Antigen capture and presentation to T lymphocytes

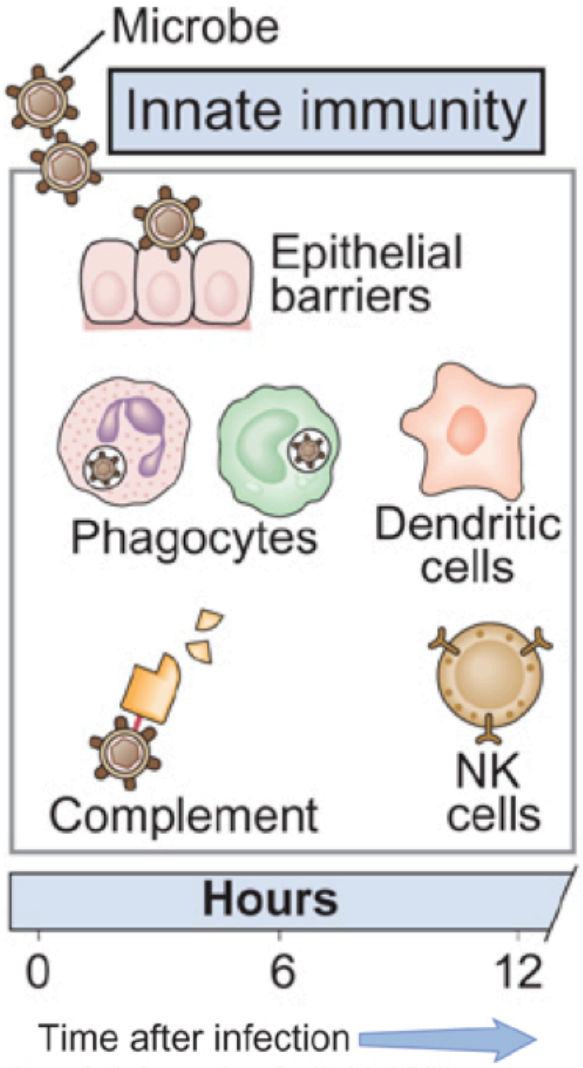
What T lymphocytes see

Innate Immunity

Immediately available

or

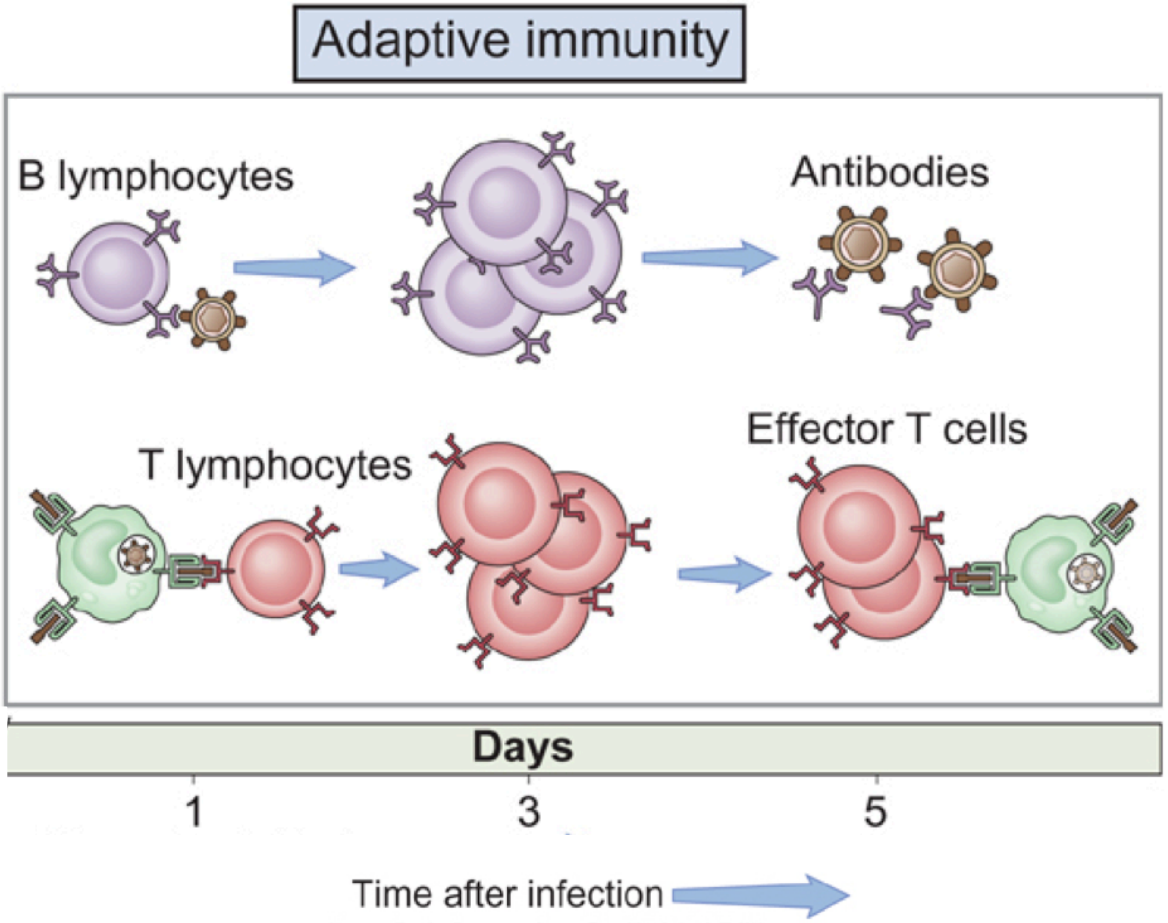
rapidly recruited



Very broad specificity

Adaptive Immunity

Rare and naïve cells require priming and expansion (i.e. a primary response takes time to develop)

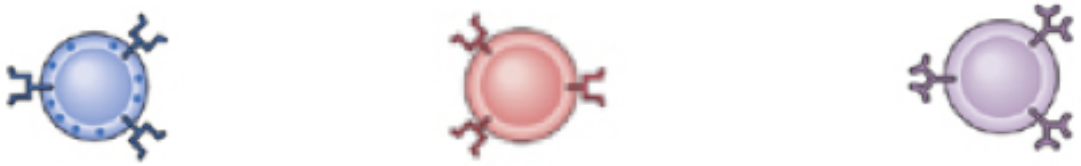


Narrow specificity

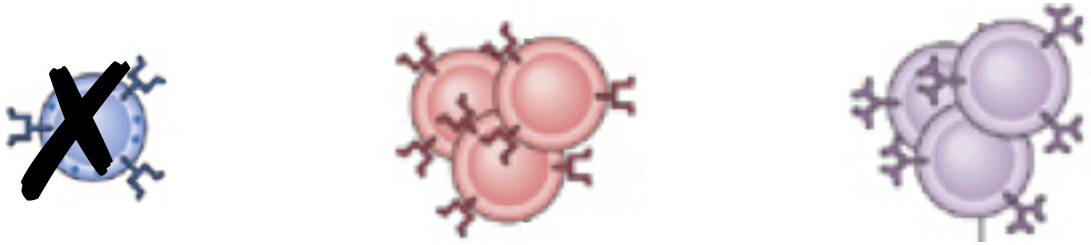
Clonally distribution

Clonal selection

Clonal Distribution & Selection

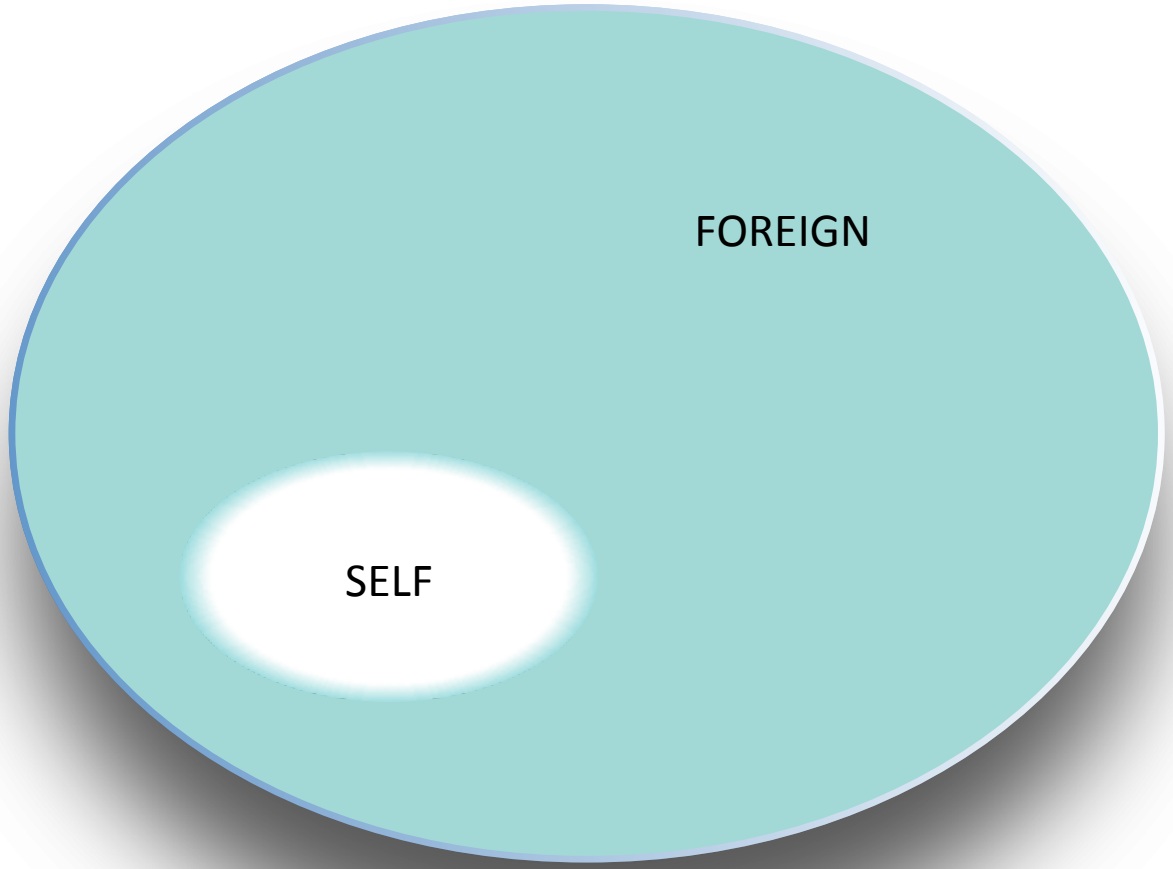


Each lymphocyte (B or T cell) express one receptor specificity (clonally distributed)



Each of these cells (i.e. specificities) can be silenced or promoted (clonally selected)

Control cells = control specificity



What is a good target for the adaptive immune system?

To be seen – targets must be accessible and easy to identify

To allow discrimination between self and foreign – targets must be highly variable

To avoid escape – targets must be difficult to conceal, change or remove

PROTEINS FULFILL THESE REQUIREMENTS – ACTUALLY PEPTIDES DO

The World of Peptide Antigens

Number of different peptides $=20^N$

where N = length of peptide

The universe of 9-mers = 512×10^9 peptides

The human proteome $\approx 12 \times 10^6$ peptides

i.e. plenty of discriminatory power in 9-mers

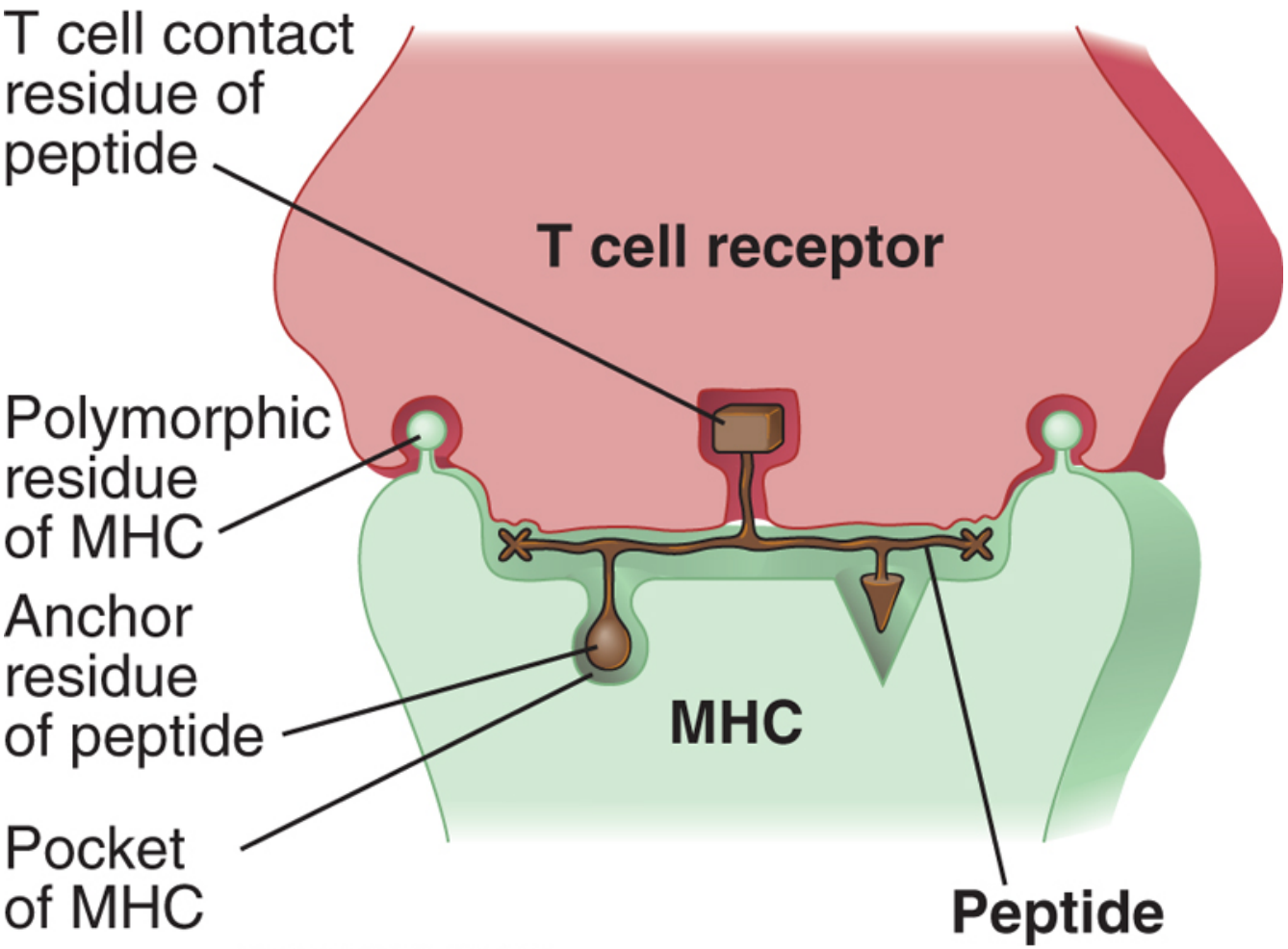
Questions

- How are source proteins captured?
- How are peptides generated?
- How are peptides displayed (presented)

Questions

- T cells of the appropriate specificity are rare - how do T cells find the antigen?
- The cellular location of a threat is important – how do T cells determine this location?
- A UNIFIED ANSWER: ANTIGEN PRESENTATION

Antigens Recognized by T Lymphocytes



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MHC RESTRICTION

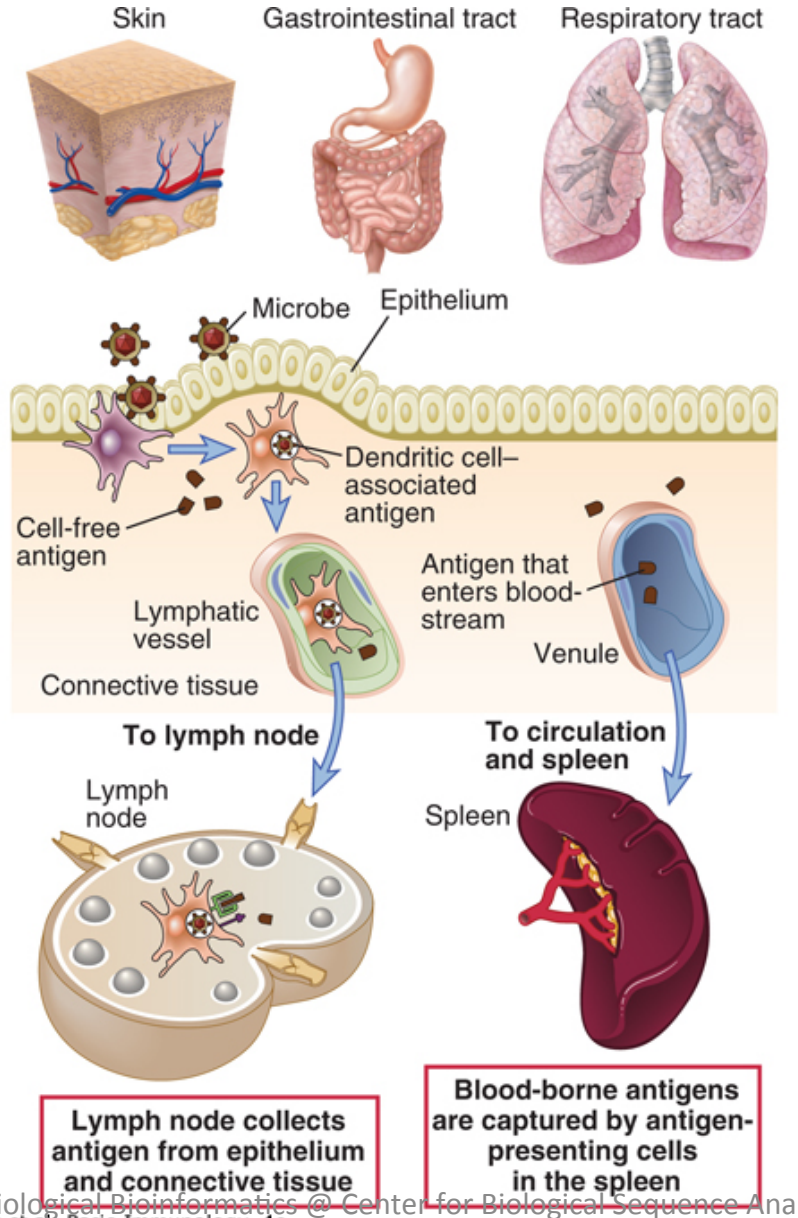
Capture & Display of Microbial Antigens

Immature DC

Antigen Capture

Mature DC

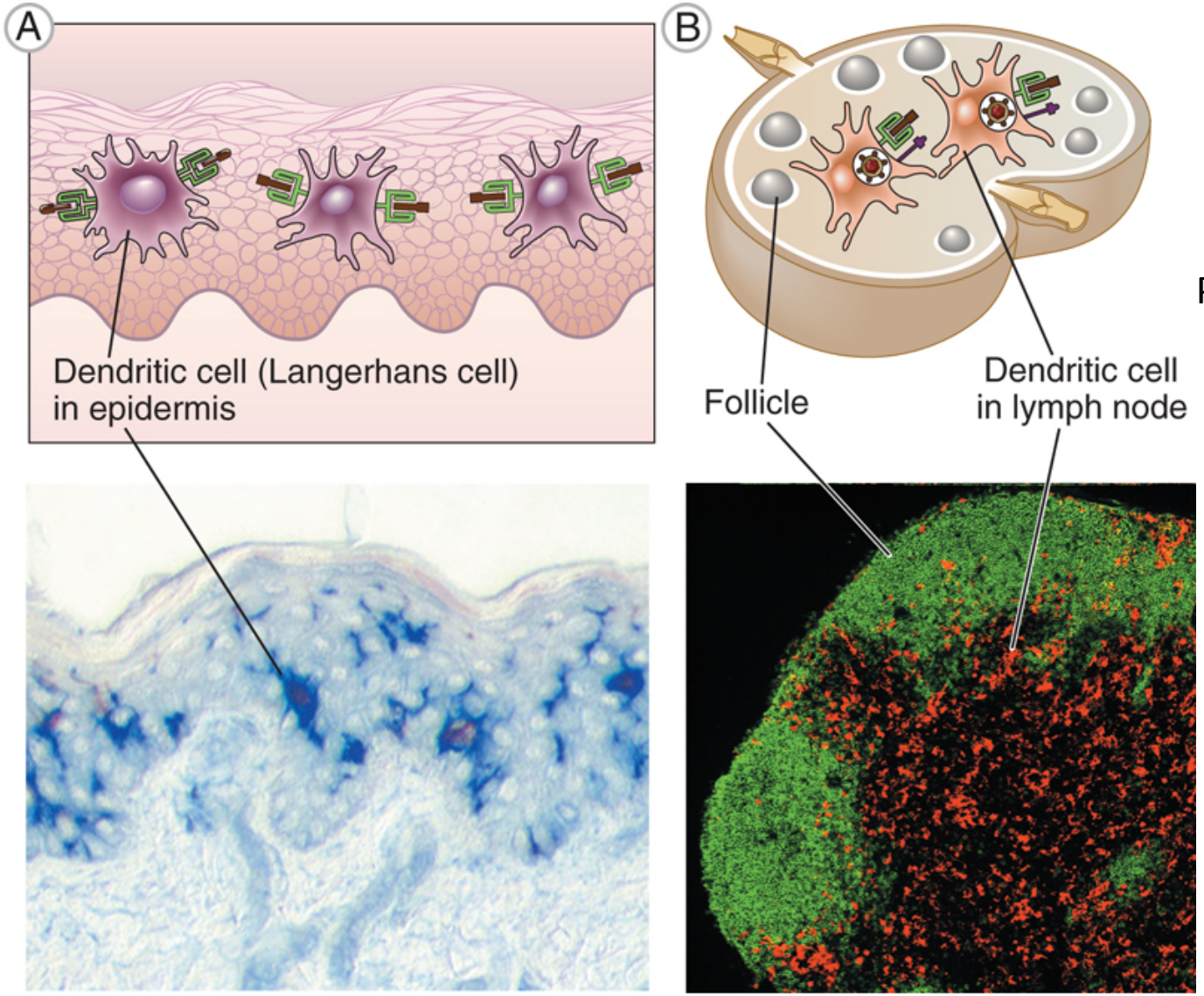
Antigen Presentation



Immature and Mature Dendritic cells

Immature DC

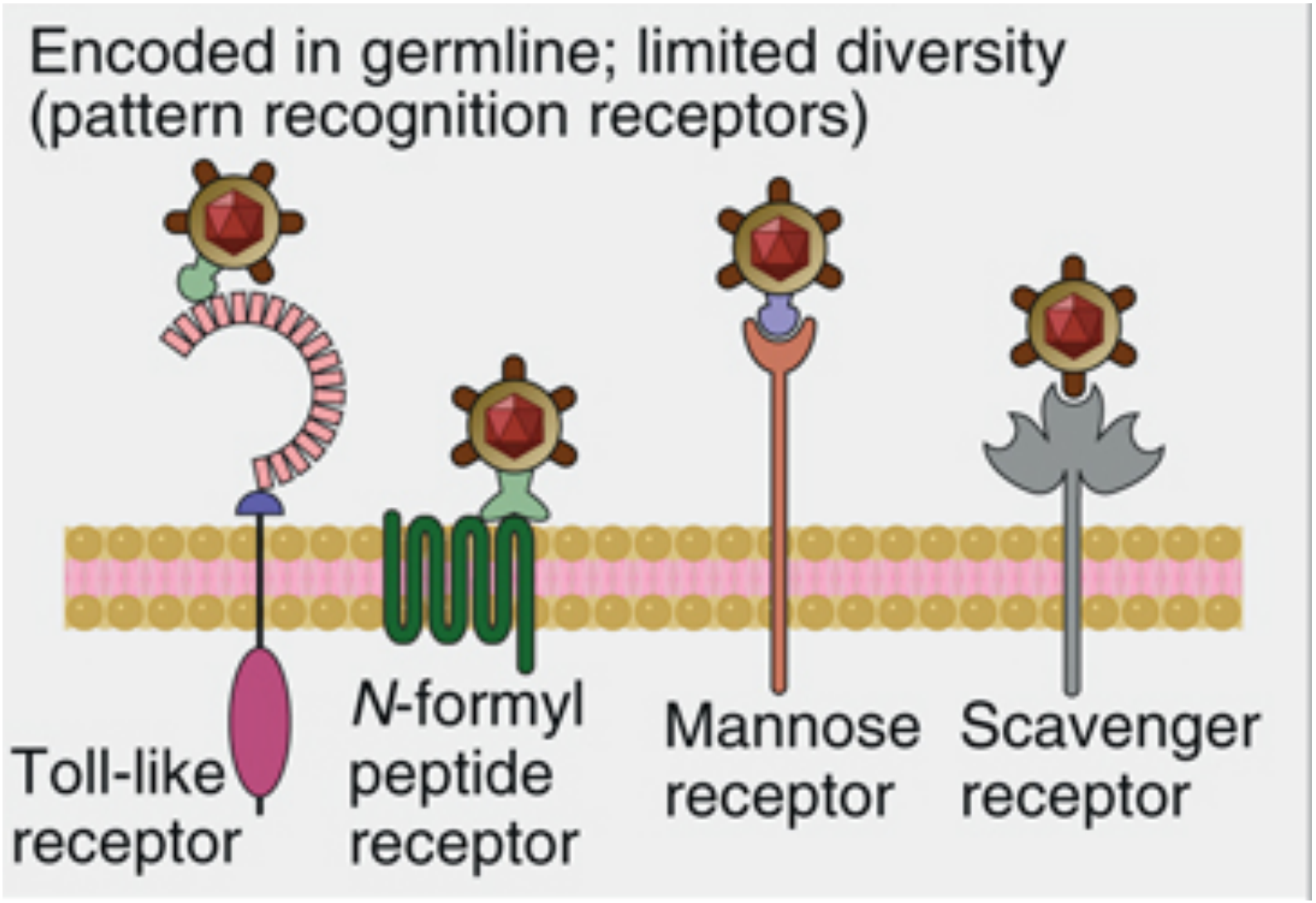
Antigen Capture



Mature DC

Antigen Presentation

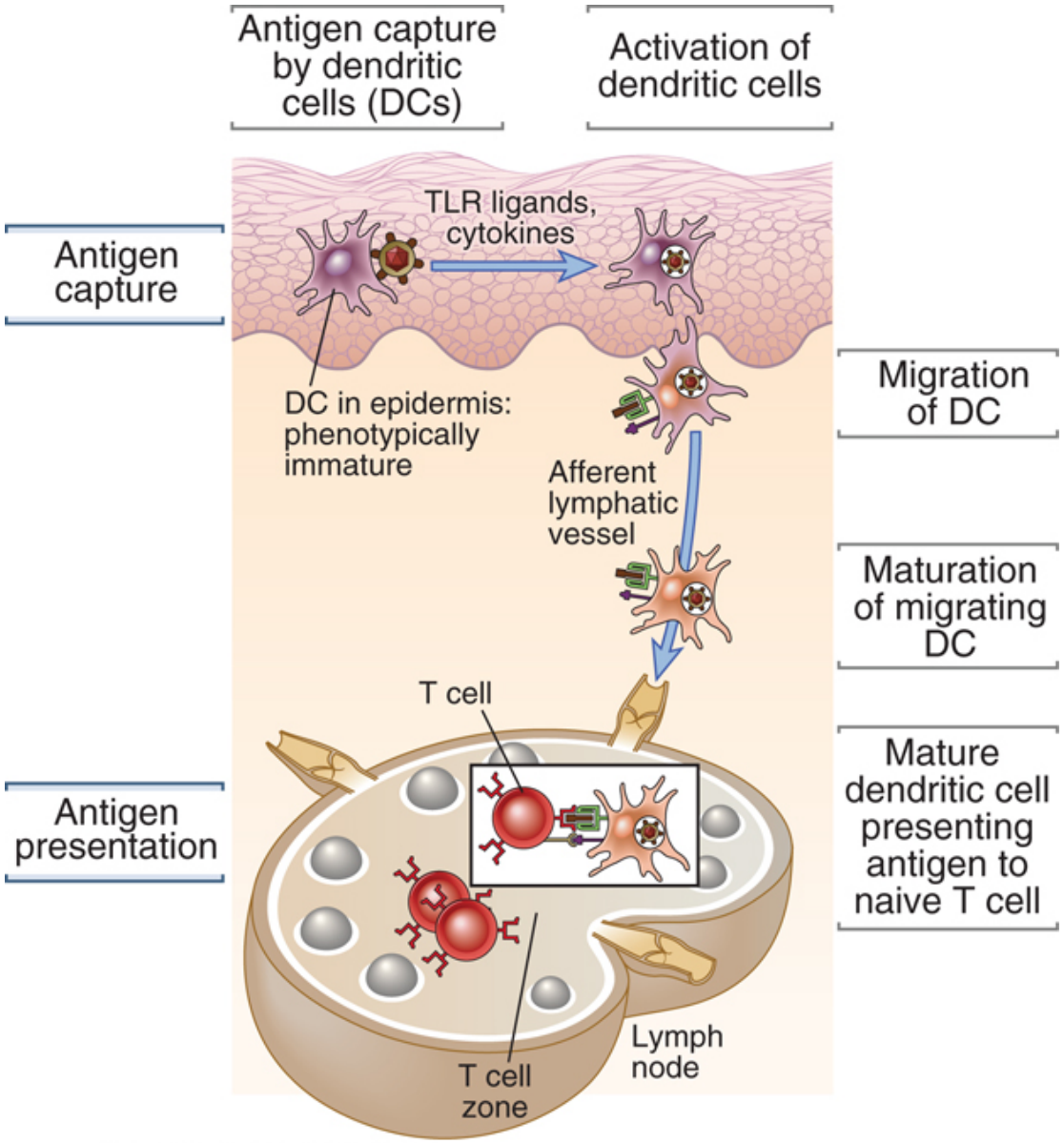
Crude Recognition of Microbes



Dendritic cells – two major classes

Feature	Conventional dendritic cells	Plasmacytoid dendritic cells
Surface markers	CD11c high CD11b high	CD11c low CD11b negative B220 high
Major location	Tissues	Blood and tissue
Expression of Toll-like receptors	TLRs 4, 5, 8 high	TLRs 7, 9 high
Major cytokines produced	TNF, IL-6, IL-12	Type I interferons
Postulated major functions	Induction of T cell responses against most antigens	Antiviral innate immunity and induction of T cell responses against viruses

Capture & Presentation by DC's



Antigens Presenting Cells (APC)

Cell type	Expression of		Principal function
	Class II MHC	Costimulators	
Dendritic cells	Constitutive; increases with maturation; increased by IFN-γ	Constitutive; increases with maturation; inducible by TLR ligands, IFN-γ, and T cells (CD40-CD40L interactions)	Initiation of T cell responses to protein antigens
Macrophages	Low or negative; inducible by IFN-γ	Low, inducible by TLR ligands, IFN-γ, and T cells (CD40-CD40L interactions)	Effector phase of cell-mediated immune responses
B lymphocytes	Constitutive; increased by IL-4	Induced by T cells (CD40-CD40L interactions), antigen receptor cross-linking	Antigen presentation to $CD4^+$ helper T cells in humoral immune responses (cognate T cell–B cell interactions)

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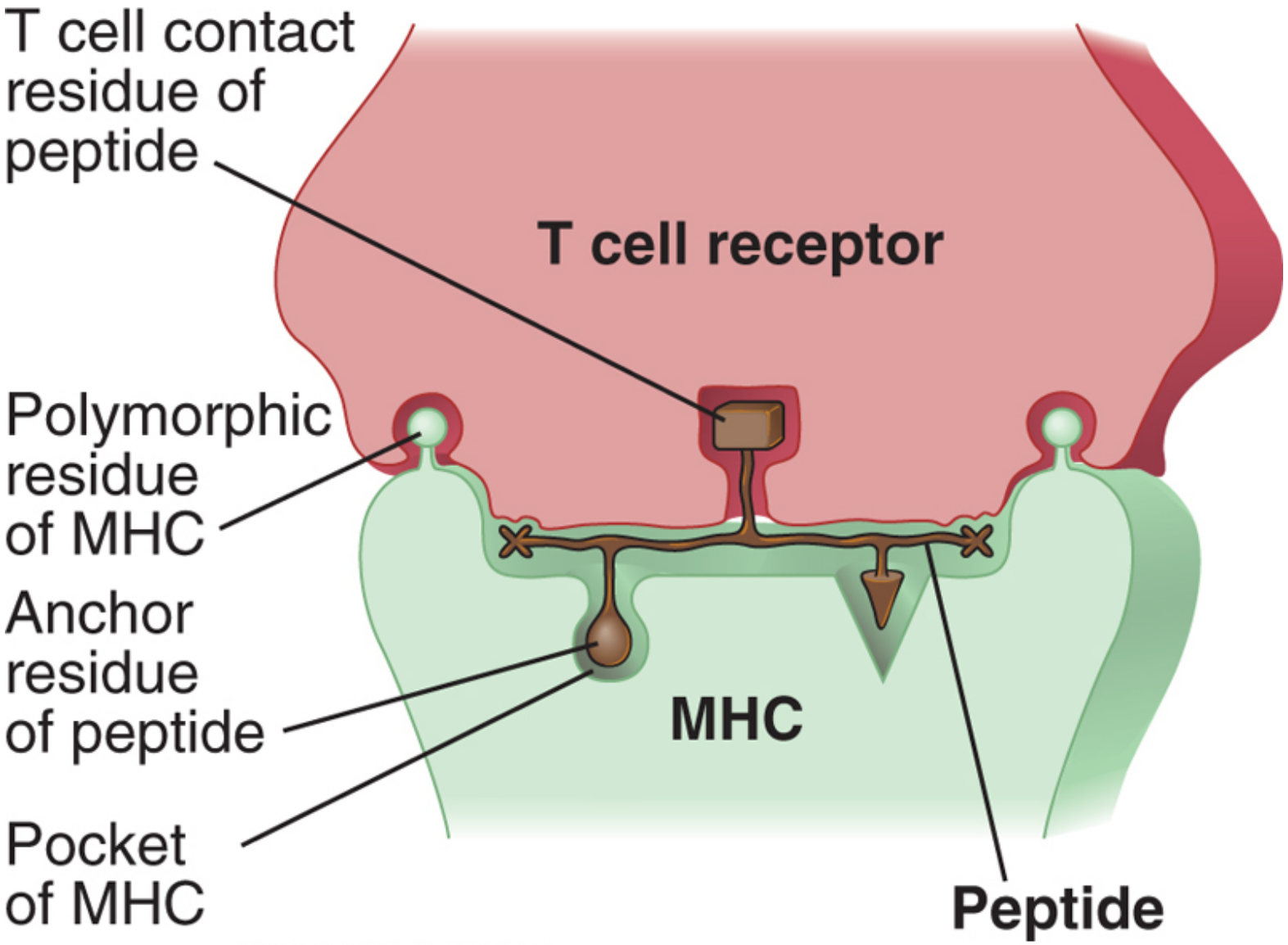
What are MHC molecules?



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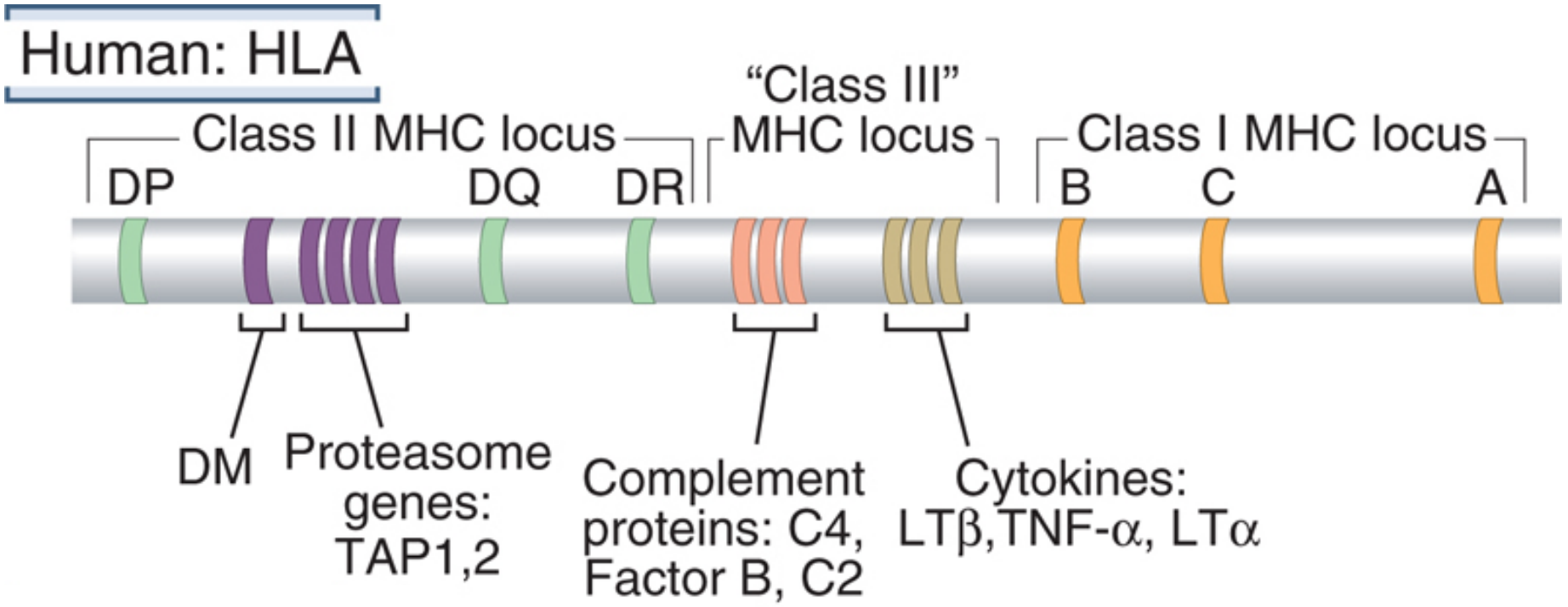
MHC (HLA) gene region



MHC / HLA polymorphism

- The most polymorphic gene region known
  - About 3500 different HLA class I registered
  - About 4500 different HLA class II registered

Gene complexity at the MHC locus in man

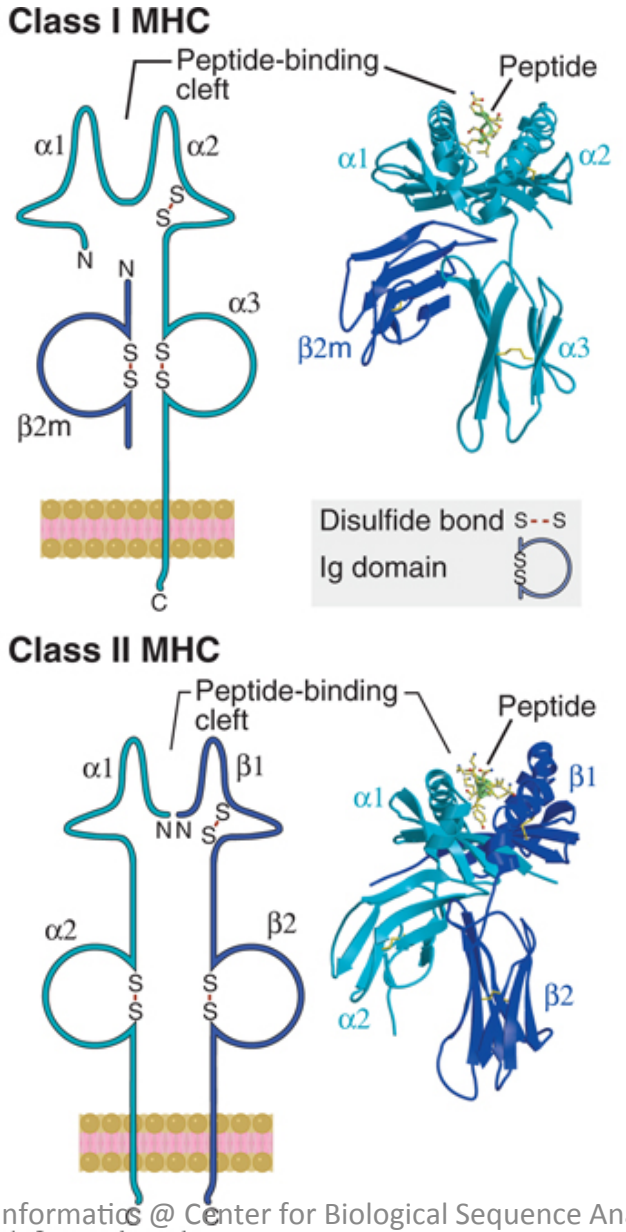
Class I		Class II			
gene	alleles	gene	A alleles	B alleles	A x B
HLA-A	1,519	DR	3	966	2,898
HLA-B	2,069	DQ	35	144	5,040
HLA-C	1,016	DP	28	145	4,060
HLA-E	10	DM	4	7	28
HLA-F	22	DO	12	9	108
HLA-G	46				

data from the European Bioinformatics Institute (EBI) server (http://www.ebi.ac.uk/imgt/hla/stats.html)

Structure of MHC / HLA molecules

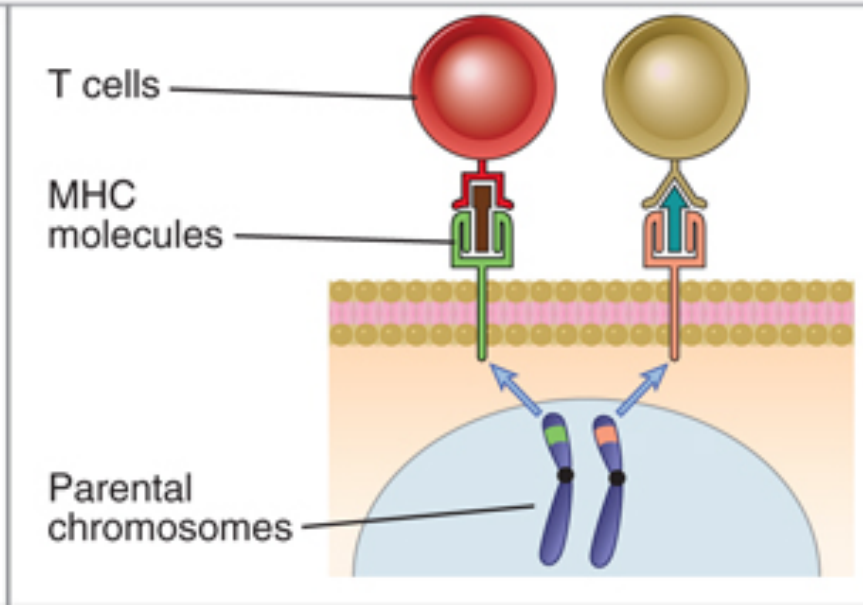
Class I

Class II



Features of MHC genes and molecules

Feature	Significance
Co-dominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells

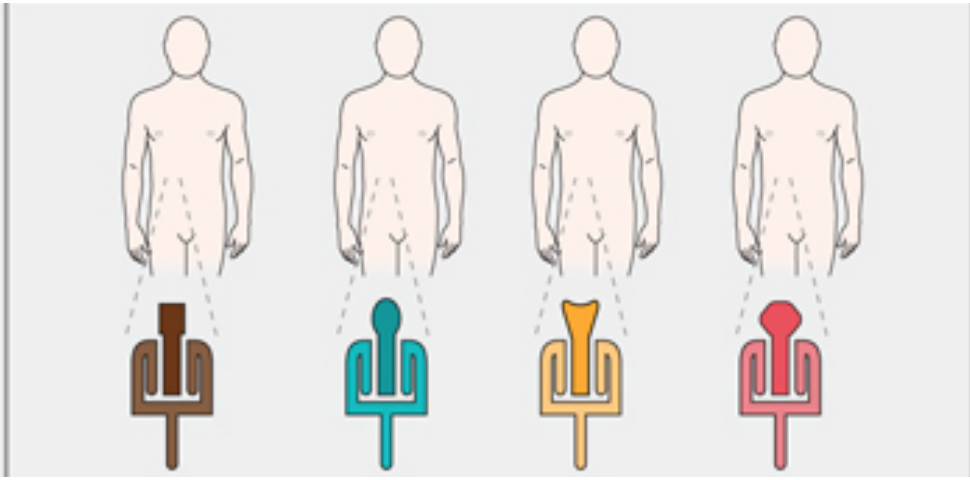


Features of MHC genes and molecules

Polymorphic genes:

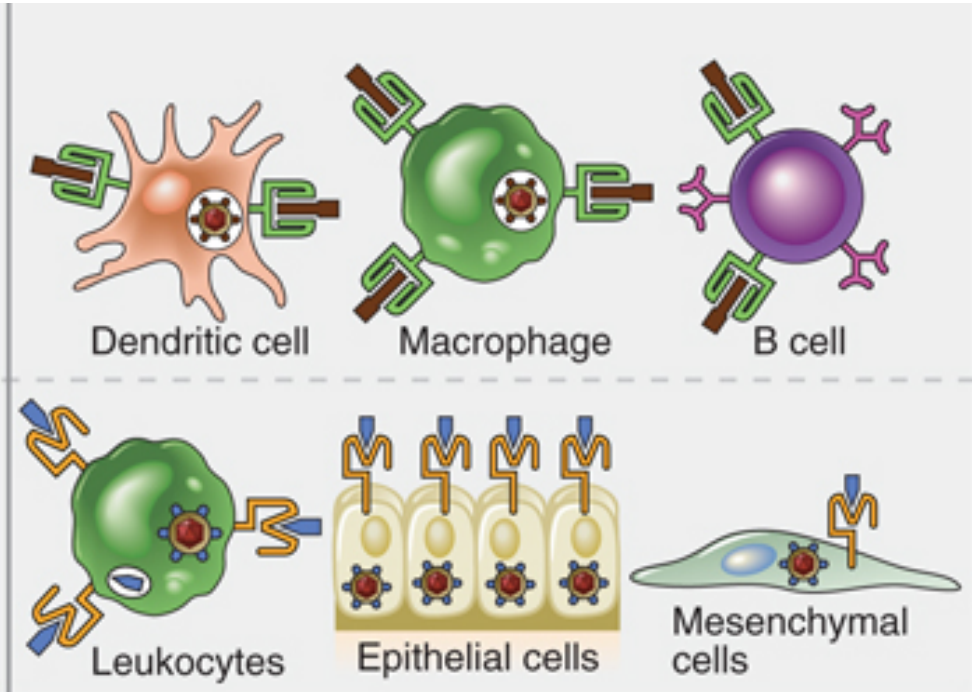
Many different alleles are present in the population

Ensures that different individuals are able to present and respond to different microbial peptides



Features of MHC genes and molecules

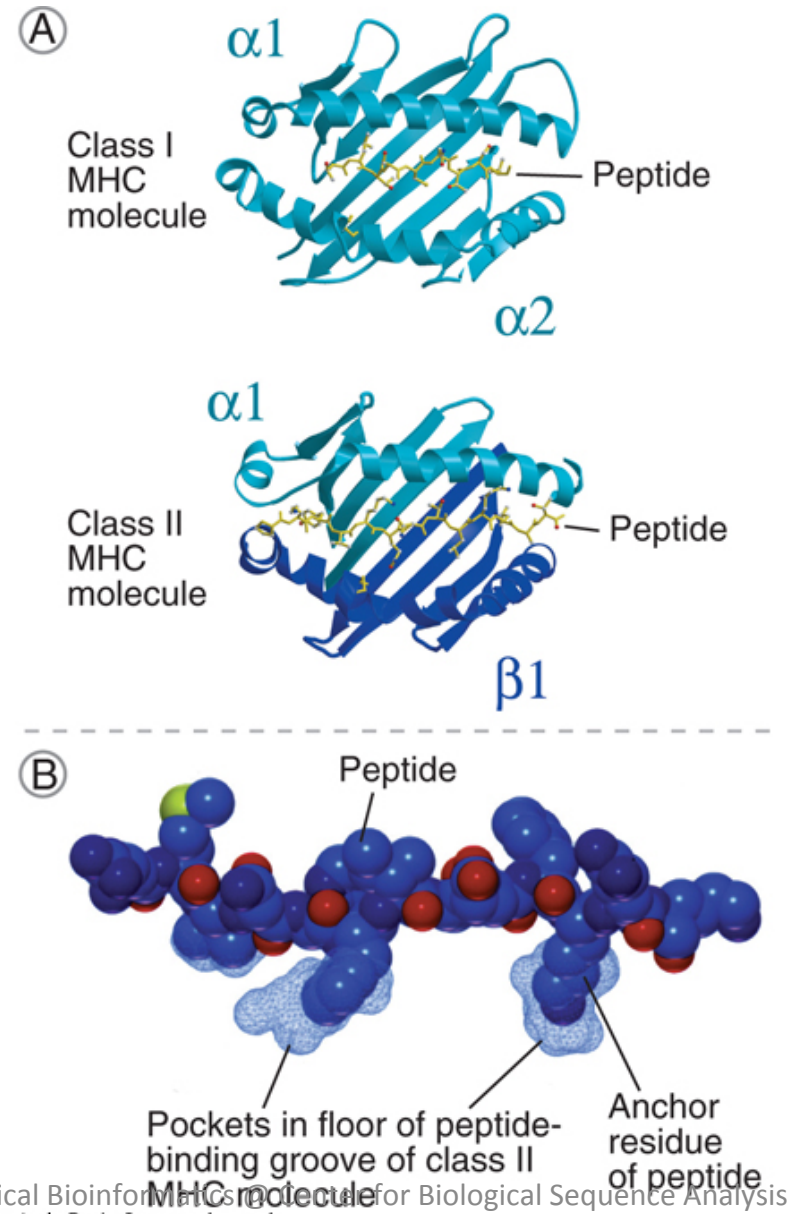
MHC-expressing cell types:	
Class II: Dendritic cells, macrophages, B cells	$CD4^+$ helper T lymphocytes interact with dendritic cells, macrophages, B lymphocytes
Class I: All nucleated cells	$CD8^+$ CTLs can kill any virus-infected cell



Binding of Peptides to MHC

MHC class I closed
Peptide short

MHC class II open
Peptide longer



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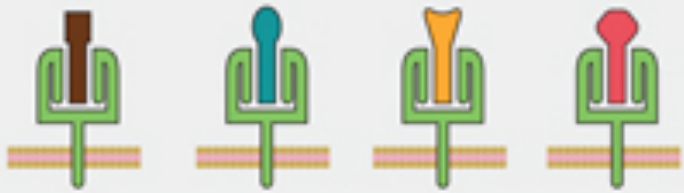
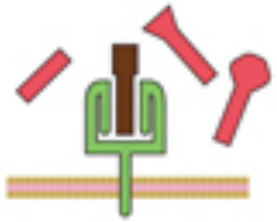
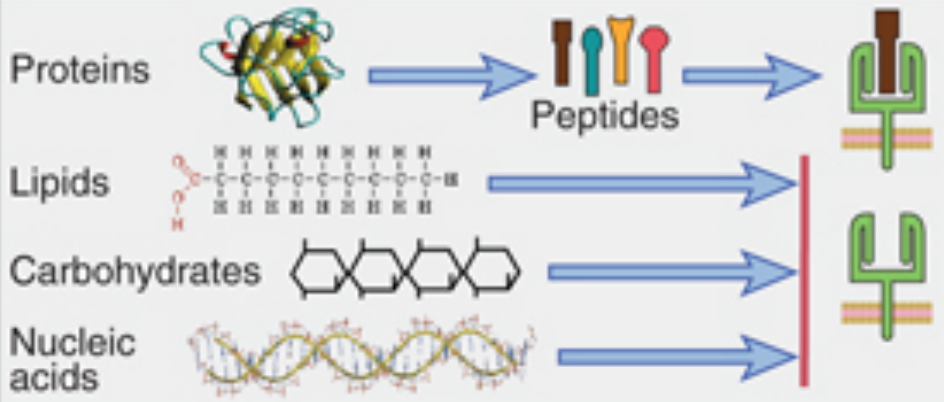
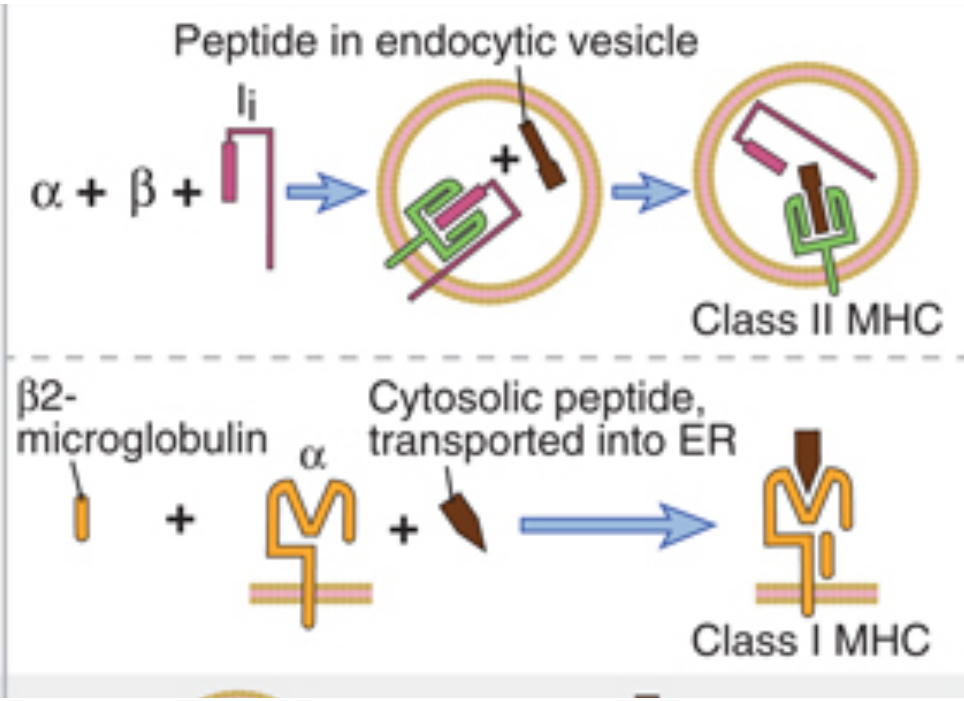
Peptide interaction with MHC

Feature	Significance	
Broad specificity	Many different peptides can bind to the same MHC molecule	
Each MHC molecule displays one peptide at a time	Each T cell responds to a single peptide bound to an MHC molecule	
MHC molecules bind only peptides	MHC-restricted T cells respond only to protein antigens, and not to other chemicals	

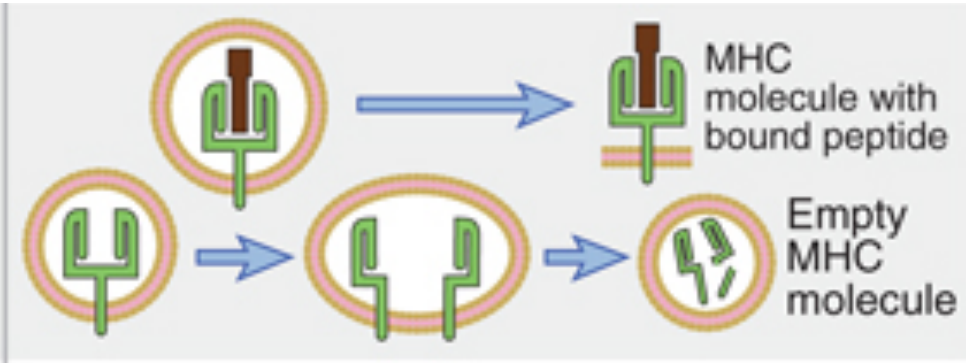
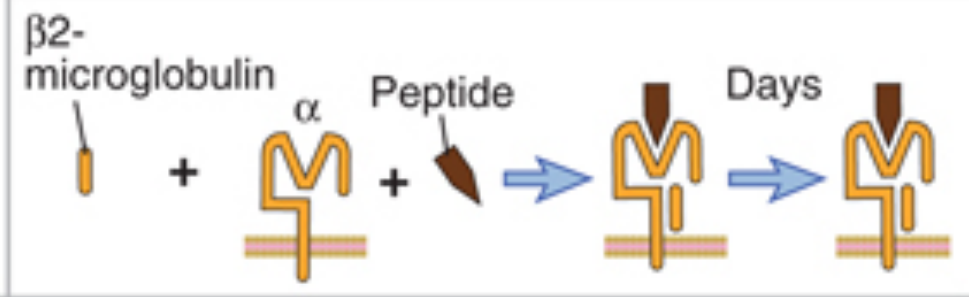
Peptide interaction with MHC

Peptides are acquired during intracellular assembly

Class I and class II MHC molecules display peptides from different cellular compartments



Peptide interaction with MHC

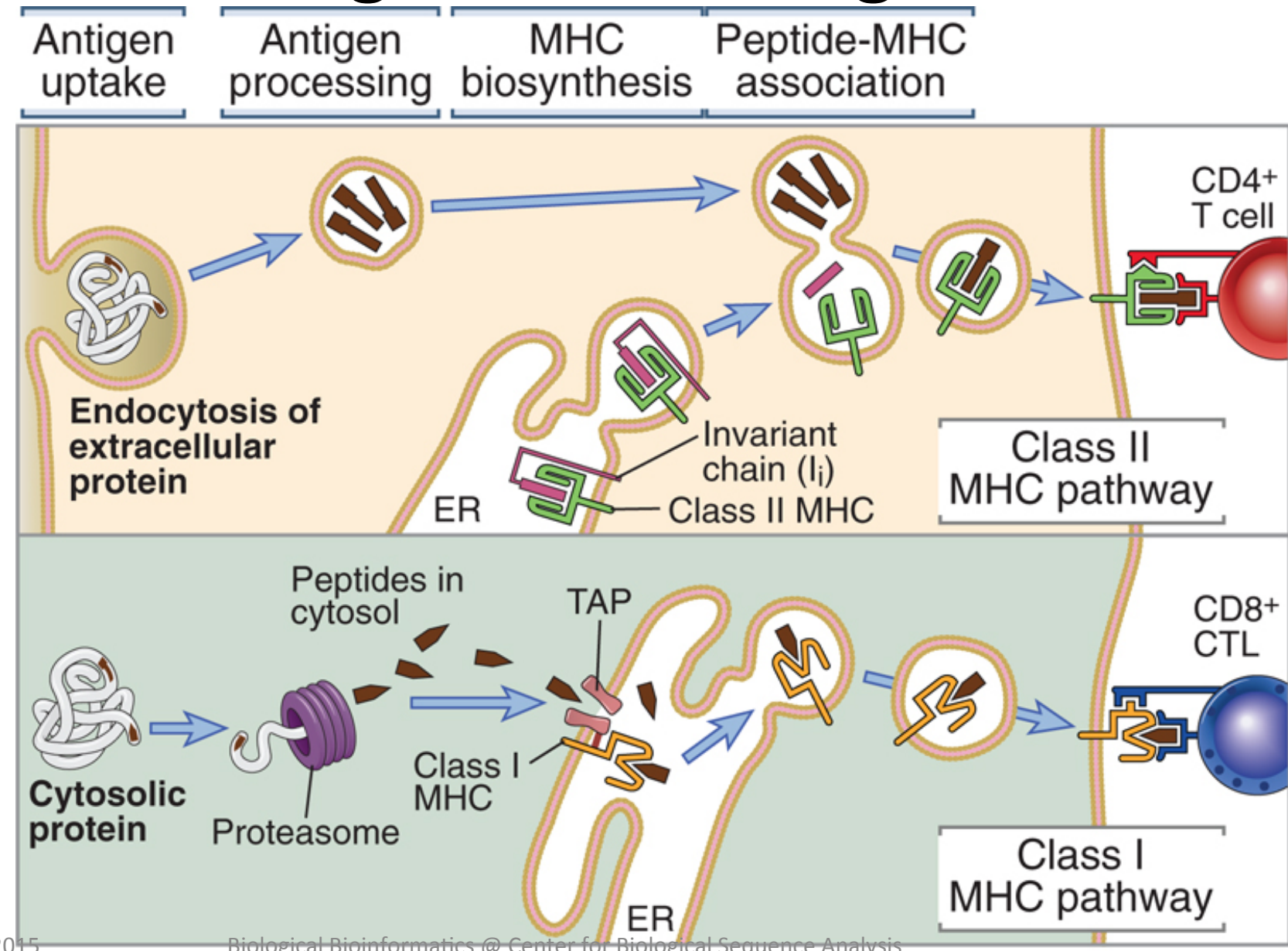
Stable surface expression of MHC molecule requires bound peptide	Only peptide-loaded MHC molecules are expressed on the cell surface for recognition by T cells	
Very slow off-rate	MHC molecule displays bound peptide for long enough to be located by T cell	

Peptide interaction with MHC

MHC samples intracellular peptides.

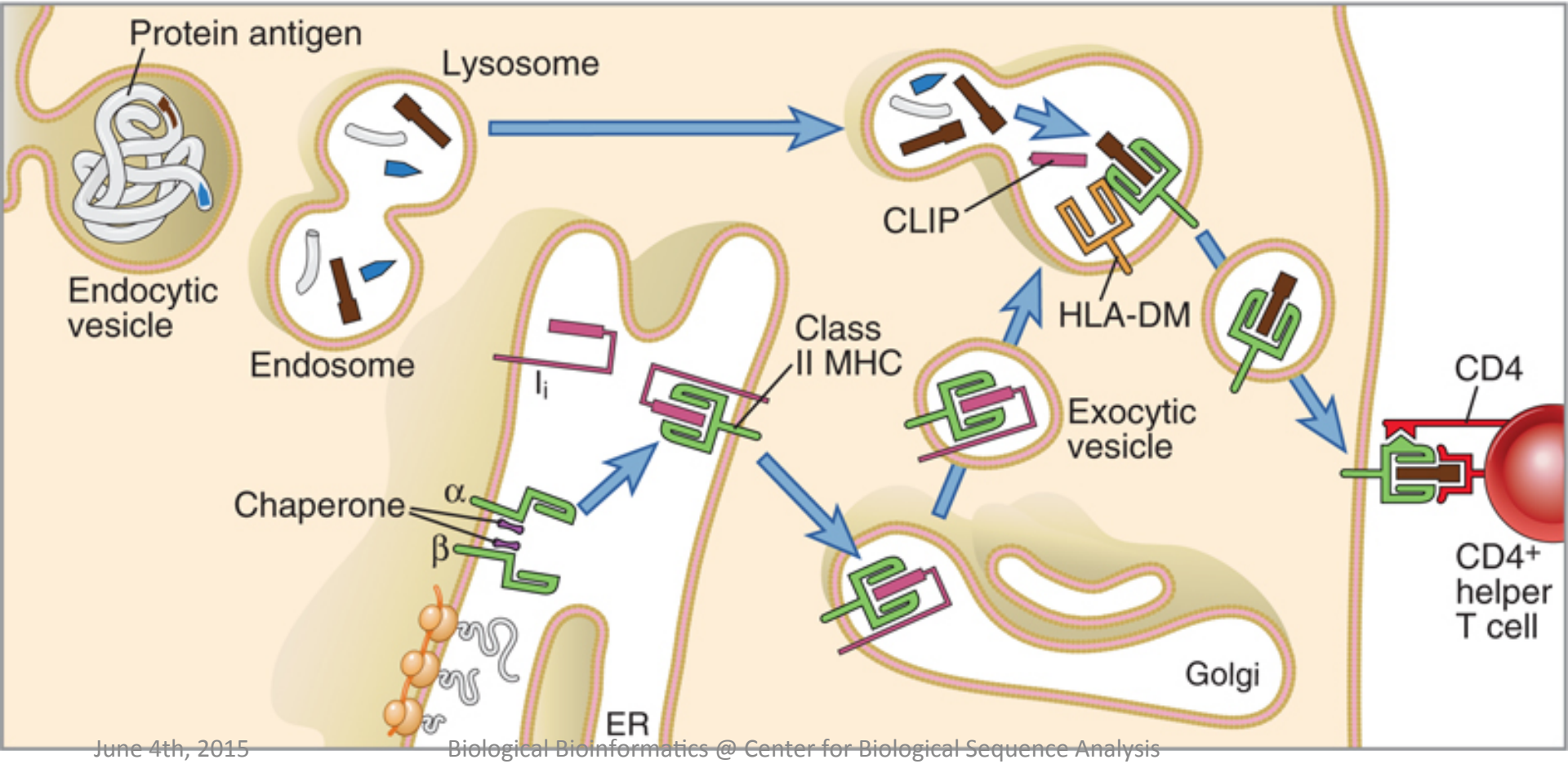
They do NOT discriminate between self and non-self

Antigen Processing

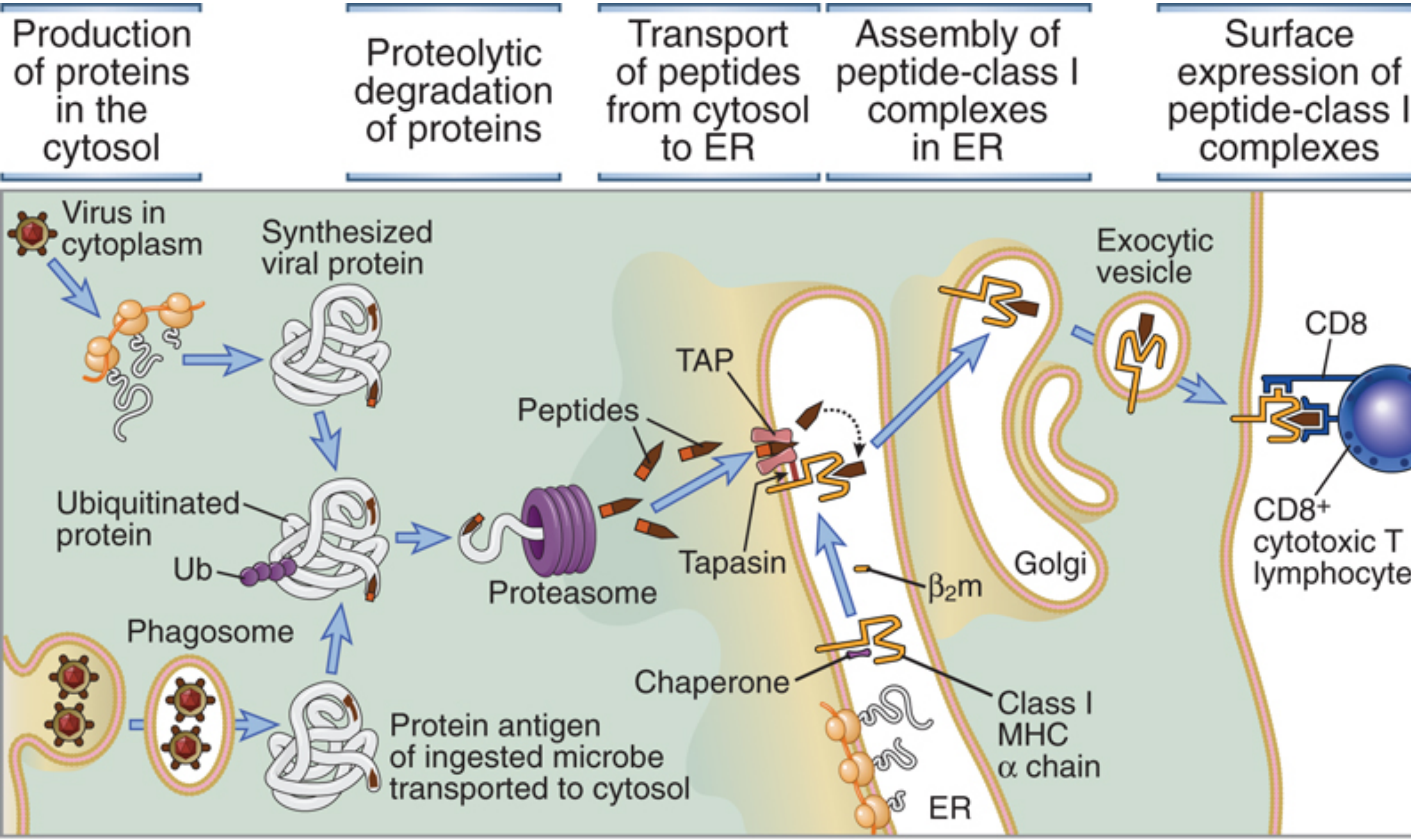


MHC class II mediated antigen processing

Uptake of extracellular proteins into vesicular compartments of APC	Processing of internalized proteins in endosomal/ lysosomal vesicles	Biosynthesis and transport of class II MHC molecules to endosomes	Association of processed peptides with class II MHC molecules in vesicles	Expression of peptide-MHC complexes on cell surface



MHC class I mediated antigen processing



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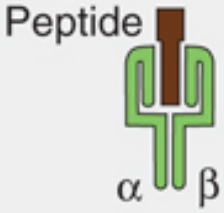
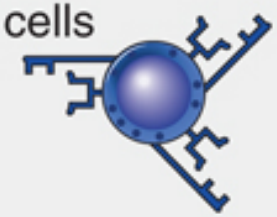
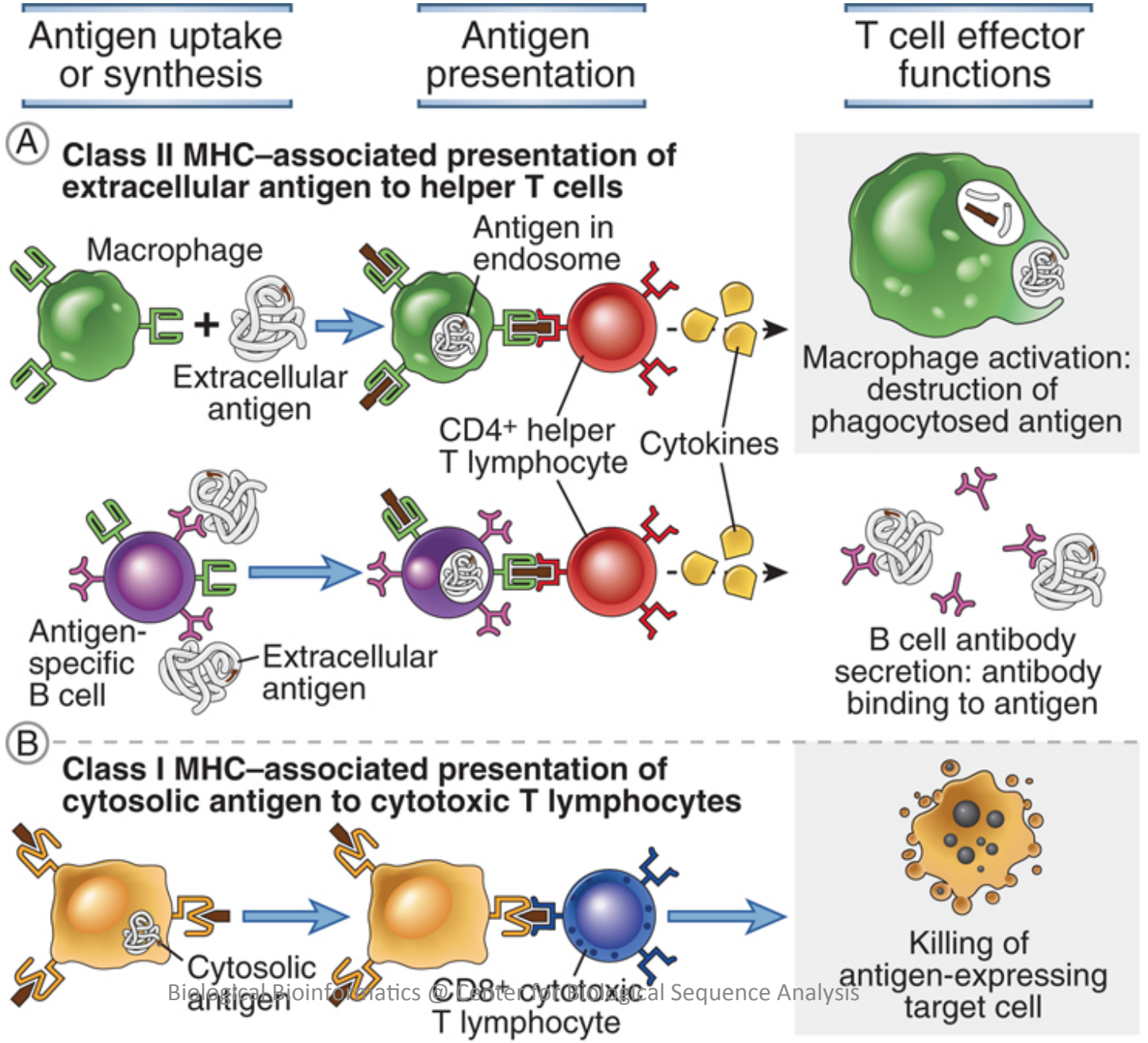
Two Antigen Processing Pathways:
one for each class of MHC

Feature	Class II MHC Pathway	Class I MHC pathway
Composition of stable peptide-MHC complex	Polymorphic α and β chains of MHC, peptide 	Polymorphic α chain of MHC, β2-microglobulin, peptide 
Cells that express MHC	Dendritic cells, mononuclear phagocytes, B lymphocytes; endothelial cells, thymic epithelium	All nucleated cells
Responsive T cells	$CD4^+$ T cells 	$CD8^+$ T cells 

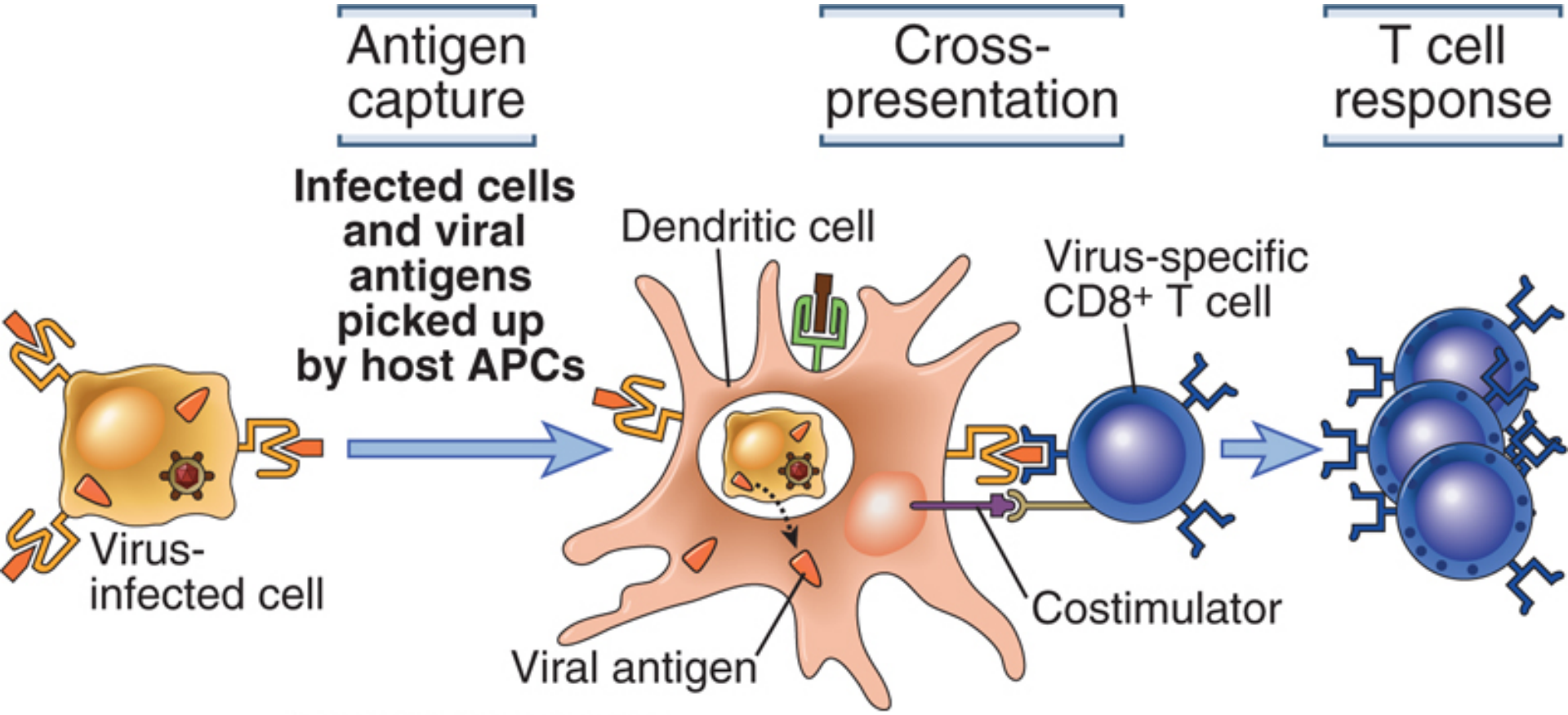
Two Antigen Processing Pathways:
one for each class of MHC

Feature	Class II MHC Pathway	Class I MHC pathway
Source of protein antigens	Endosomal/lysosomal proteins (mostly internalized from extracellular environment)	Cytosolic proteins (mostly synthesized in the cell; may enter cytosol from phagosomes)
Enzymes responsible for peptide generation	Endosomal and lysosomal proteases (e.g., cathepsins)	Cytoplasmic proteasome
Site of peptide loading of MHC	Specialized vesicles	Endoplasmic reticulum
Molecules involved in transport of peptides and loading of MHC molecules	Invariant chain, DM	TAP

Detecting the cellular antigen location



Cross-presentation



T cell recognition

- MHC molecules sample peptides from the cellular protein metabolism, and T cells recognize peptide/MHC complexes in a cell-cell interaction

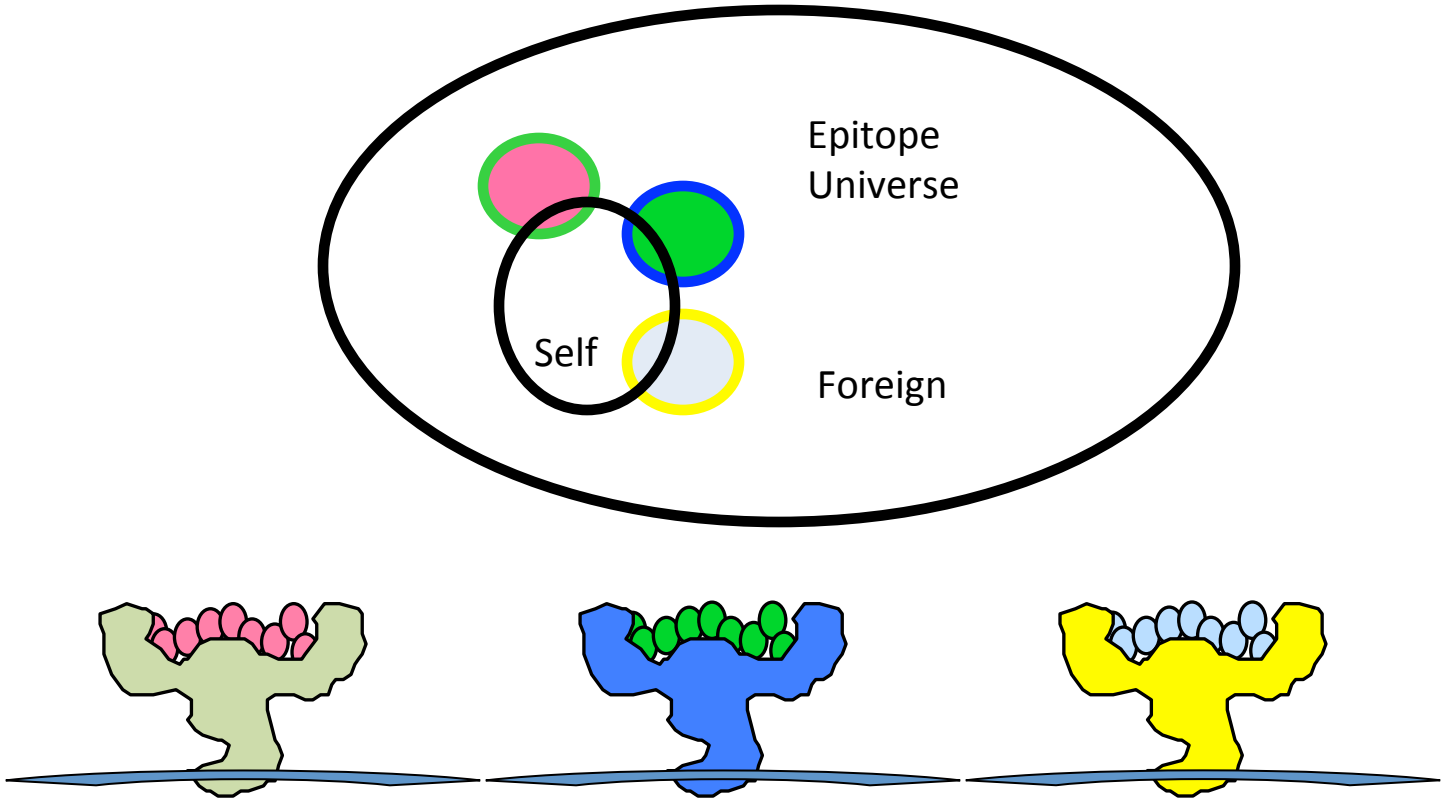
- Priming requires presentation AND co-stimulation

T cell recognition

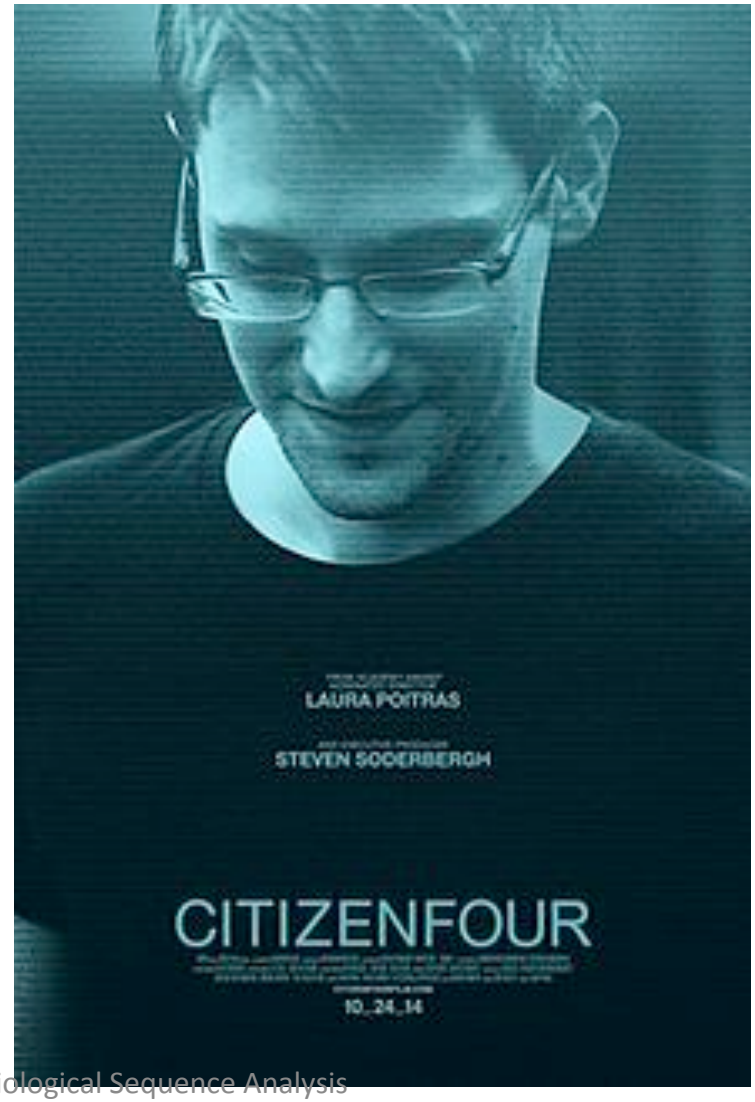
- MHC's do NOT discriminate between self and non-self – T cells do

- T cells do NOT discriminate between peptides of intra or extra-cellular protein origin– MHC pathways do

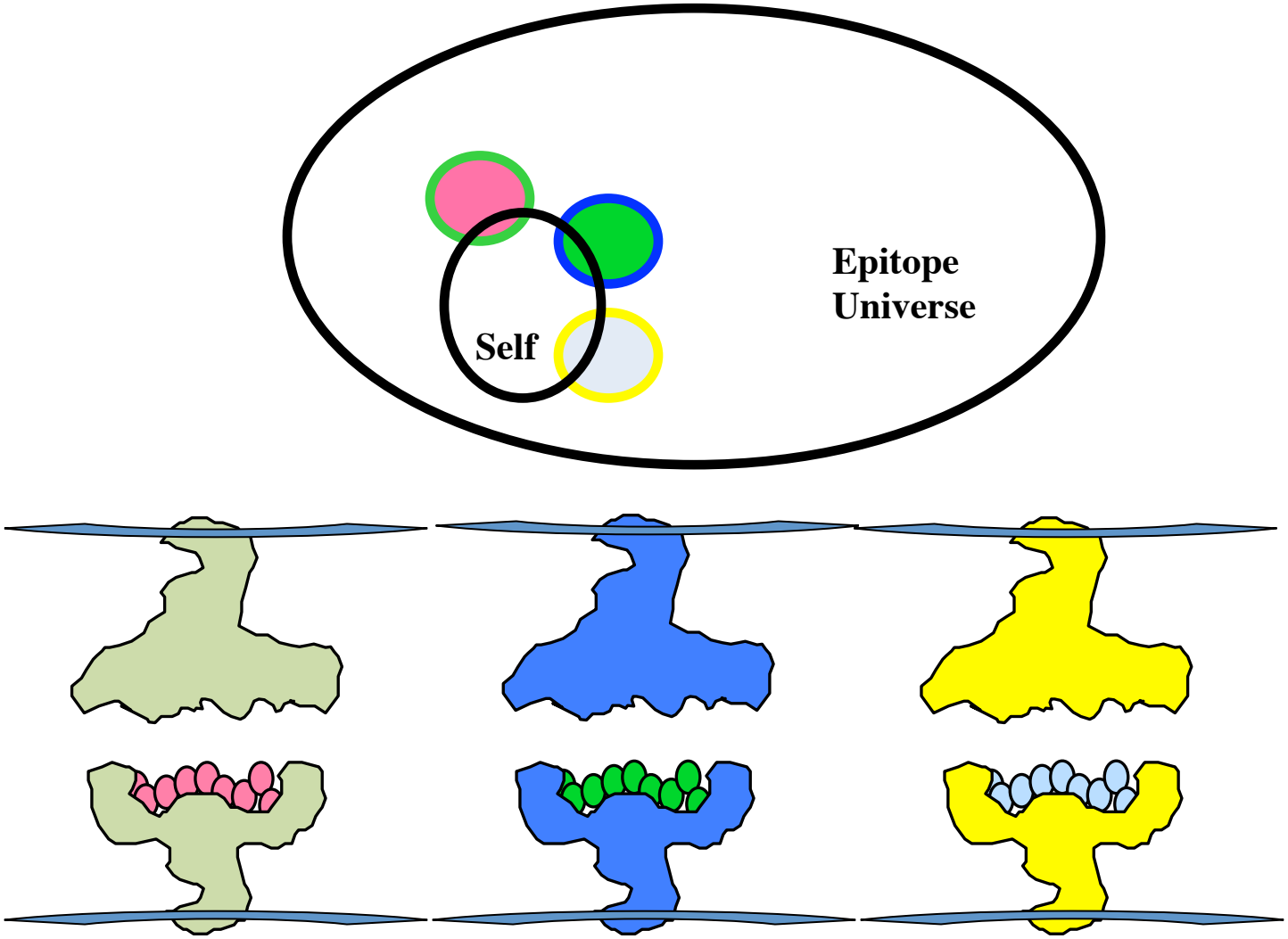
HLA polymorphism and immune specificity



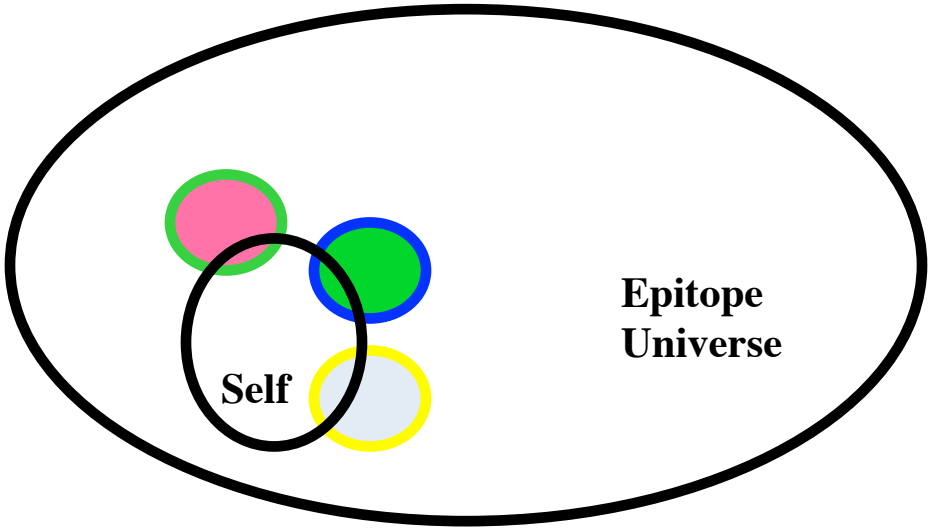
To be, or not to be - encrypted

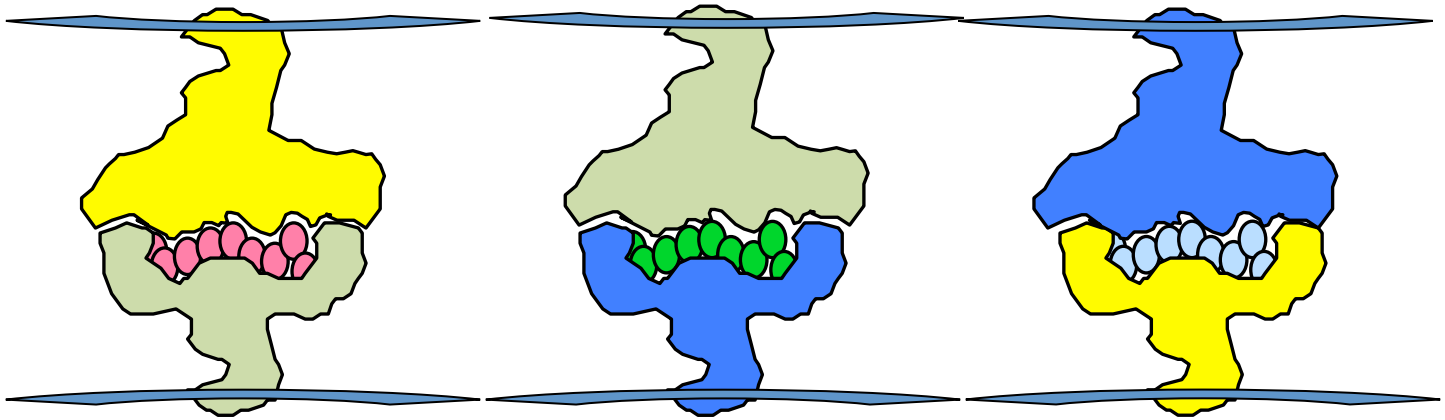


HLA polymorphism individualizes T cell responses



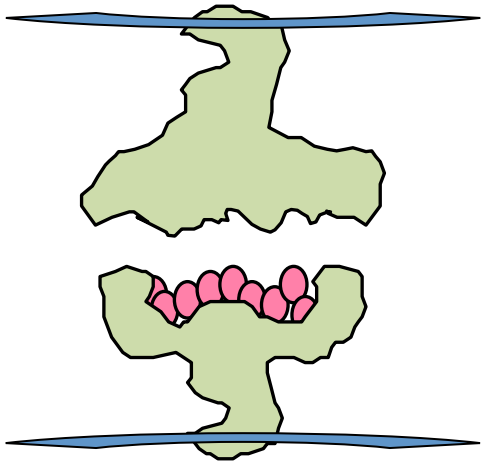
HLA polymorphism mismatch causes allo-responses





Allo-recognition in bone-marrow transplatation

Donor TcR

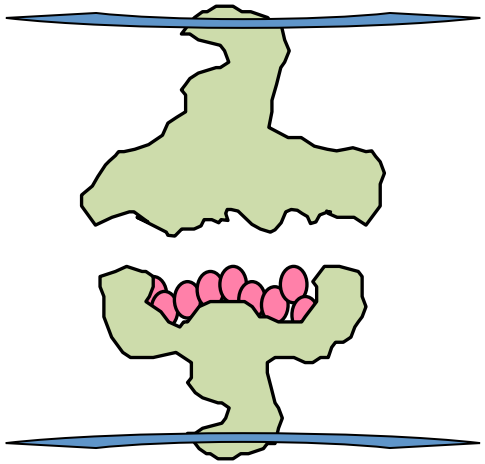


Donor APC

Auto tolerance

Allo-recognition in bone-marrow transplatation

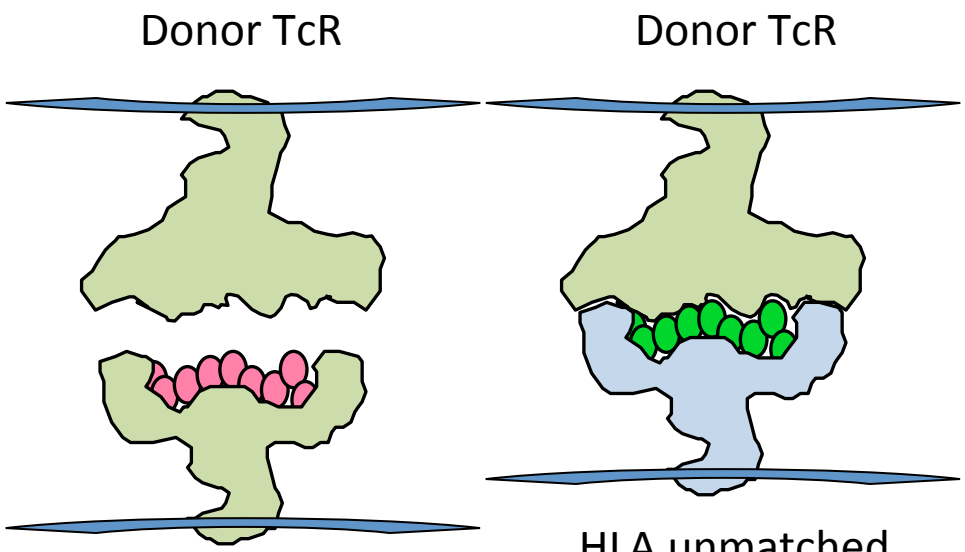
Donor TcR



Perfectly matched
APC

Auto tolerance

Allo-recognition in bone-marrow transplatation



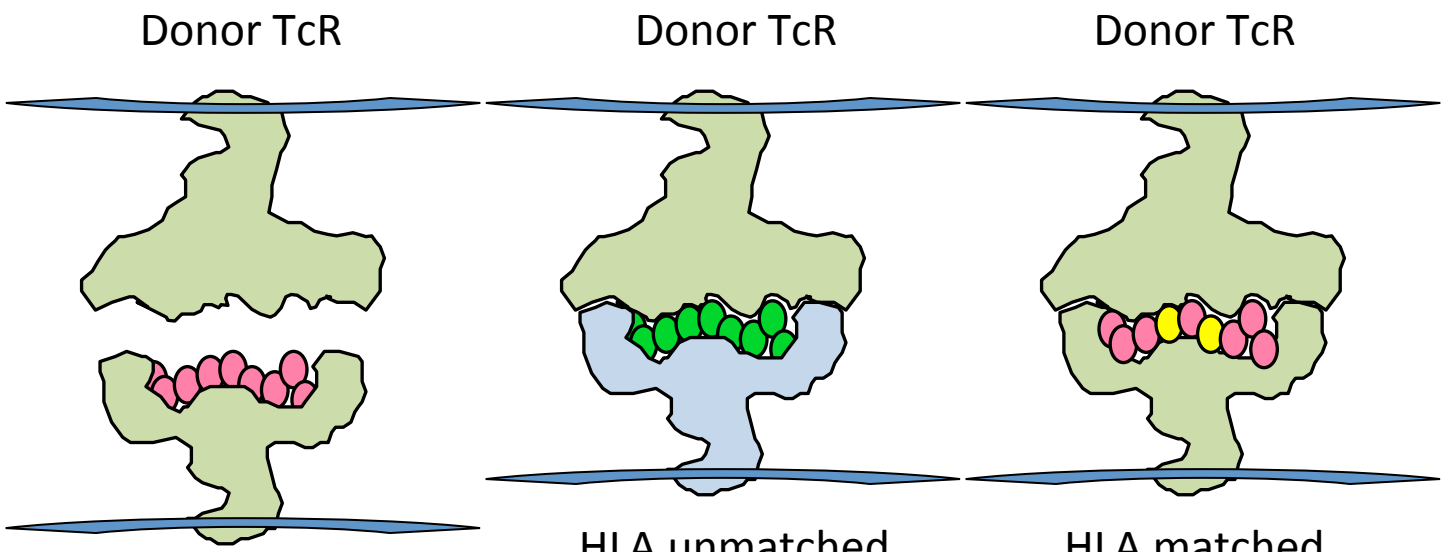
Perfectly matched APC

Auto tolerance

HLA unmatched patient APC

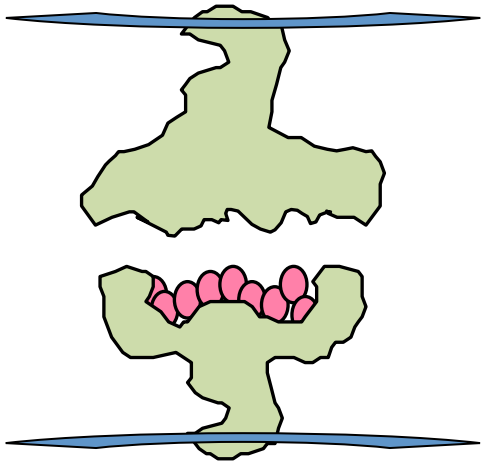
Major Histo-incompatibility

Allo-recognition in bone-marrow transplatation



Altered self-repertoire = equivalent of allo-response

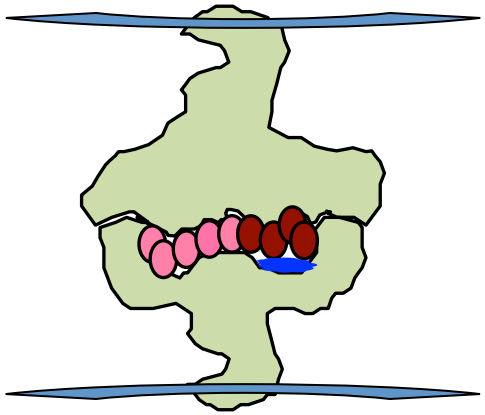
Auto TcR



HLA-B*57:01

Auto tolerance

"Allo-equivalent" TcR



HLA-B*57:01/Abacavir

ADR

B cell recognition

- Do NOT require MHC mediated antigen processing and presentation
- Use FDC for antigen display
- Recognizes targets of many kinds / intact structures
- May use a soluble receptor
- Recognize targets in the extracellular space