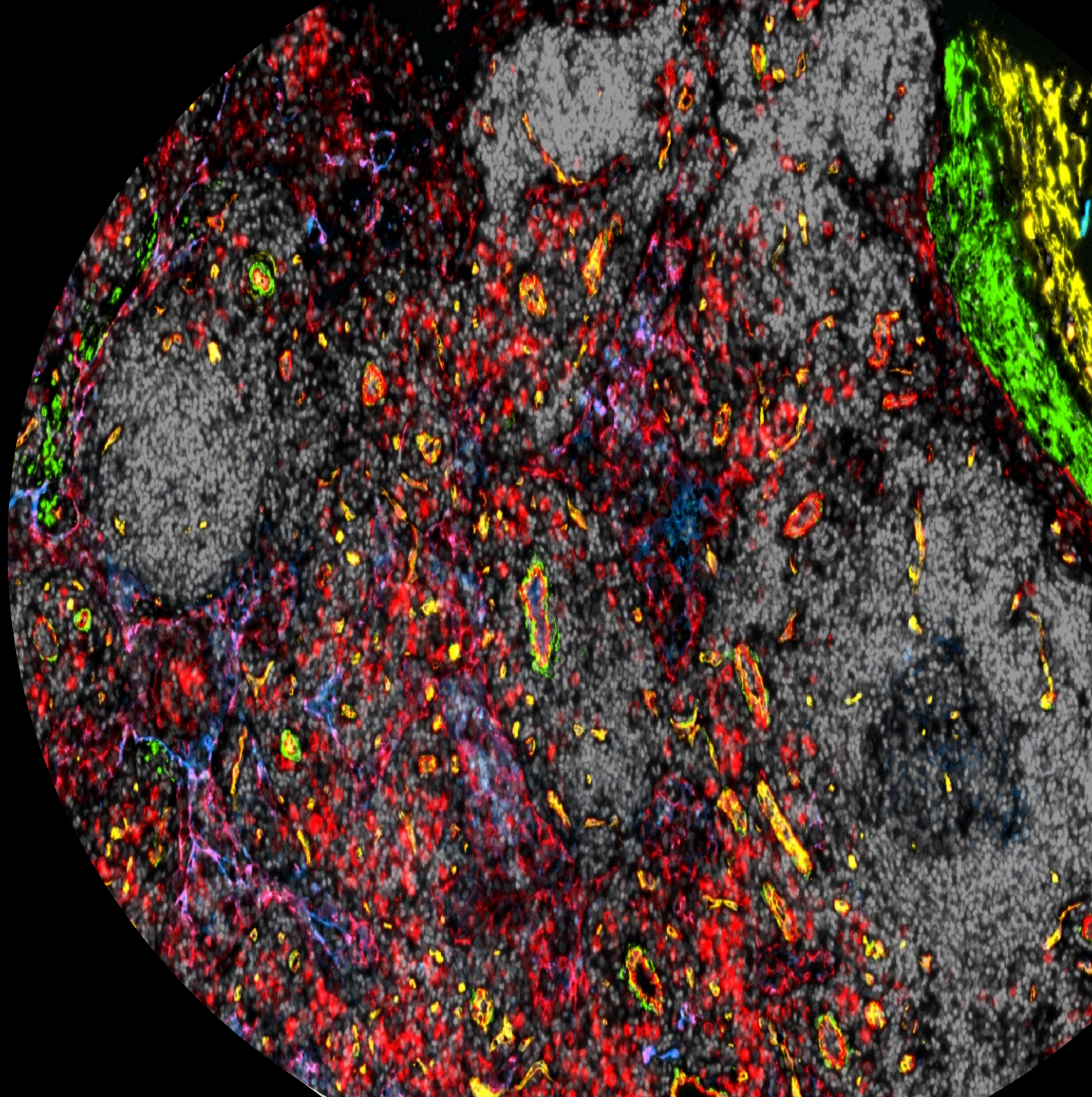
Cancer Biology I

Part-II

Week 12



AGENDA

Nov 5th: Cancer genomics- mutations

Nov 11th: Cancer genomics-copy number alteration, heterogeneity, evolution *(recording)*

Nov 18th: Cancer Epigenetics- chromatin 3D structure, cell plasticity

Nov 25th: – Major signaling pathways leading to cancer

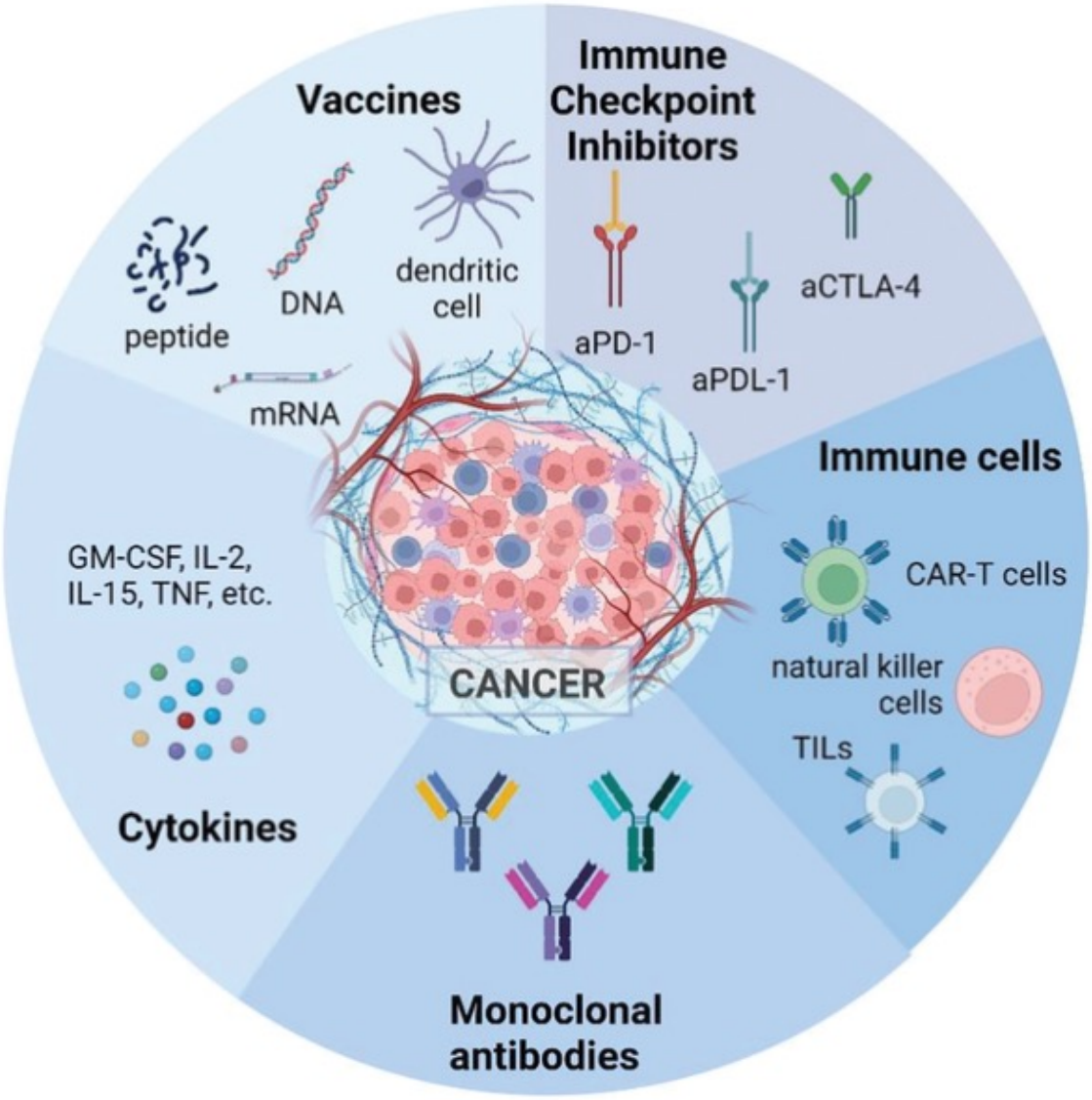
Dec 2th: Cancer Therapies – chemo and targeted therapies

Dec 9th: Introduction to immunotherapies –

Dec 16th: questions for the exam (please send me your questions by Wednesday Dec 12th)

Dec 18th: Exam 1.30 PM-3.30 PM CM 1 2

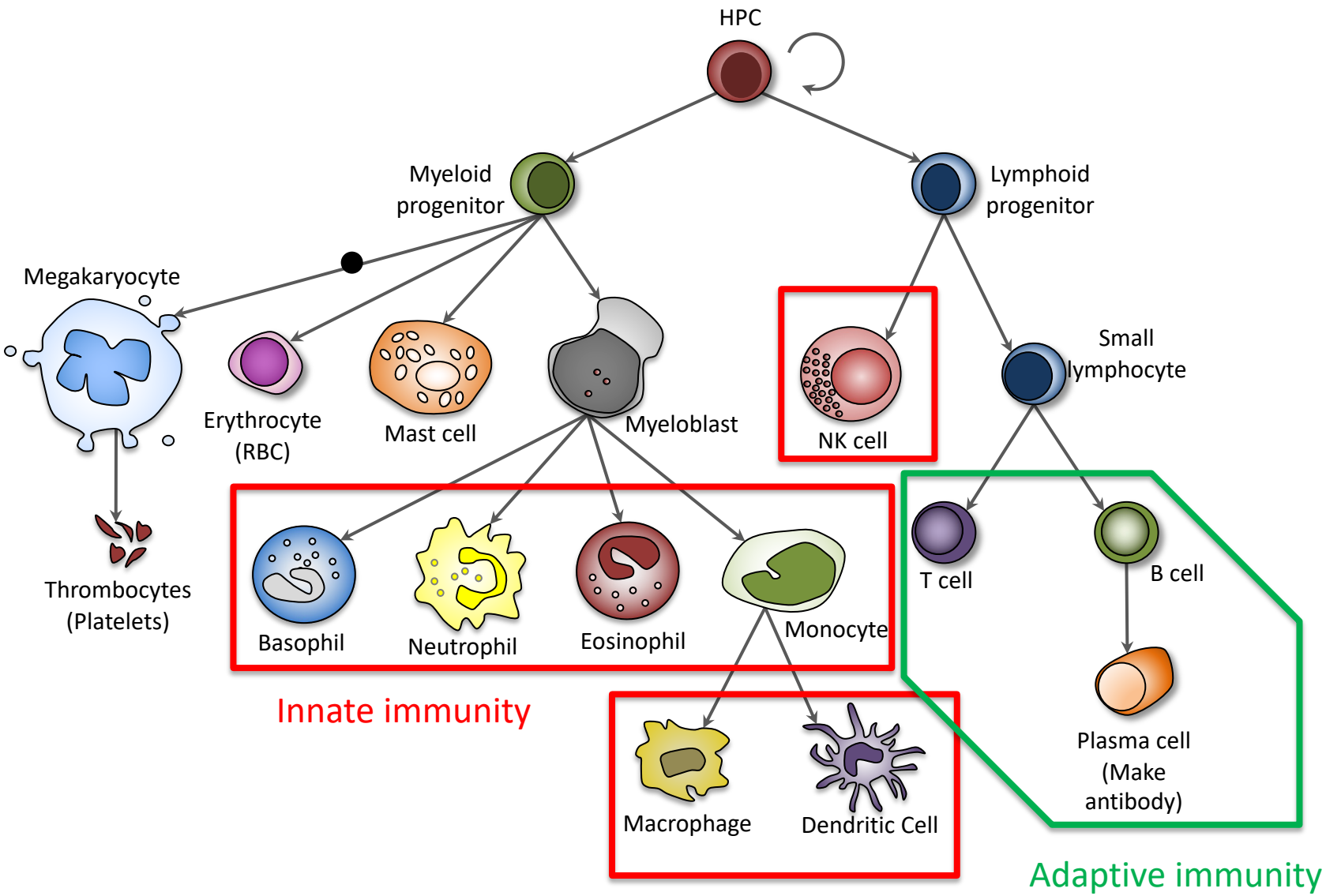
CANCER IMMUNOTHERAPIES



GOAL of cancer immunotherapies

Activate the immune-system to recognize and kill the tumor

IMMUNE SYSTEM



IMMUNOTHERAPY : PLAYERS

T-cells

B-cells

Natural Killer (NK)

Macrophages

Dendritic cells

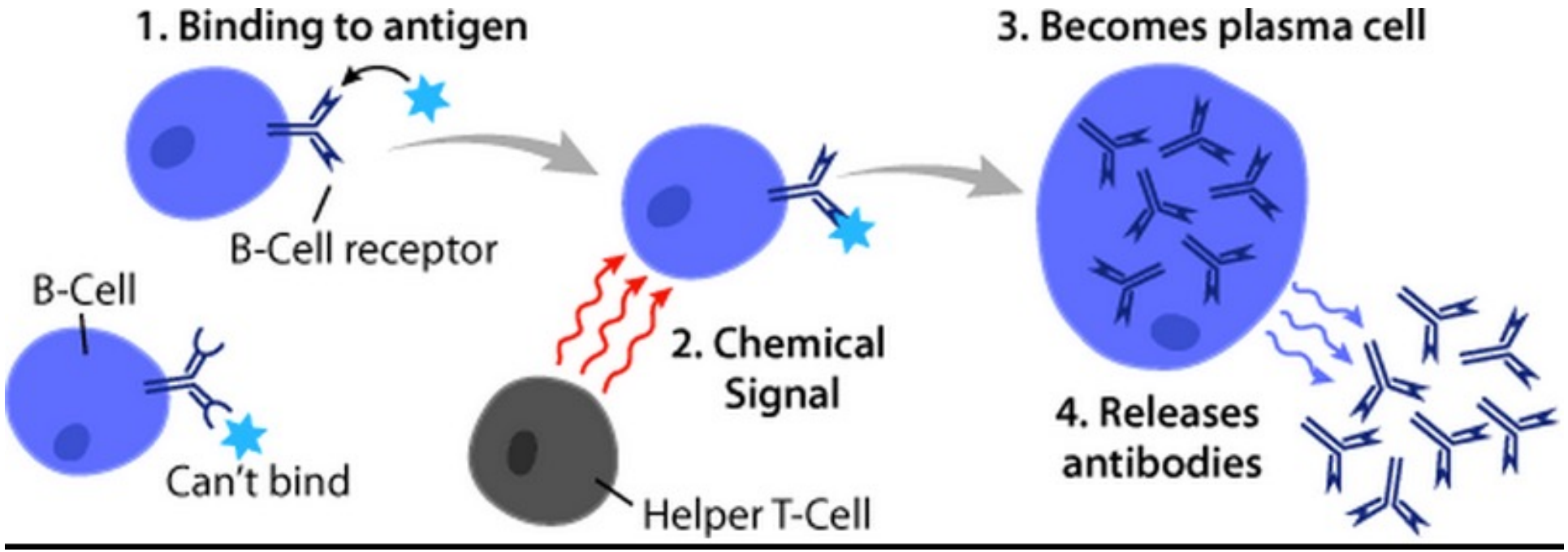
T-cells

CD4 cells/T-helper
Activation of B and T cells

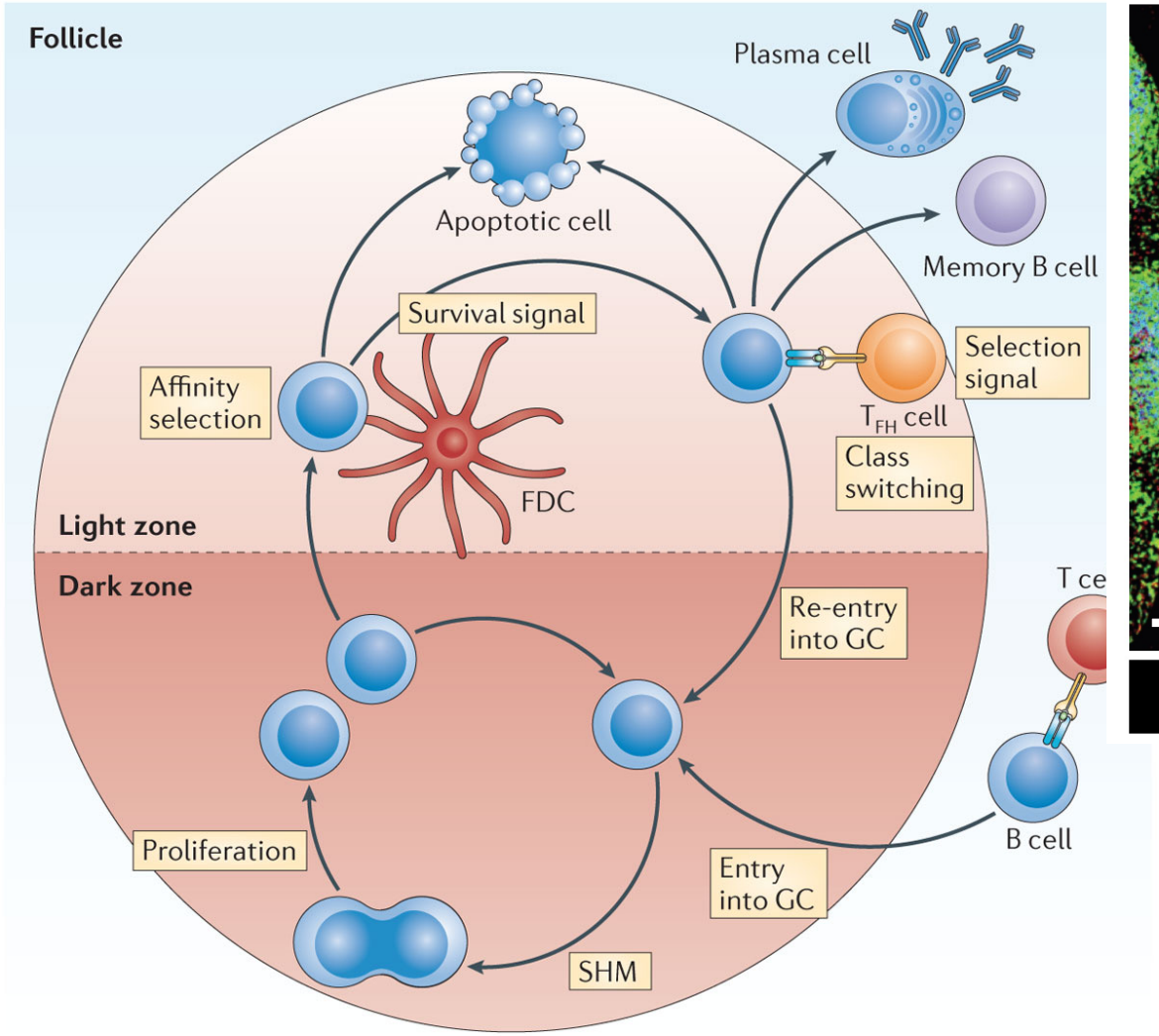
CD8
Cytotoxic
Adaptive immune system

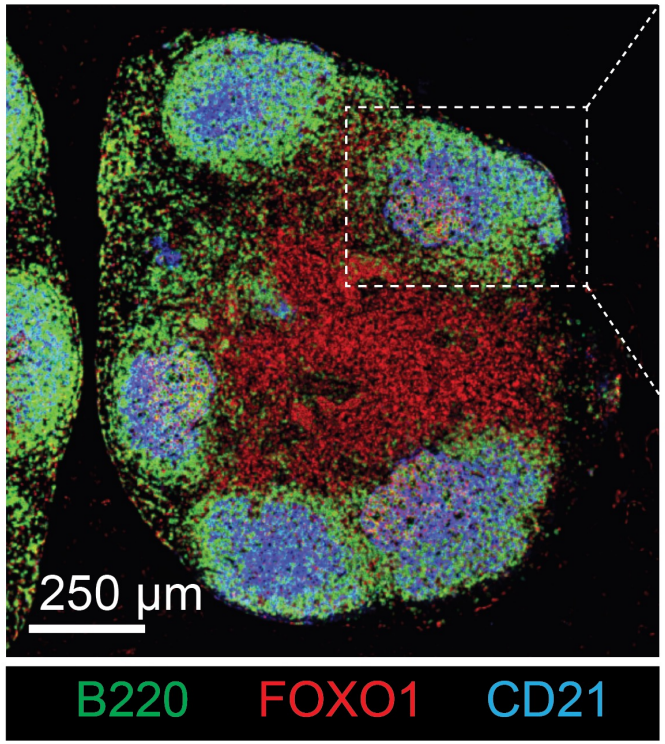
Regulator T cells (Treg)
CD4/FoxP3
Immunosuppressive

B-cells

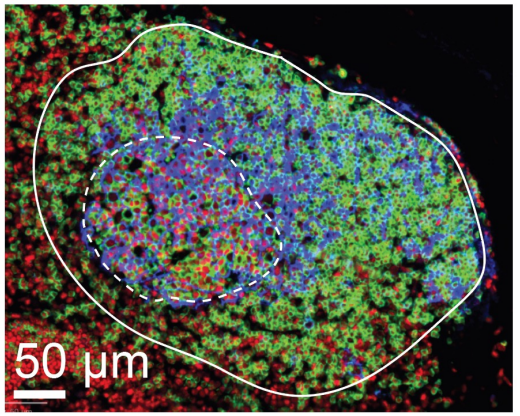

1. Binding to antigen
B-Cell receptor
B-Cell
Can't bind
2. Chemical Signal
Helper T-Cell
3. Becomes plasma cell
4. Releases antibodies

B-cells maturation in the Germinal Center to produce specific antibodies





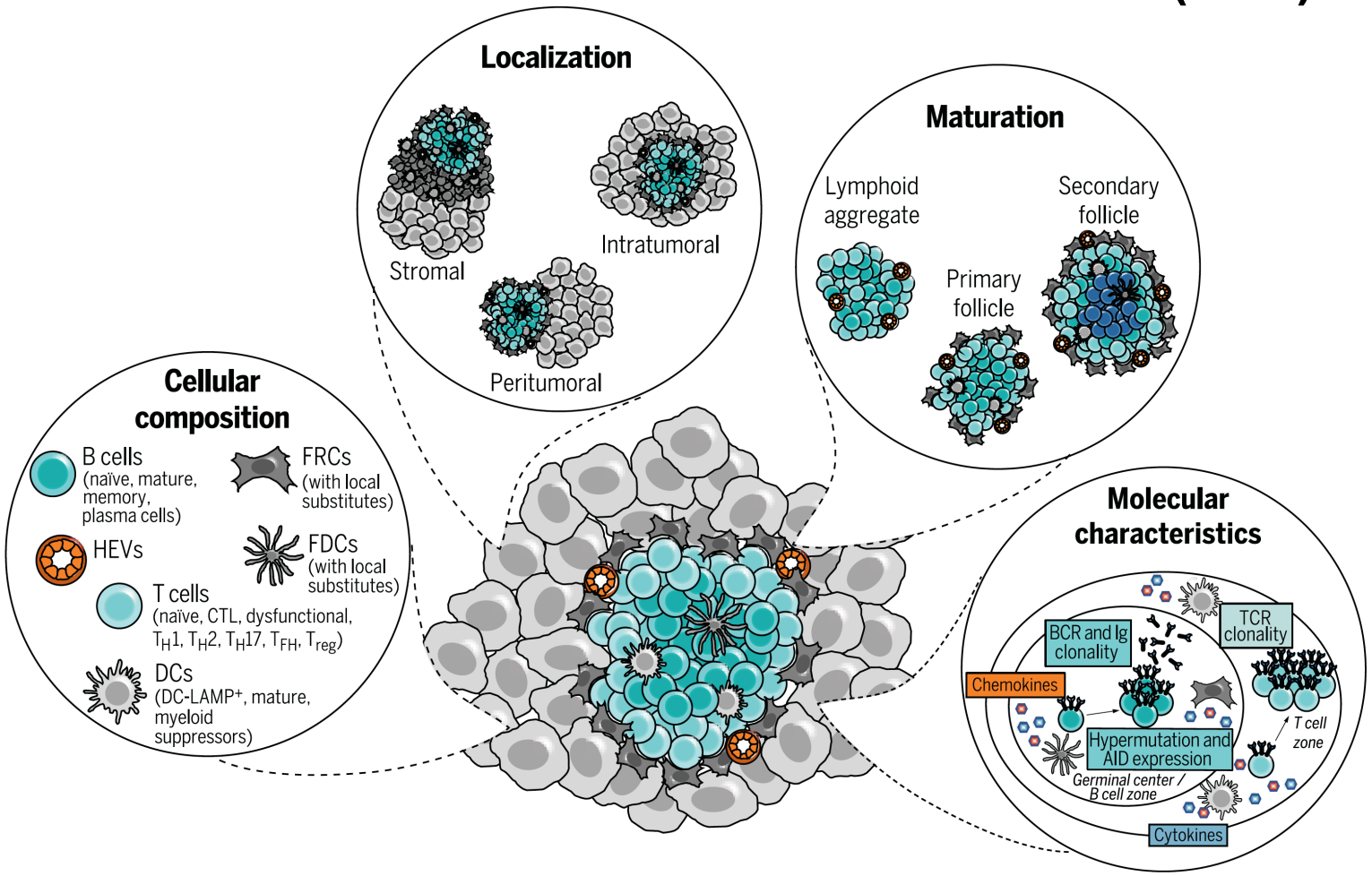
Lymph node

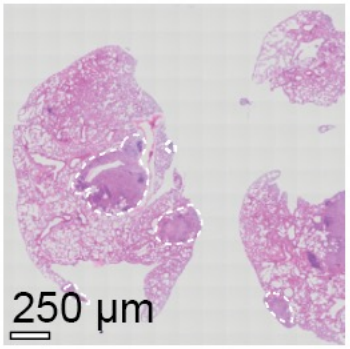


Germinal center

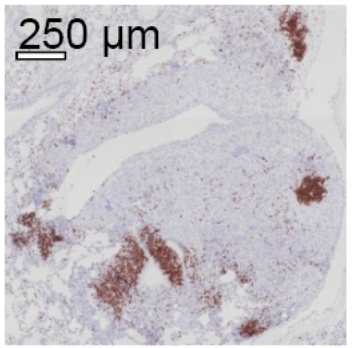
Nature Reviews | Immunology

In solid tumors: formation of structure similar to germinal centers, called Tertiary Lymphoid structure (TLS)

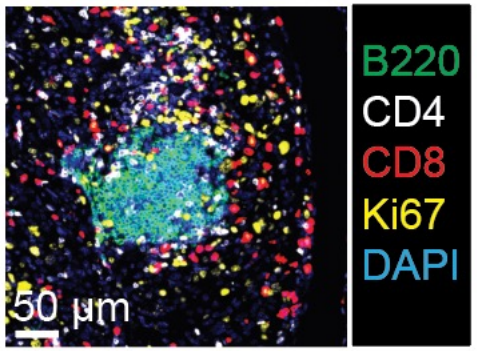




Lung cancer



Brow dots= B cells

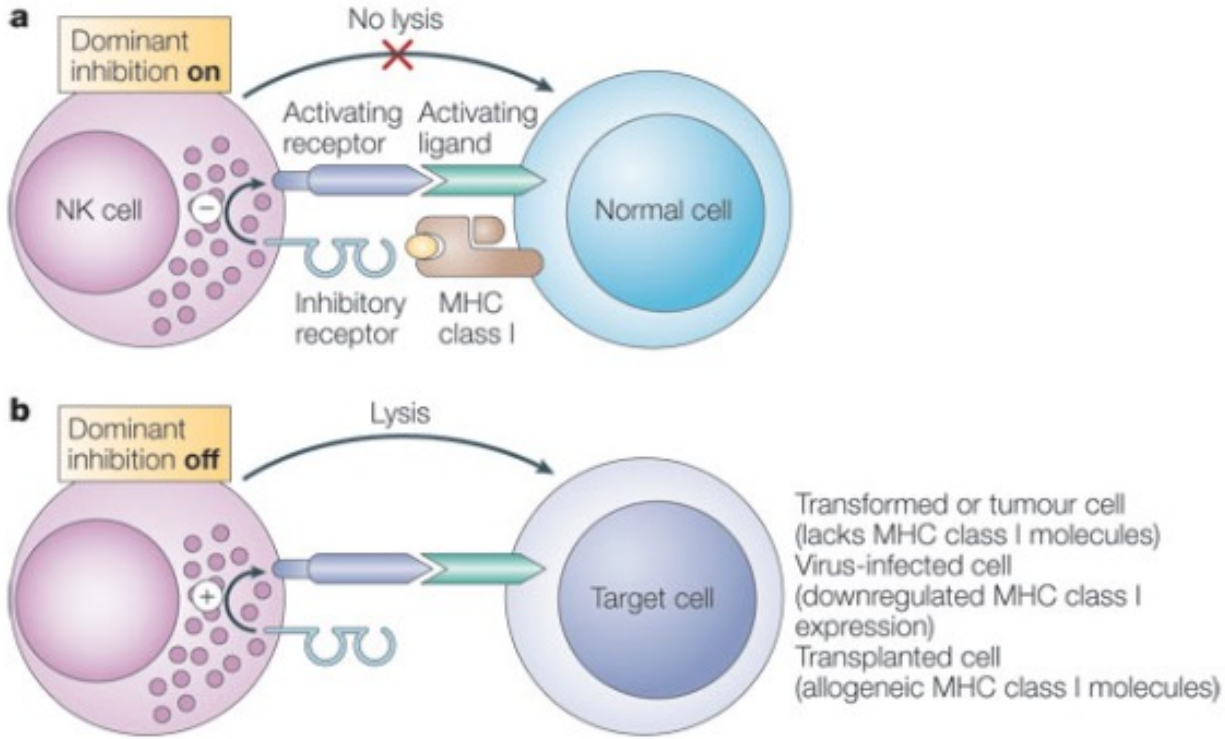


TLS

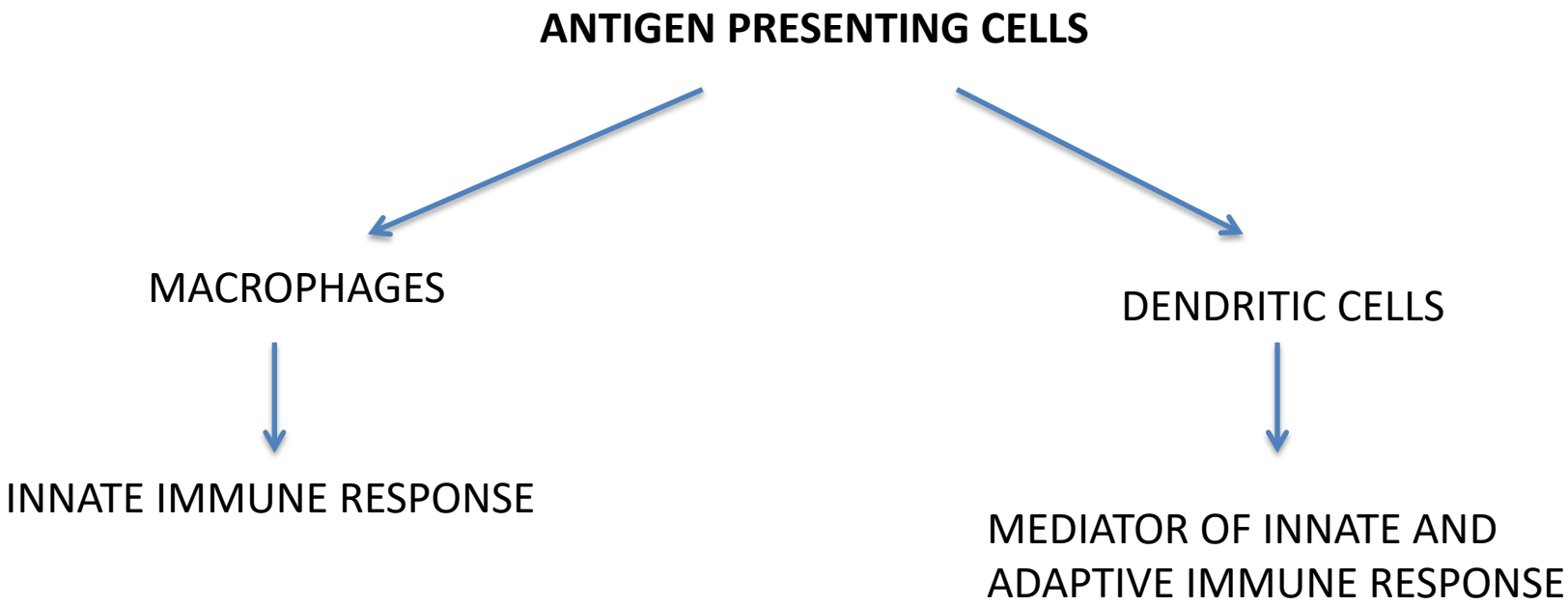
INNATE IMMUNE SYSTEM: PLAYERS

NK cells (Natural Killer cells): Cytotoxic lymphocytes

Innate Immune response (rapid response to viral infection)

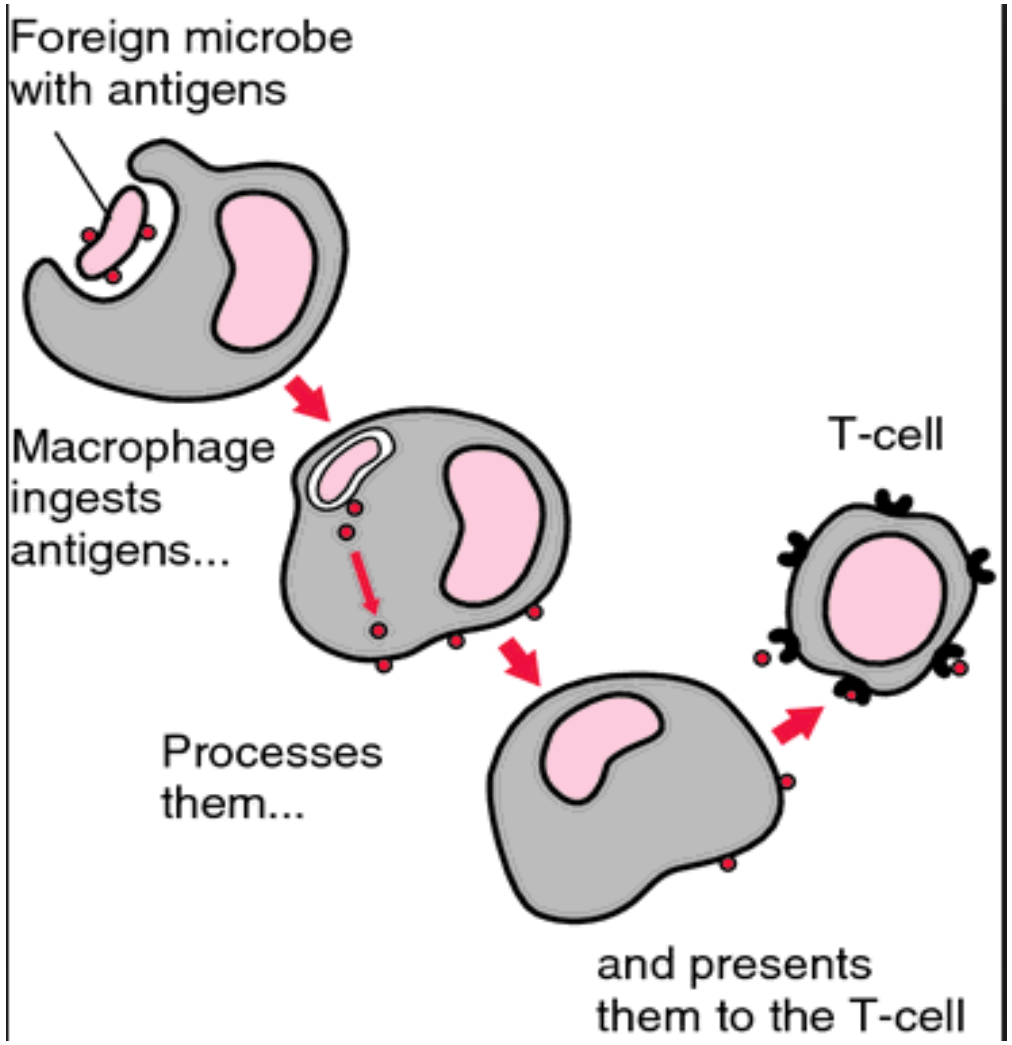


IMMUNE SYSTEM: PLAYERS



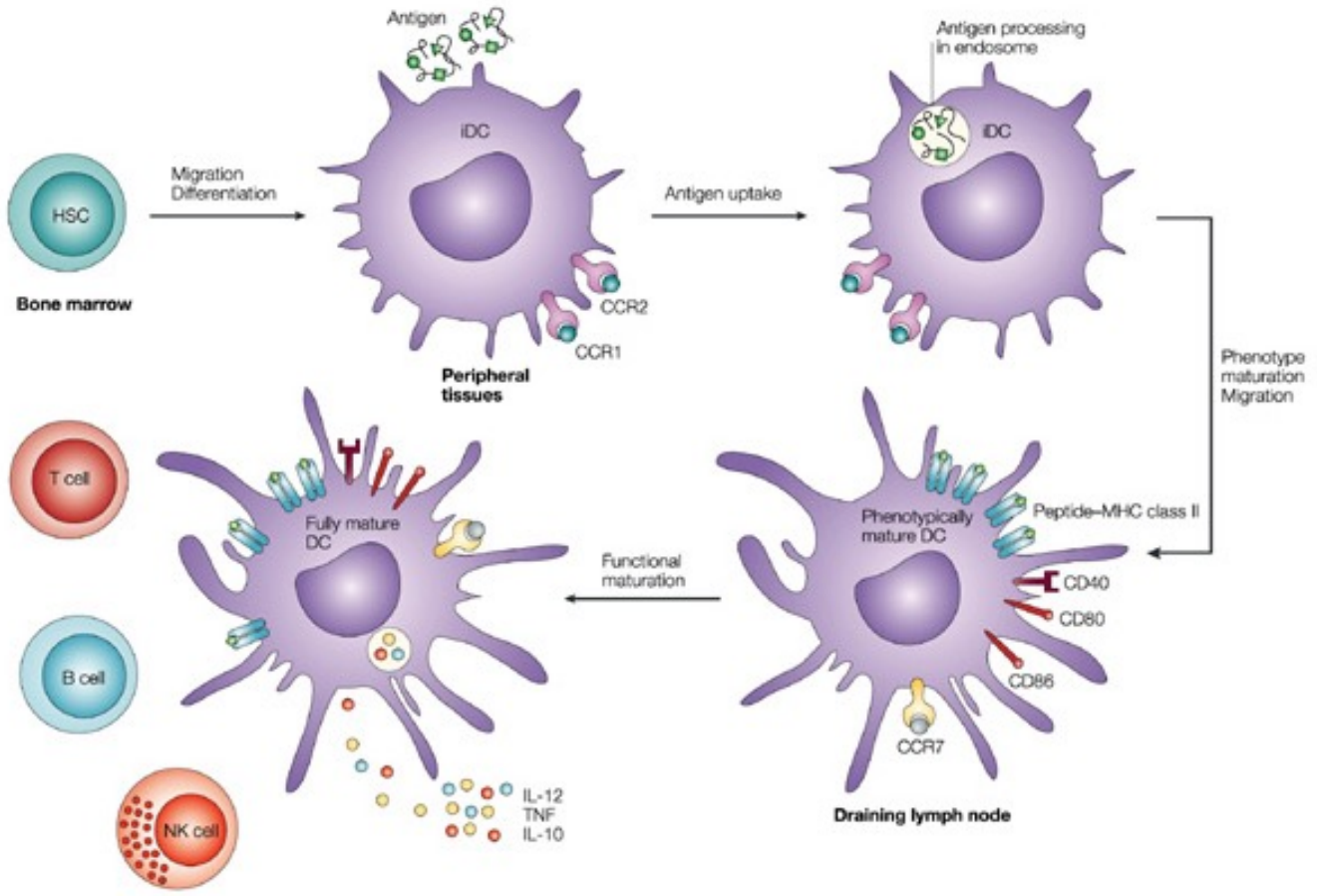
IMMUNE SYSTEM: PLAYERS

Macrophages (AP cells)

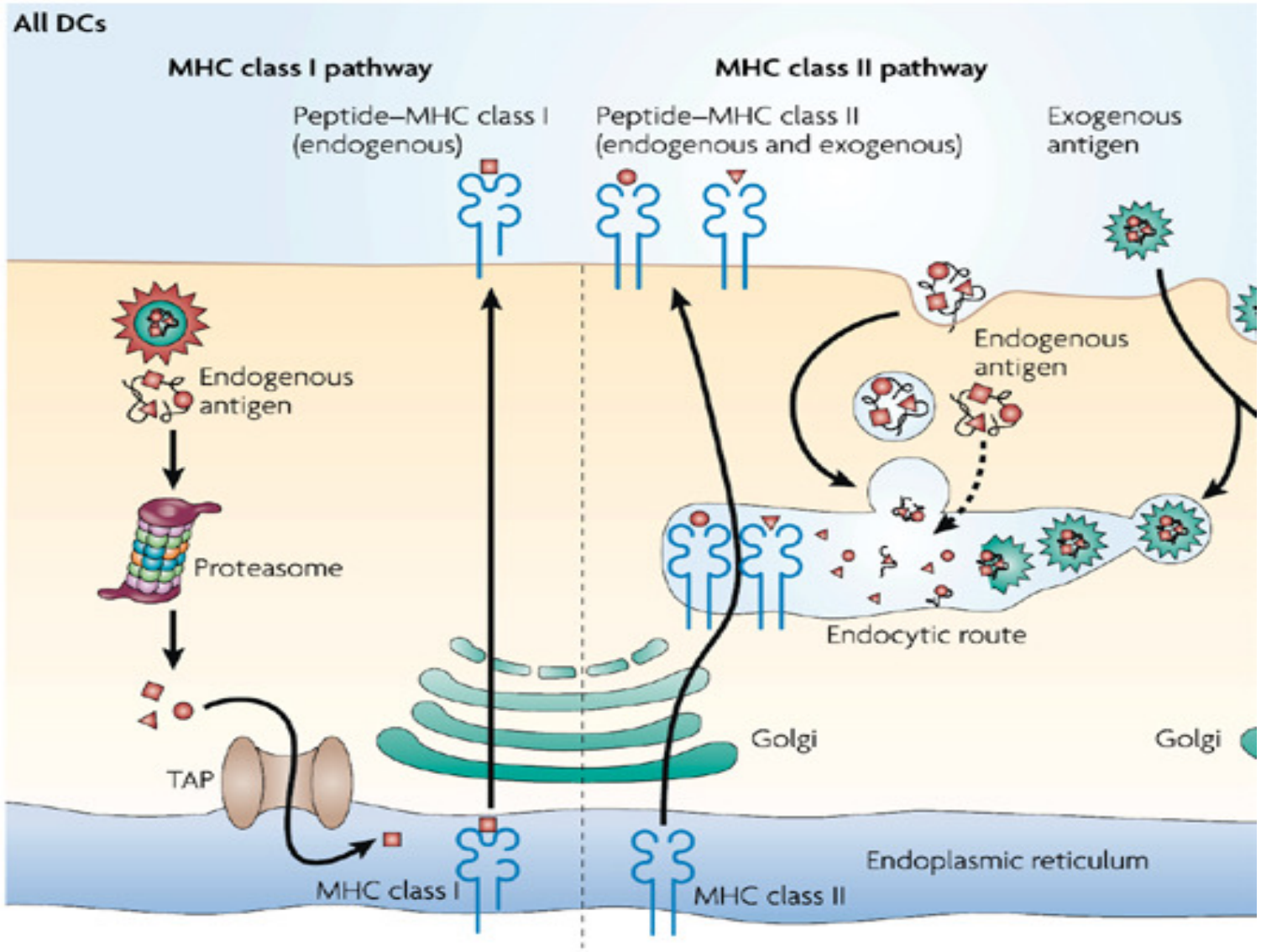


IMMUNE SYSTEM: PLAYERS

Dendritic cells= APC (Antigen Presenting cells)
mediator of innate and adaptive immune response



ANTIGENE PRESENTATION: MHC



ANTIGENE PRESENTATION: MHC I

ALL CELLS IN OUR BODY

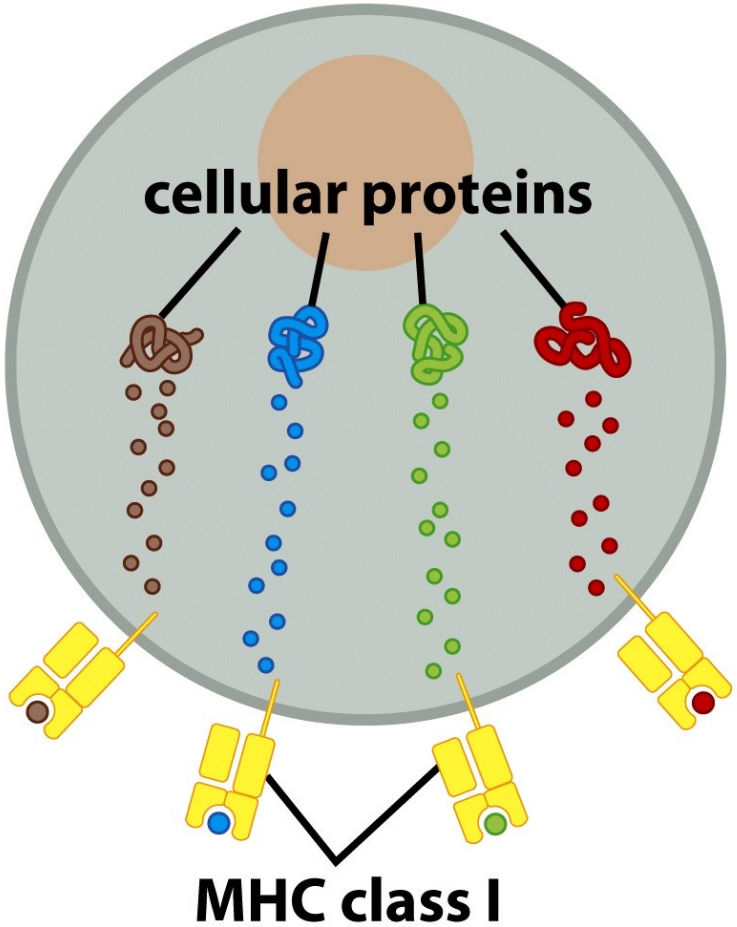
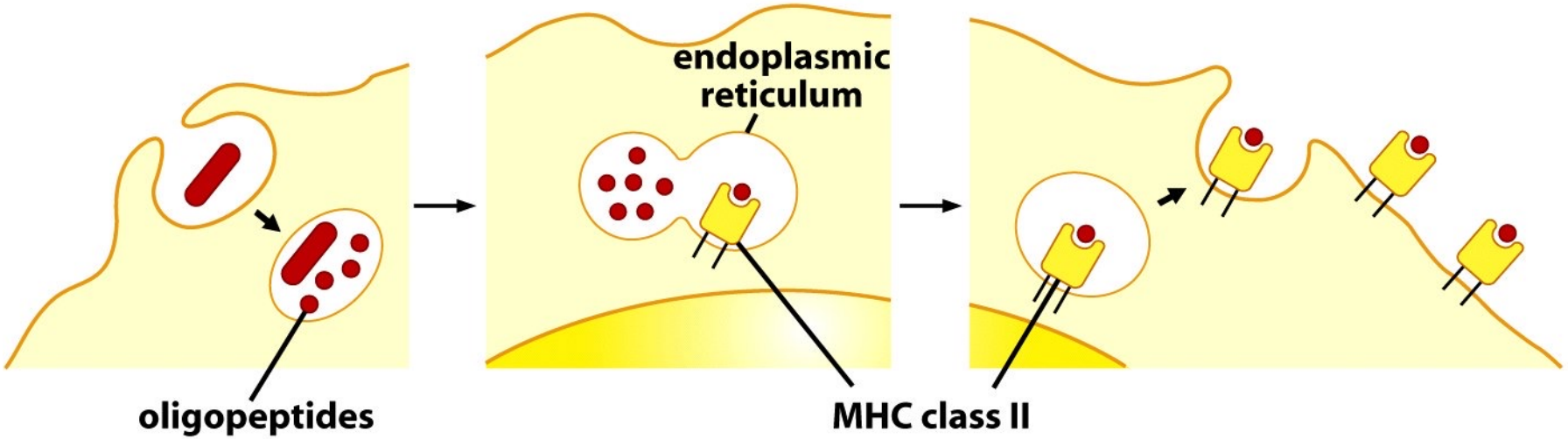


Figure 15.10b *The Biology of Cancer* (© Garland Science 2007)

ANTIGENE PRESENTATION: MHC II

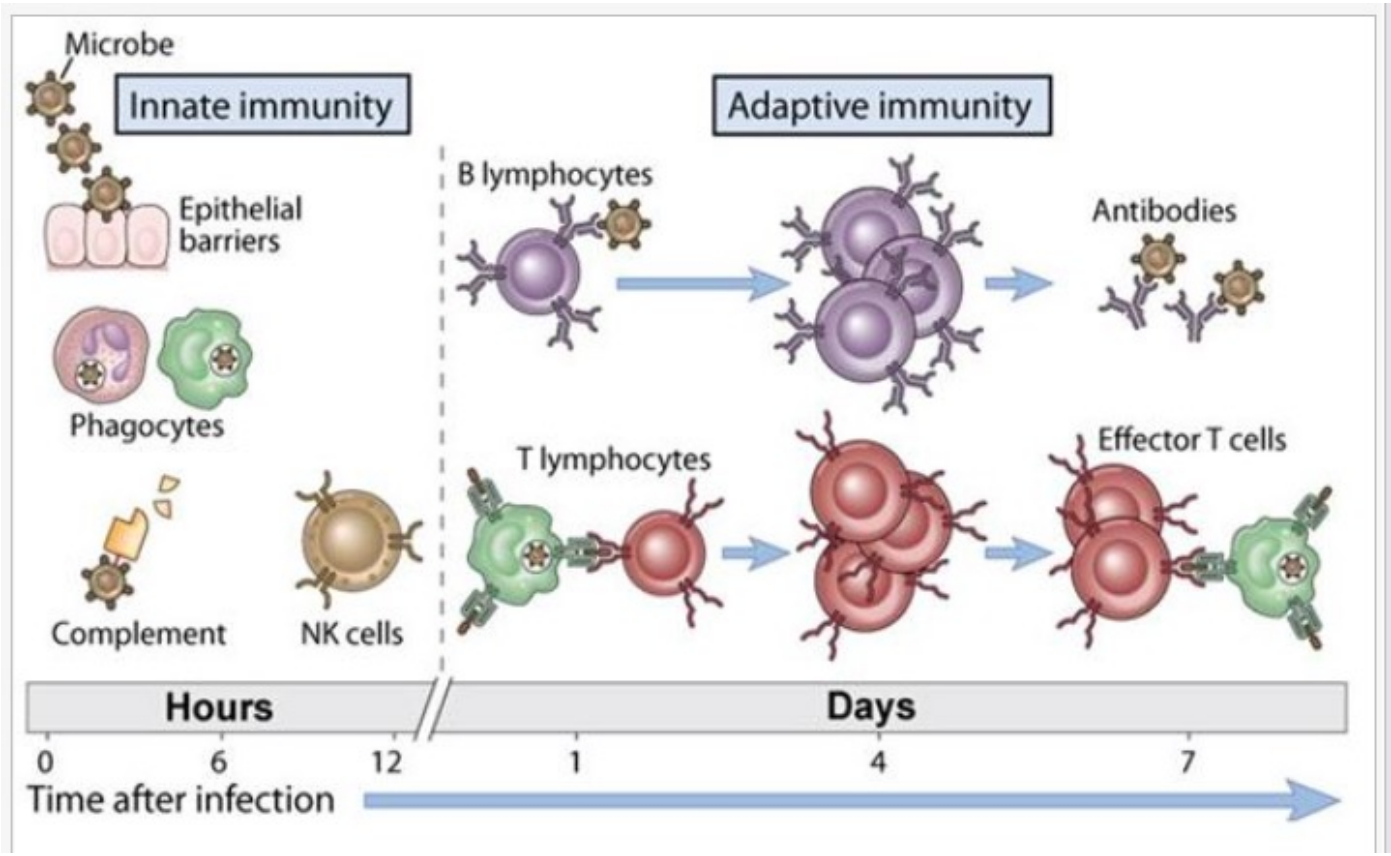
MACROPHAGES, B-CELLS , T CELLS



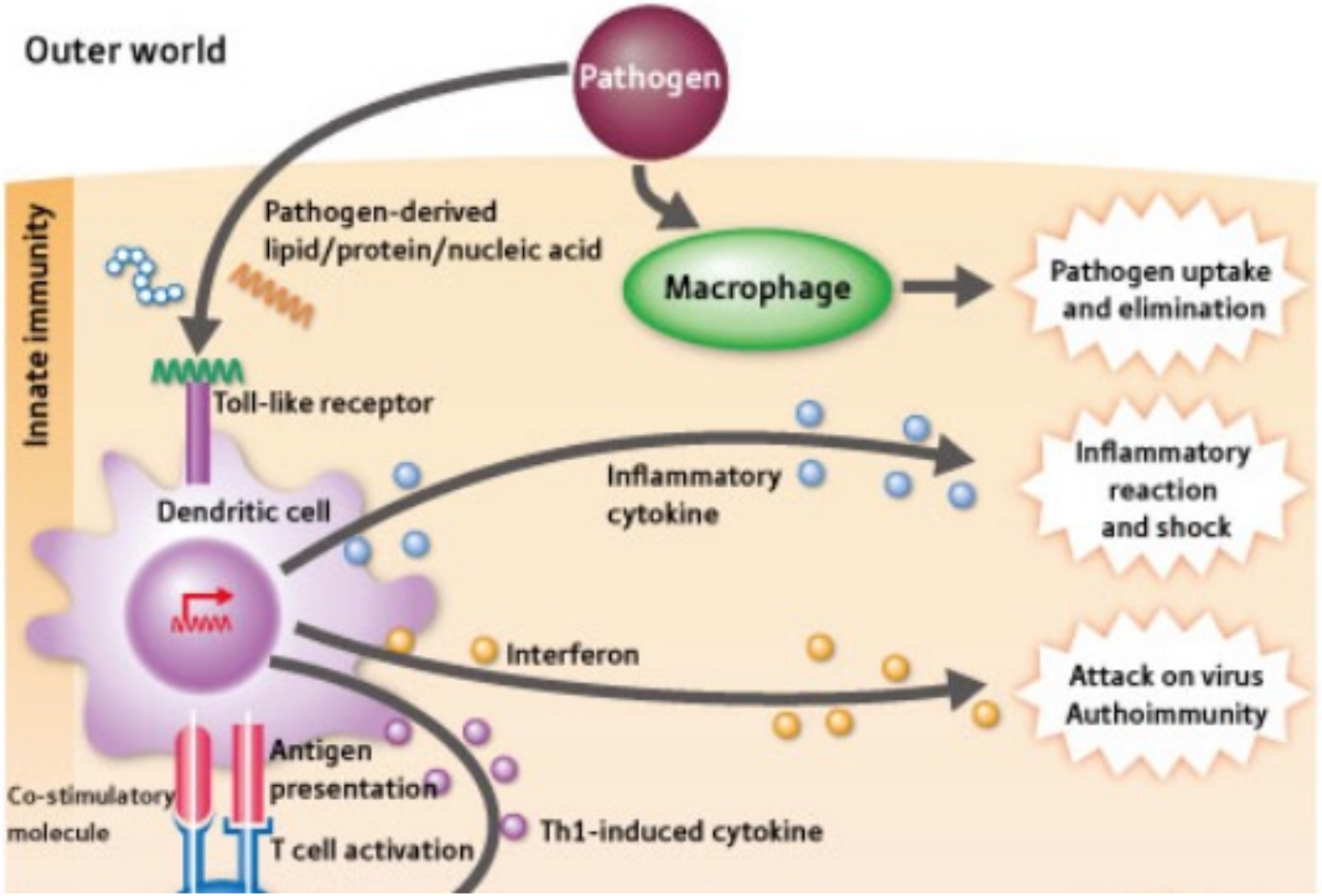
IMMUNE RESPONSE

INNATE IMMUNE RESPONSE= Fast

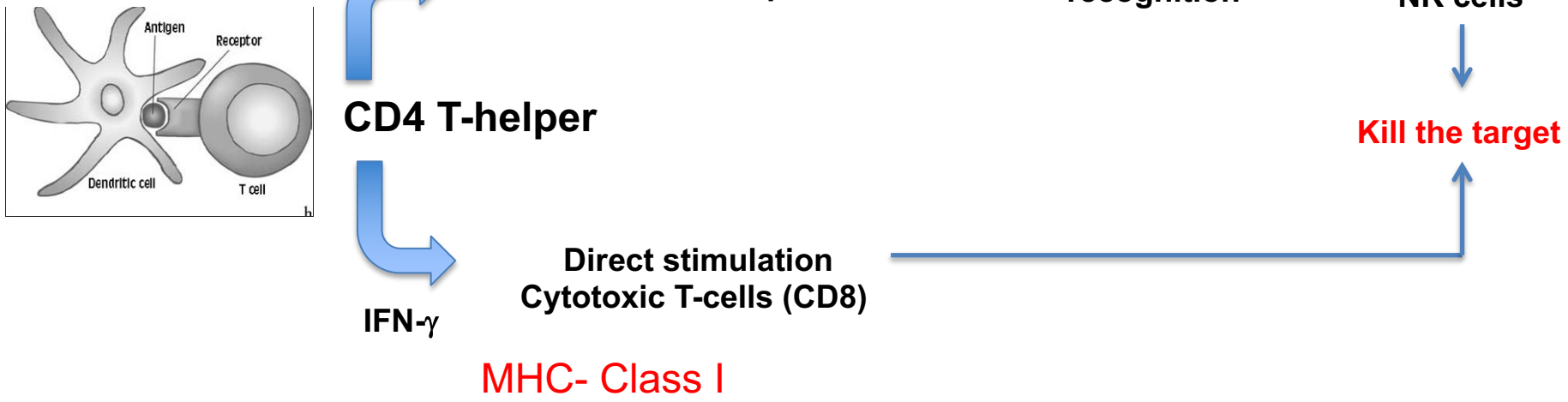
ADAPTIVE IMMUNE RESPONSE= Slow but long term memory



INNATE IMMUNE RESPONSE

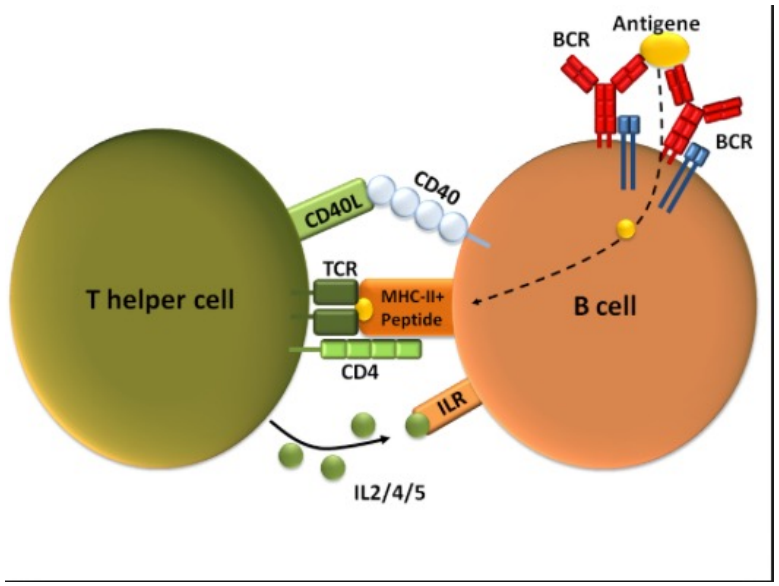


ADAPTIVE IMMUNE RESPONSE

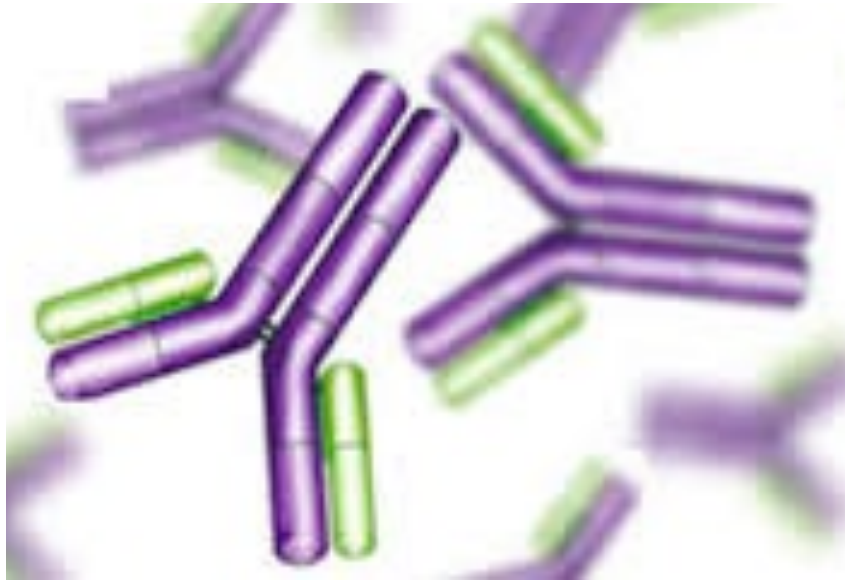


STEP1-2: Activation of B-cells to produce antibodies

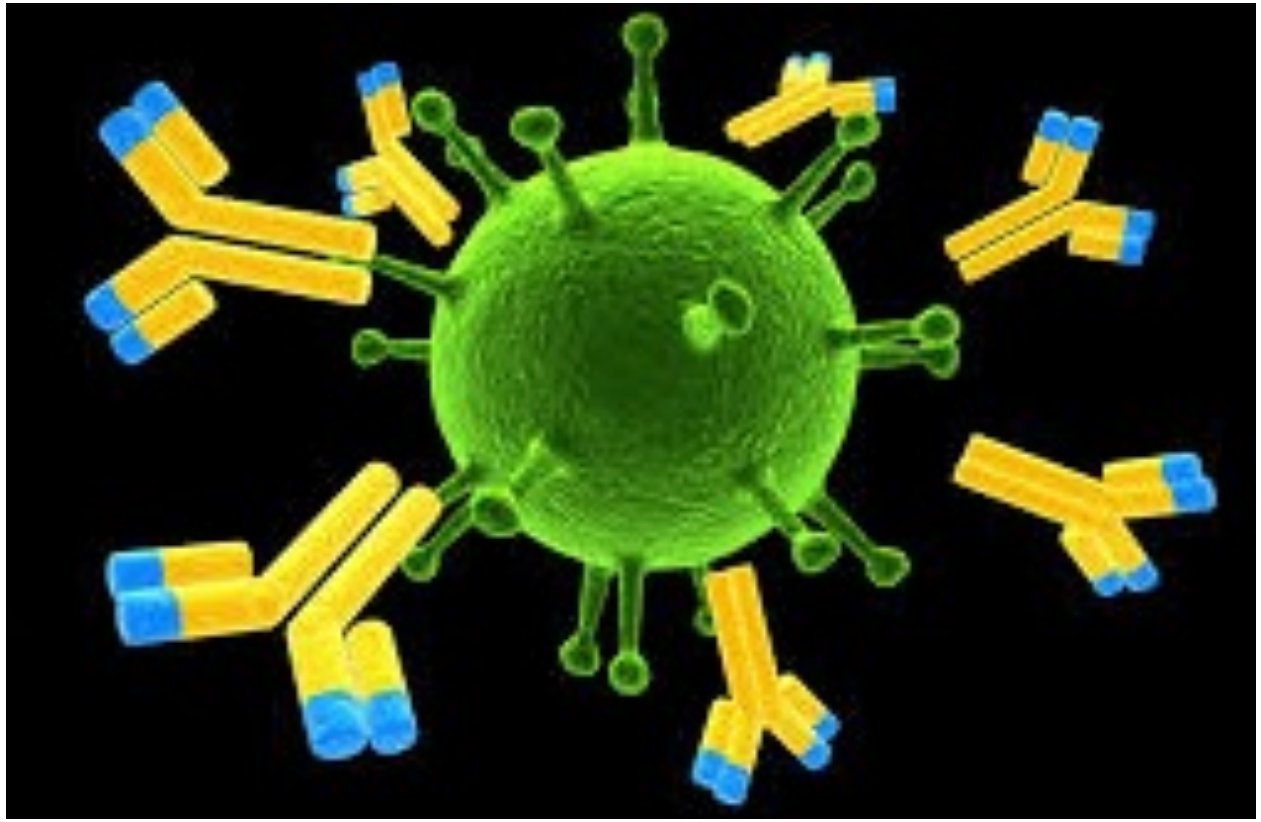
1. Activation of B-cells



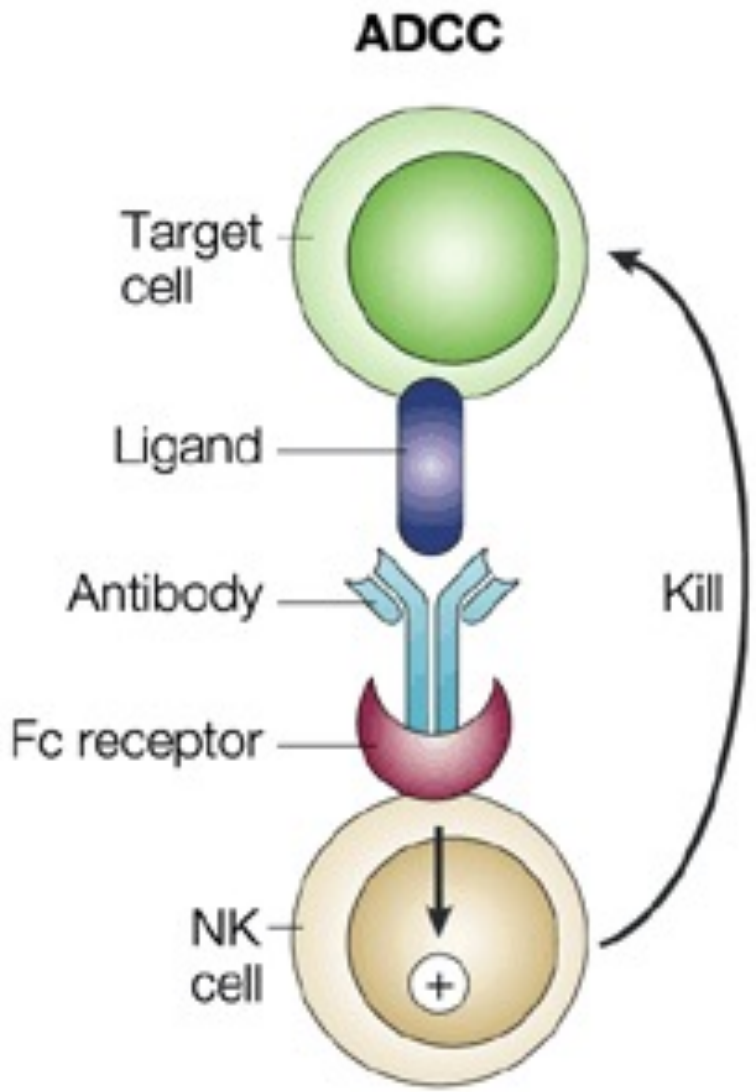
2. Antibodies production



STEP3: Recognize the target



STEP 4-5: Activation of NK cells and macrophages and kill the target

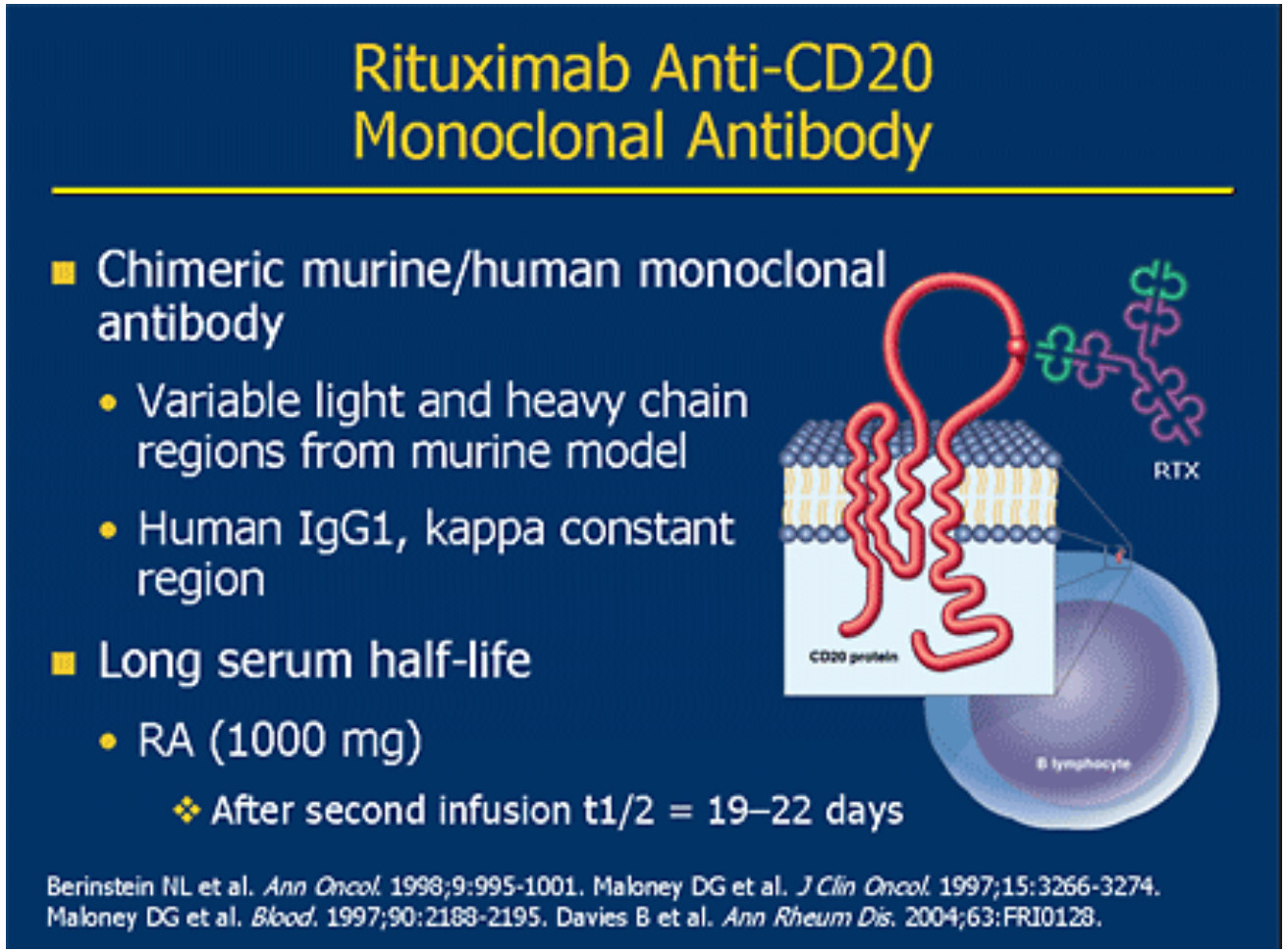


Antibodies for cancer treatment

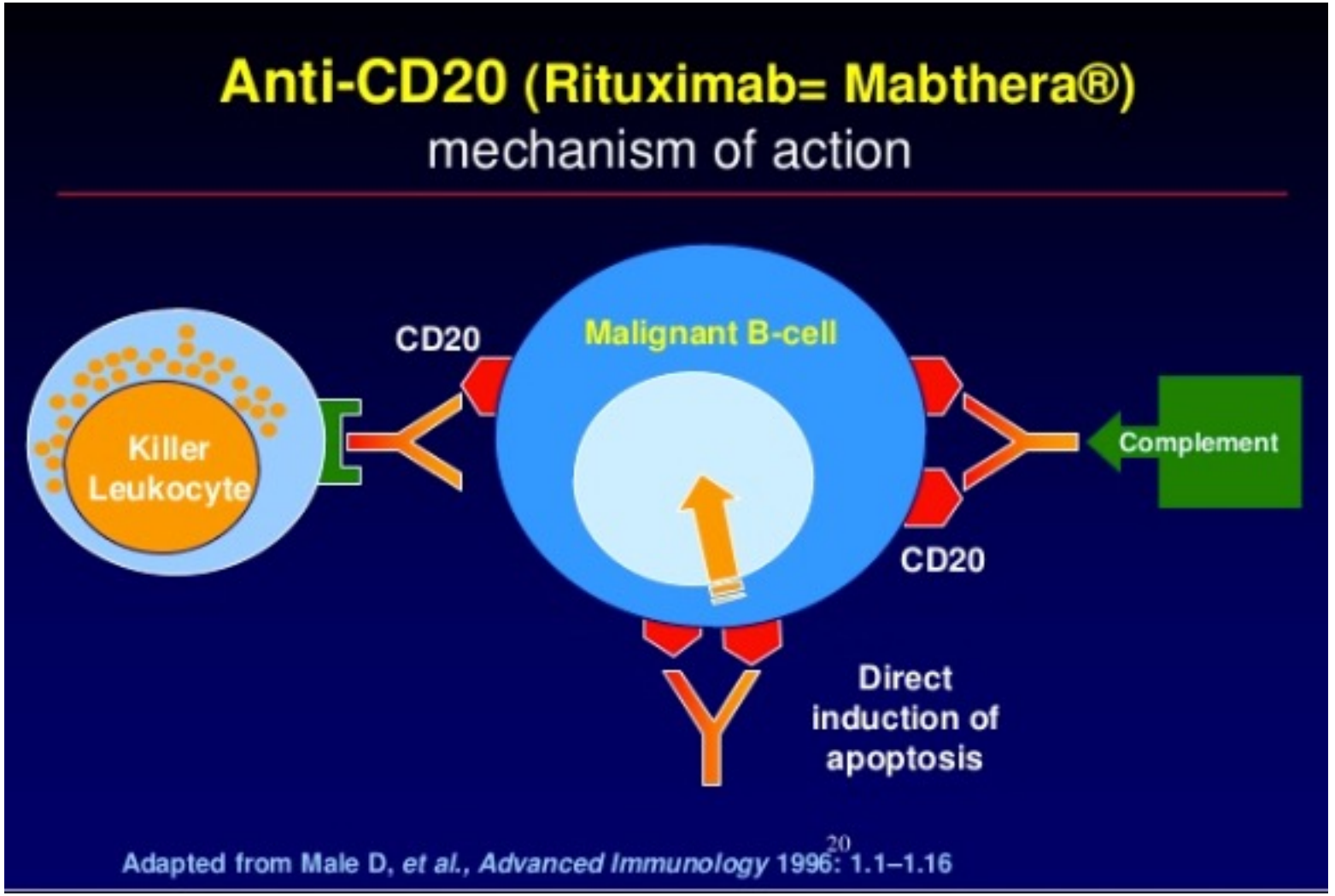
Lymphoma therapy: R-CHOP

R= Rituximab

CHOP= Chemotherapies MIX

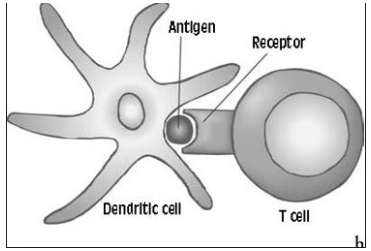


Antibodies for cancer treatment



ADAPTIVE IMMUNE RESPONSE

New Antigen



MHC- Class II

IL4

1. activation of B-cells → **2. antibodies production** → **3. Target cells recognition** → **4. Activation NK cells** → **Kill the target**

CD4 T-helper

IFN-γ

Direct stimulation Cytotoxic T-cells (CD8) → **Kill the target**

MHC- Class I

ADAPTIVE IMMUNE RESPONSE: Cytotoxic cells

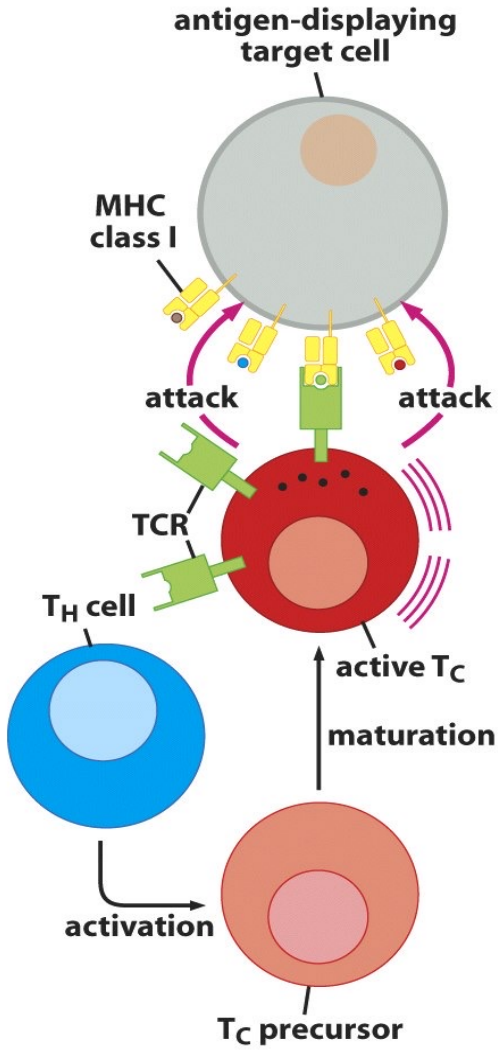


Figure 15.11 *The Biology of Cancer* (© Garland Science 2007)

INNATE VS ADAPTIVE IMMUNE RESPONSE

	Innate Immunity	Adaptive Immunity
Speed of Onset	Immediate (within minutes)	~ 3 day lag
Specificity to Antigen	Lower	Higher
Diversity of Response	Lower	Higher
Potency	Lower	Higher
Memory (Reacts quicker to subsequent exposures)	No	Yes

IMMUNE TOLERANCE

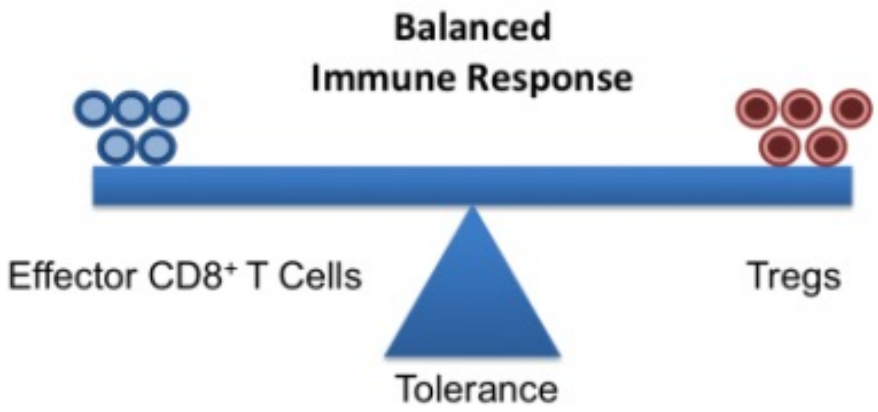
T-Regulatory cells
(Treg)
(CD4, CD25 and FoxP3)

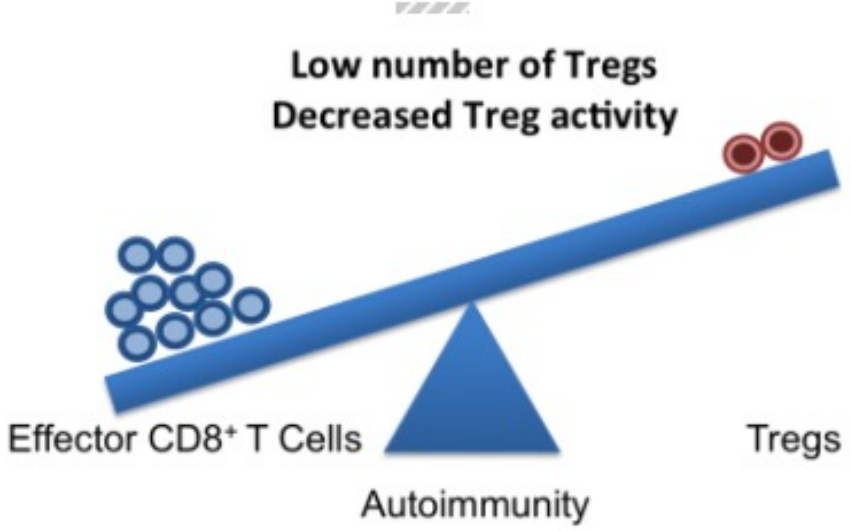
Protect the body from auto-immune disease

Release IL10/TGF-β

Inhibit T-cells activation

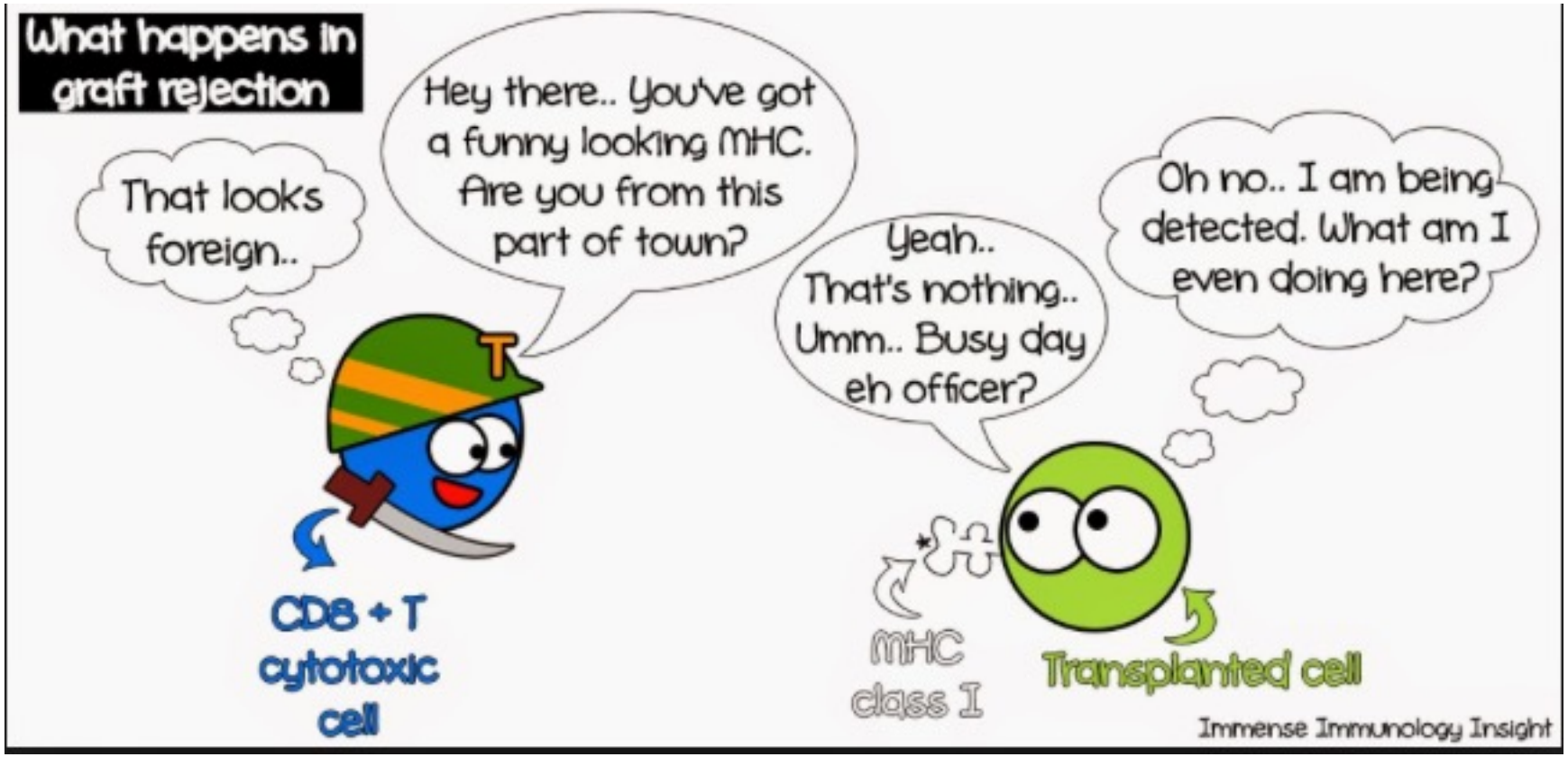
IMMUNE TOLERANCE: mediated by Treg cells





GRAFT REJECTION

Transplanted cells from donor are recognized and eliminated by the immune system



SYNGENEIC and ALLOGENEIC TRANSPLANT

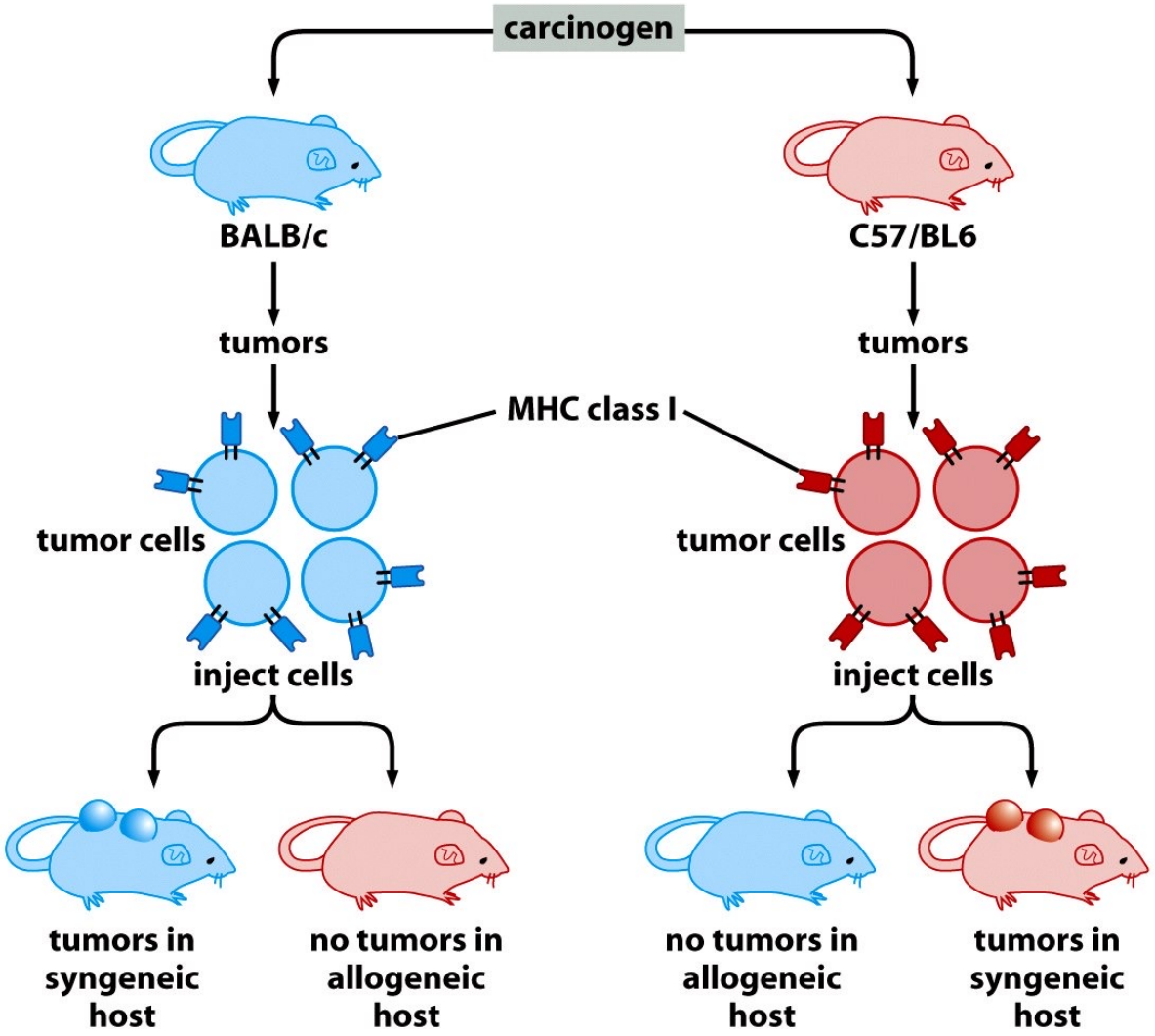
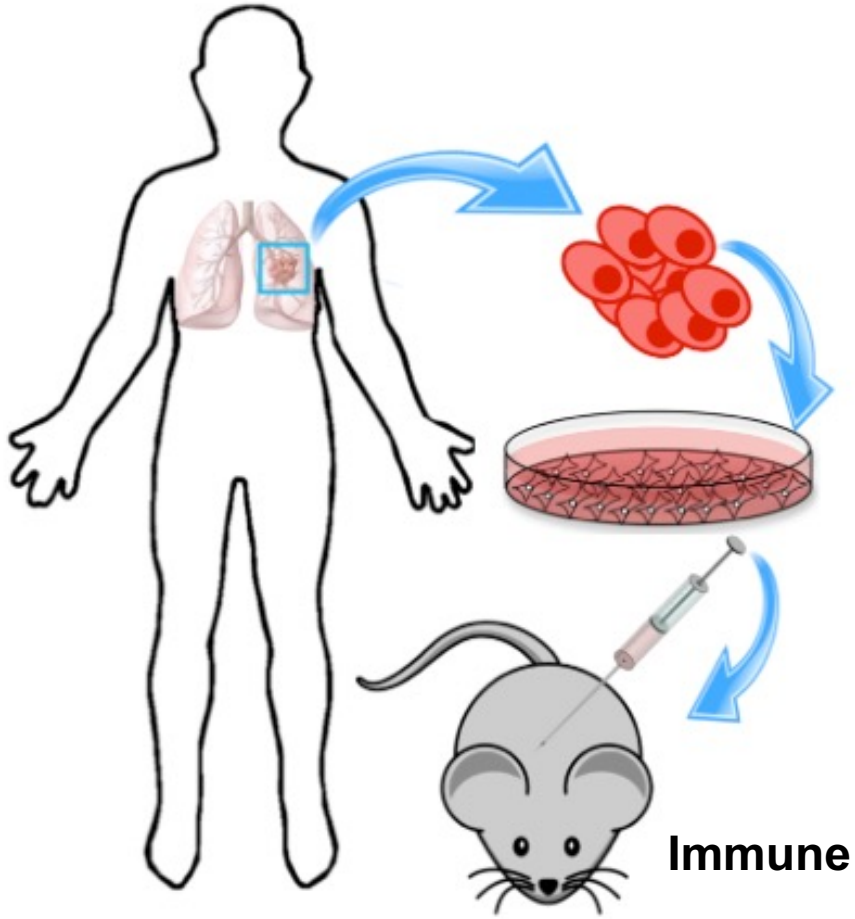


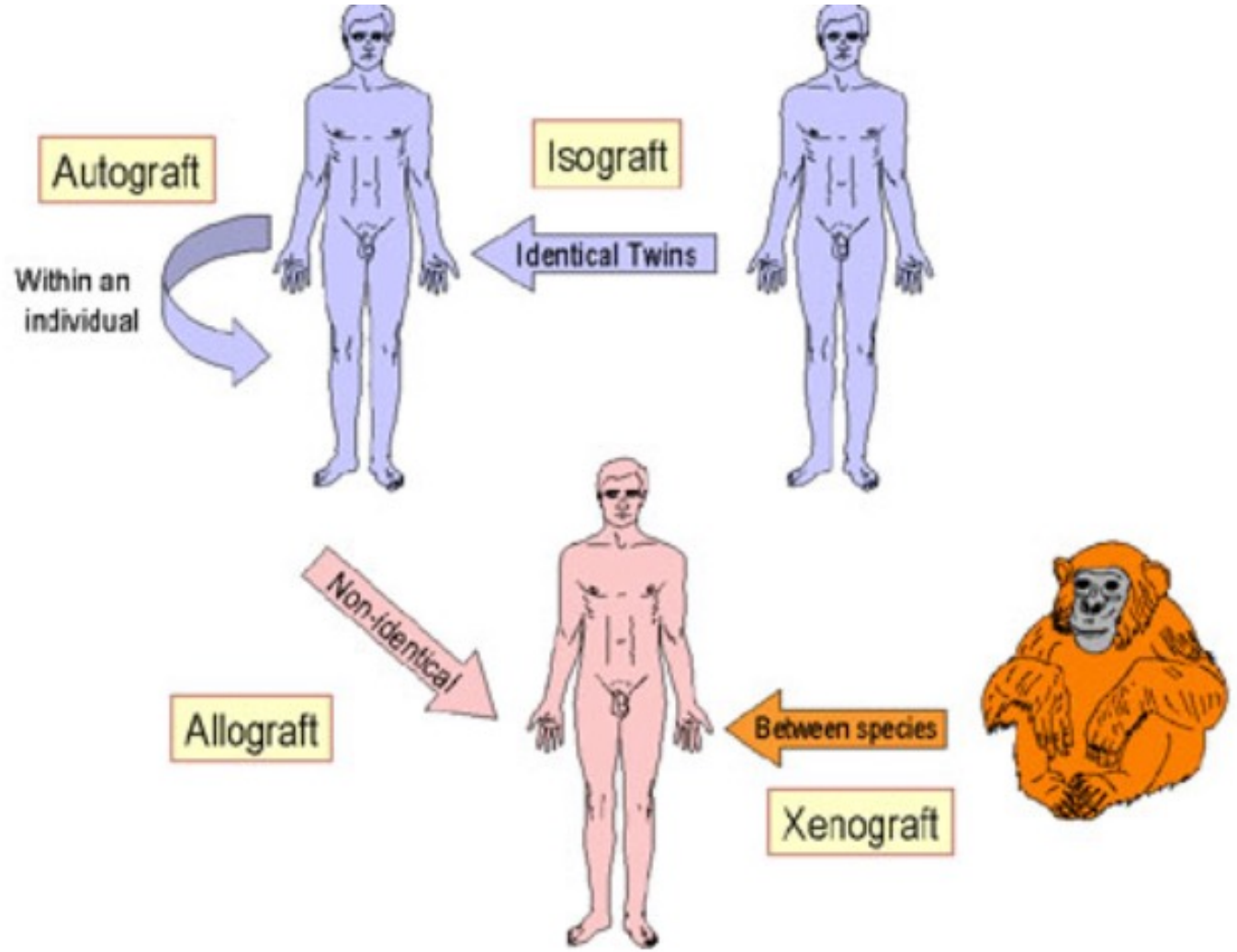
Figure 15.15 *The Biology of Cancer* (© Garland Science 2007)

XENOGRAFT TRANSPLANT

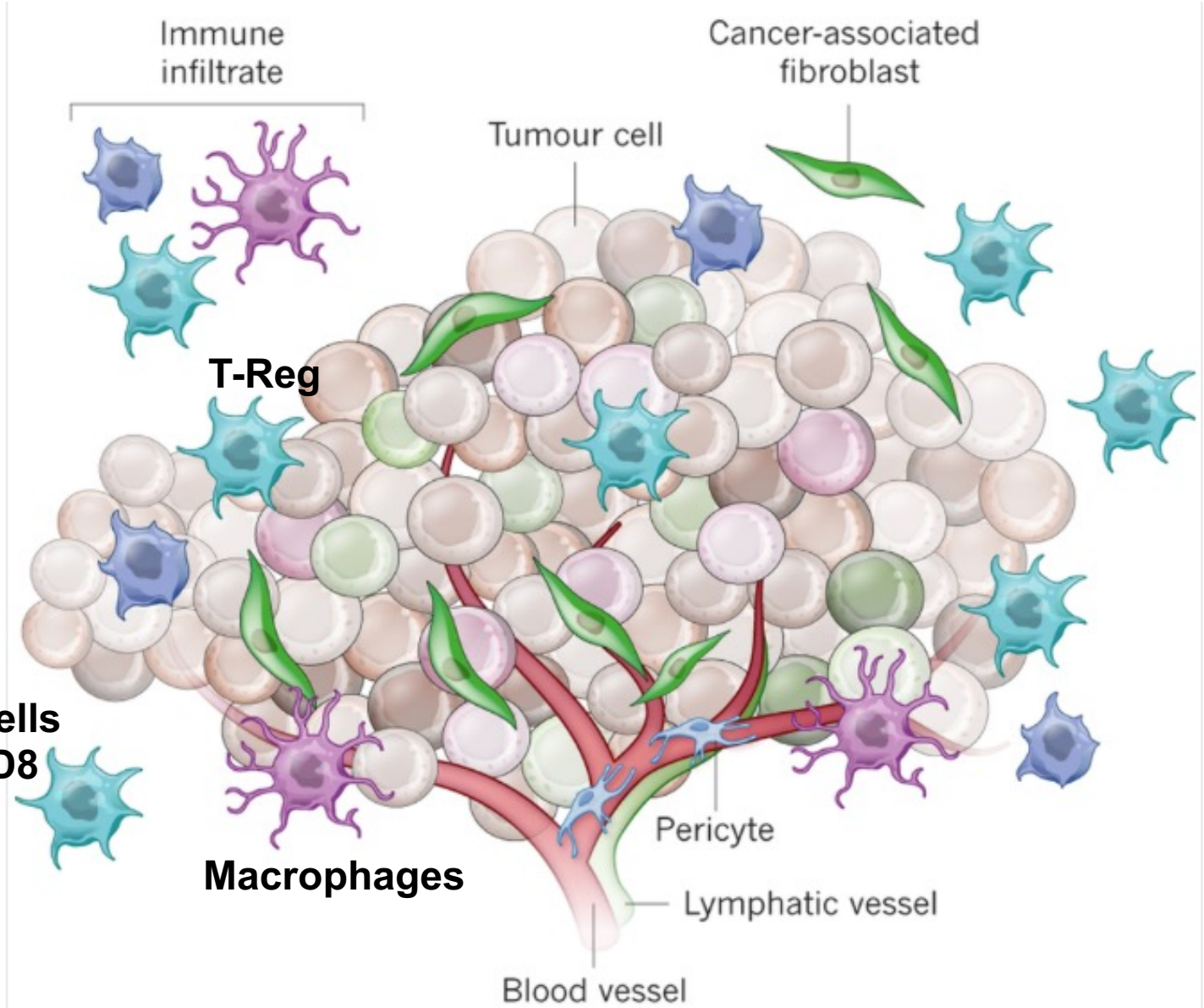


Immune deficient animals

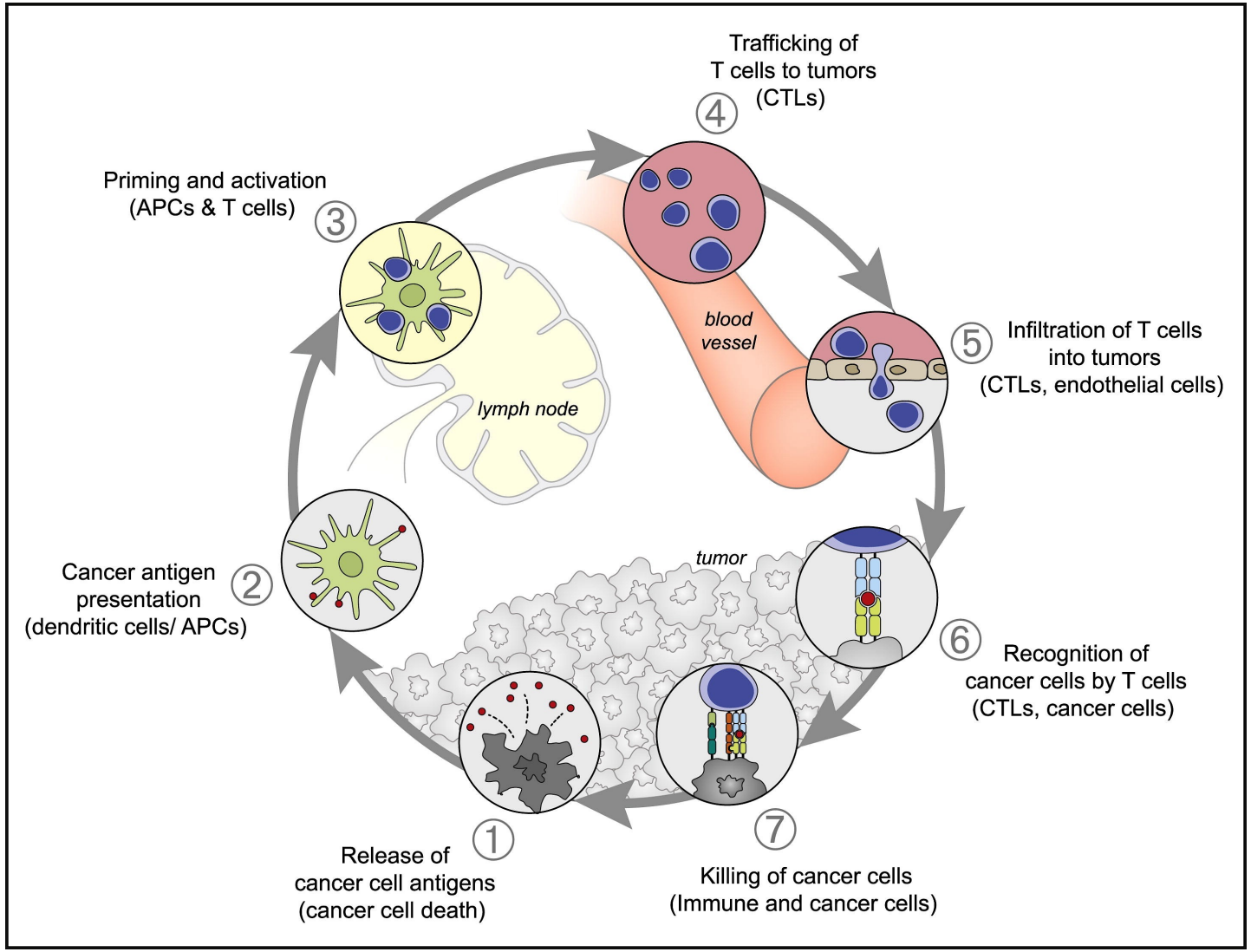
SUMMARY TRANSPLANT



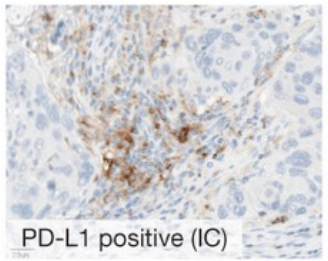
TUMOR MICROENVIROMENT

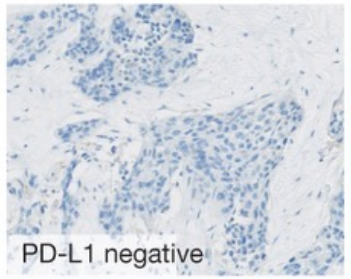


THE CANCER IMMUNITY CYCLE



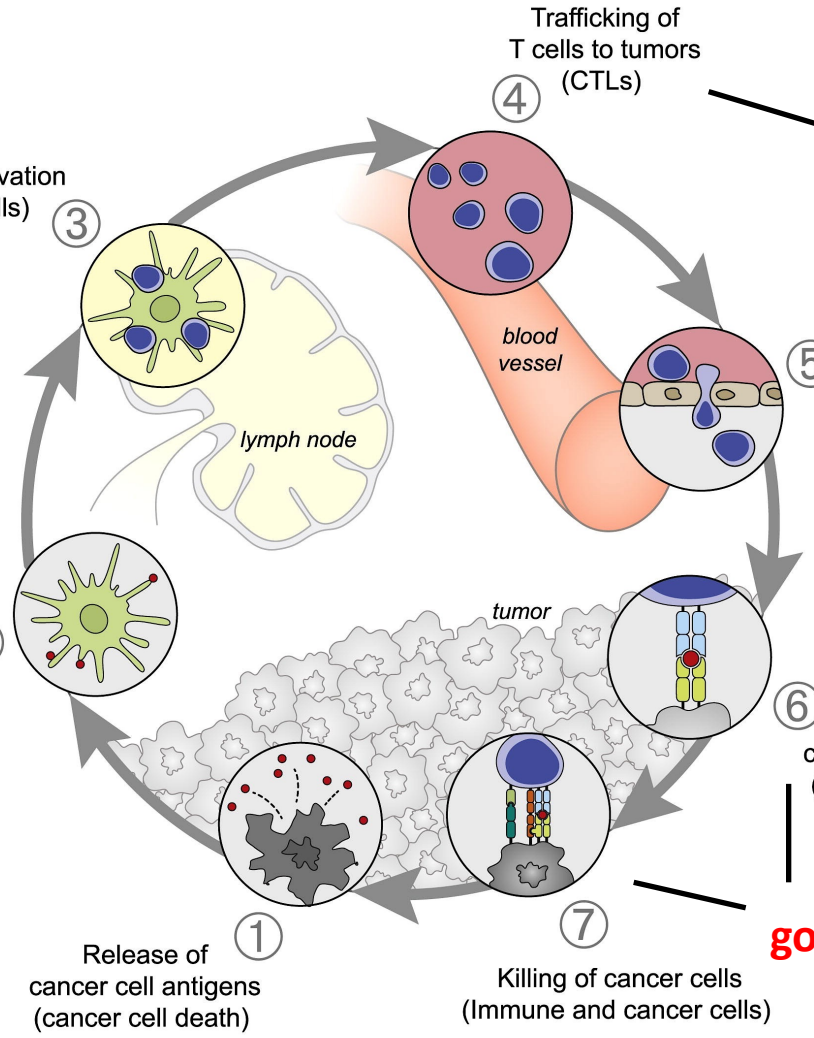
THE CANCER IMMUNITY CYCLE

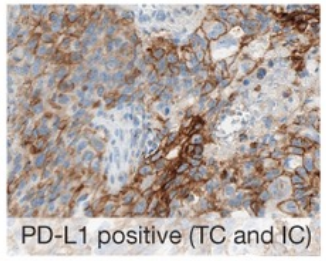




IMMUNE DESERT TUMORS

IMMUNE EXCLUDED TUMORS





INFLAMED TUMORS
good for immunotherapies

IMMUNE DESERT TUMORS ARE TUMORS THAT DON'T PRESENT ANTIGENS

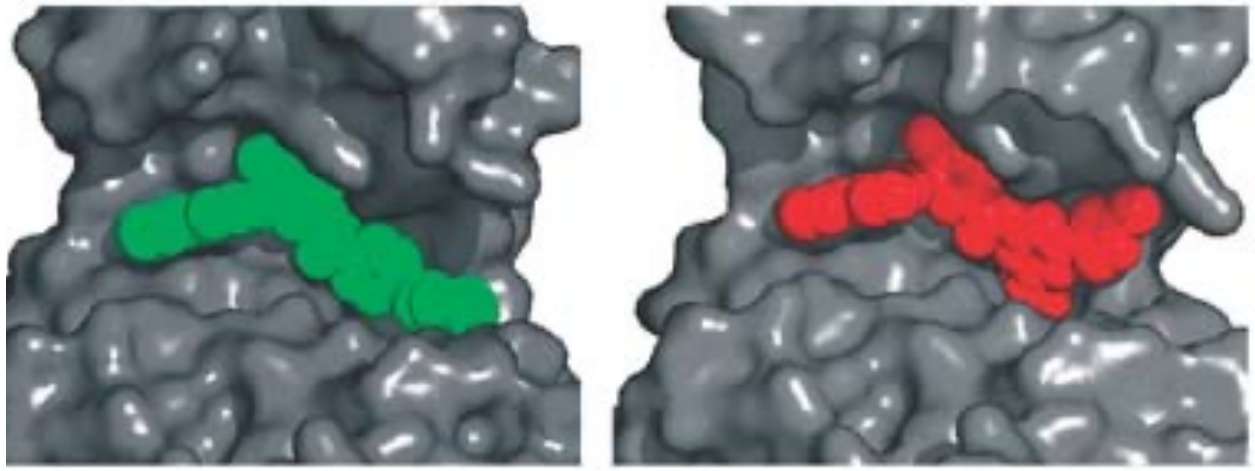
What is different between an immune desert tumor and an inflamed tumor?

An inflame tumor is:

characterized by high mutation rates

Mutate proteins can be recognized as non-self antigen and activate the immune response

TUMOR WITH HIGH LEVELS OF MUTATIONS CAN BE ATTACKED BY THE IMMUNE SYSTEM



WT MUT

Potential attack from the immune system if the mutations change the tridimensional structure of the peptide

COPY NUMBER ALTERATIONS DON'T CHANGE PROTEIN SEQUENCE

Tumors driven by high copy number changes are less immunogenic

Antigen peptides are identical
in tumor and non-tumor cells

HOW THE TUMOR ESCAPE WITH HIGH MUTATION RATE ESCAPE THE IMMUNE RESPONSE

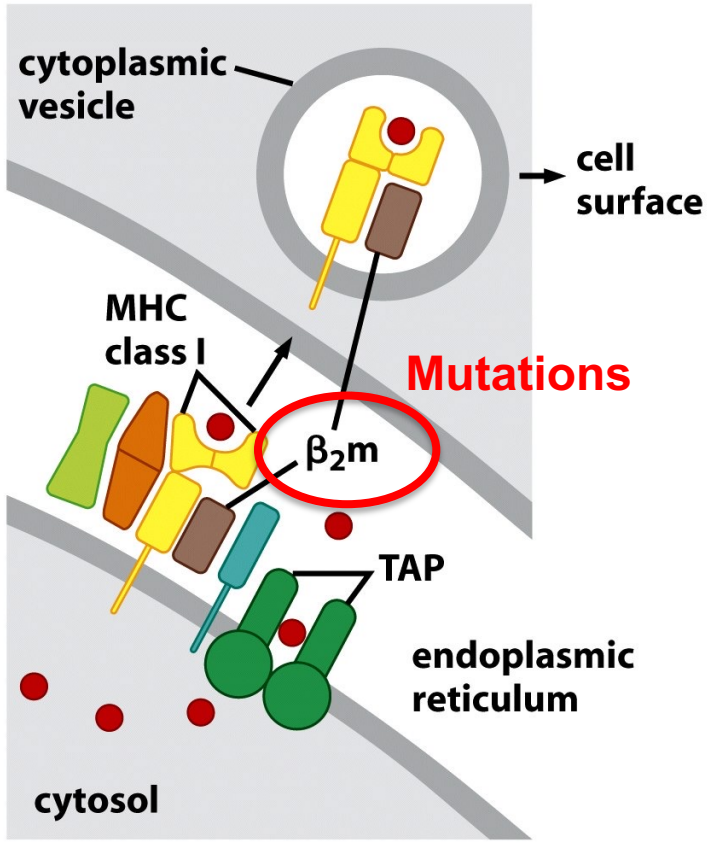
HIDE THE ANTIGEN PRESENTATION: REPRESS/MUTATE MHC class I

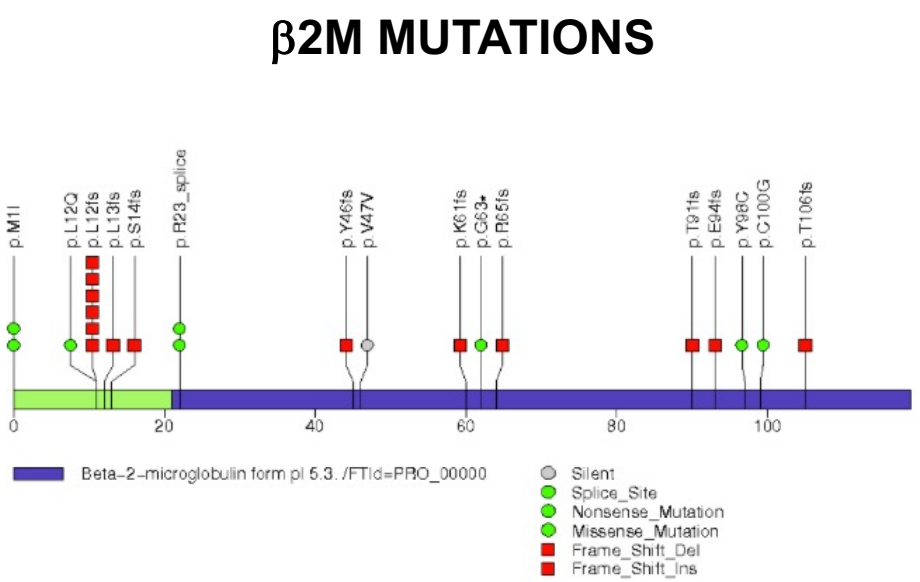
RELEASE INHIBITORY CYTOKINES (IL10 and TGF β)

Mimic the function of Treg cells

HIDE THE ANTIGEN PRESENTATION: REPRESS/MUTATE MHC class

MUTATE β2M or other component of antigen presentation



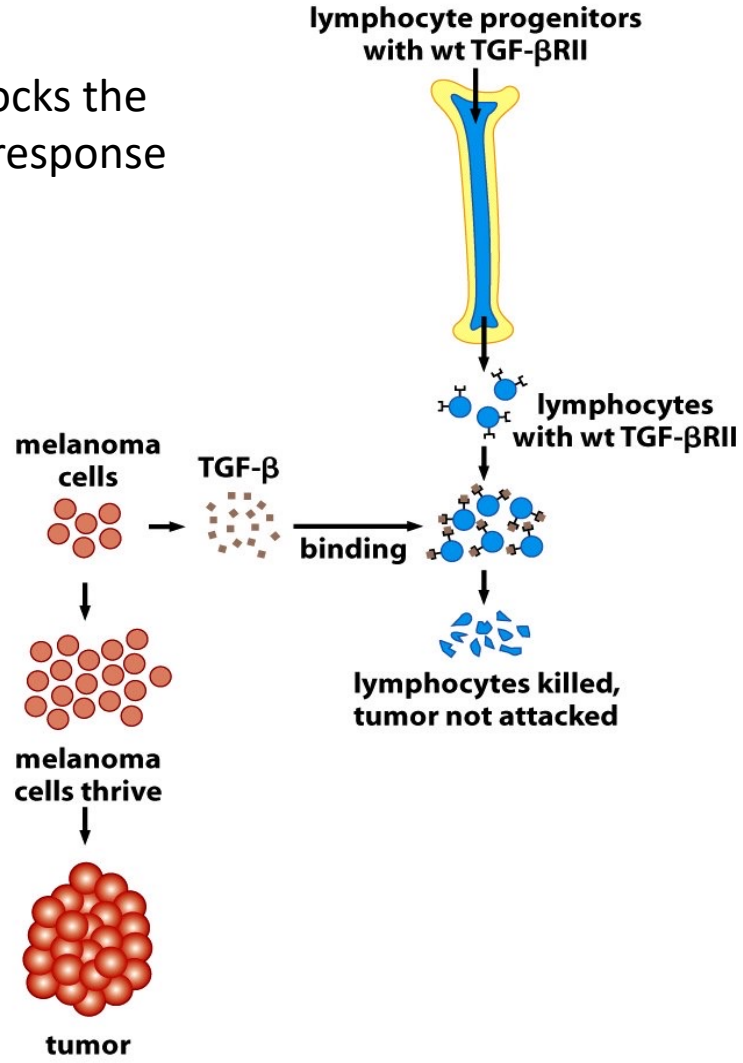


HIDE THE ANTIGEN PRESENTATION: REPRESS/MUTATE MHC class

Repress the expression of MHC-I

RELEASE INHIBITORY CYTOKINES

Tumor blocks the immune-response



lymphocyte without TGF-β receptor

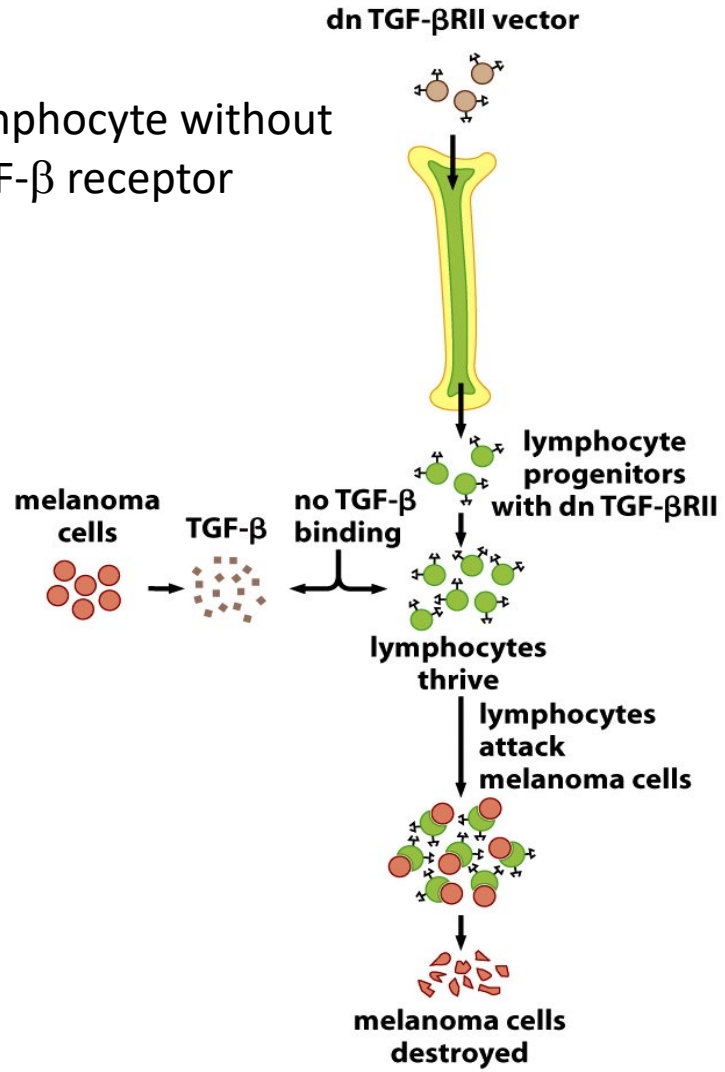
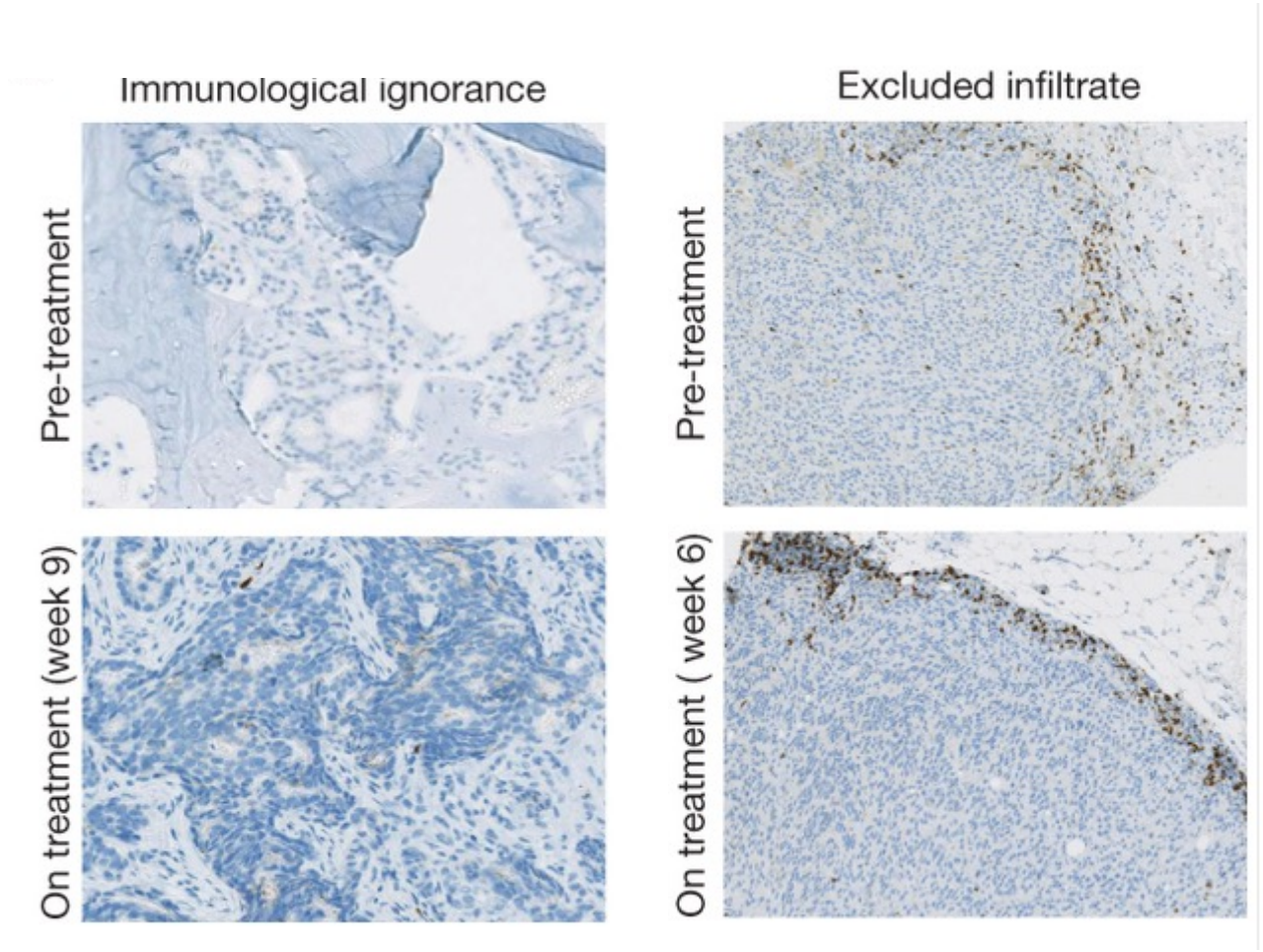


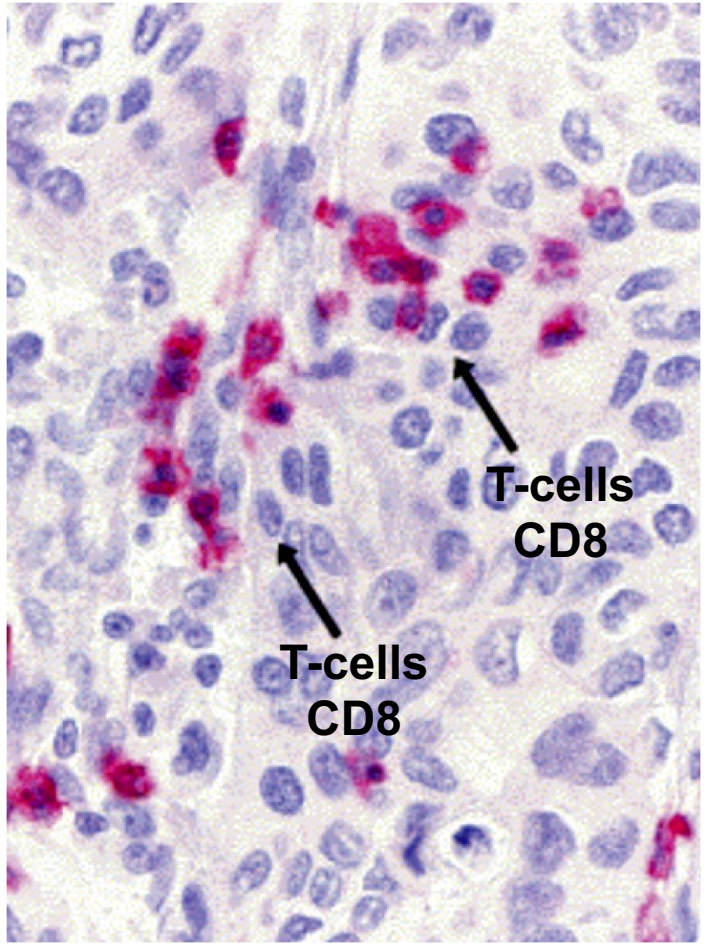
Figure 15.32a *The Biology of Cancer* (© Garland Science 2007)

2. IMMUNE EXCLUDED TUMORS



Cancer cells release factors that maintain immune cell to the periphery

3. INFLAMED TUMORS: TUMOR INFILTRATING LYMPHOCYTES



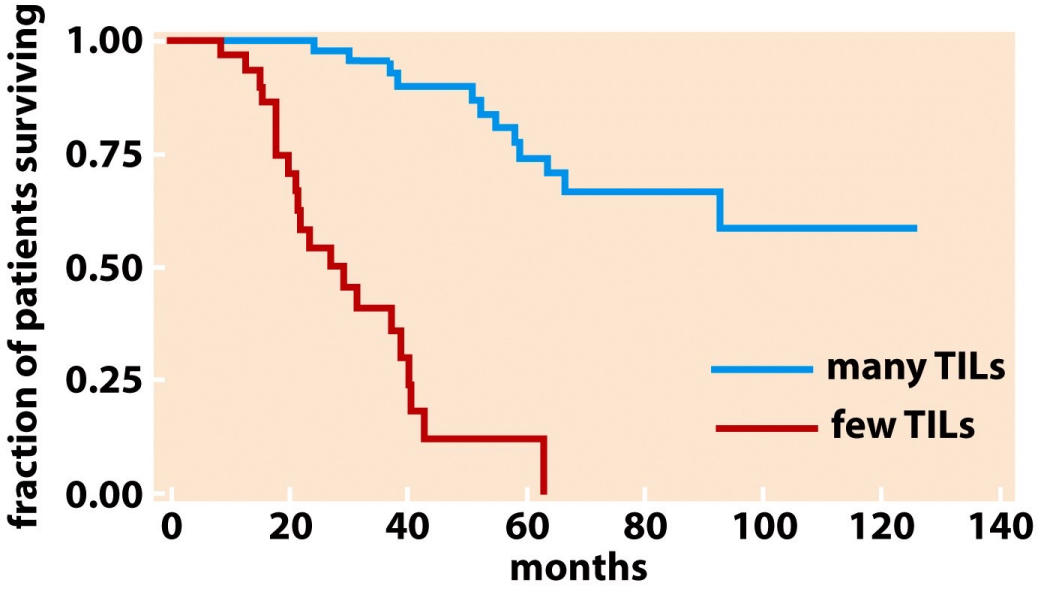


Figure 15.21c *The Biology of Cancer* (© Garland Science 2007)

MOBILIZE THE IMMUNE SYSTEM

Immune checkpoint inhibitors

Immune cell engineering: mainly T cells, but NK and Dendritic cells are also largely studied

Activate the immune system to attack the tumors

ACTIVATE T CELLS: CHECKPOINT INHIBITORS

ANTIBODIES THAT INHIBIT THE IMMUNE SUPPRESSIVE ACTIVITIES AND INDUCE ACTIVATION OF T-CELLS

anti-CTLA4 (Ipilimumab)= **Cytotoxic T-lymphocyte-associated antigen 4**

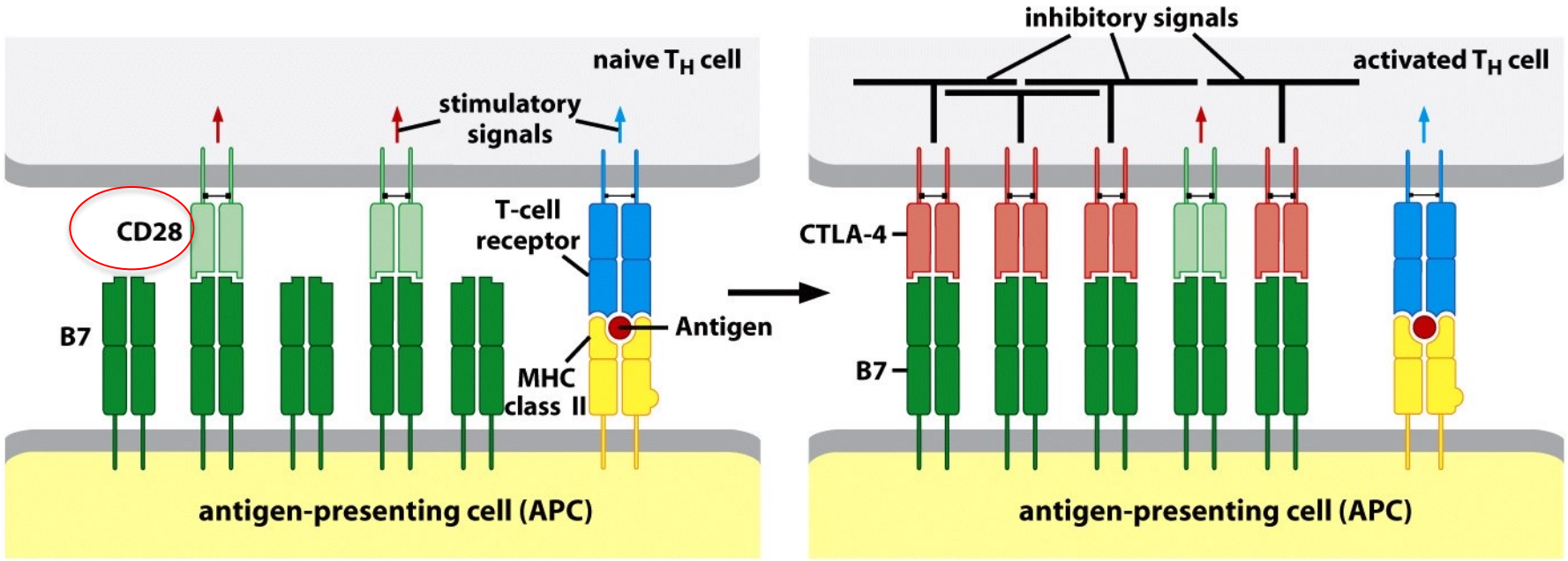
anti-PD1**= Programmed cell death protein 1**

or

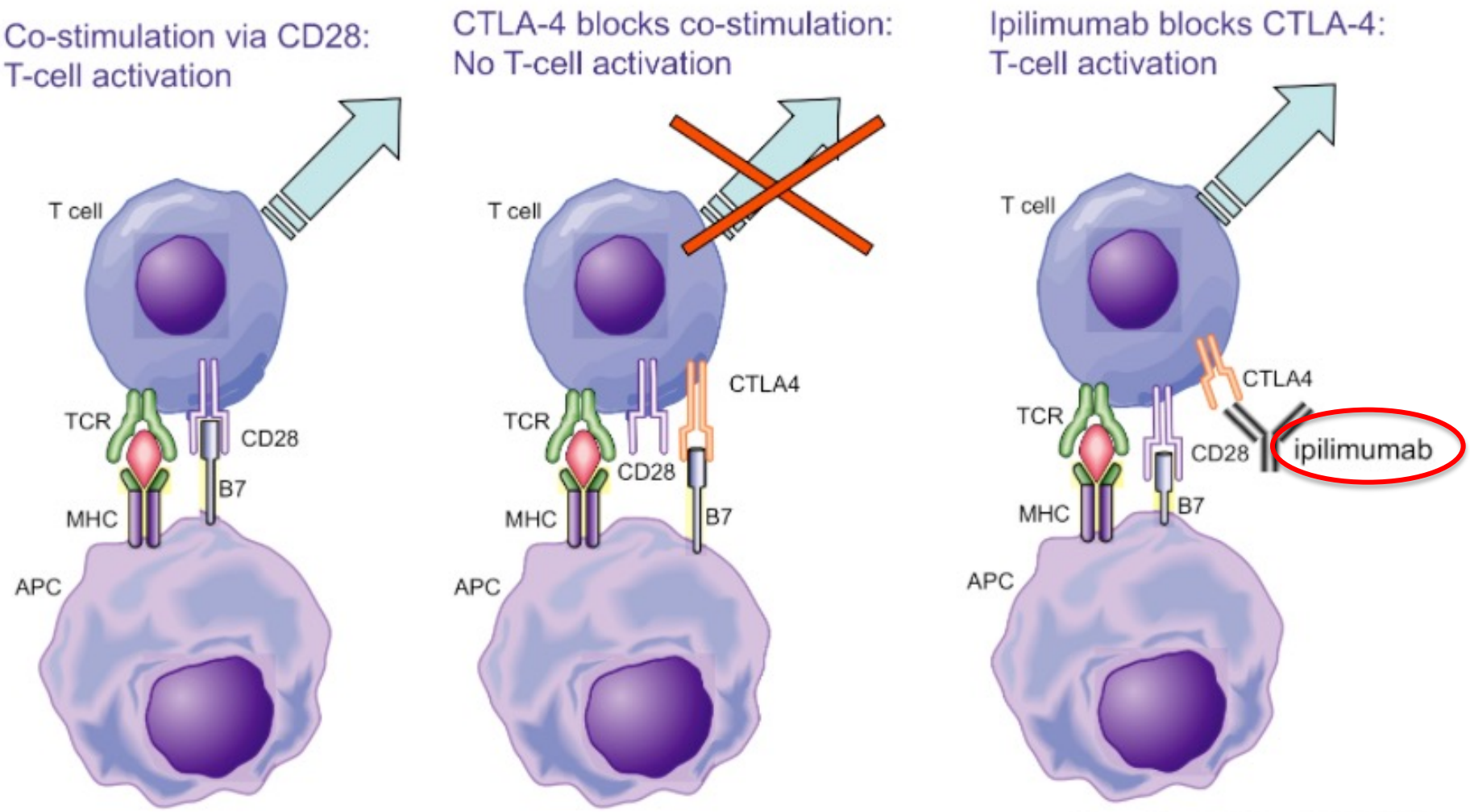
anti-PDL1**= Programmed cell death protein 1 Ligand**

http://www.nature.com/nrc/journal/v12/n4/pdf/nrc3239.pdf
(a review if you want to read more details)

CTLA4 BLOCKS T CELLS ACTIVATION



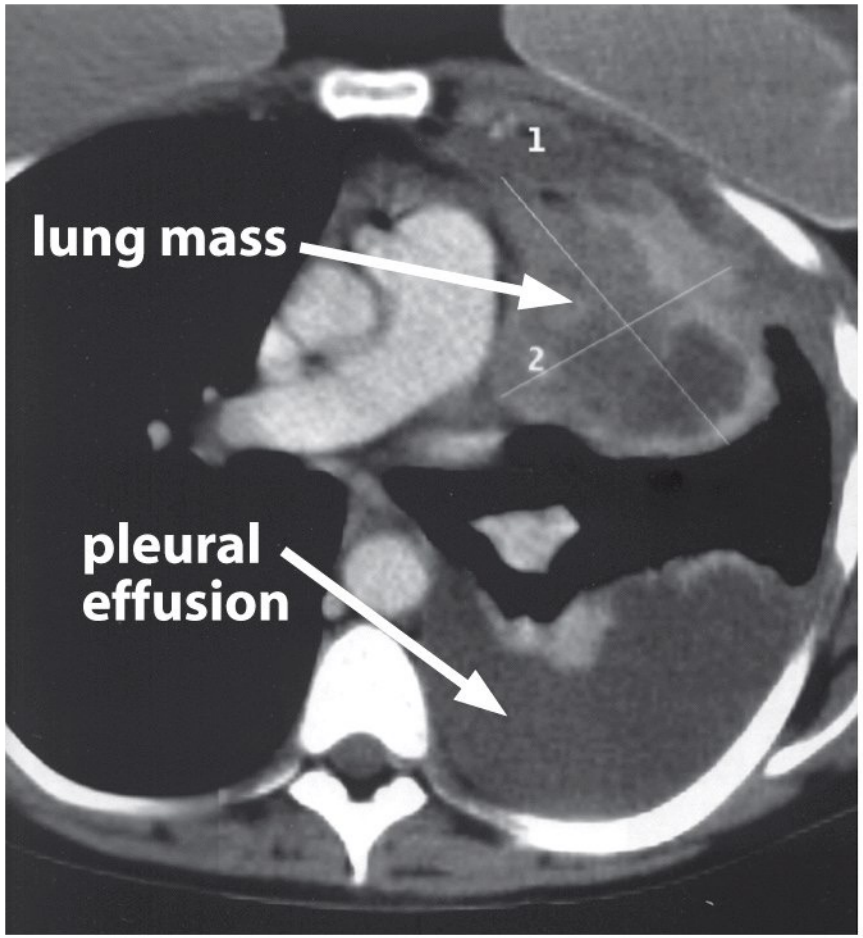
ANTI-CTLA4 INDUCES T-CELLS ACTIVATION



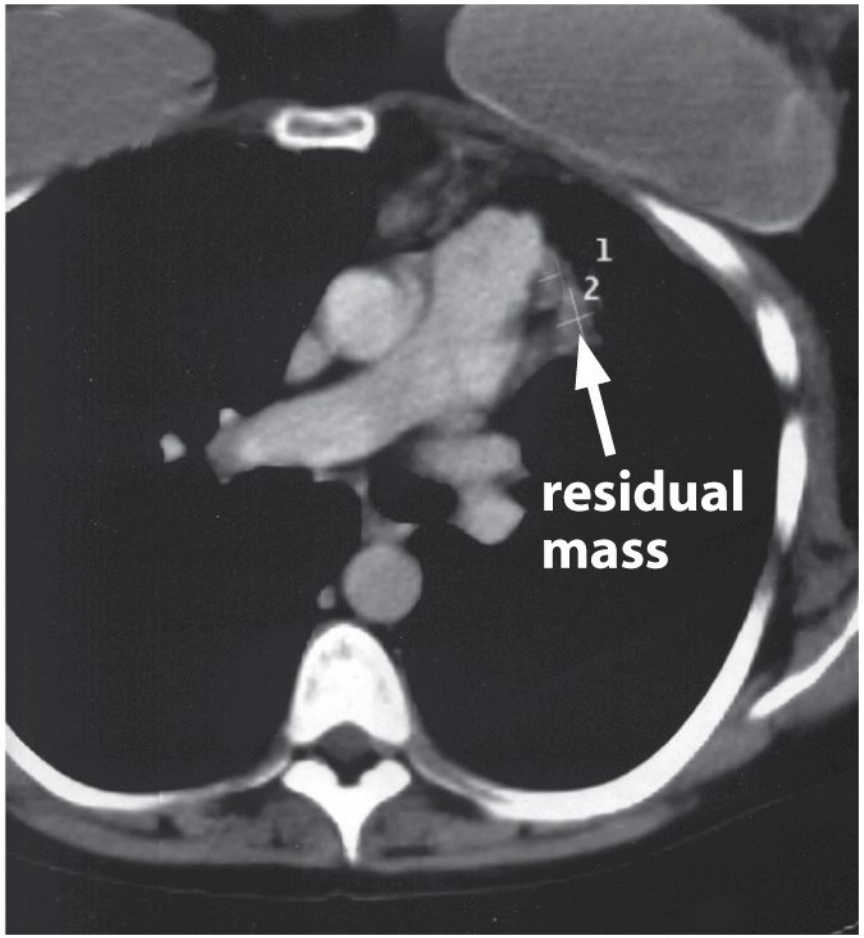
Adapted from Lebbé et al. ESMO 2008

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

ANTI-CTLA4 TUMOR RESPONSE



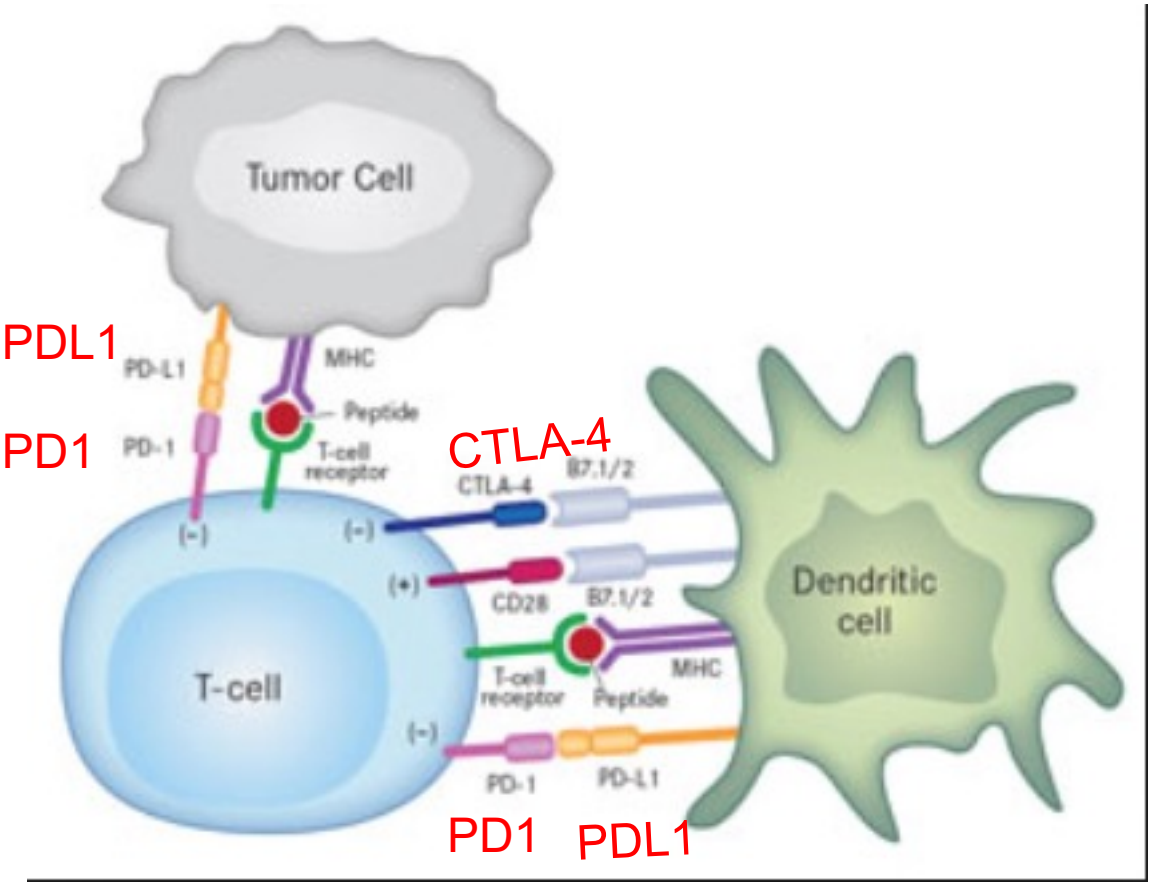
pre-treatment



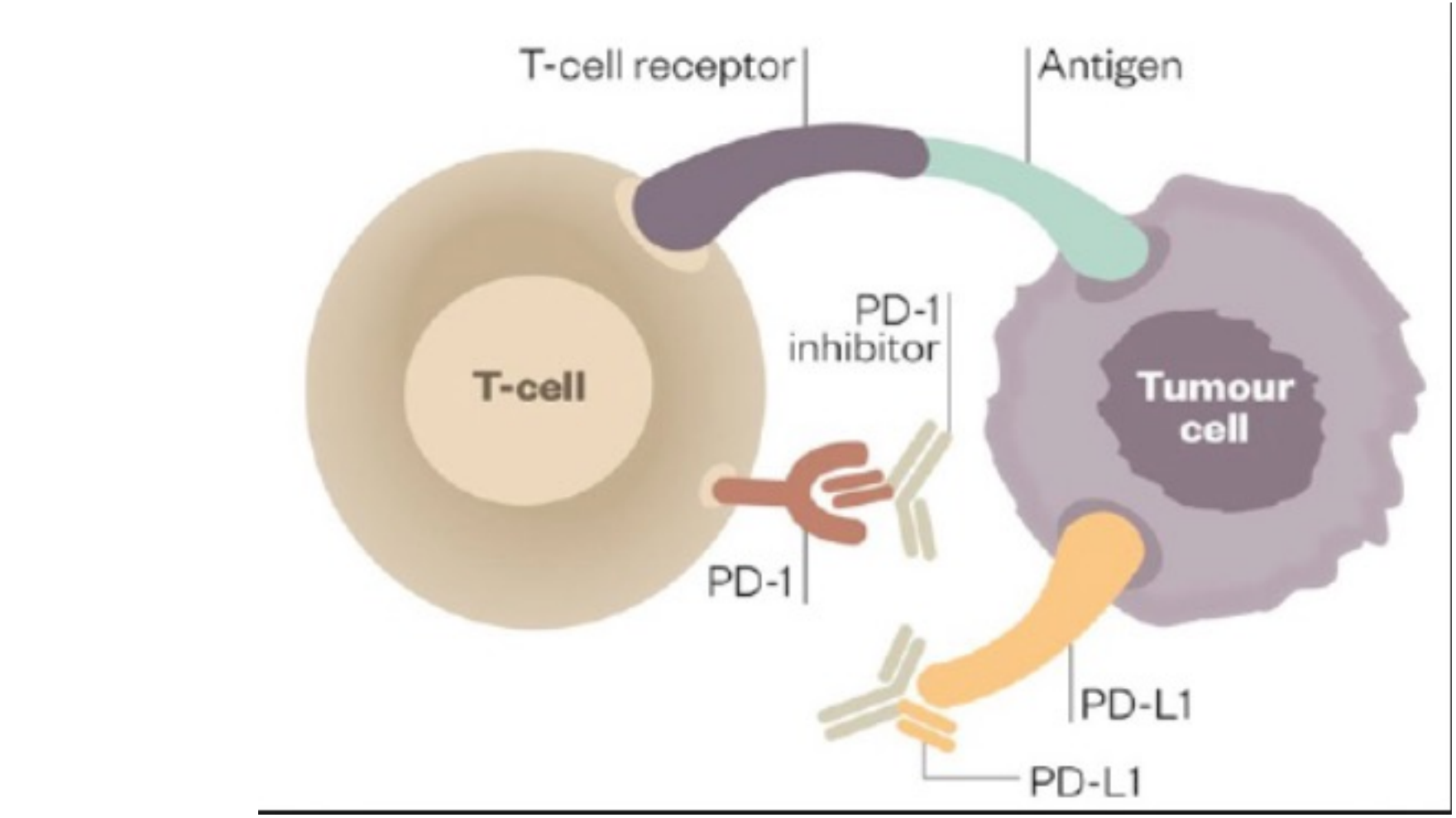
5 months post-treatment

PD1/PDL1 signal

Inhibitory signal

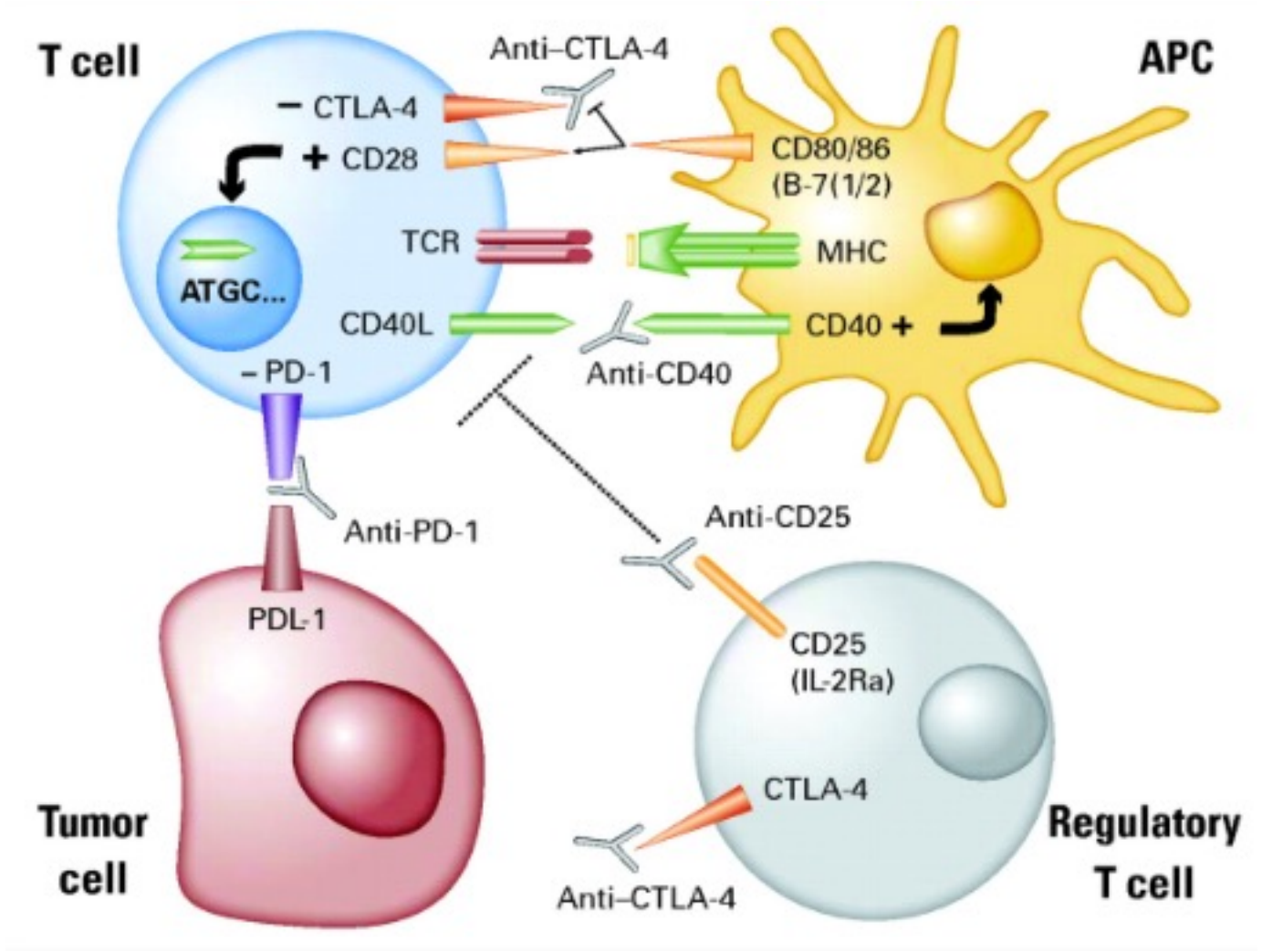


anti PD1 and anti-PDL1

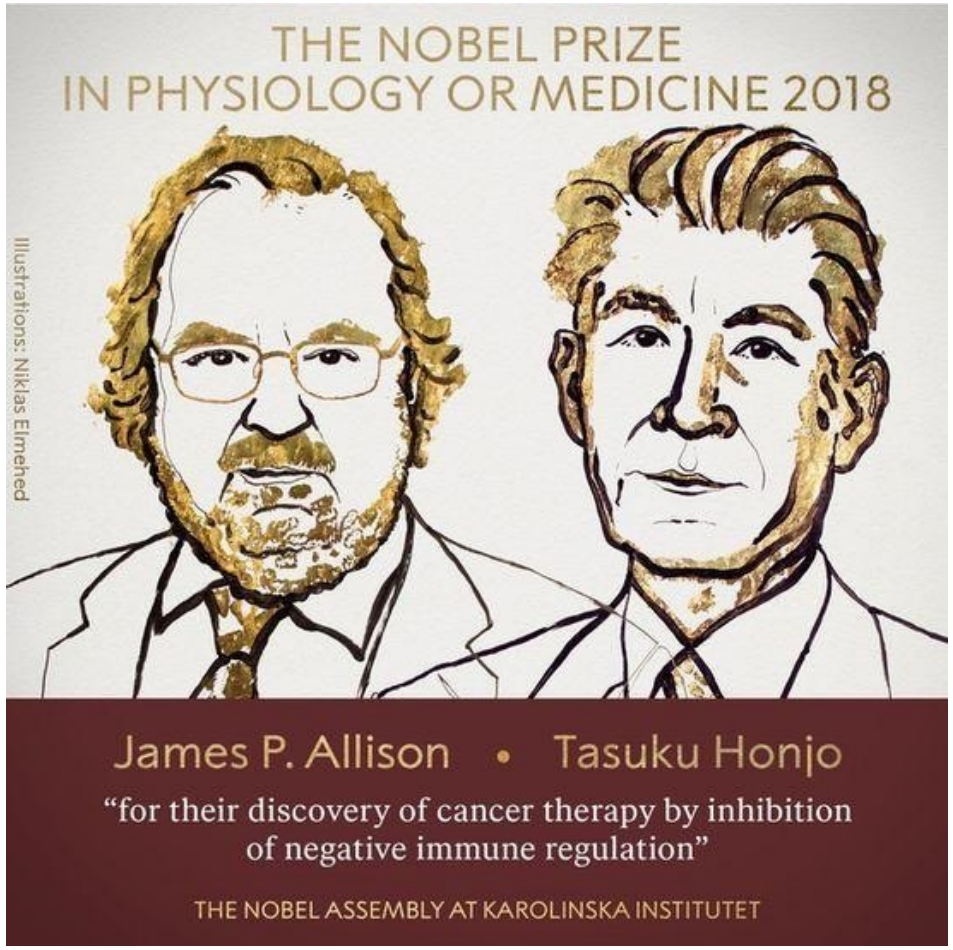


anti-PD1 = binds receptor on T-cells
anti-PDL1 = binds the ligand on tumor cells

anti-PD1/PDL1 and anti-CTLA4

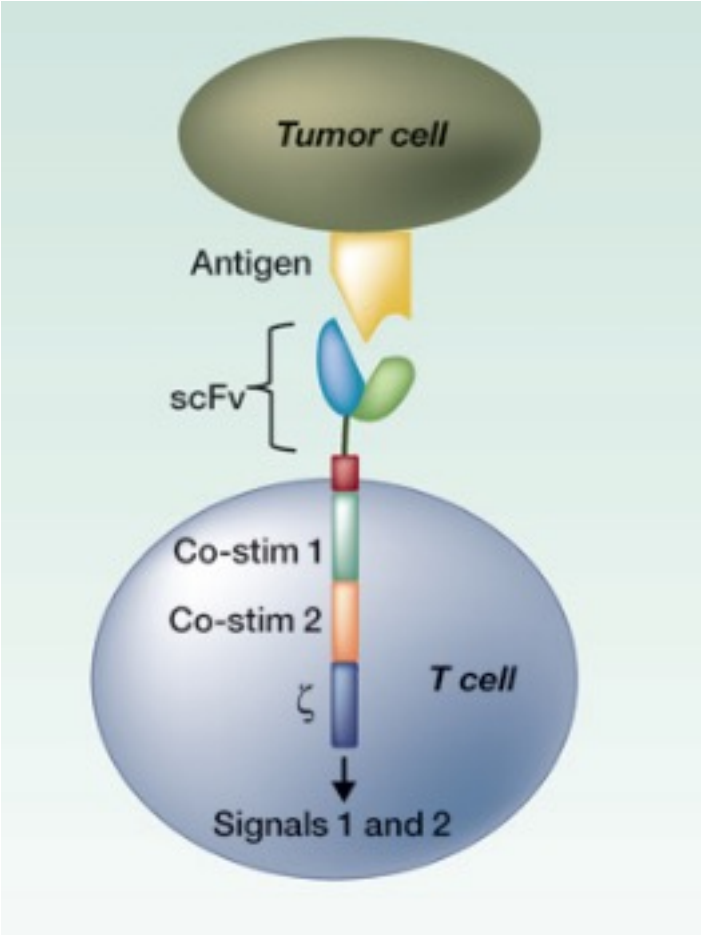


Cover of the year, 2013



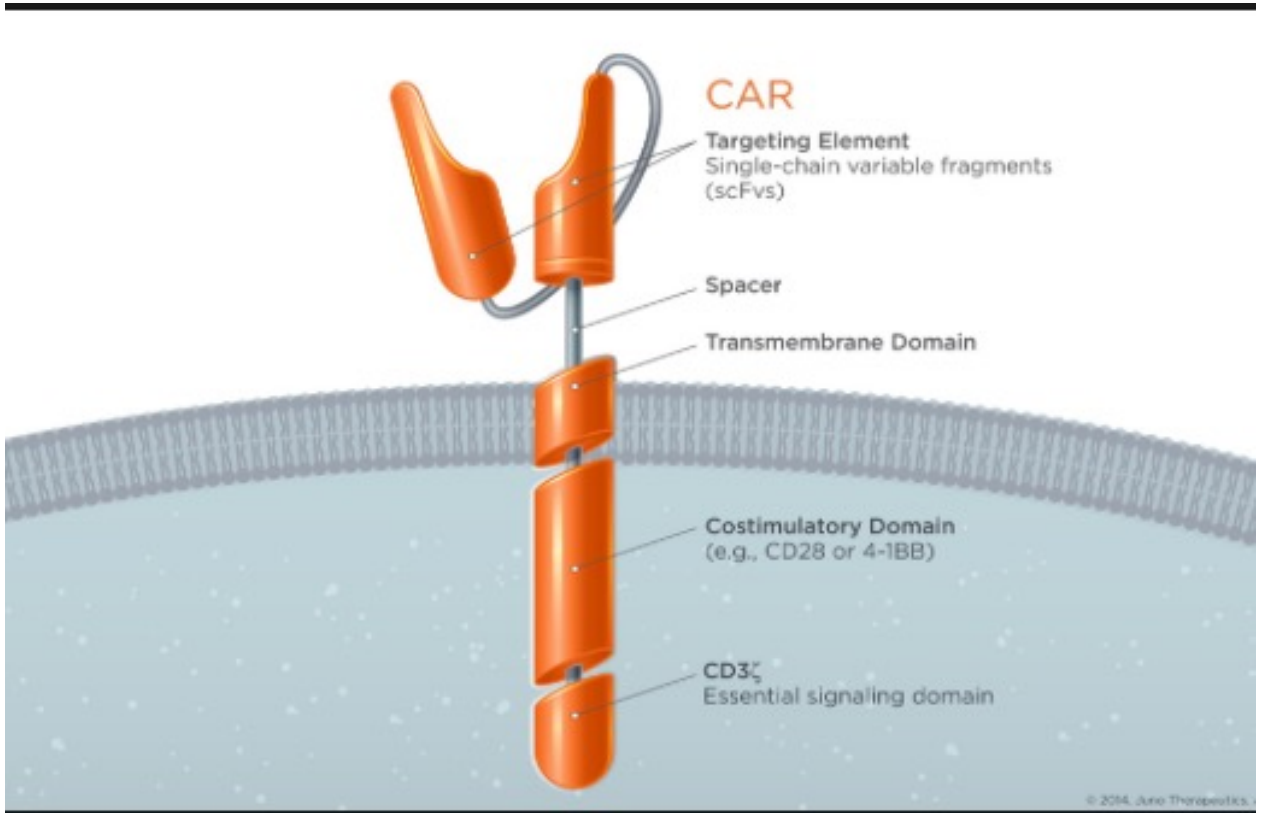
Nobel Prize, 2018

GENETICALLY ENGINEERED T-CELLS

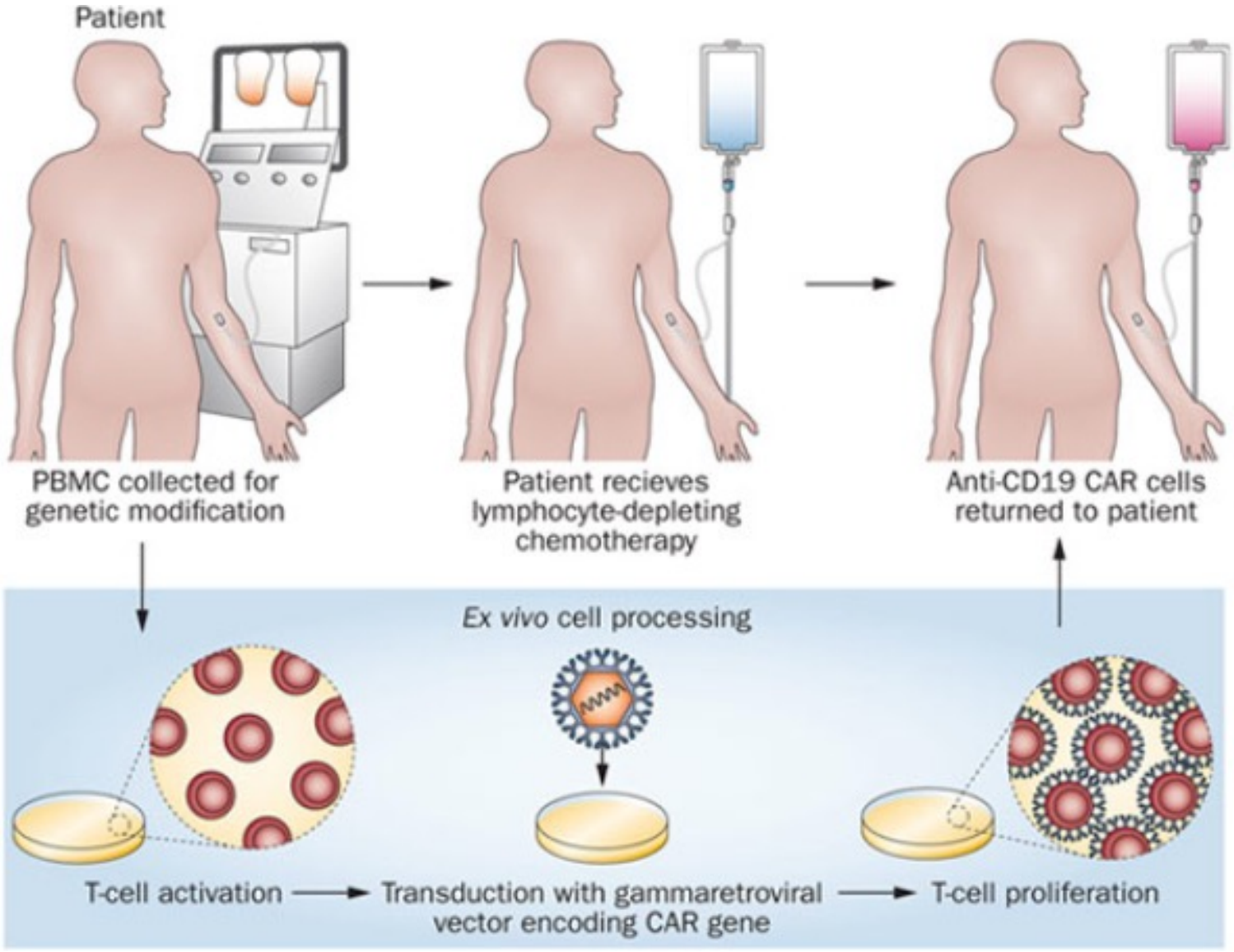


Express an exogenous stimulatory receptor in T-cells,
that it will recognize the antigen on tumor cells and activates T-cells

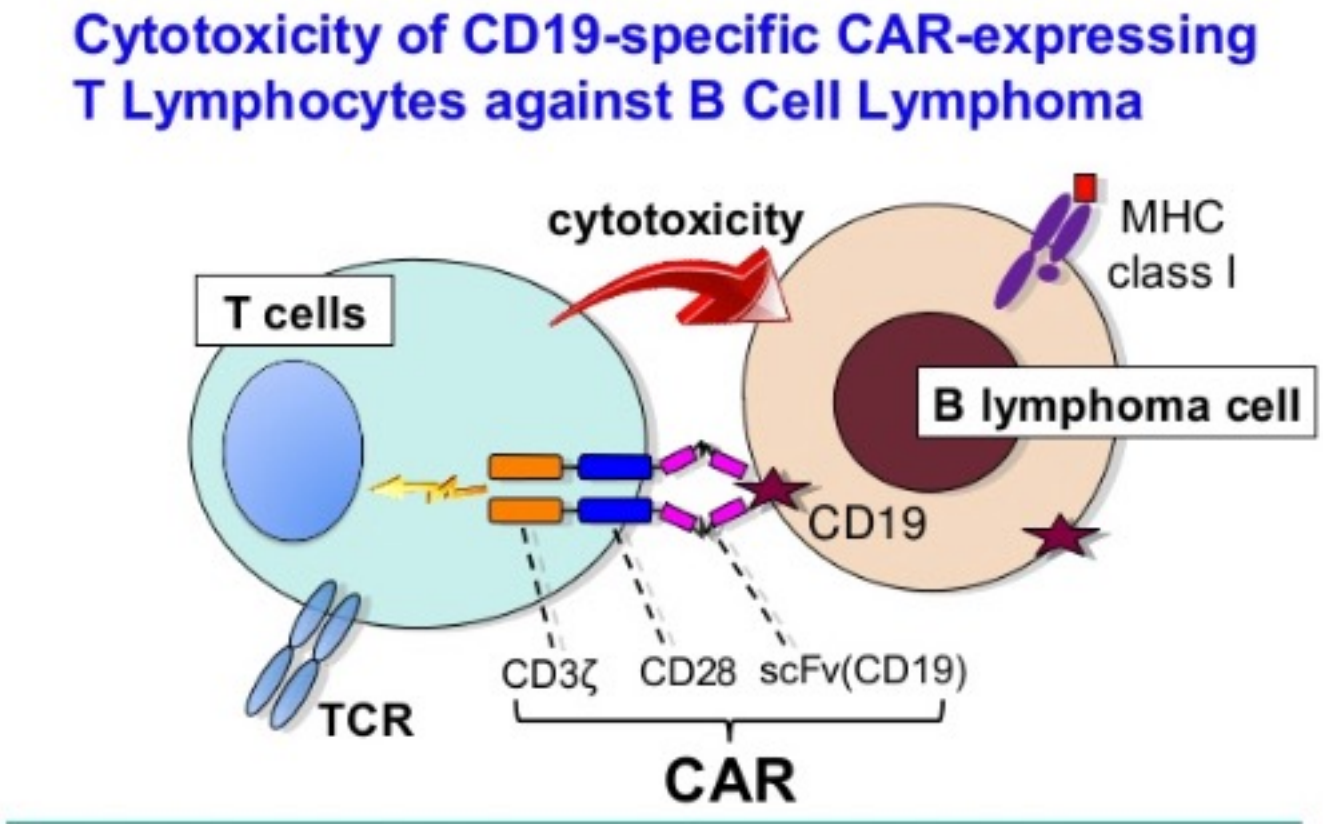
Synthetic receptor is called-CAR



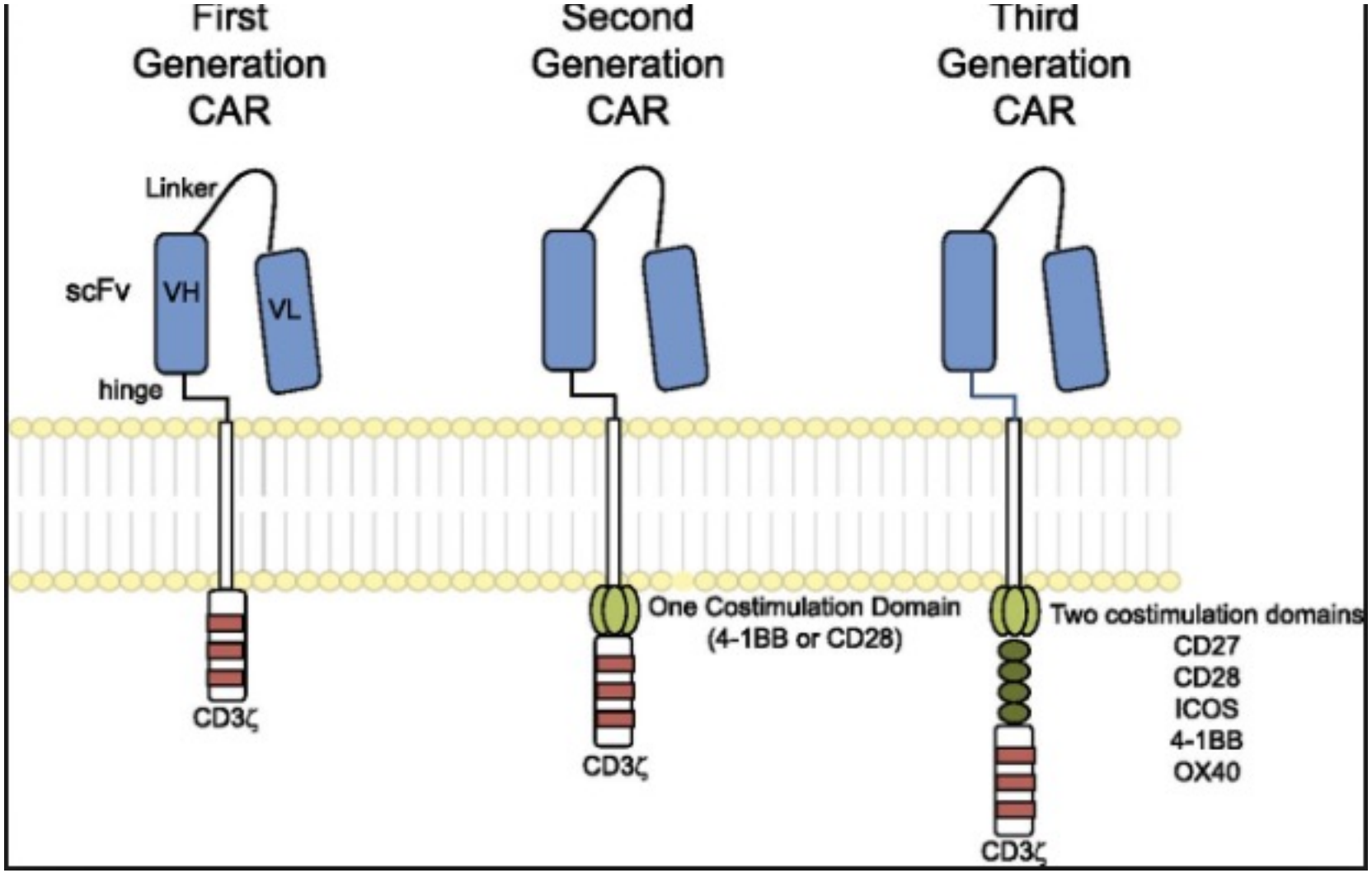
CAR-T cells Therapy



CD19 CAR-T cells therapy for B-cell malignancies



CD19 CAR-T cells Therapy



The first patient treated with CAR-T cells

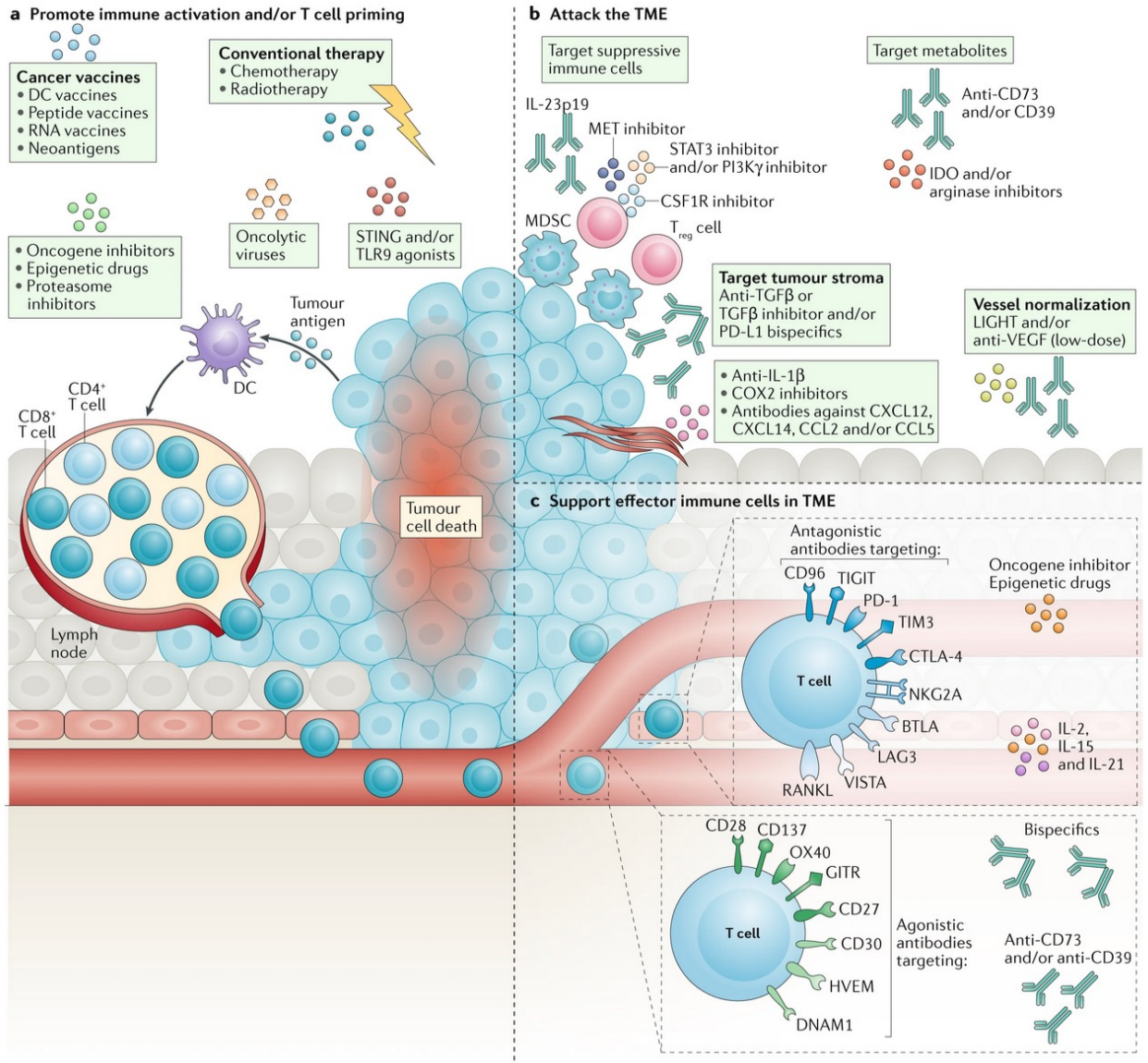
Carl June, MD
UPenn

http://www.nytimes.com/2012/12/10/health/a-breakthrough-against-leukemia-using-altered-t-cells.html?_r=0
https://emilywhiteheadfoundation.org/news/celebrating-10-years-cancer-free/

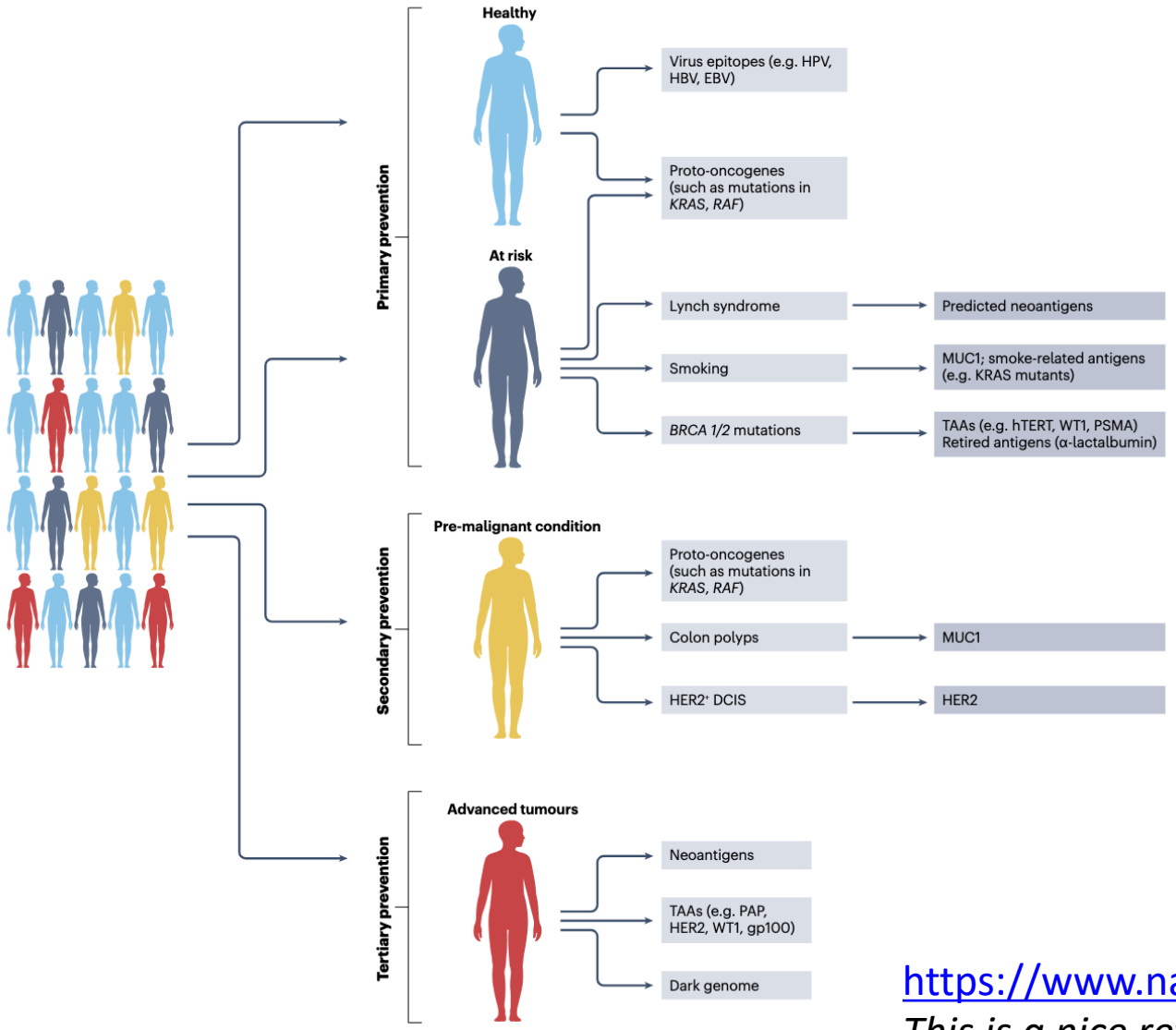
CANCER IS A DISEASE THAT RAPIDLY EVOLVED: MECHANISMs OF RESISTANCE, and COMBINATION THERAPIES

Fig. 3: Essential targets for combination immunotherapies.

From: Cancer immunoediting and resistance to T cell-based immunotherapy



PREVENTIVE CANCER VACCINE: Prevent tumor development using specific antigens



https://www.nature.com/articles/s41573-024-01081-5

This is a nice review published 3 days ago if you want to Know more about cancer vaccine

Exercise:

Discussion of the paper

https://www.cell.com/cell/fulltext/S0092-8674(17)31322-3