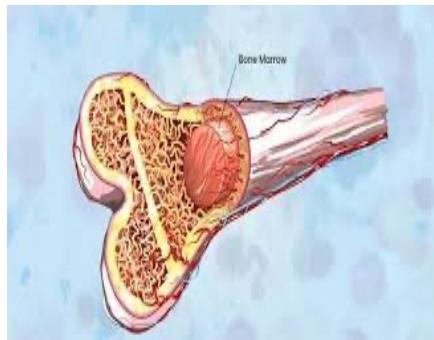
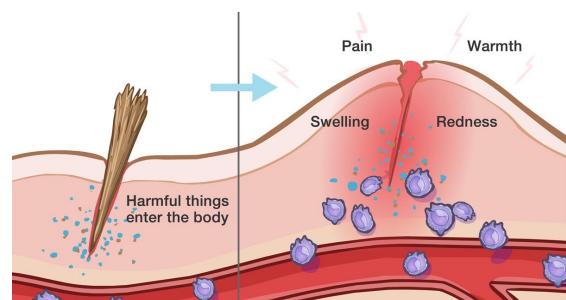
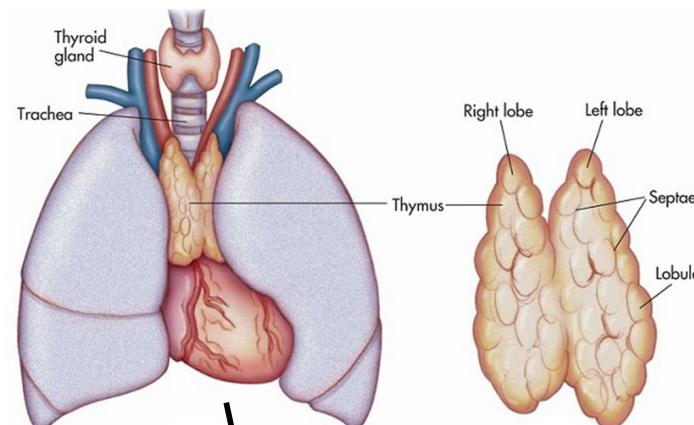


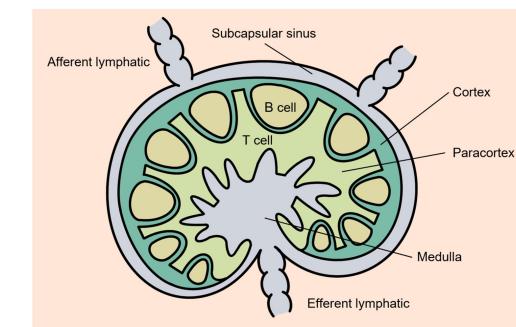
**Stem Cells Live in the Bone Marrow**



**In the Thymus Stem Cells can Mature into Naïve T cells**



**Effector T cells Migrate to Sites of Inflammation**



**Naïve T cells Circulate in the Blood and Peripheral Lymphoid Tissue**

# Everything You Need to Know About T cells

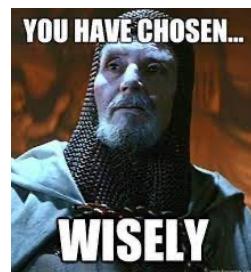
1. Where do they develop?



2. What is their function during an immune response?



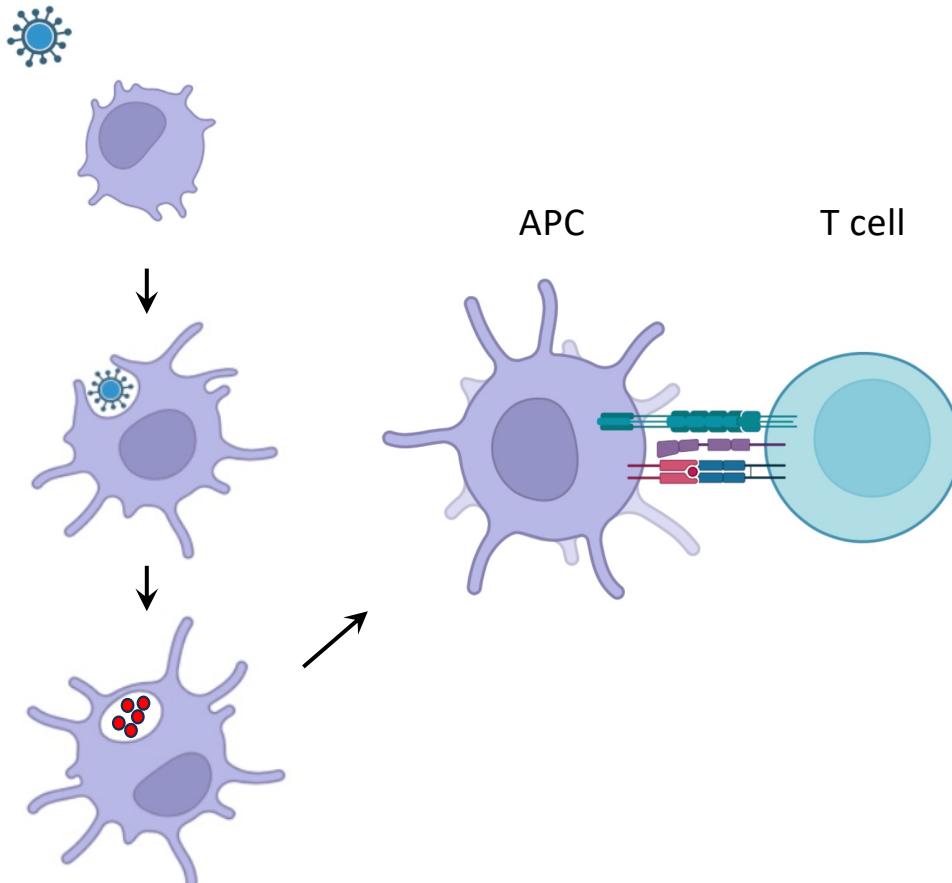
3. How do they achieve specificity?



4. What are the different types of T cells?



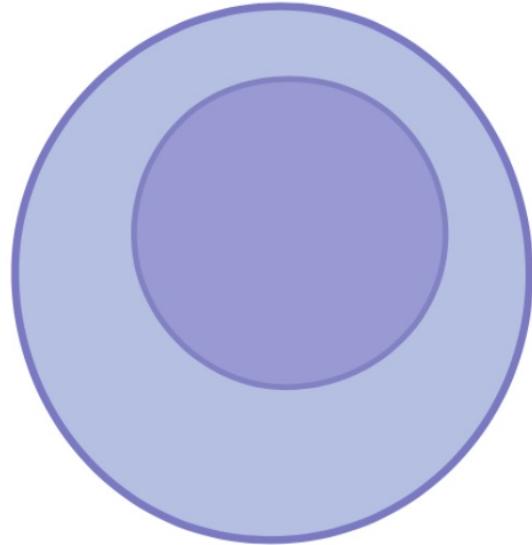
# What do T cells do in Immune Responses?



Antigen Presenting Cells (APC) take up foreign organisms/pathogens and break them down into proteins in lysosomes.

Pieces of these proteins called **peptides** are presented on the surface of the APC in either MHC Class I or Class II protein complexes

T cells use their T cell receptors to 'scan' these peptides to assess whether they are 'self' or 'non-self'

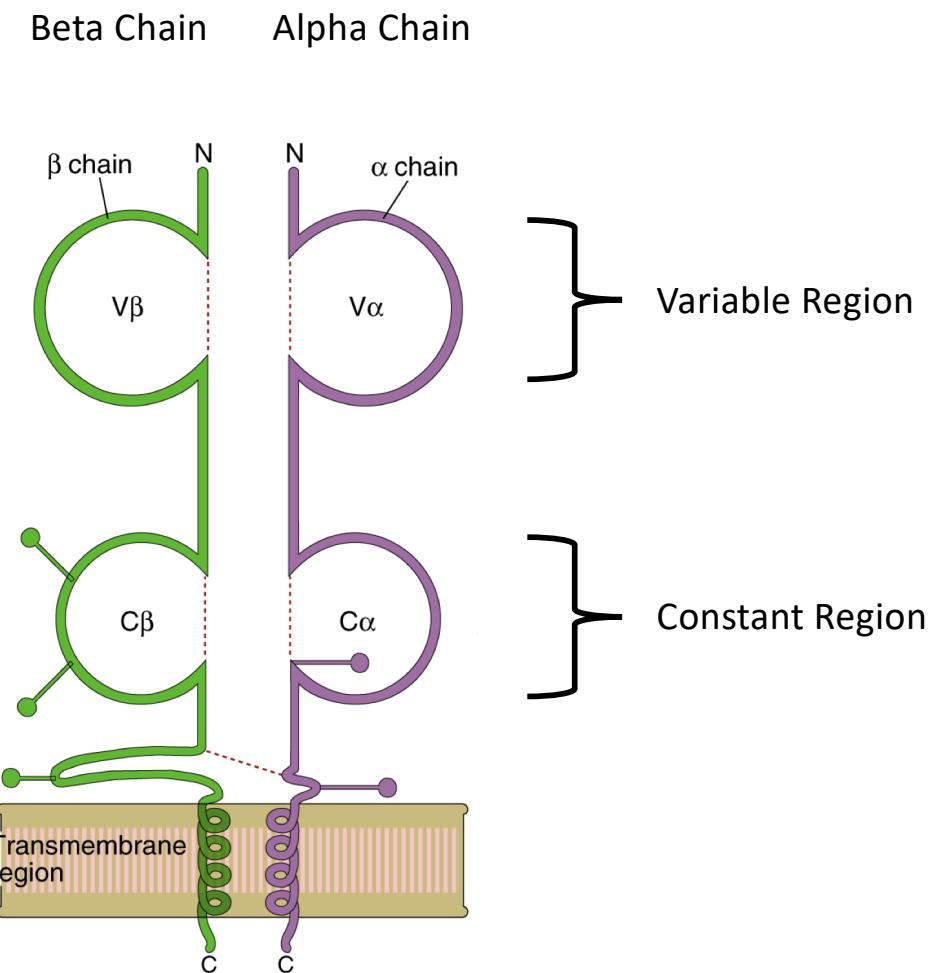
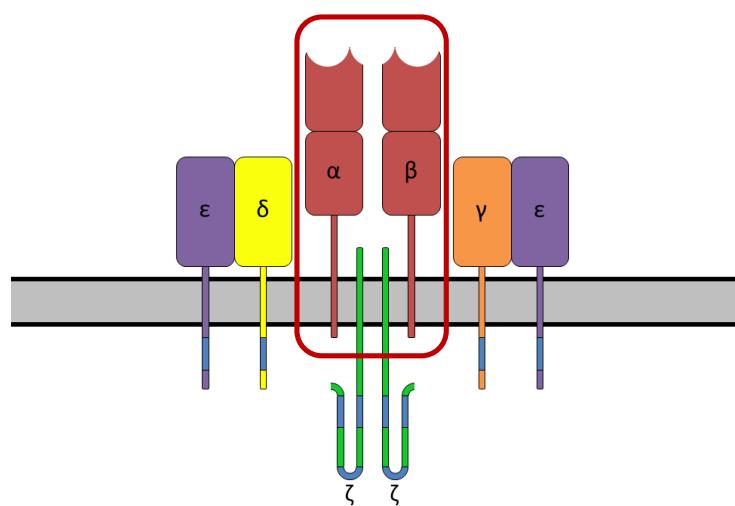


T Cell

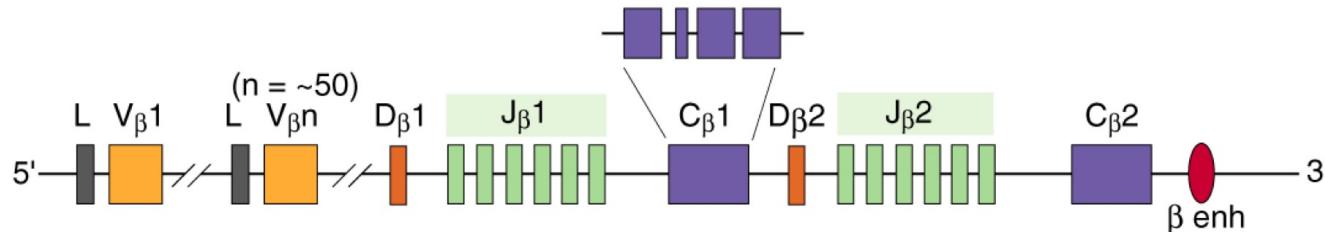
## How to Build a Mature T cell

- 
- The diagram illustrates the three steps to build a mature T cell:
- First – We need to add a T cell receptor (TCR) so that the T cell can gain **specificity****  
An illustration of a TCR consisting of four green rectangular subunits arranged in a 2x2 grid.
  - Second – We add CD4 or CD8 protein which determines whether a T cell binds to MHC Class II (CD4) or Class I (CD8) – this will determine the general ‘TYPE’ of cell it is.**  
An illustration of a CD4 protein (blue trimer) and a CD8 protein (red monomer).
  - Finally – We add receptors that direct T cells to blood and lymphoid tissues and allow them to interact with activated antigen presenting cells and infected target cells.**  
An illustration of various T cell receptors: a yellow spike-like receptor, a purple Y-shaped receptor, and an orange chain-like receptor.

# T Cell Receptor Complex

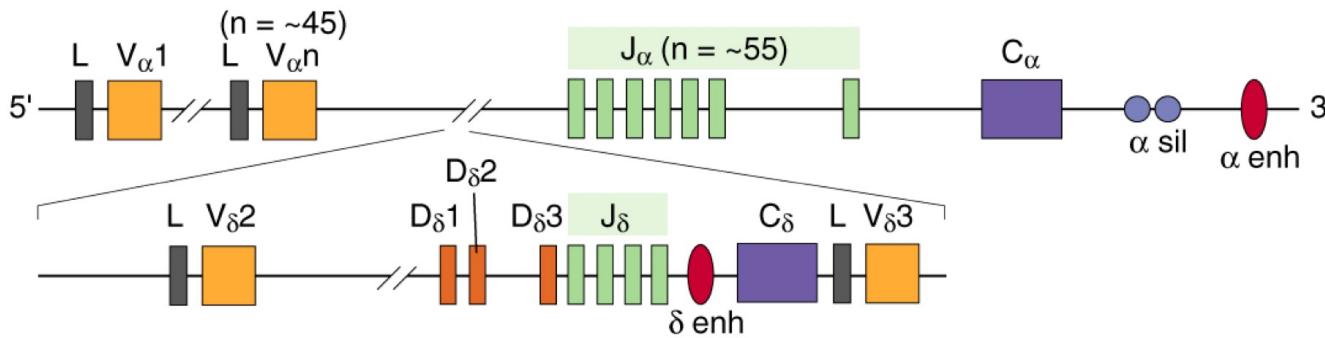


### Human TCR β chain locus (620 kb; chromosome 7)

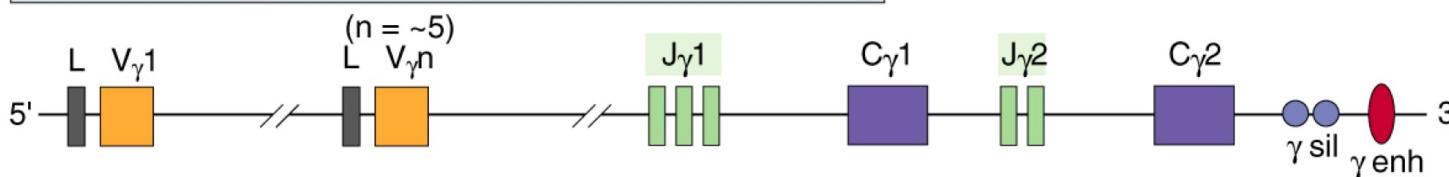


Don't Freak out....

### Human TCR α, δ chain locus (1000 kb; chromosome 14)

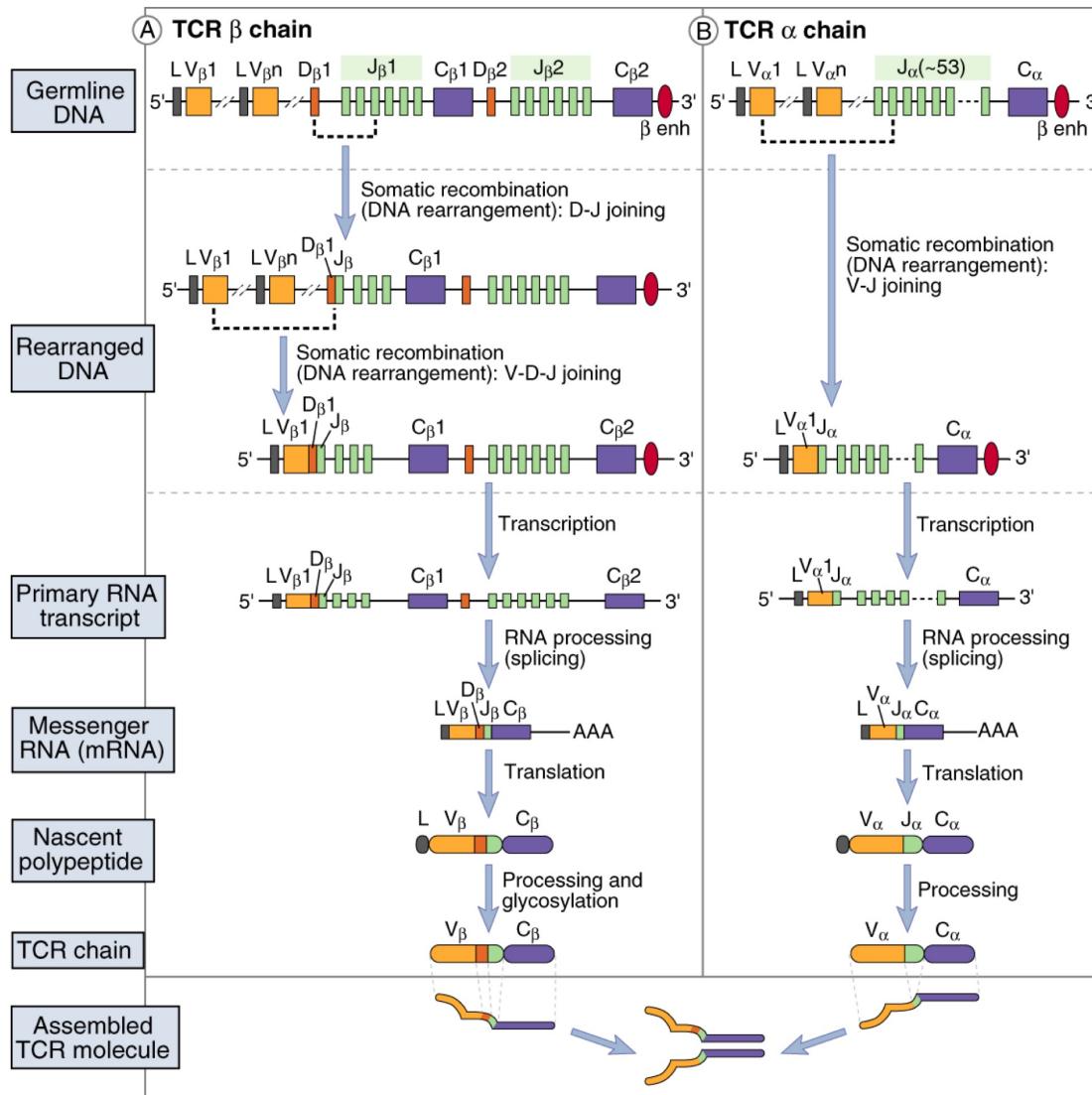


### Human TCR γ chain locus (200 kb; chromosome 7)



## DN Thymocytes

## DP Thymocytes



I stole this from a great set of lecture notes from UCSF professor Art Weiss who is one of the people who described how T cells work – you can find a link to those notes in the outline!

# What are the basic components of a TCR?

## Alpha Chain

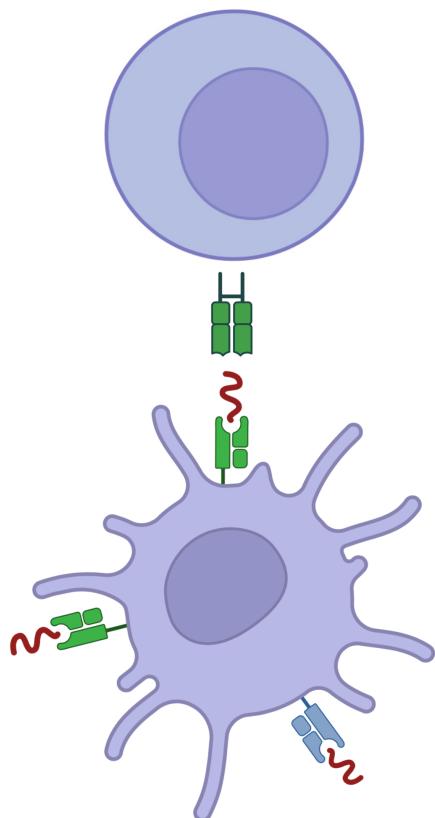


## Beta Chain



RAG1 and RAG2 join random segments together and TdT inserts random nucleotides in the joined regions!

## What are the key things to know about the TCR

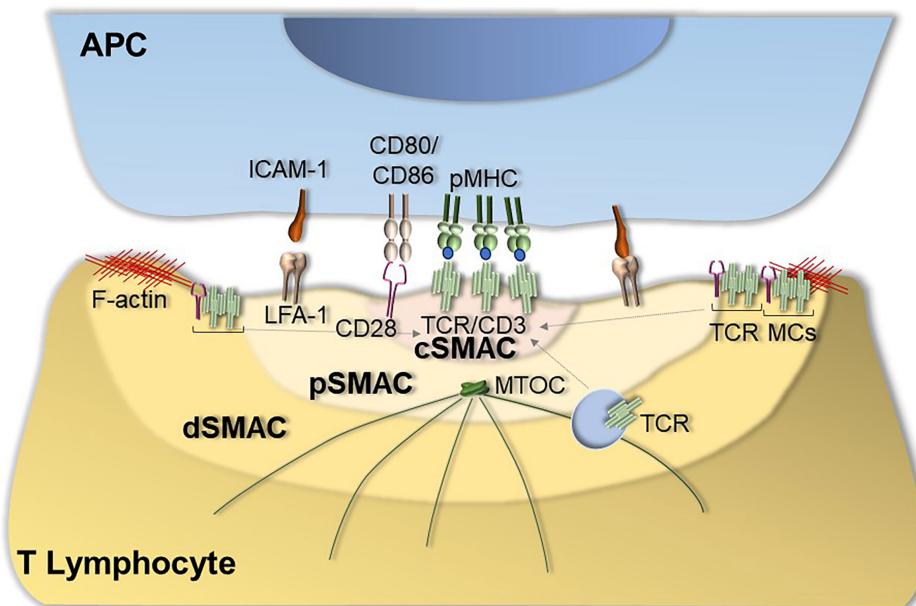


T cells must be able to respond to specific antigens

AND – they must be ‘tolerant’ of any antigens that are not dangerous

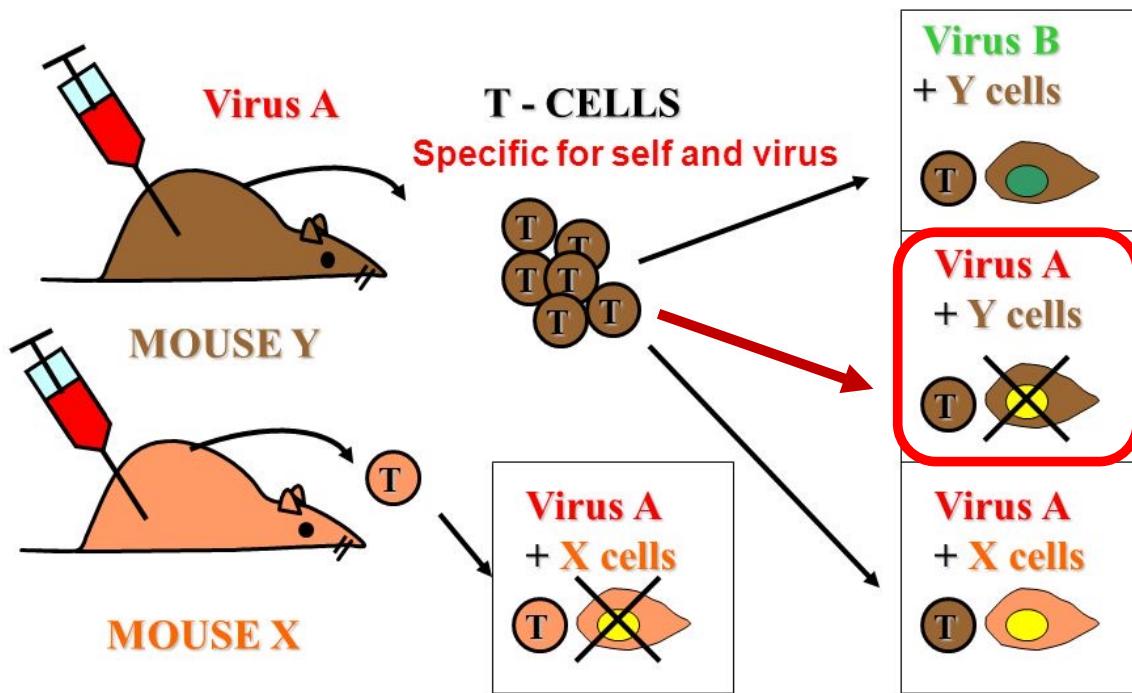
So we have to build a system from scratch that recognizes ALL foreign dangerous proteins while ignoring normal/healthy proteins

# The Way that a TCR Signals a ‘Positive’ Signal is Because of High Affinity Engagement with MHC-Peptide Complexes



**KEY POINT:** Specificity of the TCR is dependent on the strength it binds to a combination of MHC and peptide

## THE EXPERIMENT OF DOHERTY & ZINKERNAGEL 1976



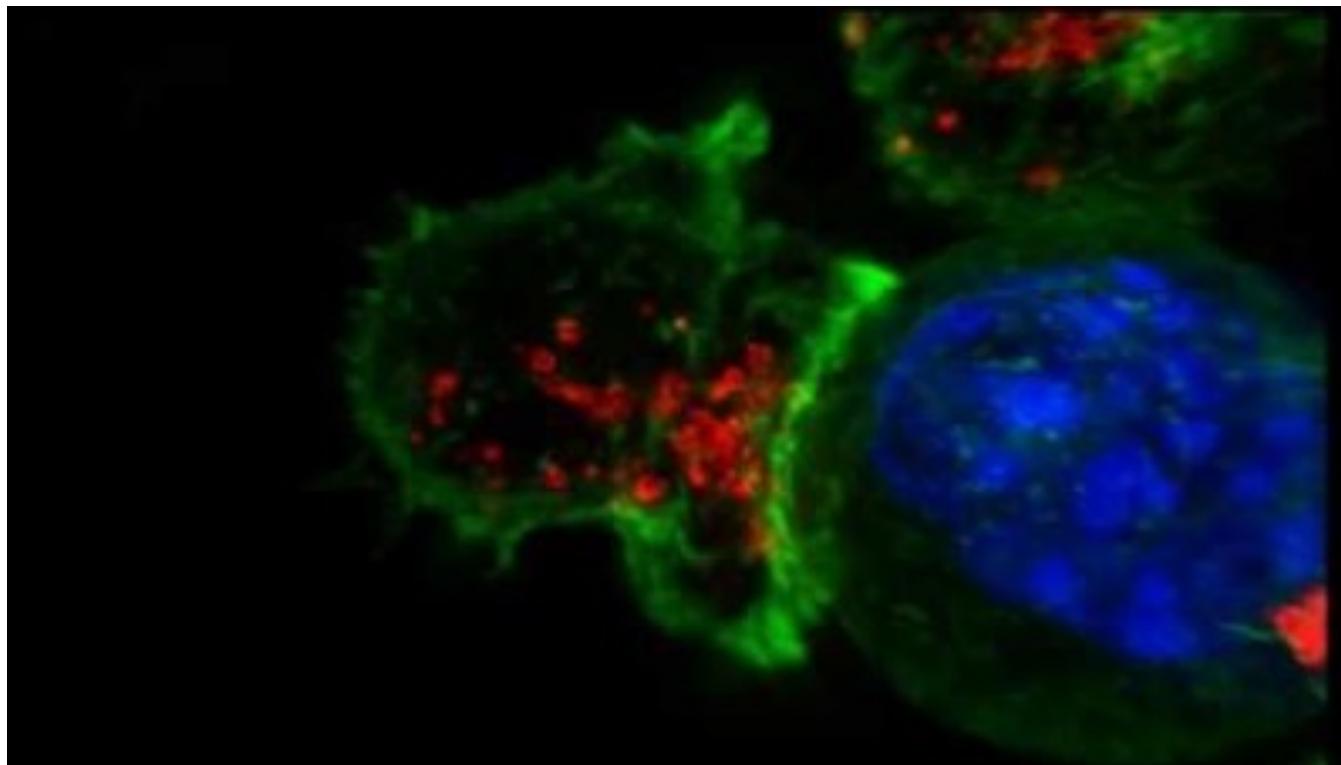
T cells recognize FOREIGN PEPTIDE  
(antigen) in the context of SELF MHC

The virus infected cell must derive from the same strain as the T cell

They have to be MHC identical

Link to this paper in your outline (online)

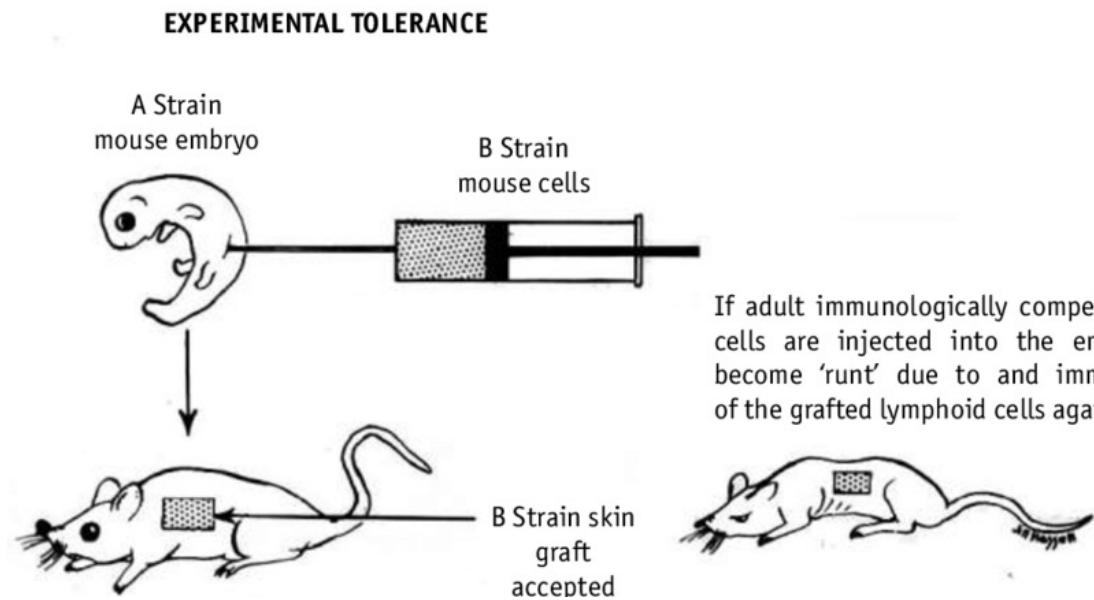
# Tolerance and Aggression in T cell Biology



# The Birth of the Concept of Immunological Tolerance

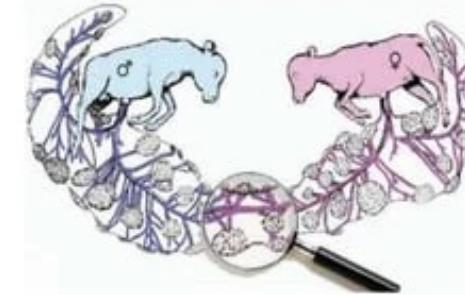
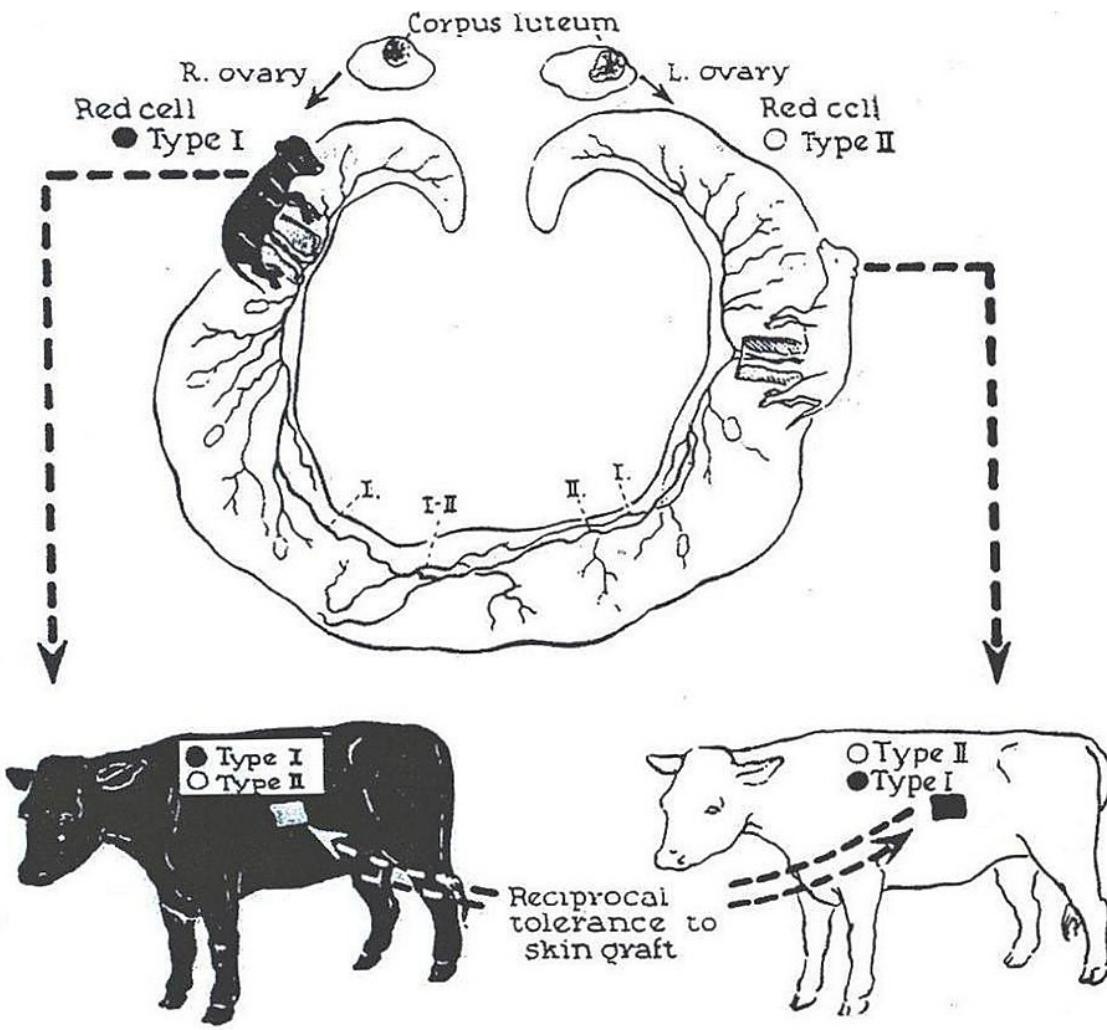


Sir Peter Medawar  
British Transplant Surgeon  
Nobel Laureate 1960  
'For the discovery of acquired  
immunological tolerance'

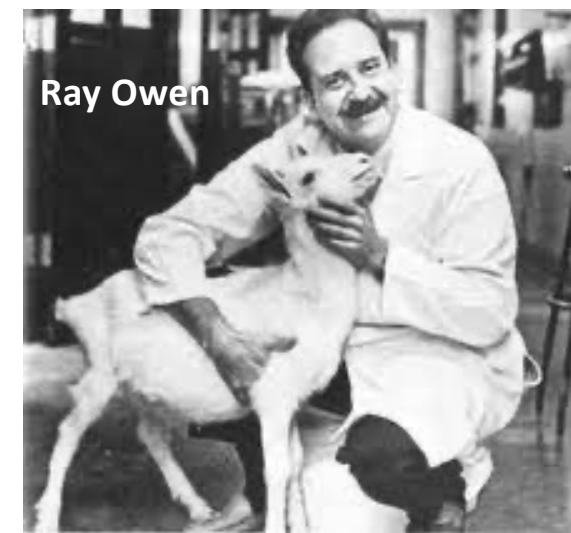


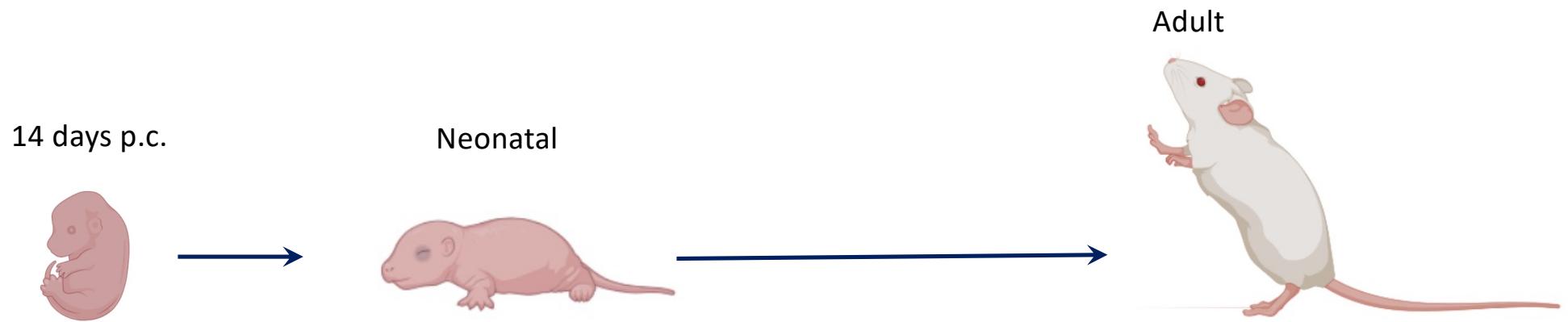
If adult immunologically competent lymphocytes are injected into the embryo, they become 'runt' due to an immune reaction of the grafted lymphoid cells against th





A peculiar observation while studying cattle infertility due to hormonal exchange in utero





No Mature  
Typical T cells

First CD4/CD8 Naïve T cells  
appear at Day 0-3 post birth

Adult



2-3 months



Active Thymus at  
10g.w. in utero

4-8 months



Peripheral Fetal T cells  
including 'activated' cells  
At 18-24g.w. in utero!

Neonatal



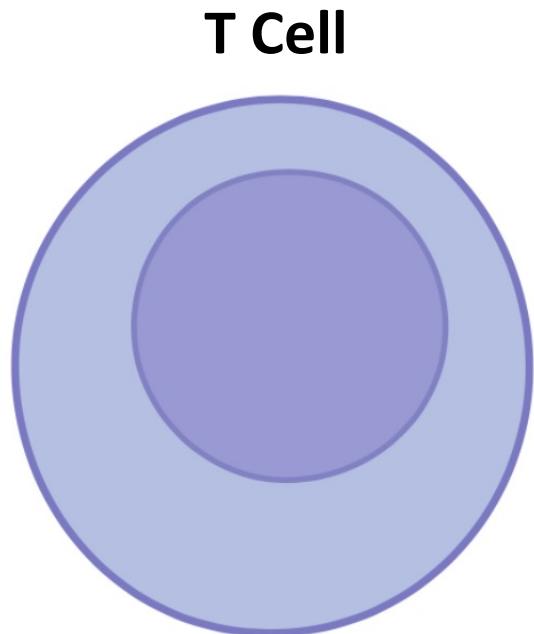
Highly developed but  
'immature' T cell  
population at birth

'Adult'



Full repertoire of  
Naive T cells in Adults

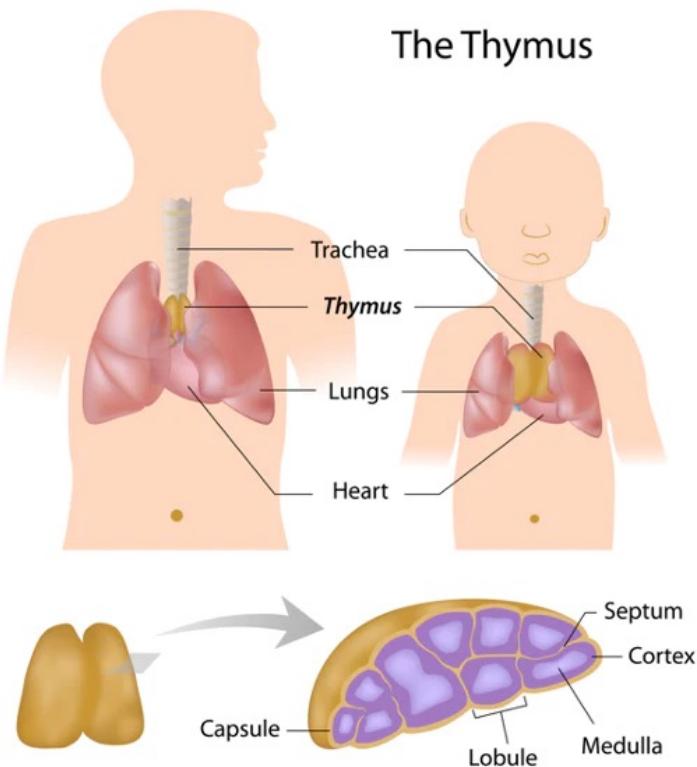
# T Cell Development



First – We need to add a T cell receptor (TCR) so that the T cell can gain **specificity**

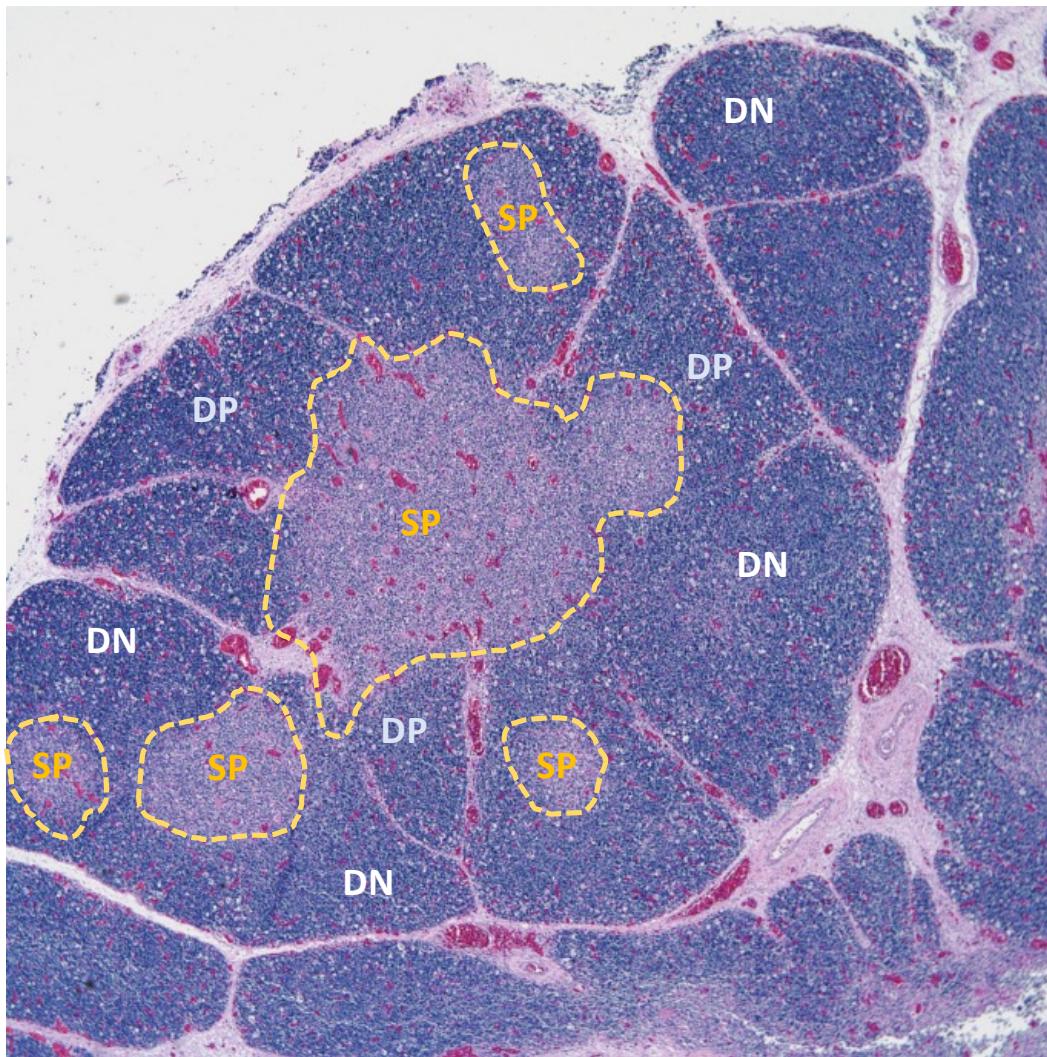
This T cell receptor has to meet these requirements:

- 1) It has to be able to bind to the MHC molecules found in the organism (Huge diversity of MHC among individuals)
- 2) It has to NOT be activated by 'self' MHC molecules
- 3) It needs to be able to potentially recognize foreign peptide on self MHC molecules
- 4) It must NOT react to 'self' peptides on 'self' MHC



The Thymus is 'School' for Developing T cells – If you remove the Thymus you have NO conventional T cells!

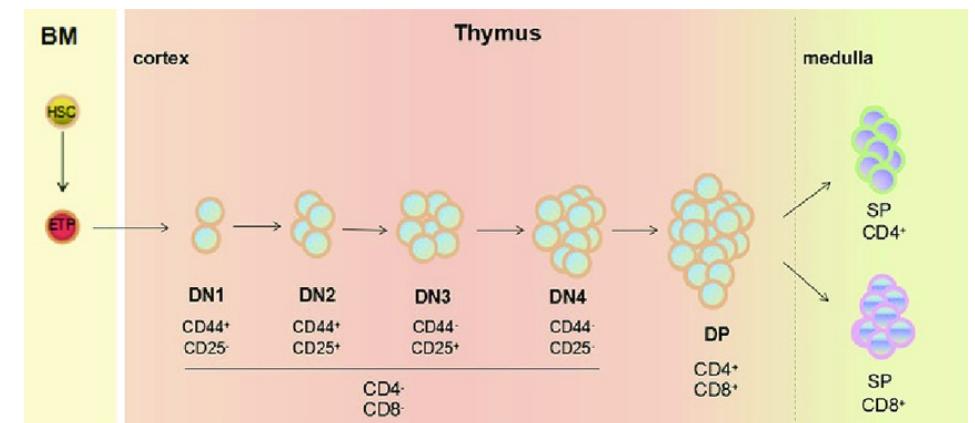
Just like school – the thymus is more important/active very early in life and goes away in adulthood.



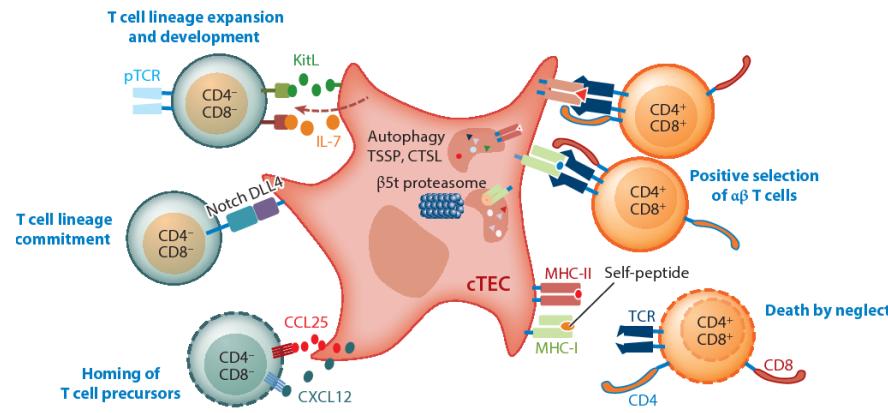
**You can break the thymus into 2 categories:**

**(1) Cortical Regions:** Densely packed with immature thymocytes (double negative (**DN**) and double positive (**DP**)))

**(2) Medullary Regions:** More diffuse regions containing more mature thymocytes (single positive (**SP**)))

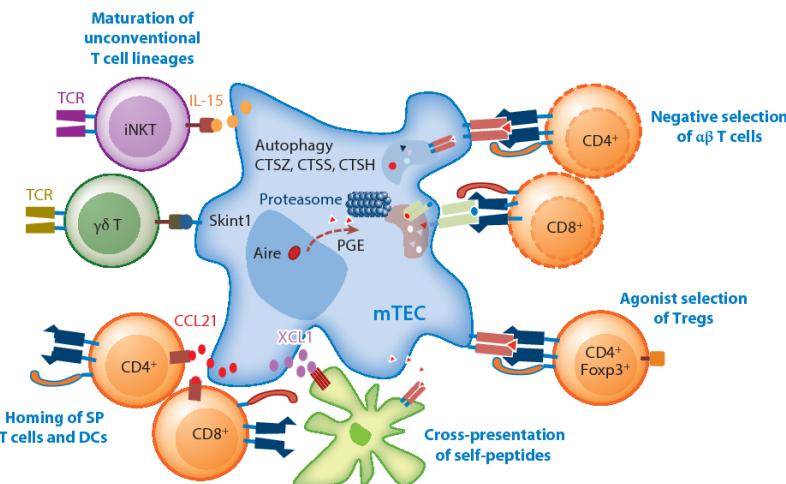


# Thymocytes are selected on specialized epithelial cells and Antigen Presenting Cells



**Positive Selection – CORTEX** – T cells ‘audition’ rearranged TCRs to see if they can bind self MHC. cTEC have special proteasomes which present different peptides for positive selection.

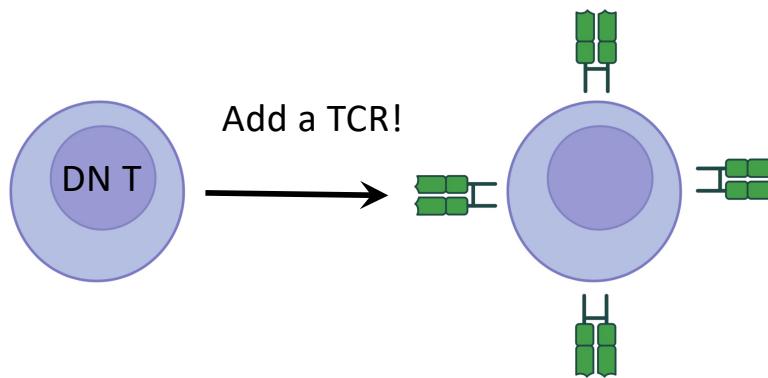
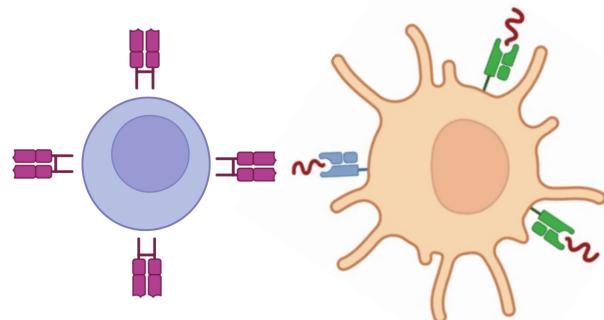
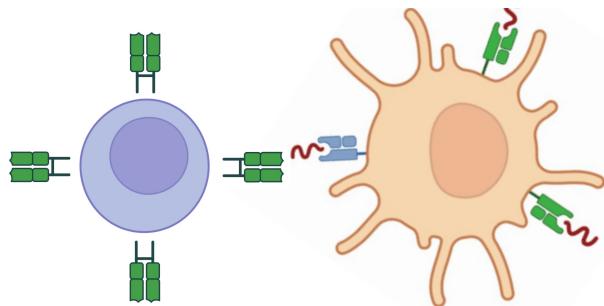
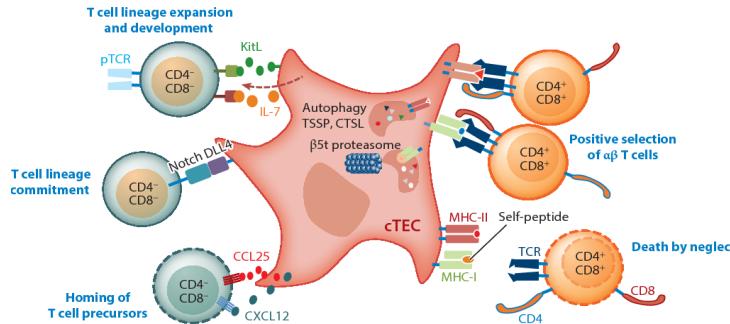
If they don't receive a signal: ‘Death by Neglect’



**Negative Selection – MEDULLA** – T cells are test TCRs to look for possibly ‘self reactivity’ to endogenous protein antigens. mTEC have special machinery to present a diverse array of ‘tissue specific antigens’ (like insulin)

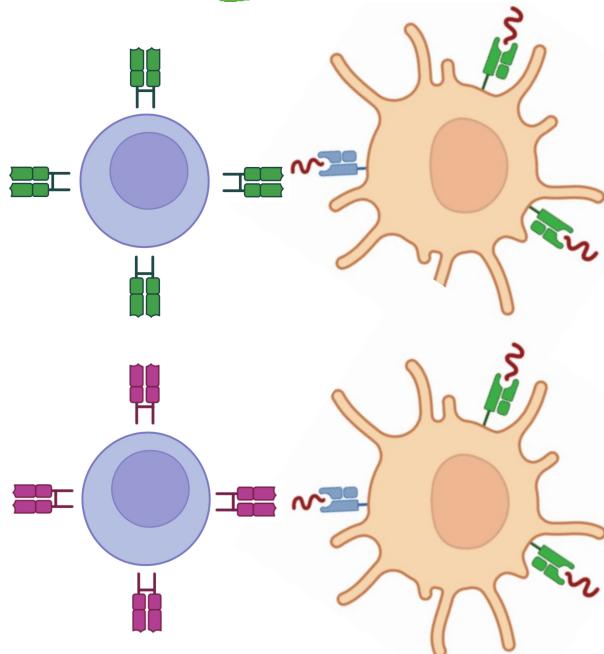
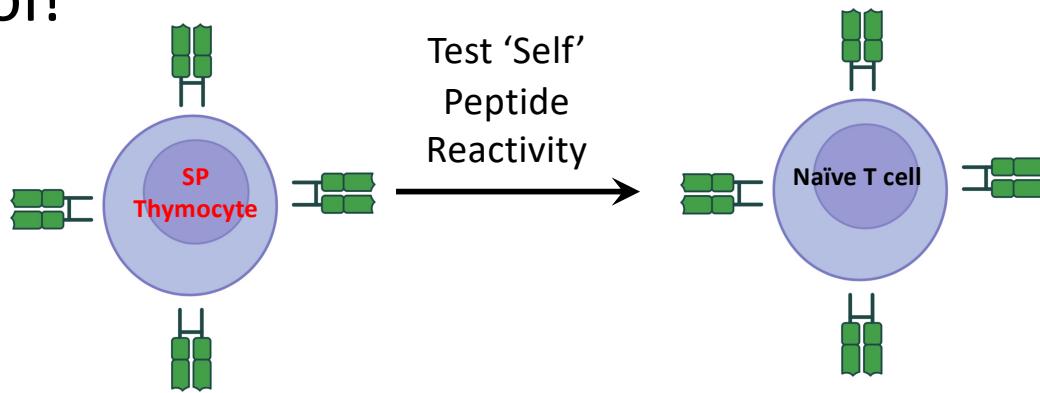
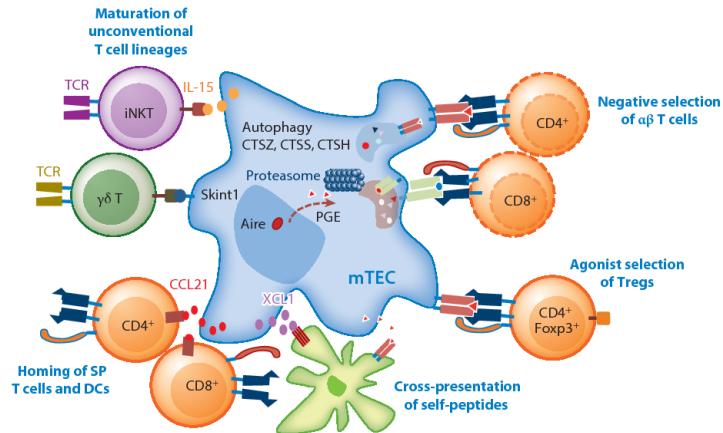
If they react strongly: ‘Death by Negative Selection’

# Positive Selection: Grade School!



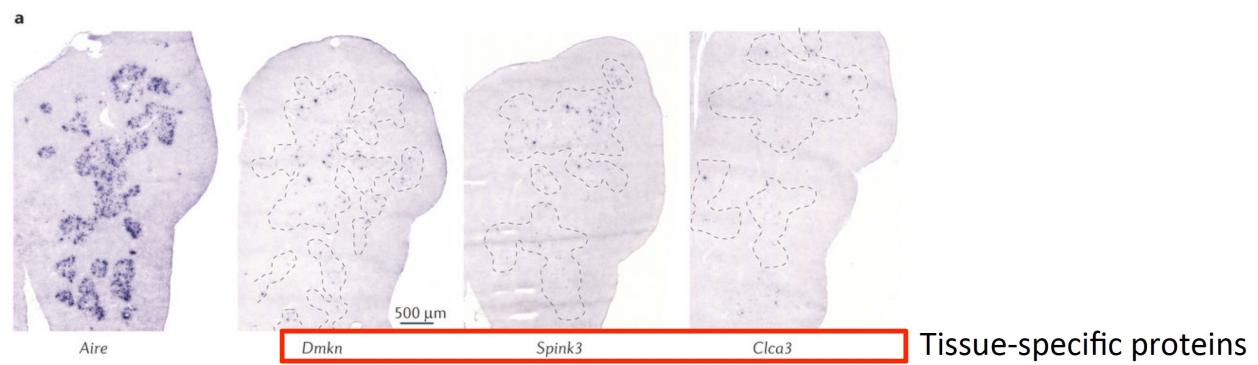
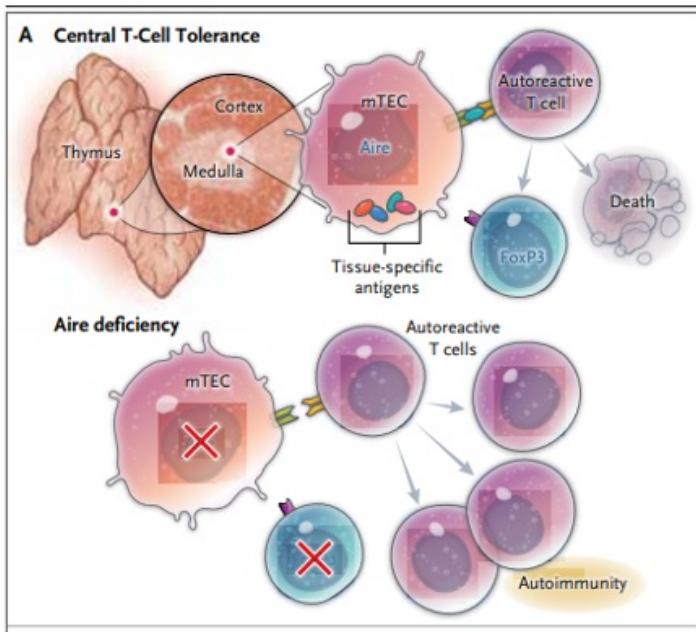
You have 2 copies of Chr7 and Chr14 -> Two tries to make a productive TCR combo!

# Negative Selection: High School!



# Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein

Mark S. Anderson,<sup>1</sup> Emily S. Venanzi,<sup>1</sup> Ludger Klein,<sup>2</sup>  
Zhibin Chen,<sup>1</sup> Stuart P. Berzins,<sup>1</sup> Shannon J. Turley,<sup>1</sup>  
Harald von Boehmer,<sup>2</sup> Roderick Bronson,<sup>3</sup> Andrée Dierich,<sup>4</sup>  
Christophe Benoist,<sup>1\*</sup> Diane Mathis<sup>1\*</sup>



**Table I Facts/Features of IPEX and APECED**

From: [Primary Immune Deficiency Disorders Presenting as Autoimmune Diseases: IPEX and APECED](#)

	IPEX	APECED
OMIM	304930	240300
Gene	<i>FOXP3</i>	<i>AIRE</i>
Onset of symptoms	Infancy	Childhood
Infections	<i>Staphylococcus</i> , <i>Enterococcus</i> species, CMV, <i>Candida</i> (infrequent)	<i>Candida</i> (up to 100%)
Auto-immune enteropathy	Frequent	10%
Skin involvement	Frequent	Frequent
Alopecia	Rare	30%
Vitiligo	Rare	15%
Nail dystrophy	Rare	50%
Enamel hypoplasia	Absent	75%
Insulin-dependent diabetes mellitus	Frequent	20%
Autoimmune thyroiditis	Frequent	6%
Hypoparathyroidism	Absent	85%
Adrenal failure	Rare	70%
Ovarian failure	Absent	60%
Autoimmune liver disease	Common	15%
Renal disease	Common *	Absent
Autoimmune hematologic diseases	Frequent	Rare
IgG, IgA, IgM	Normal	Normal
IgE	Elevated	Normal
Eosinophils	Increased	Normal
CD3, CD4, CD8, CD19	Normal	Normal
Autoantibodies	Frequent	100%
Antibody production	Normal	Normal
Treatment	Immunosuppressive agents HSCT	Antifungal Hormonal replacement
Lethality at early age	High	Low

\* It is unclear if this is autoimmune or secondary to treatment with cyclosporin A

## **Two Genetic Diseases Which Cause Failure of T cell Tolerance:**

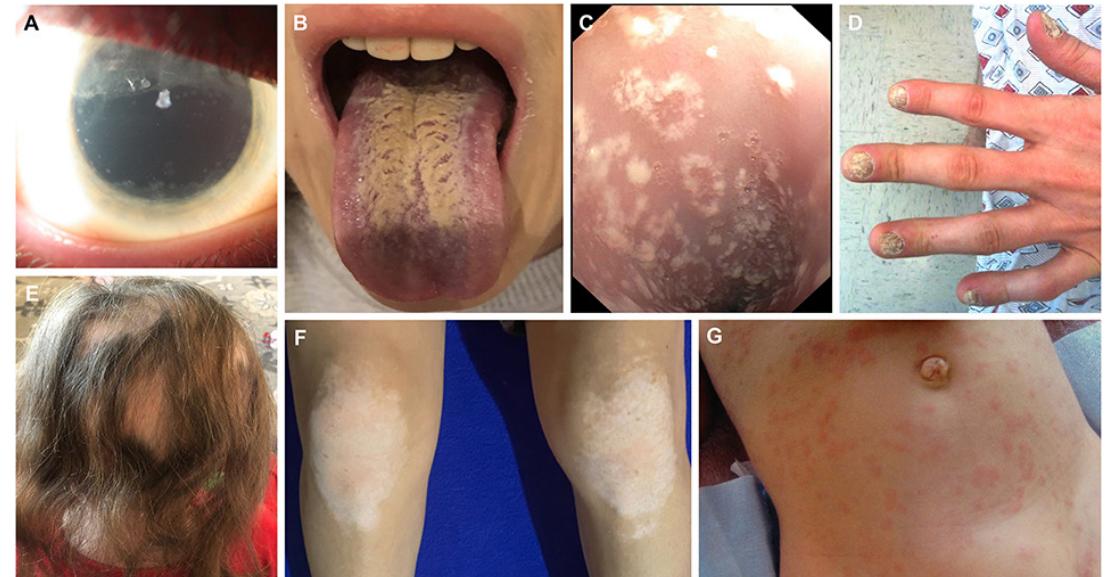
**IPEX: Dysfunctional Treg**

**APECED: Failed Negative Selection**

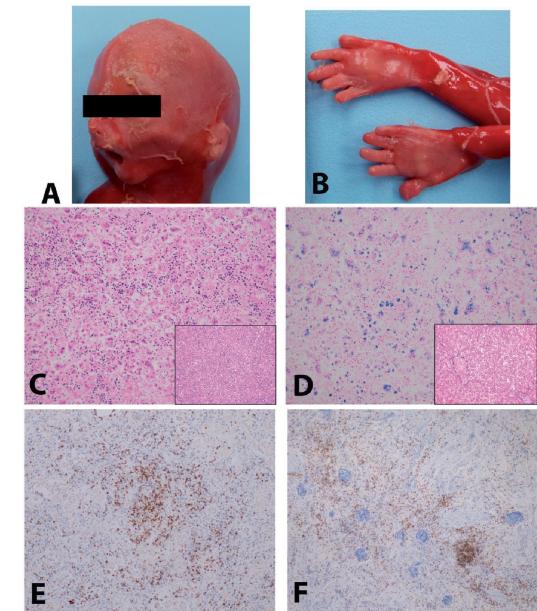
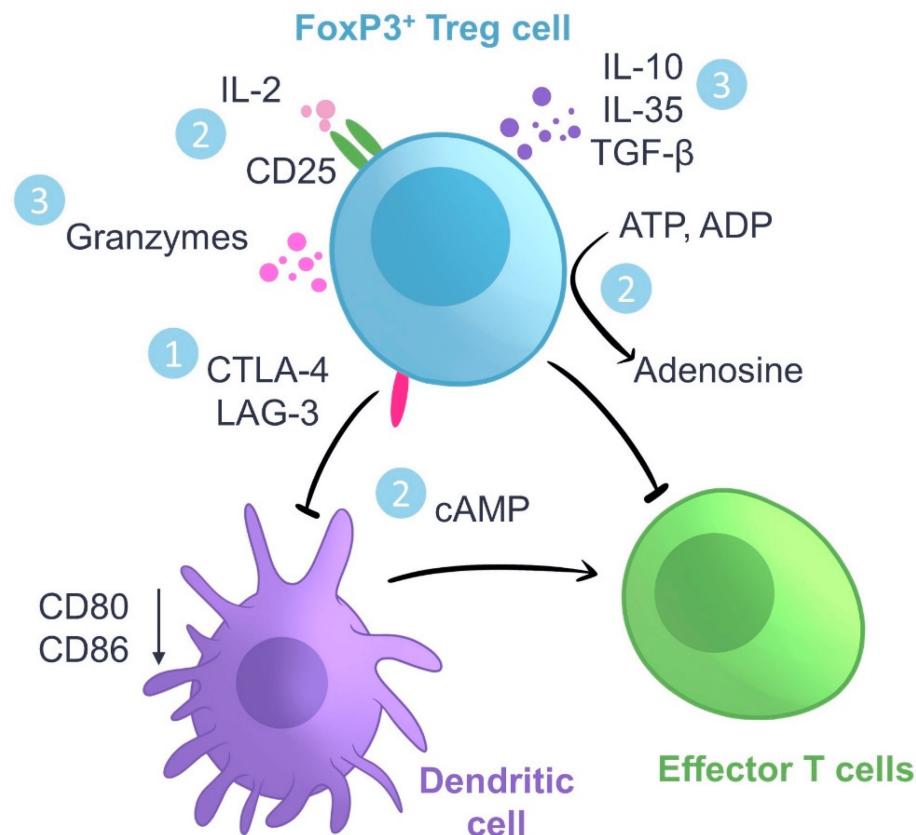
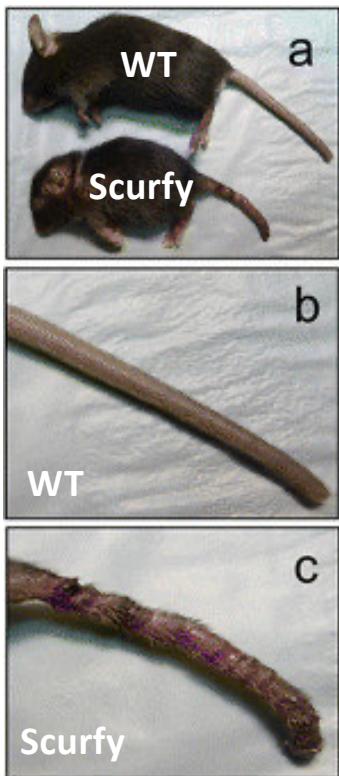
IPEX: No Tregs – Failure to Thrive



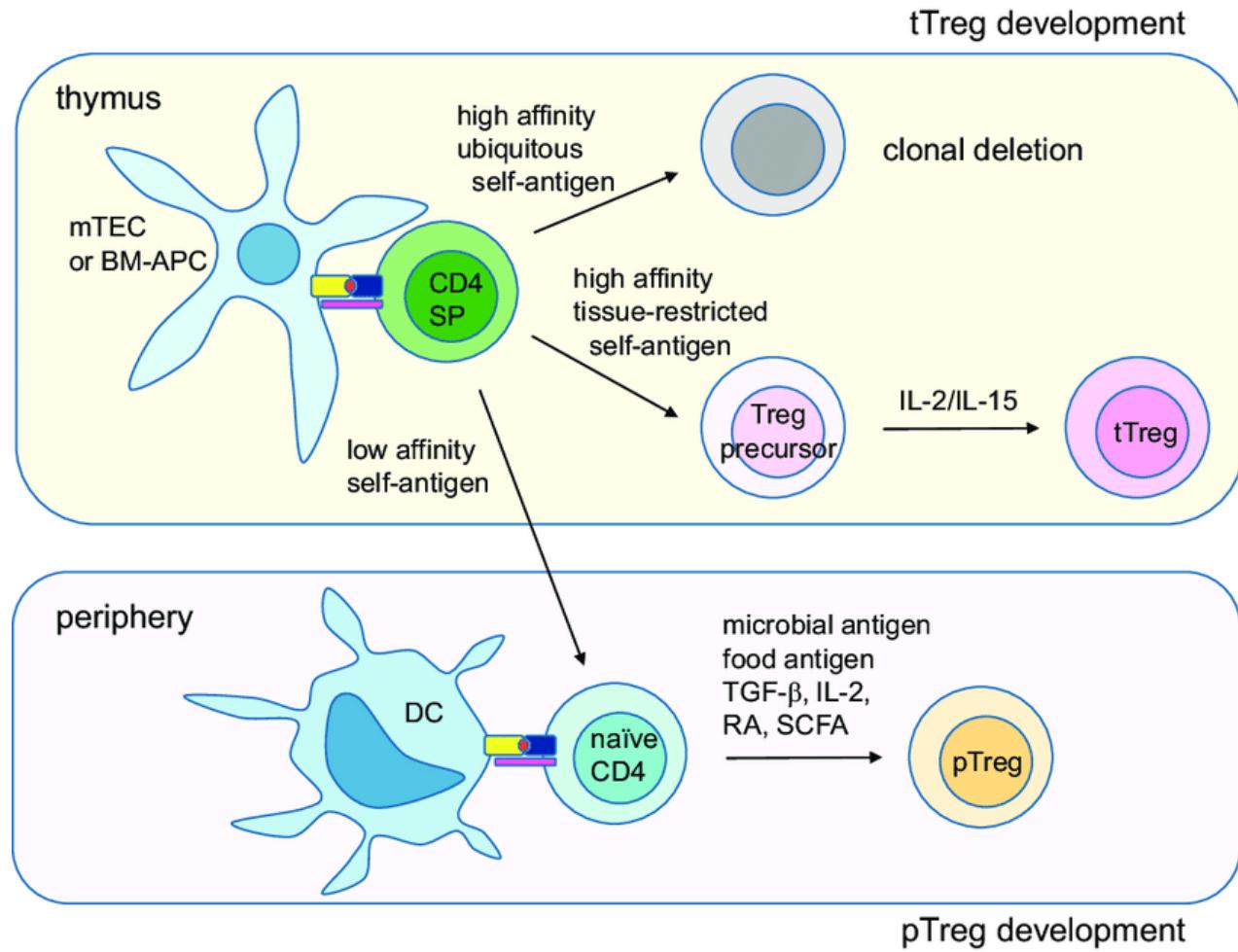
APECED: No Negative Selection – multiple autoimmune manifestations



# Let's Talk about Treg Cells



Humans often fail to develop



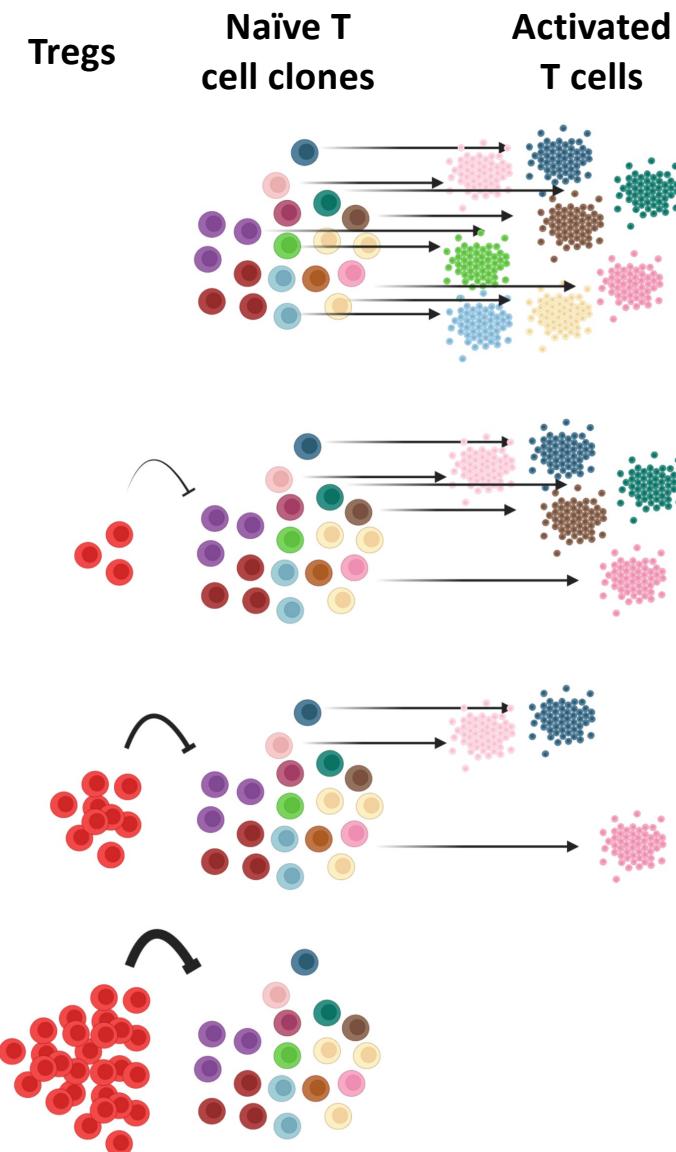
Treg can come from the thymus or be generated in the periphery –

Both processes typically involve upregulation of the transcription factor **FOXP3** (the gene affected in IPEX/Scurfy)

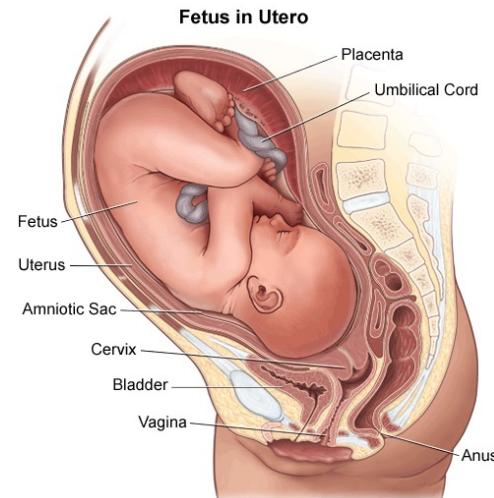
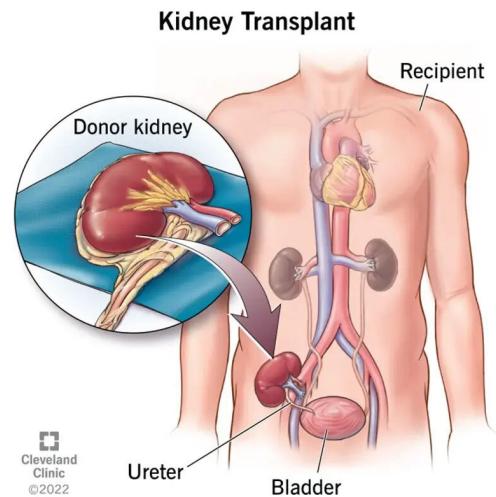
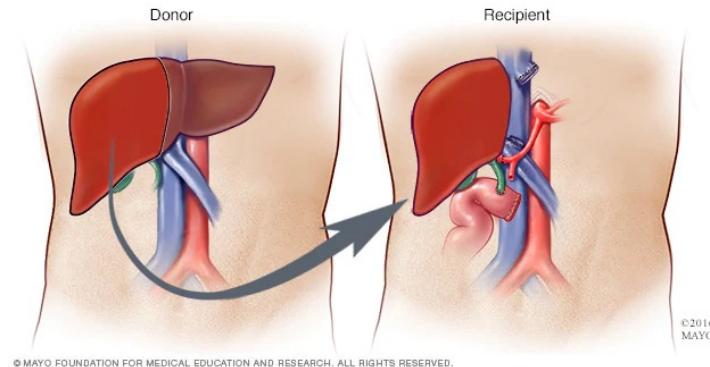
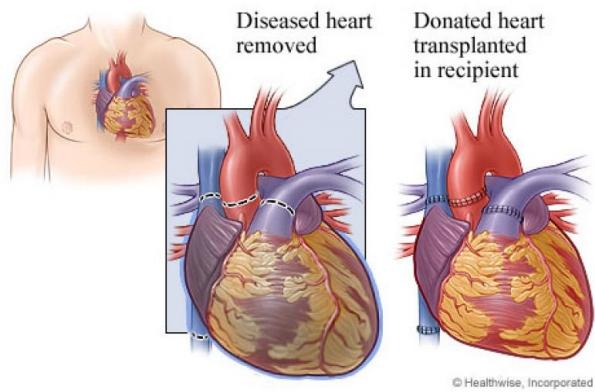
# Regulatory T Cells Increase the Avidity of Primary CD8<sup>+</sup> T Cell Responses and Promote Memory

Luigia Pace,<sup>1</sup> Andy Tempez,<sup>1\*</sup> Catharina Arnold-Schrauf,<sup>2\*</sup> Fabrice Lemaitre,<sup>3</sup> Philippe Bouso,<sup>3</sup> Luc Fetler,<sup>4†</sup> Tim Sparwasser,<sup>2†</sup> Sebastian Amigorena<sup>1‡</sup>

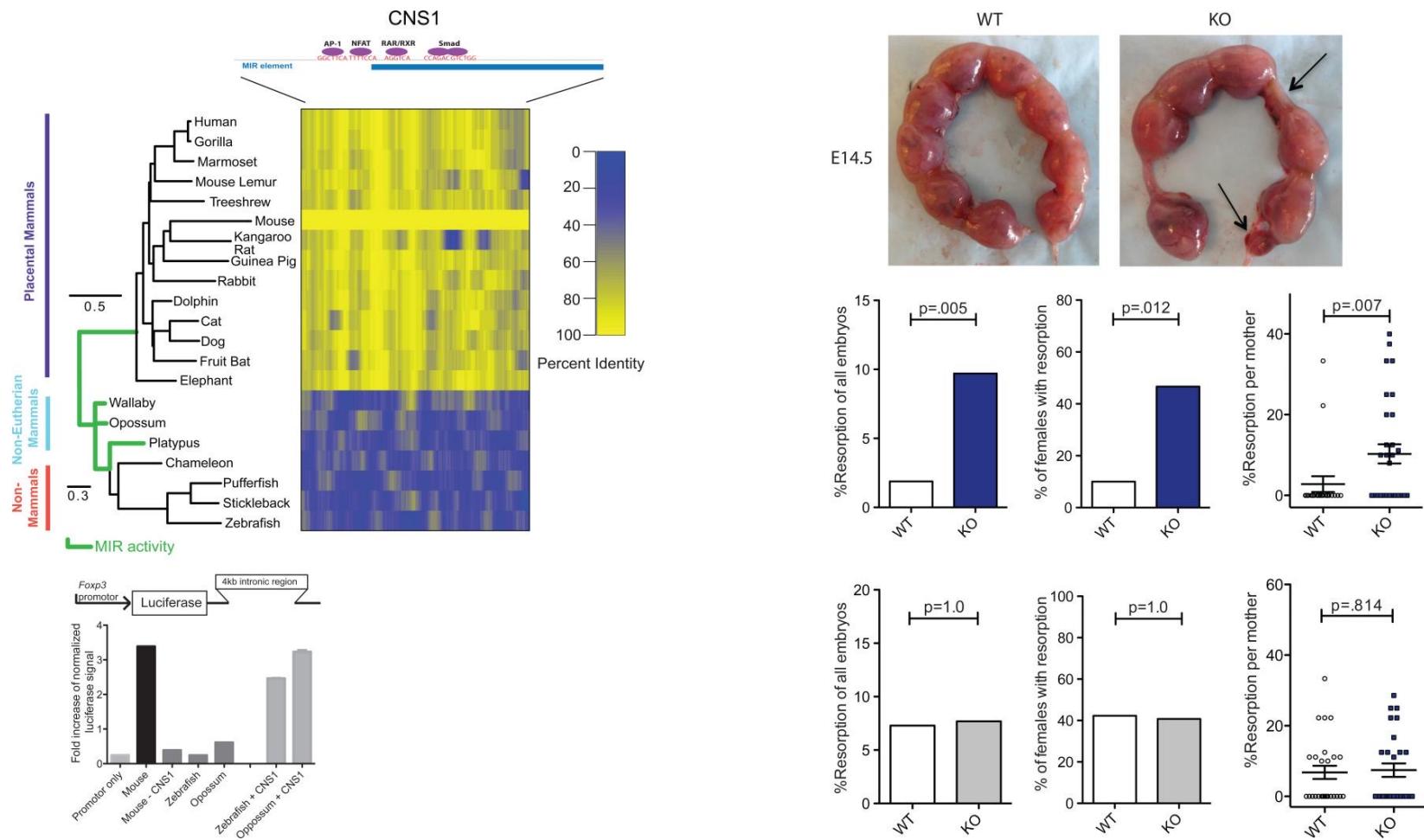
Although regulatory T cells ( $T_{reg}$ ) are known to suppress self-reactive autoimmune responses, their role during T cell responses to nonself antigens is not well understood. We show that  $T_{reg}$  play a critical role during the priming of immune responses in mice.  $T_{reg}$  depletion induced the activation and expansion of a population of low-avidity CD8<sup>+</sup> T cells because of overproduction of CCL-3/4/5 chemokines, which stabilized the interactions between antigen-presenting dendritic cells and low-avidity T cells. In the absence of  $T_{reg}$ , the avidity of the primary immune response was impaired, which resulted in reduced memory to *Listeria monocytogenes*. These results suggest that  $T_{reg}$  are important regulators of the homeostasis of CD8<sup>+</sup> T cell priming and play a critical role in the induction of high-avidity primary responses and effective memory.



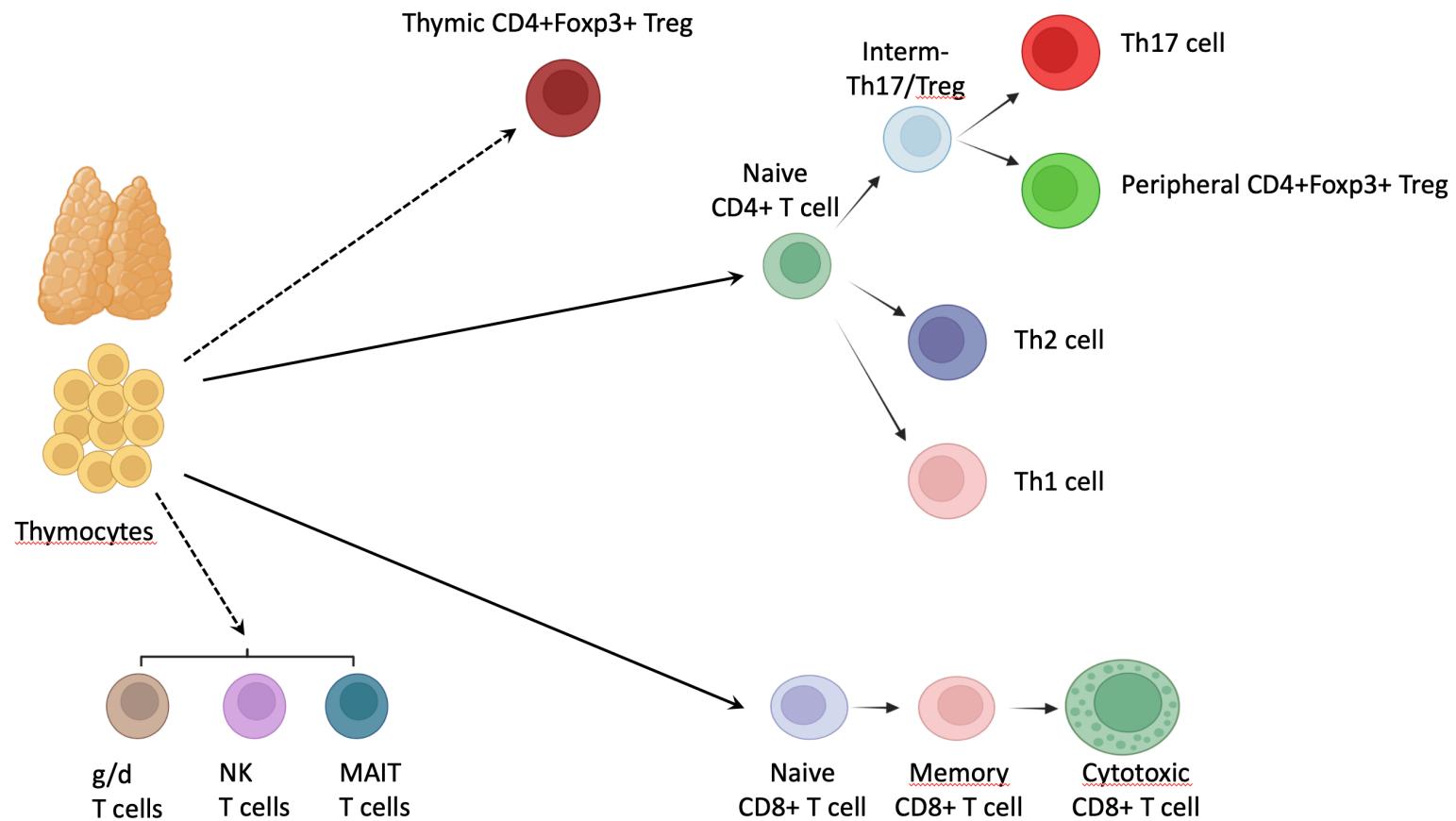
# What do these scenarios have in common?



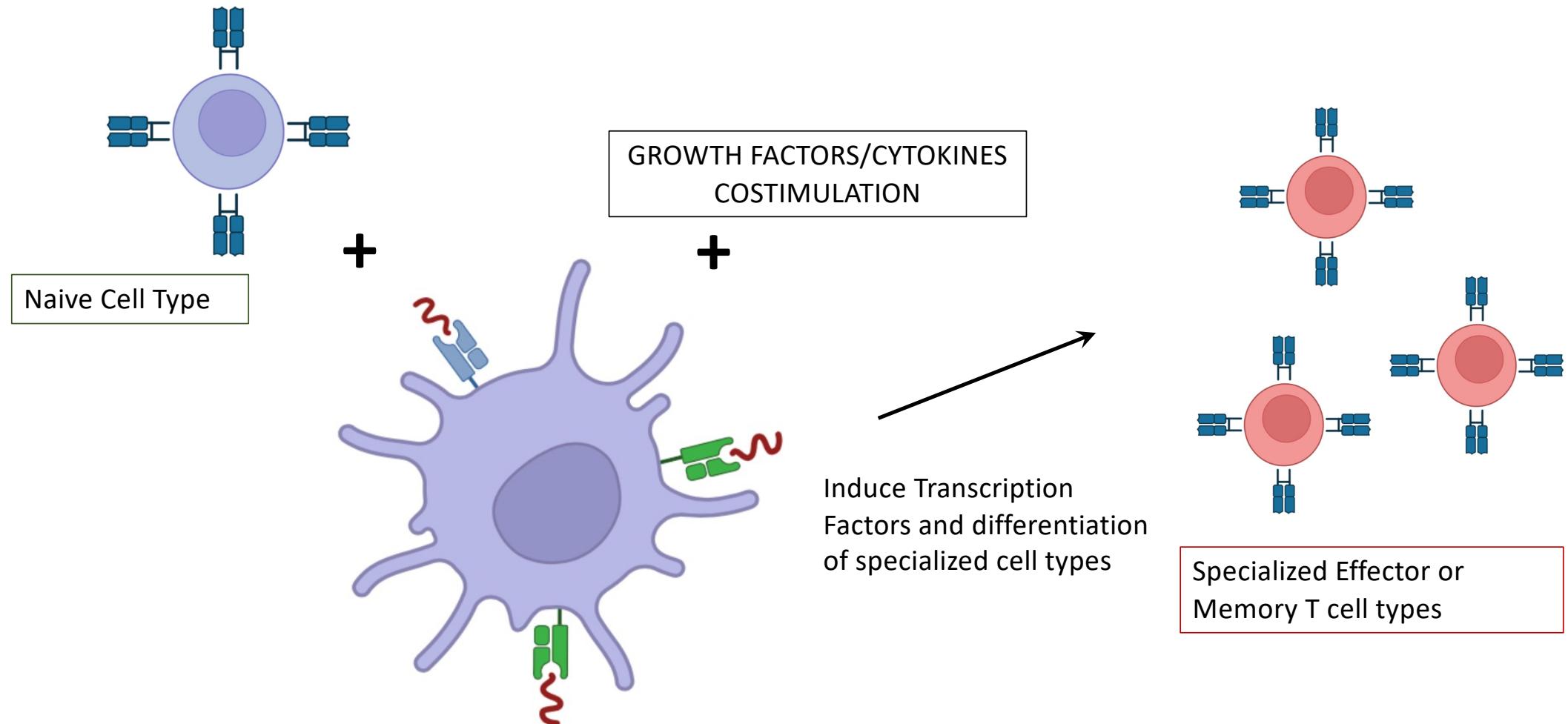
# Placental Mammals Evolved a Mechanism to Generate Tregs to Sustain Allogeneic Pregnancy



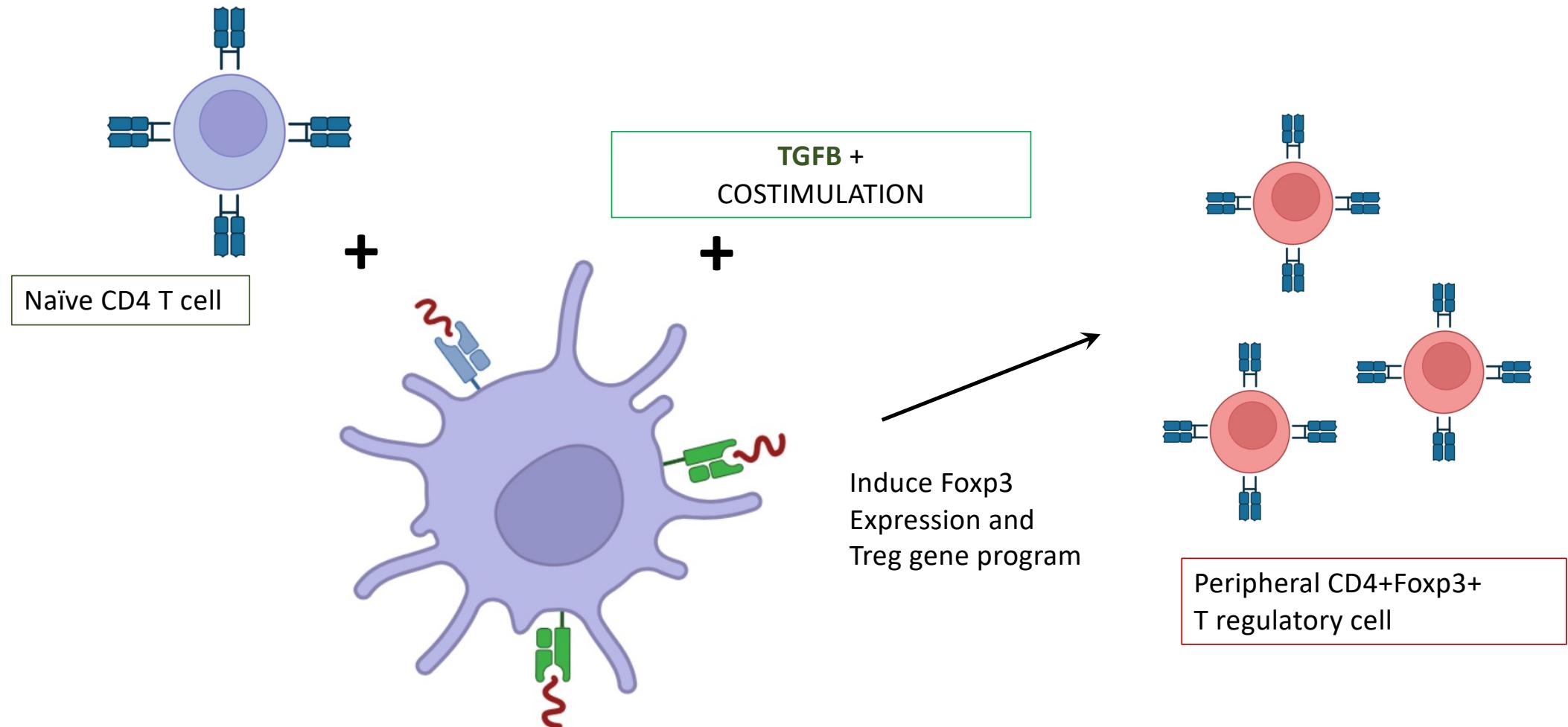
## Different Types of Mature T cells Exist – There are MANY and Growing... But These are Important Ones



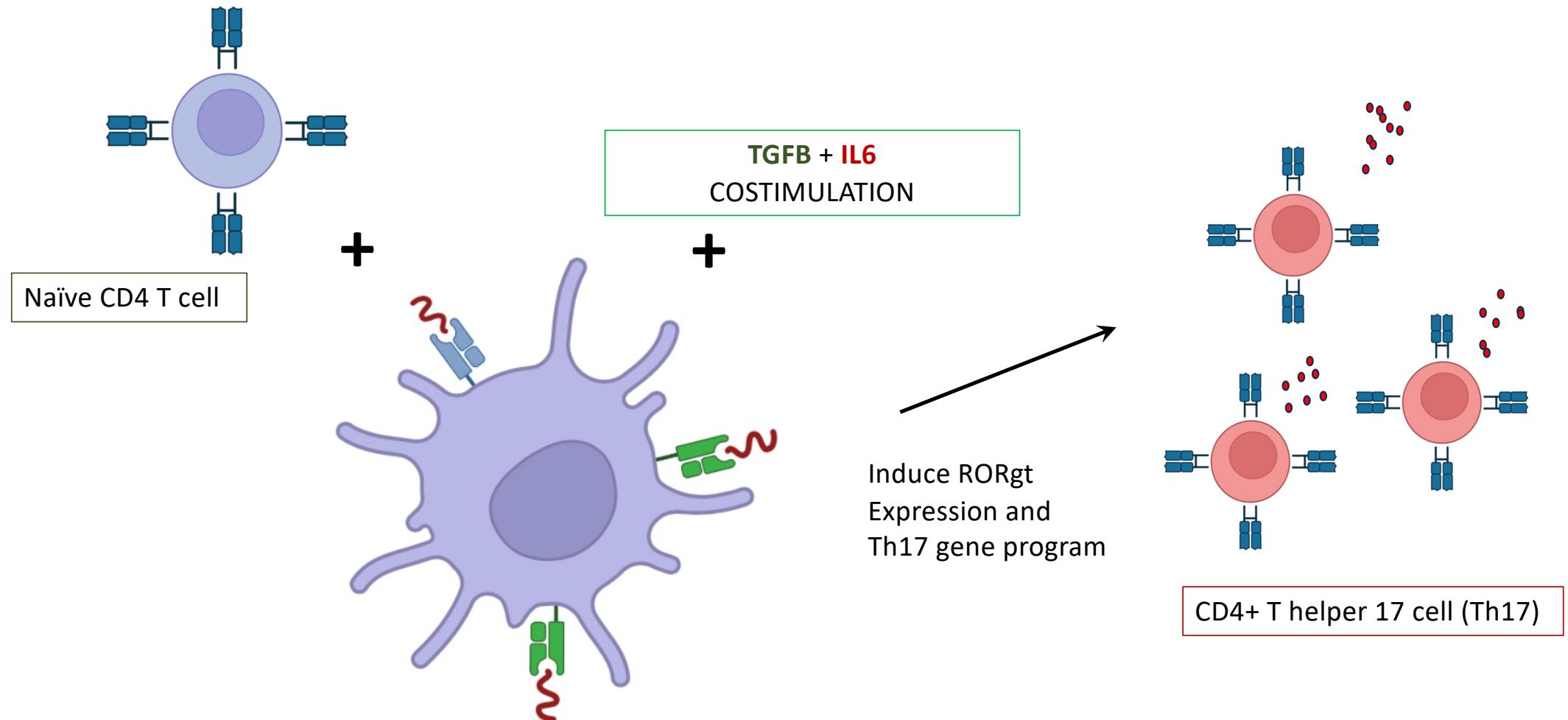
## How do you Generate an Effector or Memory T cell?



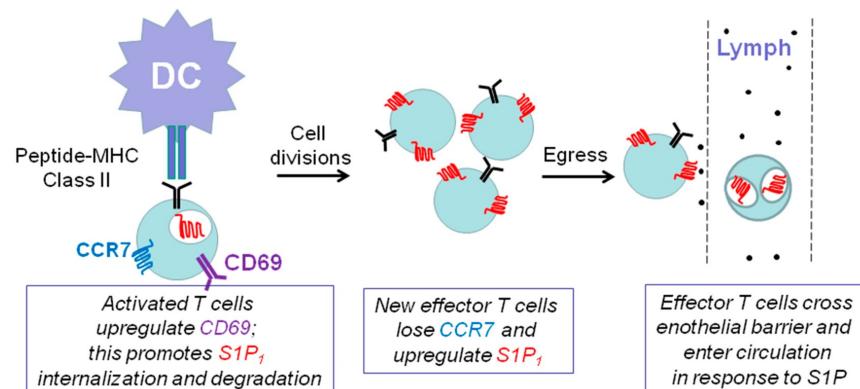
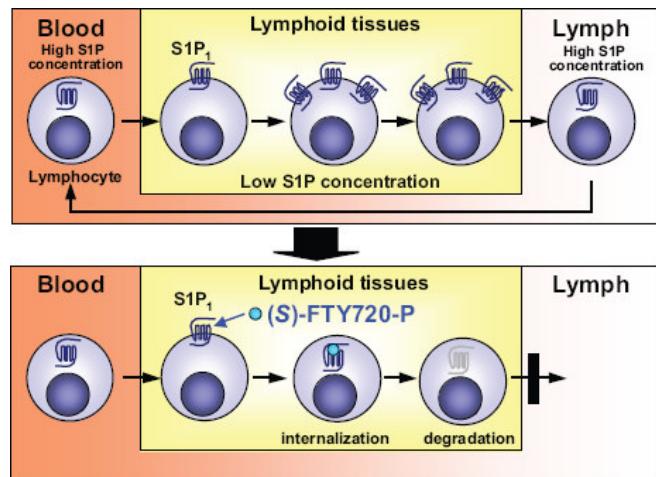
## How do you Generate an Effector or Memory T cell?



## How do you Generate an Effector or Memory T cell?

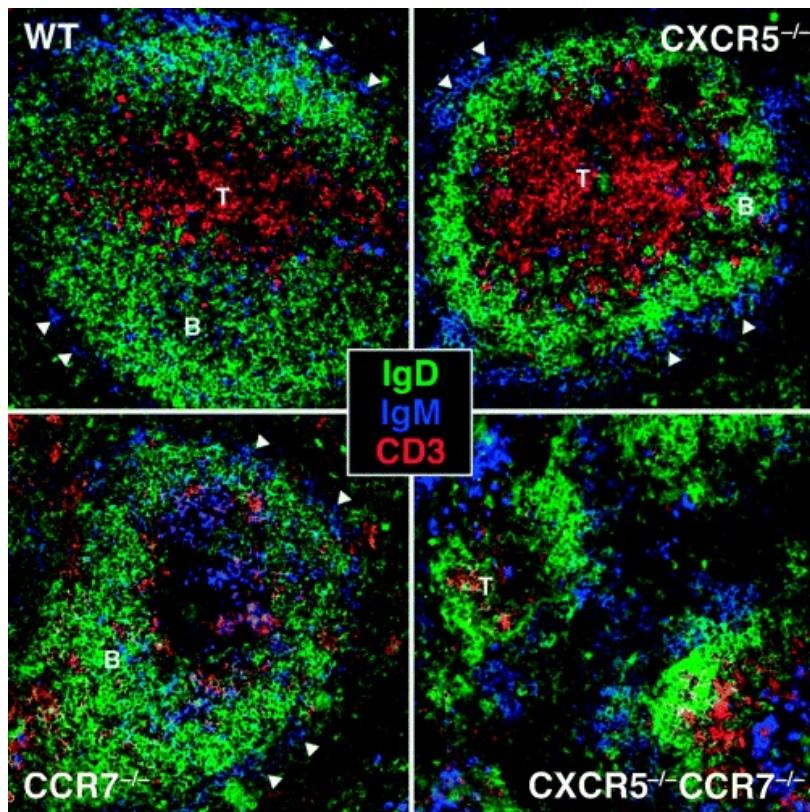


# The Migration of T cells – Sphingosine Gradients Regulate Recirculation of Lymphocytes



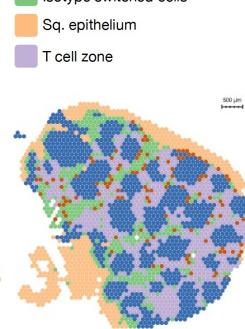
Jason Cyster's lab showed that S1PR1 blocks T cell recirculation through lymphoid tissues.

# Chemokines Specify Positions of Immune Cells in Tissues

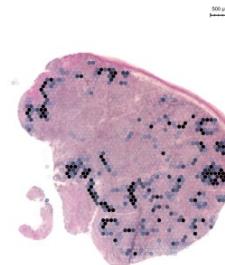


Spatial GEX Cluster group:

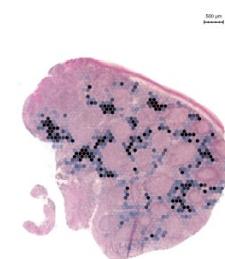
- B cell follicles/GC
- Endothelium
- Isotype switched cells
- Sq. epithelium
- T cell zone



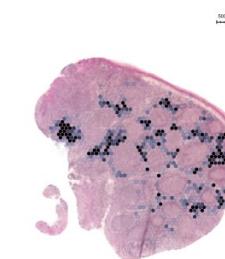
CXCL13



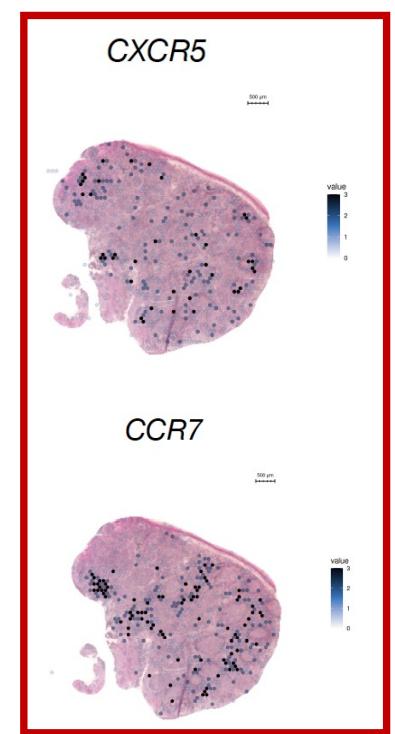
CCL19



CCL21

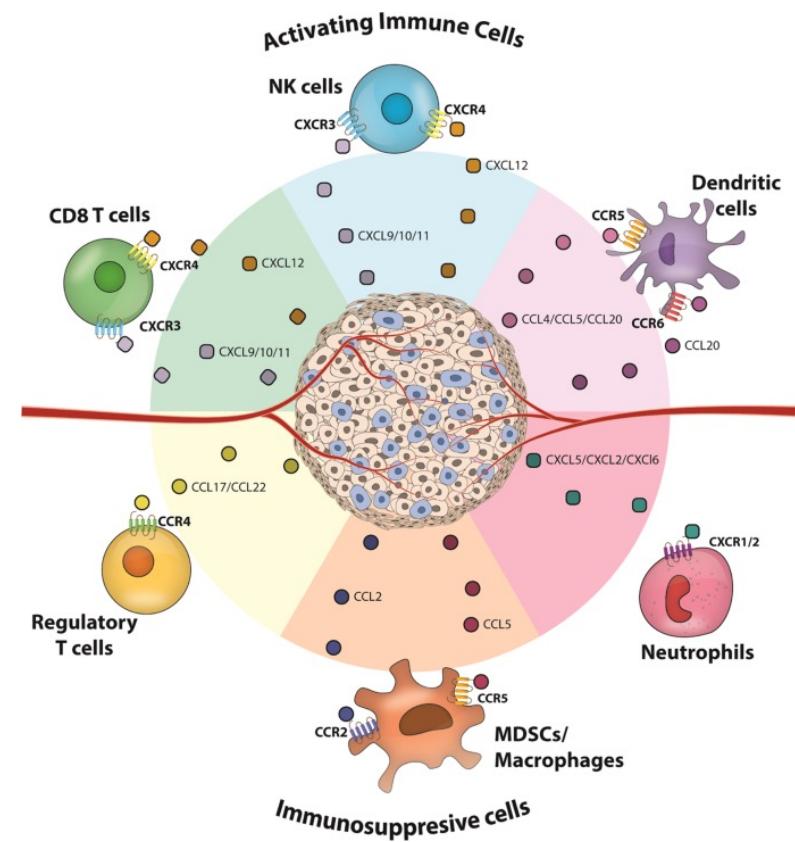
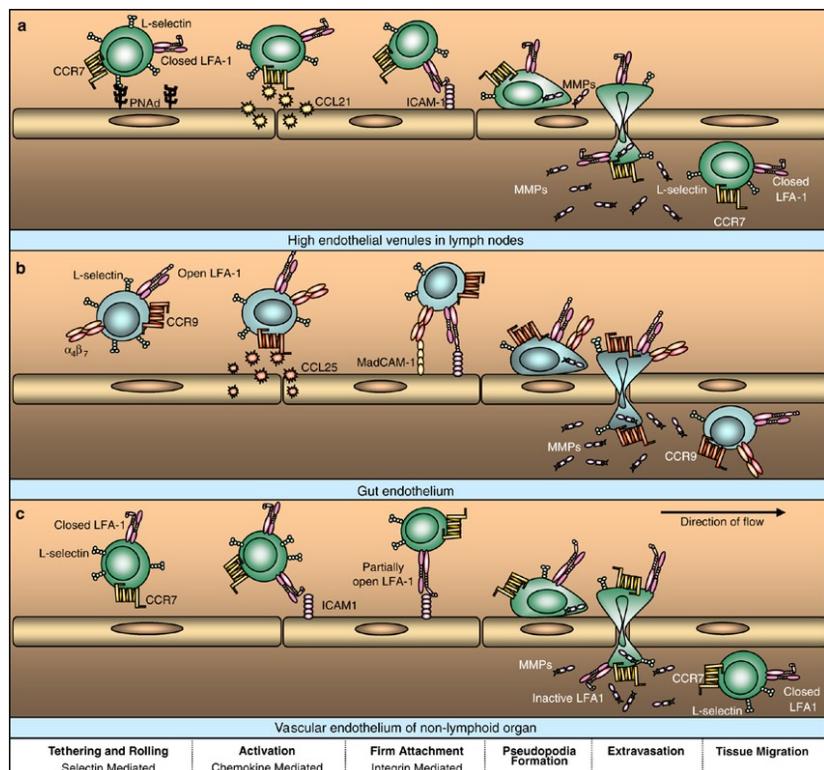


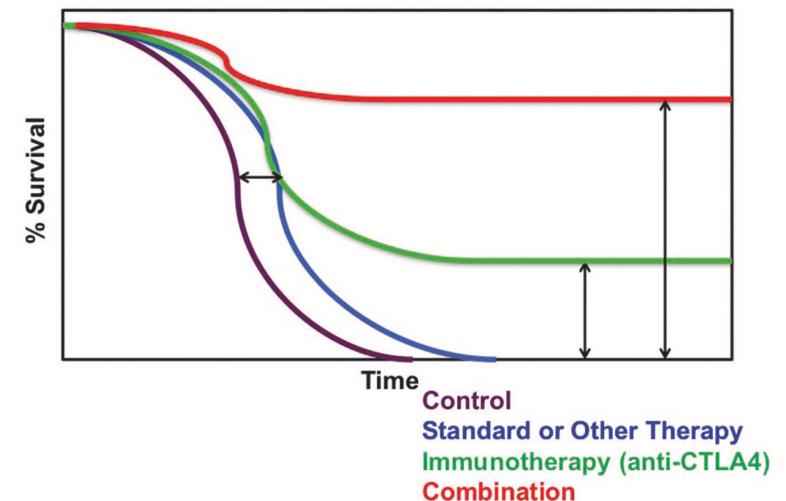
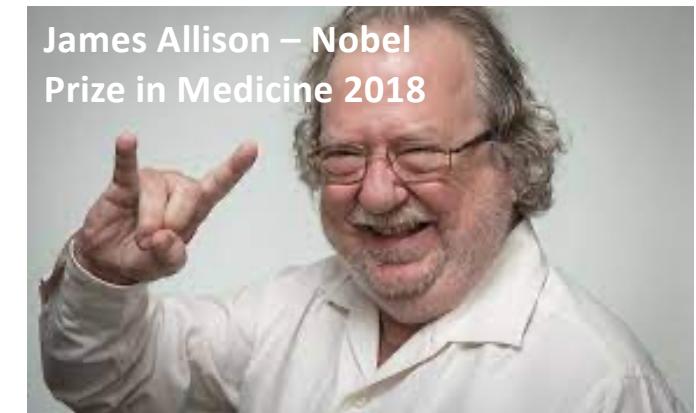
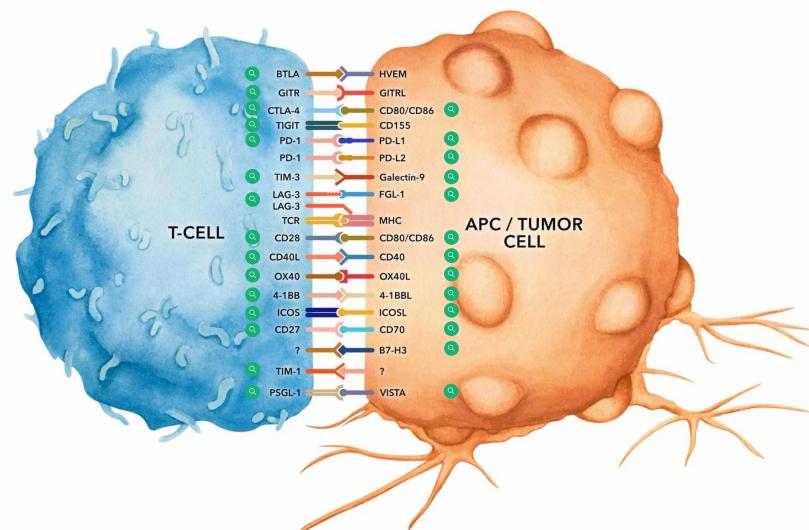
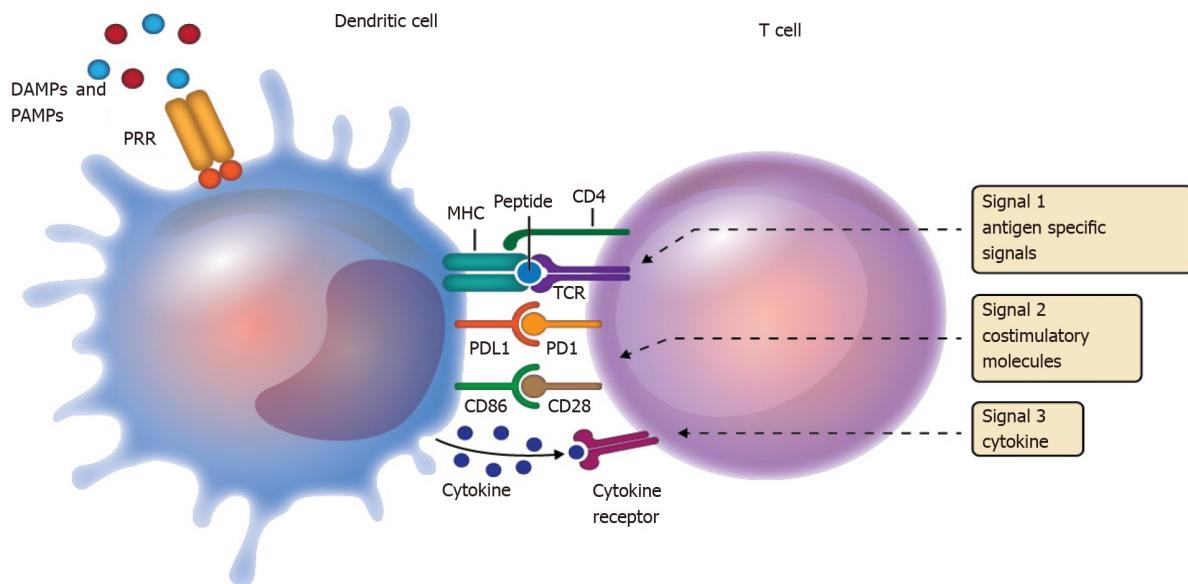
CXCR5

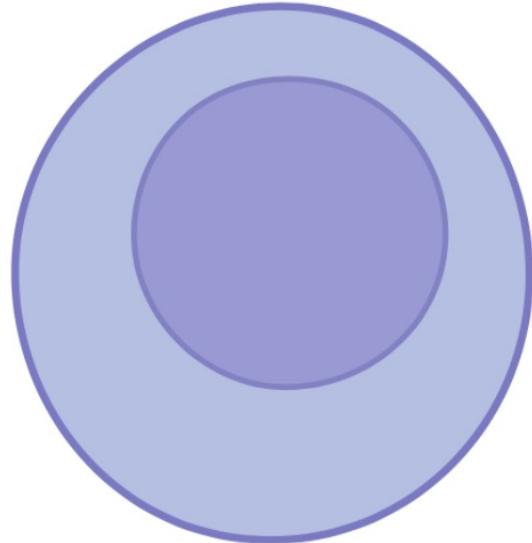


CCR7

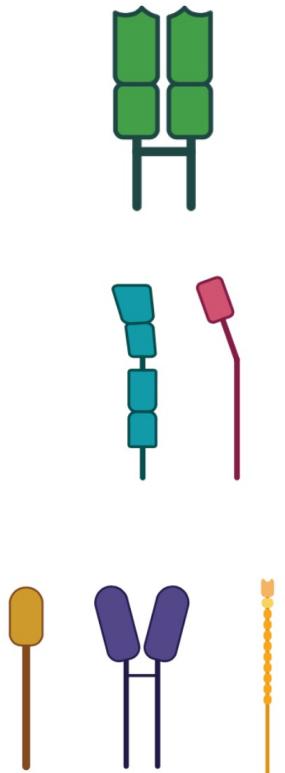
# The Migration of T cells







**T Cell**



## How to Build a Mature T cell

TCR – Defines what antigen the T cell will ‘see’

CD4/CD8 – Defines what type of T cell it will be and what MHC it will engage with.

Costimulation/Adhesion/Chemokine Receptors – Defines how the T cell will become activated and where it will go.

Let's Put it All Together...