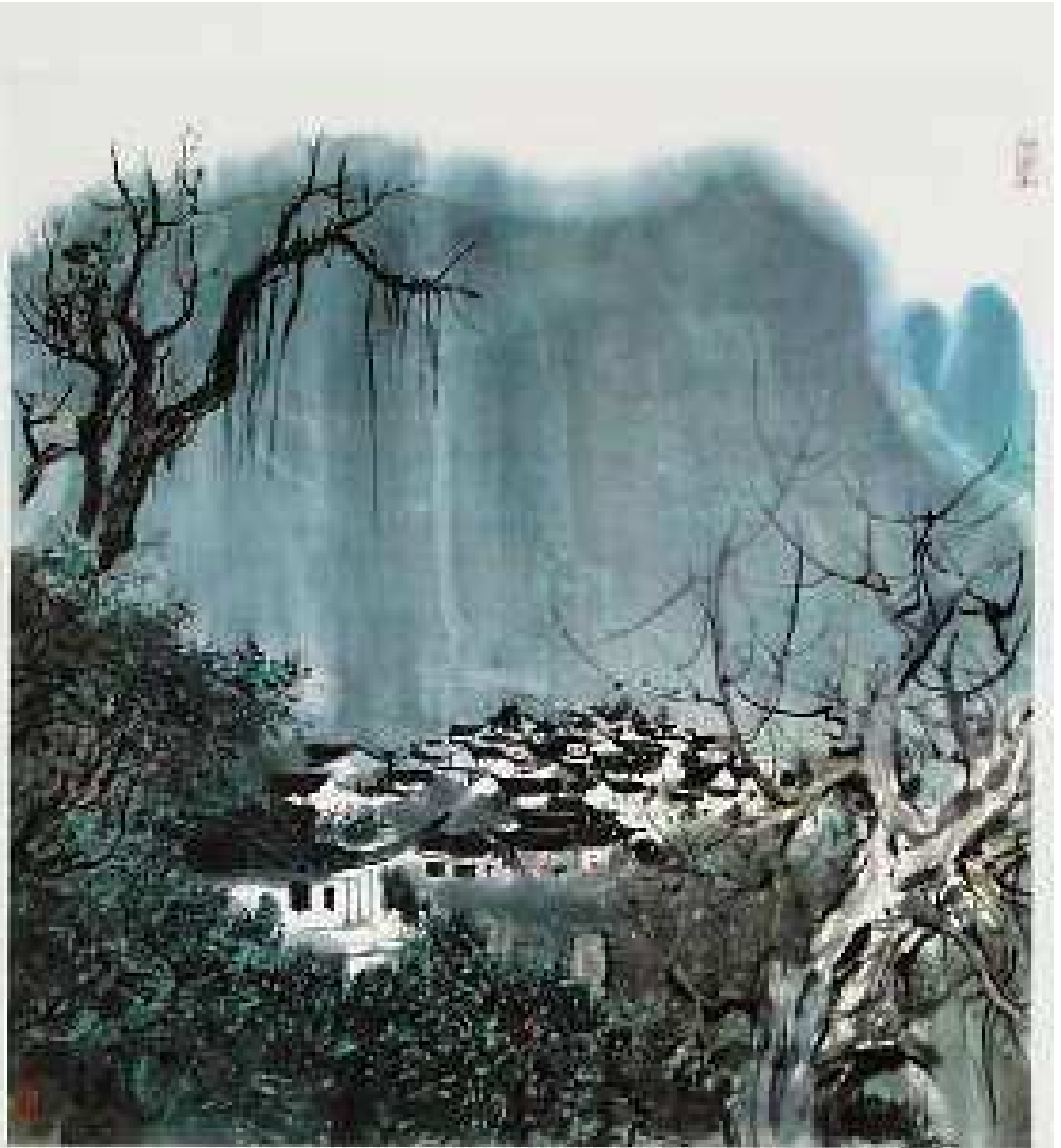


Centre for Mathematical Medicine

**“Order
from
Disorder
Sprung”**

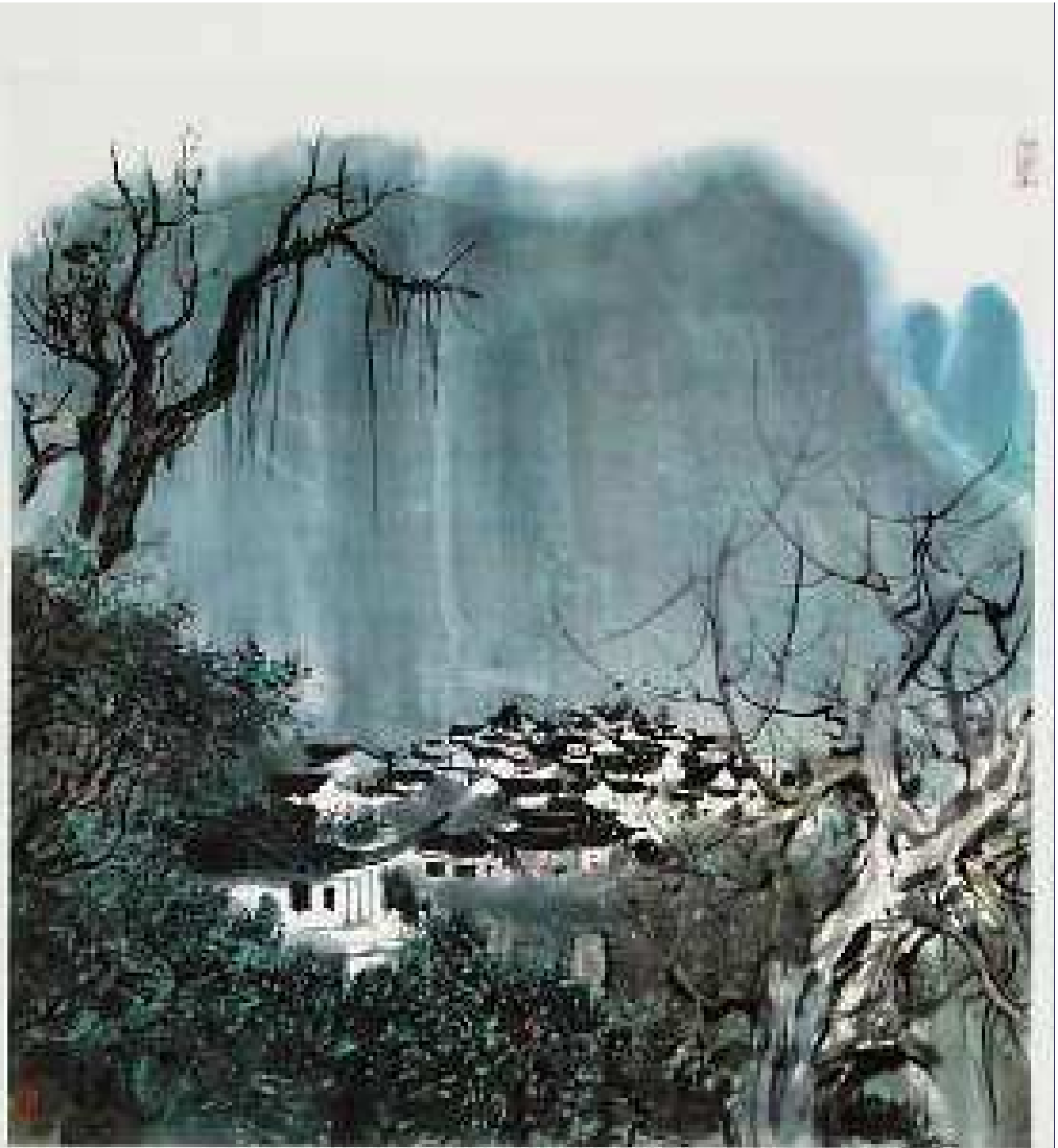




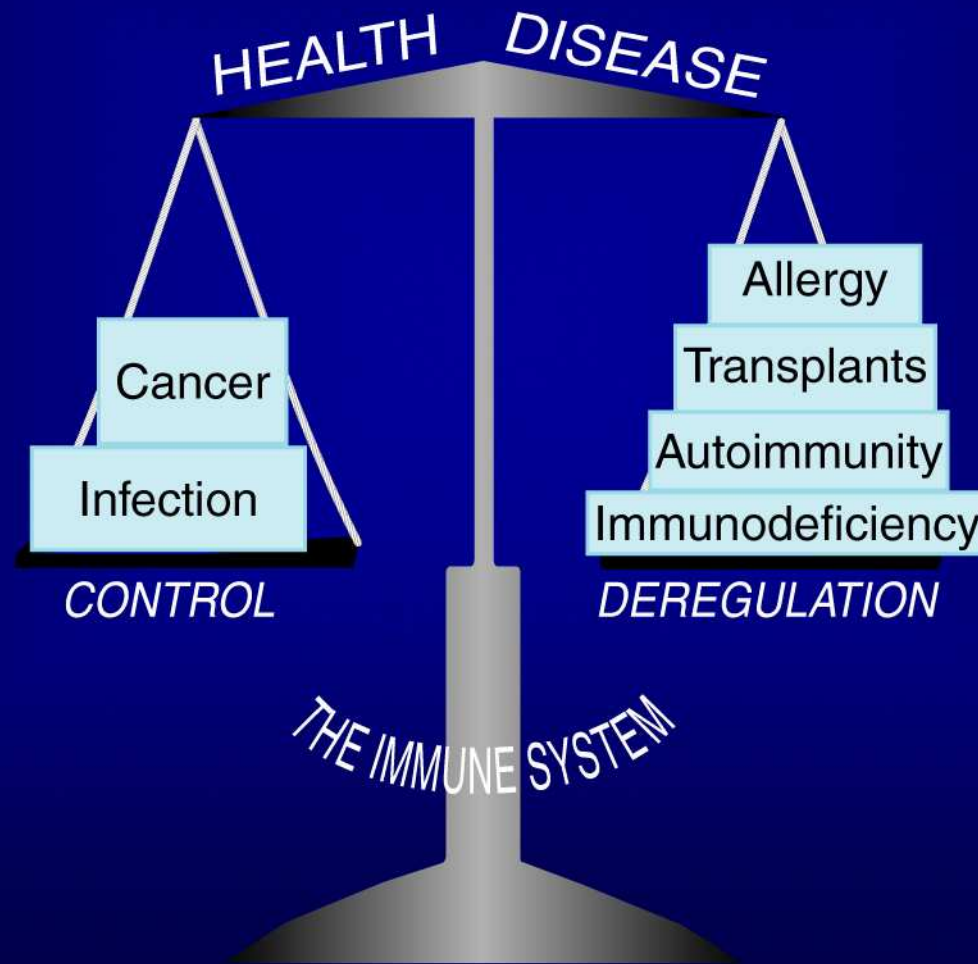
Centre for Mathematical Medicine

“Order from Disorder Sprung”

**Recognition & Regulation
Of the
Immune System**

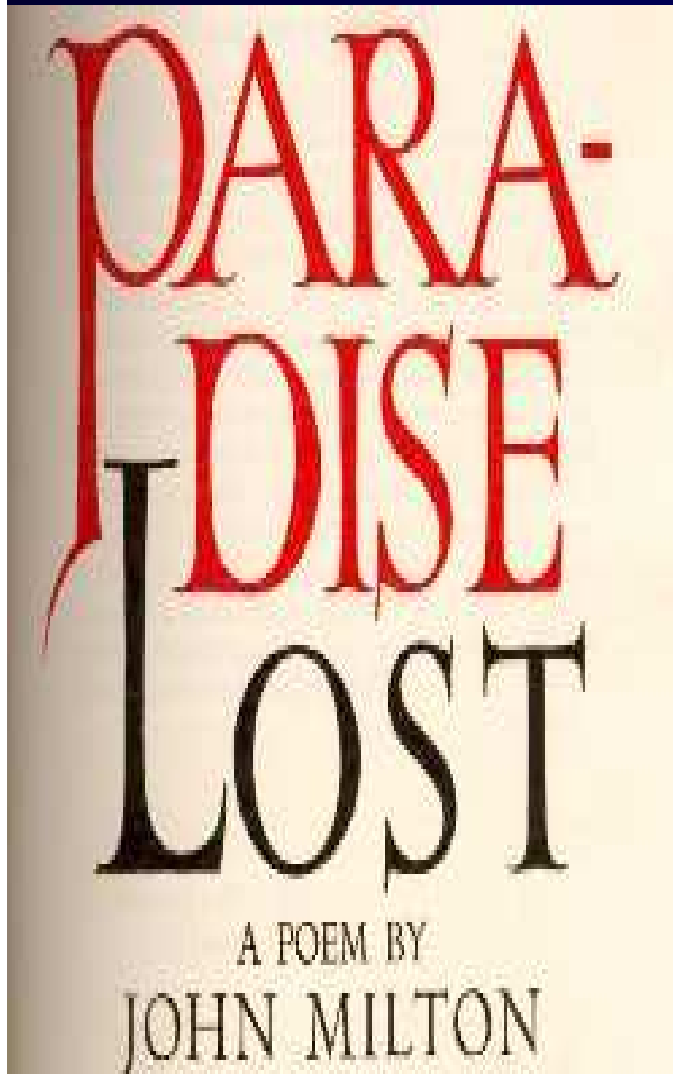


Control and Deregulation of the Immune System



The creation of the Universe and how Adam and Eve came to lose their place in Paradise

GOD brought the world out of the Chaos to establish “Order”



Metaphor

Satan pretends to praise GOD's creation, enters man's home
-pathogens played by Satan, invading to destroy the "paradise" of Our good Health

GOD brought the world out of the Chaos to regain "paradise"
-GOD creates the immune system to establish order
-GOD is "Generation Of Diversity" ie. enable it to recognize and remove all "Satans", but preserve "paradise"





“Order from Disorder Sprung”

- 1) *innate immunity - sentinel*
- 2) *acquired immunity - battle*
- 3) *Homeostasis - restoration*

Satan finds an opening to the universe within...

Confusion heard his voice...

*Till, at his second bidding, Darkness fled, Light shone, and
Order from disorder sprung ...*

Each had his place appointed, each his course;

The rest in circuit walls this Universe



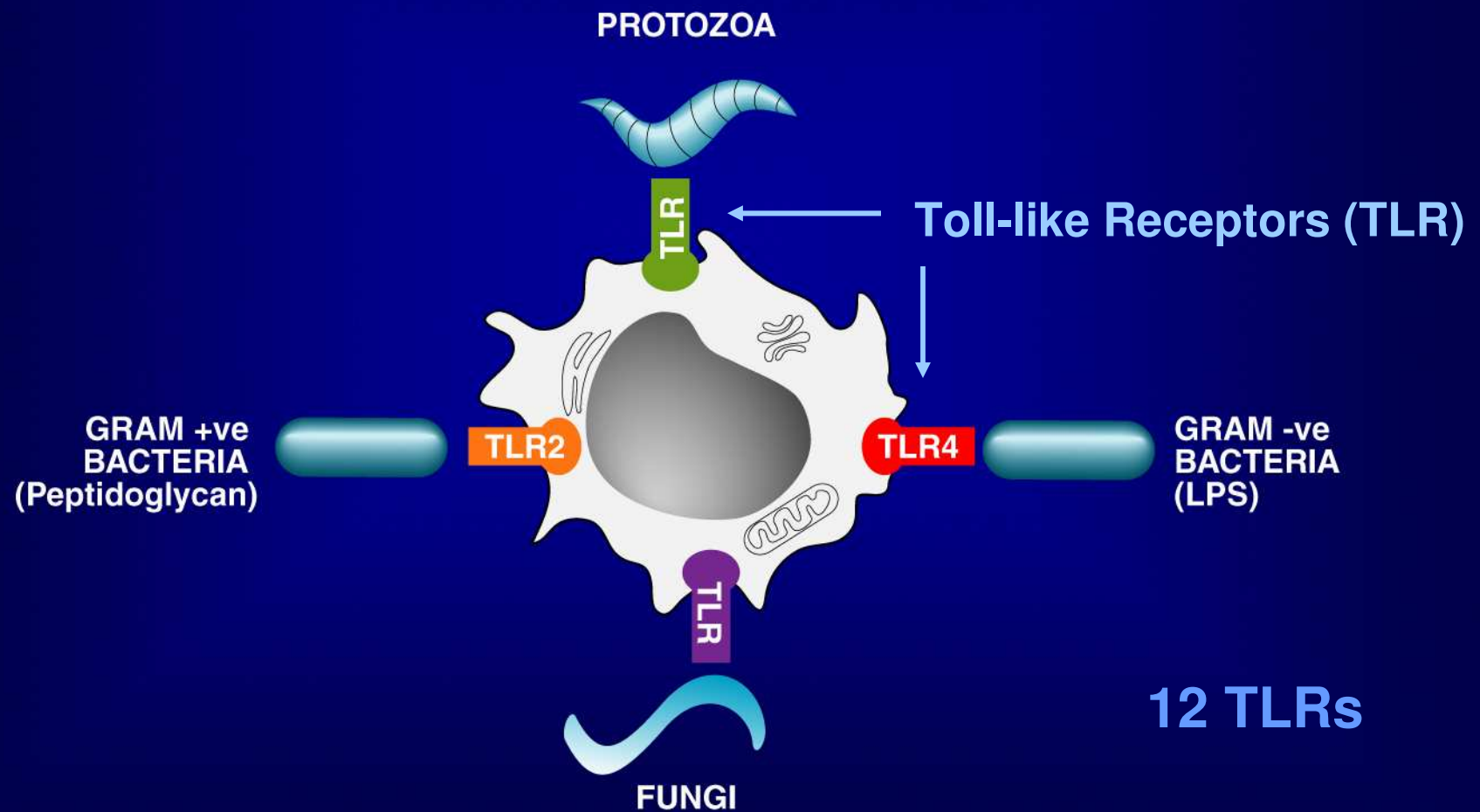


Innate Immunity

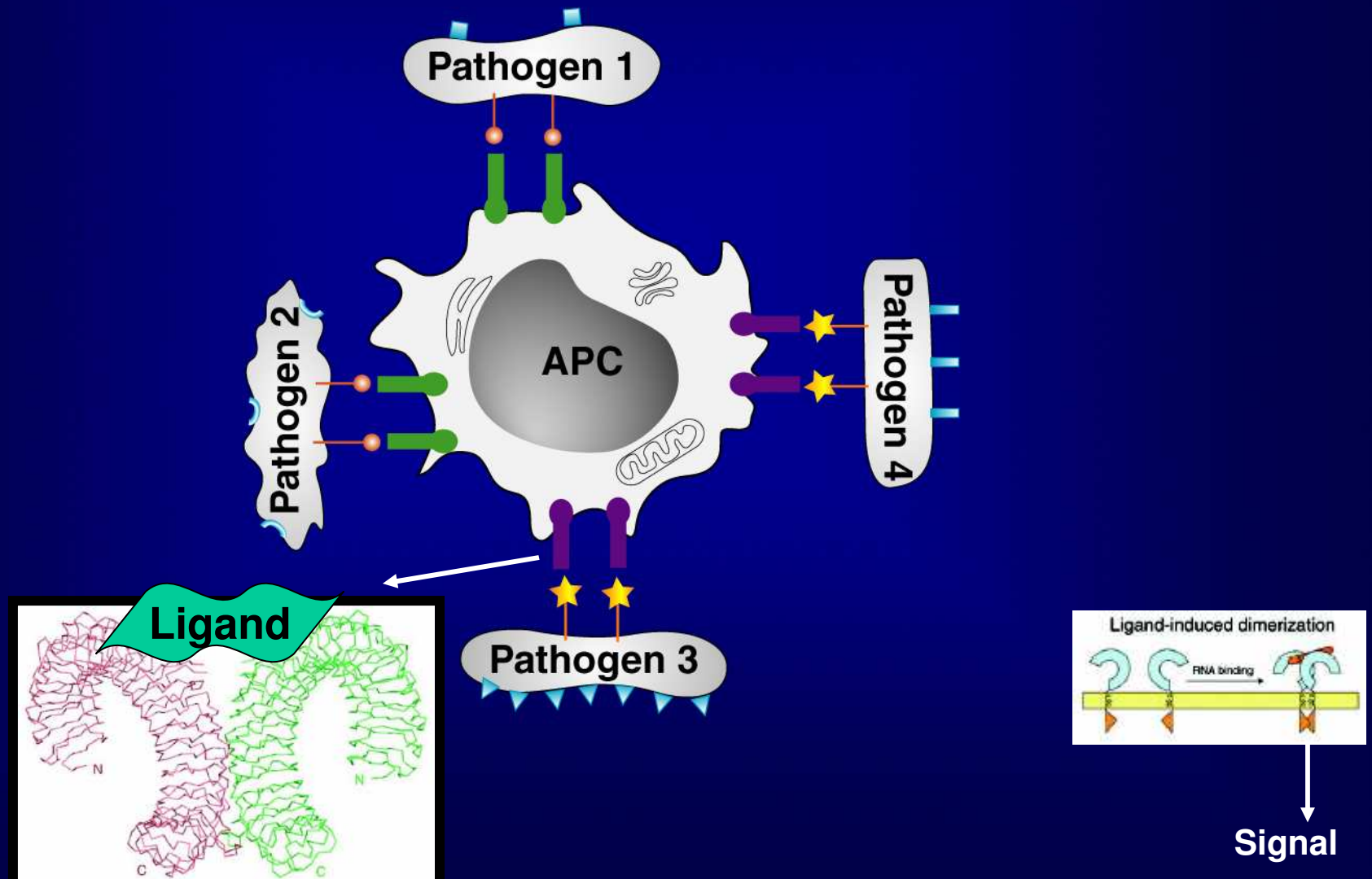
(granulocytes, macrophages, dendritic cells, natural killer cells)

- *controls pathogens*
- *primes acquired immunity*

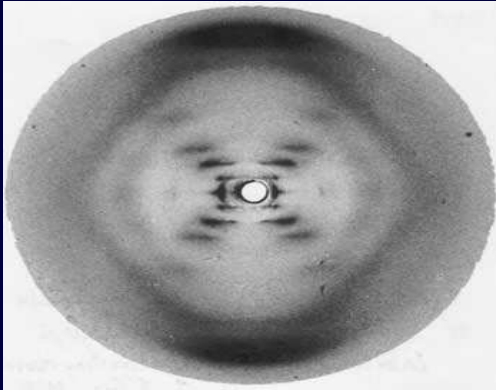
Pattern Recognition Receptors Primed by Pathogens



Pattern Recognition Receptors- Shared by Pathogens



X-ray Diffraction Crystal Structures



B form of DNA by Rosalind Franklin
in May 1952:

Allowing Watson & Crick to construct their
Nobel Prize-winning model for DNA.

Symmetry of crystals is revealed by the ordered and periodic arrangement
of atoms or groups of atoms in various space directions

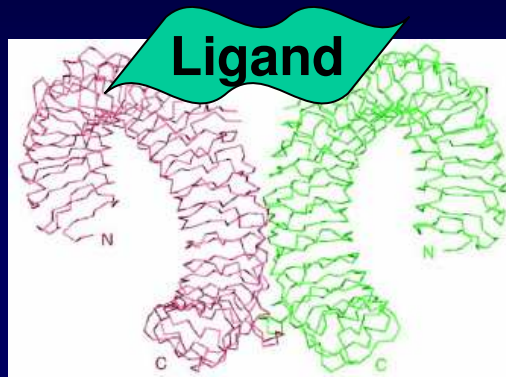
Repetition of motifs: periodic translation in two dimensions
Calculating the reciprocal lattice from a repeating pattern:

Each reciprocal lattice vector \mathbf{h} is an integer combination
of the three reciprocal basis vectors \mathbf{a}^* , \mathbf{b}^* and \mathbf{c}^* :

$$\mathbf{h} = h\mathbf{a}^* + k\mathbf{b}^* + l\mathbf{c}^*$$

where the triplet of integers (h, k, l) characterizes
uniquely each reciprocal lattice vector

Affinity of Binding of Ligands to Receptors



$$K_d = k_{\text{off}} / k_{\text{on}}$$

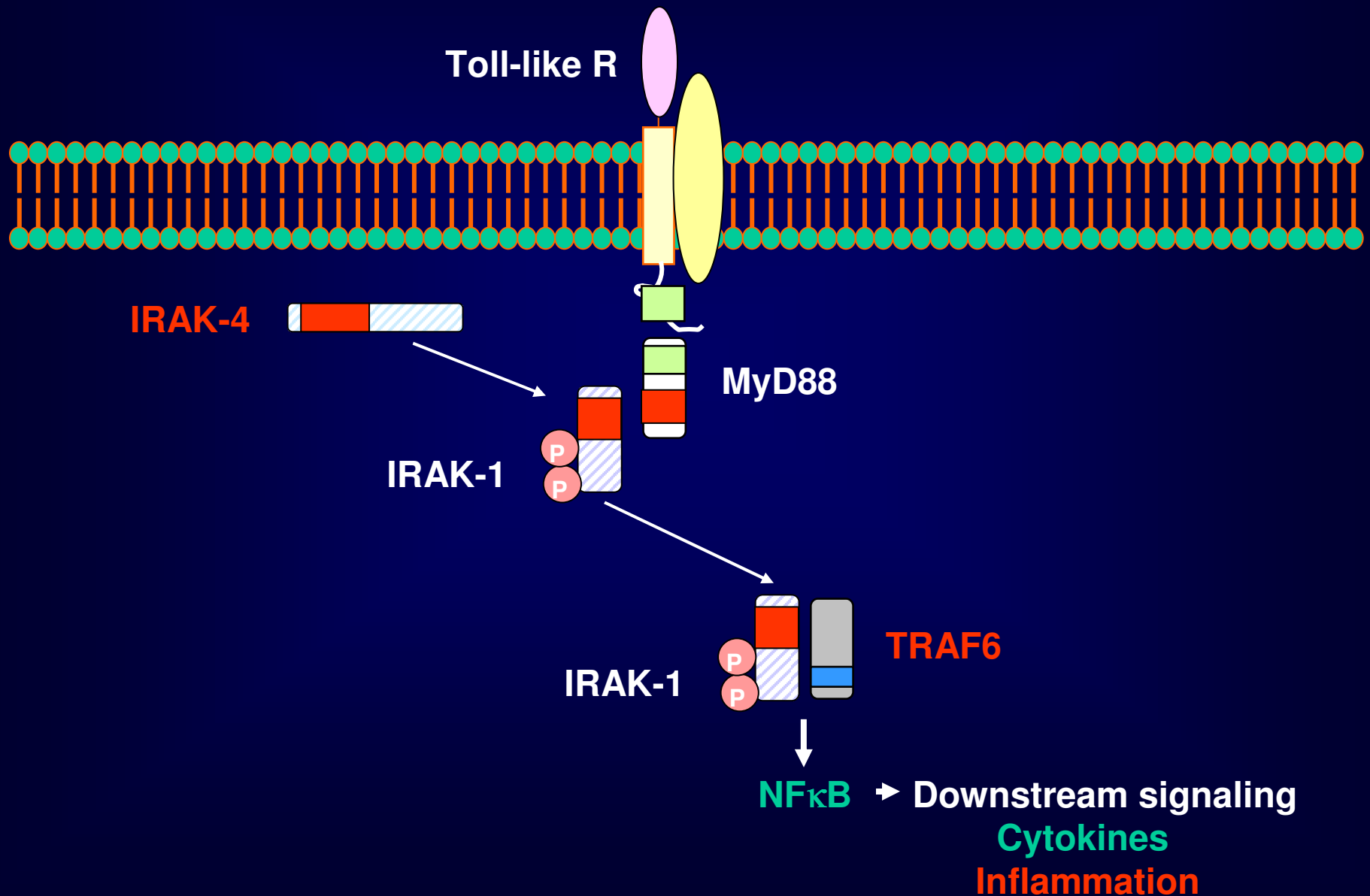
Affinity:

association rate constant k_{on} equal to $2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$

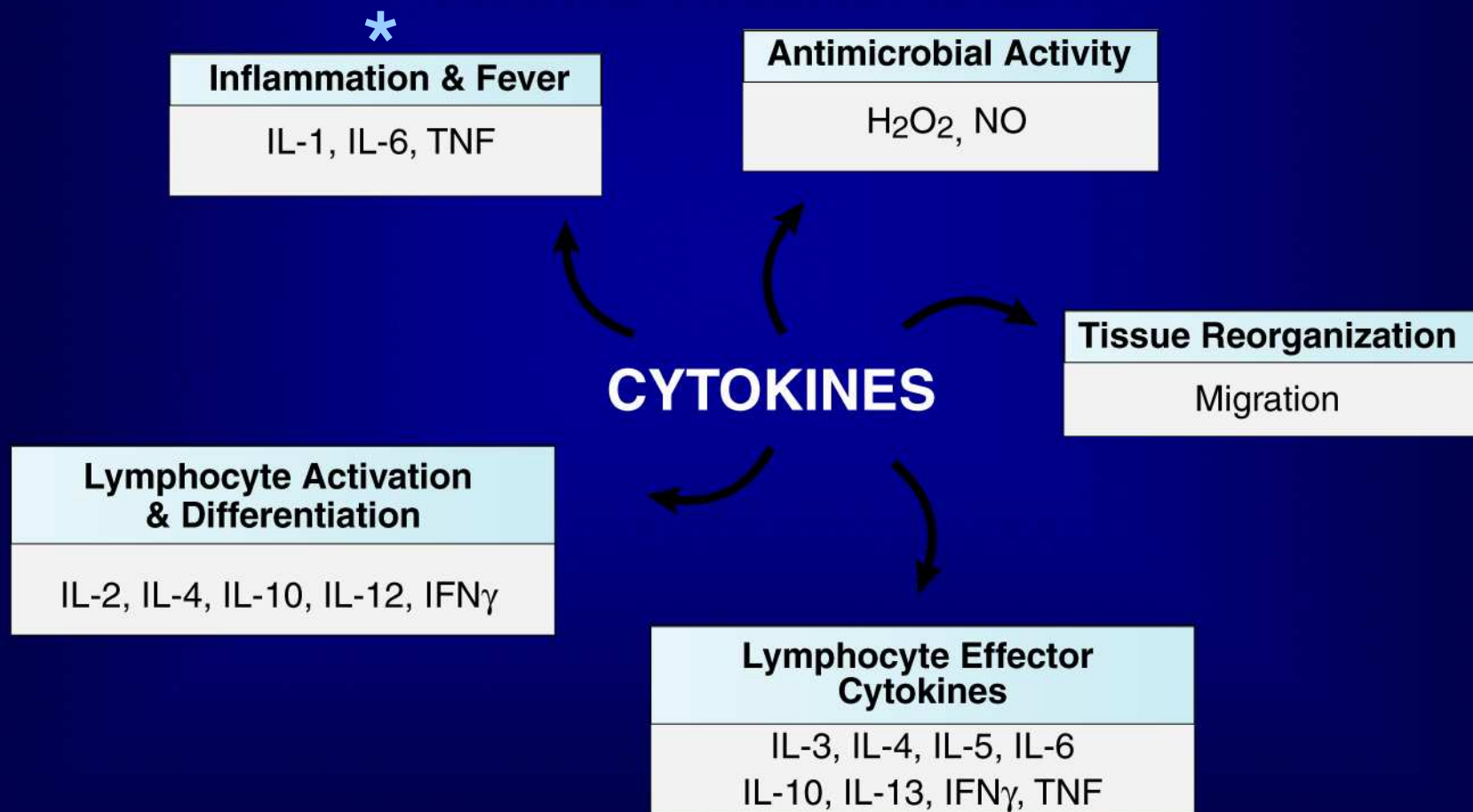
dissociation rate constant k_{off} equal to $10 \times 10^{-4} \text{ s}^{-1}$

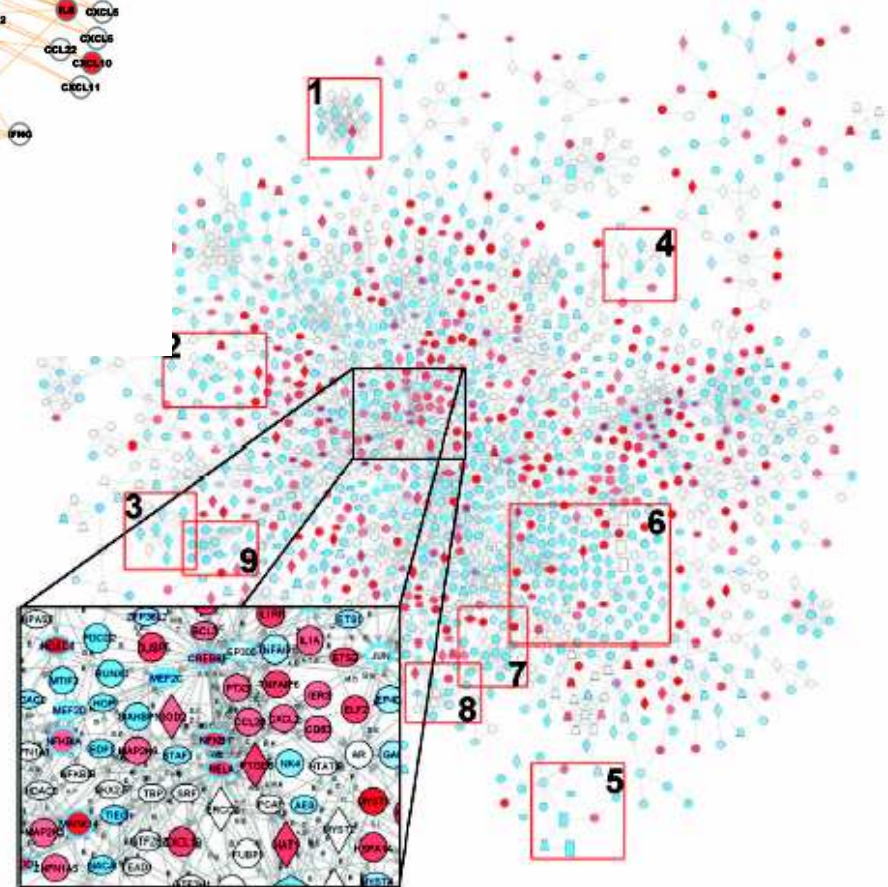
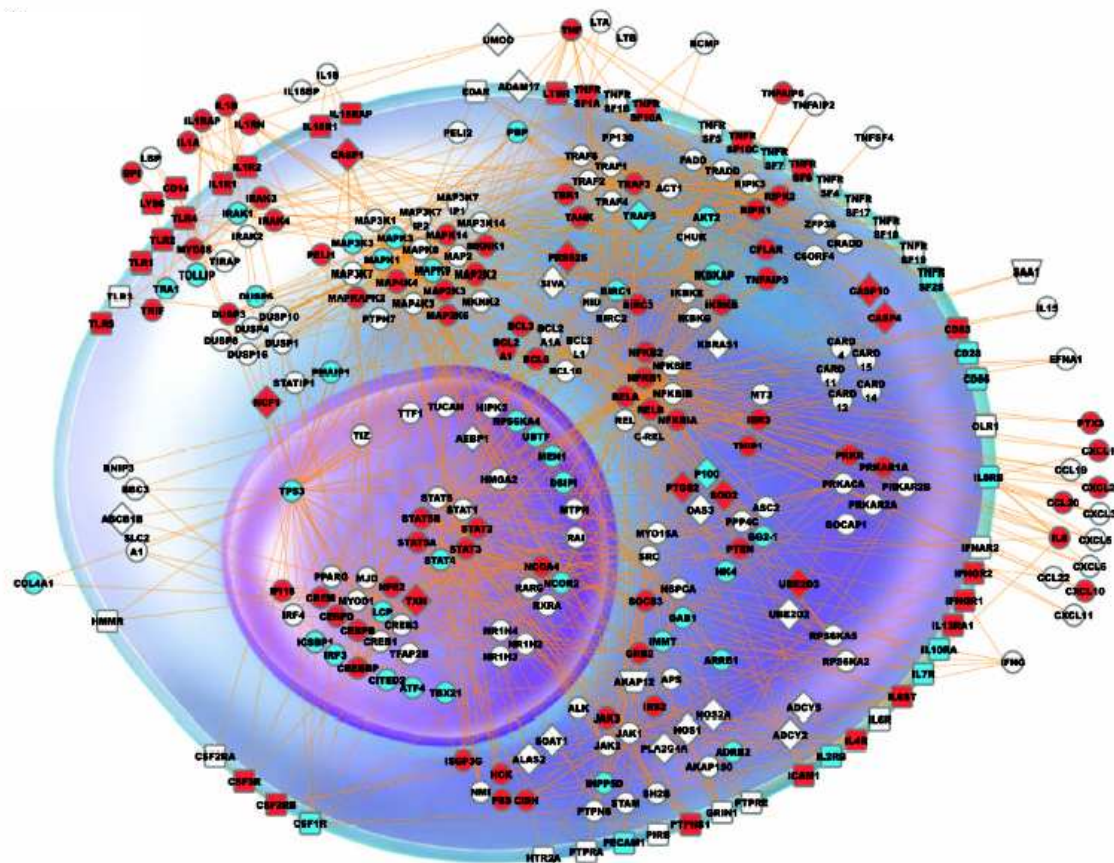
Estimate dissociation constant: $50 \times 10^{-9} \text{ M}$

Toll-like Receptors Activate Inflammatory Responses



Cytokine Effector Functions

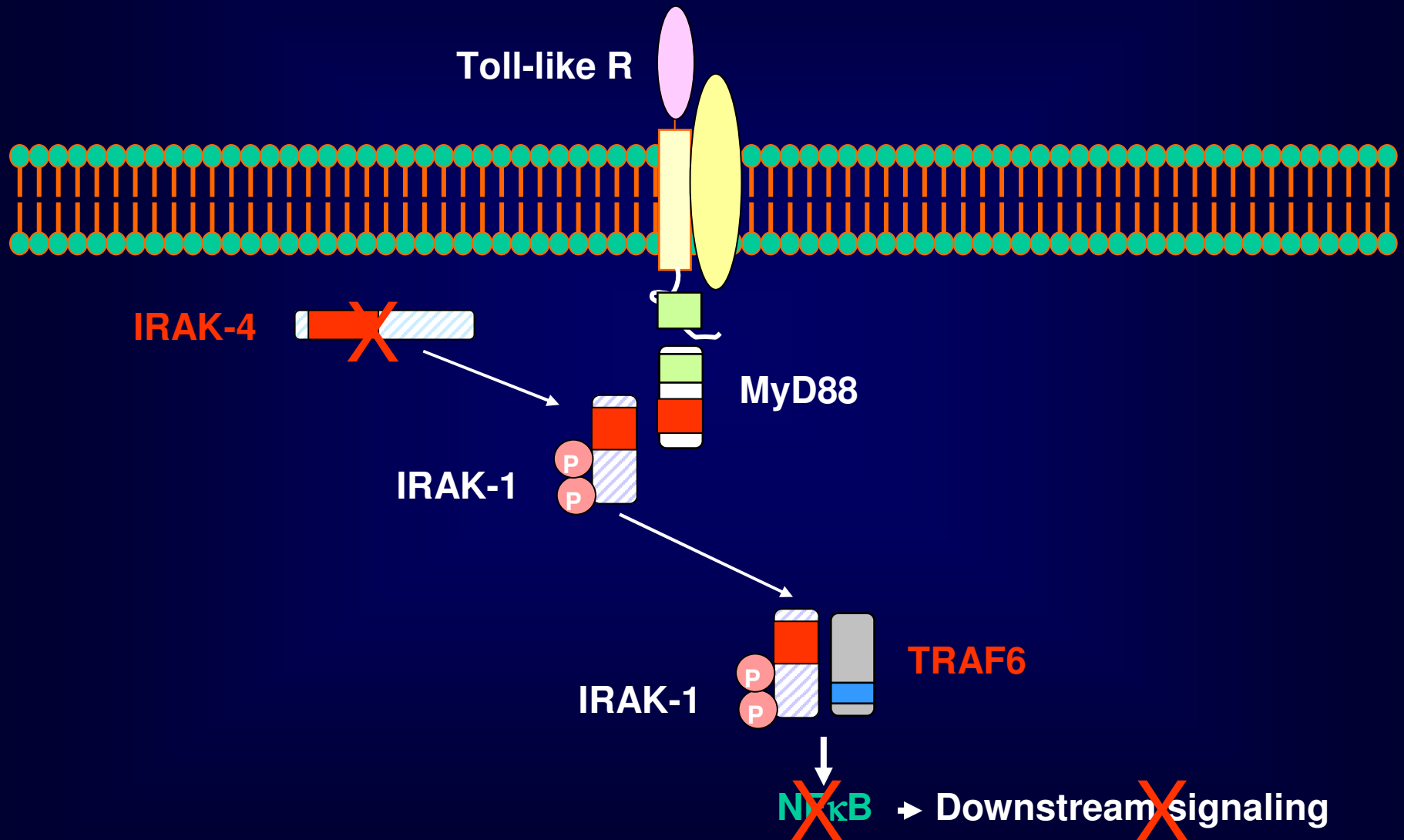




$$\text{Score} = -\log_{10} \left(1 - \sum_{i=0}^{f-1} \frac{C(G, i) C(N - G, s - i)}{C(N, s)} \right)$$

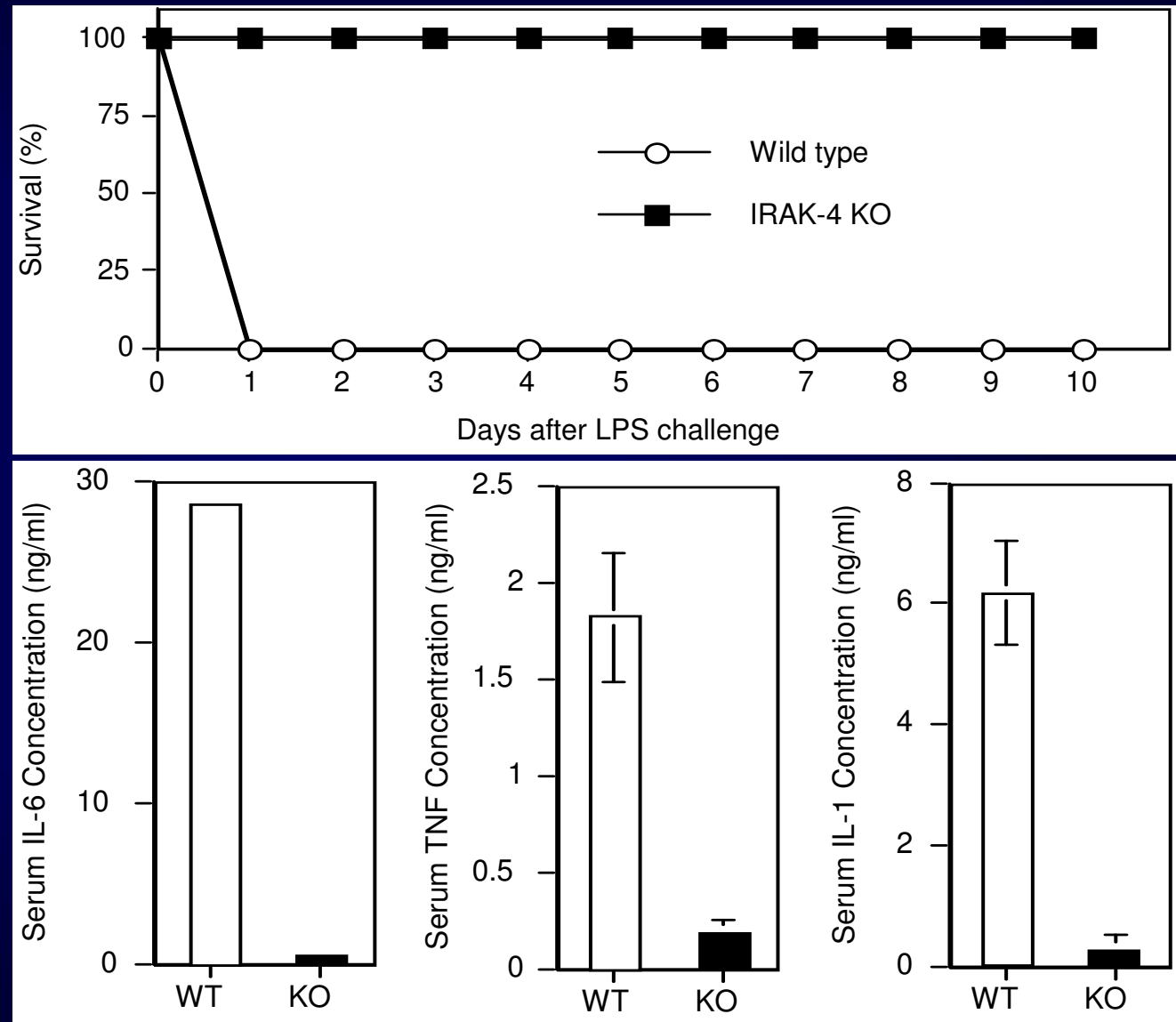
N = number of genes in network
 G = focus genes for pathway of s genes
 C(n,k) =binomial coefficient

IRAK4: Critical for Inflammatory Responses



IRAK4^{-/-} Mice are resistant to LPS Challenge

This kinase is a critical regulator of inflammatory cytokines

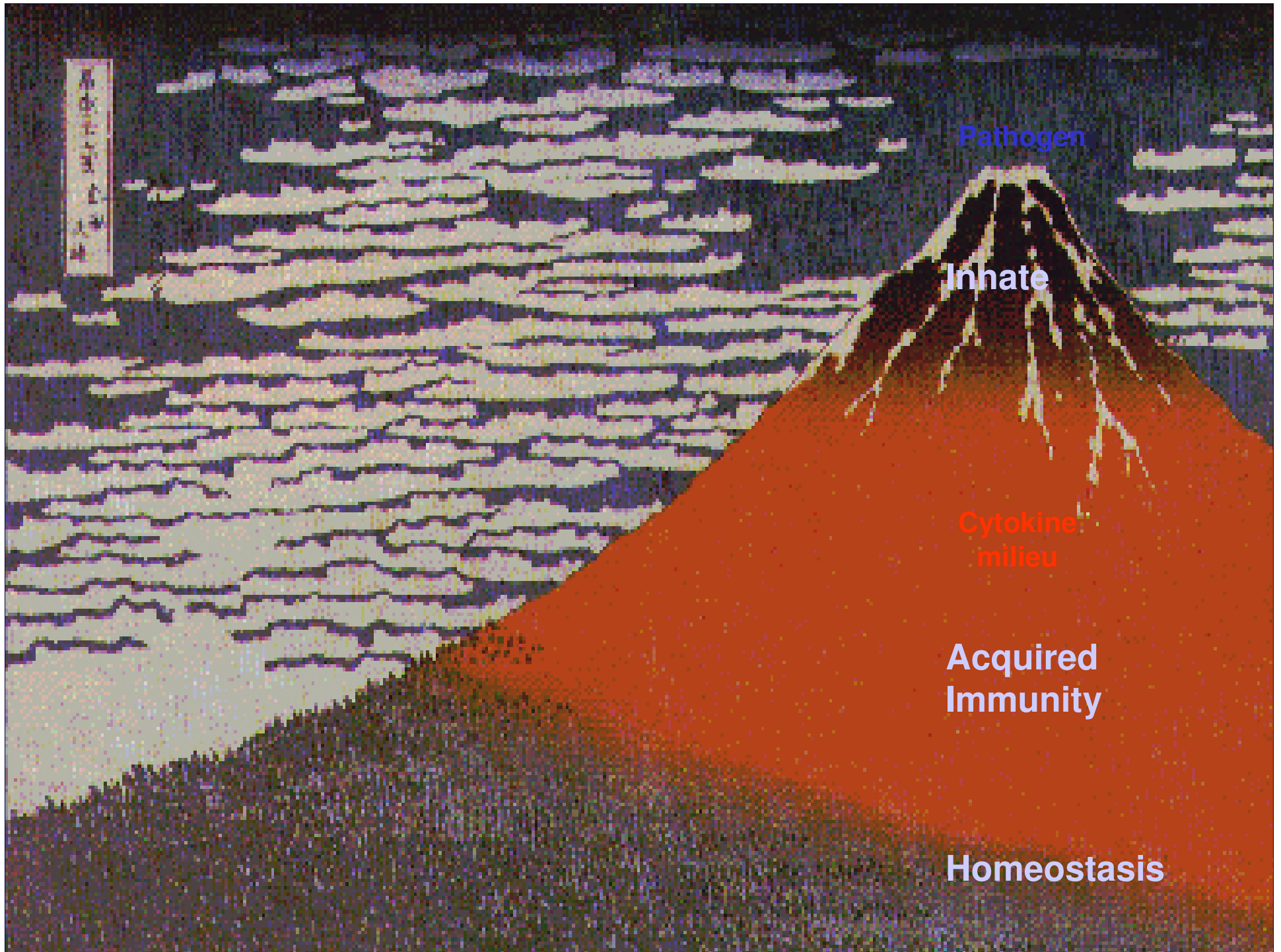


Suzuki et al *Nature* 416 750 (2002)



“Order from Disorder Sprung”

- 1) *innate immunity - sentinel*
- 2) *acquired immunity - battle*
- 3) *Homeostasis - restoration*



Pathogen

Innate

Cytokine
milieu

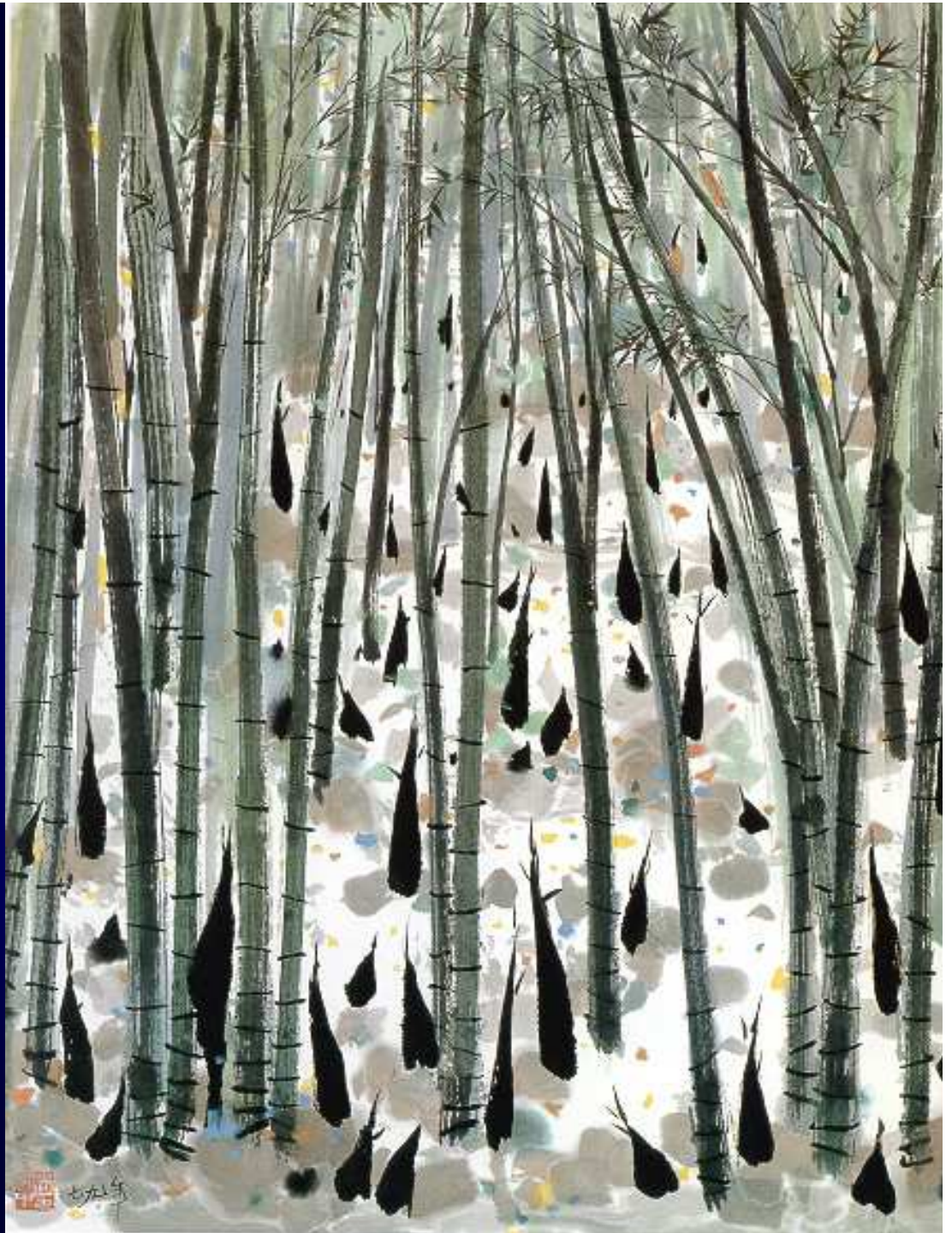
Acquired
Immunity

Homeostasis

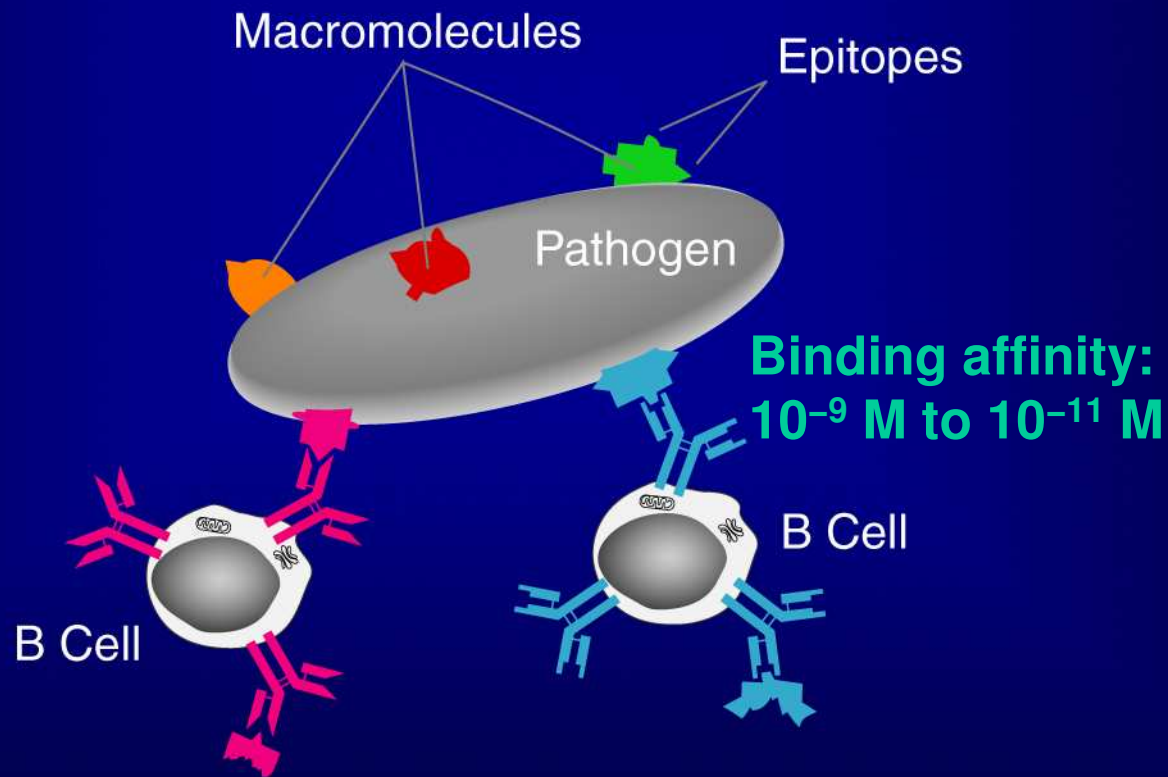
Acquired Immunity

(T & B lymphocytes)

- *specificities acquired*
- *immune tolerance to self*
- *eliminates pathogens*
- *recognition*
- *specific clonal selection*
- *expansion, effectors*
- *deactivate, homeostasis*



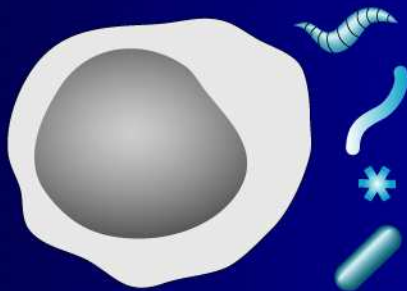
B Cell Antibody Responses Require T Cell Activation



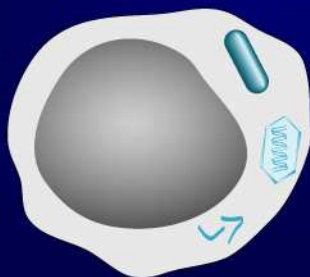
T Cell Antigen Receptors Control Specificities

TYPE OF PATHOGEN

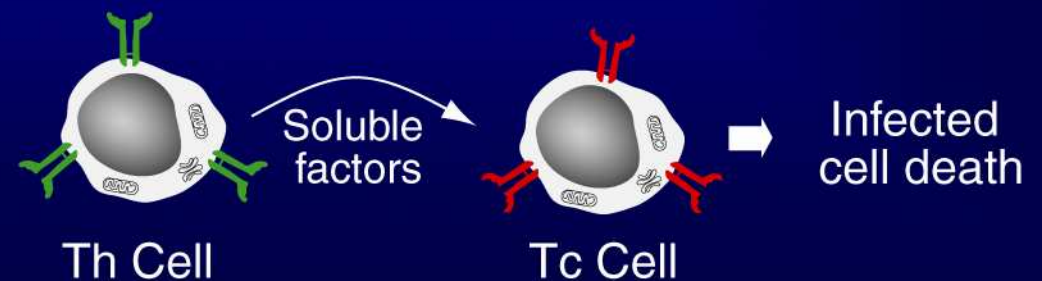
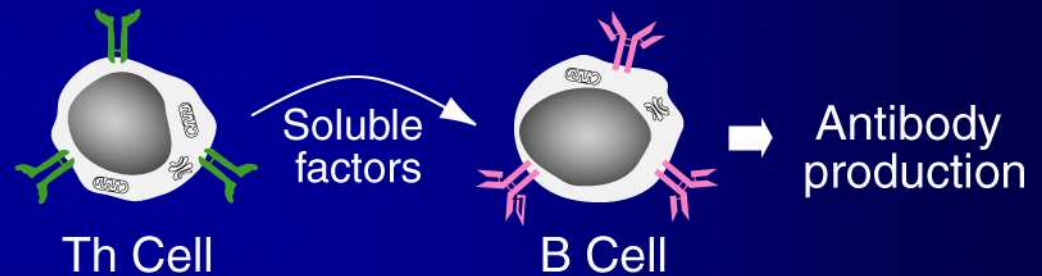
*Extracellular
pathogens*



*Intracellular
pathogens*



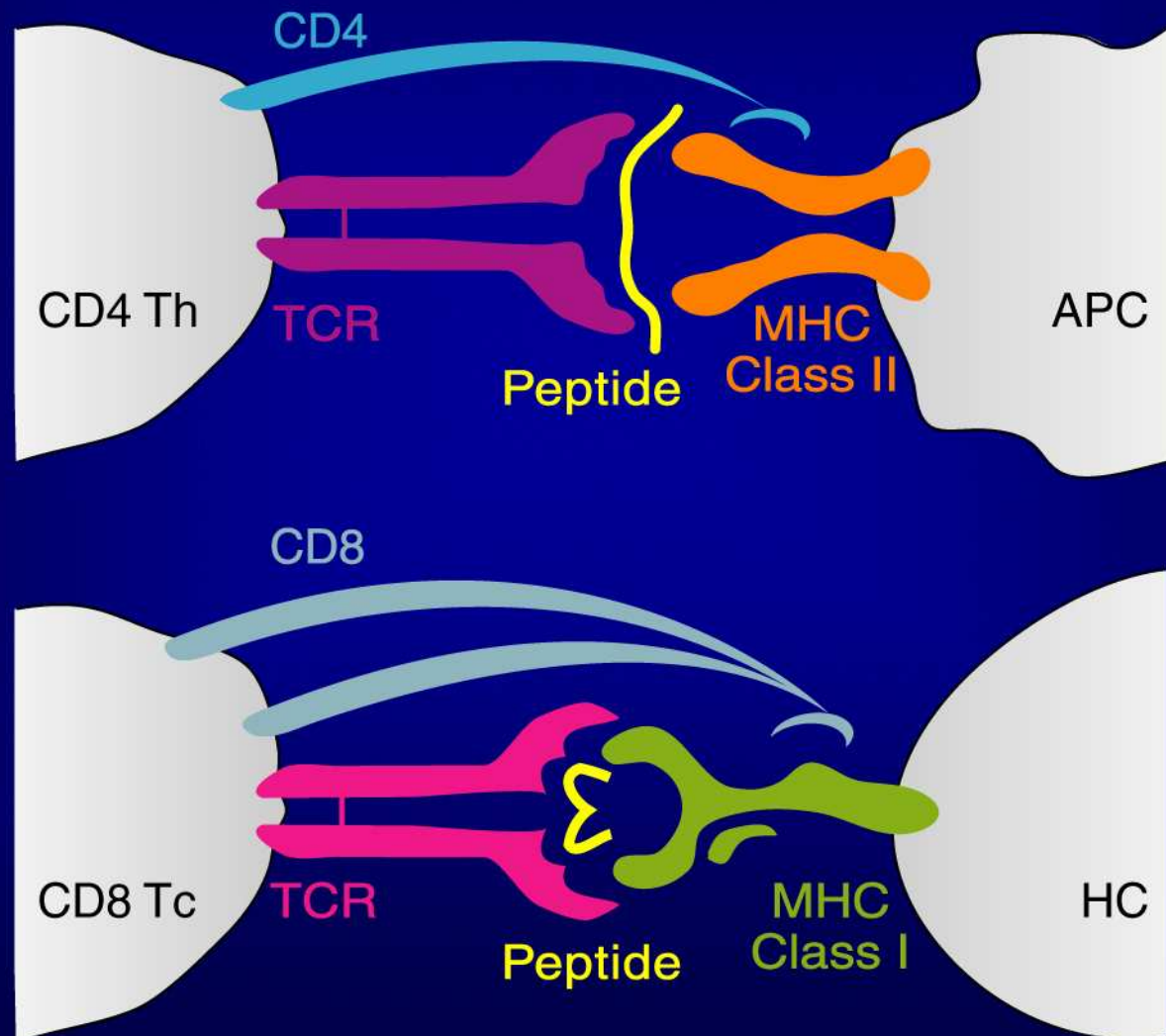
RESPONDING LYMPHOCYTES



Looking for the T Cell Receptor in Japan



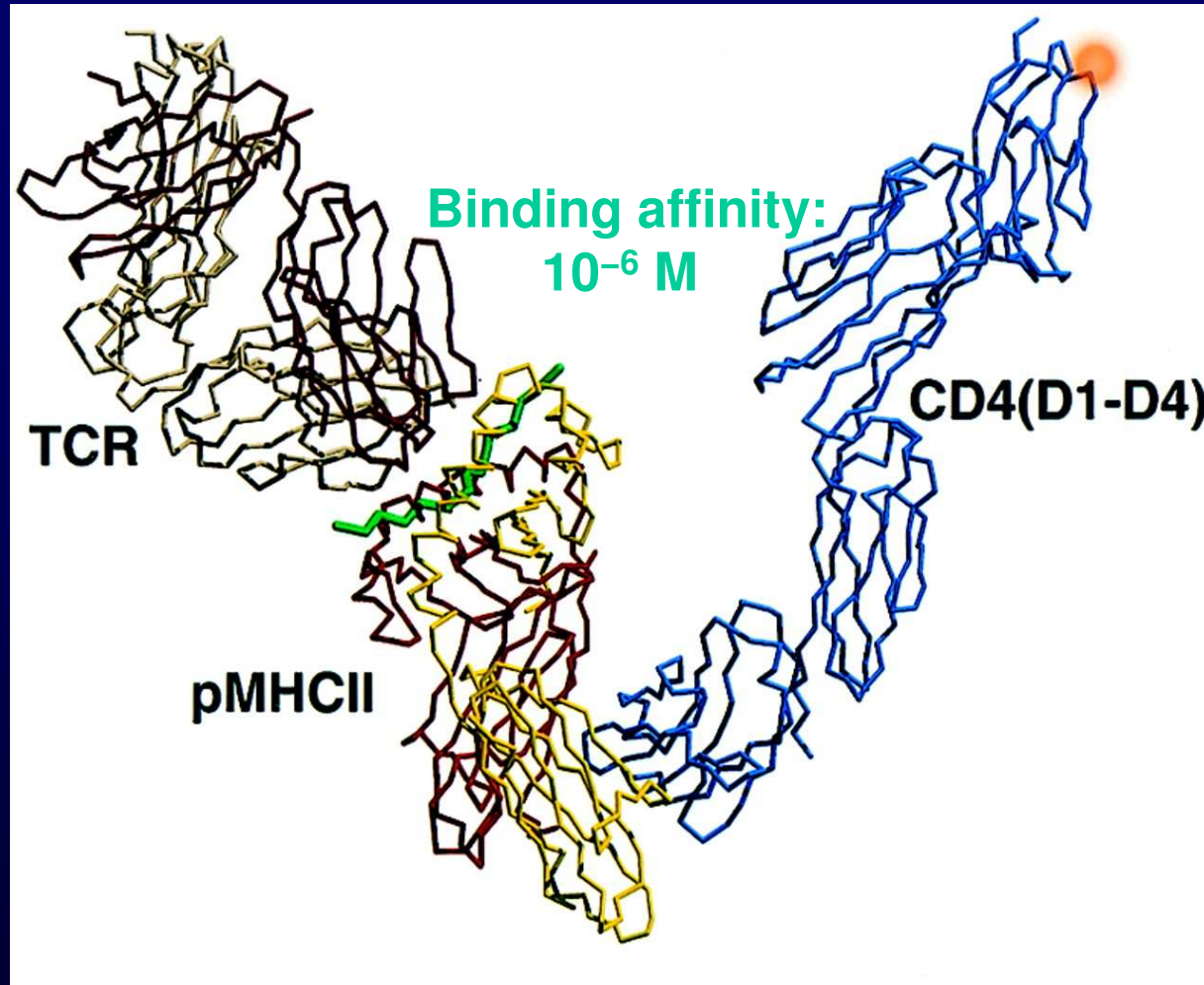
T Cell Receptors Recognize Peptides + MHC I or II



Yanagi, 1984
Hedricks 1984

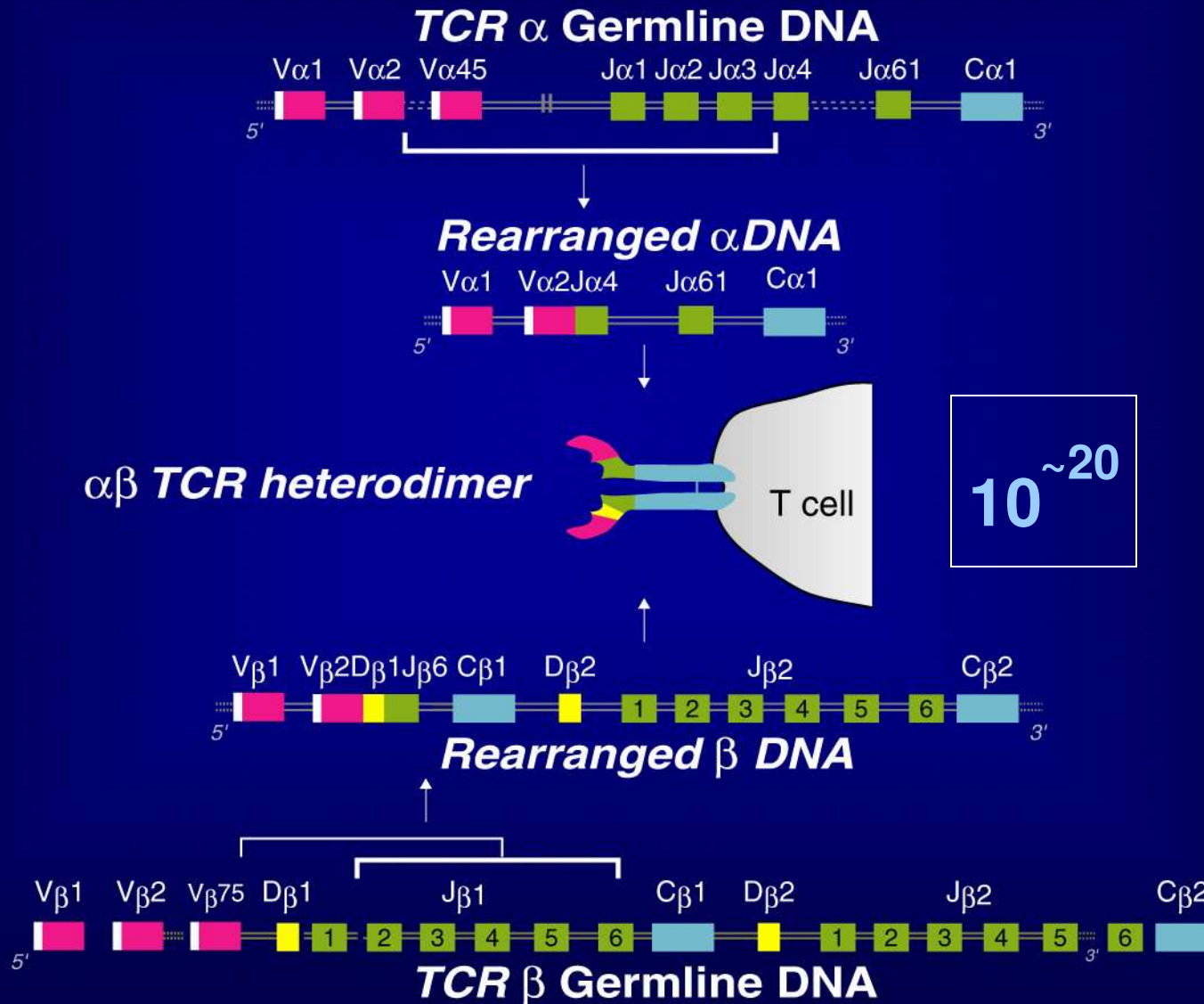
Zinkernagel &
Doherty 1974

Binding of a TCR to peptide-MHC Complex



(Wang et al. PNAS 2001)

TCR Diversity Through Somatic Rearrangements

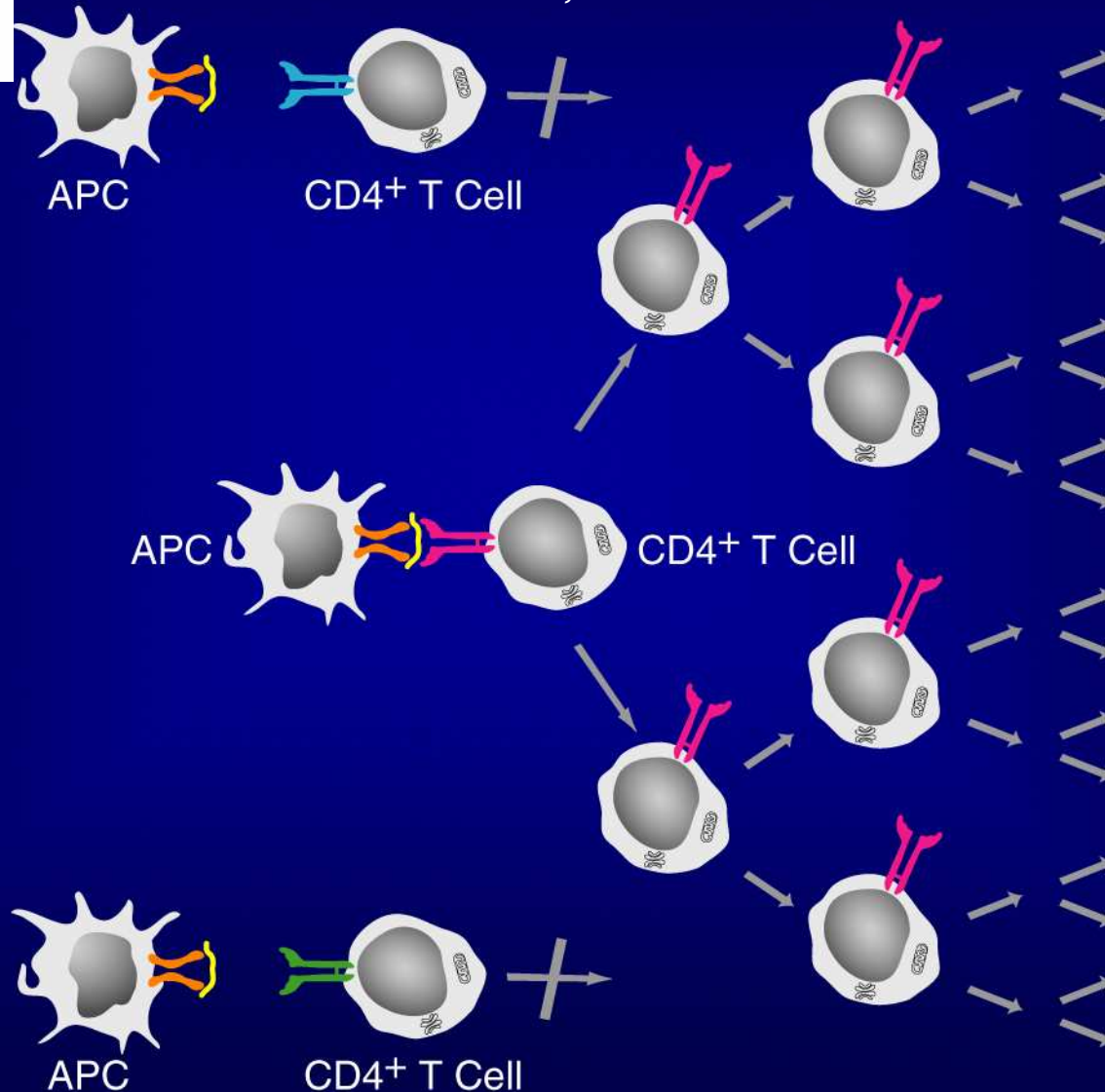


$$S_i = \frac{\left(\frac{YE_i}{A_i}\right)}{1 + \left(\frac{YE_i}{A_i}\right)}$$

level of stimulation (S_i)
 avidity for Ag (A_i)
 efficiencies ($E_A - E_C$)

Callan, 2002

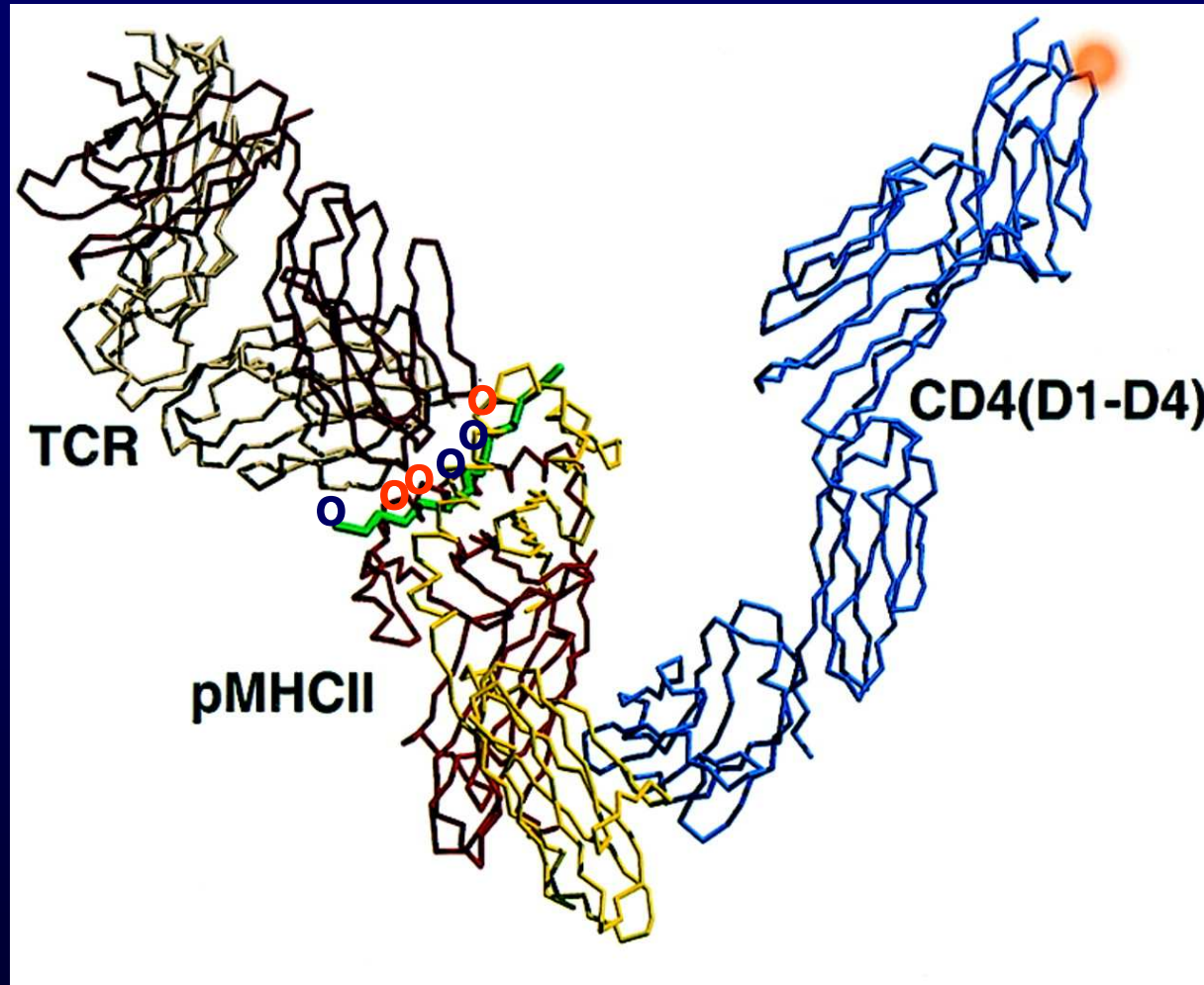
CLONAL SELECTION



CLONAL EXPANSION

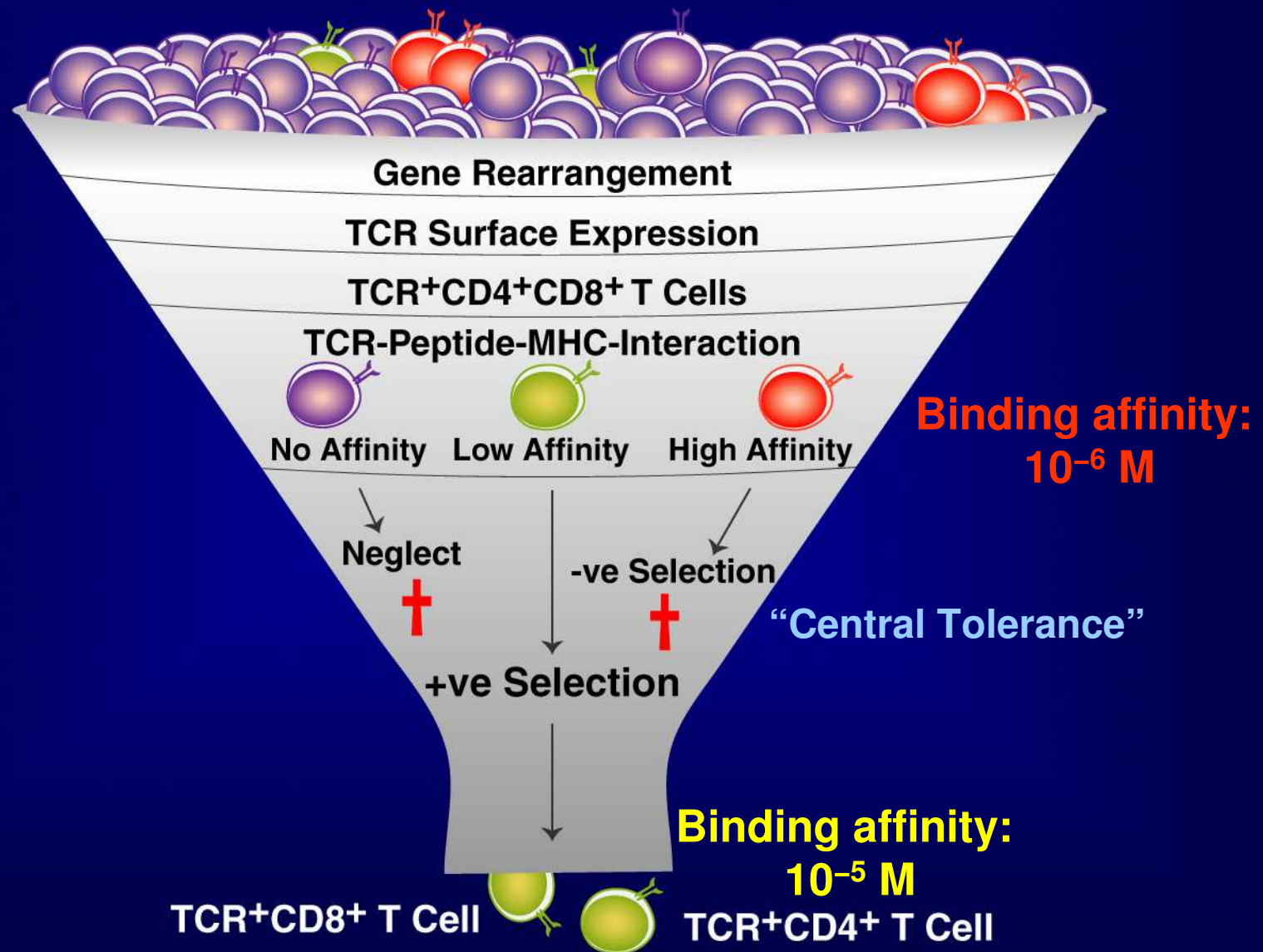
Sir Frank Macfarlane Burnet , 1950

Binding of a TCR to peptide-MHC Complex

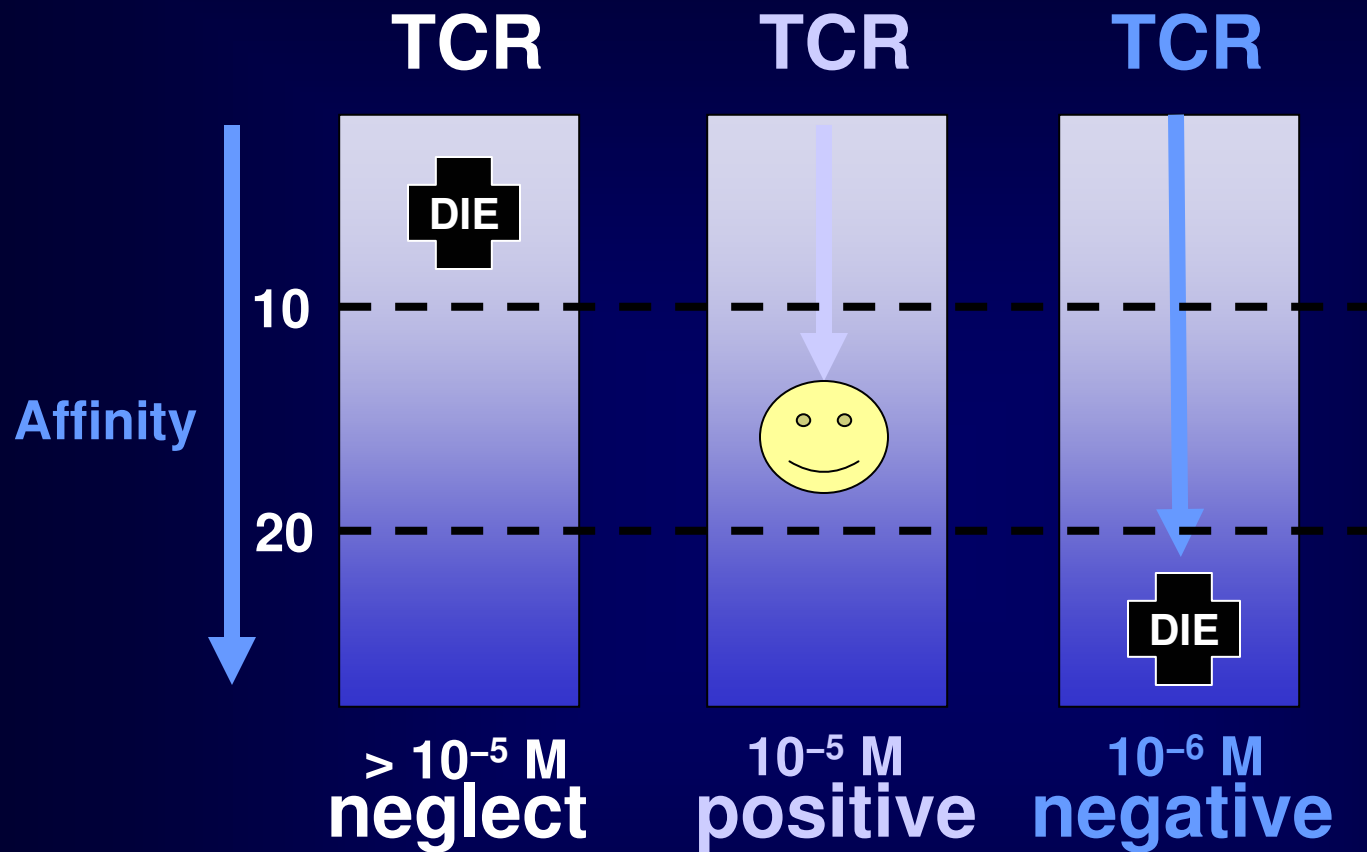


(Wang et al. PNAS 2001)

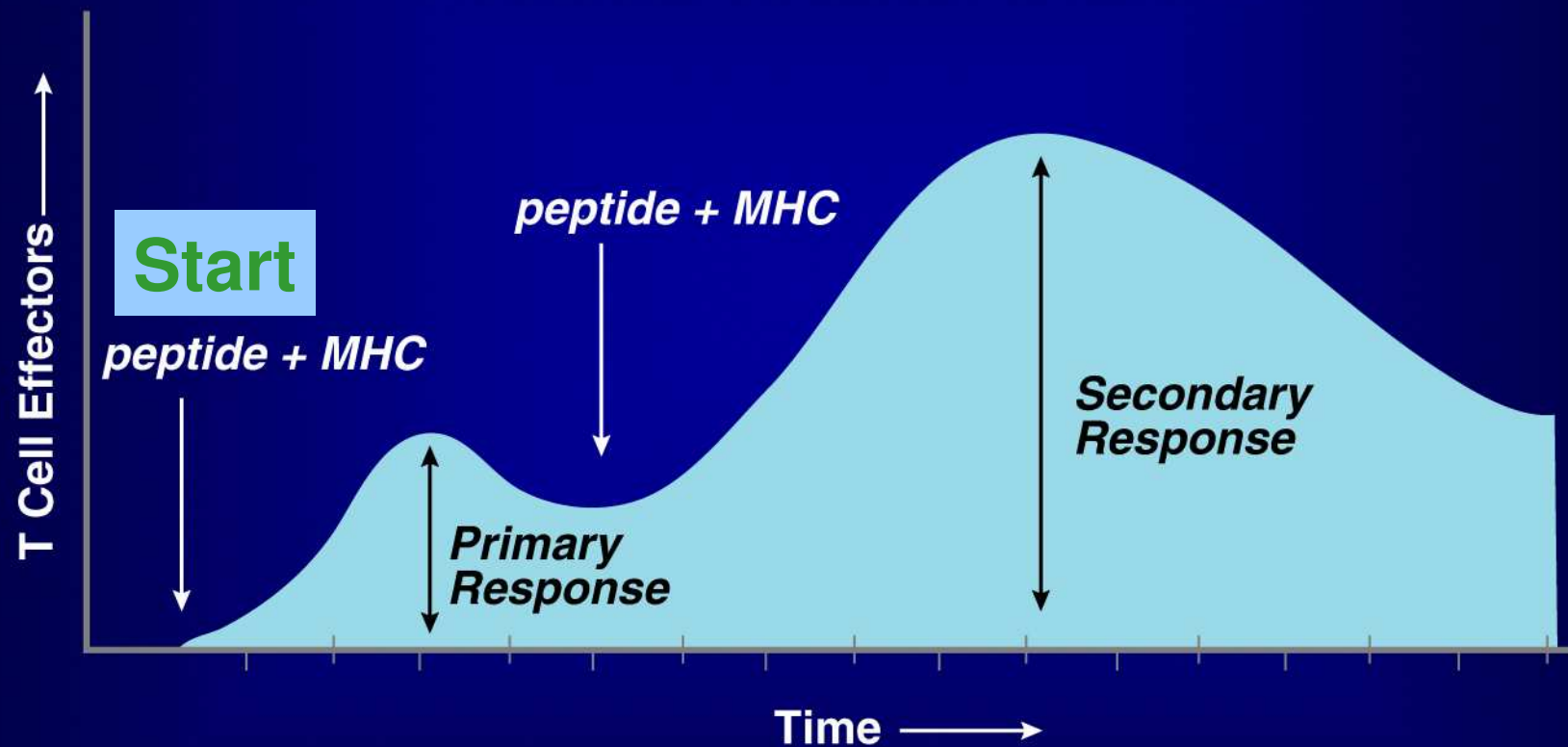
Thymic Selection Based on TCR Affinity to peptide-MHC



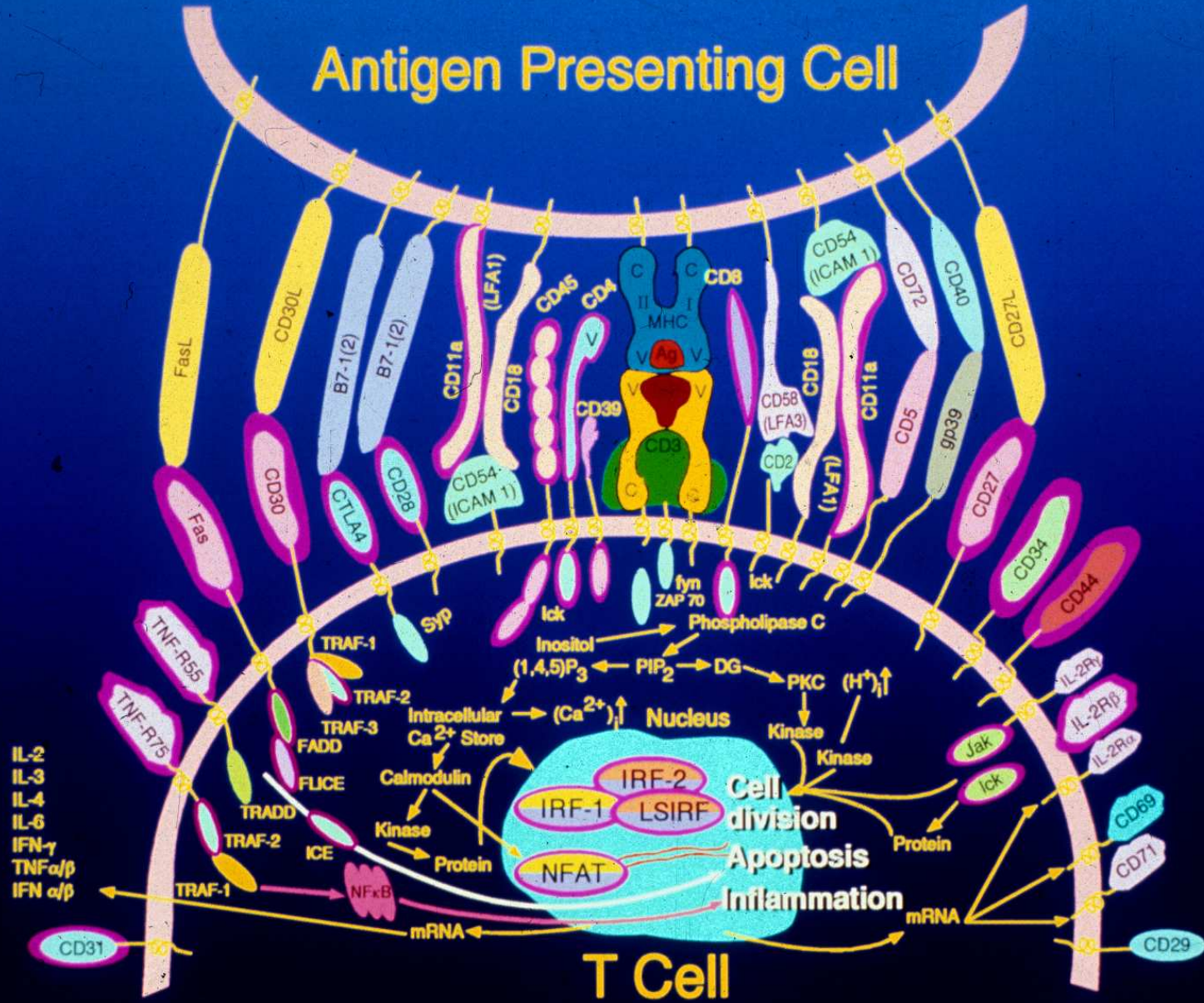
Threshold Model of Signal Strength

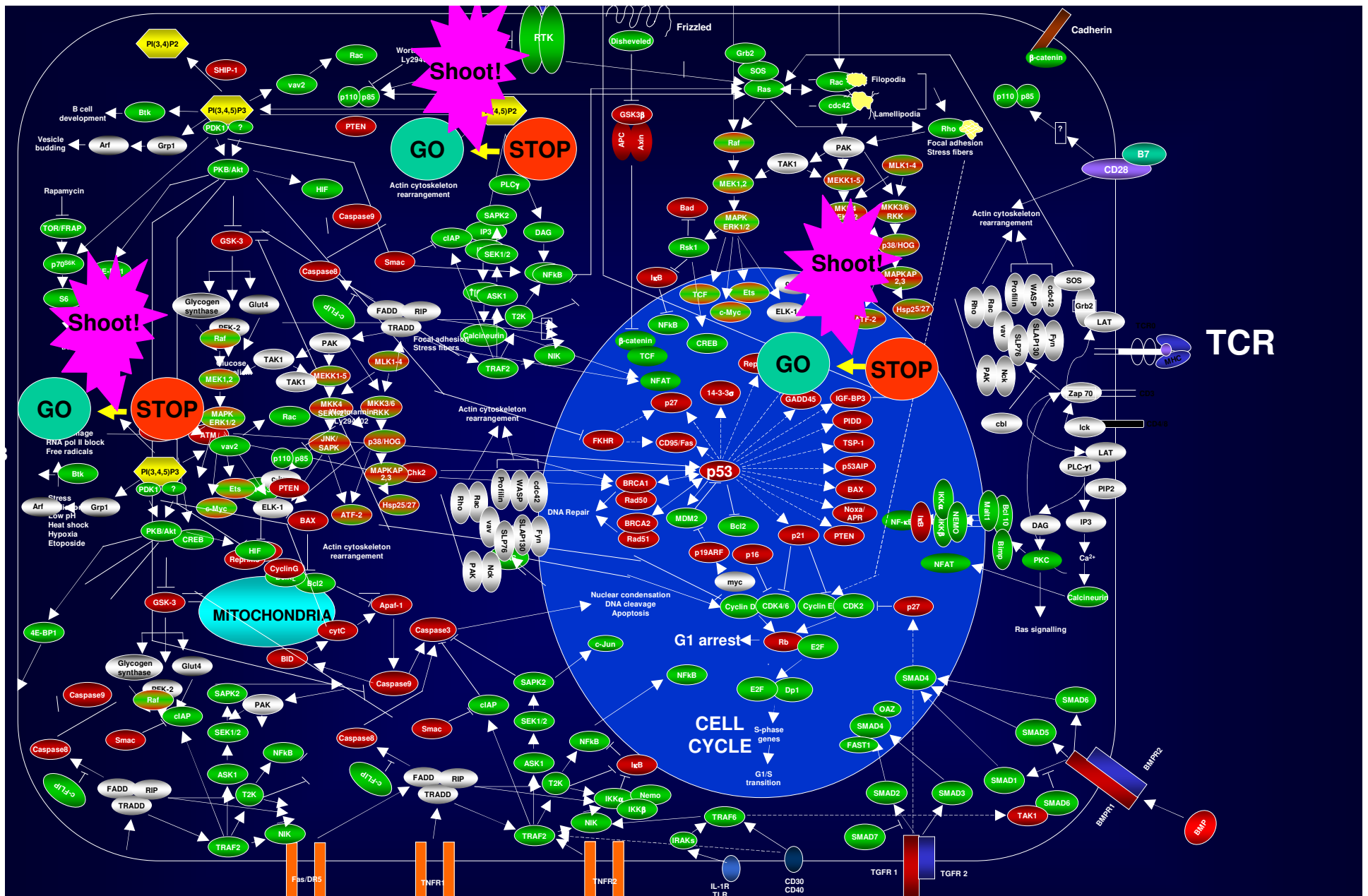


T Cells Response Profile to peptide-MHC



T cell and Antigen Presenting Cell

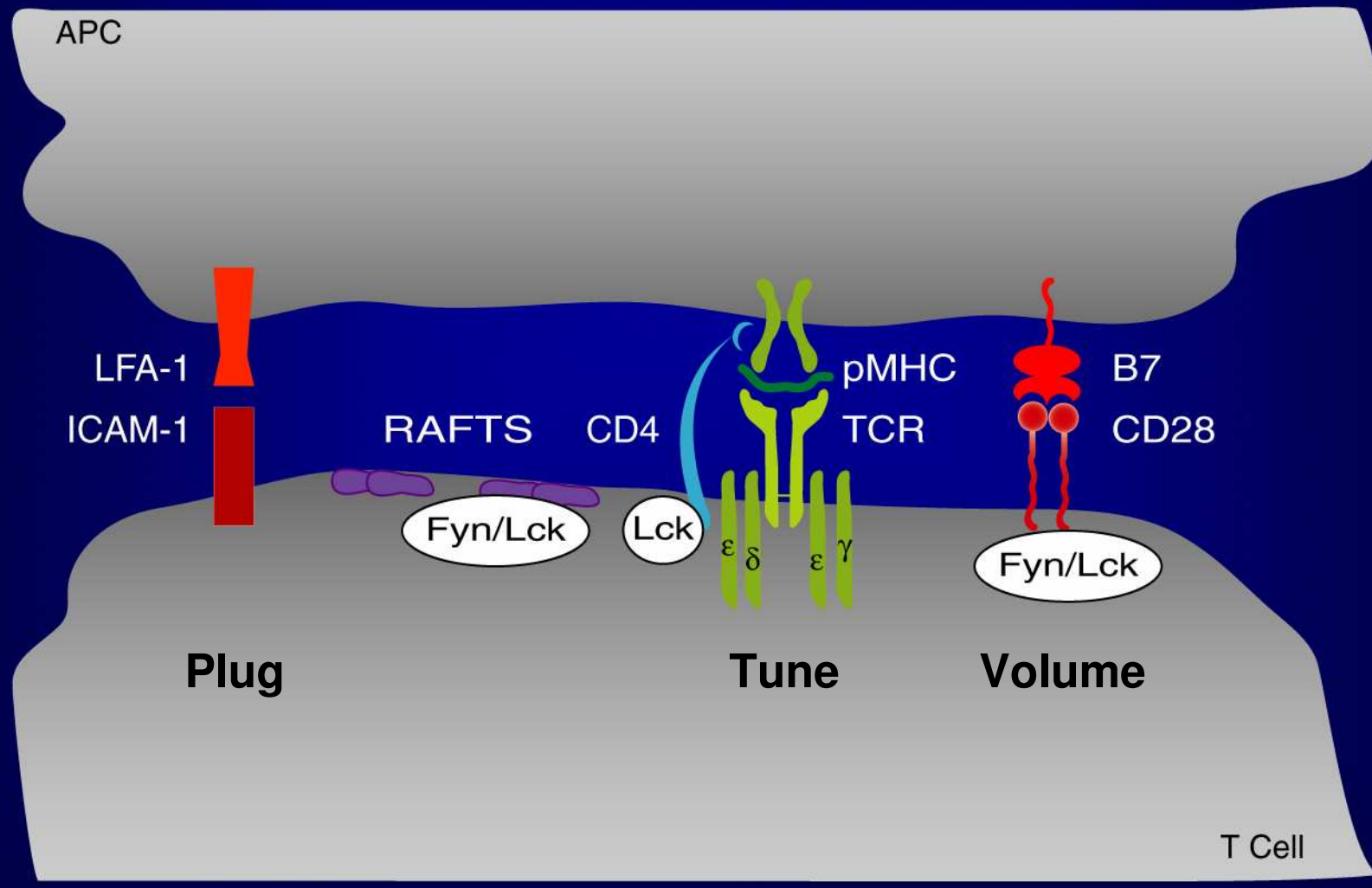




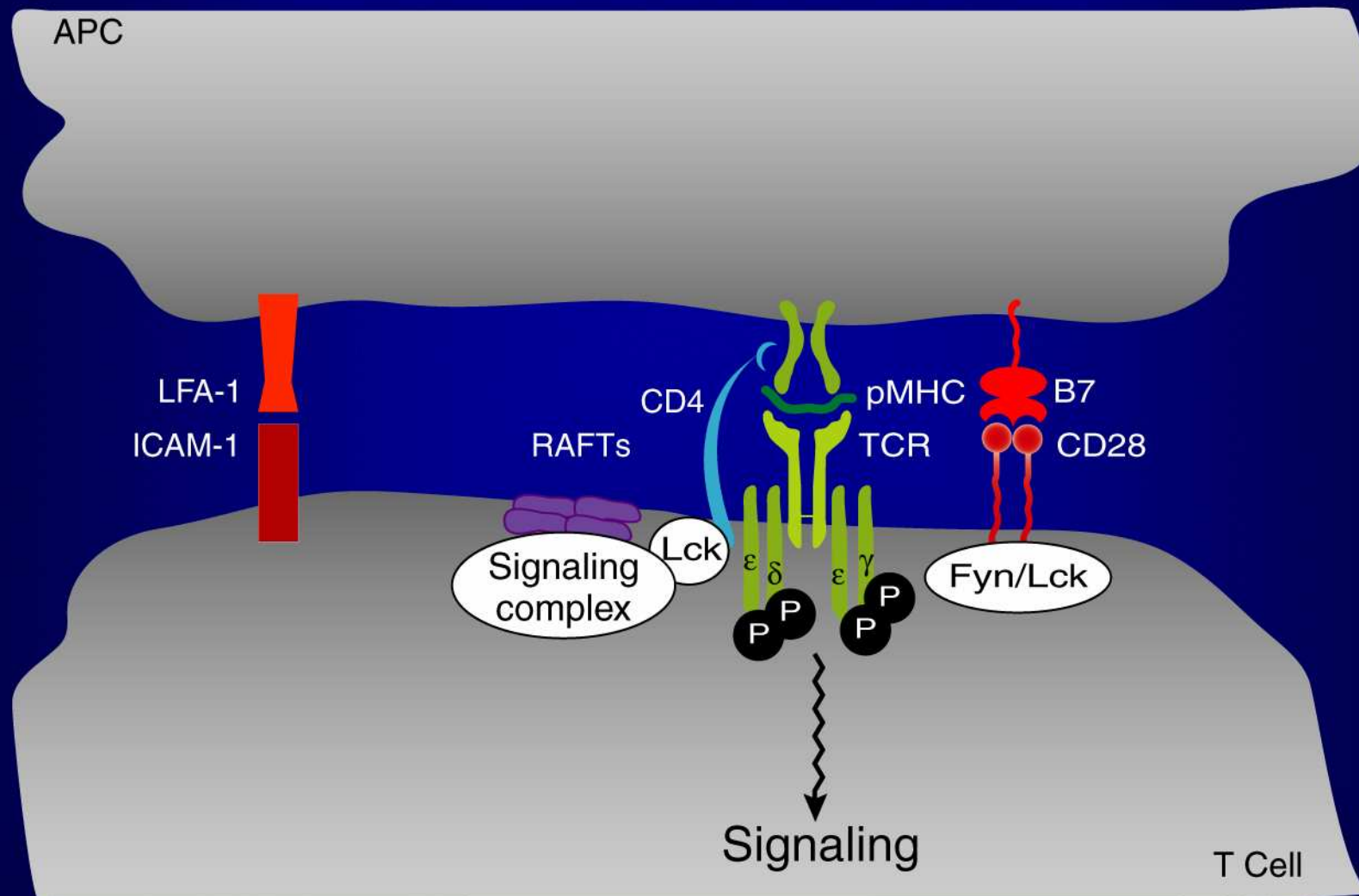
$$P(X_1, \dots, X_n) = \prod_i P(X_i | Pa_i)$$

variable X_i
probability distribution(Pa_i)

Self-assembly of the TCR Signaling Complex

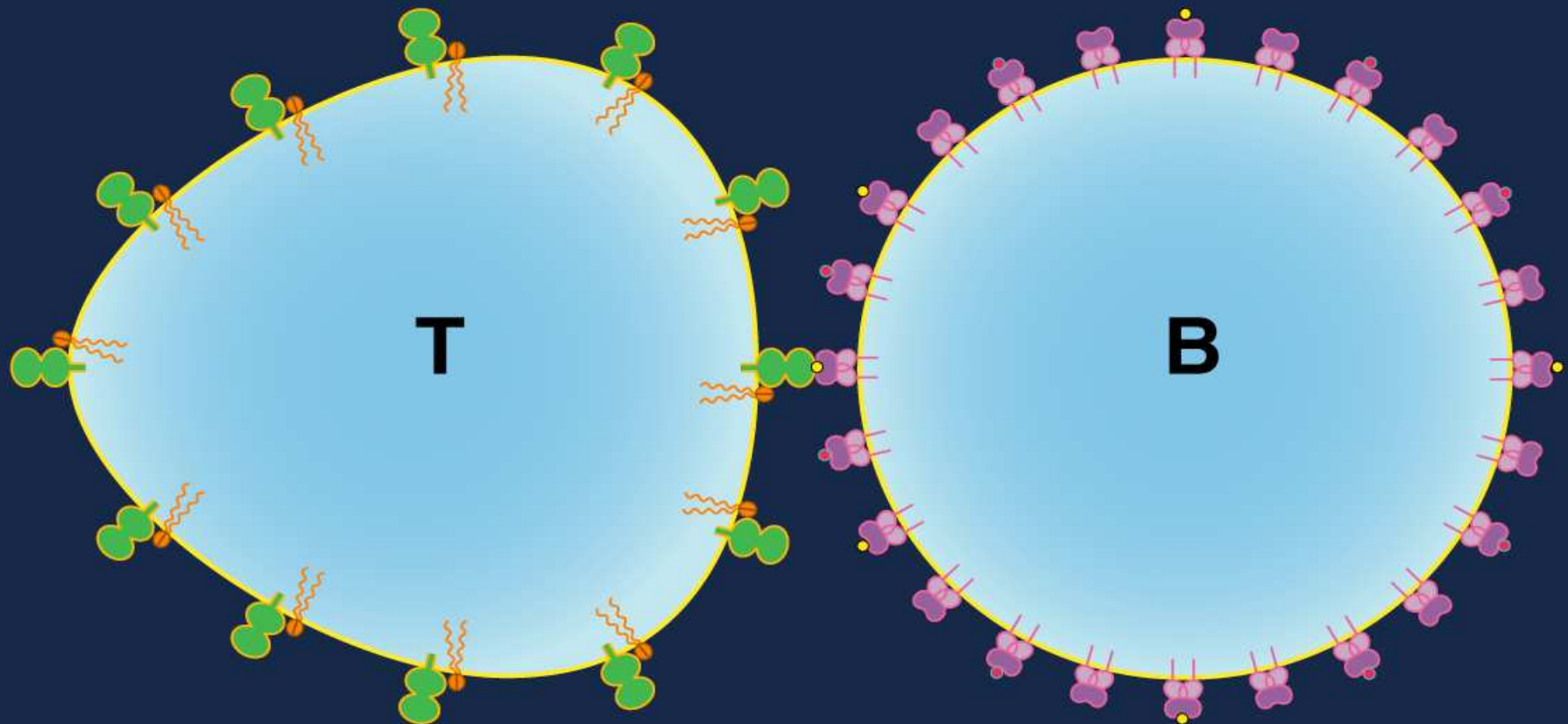


Aggregation of Signaling Complexes Activates TCR

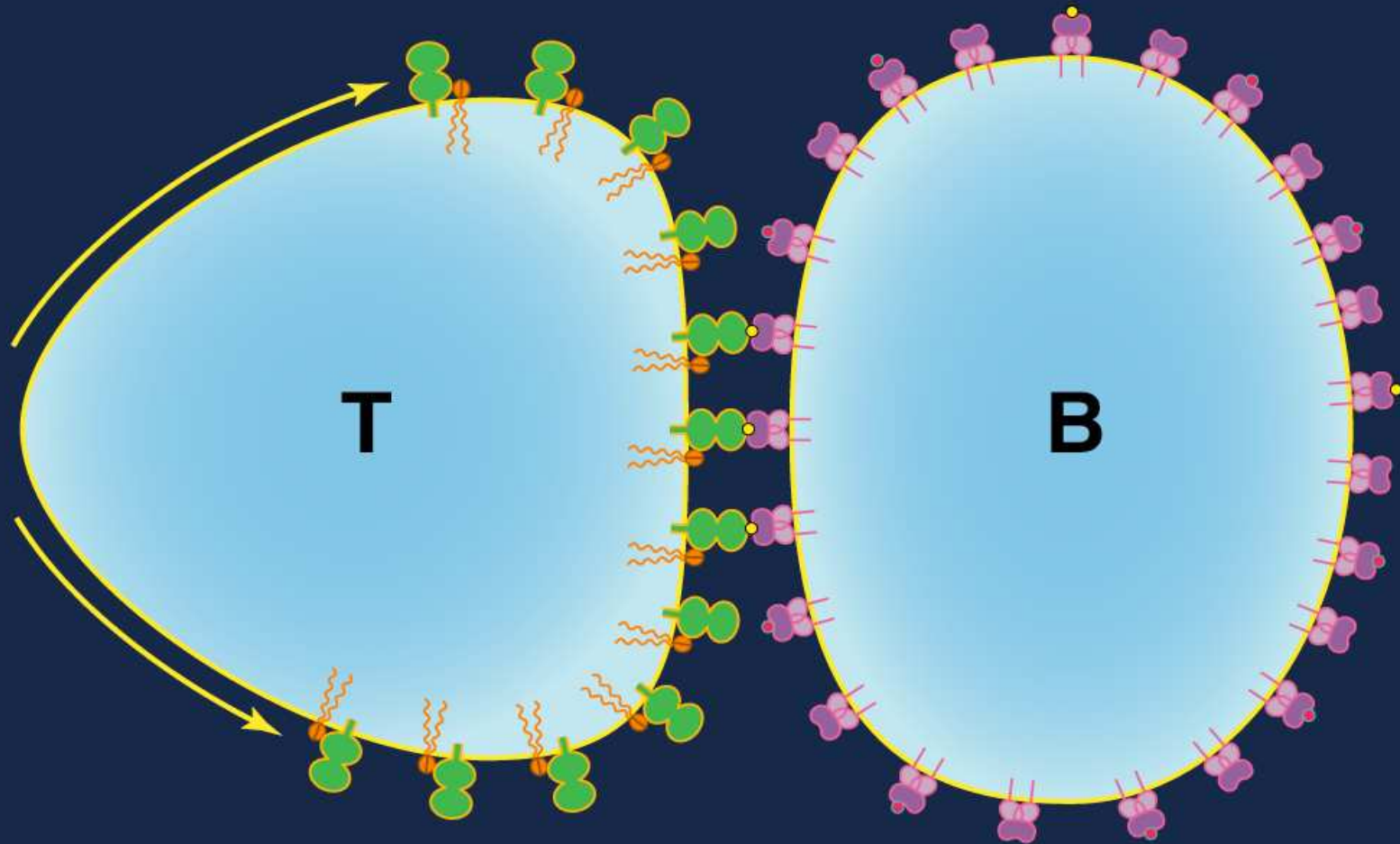


Synapse Formation of TCR

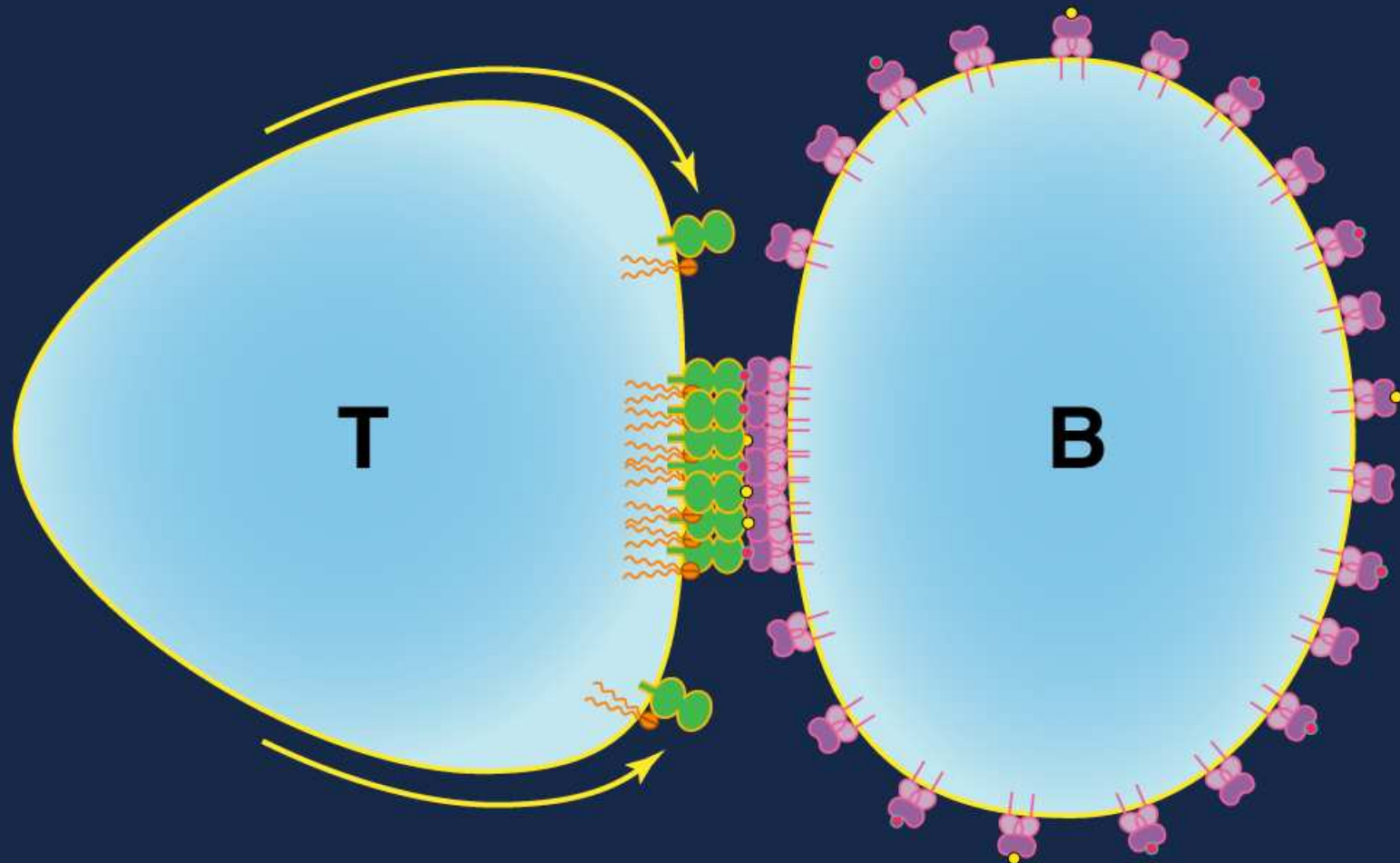
1) TCR Contacts p-MHC



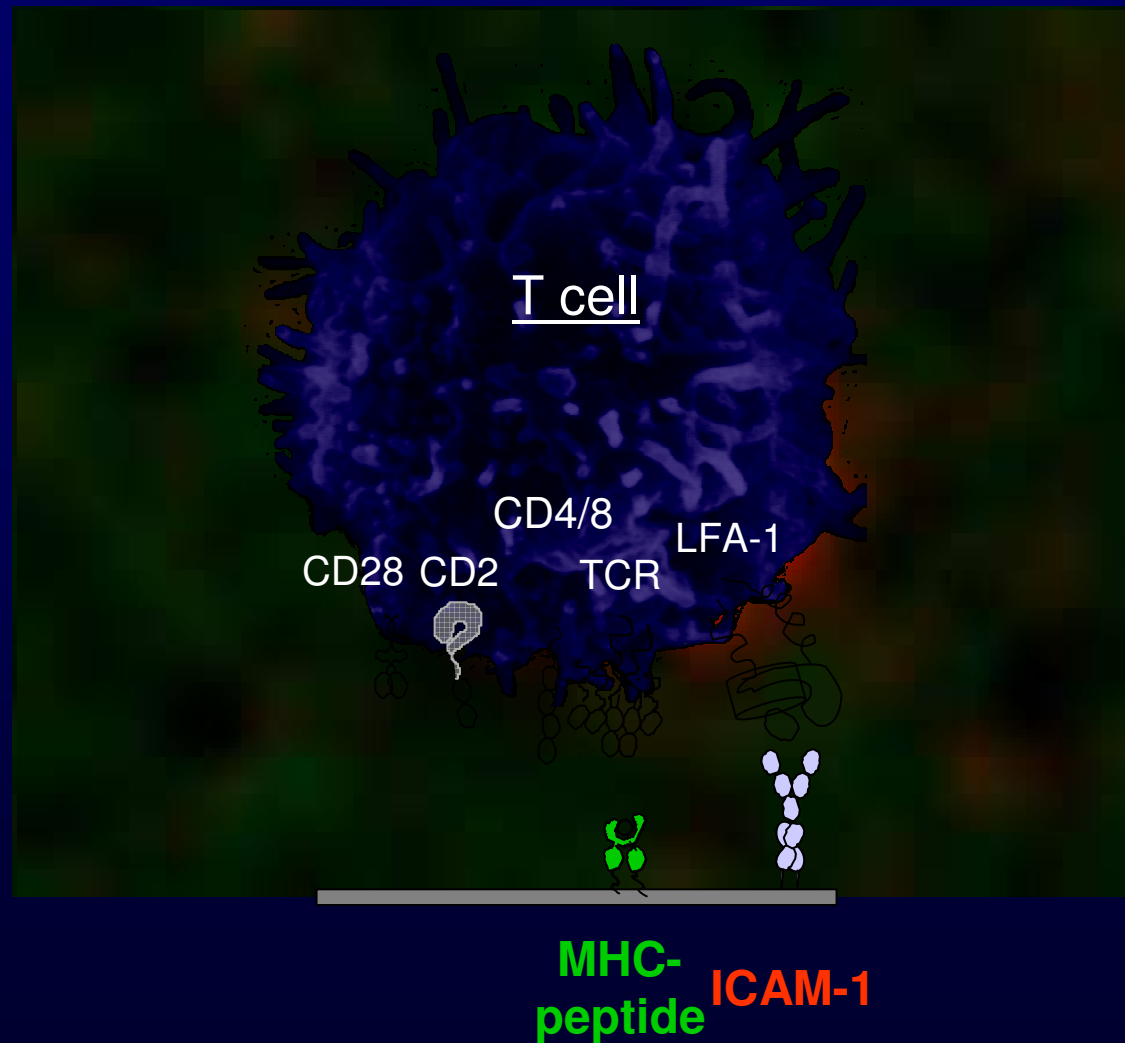
2) TCR Aggregation



3) Self-assembled Synapse Formed

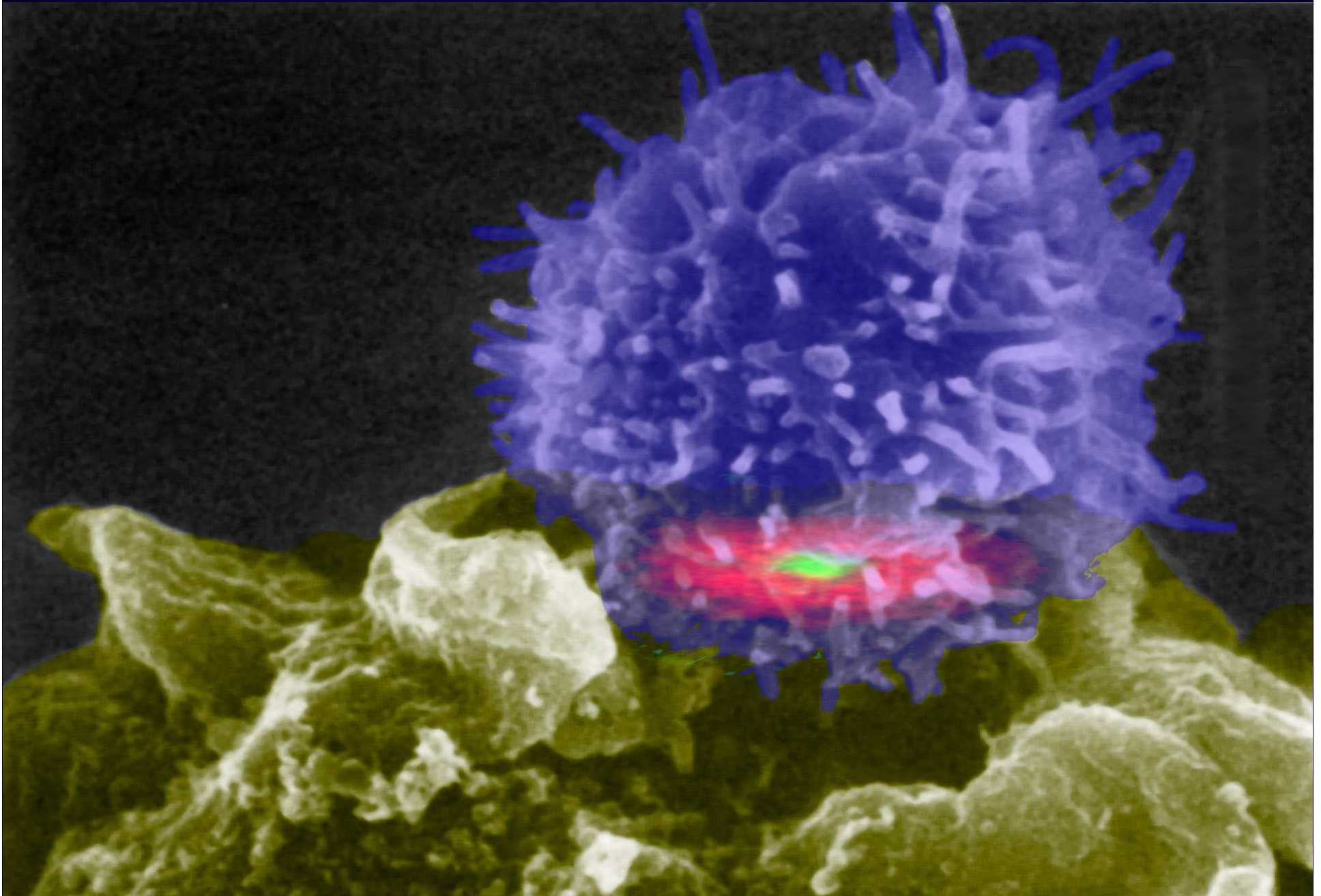


Self-assembling Immunological Synapse in Action

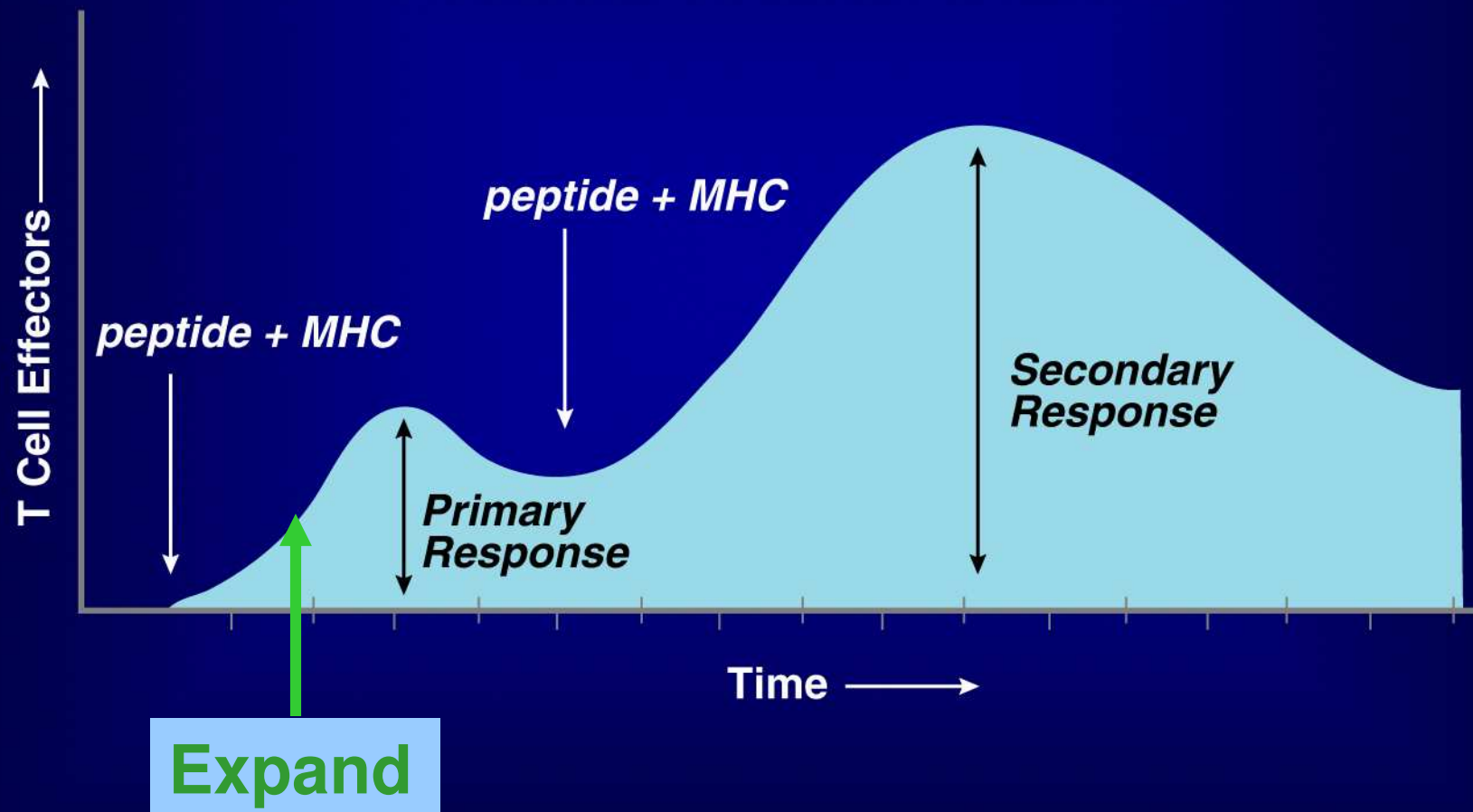


Mark Davis

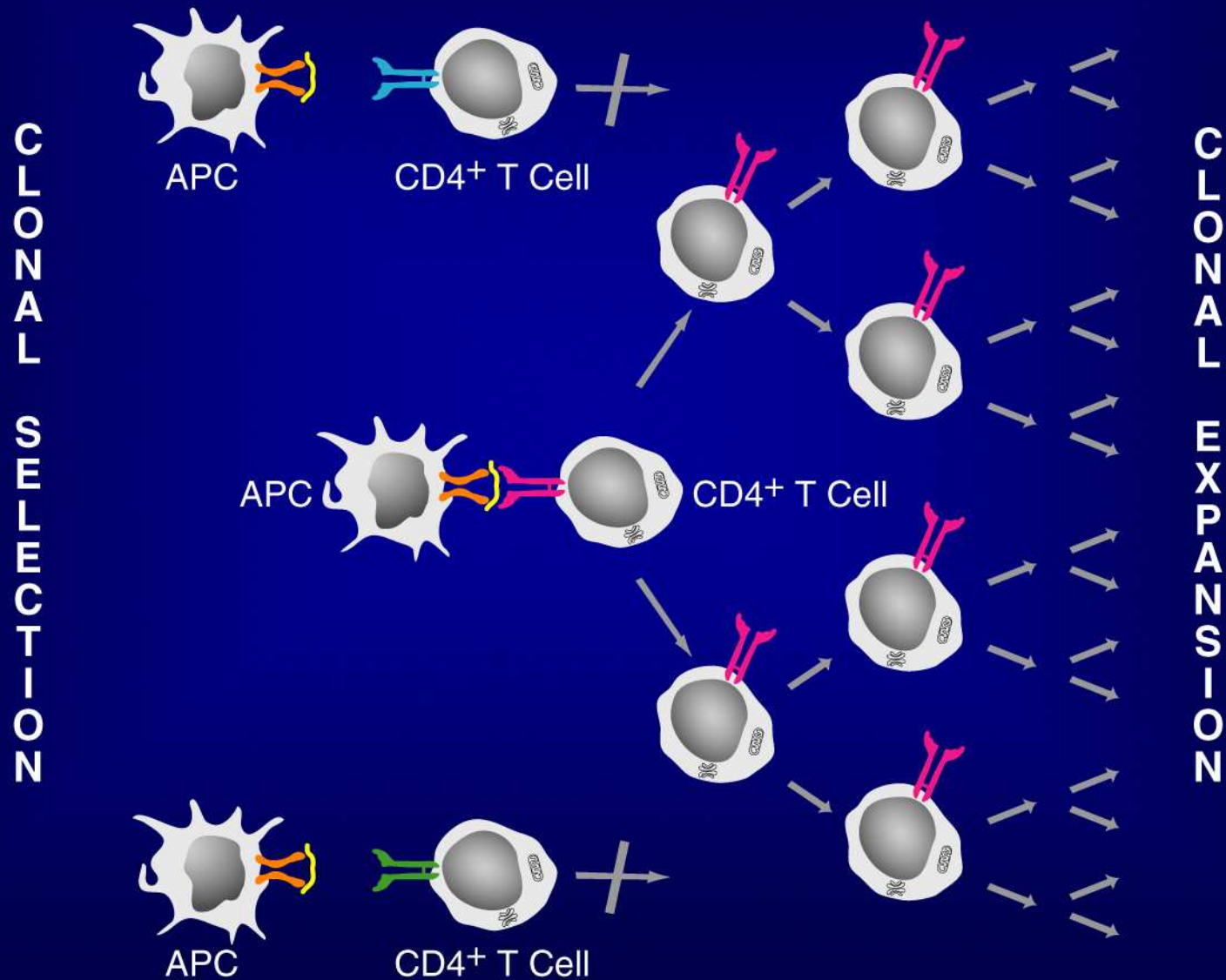
Self-assembled Immunological Synapse



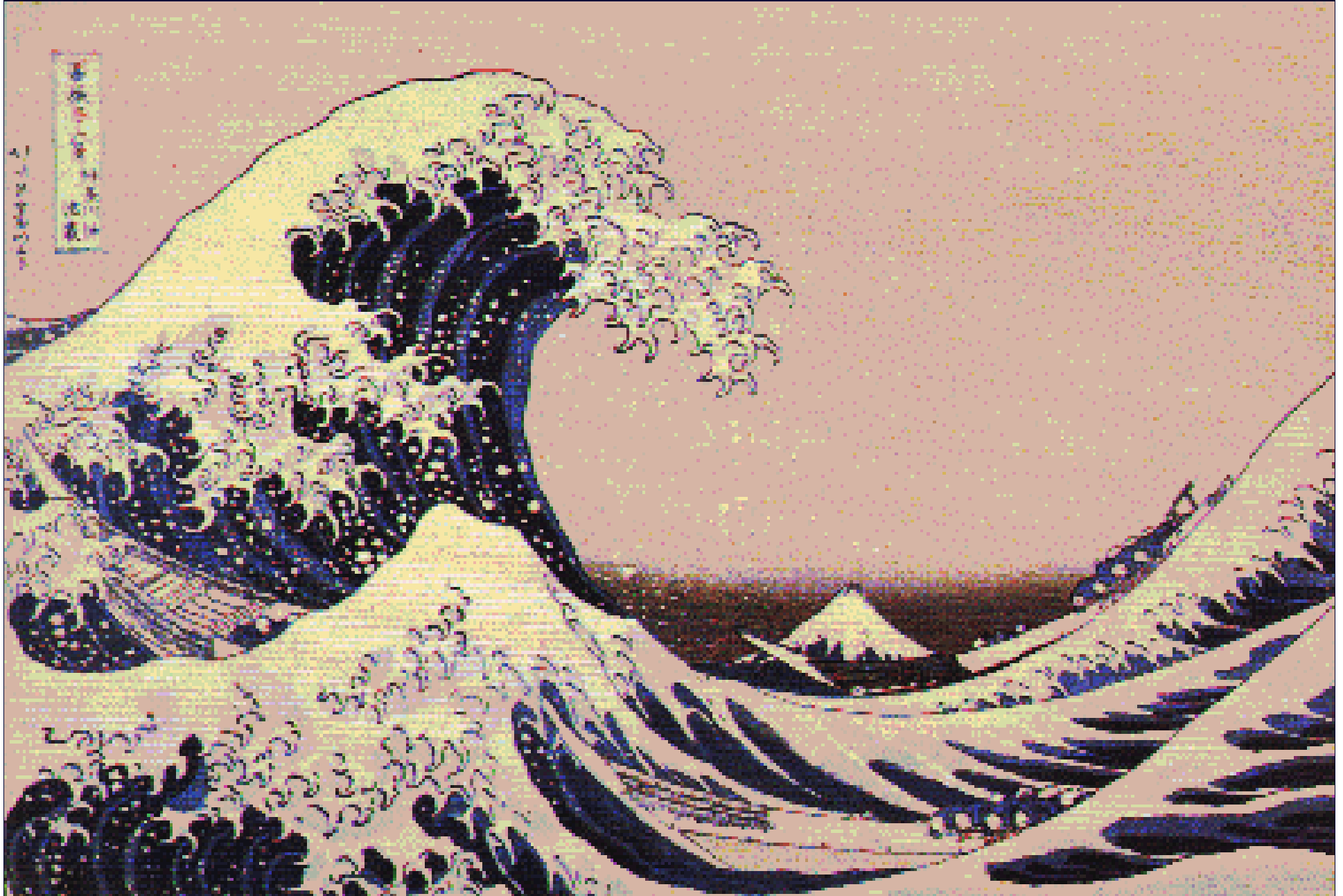
Expansion of Activated T Cells



T Cell Expansion is Directed by Clonal Selection of TCR



Tsunami



(0), 00) (x^2+10x+17)(x^2-10x+17) -4+-i 4+-i (+-sqrt(24), 100) (x^2+12x+37)(x^2-12x+26)
2+20x+101)(x^2-20x+110+-i 10+-i (+-sqrt(99),
-i 15+-i (+-sqrt(224), 900) (+-a, +-i) (+-h, k) (x
(3), 16) (x^2+6x+10)(x^2-6x+10) -3+-i 3+-i (+-
4+-i (+-sqrt(15), 64) (x^2+10x+26)(x^2-10x+
2+12x+37)(x^2-12x+26) -6+-i 6+-i (+-sqrt(35),
(99), 400) (x^2+30x+226)(x^2-30x+226) -15+
) (x^2++5)(x^2-4x+5) -2+-i 2+-i (+-sqrt(3), 16)
(8), 36) (x^2+8x+17)(x^2-8x+17) -4+-i 4+-i (+-
5+-i (+-sqrt(24), 100) (x^2+12x+37)(x^2-12x+
2+20x+101)(x^2-20x+1-10+-i 10+-i (+-sqrt(99)
-i 15+-i (+-sqrt(224), 900) (+-a, +-i) (+-h, k) x^



“Order from Disorder Sprung”

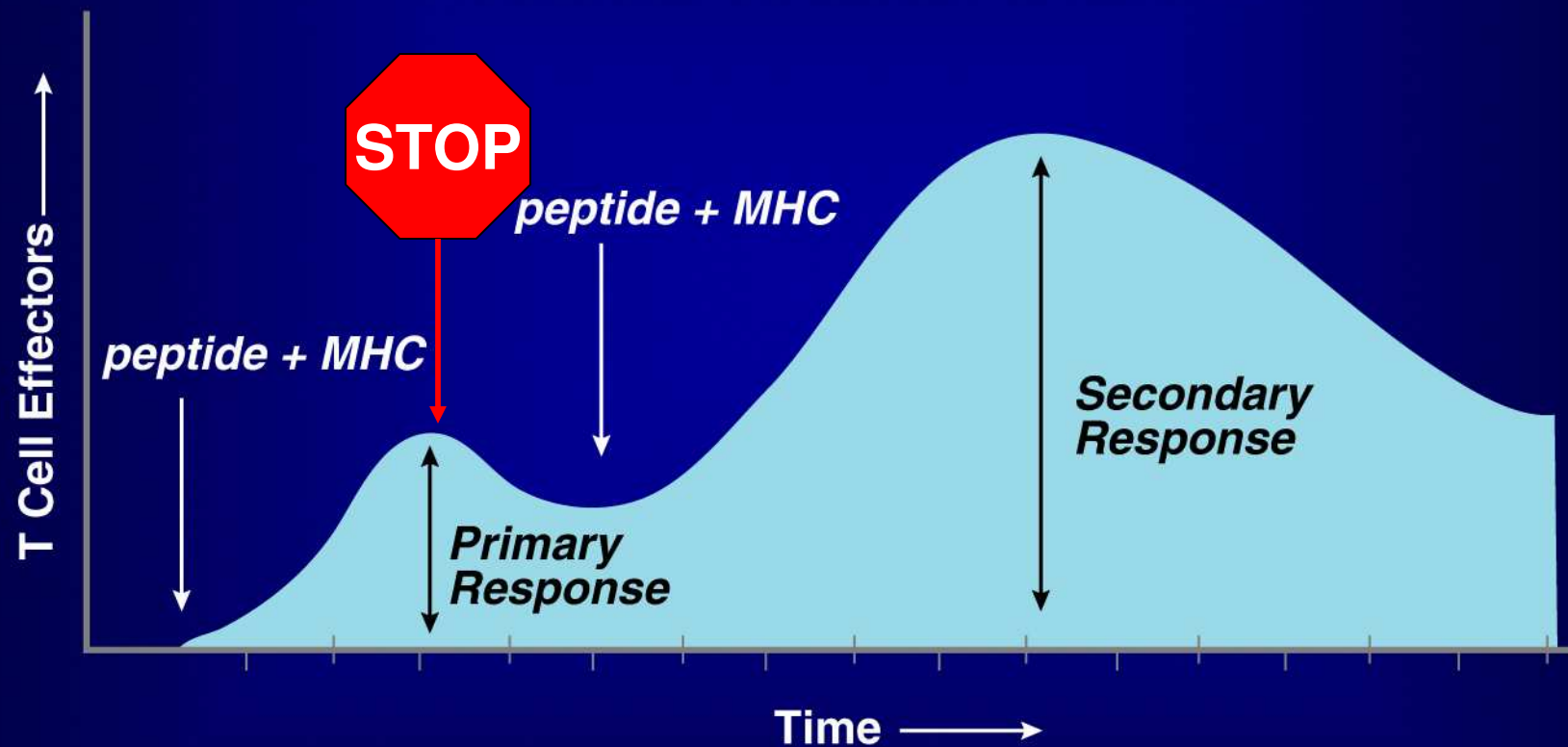
- 1) *innate immunity - sentinel*
- 2) *acquired immunity - battle*
- 3) *Homeostasis - restoration*



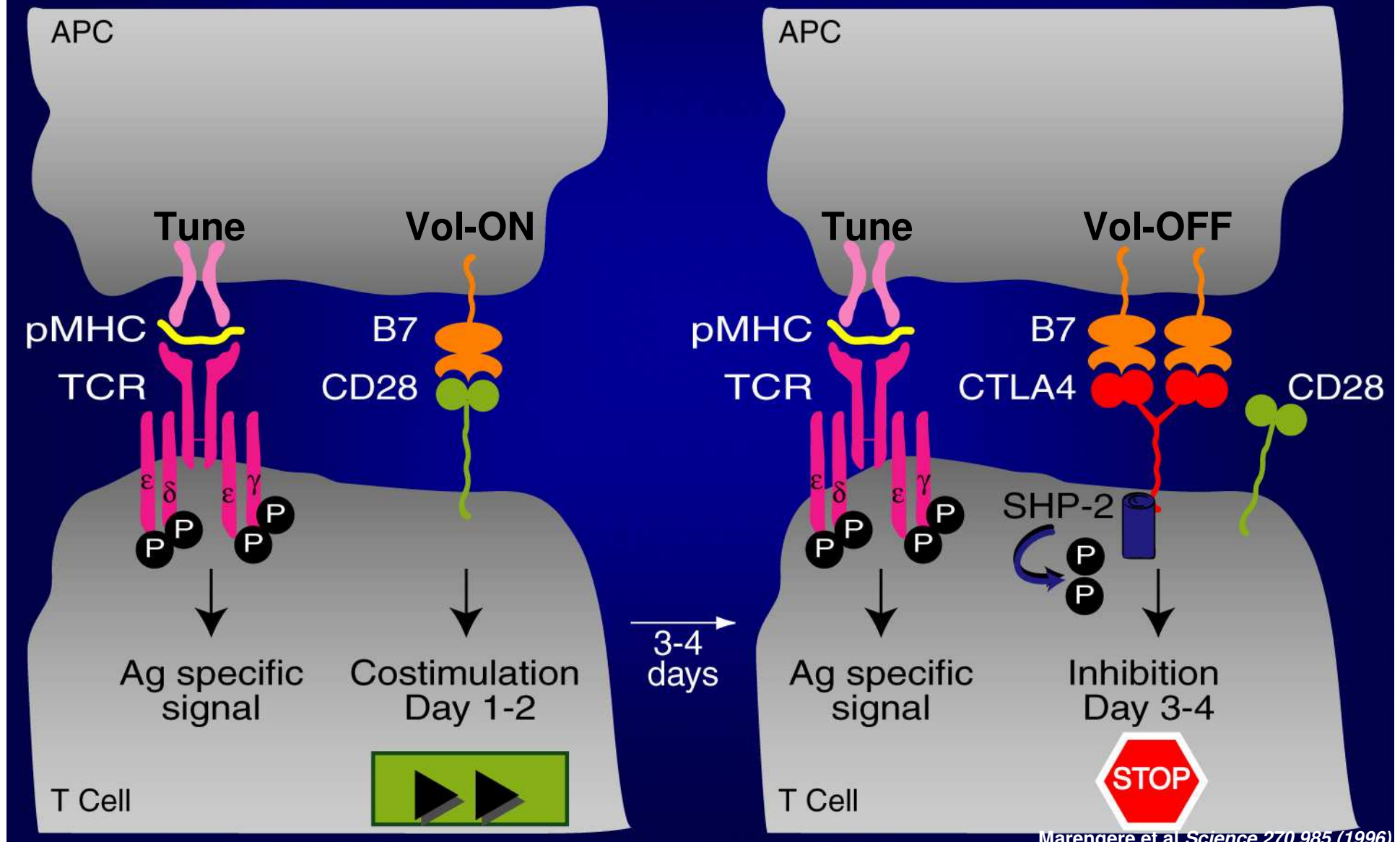
Homeostasis

- *stops immune responses*
- *reduces reactive immune cells*
- *re-establishes tolerance to self*
- *remembers specificities*

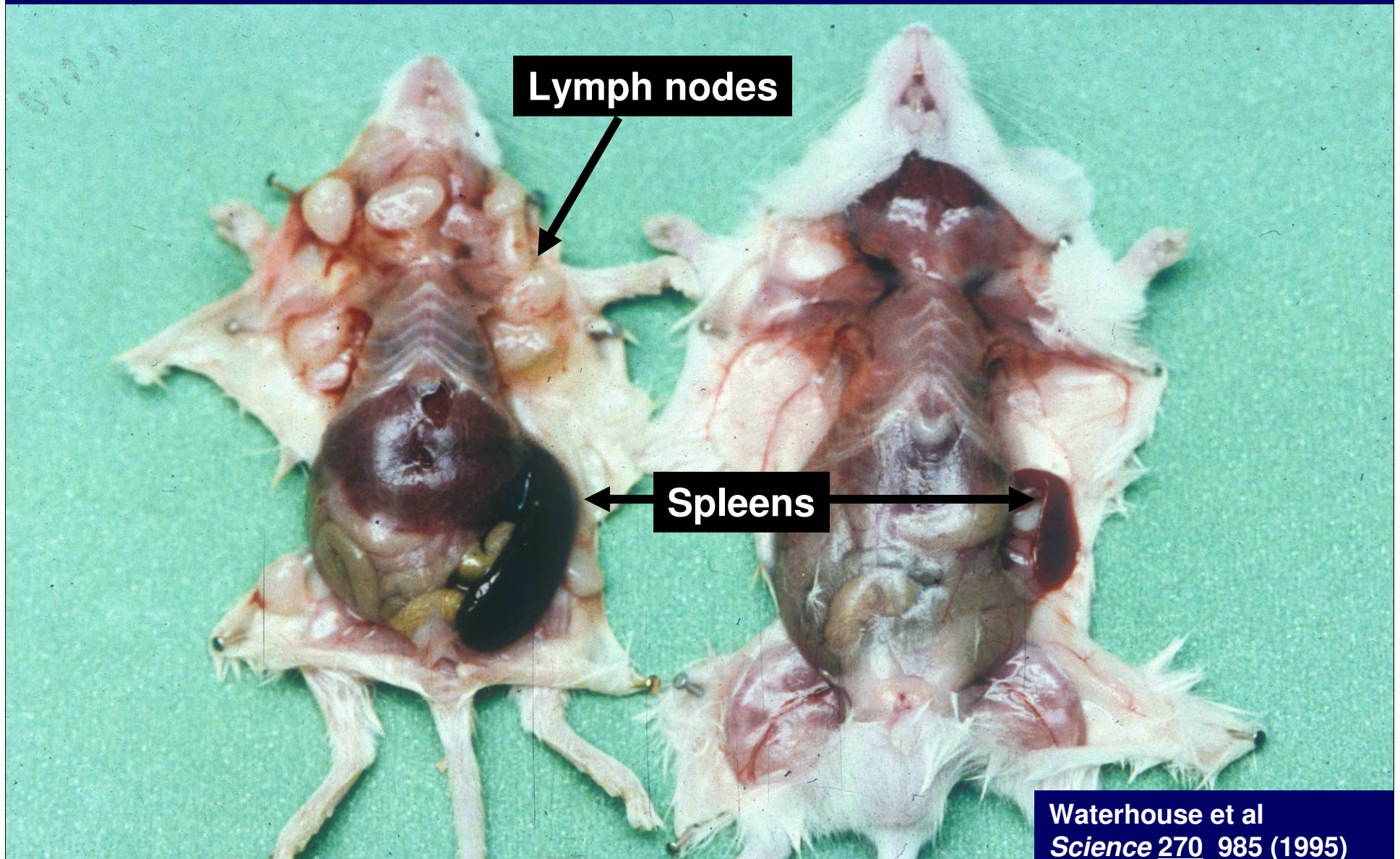
T Cell Activation Switches Off After Immune Response



CTLA4 Shuts Off T Cell Activation



Lymphoproliferation in CTLA4^{-/-} Mice



Waterhouse et al
Science 270 985 (1995)

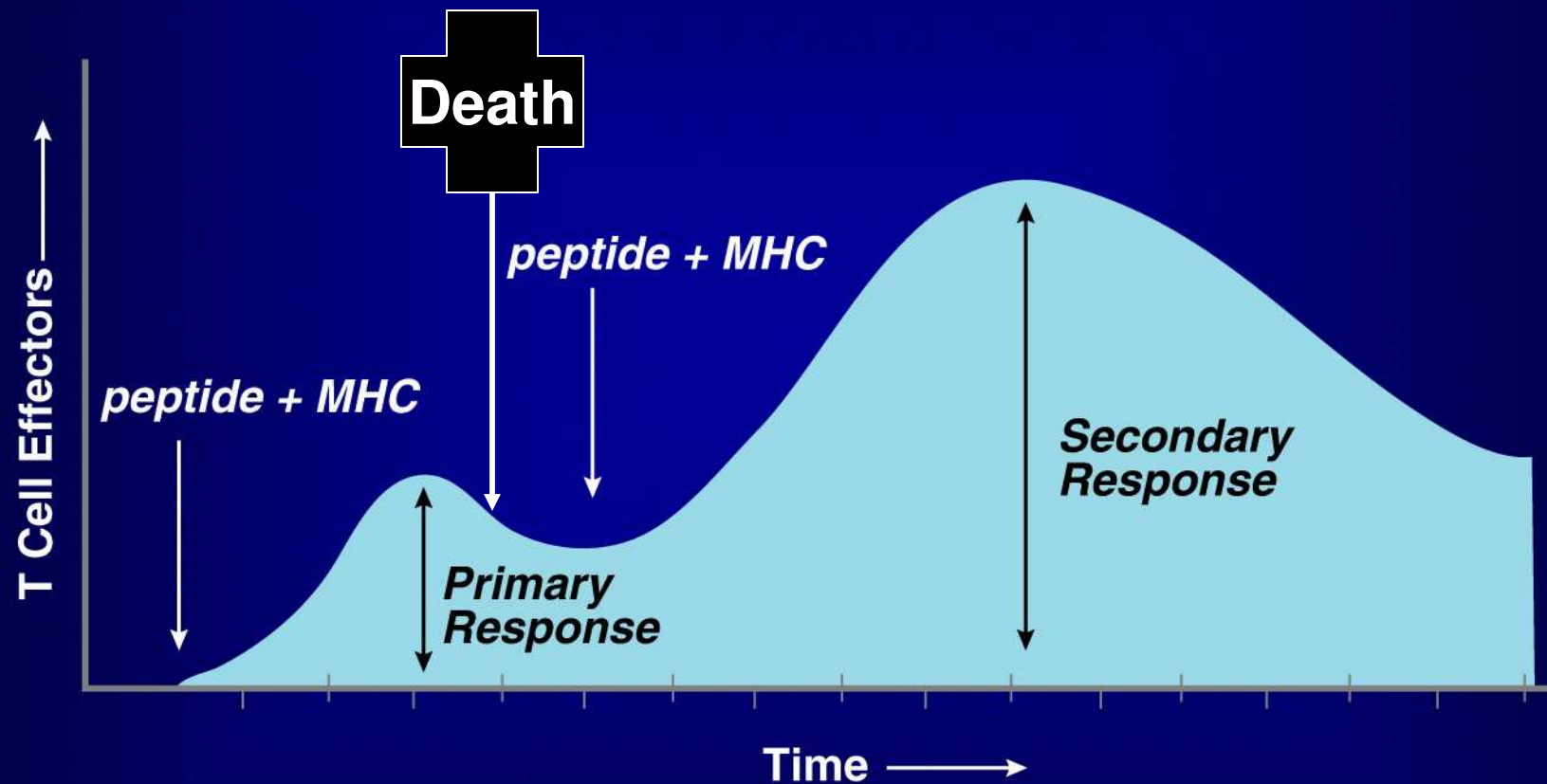
CTLA4

-/-

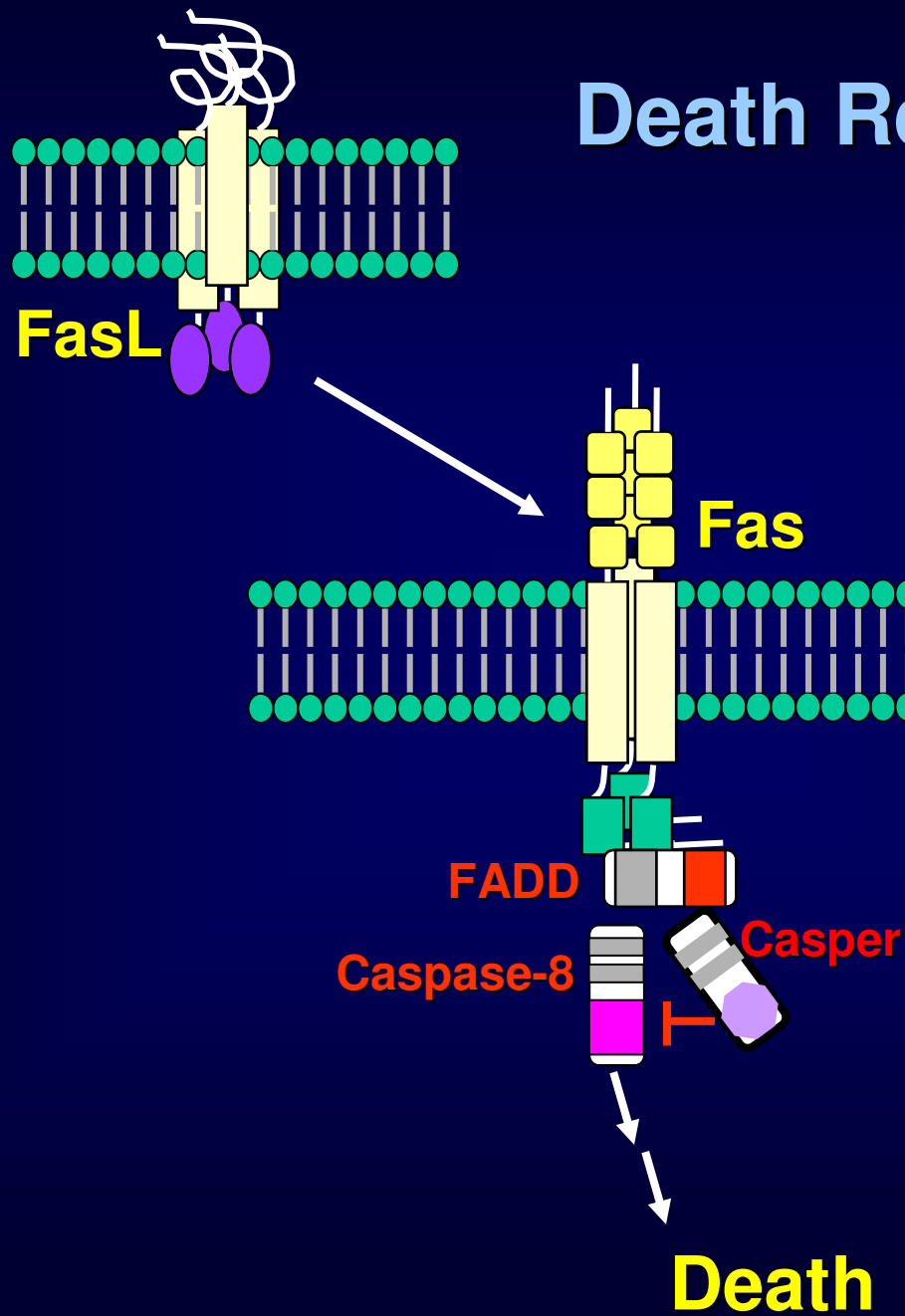
+/+

(2 Weeks)

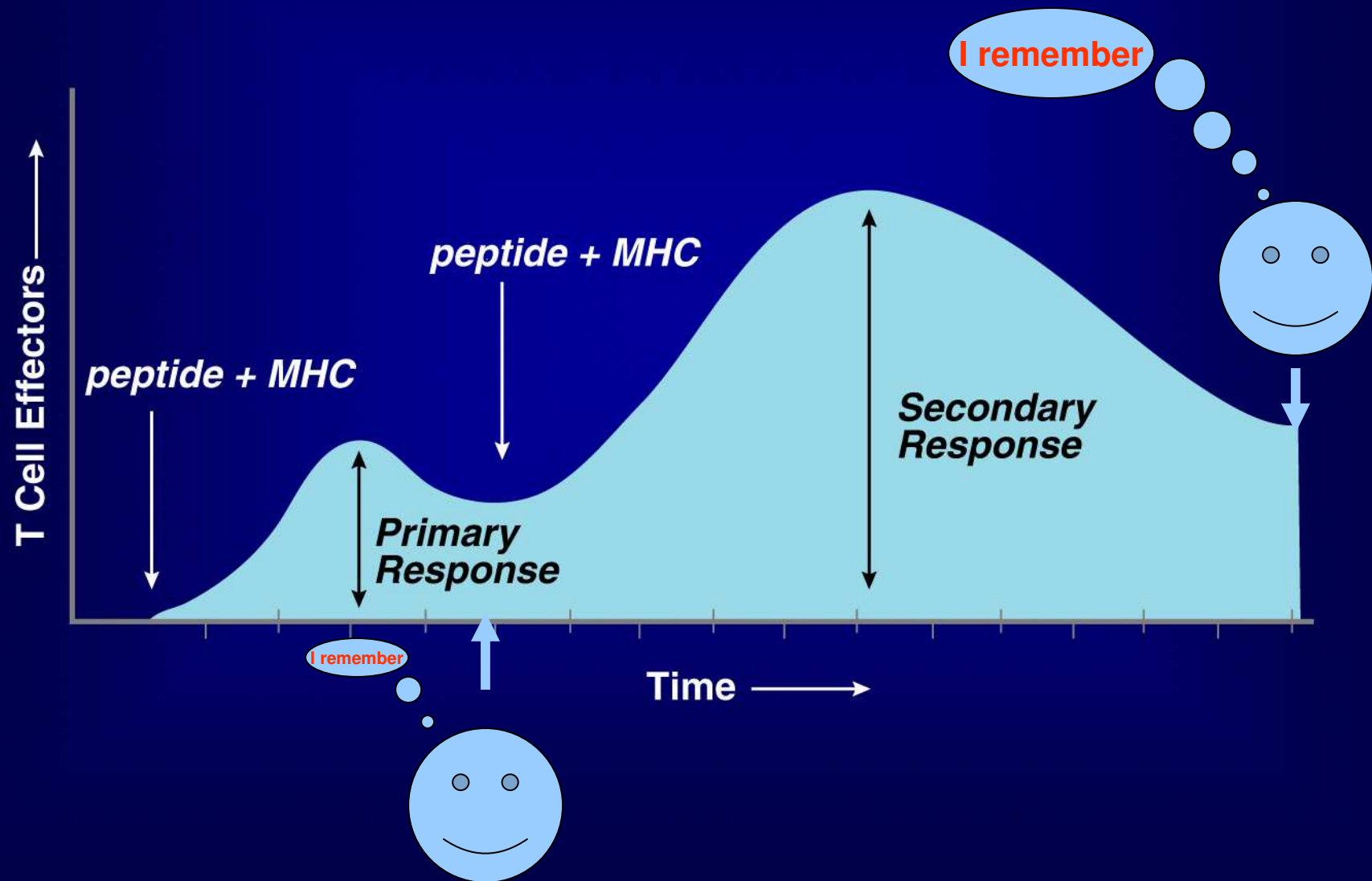
T Cells Establish Homeostasis After Immune Response



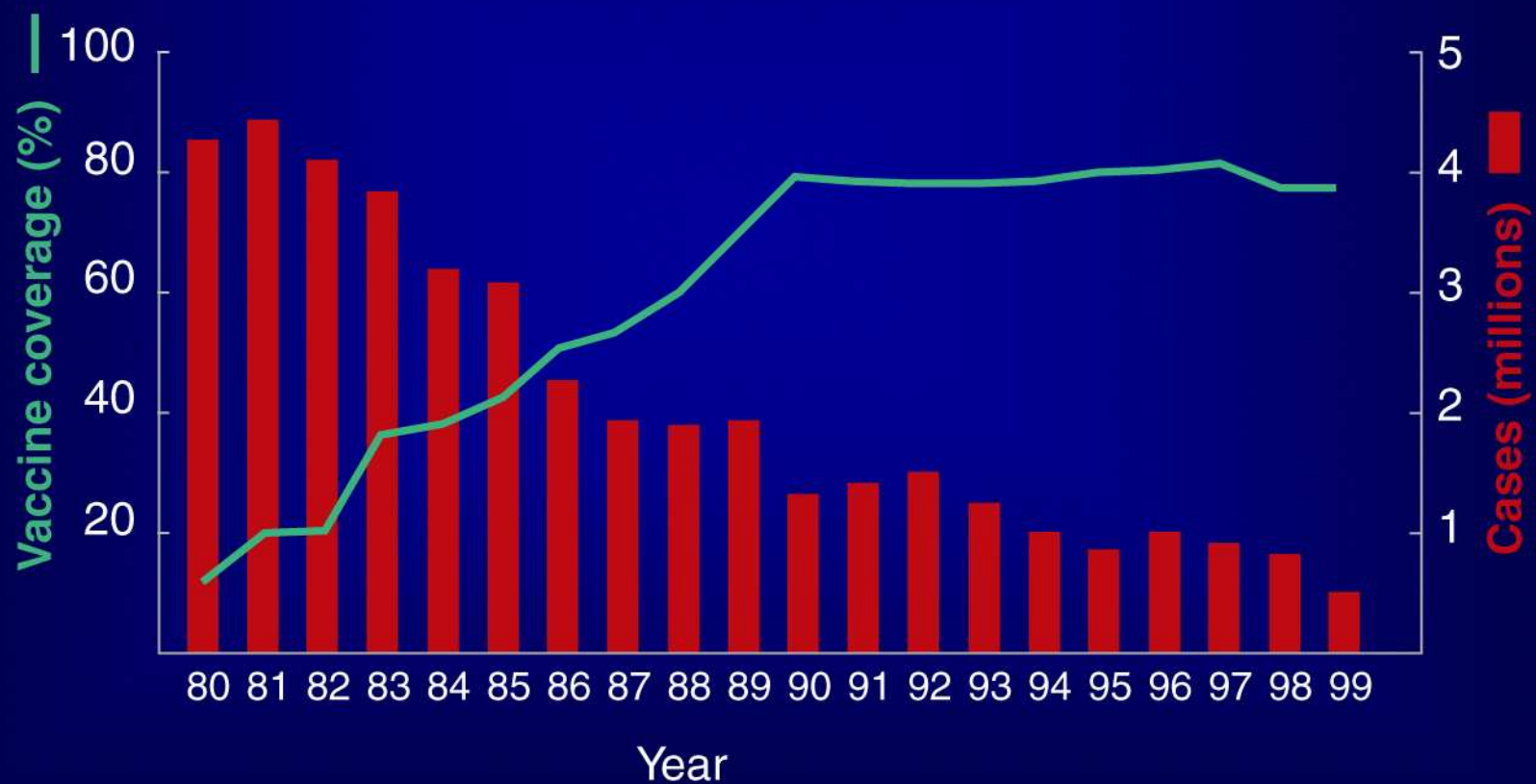
Death Receptors



Memory T Cells Persist



Success in Controlling Measles



WHO 2000

Vaccination

Successes

Smallpox

Polio

Typhoid

Hepatitis B

Measles

Challenges

Malaria

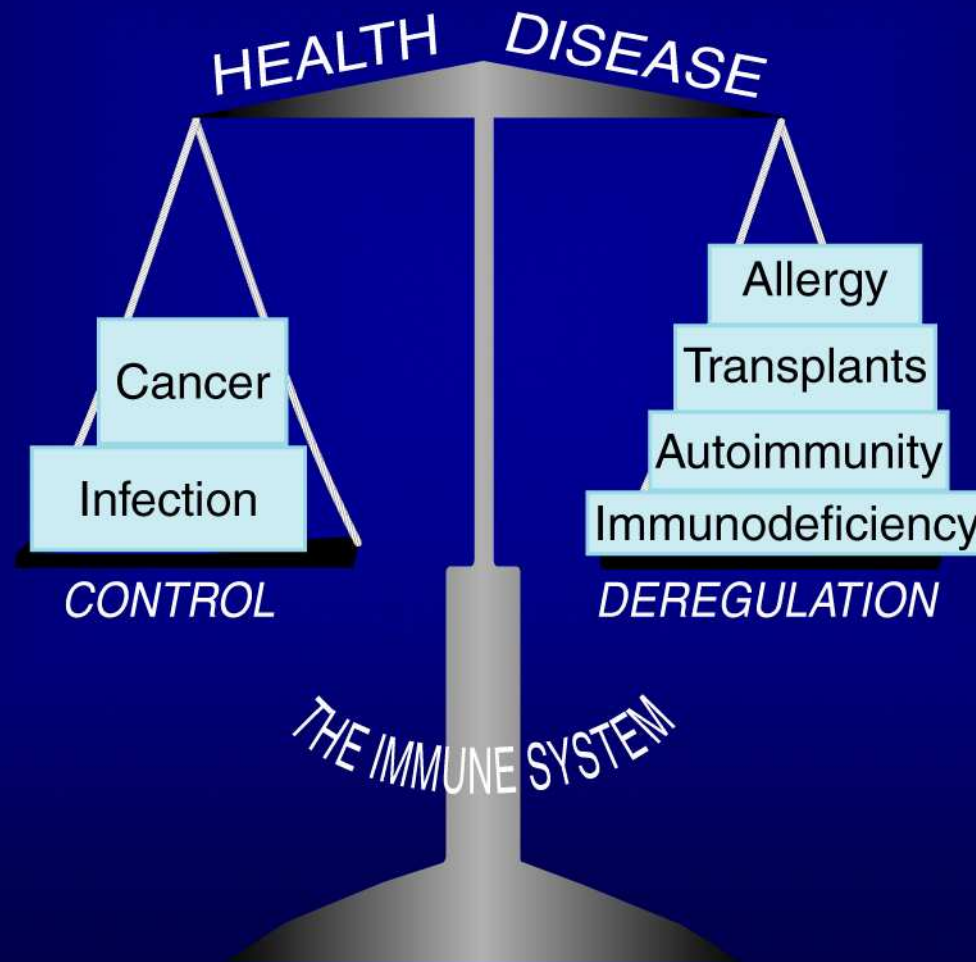
HIV

Hepatitis C

Tuberculosis

Cancer

Control and Deregulation of the Immune System



Future Challenges

Immune Tolerance:

- 1) Avoiding Autoimmunity**
- 2) Attack Cancers**

Central Tolerance (thymus)

Peripheral Tolerance

*There are, in our Countries,
Rivers which have no names,
Trees that nobody knows, and
Birds which nobody has described...*

*Our duty, then, as we understand it,
Is to express what is unheard of.*

Pablo Neruda



Acknowledgements

TCR

Yusuke Yanagi
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Pamela Ohashi
Leroy Hood - UW

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Paul Waterhouse
Luc Marengere
Hans-Willi Mittrucker

CD8

Wai Fung-Leung

NFATc

Jose de la Pompa

Inflammation/Cell Death

Wen-Chen Yeh
Mark Lomaga

Immunological Synapse

Mark Davis - Stanford

$$\text{Score} = -\log_{10} \left(1 - \sum_{i=0}^{f-1} \frac{C(G, i)C(N - G, s - i)}{C(N, s)} \right)$$

