

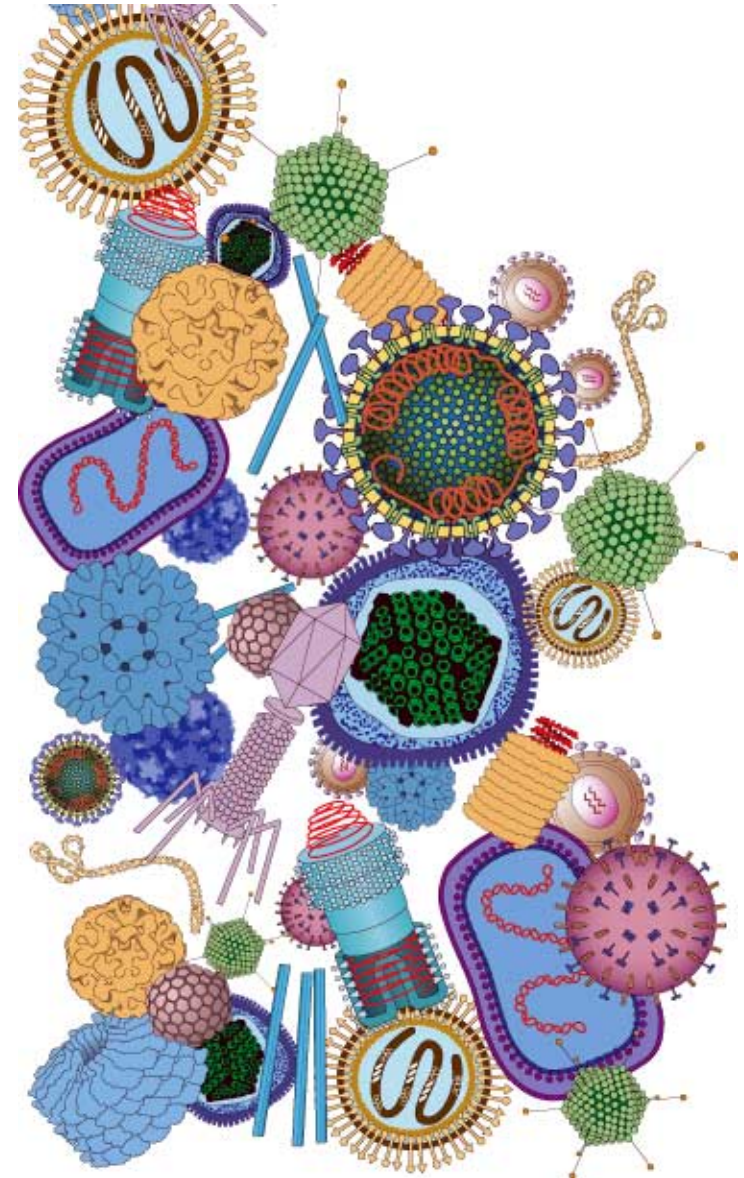


Immune Responses to Viruses

Juthathip Mongkolsapapya

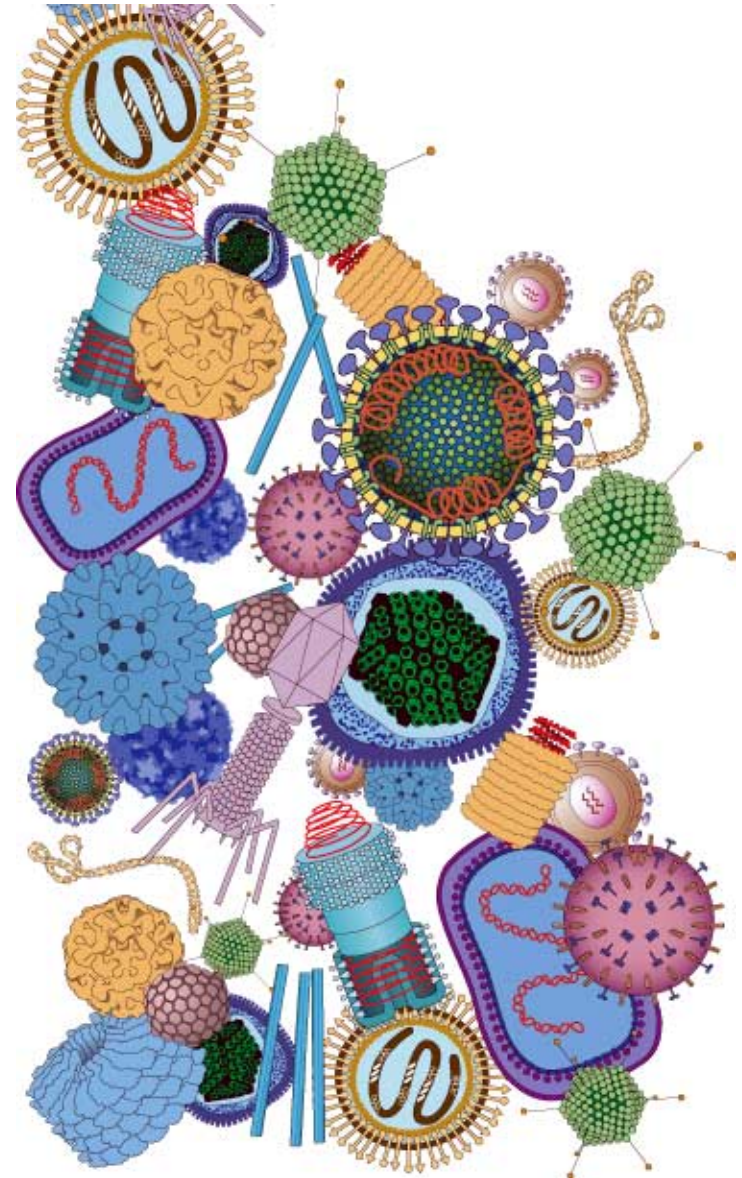
● ● ● | Overview

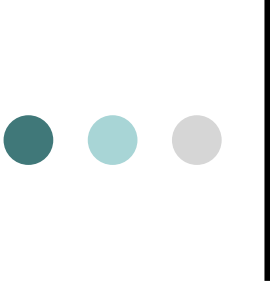
- Background
 - What is a virus?
 - Properties of viruses
- Immune responses
 - Innate responses
 - Adaptive responses
- Immune evasion/persistence



● ● ● | Overview

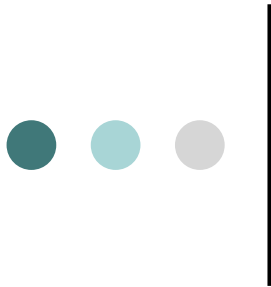
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What is a virus?

- A “filterable” agent – much smaller than bacteria
- Infects cells and has an absolute requirement for cells
- A programme for self-replication and multiplication that has:
 - Gene expression; genome replication; virus assembly; virus release and transmission.
- Classified according to genetic content and replication strategy – Baltimore Classification



Baltimore classification: examples

Class	Nucleic Acid	Examples	Envelope	Genome size (kb)
I	dsDNA	Herpes virus	Yes	120 - 220
		Poxvirus	Yes	130 - 375
		Adenovirus	No	3.0 - 4.2
		Papillomavirus	No	5.3 - 8.0
II	ssDNA	Adeno-associated virus	No	5.0
III	dsRNA	Reovirus	No	18 - 31‡
IV	(+) ssRNA	Togavirus	Yes	9.7 - 11.8
		Poliovirus	No	7.4
		Foot-and-mouth disease virus	No	7.5
		Hepatitis A virus	No	7.5
		Hepatitis C virus	Yes	10.5
V	(-) ssRNA	Influenza virus	Yes	12 - 15‡
VI	(reverse) RNA	HIV	Yes	9.7
VII	(reverse) DNA	Hepatitis B virus	Yes	3.1

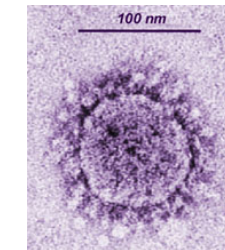
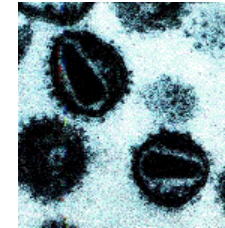


Important Human Virus Diseases

- HIV
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Human Papilloma virus (HPV)
- Rotavirus
- Measles
- Respiratory Syncytial Virus (RSV)
- Influenza A

Emerging and re-emerging Viruses

- HIV →
- Dengue
- Hantavirus
- Ebola →
- West Nile Virus
- SARS →
- Avian influenza H5N1
- Swine influenza

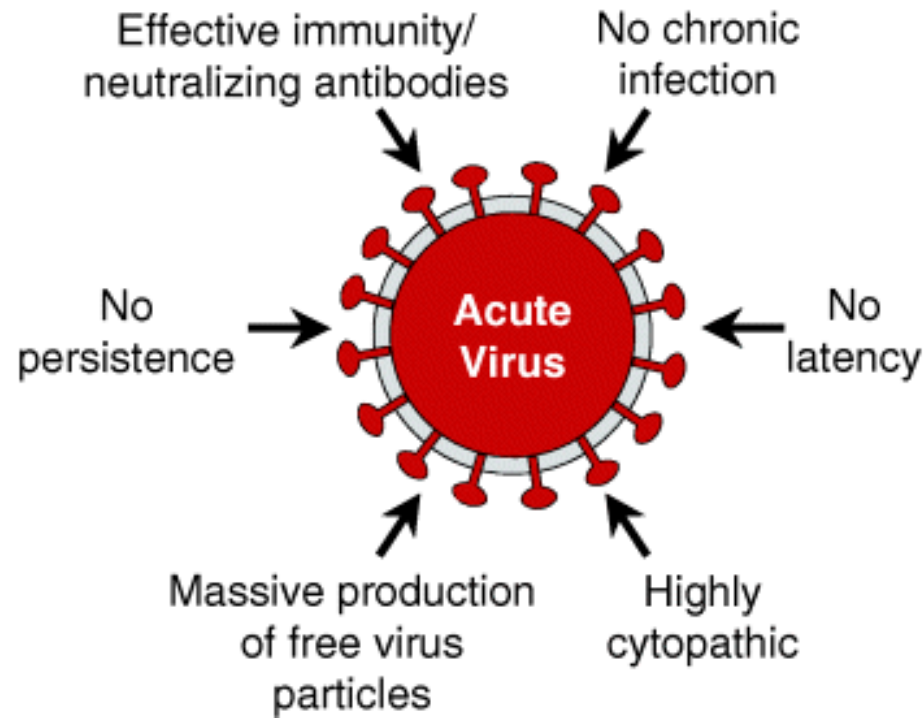




Properties of viruses I

- Cytopathic or non-cytopathic
 - Cytopathic eg: **Hep B**
 - Non-cytopathic eg: **Rhinovirus**
- Acute or Chronic
 - Acute eg: **Ebola Virus**
 - Chronic eg: **Cytomegalovirus**

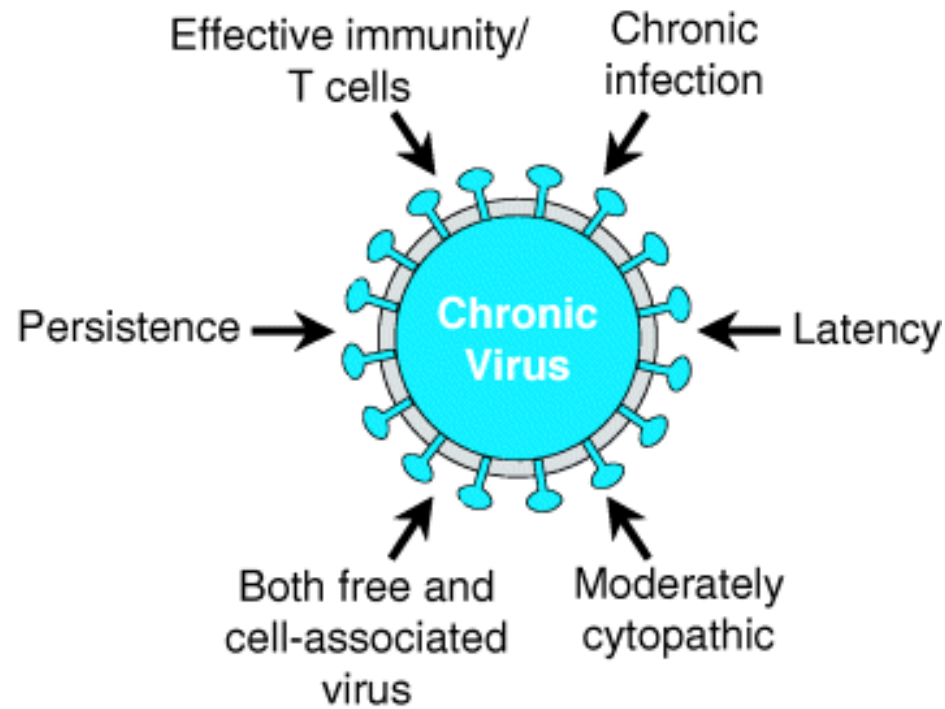
Acute vs Chronic Viruses



Acute

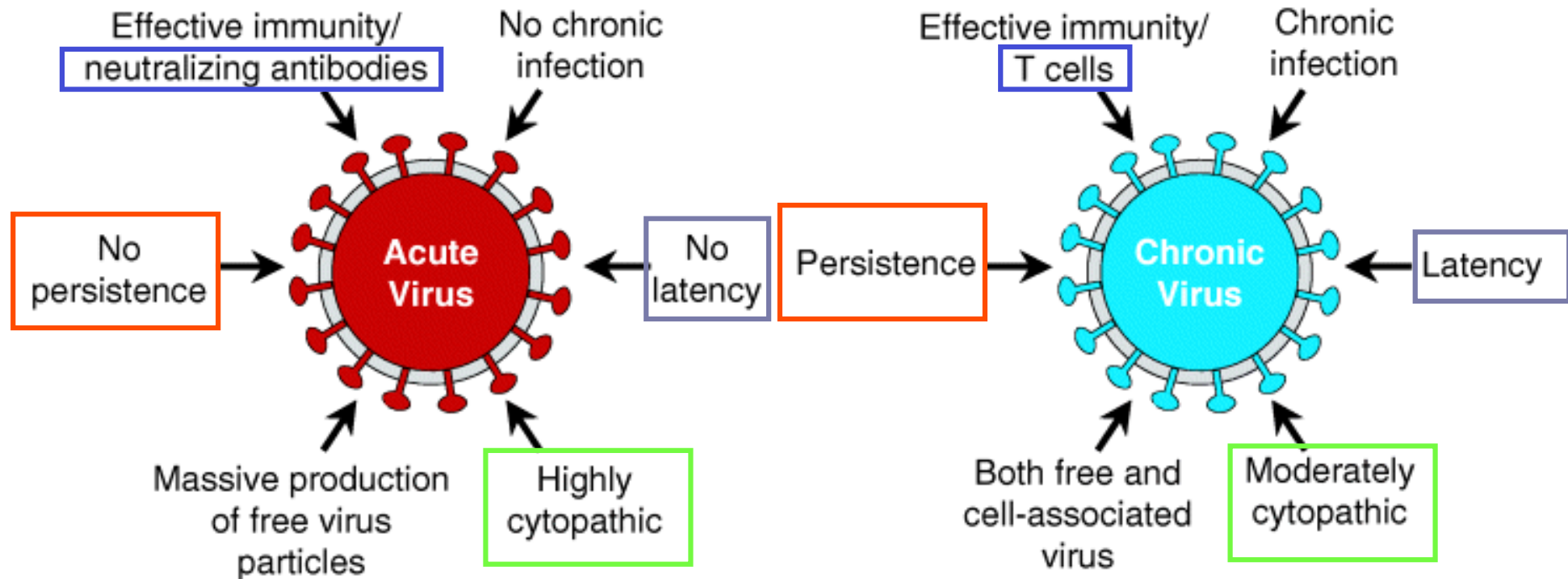


Acute vs Chronic Viruses



Chronic

Acute vs Chronic Viruses

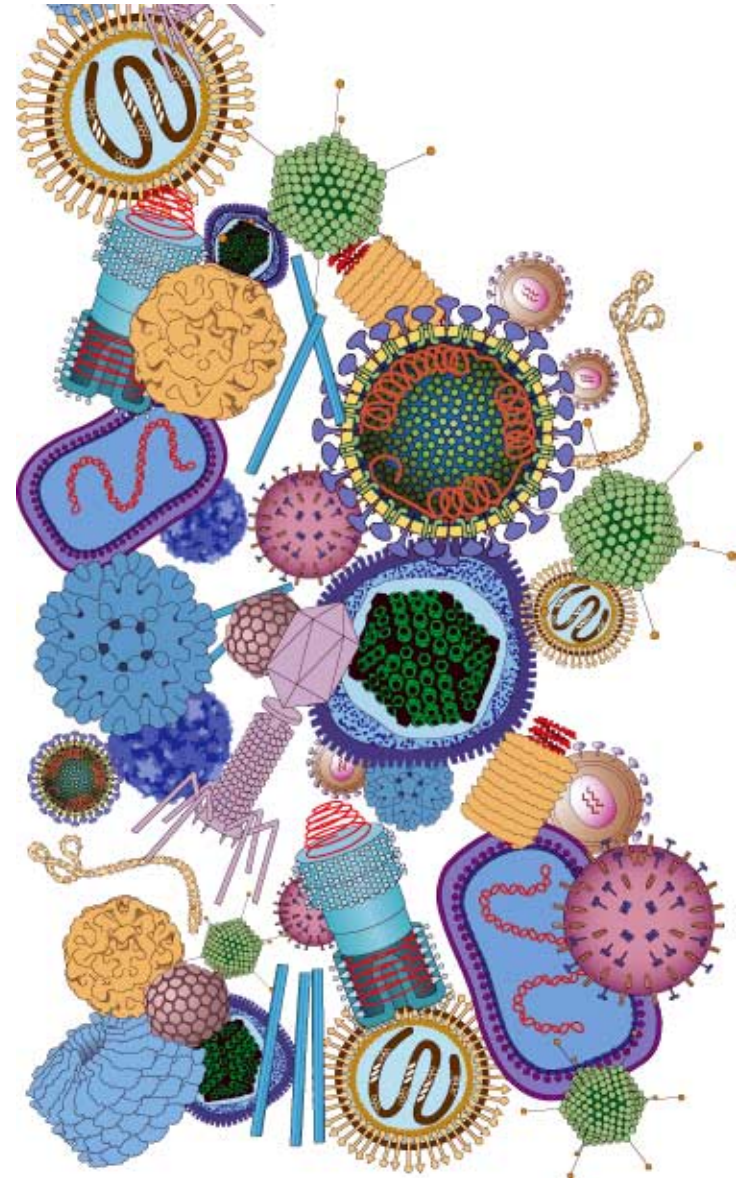


Acute

Chronic

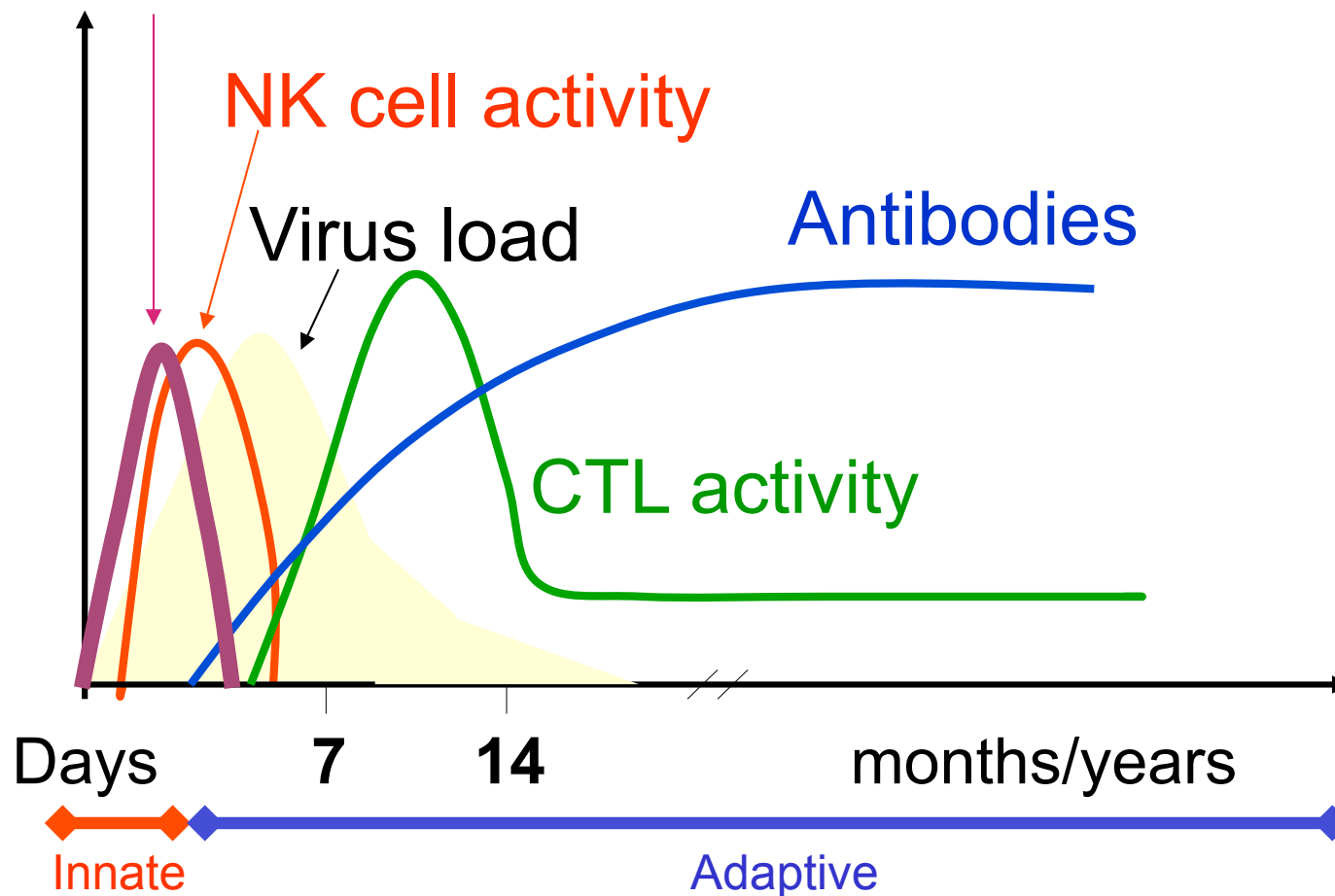
● ● ● | Overview

- Background
 - What is a virus?
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- **Immune responses**
 - Innate responses
 - Adaptive responses
- Immune evasion/persistence



Kinetics of virus induced immunity

Production of IFN- α , IFN- β , TNF- α and IL-12





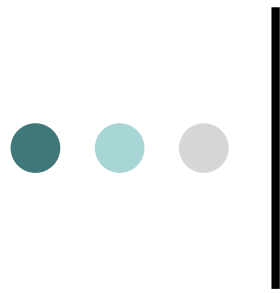
Innate and adaptive immunity I

- **Innate immunity**

- To combat the early stage of infection

- **Adaptive immunity**

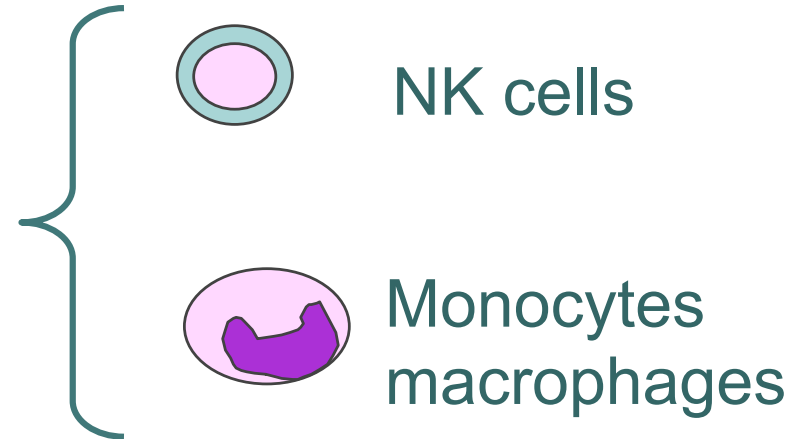
- Several days required to enable clonal expansion and differentiation of naïve lymphocytes into:
 - **Effector T cells**
 - **Antibody secreting B cells**



Innate and adaptive immunity II

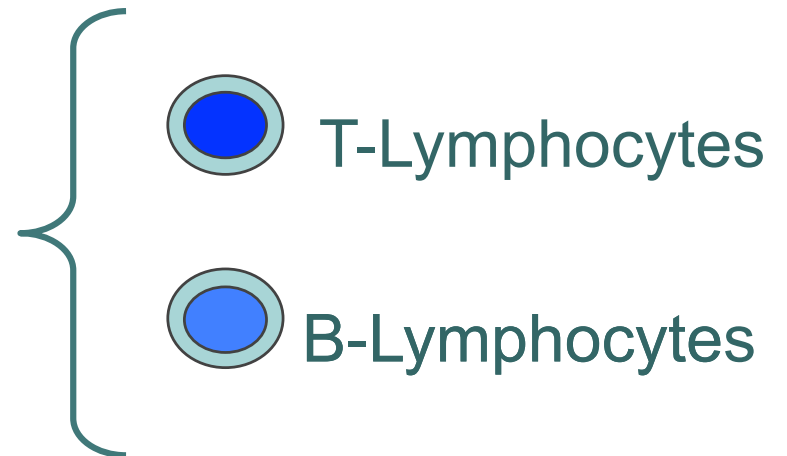
Innate

- Physical barrier
- Complement
- NK cells
- Type I Interferons



Adaptive

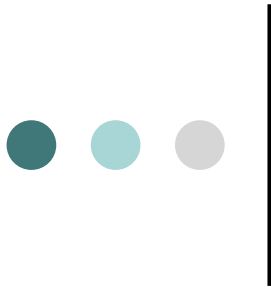
- CD4 / CD8 T cells
- B cells
- Cytokines
- Chemokines





Innate immunity to viruses

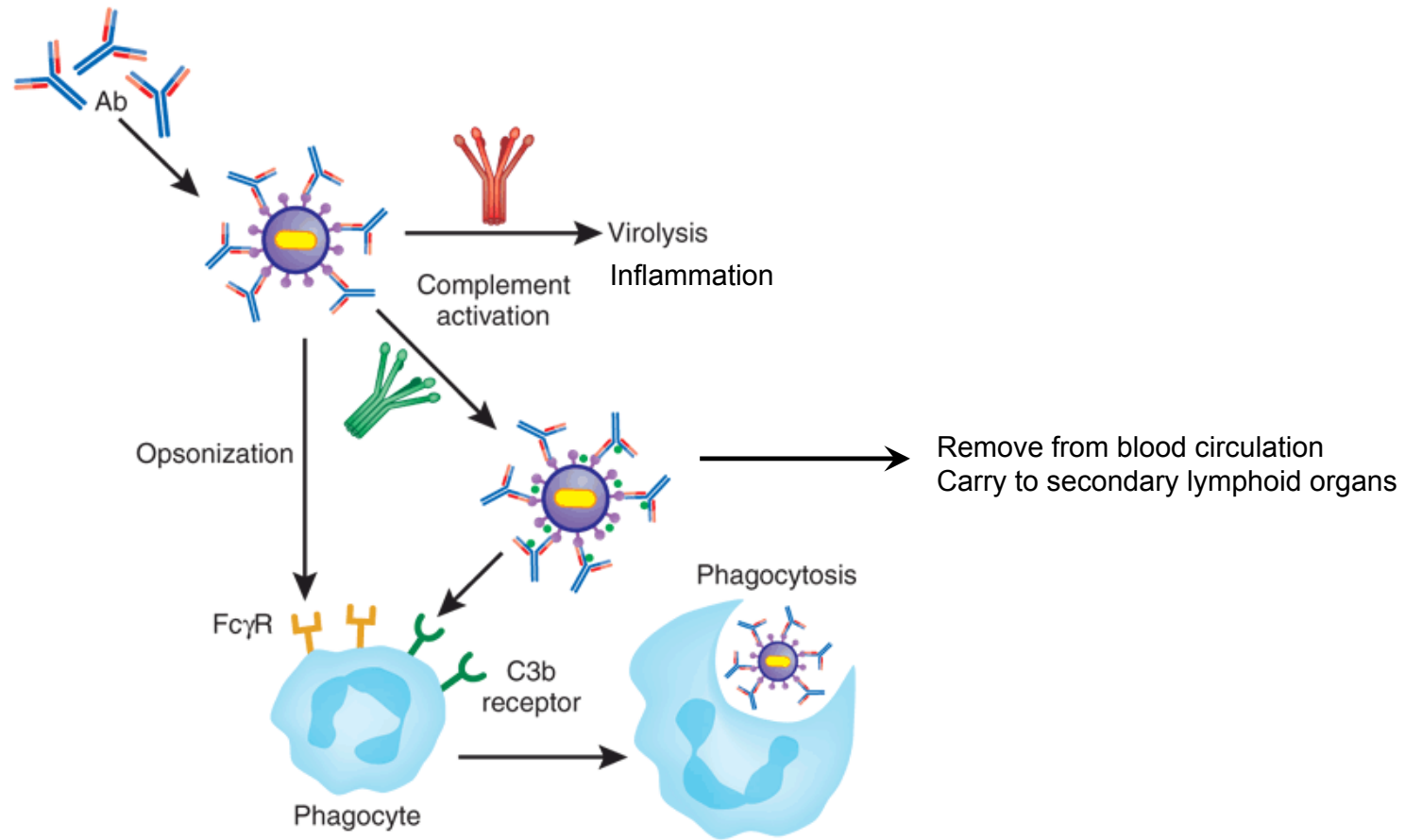
- Complement
- NK cells
- Interferons



Complement - Major Roles

- opsonisation of viruses for phagocytosis
- direct killing of viruses
- promotion of inflammation
- chemotaxis - neutrophils & leukocytes
- processing immune complexes
- Augment induction of specific antibodies

● ● ● | **Complement**





Interferons



Virus infected
host cell



IFN- α & IFN- β



1. Induce resistance to viral replication in all cells such as induce OAS
2. Increase MHC Class I expression and antigen presentation in all cells
3. Activate NK cells to kill virus-infected cells
4. Activate Dendritic cells and macrophages
5. Induce chemokine production, such as CXCL-9,-10 and -11, to recruit lymphocytes



NK cells and viruses

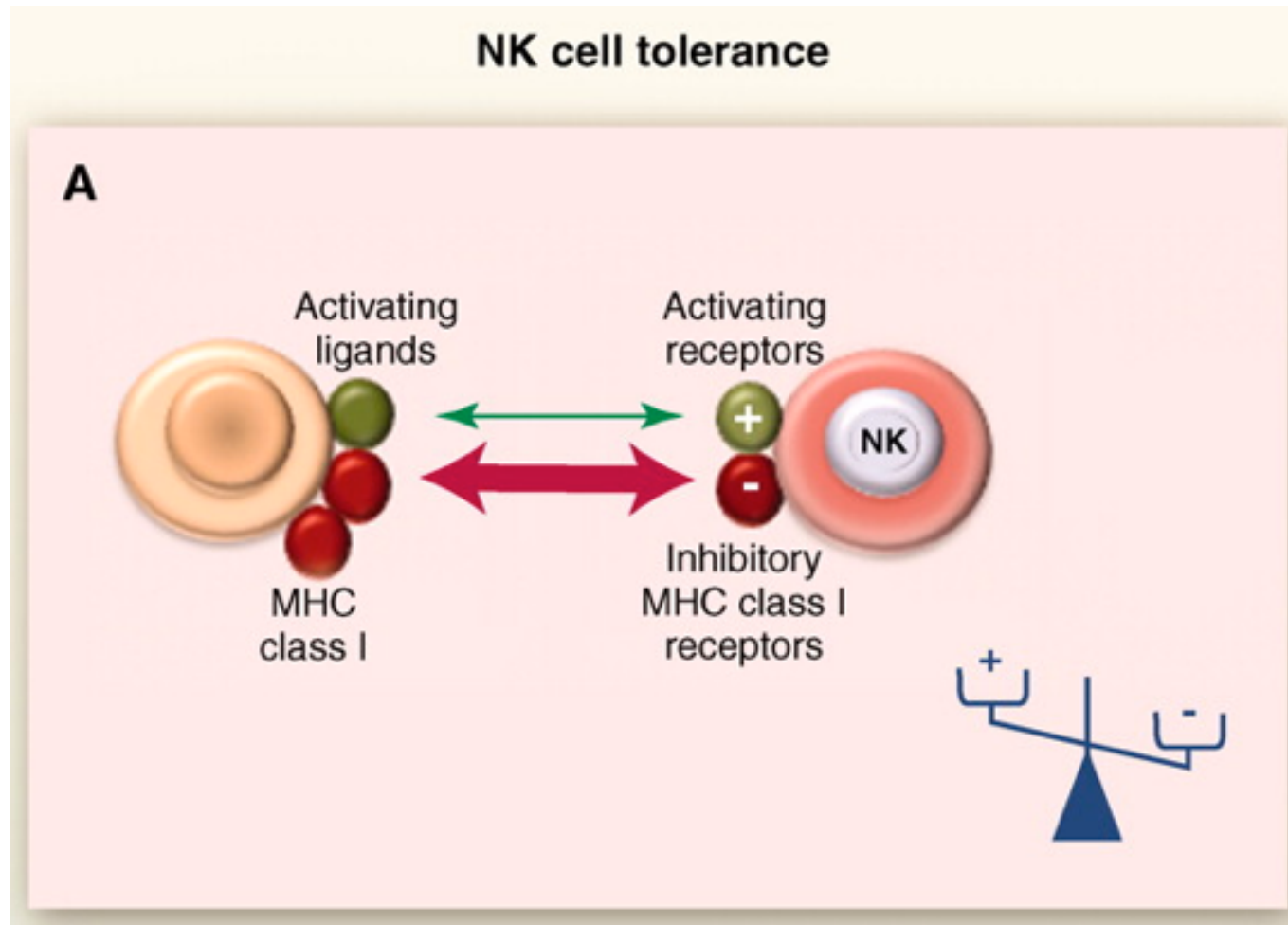
- Crucial link between innate and adaptive IR
 - Important in first five days of infection
 - Cytokine secretion
 - Differentiation of CD4⁺ T cells



NK cells and viruses

- Eliminate viral infected cells by:
 - **Cytolytic mechanisms**
 - NK cell receptors
 - ADCC
 - **Non-cytolytic mechanisms**
 - Chemokine secretion
 - Cytokine secretion
 - Effector cell recruitment

NK cell recognition of virus infected cell



NK cell recognition of virus infected cell

NK cell activation

B

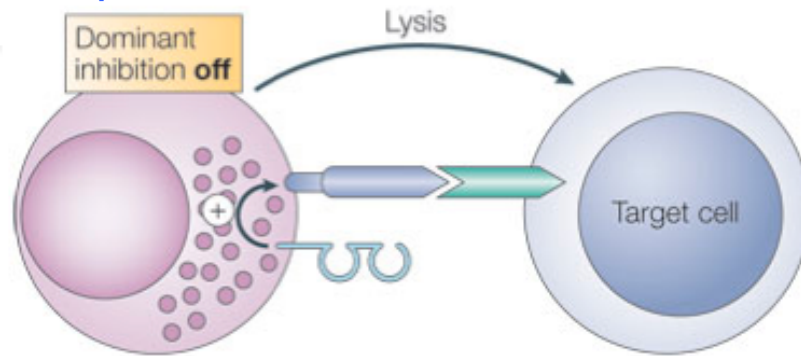


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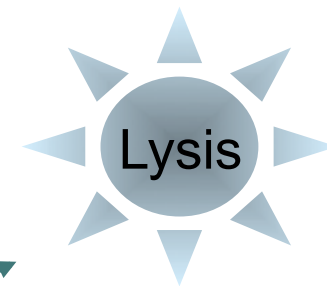
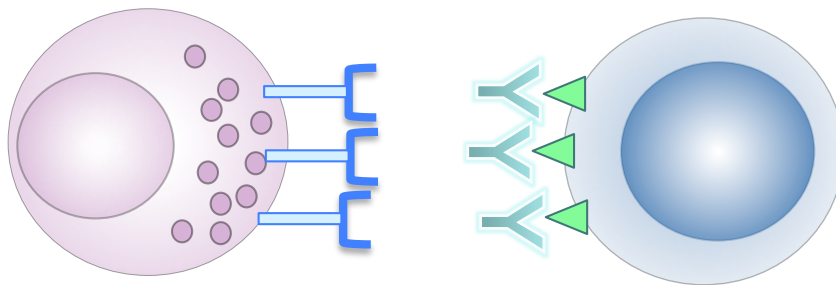


NK cell killing mechanisms – Cytolytic

Activating receptor

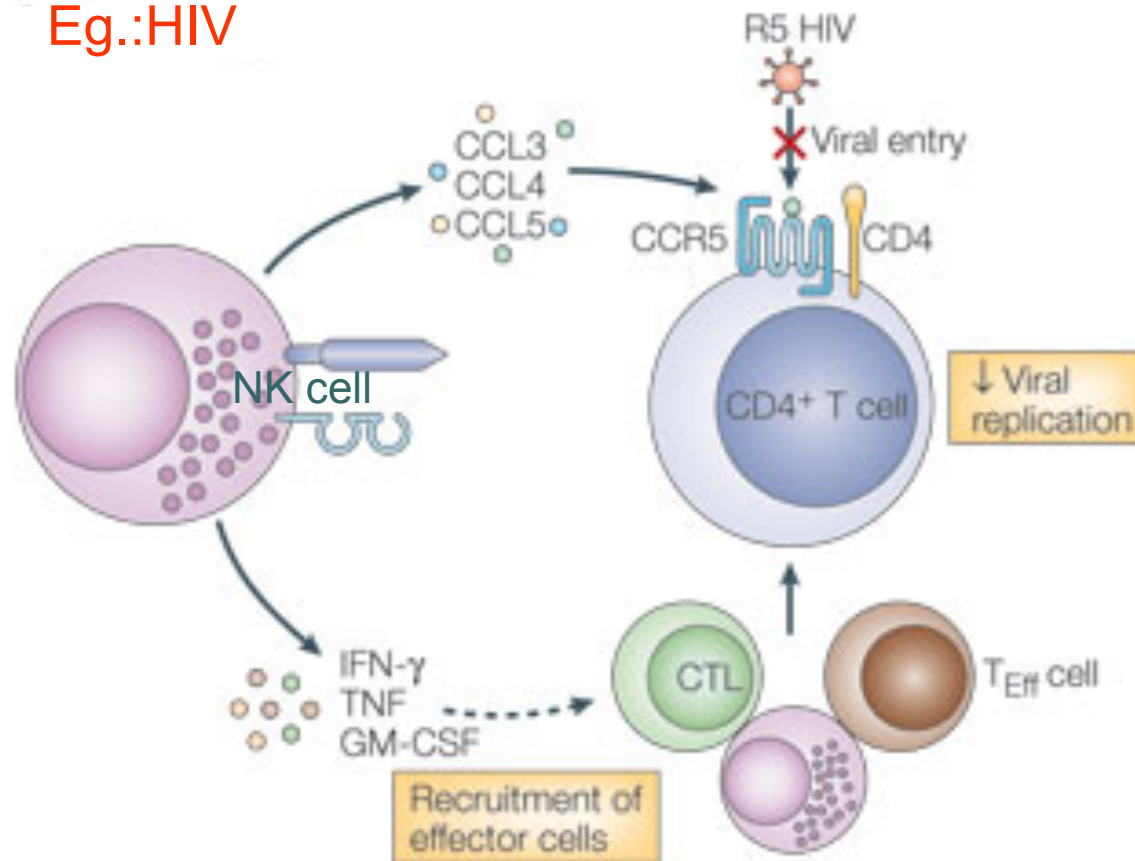


ADCC



NK cell killing mechanisms – Non-cytolytic

Eg.:HIV



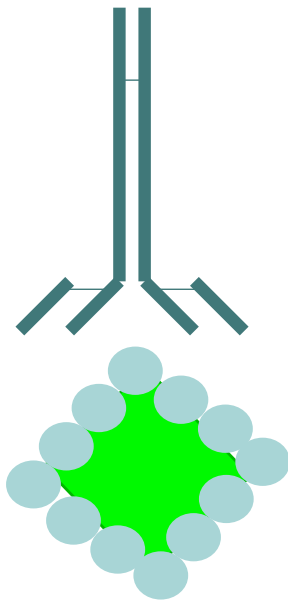


Adaptive immune response to viruses

- CD4⁺ T helper cells
- CD8⁺ T cytotoxic cells
- Regulatory T cells
- B cells

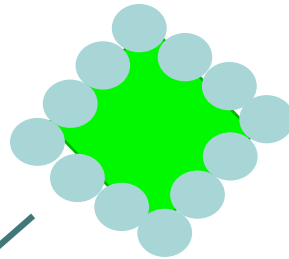
Antigen Recognition

Antibody

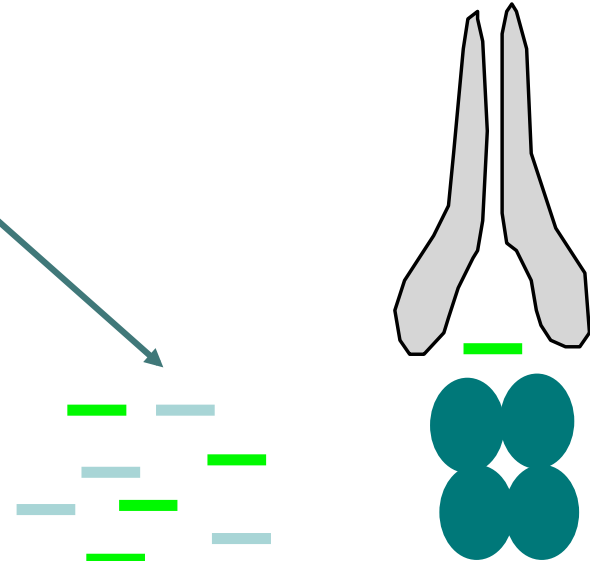


Direct
binding

Virus



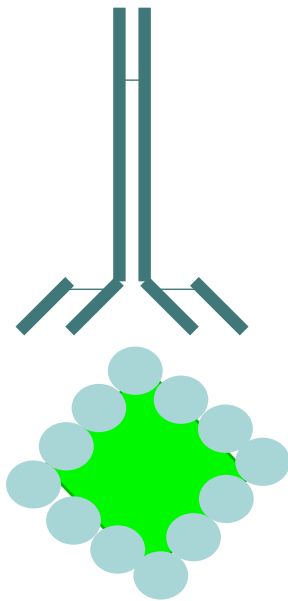
T cell receptor



MHC
restriction

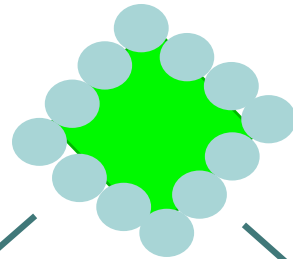
Antigen Recognition

Antibody

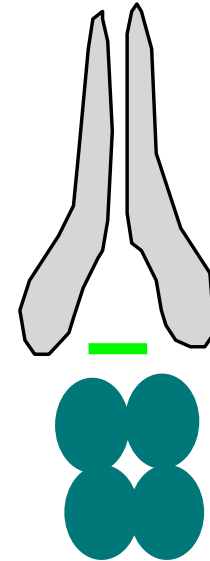


Direct
binding

Virus



T cell receptor



MHC
restriction



Dynamics of T Cell response

T cell expansion

T cell death

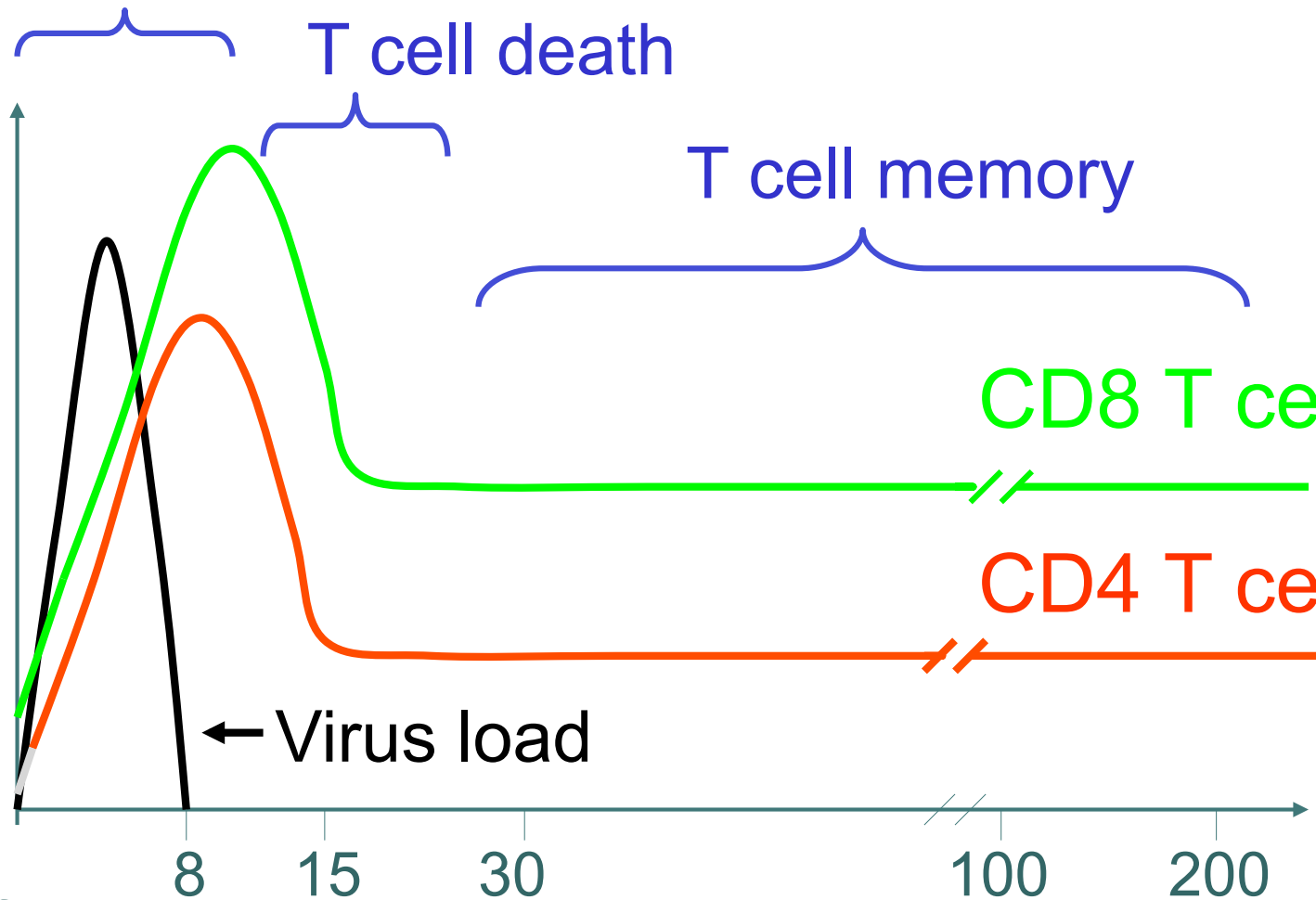
T cell memory

CD8 T cells

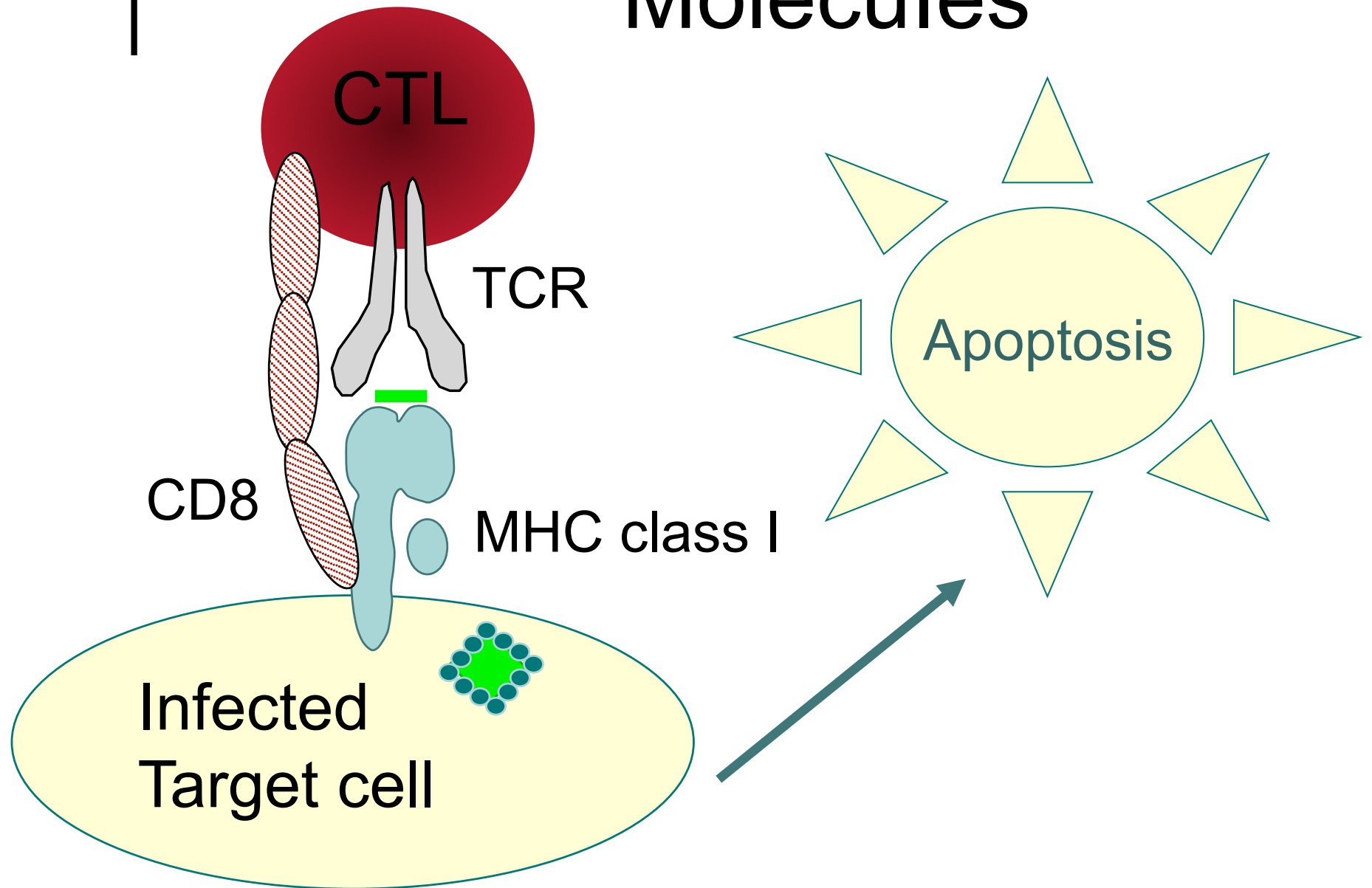
CD4 T cells

Virus load

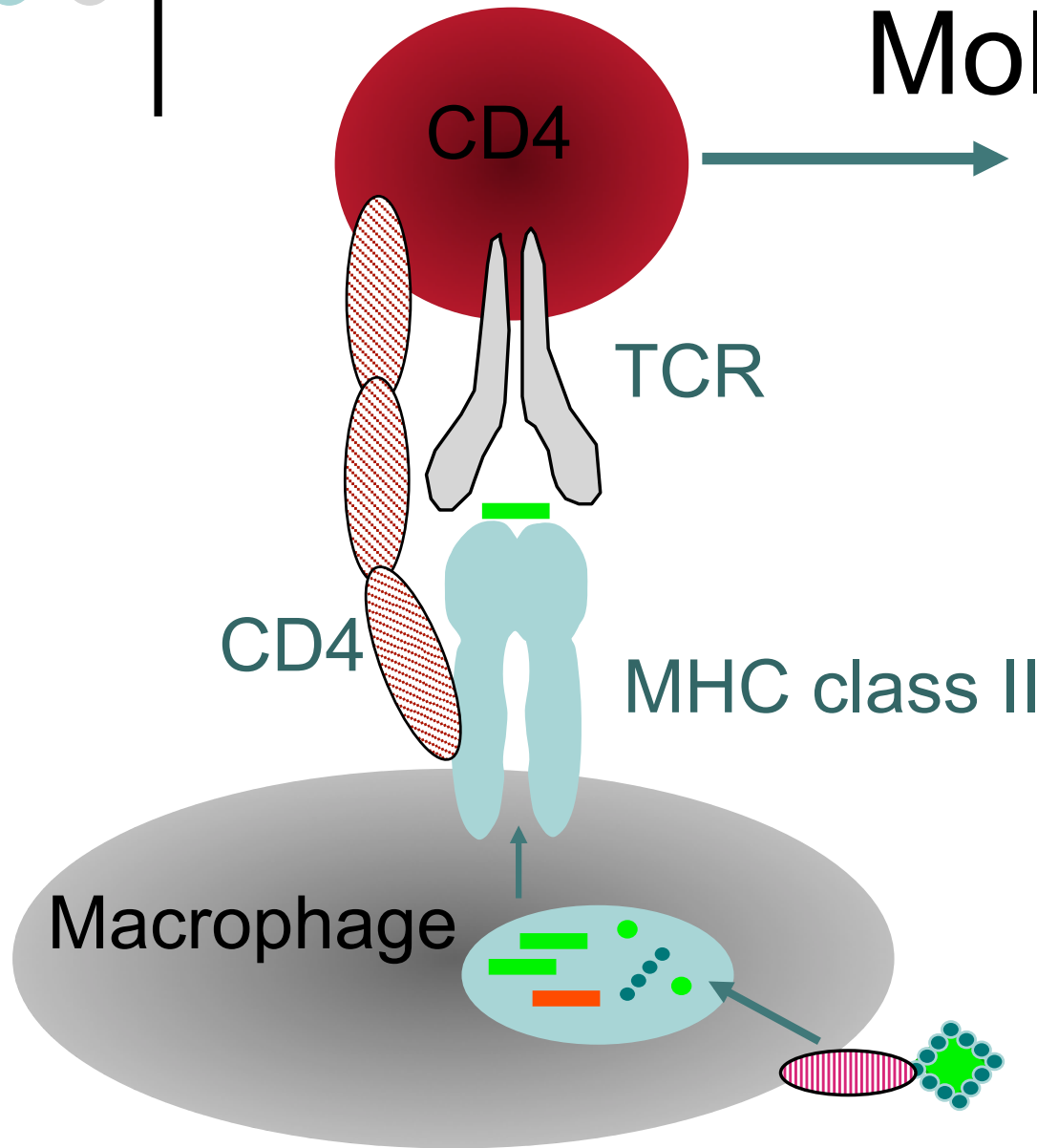
Days post infection



Role of MHC Class I Molecules



Role of MHC Class II Molecules



IFN- γ

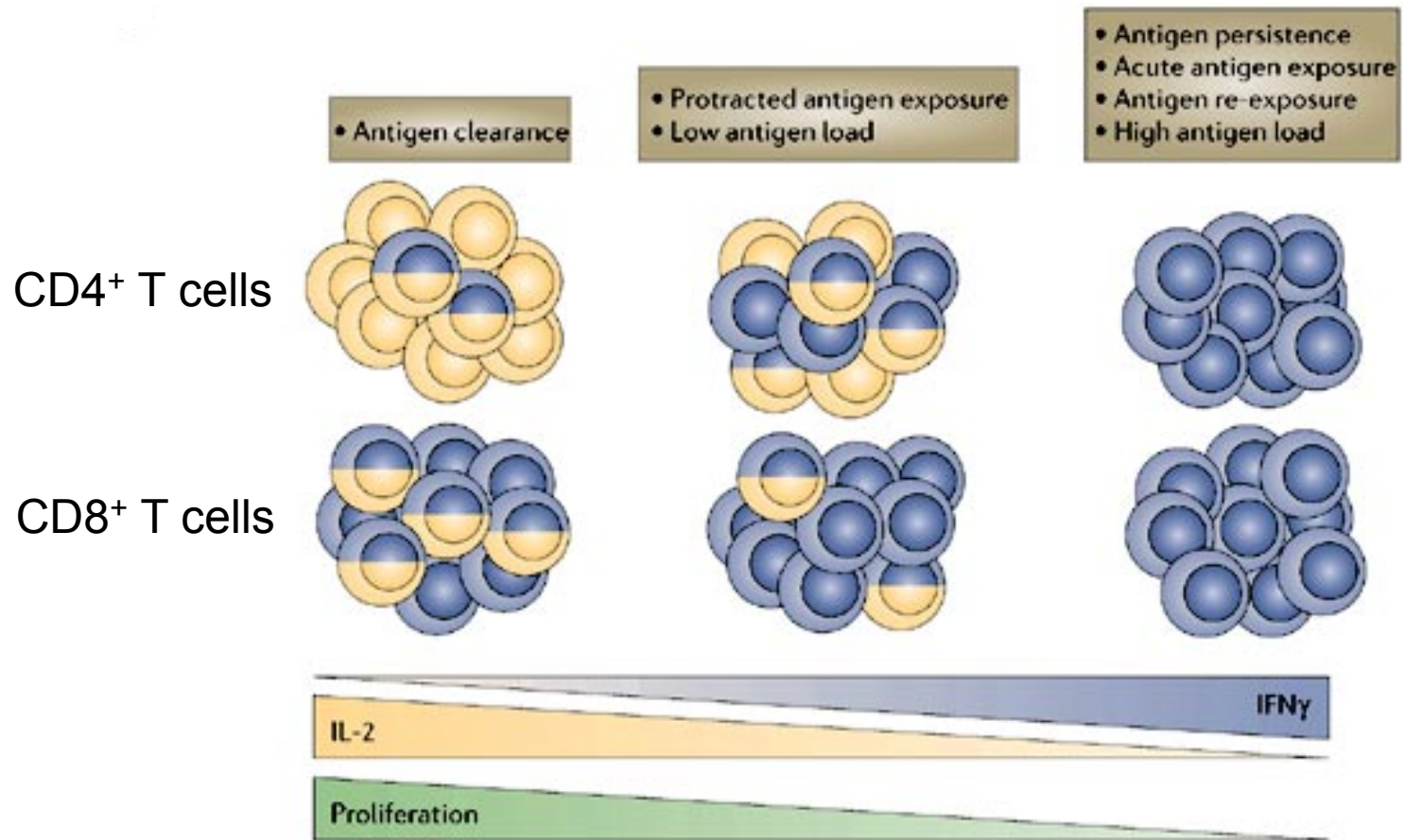
IL-4

IL-5

IL-10.....

Cytotoxicity

Functional cytokine signature Ag load





Functional Cytokine Signature – Clinical Application

- Transplantation: CMV and EBV-specific T cells
 - Correlation of specific T cell responses and reactivation of virus
- Following treatments of patients with AIDS
 - Shift from solely IFN-gamma to multifunctional CD4 response
- HCV and HBV viral infections
 - Multi-functional Hepatitis specific T cell response associated with lower levels of viraemia



Regulatory T cells (Tregs)

- Affect the magnitude and the outcome of viral infection
 - Deleterious
 - Beneficial



Deleterious Tregs

- HSV

- Animals depleted of Tregs prior to infection more effectively control the virus

- HCV and HIV

- Tregs contribute to immune dysfunction



Beneficial Tregs

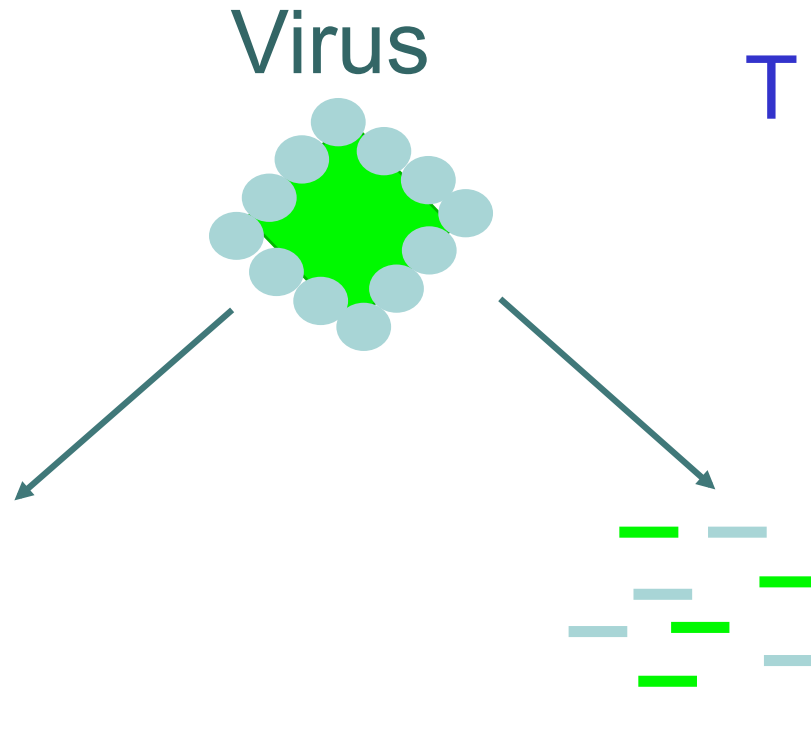
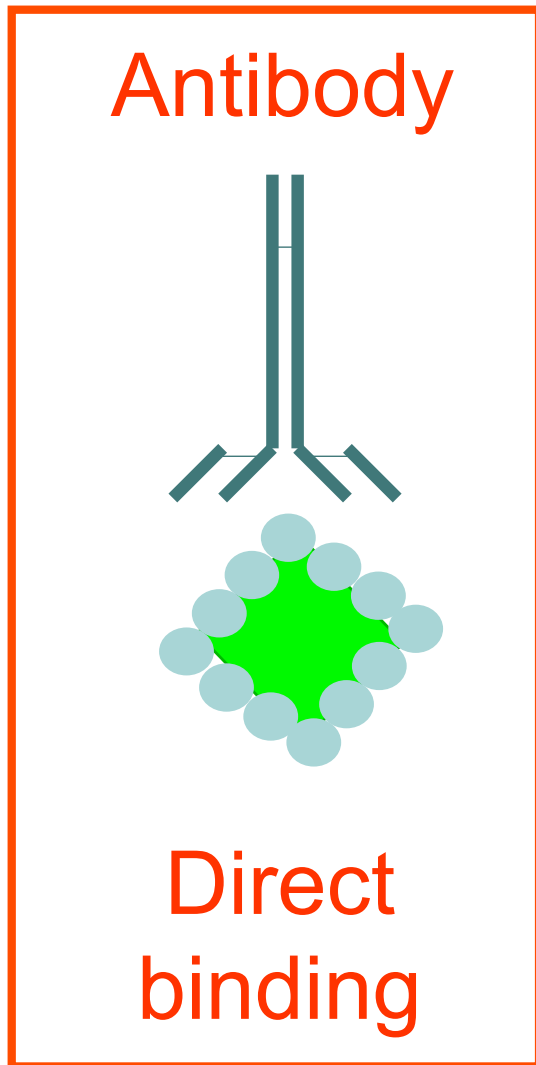
- HSV

- Tregs limit the severity of tissue damage associated with an inflammatory reaction to viral infection.

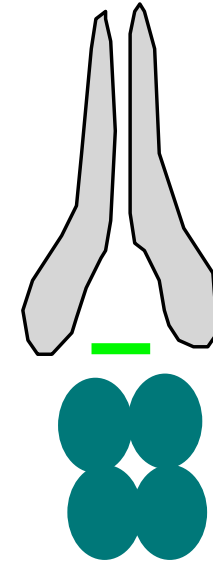
- HIV

- Limit chronic immune activation that precedes immune collapse.

Antigen Recognition



T cell receptor



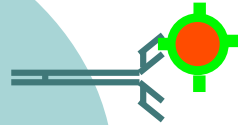
MHC restriction

B cells and anti-viral antibody



1.

B cells bind viruses through viral coat proteins



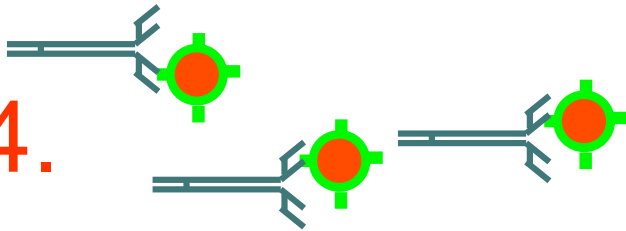
2.

Virus is Internalised & degraded



4.

Activated B cell produces antibody against viral coat protein

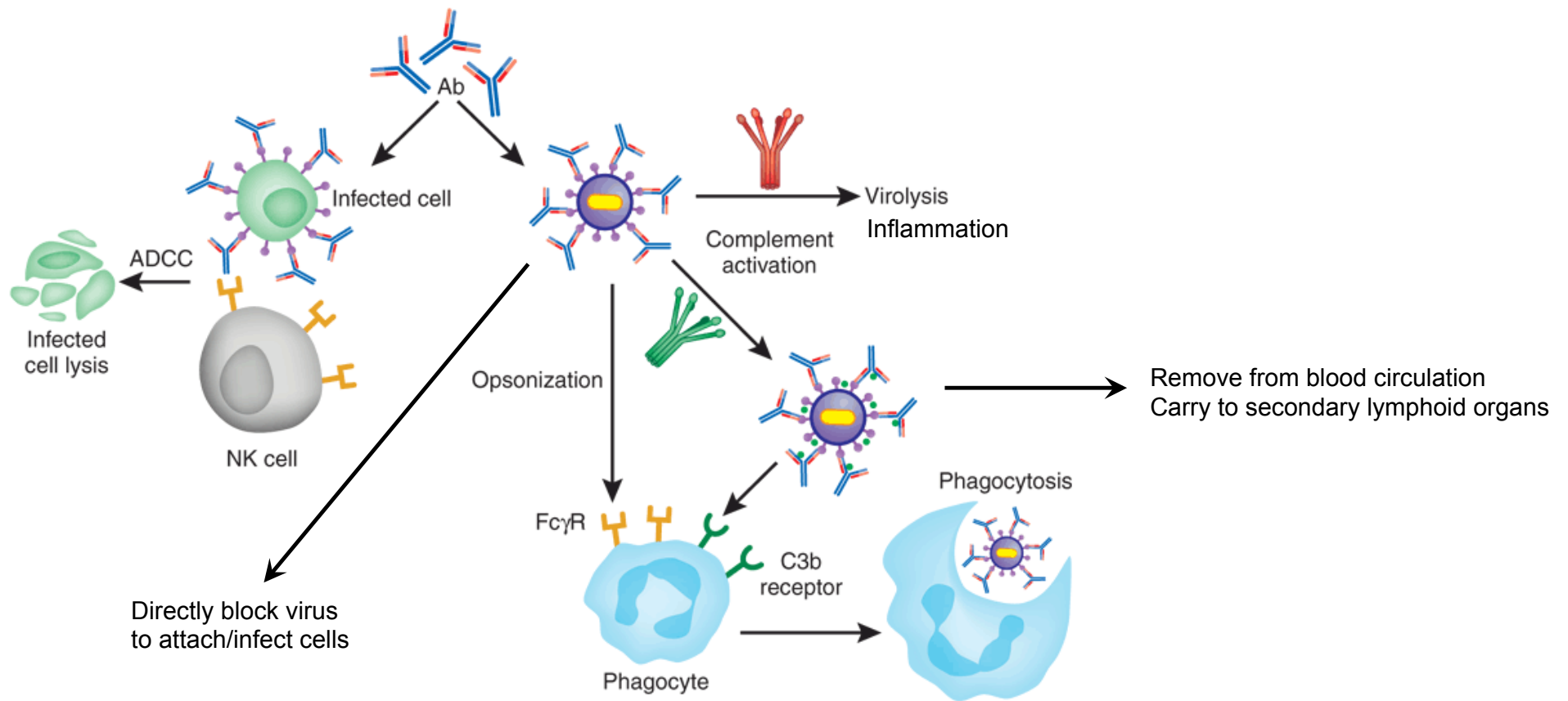


3.

Peptides of the virus are presented to the T cell which activates the B cell



Antibodies





Immunogenicity of viral surfaces

Viral Factors

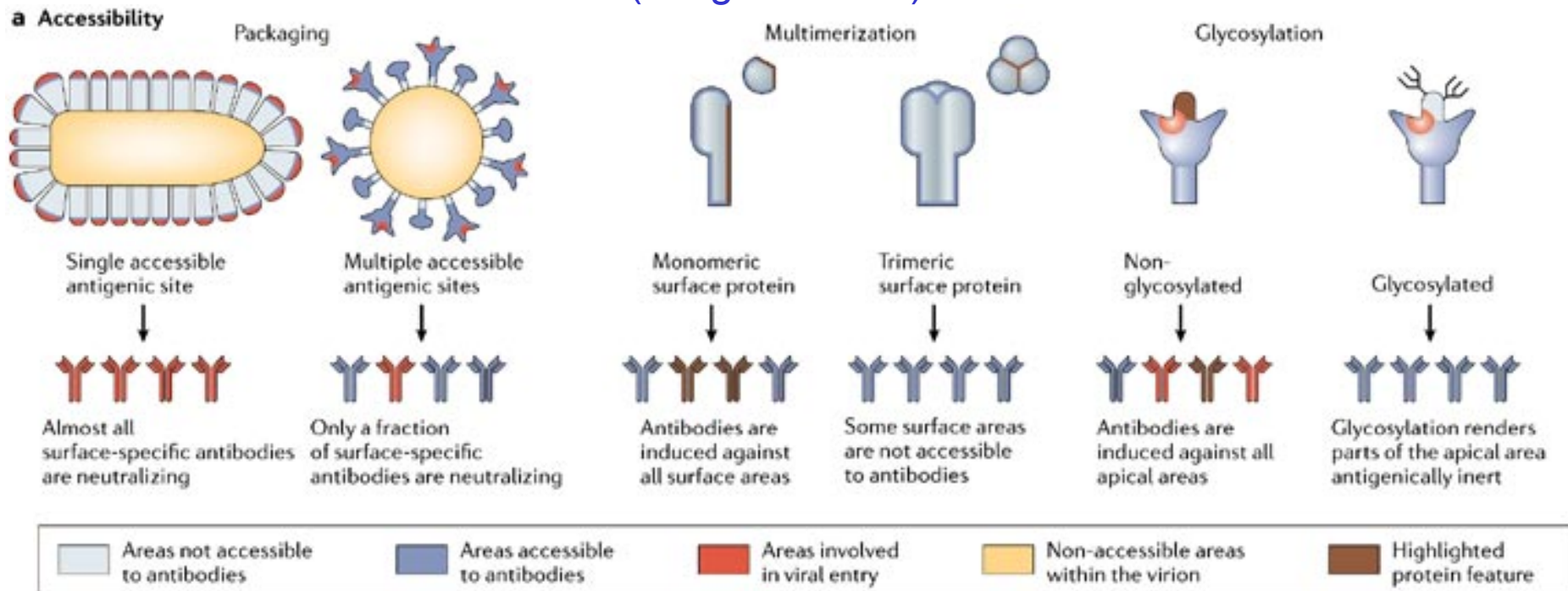
- Accessibility to Ab
- Structural arrangement of accessibility site

Host Factor

- Frequency of germ-line encoded IgG V_H - V_L region combinations with specificity for epitopes in the accessibility sites

Immunogenicity of viral surfaces

A. Accessibility (antigenic sites)

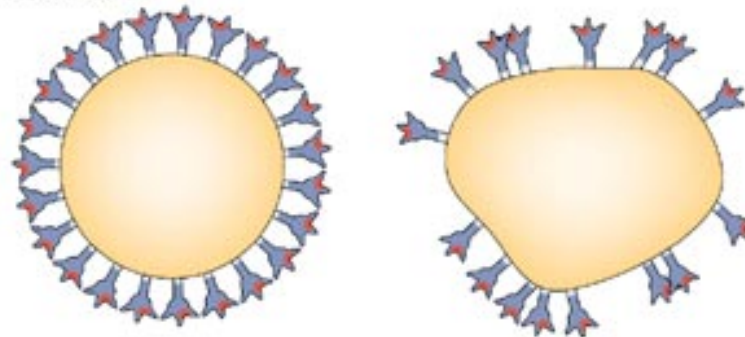




Immunogenicity of viral surfaces

B: Arrangement of Antigenic sites

b Organization



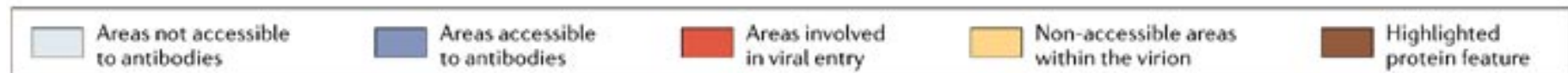
Quasi-crystalline

Random and/or mobile

T-cell-independent
antibody production

T-cell-dependent
antibody production

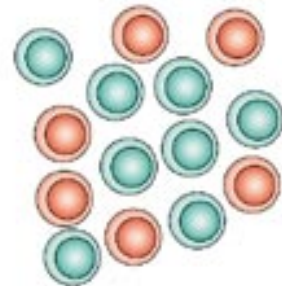
Eg: VSV





Immunogenicity of viral surfaces

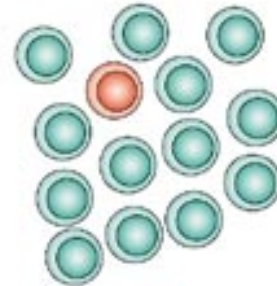
C: Frequency of IgG combinations



High-affinity
V regions frequently
encoded in germline



Protective antibody response



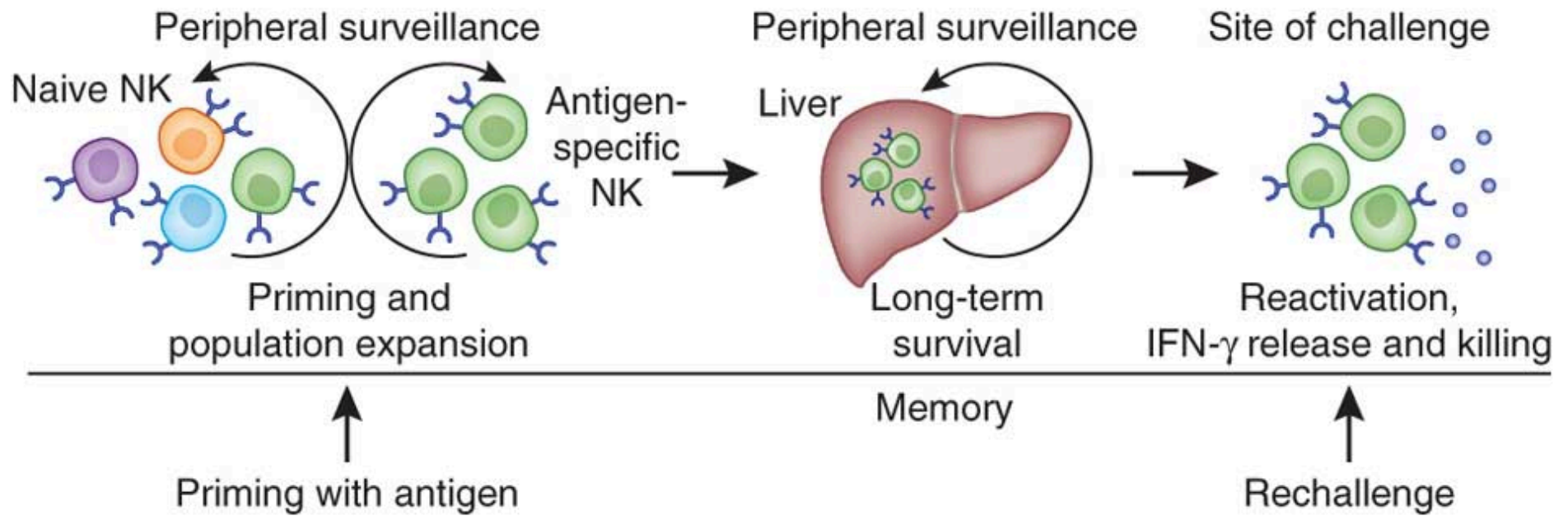
High-affinity
V regions rarely
encoded in germline



Poor antibody response



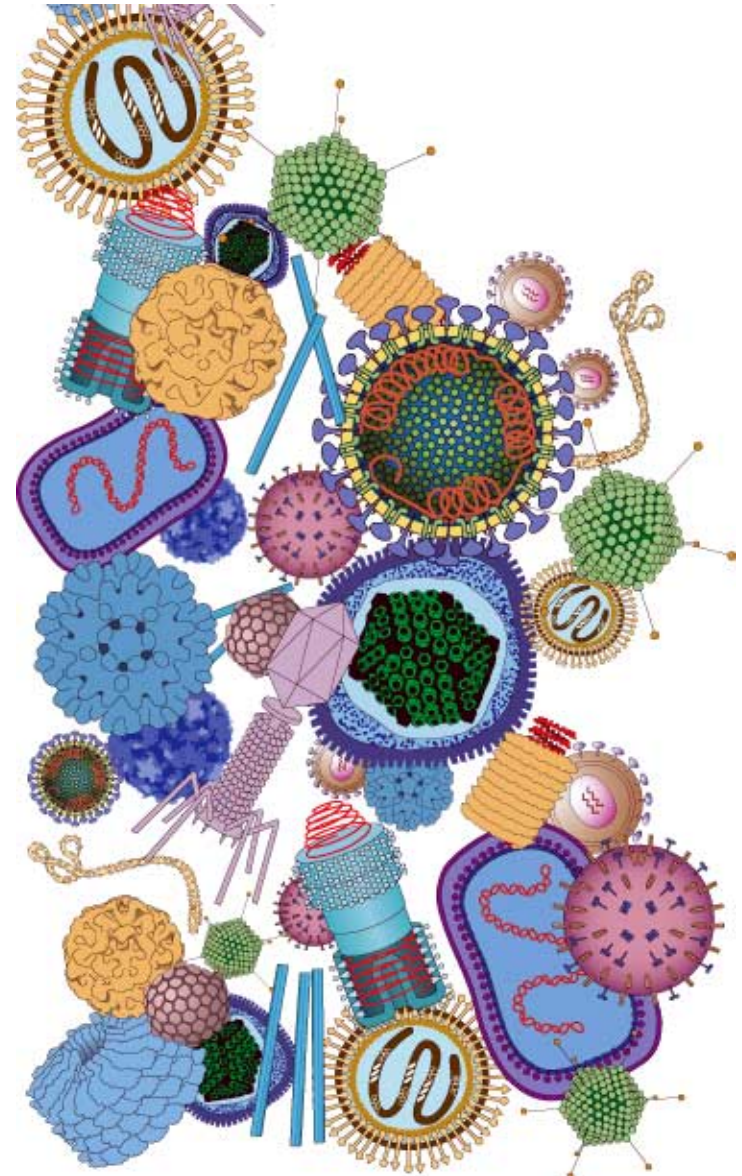
Memory NK cells





Overview

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- Immune persistence/evasion





Viral Immune evasion and subversion

Strategies employed by viruses to overcome every arm of the immune response



Immune evasion/subversion strategies

- Change viral genome
- Inhibit Complement
- Evade NK cells
- Inhibit Interferons
- Interfere with Ab responses
- Interfere with T cells responses
- Inhibit and modulate CK and CC

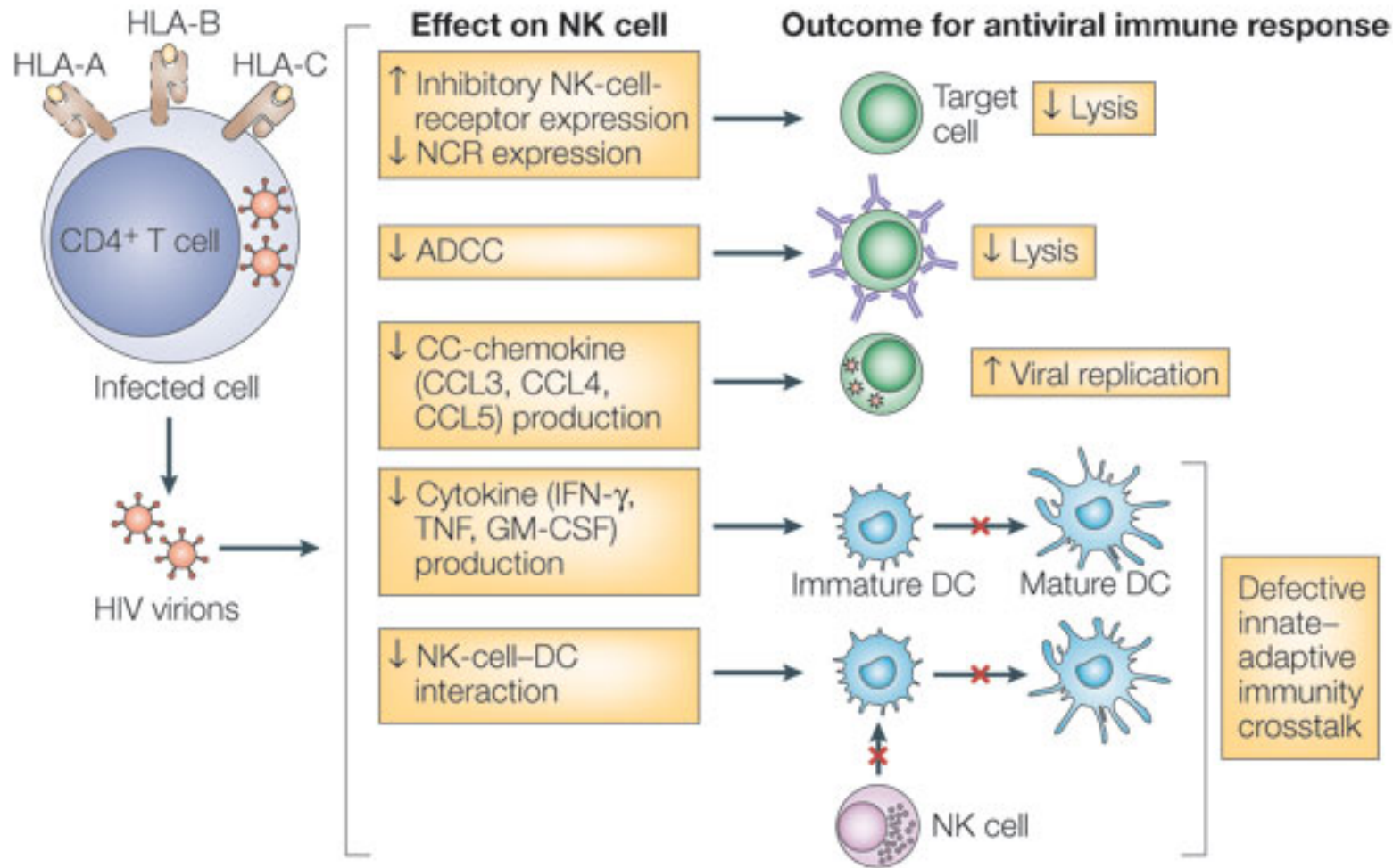


Immune evasion/subversion strategies

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Modulation of NK cell function





Interference with Antibody response

Interference with recognition by B cells

Expression of neutralizing epitopes recognized by few and low-affinity B cells



Depletion of B-cell subsets



Interference with normal T-cell-B-cell interaction

Abnormal T-helper-cell function, leading to polyclonal B-cell activation



Physical or functional depletion of T-helper cells



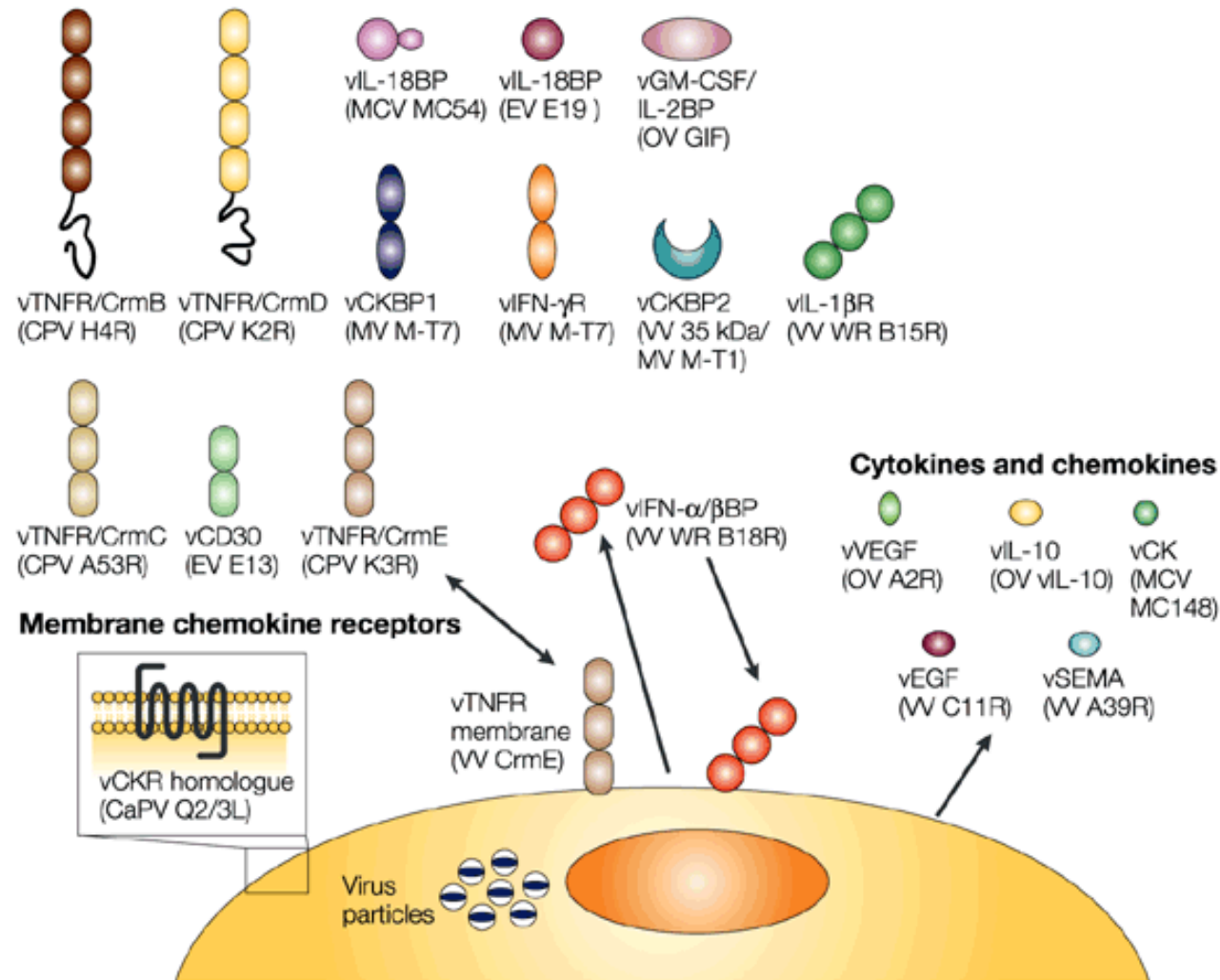
HIV

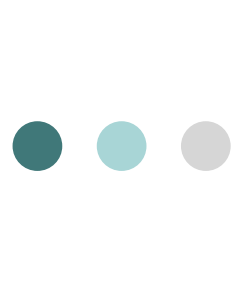
Disruption of lymphoid architecture



● T cell ● Neutralizing B cell ● ● ● Non-neutralizing or irrelevant B cell

Cytokine mimicry





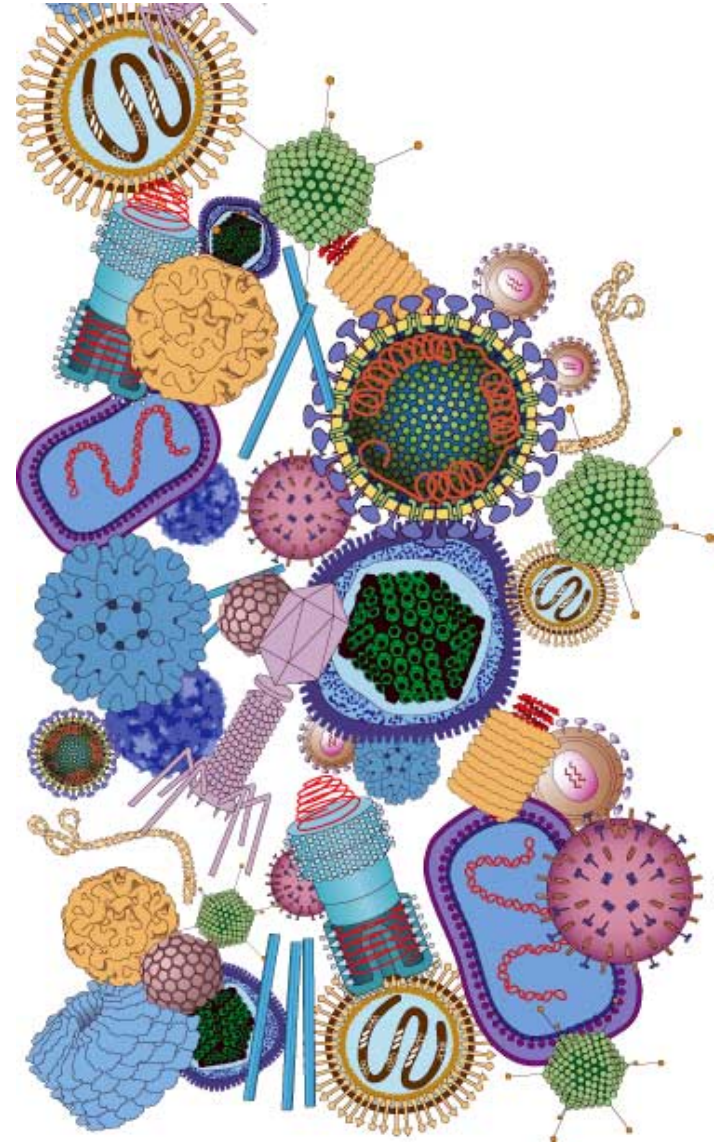
Consequences of the failure to eliminate virus

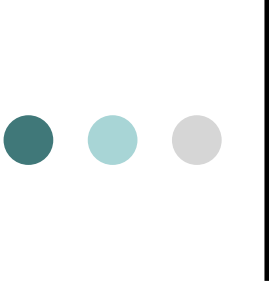
- Latent eg: Herpes Simplex Virus
 - Virus not normally detected.
 - Quiescent infection, episodes of reactivation
- Persistent eg: Epstein Barr Virus
 - Infection persists and causes prolonged disease which is slow to develop
- Oncogenic eg: Rous Sarcoma Virus
 - Part of the viral genome is incorporated into the host genome, causing malignant transformation.



Summary

- Wide variety of viruses
- Wide variety of Immune responses to viruses
- Innate responses
- Adaptive responses
- Evasion/subversion





References

- Viral immune evasion: a masterpiece of evolution. *Immunogenetics* (2002) 54: 527-542
- Anti-viral Ab responses. *Nature Reviews Immunology* (2006) 6: 231-243
- NK cells in HIV infection. *Nature Reviews Immunology* (2005) 5: 835-843
- Subversion of immune responses by Hepatitis C virus. *Current Opinion in Immunology*. (2003) 15: 443-449
- Innate or adaptive immunity? The example of natural killer cells. *Science* (2011) 331:44-49
- Natural killer cell memory. *Nature Immunology* (2011) 12:500-508