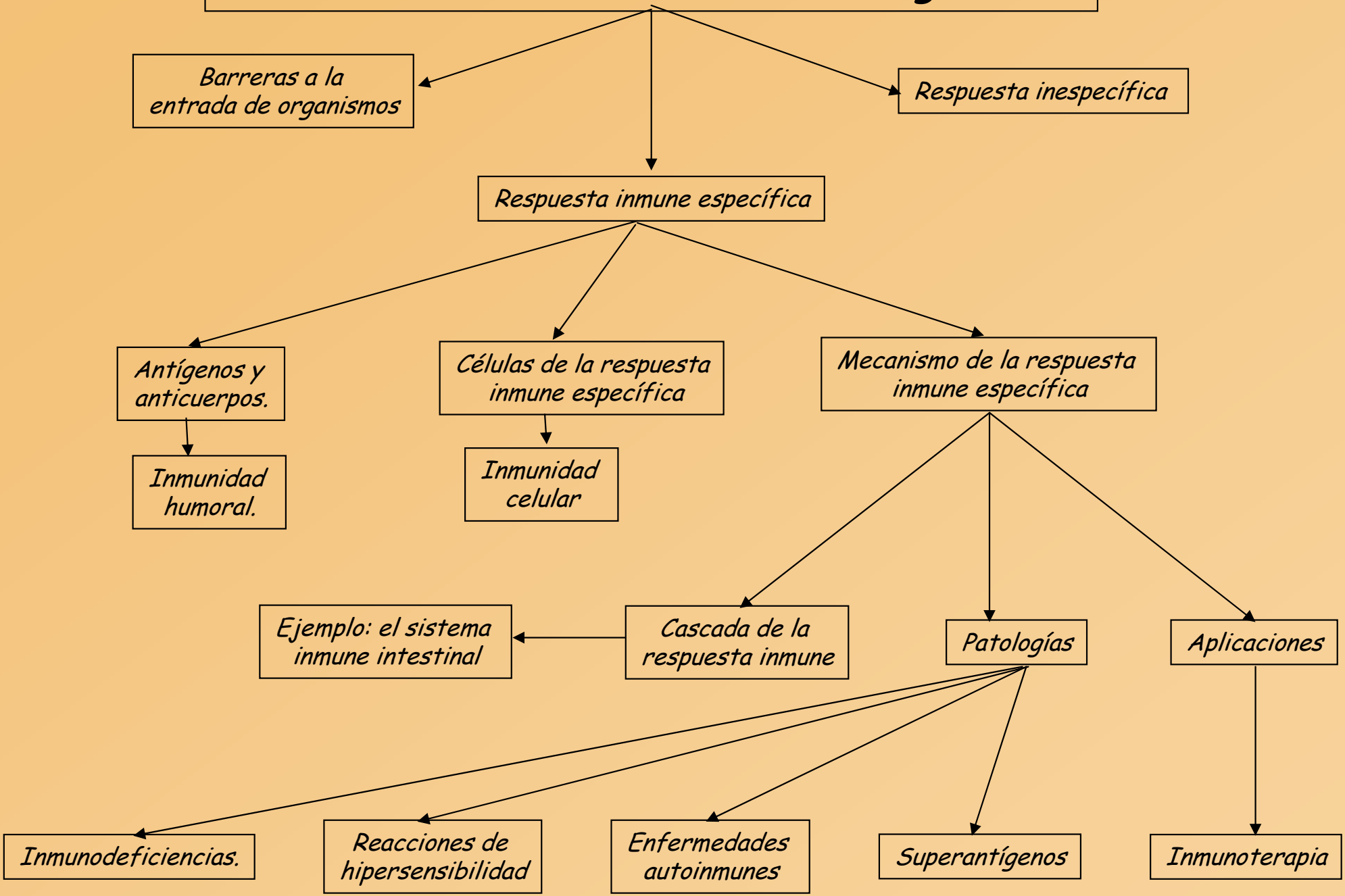
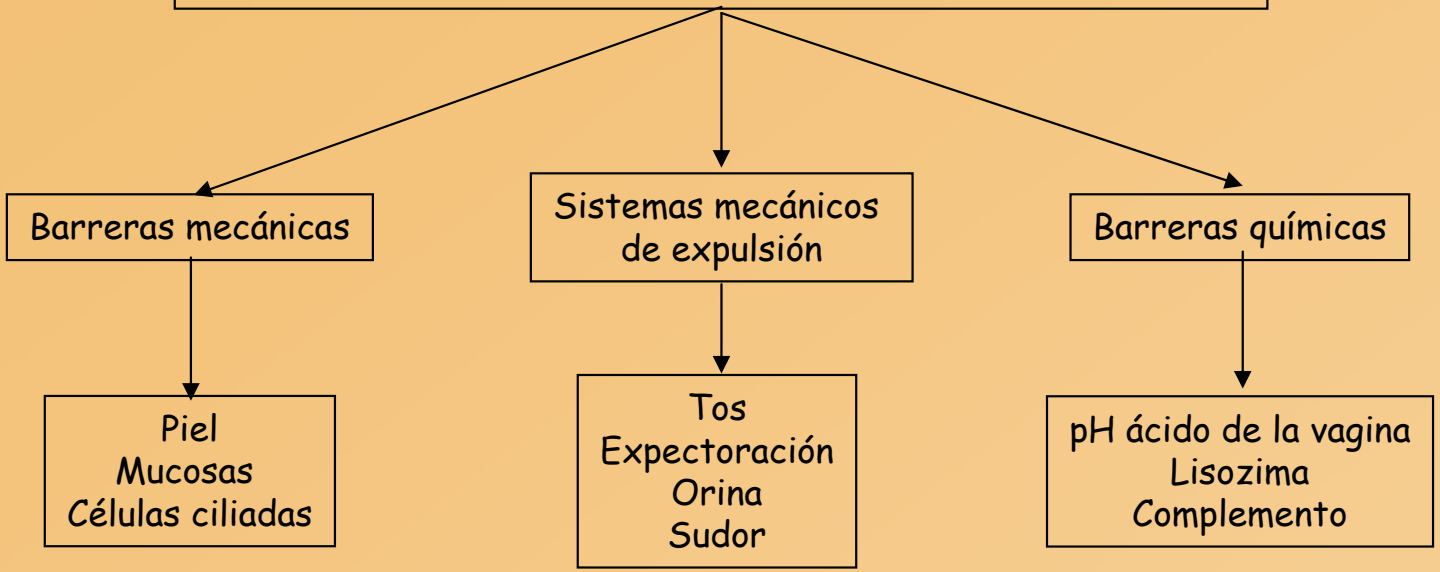
Microbiología Clínica
2006 - 2007

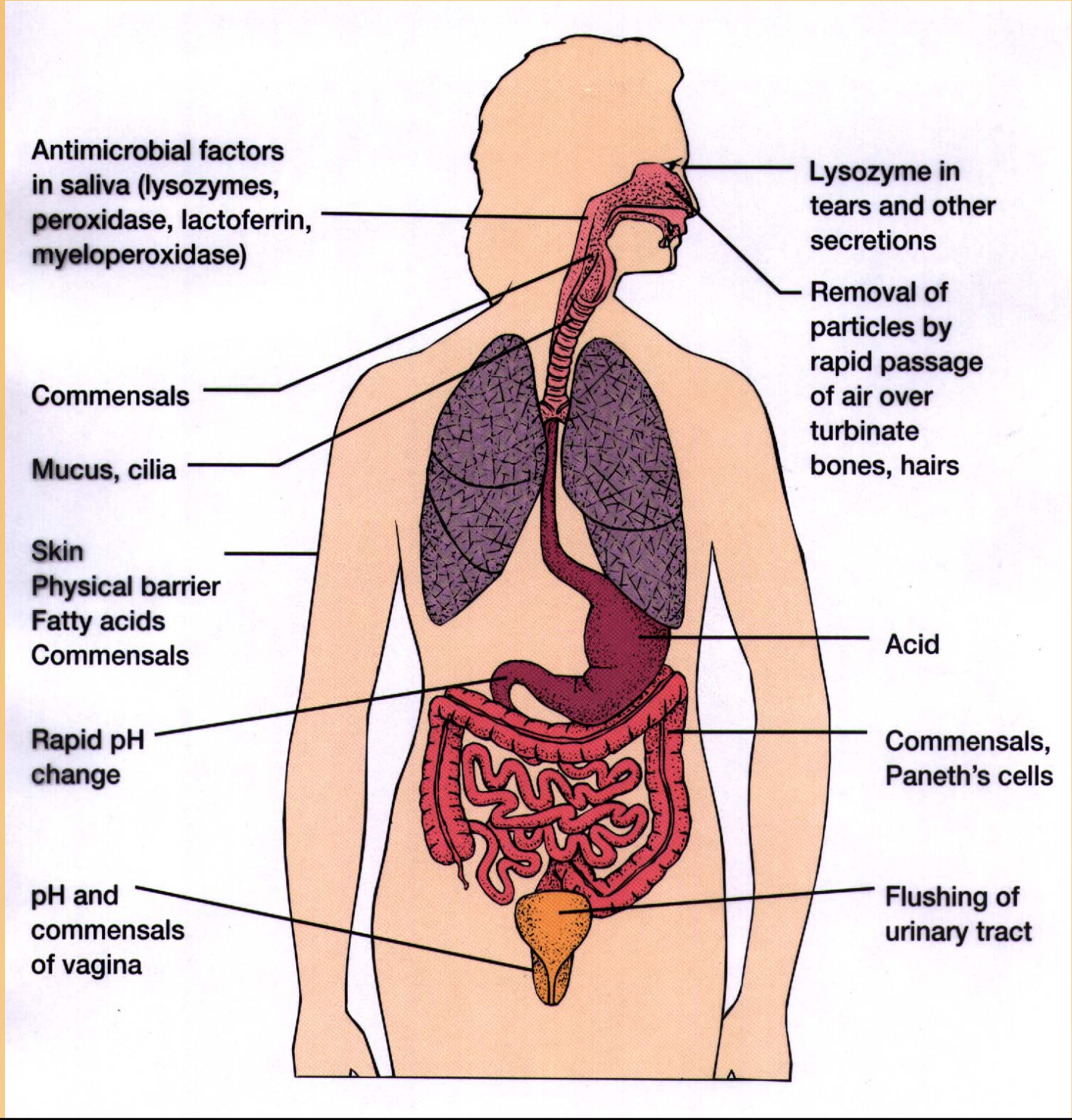
Defensa frente a los microorganismos.

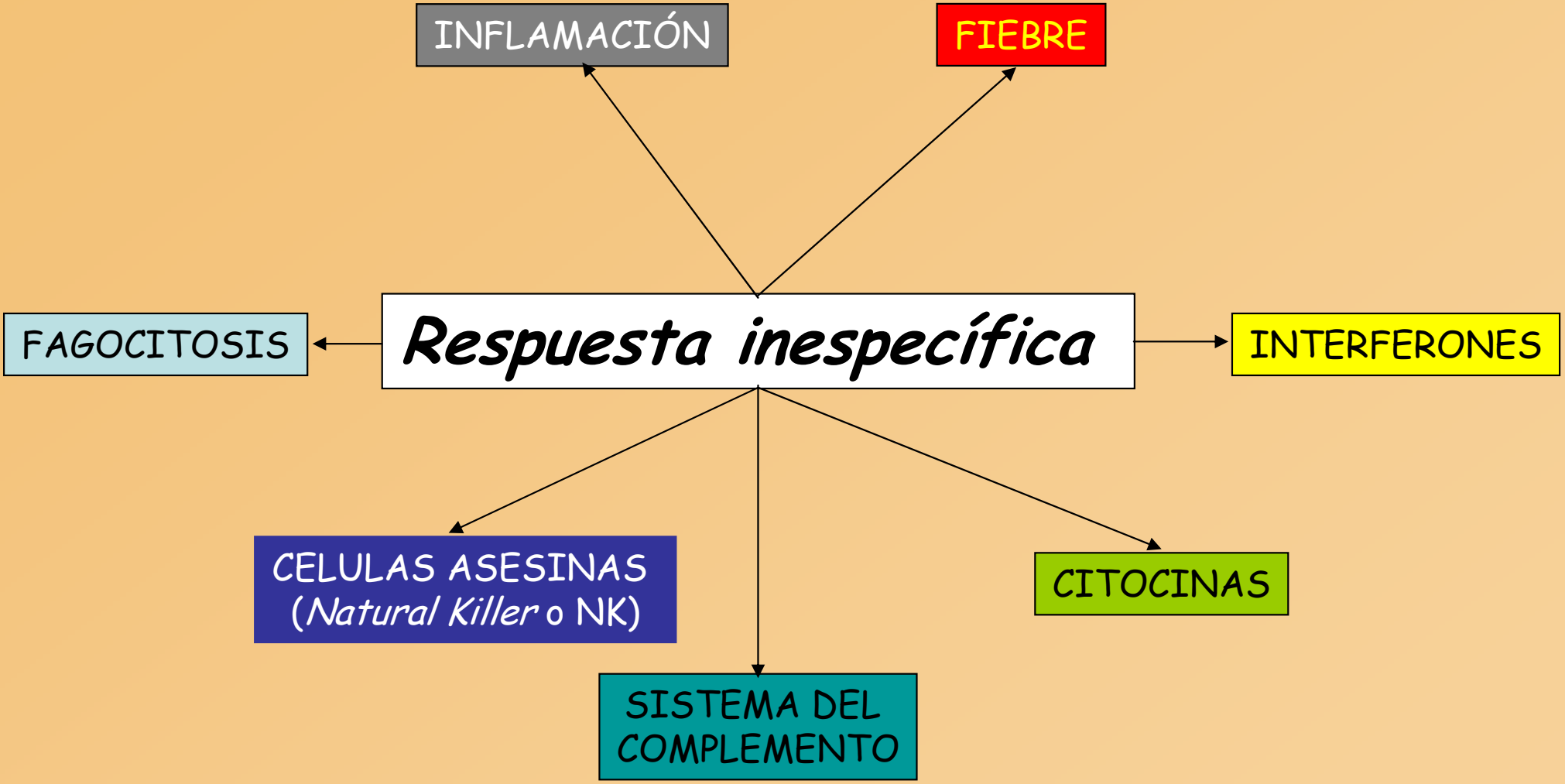
Tema 9.- Defensa frente a microorganismos



Barreras a la entrada de organismos



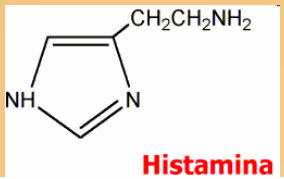

Antimicrobial factors in saliva (lysozymes, peroxidase, lactoferrin, myeloperoxidase)
Commensals
Mucus, cilia
Skin
Physical barrier
Fatty acids
Commensals
Rapid pH change
pH and commensals of vagina
Lysozyme in tears and other secretions
Removal of particles by rapid passage of air over turbinate bones, hairs
Acid
Commensals, Paneth's cells
Flushing of urinary tract


INFLAMACIÓN
FIEBRE
FAGOCITOSIS
Respuesta inespecífica
INTERFERONES
CELULAS ASESINAS
(Natural Killer o NK)
CITOCINAS
SISTEMA DEL
COMPLEMENTO

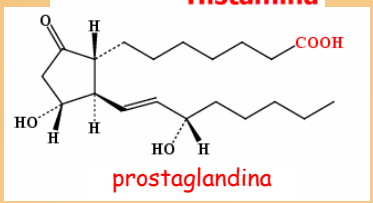
Respuesta inespecífica

INFLAMACIÓN

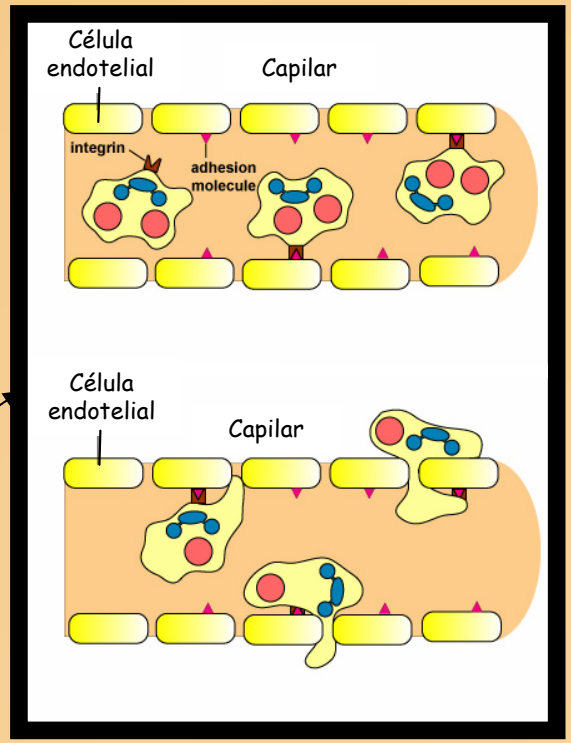
- Respuesta al daño en los tejidos
  - Substancias químicas activas
    - Histamina Prostaglandinas
      - → Vasodilatación
        - → Permeabilidad de vasos
          - → Quimiotactismo
          - → Diapedesis
- Rubor
  Calor
  Tumor
  Dolor



Histamina

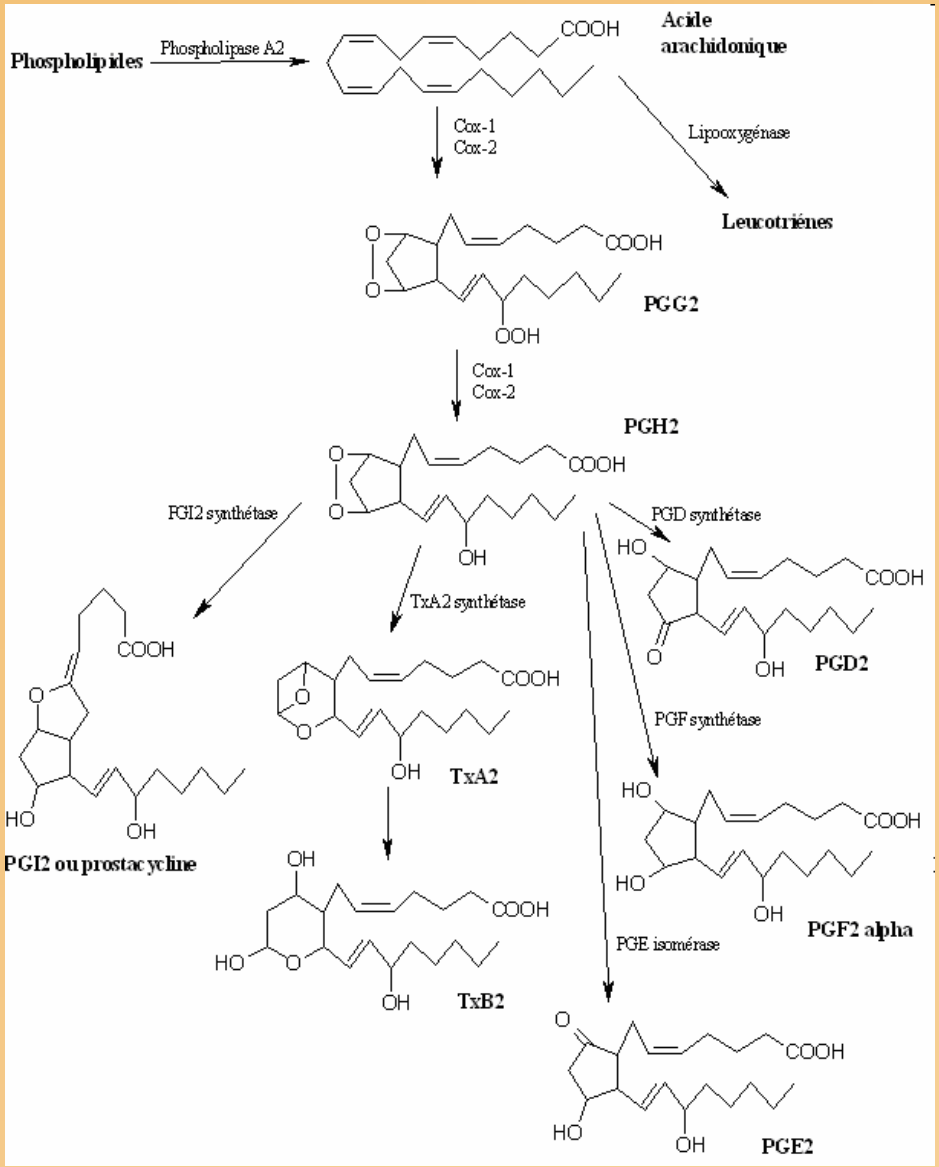


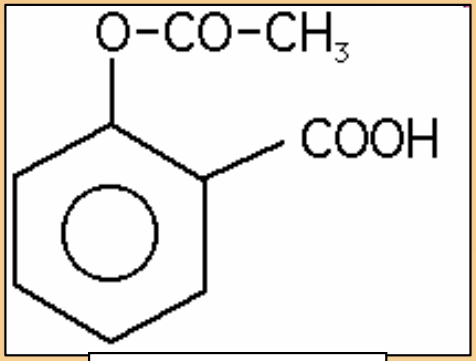
prostaglandina



Respuesta inespecífica

INFLAMACIÓN





Ácido salicílico (Aspirina)

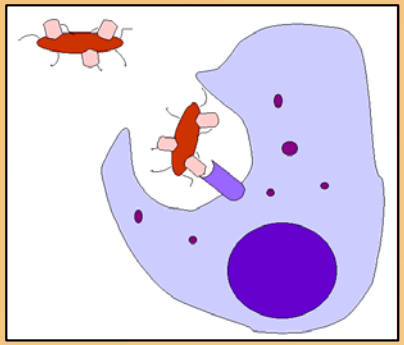
Bloqueo de la síntesis de prostaglandinas

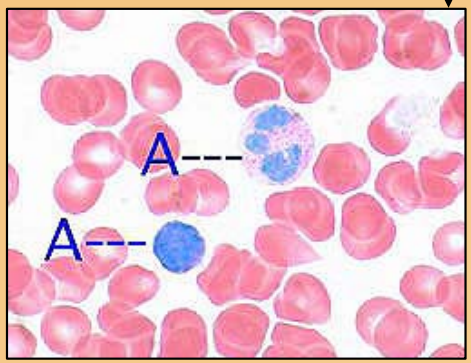
Acción antiinflamatoria

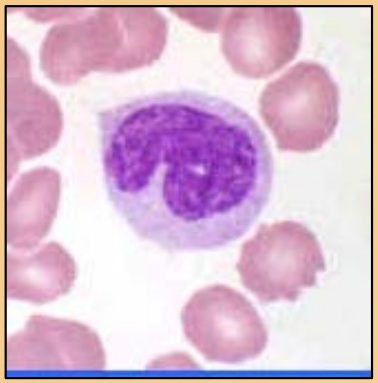
Respuesta inespecífica

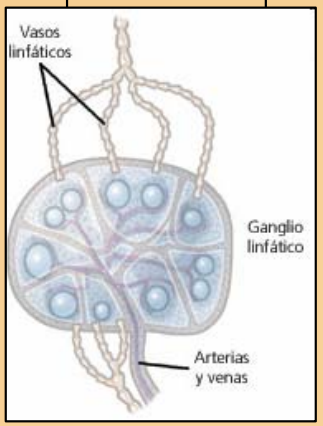
FAGOCITOSIS

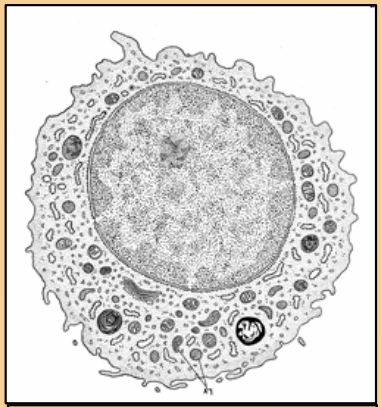
- Eliminación de cuerpos extraños
  - Opsonización
- Leucocitos polimorfonucleares
  - médula ósea
  - vida corta y acción rápida
    - células del pus
- Macrófagos
  - larga vida
  - Viajan por la sangre
    - monocitos
      - macrófagos fijos
        - ganglios linfáticos
      - macrófagos libres
  - sistema retículo endotelial.







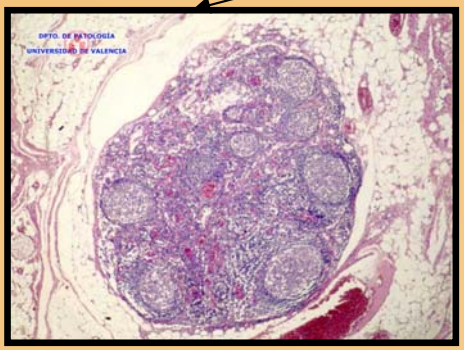


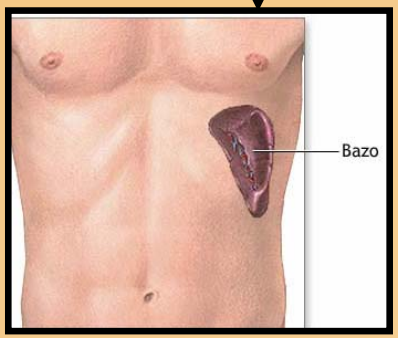


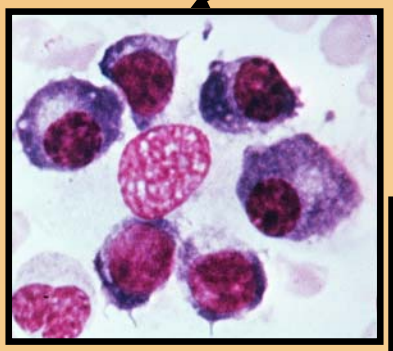
Macrófago alveolar de los pulmones

Sistema retículo endotelial

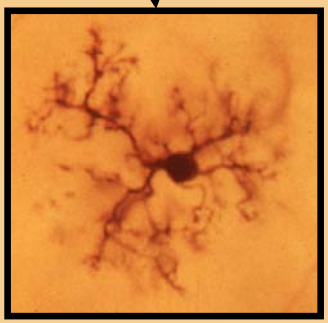
- Reserva de macrófagos del cuerpo
- Tipos de céulas
  - Células reticulares
    - ganglios linfáticos
    - bazo
    - médula ósea
  - Histiocitos
    - tejido subcutáneo
  - Microglia
    - tejido nervioso
  - macrófagos alveolares
    - pulmones
  - células Kupffer
    - hígado



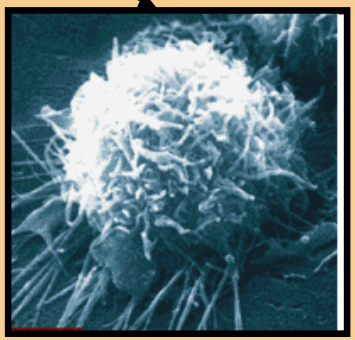




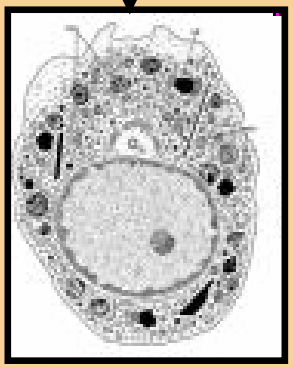
Células plasmáticas rodenado un histiocito (Univ. Alberta, Cananá)

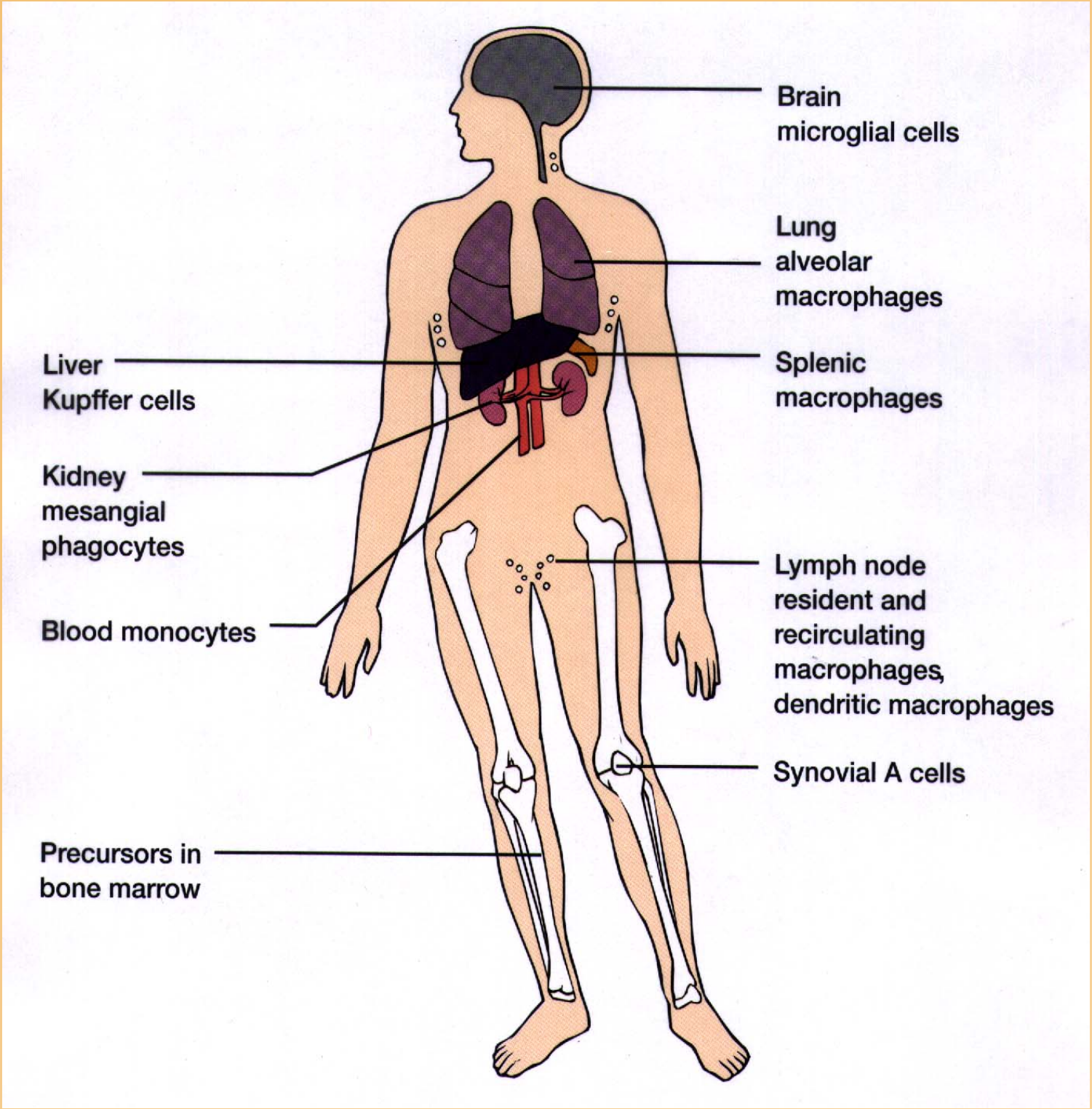


Microglía (Univ. Virginia, USA)



Boehringer-Ingelheim

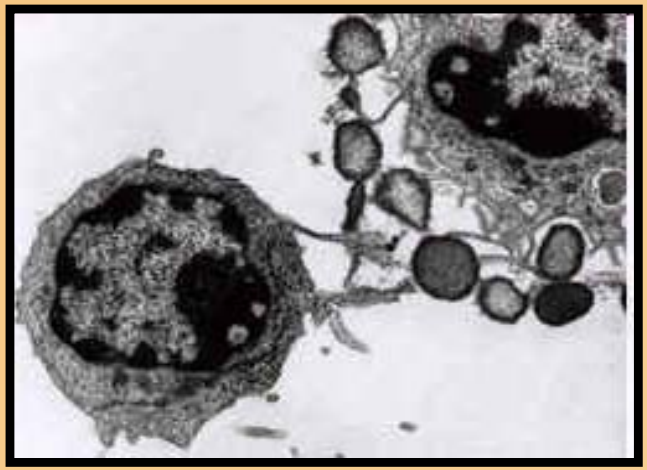


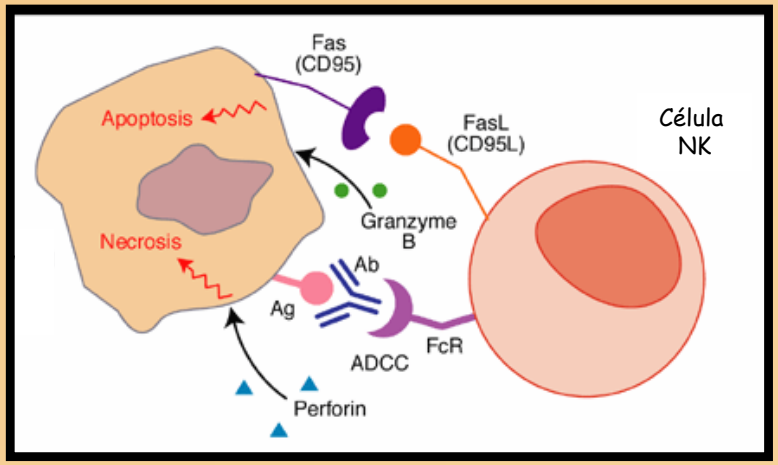

Brain
microglial cells
Lung
alveolar
macrophages
Liver
Kupffer cells
Splenic
macrophages
Kidney
mesangial
phagocytes
Blood monocytes
Lymph node
resident and
recirculating
macrophages,
dendritic macrophages
Synovial A cells
Precursors in
bone marrow

Respuesta inespecífica

CELULAS ASESINAS
(*Natural Killer* o NK)

- Linfocitos especializados en destruir
  - células infectadas
    - virus
- defensas inespecíficas
  - protozoos
  - parásitos

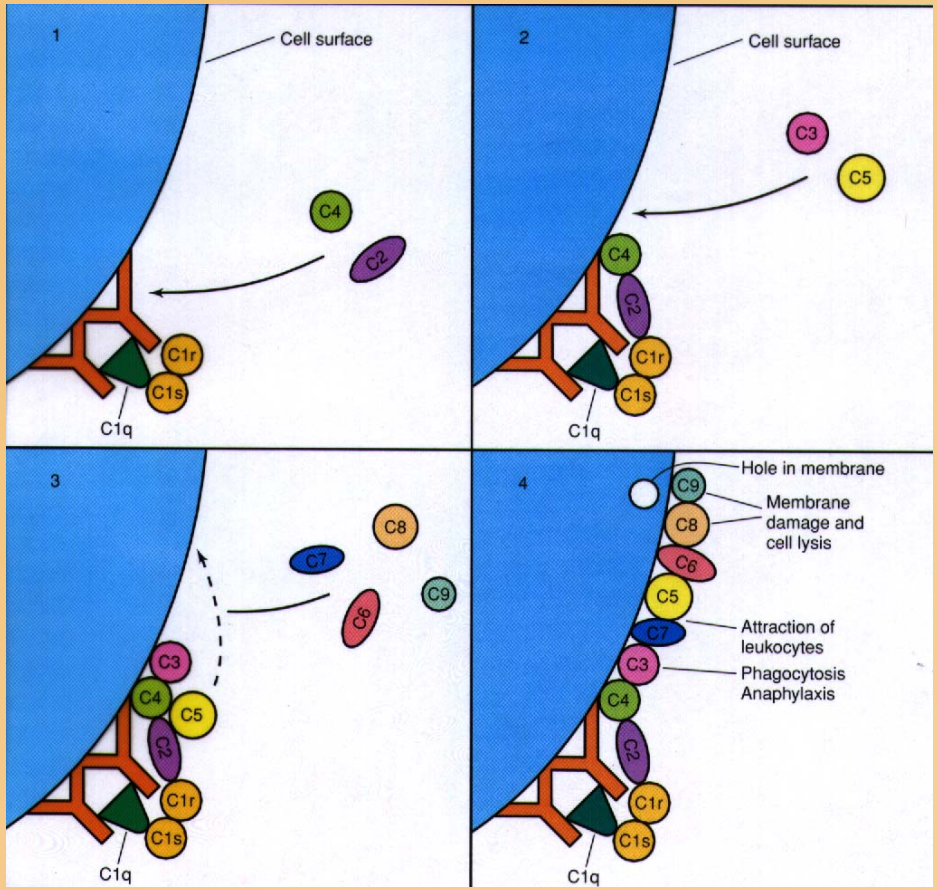




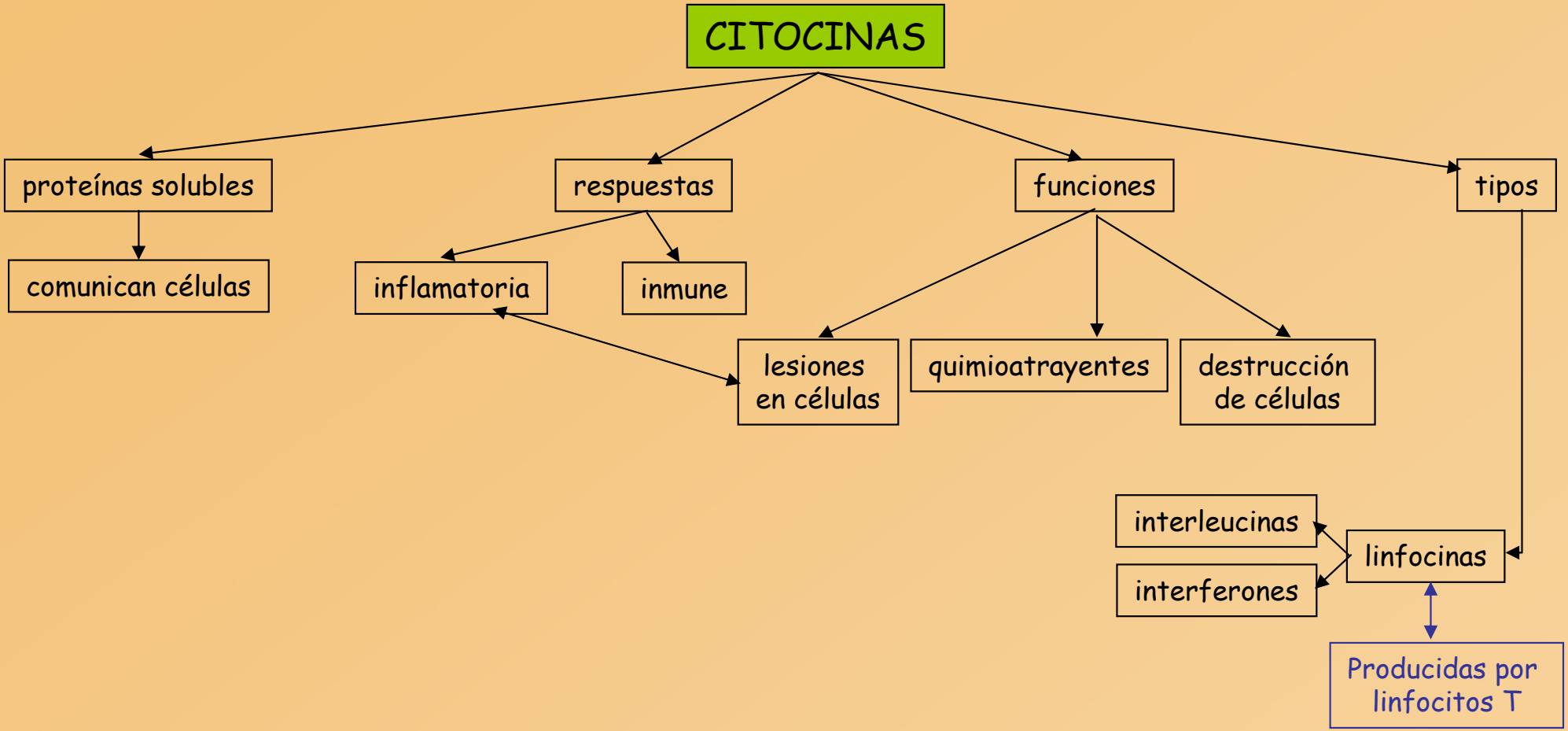
Respuesta inespecífica

SISTEMA DEL COMPLEMENTO

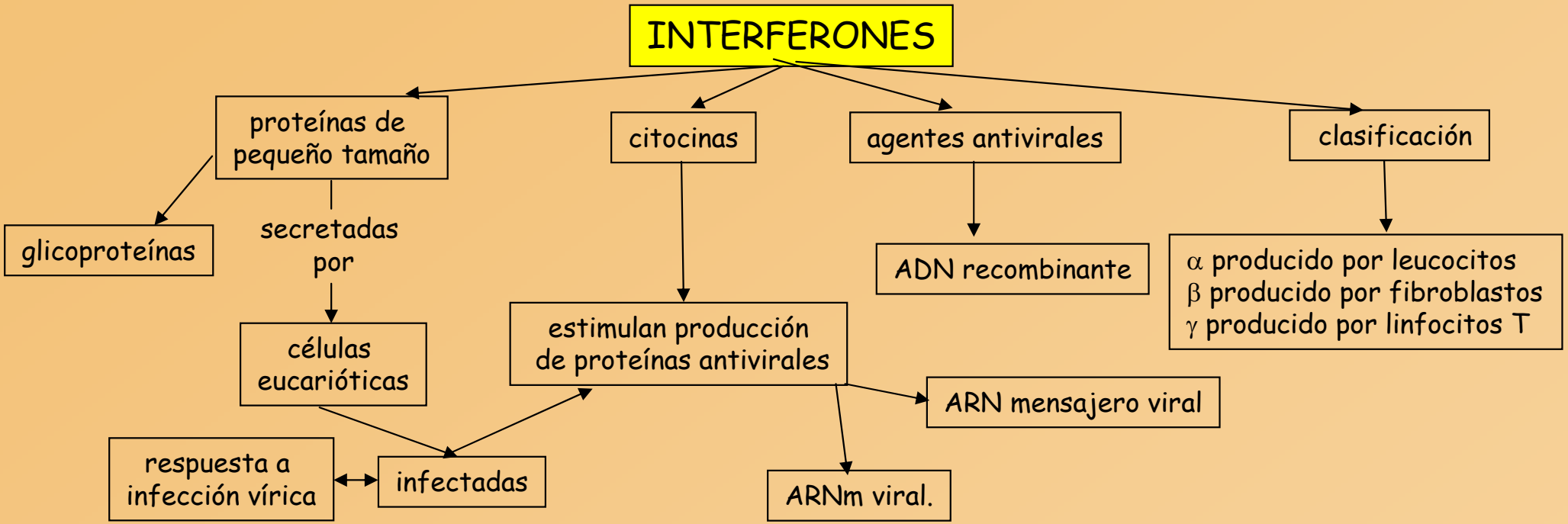
- proteínas que facilitan la actuación de determinados anticuerpos
- **cascada del complemento**
- opsonización
- respuesta inflamatoria
- actividad líticas

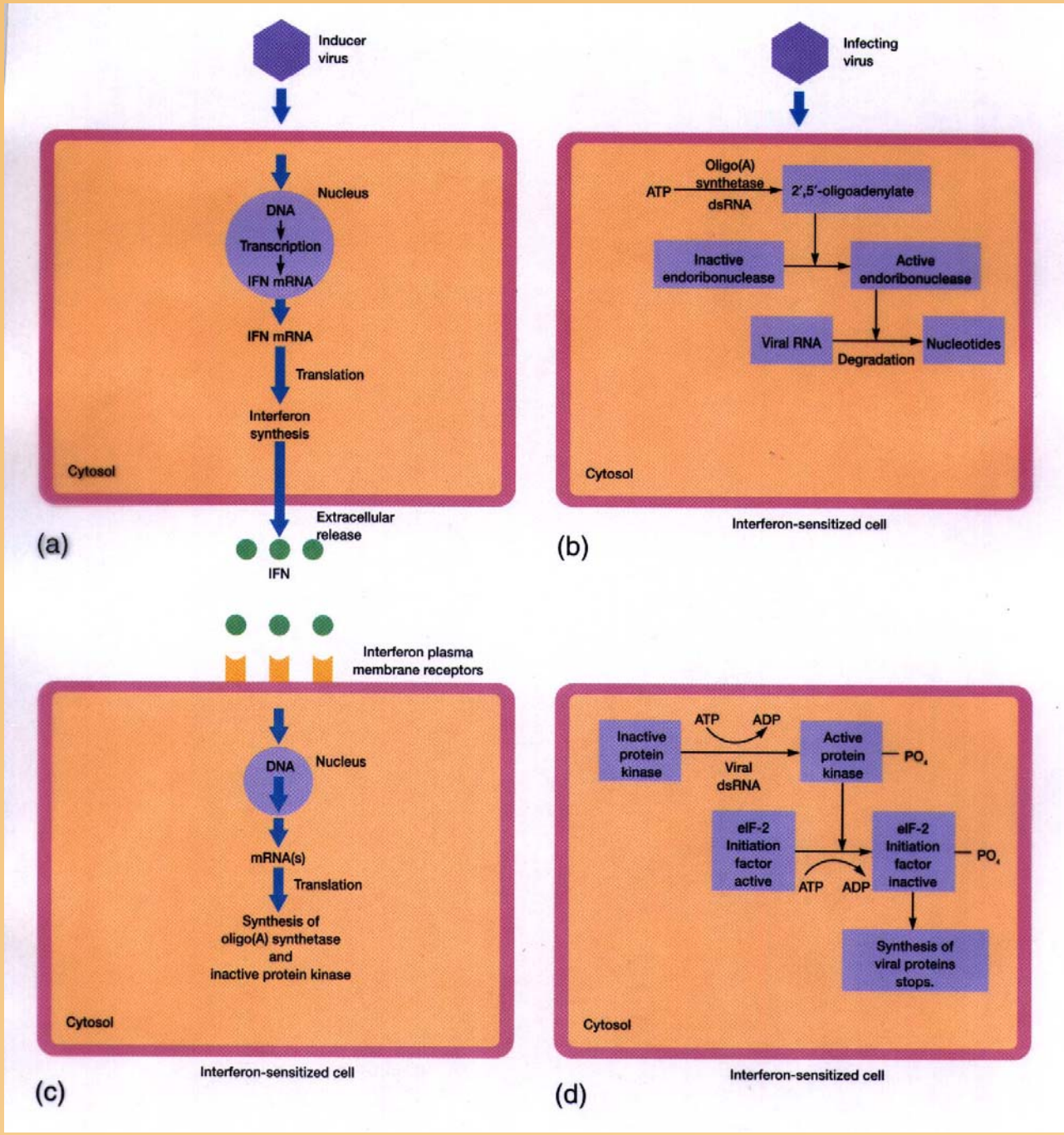


Respuesta inespecífica

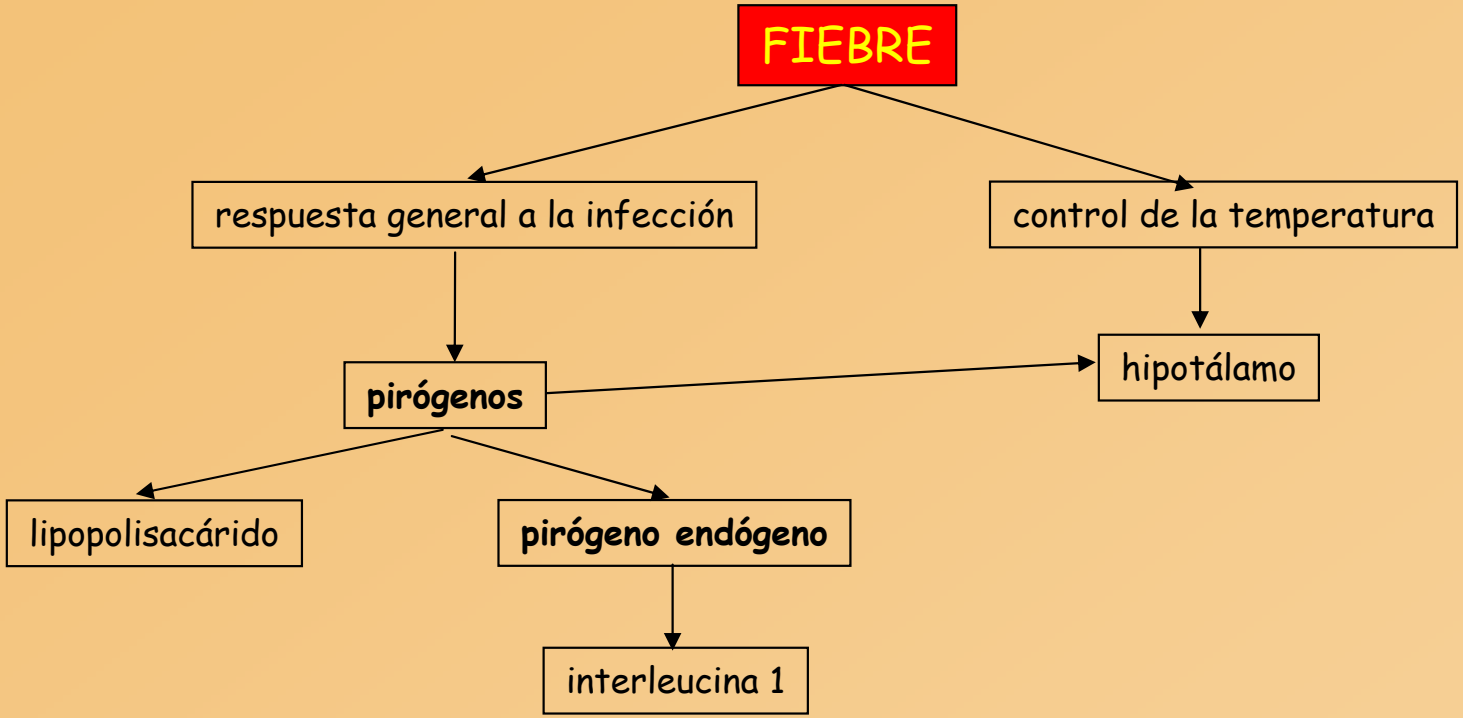


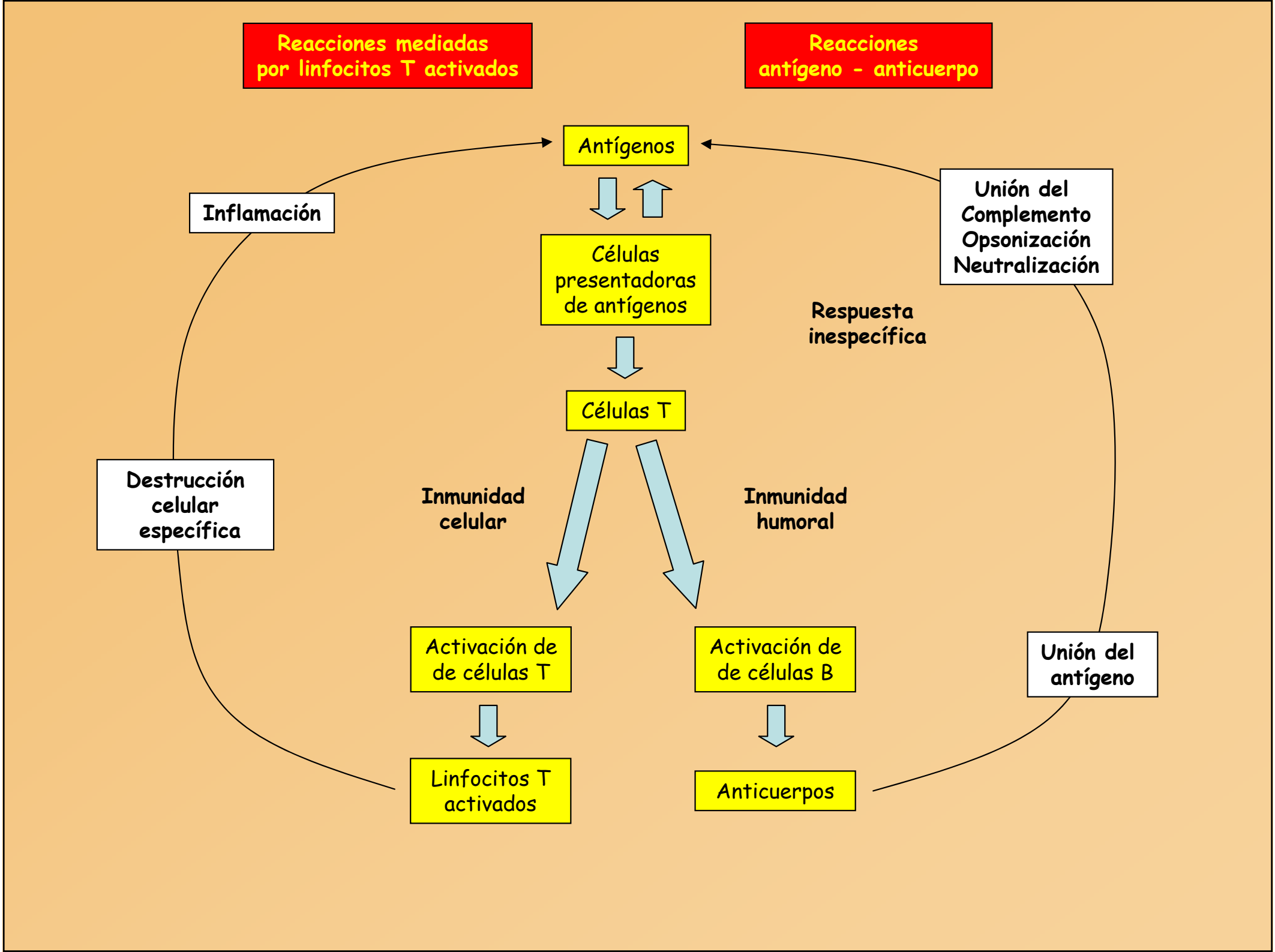
Respuesta inespecífica



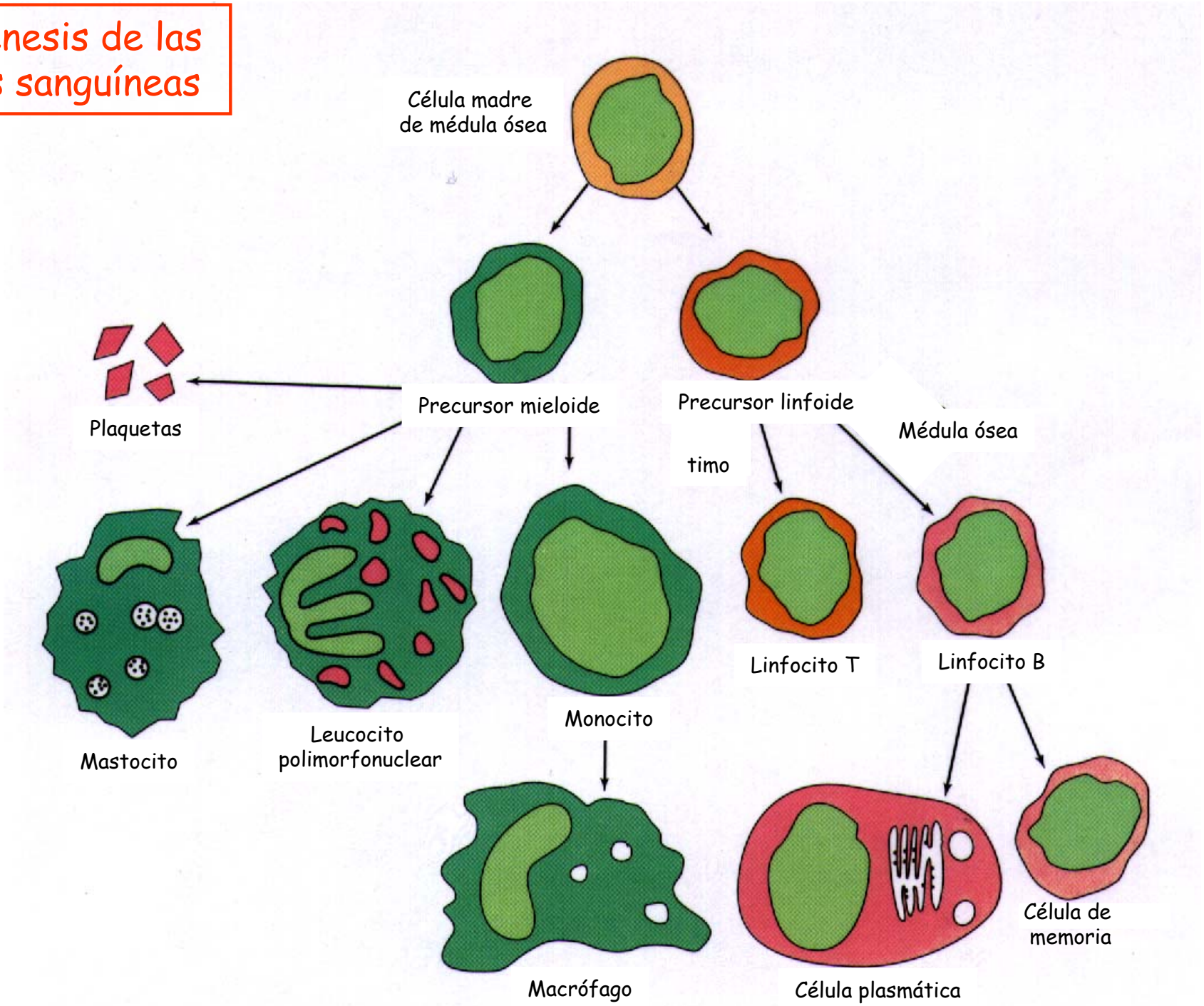

Inducer virus
Nucleus
DNA
Transcription
IFN mRNA
IFN mRNA
Translation
Interferon synthesis
Cytosol
Extracellular release
IFN
(a)
Infecting virus
Oligo(A) synthetase
ATP
dsRNA
2′,5′-oligoadenylate
Inactive endoribonuclease
Active endoribonuclease
Viral RNA
Degradation
Nucleotides
Cytosol
Interferon-sensitized cell
(b)
Interferon plasma membrane receptors
DNA
Nucleus
mRNA(s)
Translation
Synthesis of oligo(A) synthetase and inactive protein kinase
Cytosol
Interferon-sensitized cell
(c)
Inactive protein kinase
ATP
ADP
Viral dsRNA
Active protein kinase
PO4
eIF-2 Initiation factor active
ATP
ADP
eIF-2 Initiation factor inactive
PO4
Synthesis of viral proteins stops.
Cytosol
Interferon-sensitized cell
(d)

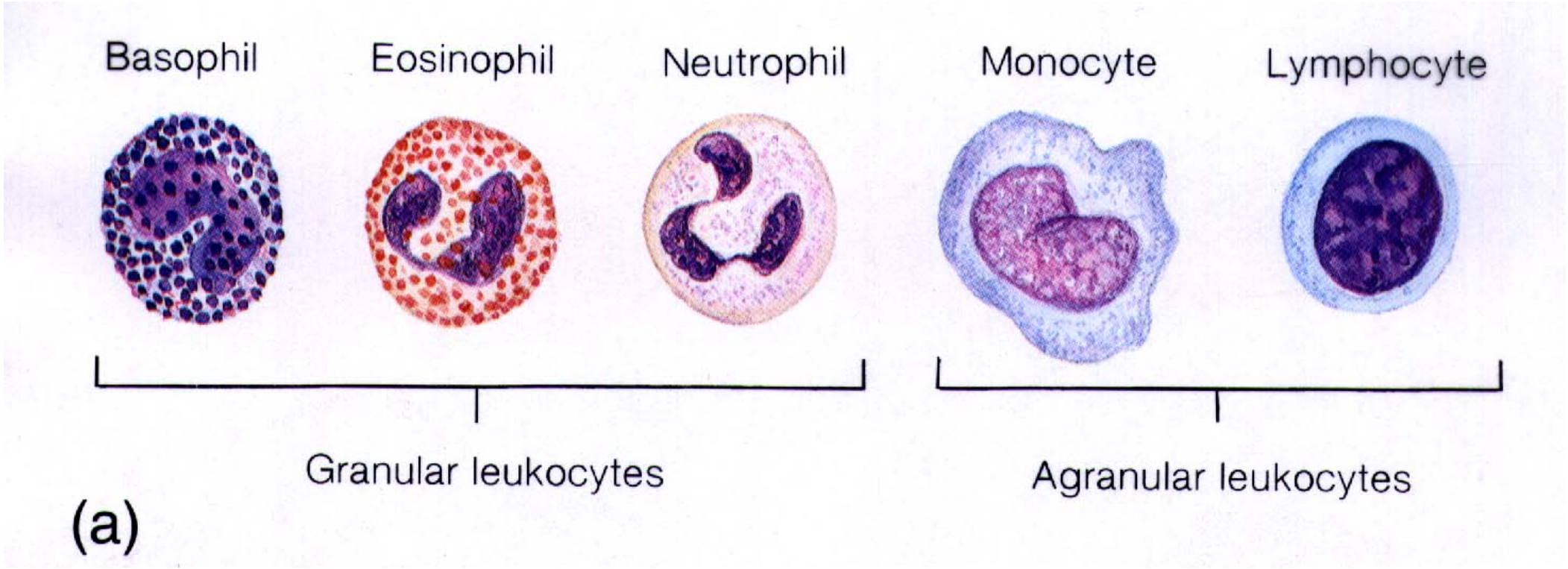
Respuesta inespecífica

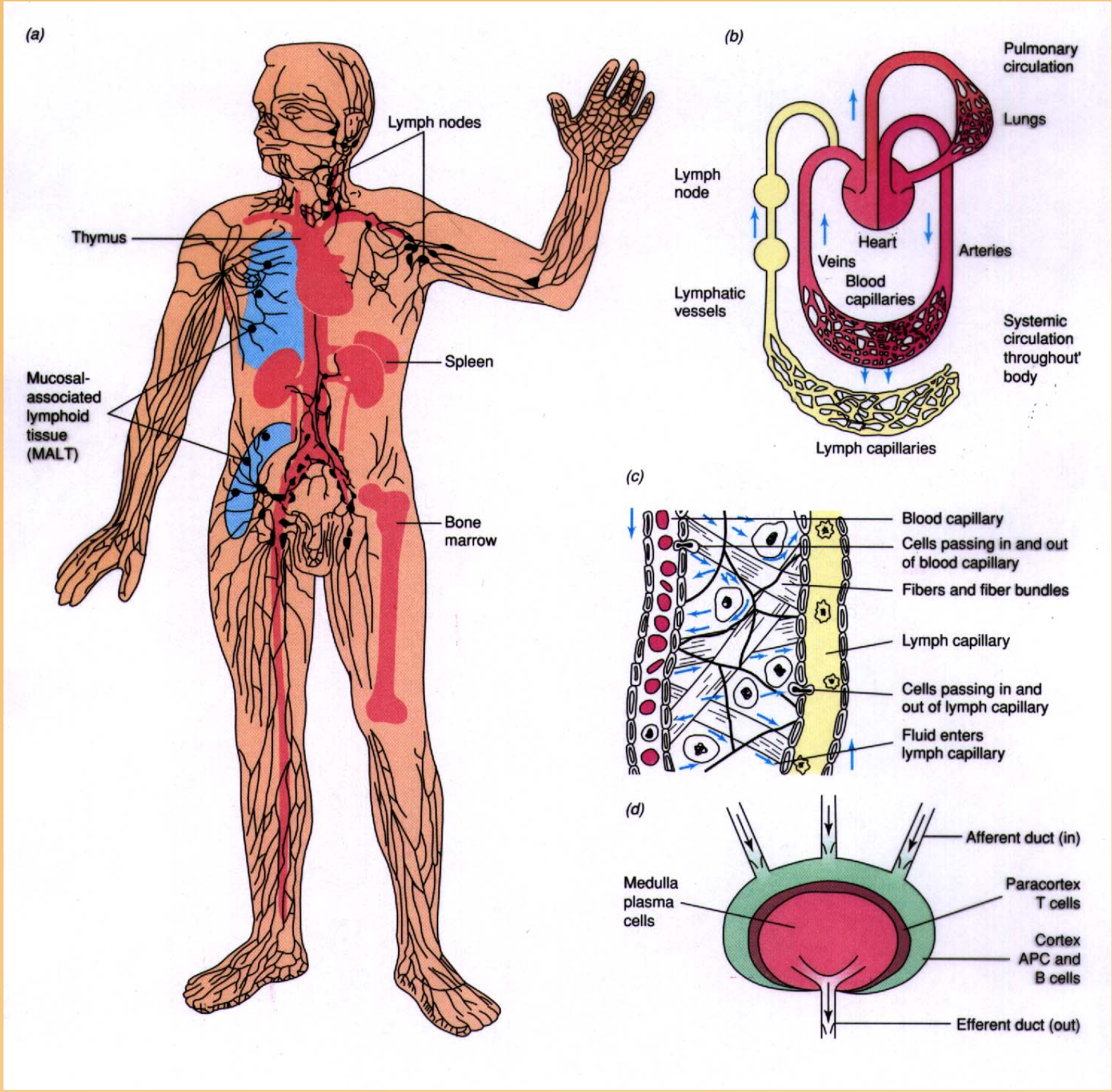


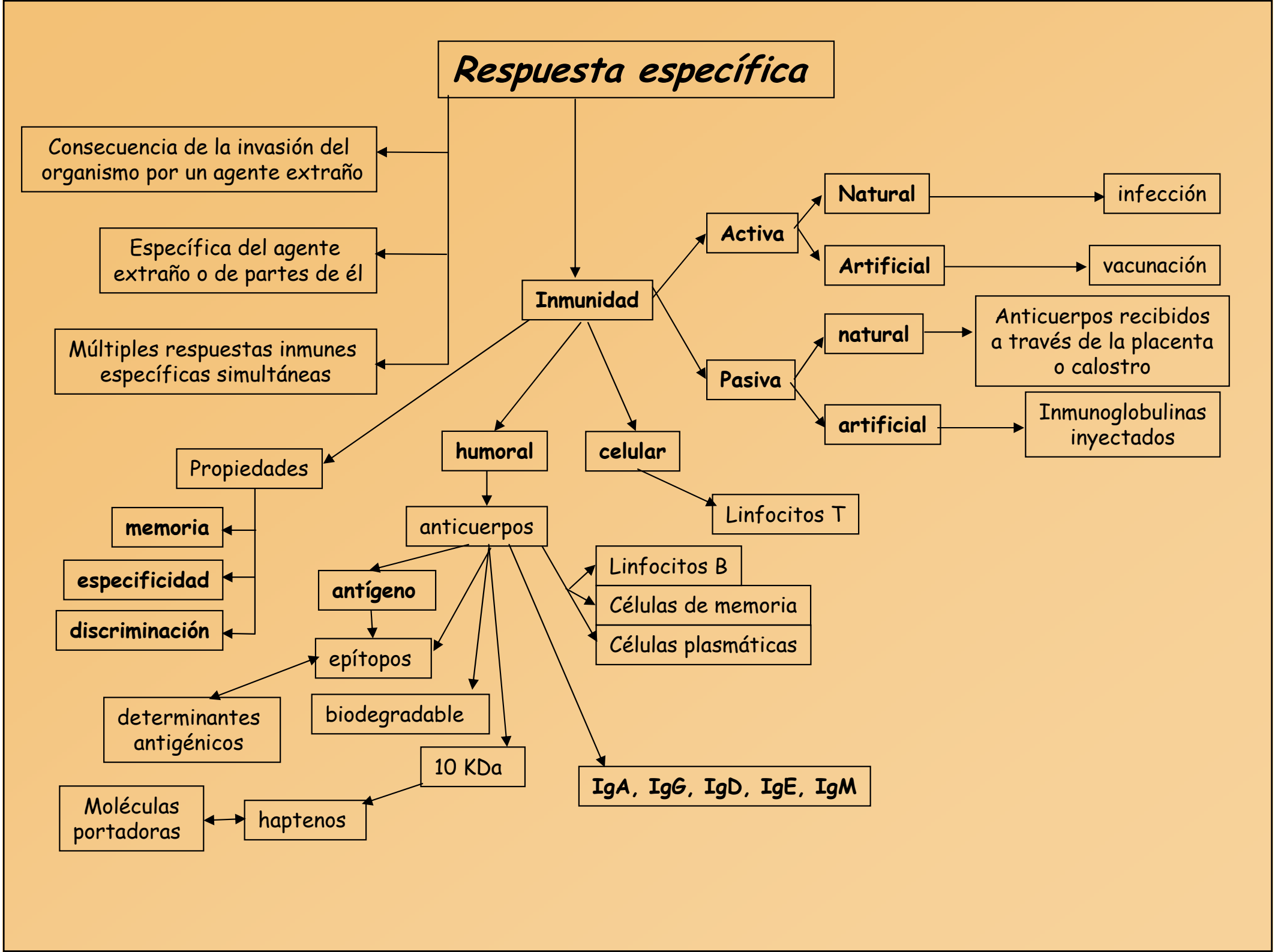

Reacciones mediadas por linfocitos T activados
Reacciones antígeno - anticuerpo
Antígenos
Células presentadoras de antígenos
Células T
Inmunidad celular
Inmunidad humoral
Activación de de células T
Activación de de células B
Linfocitos T activados
Anticuerpos
Inflamación
Destrucción celular específica
Unión del Complemento Opsonización Neutralización
Respuesta inespecífica
Unión del antígeno

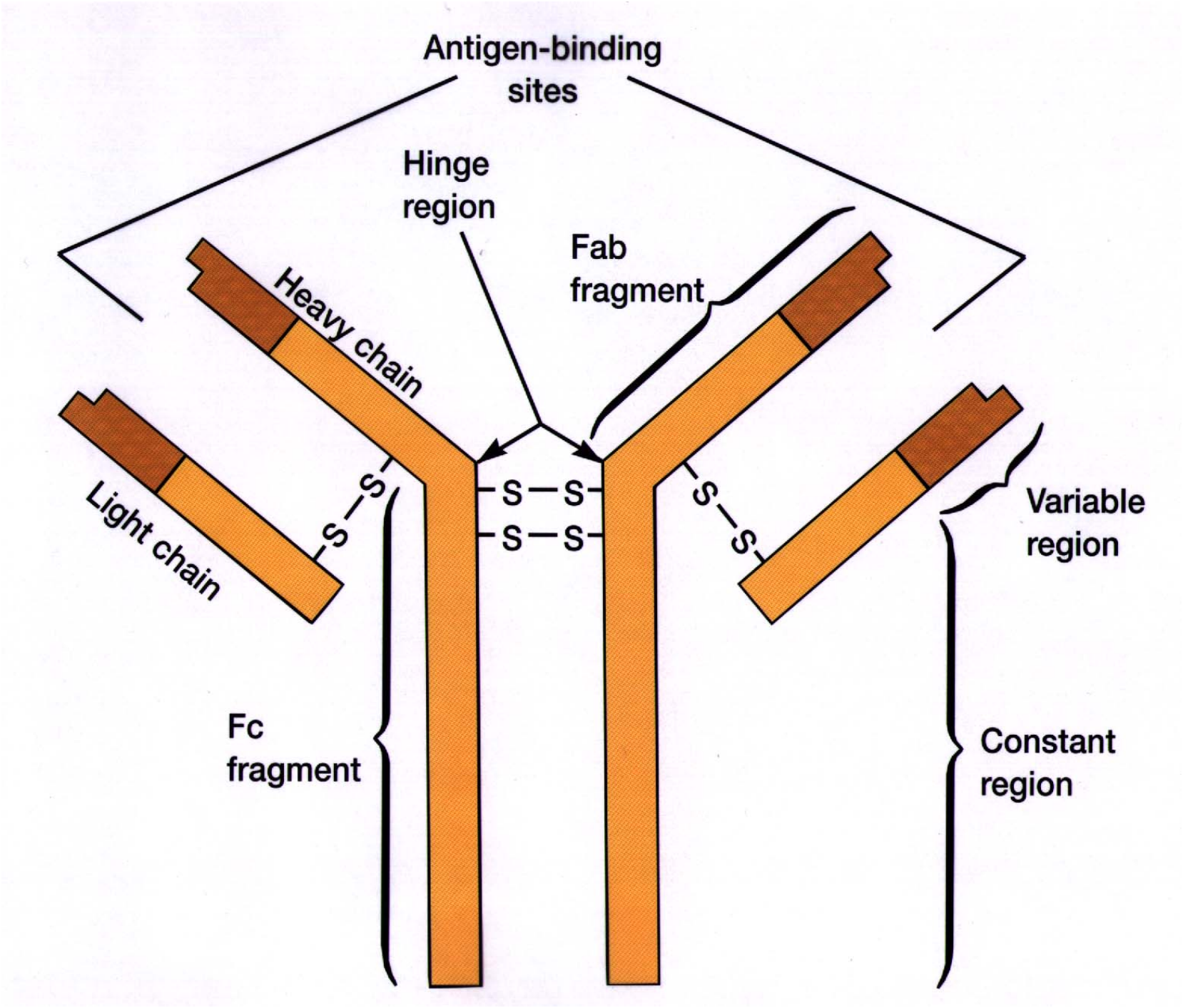
Ontogénesis de las células sanguíneas




Basophil
Eosinophil
Neutrophil
Monocyte
Lymphocyte
Granular leukocytes
Agranular leukocytes
(a)


(a)
Lymph nodes
Thymus
Spleen
Mucosal-associated lymphoid tissue (MALT)
Bone marrow
(b)
Pulmonary circulation
Lungs
Lymph node
Heart
Arteries
Veins
Blood capillaries
Lymphatic vessels
Systemic circulation throughout body
Lymph capillaries
(c)
Blood capillary
Cells passing in and out of blood capillary
Fibers and fiber bundles
Lymph capillary
Cells passing in and out of lymph capillary
Fluid enters lymph capillary
(d)
Afferent duct (in)
Medulla plasma cells
Paracortex T cells
Cortex APC and B cells
Efferent duct (out)


Respuesta específica
Consecuencia de la invasión del organismo por un agente extraño
Específica del agente extraño o de partes de él
Múltiples respuestas inmunes específicas simultáneas
Inmunidad
Activa
Natural
infección
Artificial
vacunación
Pasiva
natural
Anticuerpos recibidos a través de la placenta o calostro
artificial
Inmunoglobulinas inyectados
Propiedades
memoria
especificidad
discriminación
humoral
celular
Linfocitos T
anticuerpos
antígeno
epítopos
determinantes antigénicos
biodegradable
10 KDa
Moléculas portadoras
haptenos
Linfocitos B
Células de memoria
Células plasmáticas
IgA, IgG, IgD, IgE, IgM


Antigen-binding sites
Hinge region
Fab fragment
Heavy chain
Light chain
S—S
S—S
S—S
S—S
S—S
Variable region
Fc fragment
Constant region

ANTÍGENOS Y ANTICUERPOS

haptenos

biodegradable

tamaño mayor de 10 KDa

epítopos ↔ determinantes antigénicos

antígeno

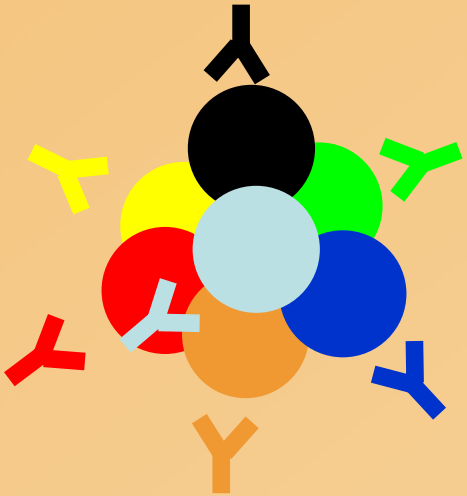
- molécula o parte de una molécula
- reconocida por sistema inmune
- provoca una reacción específica

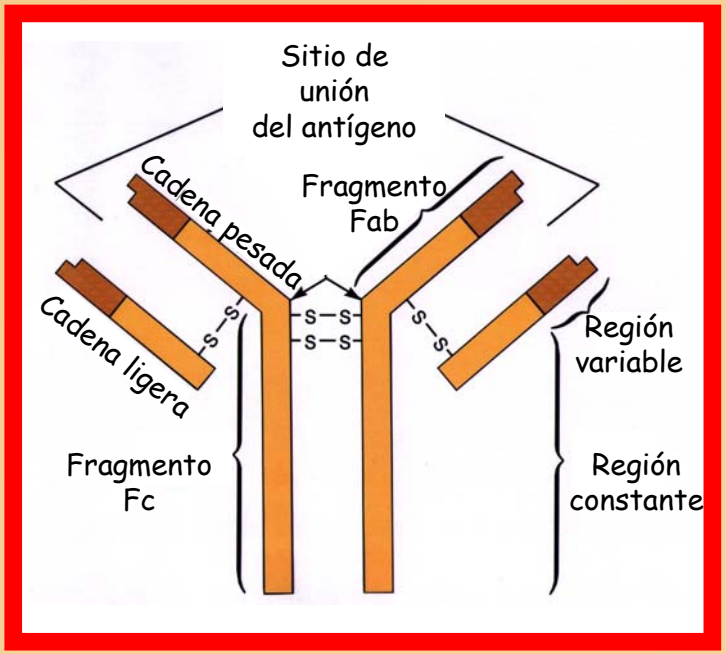
Unión específica

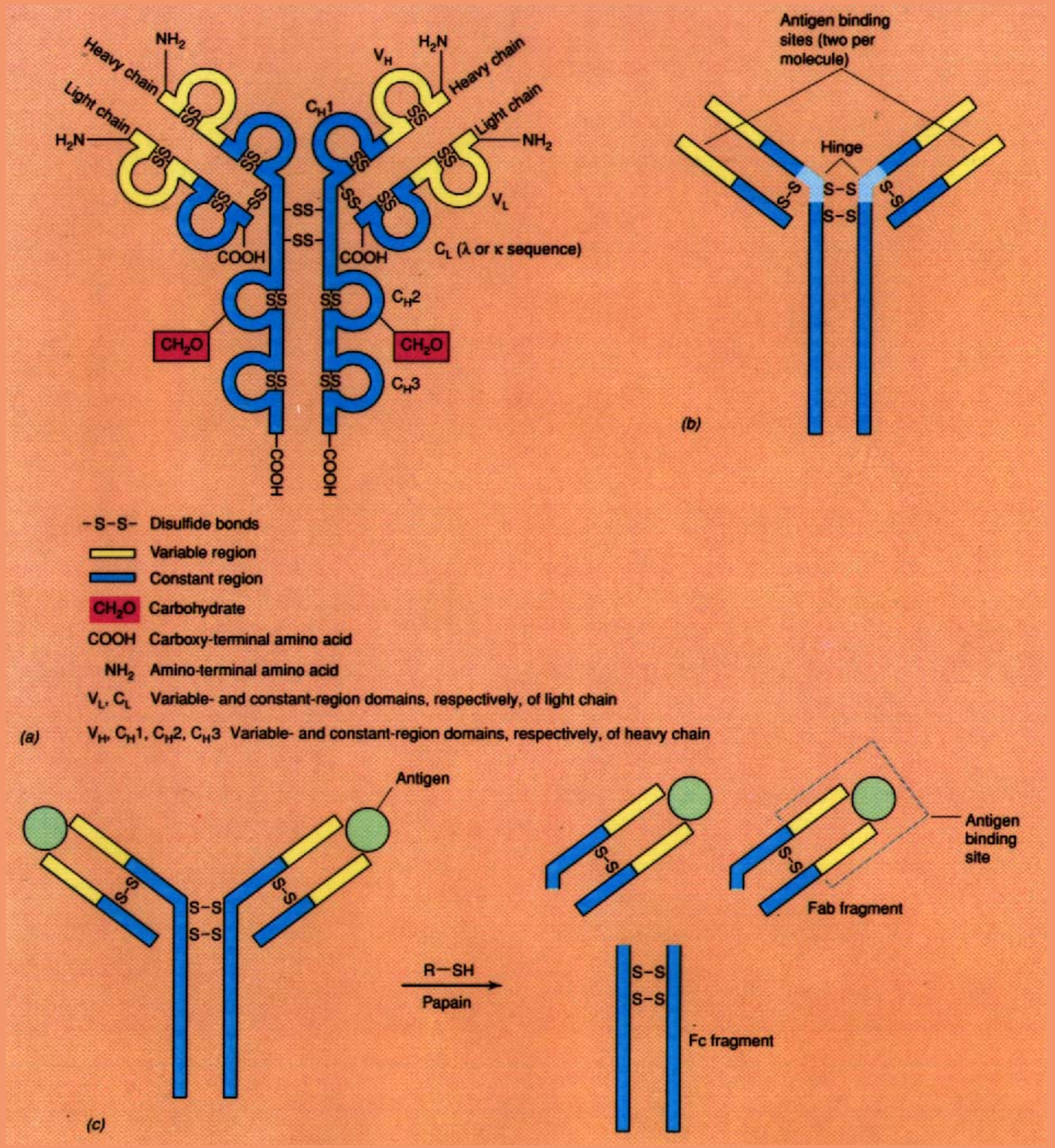
anticuerpo

- proteína
- sintetizada por sistema inmune

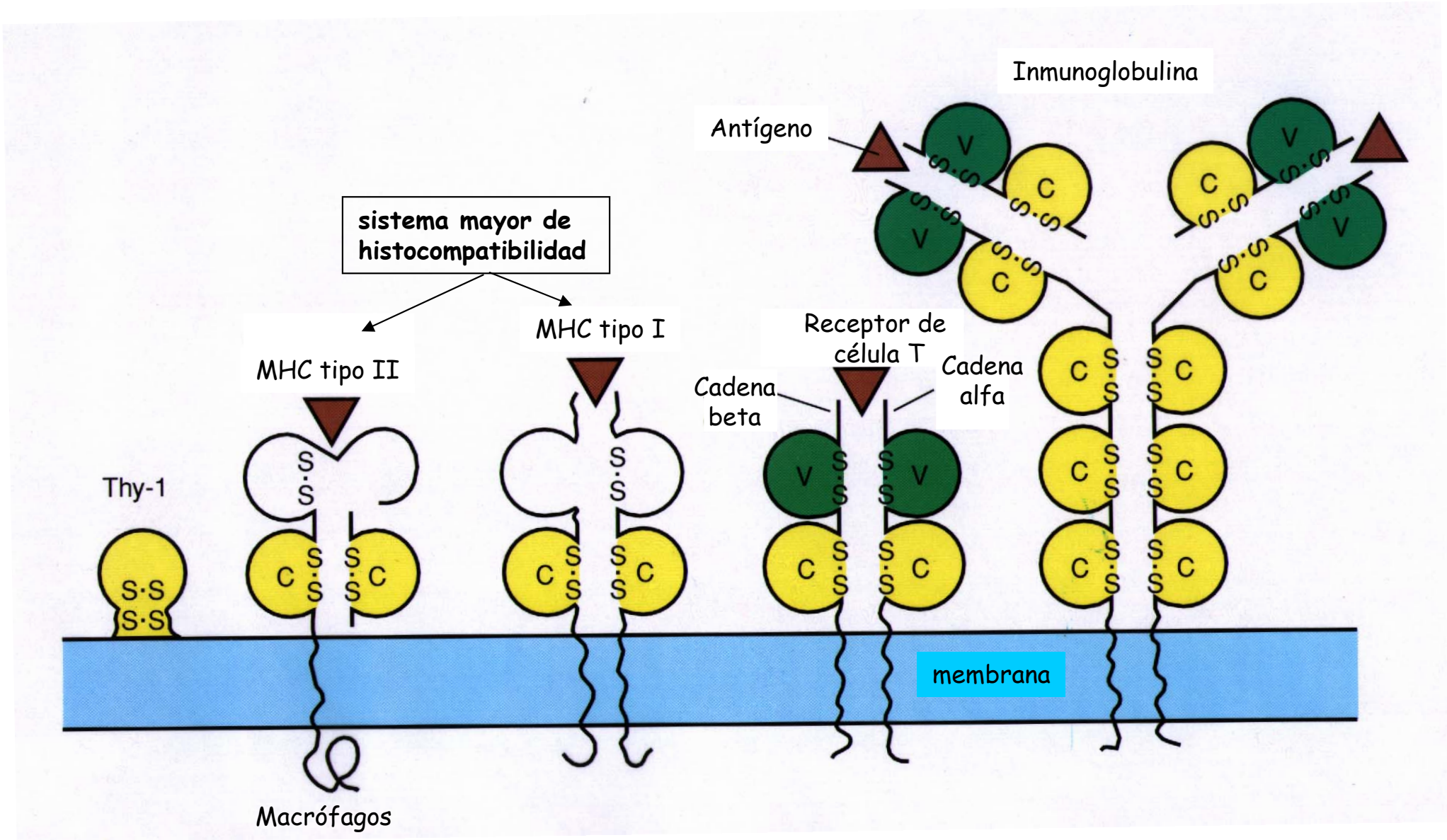
- neutralizan
  - toxinas
  - virus
- bloquean → adhesinas
- opsonizan
- activan complemento

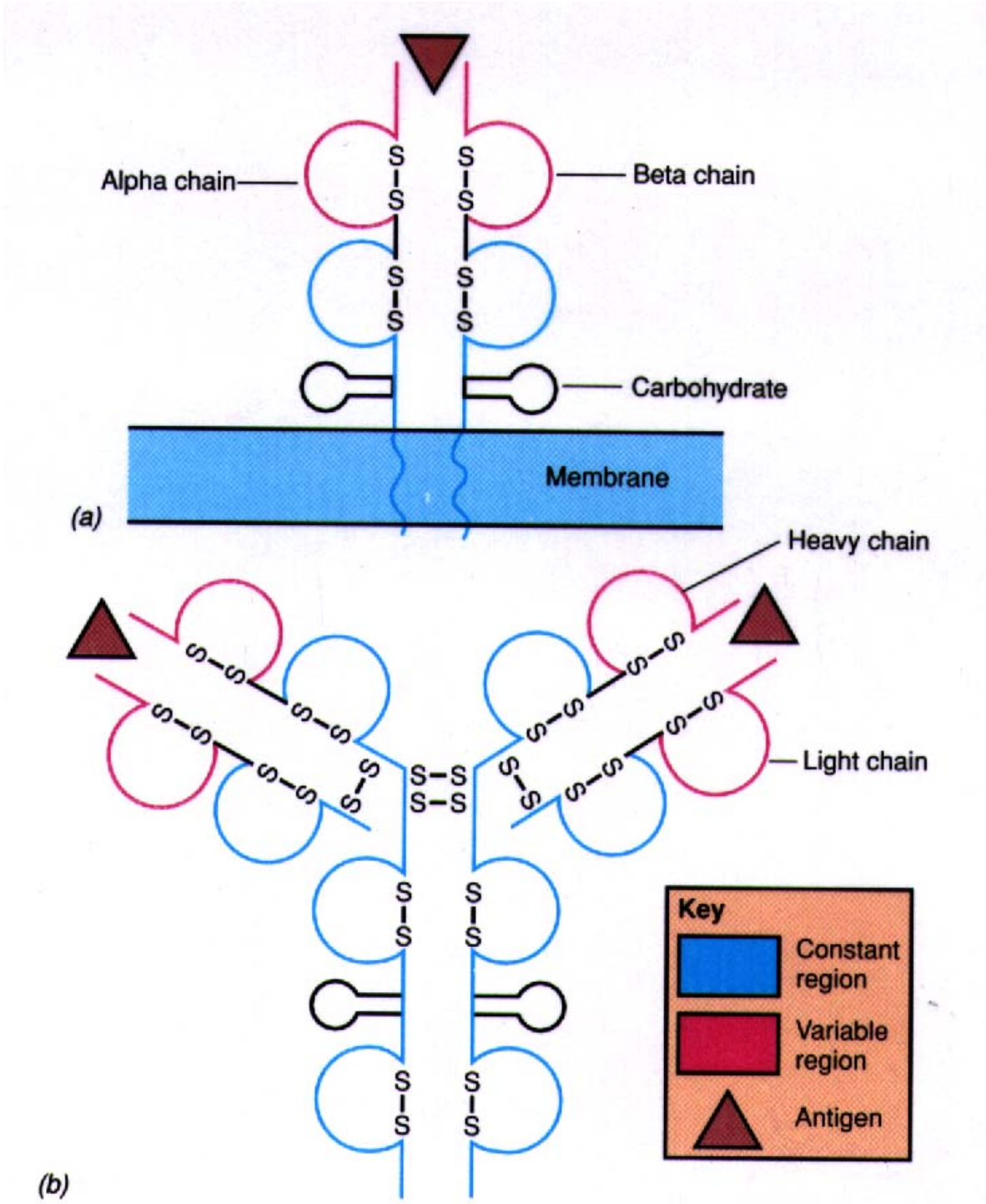


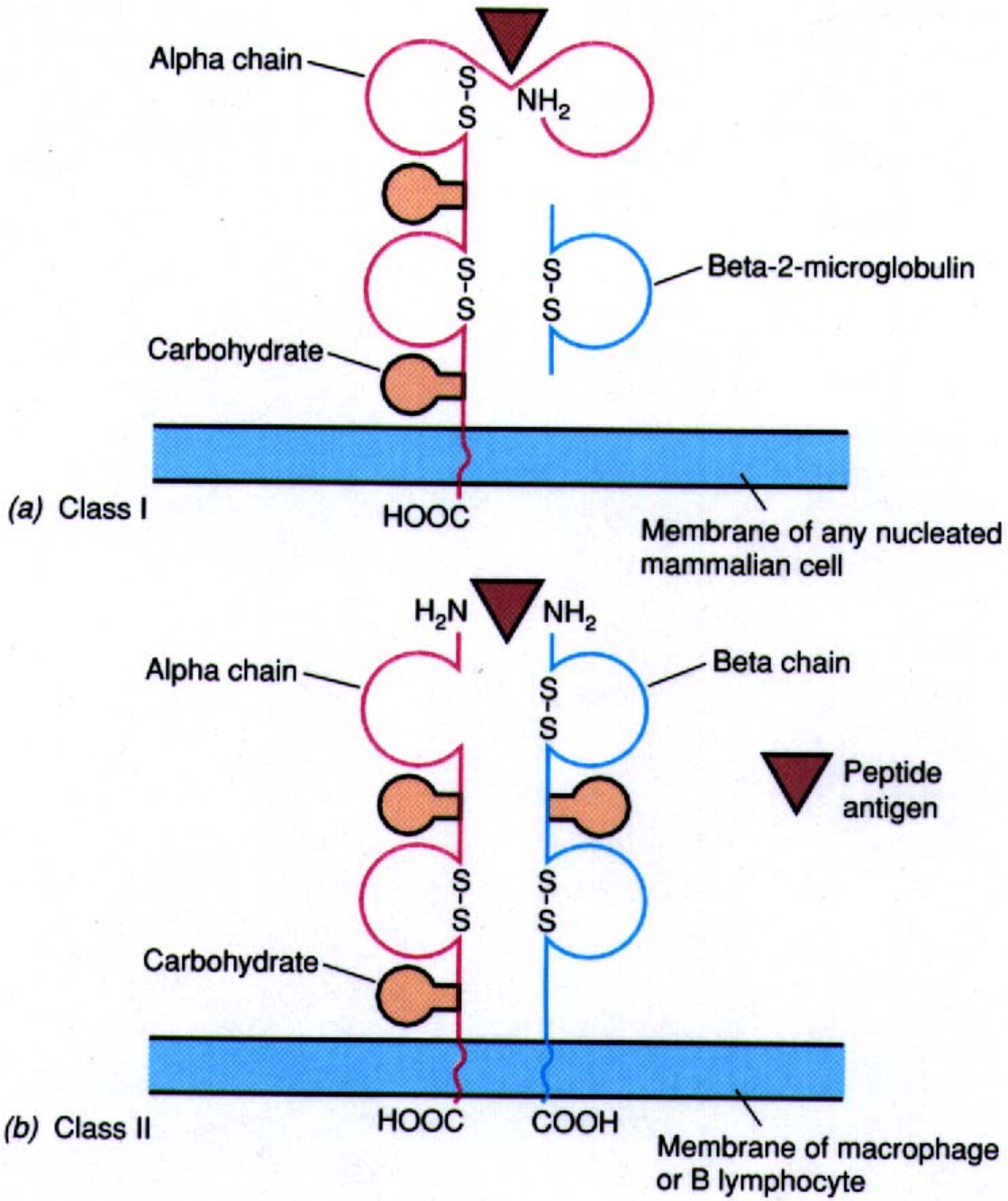



NH2
Heavy chain
Light chain
H2N
VH
H2N
Heavy chain
CH1
Light chain
NH2
VL
SS
SS
COOH
COOH
CL (λ or κ sequence)
CH2
CH2O
CH2O
CH3
COOH
COOH
(a)
Antigen binding sites (two per molecule)
Hinge
S–S
S–S
S–S
S–S
(b)
–S–S– Disulfide bonds
Variable region
Constant region
CH2O Carbohydrate
COOH Carboxy-terminal amino acid
NH2 Amino-terminal amino acid
VL, CL Variable- and constant-region domains, respectively, of light chain
VH, CH1, CH2, CH3 Variable- and constant-region domains, respectively, of heavy chain
Antigen
S–S
S–S
S–S
R–SH
Papain
S–S
S–S
Fc fragment
S–S
S–S
Antigen binding site
Fab fragment
(c)

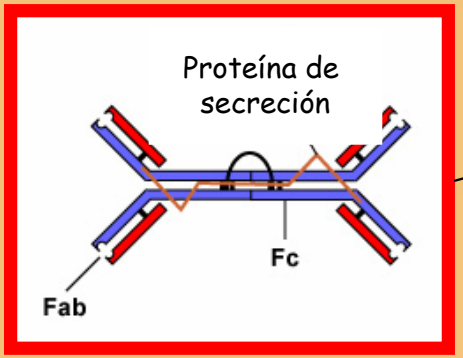
Proteínas de la familia de las Inmunoglobulinas



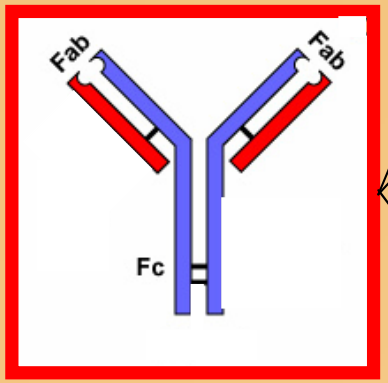

Alpha chain
Beta chain
Carbohydrate
Membrane
(a)
Heavy chain
Light chain
Key
Constant region
Variable region
Antigen
(b)


Alpha chain
S
S
NH2
Beta-2-microglobulin
S
S
S
S
Carbohydrate
(a) Class I
HOOC
Membrane of any nucleated
mammalian cell
H2N
NH2
Alpha chain
Beta chain
S
S
Peptide
antigen
S
S
S
S
Carbohydrate
(b) Class II
HOOC
COOH
Membrane of macrophage
or B lymphocyte

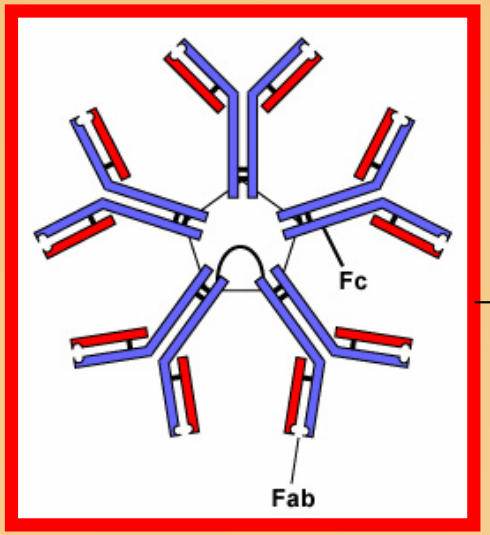
TIPOS DE INMUNOGLOBULINAS



- **IgA**
  - 6% de los anticuerpos del suero
  - 5 días de vida media
  - es la principal Ig de las secreciones (saliva, moco, calostro, lágrimas, etc)
  - dímeros en las mucosas → monómeros circulantes en el suero

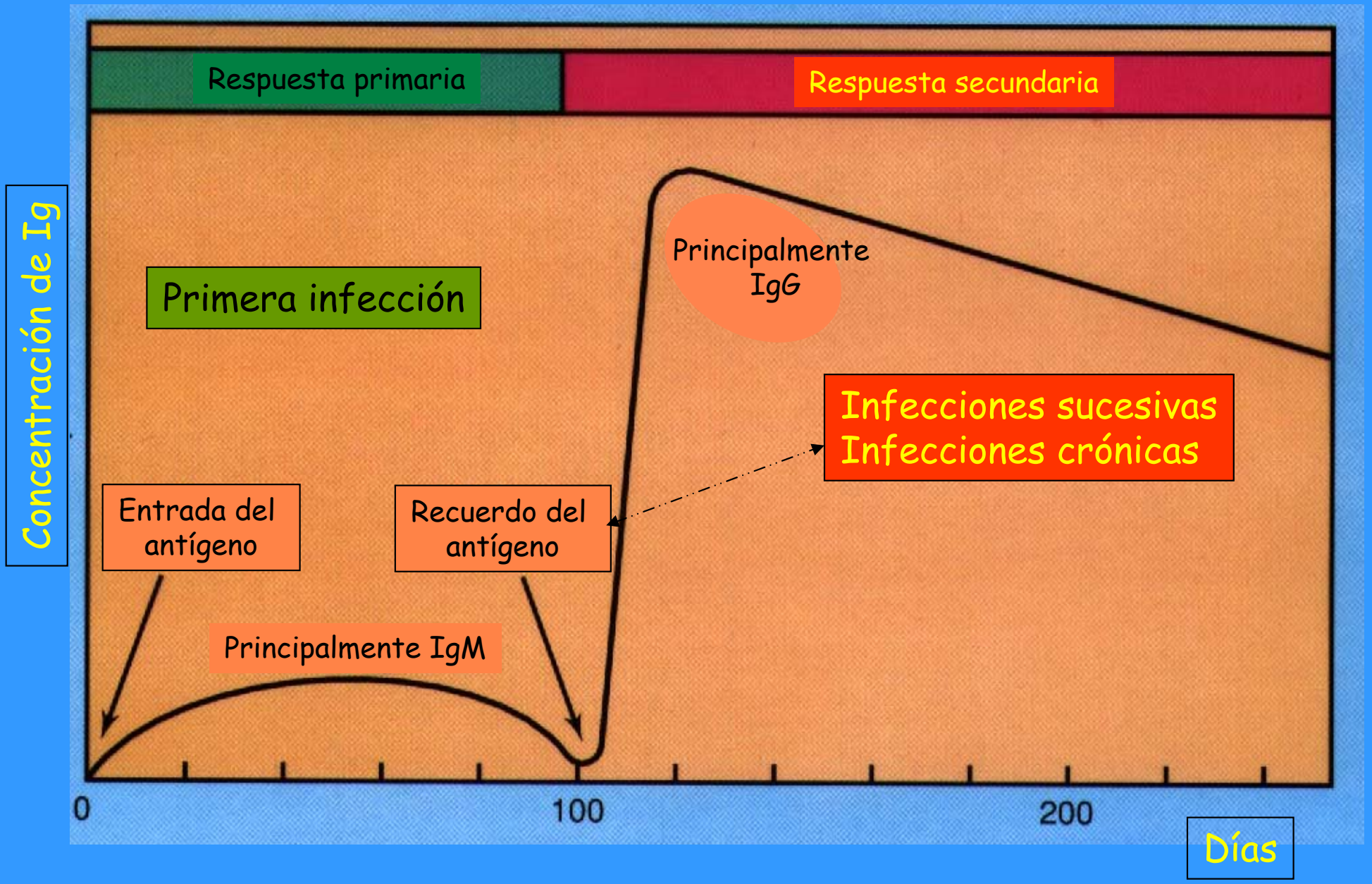


- **IgD**
  - 0.2% de los anticuerpos
- **IgE**
  - 0.002% de los anticuerpos
  - 2 días de vida media
  - Producidos frente a parásitos y alergenos
- **IgG**
  - 80% de los anticuerpos del suero
  - 7-23 días de vida media
  - atravesar la placenta → inmunidad natural pasiva
  - activación del complemento

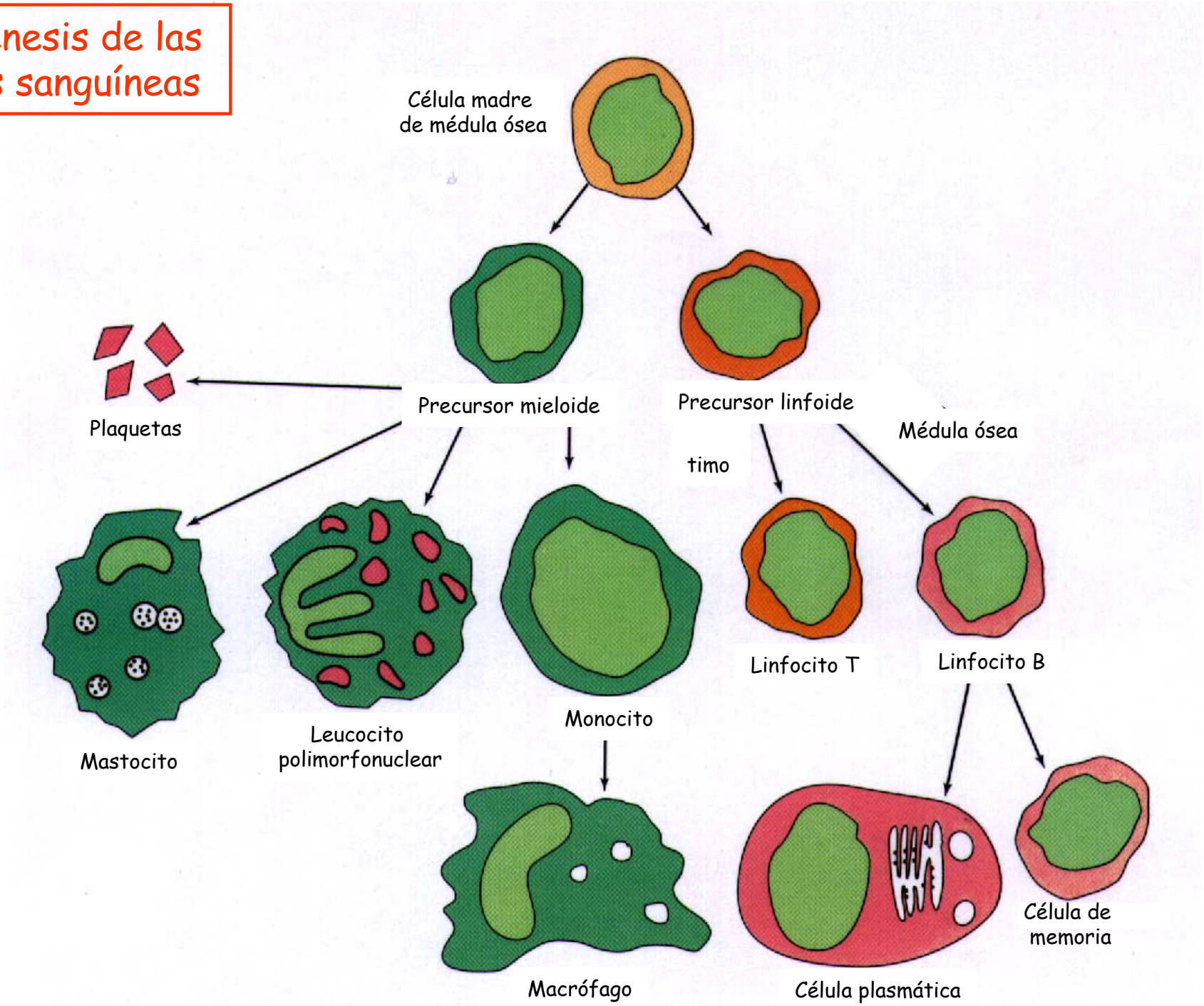


- **IgM**
  - 13% de los anticuerpos del suero
  - 5 días de vida media
  - no atraviesa la placenta
  - respuesta inmune primaria
  - activación del complemento

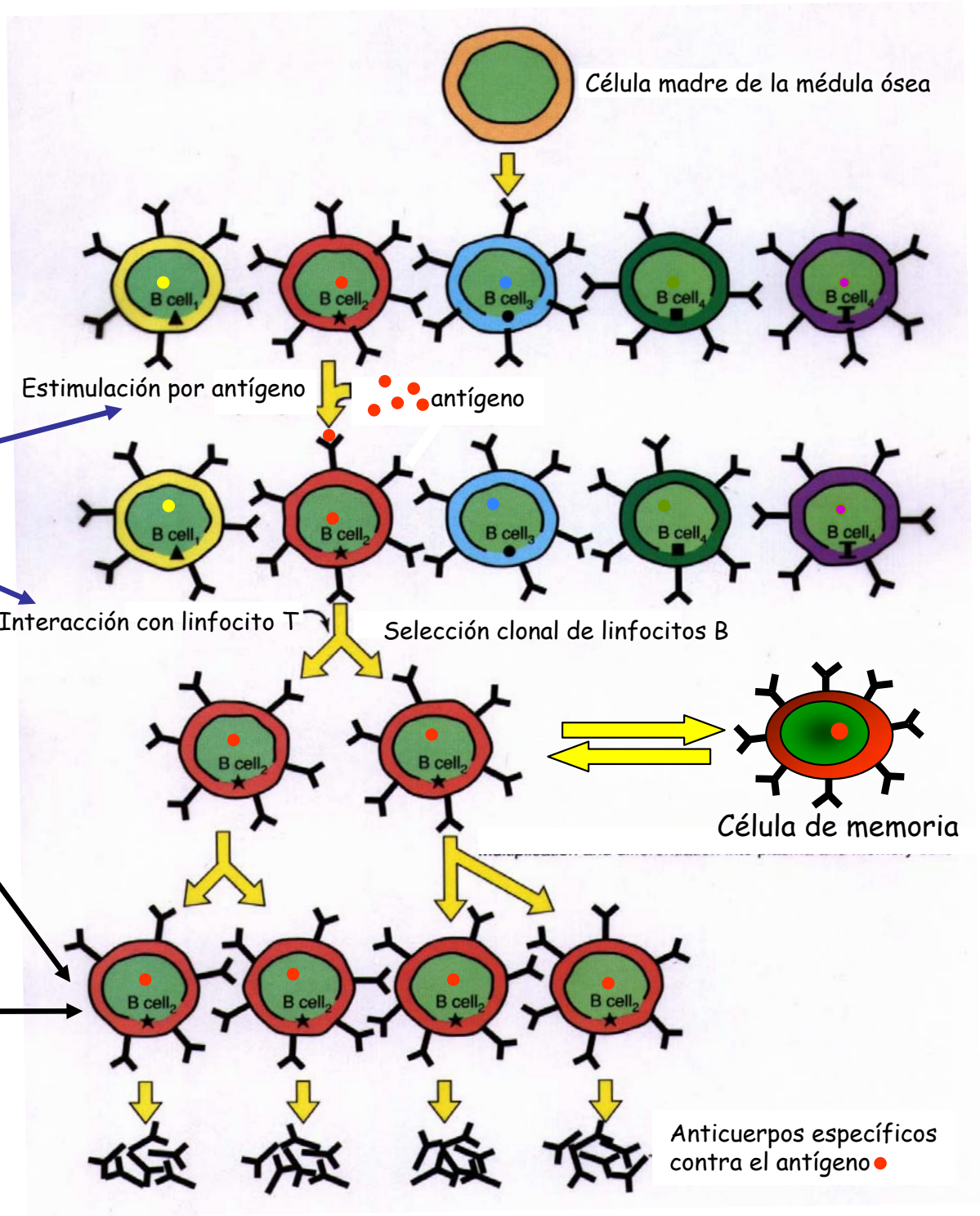
Respuestas primaria y secundaria

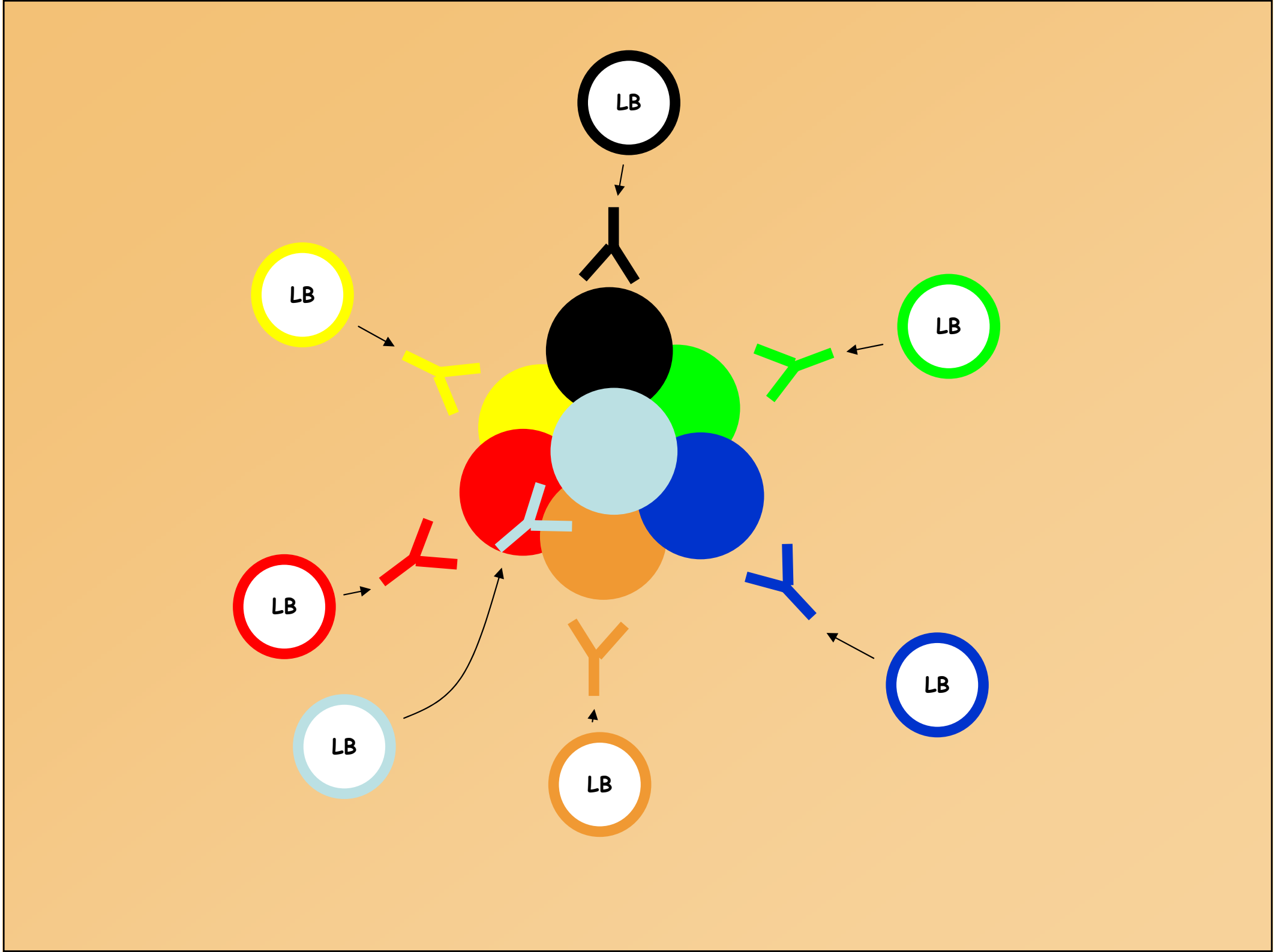


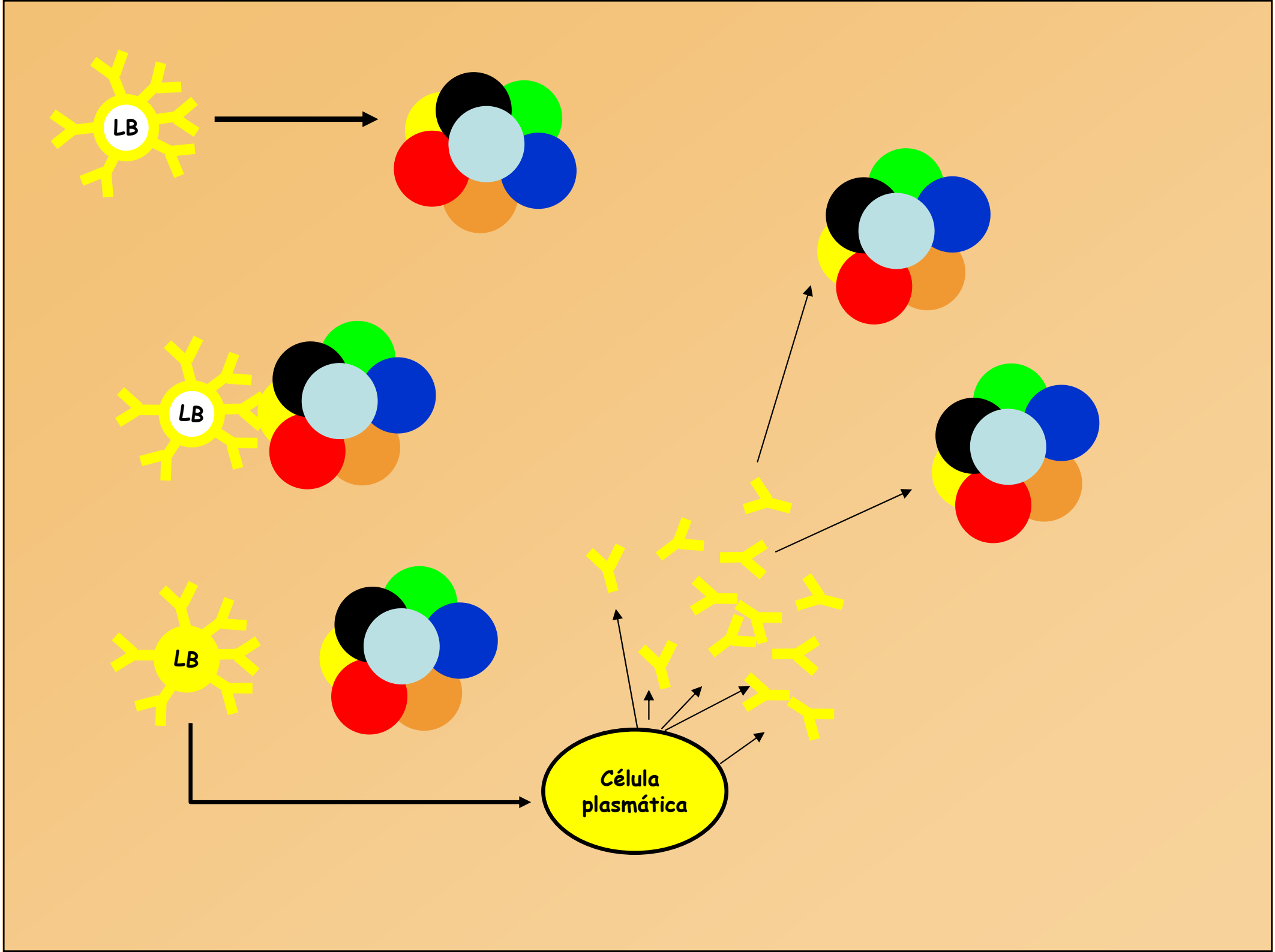
Ontogénesis de las células sanguíneas

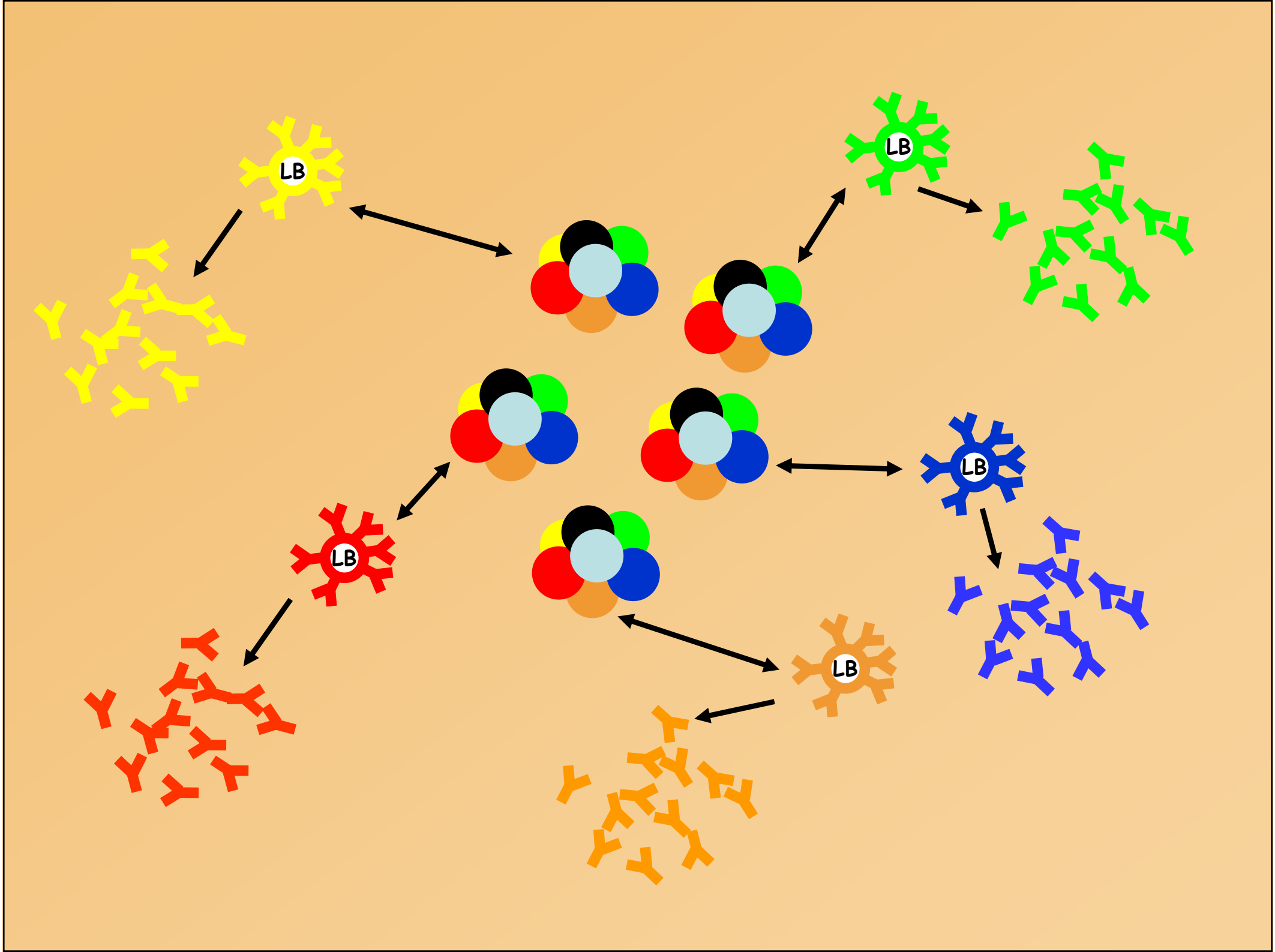


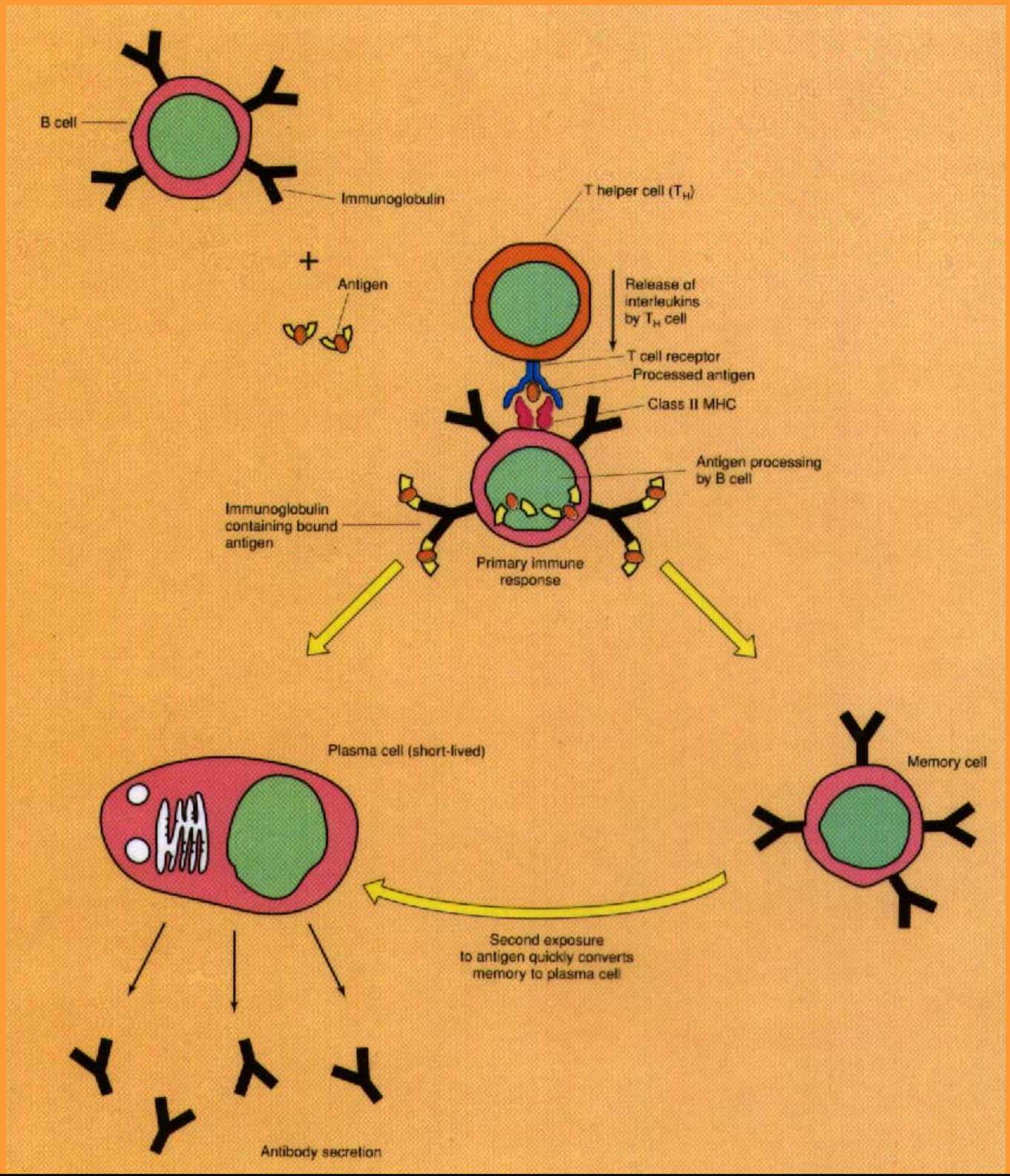
Activación de los linfocitos B



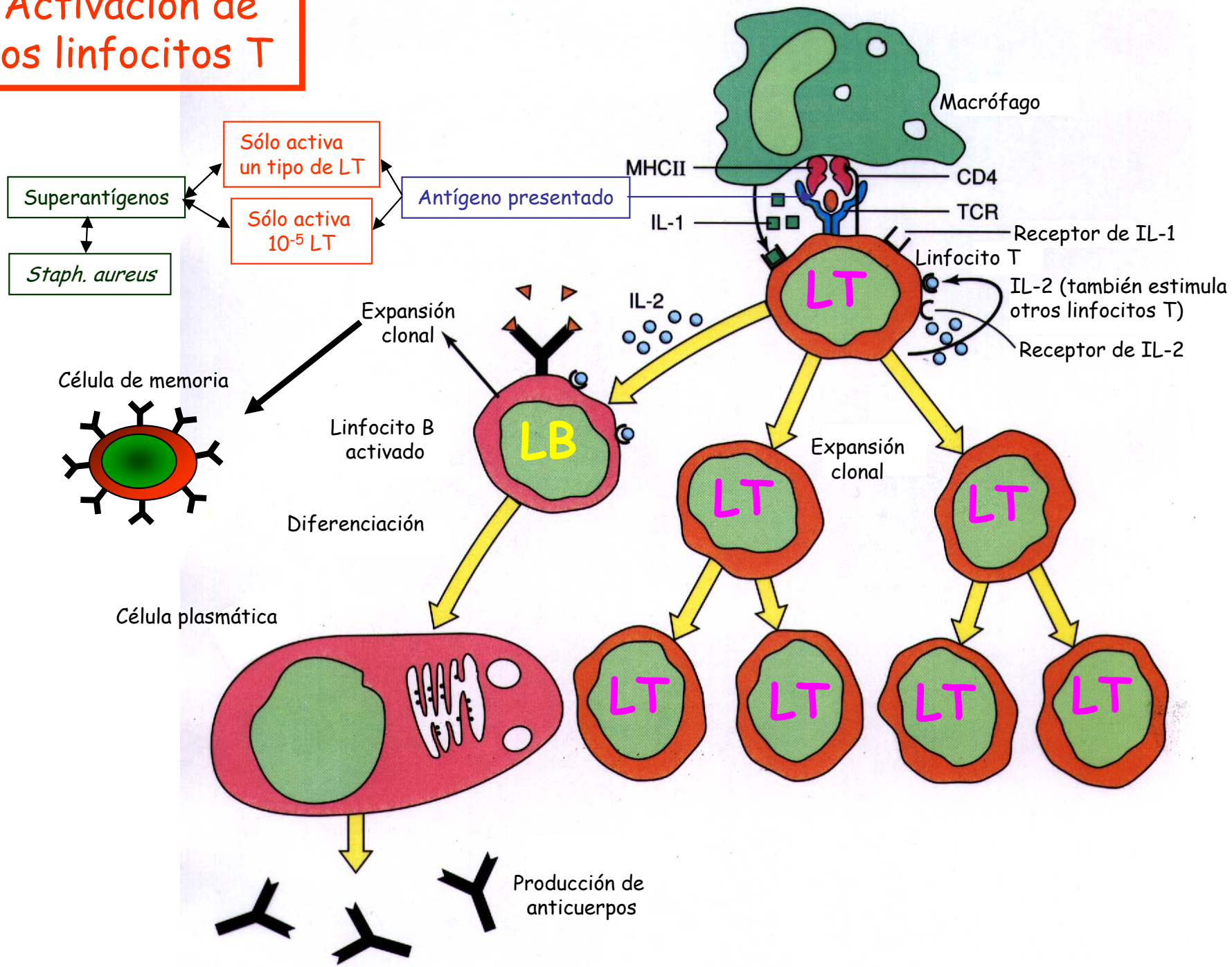

LB
LB
LB
LB
LB
LB
LB

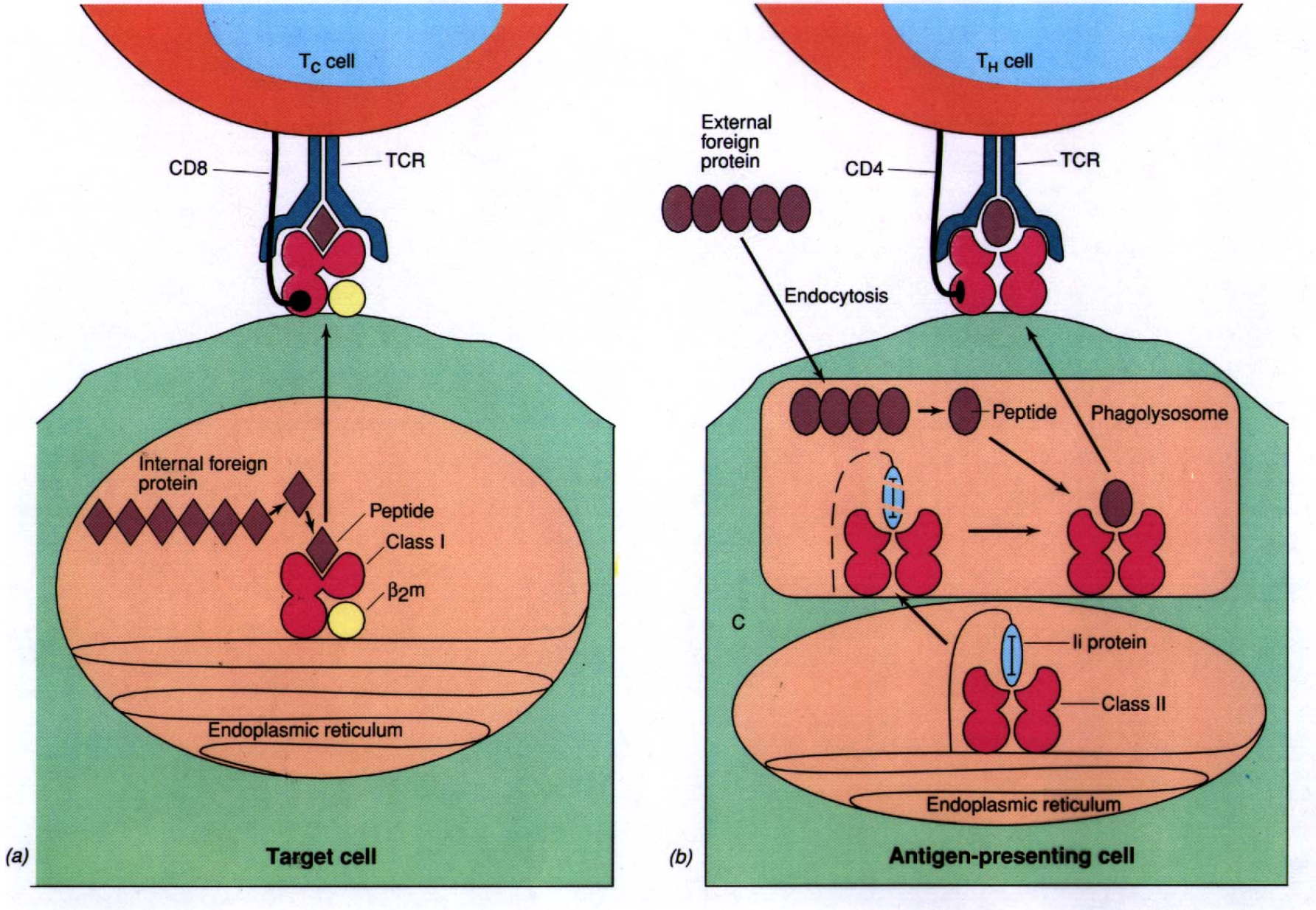

LB
LB
LB
Célula plasmática


LB
LB
LB
LB
LB

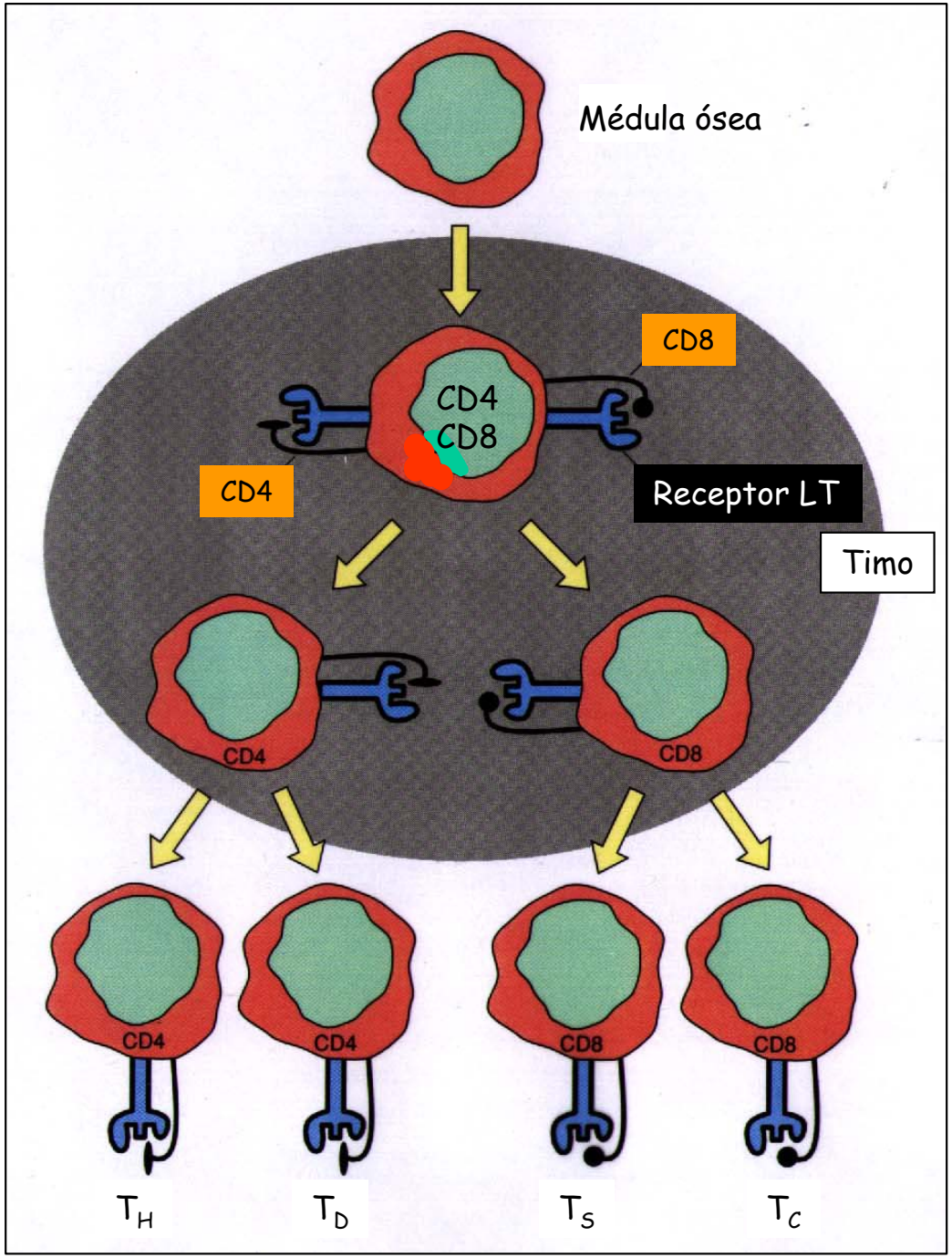

B cell
Immunoglobulin
+
Antigen
T helper cell (T_H)
Release of interleukins by T_H cell
T cell receptor
Processed antigen
Class II MHC
Antigen processing by B cell
Immunoglobulin containing bound antigen
Primary immune response
Plasma cell (short-lived)
Memory cell
Second exposure to antigen quickly converts memory to plasma cell
Antibody secretion

Activación de los linfocitos T

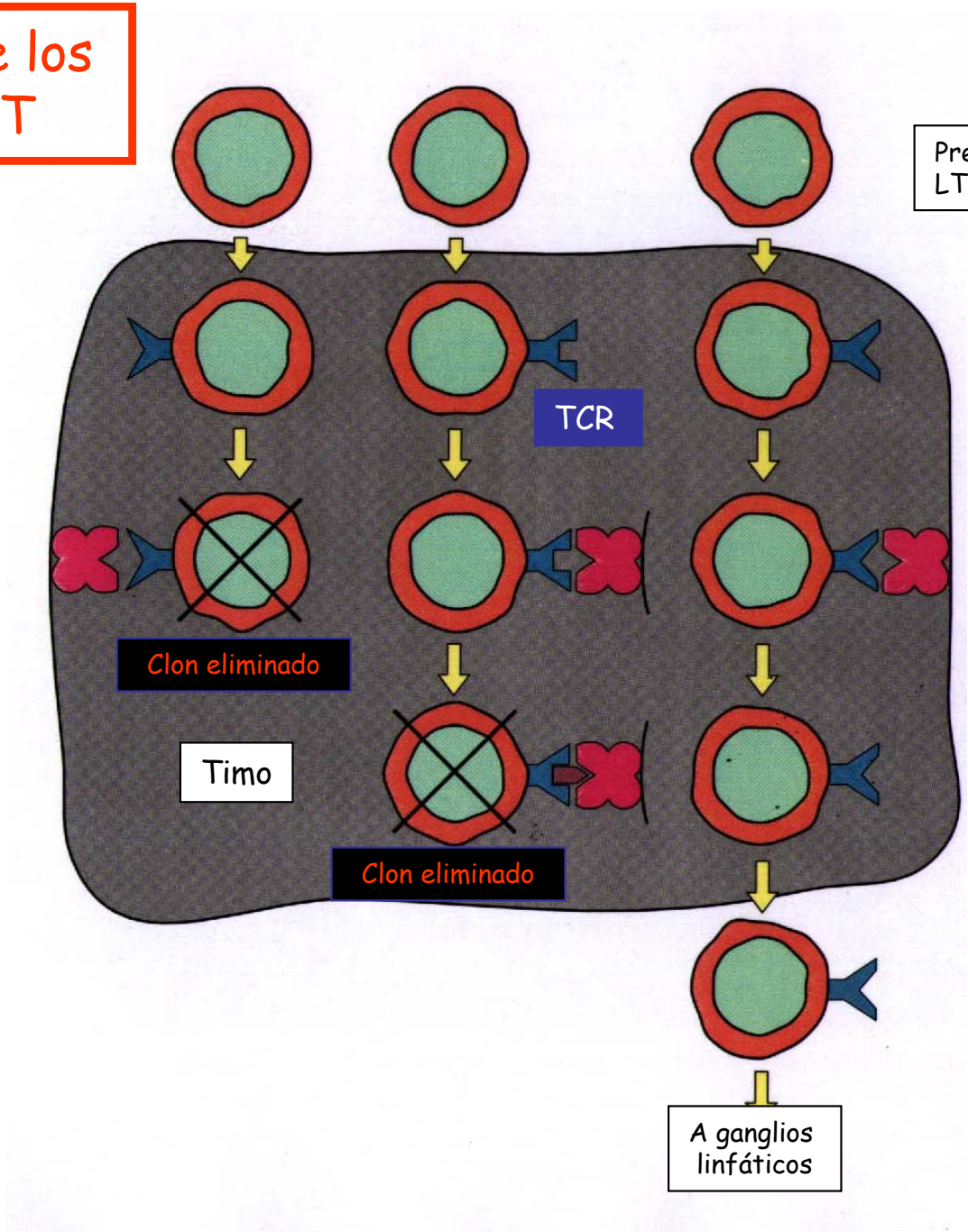



T_C cell
CD8
TCR
Internal foreign protein
Peptide
Class I
β_2m
Endoplasmic reticulum
(a)
Target cell
T_H cell
External foreign protein
CD4
TCR
Endocytosis
Peptide
Phagolysosome
C
Ii protein
Class II
Endoplasmic reticulum
(b)
Antigen-presenting cell

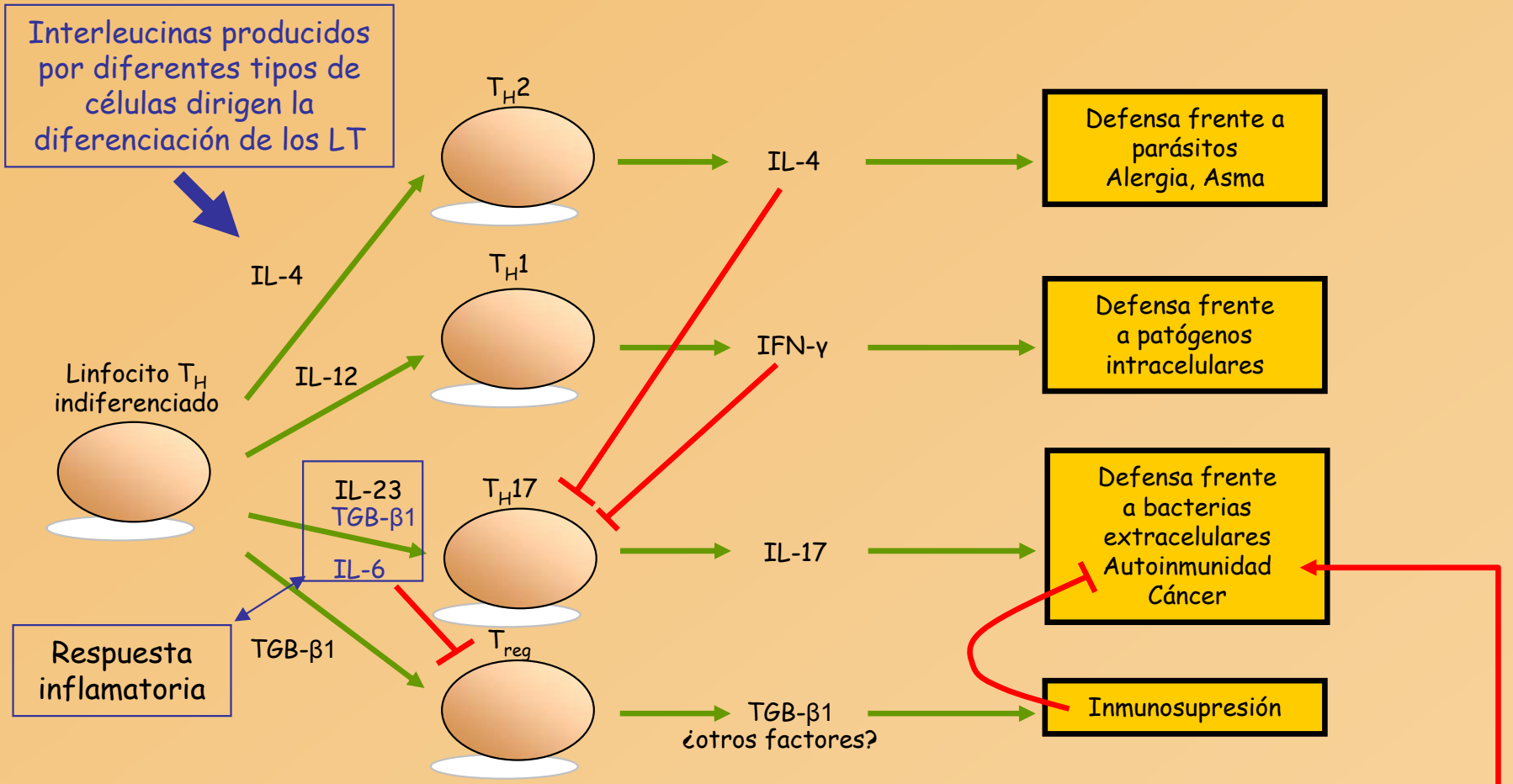
Activación de los linfocitos T



Desarrollo de los Linfocitos T

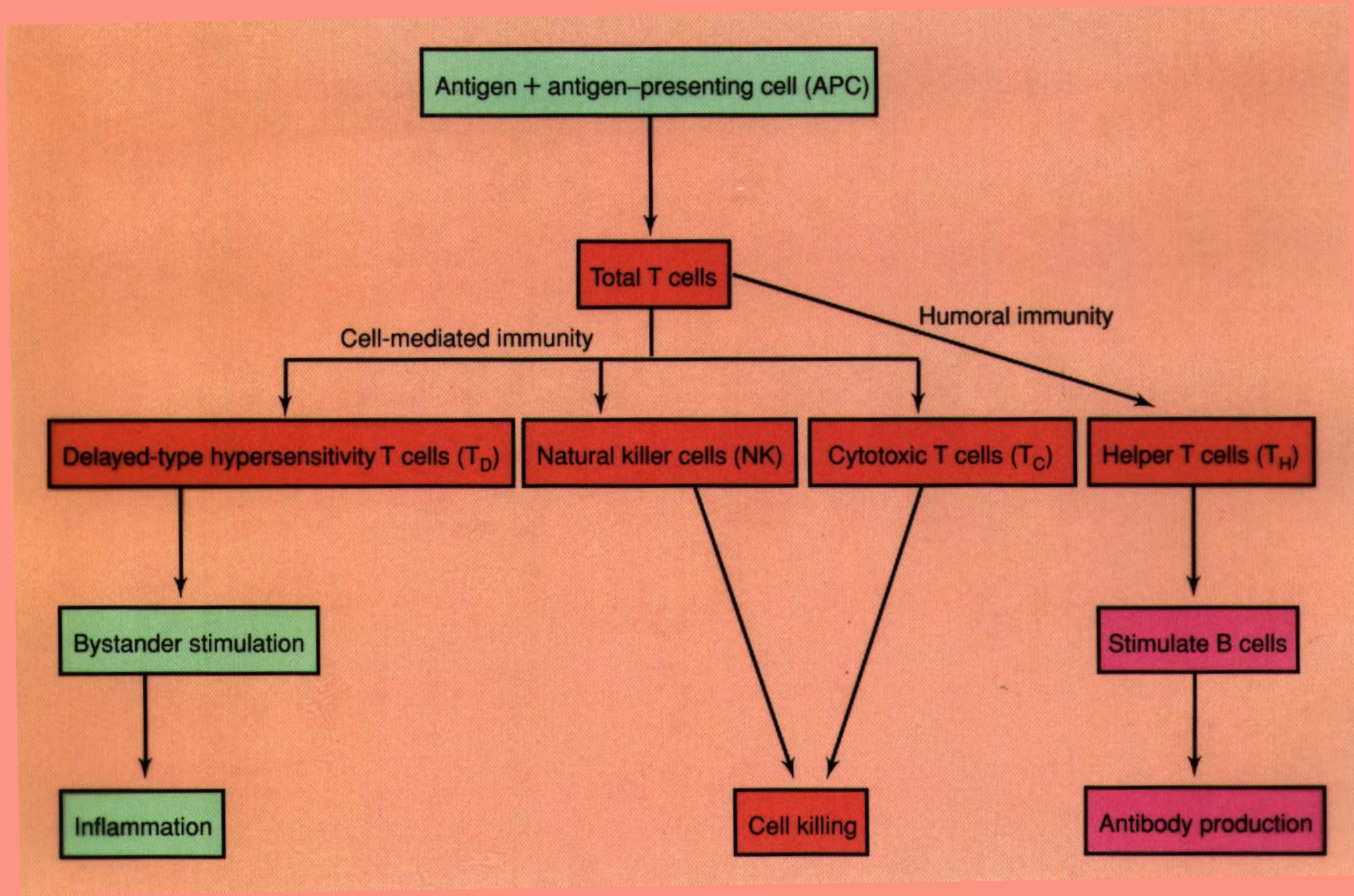


Diferenciación de los linfocitos T_H



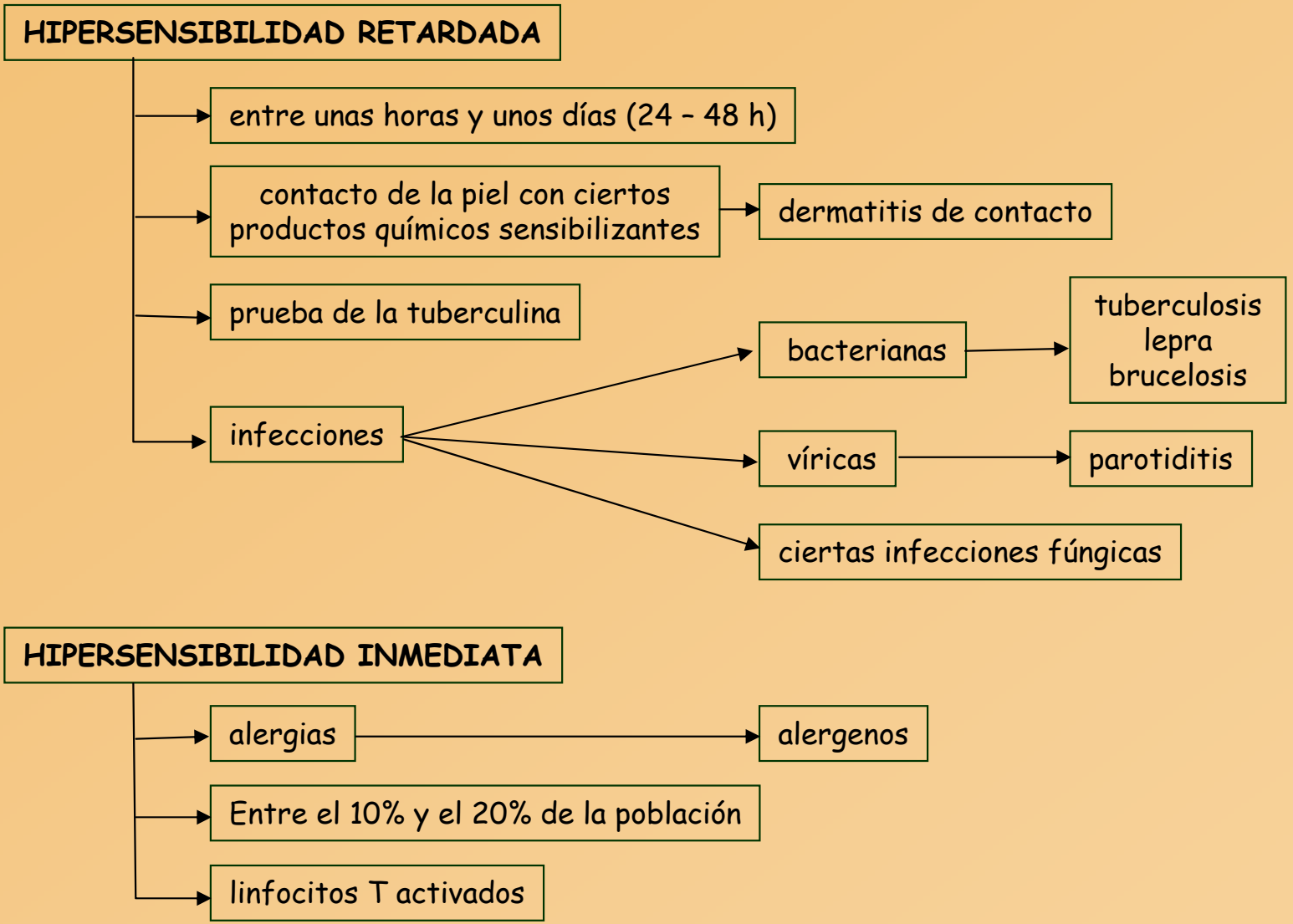
Hay, al menos, cuatro tipos diferentes de LT_H. Al menos dos de ellos participan en la respuesta inflamatoria en la repuesta inflamatoria en algunas circunstancias

Nature 441: 166-168, 231-234, 235-238


Antigen + antigen–presenting cell (APC)
Total T cells
Cell-mediated immunity
Humoral immunity
Delayed-type hypersensitivity T cells (T_D)
Natural killer cells (NK)
Cytotoxic T cells (T_C)
Helper T cells (T_H)
Bystander stimulation
Stimulate B cells
Inflammation
Cell killing
Antibody production

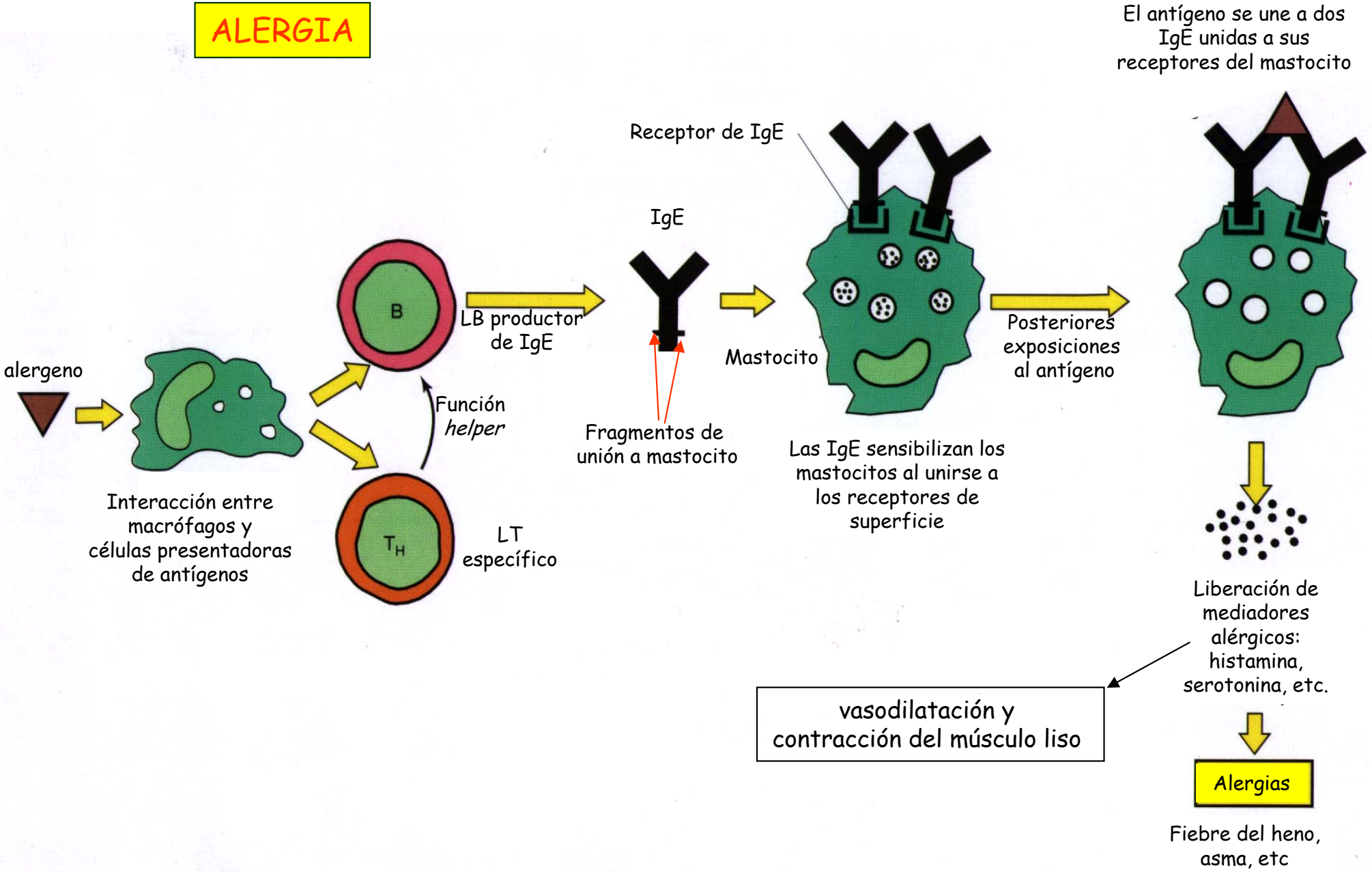
REACCIONES DE HIPERSENSIBILIDAD

alergias



Reacción de hipersensibilidad inmediata

ALERGIA



programa nacional de vacunación

(agrupadas por las vacunas que se administran simultáneamente)

poliomielitis

difteria, tétanos, tos ferina

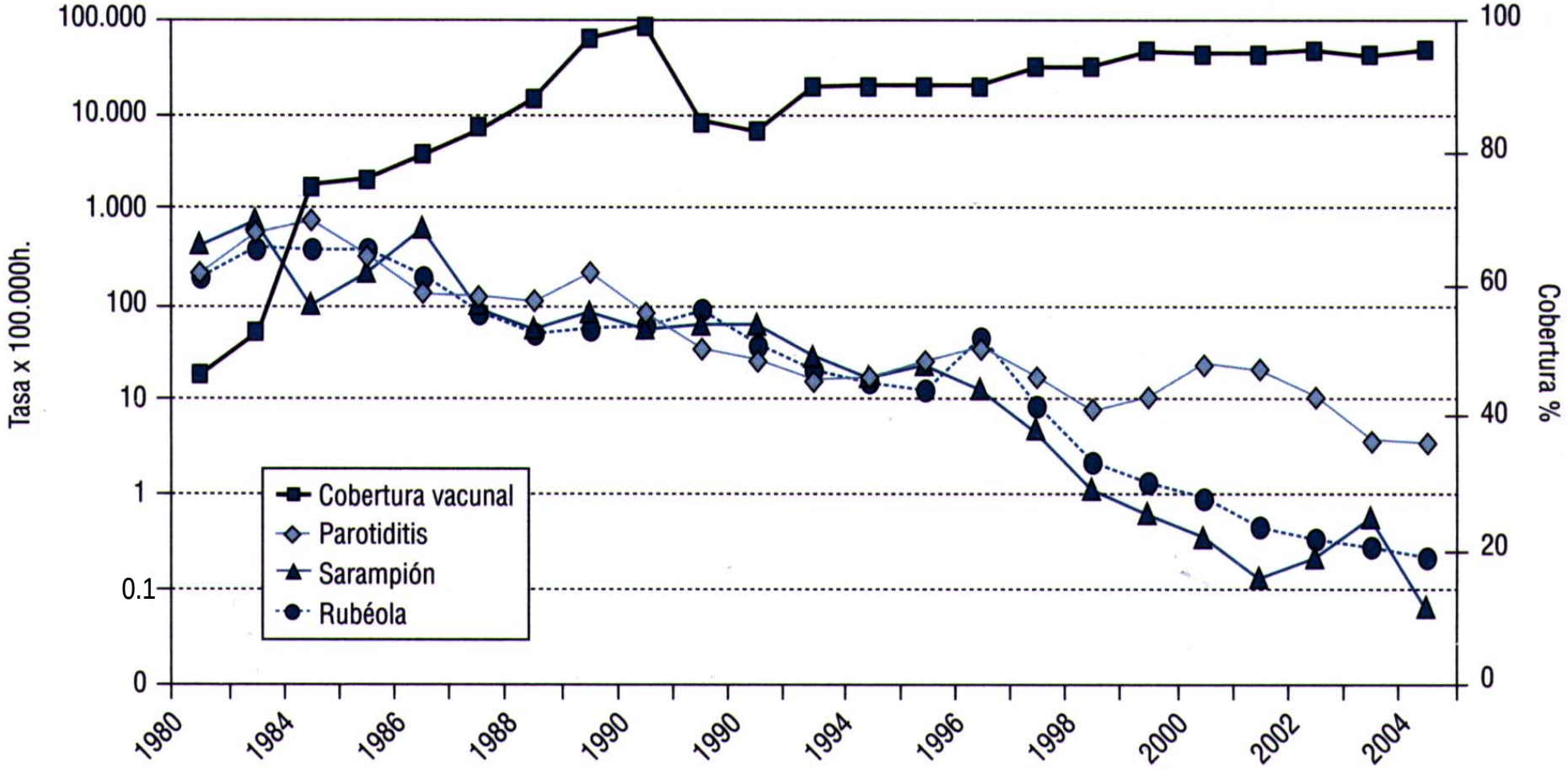
sarampión, rubéola, parotiditis

hepatitis B

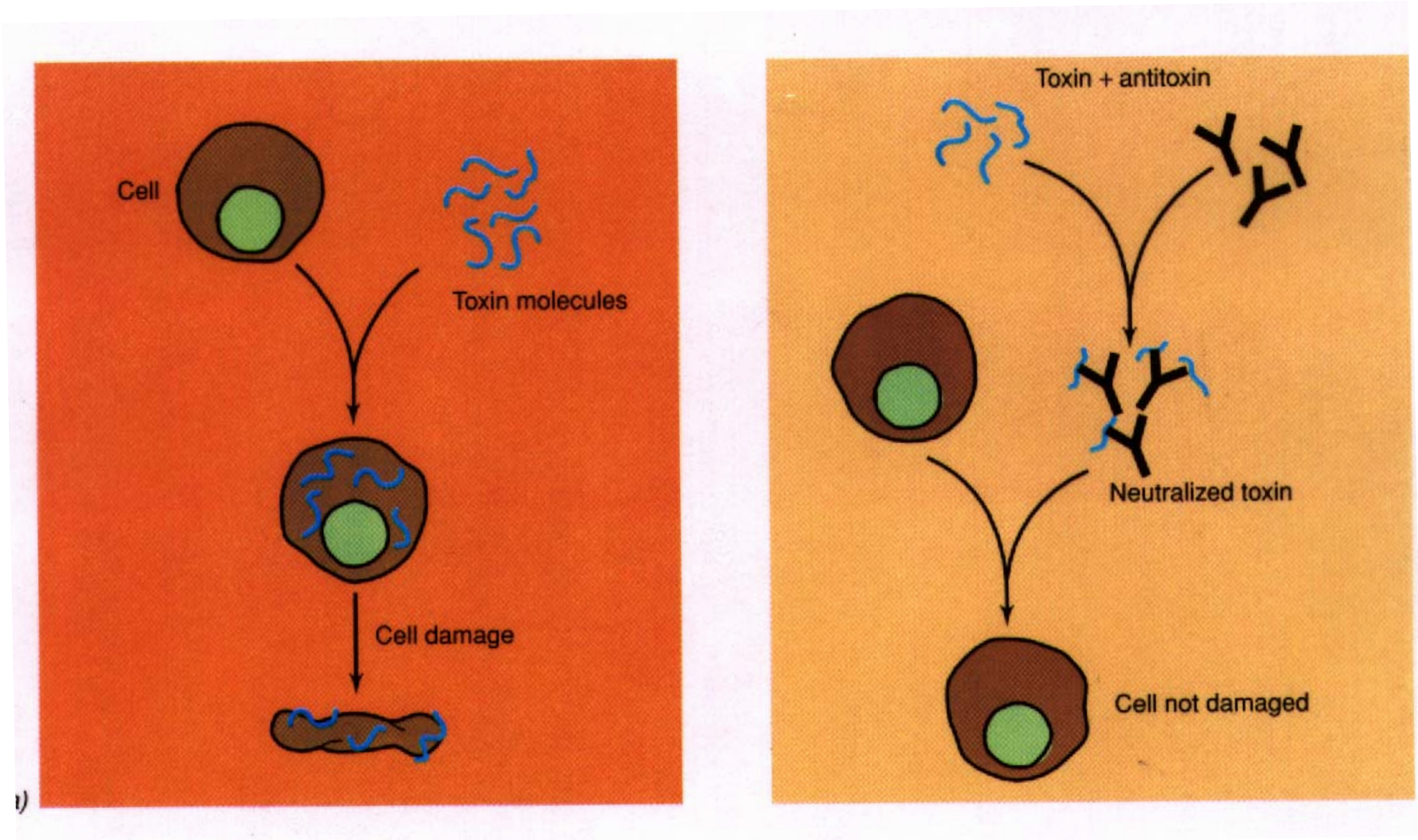
H. influenzae

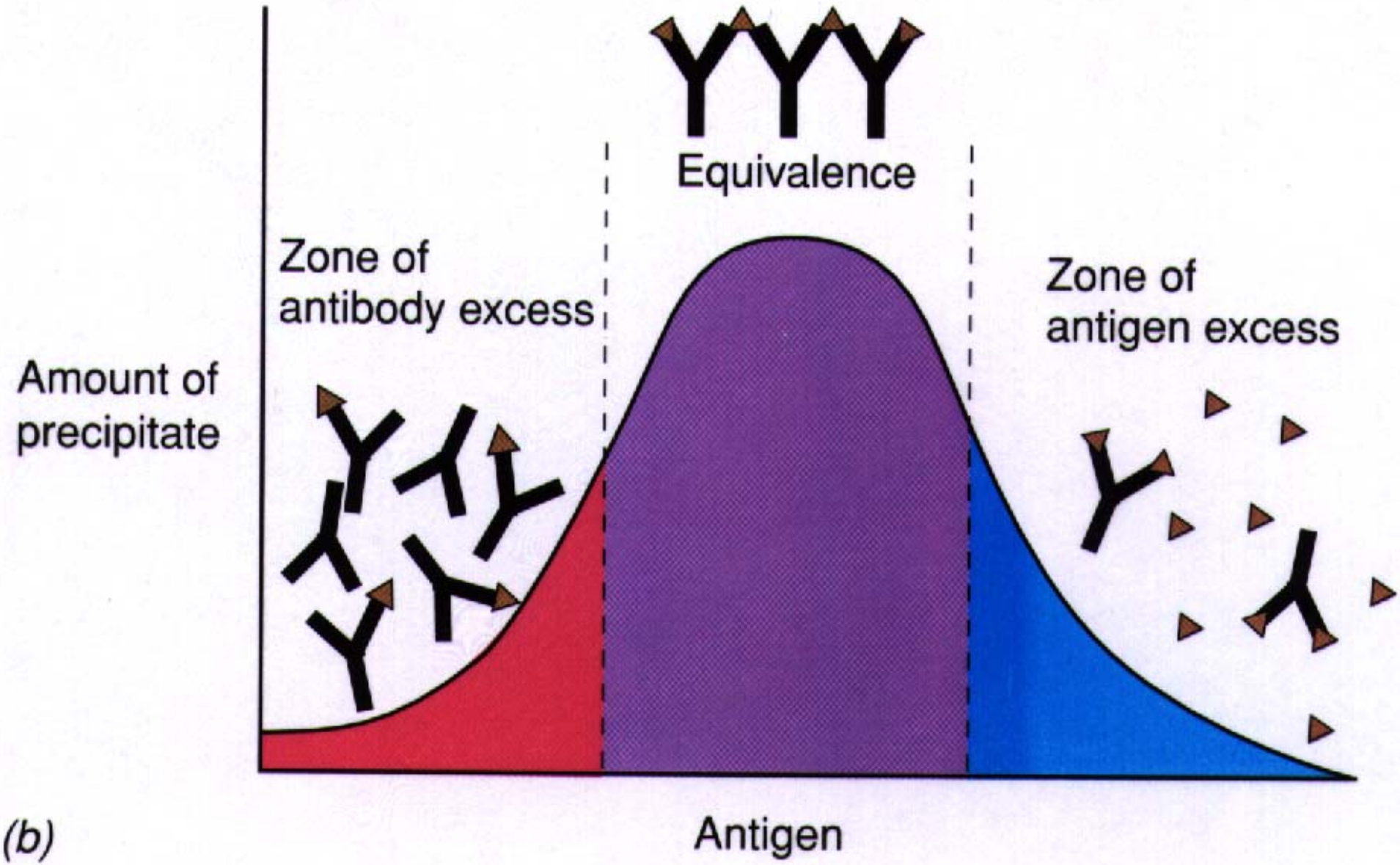
Meningococo

Vigilancia de Sarampión, Rubéola y Parotiditis España 1982-2004
Incidencia anual por 100.000 habitantes y cobertura vacunal

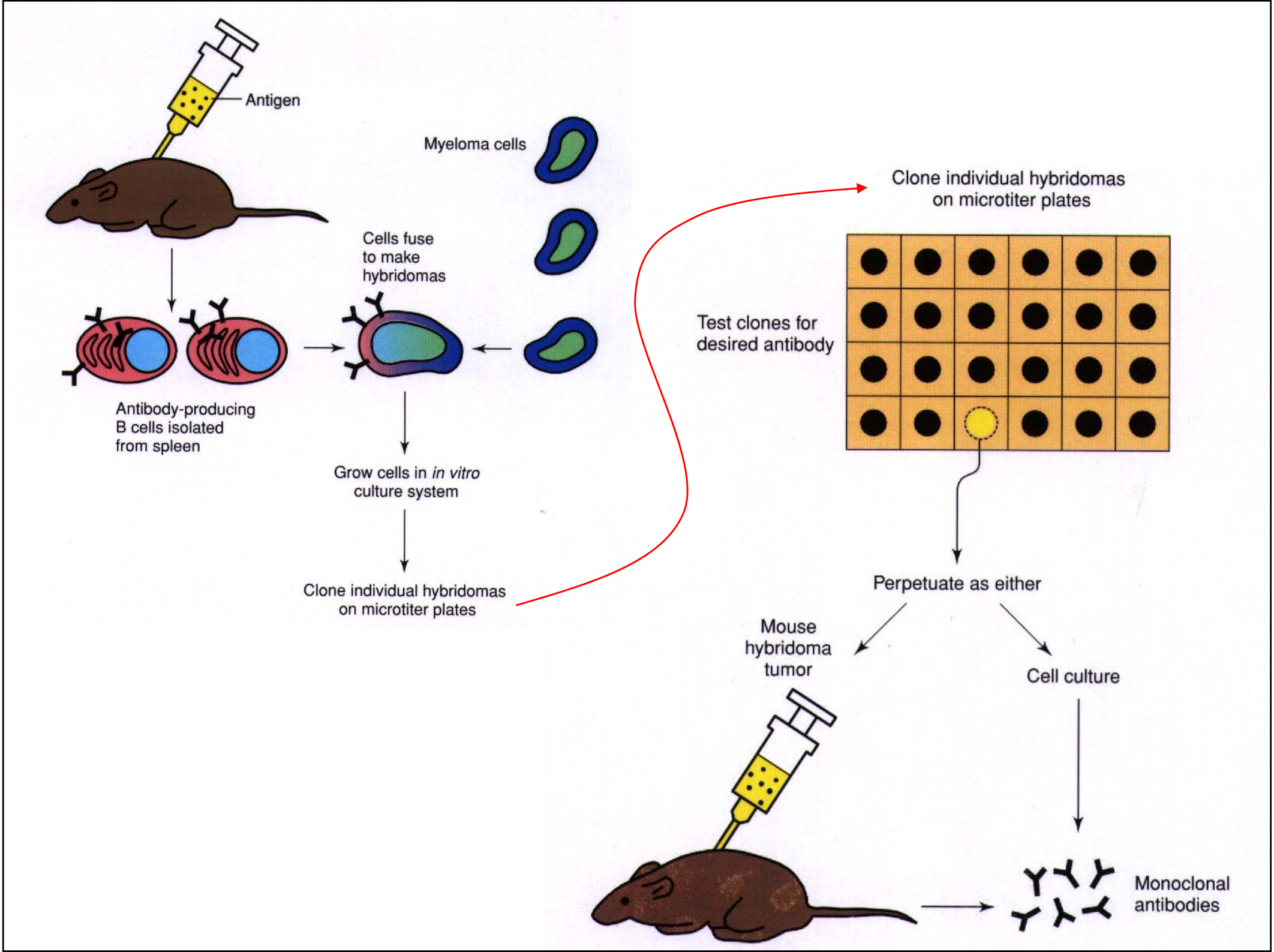


Boletín Epidemiológico **13**: 109-120 (2005)


Cell
Toxin molecules
Cell damage
Toxin + antitoxin
Neutralized toxin
Cell not damaged


Equivalence
Zone of
antibody excess
Zone of
antigen excess
Amount of
precipitate
Antigen

(b)


Antigen
Myeloma cells
Cells fuse to make hybridomas
Antibody-producing B cells isolated from spleen
Grow cells in *in vitro* culture system
Clone individual hybridomas on microtiter plates
Clone individual hybridomas on microtiter plates
Test clones for desired antibody
Perpetuate as either
Mouse hybridoma tumor
Cell culture
Monoclonal antibodies