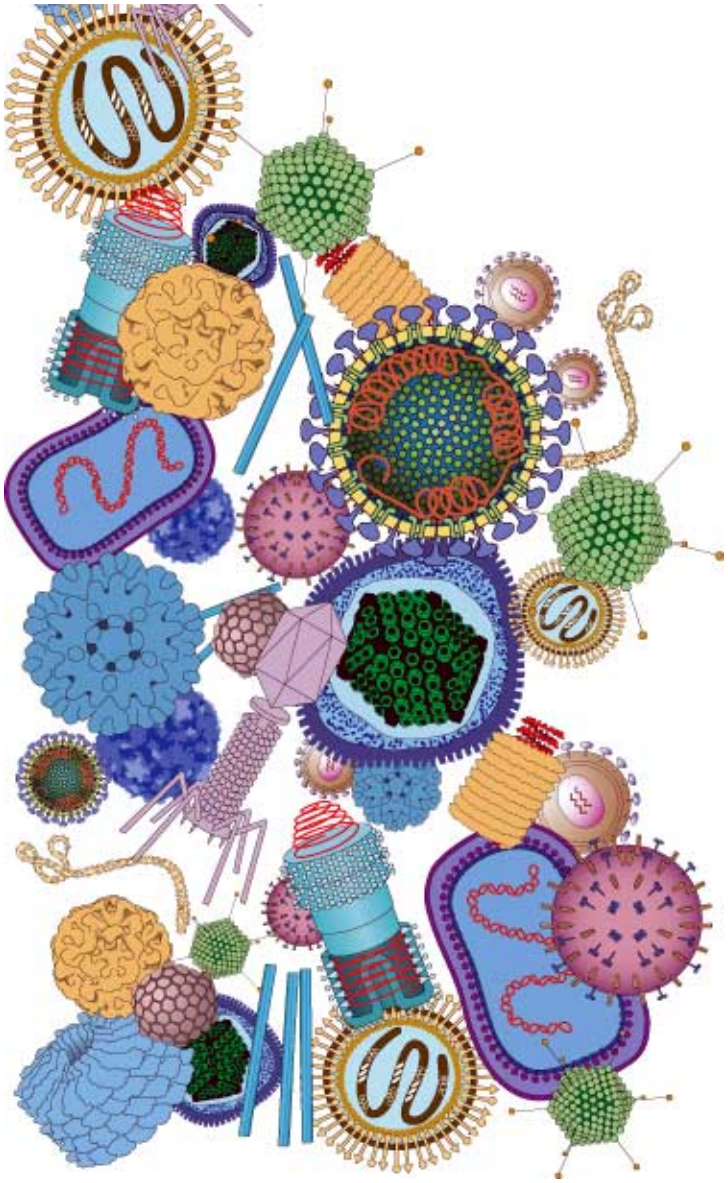
Immune Responses to Viruses

Juthathip Mongkolsapapya

Overview

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



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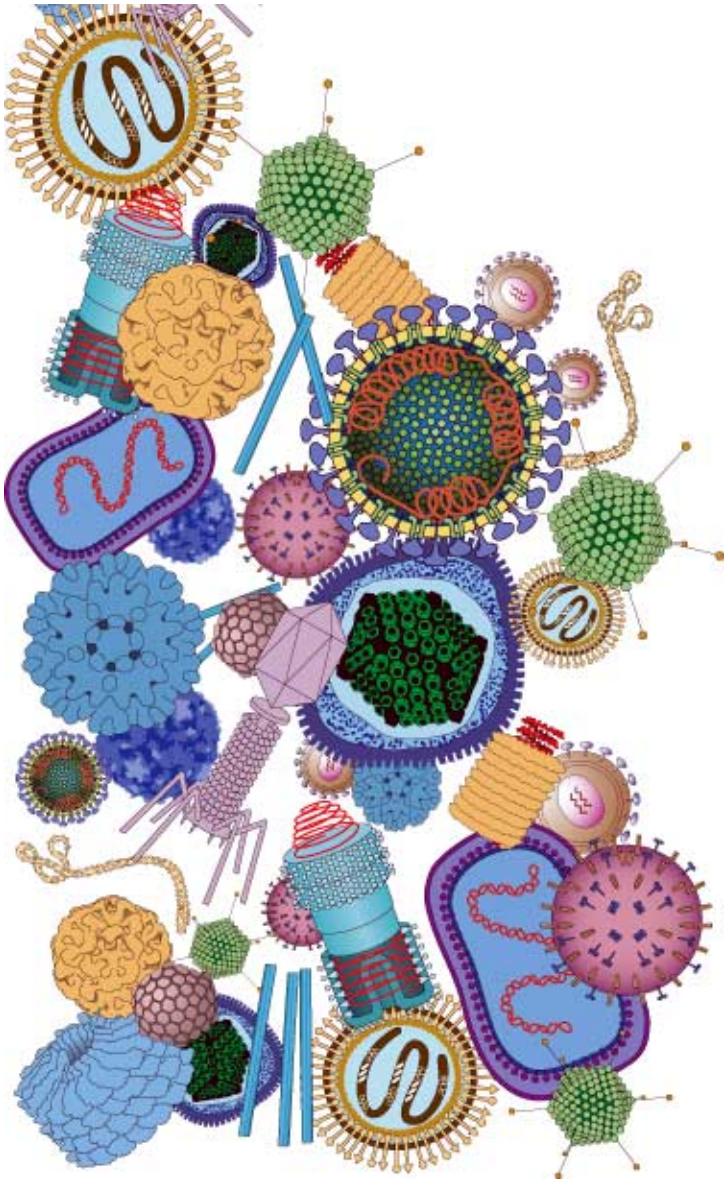


What is a virus?

- 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

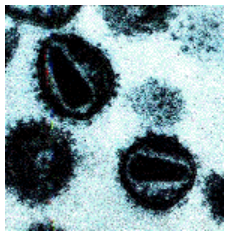
www.web-books.com/mobio/free/Ch1E2.htm

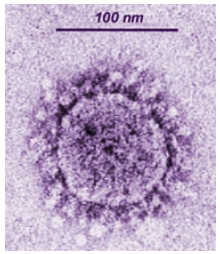
Important Human Virus Diseases

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

Emerging and re-emerging Viruses

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

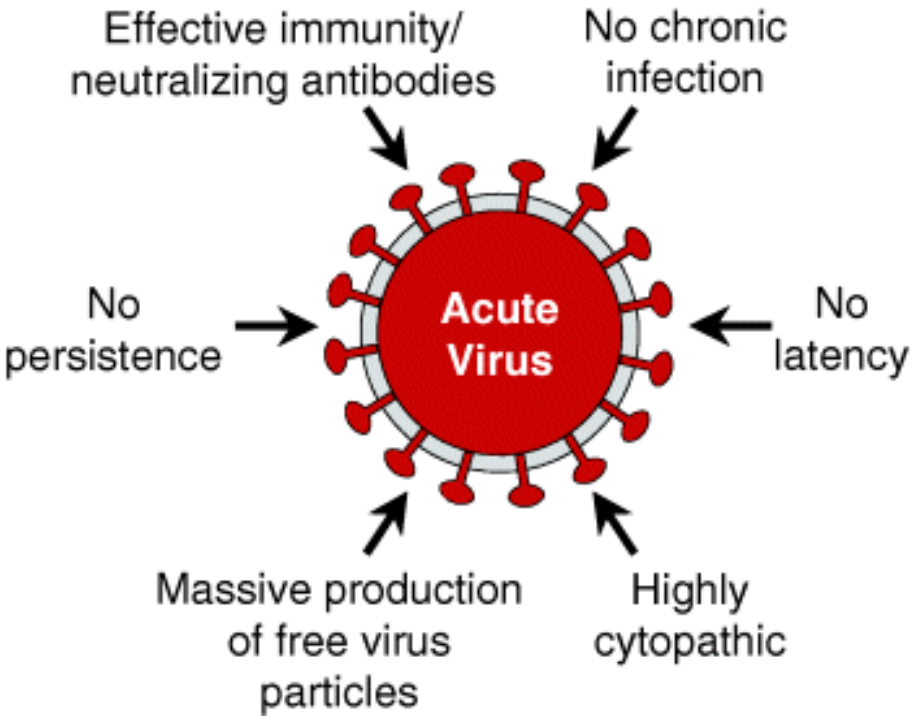




Properties of viruses I

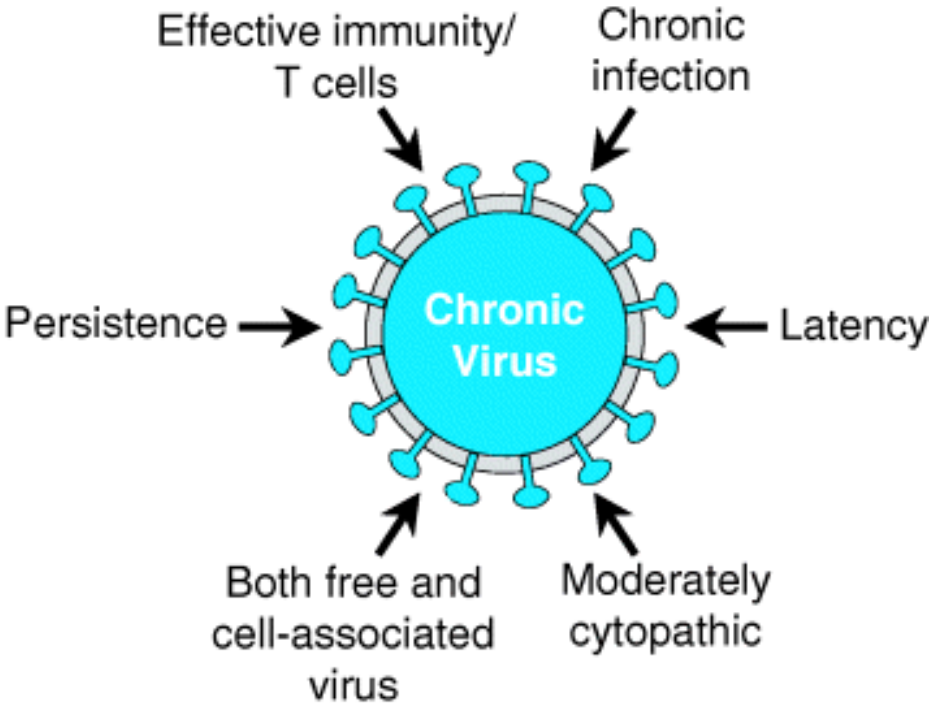
- Cytopathic or non-cytopathic
  - Cytopathic eg: Hep B
  - Non-cytopathic eg: Rhinovirus
- Acute or Chronic
  - Acute eg: Ebola Virus
  - Chronic eg: Cytomegalovirus

Acute vs Chronic Viruses



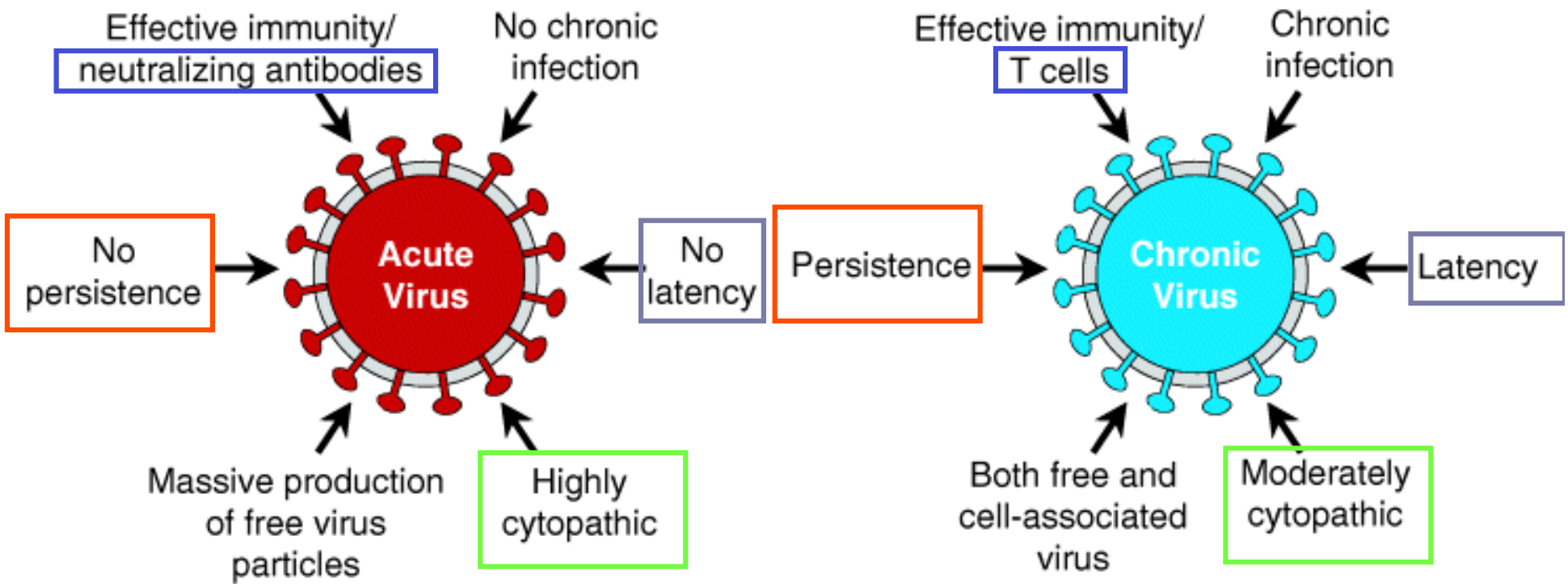
Acute

Acute vs Chronic Viruses



Chronic

Acute vs Chronic Viruses



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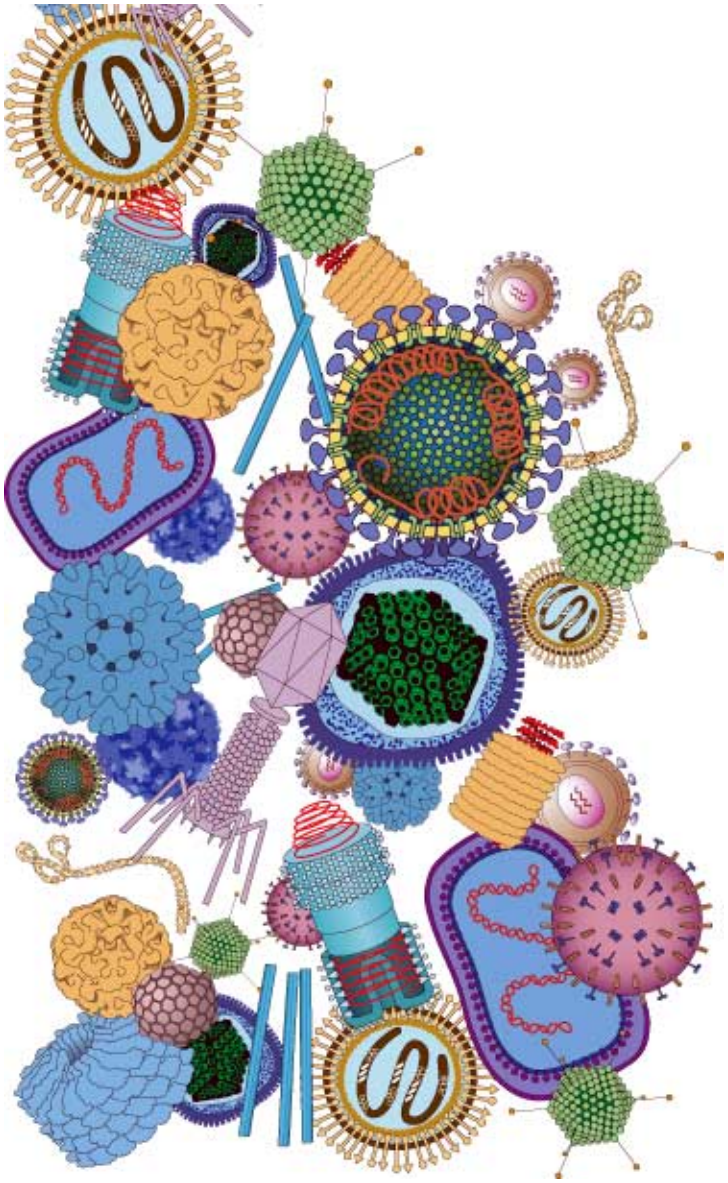
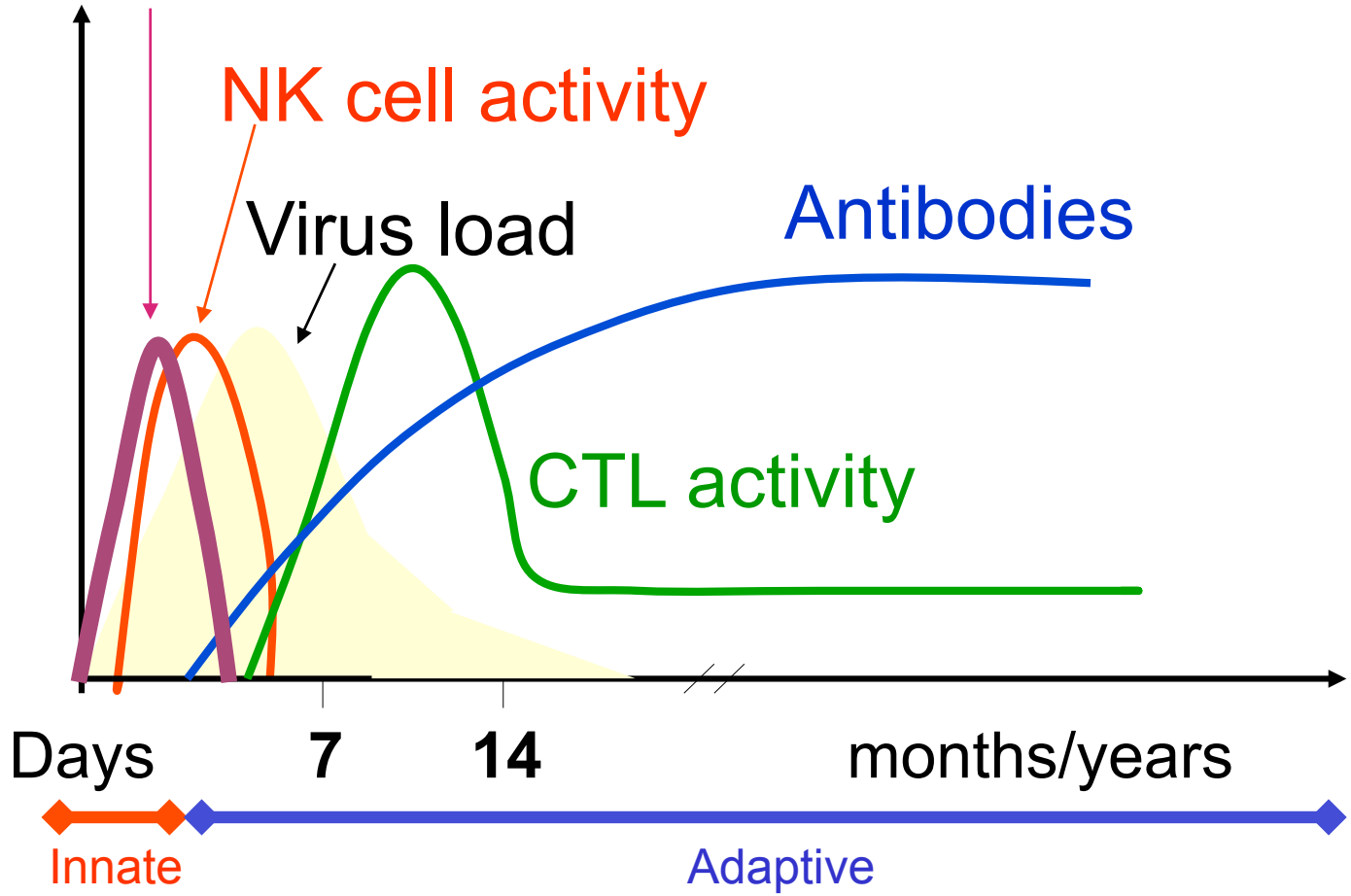


Kinetics of virus induced immunity

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



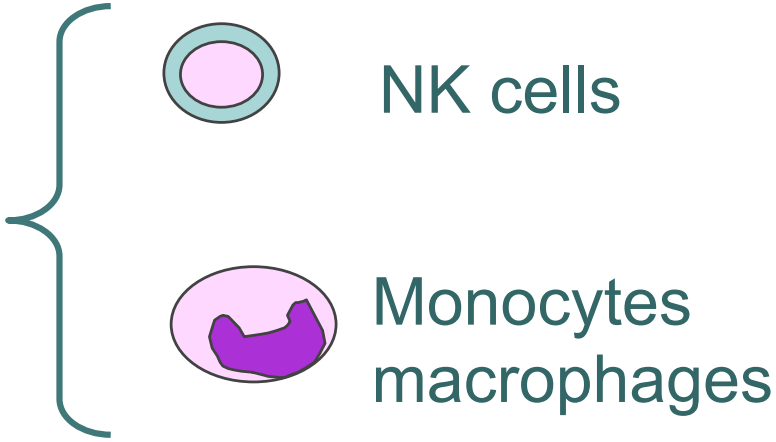
Innate and adaptive immunity I

- 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

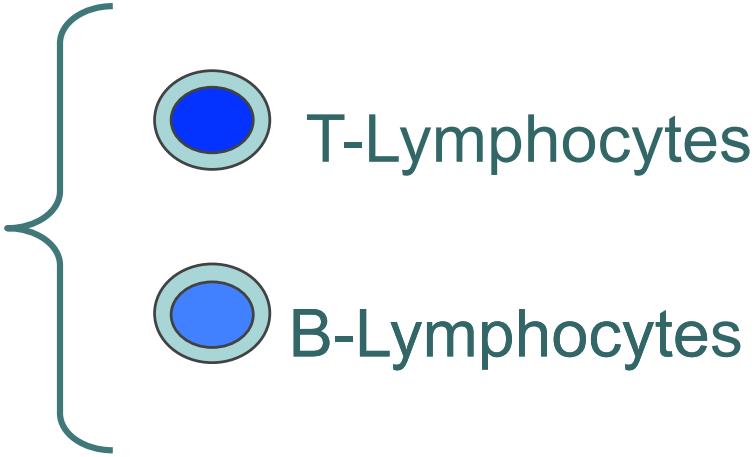
Innate

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



Adaptive

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



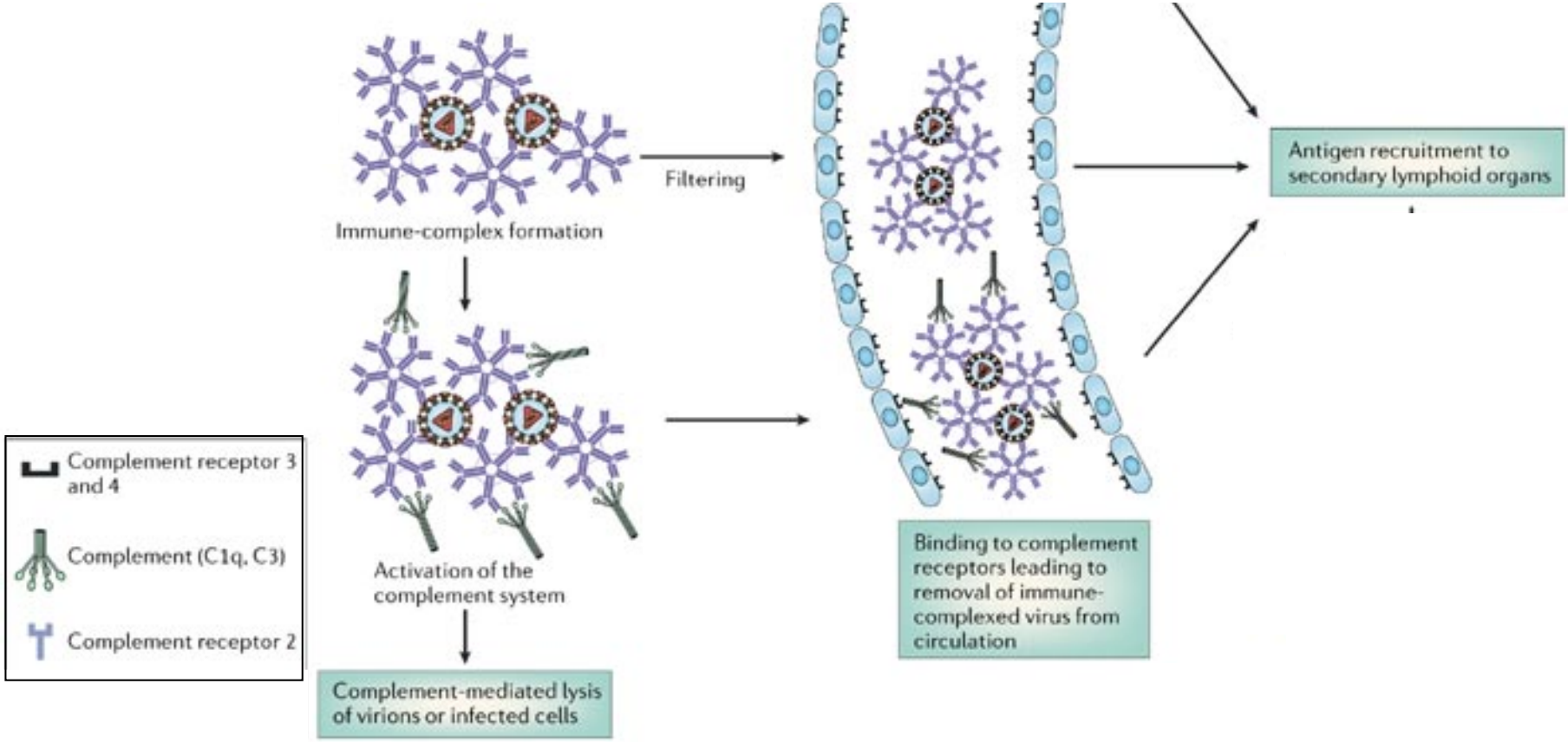
Innate immunity to viruses

- 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


Complement receptor 3 and 4
Complement (C1q, C3)
Complement receptor 2
Immune-complex formation
Filtering
Activation of the complement system
Complement-mediated lysis of virions or infected cells
Binding to complement receptors leading to removal of immune-complexed virus from circulation
Antigen recruitment to secondary lymphoid organs

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

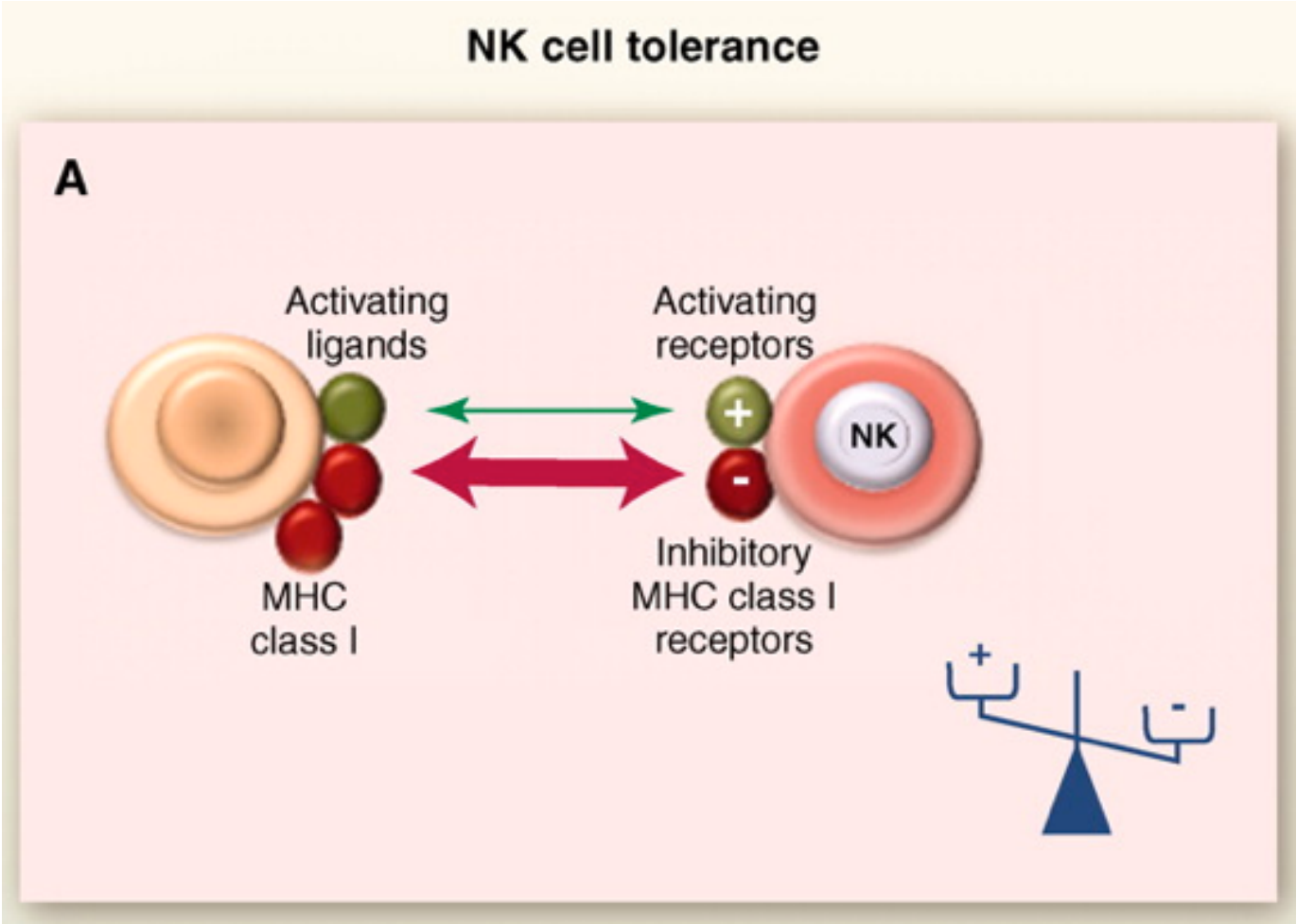
NK cells and viruses

- 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

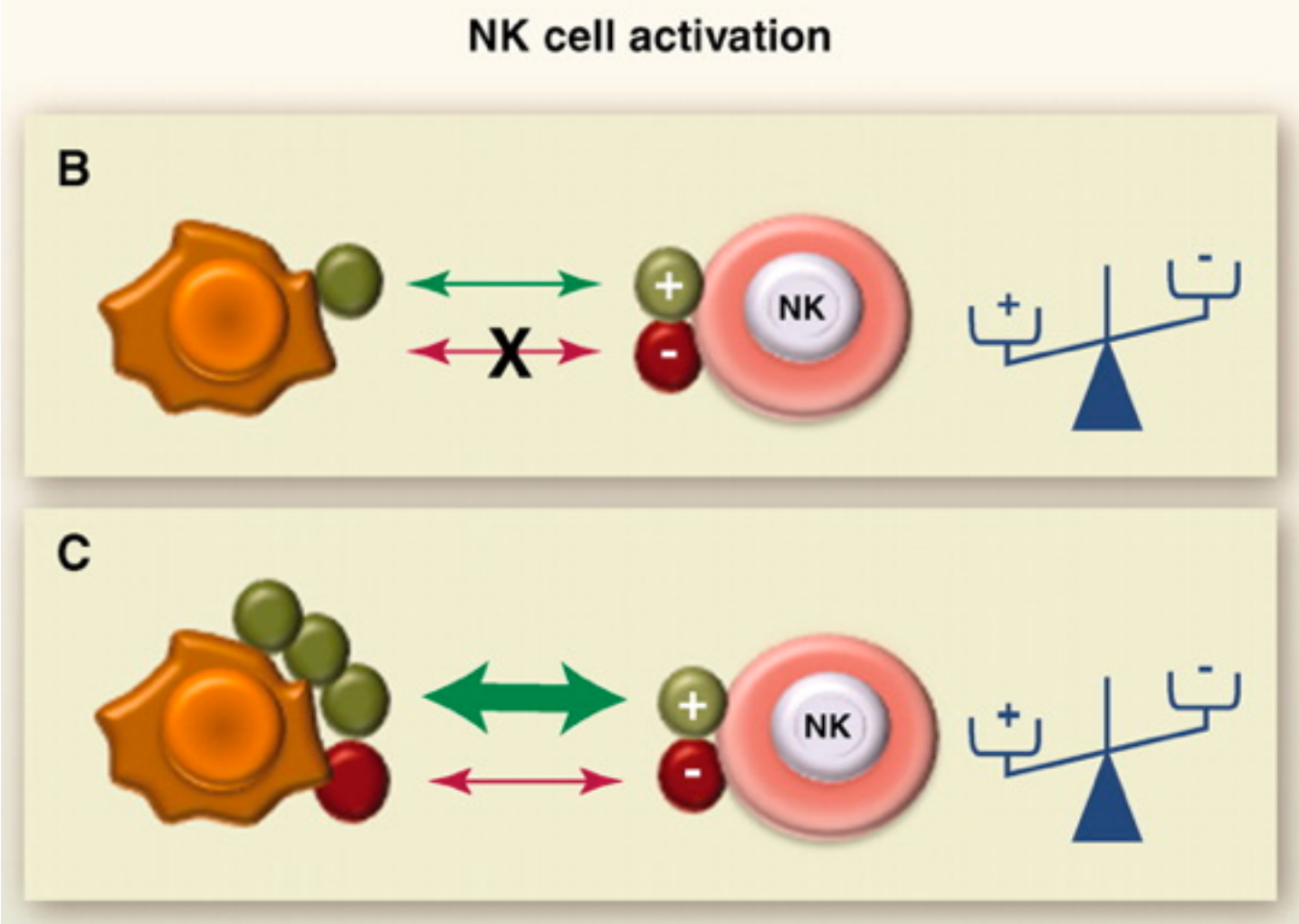
- Eliminate viral infected cells by:
  - Cytolytic mechanisms
    - NK cell receptors
    - ADCC
  - Non-cytolytic mechanisms
    - Chemokine secretion
    - Cytokine secretion
    - Effector cell recruitment

NK cell recognition of virus infected cell



Science (2011) 331:44-49

NK cell recognition of virus infected cell



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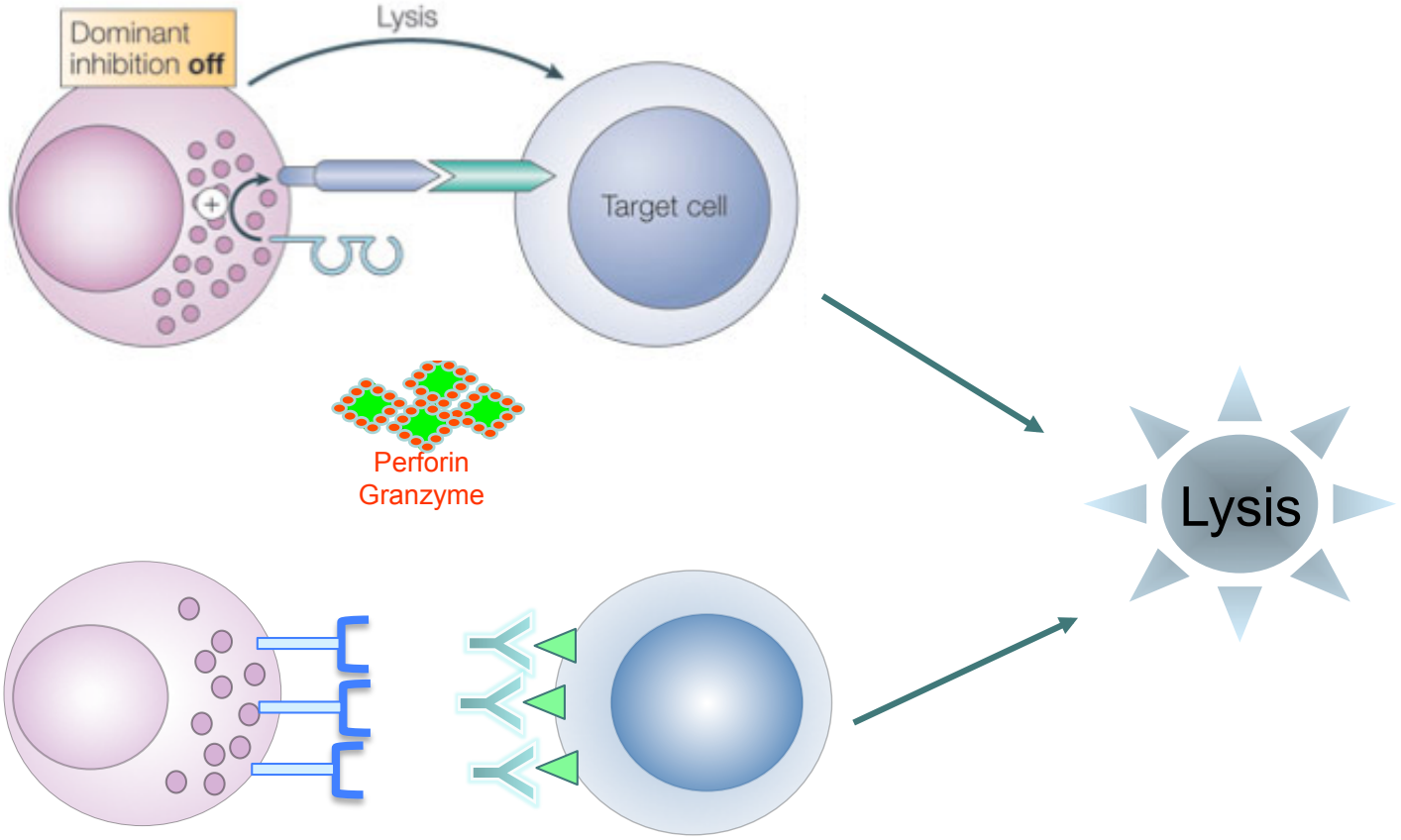
NK cell killing mechanisms – Cytolytic

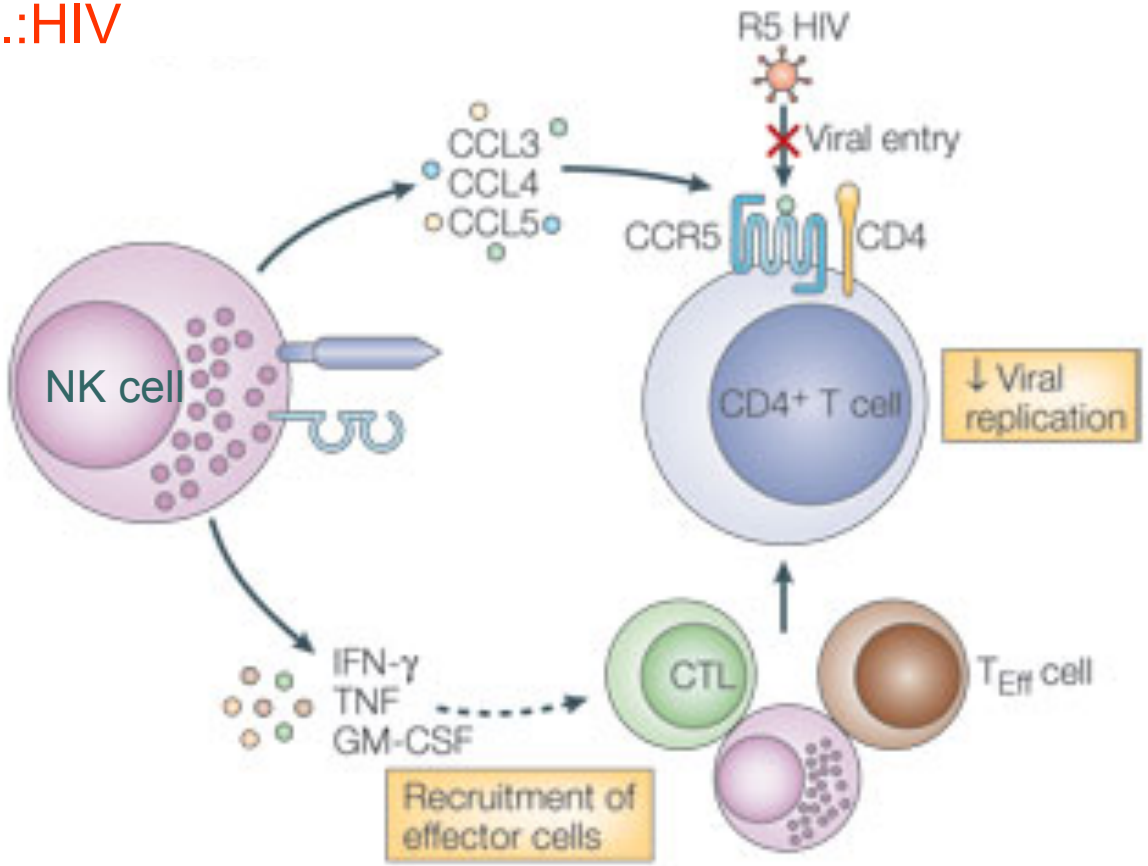
Activating receptor



ADCC

NK cell killing mechanisms – Non-cytolytic

Eg.:HIV



Adaptive immune response to viruses

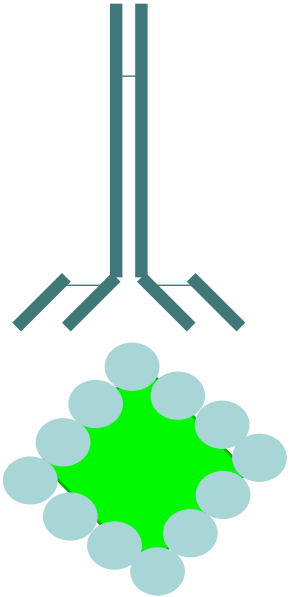
- $CD4^+$ T helper cells
- $CD8^+$ T cytotoxic cells
- Regulatory T cells
- B cells

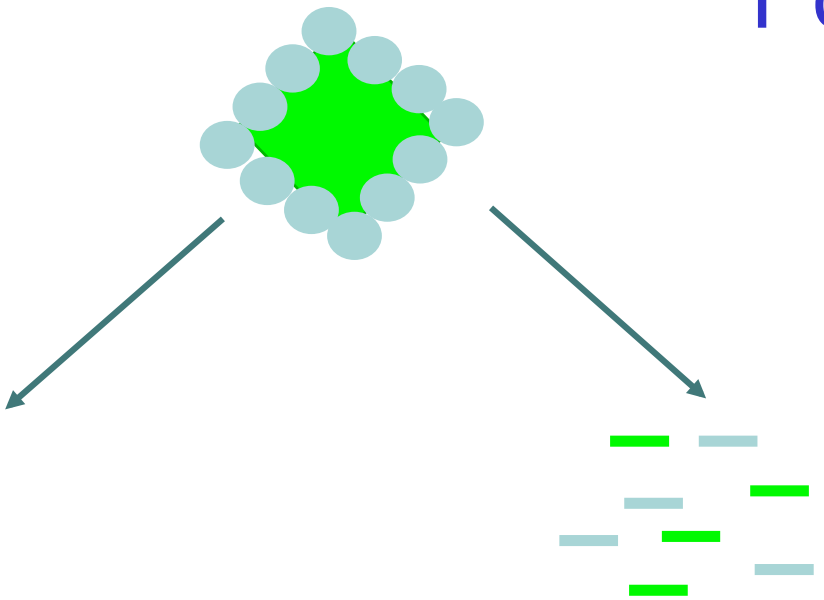
Antigen Recognition

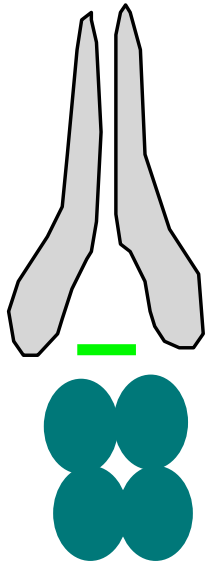
Antibody

Virus

T cell receptor



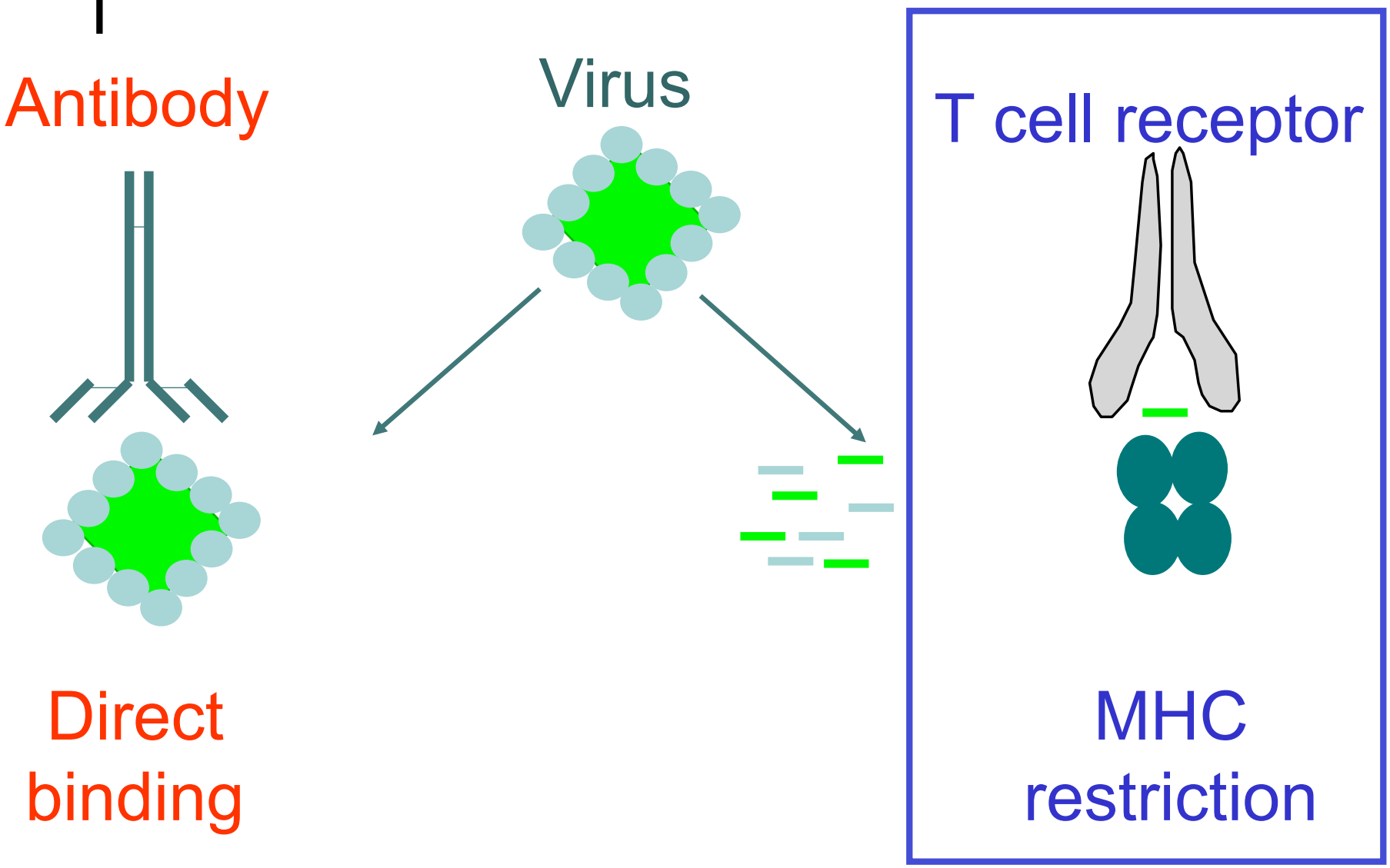




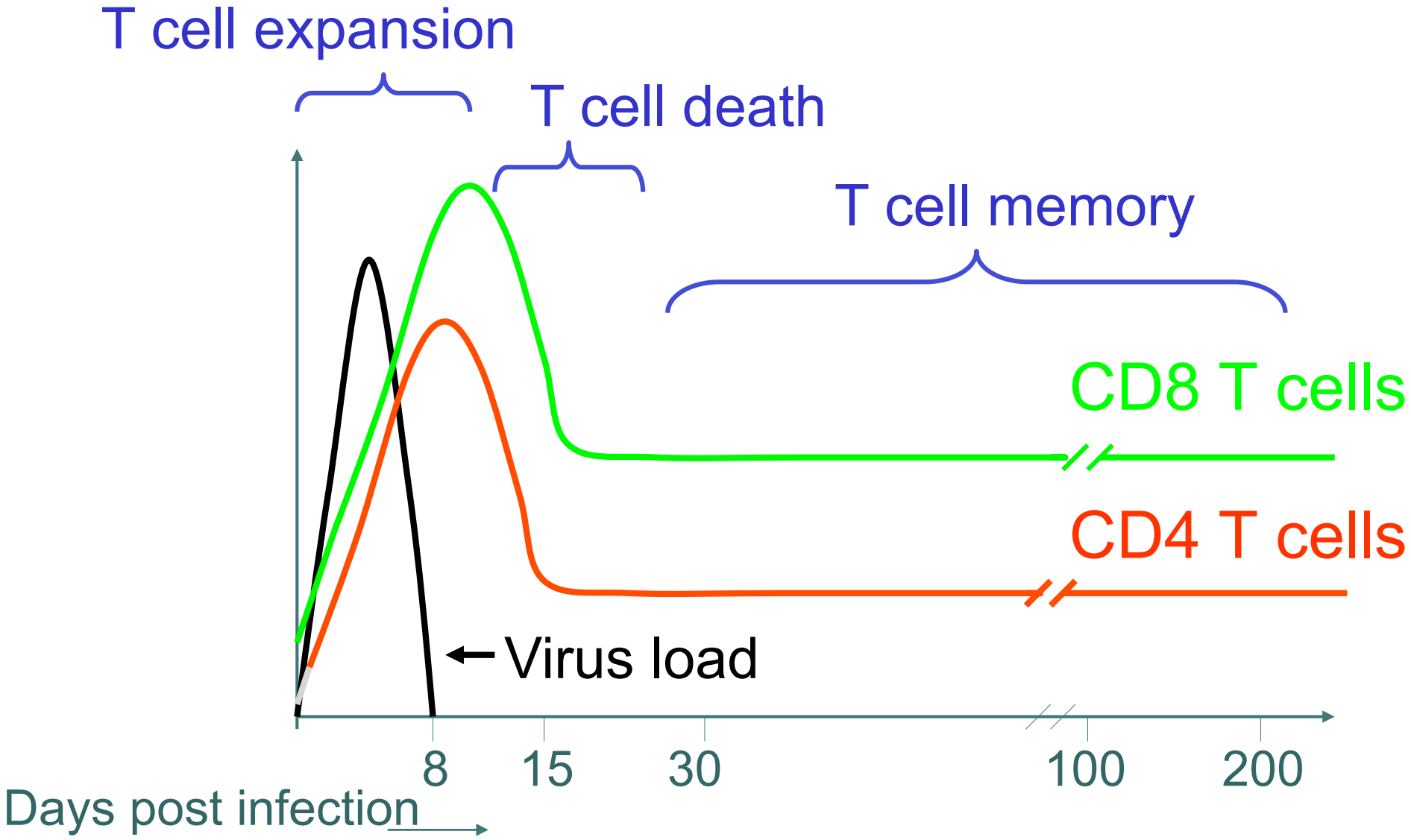
Direct binding

MHC restriction

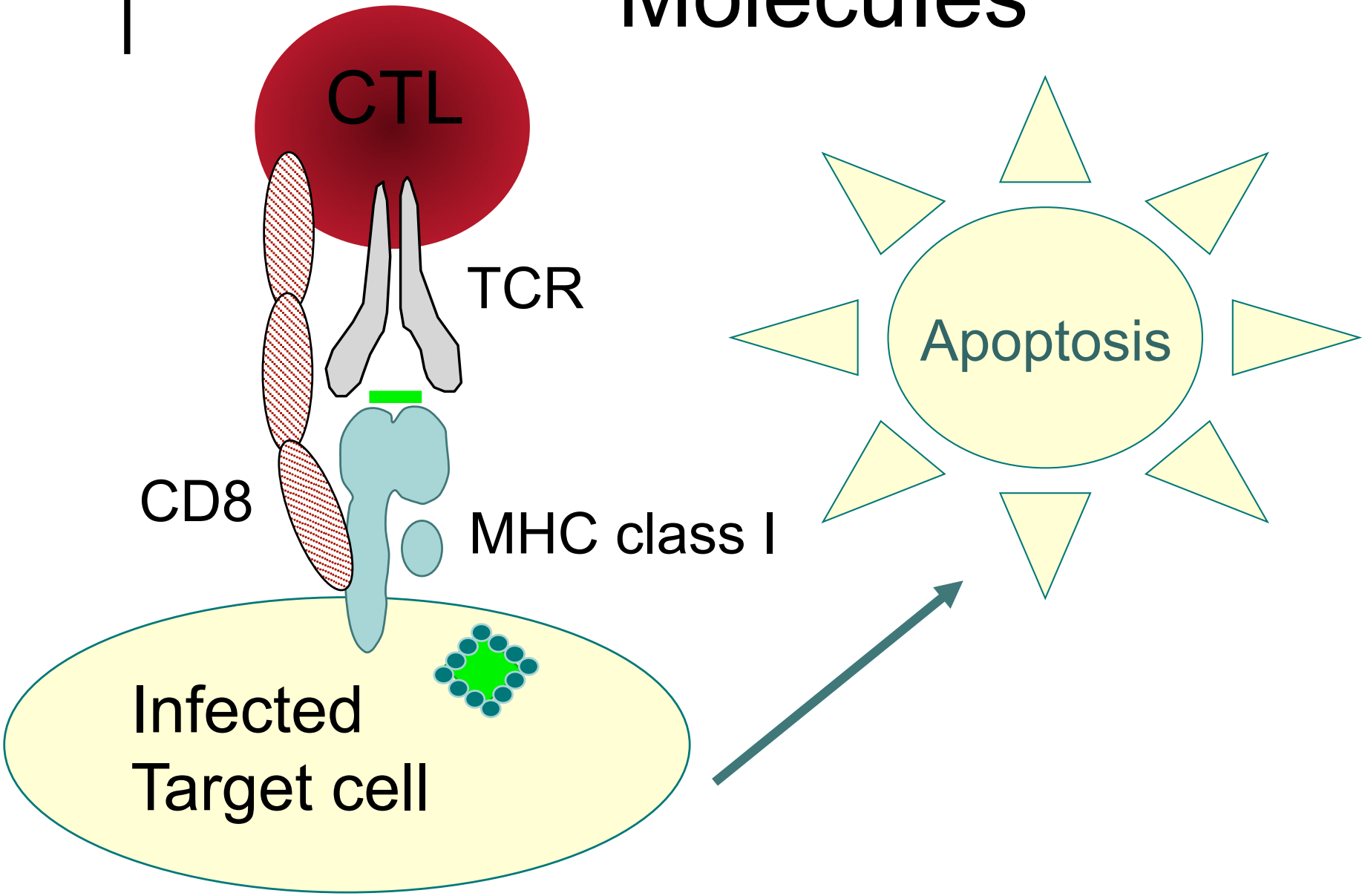
Antigen Recognition



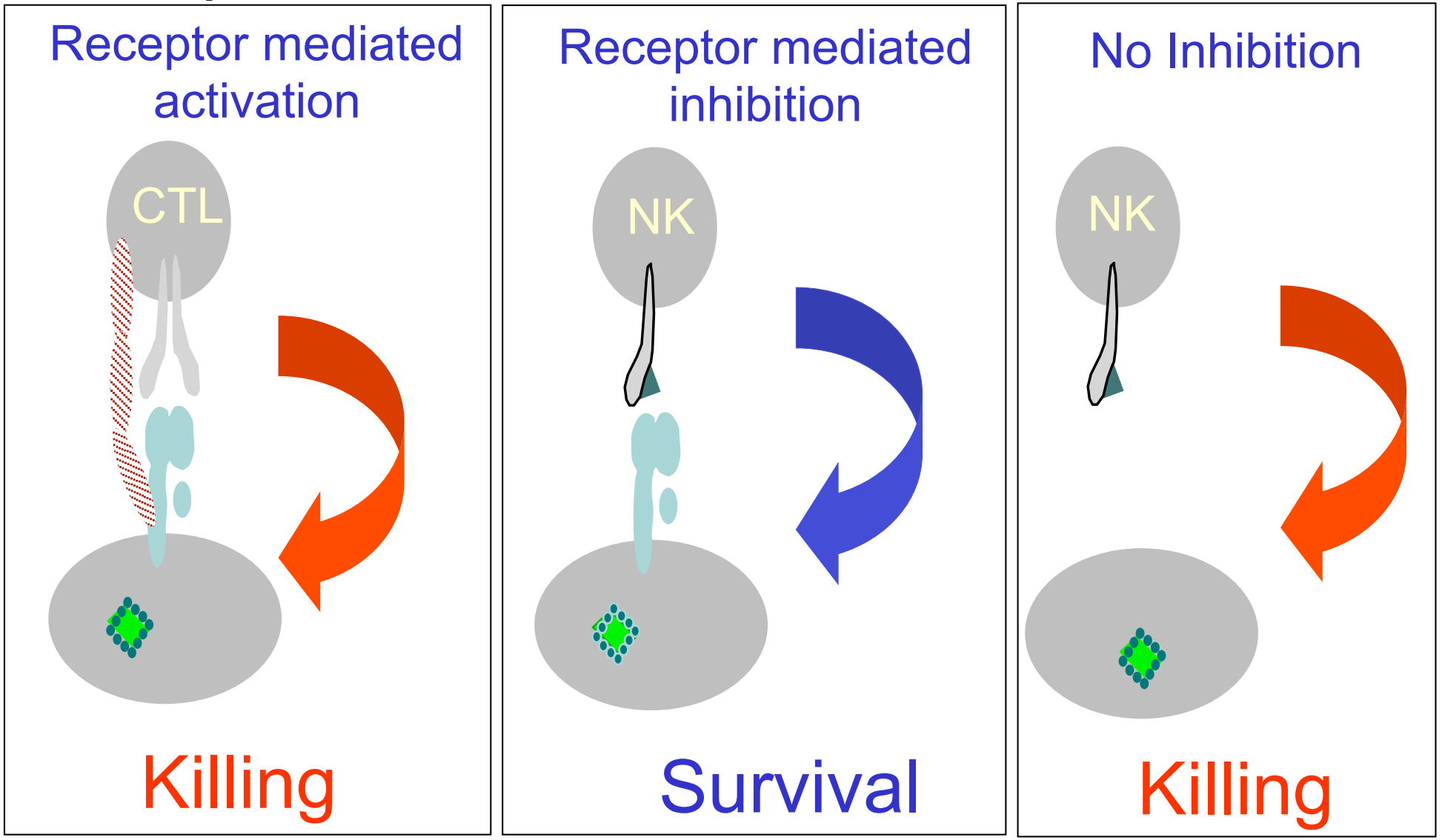
Dynamics of T Cell response



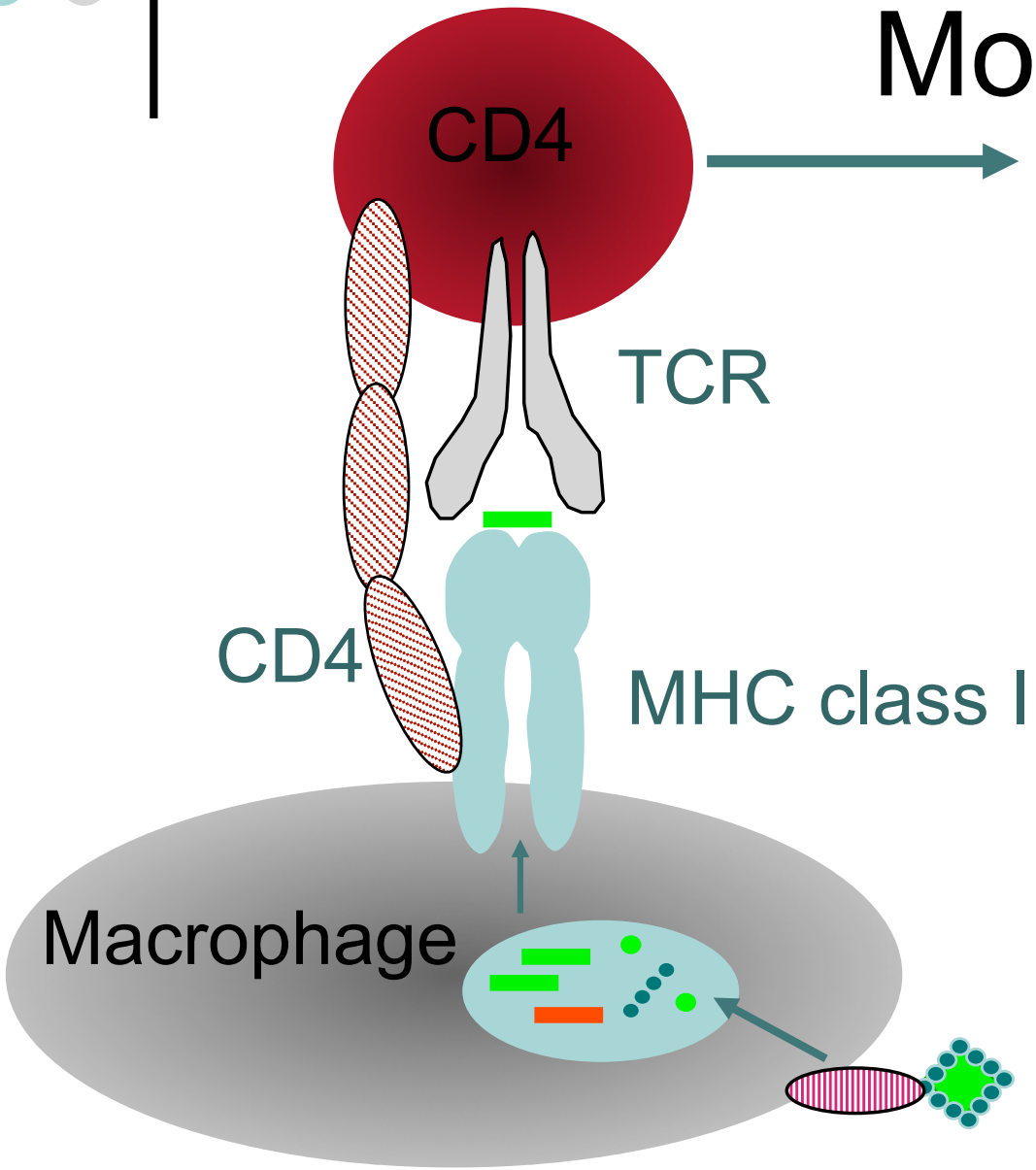
Role of MHC Class I Molecules



Target cell recognition by CTL and NK cells

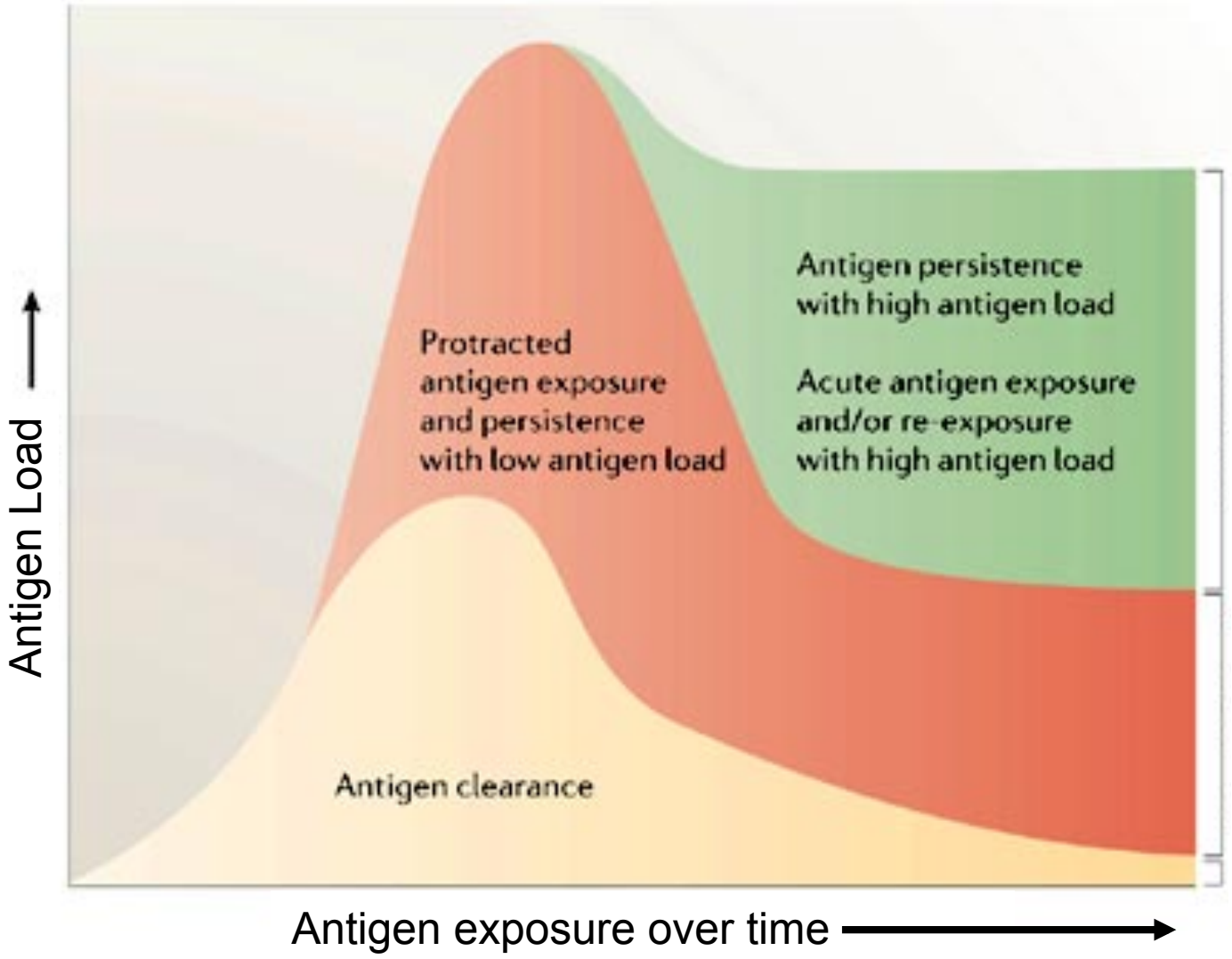


Role of MHC Class II Molecules



IFN- γ
IL- 4
IL- 5
IL-10…….

Viral expression model – antigen load and exposure

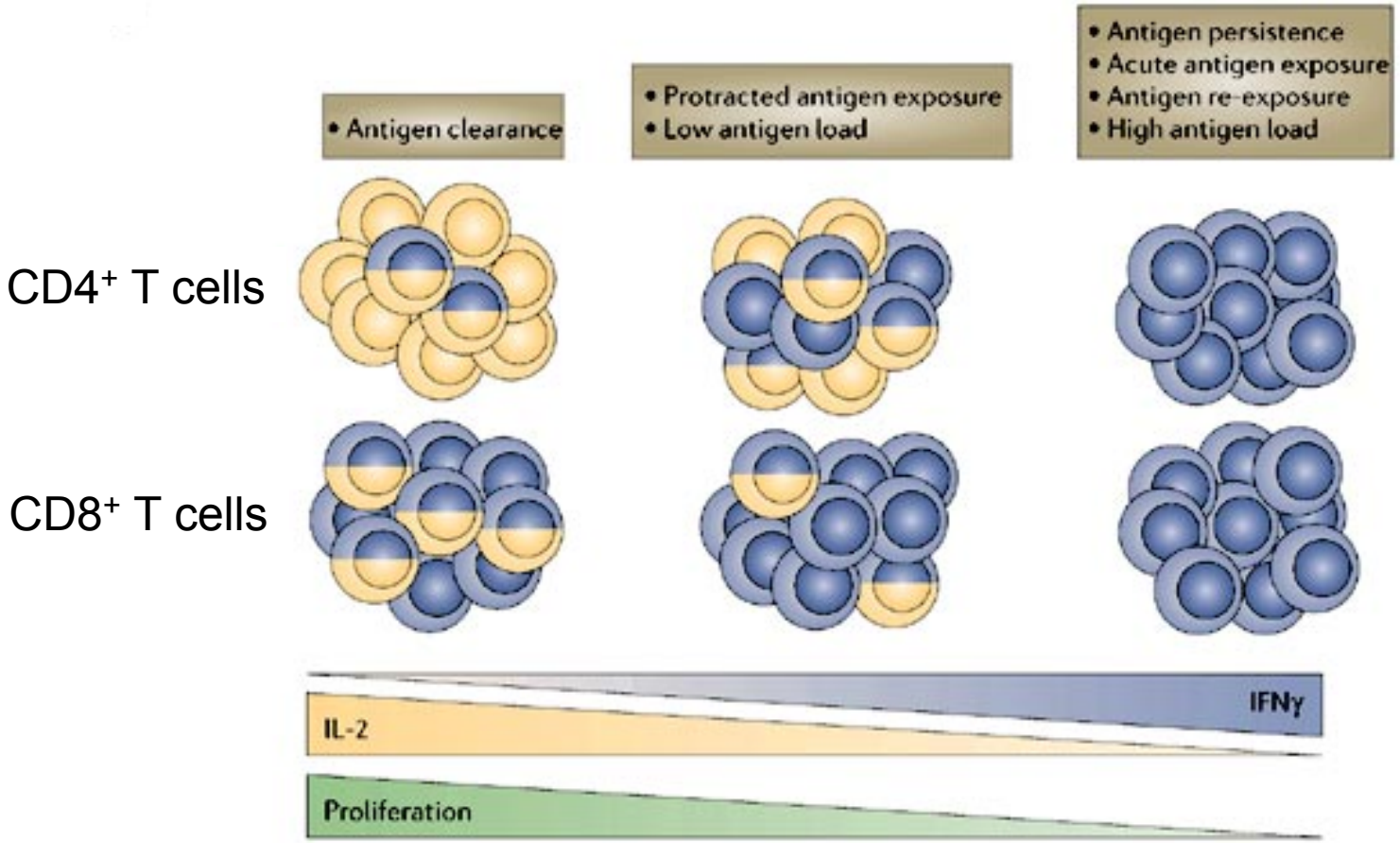


Chronic and/or progressive HIV-1 infection

Chronic CMV Infection

Influenza infection

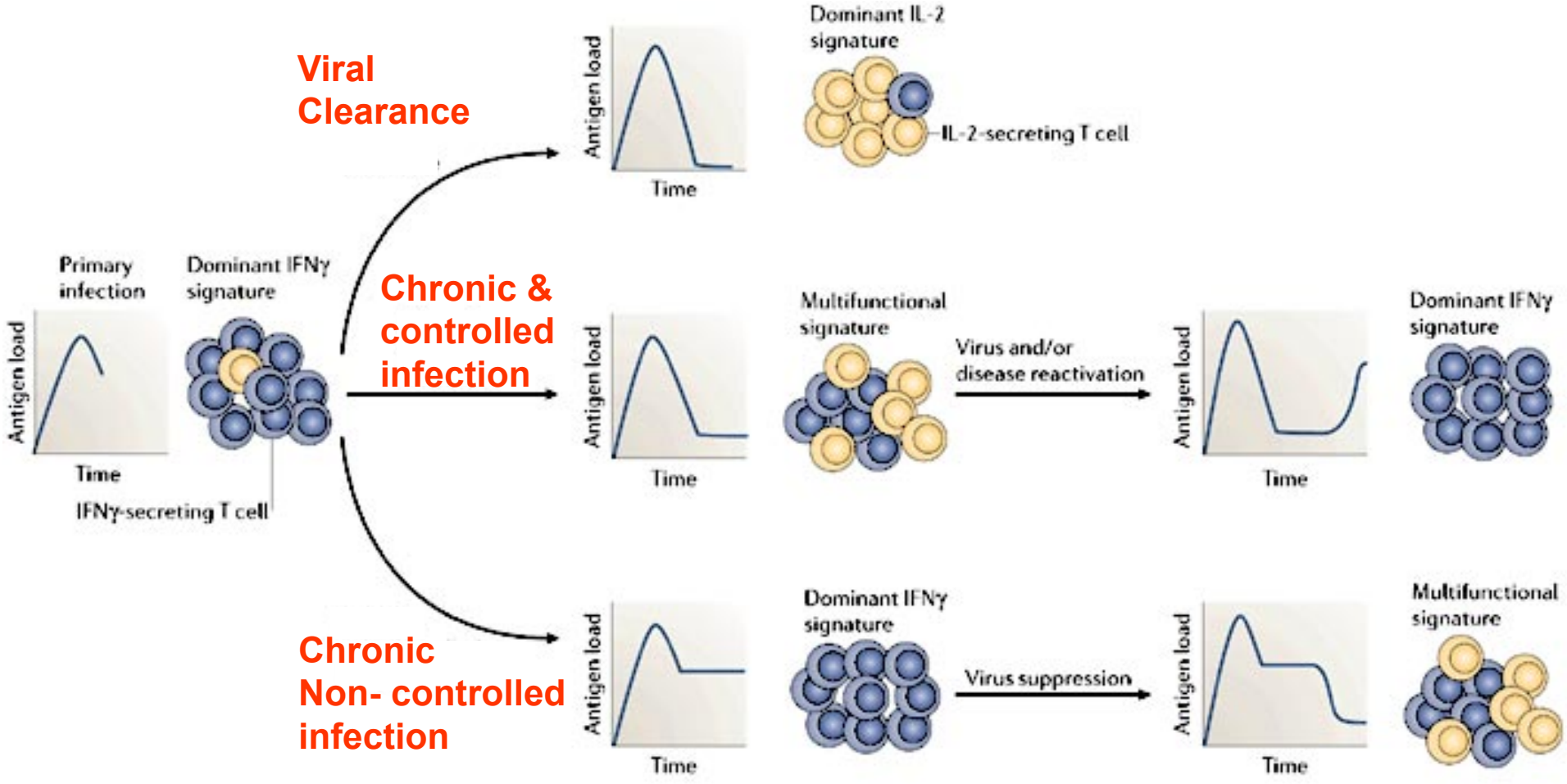
Functional cytokine signature Ag load



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

Functional Cytokine signature – Clinical Application



Regulatory T cells (Tregs)

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

Deleterious Tregs

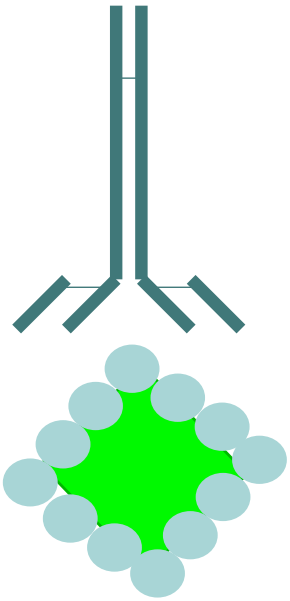
- HSV
  - Animals depleted of Tregs prior to infection more effectively control the virus
- HCV and HIV
  - Tregs contribute to immune disfunction

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

Antibody



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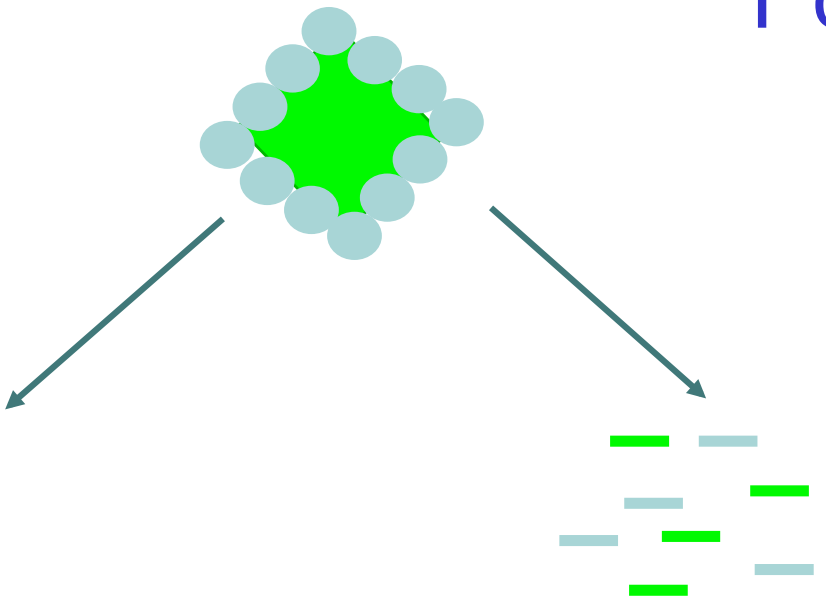
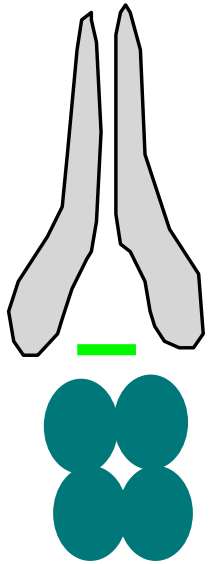
Virus



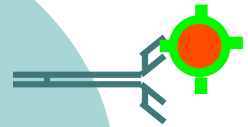
T cell receptor



MHC restriction

B cells and anti-viral antibody

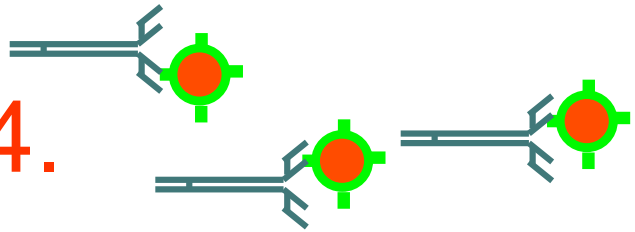
1. B cells bind viruses through viral coat proteins



2. Virus is Internalised & degraded

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

4. Activated B cell produces antibody against viral coat protein



Antibodies

- IgM
  - low affinity
- IgG
  - high affinity
- Complement activation
- Neutralisation
  - blockade of viral production by interfering with viral binding/entry/fusion

Immunogenicity of viral surfaces

Viral Factors

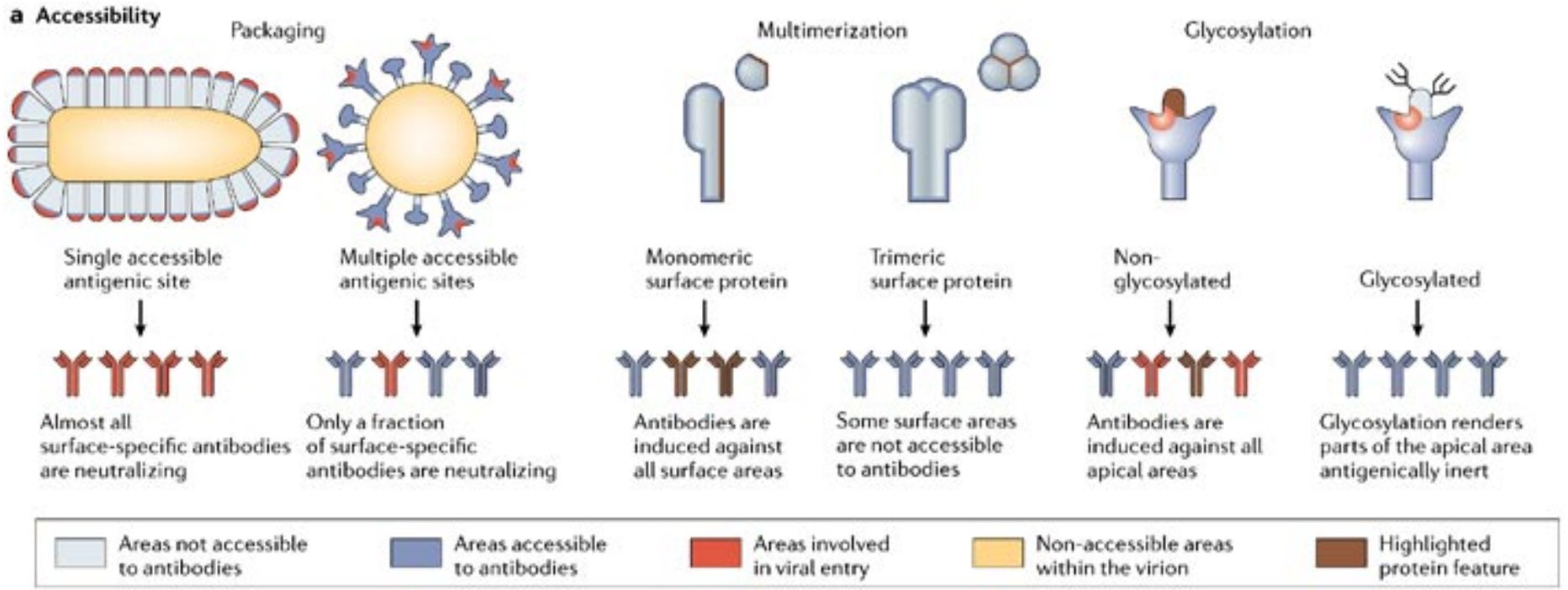
- Accessibility to Ab
- Structural arrangement of accessibility site

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

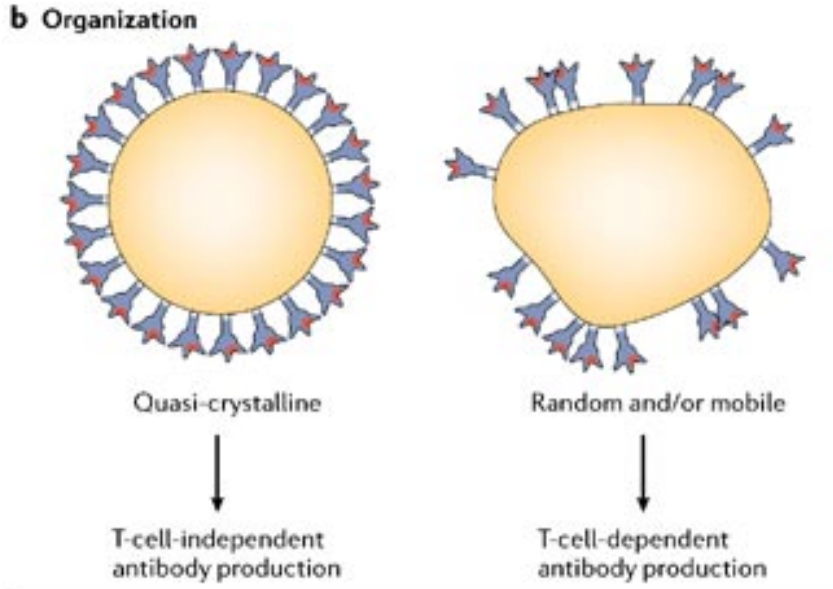


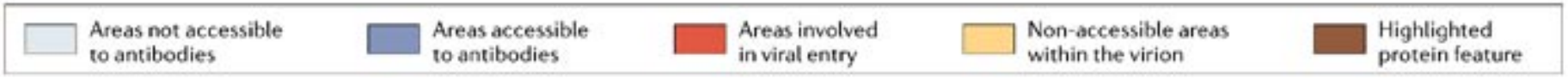
NRI: 2006: 6: 231-243

Immunogenicity of viral surfaces

B: Arrangement of Antigenic sites

Eg: VSV





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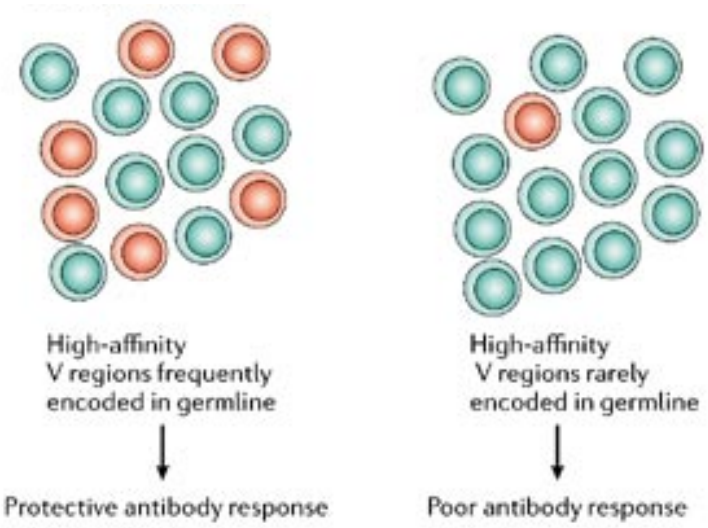
Immunogenicity of viral surfaces

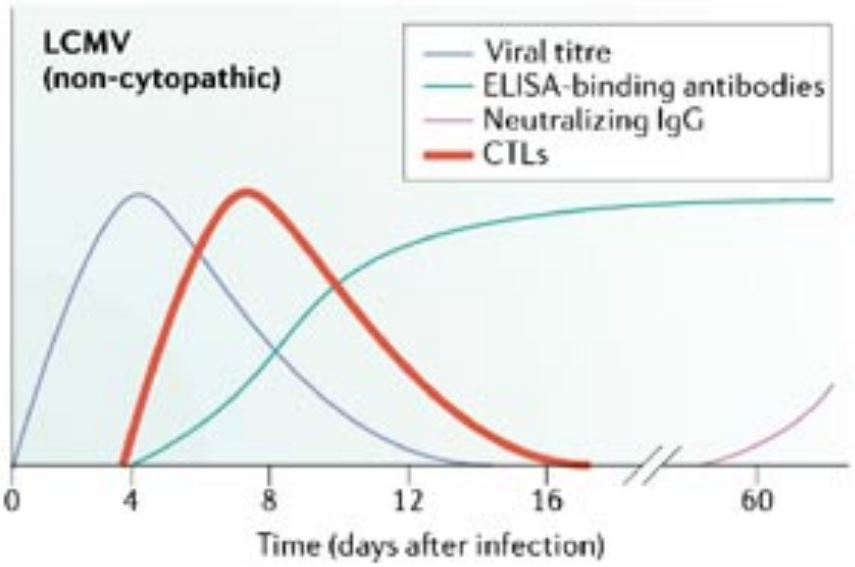
C: Frequency of IgG combinations



NRI: 2006: 6: 231-243

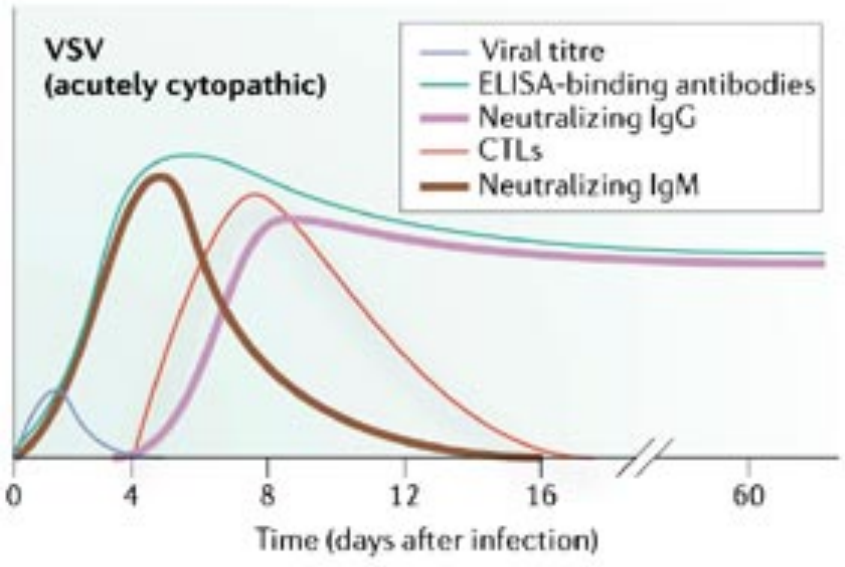
Ab responses to Cytopathic vs Non-cytopathic viruses

ELISA detected Ab DO NOT correlate with in vitro neutralisation titre



ELISA detectable Ab appear early
Neutralising Ab detected weeks-months later

ELISA detected Ab correlate with in vitro neutralisation titre



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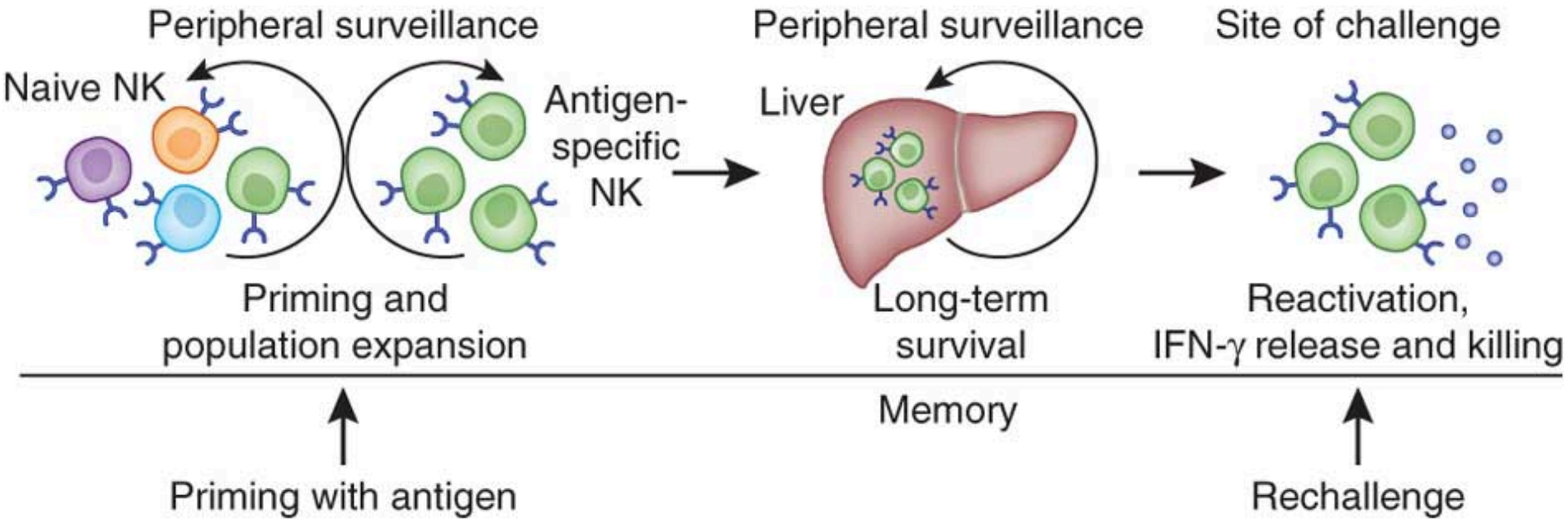
Memory NK cells



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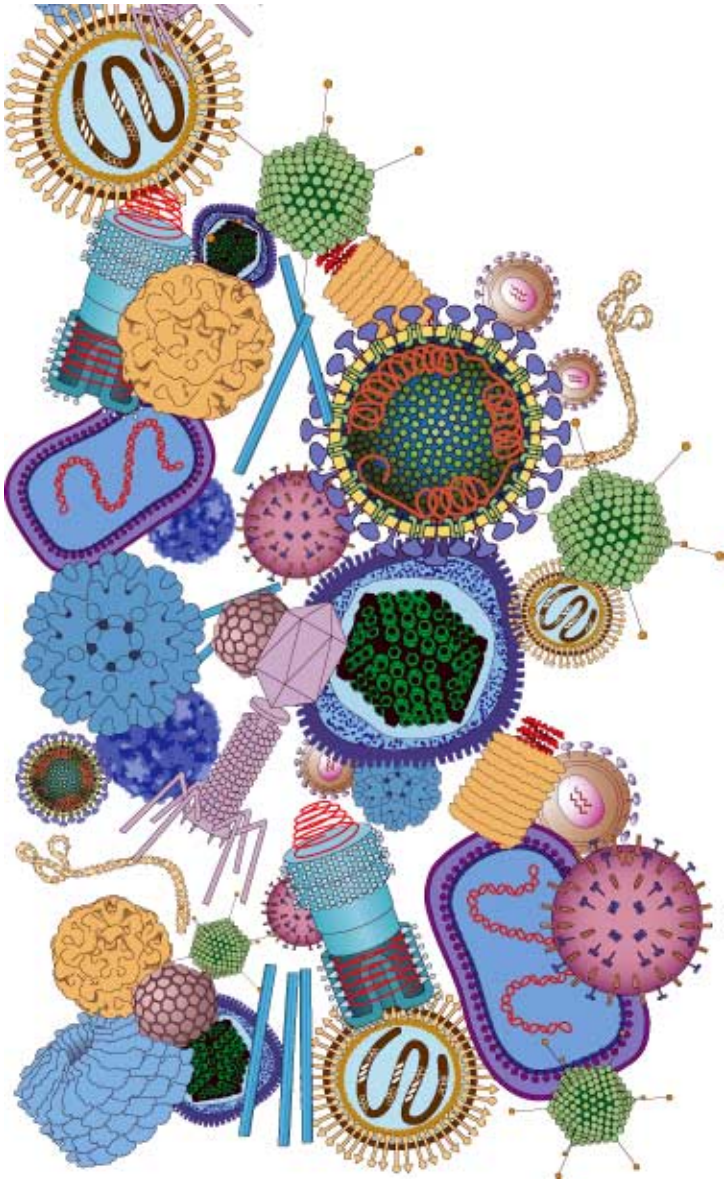
- Immune persistence/evasion



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

- Change viral genome
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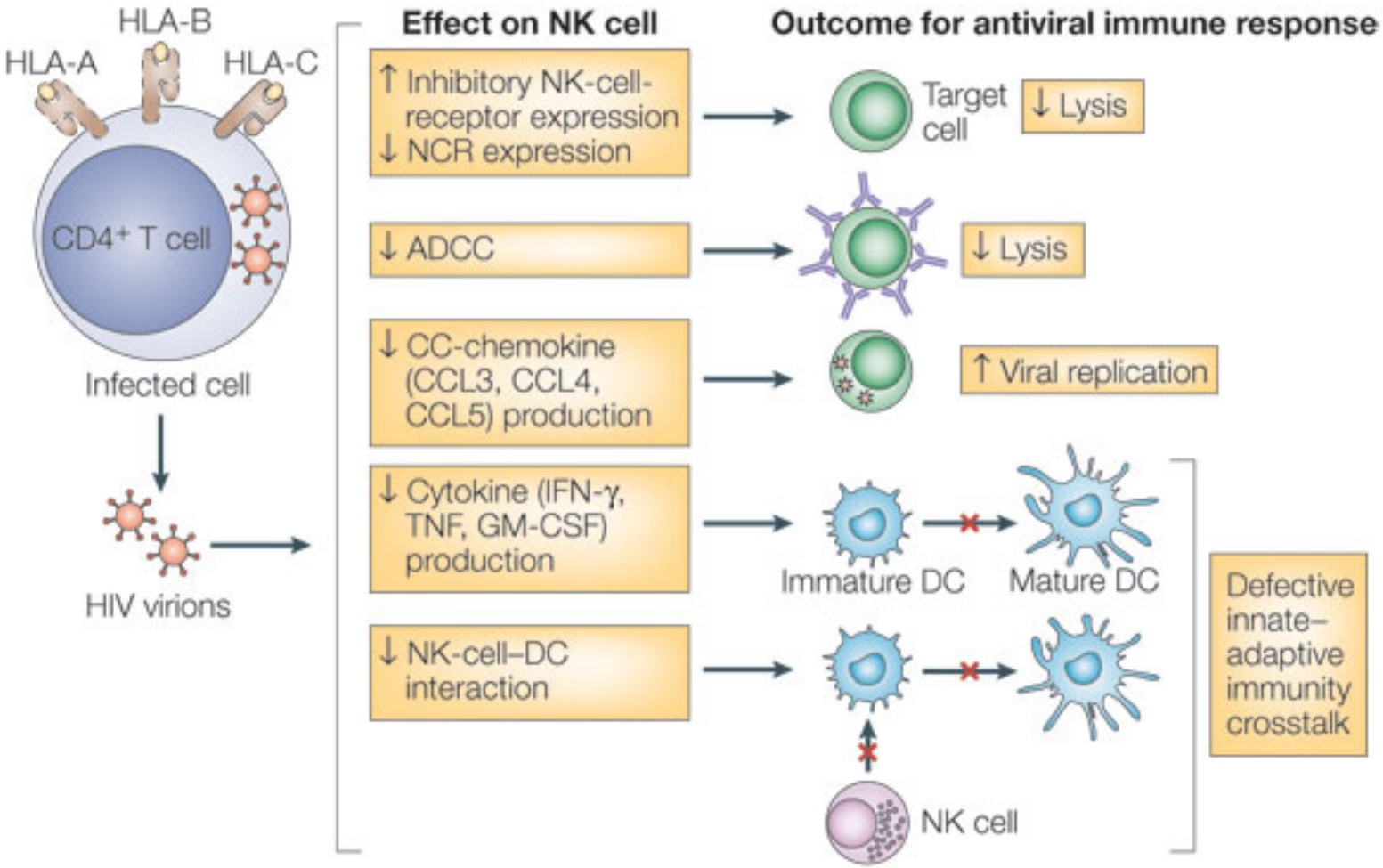
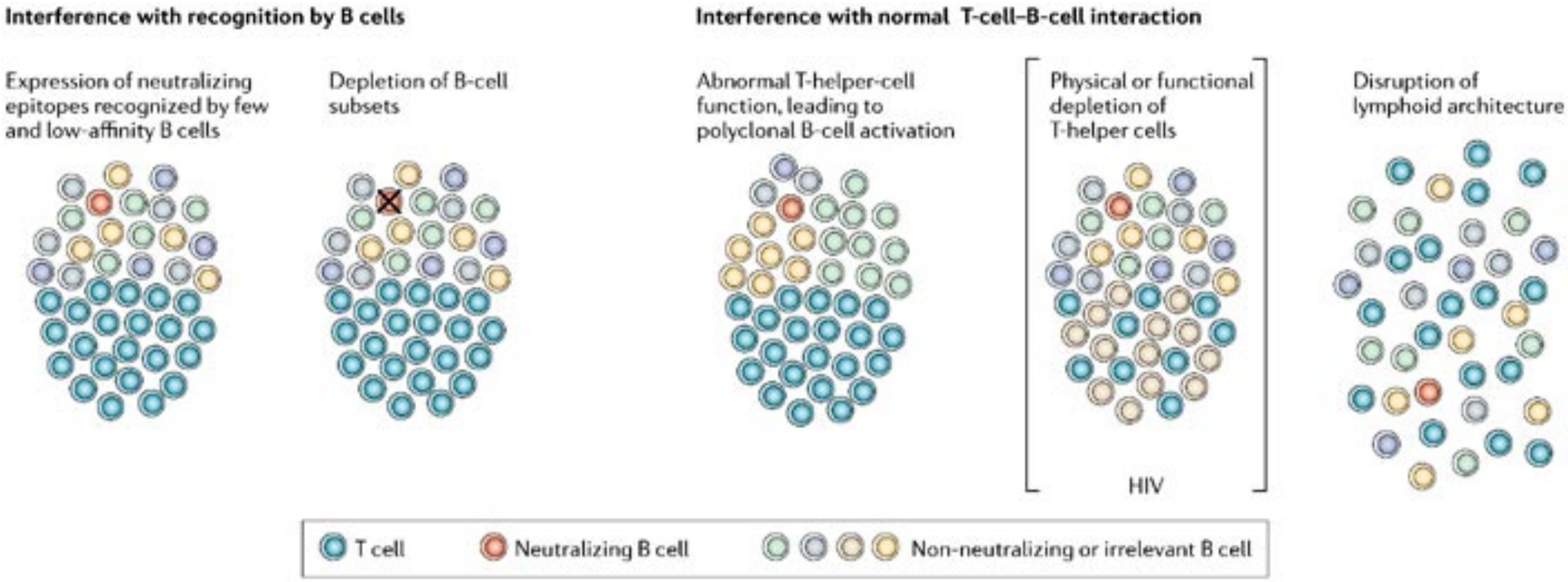
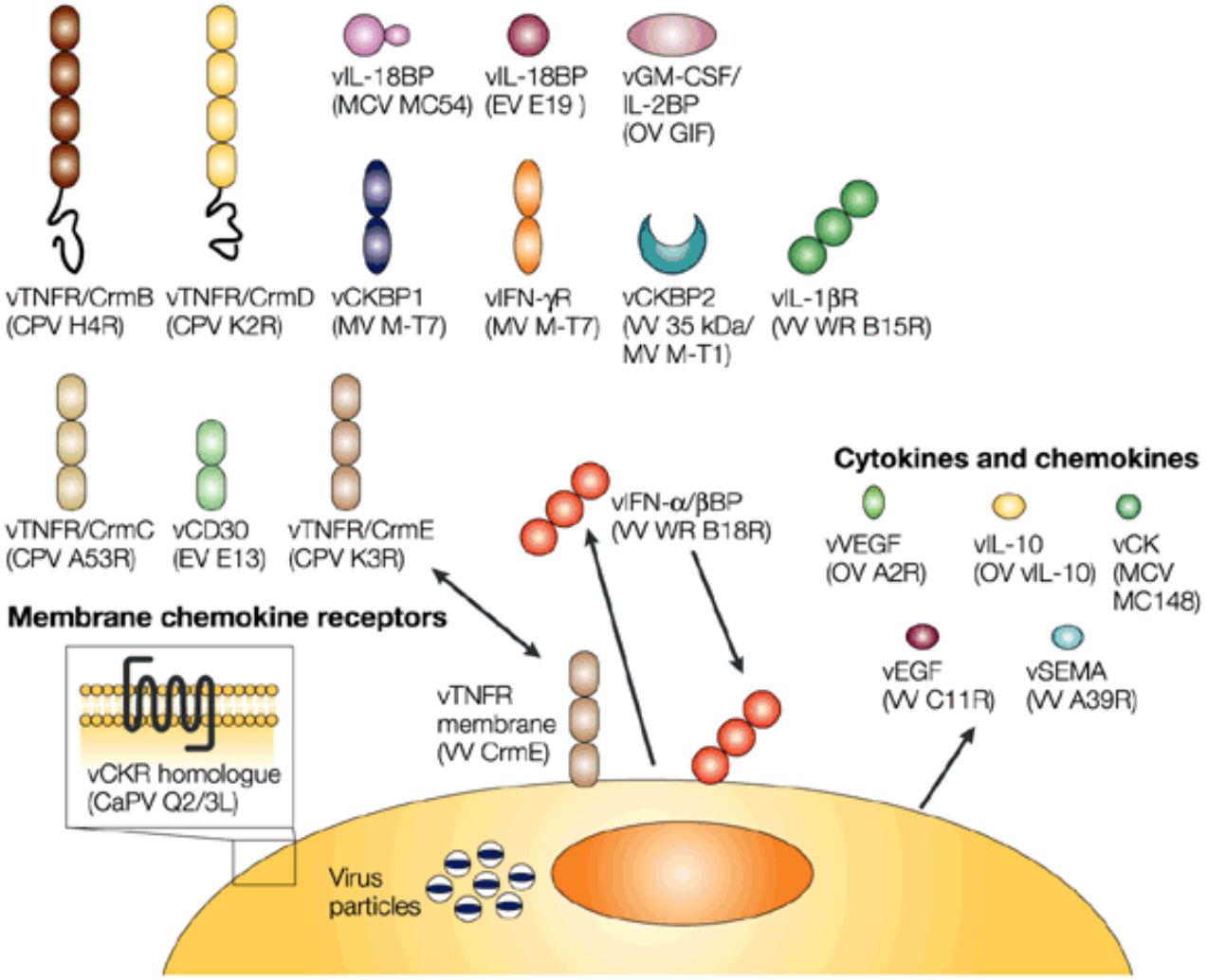
Modulation of NK cell function



Interference with Antibody response



Cytokine mimicry

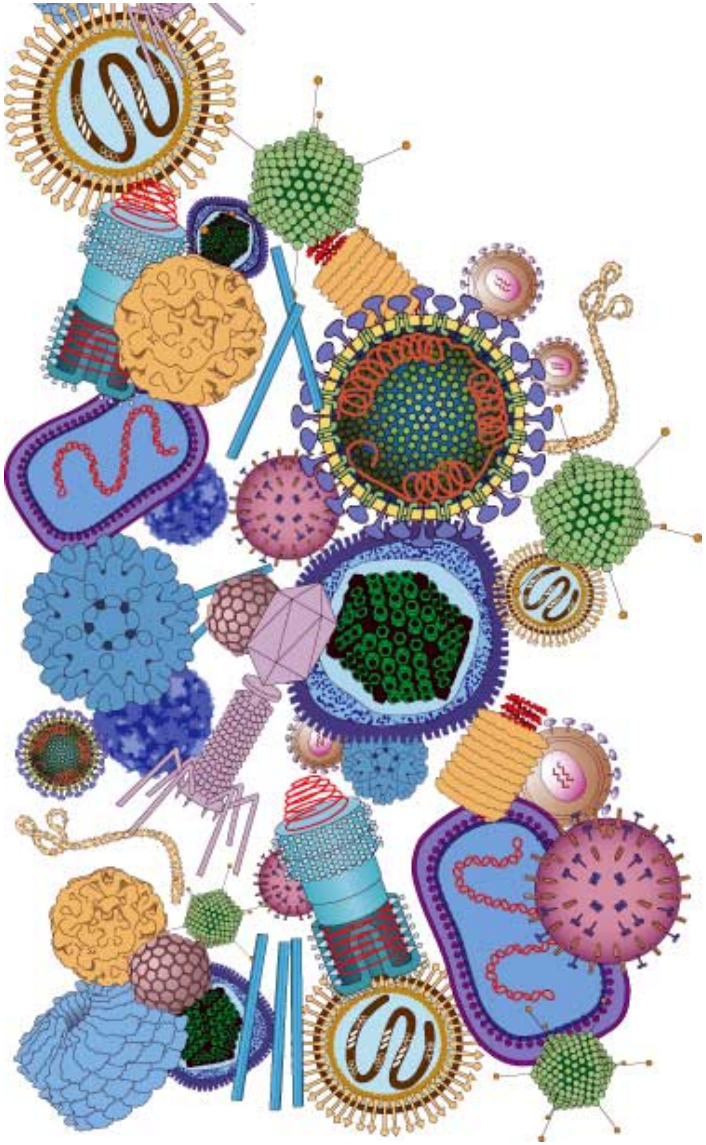


Consequences of the failure to eliminate virus

- Latent eg: Herpes Simplex Virus
  - Virus not normally detected.
  - Quiescent infection, episodes of reactivation
- Persistant 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