INMUNODEFICIENCIAS PRIMARIAS

Dra: Alexis Strickler Prouvay

Immune system

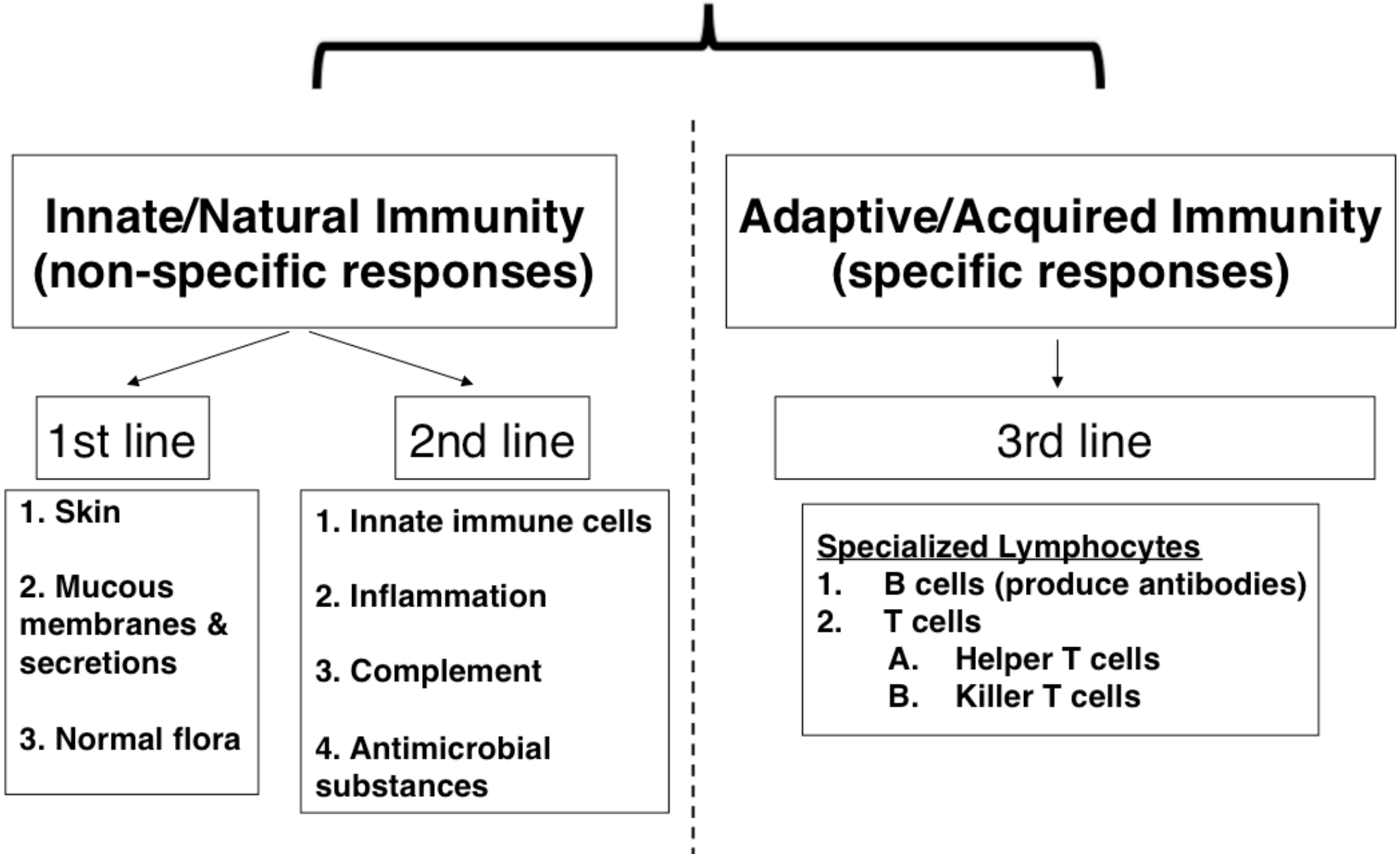
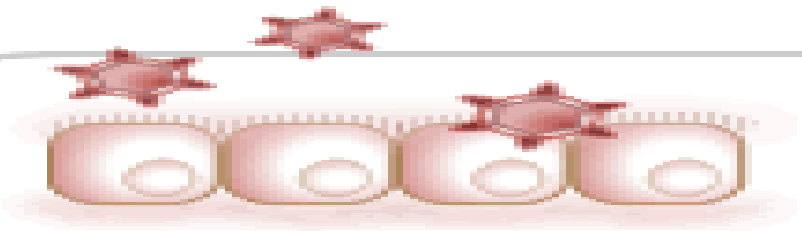


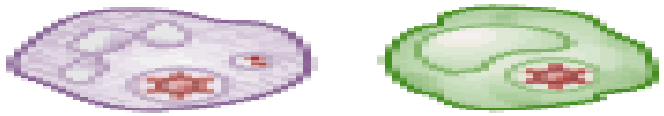
Table 1. Properties of Pattern Recognition Receptors

PRR	Localization	Ligands	Ligand Sources
TLR Toll-like receptors	Plasma membrane	lipoproteins, DNA, RNA, endotoxin, endogenous danger signals	bacteria, viruses, parasites, self
NLR NOD-like receptors	Cytoplasm	endogenous danger signals, muramyl dipeptides	self, bacteria
CLR C-type lectin receptors	Plasma membrane	beta-glucans	fungi
RLR Retinoic acid-inducible gene-1-like receptors	Cytoplasm	double-stranded RNAs	RNA viruses

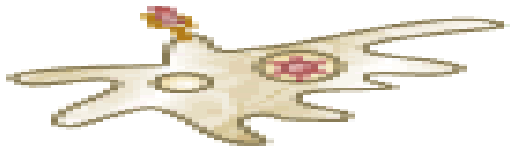
Innate Immunity



Epithelial barriers

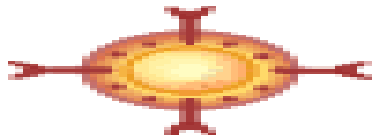


Phagocytes



Dendritic cells

Plasma proteins



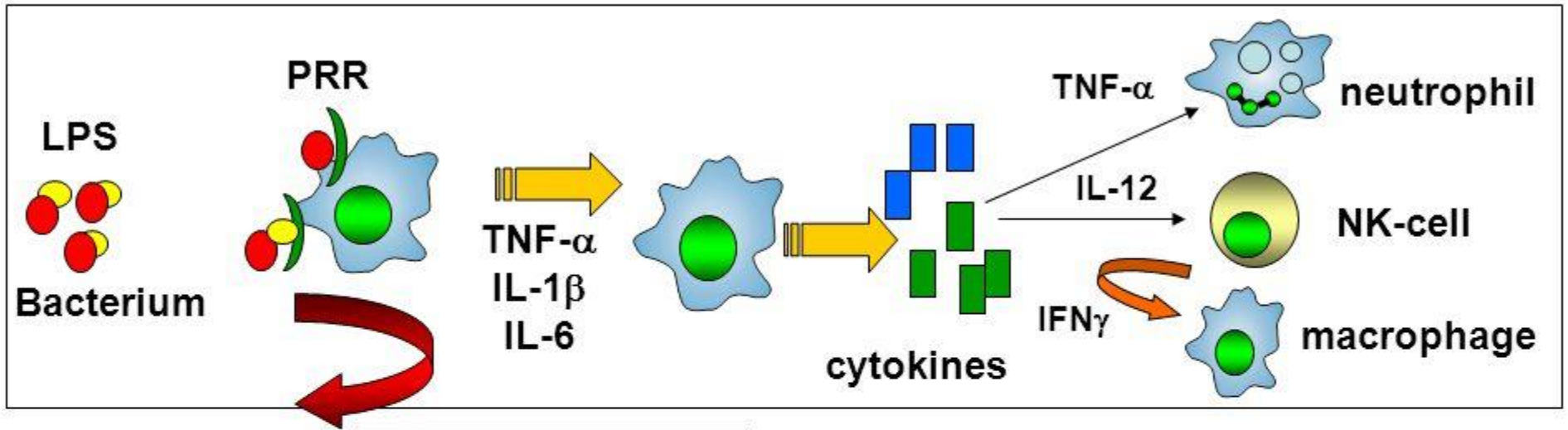
NK cells

Hours

0 6 12

MECHANISMS OF INNATE IMMUNITY

INFLAMMATION – ACUTE PHASE RESPONSE



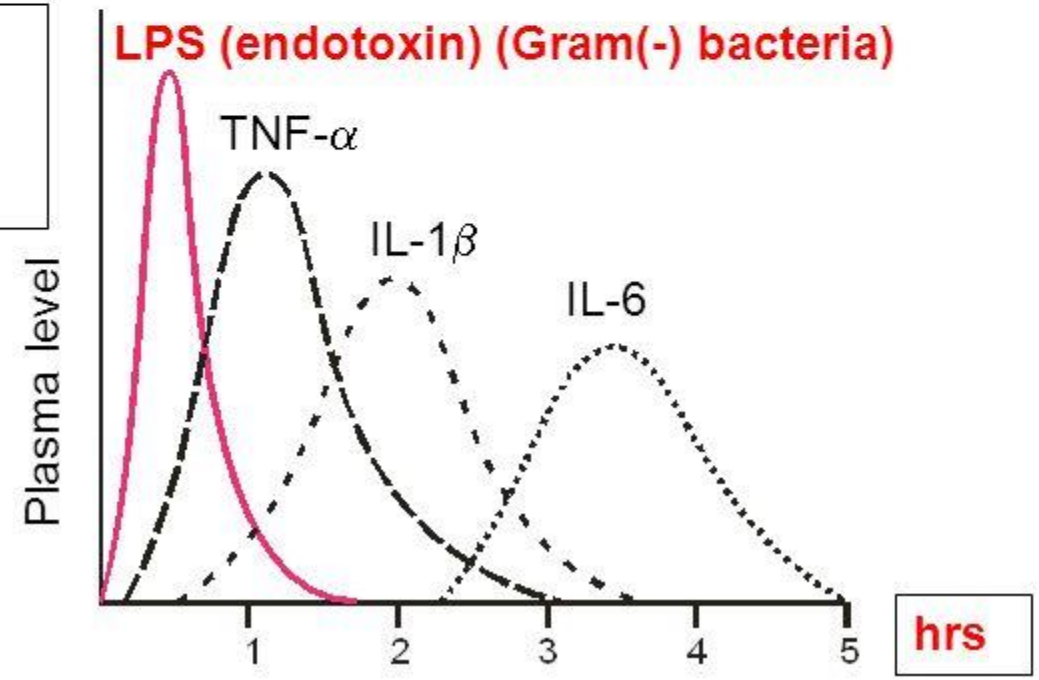
DANGER SIGNAL

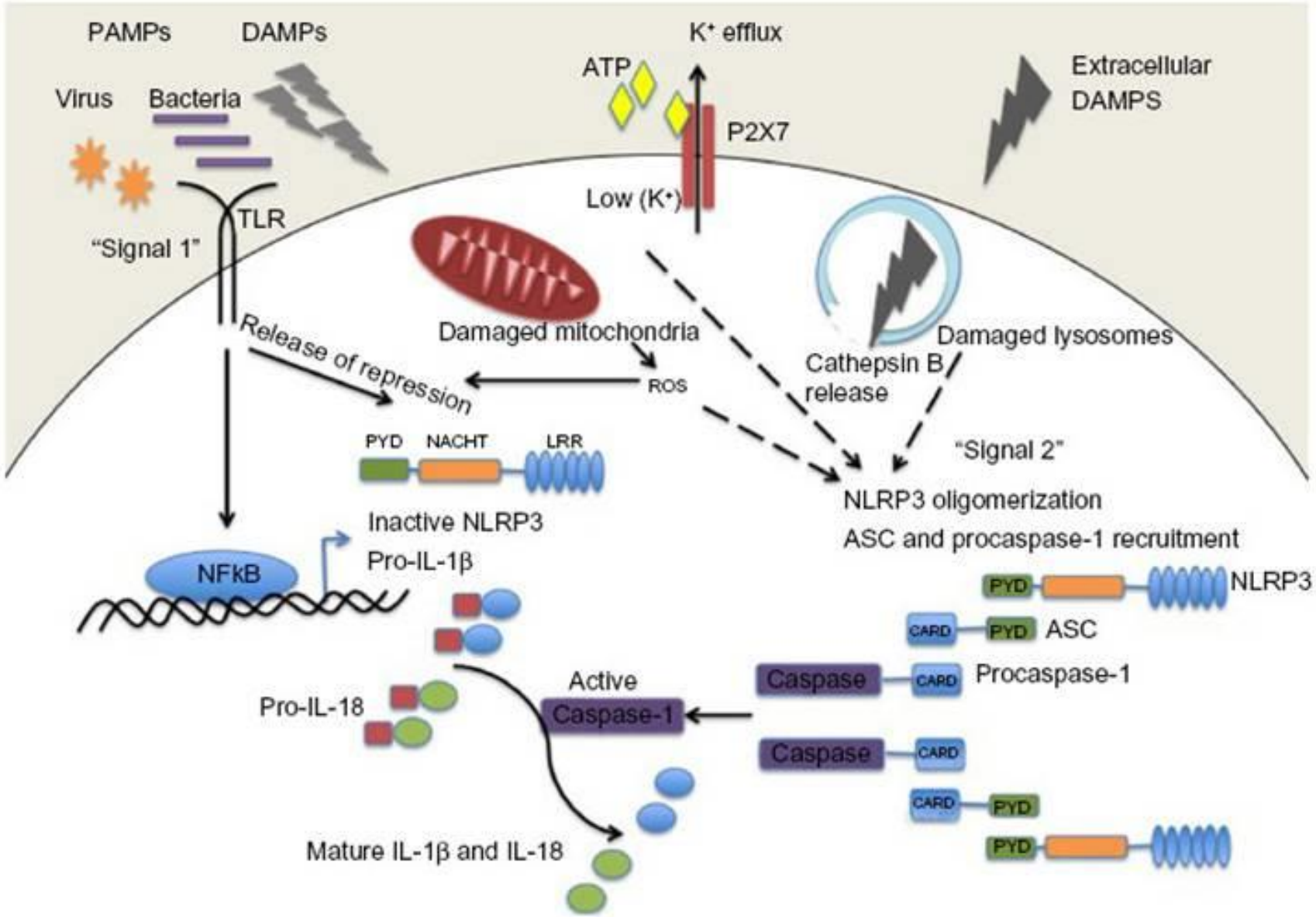
ACTIVATION

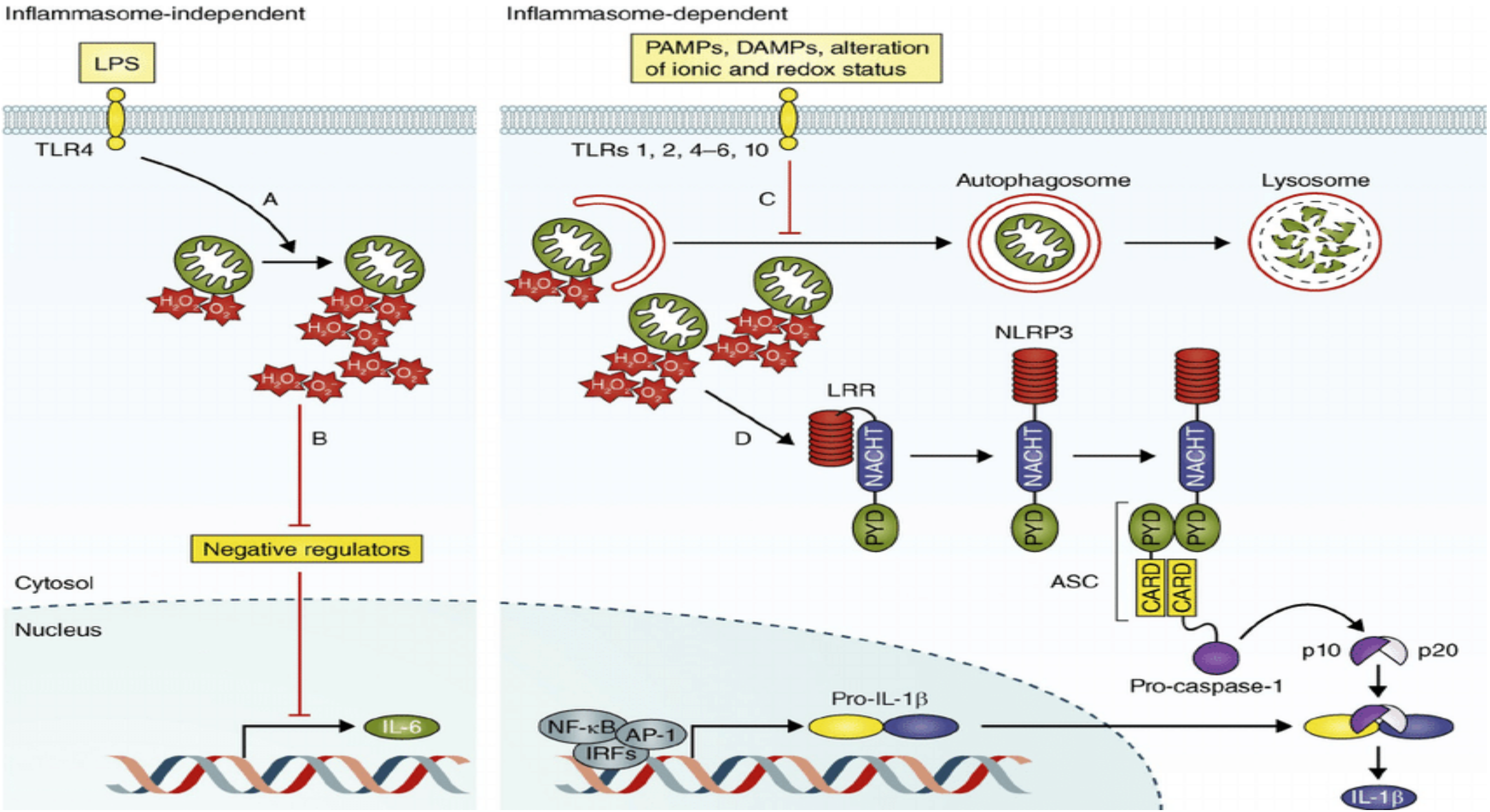
→ **Few hours**

ACUTE PHASE RESPONSE

Kinetics of the release of pro-inflammatory citokines in bacterial infection

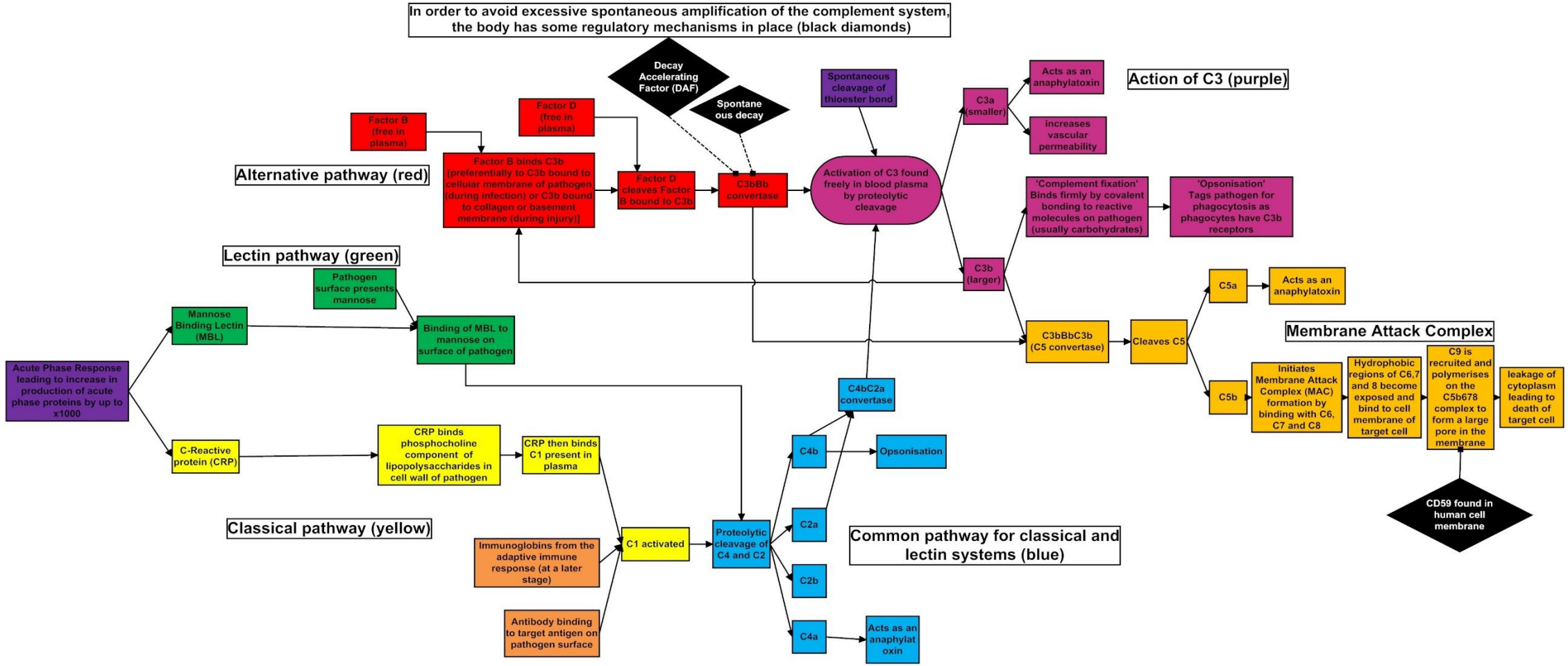



PAMPs
DAMPs
Virus
Bacteria
TLR
"Signal 1"
K⁺ efflux
ATP
P2X7
Low (K⁺)
Extracellular DAMPS
Damaged mitochondria
Damaged lysosomes
Cathepsin B release
ROS
Release of repression
PYD
NACHT
LRR
Inactive NLRP3
"Signal 2"
NLRP3 oligomerization
ASC and procaspase-1 recruitment
NFkB
Pro-IL-1β
NLRP3
CARD
PYD
ASC
Caspase
Procaspase-1
Active
Caspase-1
Pro-IL-18
Mature IL-1β and IL-18


Inflammasome-independent
LPS
TLR4
A
B
Negative regulators
Cytosol
Nucleus
IL-6
Inflammasome-dependent
PAMPs, DAMPs, alteration of ionic and redox status
TLRs 1, 2, 4–6, 10
C
Autophagosome
Lysosome
D
NLRP3
LRR
NACHT
PYD
ASC
CARD
Pro-caspase-1
p10
p20
Pro-IL-1β
NF-κB
AP-1
IRFs
IL-1β

By Architha Srinivasan
Cambridge University

COMPLEMENT SYSTEM

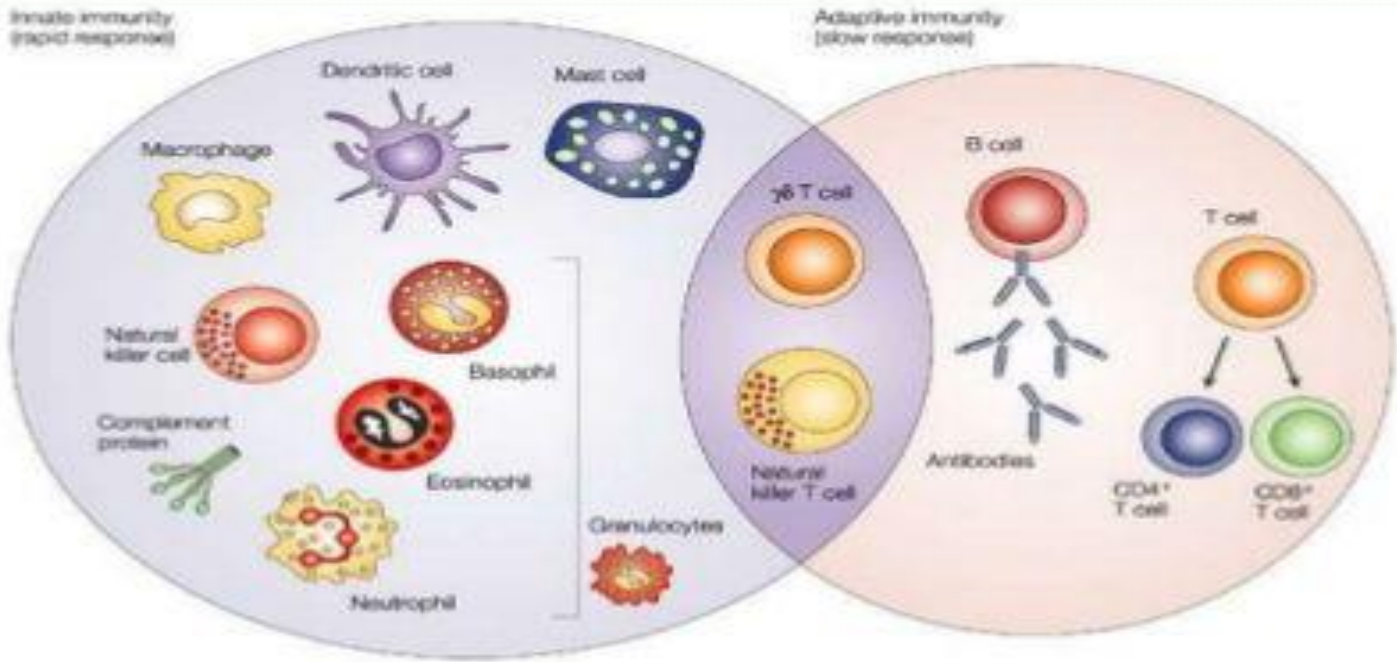


Alternative pathway acts first. Classical and Lectin pathways rely on the activation of Acute Phase Response and hence take longer.

Immune System – Innate vs Adaptive

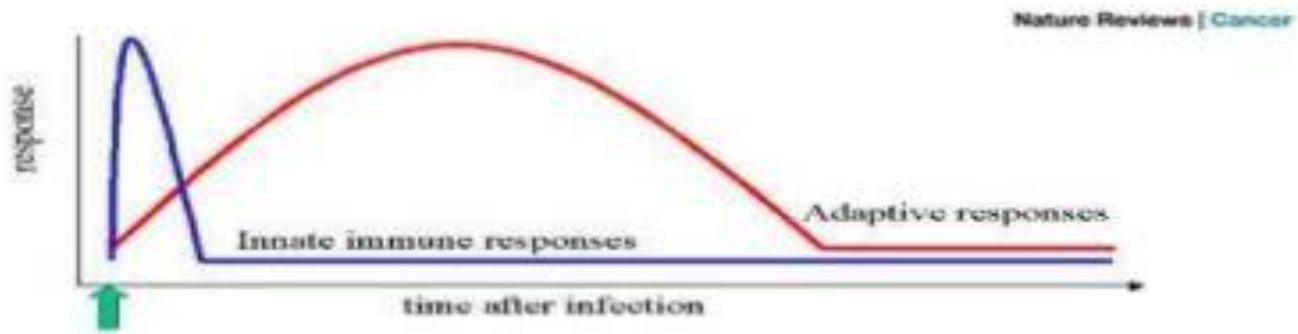
Innate:

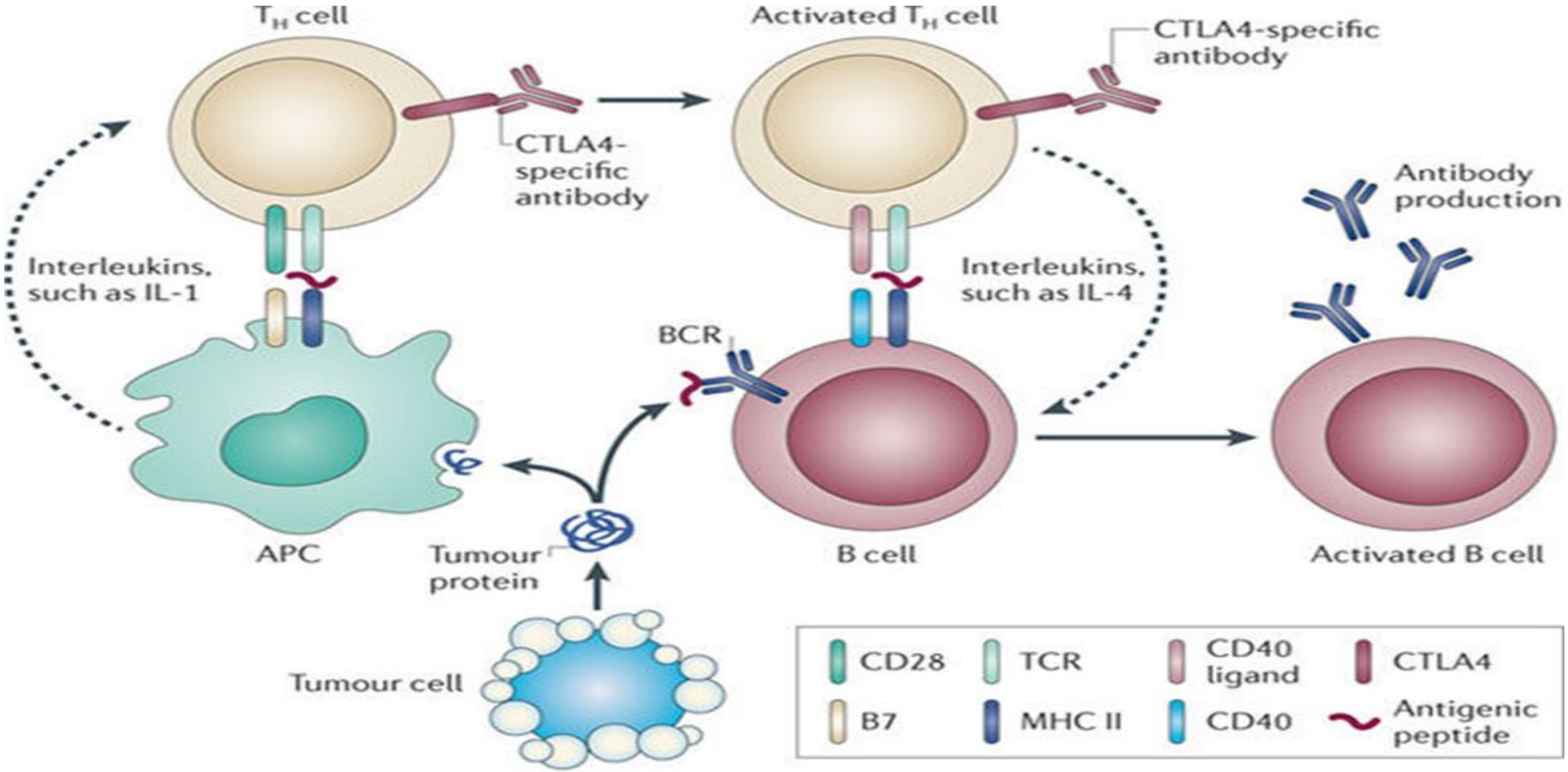
- Nonspecific
- Responds quickly



Adaptive:

- Specific
- Responds Slowly the 1st time





Nature Reviews | Cancer

Phases of T Cell Responses

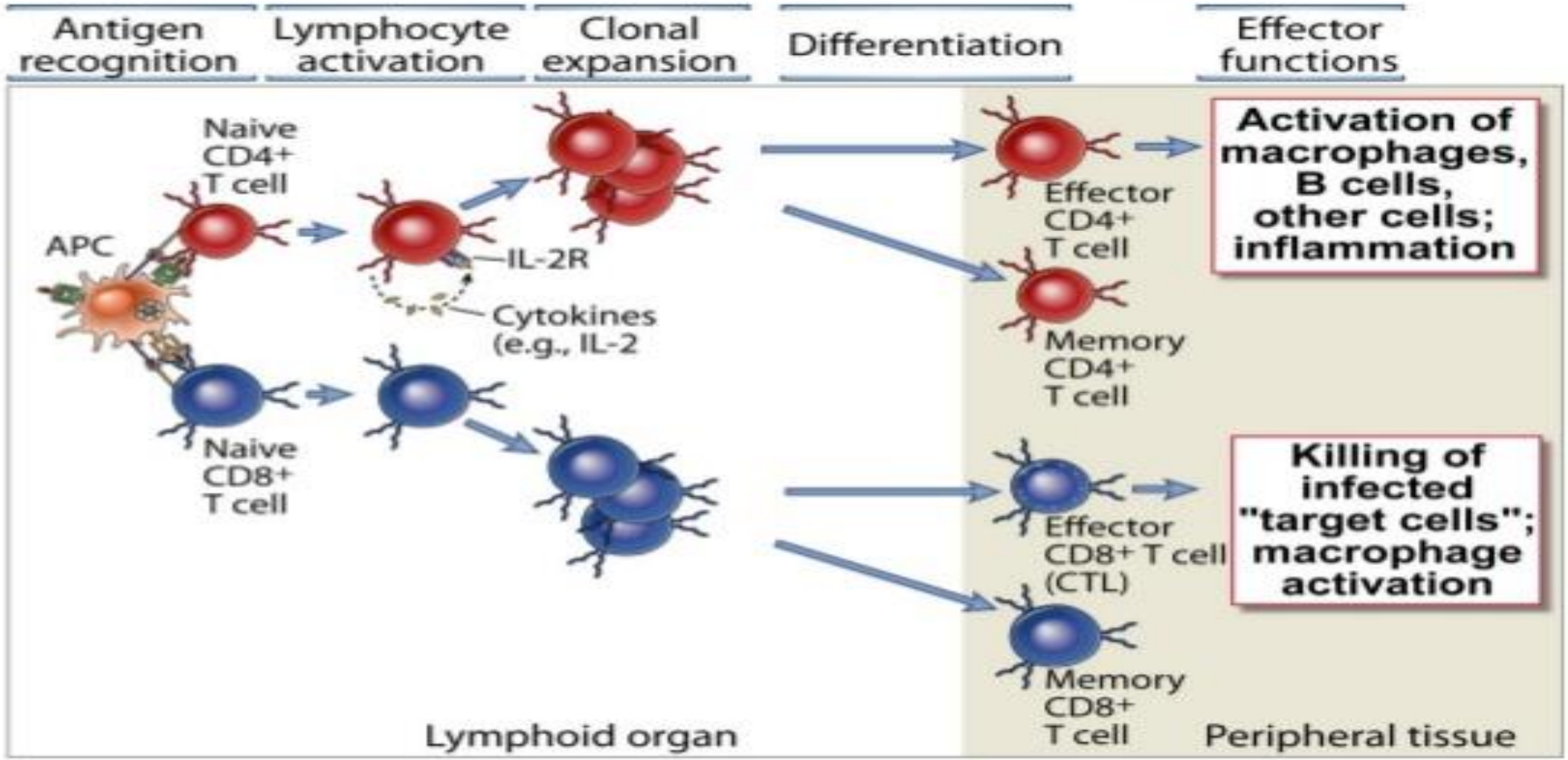
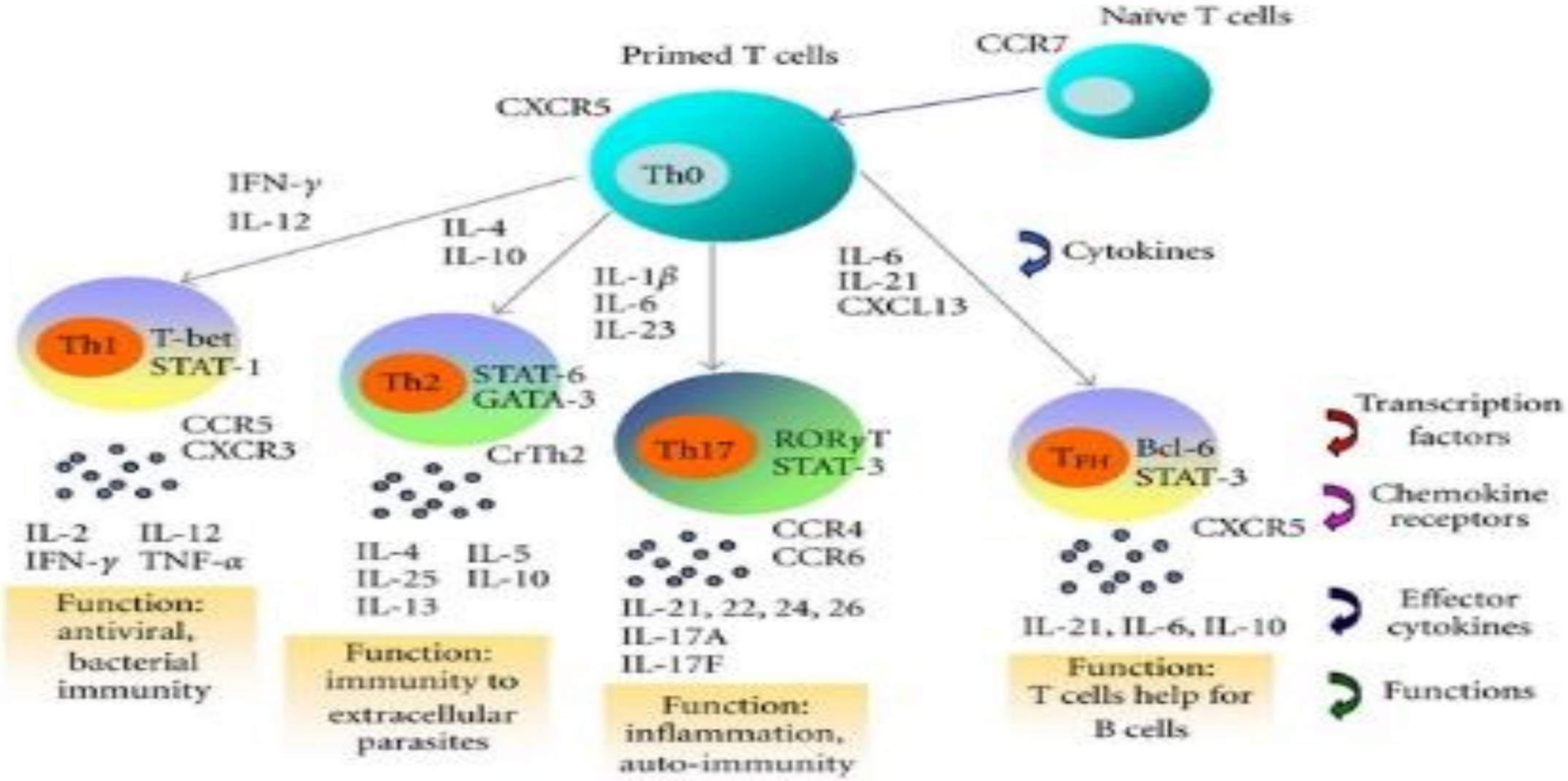
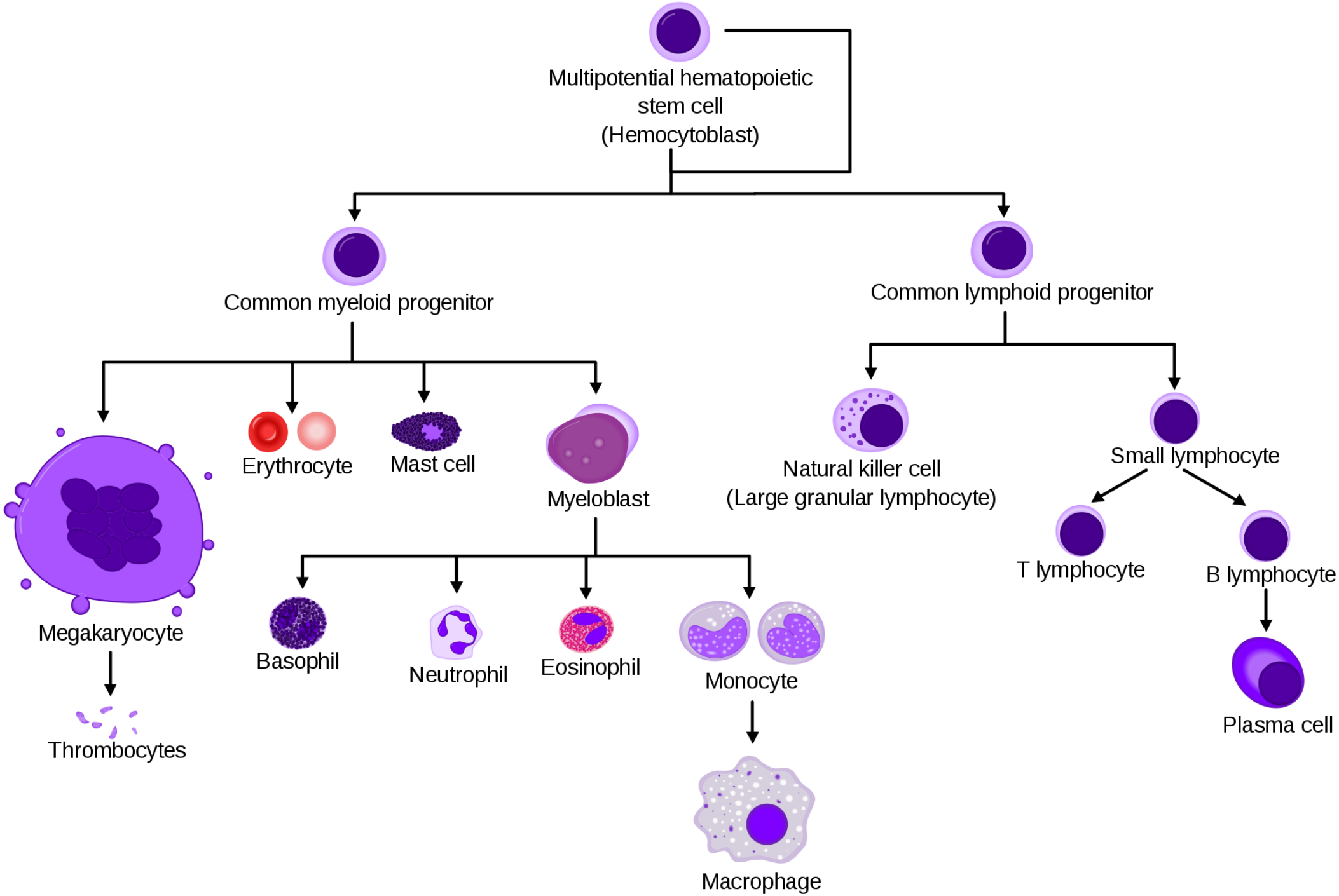
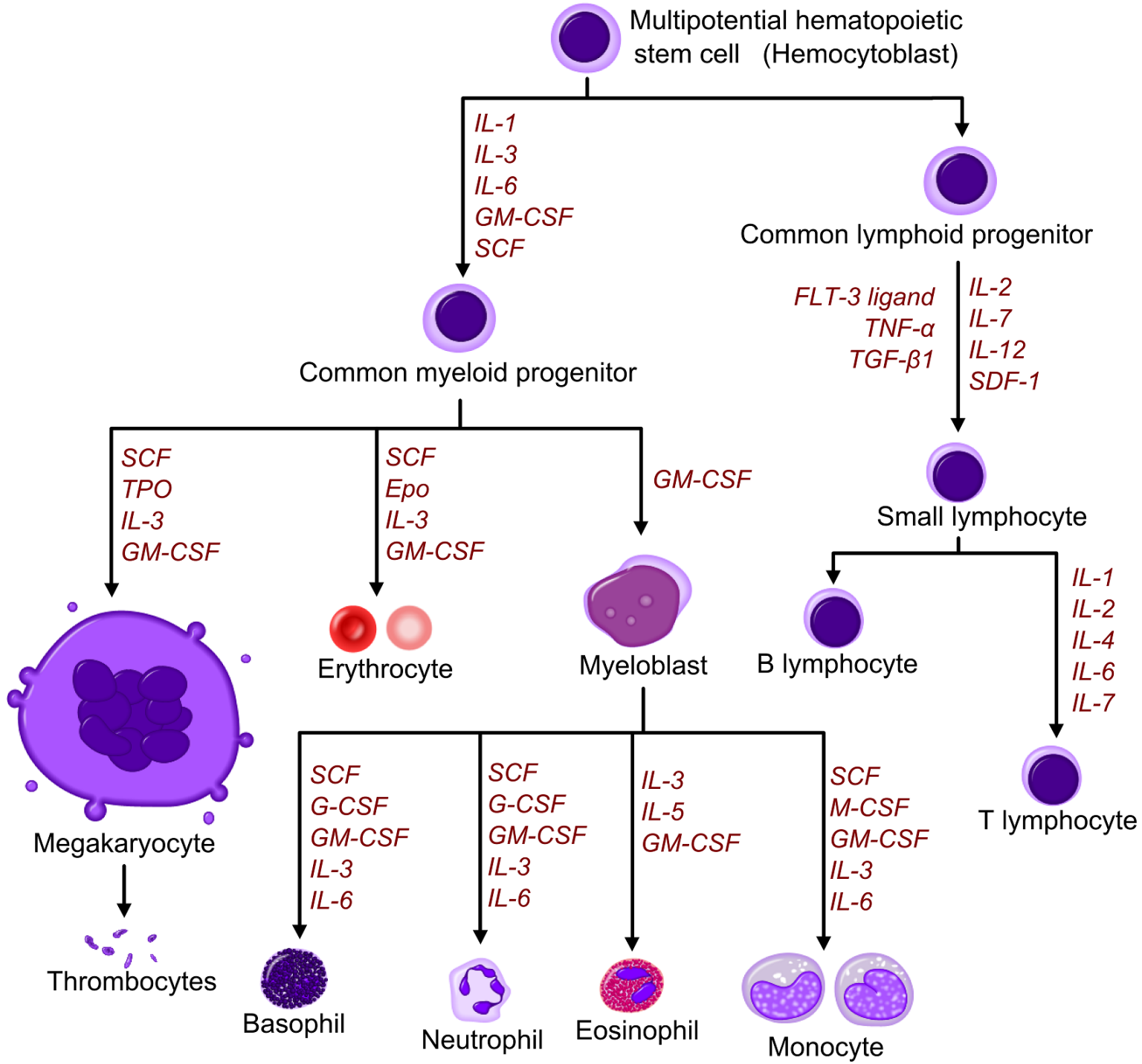
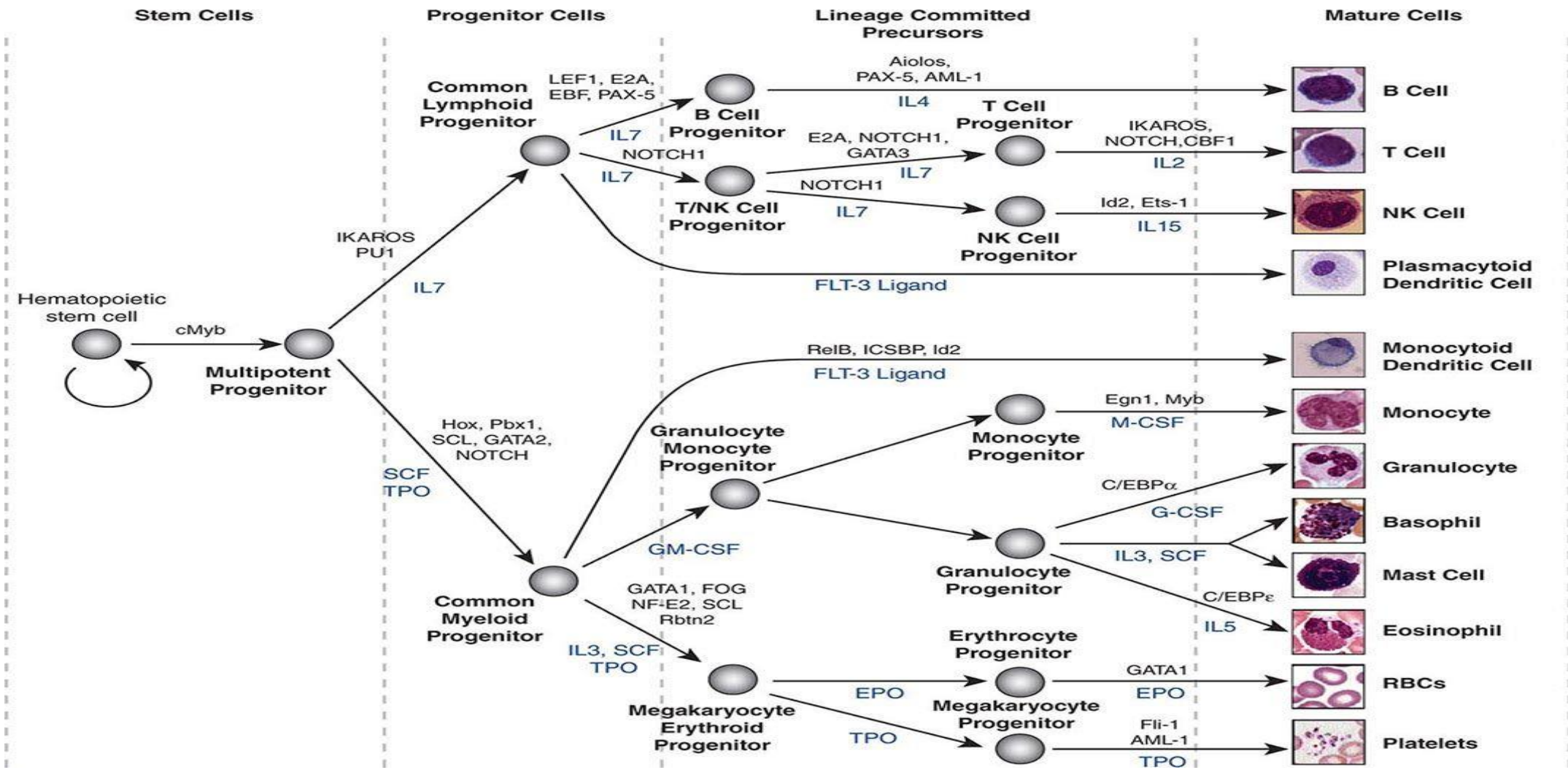


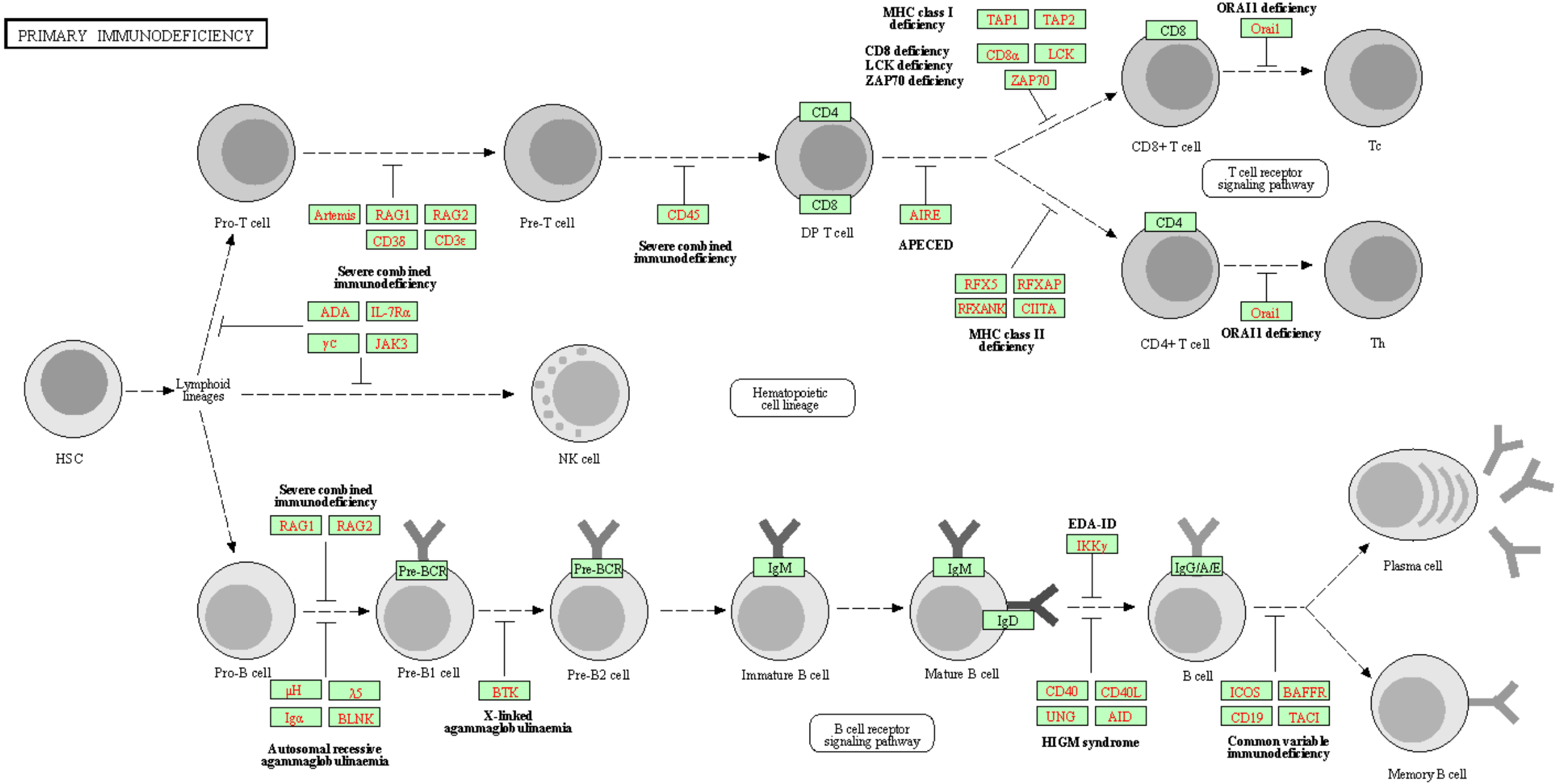
Fig. 9-2


Naive T cells
CCR7
Primed T cells
CXCR5
Th0
IFN-γ
IL-12
IL-4
IL-10
IL-1β
IL-6
IL-23
IL-6
IL-21
CXCL13
Cytokines
Th1
T-bet
STAT-1
CCR5
CXCR3
IL-2
IFN-γ
IL-12
TNF-α
Function:
antiviral,
bacterial
immunity
Th2
STAT-6
GATA-3
CrTh2
IL-4
IL-25
IL-13
IL-5
IL-10
Function:
immunity to
extracellular
parasites
Th17
RORγT
STAT-3
CCR4
CCR6
IL-21, 22, 24, 26
IL-17A
IL-17F
Function:
inflammation,
auto-immunity
TFH
Bcl-6
STAT-3
CXCR5
IL-21, IL-6, IL-10
Function:
T cells help for
B cells
Transcription
factors
Chemokine
receptors
Effector
cytokines
Functions


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
Macrophage
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
T lymphocyte
B lymphocyte
Plasma cell


Multipotential hematopoietic stem cell (Hemocytoblast)
IL-1
IL-3
IL-6
GM-CSF
SCF
Common myeloid progenitor
Common lymphoid progenitor
FLT-3 ligand
TNF-α
TGF-β1
IL-2
IL-7
IL-12
SDF-1
Small lymphocyte
SCF
TPO
IL-3
GM-CSF
SCF
Epo
IL-3
GM-CSF
GM-CSF
Megakaryocyte
Erythrocyte
Myeloblast
B lymphocyte
IL-1
IL-2
IL-4
IL-6
IL-7
T lymphocyte
Thrombocytes
SCF
G-CSF
GM-CSF
IL-3
IL-6
SCF
G-CSF
GM-CSF
IL-3
IL-6
IL-3
IL-5
GM-CSF
SCF
M-CSF
GM-CSF
IL-3
IL-6
Basophil
Neutrophil
Eosinophil
Monocyte


Stem Cells
Progenitor Cells
Lineage Committed Precursors
Mature Cells
Hematopoietic stem cell
cMyb
Multipotent Progenitor
IKAROS
PU1
IL7
Hox, Pbx1, SCL, GATA2, NOTCH
SCF
TPO
Common Lymphoid Progenitor
LEF1, E2A, EBF, PAX-5
IL7
NOTCH1
IL7
B Cell Progenitor
T/NK Cell Progenitor
Aiolos, PAX-5, AML-1
IL4
B Cell
T Cell Progenitor
E2A, NOTCH1, GATA3
IL7
IKAROS, NOTCH,CBF1
IL2
T Cell
NOTCH1
IL7
NK Cell Progenitor
Id2, Ets-1
IL15
NK Cell
FLT-3 Ligand
Plasmacytoid Dendritic Cell
RelB, ICSBP, Id2
FLT-3 Ligand
Monocytoid Dendritic Cell
Granulocyte Monocyte Progenitor
GM-CSF
Monocyte Progenitor
Egn1, Myb
M-CSF
Monocyte
Granulocyte Progenitor
C/EBPα
G-CSF
Granulocyte
IL3, SCF
Basophil
Mast Cell
C/EBPε
IL5
Eosinophil
Common Myeloid Progenitor
GATA1, FOG NF-E2, SCL Rbtn2
IL3, SCF TPO
Megakaryocyte Erythroid Progenitor
EPO
Erythrocyte Progenitor
GATA1
EPO
RBCs
TPO
Megakaryocyte Progenitor
Fli-1
AML-1
TPO
Platelets



05340 8/22/13

Approach to the patients with suspected immunodeficiency

- The medical history in immunodeficiency
- Physical examination
- Laboratory investigation

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

Presented as a public service by:

Jeffrey Modell Foundation | Caring for PI Worldwide

Funding was made possible in part by a grant from the U.S. Centers for Disease Control and Prevention (CDC).

National Heart, Lung, and Blood Institute (NHLBI) | National Institute of Allergy and Infectious Diseases (NIAID) | PPTA Plasma Protein Therapeutics Association | NICHD

Baxter | Biotest | CSL Behring | GRIFOLS | KEDRION BIOPHARMA | octapharma

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested.

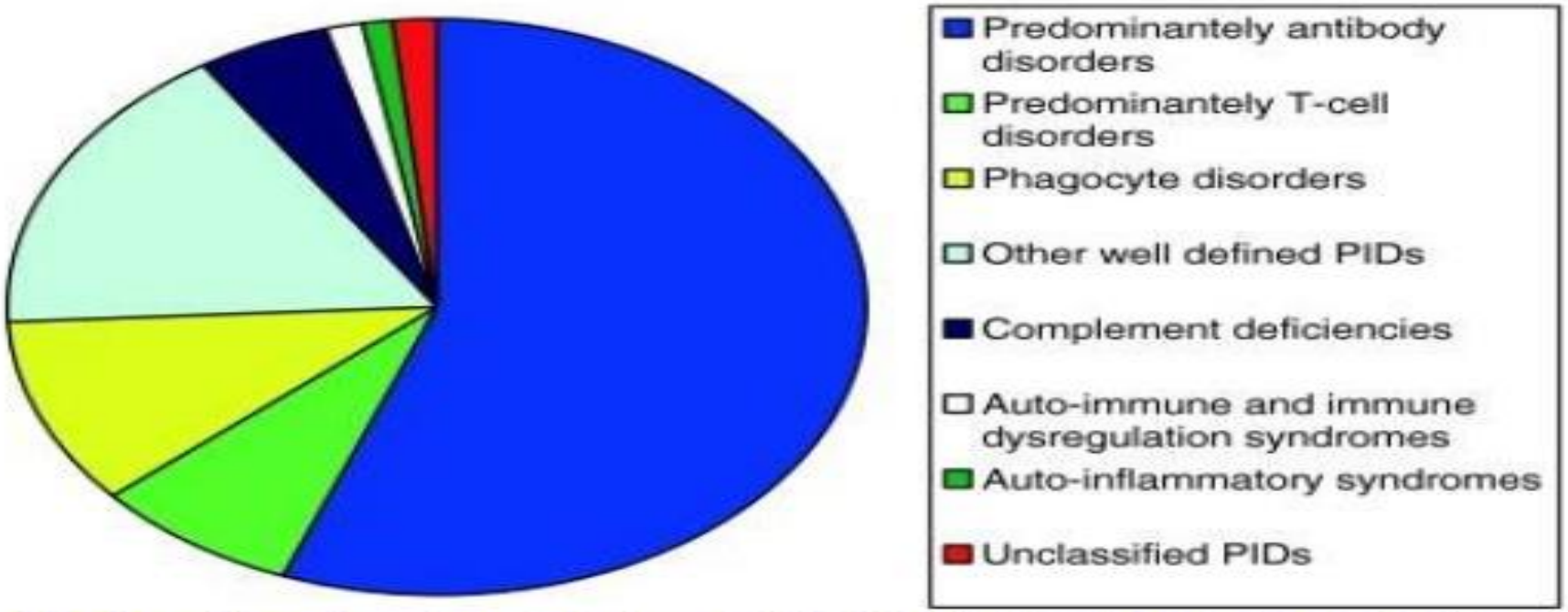
For information or referrals, contact the Jeffrey Modell Foundation: **info4pi.org | 866-INFO-4-PI**

Diagnosis of Primary Immunodeficiency

History of Symptoms

- Birth to 3 months
  - Phagocytic cell defects
  - Complement defects
  - DiGeorge syndrome
- 3 to 6 months
  - Severe combined immunodeficiency (SCID)
- 6 to 18 months
  - X-linked agammaglobulinemia
- 18 months through adulthood
  - Common variable immunodeficiency
  - Complement defects

Distribution of Primary Immunodeficiency Diseases



http://www.biomedsearch.com/attachments/00/21/17/05/21170549/431_2010_1358_Fig1_HTML.jpg
Accessed on 1/22/13 - Images

pediatric home service

Importancia de diagnóstico temprano

- Vida – muerte.
- Evita daño a órganos vitales (pulmón)
- Evita o pesquisa precoz autoinmunidad.
- Evita o pesquisa precoz malignidad.

Neonato y lactante

- ID transitorios.
- Lactancia materna y medio ambiente.
- Evitar uso indebido de antibióticos.
- Asepsia excesiva.

Estudio de la respuesta inmune inespecífica

Fagocitos

- **Determinación cuantitativa y morfolología de granulocitos y monocitos.**

- **Estudio de mecanismos microbicidas oxígeno dependientes:**
  - **Prueba de reducción del nitroazul de tetrazolio (NBT).**
  - **Quimioluminiscencia, dihidrorodamina (DHR),**
    Producción de anión superóxido.

- **Estudio de la expresión de moléculas de adhesión: CD11, CD18, CD15.**

- **Estudios de actividad enzimática:**
  Mieloperoxidasa, Glucosa 6 fosfato dehidrogenasa.

- **Actividad bactericida.**

Cont.

Estudio de la respuesta inmune inespecífica

(cont.)

Sistema del Complemento

- **Actividad lítica del complemento: CH50.**
- **Determinación de la concentración sérica de componentes del complemento.**
- **Evaluación funcional de componentes del complemento.**
- **Determinación cuantitativa y funcional de inhibidores del complemento.**

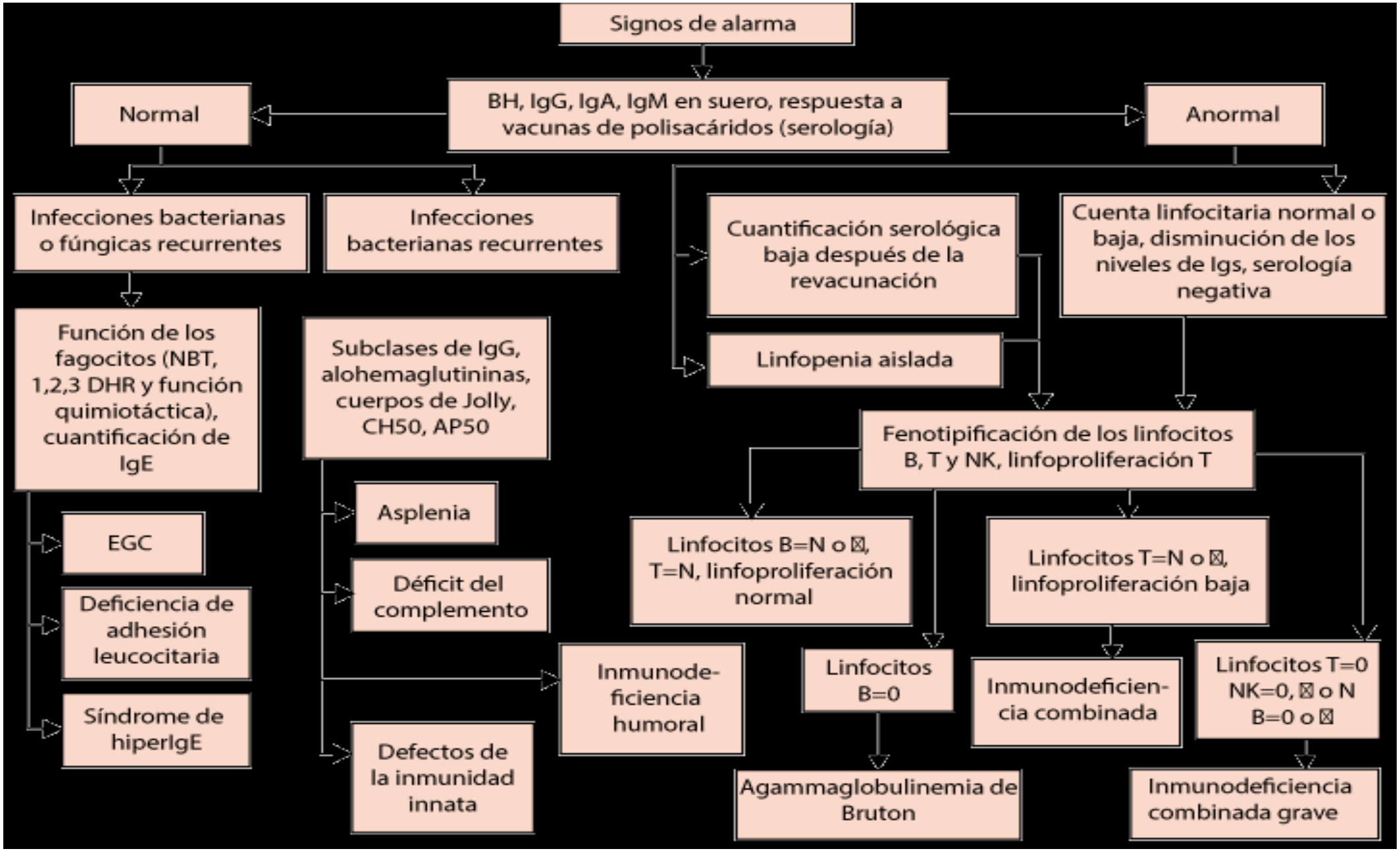
Estudio de la respuesta inmune humoral

- **Determinación de la concentración sérica de IgG, IgM, IgA e IgE.**
- **Recuento de LB por expresión de antígenos de diferenciación (CD19, CD20).**
- **Búsqueda de anticuerpos preexistentes (Isohemaglutininas antiA y antiB)**
- **Búsqueda de respuesta de Acs a la inmunización activa con:**
  - **Ags proteicos : Ac anti-tetánico, Ac anti-diftérico.**
  - **Ags polisacáridos: Ac anti- neumococo.**
- **Determinación de la concentración sérica de subclases de IgG:**
  IgG1, IgG2, IgG3, IgG4.
- **Producción de Igs *in vitro* mediante estimulación con mitógenos (PWM).**

Estudio de la respuesta inmune celular

- **Determinación del valor absoluto de linfocitos/μl**
- **Recuento de LT por expresión de antígenos de diferenciación: CD3, CD4, CD8.**
- **Pruebas de hipersensibilidad retardada** a distintos antígenos: PPD, candidina, etc.
- **Respuesta proliferativa *in vitro* a mitógenos**: PHA, ConA, PMA+Ionomicina.
- Respuesta proliferativa a:
  - **Ags** : candidina, PPD, toxoide tetánico.
  - **Células alogeneicas**: cultivo mixto linfocitario.
- **Producción de ILs: IL-1, IL-2, IFNγ, TNF-alfa, IL-4**, etc., en sobrenadantes de cultivos o detección intracitoplasmática en respuesta a mitógenos.
- **Estudios de actividad enzimática: ADA, PNP**.

PMA, Acetato de forbol mirístico; PPD, Tuberculina; PHA, Fitohemaglutinina


Signos de alarma
BH, IgG, IgA, IgM en suero, respuesta a vacunas de polisacáridos (serología)
Normal
Anormal
Infecciones bacterianas o fúngicas recurrentes
Infecciones bacterianas recurrentes
Cuantificación serológica baja después de la revacunación
Cuenta linfocitaria normal o baja, disminución de los niveles de Igs, serología negativa
Linfopenia aislada
Función de los fagocitos (NBT, 1,2,3 DHR y función quimiotáctica), cuantificación de IgE
Subclases de IgG, alohemaglutininas, cuerpos de Jolly, CH50, AP50
Fenotipificación de los linfocitos B, T y NK, linfoproliferación T
Asplenia
EGC
Déficit del complemento
Deficiencia de adhesión leucocitaria
Síndrome de hiperIgE
Defectos de la inmunidad innata
Inmunodeficiencia humoral
Linfocitos B=N o ⊠, T=N, linfoproliferación normal
Linfocitos T=N o ⊠, linfoproliferación baja
Linfocitos B=0
Inmunodeficiencia combinada
Linfocitos T=0 NK=0, ⊠ o N B=0 o ⊠
Agammaglobulinemia de Bruton
Inmunodeficiencia combinada grave

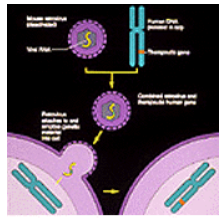
IDP

Tratamiento

Tratamiento sustitutivo

- **Gammaglobulina**

- **Trasplante de MO y Timo**
- **Reemplazo enzimático (Adenosin-deaminasa, ADA)**



Gene therapy has been attempted to treat severe combined immunodeficiency caused by a missing enzyme, adenosine deaminase. [Image credit: National Cancer Institute.]

- **Terapia génica**
- **Antibióticos**