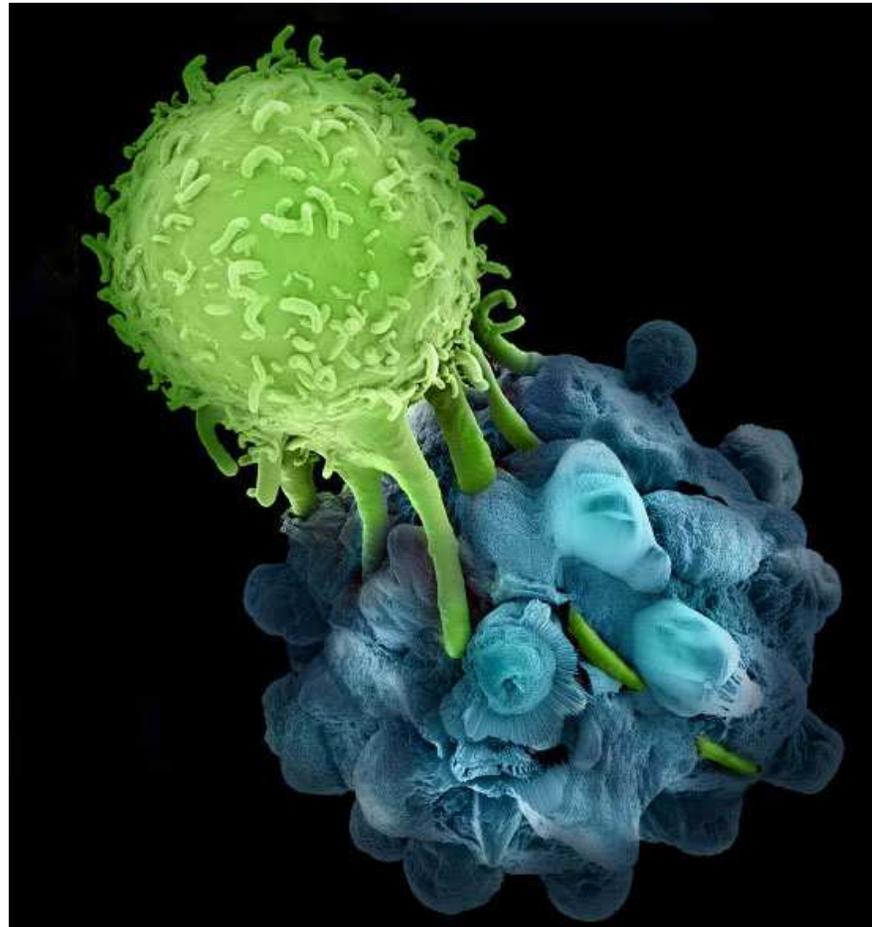


The Adaptive Immune Response

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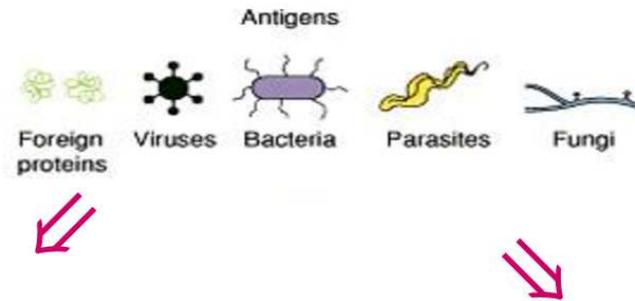
The exquisite specificity of the Adaptive Immune Response makes it a powerful modality for the treatment of cancer



2013 Cancer Immunotherapy Trials Network

YOUR ACTIVE IMMUNE DEFENSES

1



Innate Immunity

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

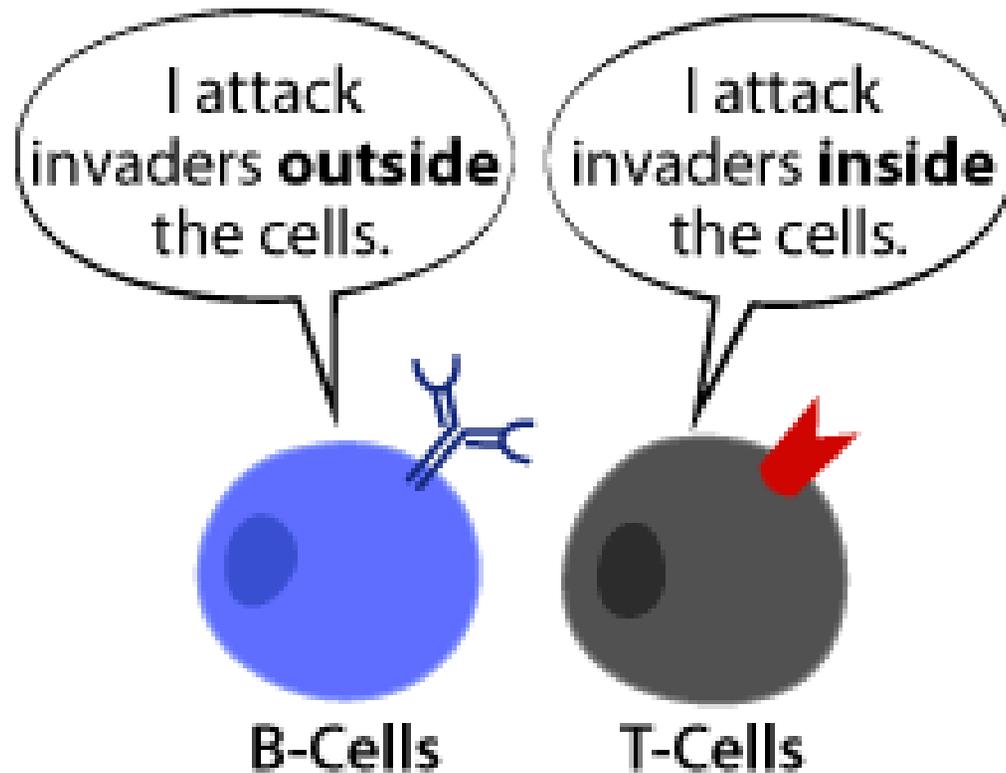
1. Barriers - skin, tears
2. Phagocytes - neutrophils, macrophages
3. NK cells and mast cells
4. Complement and other proteins

Adaptive Immunity

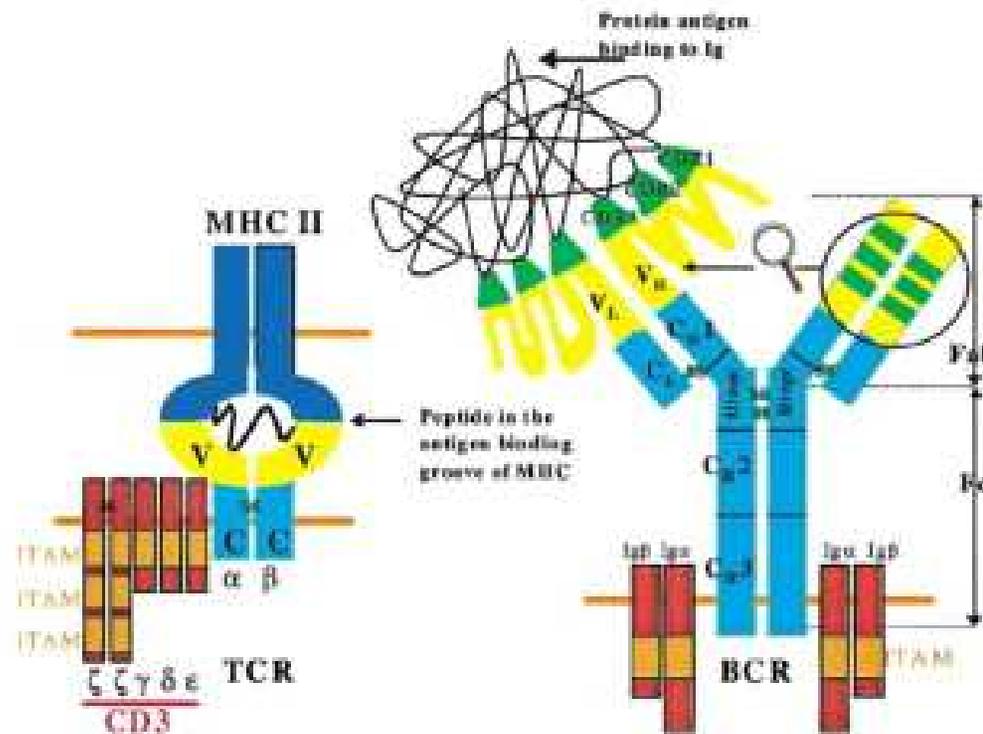
- variable (custom)
- later, highly specific
- “remembers” infection

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



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



2 key features of the adaptive immune response

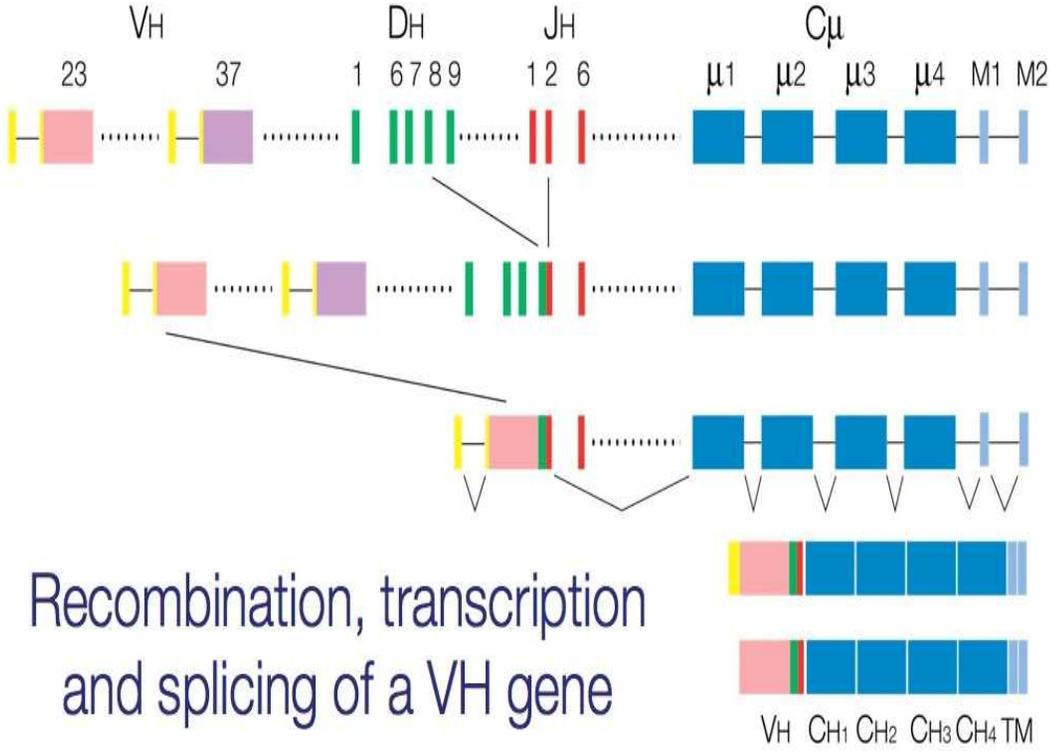
- A vast array of incredibly diverse antigen specific receptors
- Memory, that is the ability to respond rapidly upon rechallenge by the same pathogen



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

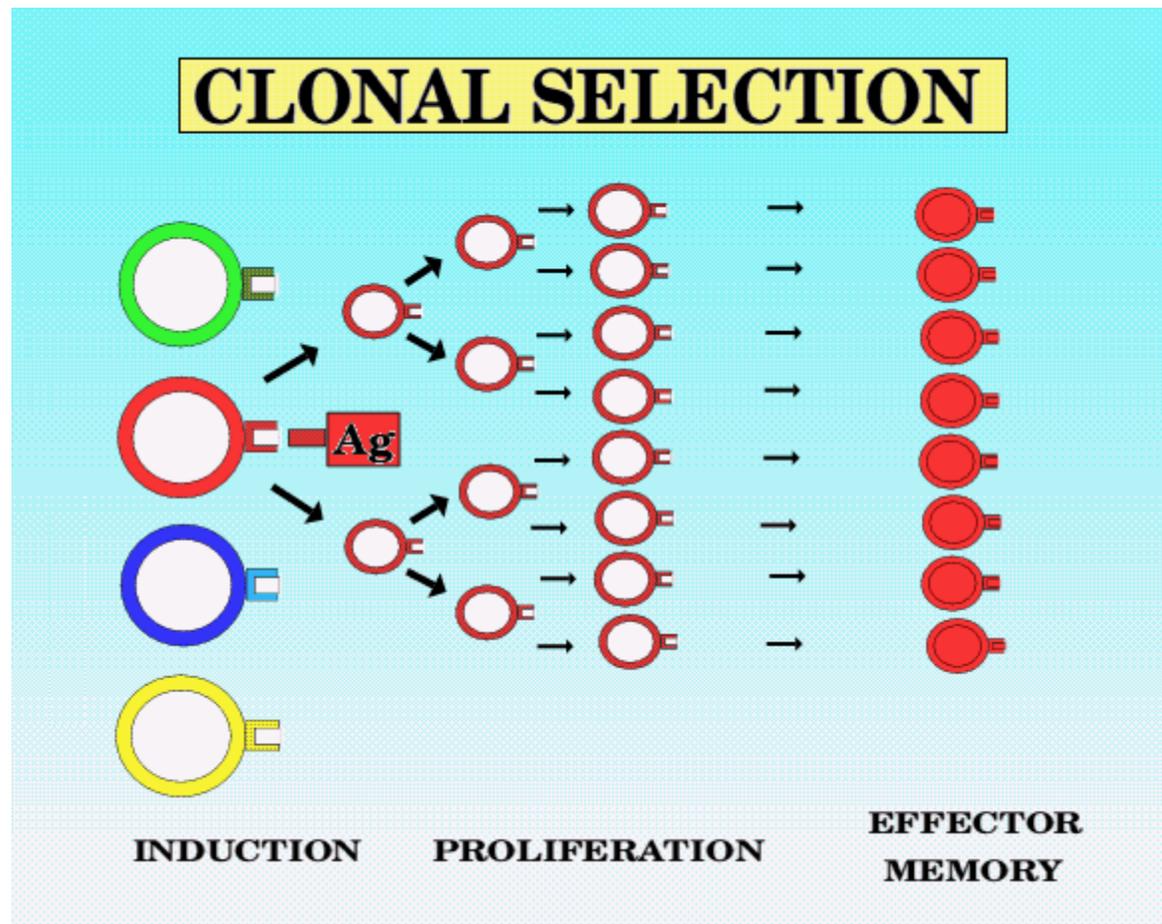


Do the math

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

Antibodies (BCRs)	Gene Segments	Combinations
V _κ	40	
J _κ	5	200 κ chains
V _λ	31	
J _λ	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)		2.5×10^6

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

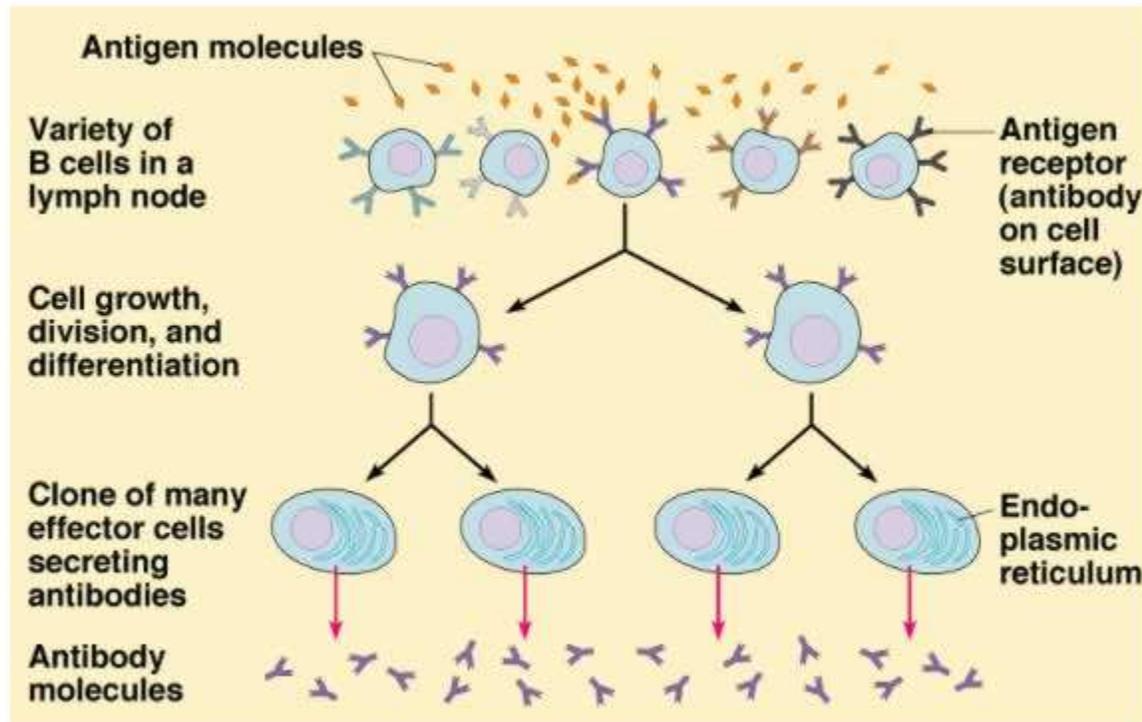


Steve Cobold

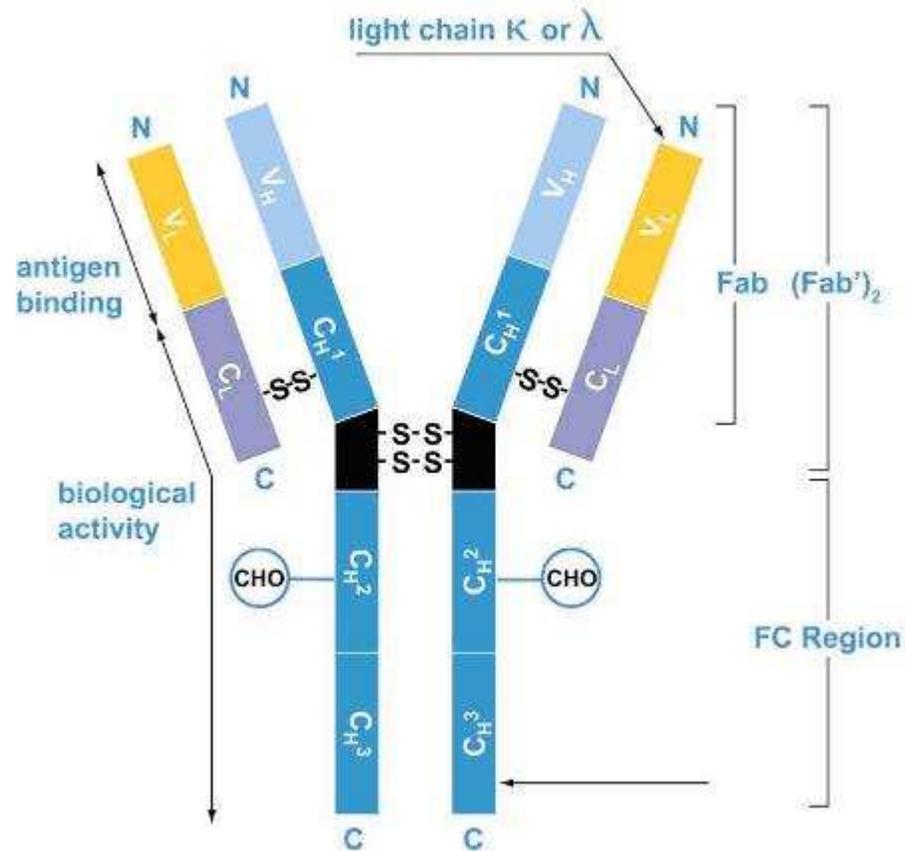
Thus, clonal selection....

- Promotes robust, antigen specific effector responses
- Leads to the generation of memory

B cells make antibodies

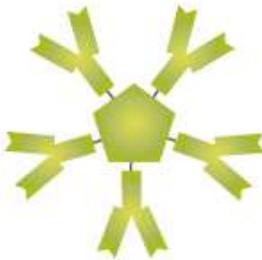


Basic structure of antibodies

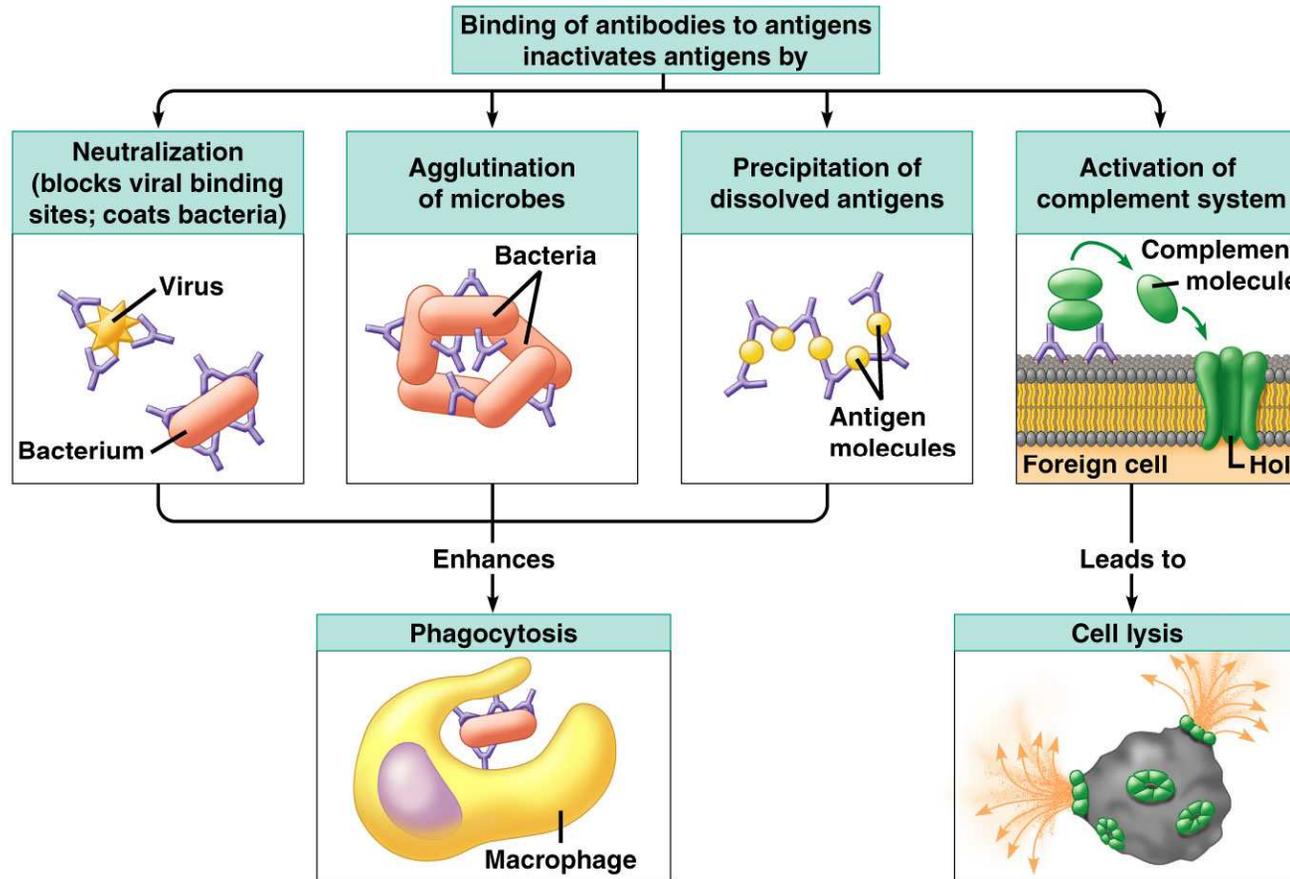


Antibodies come in different flavors

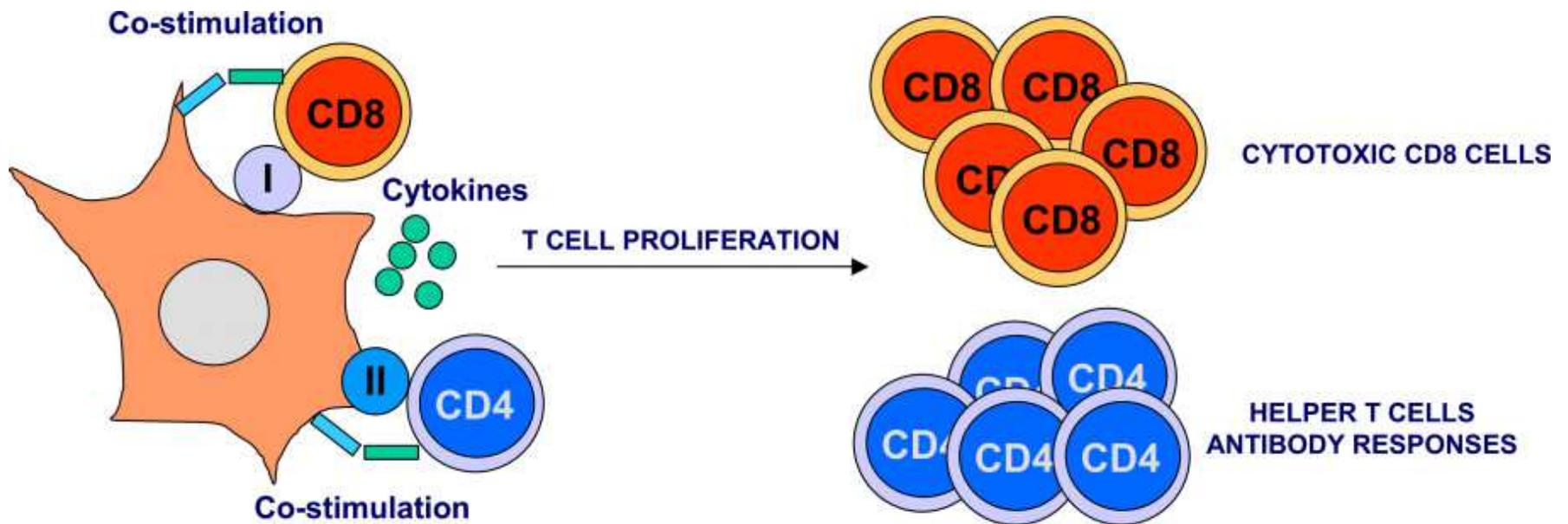
Antibody isotypes of mammals

Name	Types	Description	Antibody Complexes
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.	 Monomer IgD, IgE, IgG
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.	 Dimer IgA
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.	 Pentamer IgM

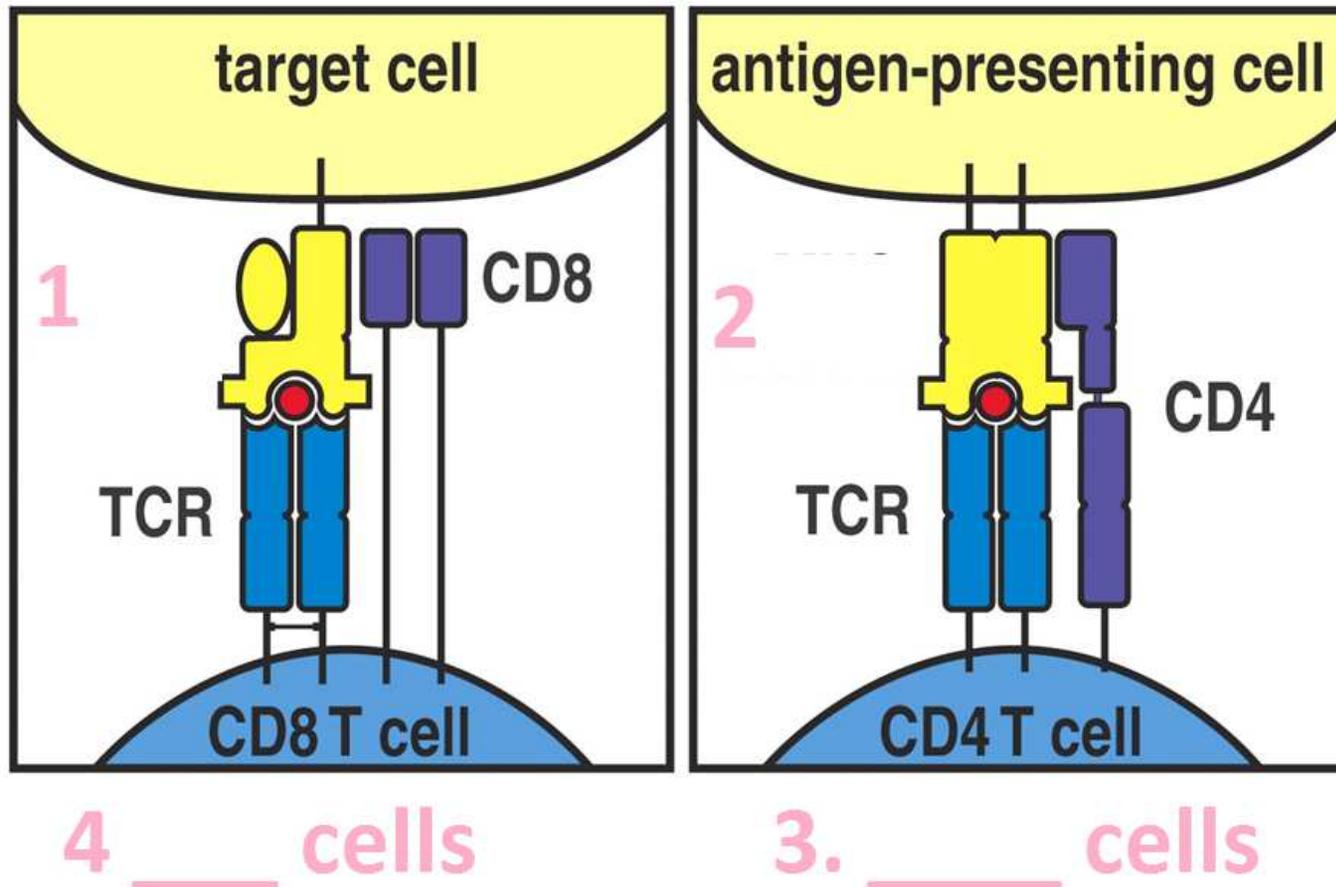
Antibody effector mechanisms



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

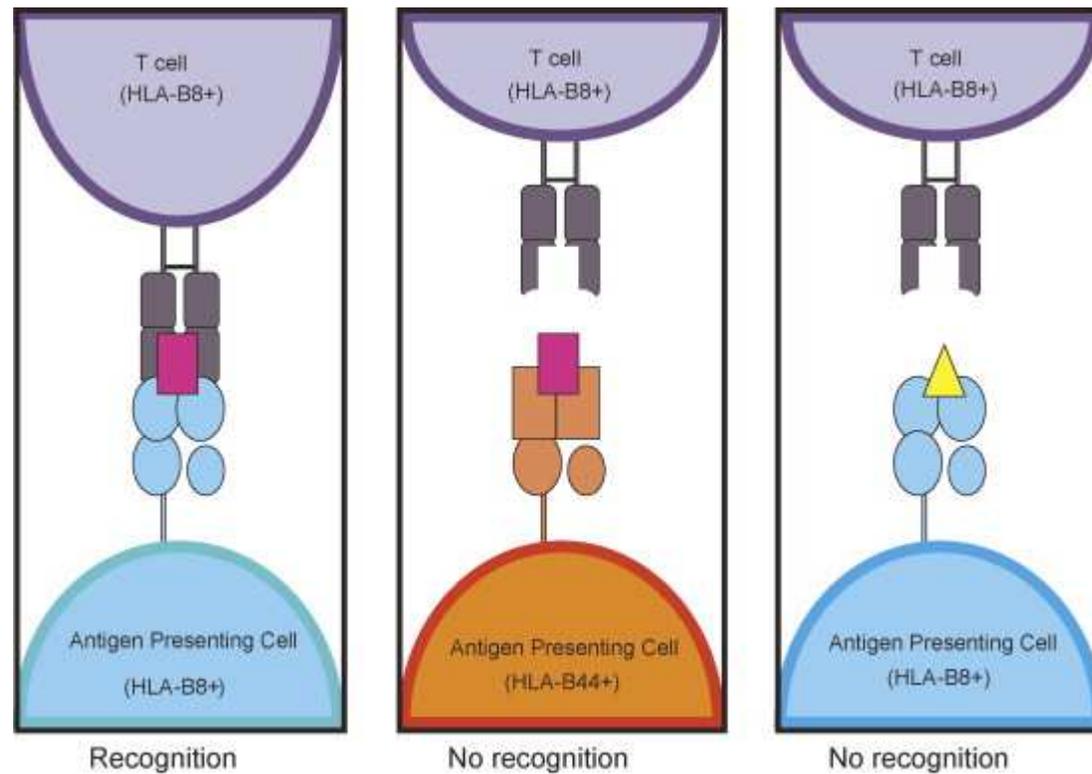


Class I and Class II recognition relates to different functions of CD4 & CD8 cells

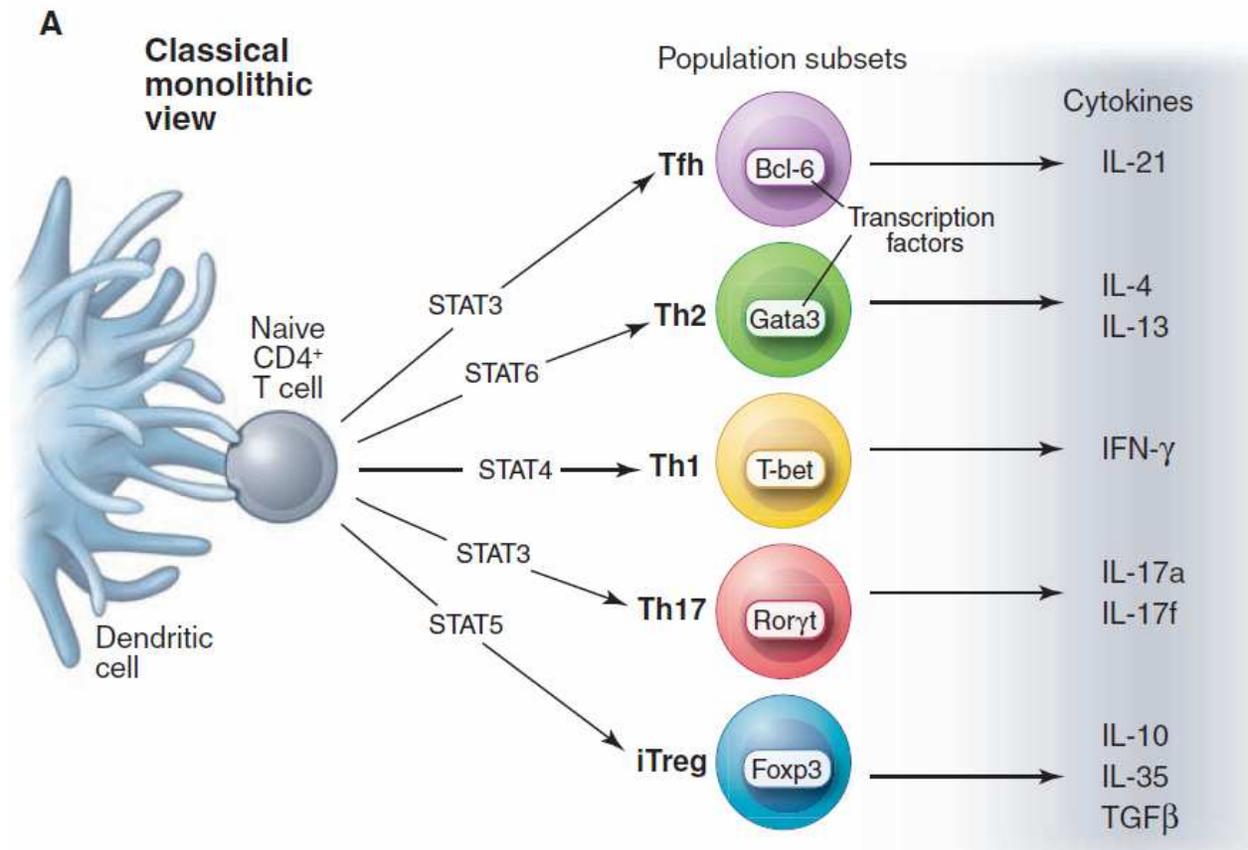
Table 2. Characteristics of the antigen processing pathways

Characteristic	MHC-I pathway	MHC-II pathway
Composition of the stable peptide-MHC complex	Polymorphic chain α and β 2 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 synthesized by the cell; may also enter from the extracellular medium via phagosomes)	Proteins present in endosomes or lysosomes (mostly internalized from extracellular medium)

Briefly, what is meant by MHC restriction?

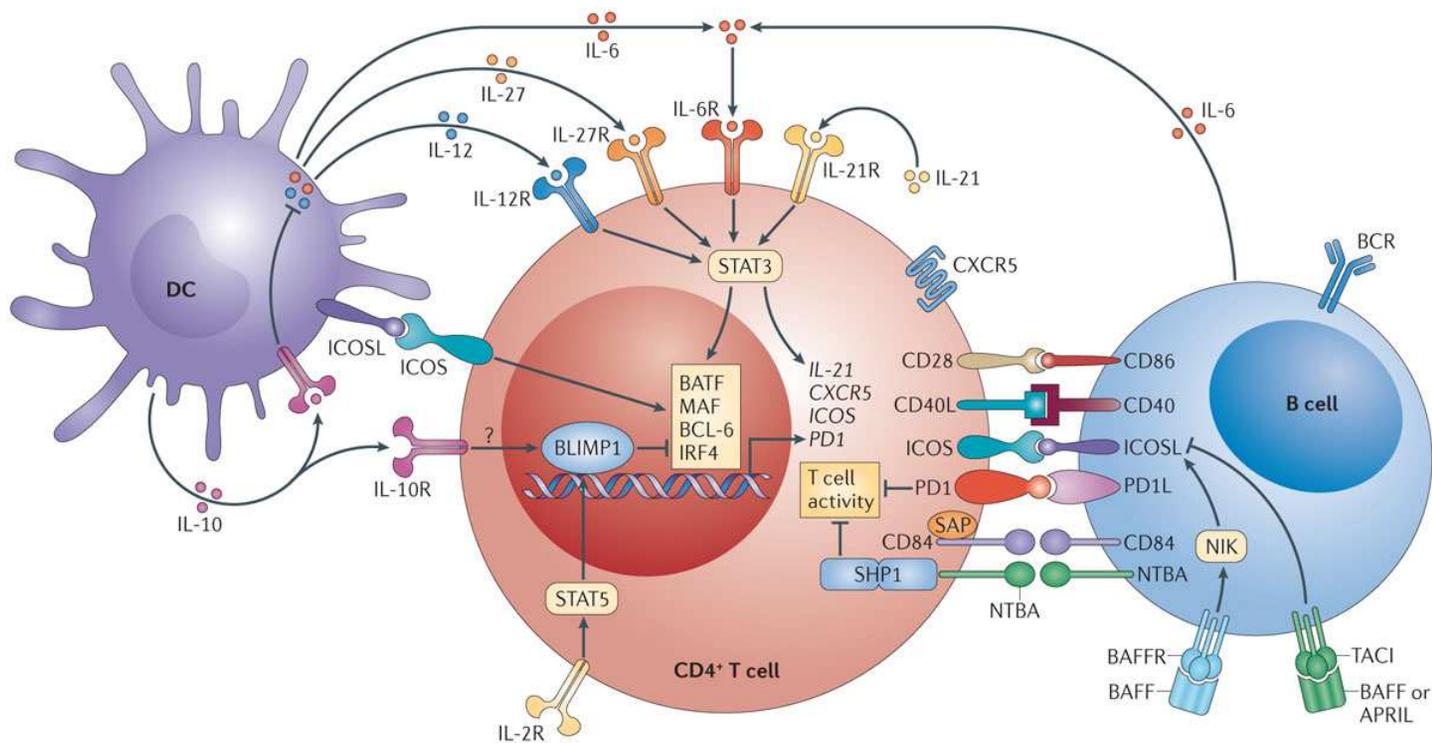


Different Types of CD4 effector cells

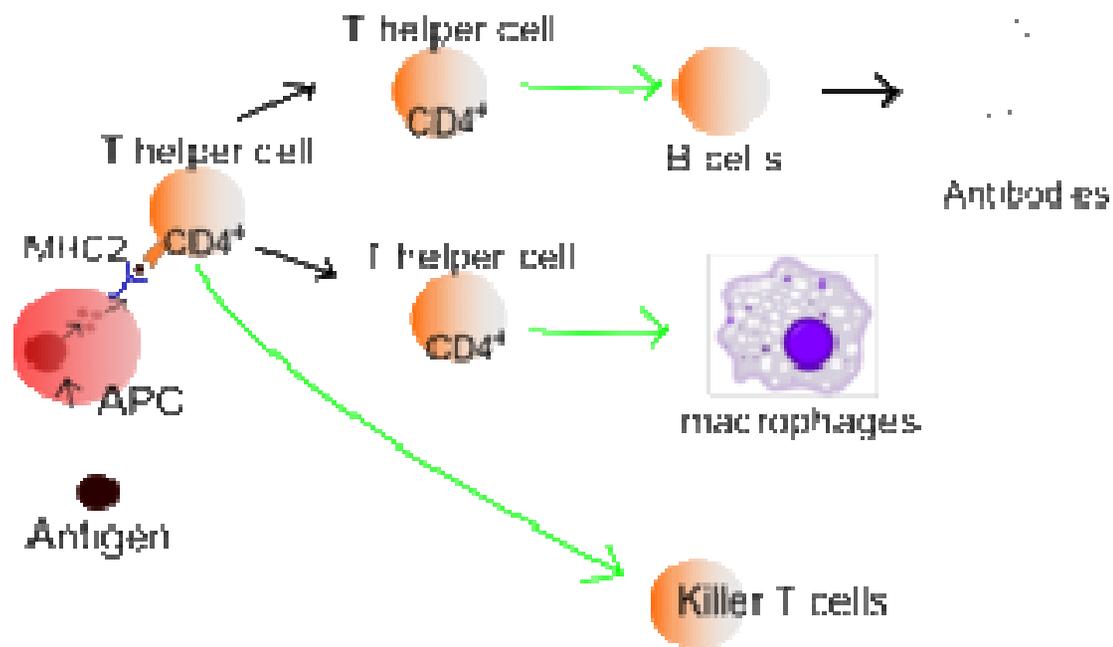


O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4⁺ T cells. *Science*. 2010 Feb 26;327(5969):1098-102.

CD4+ T cells “Help” B cells



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



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

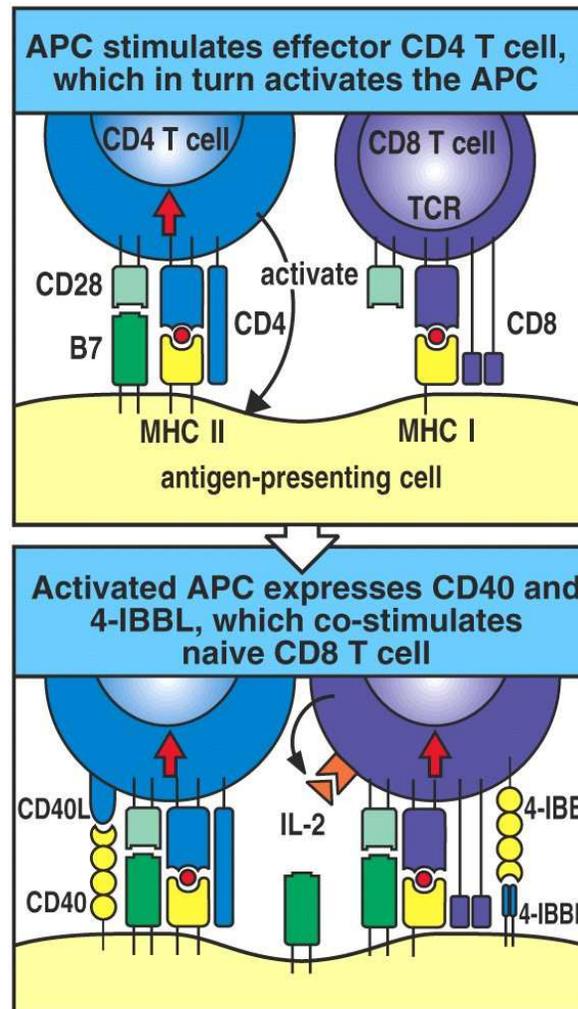


Figure 8-26 Immunobiology, 6/e. (© Garland Science 2005)

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

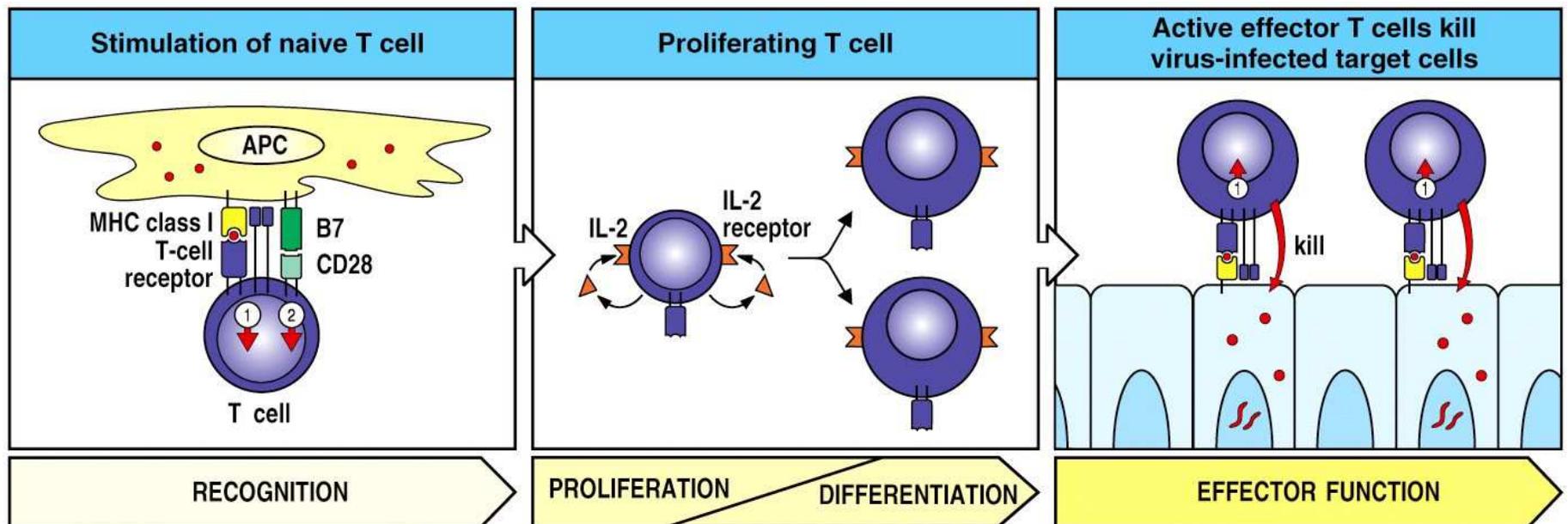
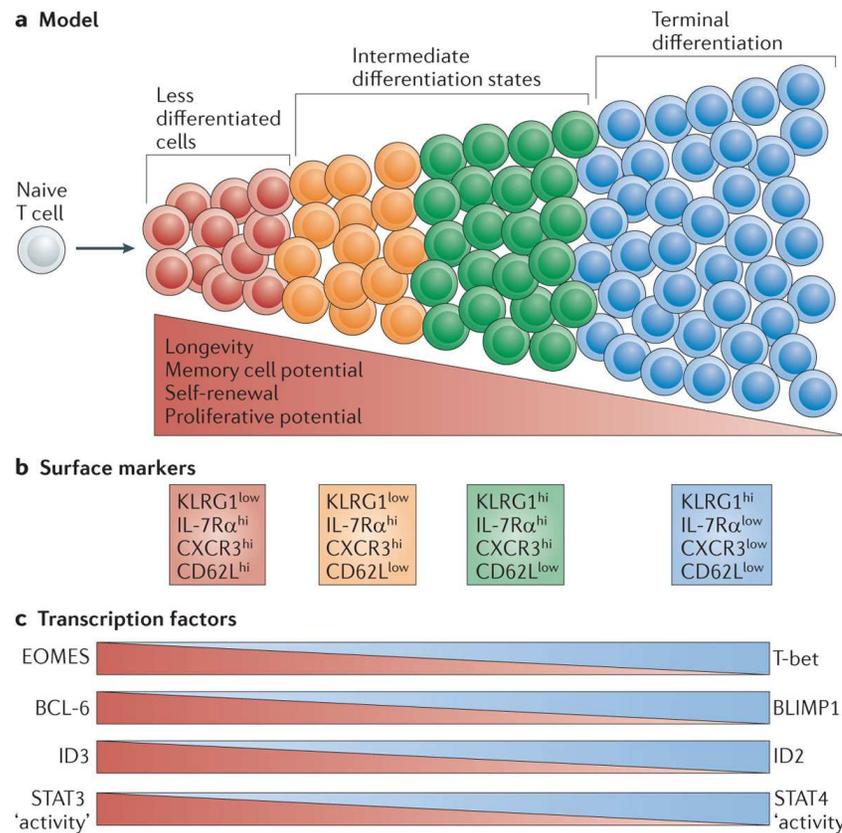
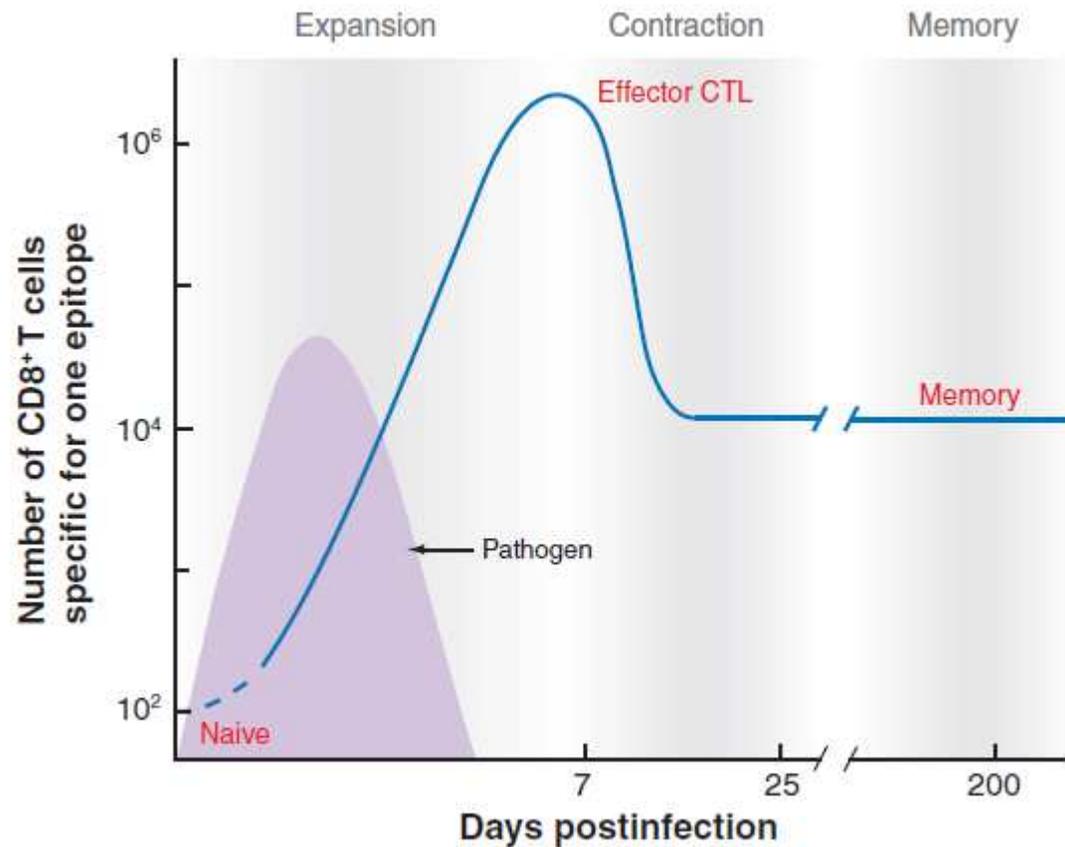


Figure 8-22 Immunobiology, 6/e. (© Garland Science 2005)

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



Generalized CD8+ T cell response



Summary of T cell functions

	CD8 cytotoxic T cells	CD4 T _H 1 cells	CD4 T _H 2 cells	CD4 T _H 17 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, <i>Listeria</i> , <i>Leishmania donovani</i> , <i>Pneumocystis carinii</i>) Extracellular bacteria	Helminth parasites	<i>Klebsiella pneumoniae</i> Fungi (<i>Candida albicans</i>)	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

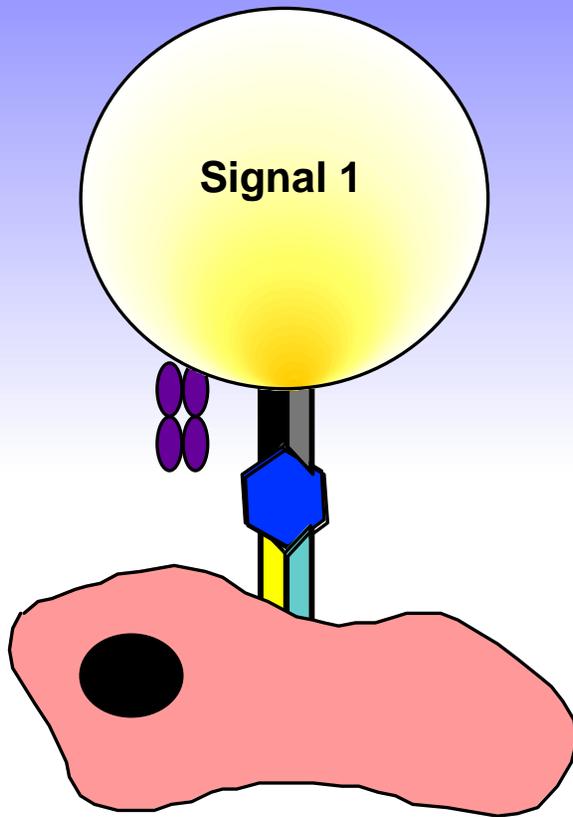
New

- Context Models
- Circumstance Driven
- Determined by milieu

Executing the Will of APC's

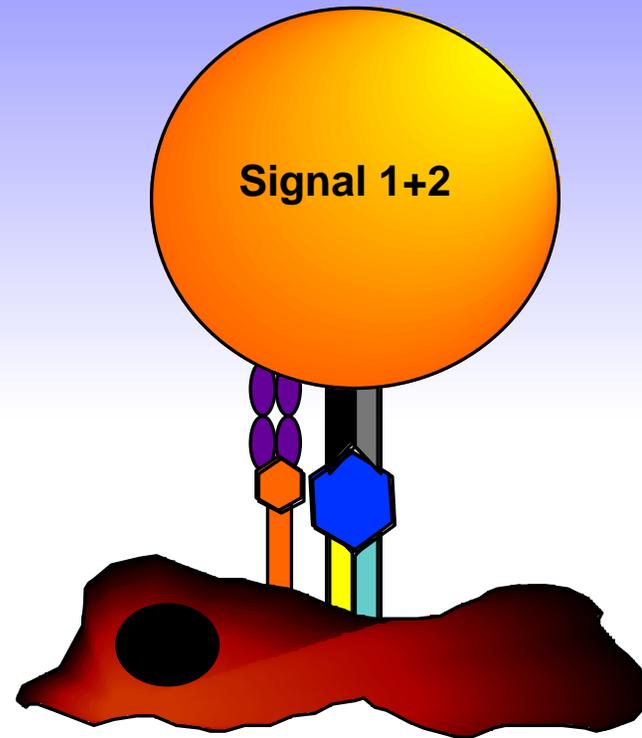
Executing the Decision

Tolerogenic



Resting APC

Immunogenic



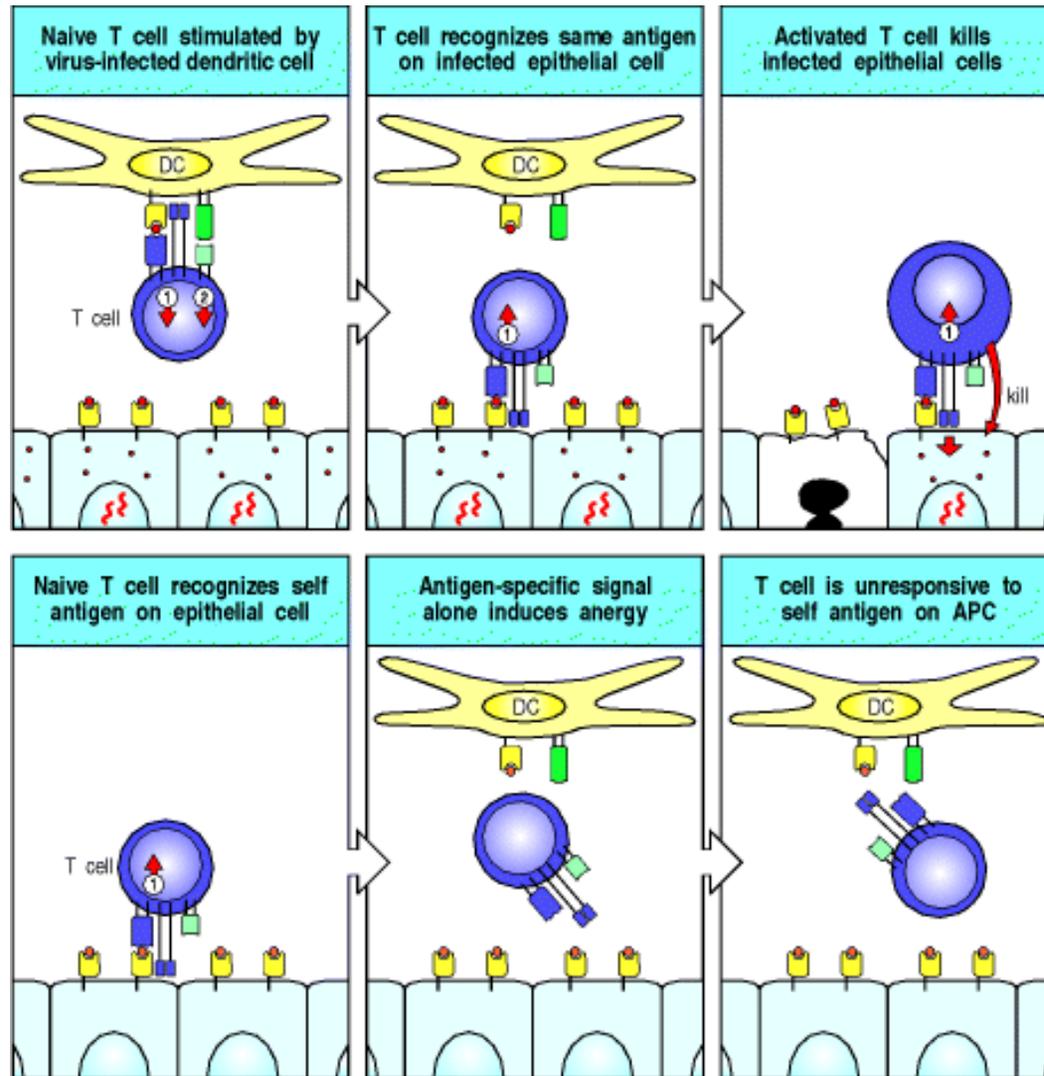
Activated APC

The Decision

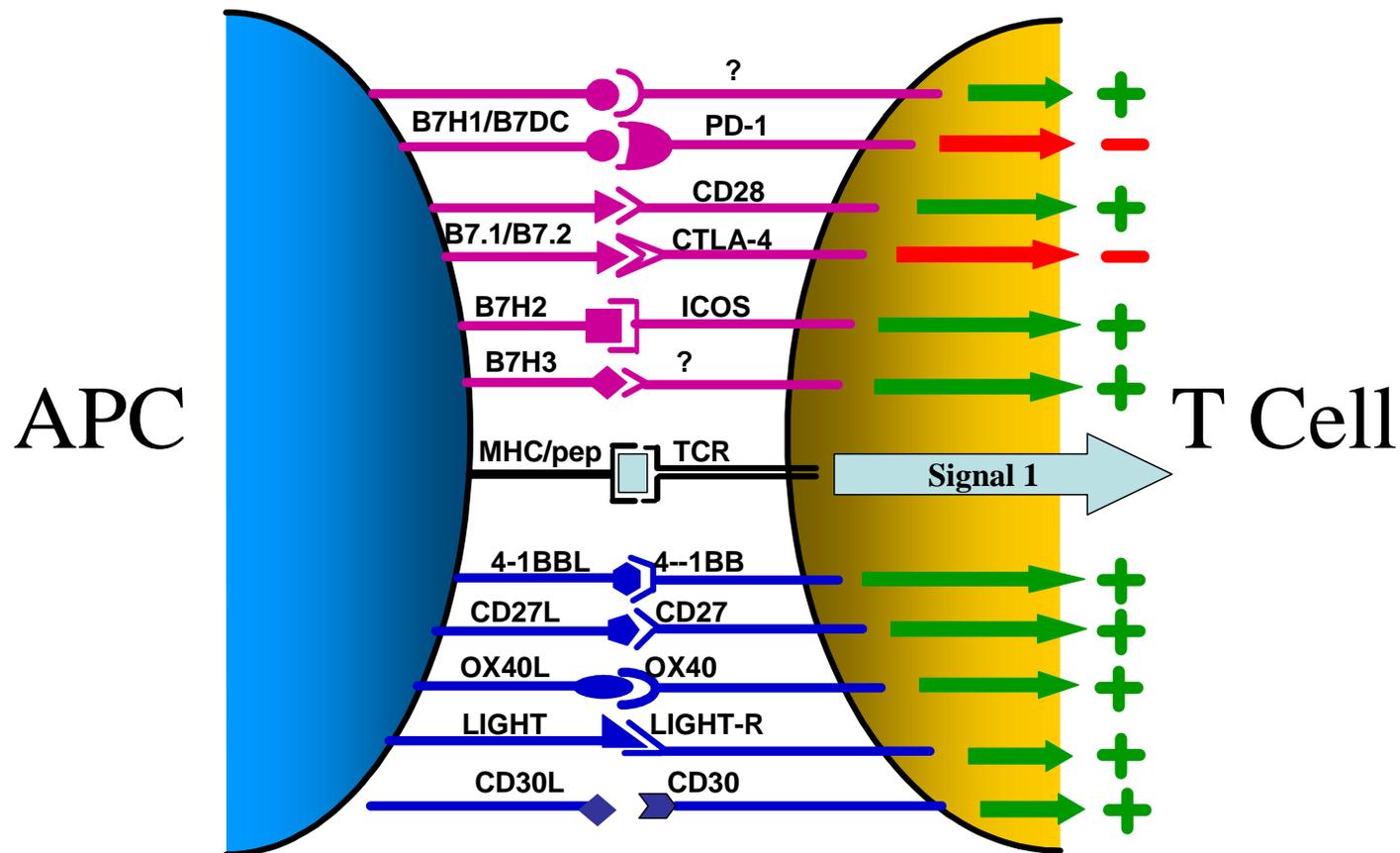
Activated APCs express costimulatory molecules (Signal 2)

- **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

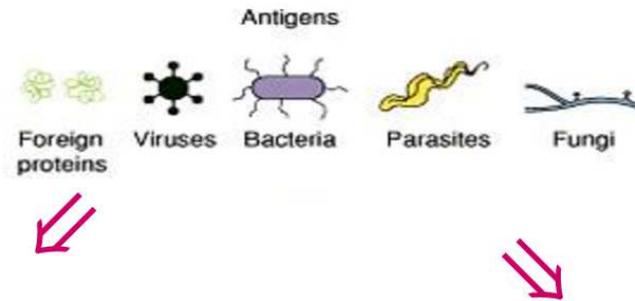


Based on what I told you how can we exploit the Adaptive Immune Response to Kill tumors?

- 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)

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