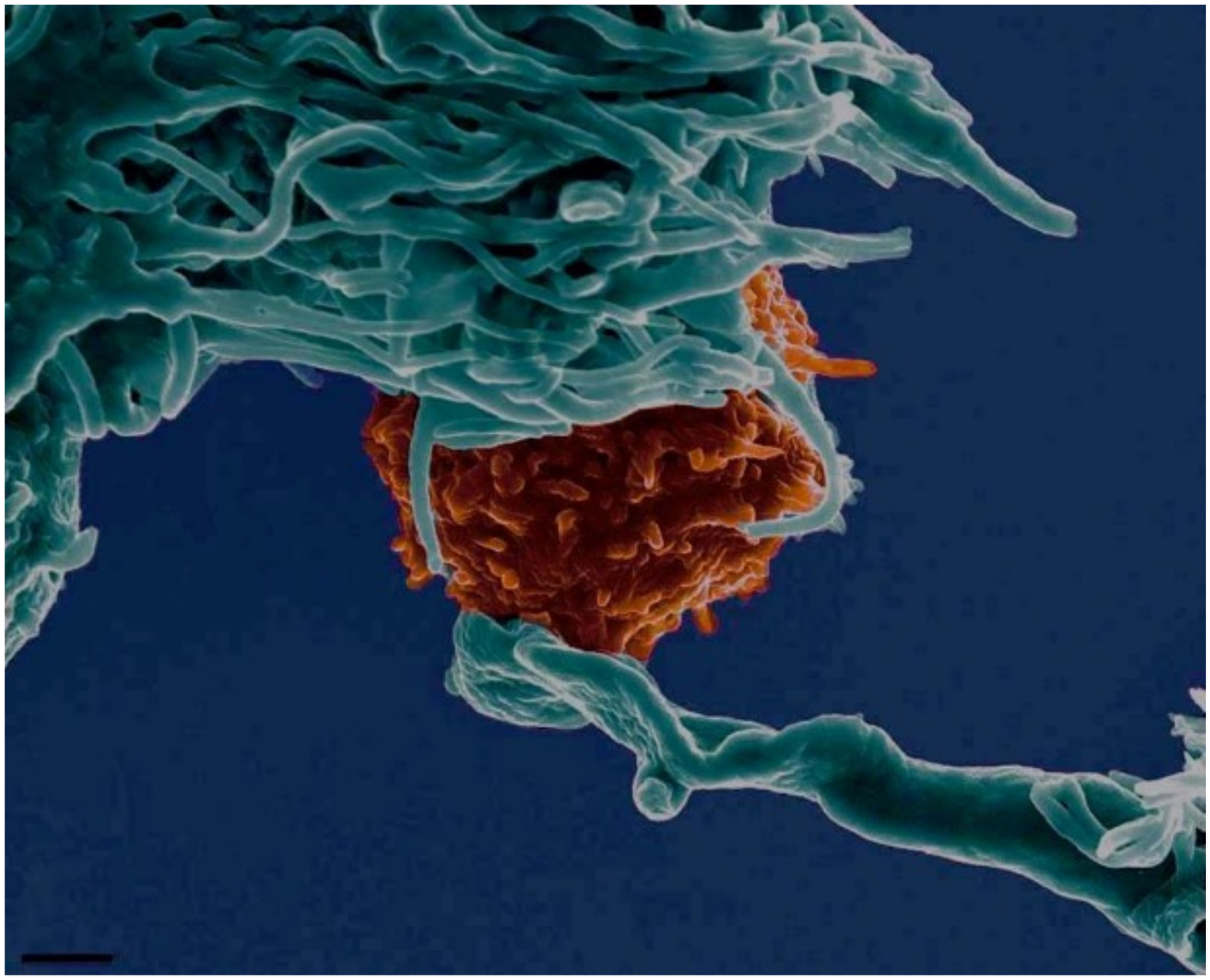
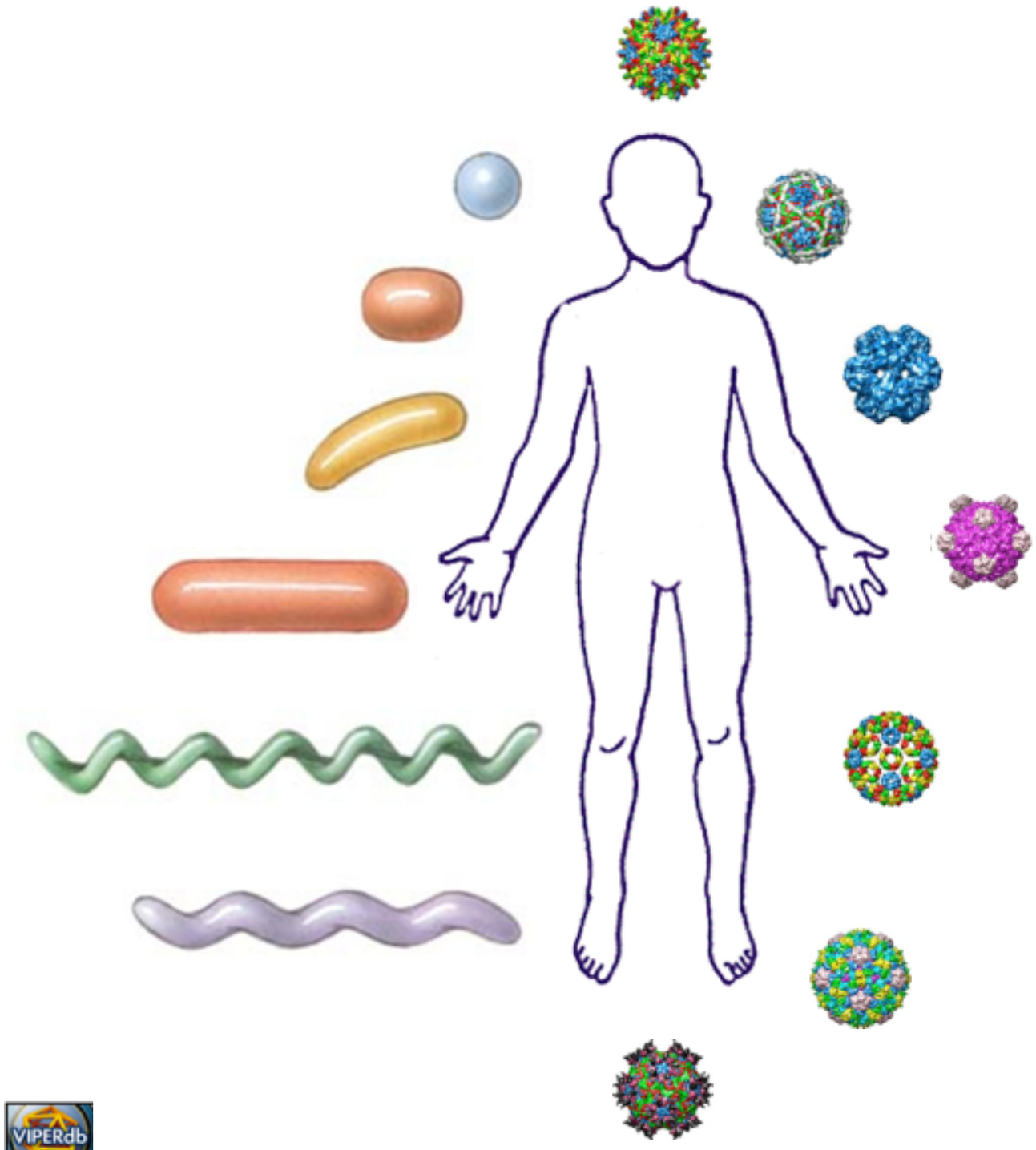
MAE 545: Lecture 24 (12/17)

Immune system



Immune system



Immune system protects us from a diverse world of pathogens (viruses, bacteria) that are still evolving.

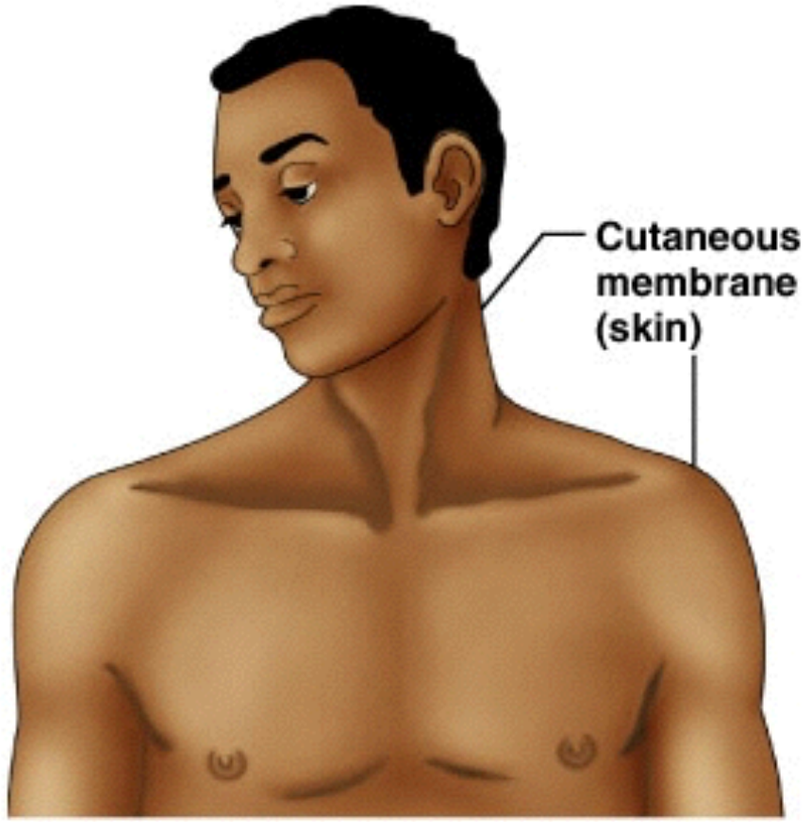
Innate (nonspecific) immune system

Physical barriers

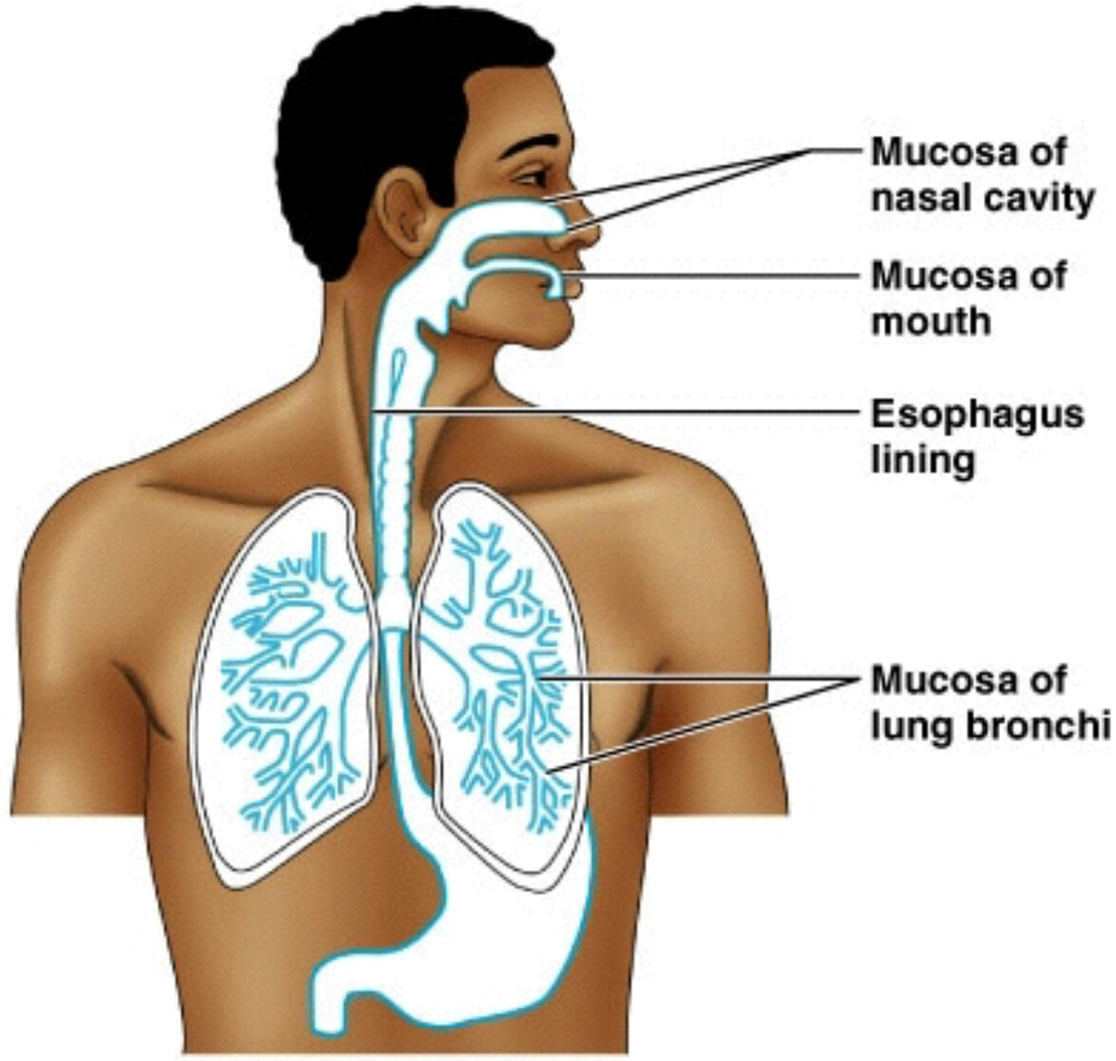
skin

mucous membranes

(cover body cavities with exterior openings)



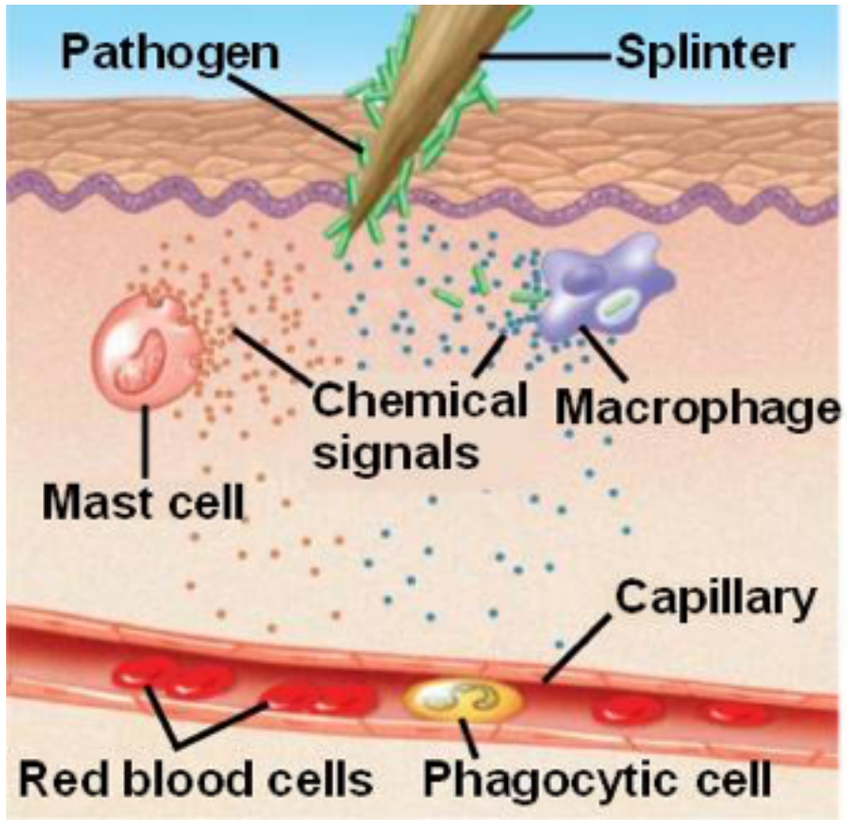
(a) Cutaneous membrane



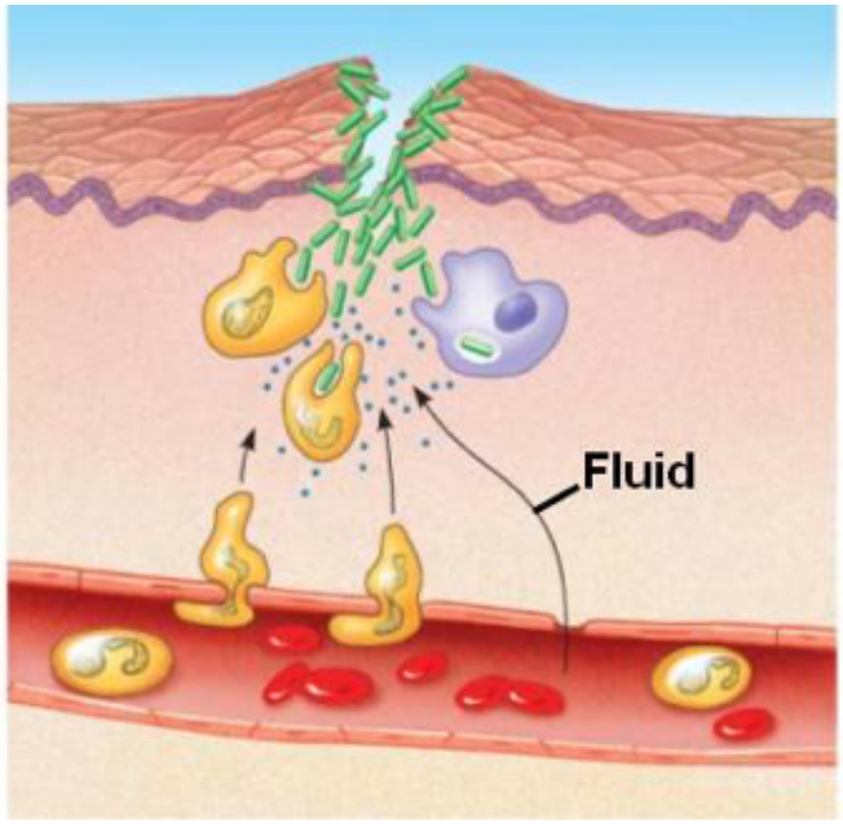
(b) Mucous membranes

Innate (nonspecific) immune system

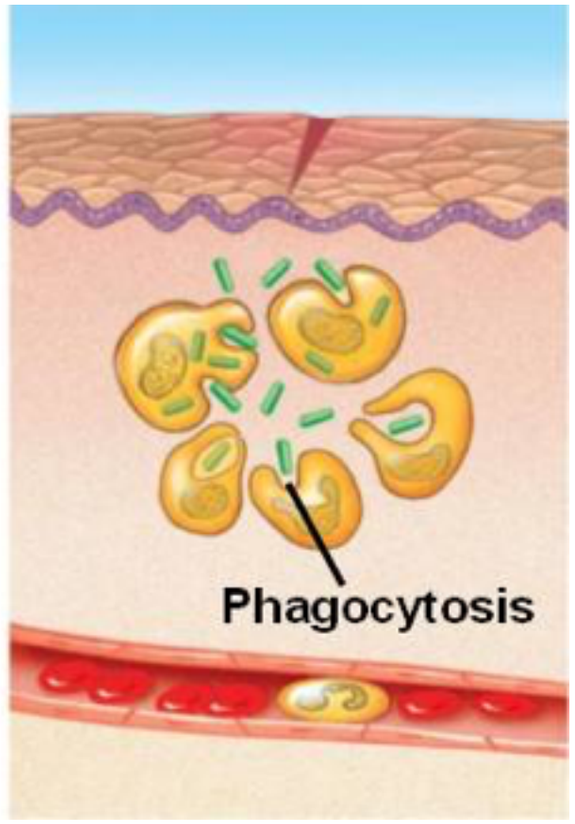
Response to damaged tissues (inflammation)



injured tissues release chemical signals



increased leakiness of local blood vessels (swelling)



phagocytes consume bacteria and tissue debris; tissue heals

Cells of innate immune system express receptors that recognize molecules that are broadly shared by pathogens.

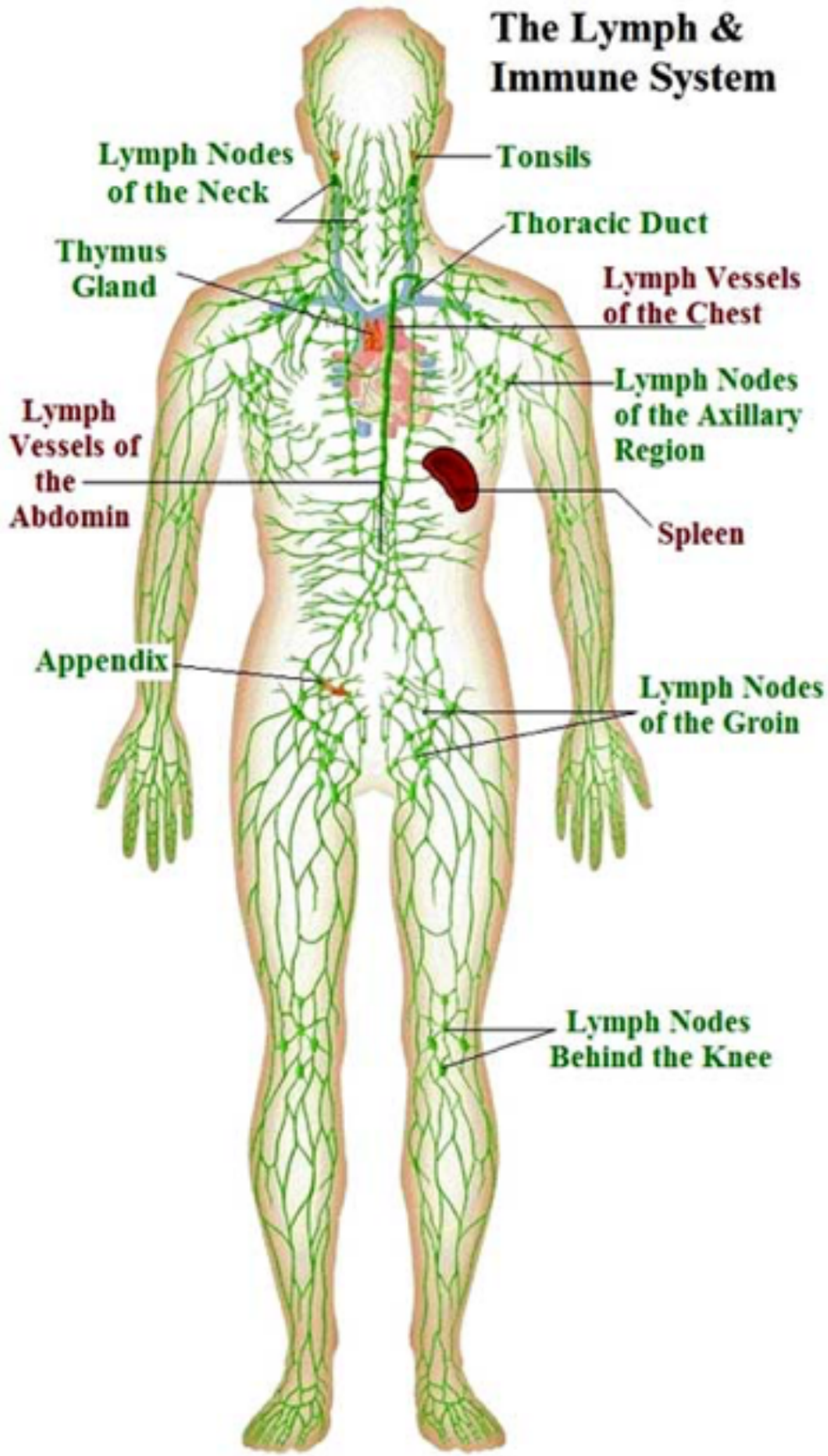
Many pathogens have evolved to escape this recognition!

Lymphatic system

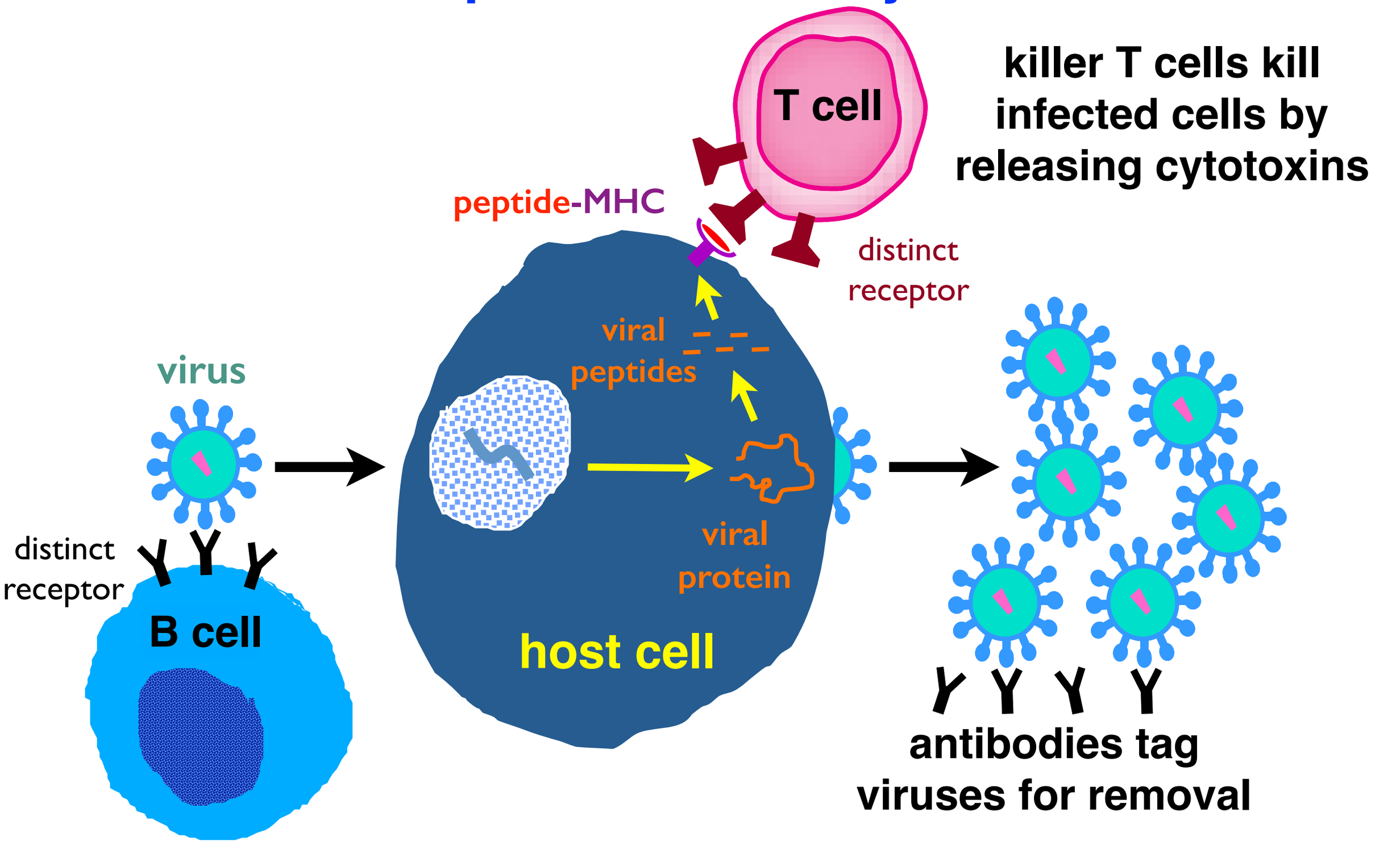
Excess fluid containing tissue debris and pathogens is flushed through the lymphatic system.

Here this fluid gets cleaned and checked for pathogens before it is returned to blood stream.

Lymph nodes contain many lymphocytes (B and T cells) that check for pathogens.

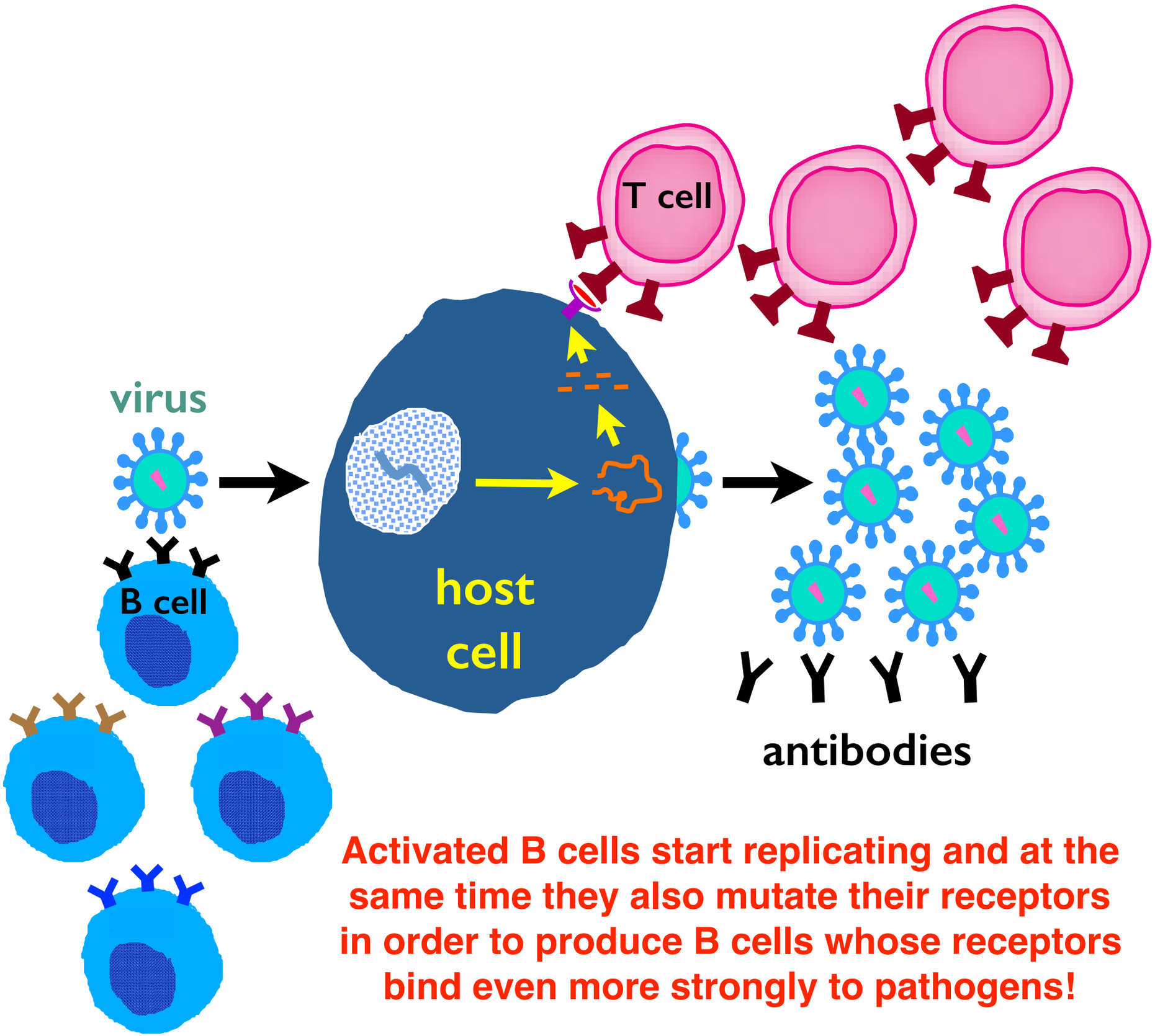


Adaptive immune system



Different B cells and T cells have different receptors and only those that are specific for pathogens get activated.

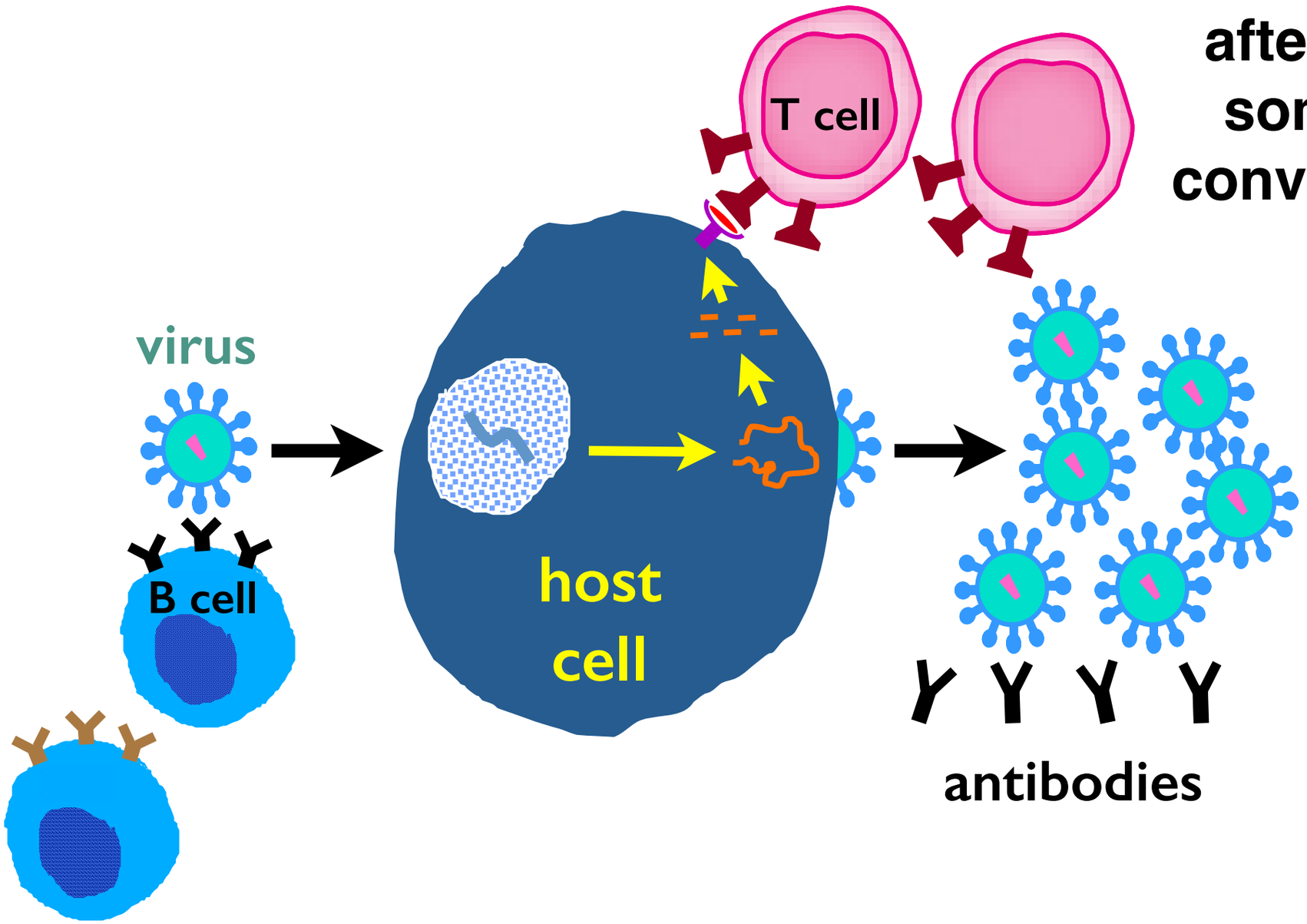
Activated adaptive immune system



Activated T cells produce multiple copies with identical receptors in order to quickly kill other infected cells.

Activated B cells start replicating and at the same time they also mutate their receptors in order to produce B cells whose receptors bind even more strongly to pathogens!

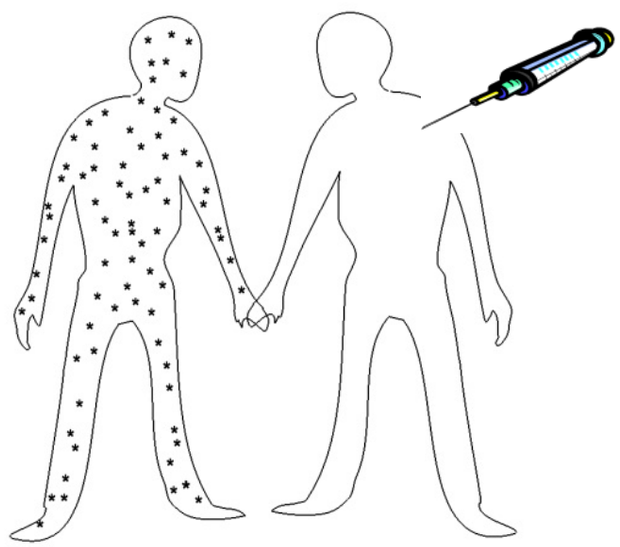
Memory of past infection



after infection is cleared some B and T cells are converted to memory cells

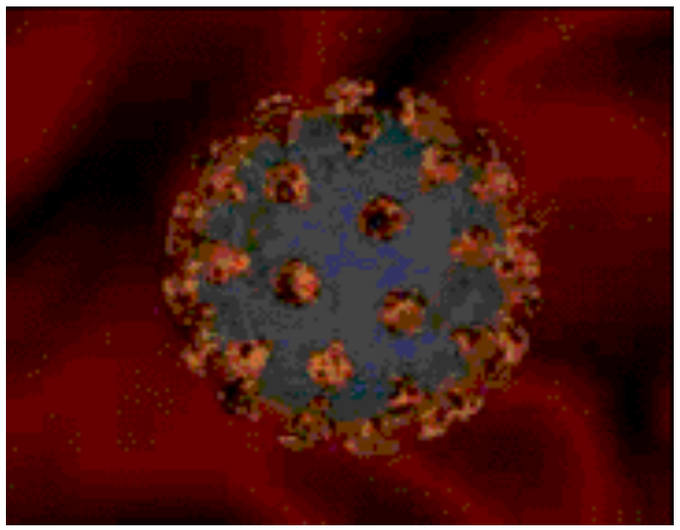
vaccination

inject certain virus markers to prepare immune system for a fight against real virus

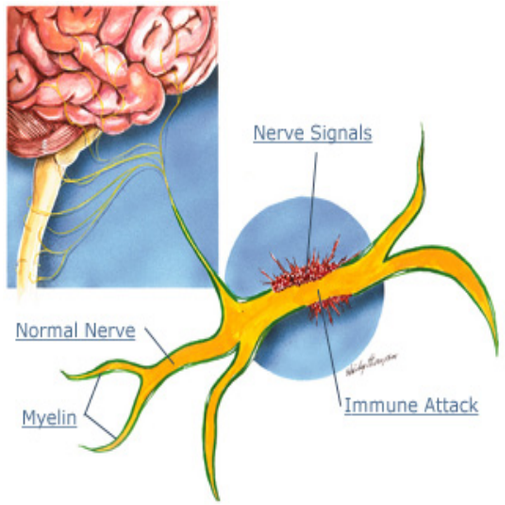


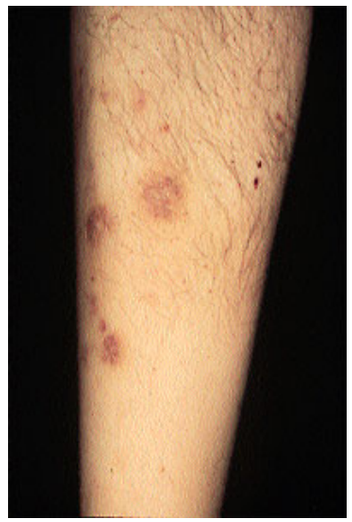
Adaptive immunity in health and disease

Combating infectious disease-causing agents



Mis-regulation leads to autoimmune diseases





Multiple Sclerosis Diabetes

<u>The challenge:</u> develop **principles** that govern the emergence of a **sytemic** immune or autoimmune response and **design rules** for therapies/vaccines

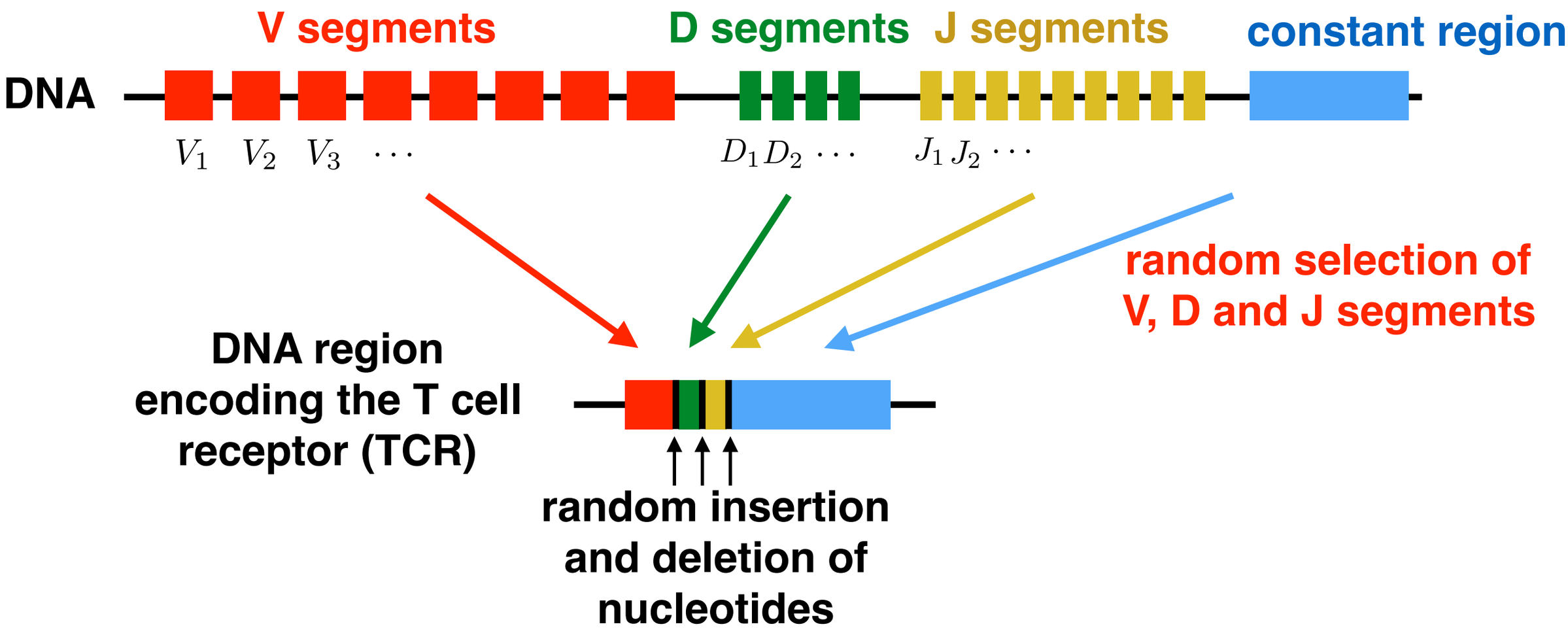
Outline

1. Mechanisms for T cell specificity for foreign peptides
2. Implications for the influence of host genetics on HIV control

Diversity of T cell receptors

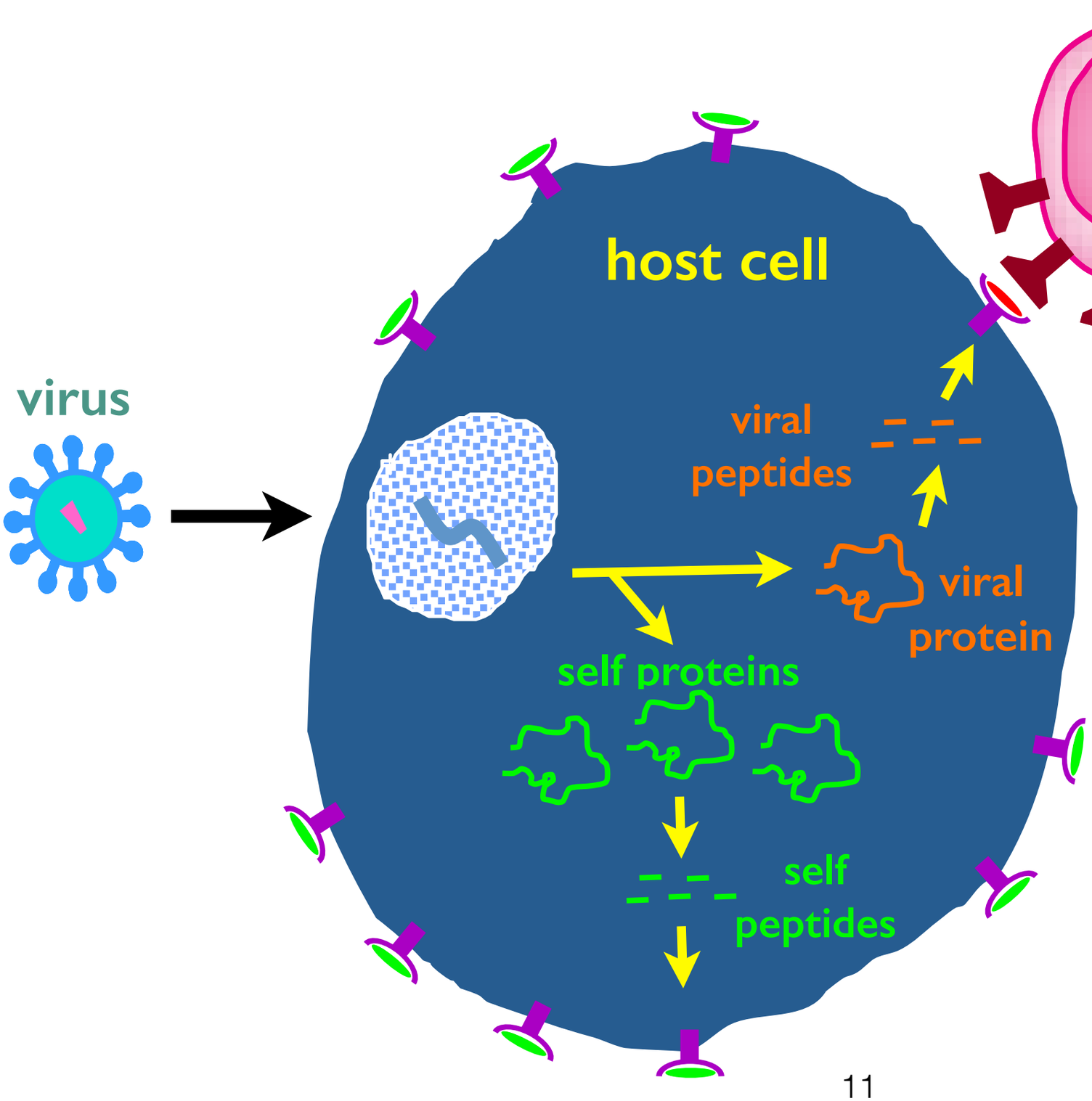
In adults there are ~10^{12} T cells in total (~10^{10} T cells in blood) and there are ~10^{8} distinct T cells.

Diverse T cell receptors are generated with VDJ recombination.



Note: VDJ recombination is also responsible for huge diversity of B cell receptors.

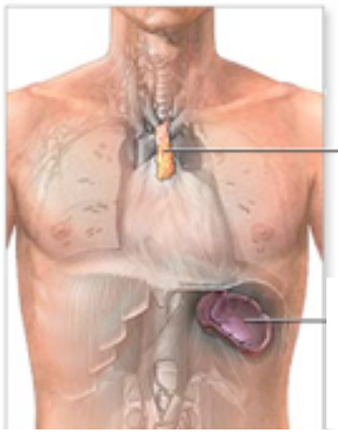
T cell recognition of foreign peptides is very sensitive



T cells can recognize 3-5 foreign peptides in a sea of ~30,000 self peptides

Recognition: strong binding of T cell receptors to foreign peptides

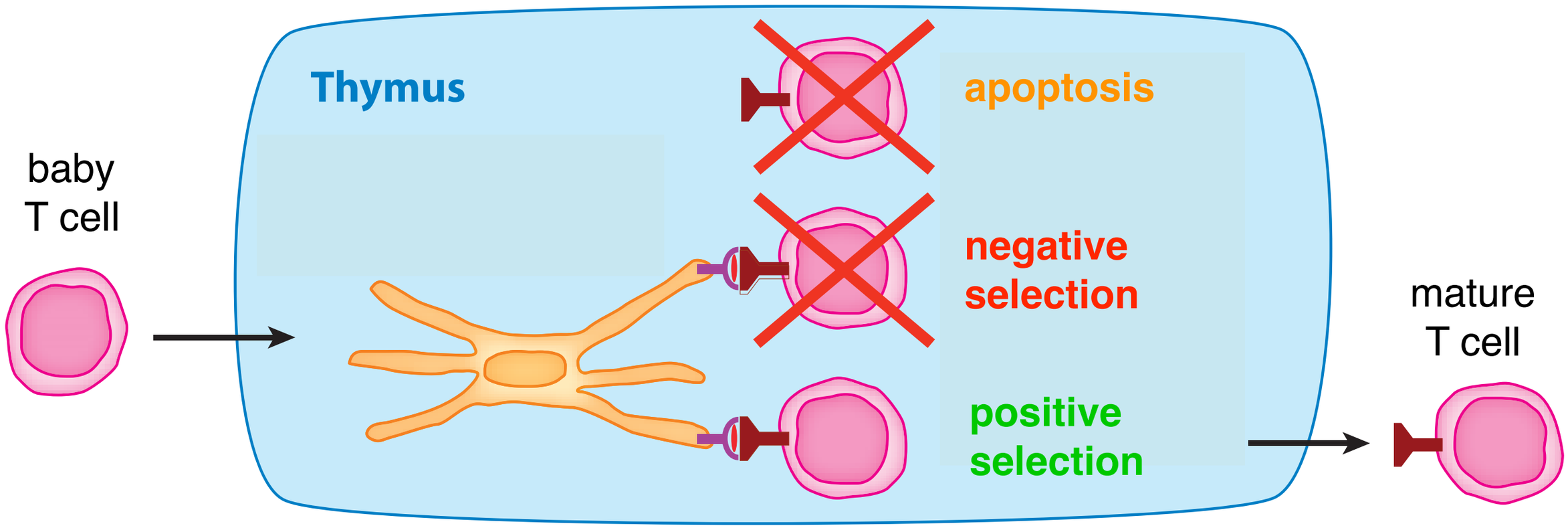
T cell development in the thymus



thymus

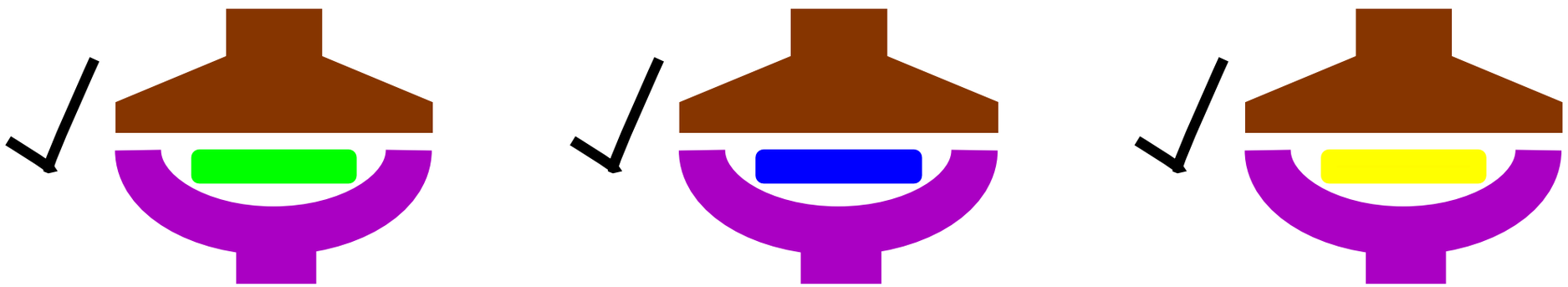
T cells scan thymus gland for 4-5 days, where they are selected against ~10^3-10^4 self-peptides.

AIRE (autoimmune regulator) causes transcription of a wide selection of genes/proteins in the thymus

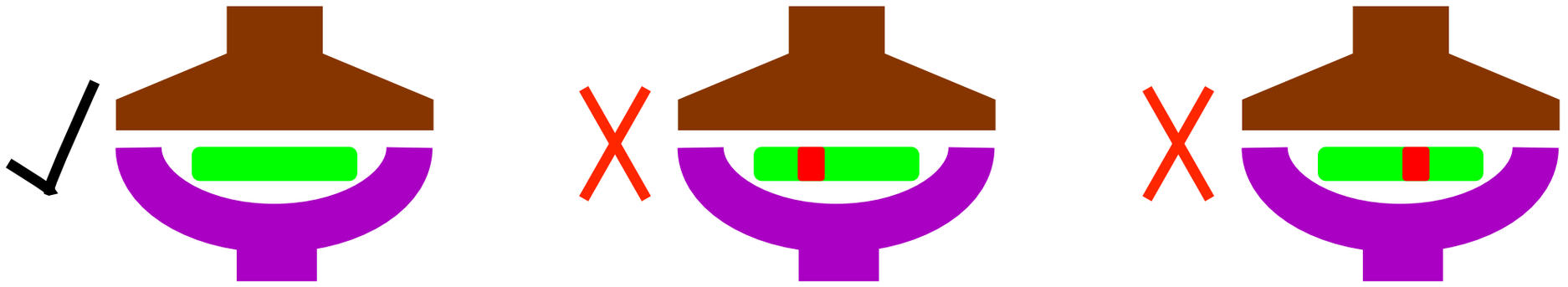


T cell recognition of foreign peptide is both degenerate and specific

degeneracy - each TCR can be activated by many different foreign peptides



specificity - most single point amino acid mutations of the foreign peptide are not recognized by the same TCR



How does the thymus gland design T cell receptors that are self-tolerant and degenerate/specific for foreign peptides?

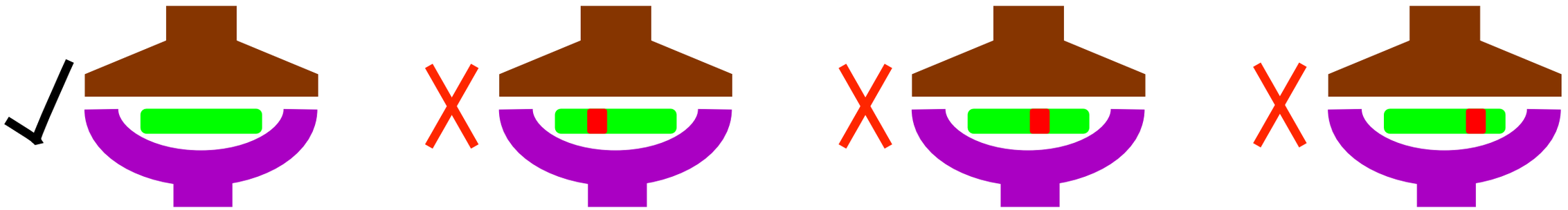
Thymic selection against one or many types of self peptides

E. Huseby *et al*., Cell **122**, 247 (2005)
E. Huseby *et al*., Nat. Immunol. **7**, 1191 (2006)

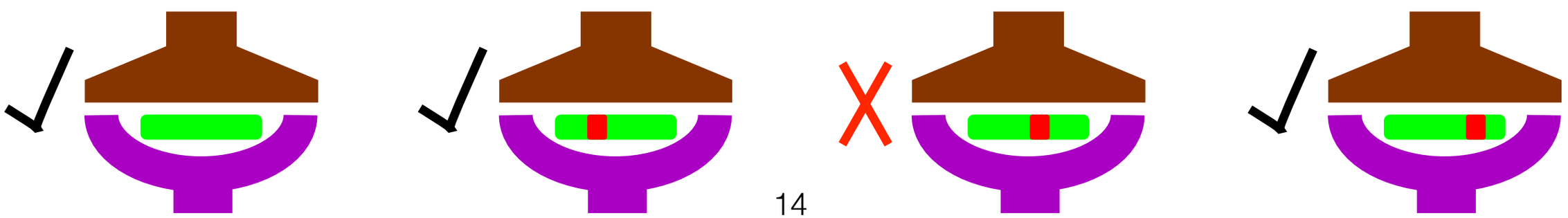
Compare properties of T cells developed in normal mouse and in engineered mouse that express only one type of self peptide in thymus.

Find T cells that recognize a particular foreign peptide. Check whether T cells can recognize point amino acid mutations of the peptide.

Normal mouse - selection against **many peptides**
selected T cells are **specific** to point mutations

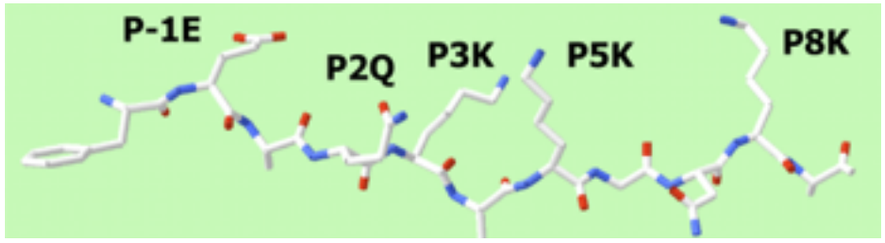


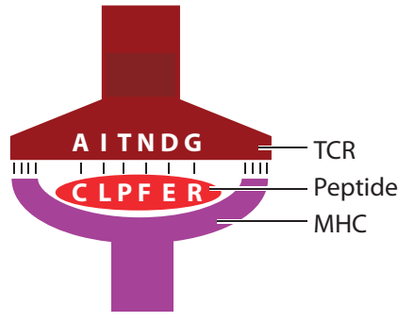
Engineered mouse - selection against **one peptide type**
selected T cells are **cross-reactive** to point mutations



Thymic selection against one or many types of self peptides

E. Huseby *et al*., Cell **122**, 247 (2005)



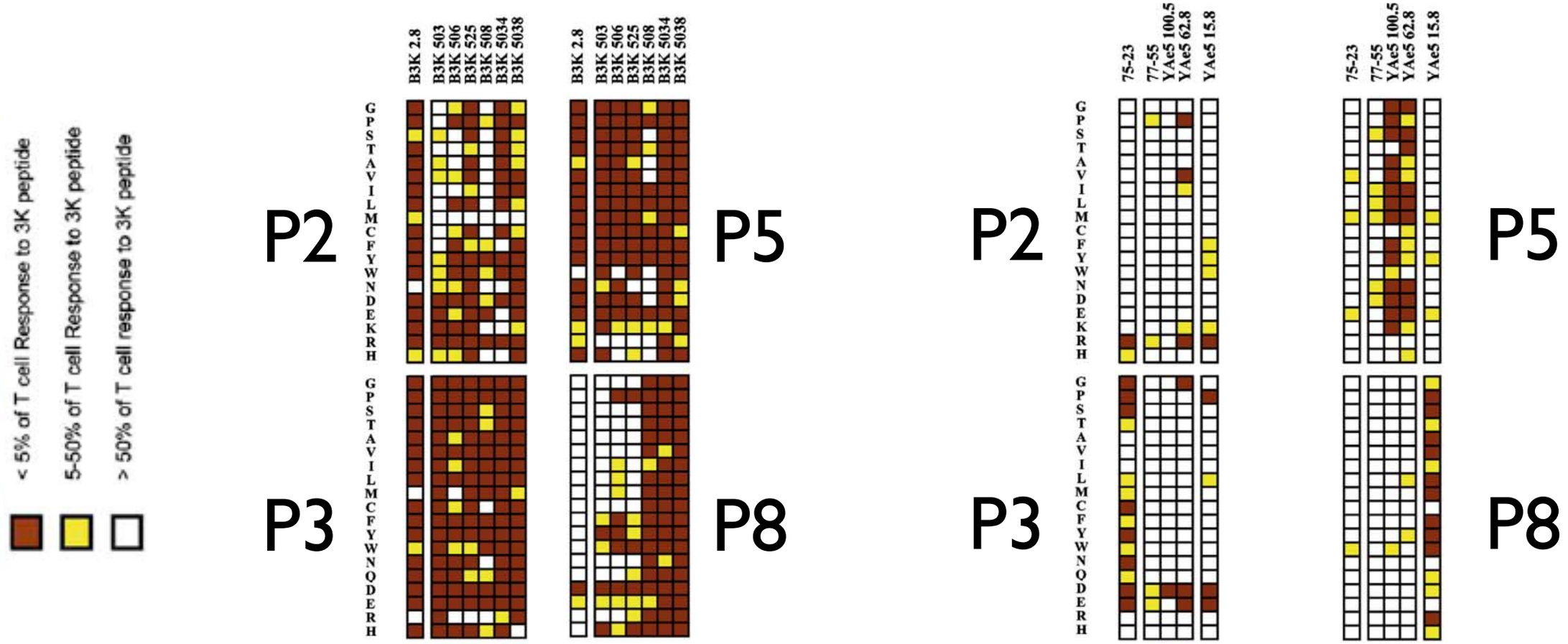


selection against many self-peptides

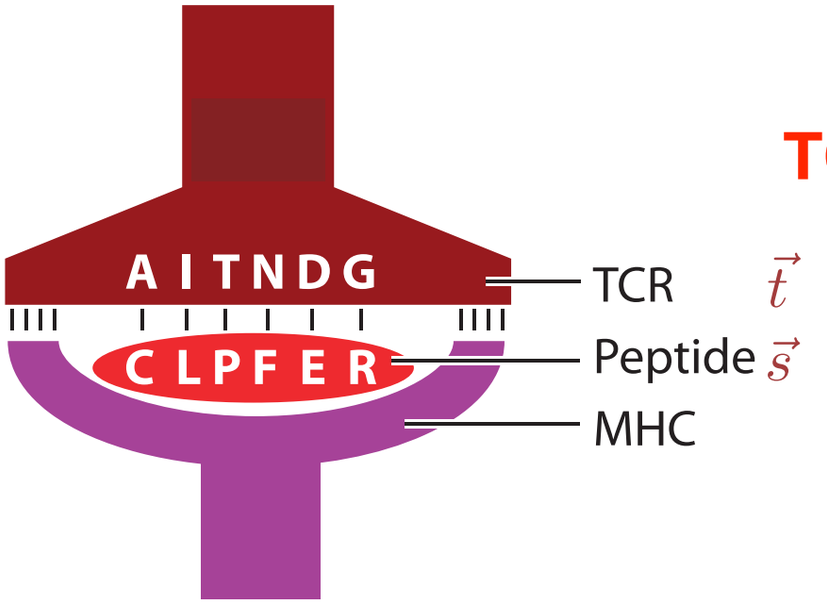
specific recognition

selection against one self-peptide

cross-reactive recognition



Model



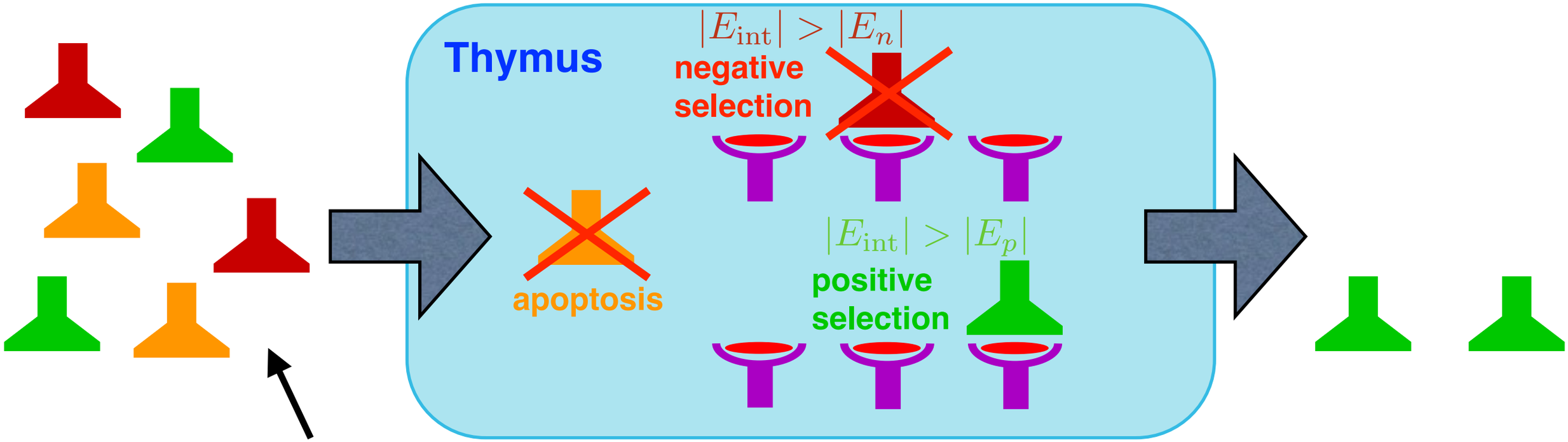
TCR-peptide-MHC interaction free energy:

$$E_{\rm int}(\vec{t},\vec{s}) = E_c + \sum_{i=1}^{N} J(t_i, s_i)$$

Miyazawa-Jernigan

TCR-peptide contacts: $N \approx 5$

collection of $M \approx 10^3 - 10^4$ random peptides

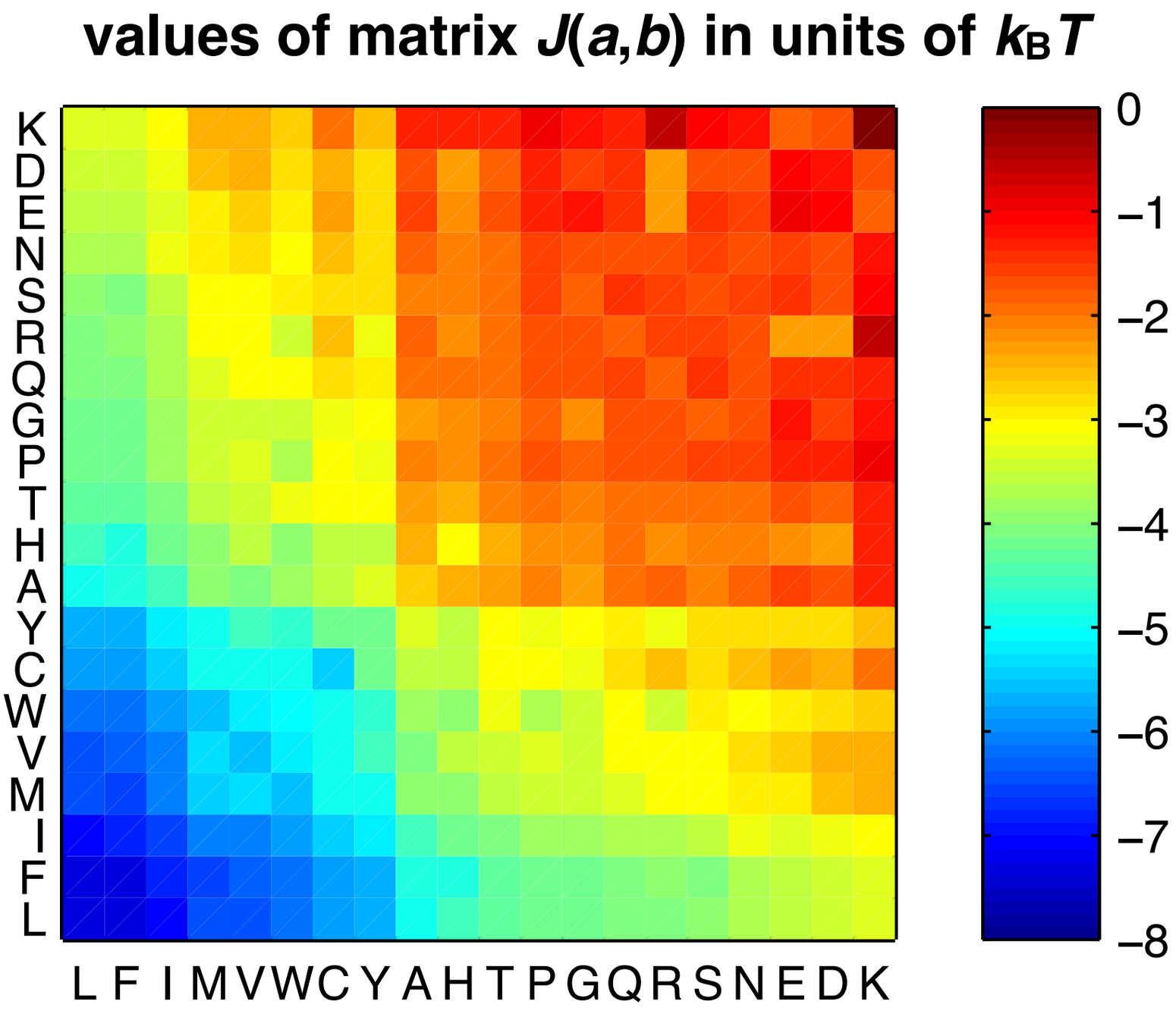


randomly generated TCR sequences, where amino acids are chosen with probability f_a with which they appear in human proteome.

A. Košmrlj *et al*., PNAS **105**, 16671 (2008)
A. Košmrlj *et al*., PRL **103**, 068103 (2009)

Miyazawa-Jernigan matrix describing interactions between amino acids

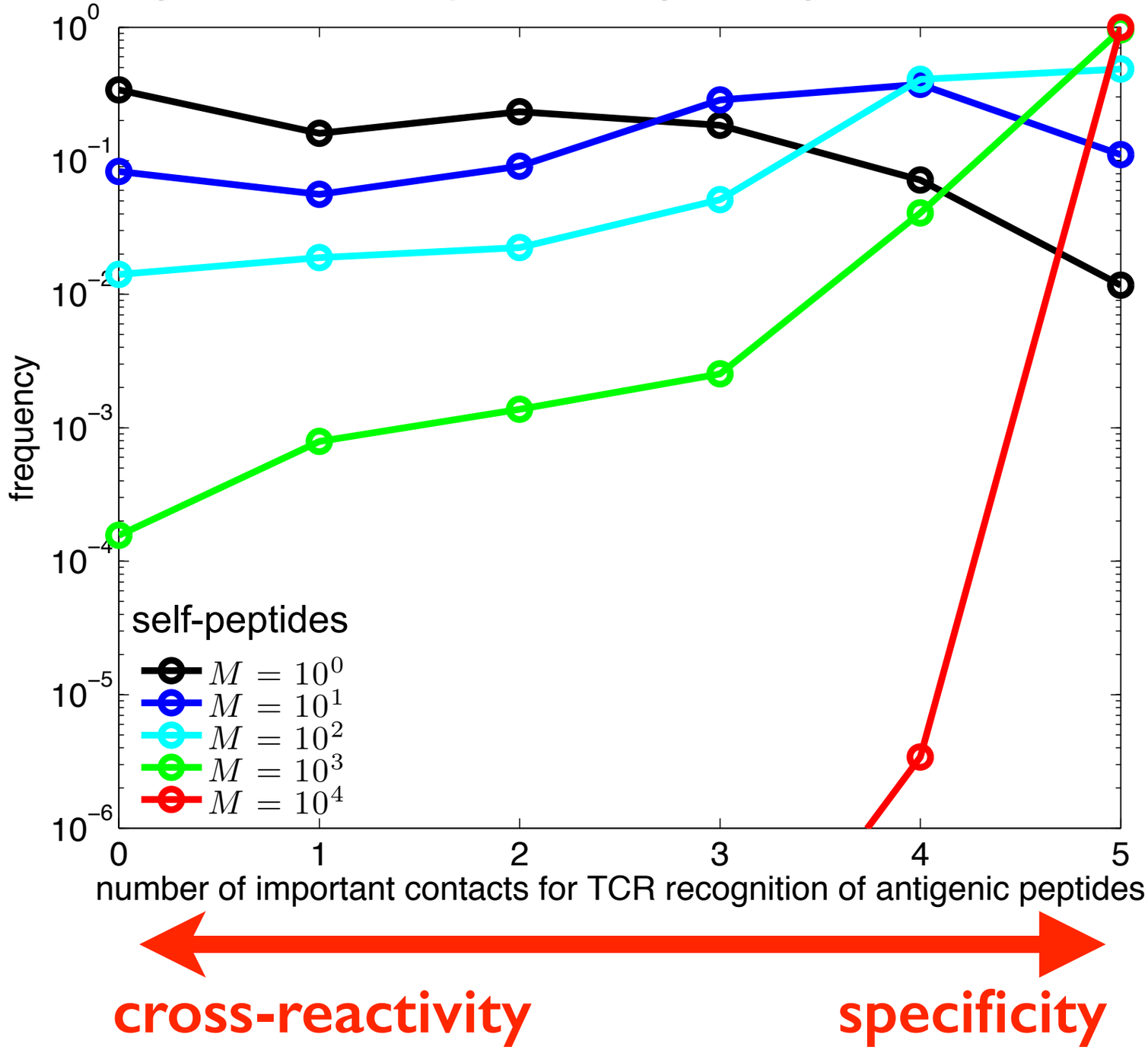
Miyazawa-Jernigan matrix was obtained by fitting the free energy values of folded proteins.

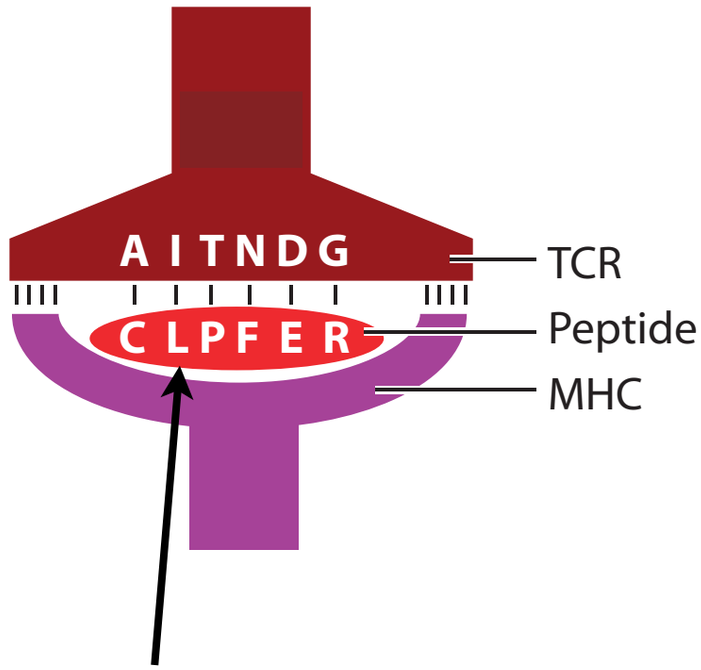


S. Miyazawa and R.L. Jernigan,
J.Mol.Biol. **256**, 623 (1996)

Model recapitulates the specificity/cross-reactivity results from mice experiments

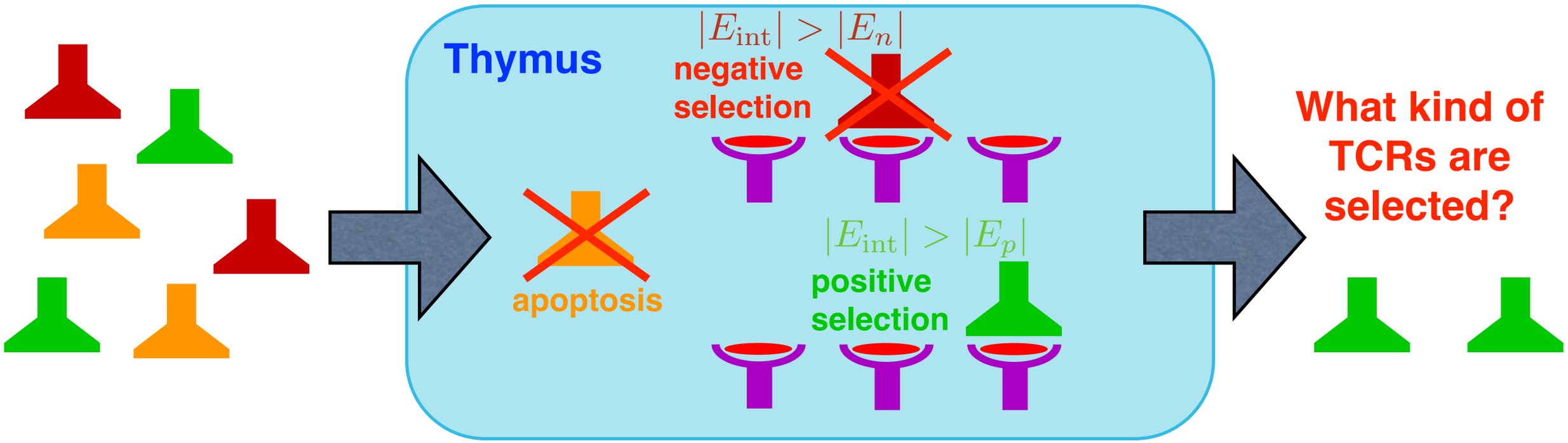
Challenge selected TCRs with foreign peptide and check how good are they at recognizing mutations of foreign peptide.





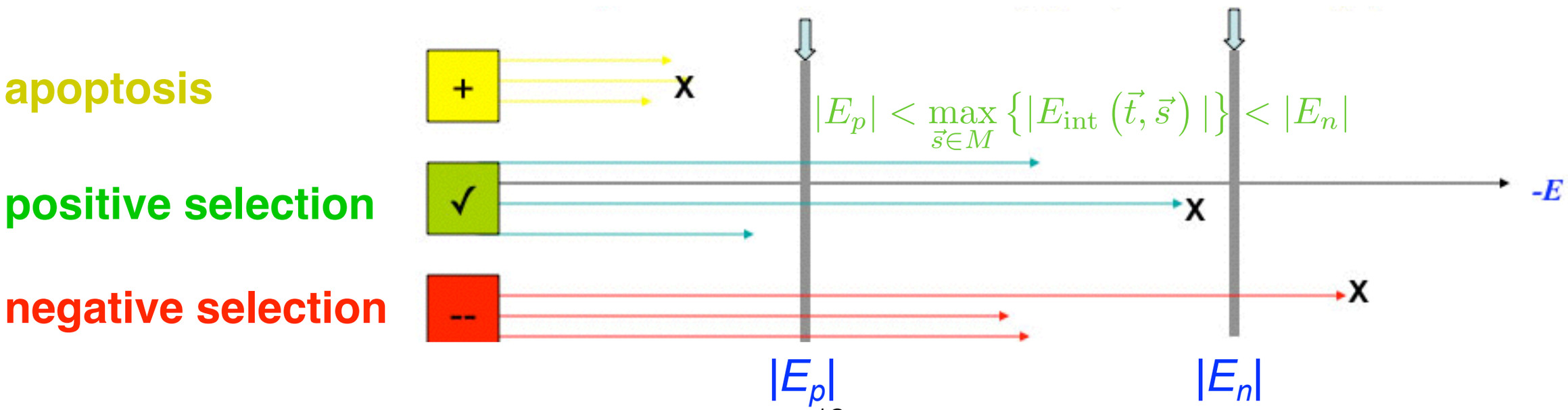
important contact: more than half of 19 amino acid mutations prevents recognition from the same TCR

Selection condition - extreme value problem



Surviving T cells: $|E_{int}| < |E_n|$ for all peptides; $|E_{int}| > |E_p|$ for at least one peptide

Selection condition is equivalent to the choice of the **Extreme Value**



Extreme value distribution

Selection condition for TCR $\vec{t}$

$$E_n < \min_{\vec{s}\in M} \left\{ E_{\rm int}\left(\vec{t},\vec{s}\right)\right\} < E_p$$

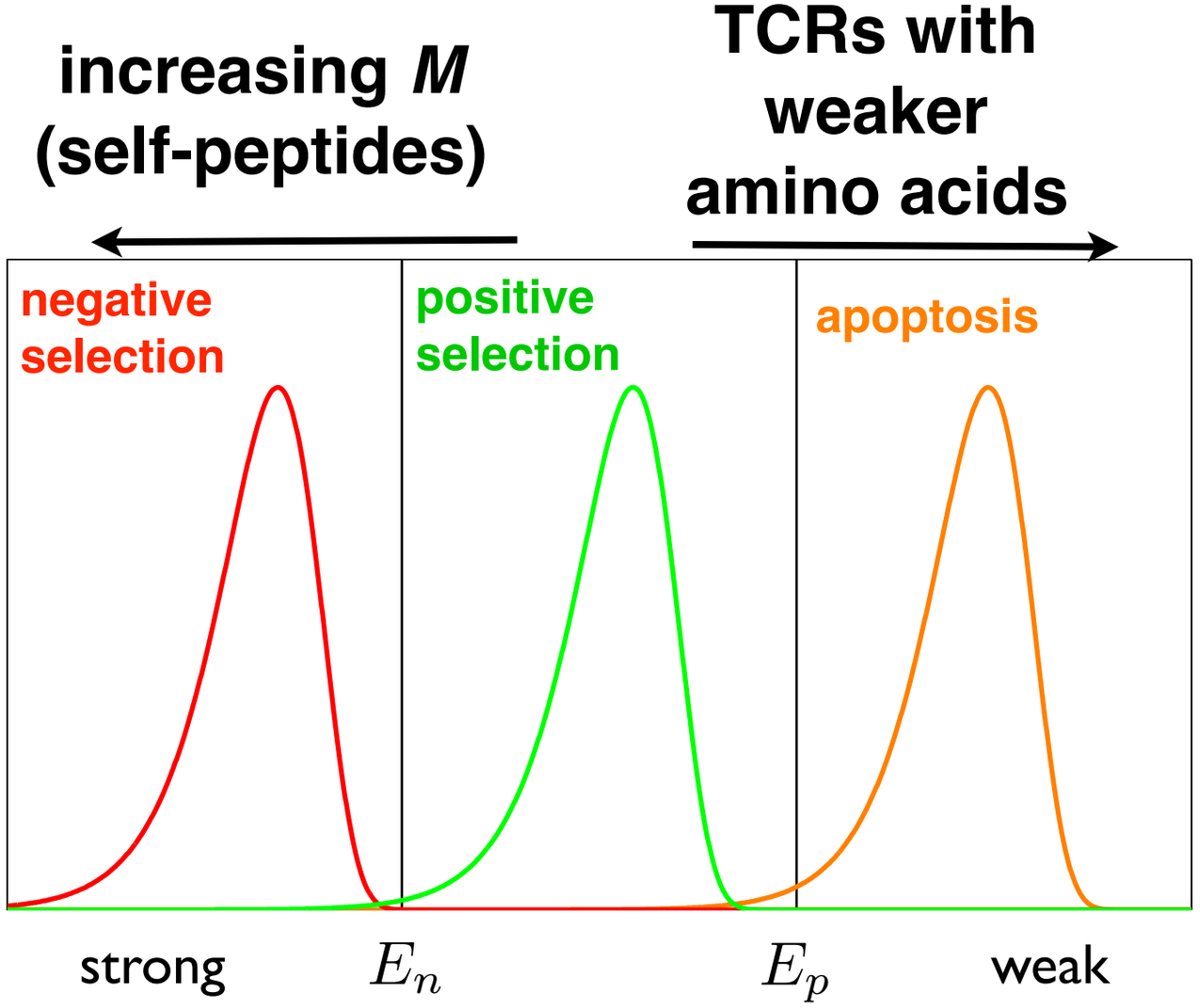
$$E_{\rm int}\left(\vec{t},\vec{s}\right) = E_c + \sum_{i=1}^{N} J(t_i,s_i)$$

$$\rho(E_{\rm int}|\vec{t})$$

Probability of TCR selection:

$$P_{\rm sel}\left(\vec{t}\right) = \int_{E_n}^{E_p} \Pi\left(x|\vec{t}\right) dx$$

$$\Pi\left(x|\vec{t}\right) = M\rho\left(x|\vec{t}\right)\left(1-P\left(E<x|\vec{t}\right)\right)^{M-1}$$



Properties of $\Pi(x|\vec{t})$

mean value: $E_0(\vec{t}) = E_c + \sum_{i=1}^{N} \mathcal{E}(t_i) - \sqrt{2\ln M \sum_{i=1}^{N} \mathcal{V}(t_i)}$

standard deviation: $\Sigma_0(\vec{t}) = \sqrt{\pi^2 \sum_{i=1}^{N} \mathcal{V}(t_i)/12\ln M}$

$$\mathcal{E}(a) = \langle J(a,b)\rangle_b$$

$$\mathcal{V}(a) = \langle [J(a,b)-\mathcal{E}(a)]^2\rangle_b$$

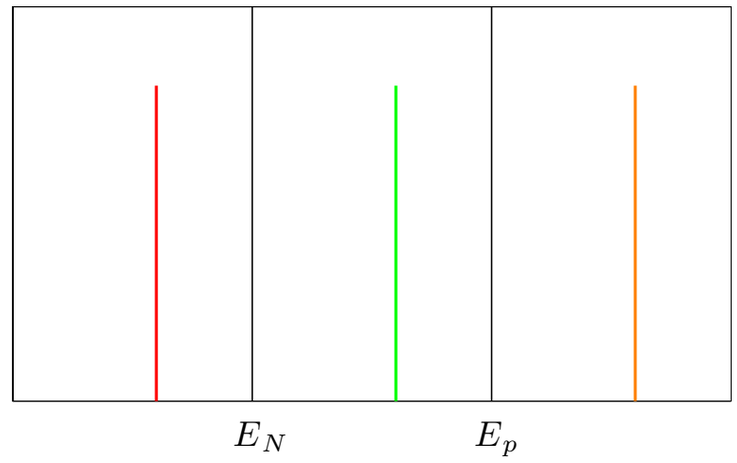
A. Košmrlj *et al.*, PRL **103**, 068103 (2009)

The limit of large peptides (N)

Scaling in the large peptide (N) limit: $\{E_c, E_p, E_n, \ln M\} \propto N$

mean value: $E_0(\vec{t}) = E_c + \sum_{i=1}^{N} \mathcal{E}(t_i) - \sqrt{2 \ln M \sum_{i=1}^{N} \mathcal{V}(t_i)}$ $\mathcal{O}(N)$

standard deviation: $\Sigma_0(\vec{t}) = \sqrt{\pi^2 \sum_{i=1}^{N} \mathcal{V}(t_i)/12 \ln M}$ $\mathcal{O}(1)$



Selection condition for TCR $\vec{t}$

$E_n < E_0\left(\vec{t}\right) < E_p$ like micro-canonical constraint in Statistical Physics

Probability of selection: $p(\vec{t}) \propto \exp\left[-\beta E_0(\vec{t})\right]$

Amino acid composition of selected TCRs:

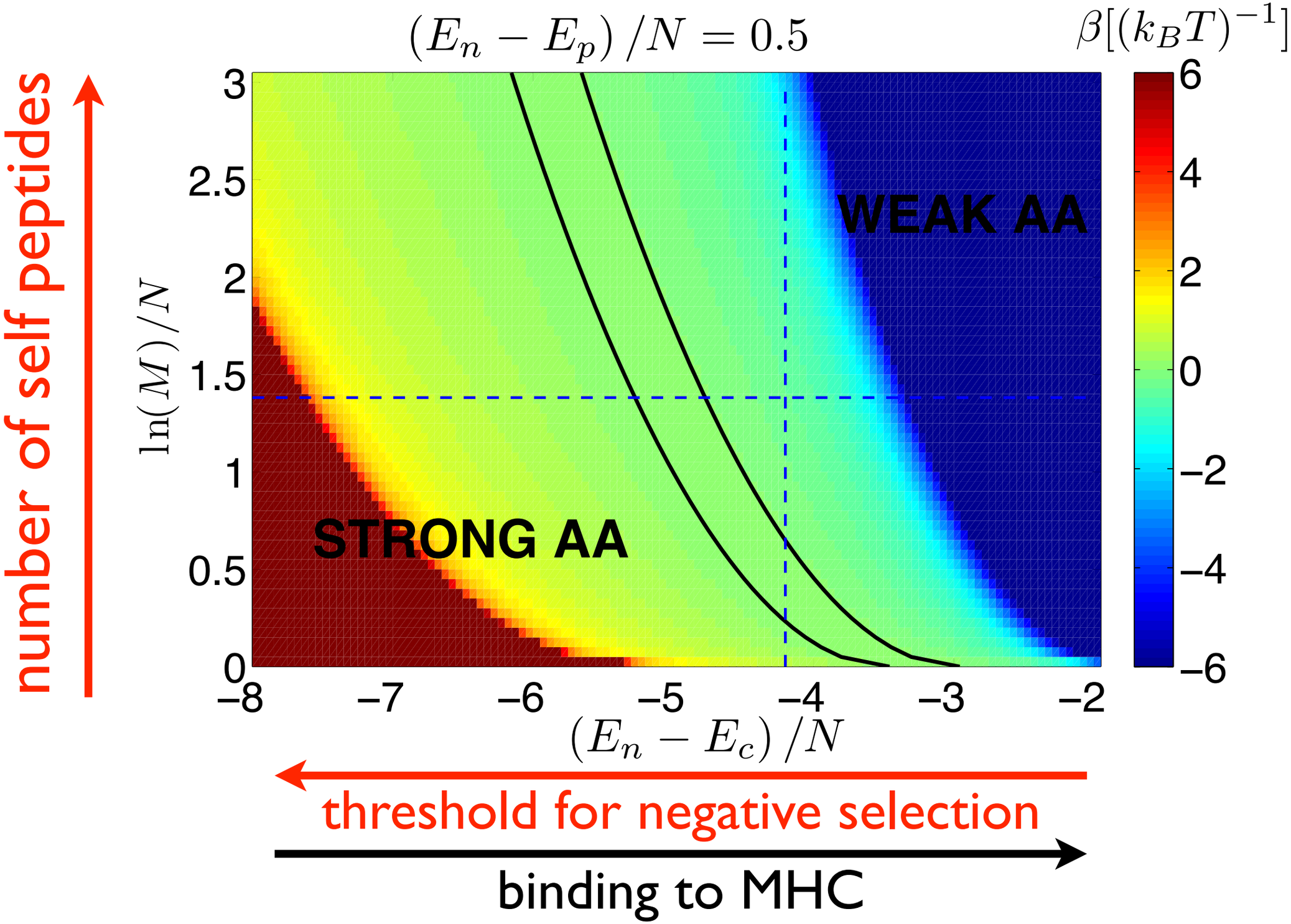
$$f_a^{(\mathrm{sel})} = \frac{f_a \exp\left[-\beta\left(\mathcal{E}(a) - \gamma \mathcal{V}(a)\right)\right]}{\sum_{b=1}^{20} f_b \exp\left[-\beta\left(\mathcal{E}(b) - \gamma \mathcal{V}(b)\right)\right]}$$

$\beta > 0$ STRONG AA

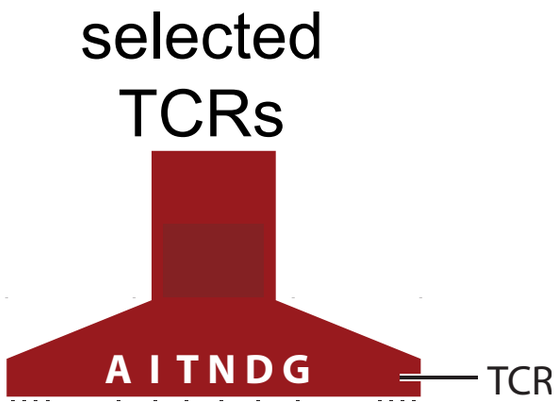
$\beta < 0$ WEAK AA

A. Košmrlj *et al.*, PRL **103**, 068103 (2009)

Phase diagram

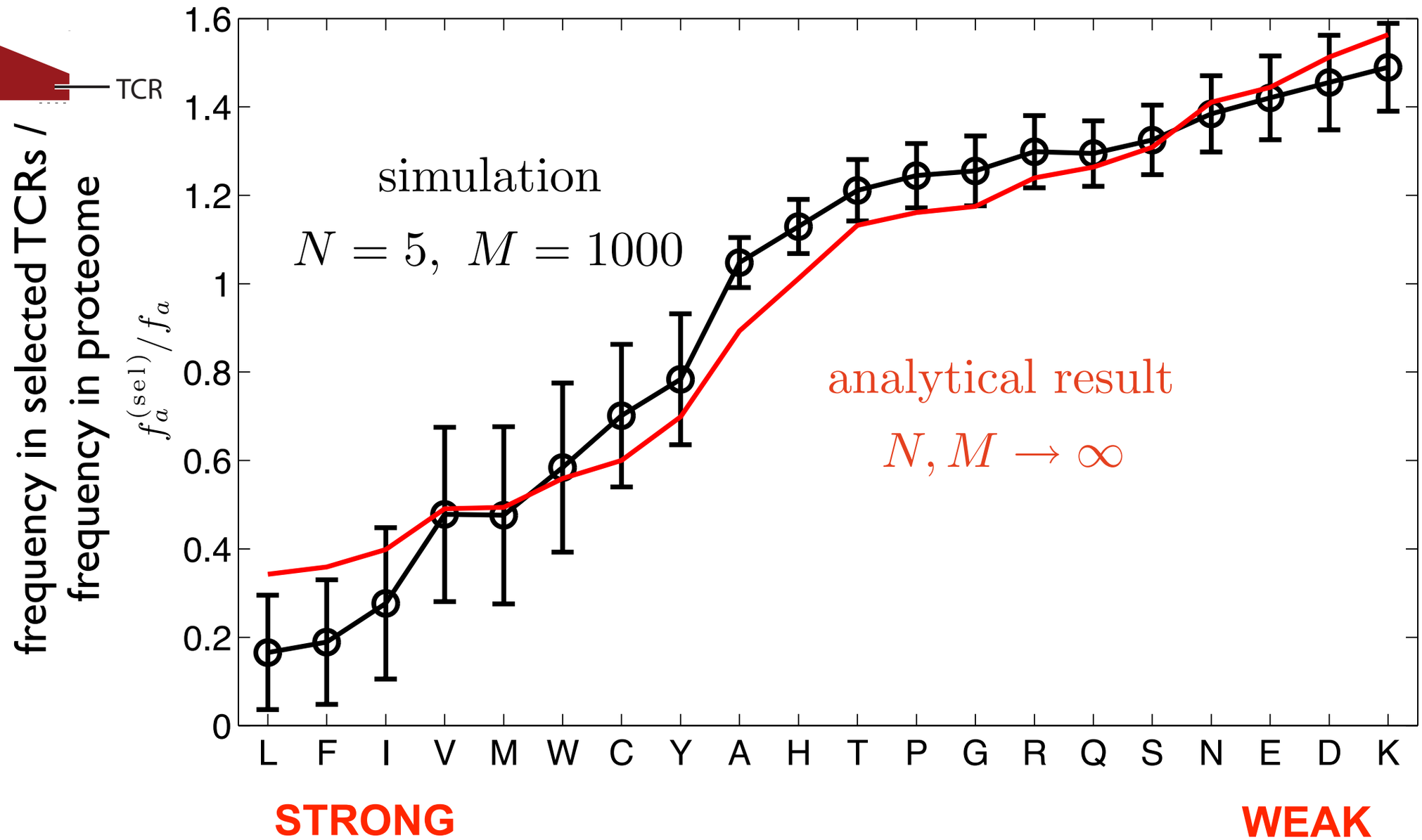


How good is analytical result for short peptides (N=5)?

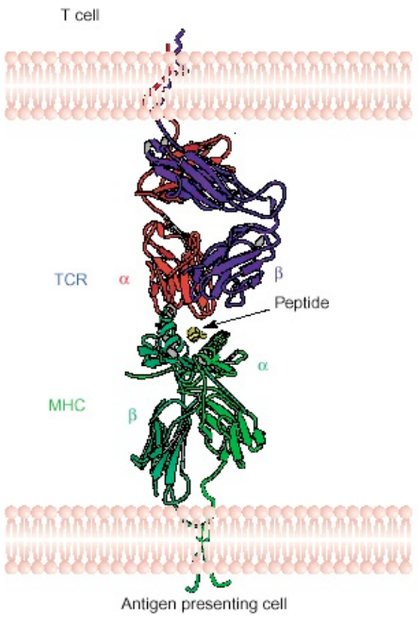


$$f_a^{(\mathrm{sel})} = \frac{f_a \exp\left[-\beta\big(\mathcal{E}(a) - \gamma\mathcal{V}(a)\big)\right]}{\sum_{b=1}^{20} f_b \exp\left[-\beta\big(\mathcal{E}(b) - \gamma\mathcal{V}(b)\big)\right]}$$

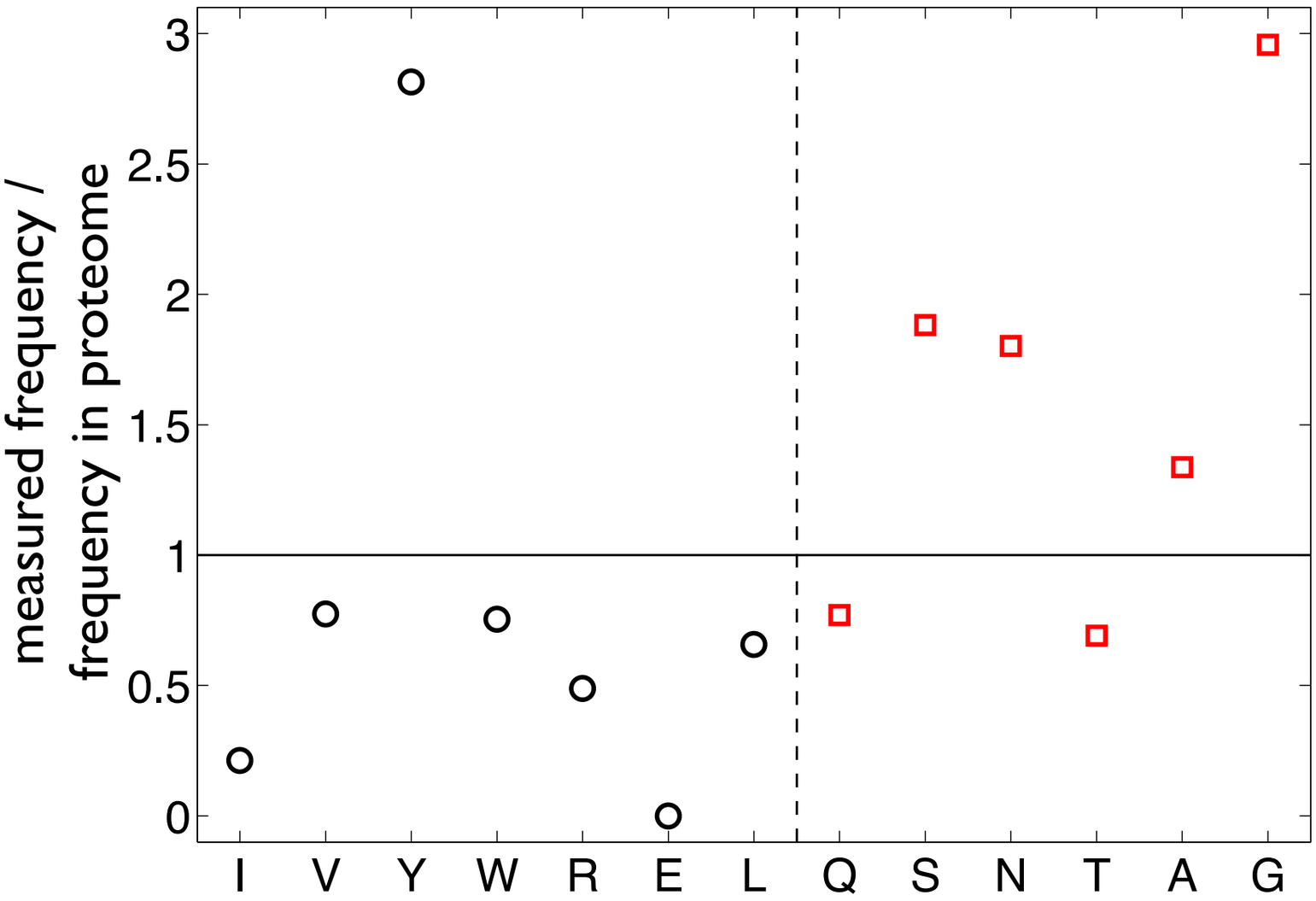
$$\beta = -0.37(k_B T)^{-1}$$
$$\gamma = 0.83(k_B T)^{-1}$$



Selected TCRs are enriched with weak amino acids



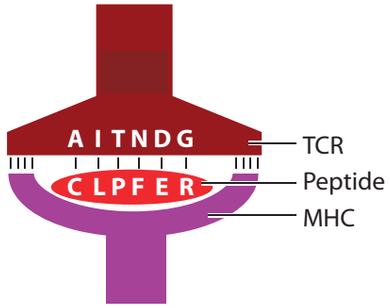
analyzed 18 crystal structures



(E. Shakhnovich et al., PLoS, 2007)

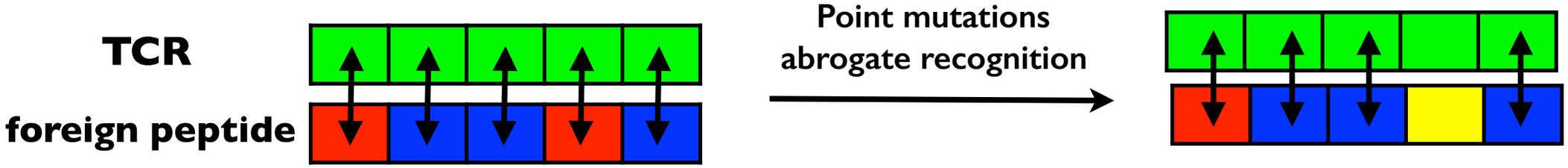
A. Košmrlj *et al*., PNAS **105**, 16671 (2008)

TCR recognition of foreign peptide is both specific and degenerate

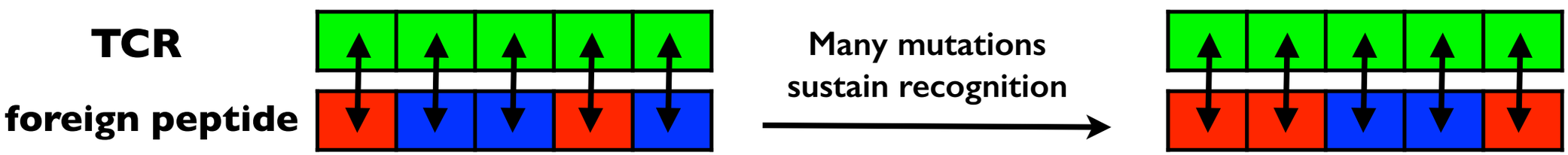


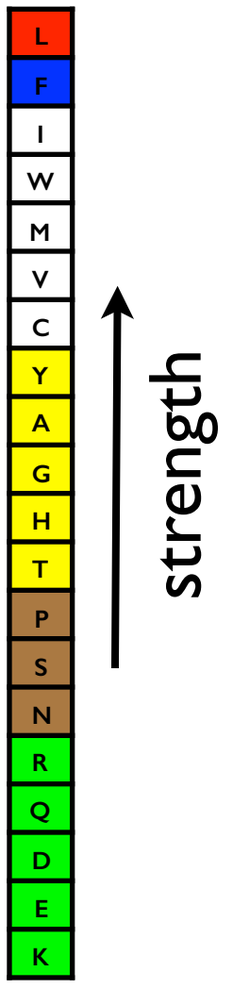
"Weak" peptide contact residues on TCR must bind a sufficient number of its stronger complementary amino acids for recognition via multiple moderate interactions

Specificity:

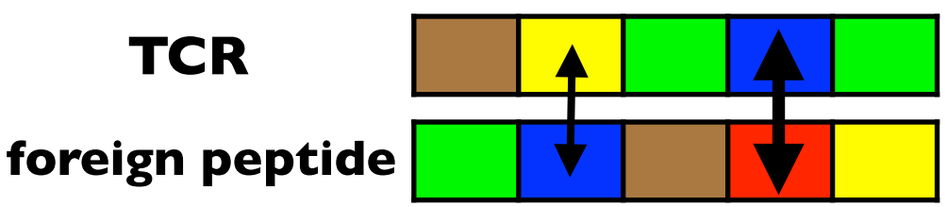


Degeneracy:



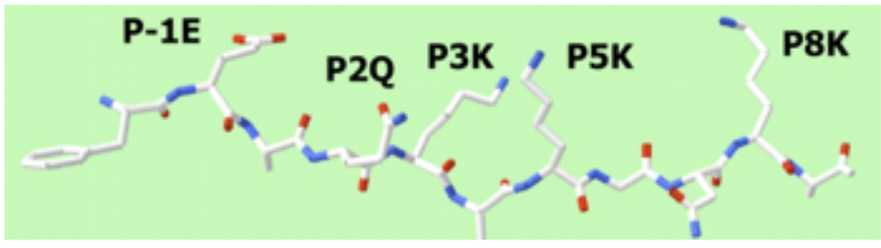


Selection against one peptide - only few important contacts



Number of important contacts for specific/cross-reactive T cells

E. Huseby *et al*., Cell **122**, 247 (2005)
E. Huseby *et al*., Nat. Immunol. **7**, 1191 (2006)

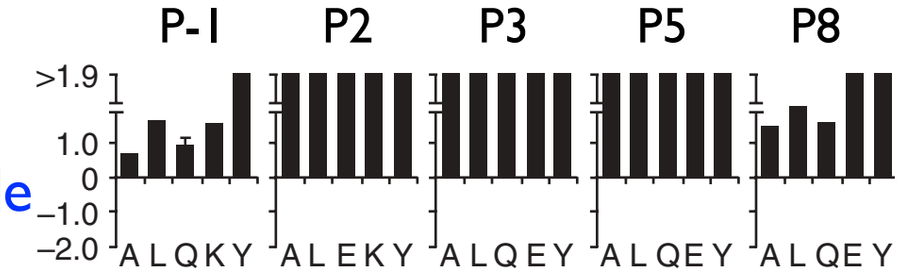


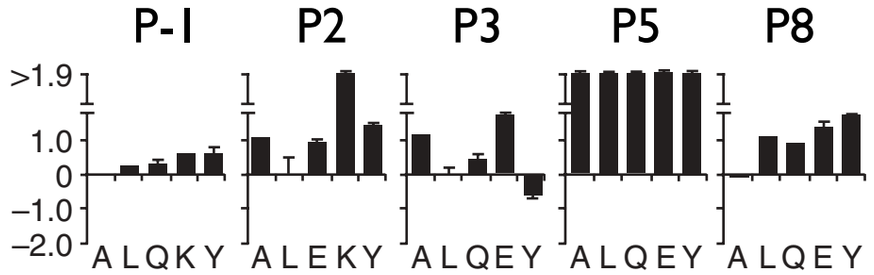
Thymic selection against

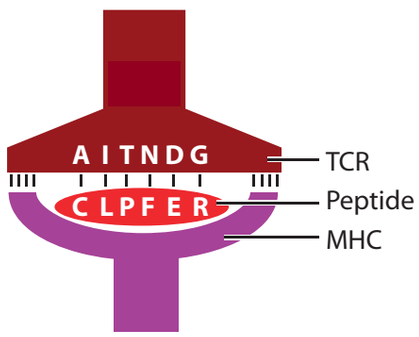
many self peptides (normal mouse)

one self peptide (engineered mouse)

change of binding free energy between TCRs and peptides with single amino acid change





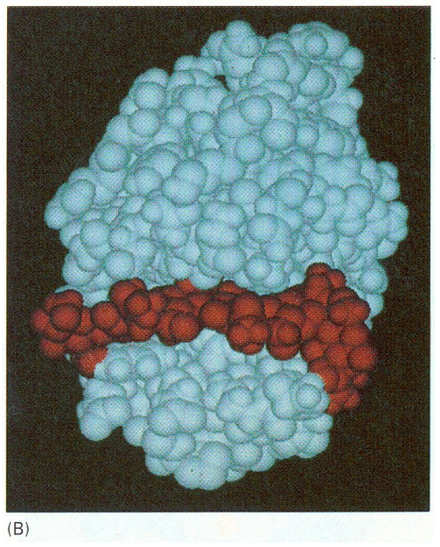


specific T cells:
many important contacts where mutations abrogate recognition

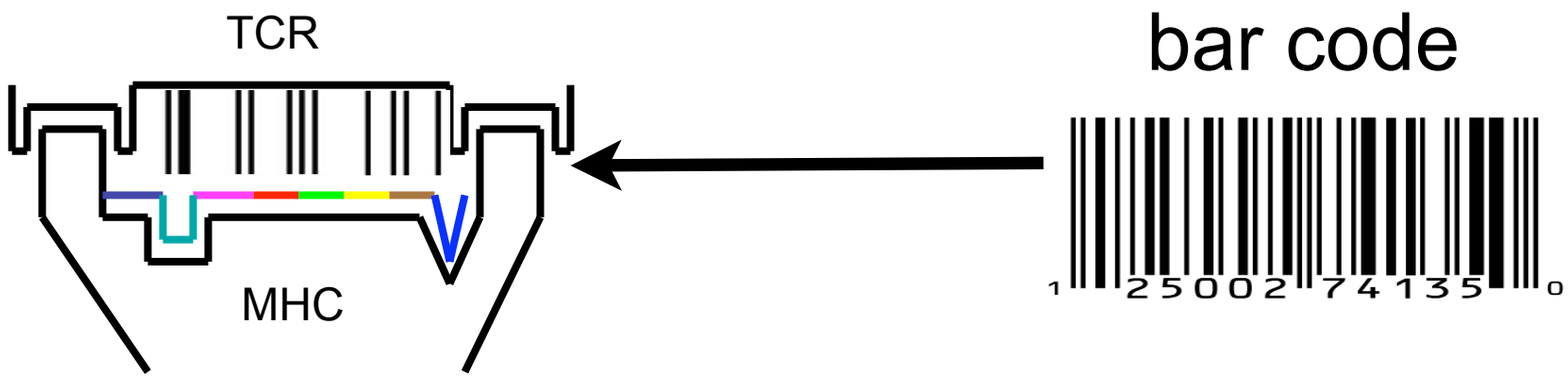
cross-reactive T cells:
only mutations at the few important contacts abrogate recognition

TCR specificity ~ statistical scan of a “bar code”

Enzyme and substrate fit together like a lock and key.

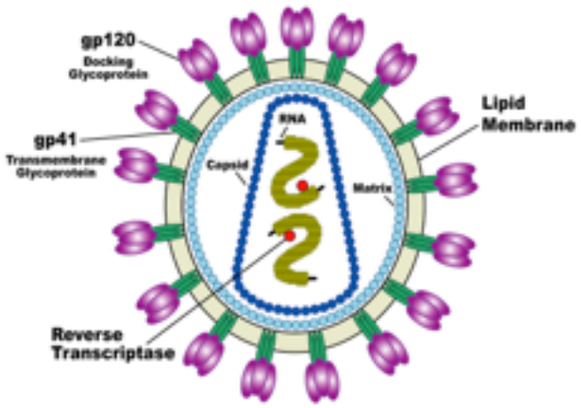


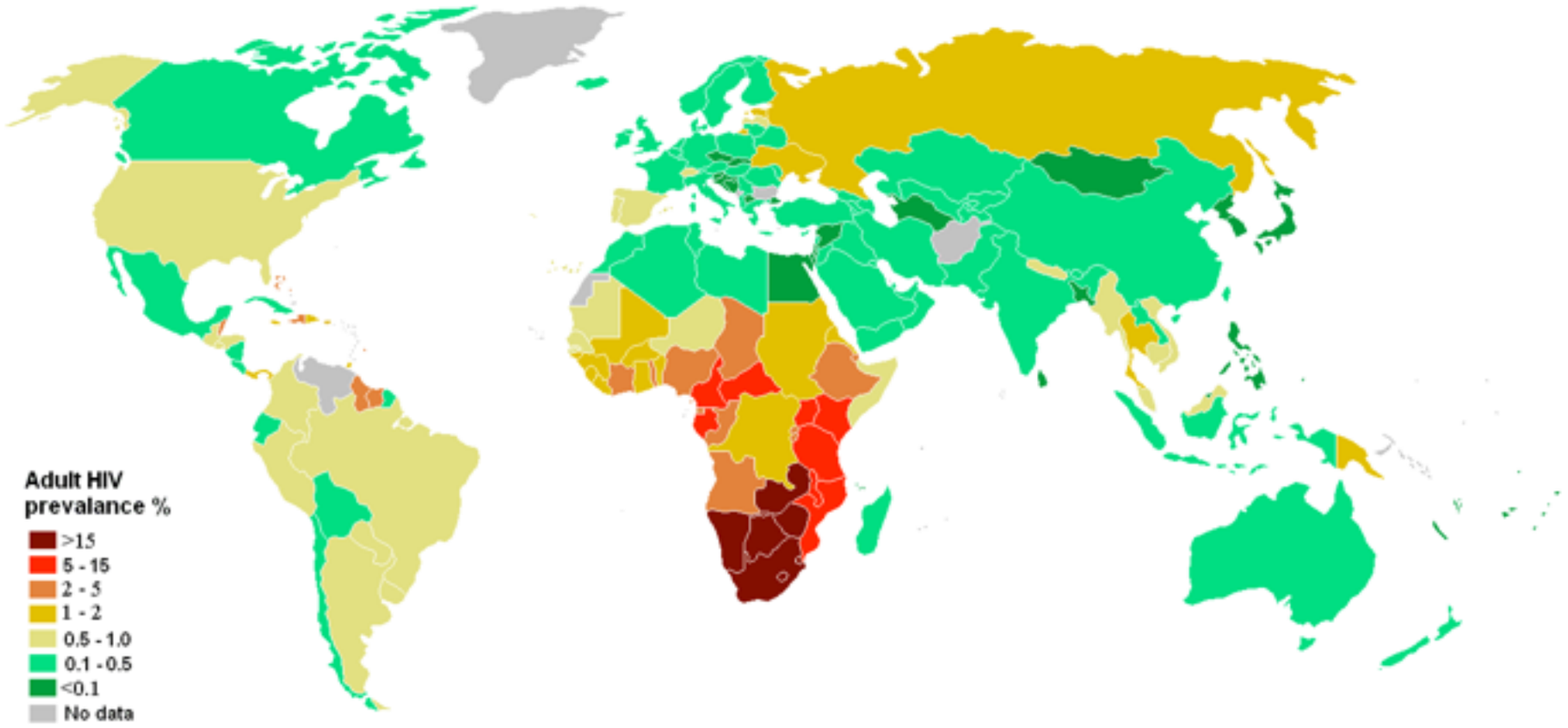
TCR like a bar code scanner -
“counts” the number of moderate interactions

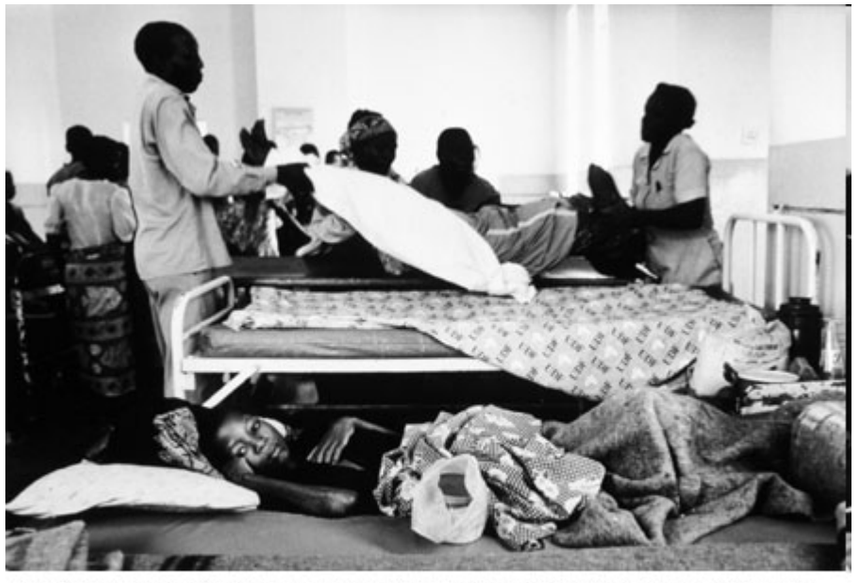


The HIV/AIDS epidemic

HIV

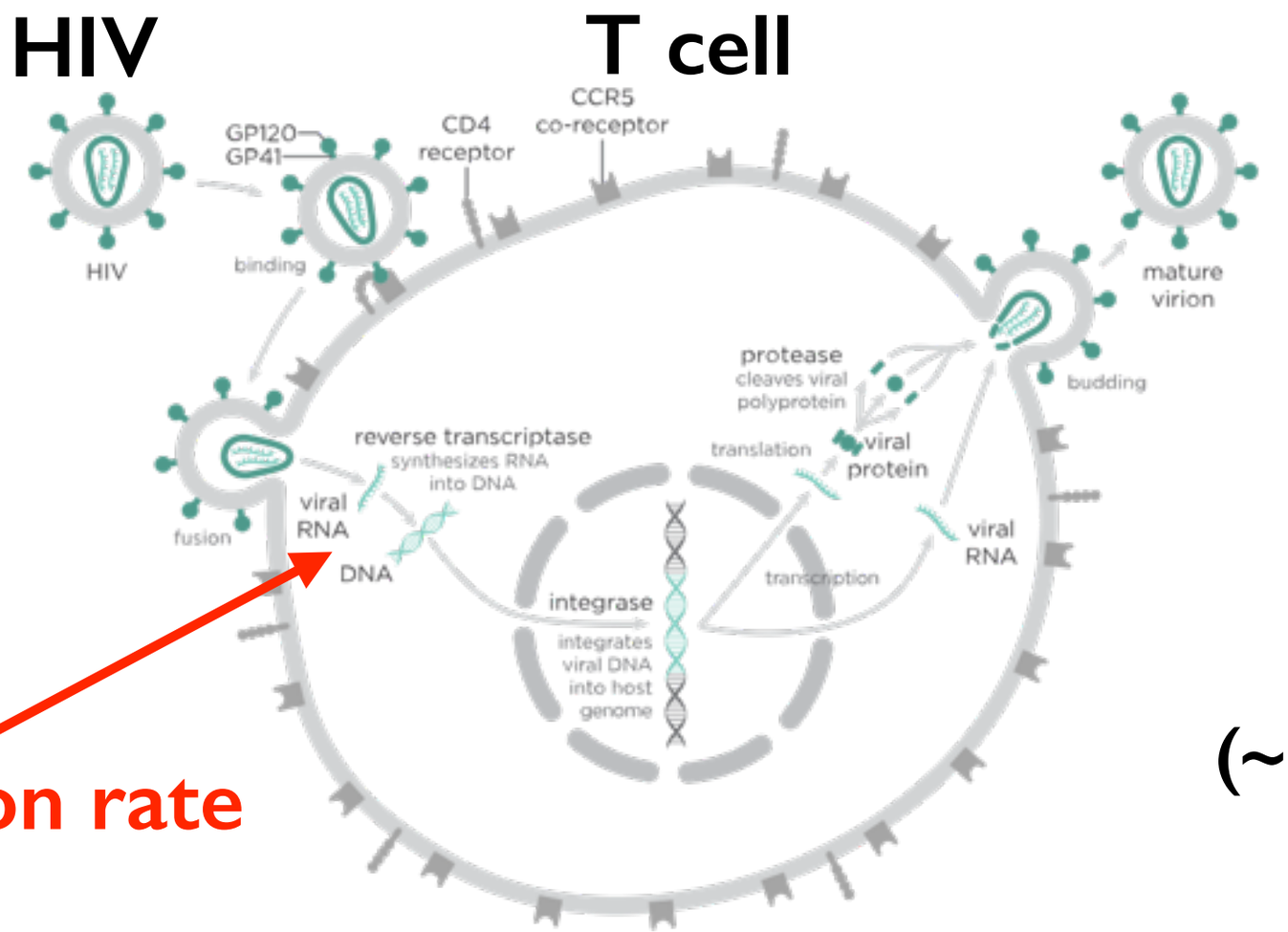






An AIDS patient lies in bed while hospital workers remove the body of a victim of AIDS in Chiradzulu Hospital in Malawi.

HIV hurts immune system by infecting and killing T cells

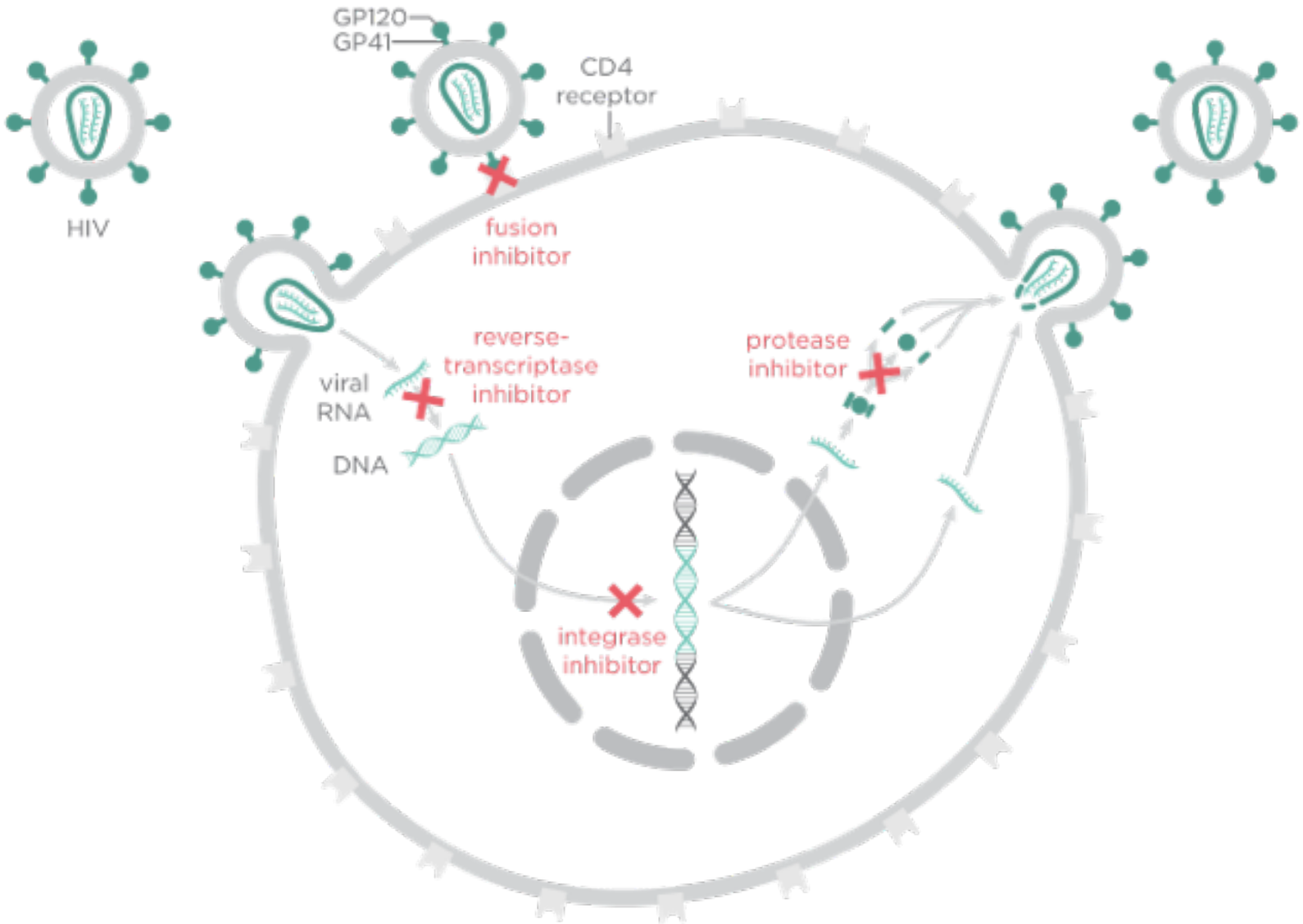


high mutation rate

high production rate of new HIV virions (~10^{10} per day)

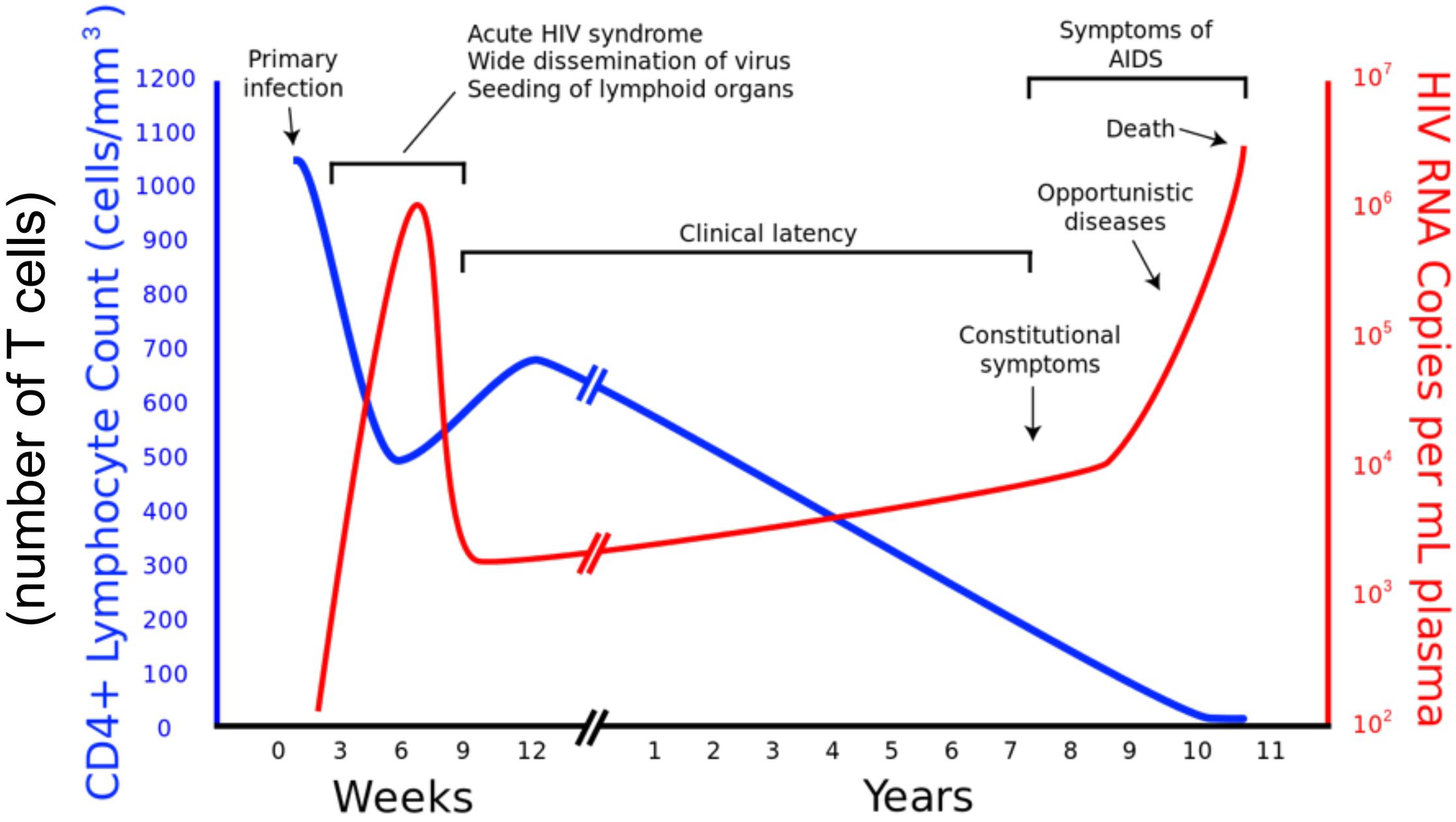
Highly mutating HIV may quickly produce mutants, that cannot be detected by immune system.

Highly active anti-retroviral therapy (HAART)



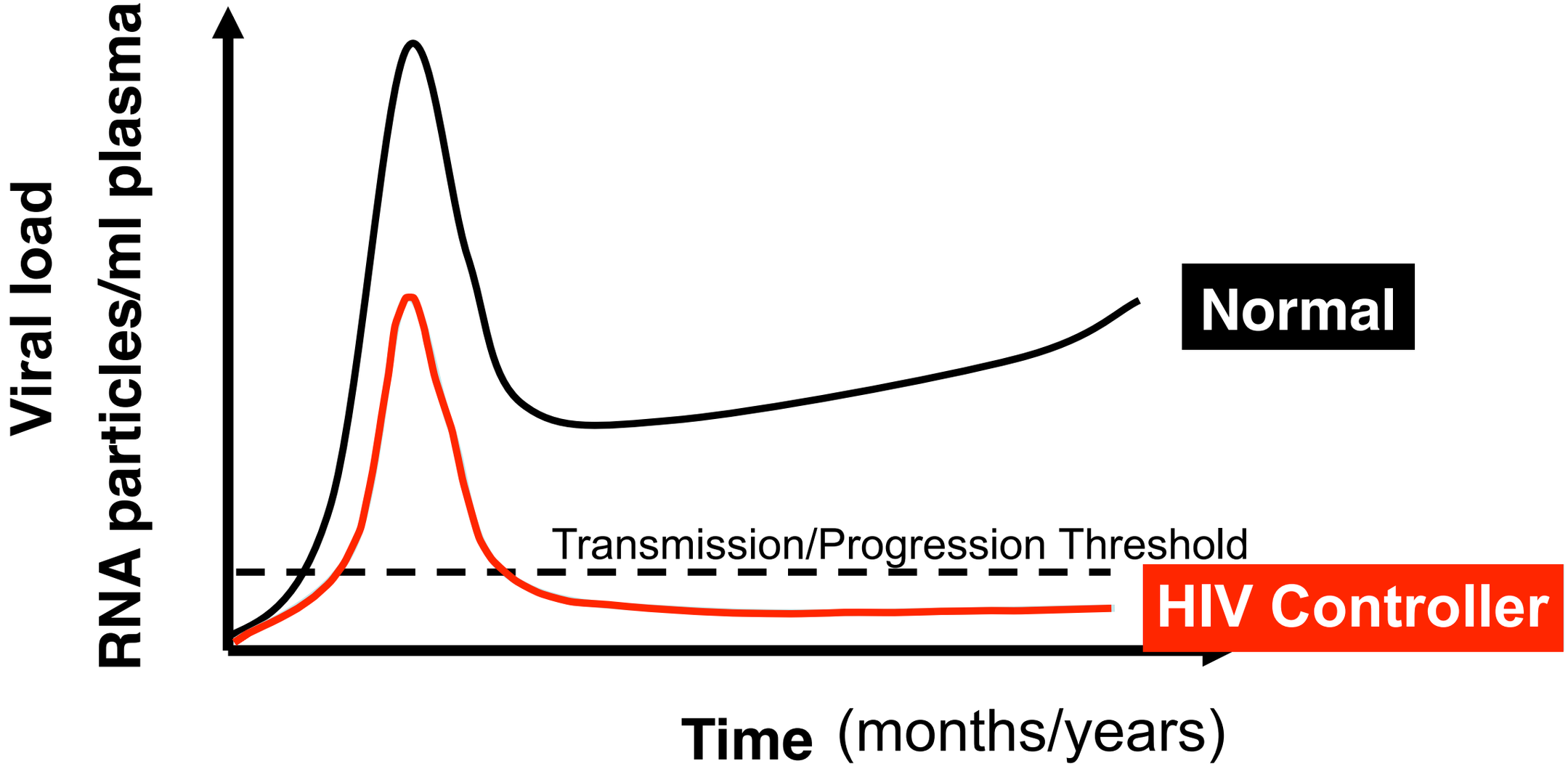
Current drug therapies can prevent infection of new T cells, but they cannot remove already infected T cells. When therapy is stopped, virus can become active again.

Typical time course of HIV infection



(from Wikipedia)

HIV Elite Controllers



Certain MHC types appear more frequently in HIV elite controllers: HLA-B57.

HLA-B57 binds fewer types of self peptides

Immune Epitope Database
(http://www.immuneepitope.org)

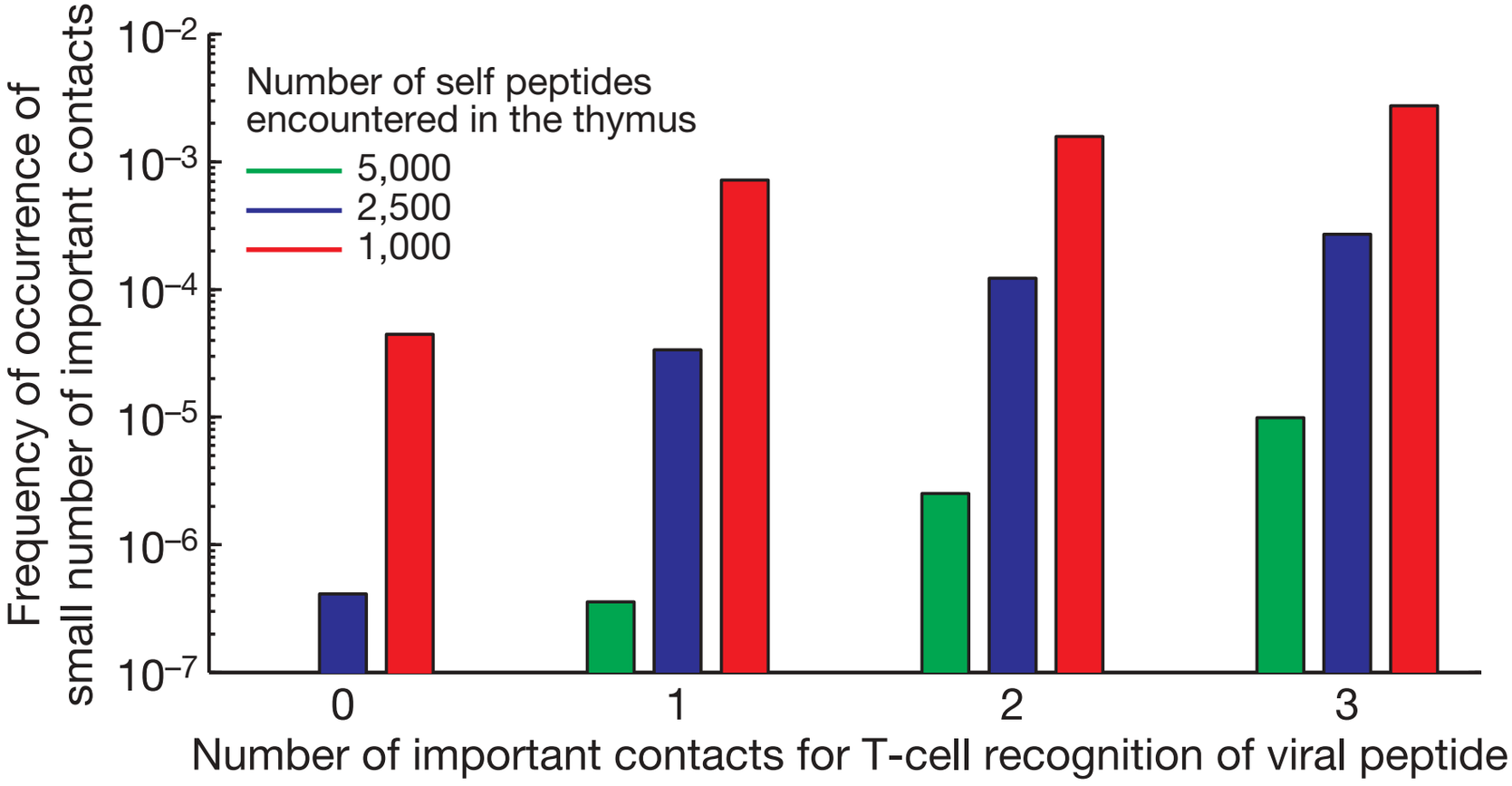
- Generate all possible peptides from the human proteome and use predictive algorithms to determine how many types of peptides bind to each HLA-B type

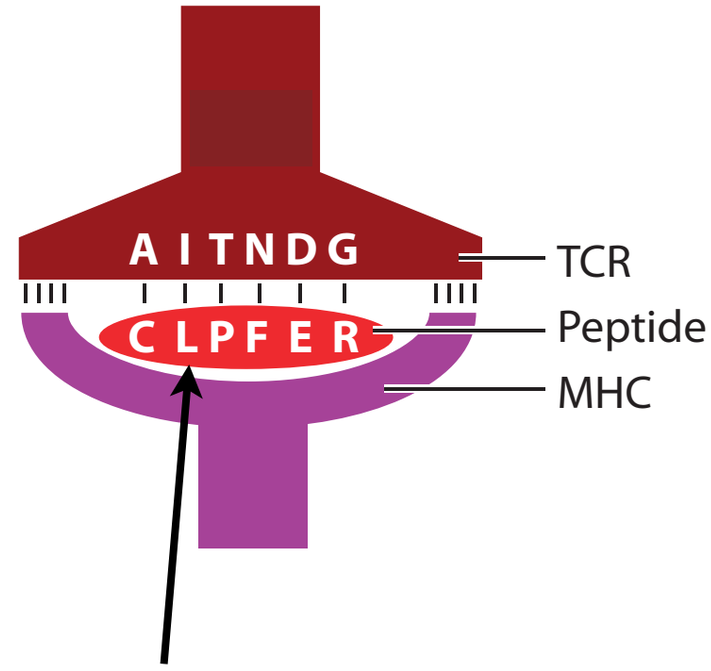
- HLA-B57 binds ~ 2-3 times fewer types of self peptides derived from human proteome than a typical HLA-B type and ~5-6 times fewer than HLA-B types that are associated with faster progression to AIDS.

- rhesus macaques: Mamu-B*17 allele (protective for SIV) binds ~ 4-10 times fewer types of peptides than other Mamu alleles

A. Košmrlj *et al.*, Nature **465**, 350 (2010)

T cell repertoire in a HLA-B57 individual is more cross-reactive to mutants of targeted viral epitopes





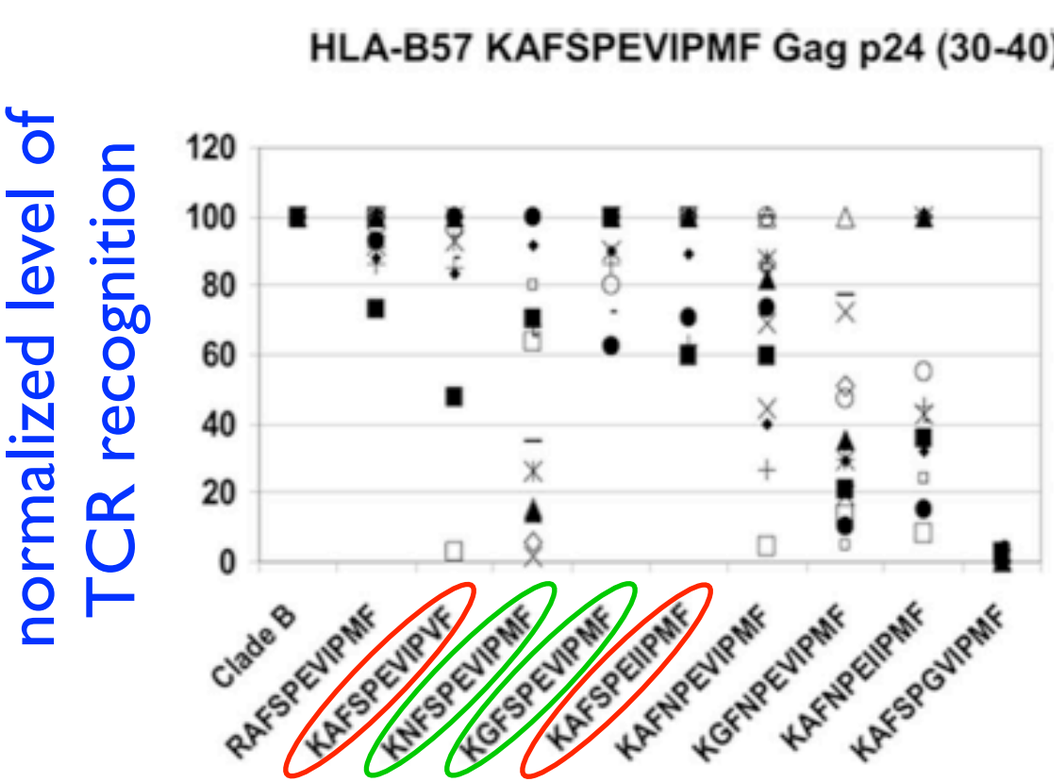
important contact: more than half of 19 amino acid mutations abrogates recognition

A. Košmrlj *et al.*, Nature **465**, 350 (2010)

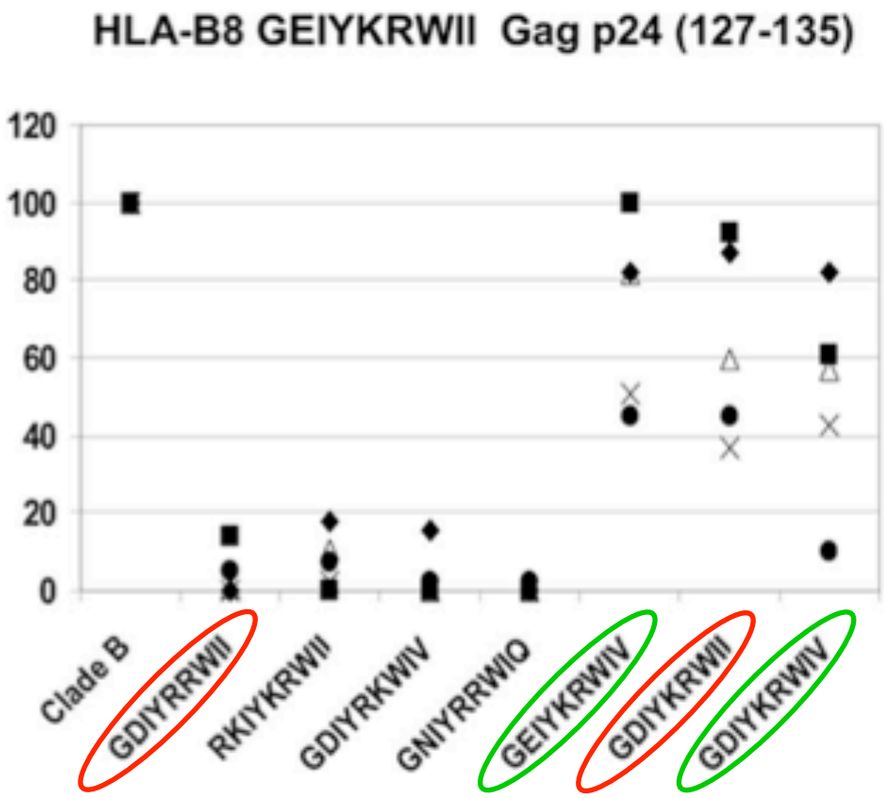
HLA-B57 individuals infected with HIV seem to have more cross-reactive TCRs

E. Turnbull *et al*., J. Immunol. **176**, 6130 (2006)

HLA-B57 (protective)



HLA-B8 (non-protective)

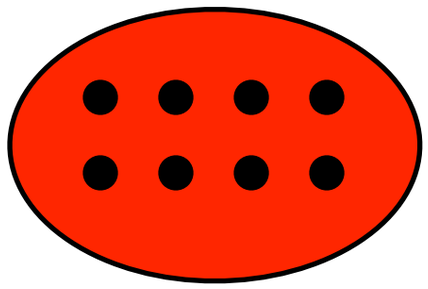


common HIV peptides and their mutants

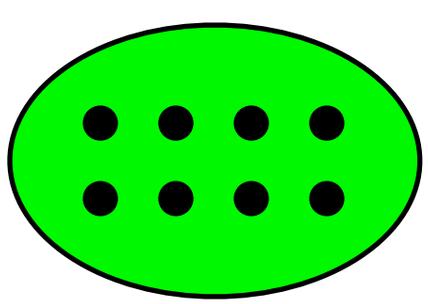
Prediction: people expressing MHC molecules that bind fewer (more) types of self peptides are better (worse) at controlling the HIV infection?

HLA associated control of HIV

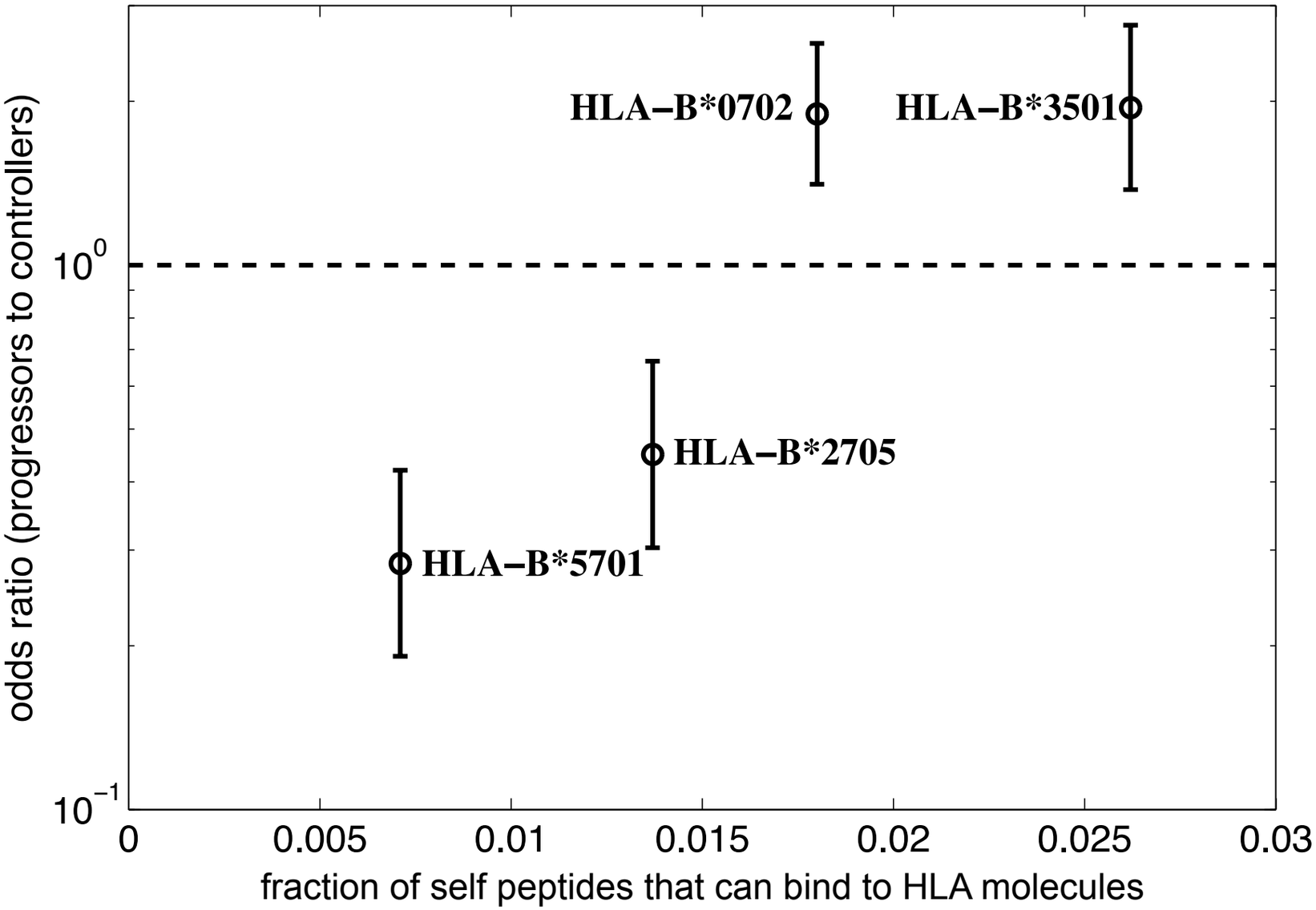
progressors

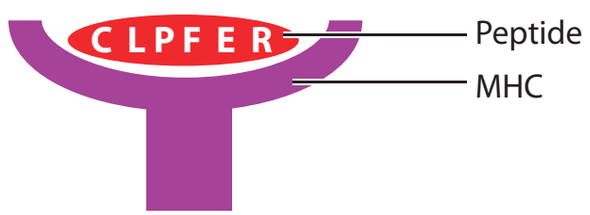


HIV controllers



probability of progressing to high viral load



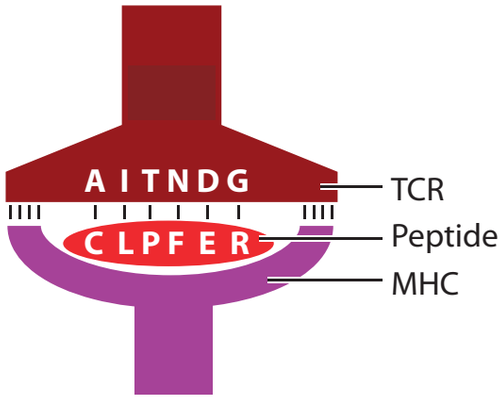


A. Košmrlj *et al.*, Nature **465**, 350 (2010)

Summary

- **How can TCR recognition of foreign peptides be both degenerate and specific?**

- **TCRs are enriched with weakly interacting amino acids. TCR recognition of foreign peptide occurs via multiple moderate contacts, each of which has a significant contribution. Breaking any contact by mutating the peptide may prevent recognition (specificity), but there are several different peptides that can be recognized (degeneracy).**



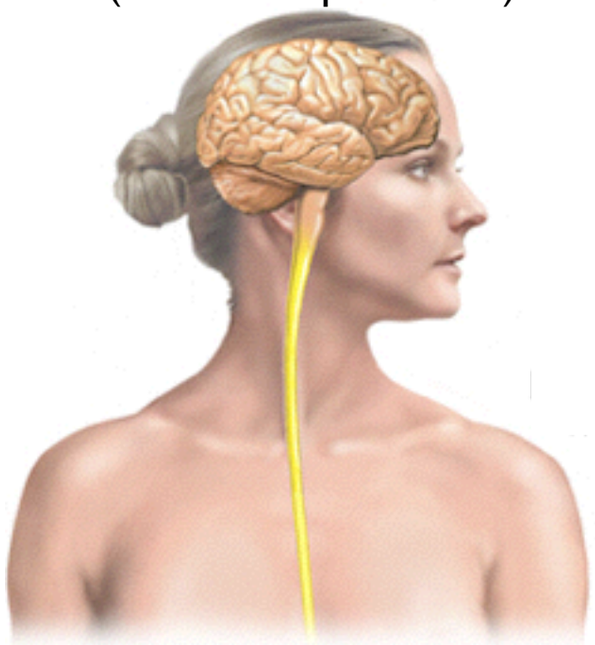
- **Certain MHC types (HLA-B57) appear more frequently in HIV elite controllers. These MHC types bind fewer types of self peptides. T cells developed against fewer self peptides are better at recognizing mutations of foreign peptides.**

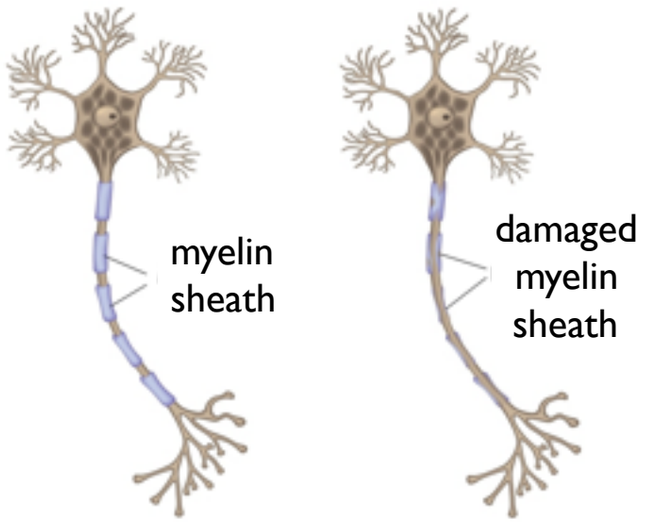
Autoimmune diseases

What goes wrong that immune system starts attacking host tissues?

Multiple Sclerosis

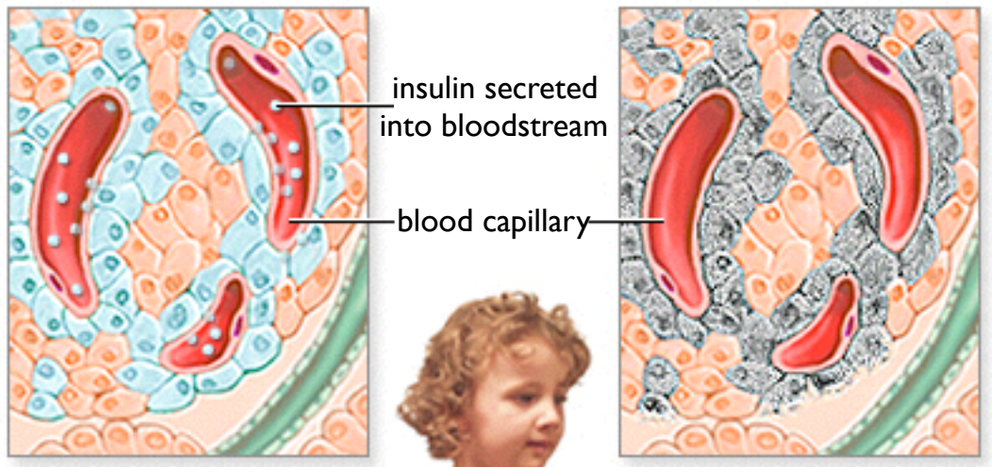
Central nervous system (brain and spinal cord)





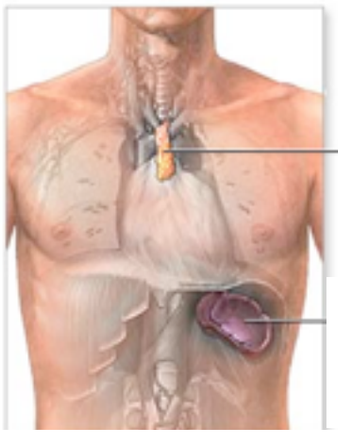
A.D.A.M.

Type I Diabetes



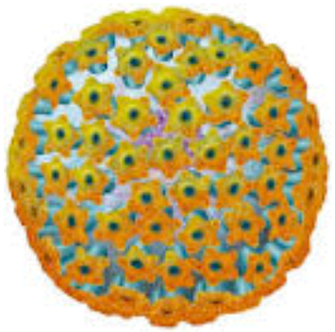
A.D.A.M.

Autoimmune diseases



thymus

What happens if some self peptides are not presented during the development in thymus? How different should these missing peptides be from other self peptides, so that immune system treats them as foreign?



Epstein-Barr virus

Why certain viral infections evolve the immune system to a state that is more prone for autoimmunity? Are these viral peptides correlated with self peptides from attacked tissues?

Certain MHC types are associated with higher risk for autoimmune diseases. How these particular MHC types affect the development in thymus and evolution in response to viral infections?

Questions about final projects?

Due Tuesday, Jan 12, in paper or electronic form.

I am traveling from Dec 24-Jan 5

During that period you can reach me via

email: andrej@princeton.edu

skype: akosmrlj