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Society for Immunotherapy of Cancer

Overview of Adaptive Immunity

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

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Audience Response Question 1

The following are characteristics of the Adaptive Immune Response:

A. Receptor Diversity
B. Memory Response
C. Rapid, first line of defense
D. (A) and (B)
E. (A), (B), and (C)

Audience Response Question 2

Which of the following is not true?

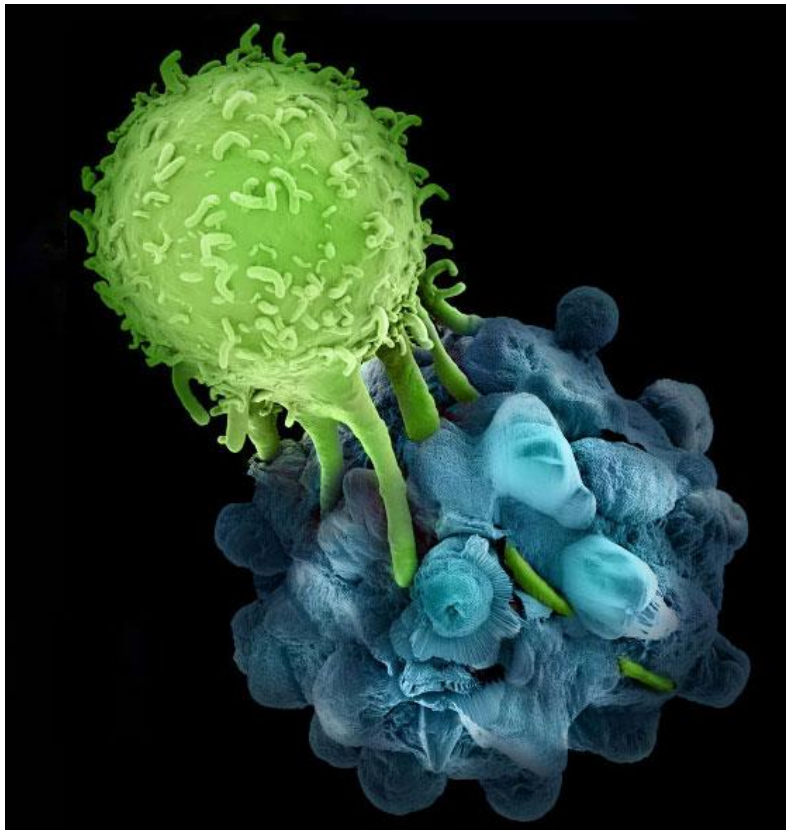
A. Antibodies recognize soluble antigen
B. TCR recognizes antigen presented on the cell surface
C. TCR can also recognize soluble antigen
D. The BCR is antibody on the surface of the B cell
E. All of the above are in fact true

Audience Response Question 3

True or false: For a particular individual, the DNA found in a liver cell is the same as DNA from a mature B cell:

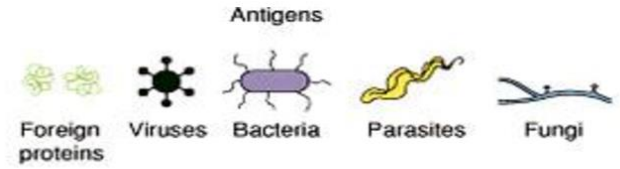
- True
- False

The exquisite specificity of the Adaptive Immune Response makes it a powerful modality for the treatment of cancer



2013 Cancer Immunotherapy Trials Network

YOUR ACTIVE IMMUNE DEFENSES



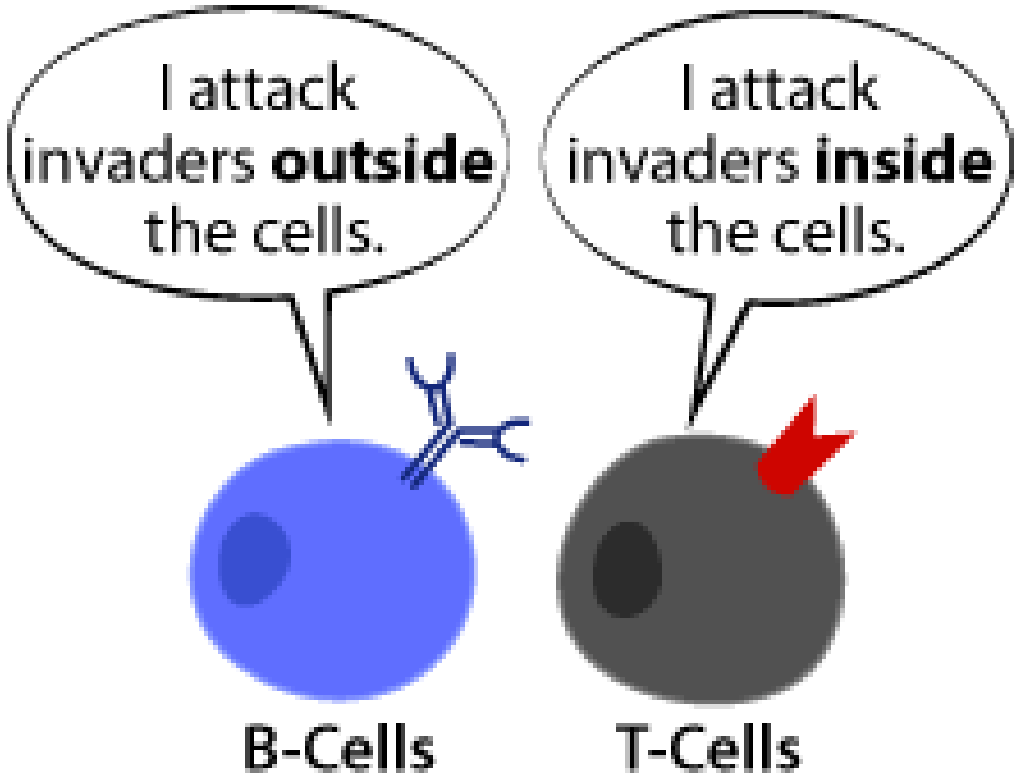
Innate Immunity
- invariant (generalized)
- early, limited specificity
- the first line of defense

1. Barriers - skin, tears
2. Phagocytes - neutrophils, macrophages
3. NK cells and mast cells
4. Complement and other proteins

Adaptive Immunity
- variable (custom)
- later, highly specific
- "remembers" infection

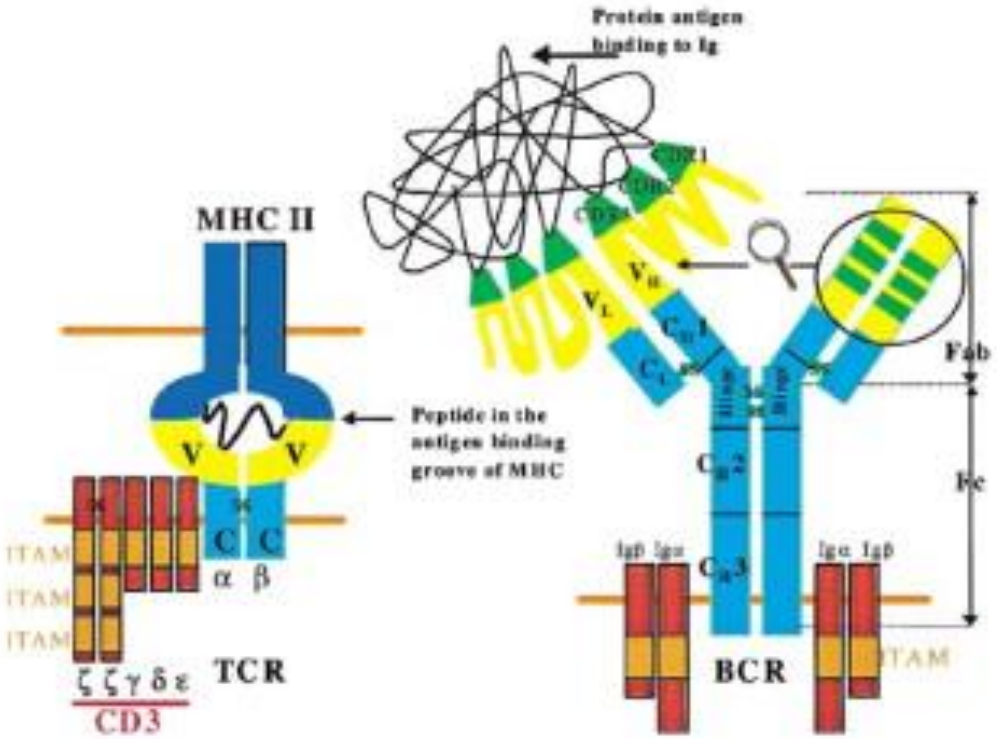
1. APCs present Ag to T cells
2. Activated T cells provide help to B cells and kill abnormal and infected cells
3. B cells - produce antibody specific for antigen

T Cells and B cells make up the Adaptive Immune Response



Ask A Biologist funded in part by the National Science Foundation and NSDL

T Cell Receptors (TCR) recognize antigen presented on the surface of cells while B Cell Receptors (BCR, AKA antibodies) recognize soluble antigen

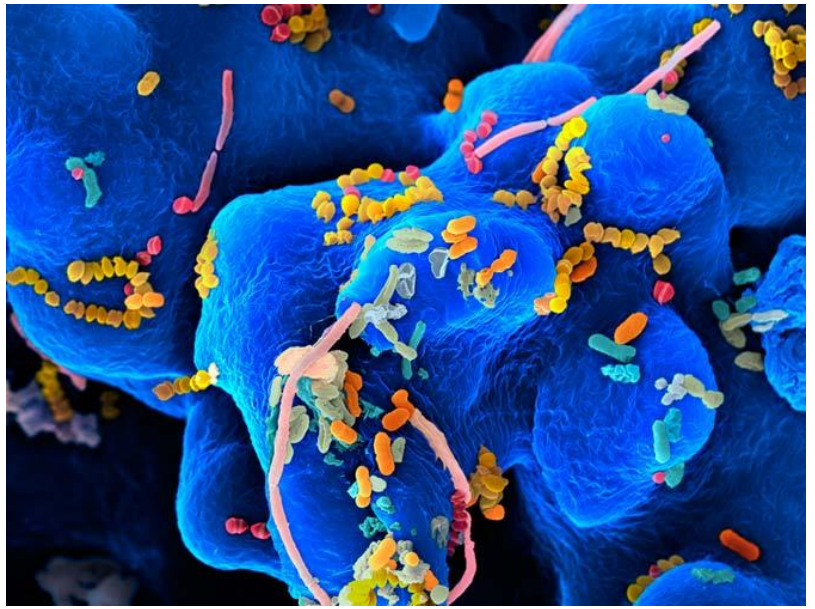


Rafeul Alam, MD, PhD, Magdalena Gorska, MD J ALLERGY CLIN IMMUNOL VOLUME 111, NUMBER 2

2 key features of the adaptive immune response

A vast array of incredibly diverse antigen specific receptors

Memory, that is the ability to respond rapidly upon rechallenge by the same pathogen

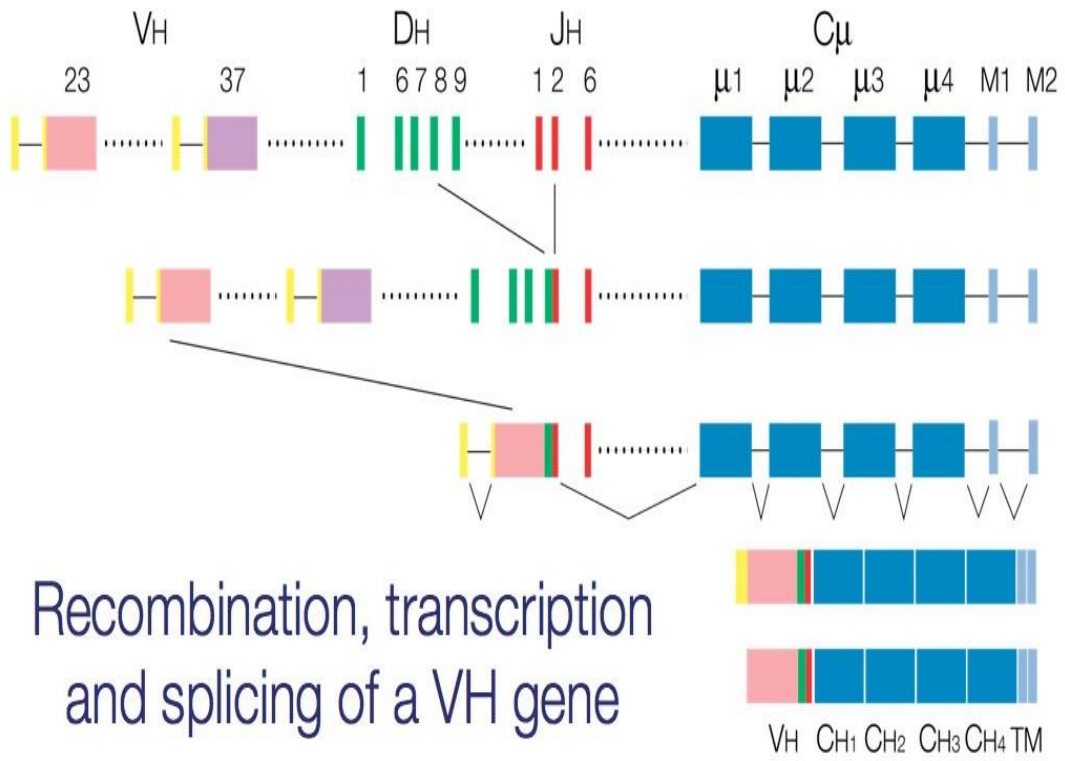


Generation of Diversity

The diverse number of antigen specific TCR and BCR are NOT encoded by germline genes

Rather, each receptor is generated through recombining different combinations of genes

Generation of Diversity through recombination



UNIPV, Italy

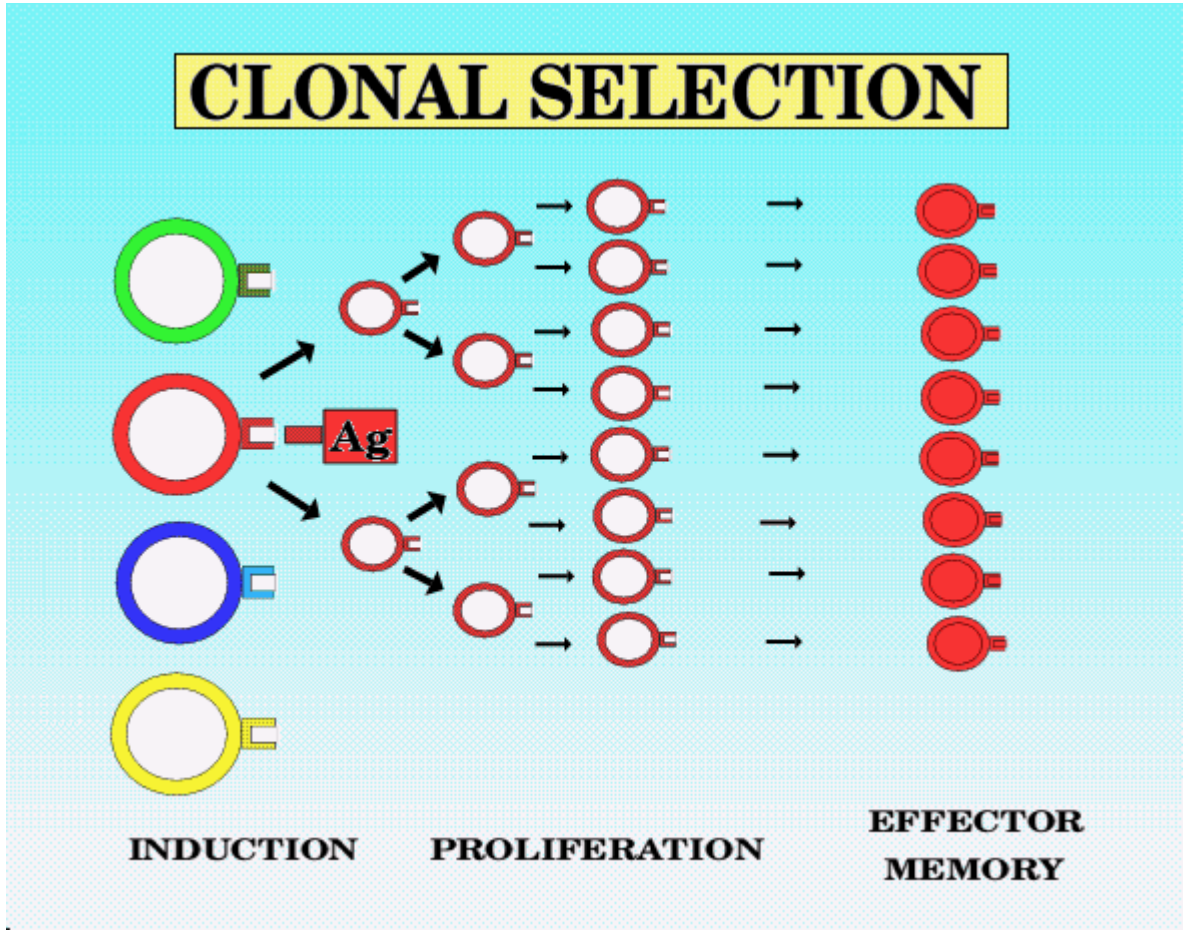
Do the math

The human genome is presently estimated to contain 20–25 thousand genes. The number of T-cell receptors for antigen (**TCR**s) that we make is estimated at 2.5 x 10^7; the number of different kinds of antibody molecules (**BCR**s) is probably about the same.

Antibodies (BCRs)	Gene Segments	Combinations
Vκ	40	
Jκ	5	200 κ chains
Vλ	31	
Jλ	4	124 λ chains
V_H	51	
D_H	25	
J_H	6	7,650 H chains
Any H chain with any L chain (324)		2.5 x 10^6

Kimball's Biology Pages

If there are so many different receptors how does an effective immune response generated?



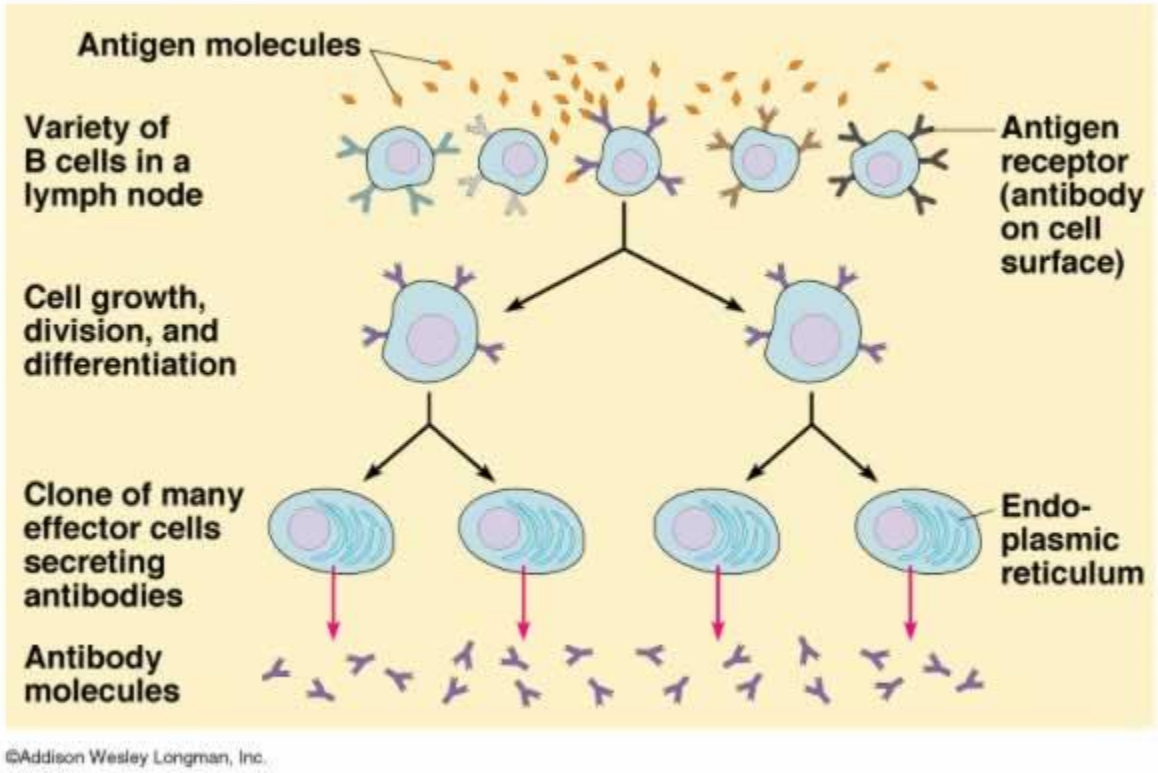
Steve Cobold

Thus, clonal selection….

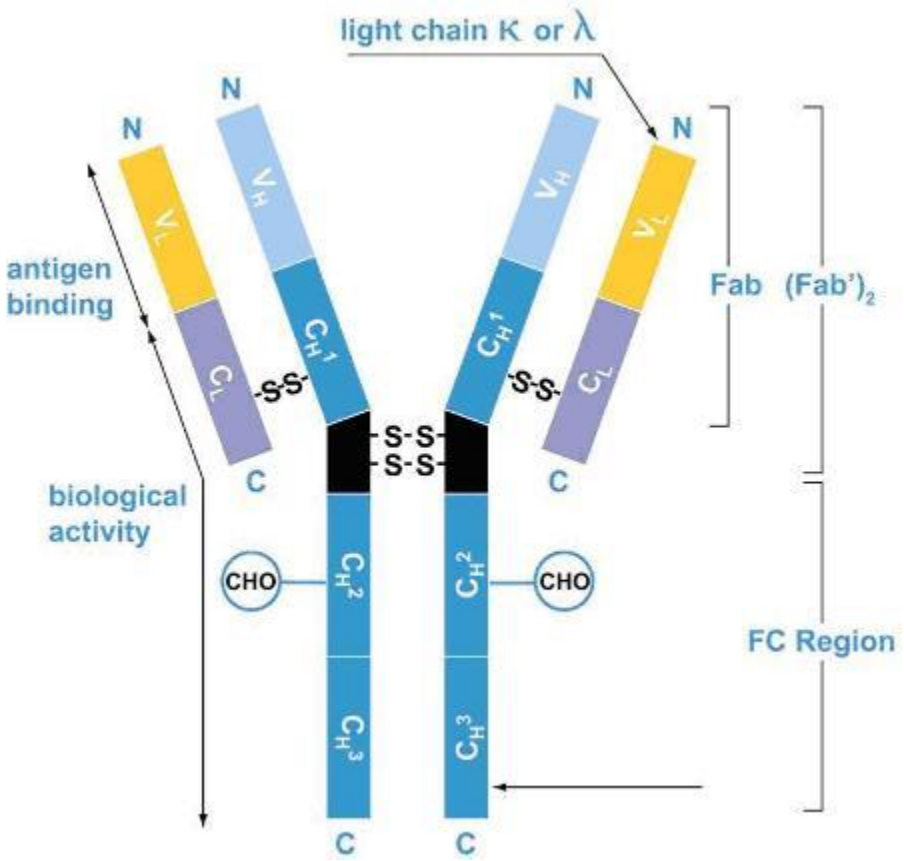
Promotes robust, antigen specific effector responses

Leads to the generation of memory

B cells make antibodies



Basic structure of antibodies



Abcam

Antibody isotypes of mammals

Name	Types	Description
IgA	2	Found in mucosal areas, such as the gut, respiratory tract and urogenital tract, and prevents colonization by pathogens. Also found in saliva, tears, and breast milk.
IgD	1	Functions mainly as an antigen receptor on B cells that have not been exposed to antigens. It has been shown to activate basophils and mast cells to produce antimicrobial factors.
IgE	1	Binds to allergens and triggers histamine release from mast cells and basophils, and is involved in allergy. Also protects against parasitic worms.
IgG	4	In its four forms, provides the majority of antibody-based immunity against invading pathogens. The only antibody capable of crossing the placenta to give passive immunity to fetus.
IgM	1	Expressed on the surface of B cells and in a secreted form with very high avidity. Eliminates pathogens in the early stages of B cell mediated (humoral) immunity before there is sufficient IgG.

Antibody Complexes

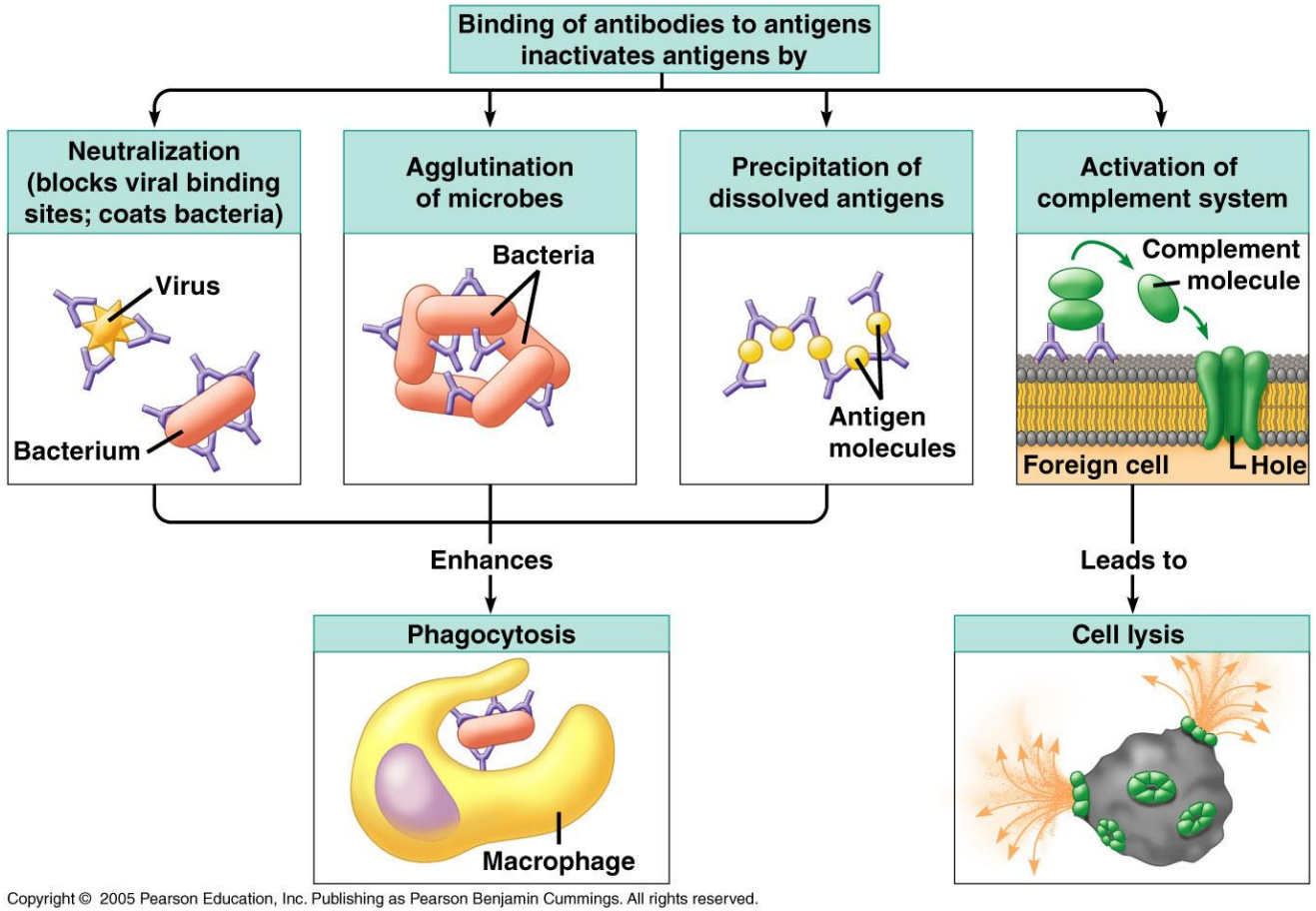
Monomer
IgD, IgE, IgG

Dimer
IgA

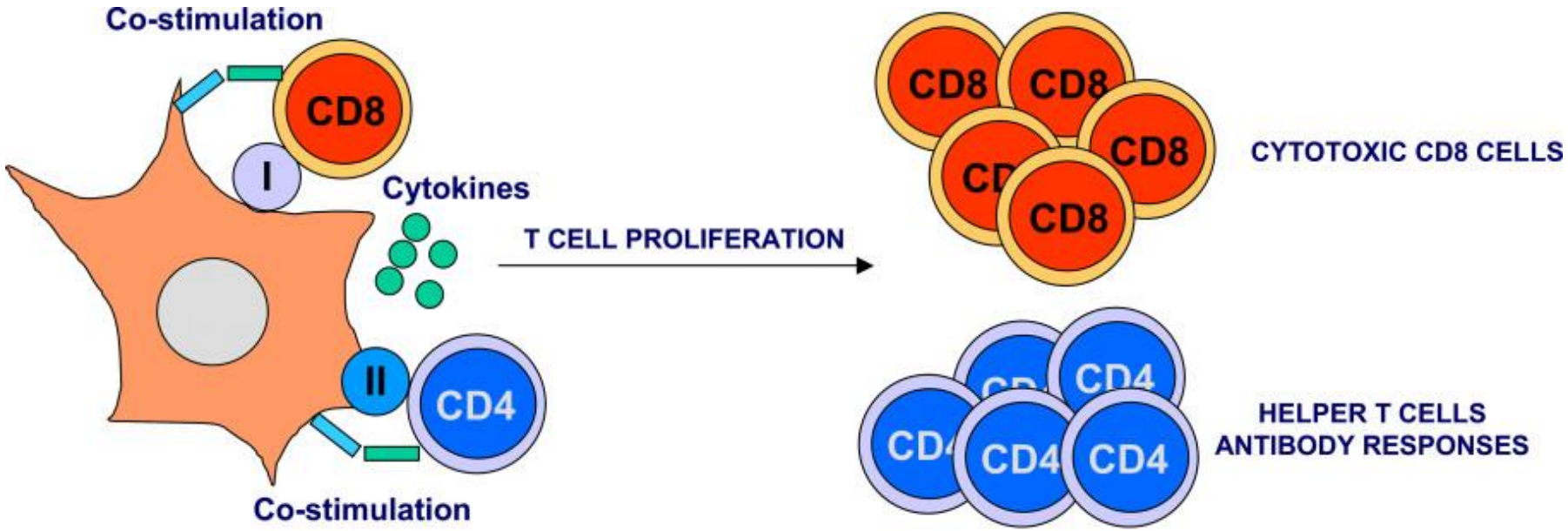
Pentamer
IgM

Adapted from Wikipedia, the free encyclopedia.

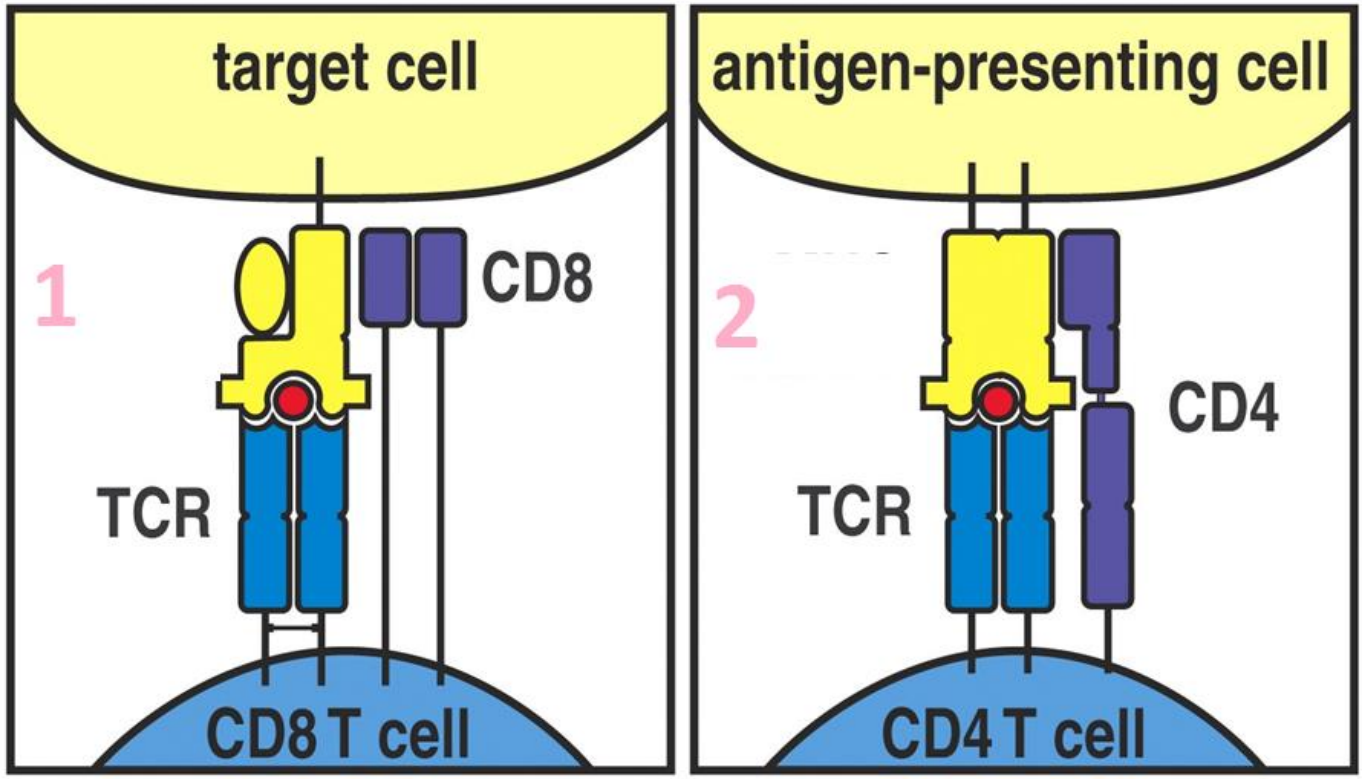
Antibody effector mechanisms



T cells come in Two flavors



CD8 T cells recognize antigen presented by MHC class I and CD4 T cells recognize antigen presented by MHC class II



Study Blue

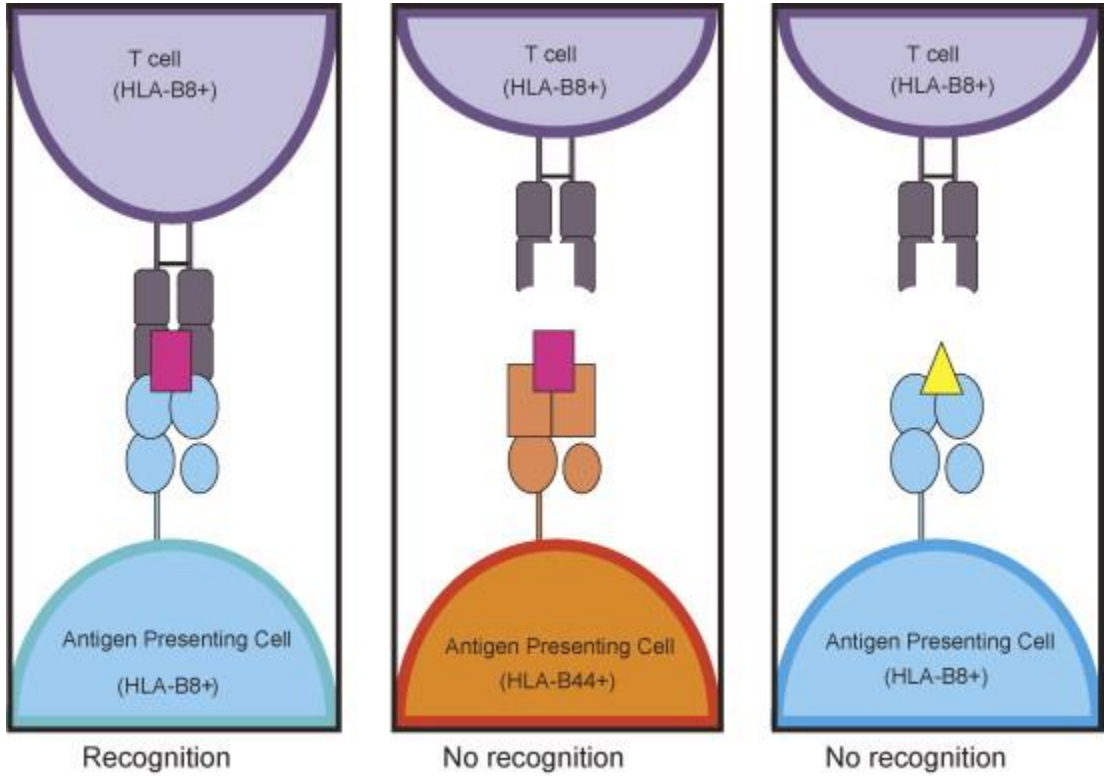
Class I and Class II recognition relates to different functions of CD4 & CD8 cells

Table 2. Characteristics of the antigen processing pathways

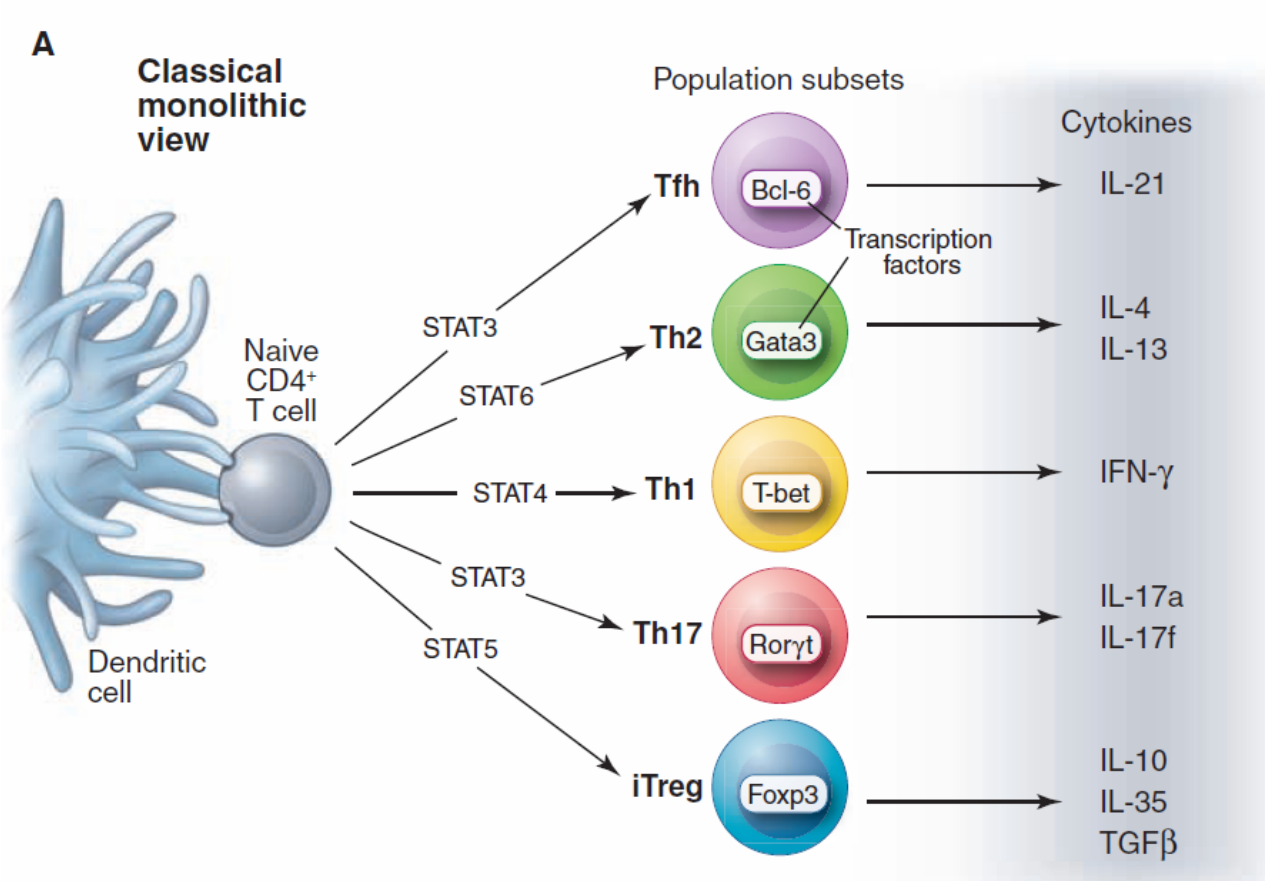
Characteristic	MHC-I pathway	MHC-II pathway
Composition of the stable peptide-MHC complex	Polymorphic chain α and β2 microglobulin, peptide bound to α chain	Polymorphic chains α and β, peptide binds to both
Types of antigen presenting cells (APC)	All nucleated cells	Dendritic cells, mononuclear phagocytes, B lymphocytes, some endothelial cells, epithelium of thymus
T lymphocytes able to respond	Cytotoxic T lymphocytes (CD8+)	Helper T lymphocytes (CD4+)
Origin of antigenic proteins	cytosolic proteins (mostly synthetized by the cell; may also enter from the extracellular medium via phagosomes)	Proteins present in endosomes or lysosomes (mostly internalized from extracellular medium

Wikipedia

Briefly, what is meant by MHC restriction?

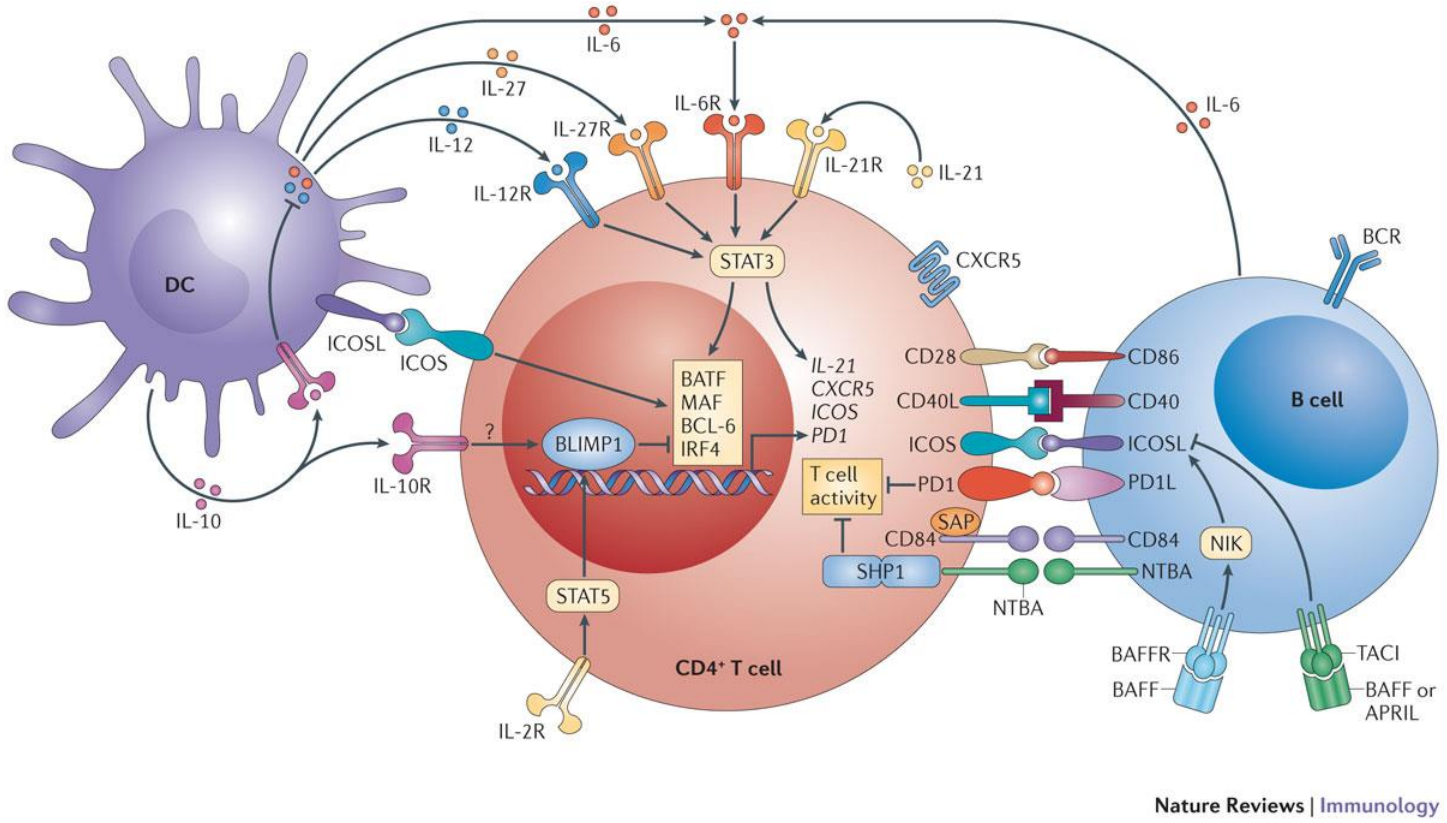


Different Types of CD4 effector cells



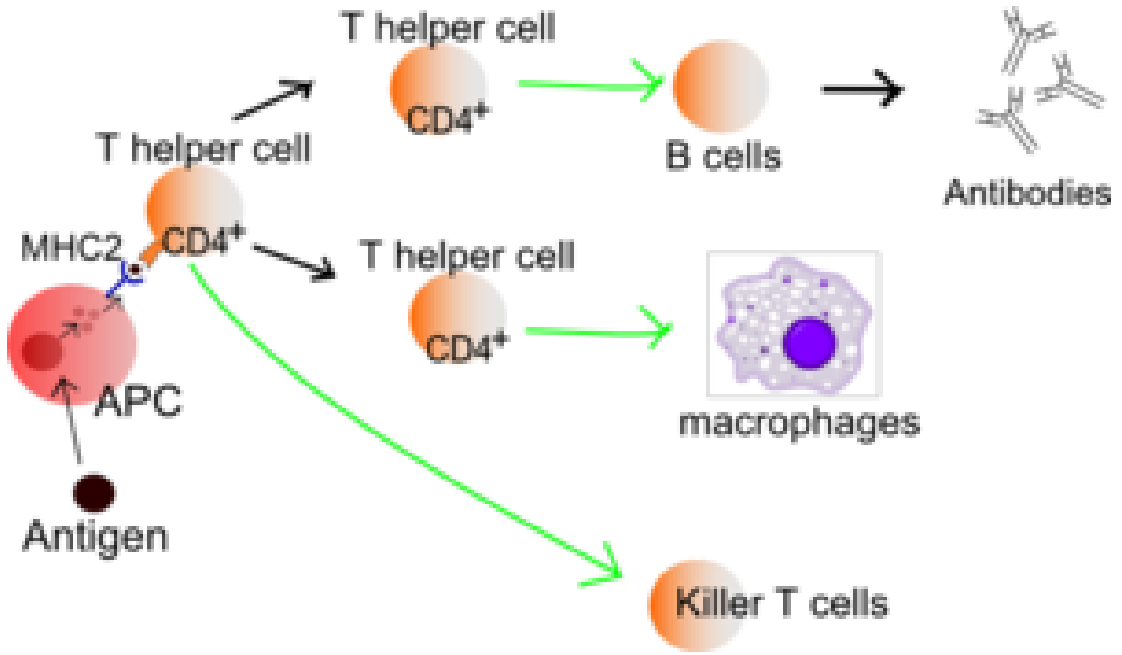
O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. Science. 2010 Feb 26;327(5969):1098-102.

CD4+ T cells "Help" B cells



Nature Reviews | Immunology

CD4+ T cells also “Help” macrophages and CD8+ CTL’s



CD8+ T cells kill infected cells
But first they must be activated

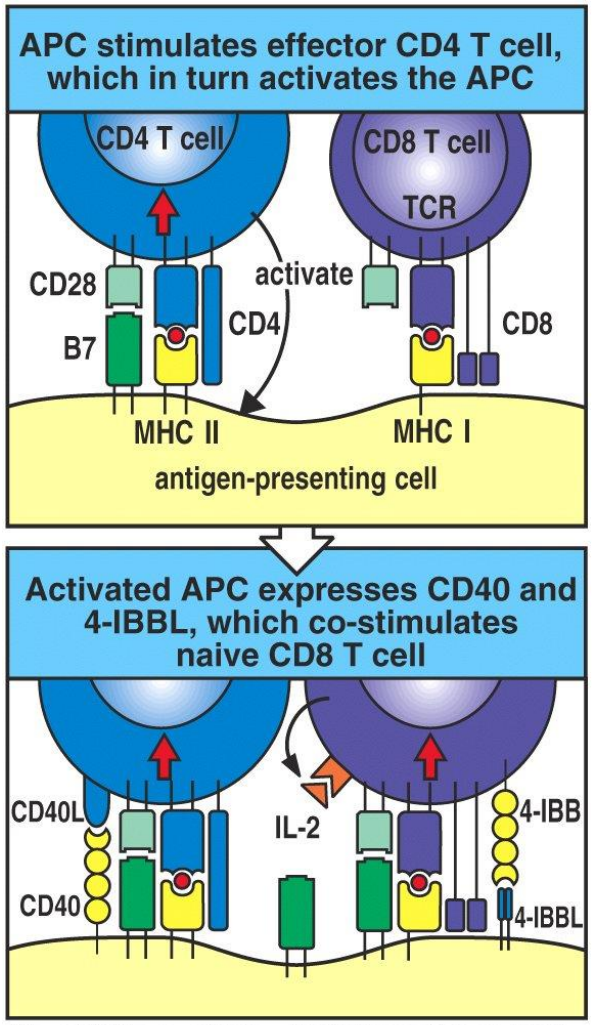


Figure 8-26 Immunobiology, 6/e. (© Garland Science 2005)

Effector CD8+ T cells expand, kill their targets, then die

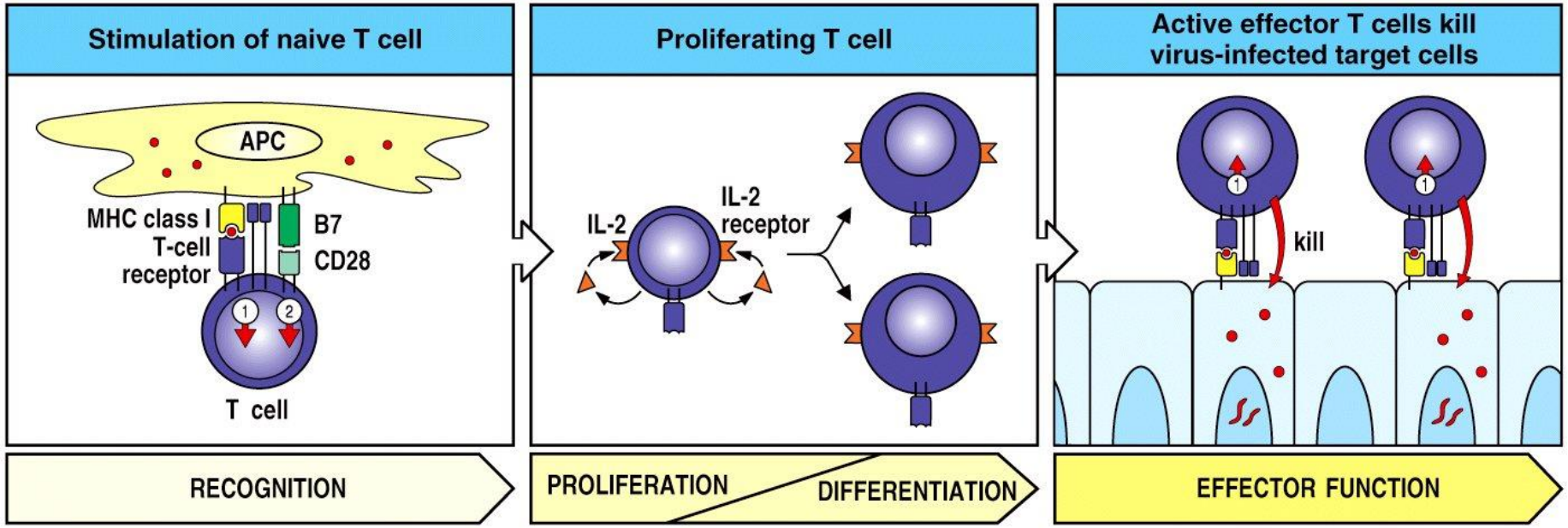
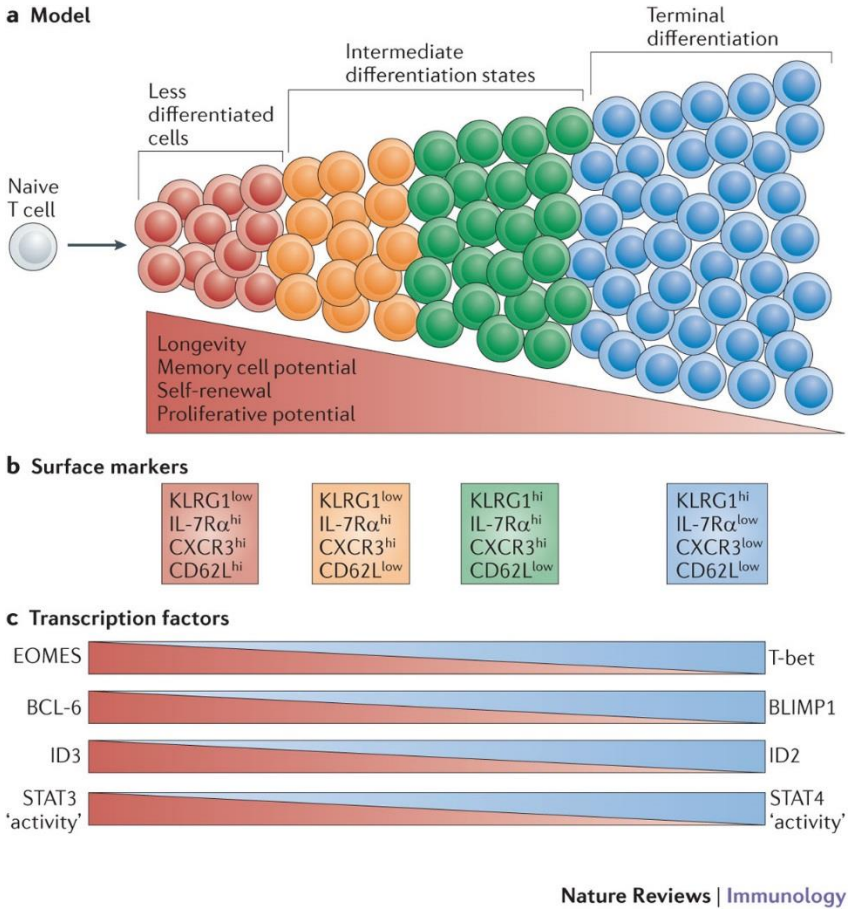


Figure 8-22 Immunobiology, 6/e. (© Garland Science 2005)

Some of the activated CD8+ T cells become long lived memory cells



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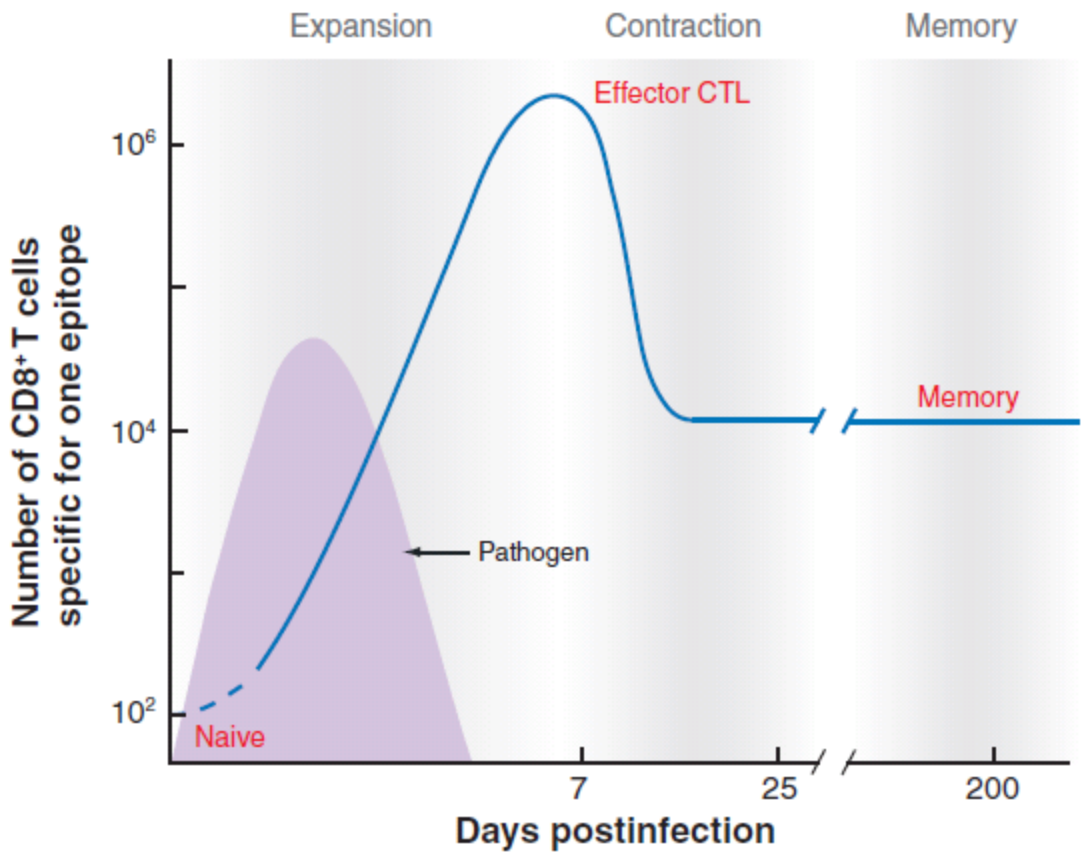
Generalized CD8+ T cell response



Summary of T cell functions

	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	T_{FH} cells	CD4 regulatory T cells (various types)
Types of effector T cell						
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response Promote barrier integrity (skin, intestine)	B-cell help Isotype switching Antibody production	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	*Klebsiella pneumoniae* Fungi (*Candida albicans*)	All types	

Figure 9.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Since the generation of diversity is a stochastic post-germline encoded event, a critical component of the immune response must subsequently be the ability to discern between harmful and innocuous antigens in a tolerance process.

On the one hand in order to deal with any and all potential pathogens the immune system generates at random a diverse array of receptors.

On the other hand a mechanism (tolerance) must be in place in order to prevent these receptors from recognizing and destroying the organism it is designed to protect.

Does the immune system recognize Good versus Evil or Self versus Non-self?

Shifting Paradigms

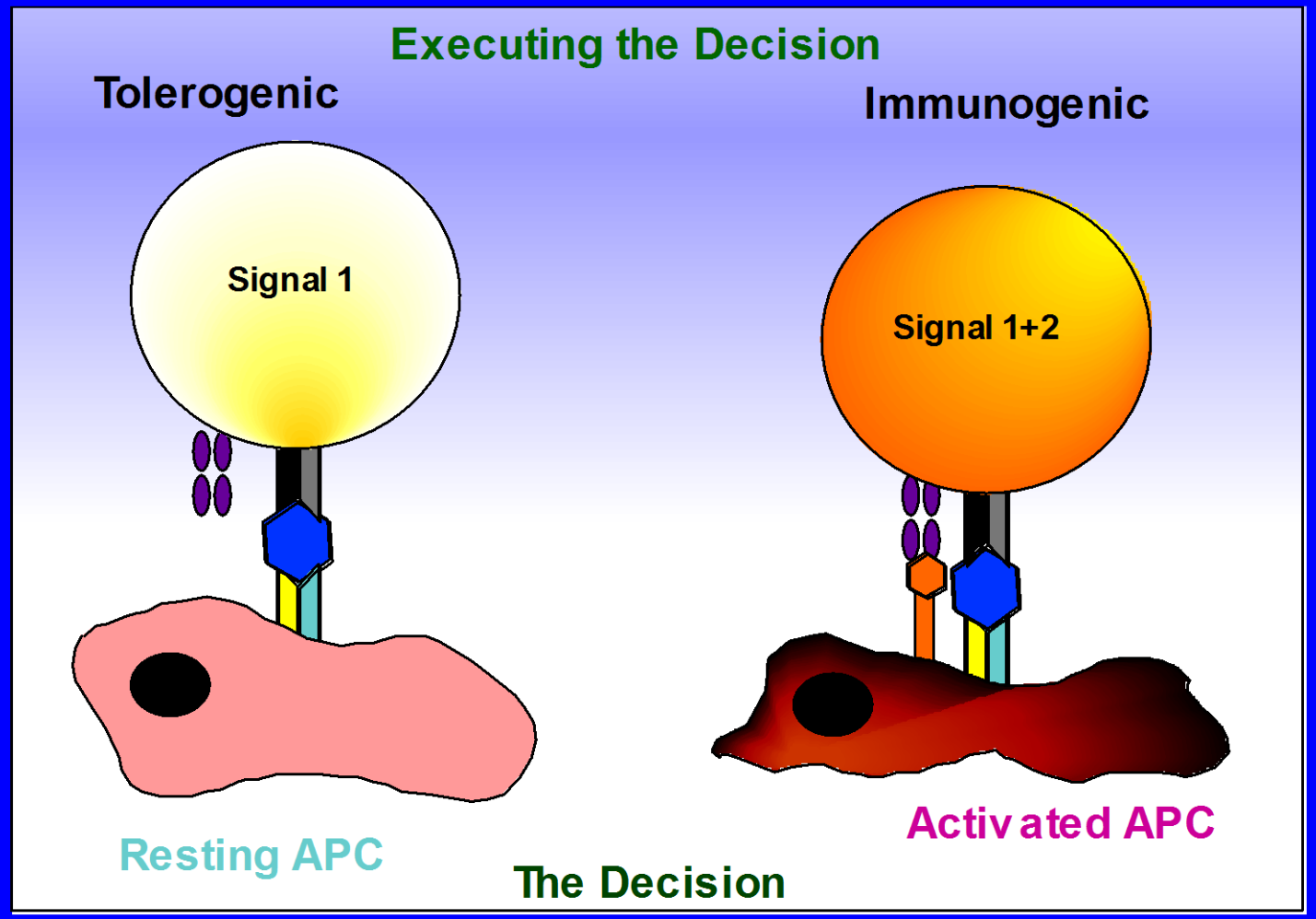
Old

- Self-Non self
- Antigen Driven
- Developmentally Determined

New

- Context Models
- Circumstance Driven
- Determined by milieu

Executing the Will of APC's



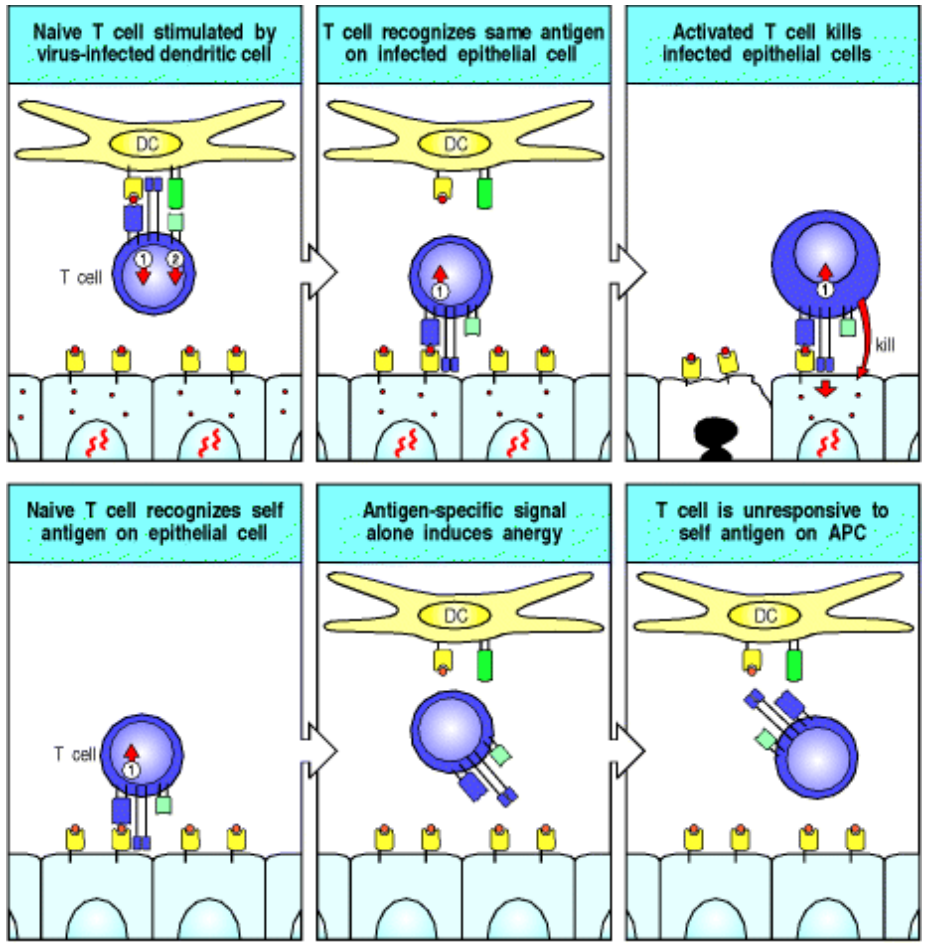
Activated APCs express costimulatory molecules (Signal 2)

Signal 1: Refers to T cell receptor (TCR) recognition of antigen. Signal 1 alone leads to anergy or deletion.

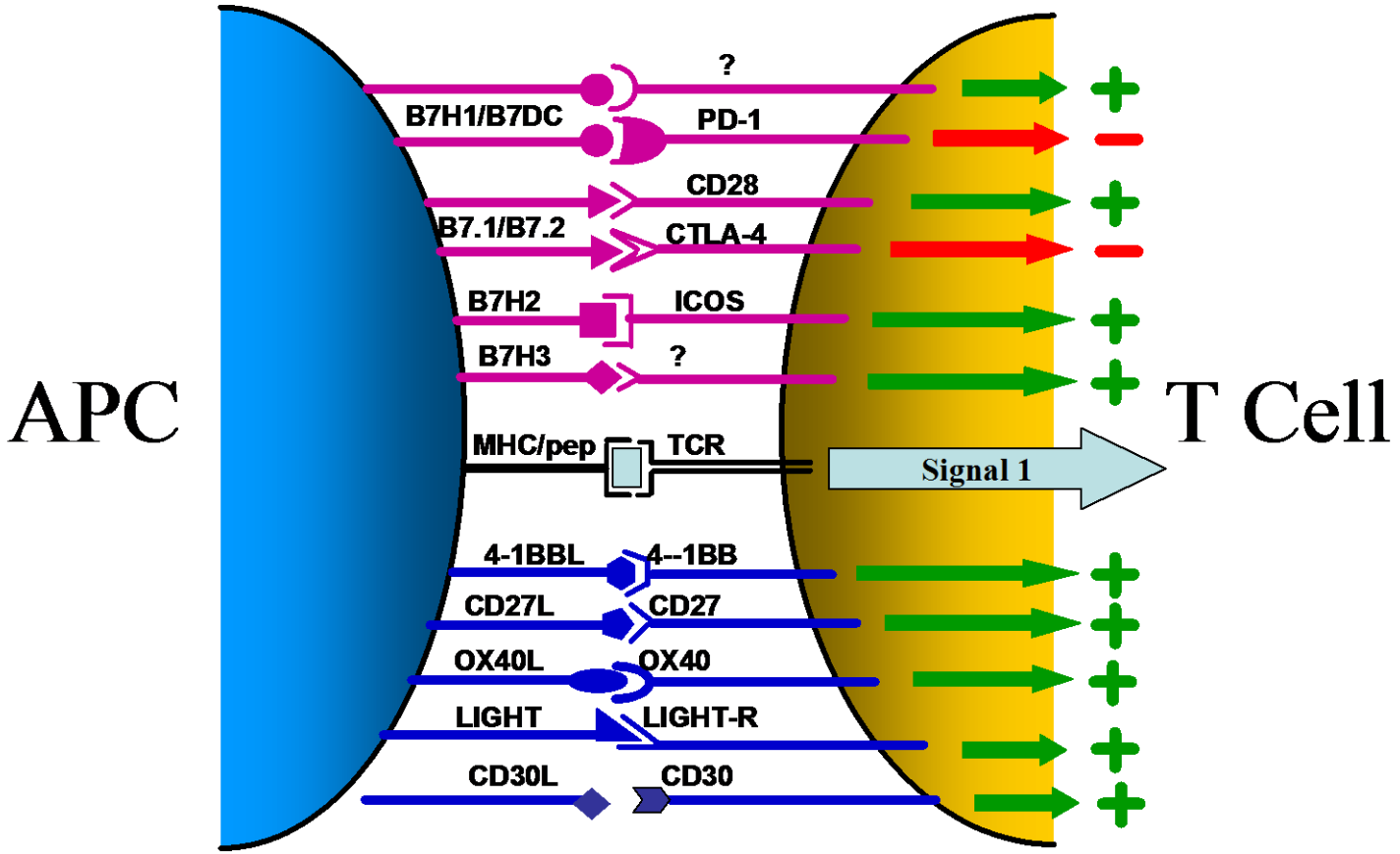
Signal 2: Refers to costimulatory molecule engagement (example CD28).

Signal 1+2 leads to full T cell activation.

Consequences of Signal 1 versus Signal 1+2



In reality Signal 2 is the sum of both costimulatory signals AND co-inhibitory signals



Based on what I told you how can we exploit the Adaptive Immune Response to Kill tumors?

Vaccine to induce clonal selection and memory response

Passively give antibodies that are directed against tumors

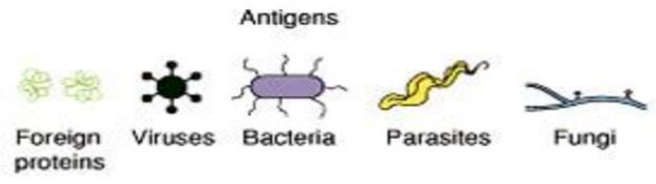
Grow up large quantities of tumor-specific T cells and then give them back to patient.

Promote the activation of APC's (Rev up Signal 2)

Inhibit/ destroy regulatory cells

Block co-inhibitory signals (Checkpoint Blockade)

YOUR ACTIVE IMMUNE DEFENSES



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