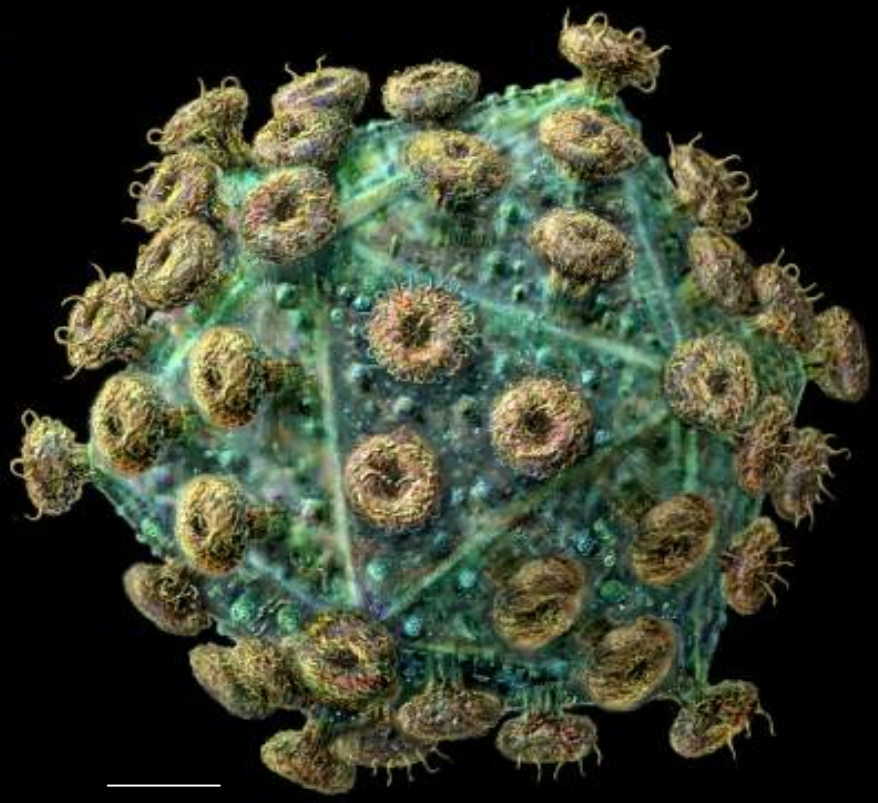
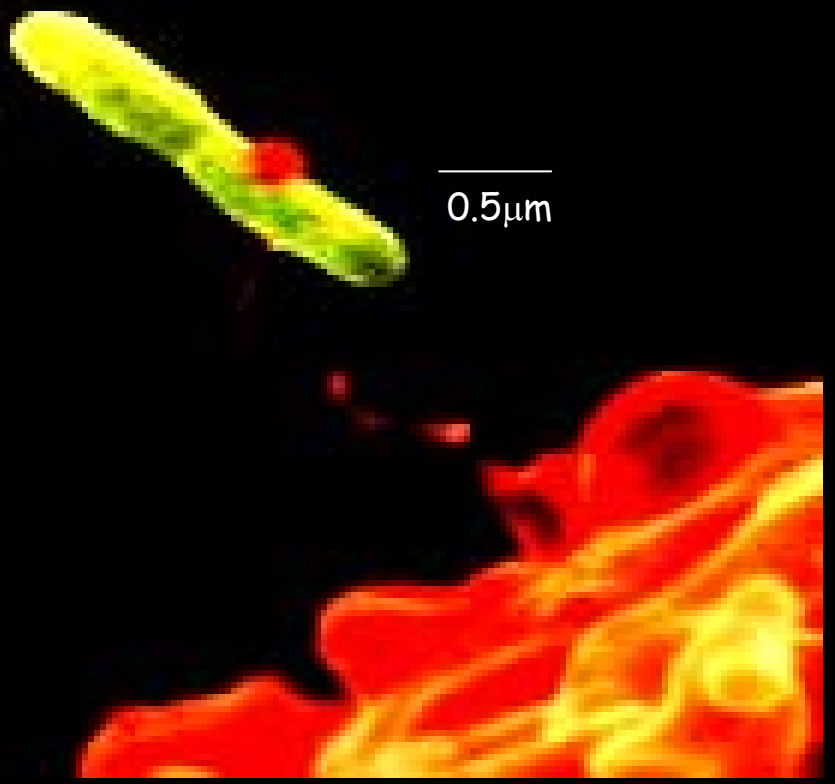
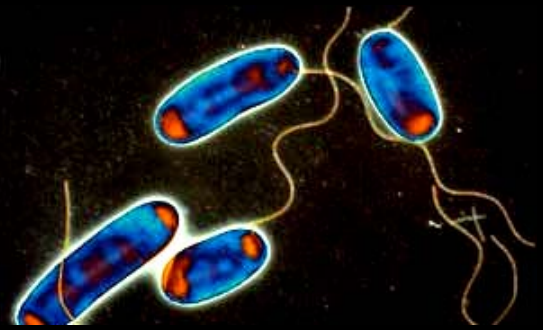
Facets of immunity to infection





Pathogen

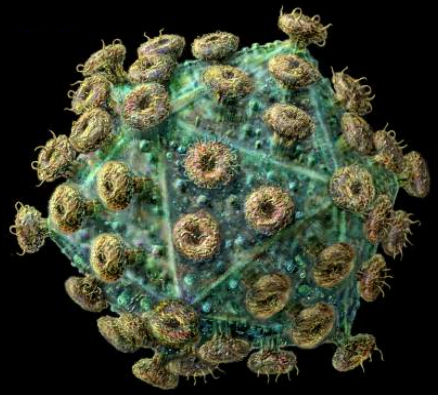
Immune response



Infection
Activation

innate (95%)

adaptive (5%)



Defense
(eradication, control)

Innate Immune Response (unspecific)

Soluble mediators (interferons, interleukins)

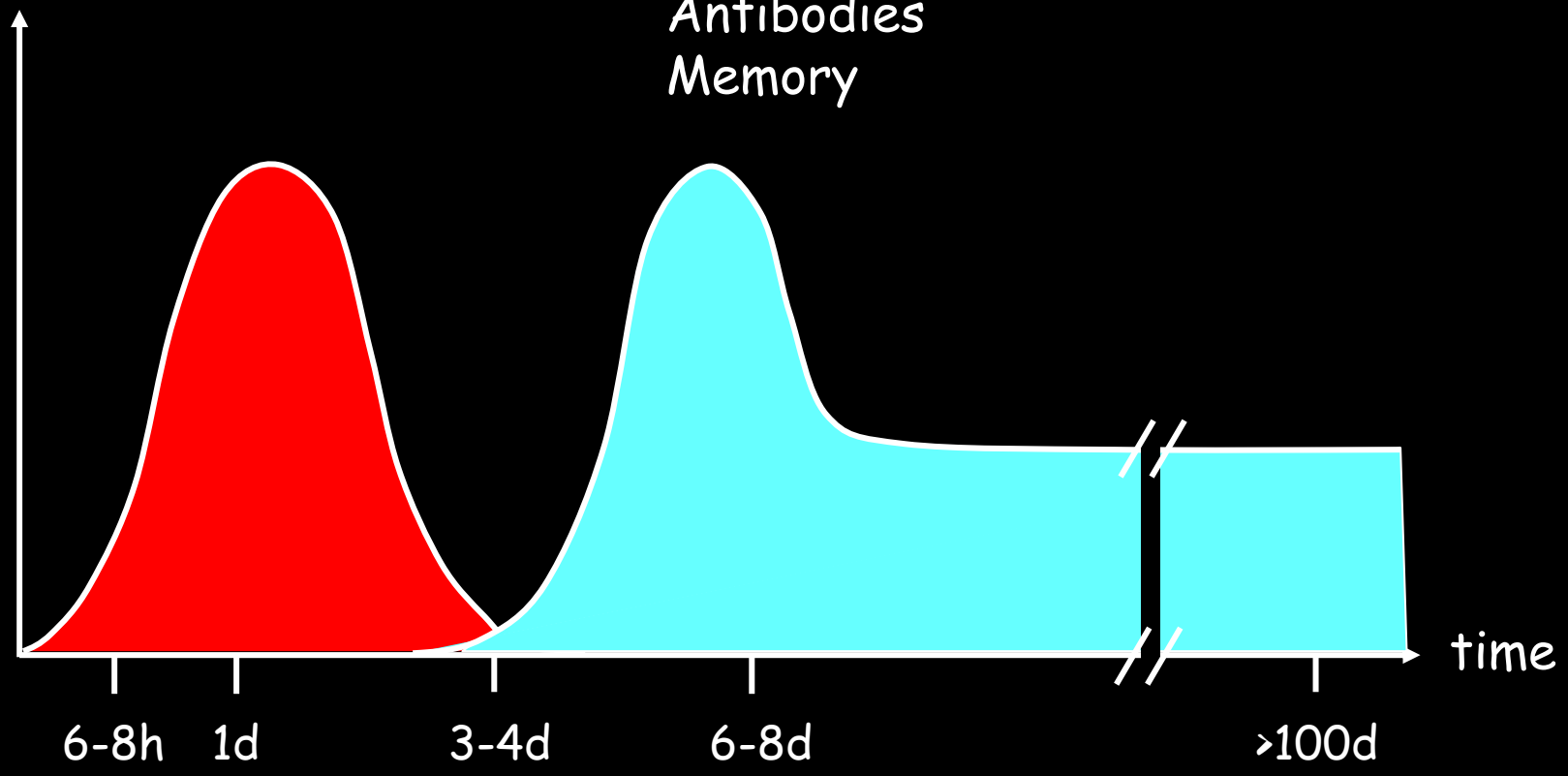
Phagocytosis

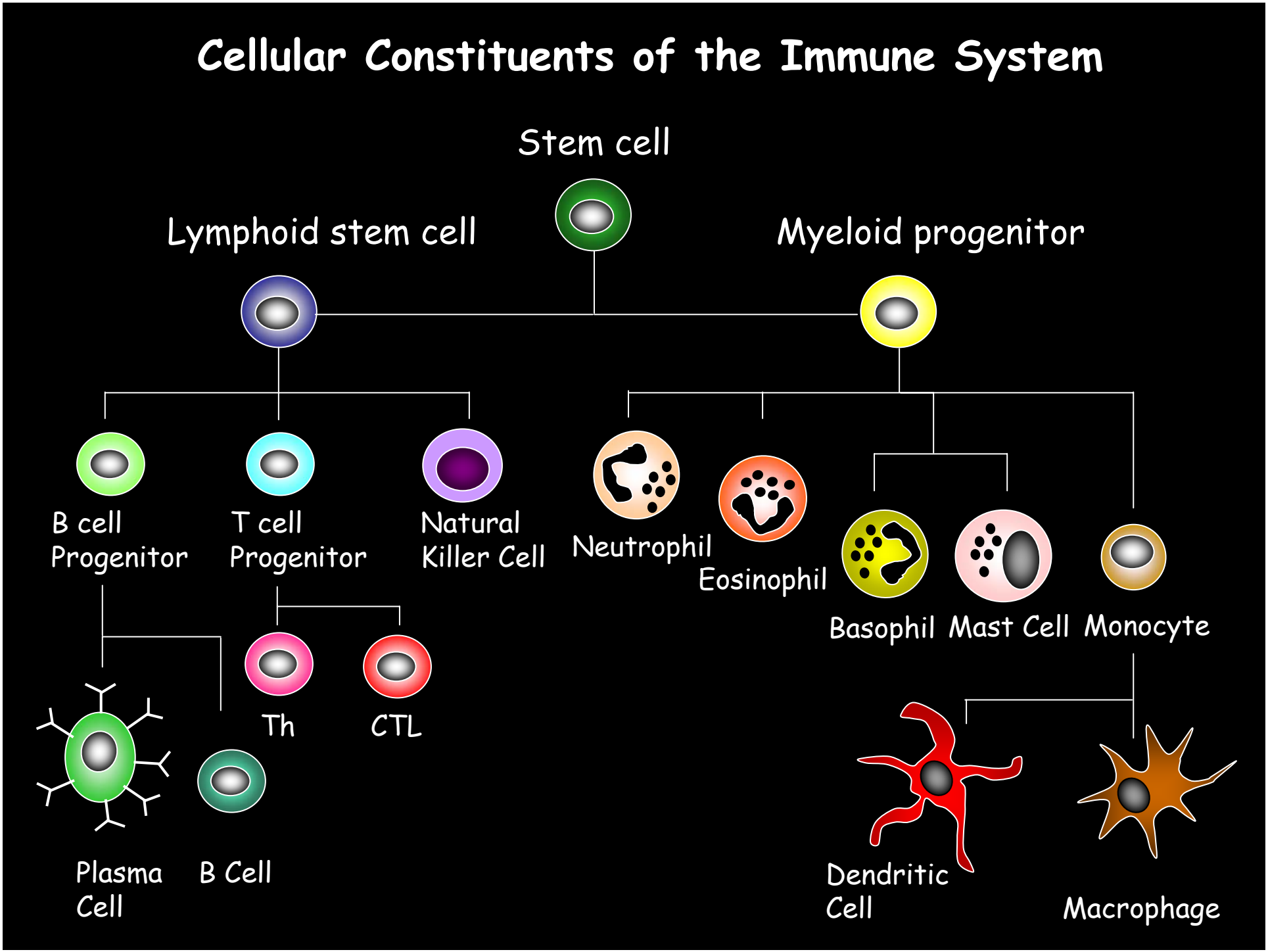
Adaptive Immune Response (specific)

Cellular effector functions

Antibodies

Memory




Cellular Constituents of the Immune System
Stem cell
Lymphoid stem cell
Myeloid progenitor
B cell Progenitor
T cell Progenitor
Natural Killer Cell
Neutrophil
Eosinophil
Basophil
Mast Cell
Monocyte
Th
CTL
Plasma Cell
B Cell
Dendritic Cell
Macrophage

Pathogen

Immune response

Legionella pneumophila

Activation

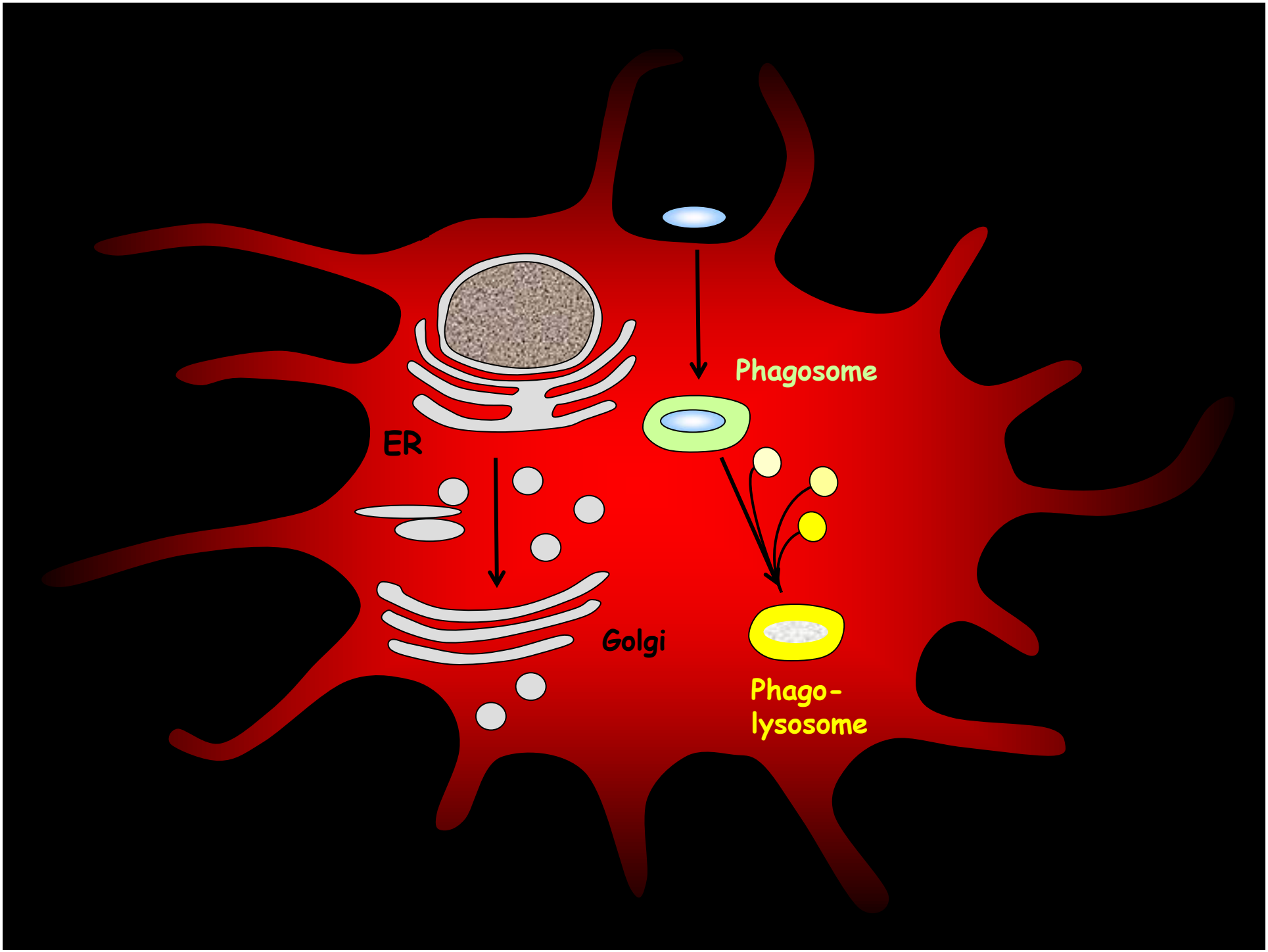
innate

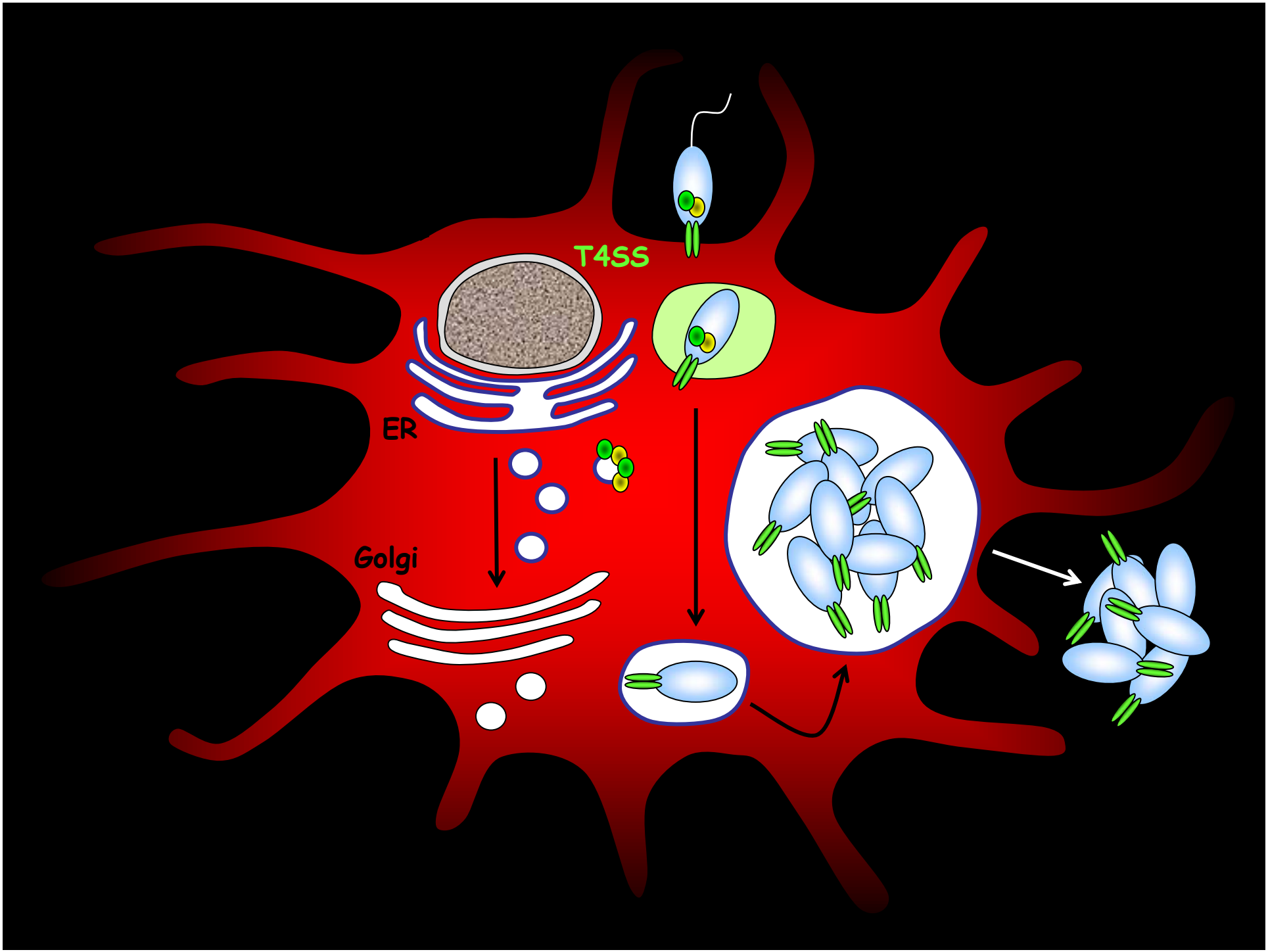
Defense
(eradication)

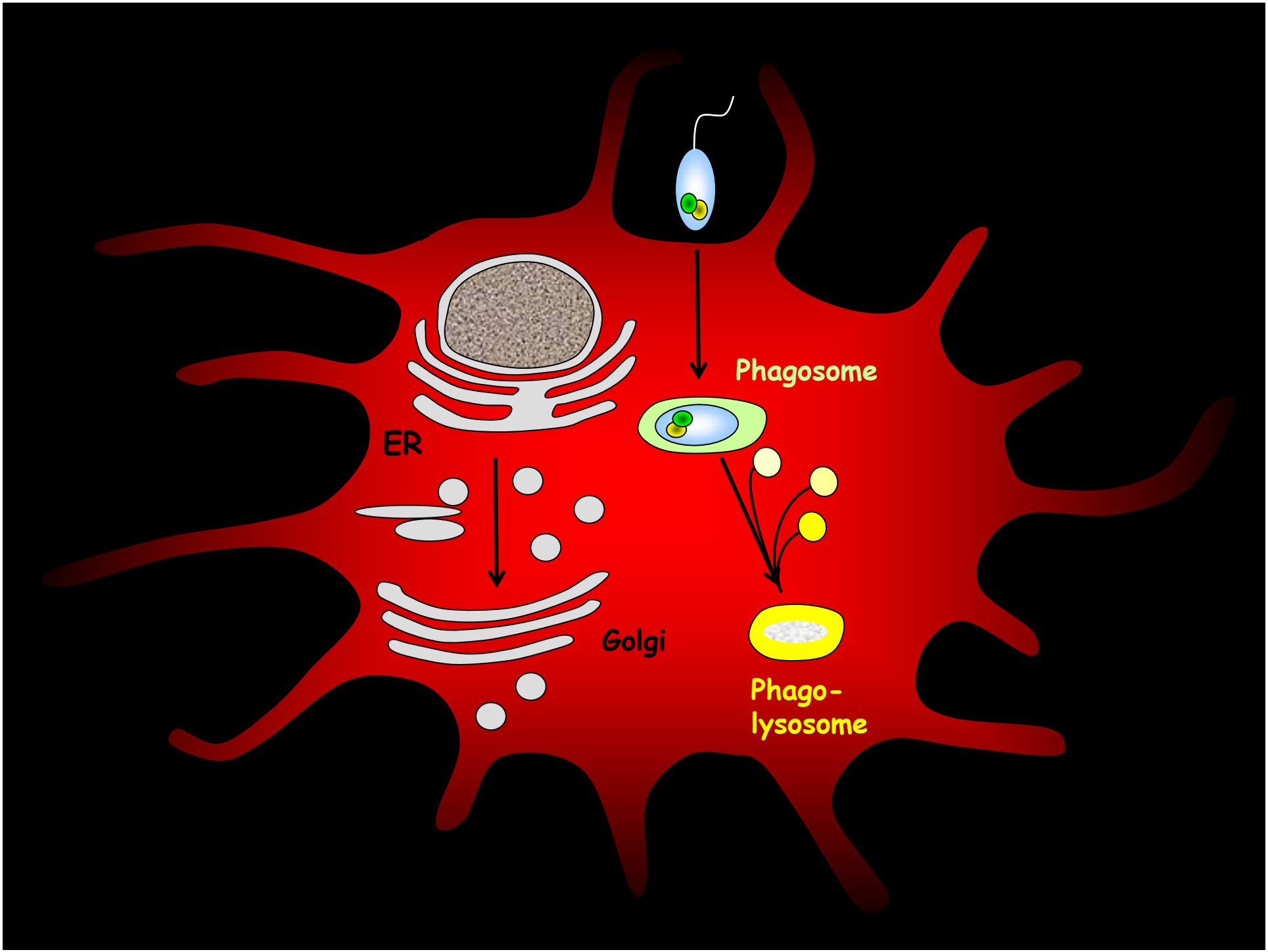
Legionella pneumophila
the causative agent of Legionnaires' disease

- *Legionella*: > 40 species, 60 serogroups
- *L. pneumophila* (serogroup 1) causes ca. 90% of clinical infections (Legionnaires' disease, Pontiac fever)

- Habitats: ubiquitous in water and soil
- Replication: facultative intracellular


Phagosome
ER
Golgi
Phago-
lysosome


T4SS
ER
Golgi

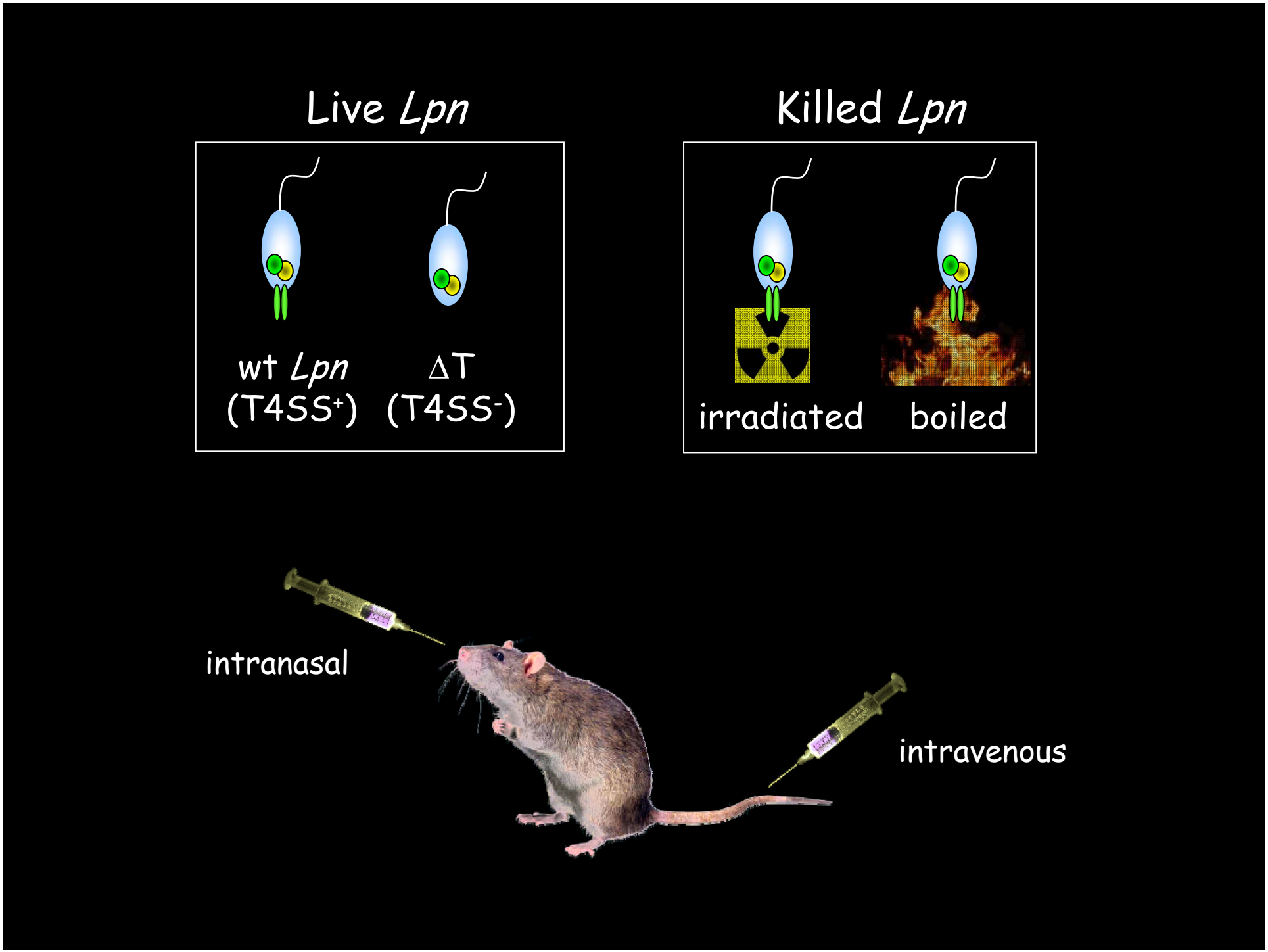

Phagosome
ER
Golgi
Phago-
lysosome

Questions

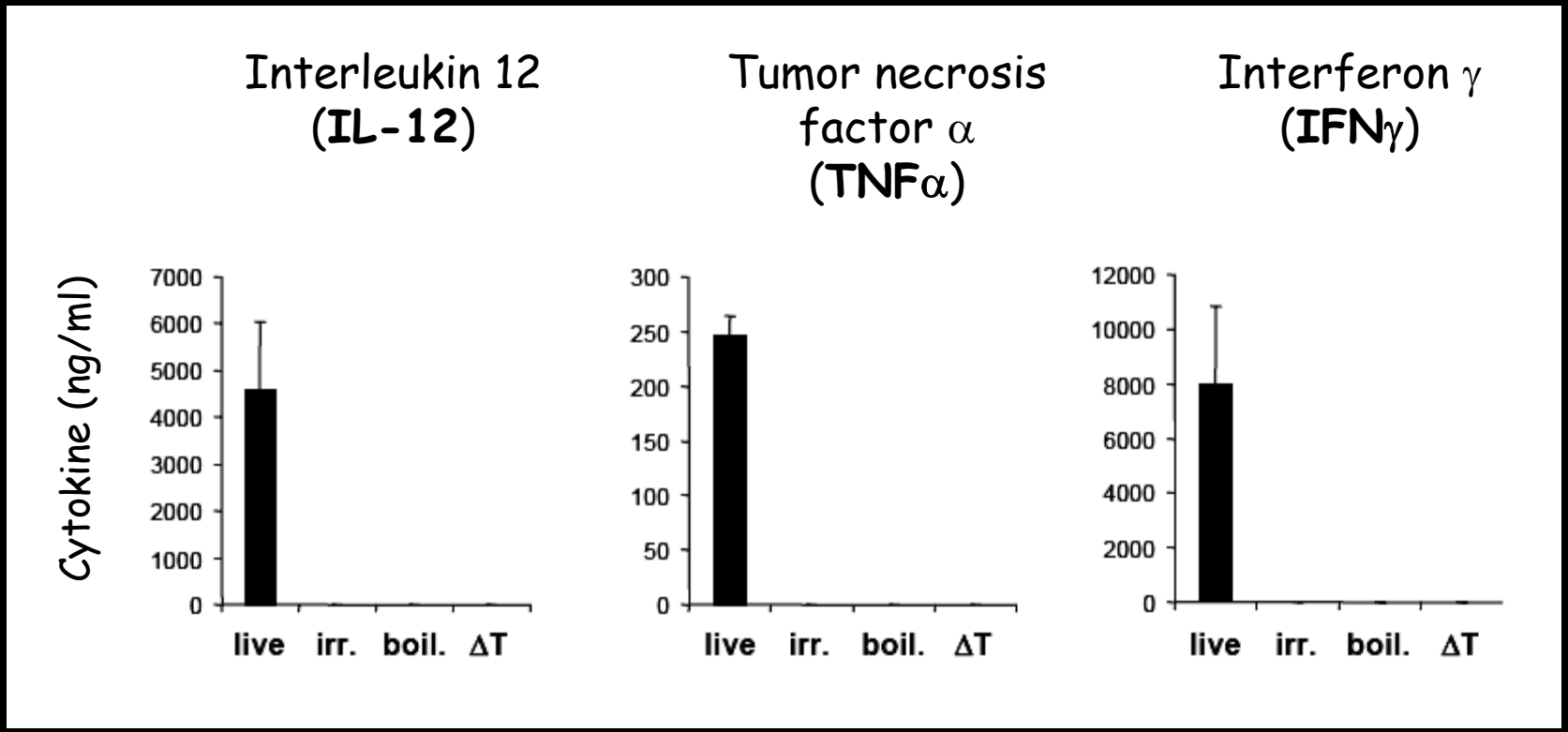
- How does *Legionella pneumophila* (*Lpn*) induce innate immune response?

- Which arms of innate immune response are important for control of *Lpn* infection?

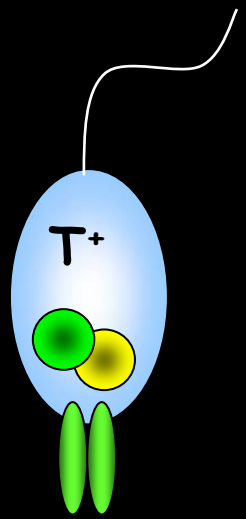
Mouse model of *Lpn* infection


Live *Lpn*
wt *Lpn* (T4SS+)
ΔT (T4SS-)
Killed *Lpn*
irradiated
boiled
intranasal
intravenous

Only live T4SS$^+$ *Lpn* induce inflammation

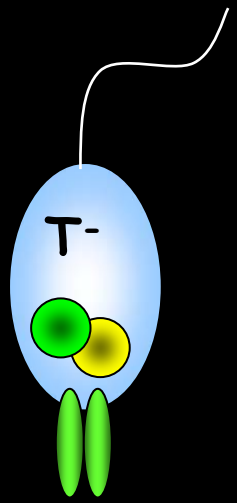


Is intracellular bacterial replication required?



wt *Lpn*
(T4SS+)

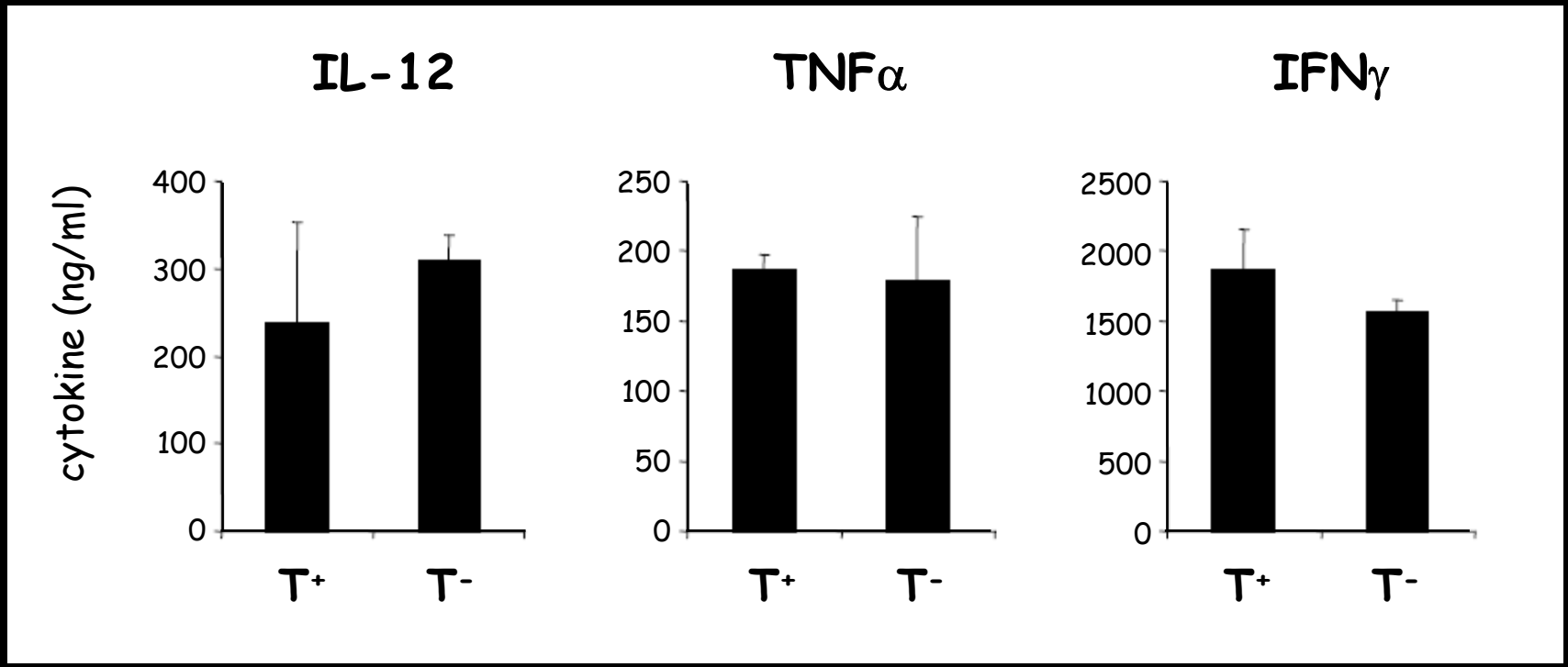
Thymidine prototroph



wt *Lpn*
(T4SS+)

Thymidine auxotroph

Intracellular bacterial replication is not required

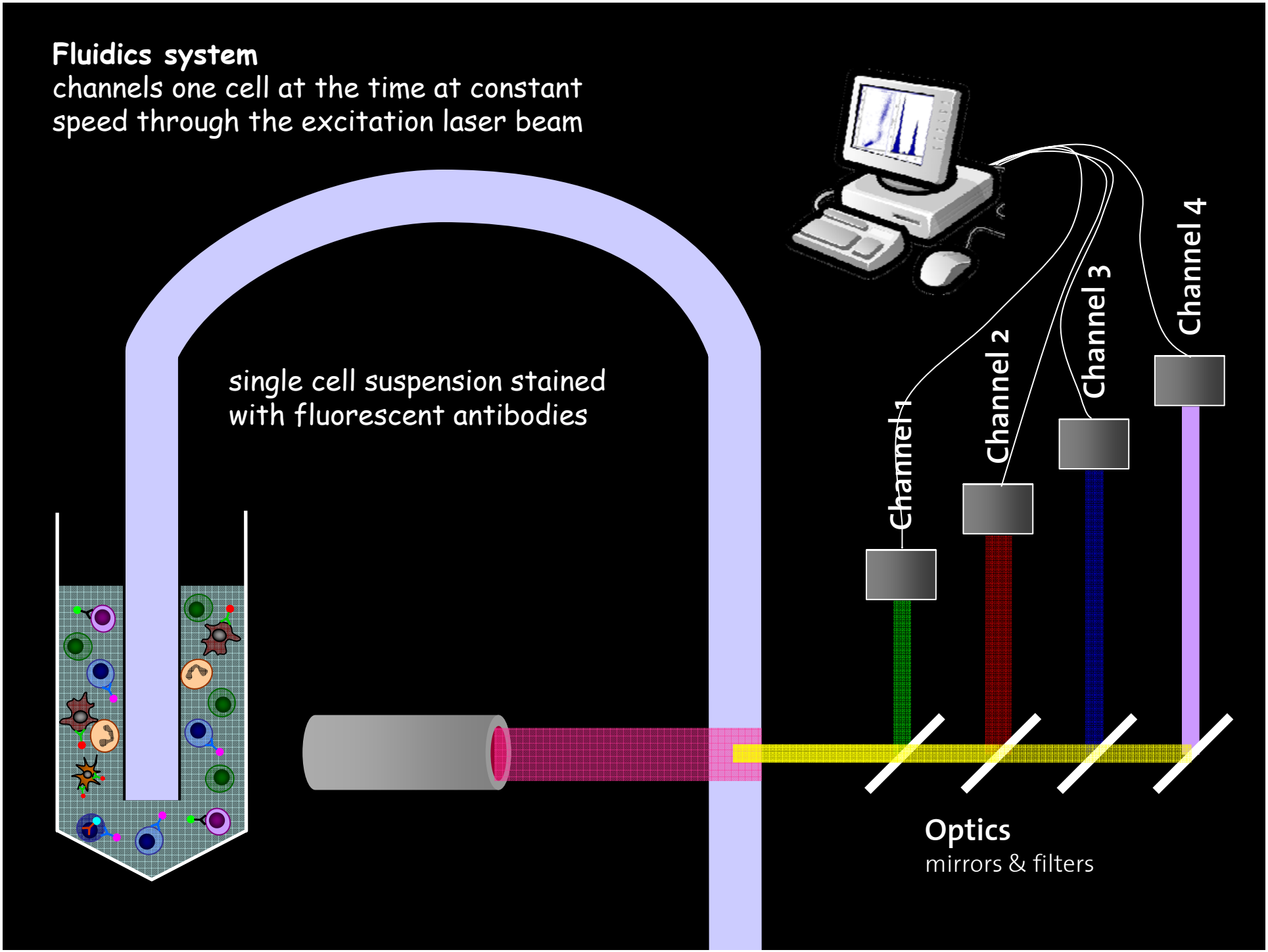


Which inflammatory cytokines are relevant for control of *Lpn* infection?

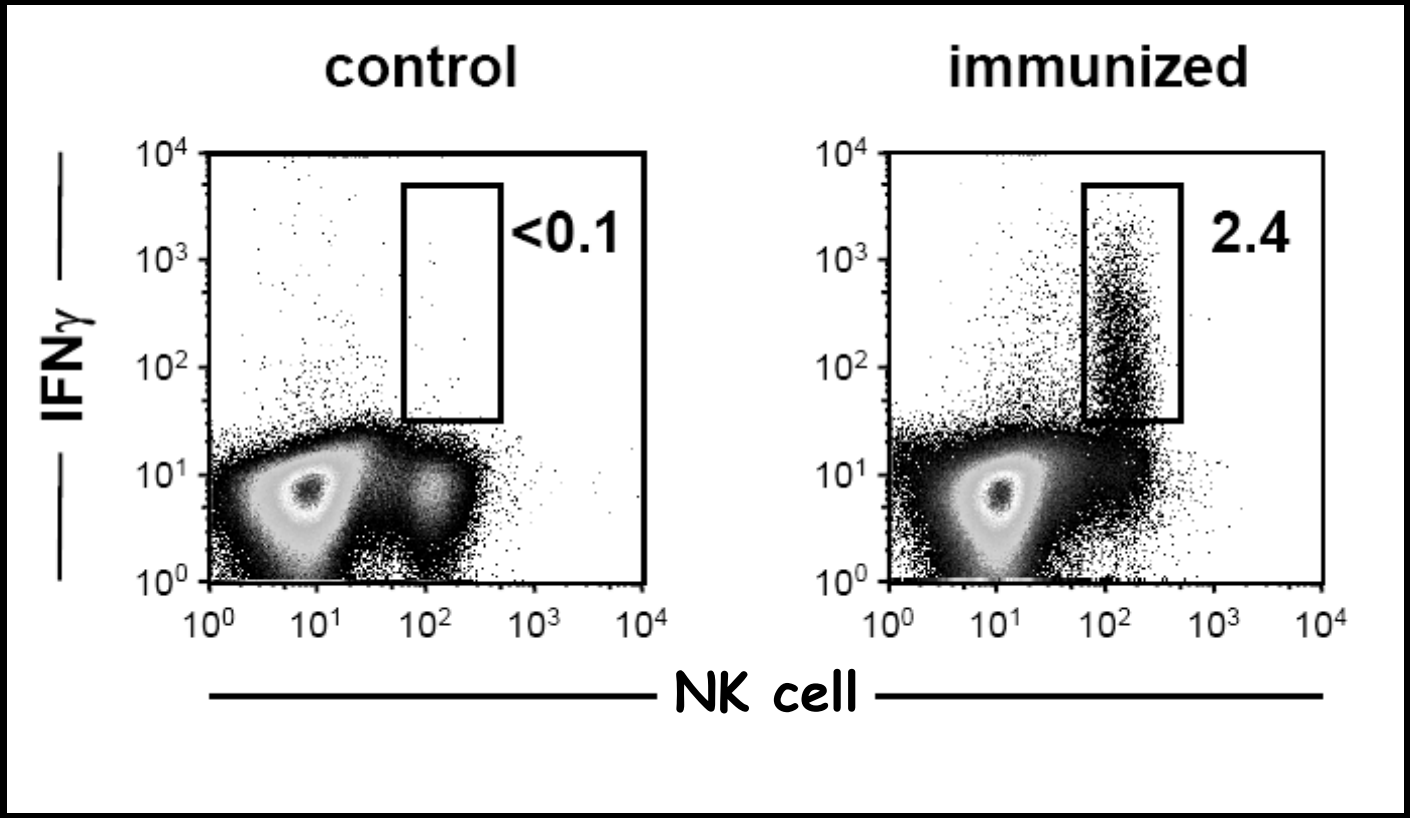
Cytokine	mouse strain	*Lpn* control
IFNα/β	IFNα/βR-/- mice	yes
TNFα	TNFR-/- mice	yes
IFNγ	IFNγR-/- mice	NO

Which cells produce IFNγ?

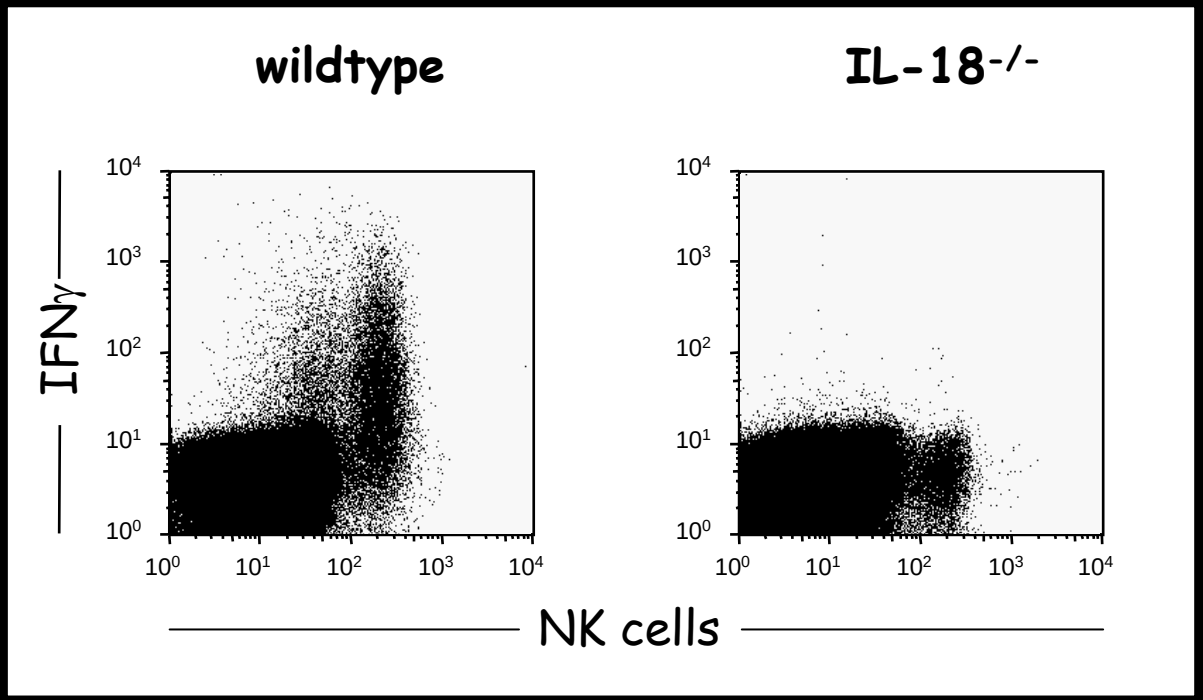
Detection of individual cytokine-producing cells
by flow cytometry


Fluidics system
channels one cell at the time at constant speed through the excitation laser beam
single cell suspension stained with fluorescent antibodies
Channel 1
Channel 2
Channel 3
Channel 4
Optics
mirrors & filters

Natural killer (NK) cells produce IFNγ

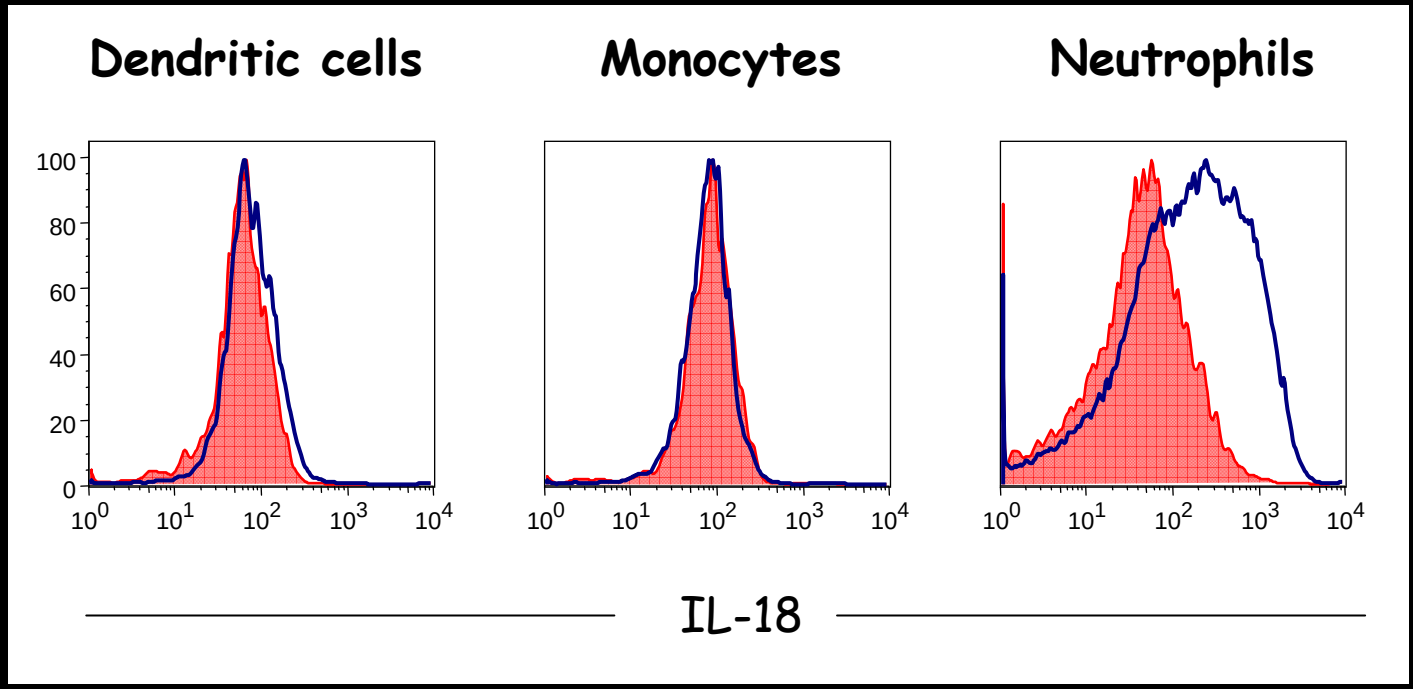


Which signals induce IFNγ production by NK cells?



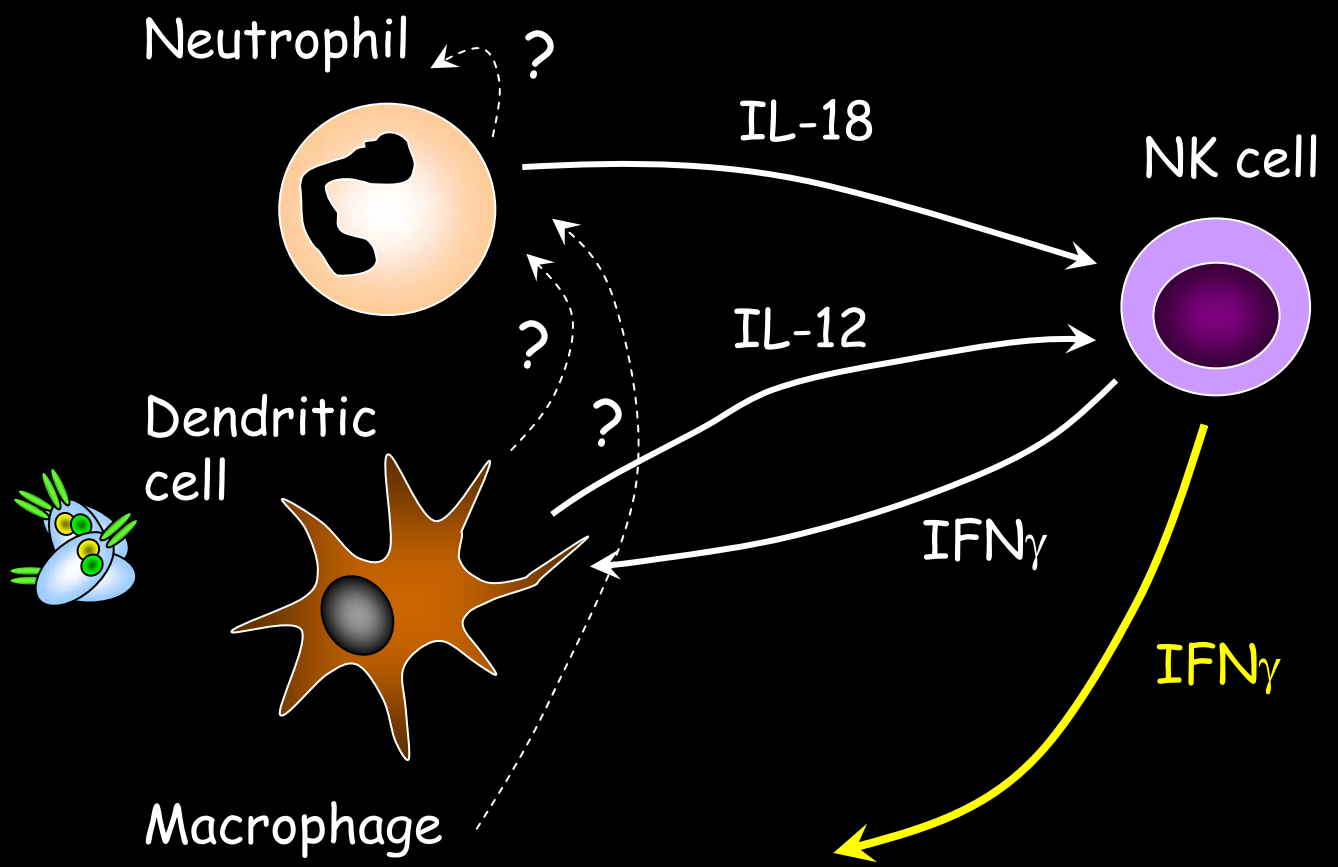
→IL-18 (and IL-12) is essential for IFNγ production

Cellular source of *Lpn*-induced IL-18



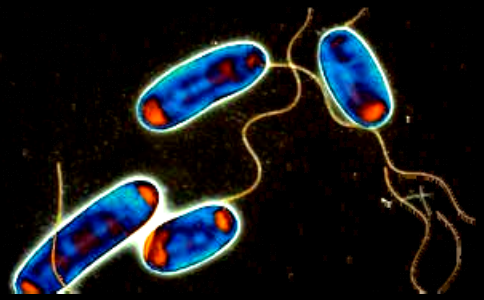
→ IL-18 is produced by neutrophils

Conclusions



Innate Immune Response

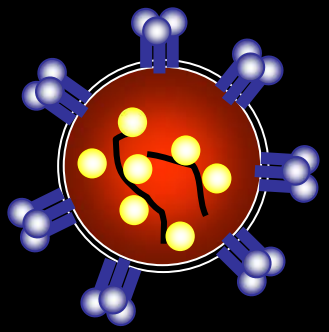
Legionella pneumophila (Lpn)



Adaptive Immune Response

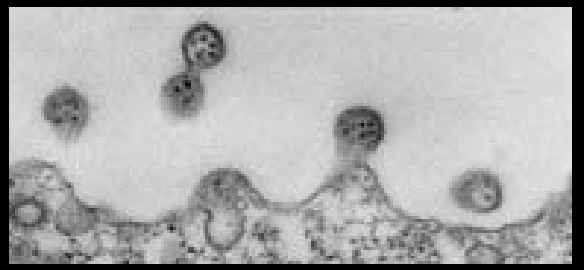
Lymphocytic choriomeningitis virus (LCMV)

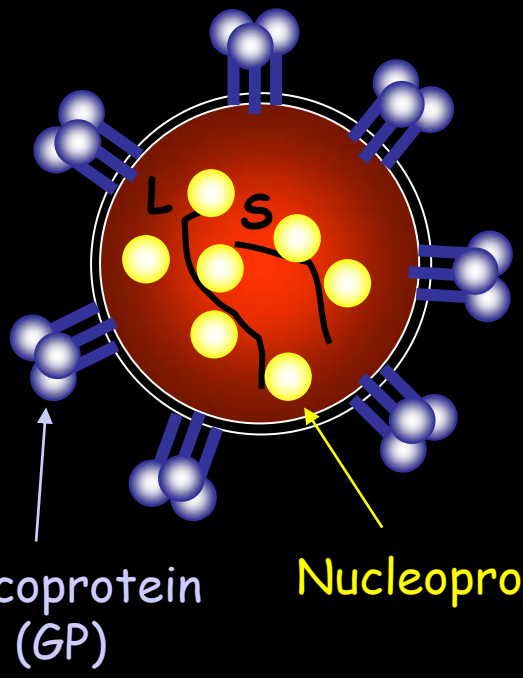
→ Effector functions of T cells



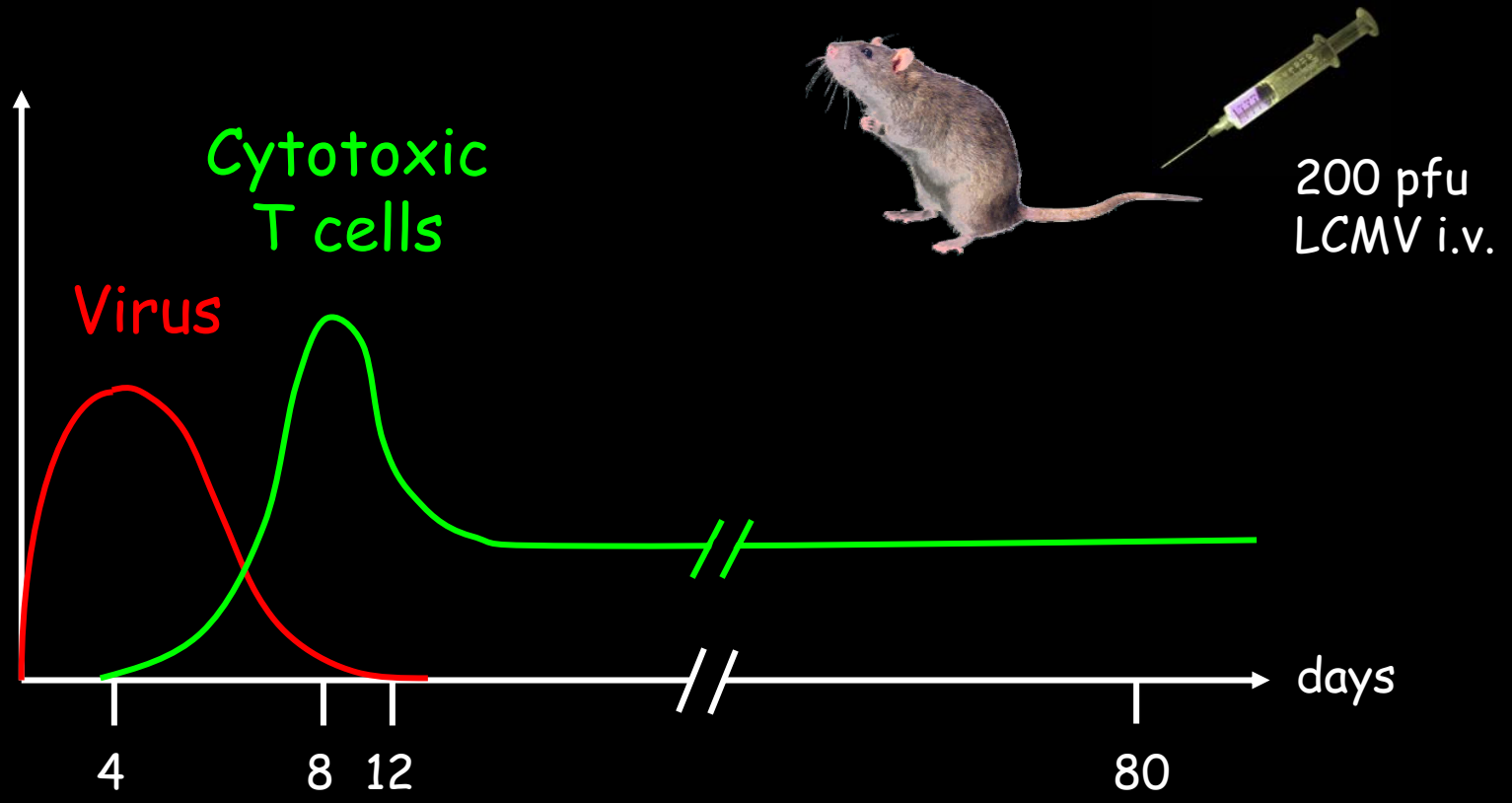
LCMV: ARENAVIRUS

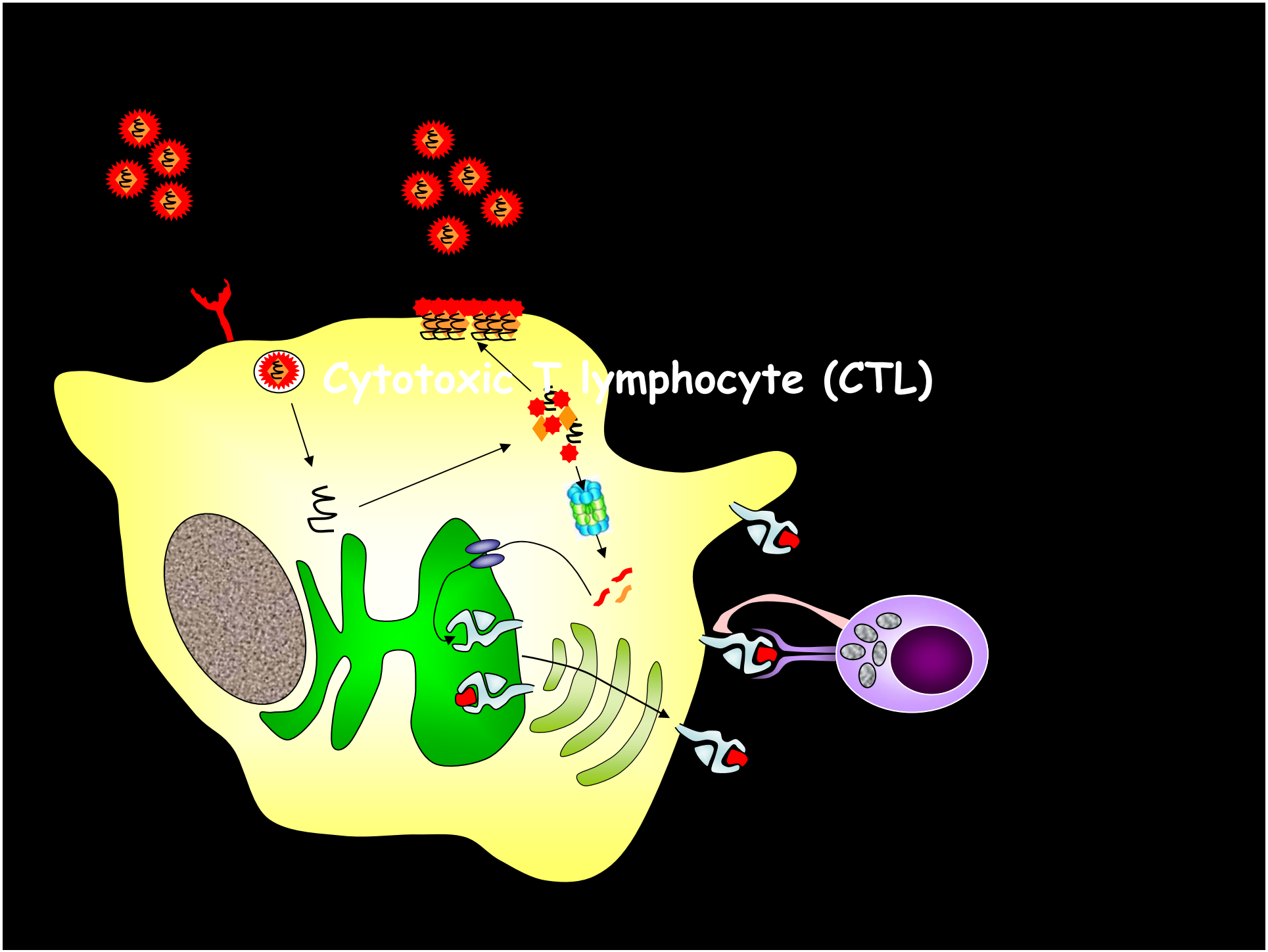
- SS negative sense RNA
- 2 segments: L (7.2 kb) and S (3.4 kb)
- 4 proteins:
  - **Glycoprotein**
  - **Nucleoprotein**
  - Polymerase
  - Zn-binding protein
- Enveloped nucleocapsid (~90 nm)
- Acute or chronic infection in rodents





Acute LCMV infection

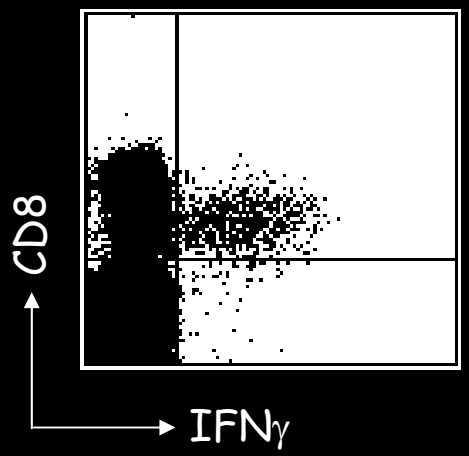



Cytotoxic T lymphocyte (CTL)

Anti-viral CD8+ T cell effector function: cytokine production and cytotoxicity

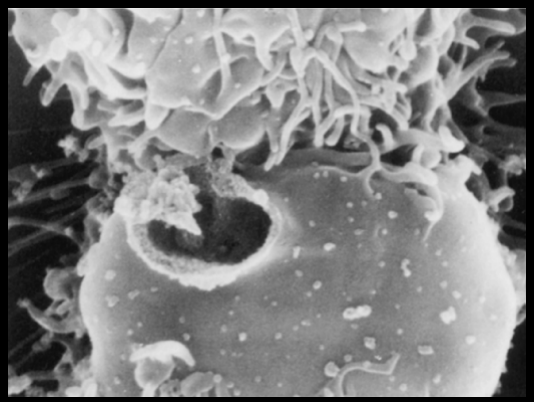
Cytokine Production

- Requires new gene transcription

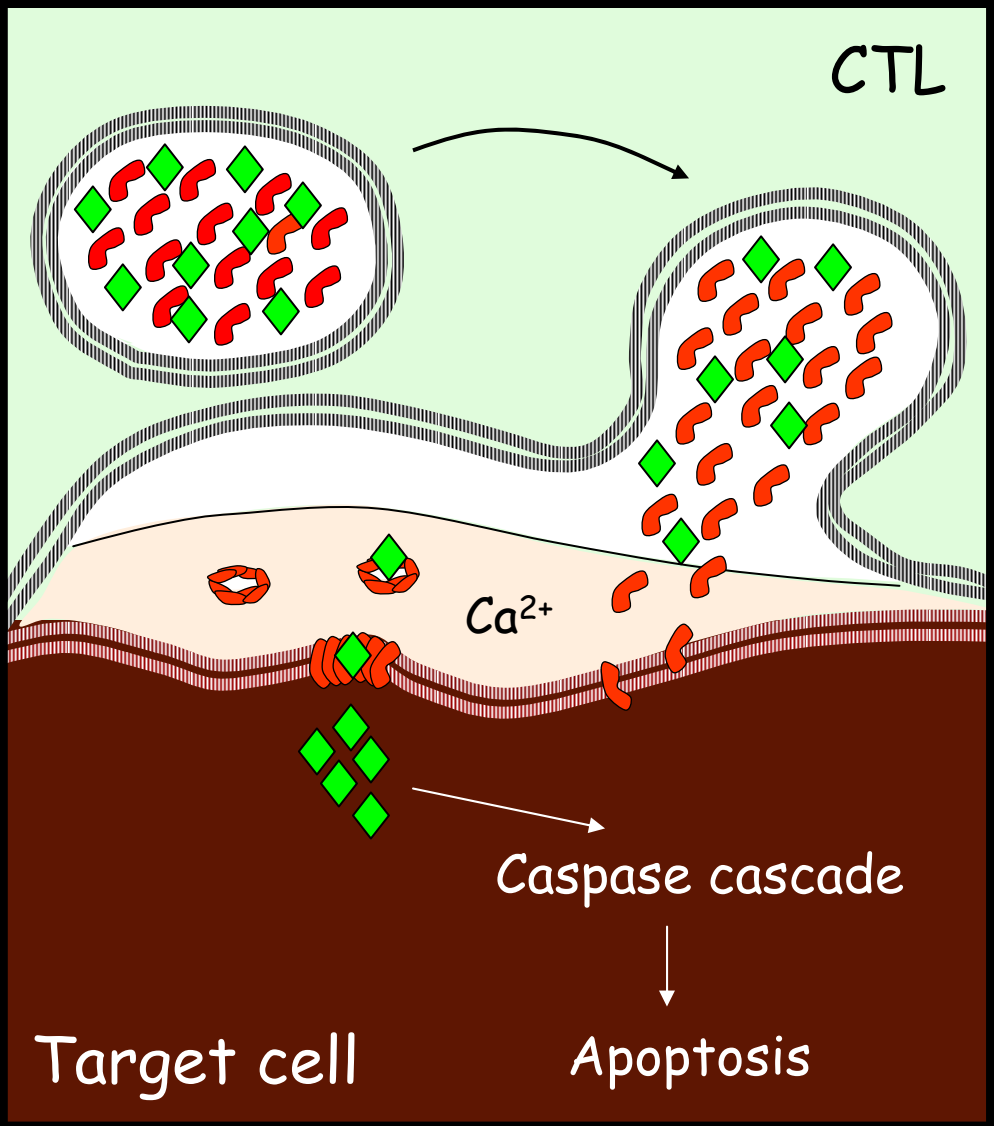


Cytotoxicity

- Exocytosis of pre-formed granules (degranulation)
- Target cell apoptosis



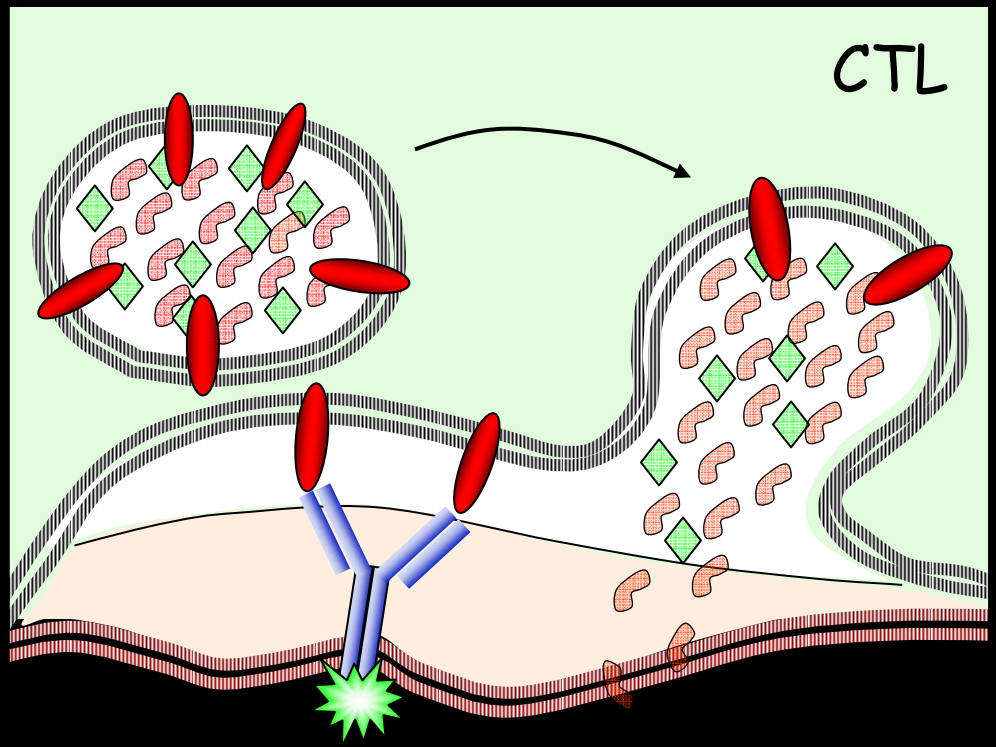
Granule exocytosis pathway



Perforin

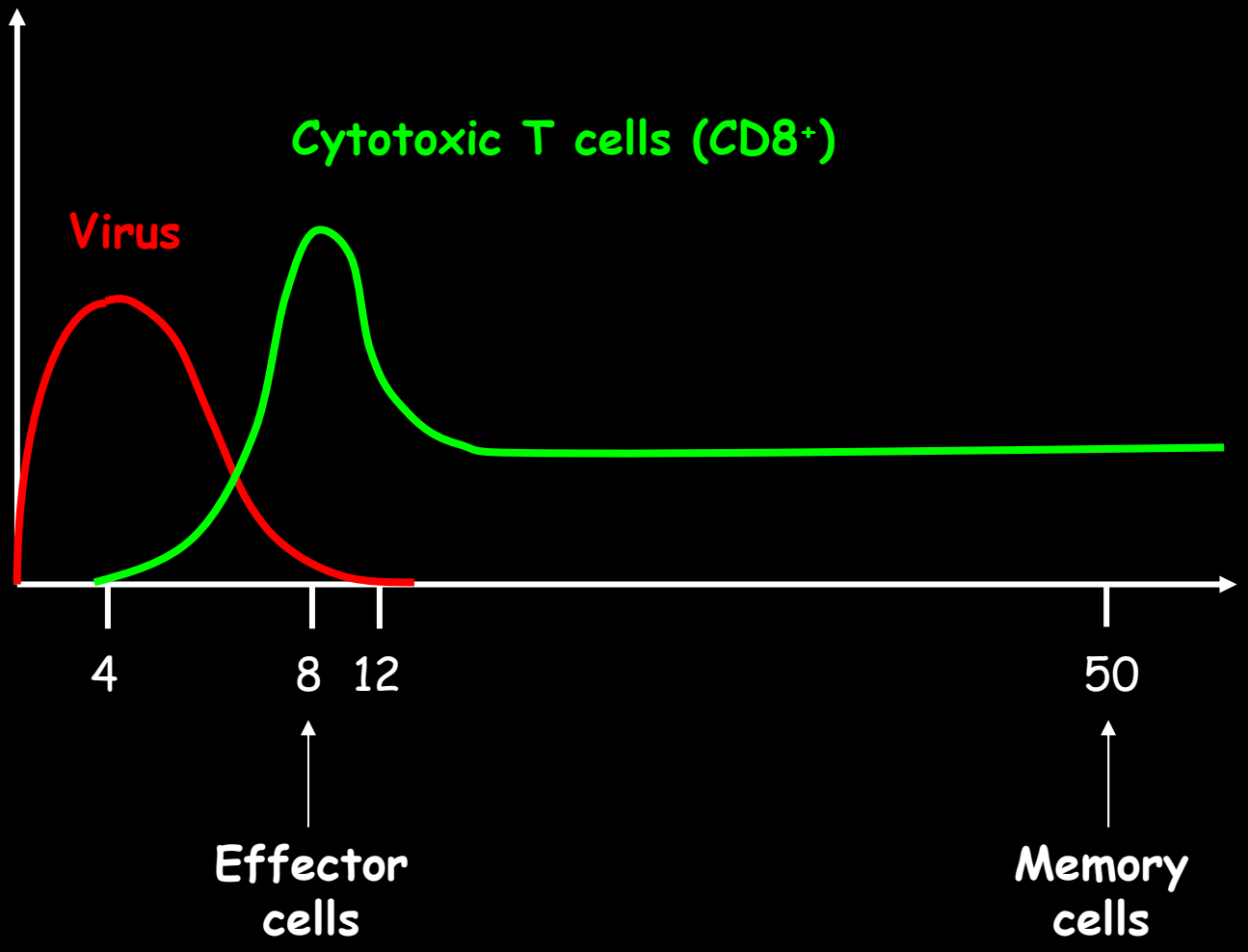
Granyzme

Assessment of antigen-induced degranulation

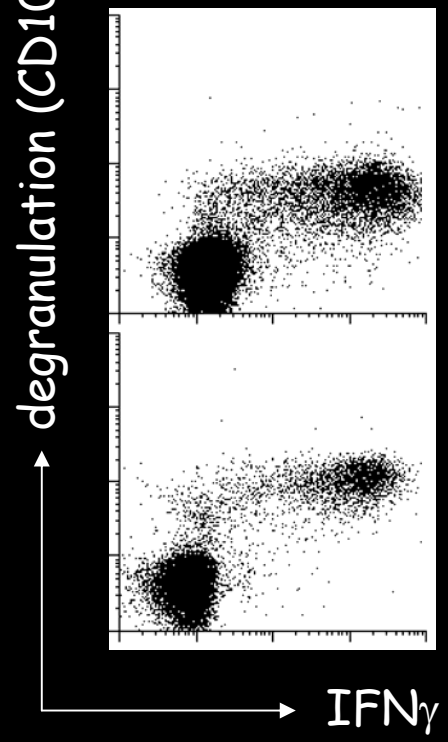


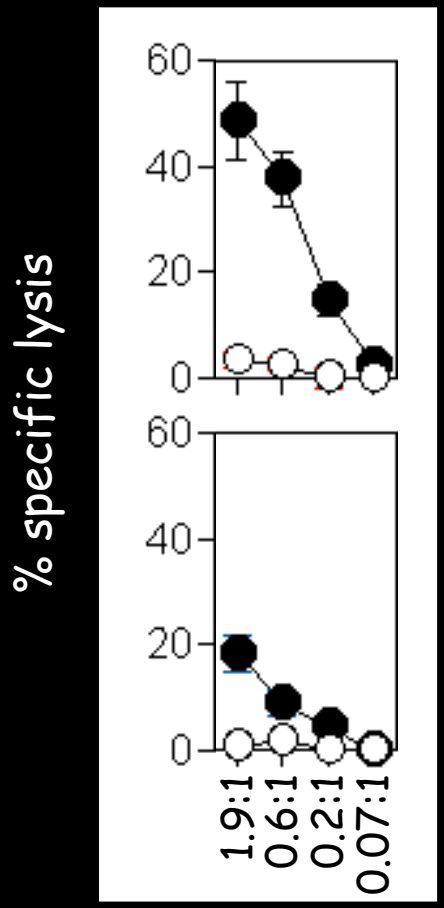
CD107
(Lamp-1)

Functions of effector and memory T cells



Degranulation and killing of LCMV-specific CD8$^+$ T cells





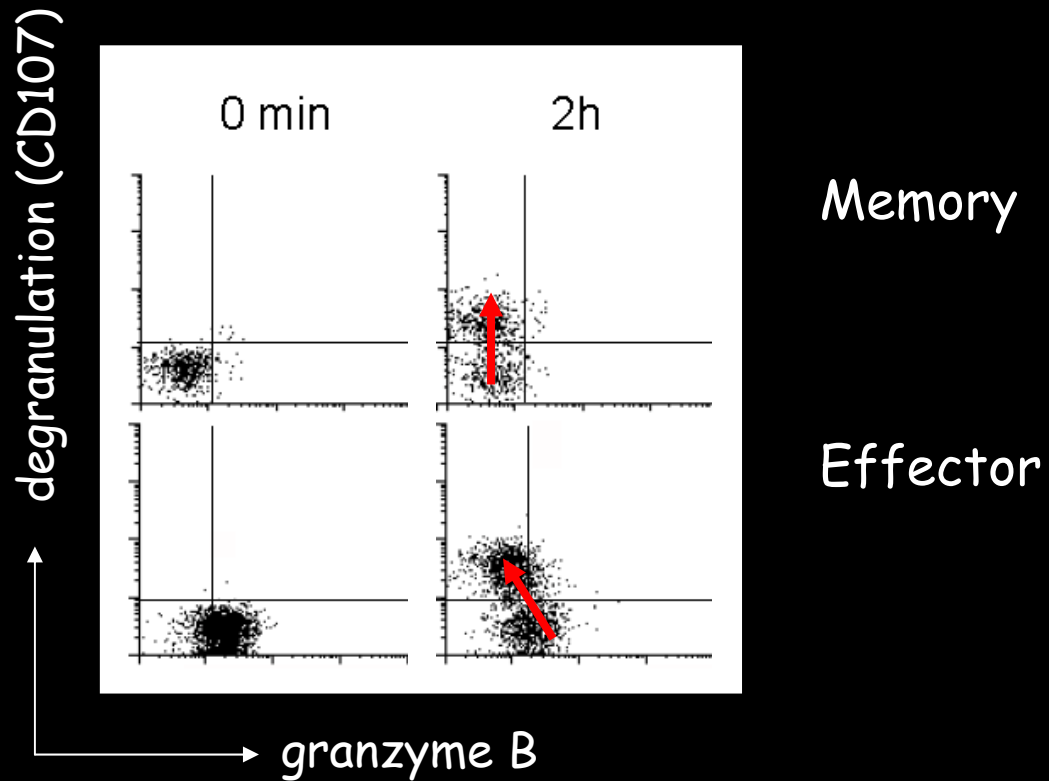
○ LCMV-infected target cells

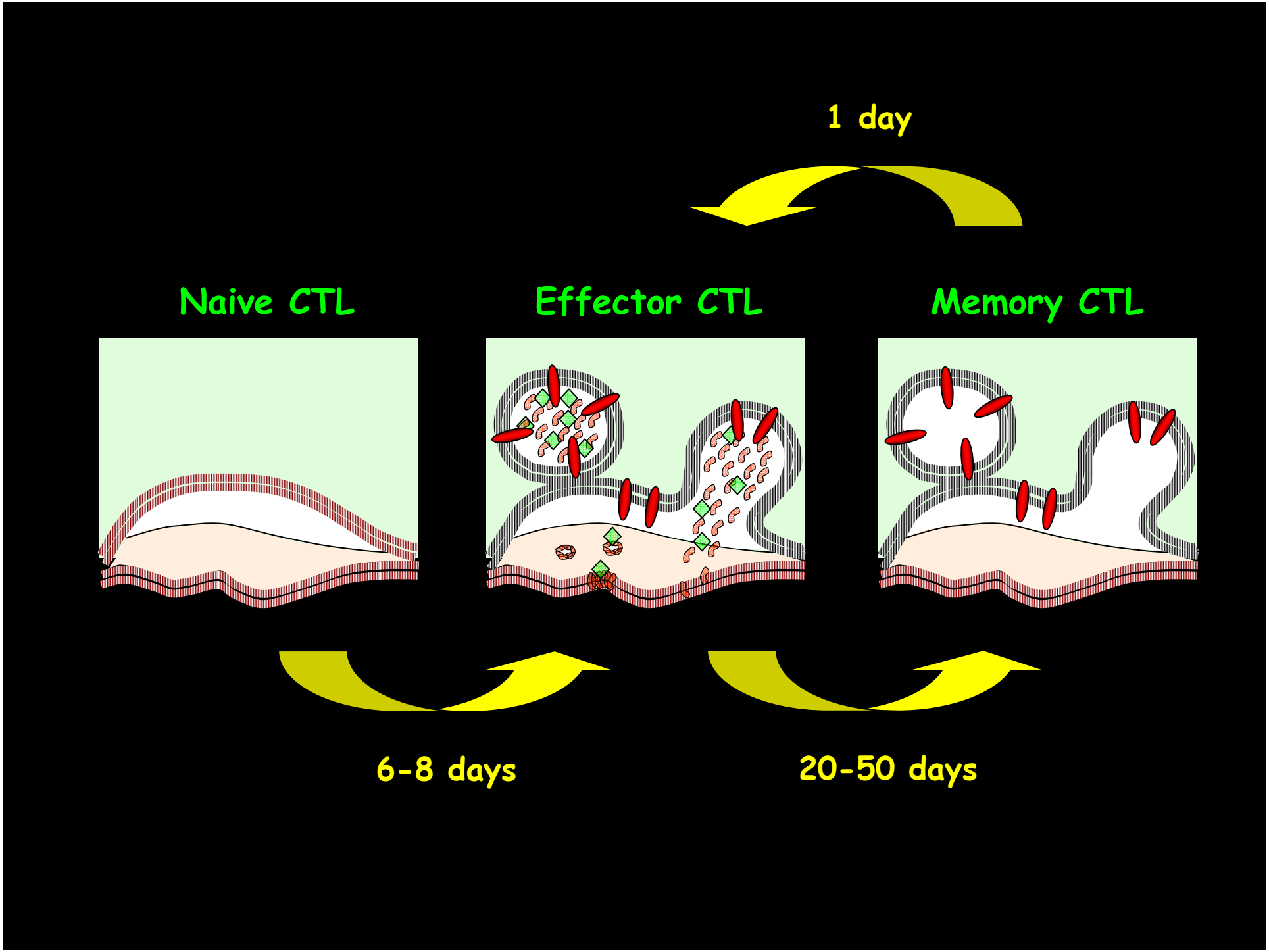
● uninfected target cells

Epitope:
gp33-41 (gp33)
from LCMV glycoprotein

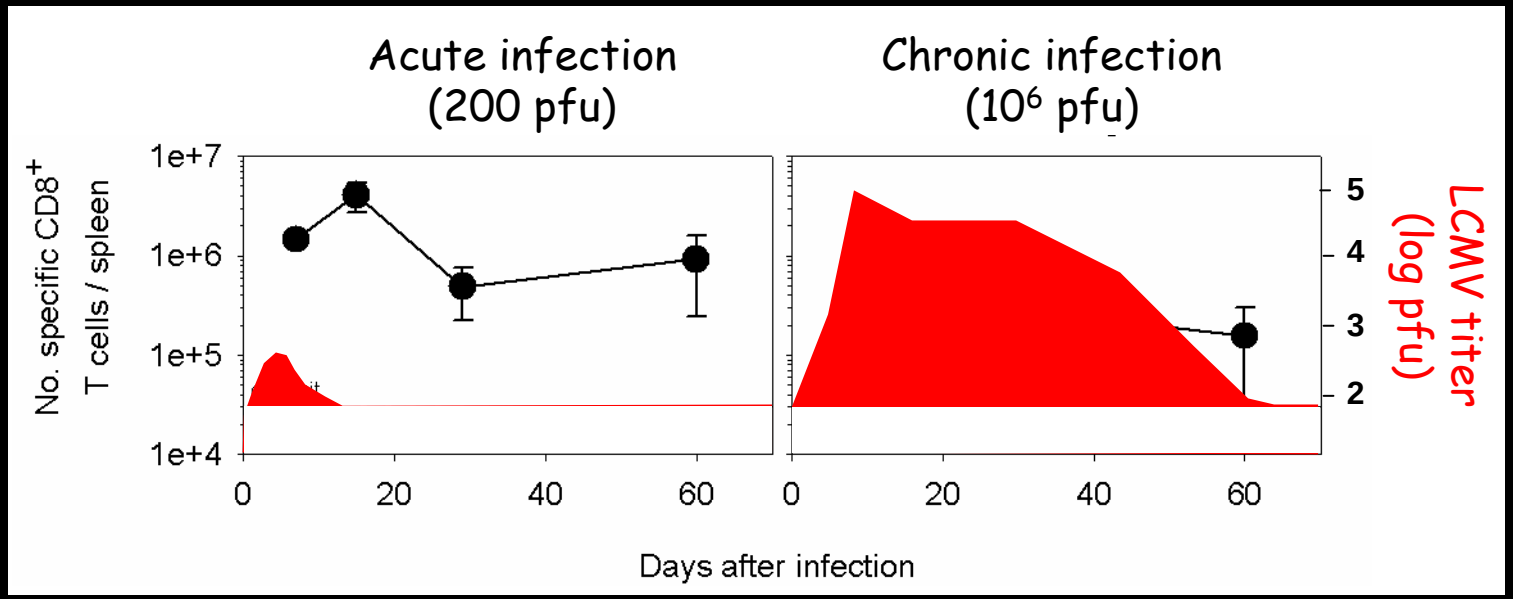
(Effector : target ratio)

Degranulation leads to loss of intracellular granzyme B




1 day
Naive CTL
Effector CTL
Memory CTL
6-8 days
20-50 days

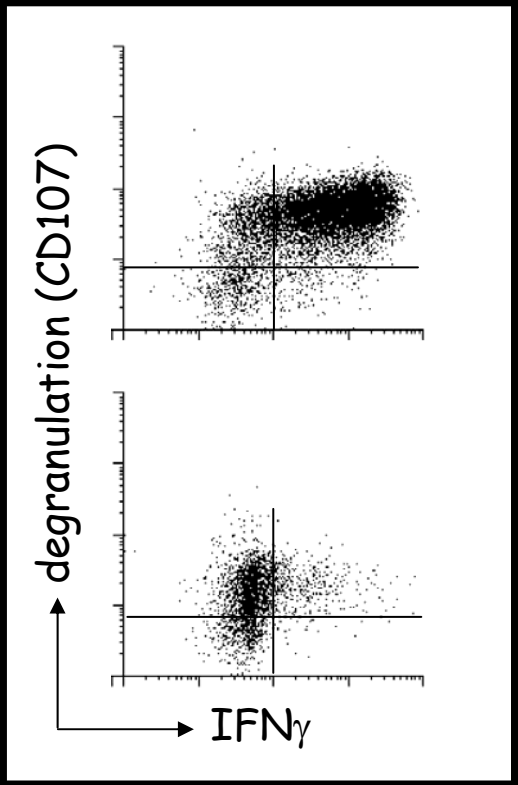
Effector functions of CD8+ T cells during persistent infection



- LCMV gp33-specific CD8+ T cells

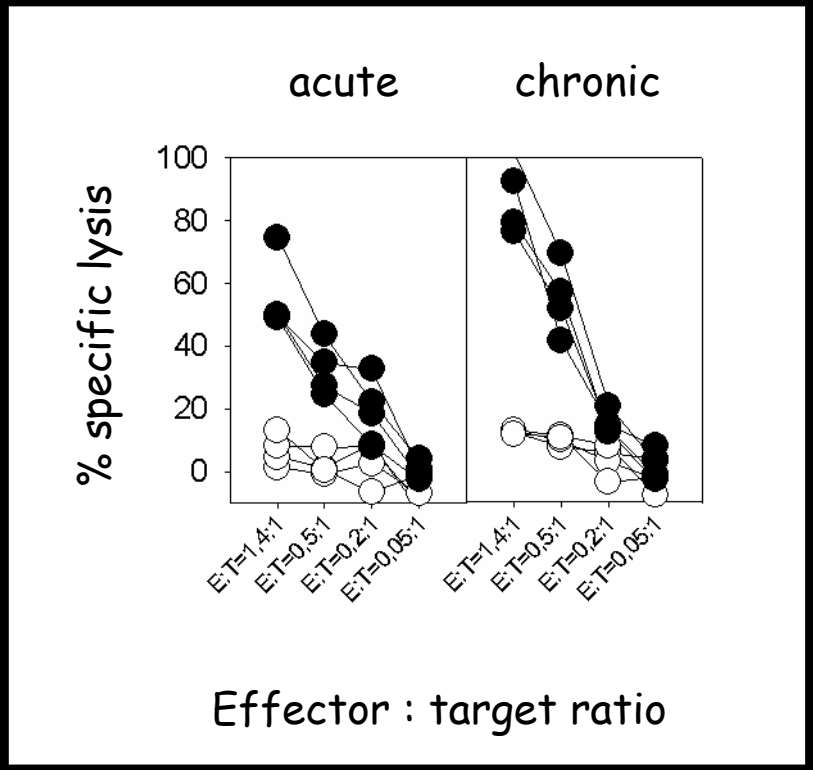
Gradual loss of cytokine production; maintenance of degranulation

d16 after infection



Direct cytotoxicity during chronic infection

d16 after infection



○ LCMV-infected target cell

● uninfected target cell

During chronic LCMV infection, $CD8^+$ T cells

- maintain degranulation capacity
- maintain direct cytotoxicity
- gradually loose cytokine production potential (IL-2 > TNFα > IFNγ)

→ „Split exhaustion" of effector cell functions