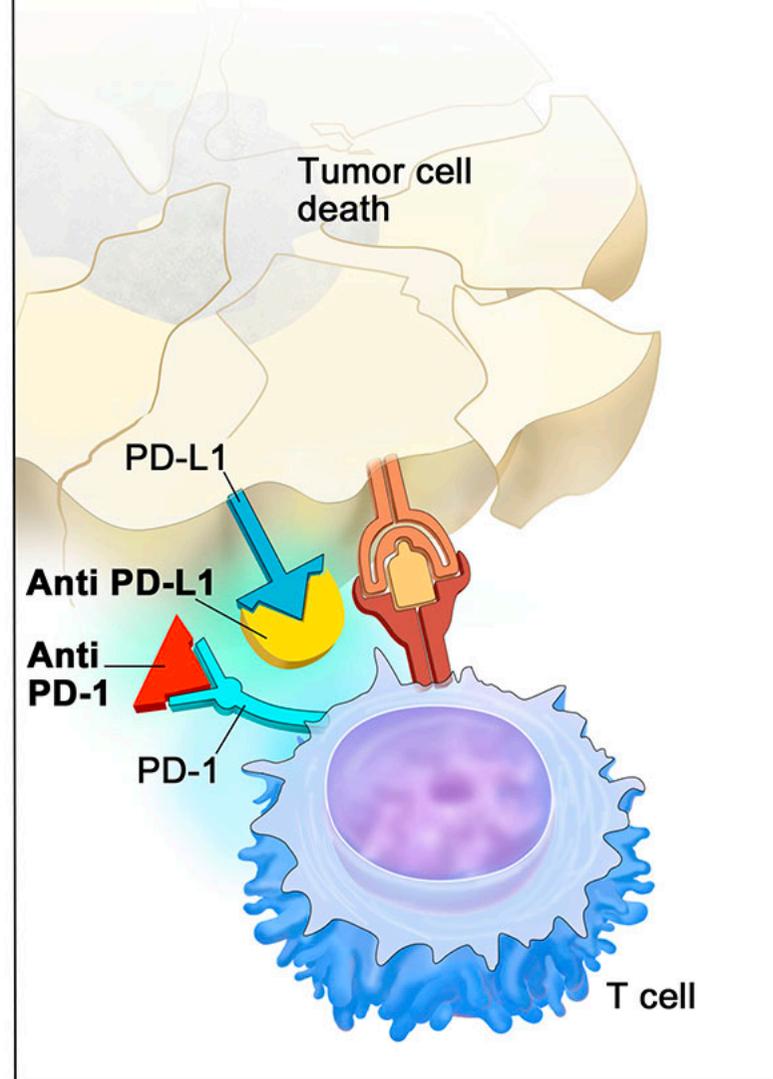
This treatment, although still in its experimental stage, has had preliminary results on lung, kidney and skin cancers.

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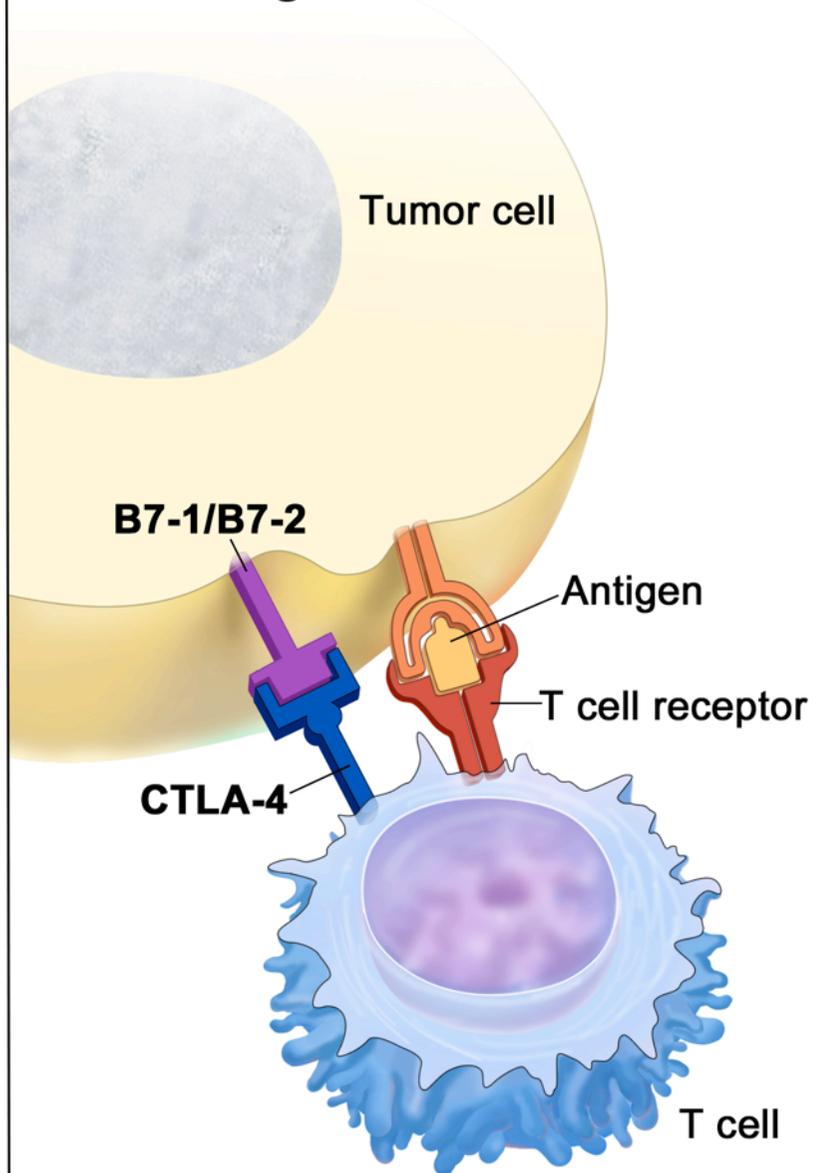
PD-L1/PD-1 binding inhibits T cell killing of tumor cell



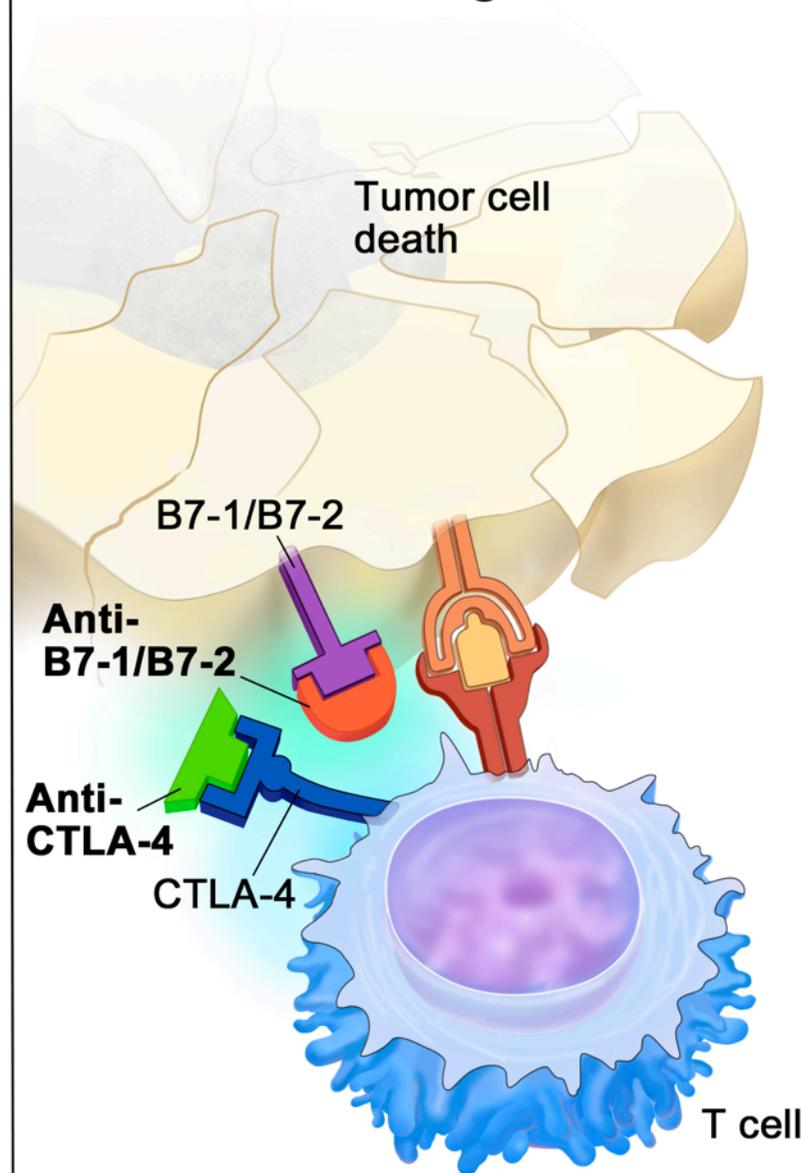
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell



B7-1/B7-2 binding to CTLA-4 inhibits T cell killing of tumor cell



Blocking B7-1/B7-2 or CTLA-4 allows T cell killing of tumor cell



Checkpoint Inhibitoren

- **PD-1 inhibitors**
 - Pembrolizumab (Keytruda®)
 - Nivolumab (Opdivo®)
- **PD-L1 inhibitors:**
 - Atezolizumab (Tecentriq®)
- **Anti-CTLA-4**
 - Ipilimumab (Yervoy®)



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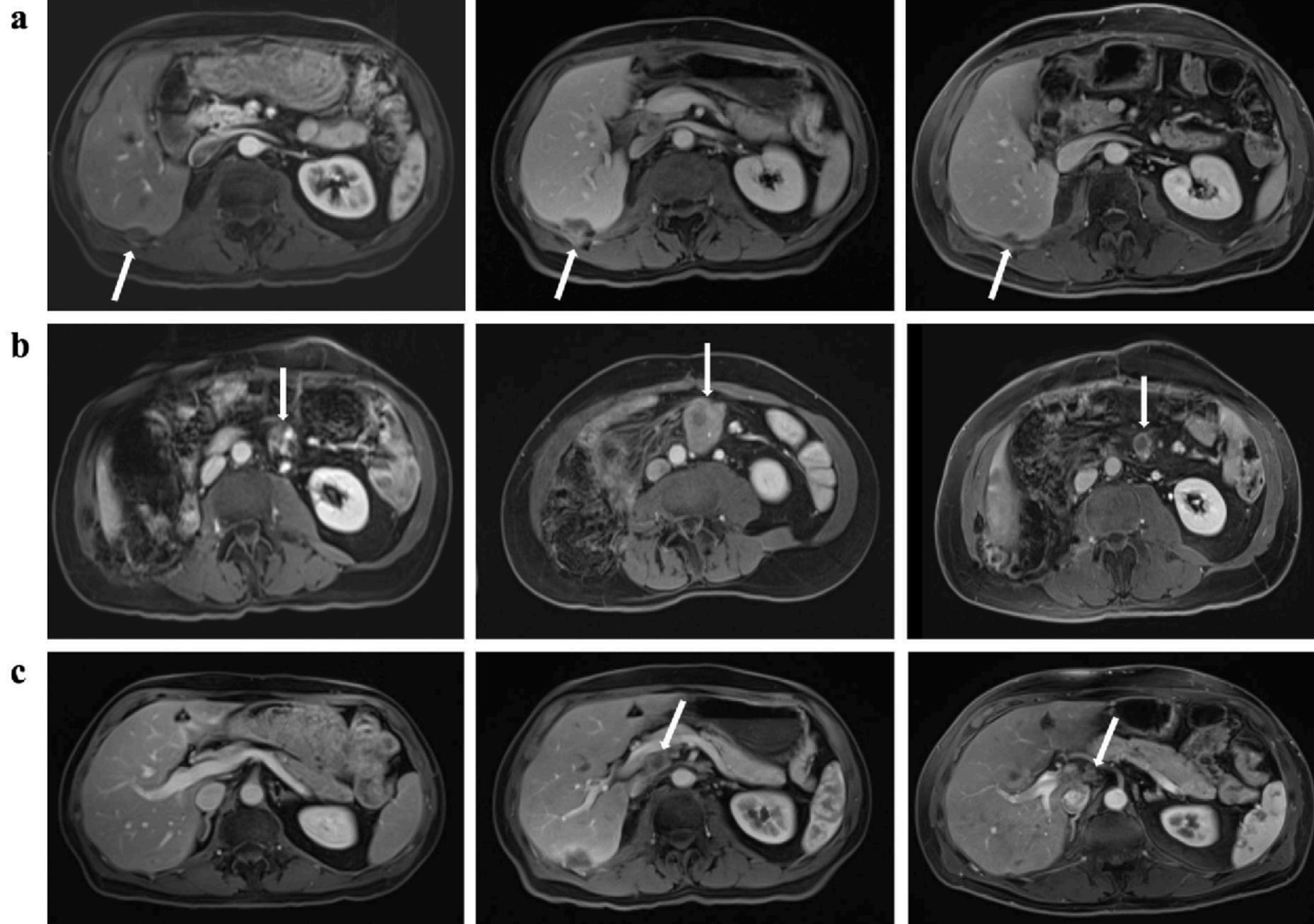
Response Rates

- **Hodgkin Lymphoma > 80%**
- **Melanoom 30%**
- **LongCa (grootcellig) 20%**
- **NierCa 20-25%**
- **BlaasCa 20%**
- **Hoofd-Halsca 15-20%**
- ~~**Borst – Prostaat – Colorectaal**~~
10-15% langdurige respons

Baseline

Week 10

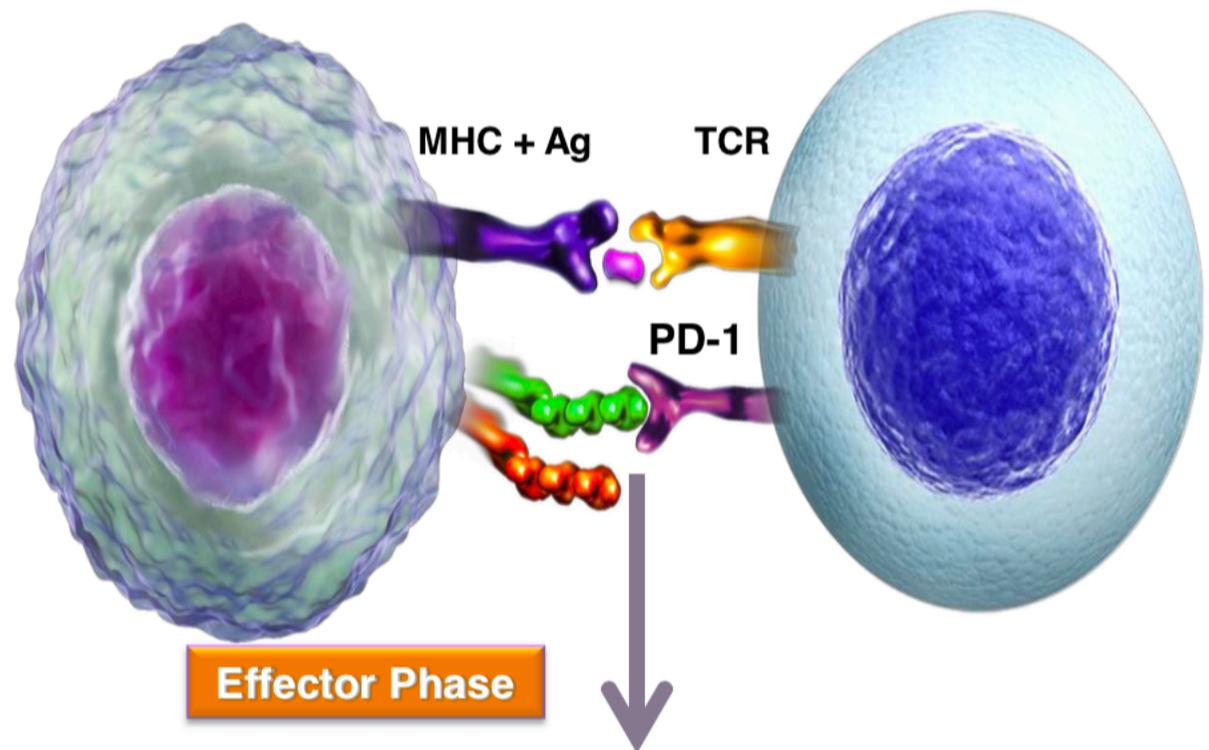
Week 18

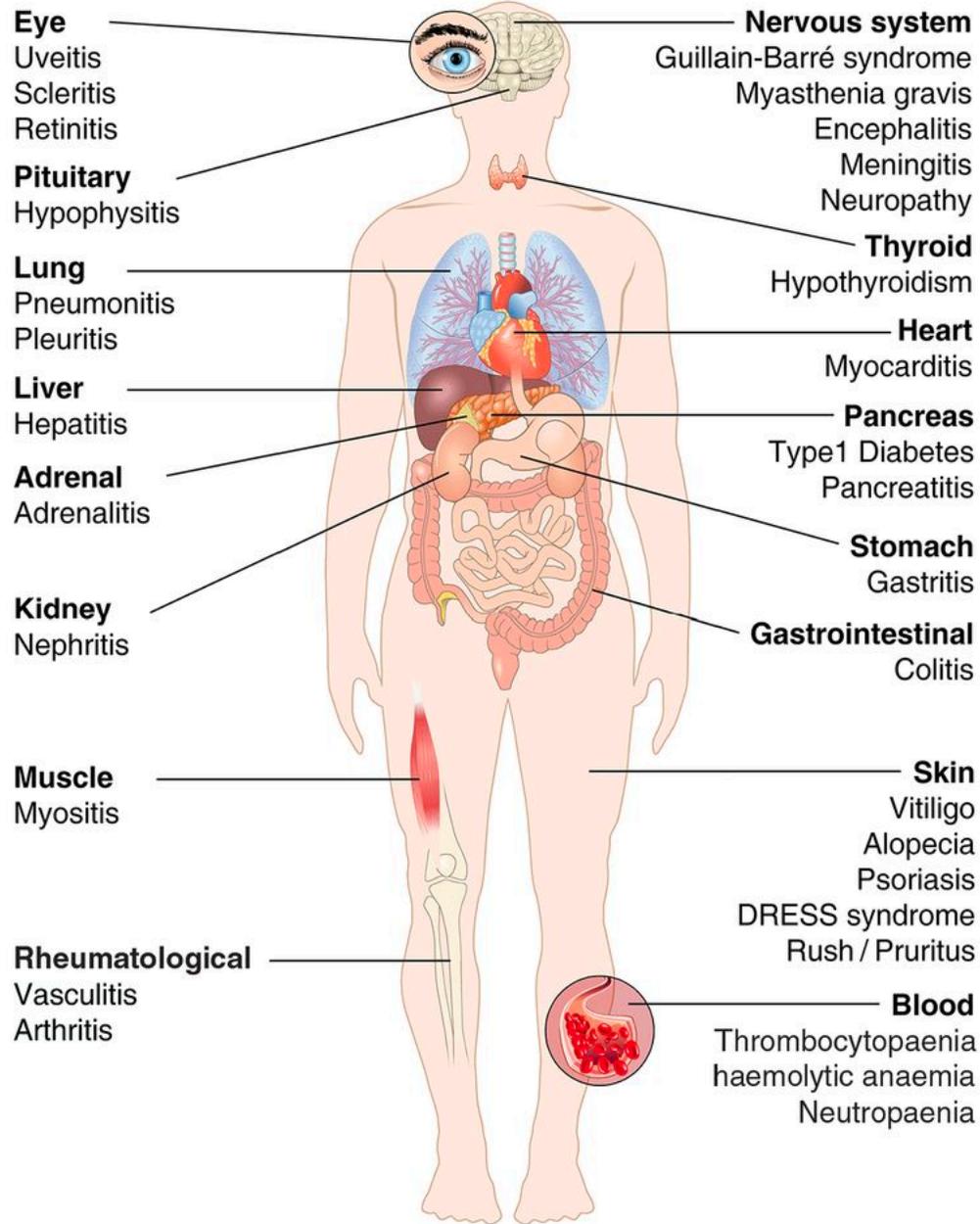




Normal Cell

Effector T cell







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AUTOIMMUNE DISEASES

Brain
Multiple Sclerosis
Guillain-Barre Syndrome
Autism



Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

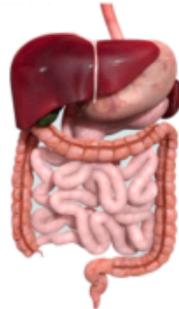
Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia



Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

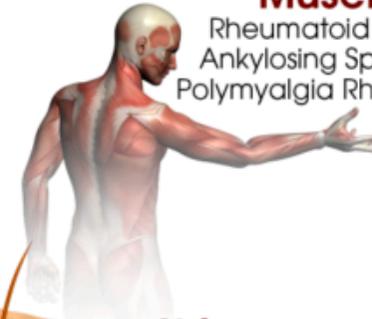


GI Tract
Celiac's Disease
Crohn's Disease
Ulcerative Colitis
Diabetes Type I



**Over 100
Different Types of
Autoimmune
Disorders**

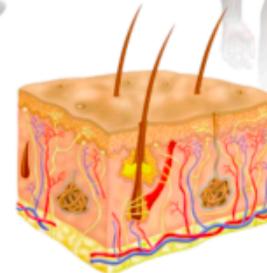
Muscles
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica



Nerves
Peripheral Neuropathy
Diabetic Neuropathy



Skin
Psoriasis
Vitiligo
Eczema
Scleroderma



Lung
Fibromyalgia
Wegener's Granulomatosis





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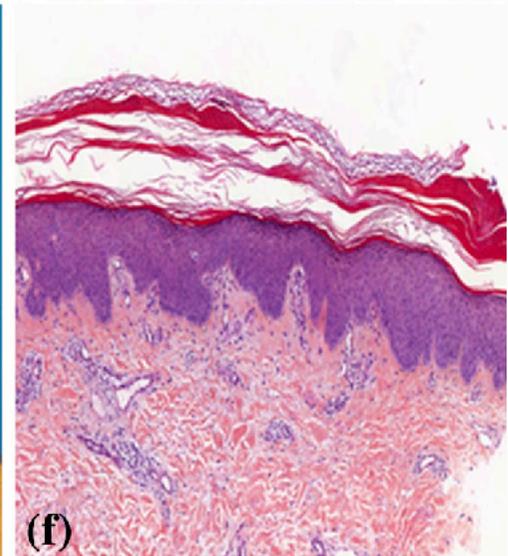
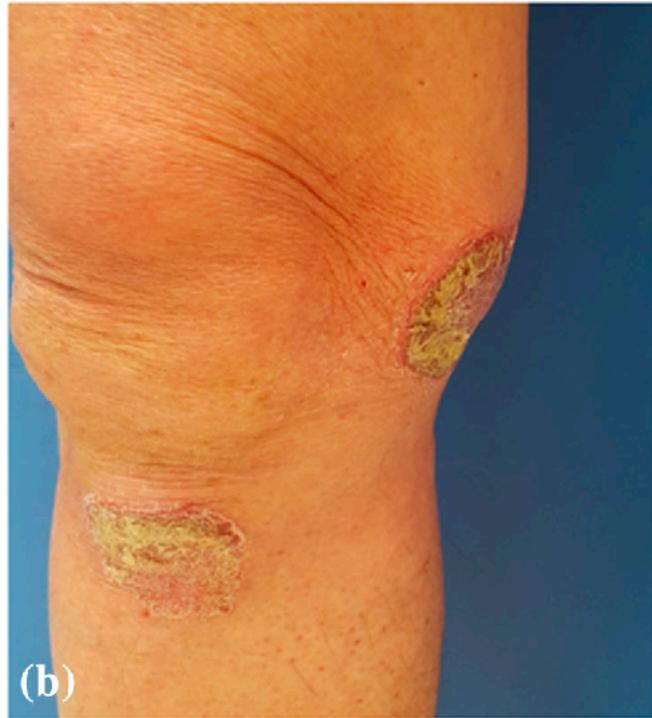
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(a)



(b)







(a)

(b)

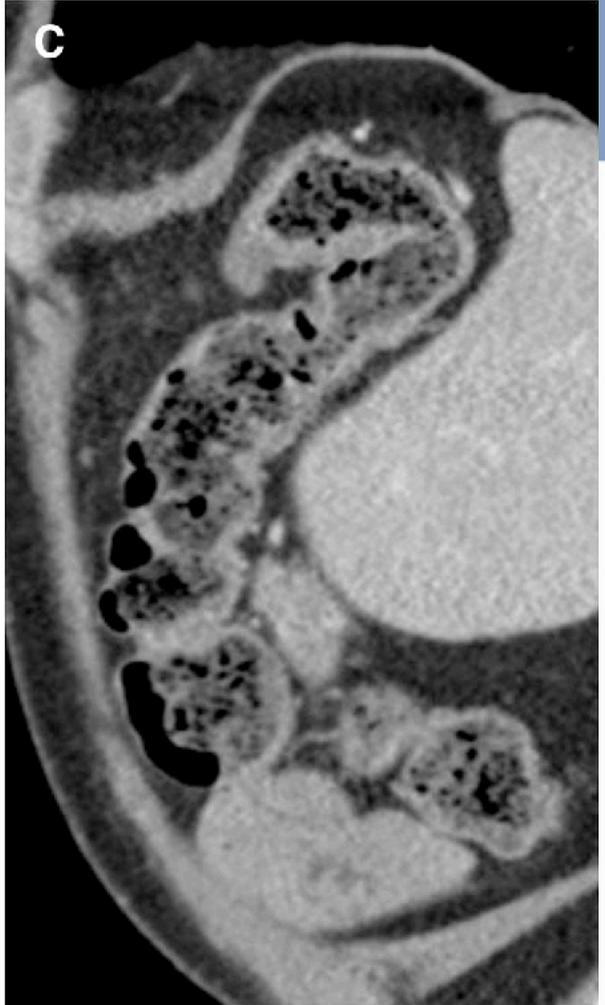


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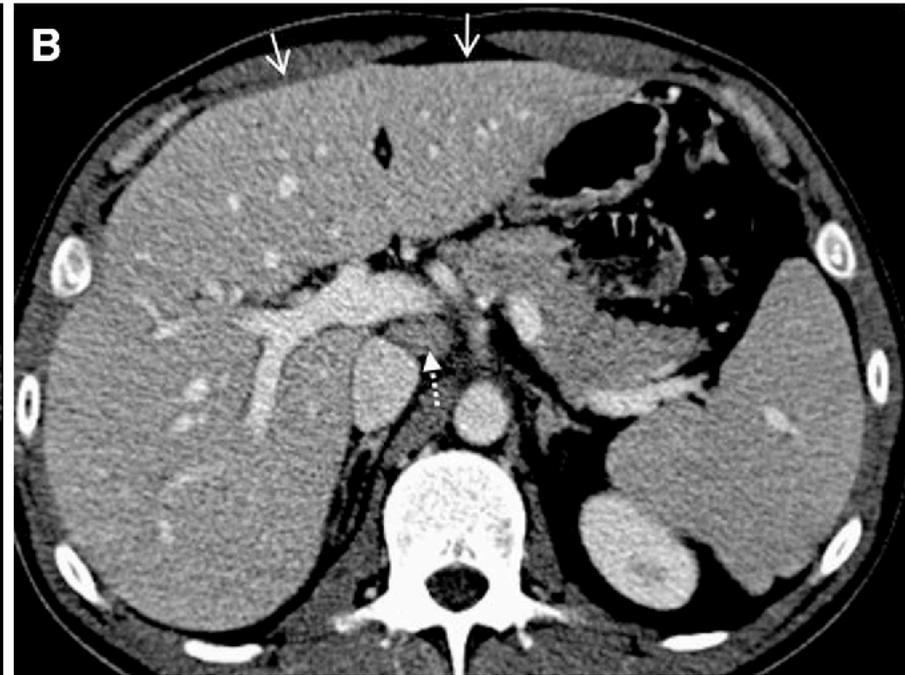


Colitis - Diarrhee

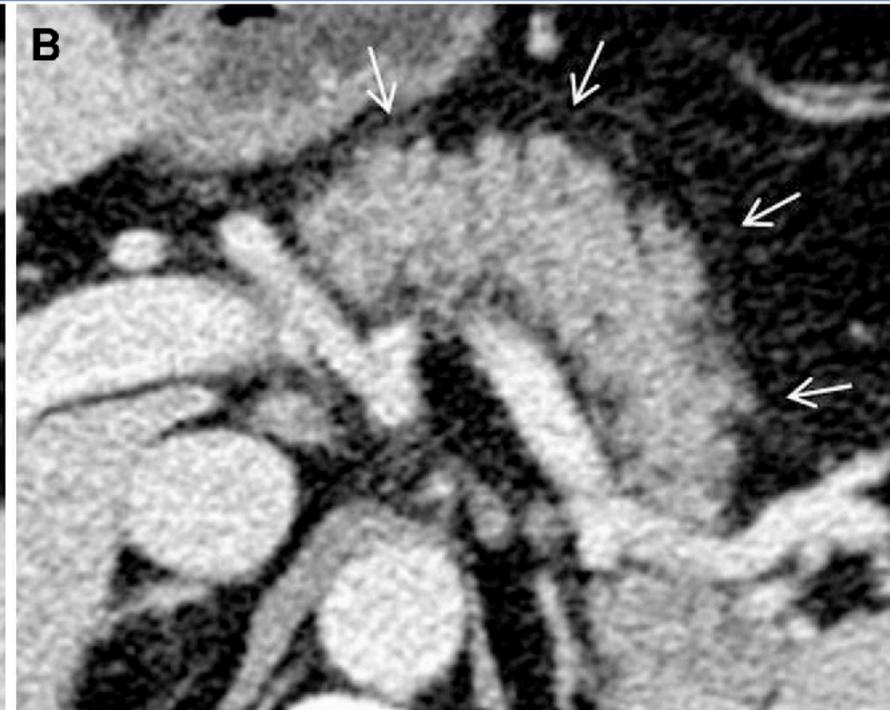
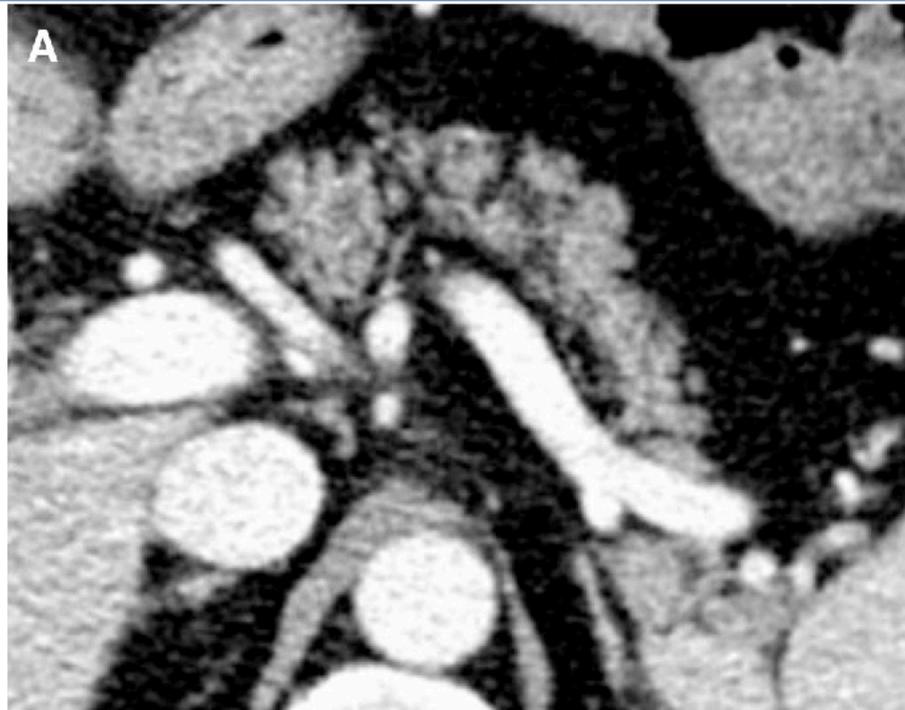




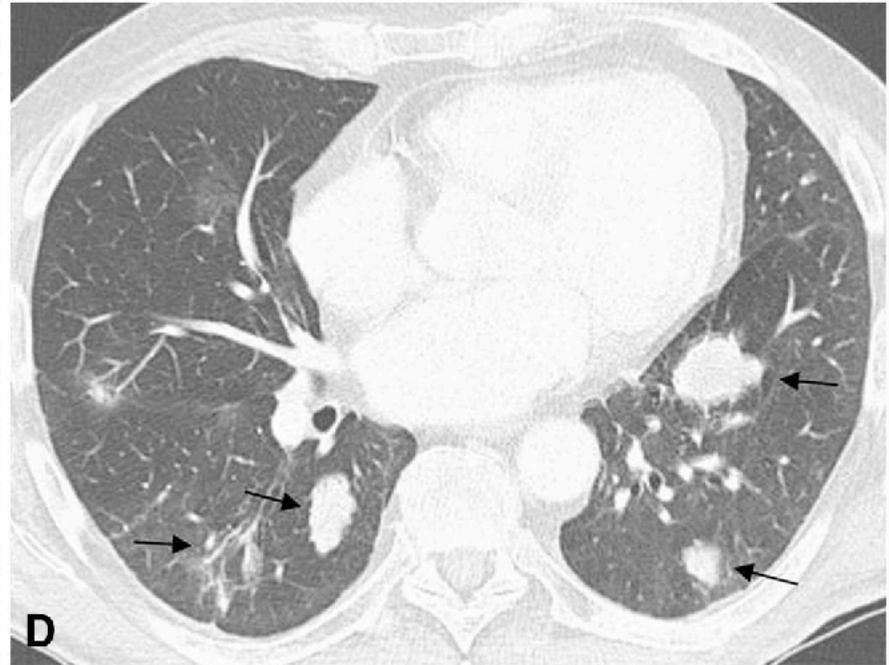
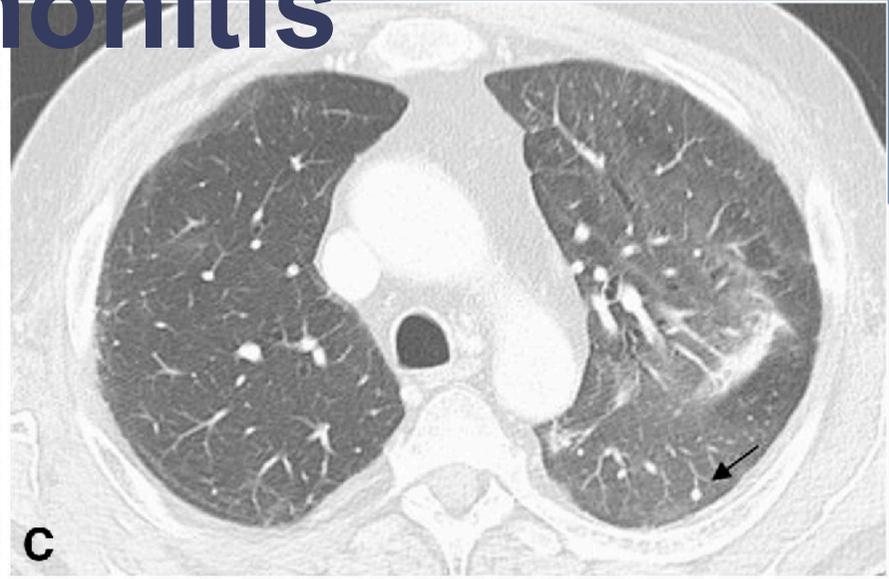
Hepatitis

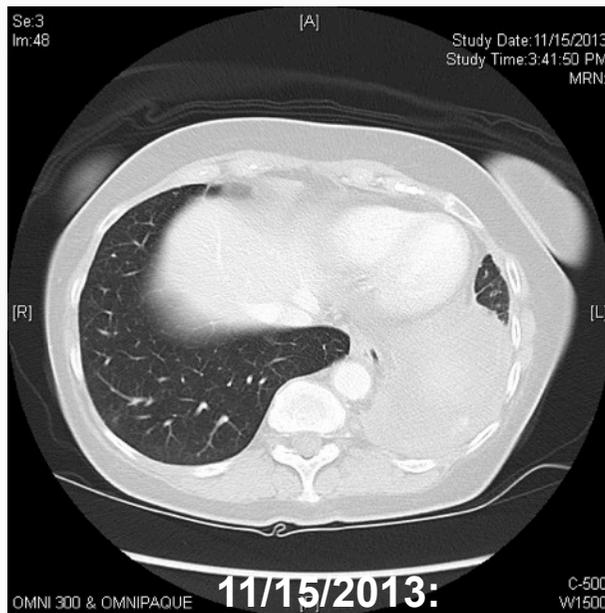


Pancreatitis

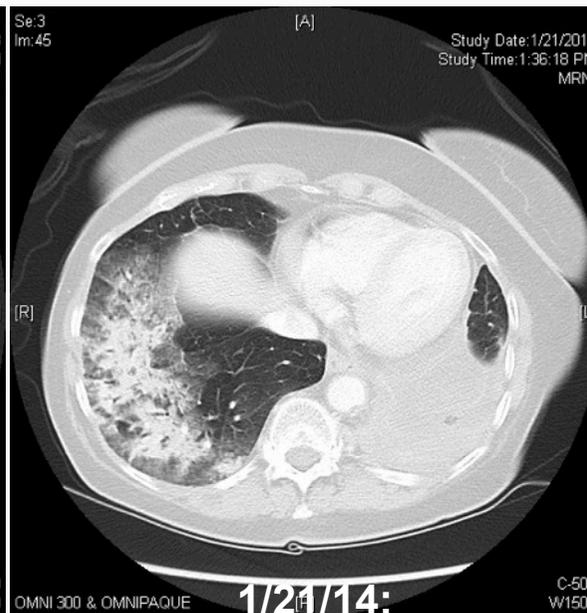


Pneumonitis

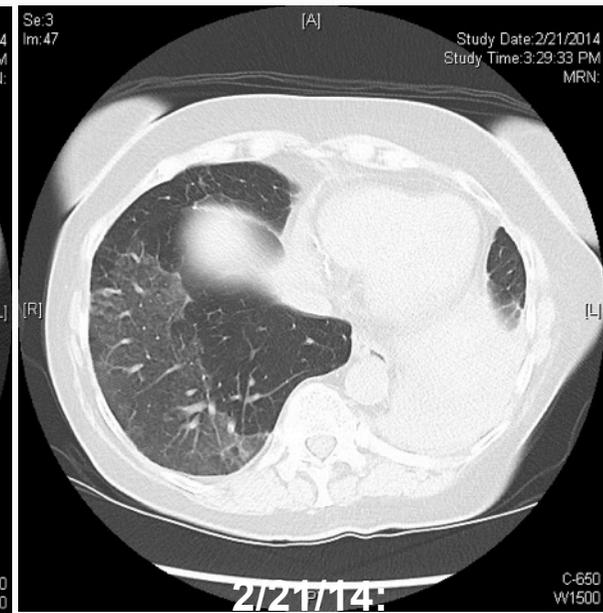




Pre-pneumonitis

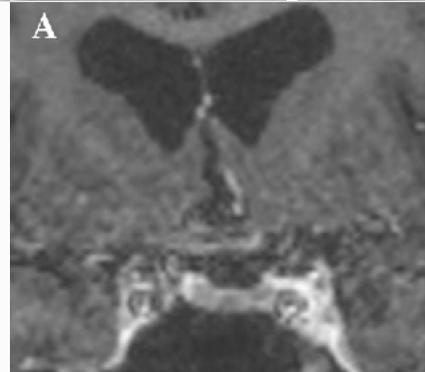
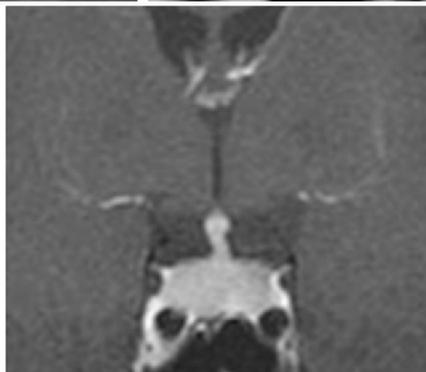
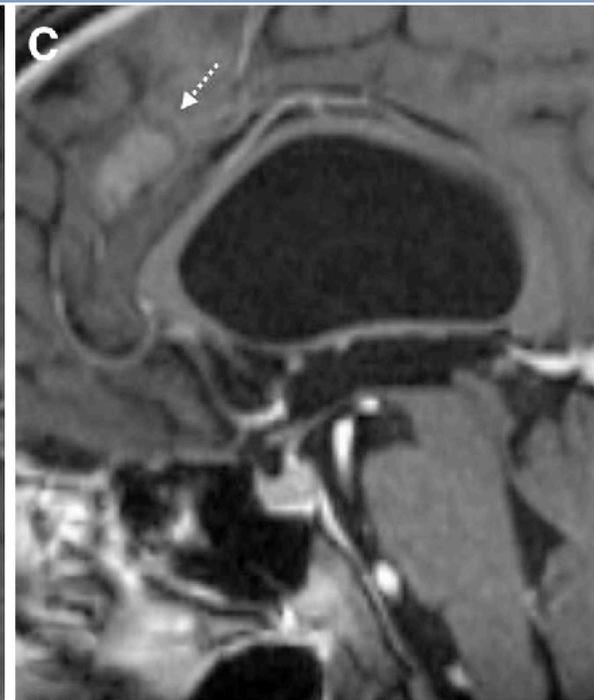


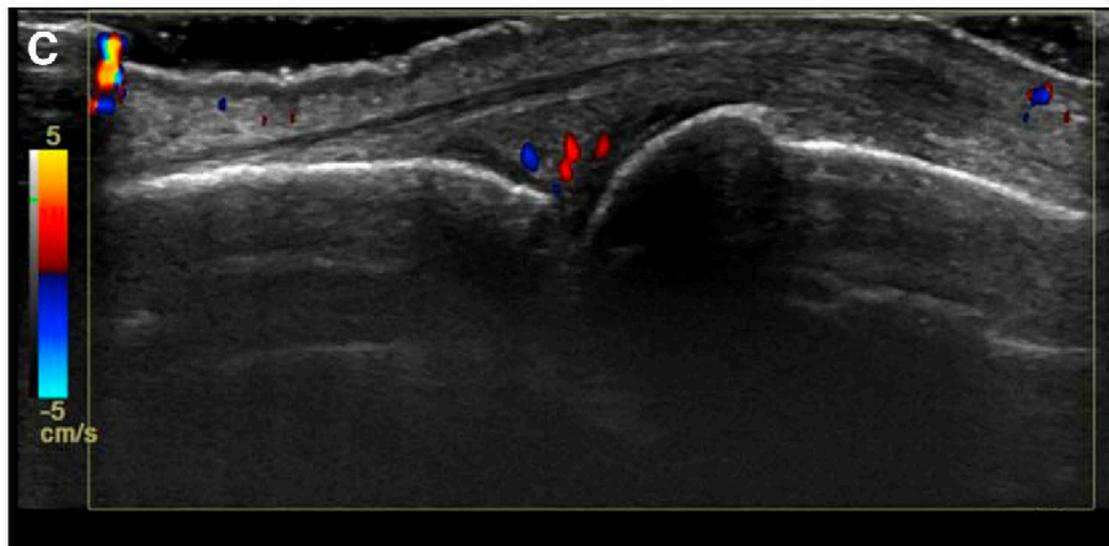
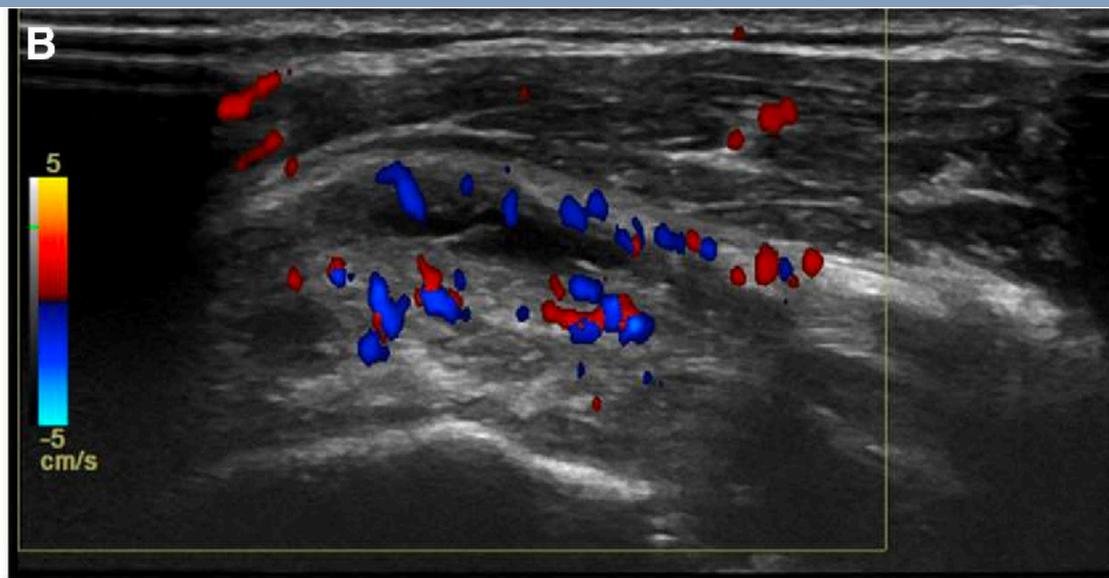
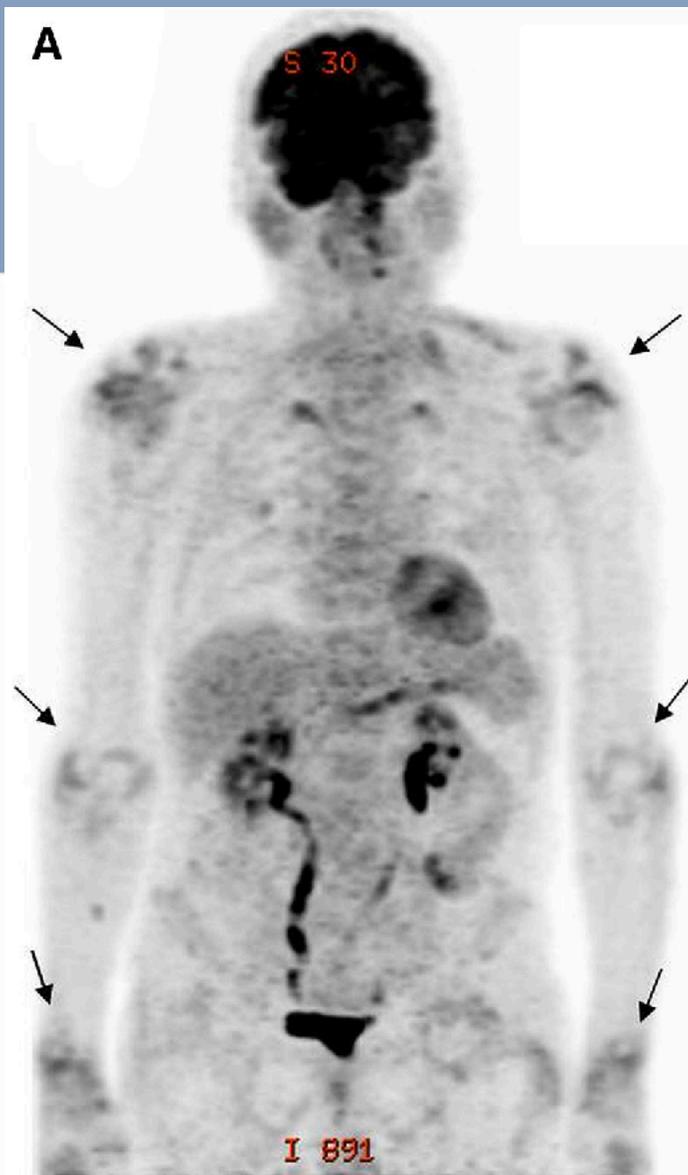
Pneumonitis



Improved with steroids;
taper completed 3/7/14

Hypophysitis

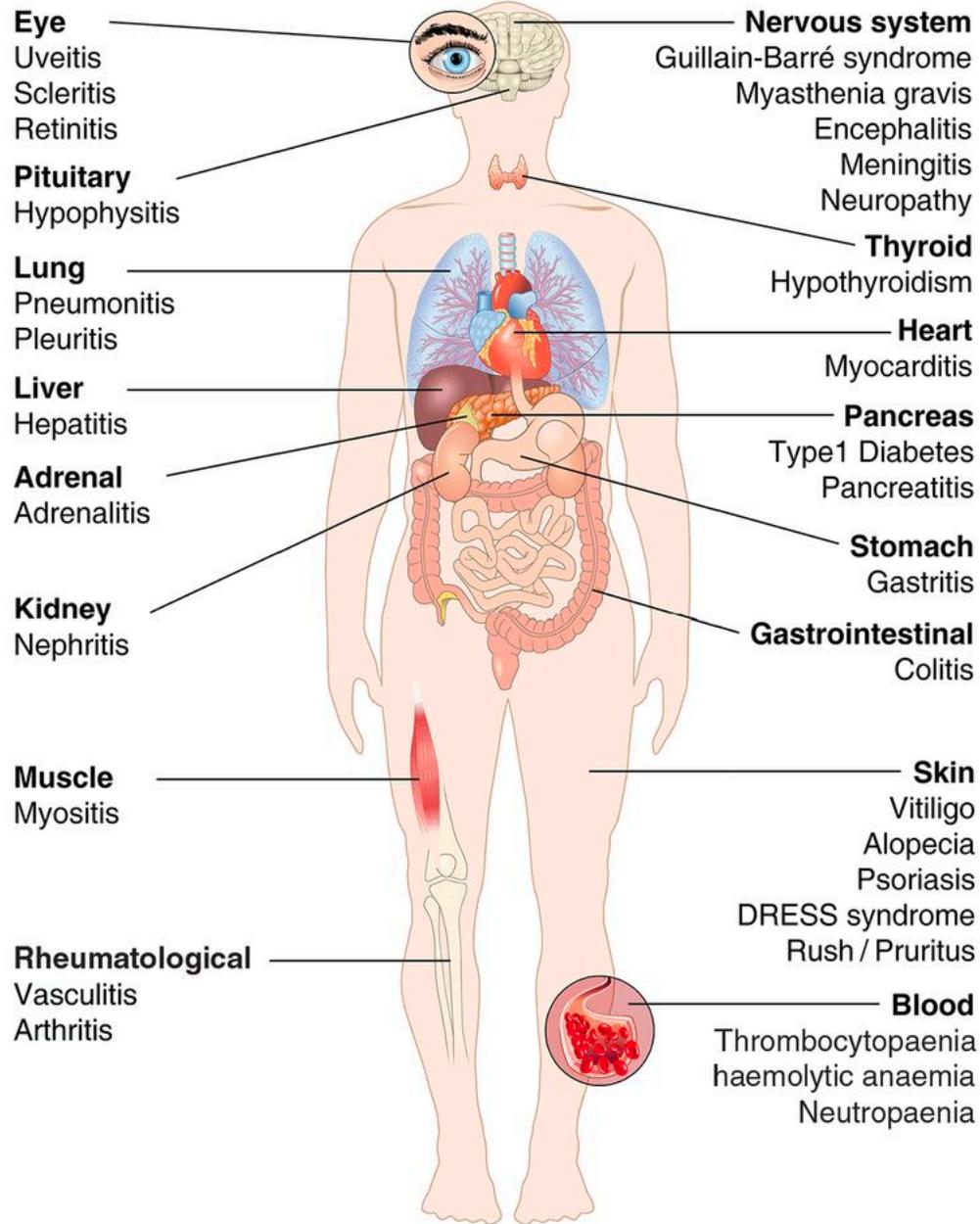




Mortaliteit < 1%

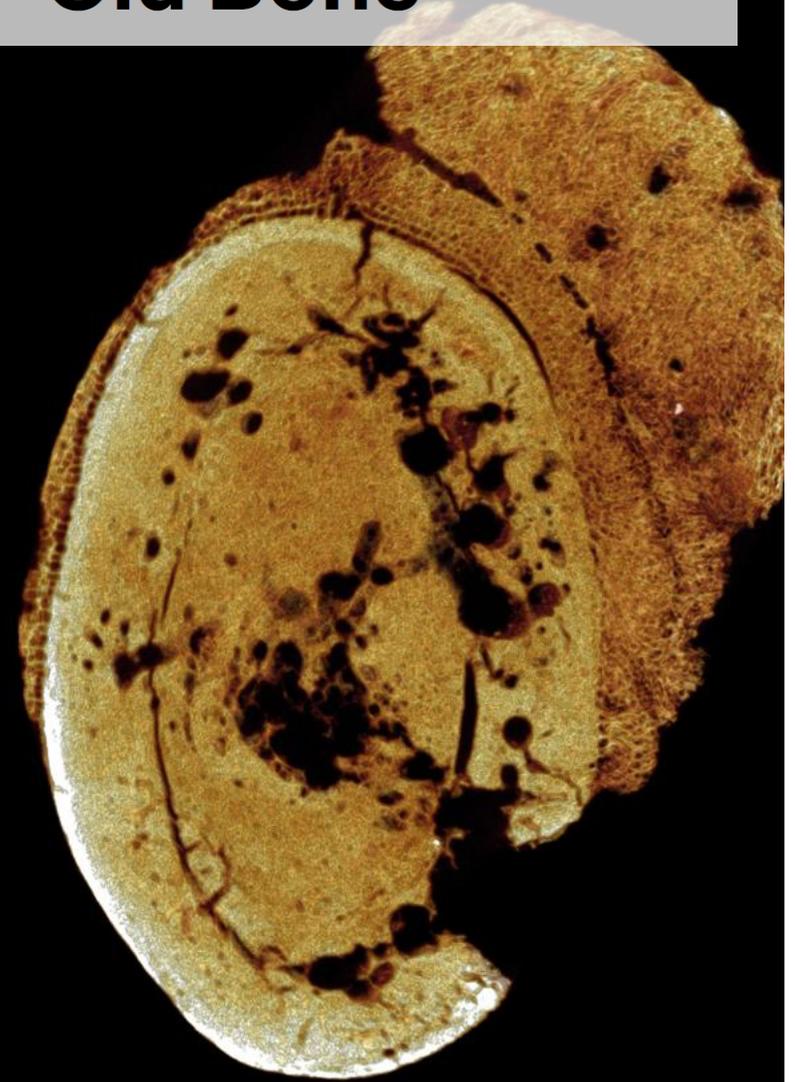
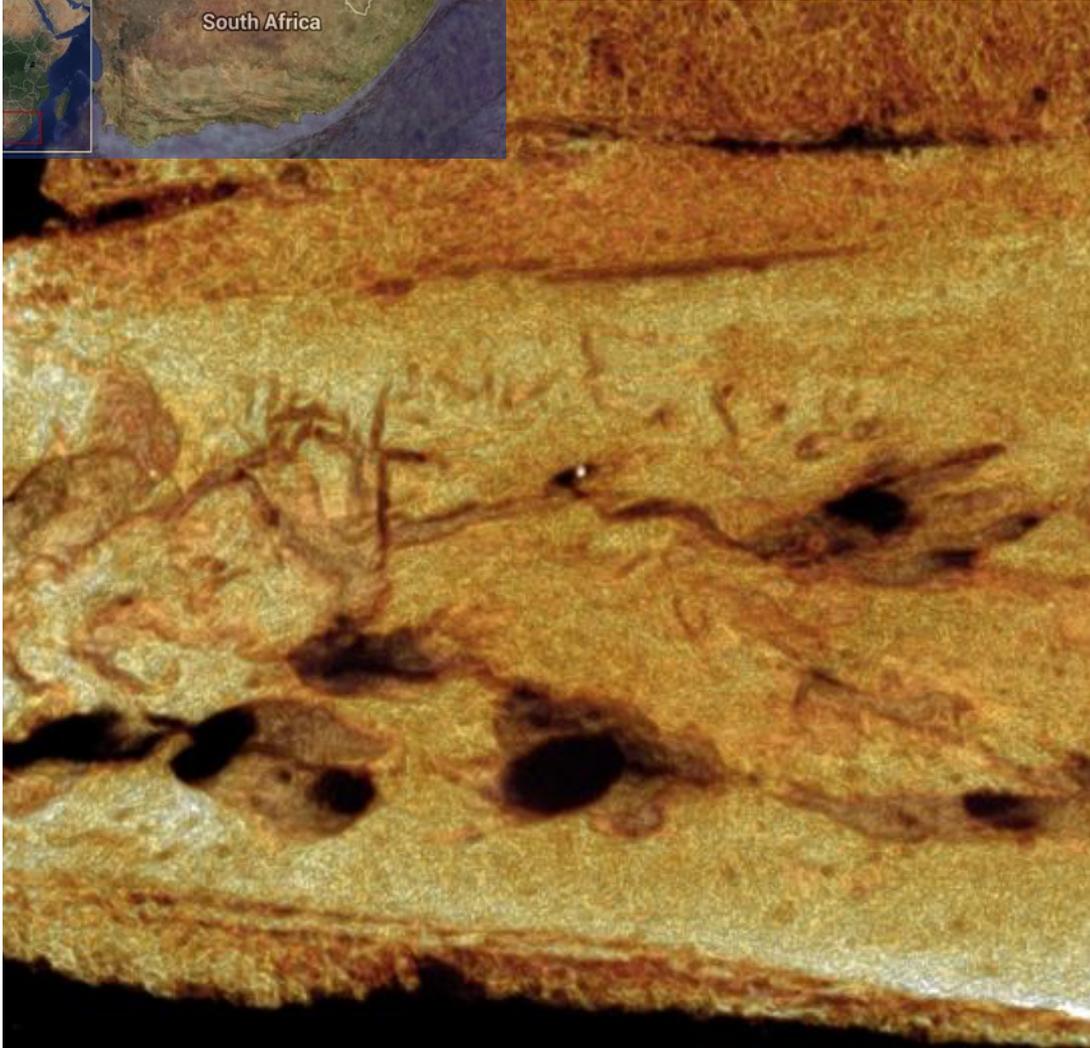
az sint-jan
Kliniek Sint-Jansdal

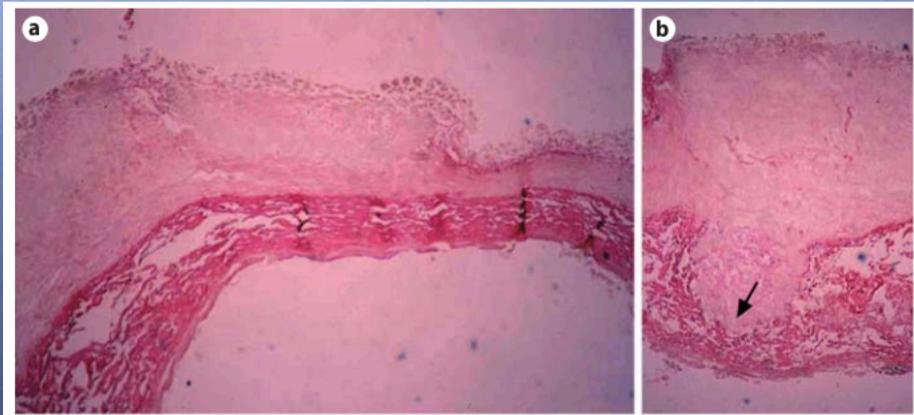
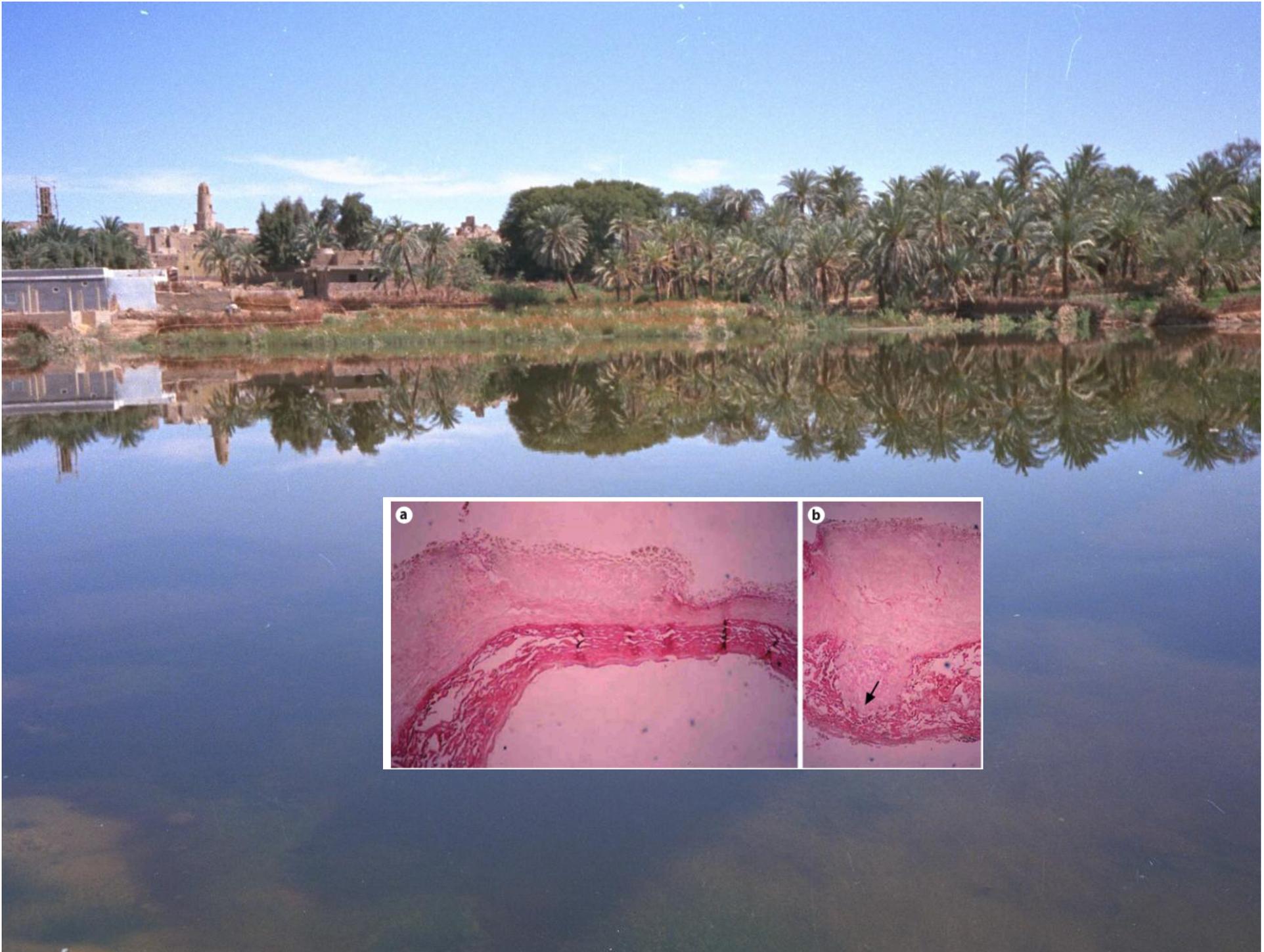






Earliest Human Cancer Found in 1.7-Million-Year-Old Bone



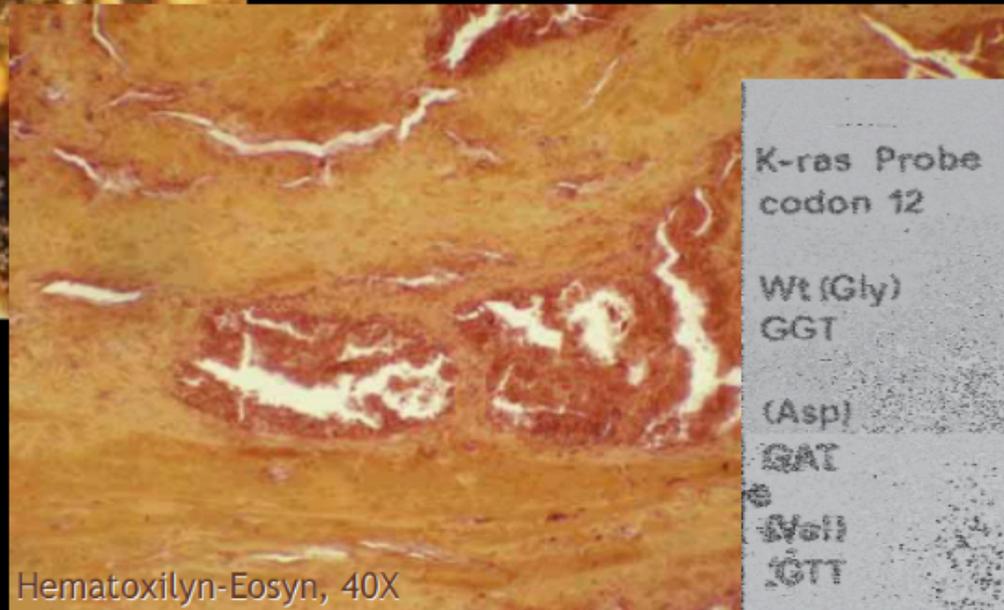




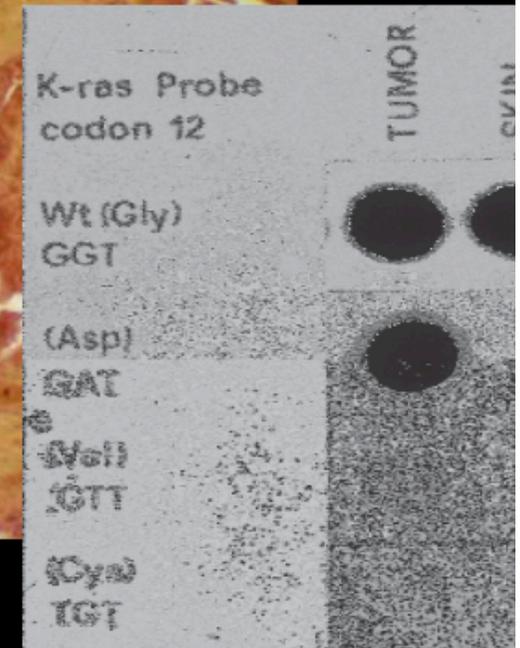
The adenocarcinoma of King Ferrante I



Tumor section after rehydration



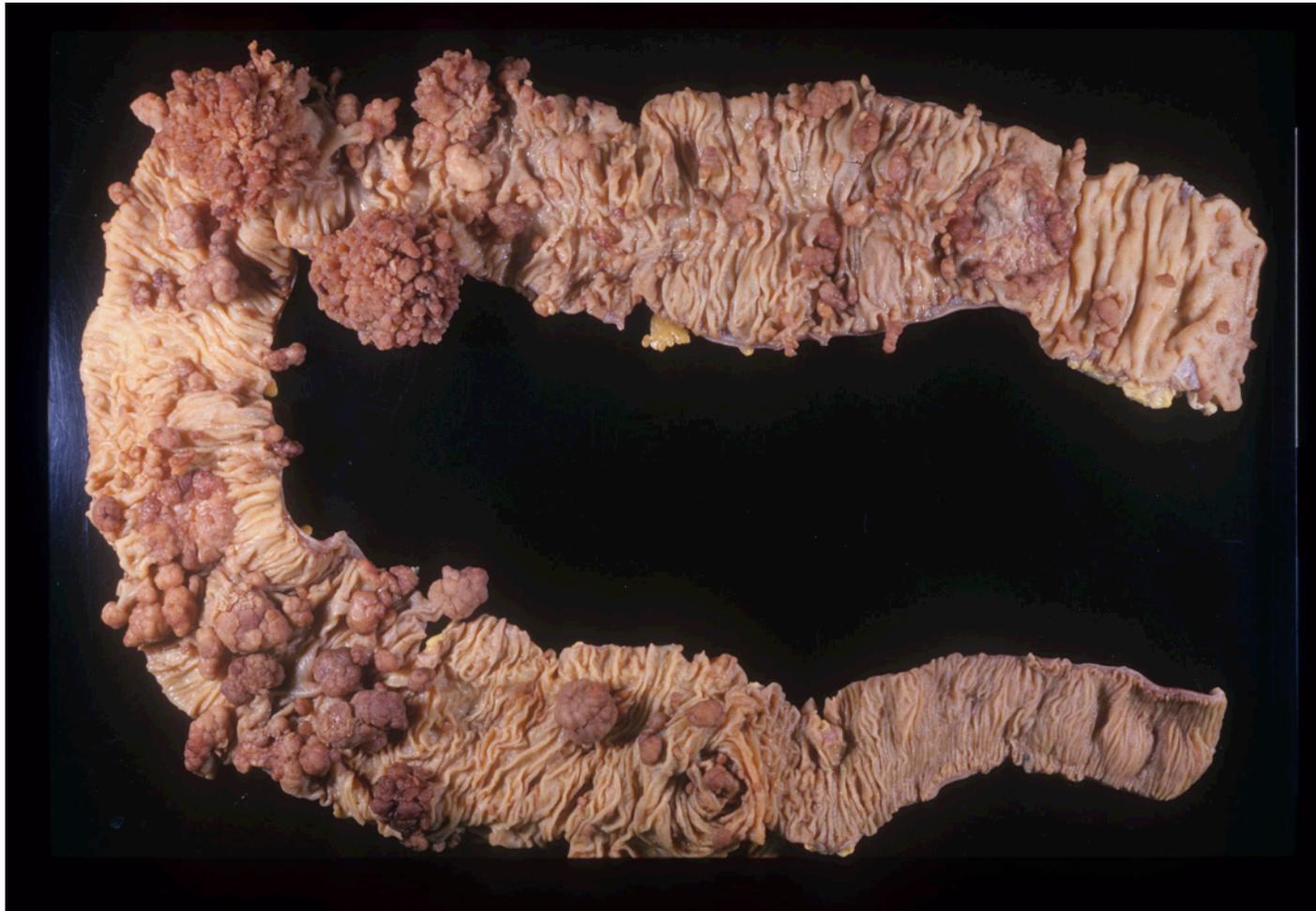
Hematoxylin-Eosyn, 40X



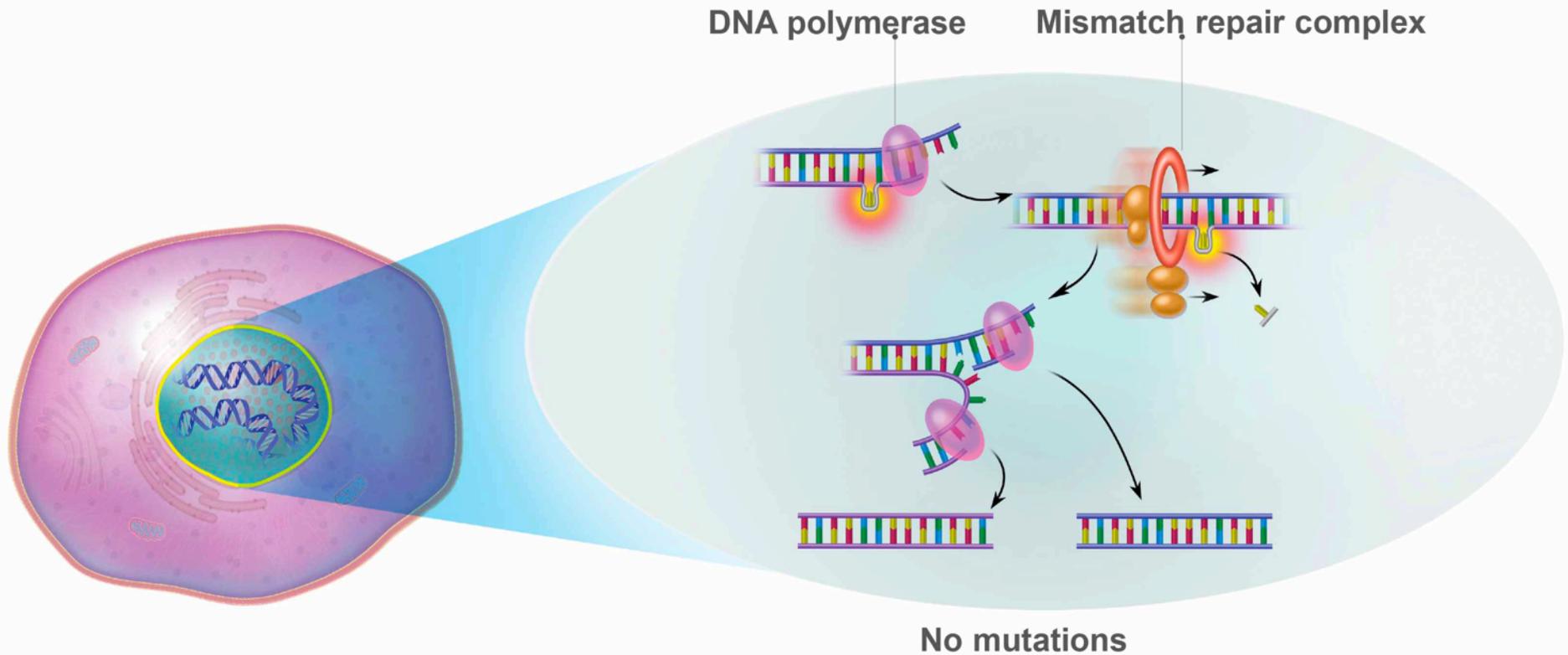
Detection of a Tumor Suppressor Gene Variant Predisposing to Colorectal Cancer in an 18th Century Hungarian Mummy

Michal Feldman , Israel Hershkovitz, Ella H. Sklan, Gila Kahila Bar-Gal, Ildikó Pap, Ildikó Szikossy, Rina Rosin-Arbesfeld

Published: February 10, 2016 • <https://doi.org/10.1371/journal.pone.0147217>

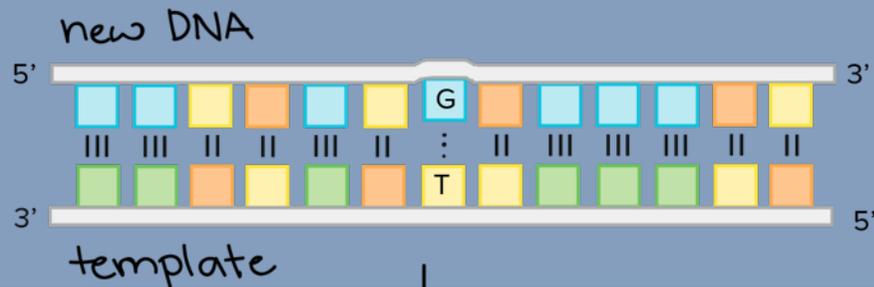


Mismatch Repair MMR

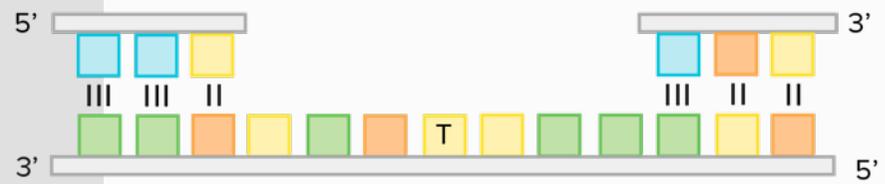


Successful repair of mismatched base pair by pMMR system

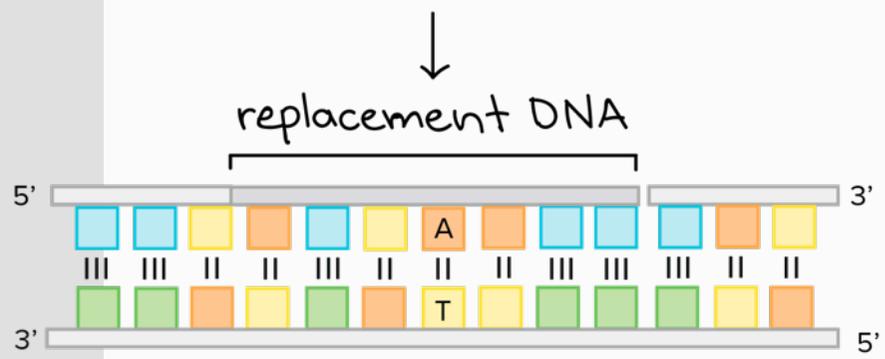
Adapted from Li et al.



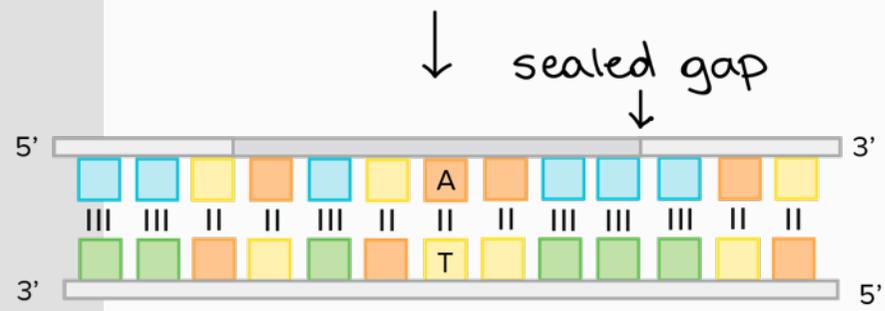
A mismatch is detected in newly synthesized DNA.



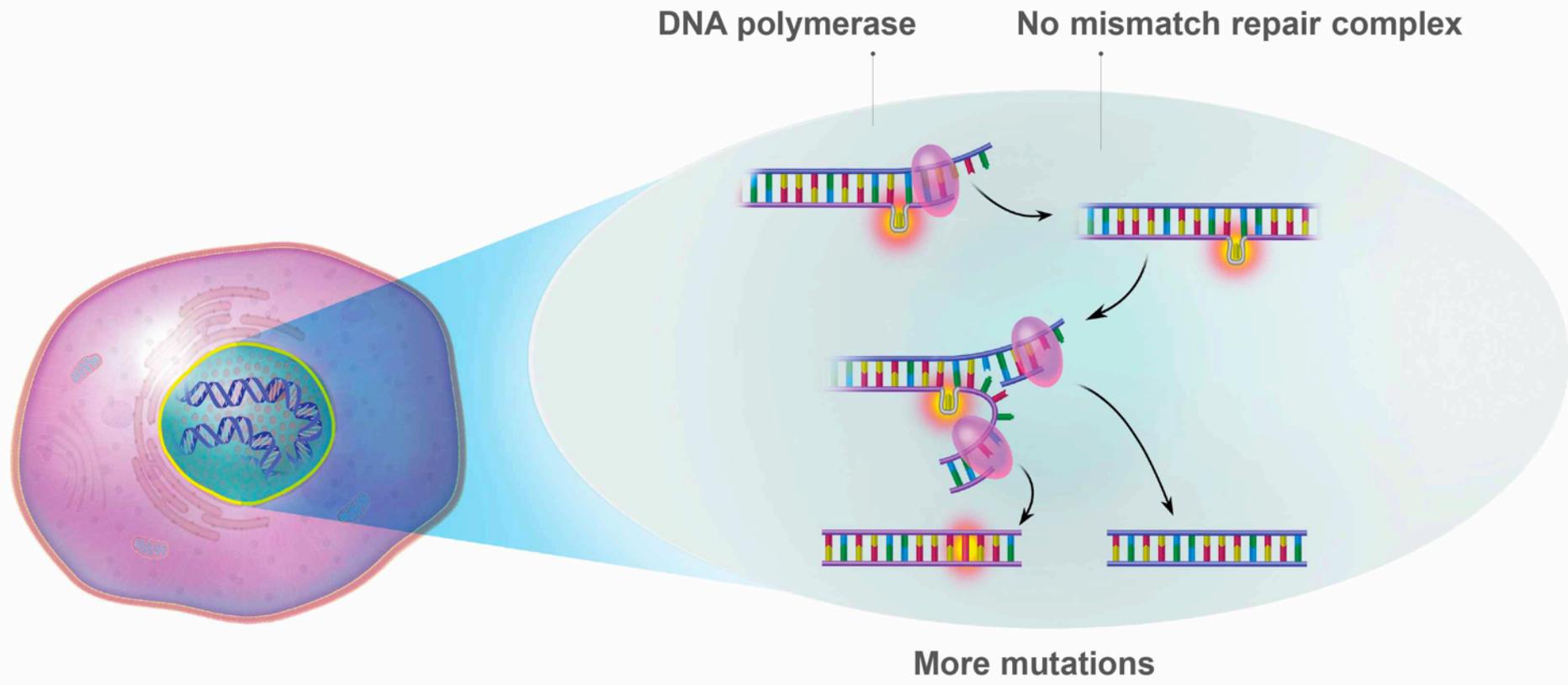
The new DNA strand is cut, and the mispaired nucleotide and its neighbors are removed.



The missing patch is replaced with correct nucleotides by a DNA polymerase.



A DNA ligase seals the gap in the DNA backbone.

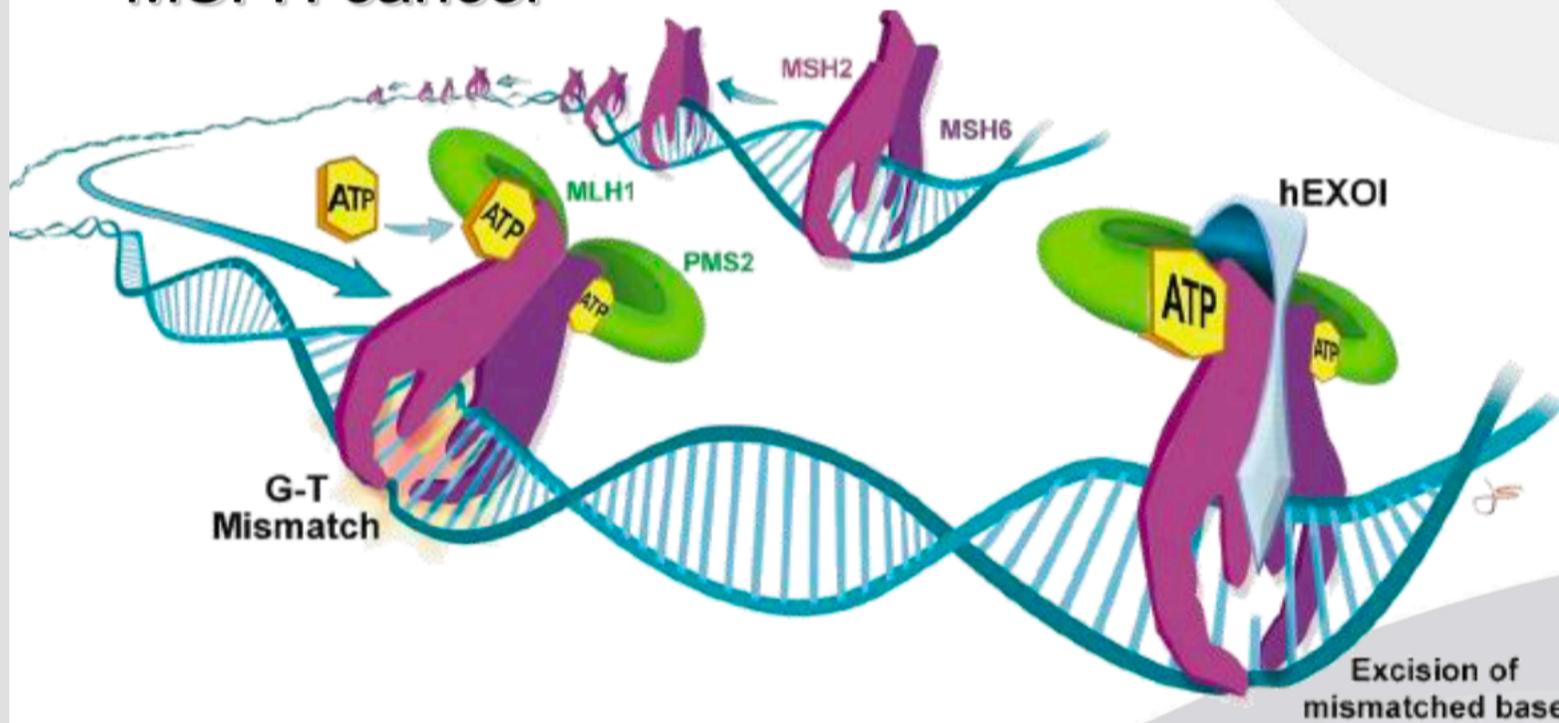


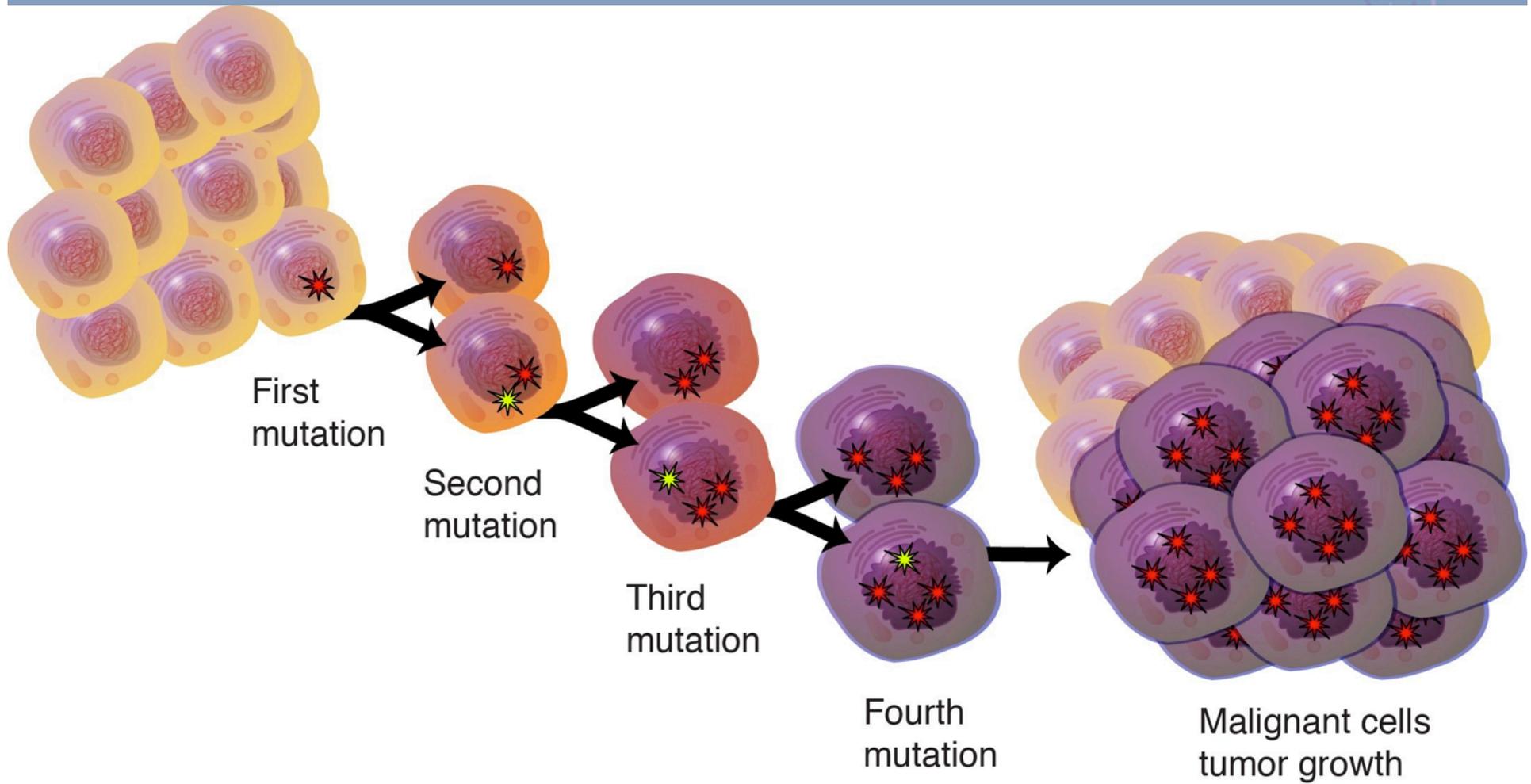
Failure to repair mismatched base pair due to dMMR system

Adapted from Li et al.

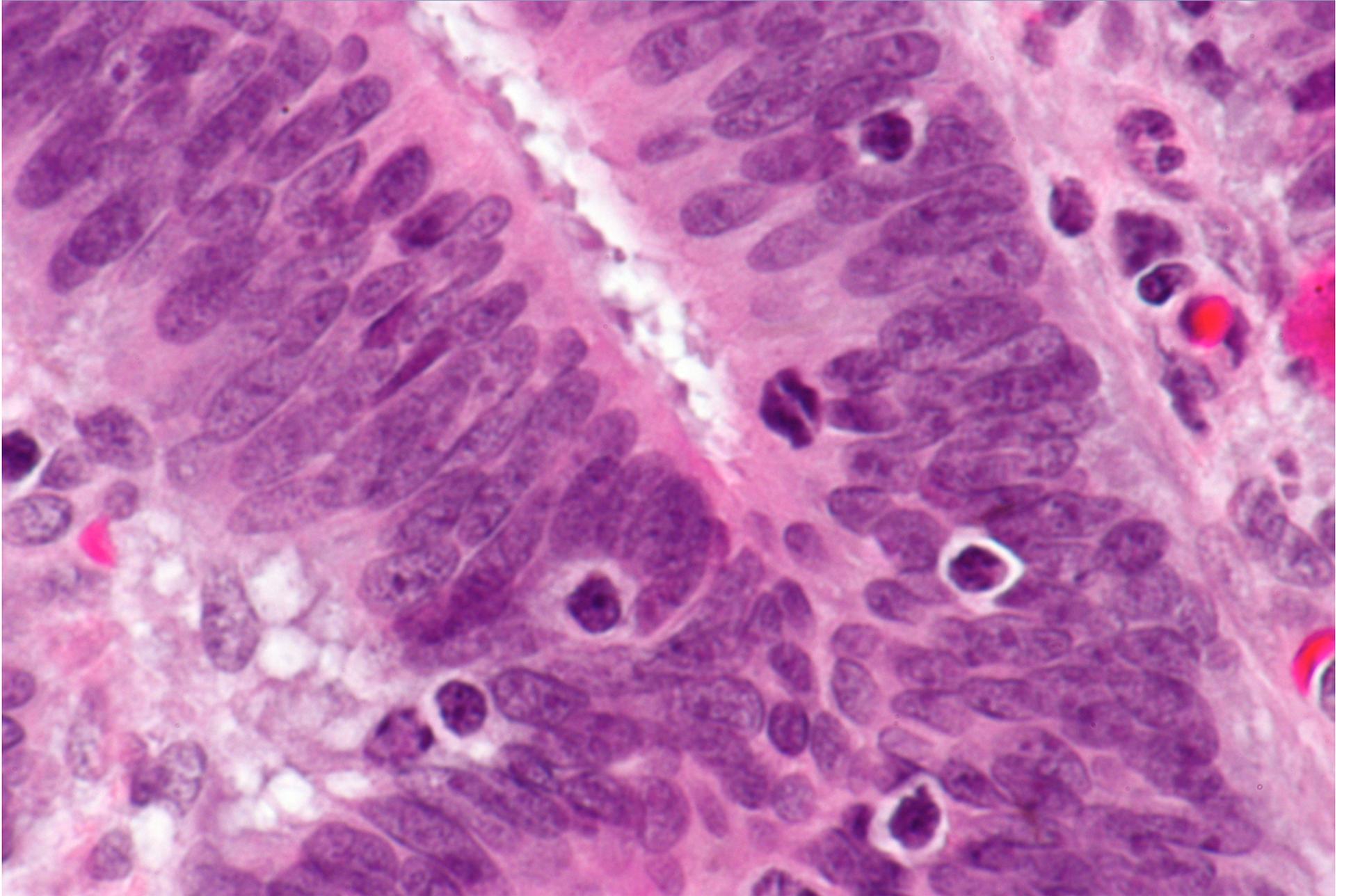
Microsatellite instability (MSI)

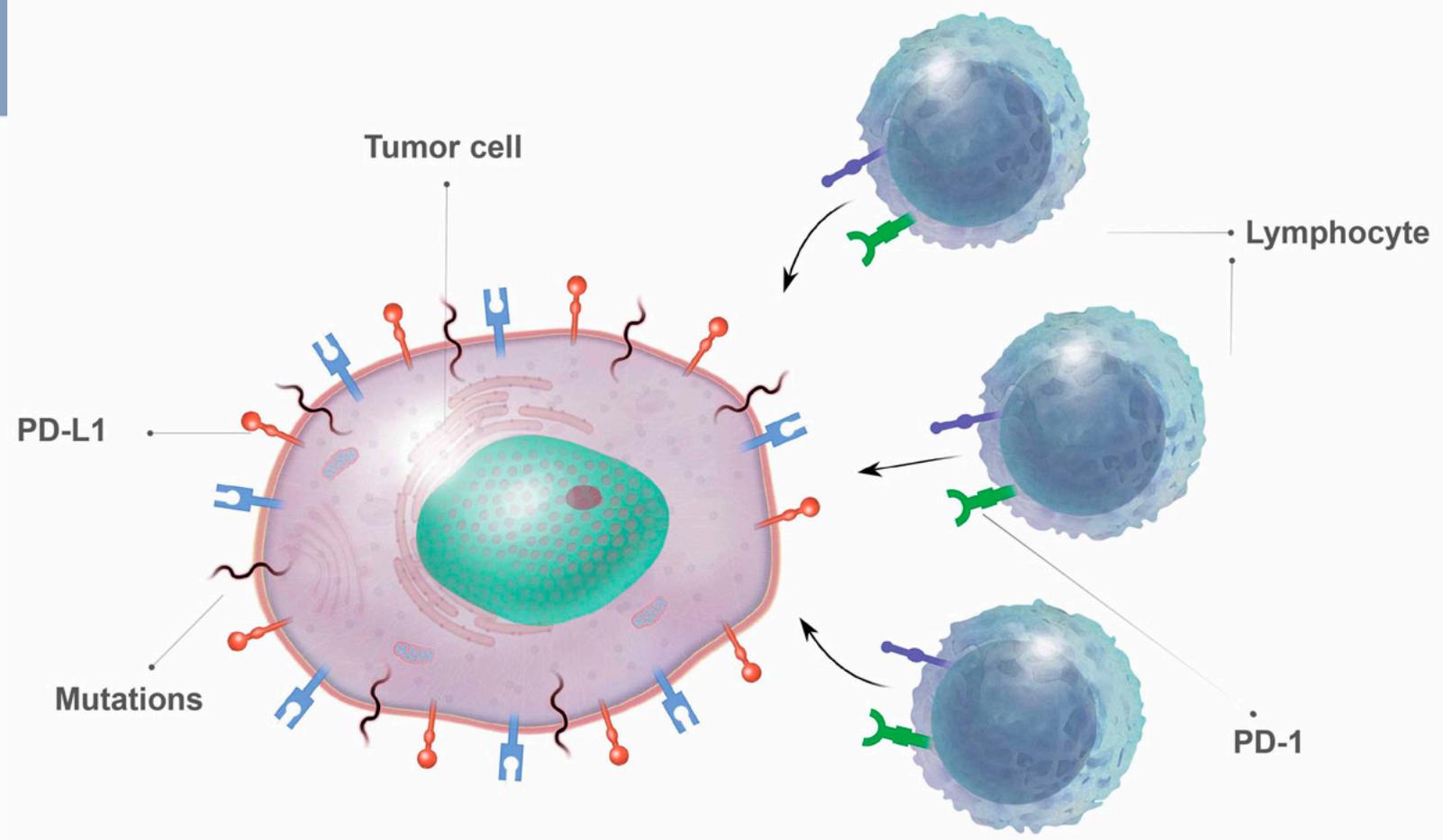
- Mutations in MMR genes lead to accumulation of altered length microsatellites (MSI)
- MLH-1, MSH-2, MSH-6, PMS-2 alterations cause MSI-H cancer



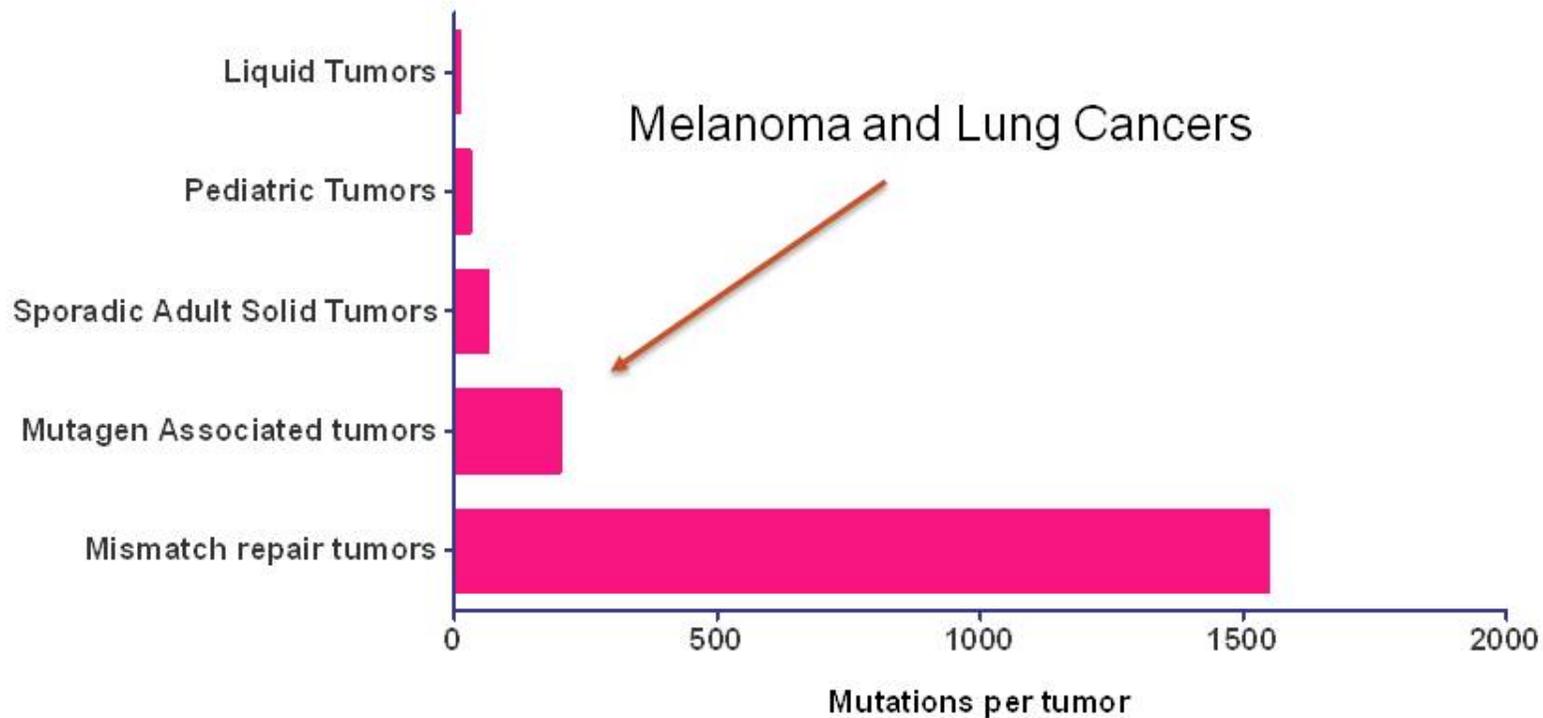


**Des te meer mutaties in een tumor
des te meer ontstekingsreactie**

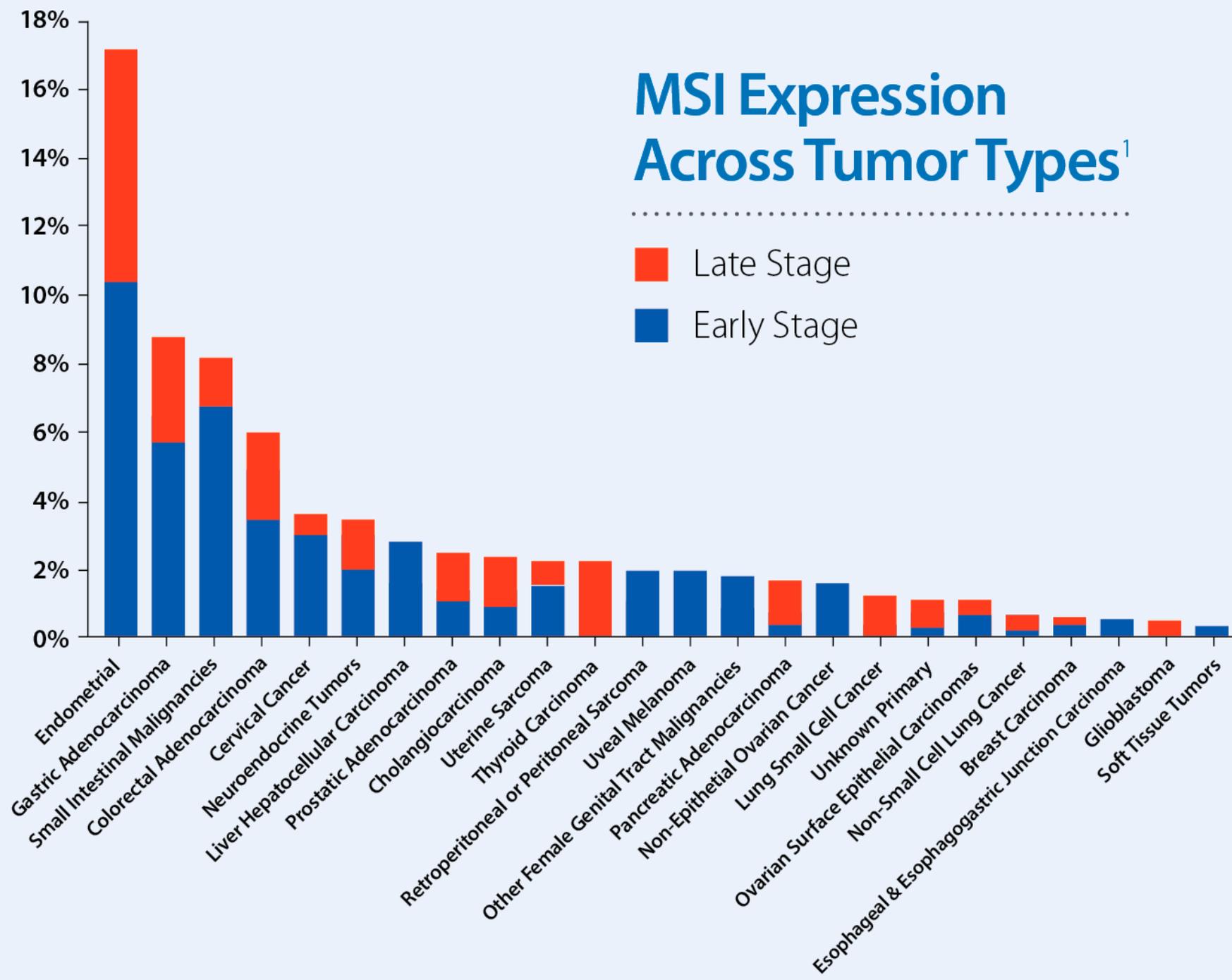


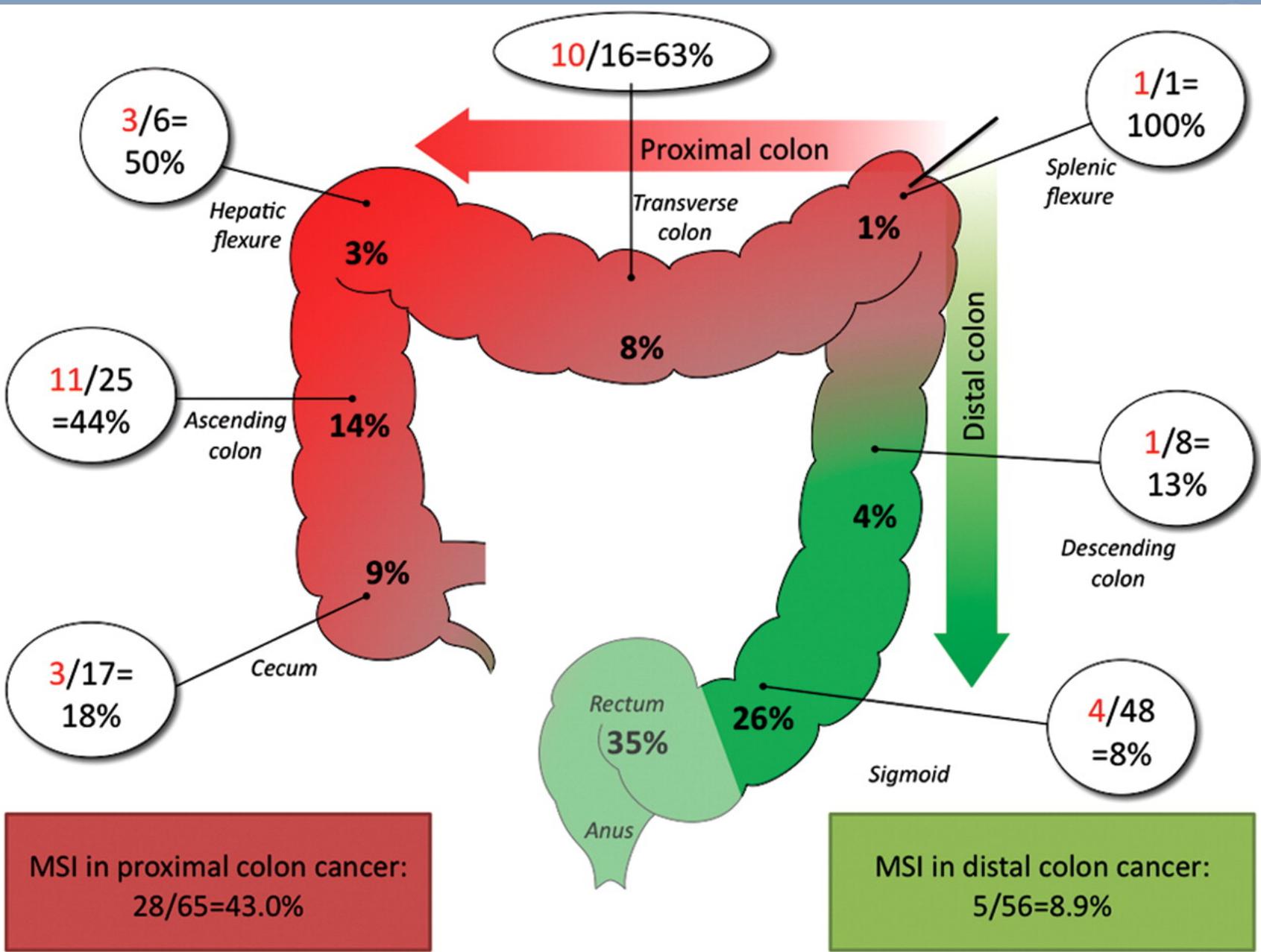


Mutations per tumor



MSI Expression Across Tumor Types¹

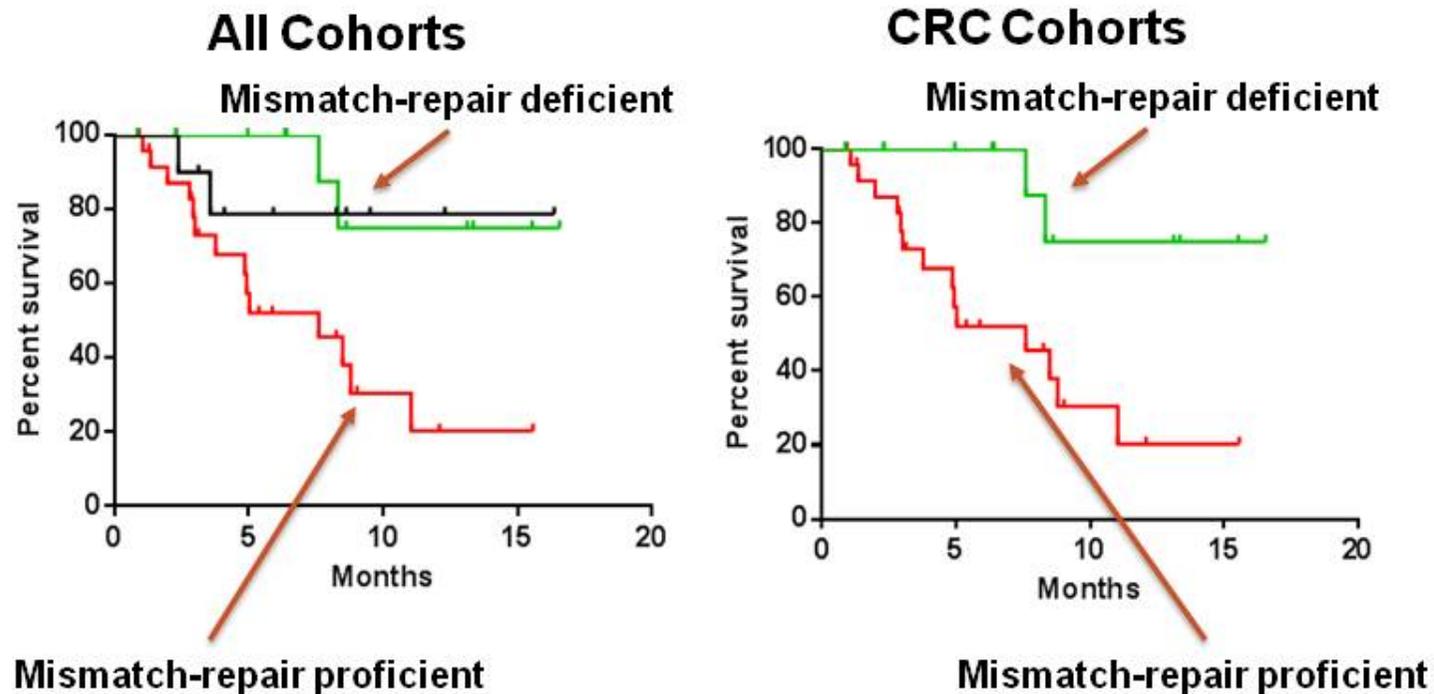




Objective Responses

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
<i>N</i>	13	25	10
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

Overall Survival



Response Rates

- Hodgkin Lymphoma > 80%
 - **MSI-H ColorectaalCa (M+ 5%) 40-70%**
 - Melanoom 30%
 - LongCa (grootcellig) 20-25%
 - NierCa 20%
 - BlaasCa 20%
 - Hoofd-Halsca 15-20%
- 10-15% langdurige respons**

Response Rates



- Hodgkin Lymphoma > 80%
- **MSI-H ColorectalCa (M+ 5%) 40-70%**

FDA Grants Priority Review for KEYTRUDA® IN MSI-H Cancers

On **November 28**, the U.S. Food and Drug Administration granted Priority Review to Merck's Supplemental New Drug Application (sNDA) for KEYTRUDA® (pembrolizumab) in the new indication of microsatellite instability-high (MSI-H) colorectal cancer. MSI-H is a biomarker caused by a deficiency in a cell's ability to repair errors in DNA sequences that occur during cell division. The FDA is expected to announce its decision on KEYTRUDA's approval in this new indication by March 2020. Merck previously granted Breakthrough Therapy Designation to KEYTRUDA for unresectable or metastatic MSI-H colorectal cancer, and previously granted it for the treatment of patients with unresectable or metastatic MSI-H colorectal cancer.