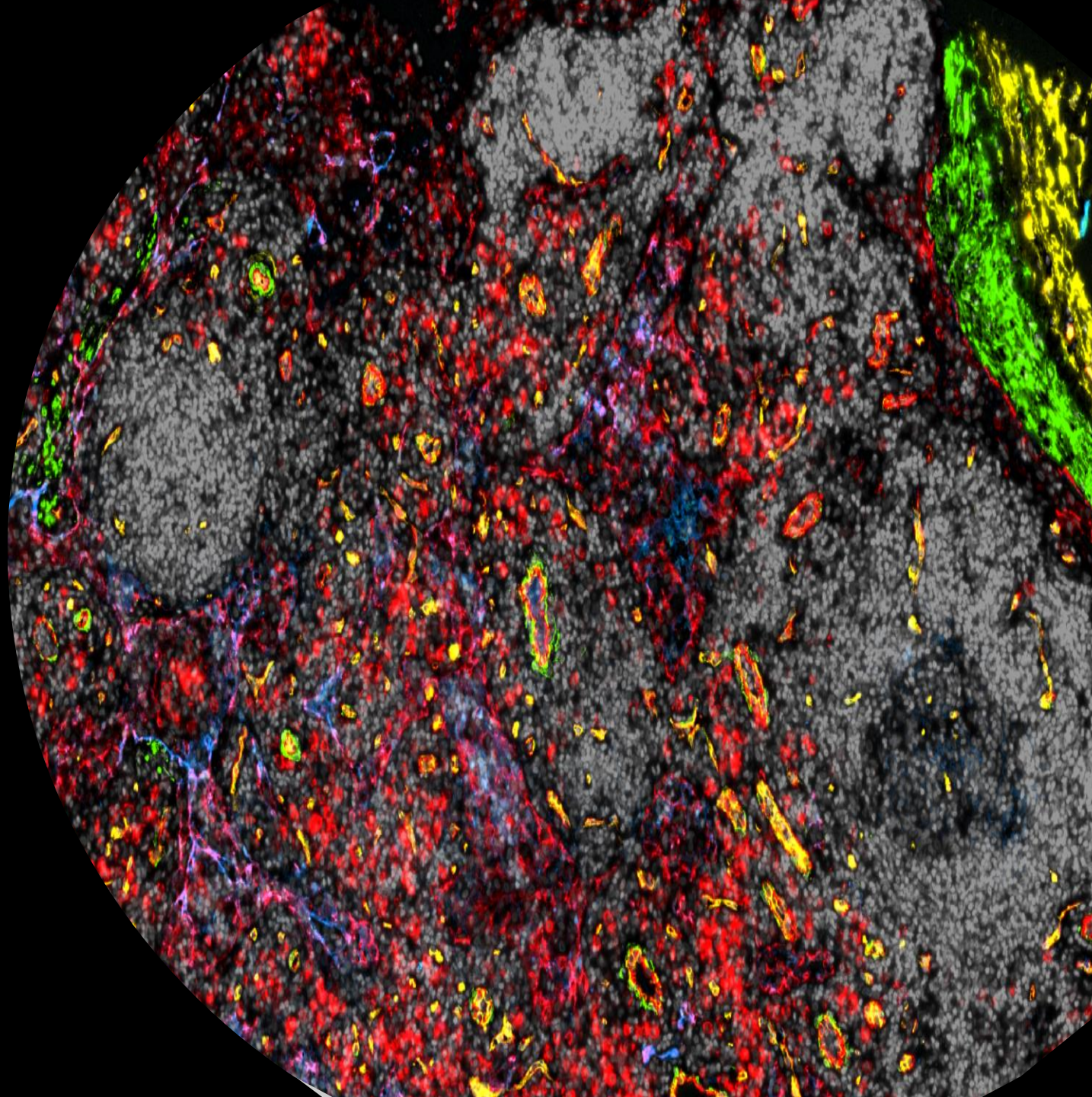
Cancer Biology I

Part-II

Week 12



AGENDA

Nov 3rd: Cancer genomics- mutations

Nov 10th: Cancer genomics-copy number alterations, heterogeneity, tumor evolution

Nov 17th: Cancer Epigenetics- chromatin 3D structure, cell plasticity

Nov 24th: – Major signaling pathways leading to cancer

Dec 1st: Cancer Therapies – chemo and targeted therapies

Dec 8th: Introduction to immunotherapies

Dec 15th: discussion of unclear points and career development discussion towards a PhD

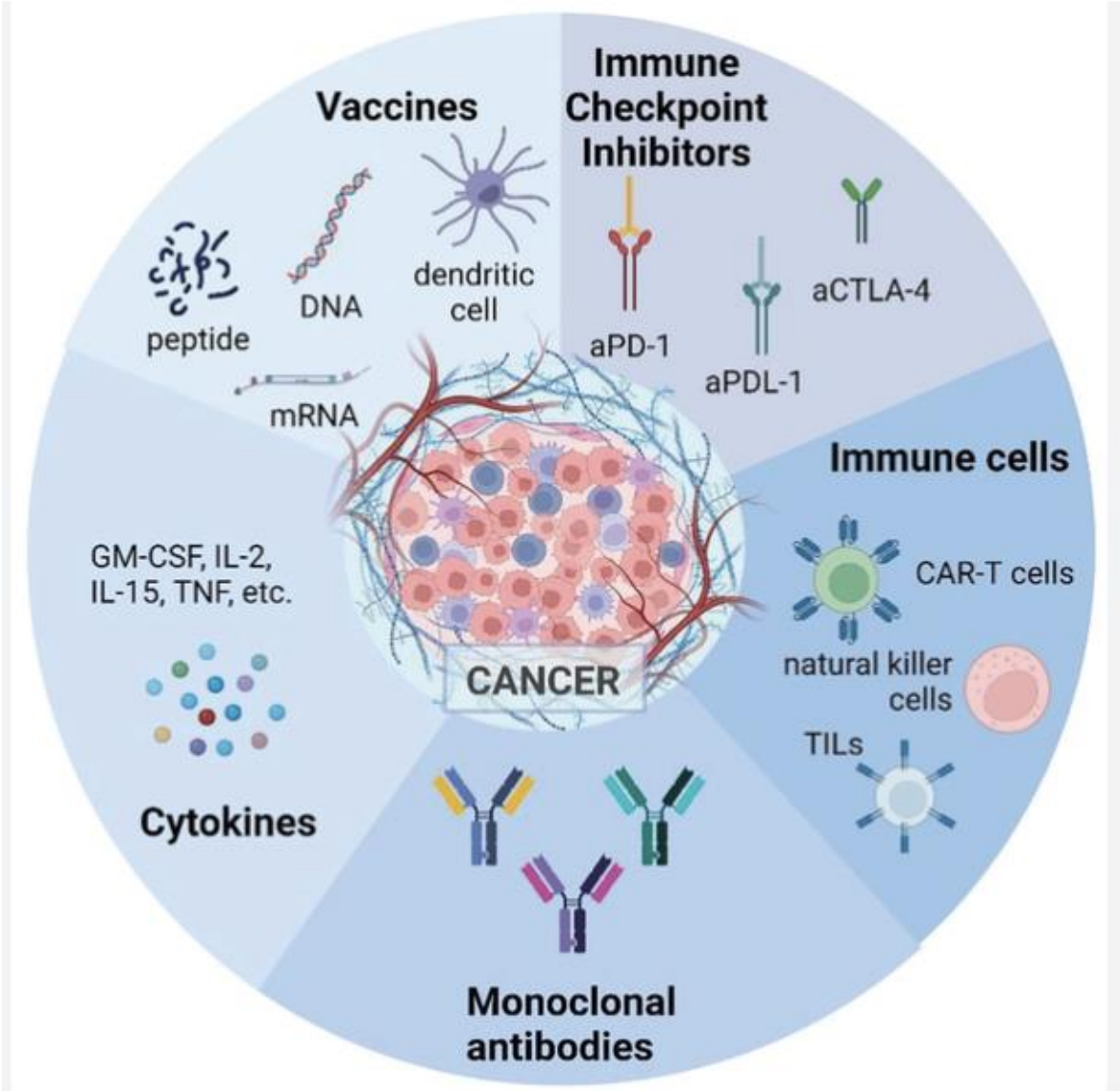
Dec 17th: Exam 2-4 PM – **GC A3 30**

CANCER IMMUNOTHERAPIES

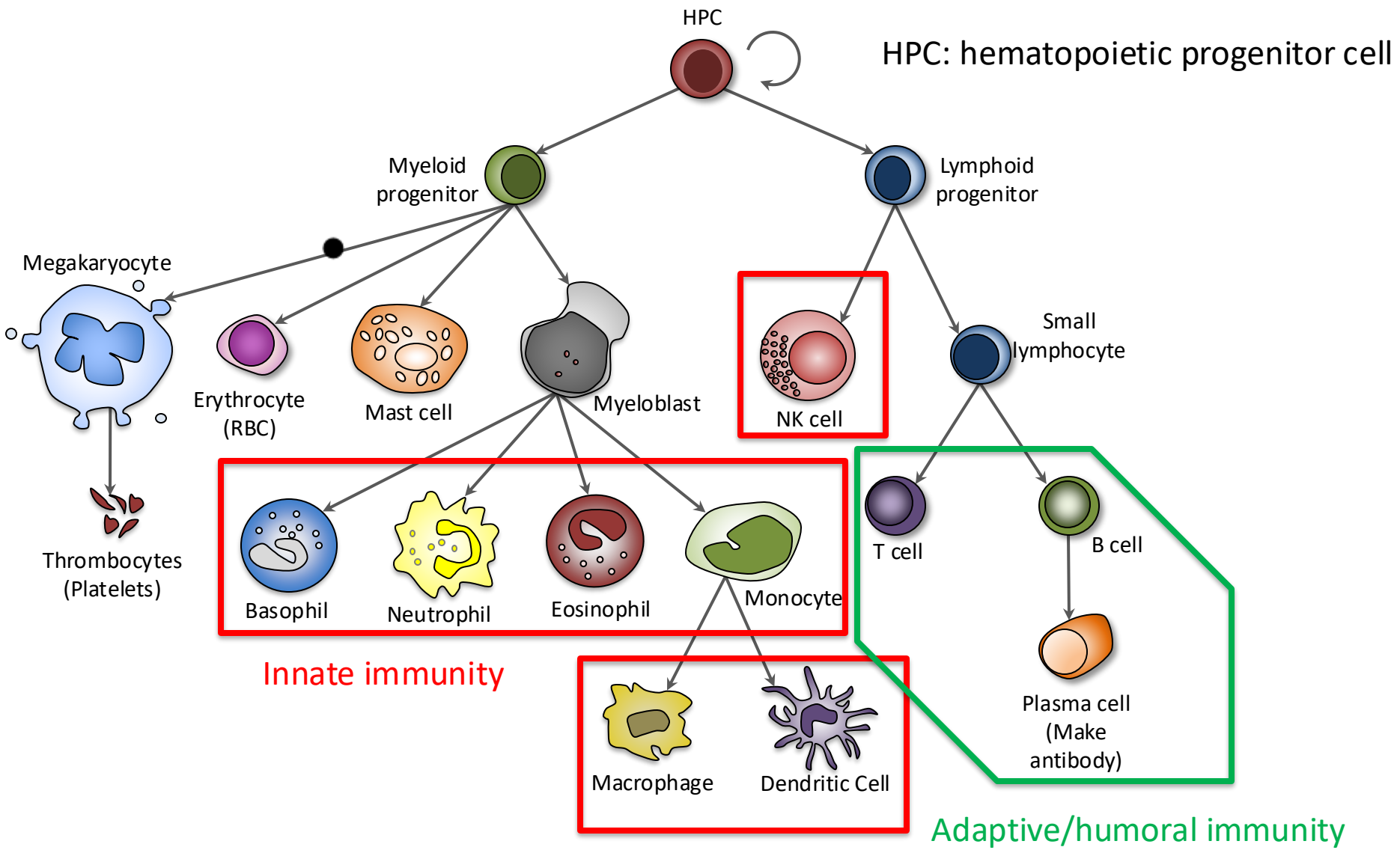
What is the GOAL/ or the principle for the design of cancer immunotherapies?

Activate the immune-system to recognize and kill the tumor

CANCER IMMUNOTHERAPIES: VARIOUS POSSIBILITIES

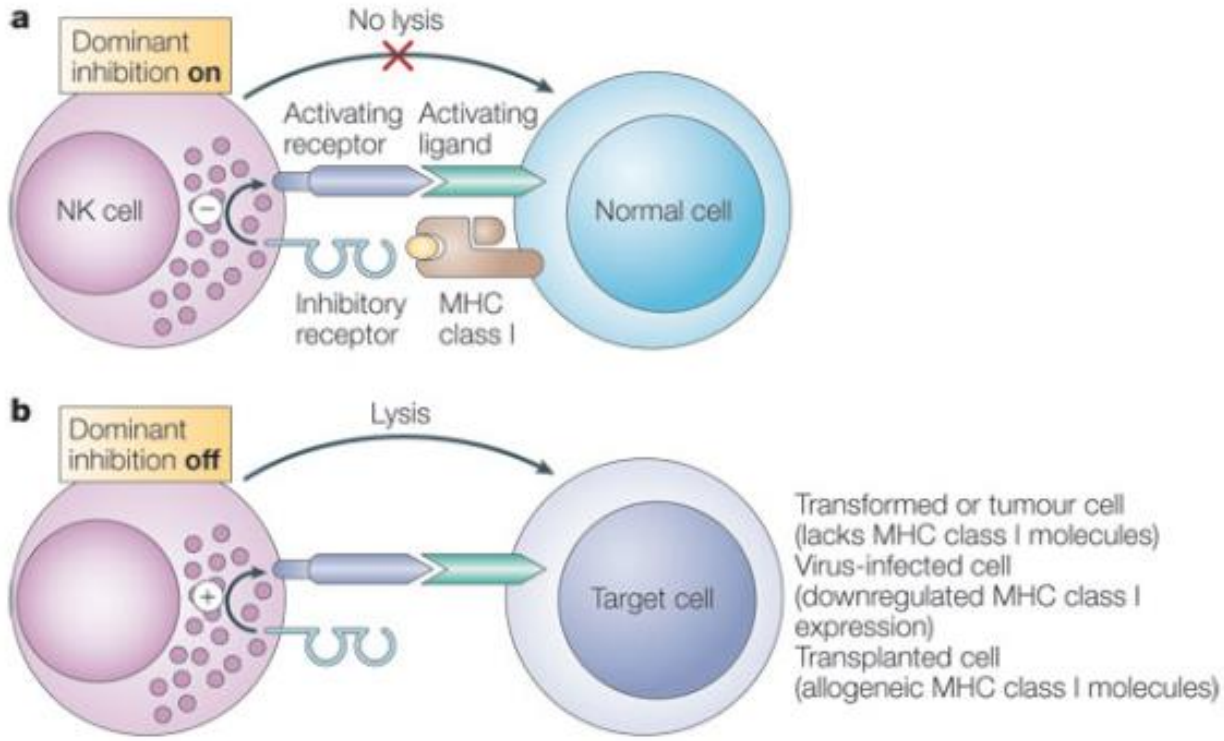


IMMUNE SYSTEM

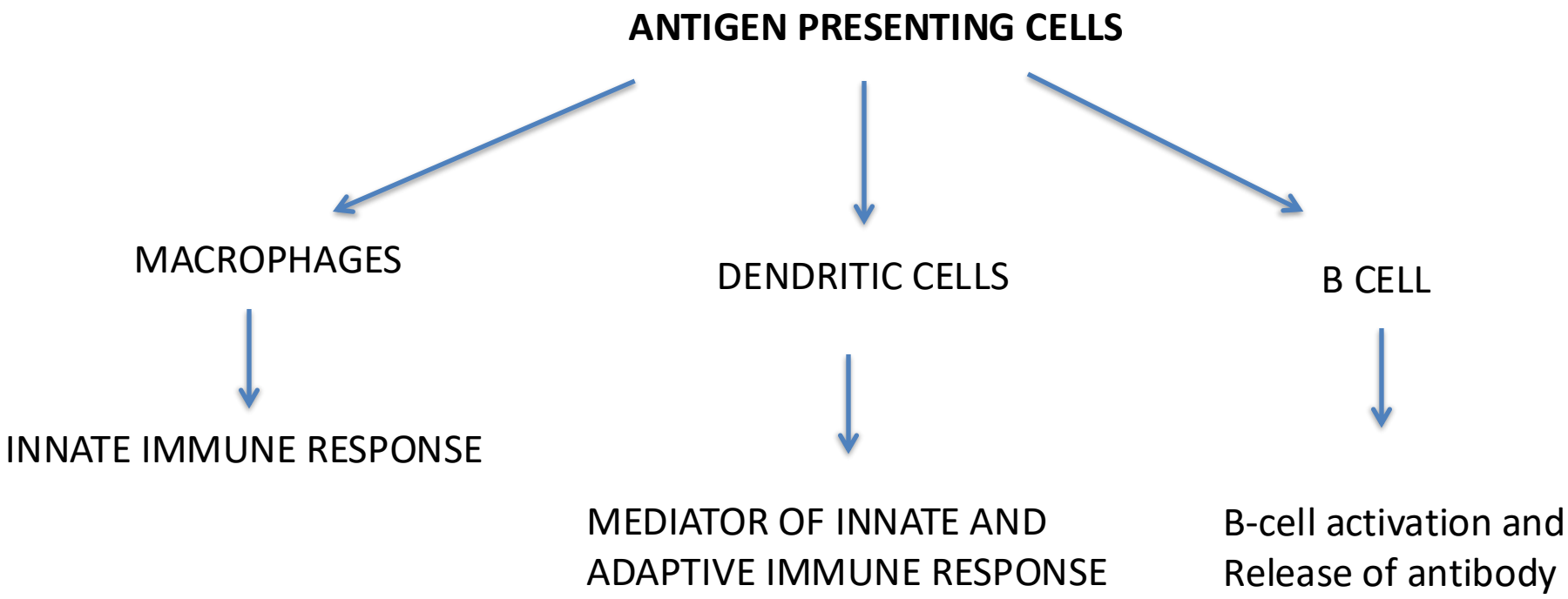


NK cells (Natural Killer cells): Cytotoxic lymphocytes

Innate Immune response (rapid response to viral infection)

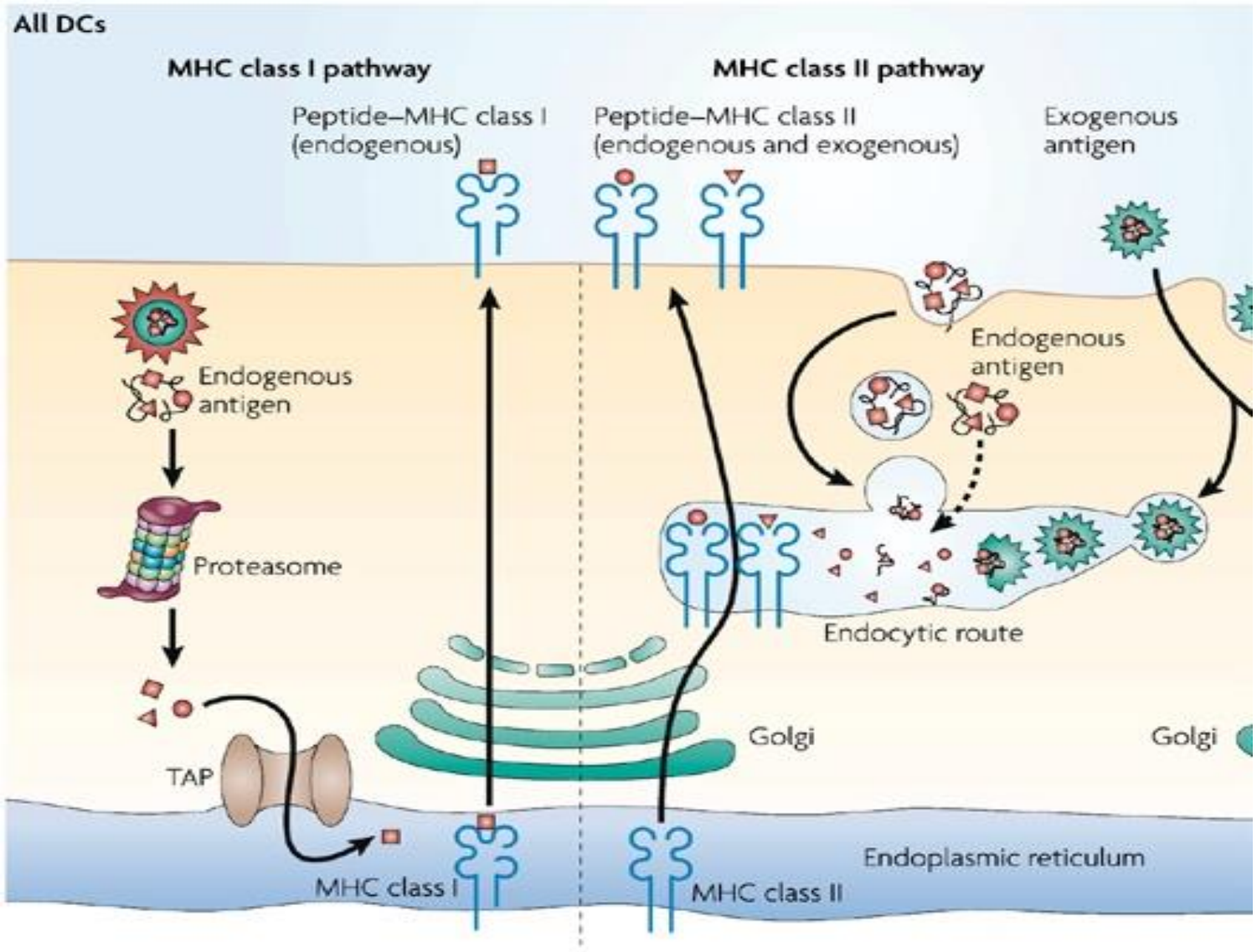


IMMUNE SYSTEM: ANTIGEN Presenting cells



WHAT DOES IT MEAN ANTIGEN PRESENTING CELLS?

ANTIGEN PRESENTATION: MHC



ANTIGEN PRESENTATION: MHC I

ALL CELLS IN OUR BODY

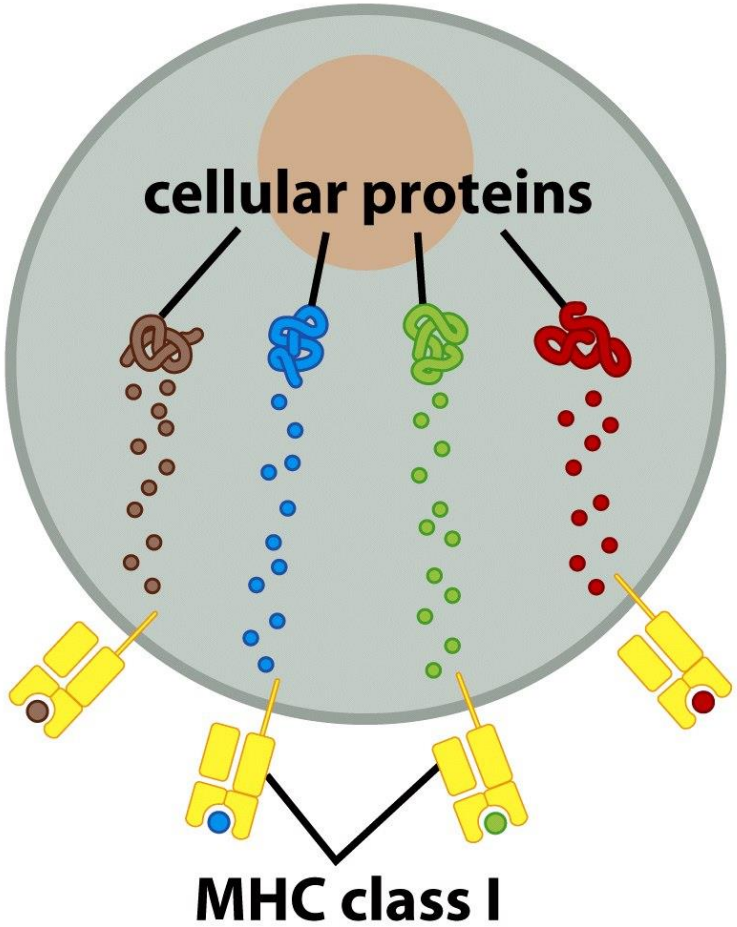
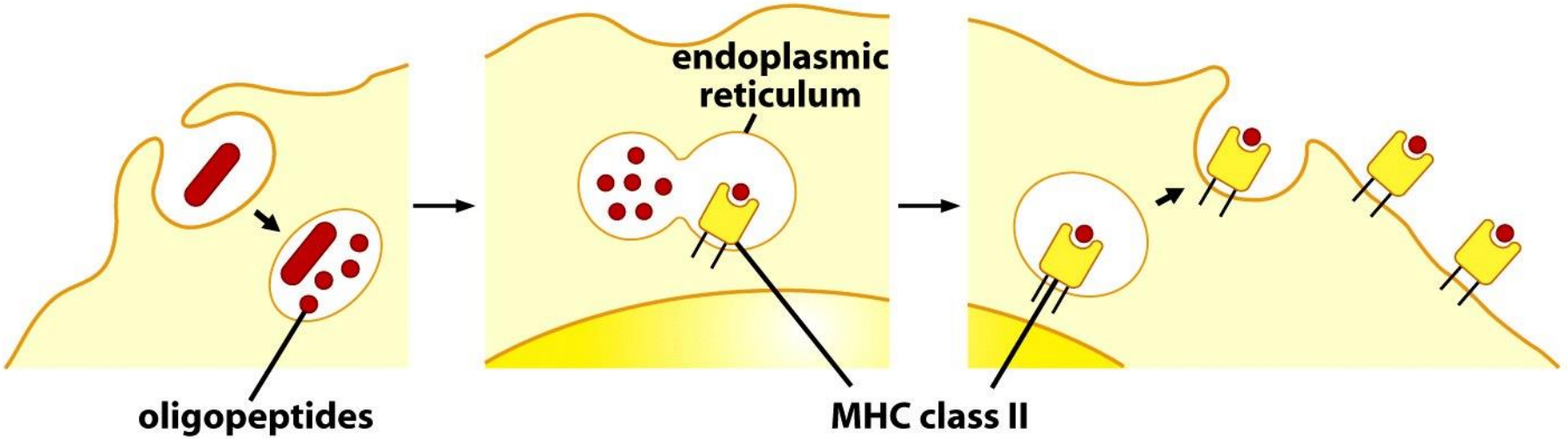


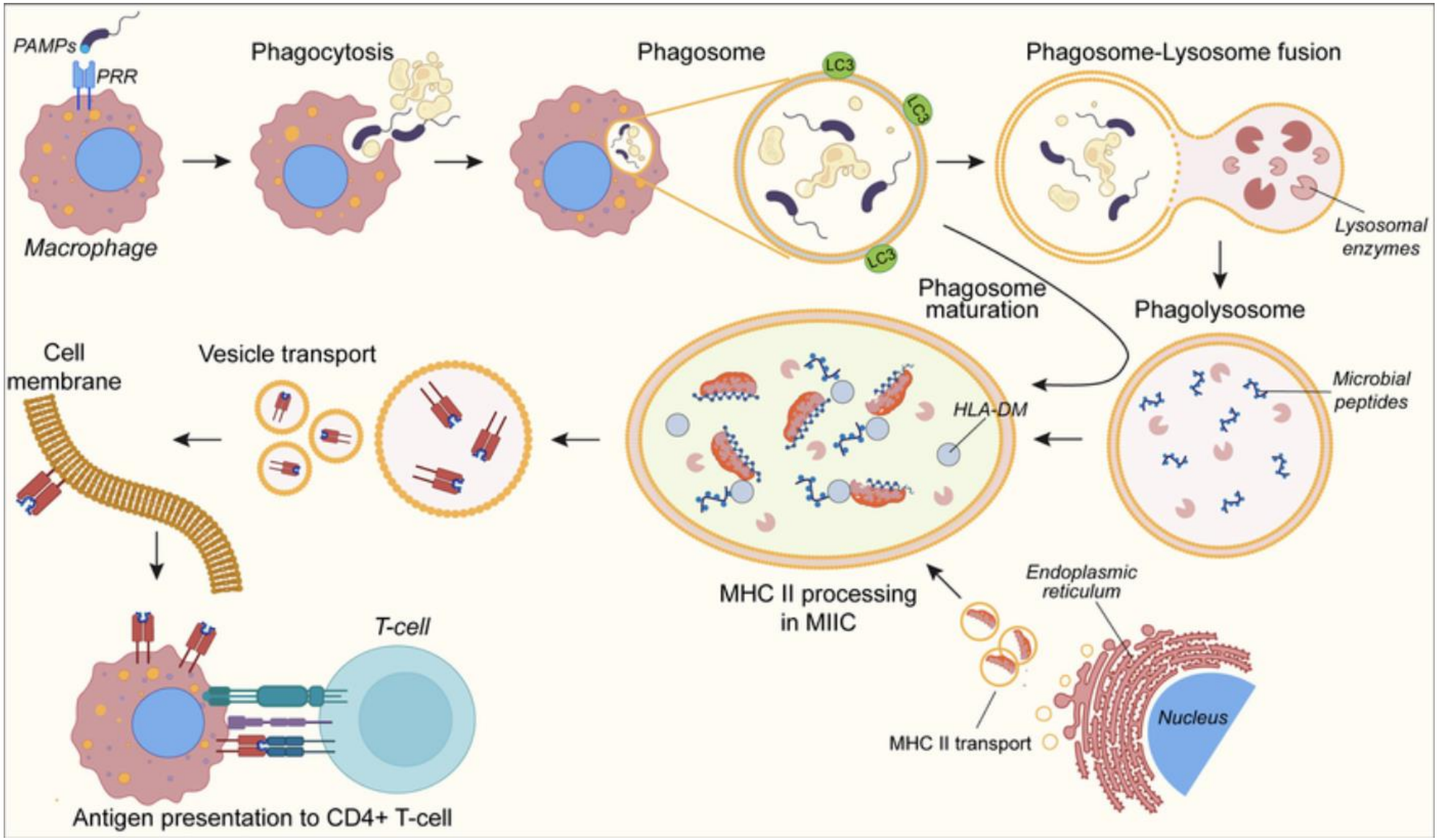
Figure 15.10b *The Biology of Cancer* (© Garland Science 2007)

ANTIGEN PRESENTATION: MHC II

MACROPHAGES, B-CELLS , T CELLS

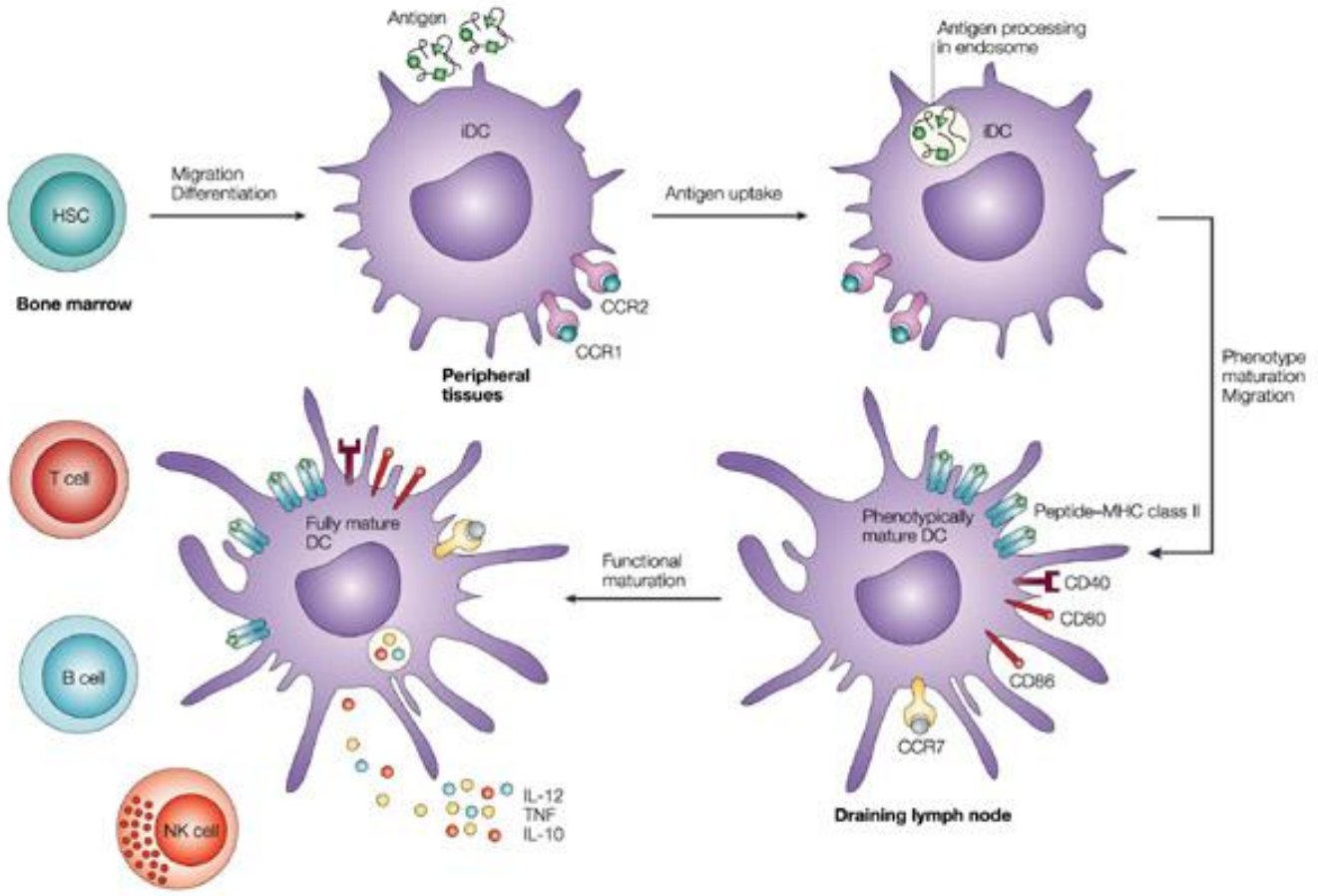


IMMUNE SYSTEM: PLAYERS

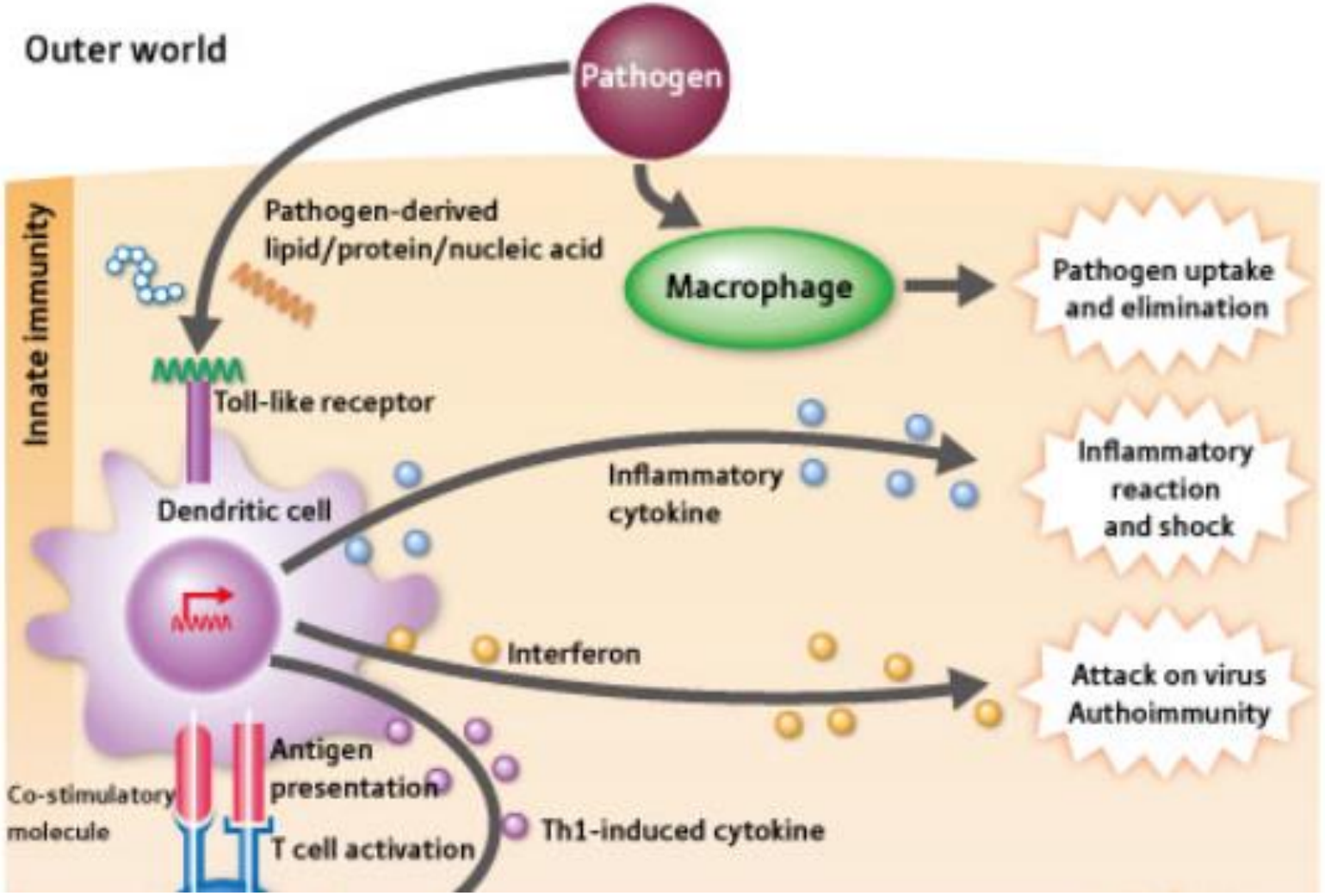


IMMUNE SYSTEM: PLAYERS

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



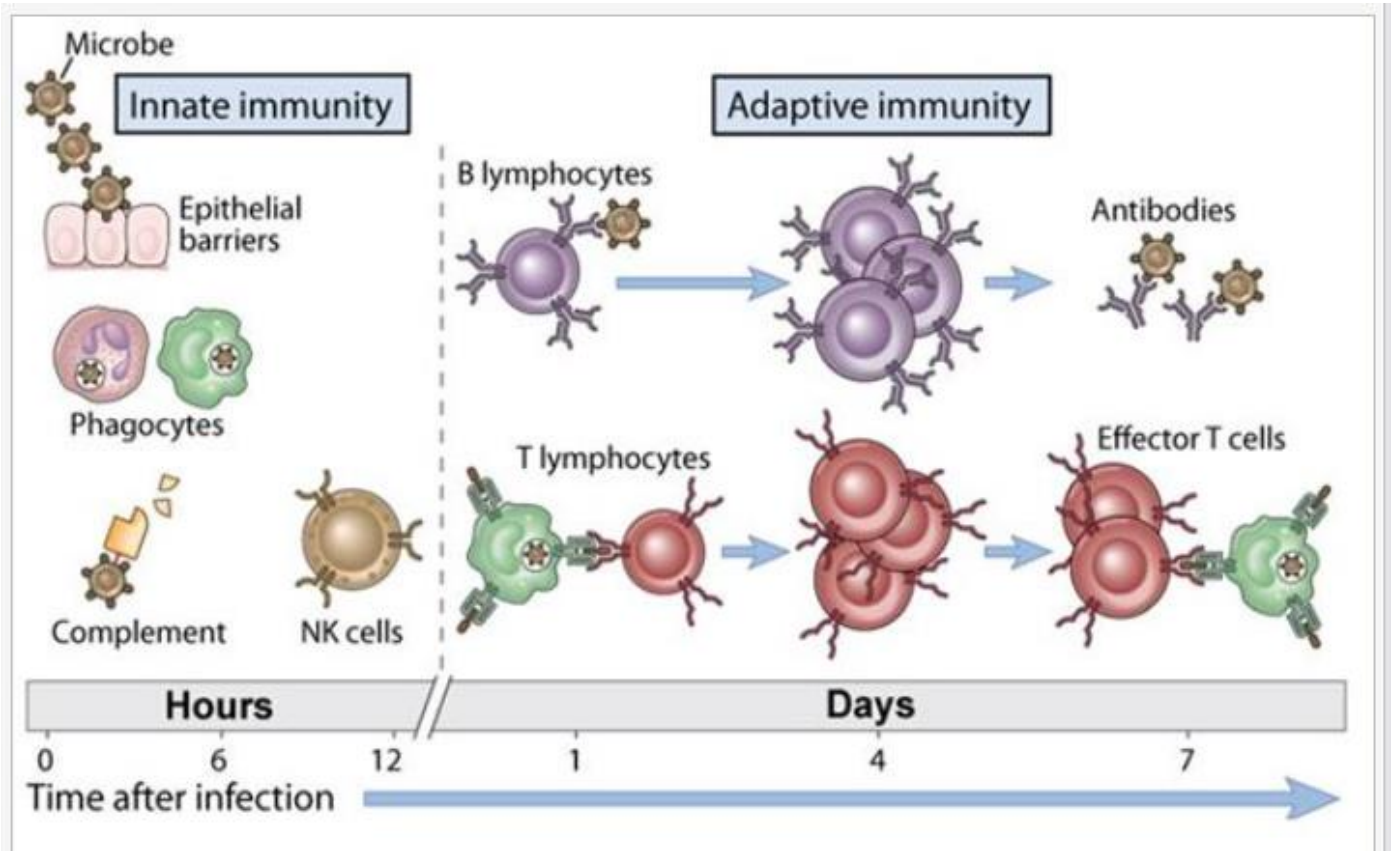
INNATE IMMUNE RESPONSE



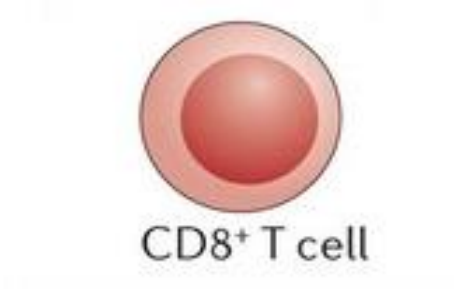
IMMUNE RESPONSE

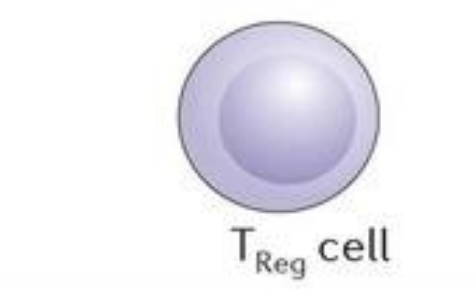
INNATE IMMUNE RESPONSE= Fast

ADAPTIVE IMMUNE RESPONSE= Slow but long term memory



T-cells



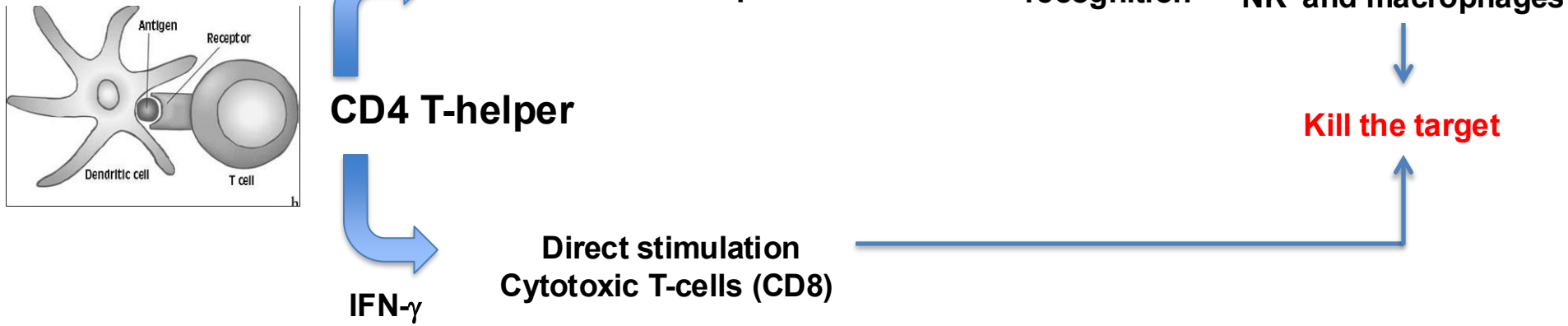


CD4 cells/T-helper
Activation of B and T cells

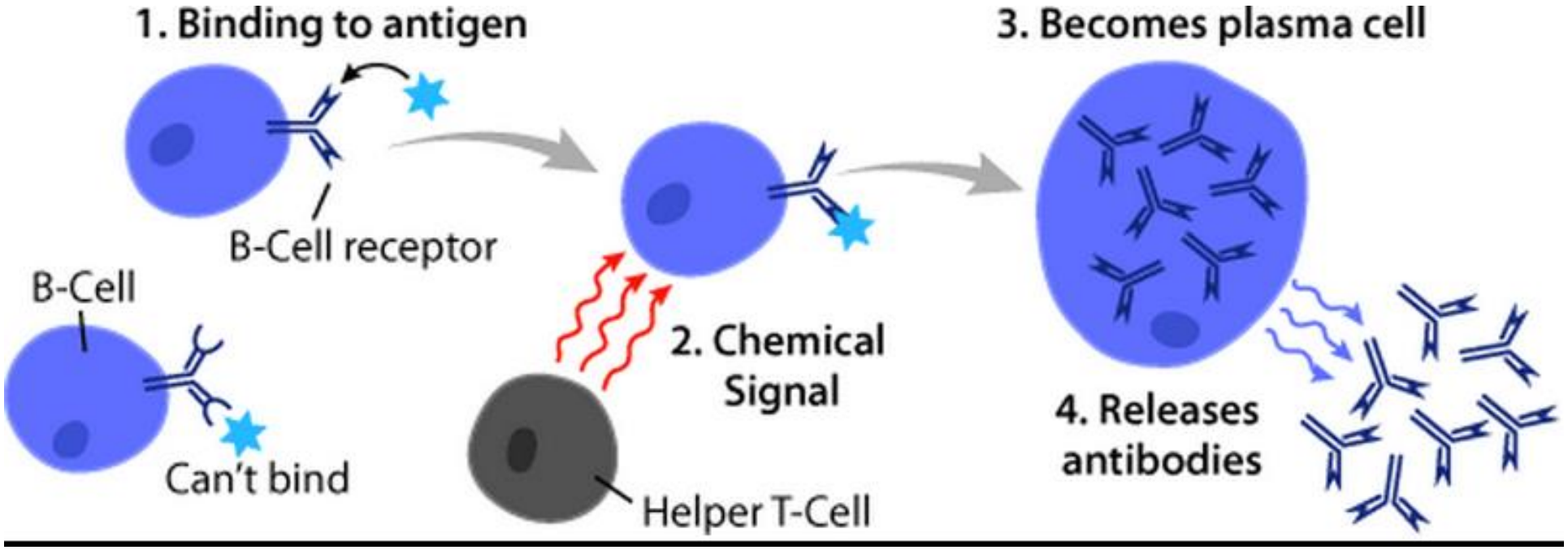
CD8
Cytotoxic
Adaptive immune system

Regulator T cells (Treg)
CD4/FoxP3
Immunosuppressive

ADAPTIVE IMMUNE RESPONSE



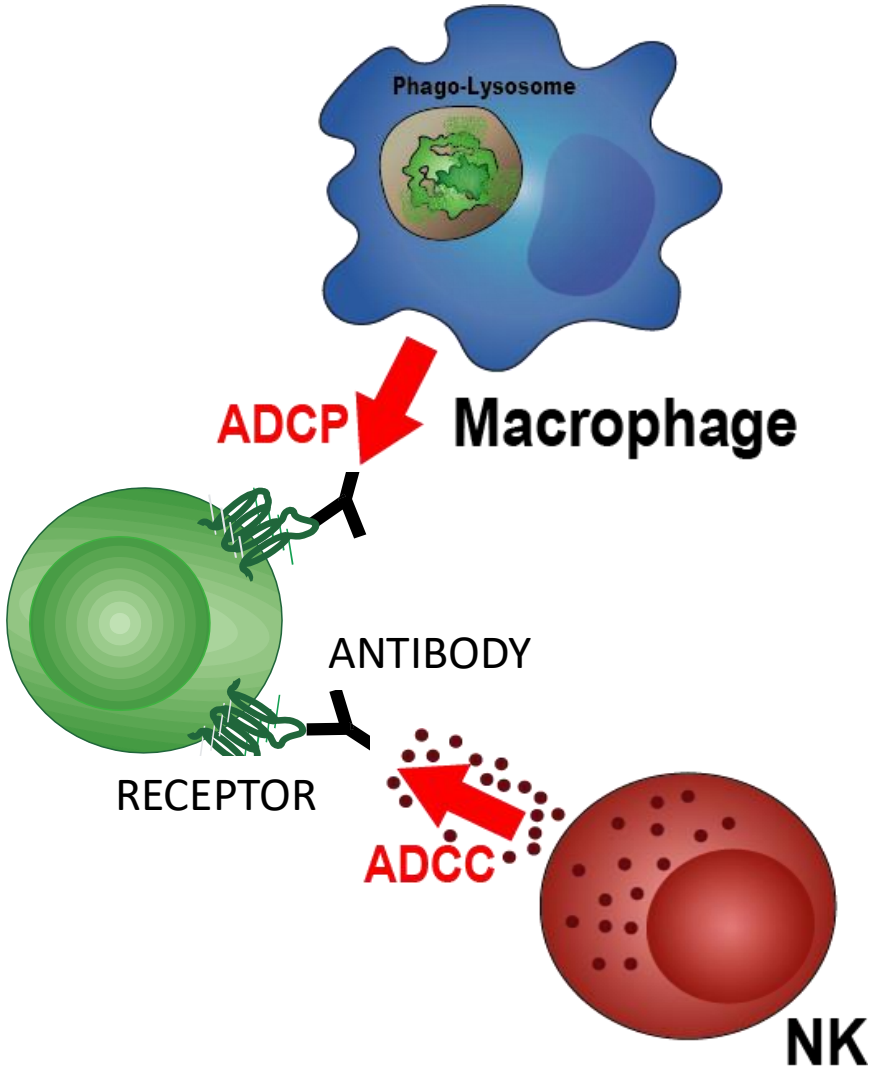
B-cells


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

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

Antibody-mediated cellular cytotoxicity = NK (ADCC)

Antibody-mediated cellular phagocytosis=macrophages (ADCP)



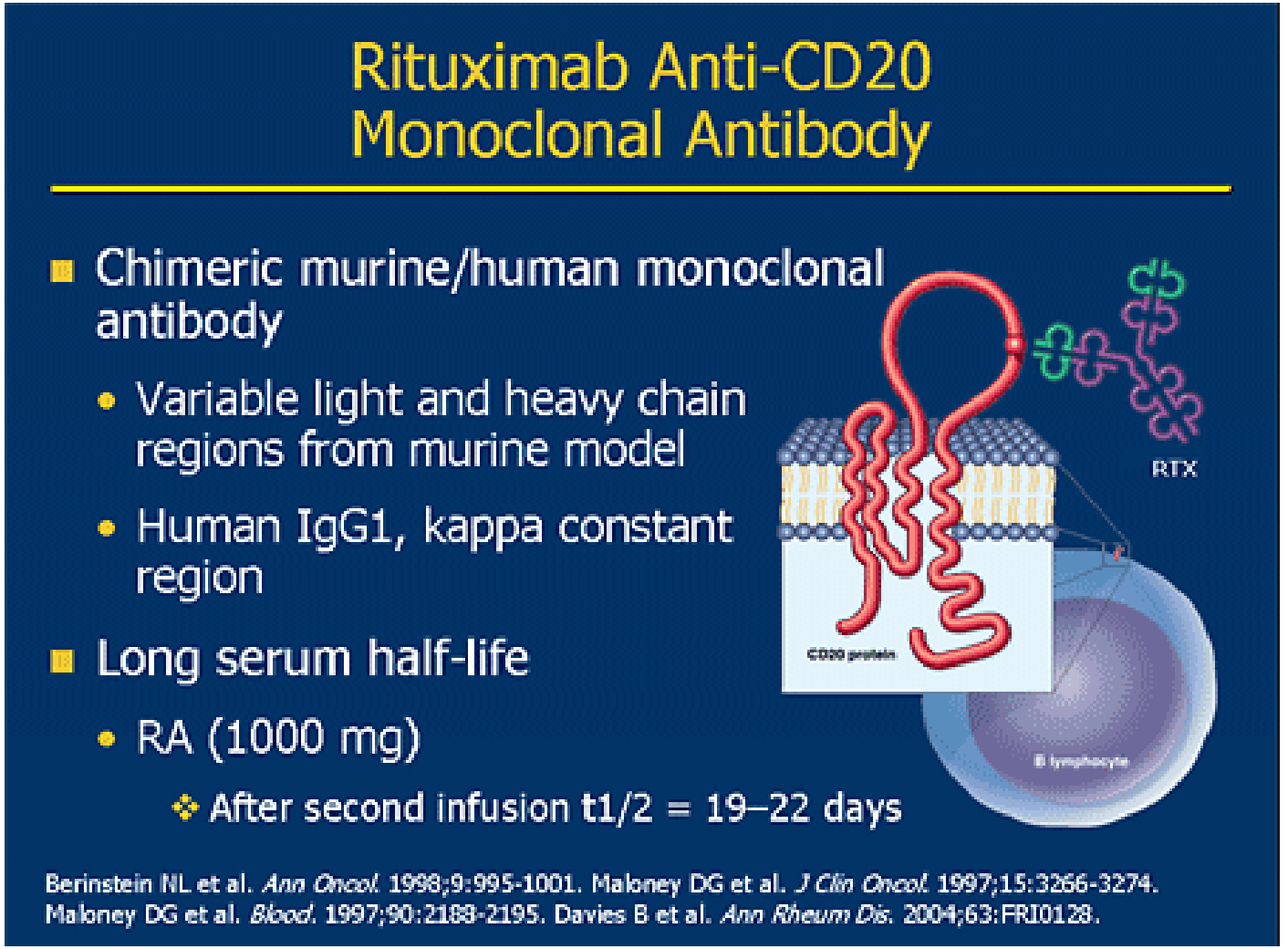
ANTIBODY BASED IMMUNOTHERAPIES to ACTIVATE IMMUNO RESPONSES

Lymphoma therapy: R-CHOP

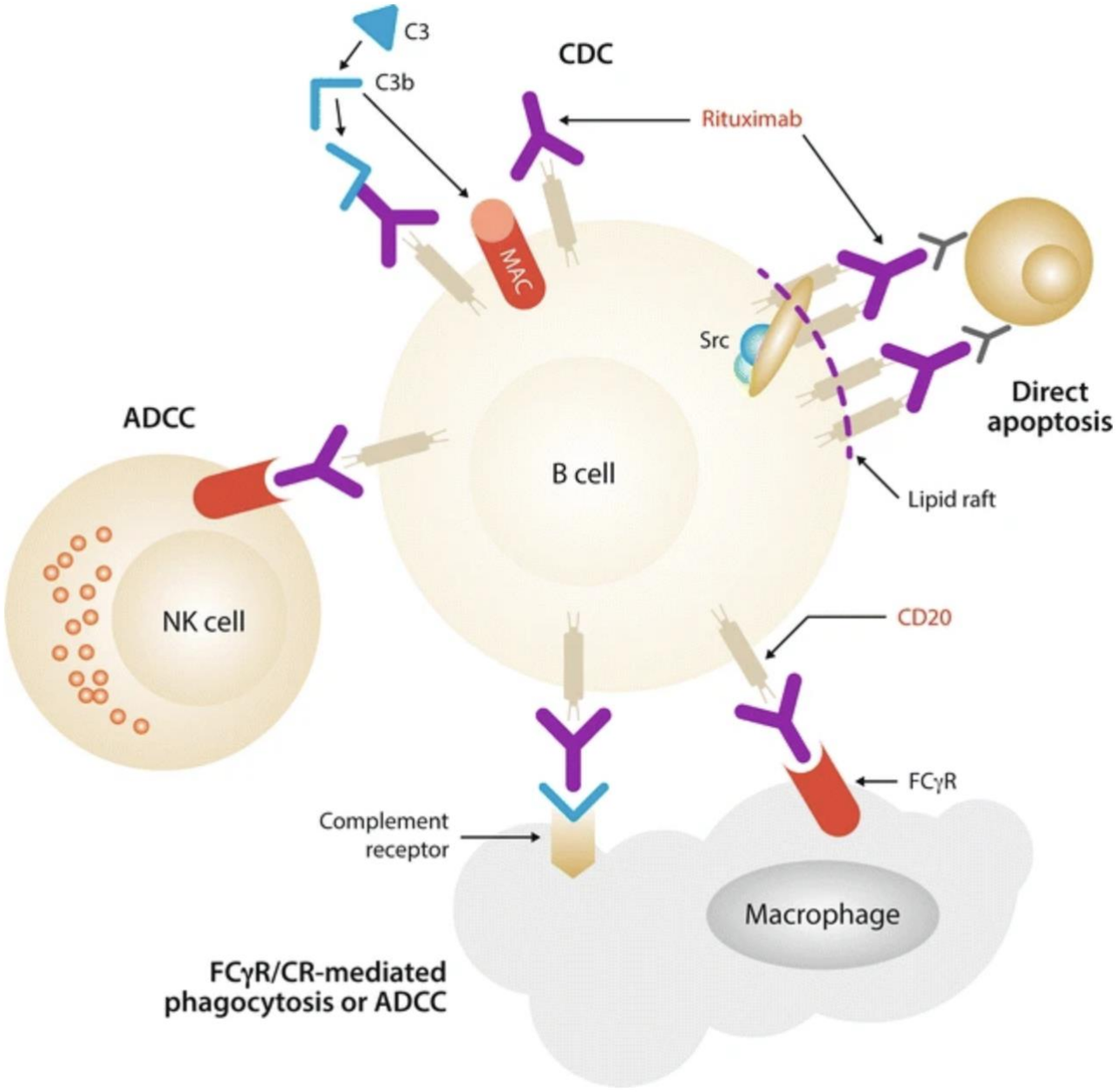
R= Rituximab

CHOP= Chemotherapies MIX

1997



Antibodies for cancer treatment

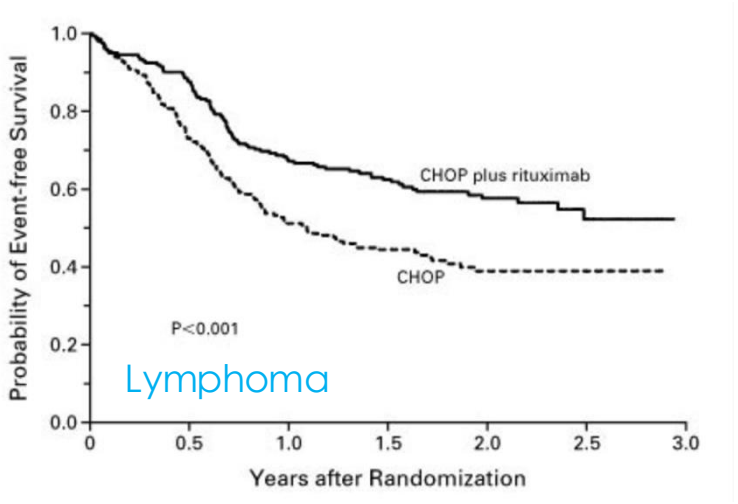


Antibody-based therapies in cancer

Rituximab
anti-CD20

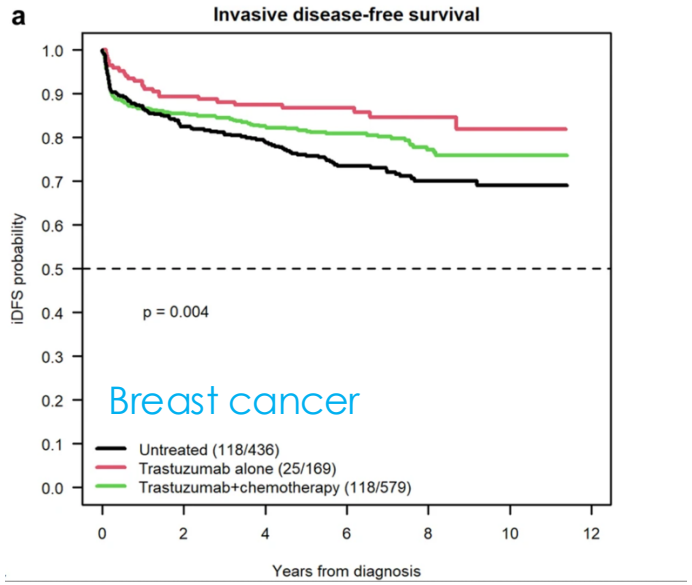
Trastuzumab
anti-HER2

Rituximab+ chemotherapies



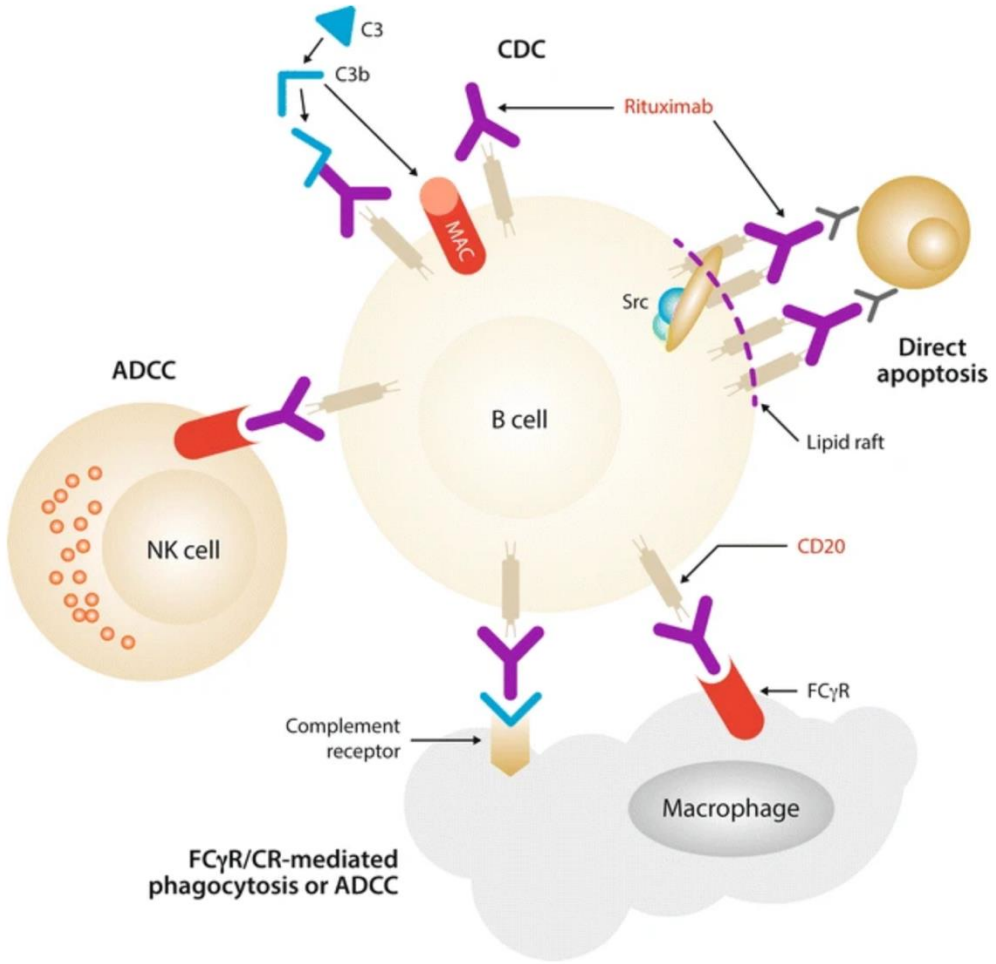
Coiffier et al. NEJM, 2002

Trastuzumab+ chemotherapies



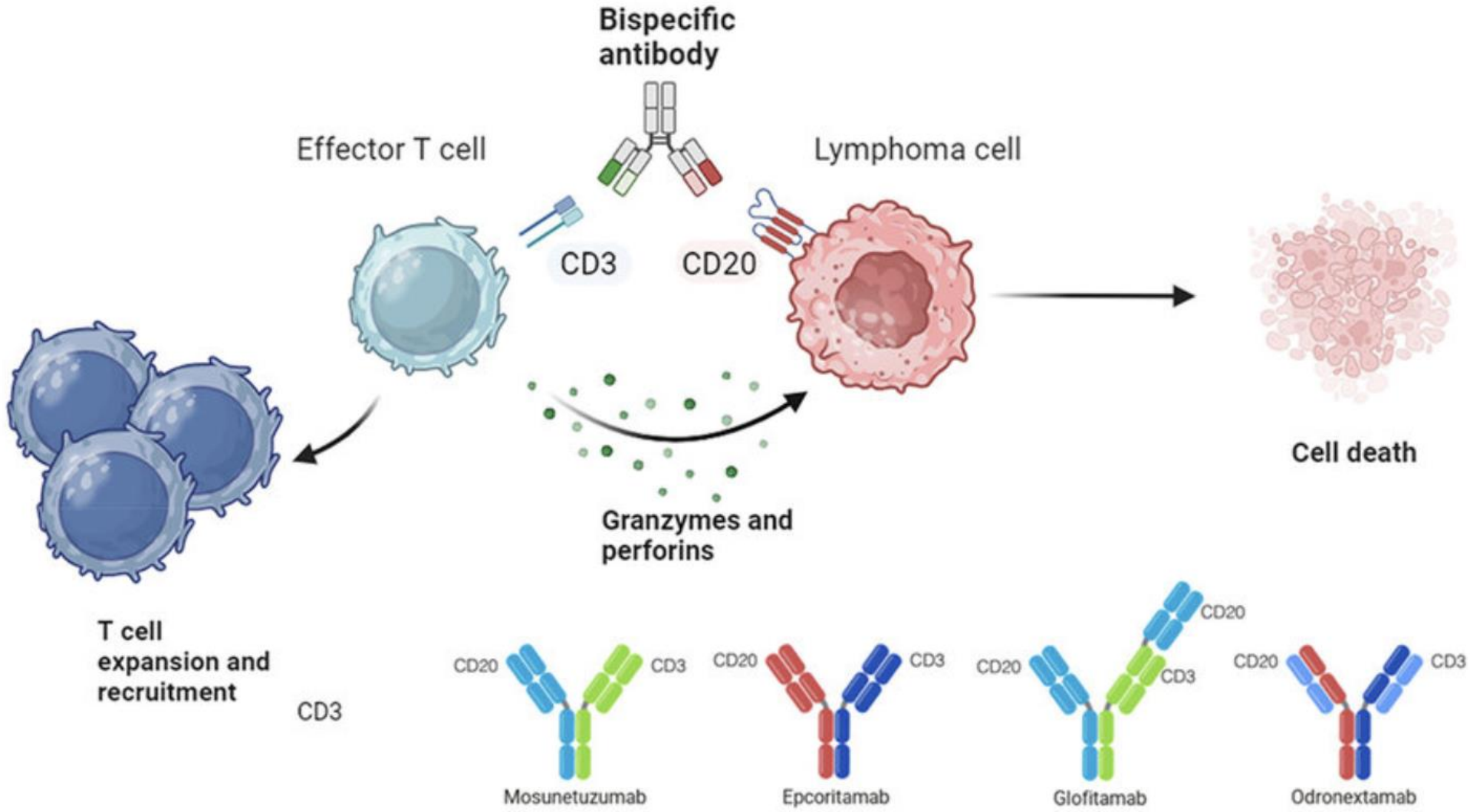
It improves but do not eliminate the tumor

Antibodies for cancer treatment

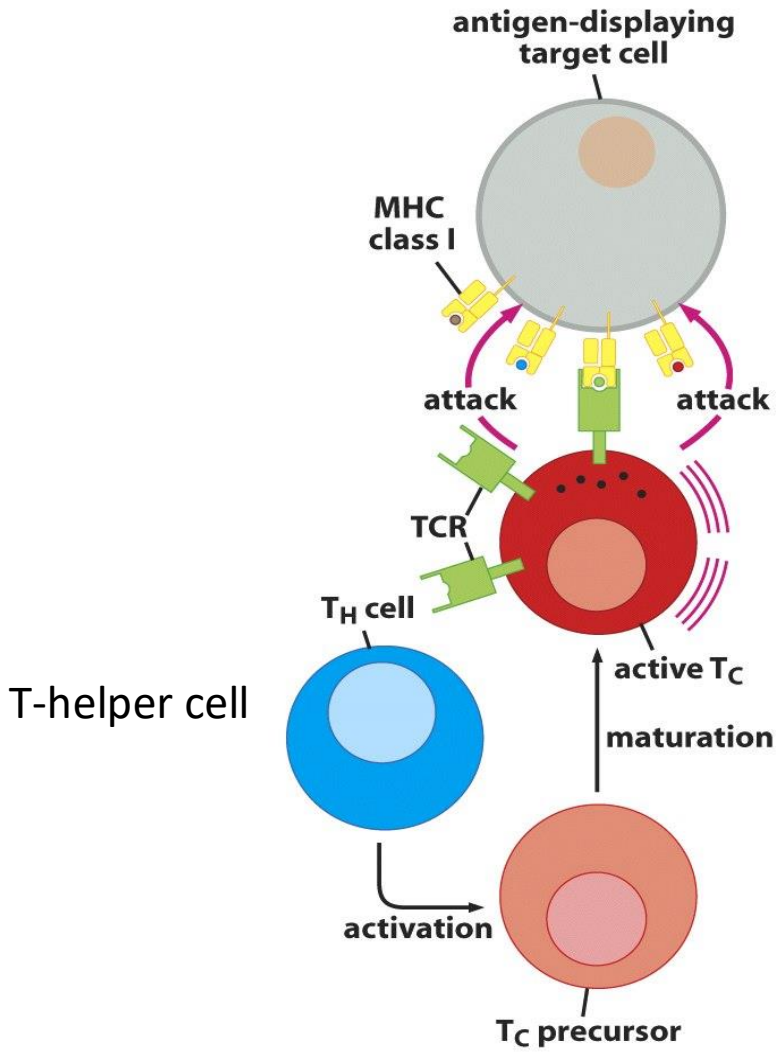


Which immune cells are missing to kill the cancer cells?

Bi-specific antibody



ADAPTIVE IMMUNE RESPONSE: Cytotoxic cells



T-helper cell

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

WHY DOES the IMMUNE SYSTEM NOT KILL CANCER CELLS?

IMMUNE TOLERANCE

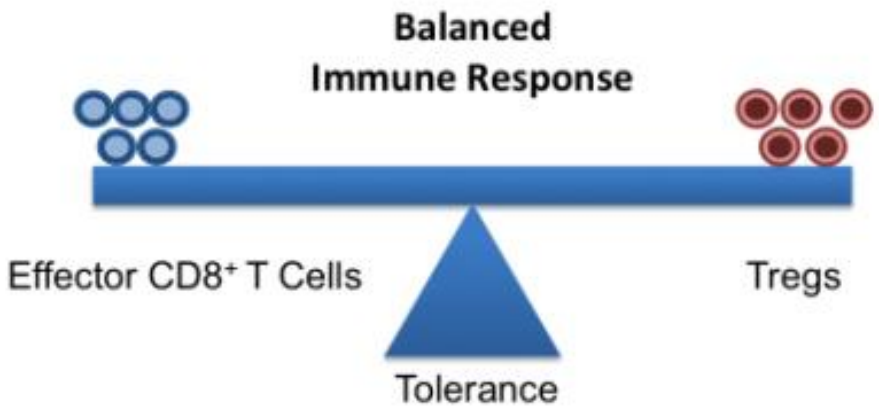
T-Regulatory cells
(Treg)
(CD4, CD25 and FoxP3)

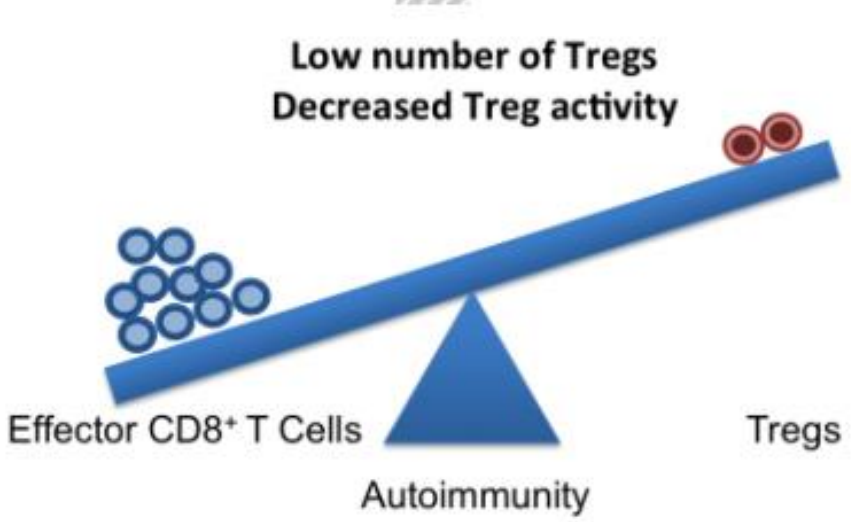
Protect the body from auto-immune disease

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

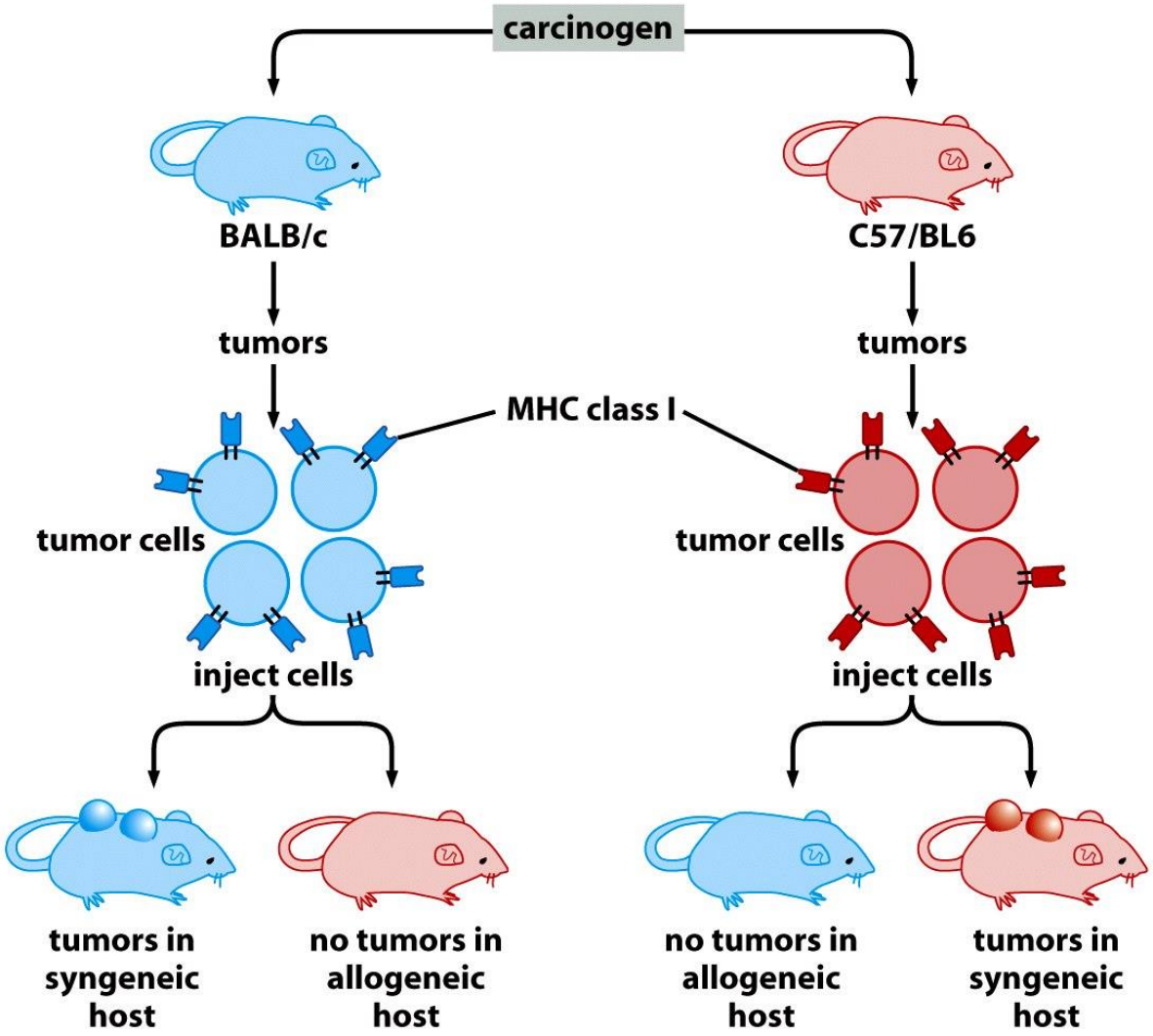
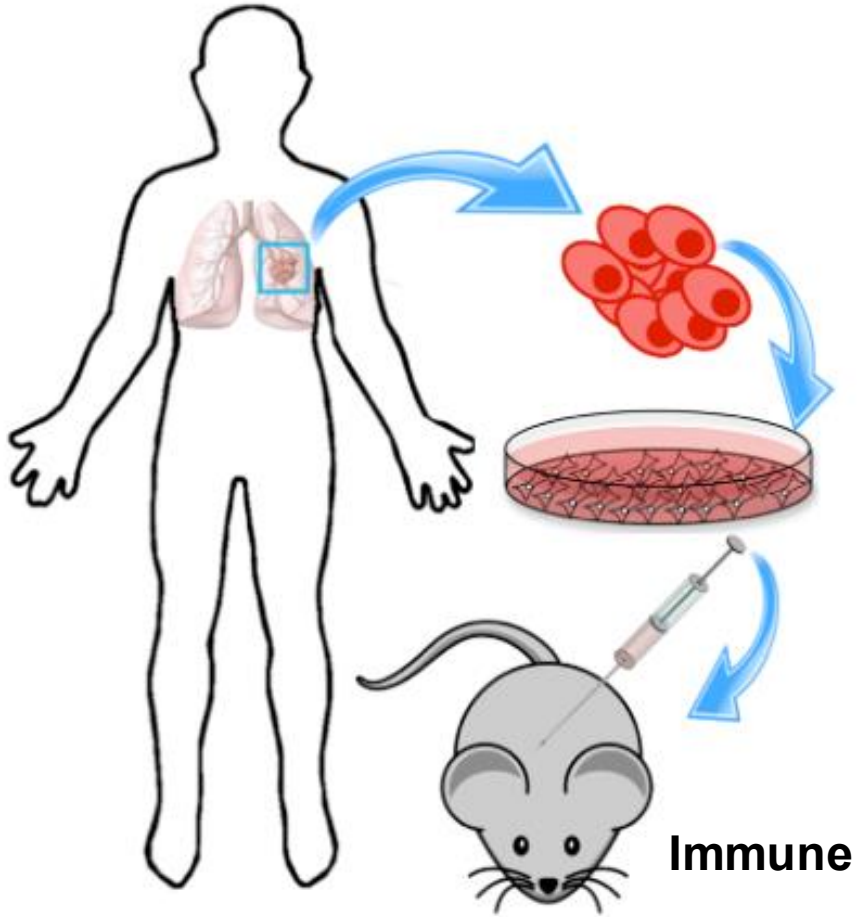


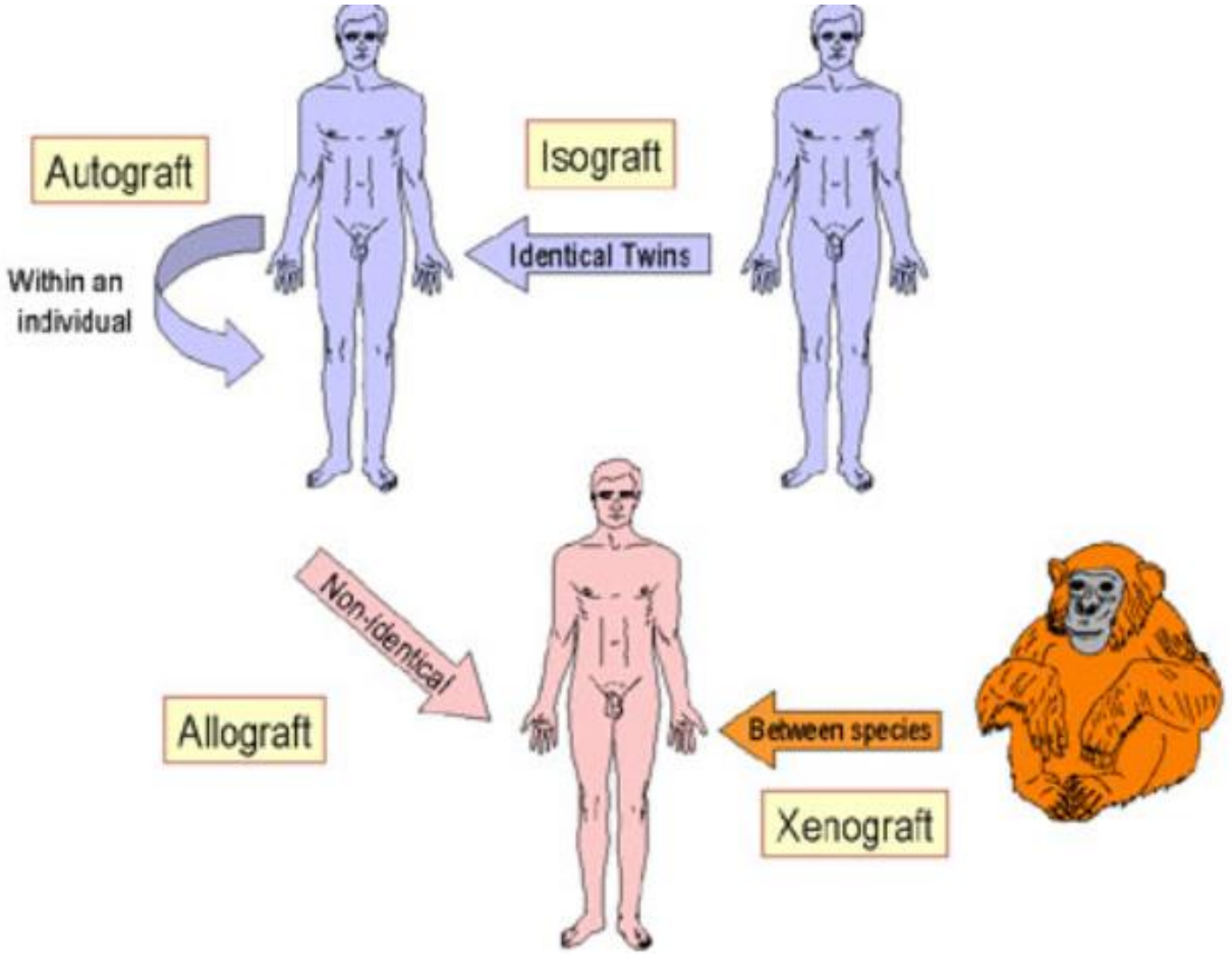
Figure 15.15 *The Biology of Cancer* (© Garland Science 2007)

XENOGRAFT TRANSPLANT

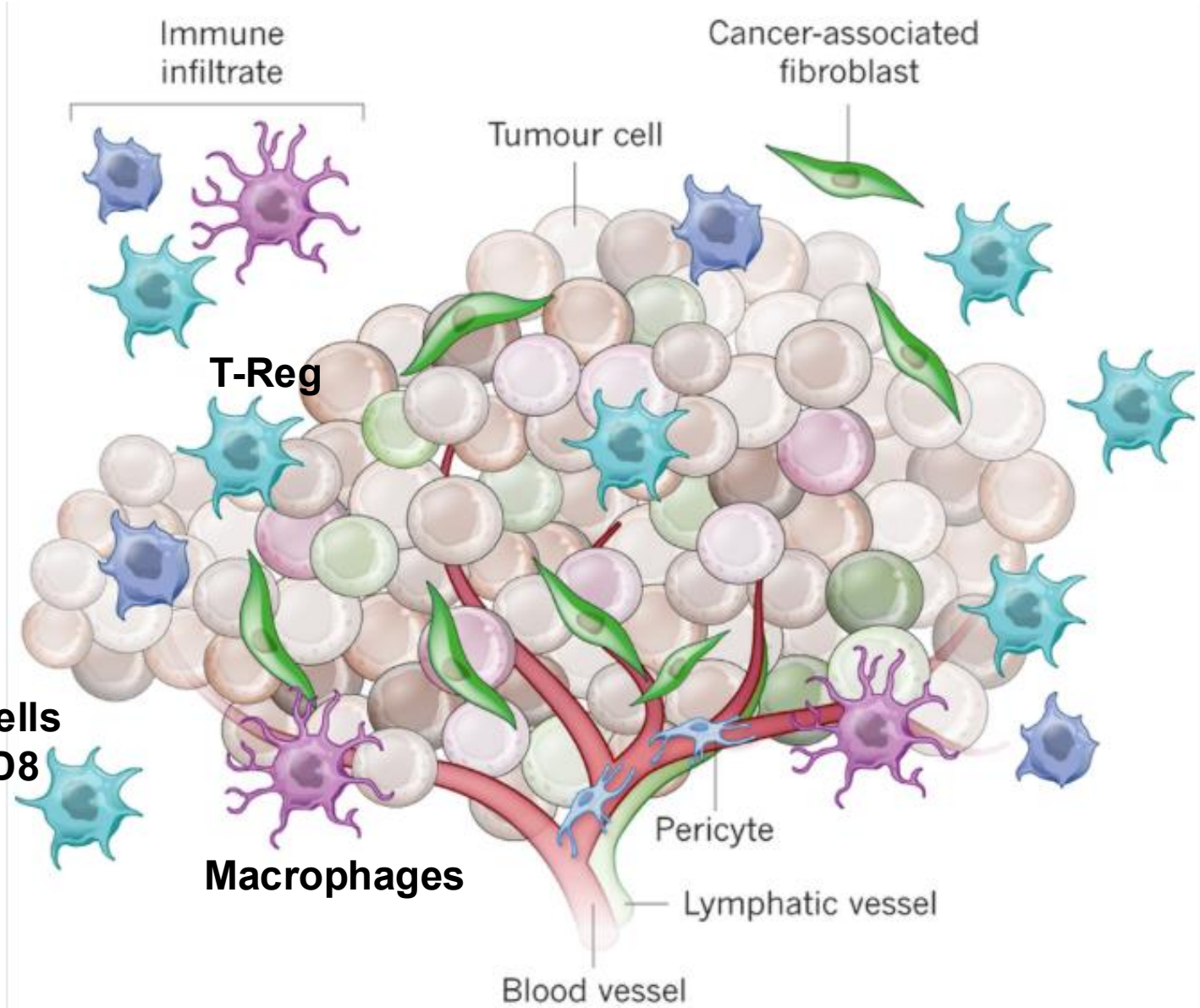


Immune deficient animals

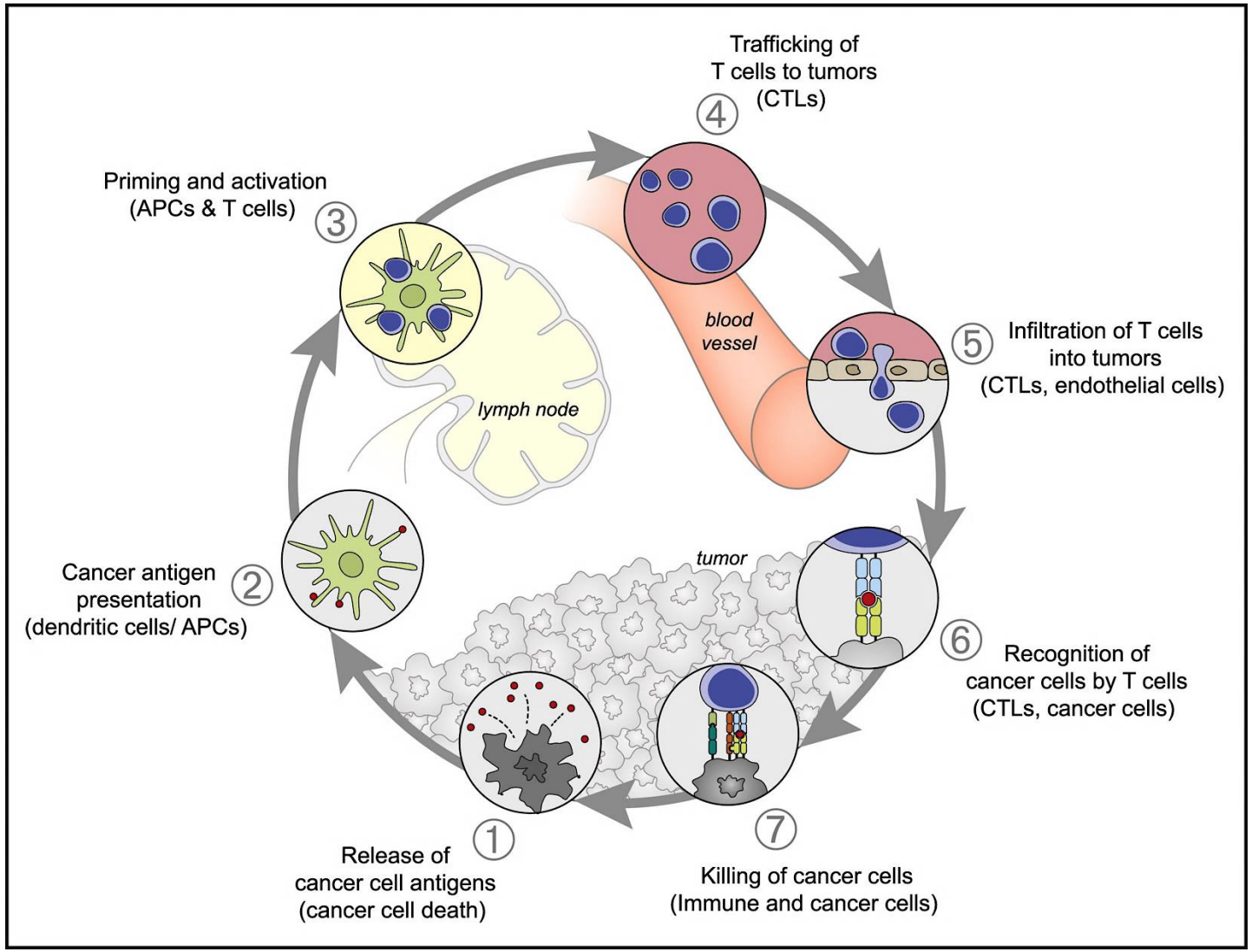
SUMMARY TRANSPLANT



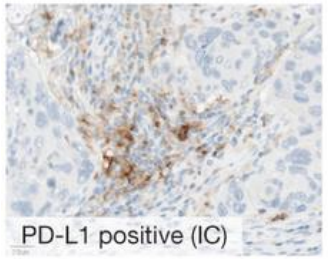
TUMOR MICROENVIROMENT



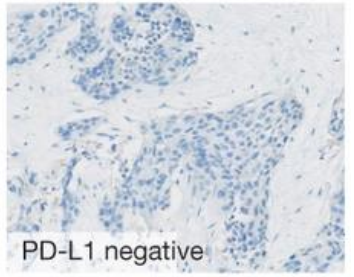
THE CANCER IMMUNITY CYCLE



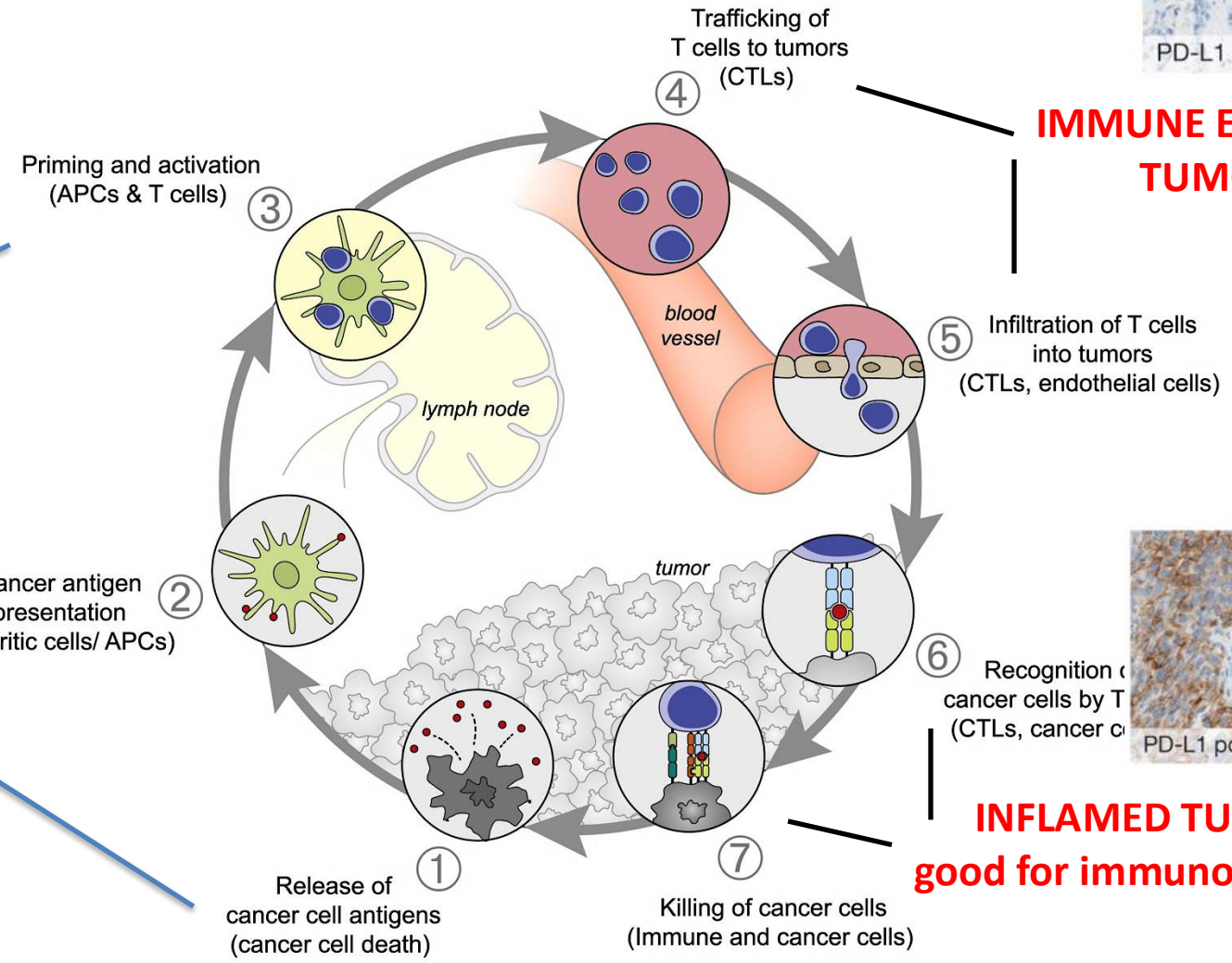
THE CANCER IMMUNITY CYCLE

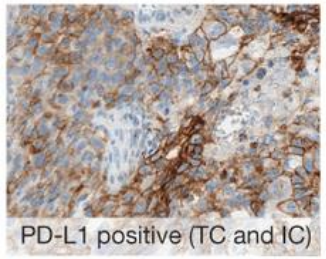


IMMUNE DESERT TUMORS



IMMUNE EXCLUDED TUMORS





INFLAMED TUMORS
good for immunotherapies

IMMUNE DESERT TUMORS ARE TUMORS THAT DON'T PRESENT ANTIGENS

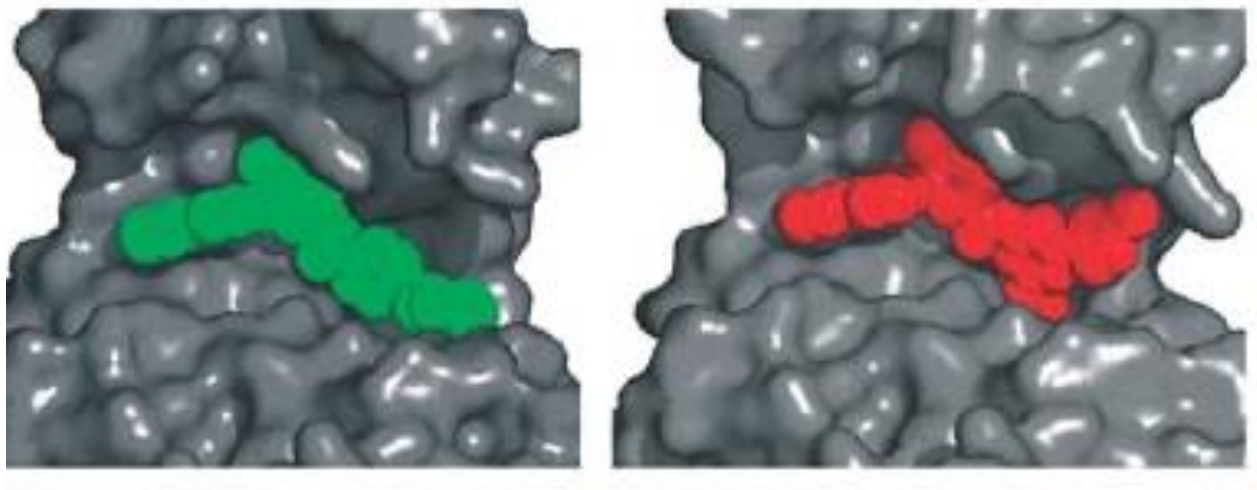
What is different between an immune desert tumor and an inflamed tumor?

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

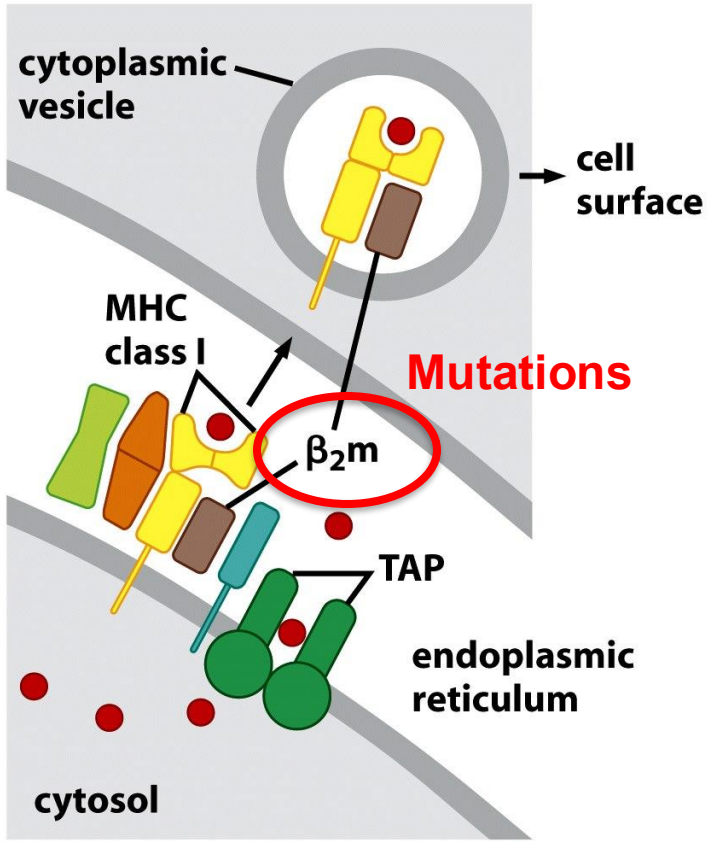
HIDE THE ANTIGEN PRESENTATION: REPRESS/MUTATE MHC class I

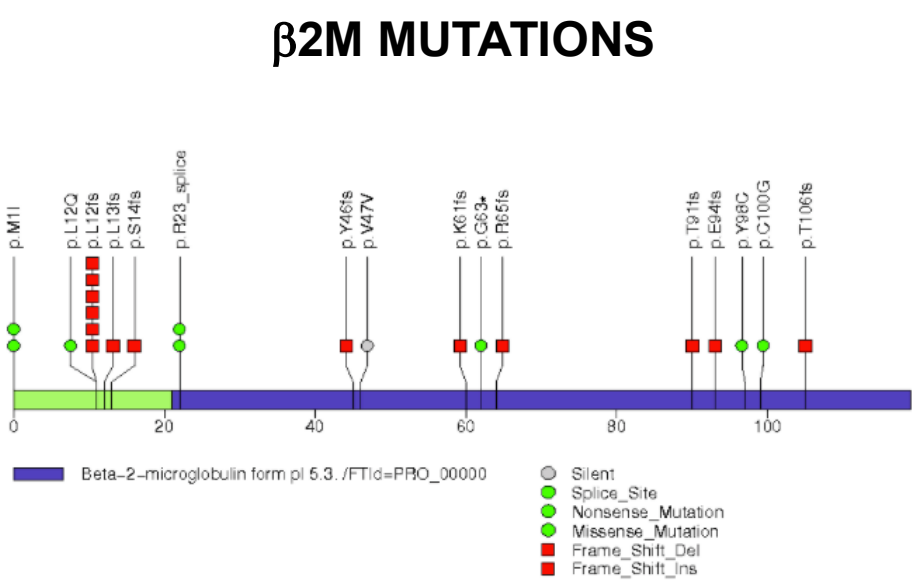
RELEASE INHIBITORY CYTOKINES (IL10 and TGF β)

Mimic the function of Treg cells

HIDE THE ANTIGEN PRESENTATION: REPRESS/MUTATE MHC class

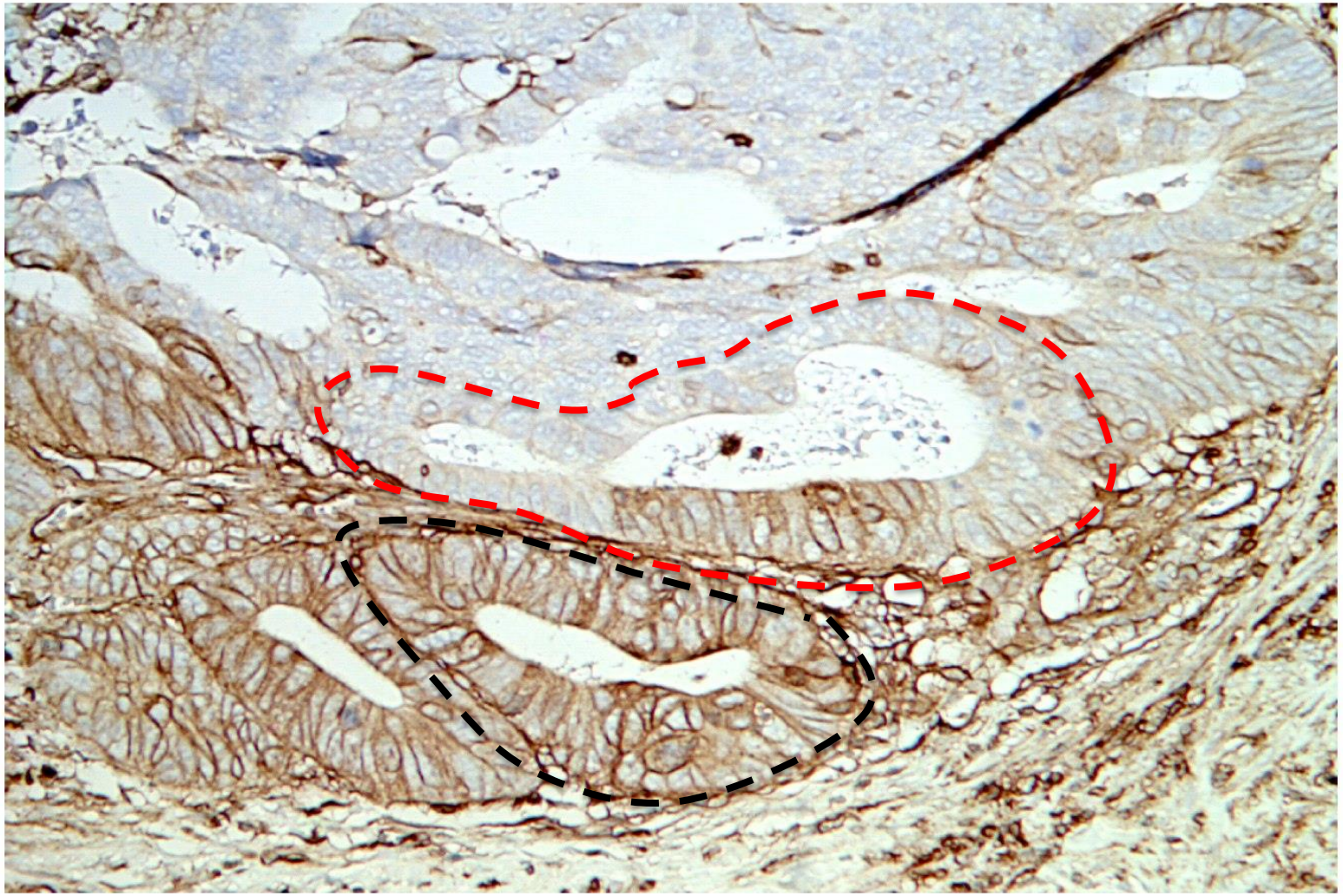
MUTATE β2M or other component of antigen presentation





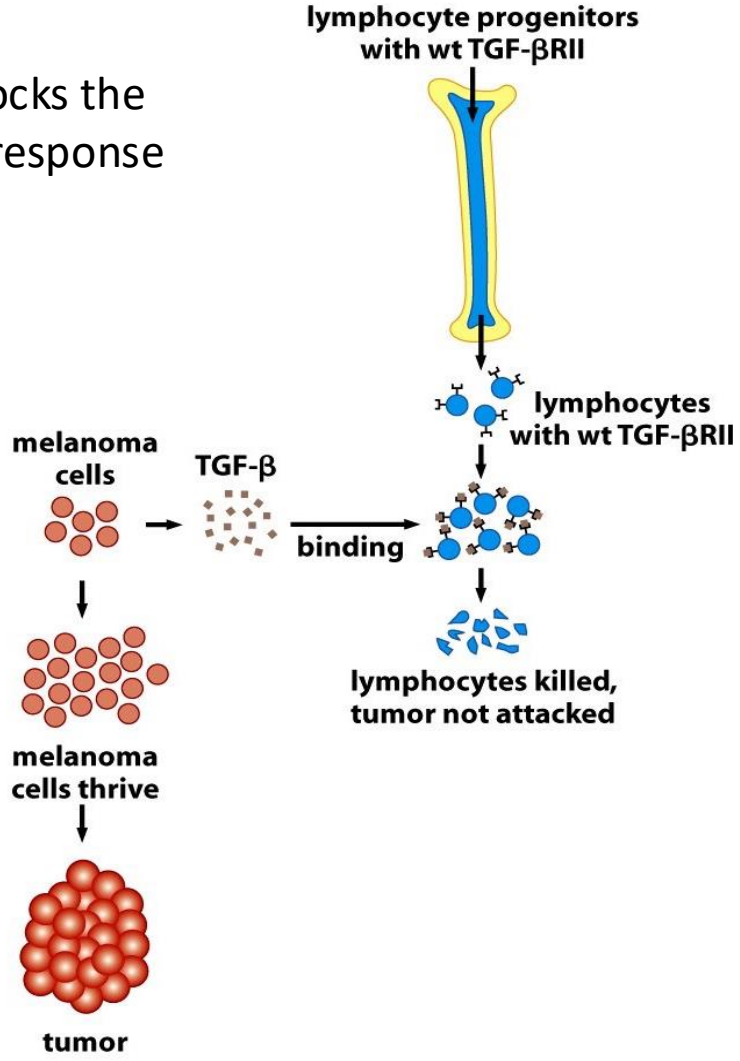
HIDE THE ANTIGEN PRESENTATION: REPRESS/MUTATE MHC class

Repress the expression of MHC-I



RELEASE INHIBITORY CYTOKINES

Tumor blocks the immune-response



lymphocyte without TGF-β receptor

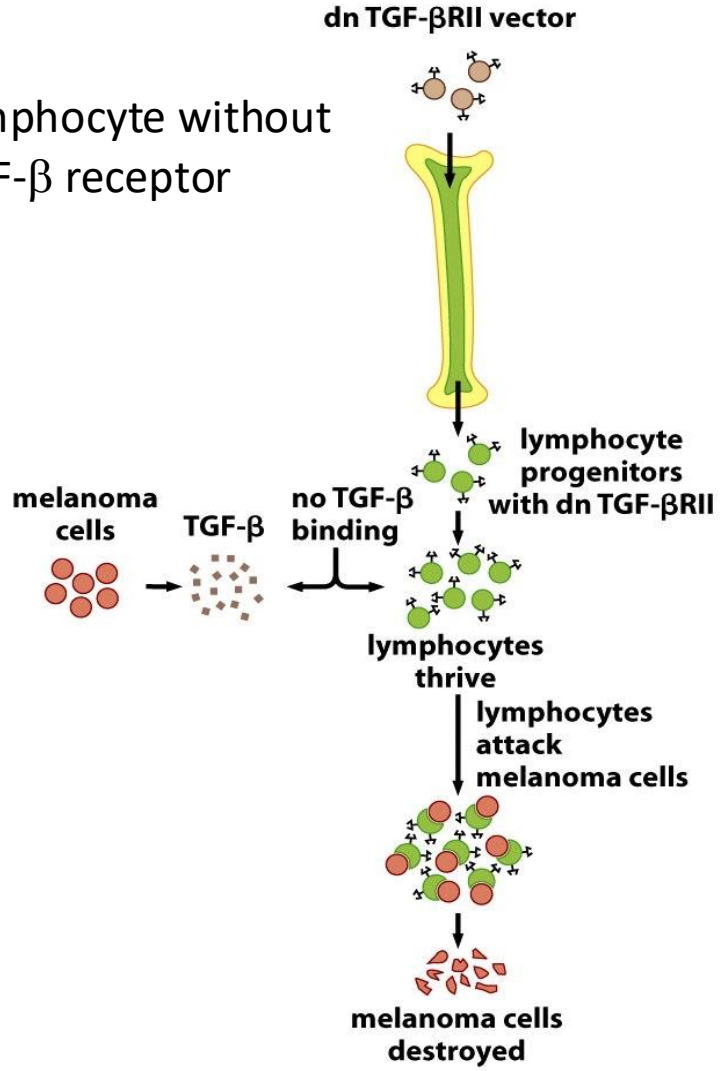
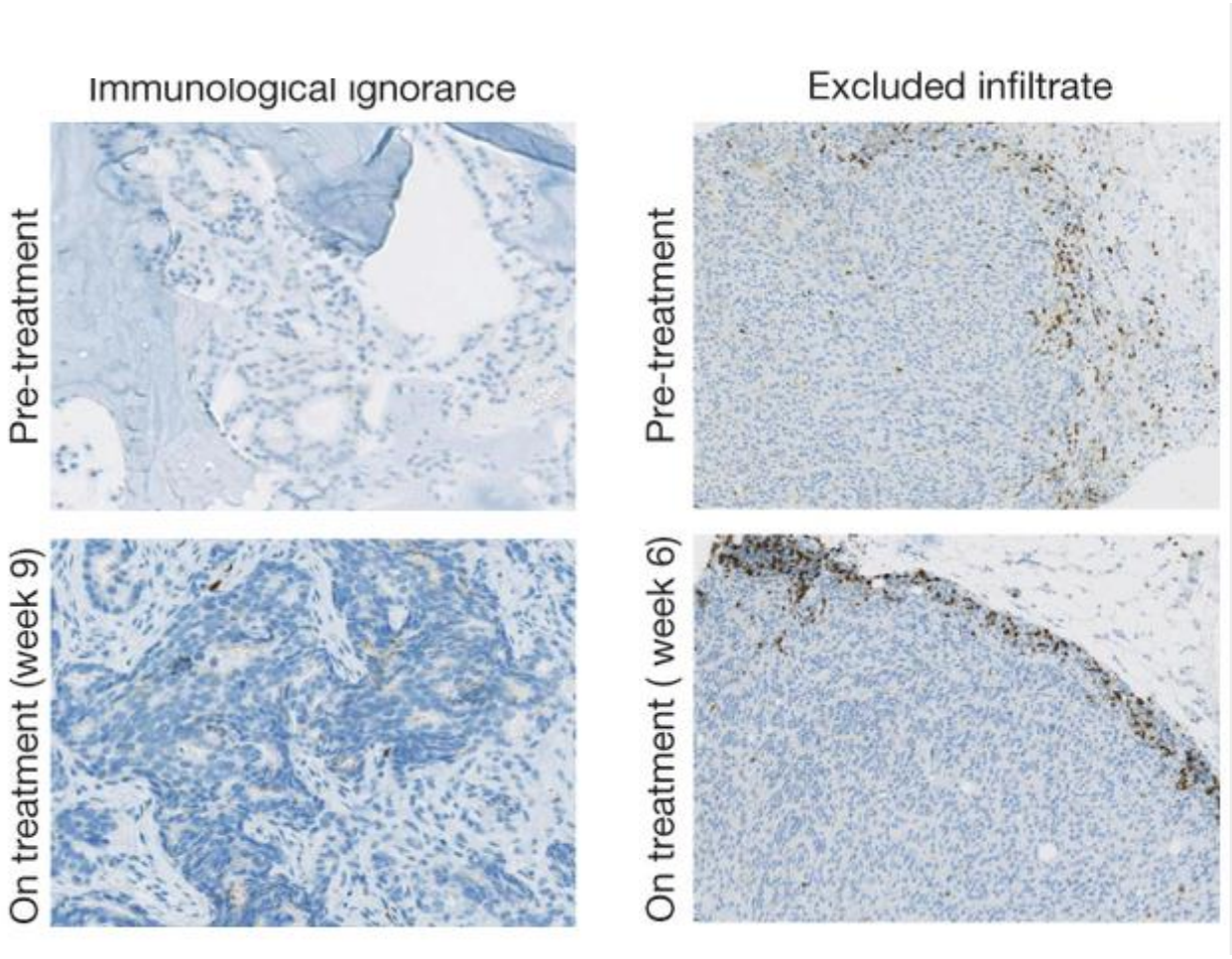


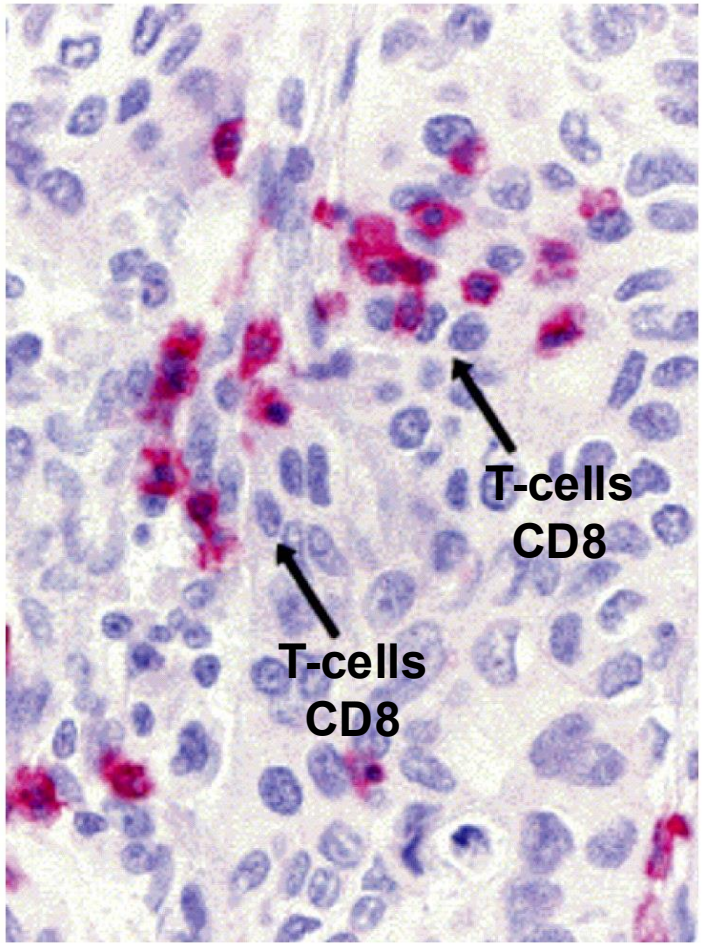
Figure 15.32a *The Biology of Cancer* (© Garland Science 2007)

2. IMMUNE EXCLUDED TUMORS



Cancer cells release factors that maintain immune cell to the periphery

3. INFLAMED TUMORS: TUMOR INFILTRATING LYMPHOCYTES



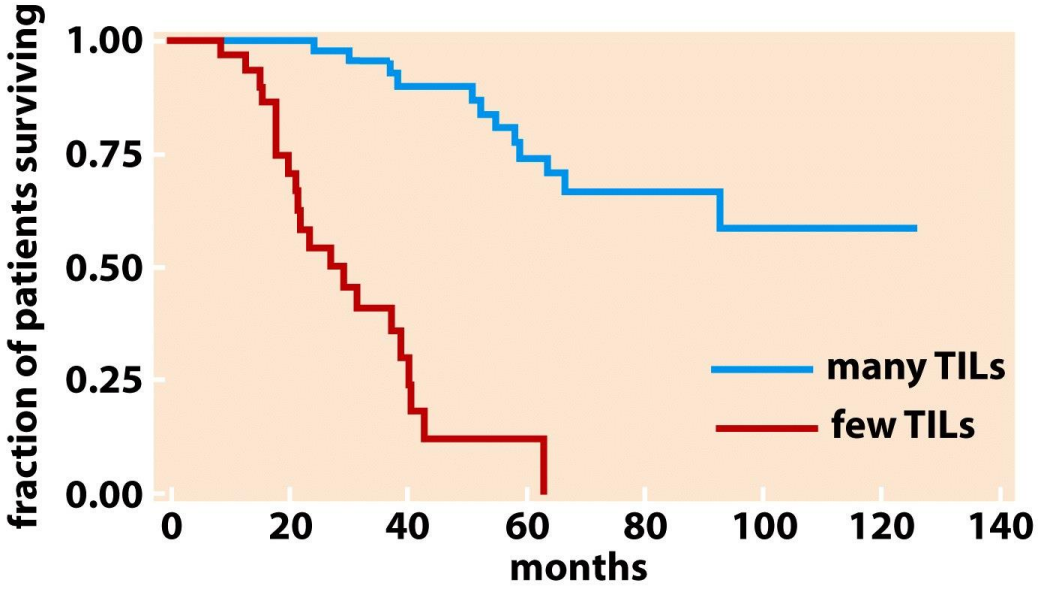
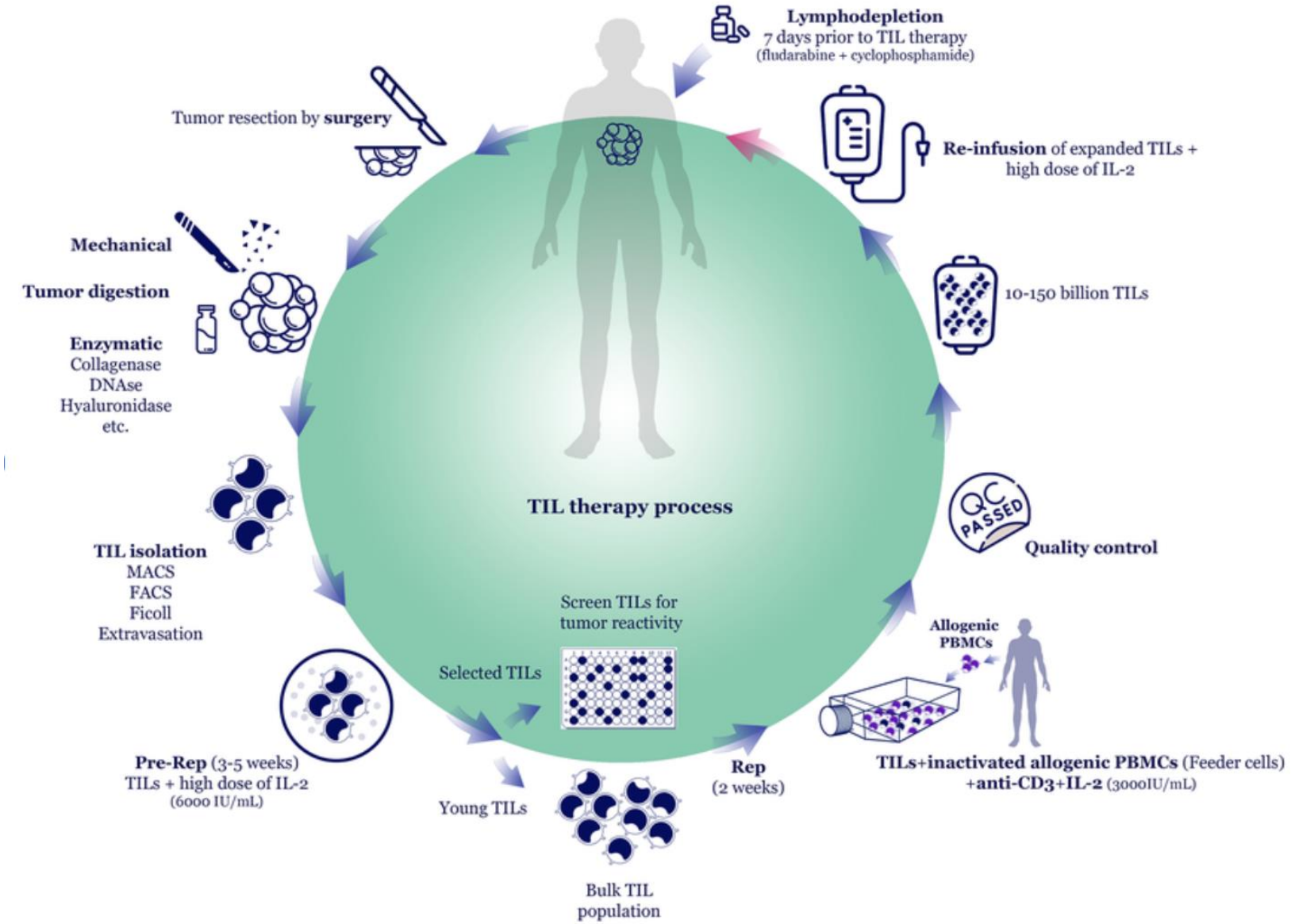


Figure 15.21c *The Biology of Cancer* (© Garland Science 2007)

IMMUNE THERAPIES BASED ON TIL



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**

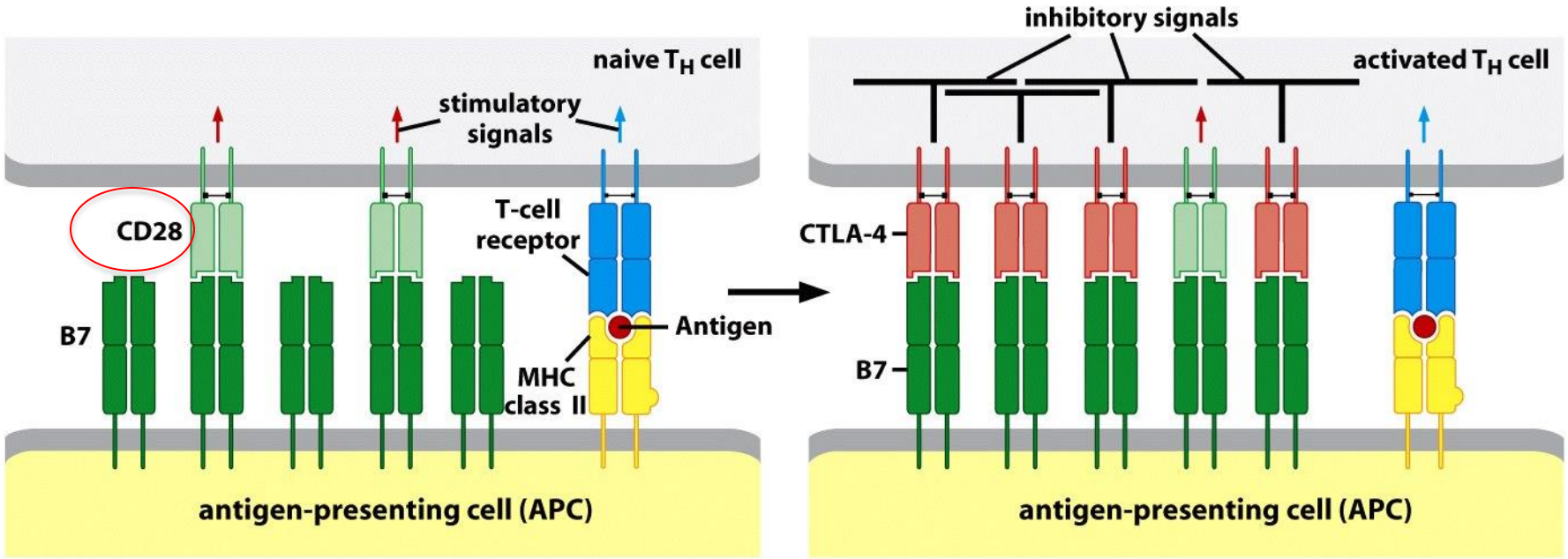
anti-PD1**= Programmed cell death protein 1**

or

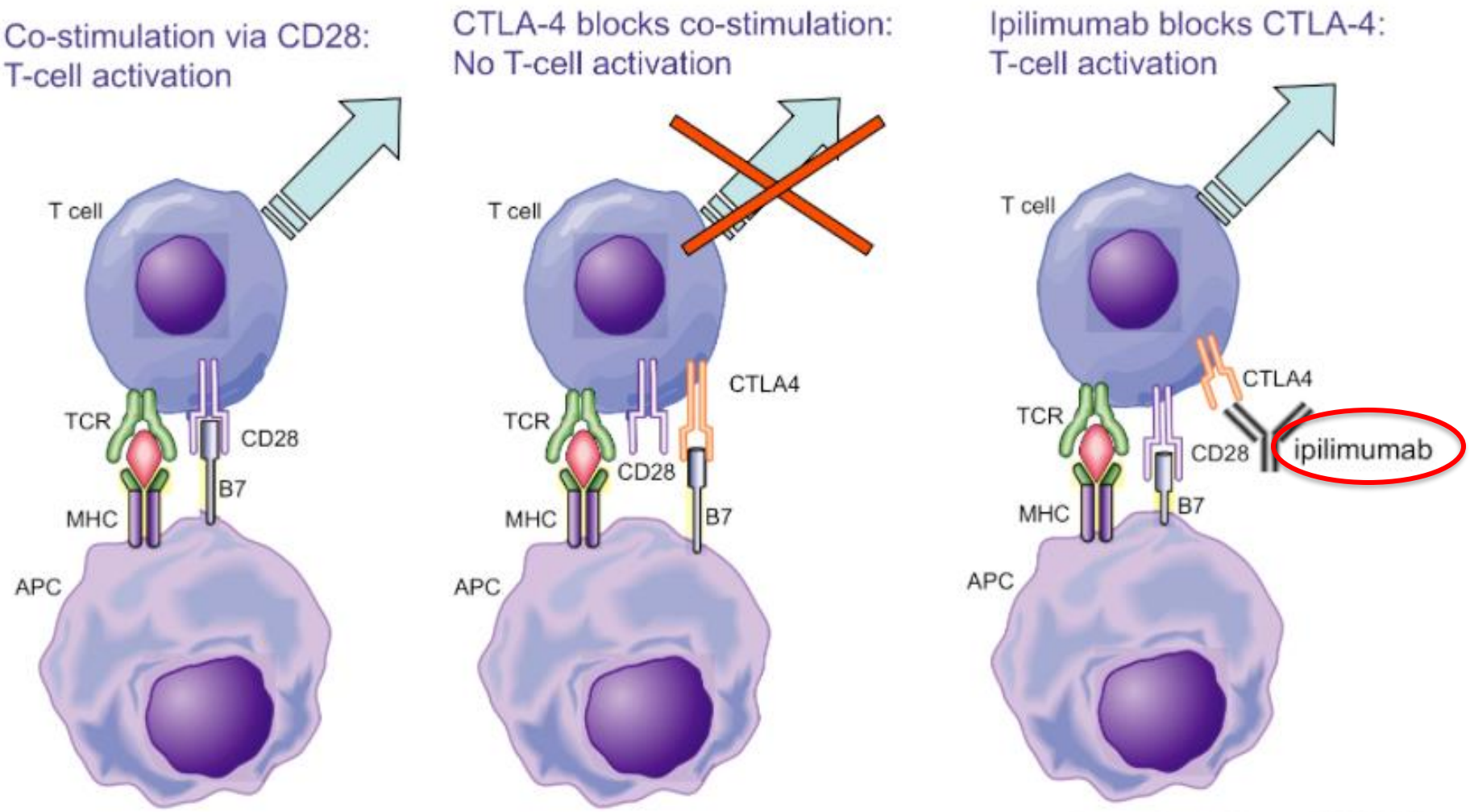
anti-PDL1**= Programmed cell death protein 1 Ligand**

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



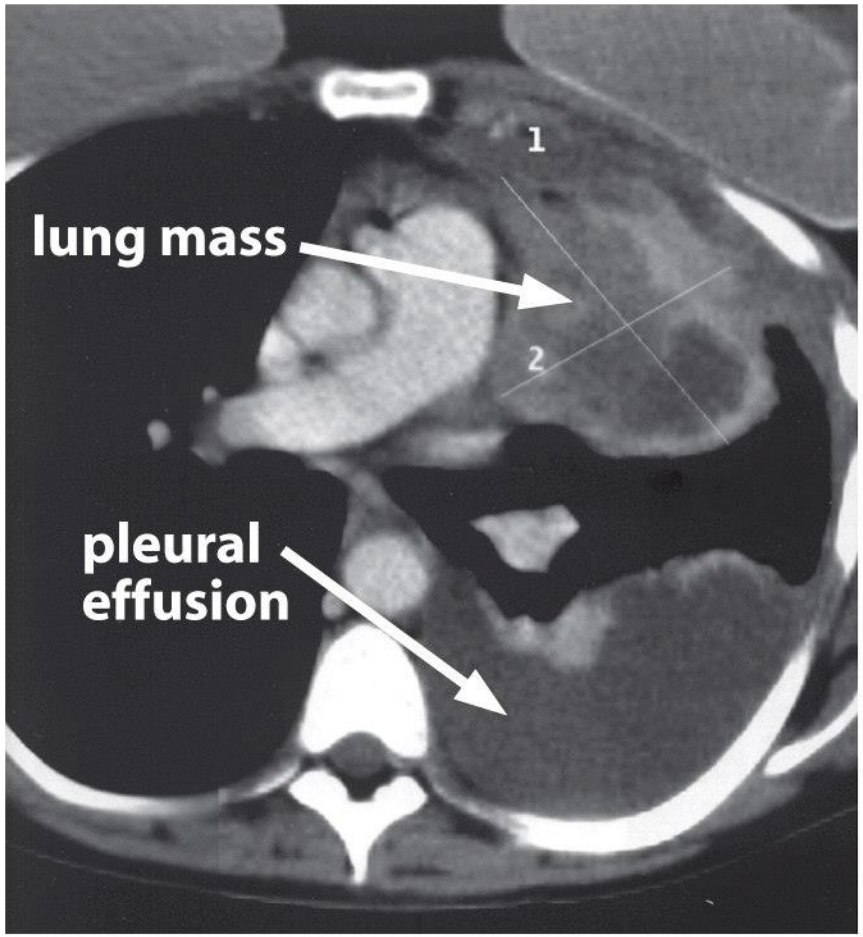
ANTI-CTLA4 INDUCES T-CELLS ACTIVATION



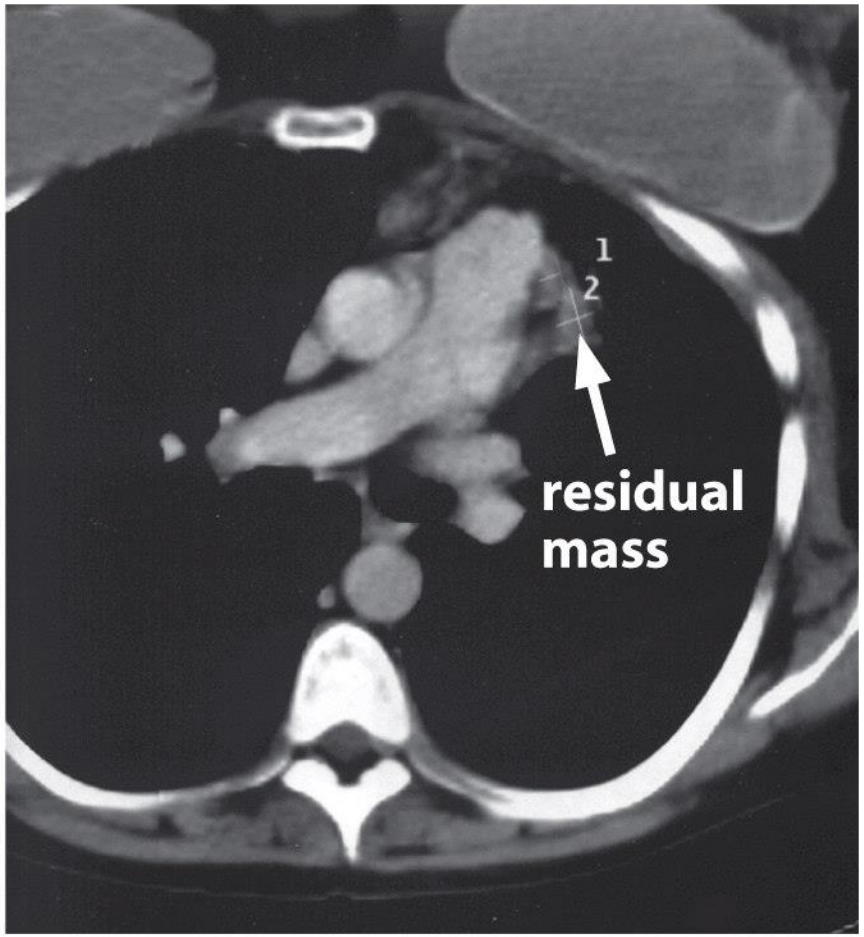
Adapted from Lebbé et al. ESMO 2008

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

ANTI-CTLA4 TUMOR RESPONSE



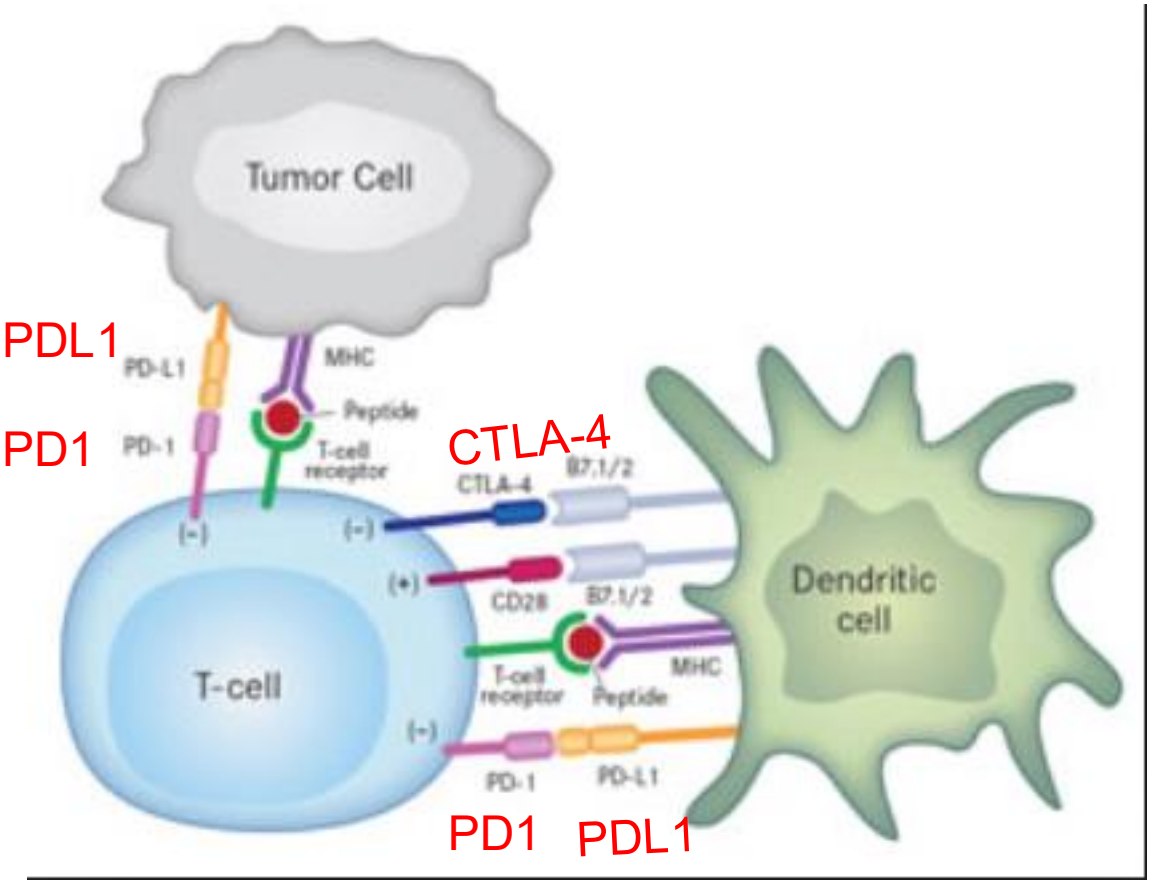
pre-treatment



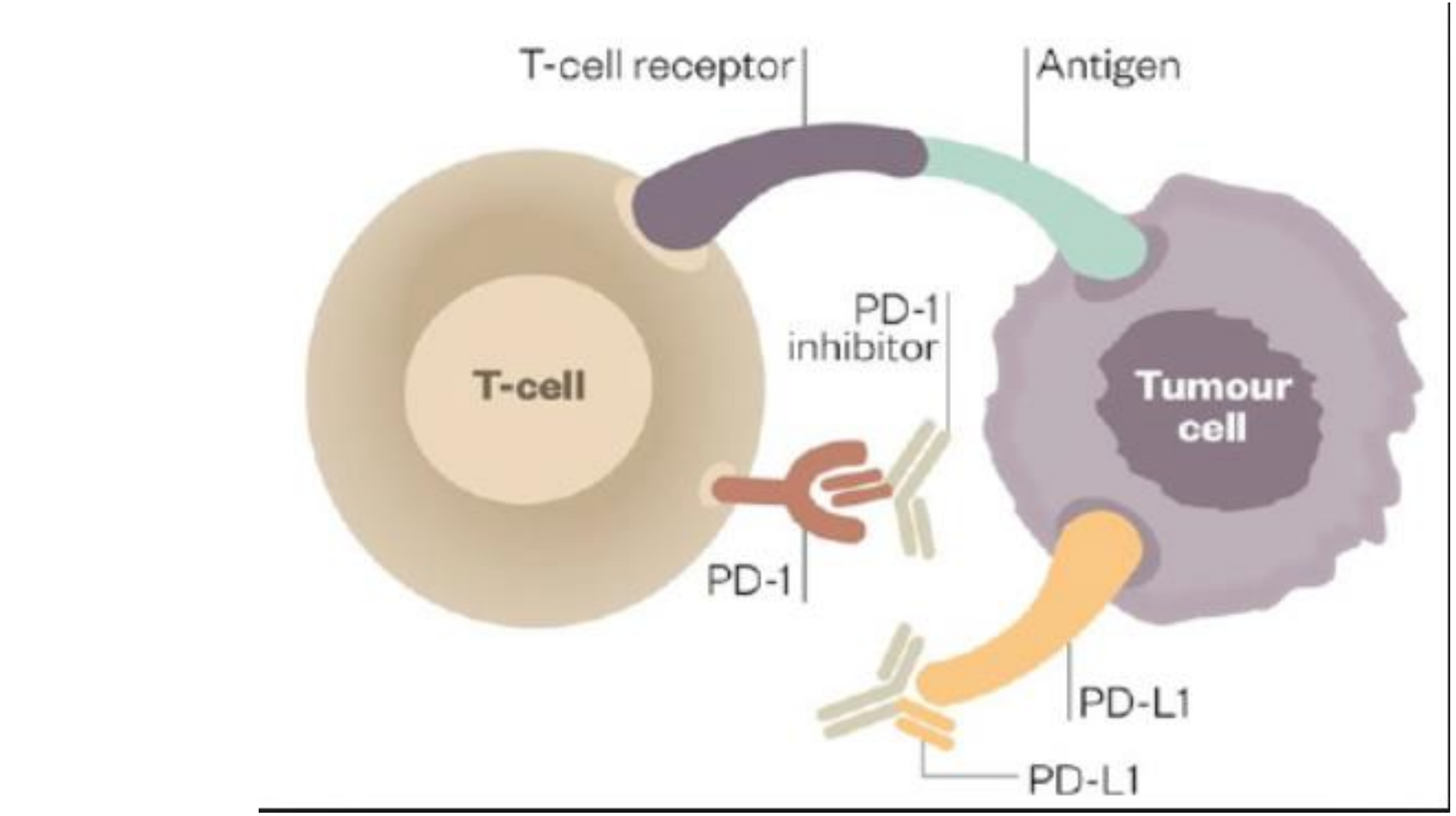
5 months post-treatment

PD1/PDL1 signal

Inhibitory signal

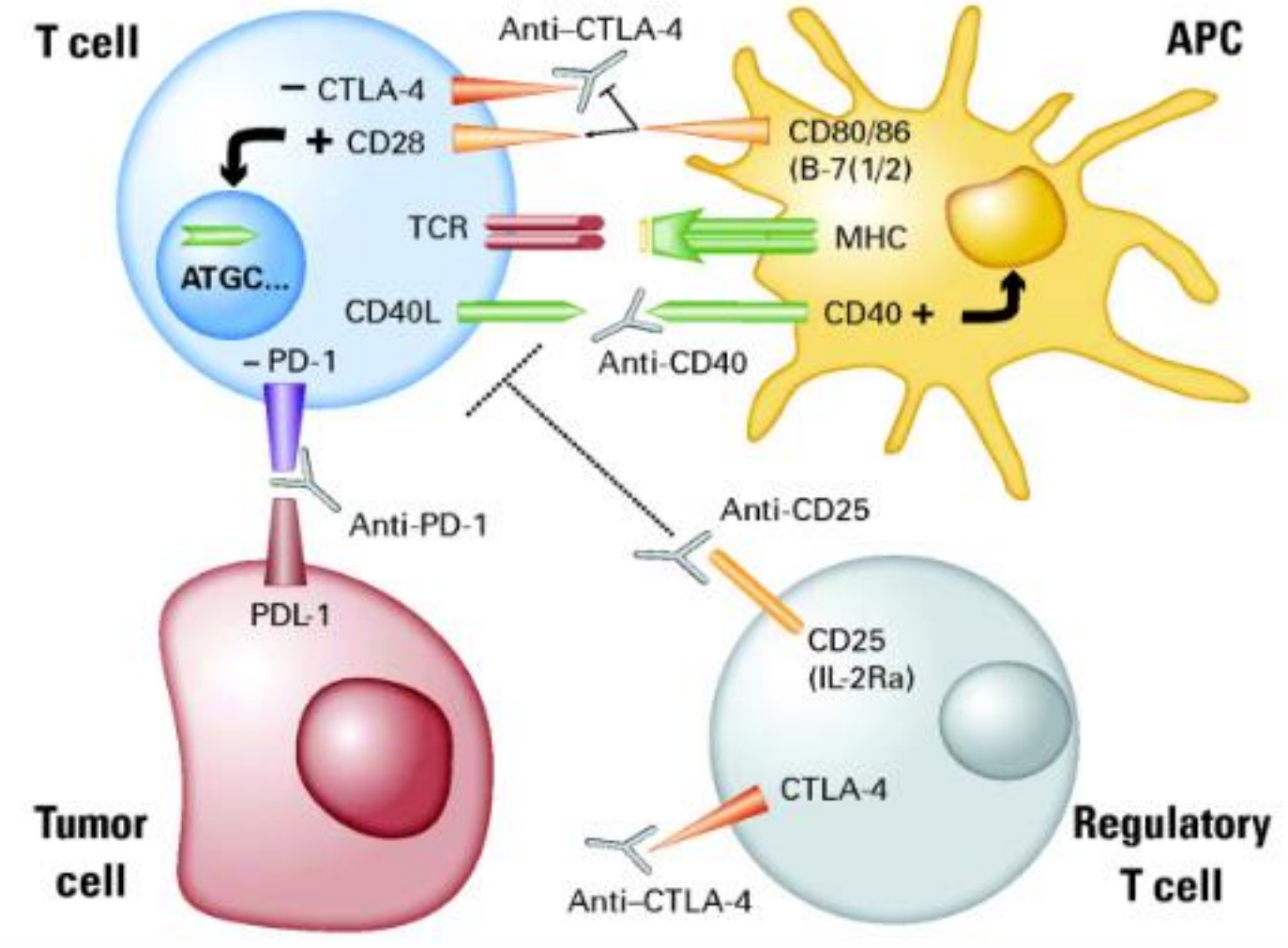


anti PD1 and anti-PDL1

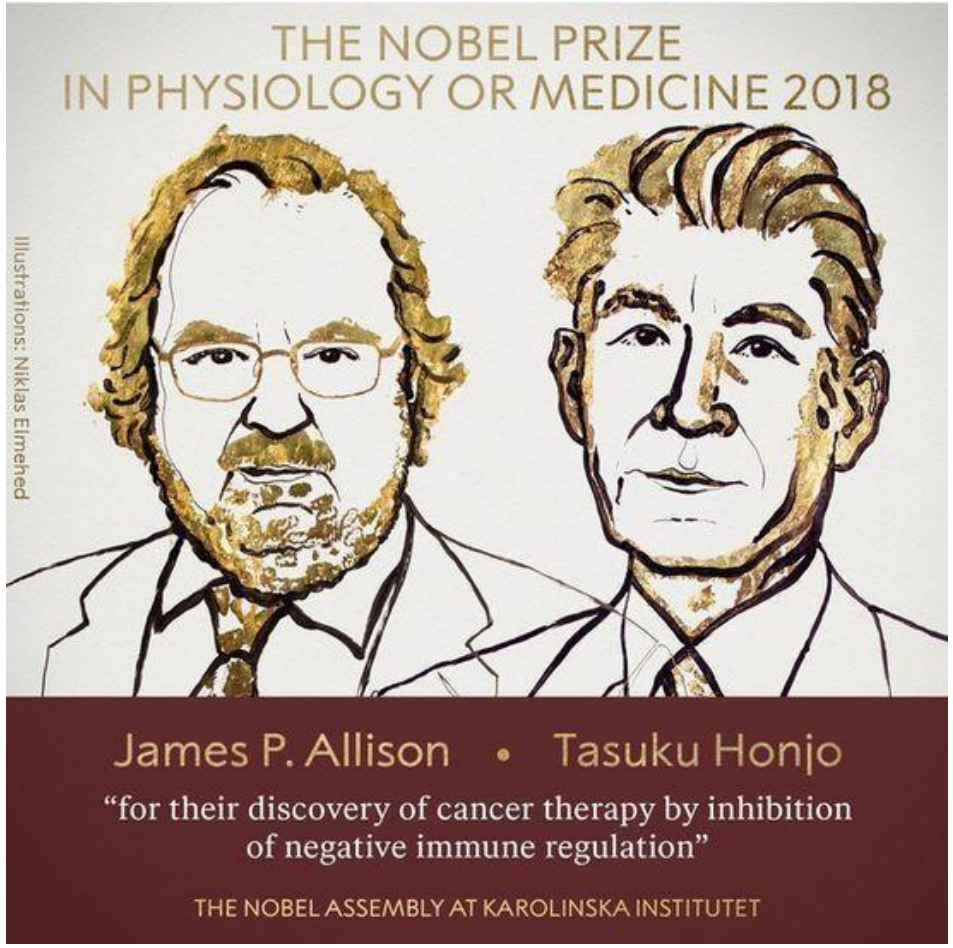


anti-PD1 = binds receptor on T-cells
anti-PDL1 = binds the ligand on tumor cells

anti-PD1/PDL1 and anti-CTLA4

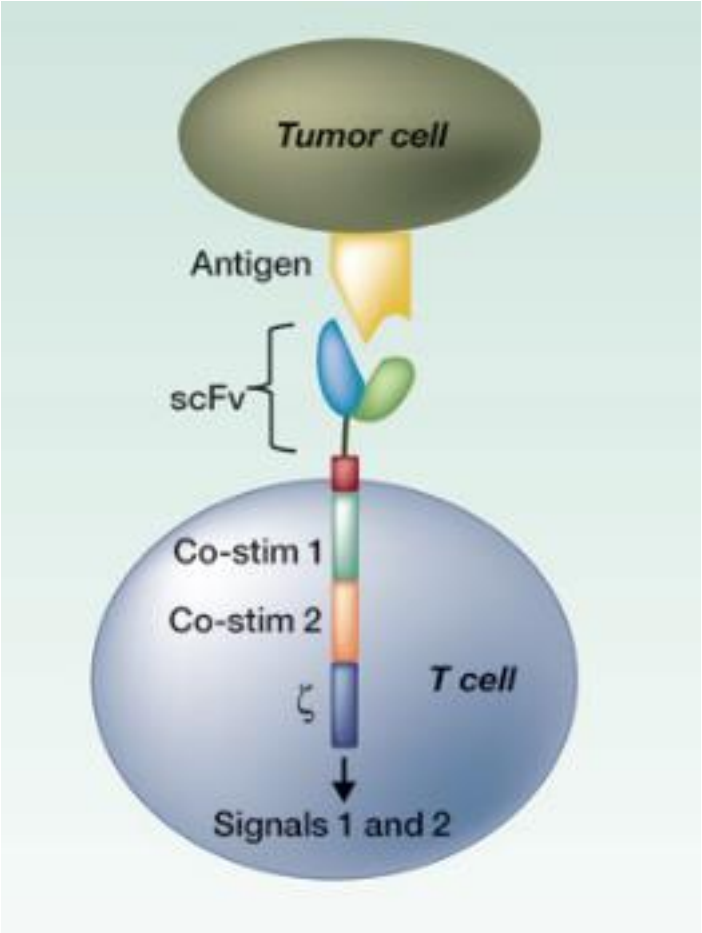


Cover of the year, 2013



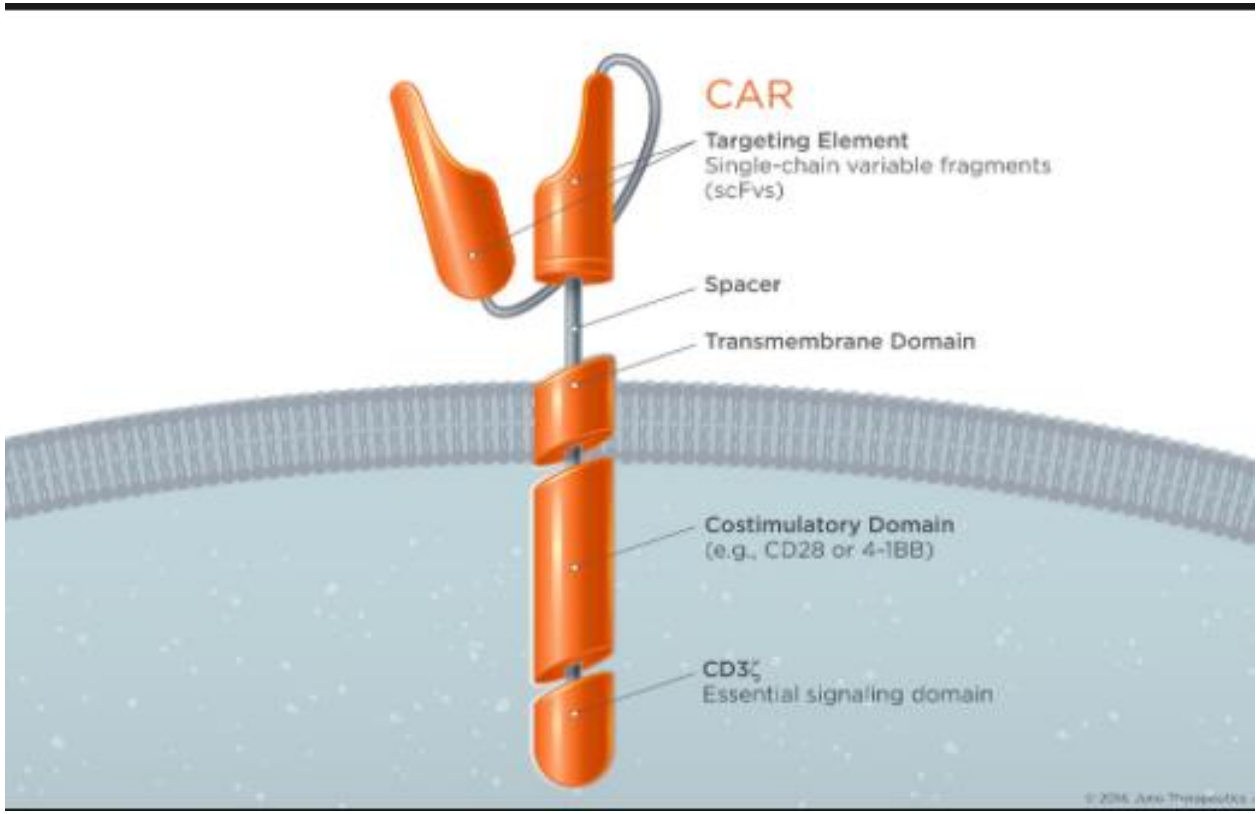
Nobel Prize, 2018

GENETICALLY ENGINEERED T-CELLS

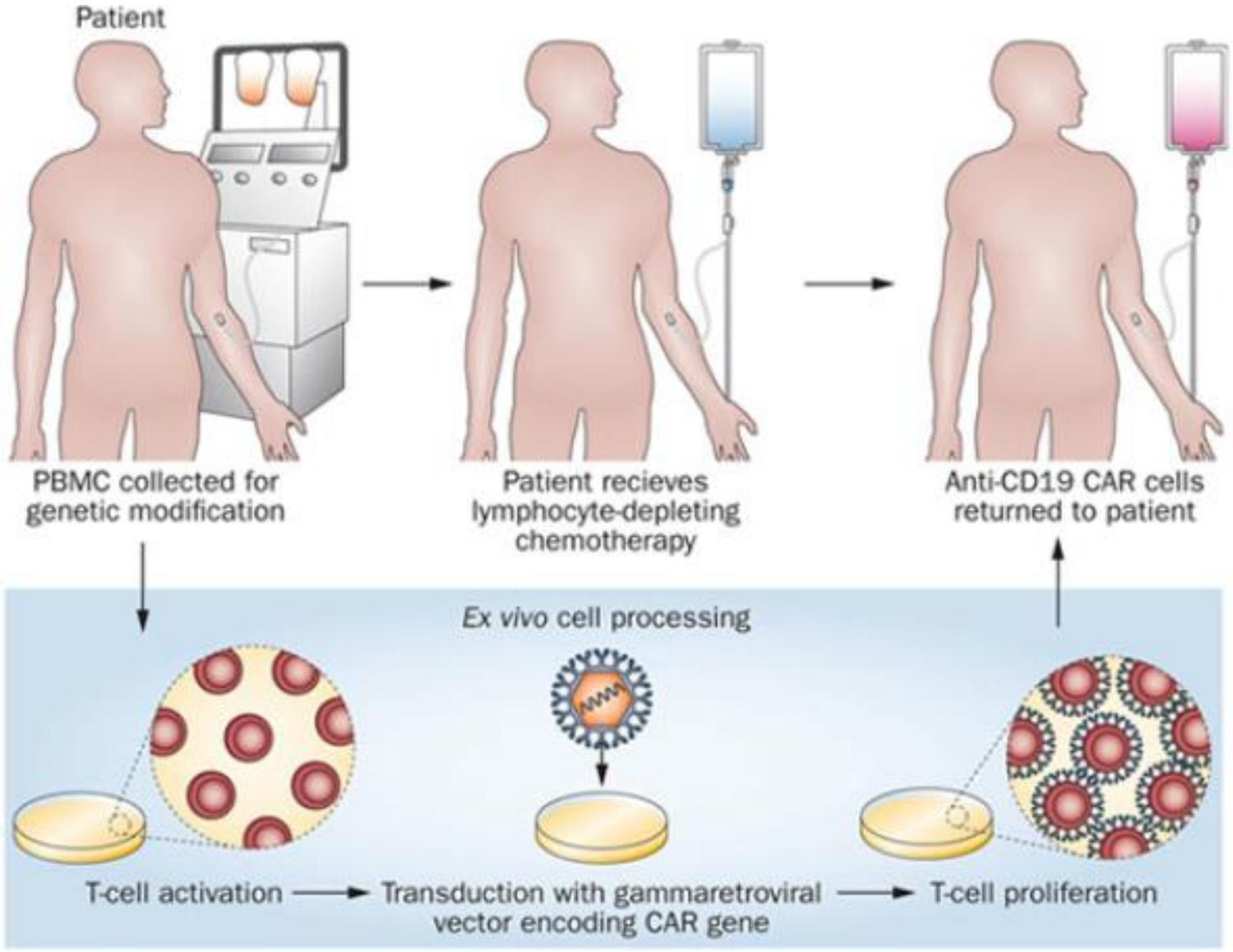


Express an exogenous stimulatory receptor in T-cells,
that it will recognize the antigen on tumor cells and activates T-cells

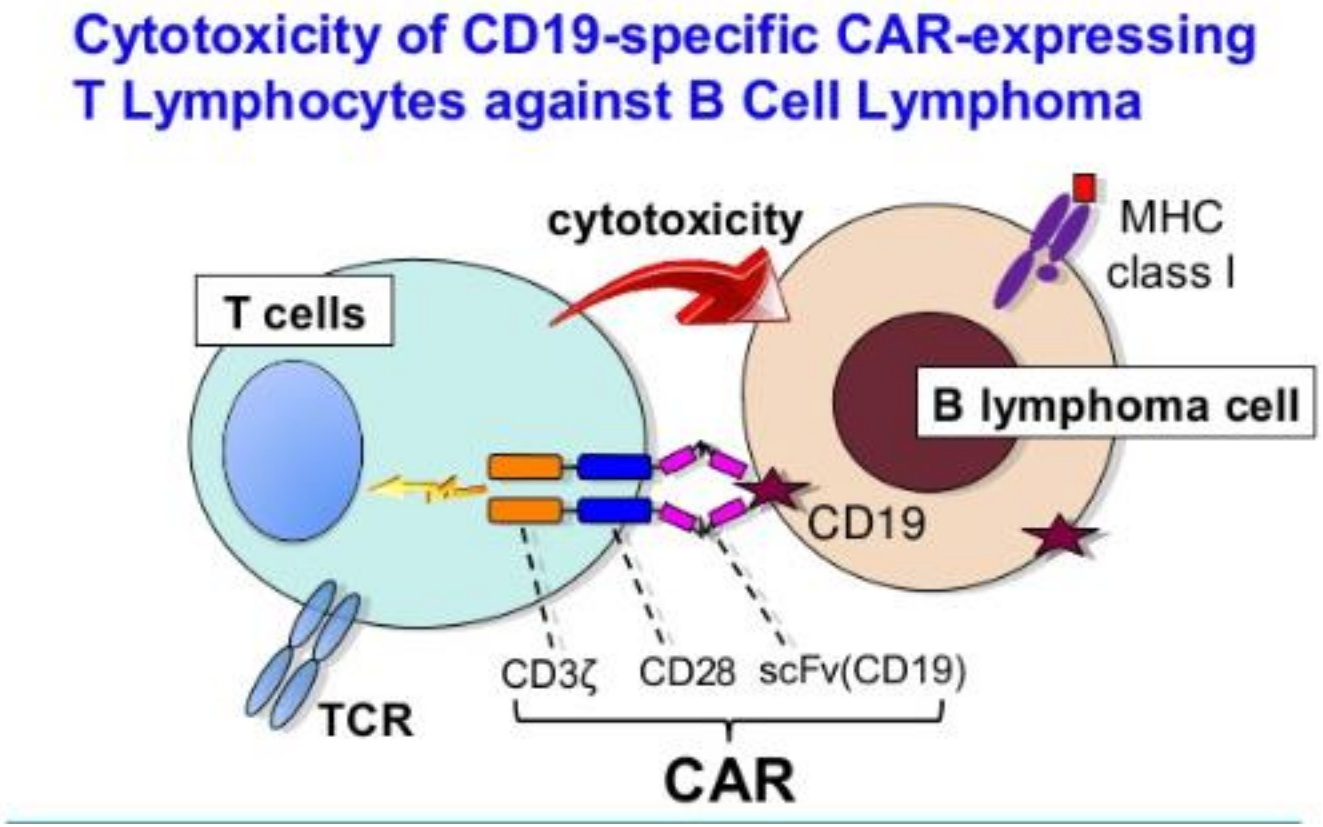
Synthetic receptor is called-CAR



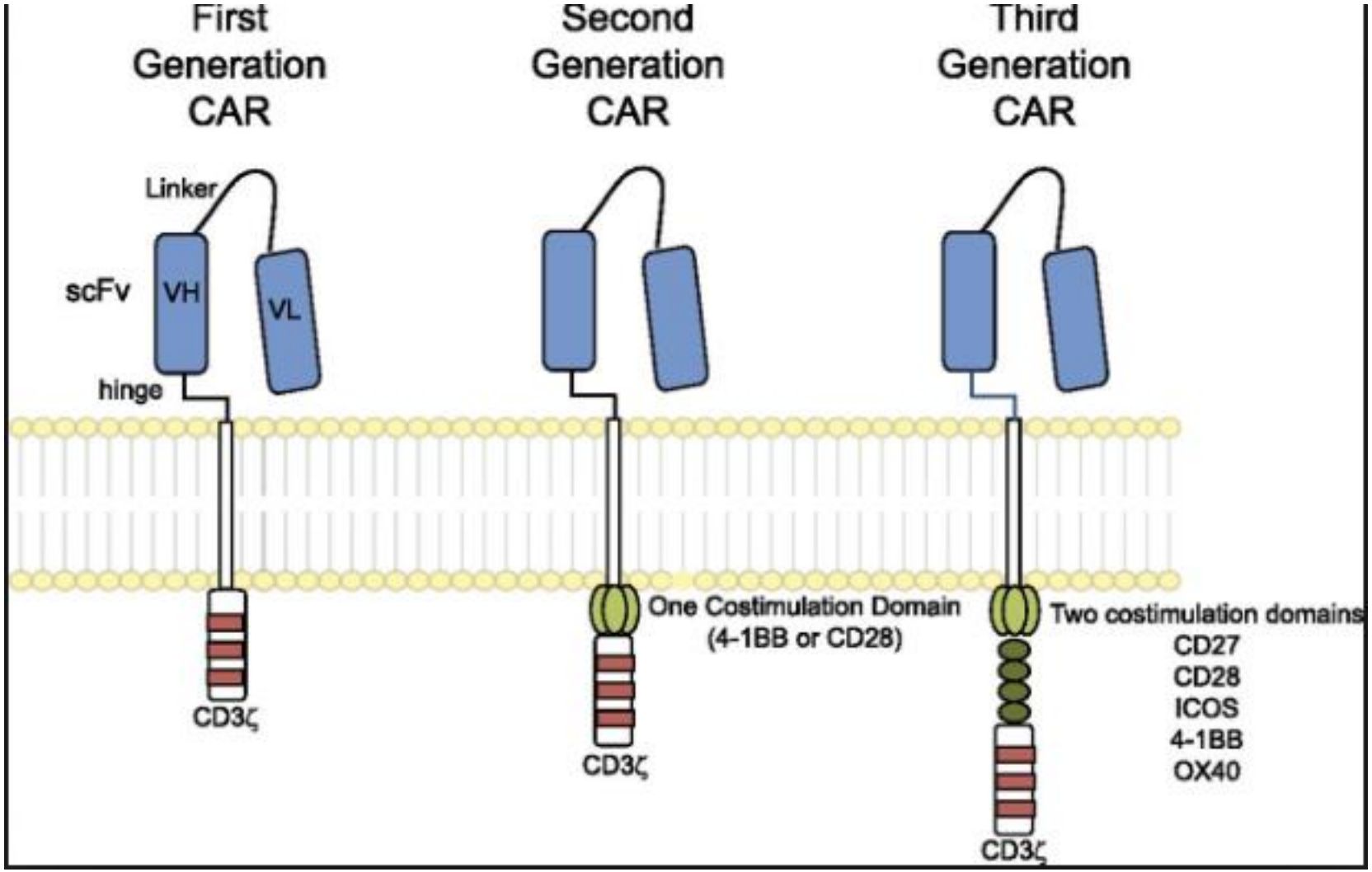
CAR-T cells Therapy



CD19 CAR-T cells therapy for B-cell malignancies



CD19 CAR-T cells Therapy



The first patient treated with CAR-T cells

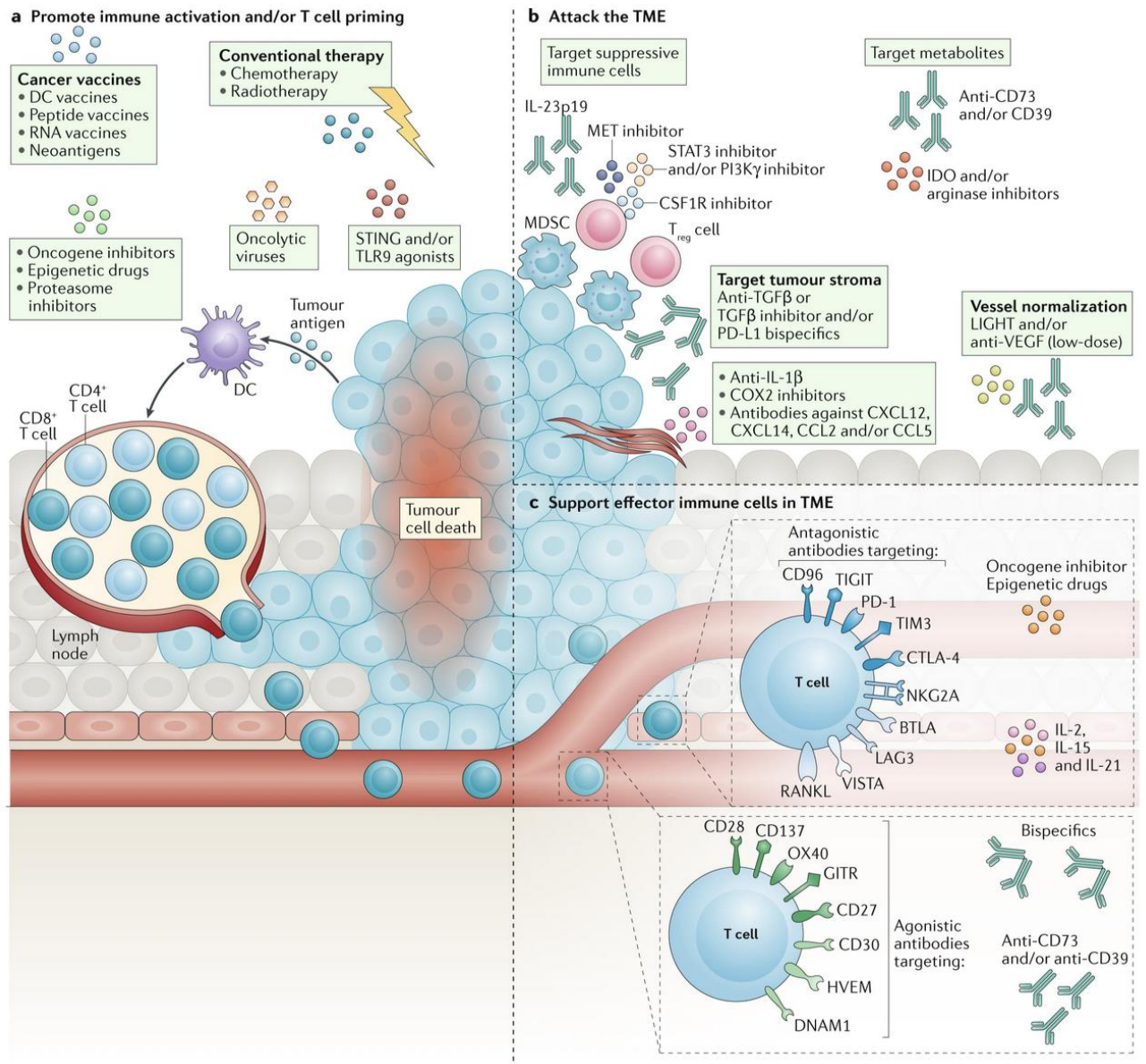
Carl June, MD
UPenn

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/

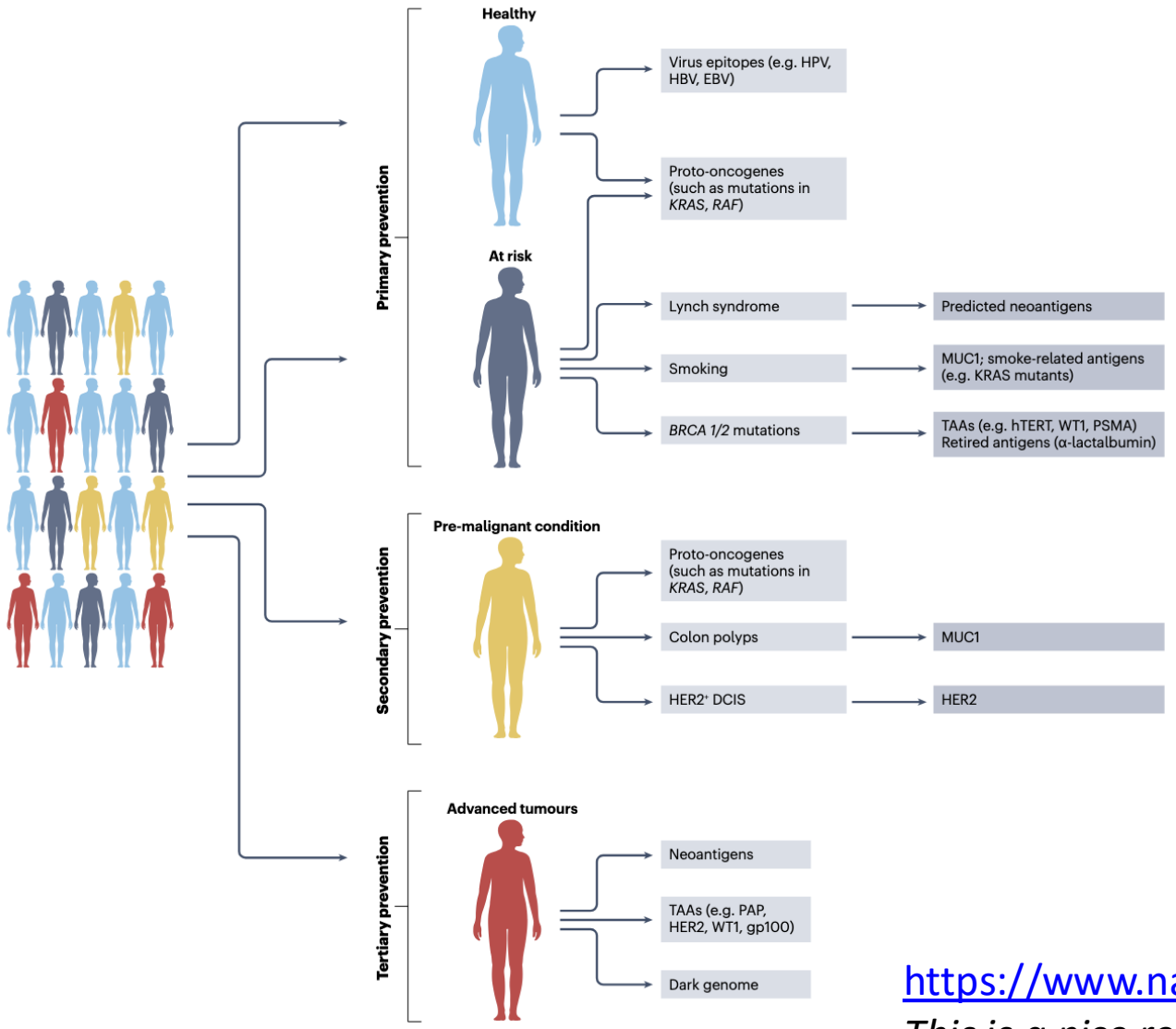
CANCER IS A DISEASE THAT RAPIDLY EVOLVED: MECHANISMs OF RESISTANCE, and COMBINATION THERAPIES

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 last year 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