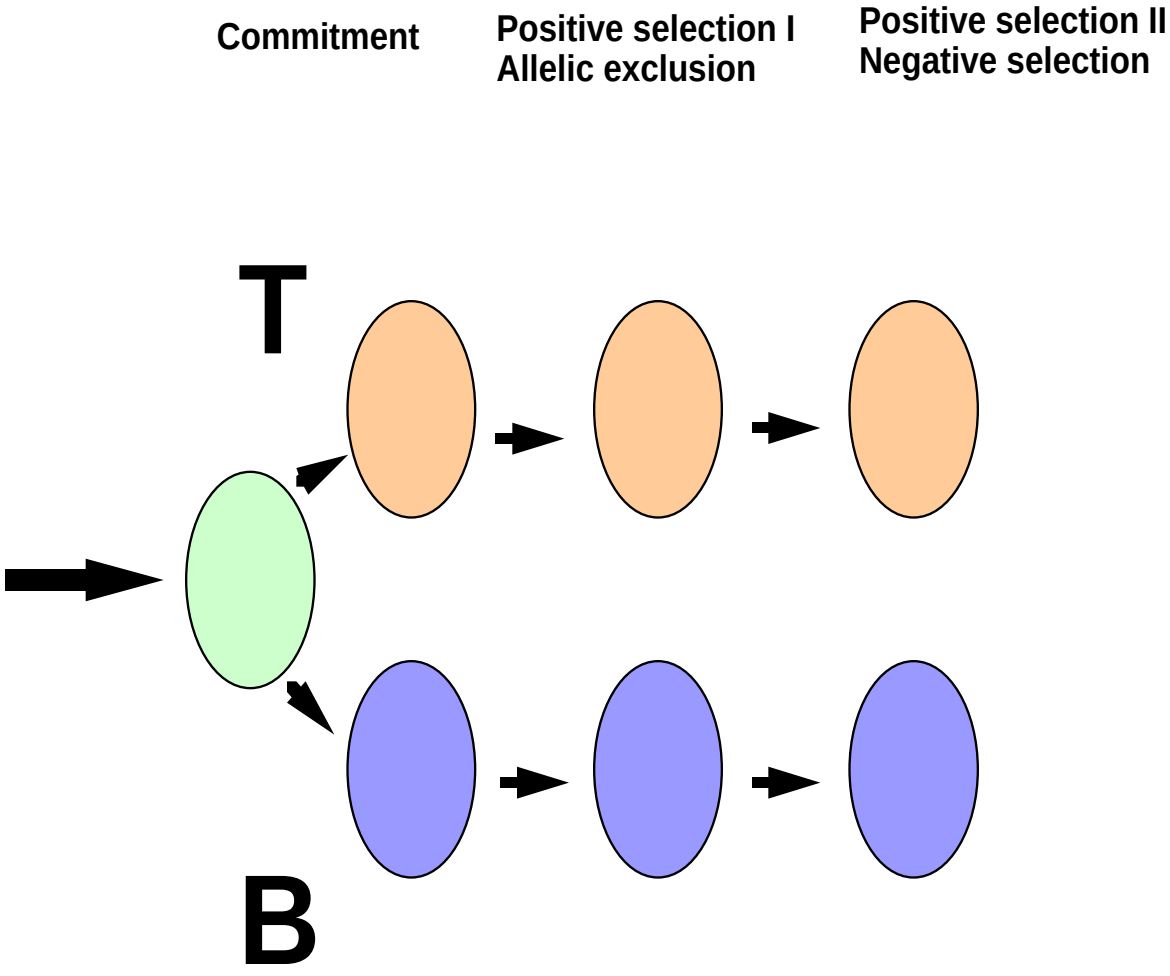
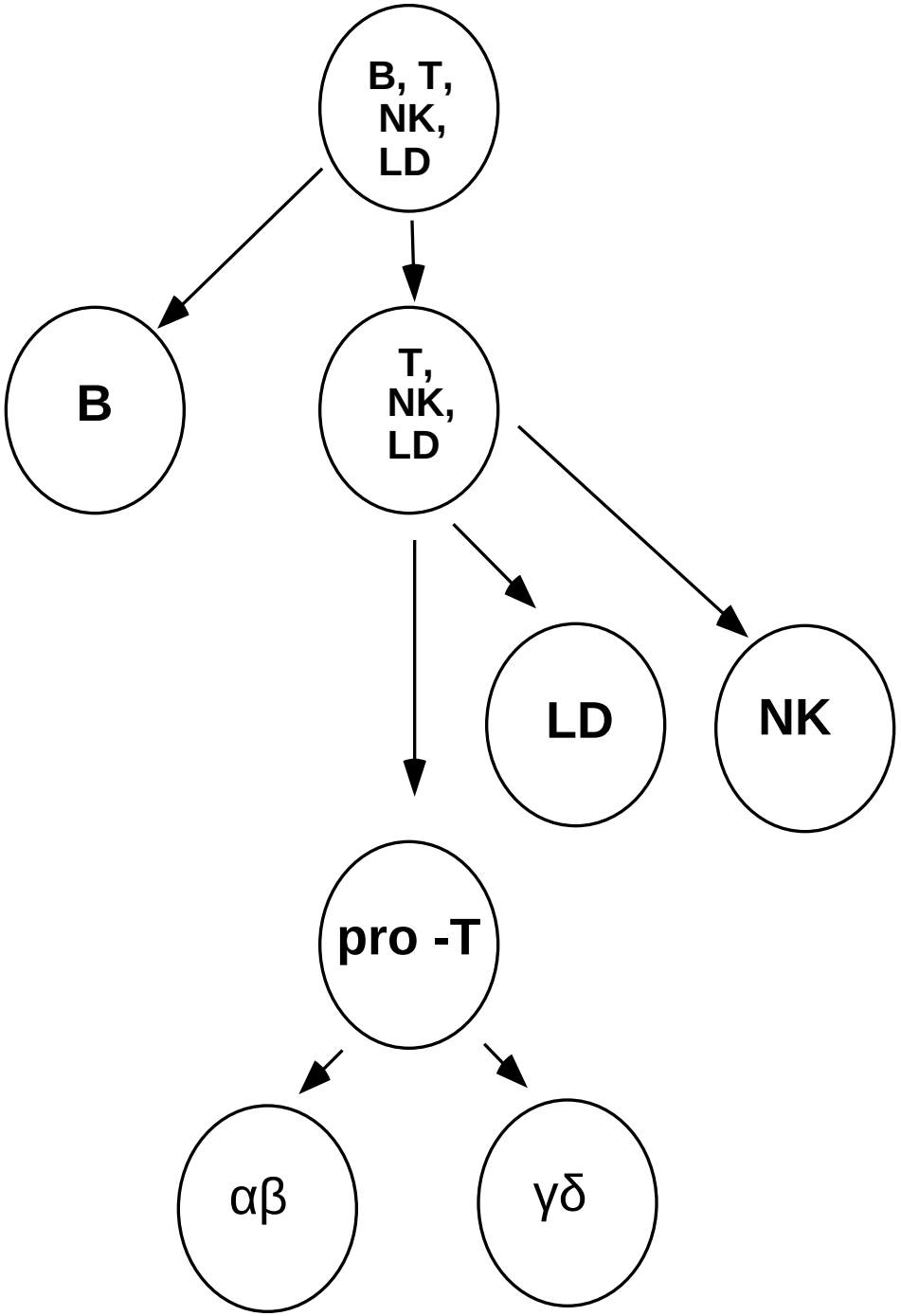
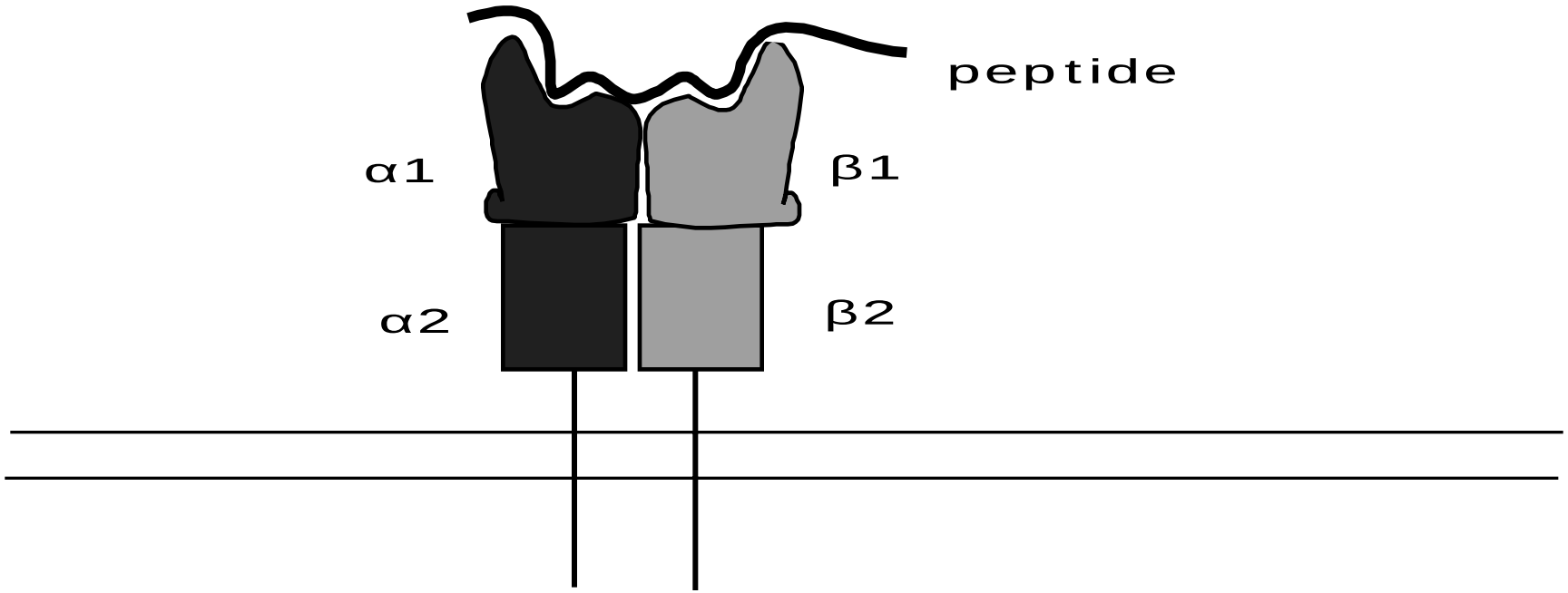
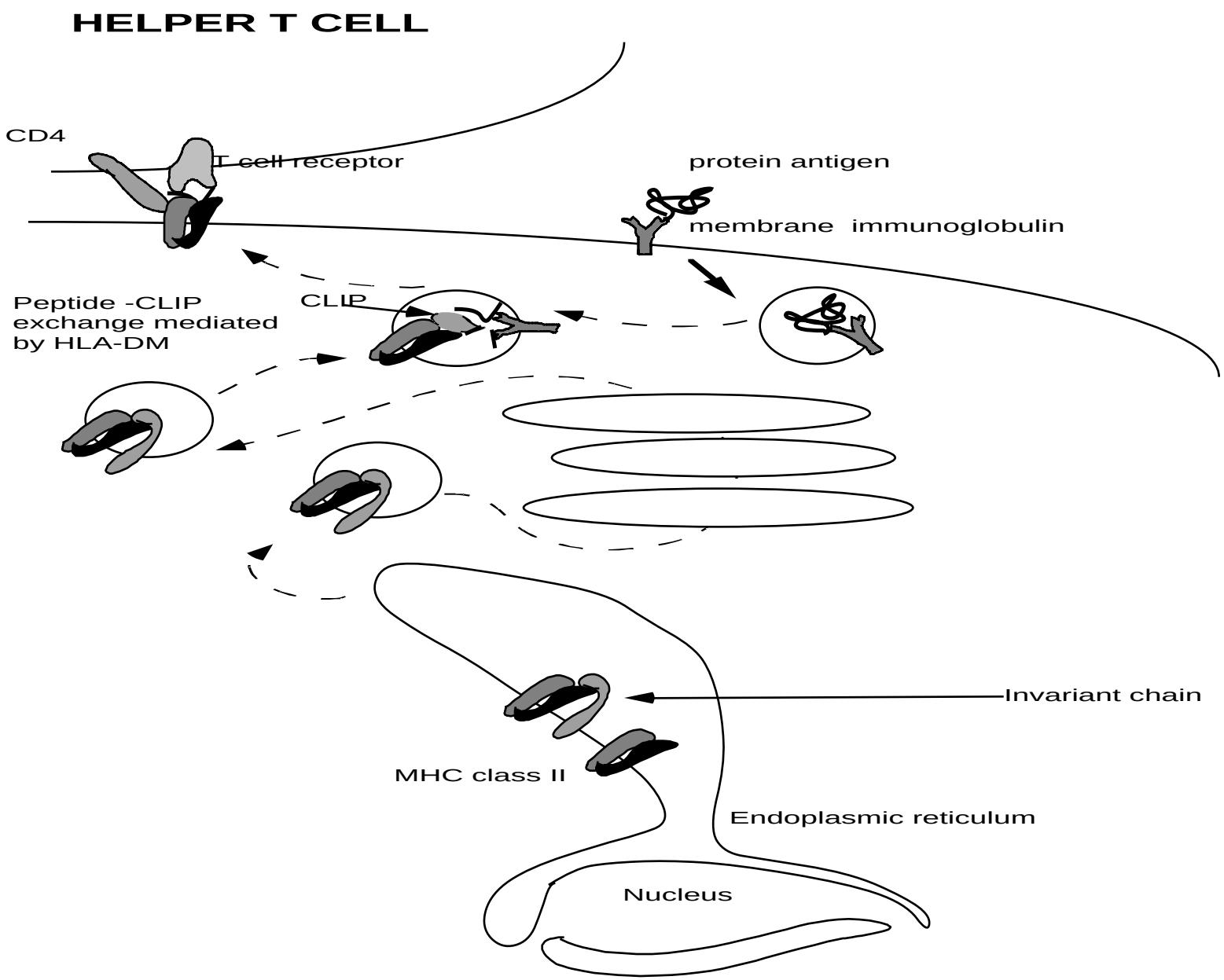

Commitment
Positive selection I
Allelic exclusion
Positive selection II
Negative selection
T
B

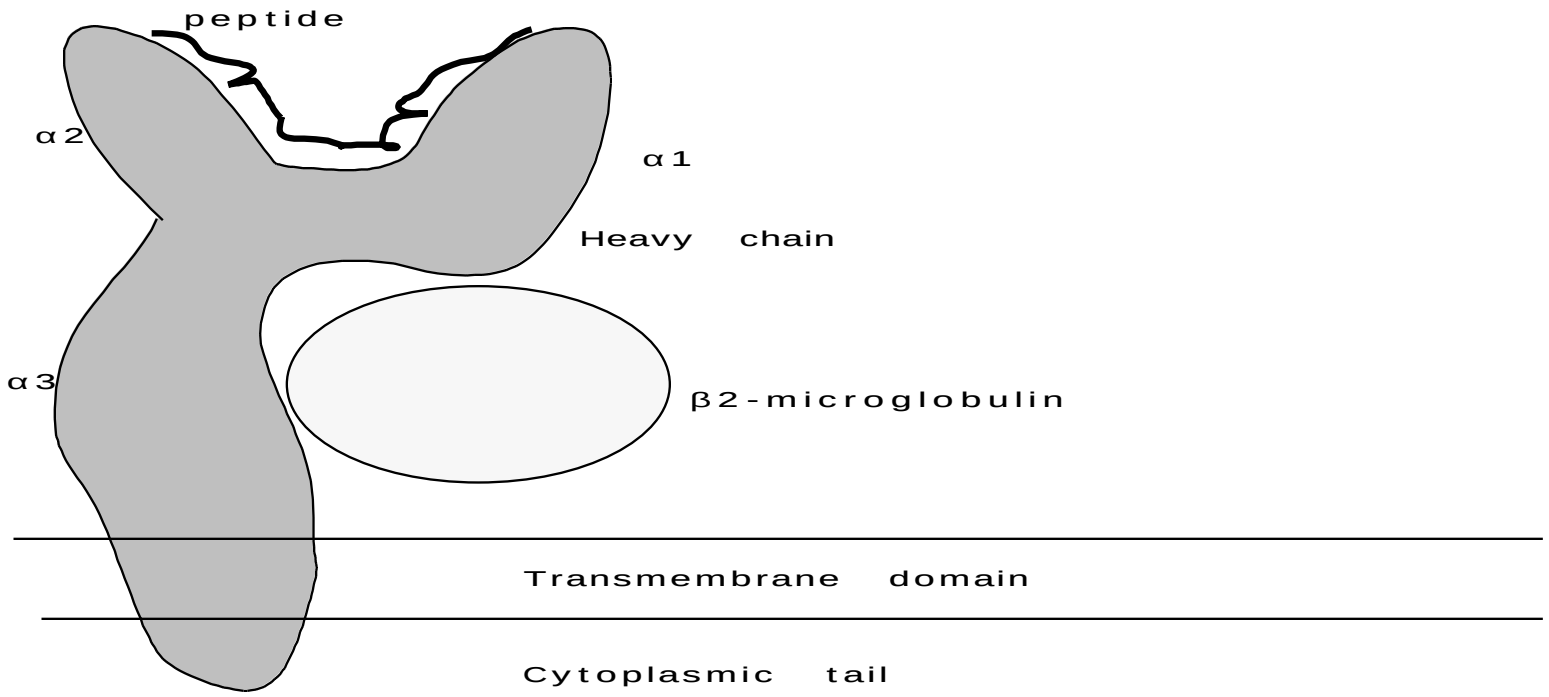

B, T, NK, LD
B
T, NK, LD
LD
NK
pro -T
αβ
γδ

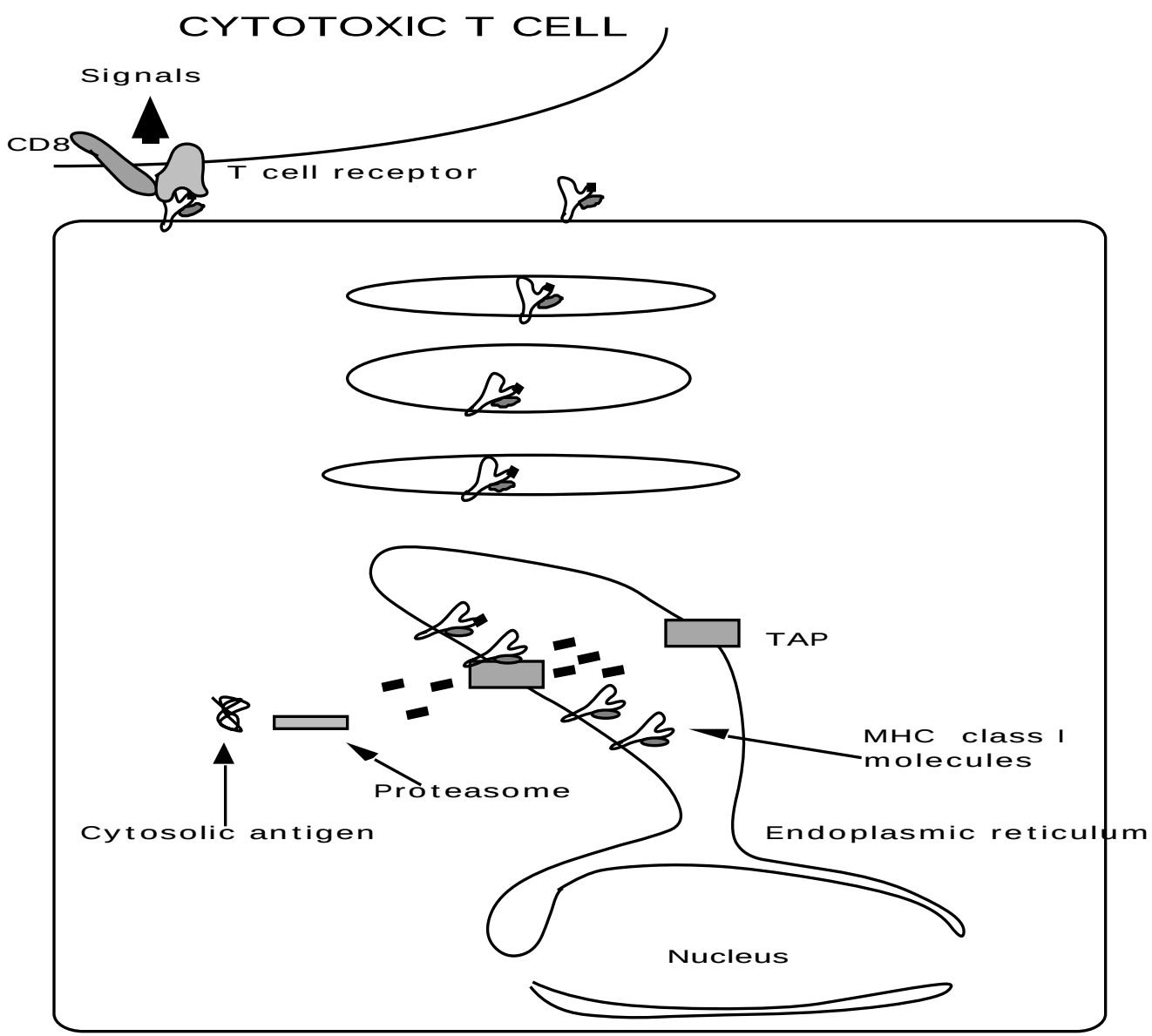
A schematic view of an HLA class II molecule




HELPER T CELL
CD4
T cell receptor
protein antigen
membrane immunoglobulin
Peptide -CLIP
exchange mediated
by HLA-DM
CLIP
Invariant chain
MHC class II
Endoplasmic reticulum
Nucleus

A schematic view of an HLA class I molecule




CYTOTOXIC T CELL
Signals
CD8
T cell receptor
TAP
MHC class I
molecules
Proteasome
Cytosolic antigen
Endoplasmic reticulum
Nucleus

MHC RESTRICTION

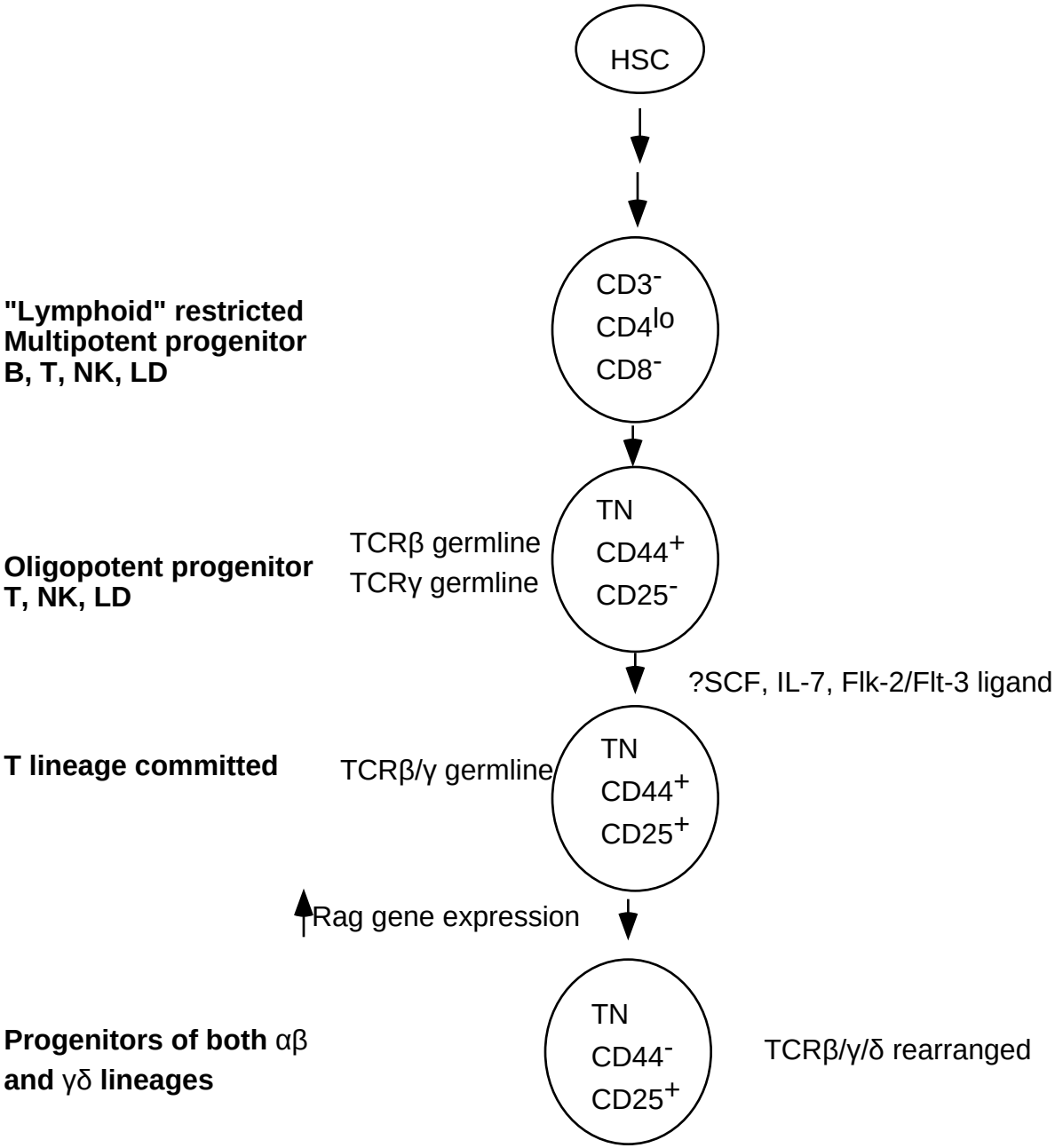
αβ T CELL DEVELOPMENT

1. Development occurs in the thymus

2. T cells with receptors biased towards self MHC must be generated

3. Self-reactive T cells must be tolerized

4. CD4 T cells which see MHC class II-peptide complexes and CD8 T cells which recognize MHC class I-peptide complexes must be generated


HSC
"Lymphoid" restricted
Multipotent progenitor
B, T, NK, LD
CD3-
CD4lo
CD8-
Oligopotent progenitor
T, NK, LD
TCRβ germline
TCRγ germline
TN
CD44+
CD25-
?SCF, IL-7, Flk-2/Flt-3 ligand
T lineage committed
TCRβ/γ germline
TN
CD44+
CD25+
Rag gene expression
Progenitors of both αβ
and γδ lineages
TN
CD44-
CD25+
TCRβ/γ/δ rearranged

Thymic versus extra-thymic development

1. Most αβ T cell develop in the thymus

2. Feedback effect: recently generated mature αβ T cells inhibit the further development of precursors

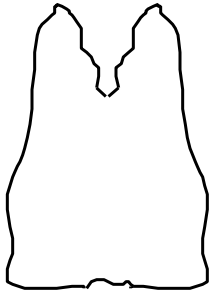
3. The thymus provides a compartmentalization function separating precursors from mature T cells

4. Many γδ T cells and some αβ T cells develop in extra-thymic sites. Intestinal "cryptopatches" are an important site for the development of intra-epithelial γδ and αβ T cells

Thymic Epithelium formed
from endoderm of third pharyngeal pouch
and ectoderm of third branchial cleft.

↓

whn is required for
thymic epithelial cell differentiation and
the ability of the thymus to attract lymphoid progenitors.



↓

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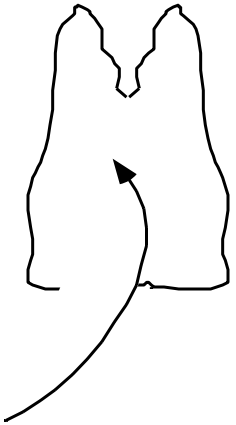


Migration of thymic progenitors starts soon after.
Bone-marrow also provides macrophages
and dendritic cells. Stromal development
completed by end of gestation.
Cell-cell and ECM-cell interactions,
IL-7, and SCF contribute to T cell
commitment and development.

↓

Proper formation of cortex requires
development of early T cells. A block at
the pro-Tp ($CD44^{+}$ $CD25^{-}$) stage
leads to cortical disruption.

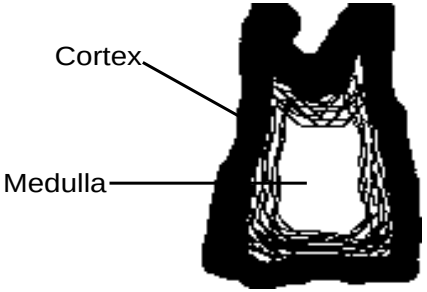
↓

Thymic progenitors and
Bone-marrow derived stromal
components

↓

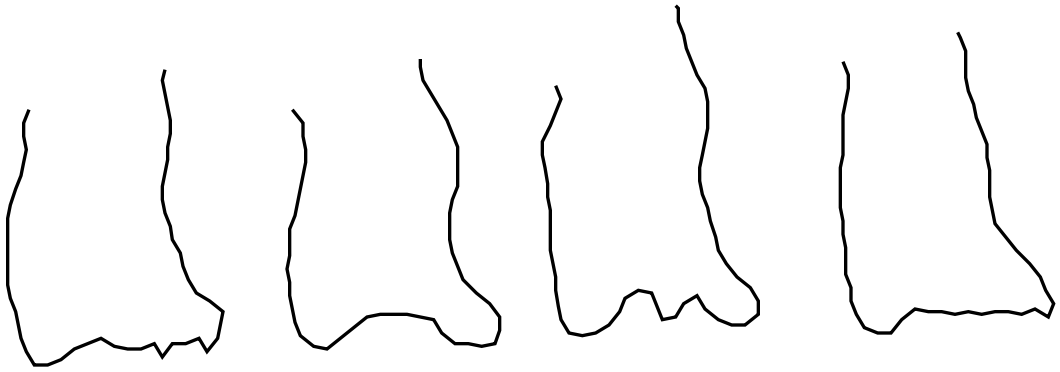
A block at the Early pre-T ($CD44^{-}CD25^{+}$) stage
leads to specific medullary defects
A block at the $CD4^{+}CD8^{+}$ DP stage also leads
to medullary defects

↓



Stroma necessary for positive
and negative selection

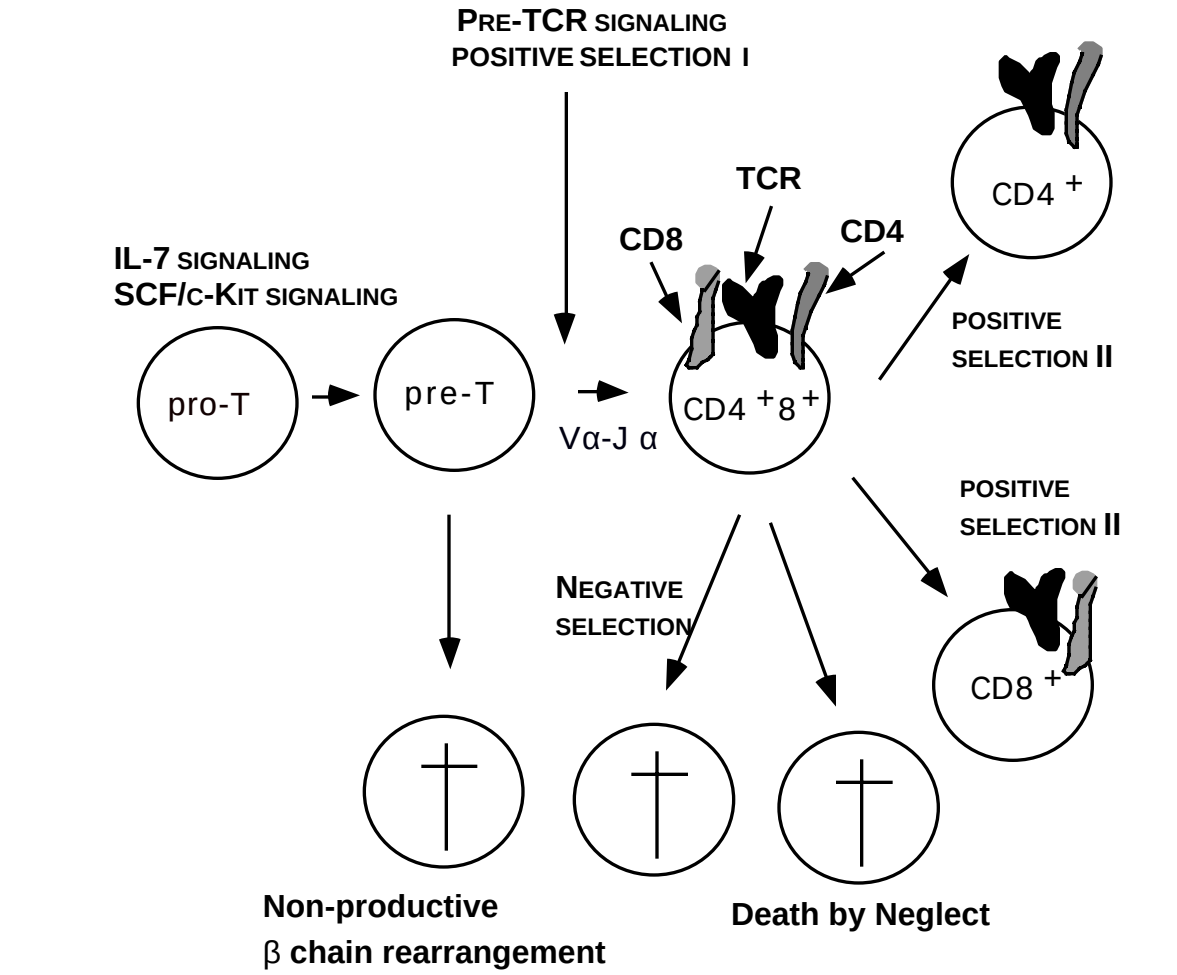
Developing T cells are required
for the architectural development
of the cortex and the medulla

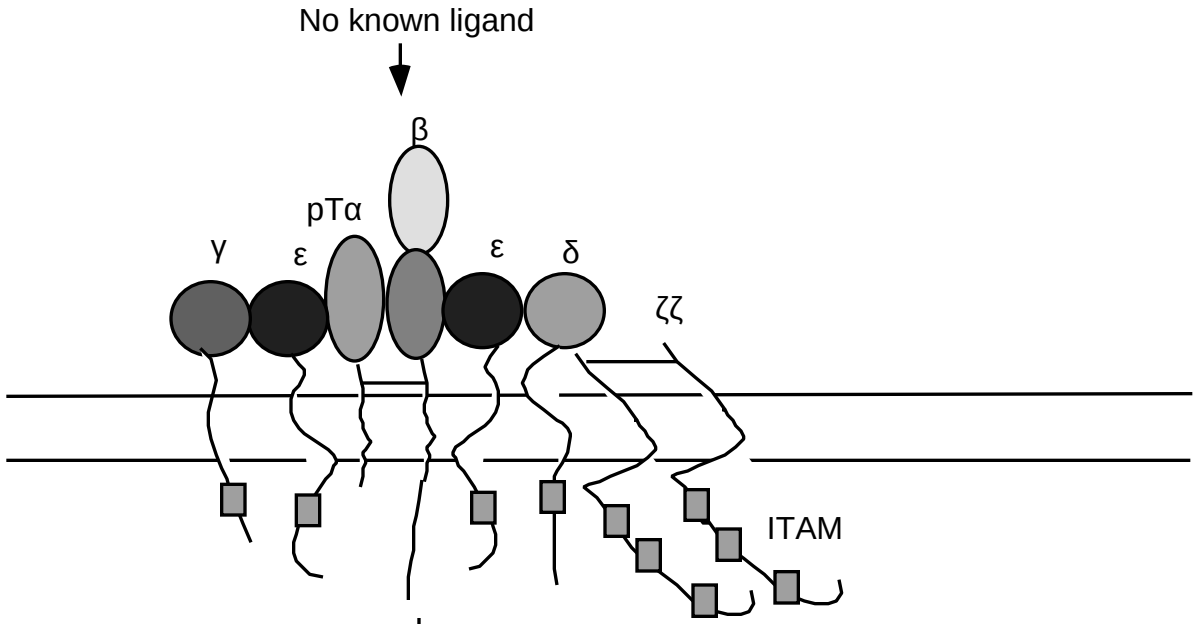


T CELL RECEPTOR BINDING SITES

Model 1: Initial repertoire like Ig
Thymic education selects a small fraction of cells

Model 2: Initial repertoire already has structural bias for MHC


PRE-TCR SIGNALING
POSITIVE SELECTION I
IL-7 SIGNALING
SCF/C-KIT SIGNALING
pro-T
pre-T
Vα-J α
CD4 +8 +
TCR
CD8
CD4
CD4 +
POSITIVE
SELECTION II
POSITIVE
SELECTION II
NEGATIVE
SELECTION
CD8 +
Non-productive
β chain rearrangement
Death by Neglect
Double Negative
Double positive
Single positive
REARRANGEMENT
ELIMINATION
RESPONDERS

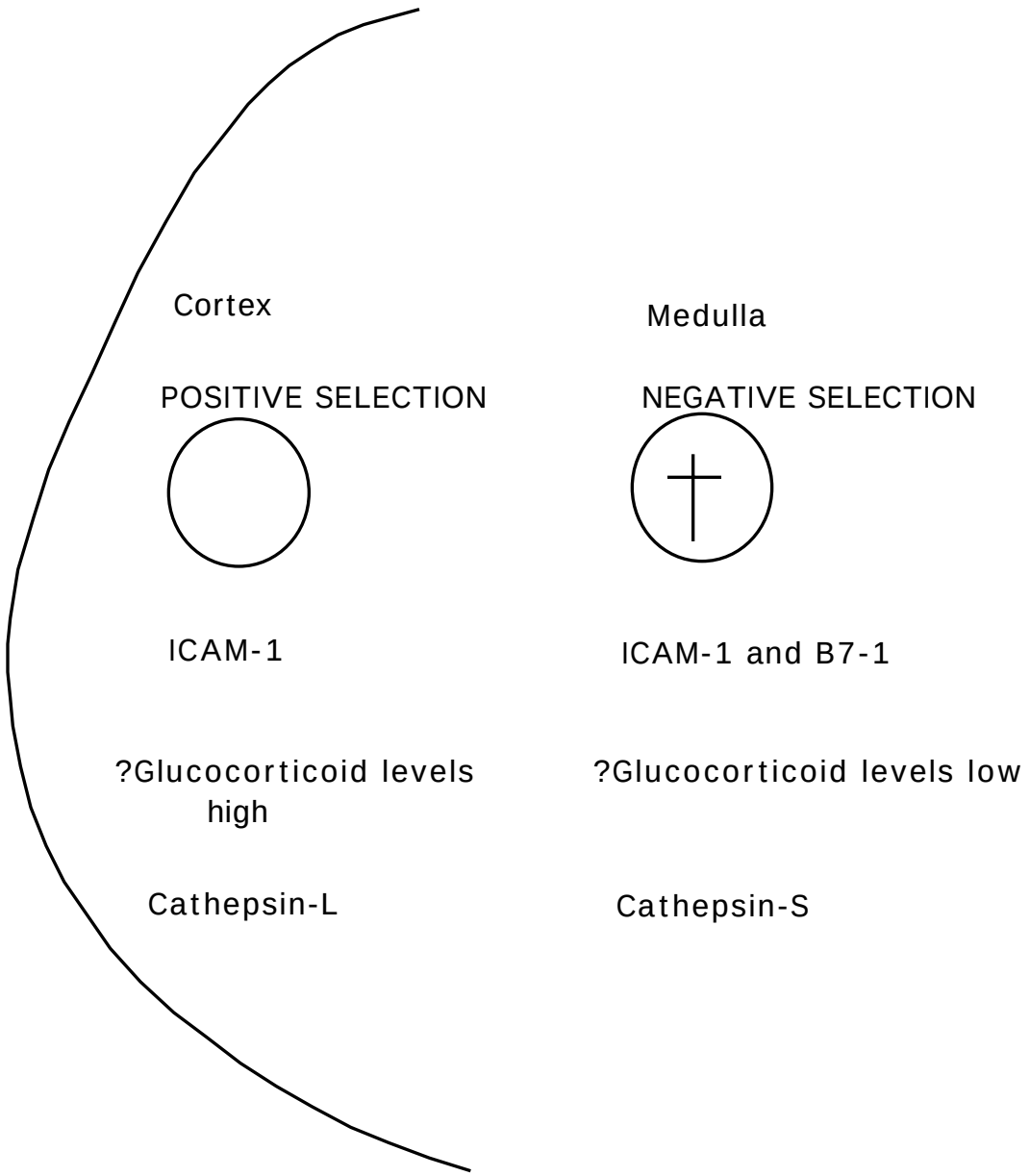


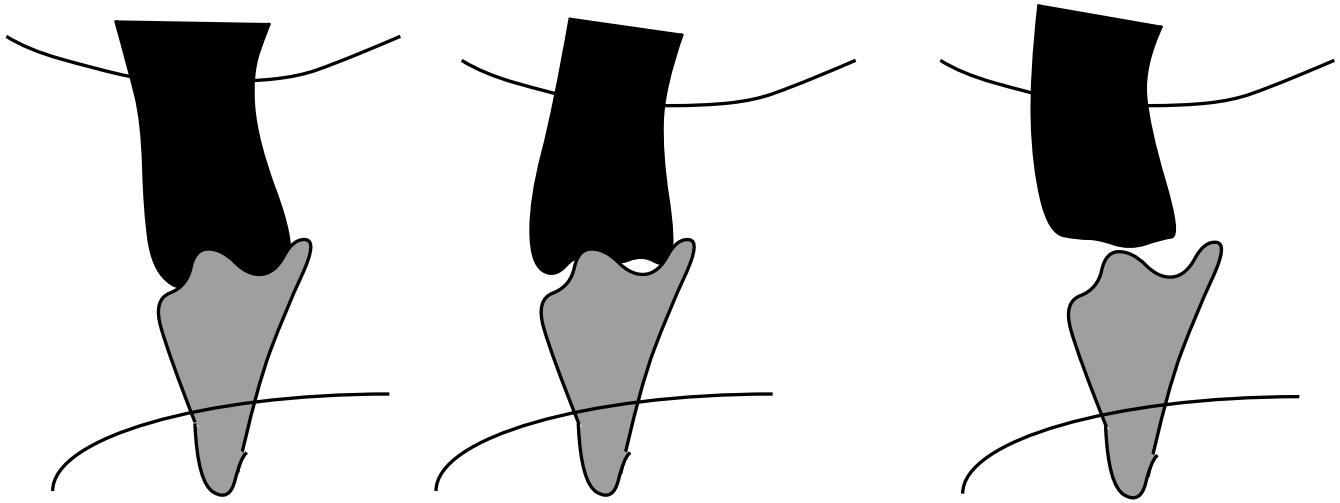
CD3δ not essential for pre-TCR signaling

Src-family kinases (Lck and Fyn)

Syk family kinases (Syk and ZAP70)

1) Survival and proliferation signals
2) Allelic exclusion at TCR β locus
3) Induction of TCR α rearrangement
d) Shut-off of pTα expression


Cortex
Medulla
POSITIVE SELECTION
NEGATIVE SELECTION
ICAM-1
ICAM-1 and B7-1
?Glucocorticoid levels high
?Glucocorticoid levels low
Cathepsin-L
Cathepsin-S



High affinity TCR-MHC interactions

"negative selection"

Low affinity TCR-MHC interactions

"positive selection"

No affinity of TCR for MHC

"death by neglect"

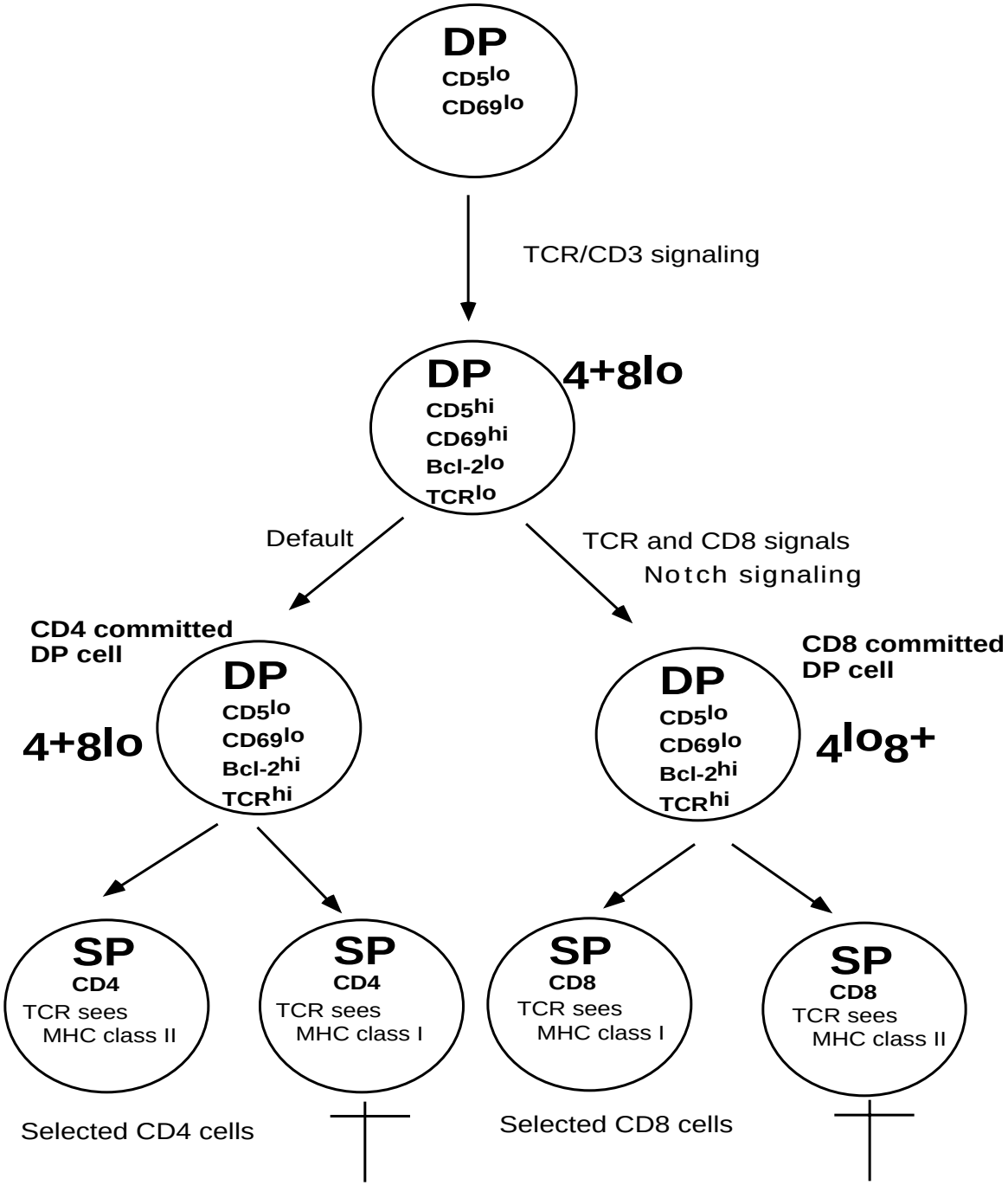
Lineage Commitment - CD4+ versus CD8+

Stochastic versus instructive

TCR Signal strength

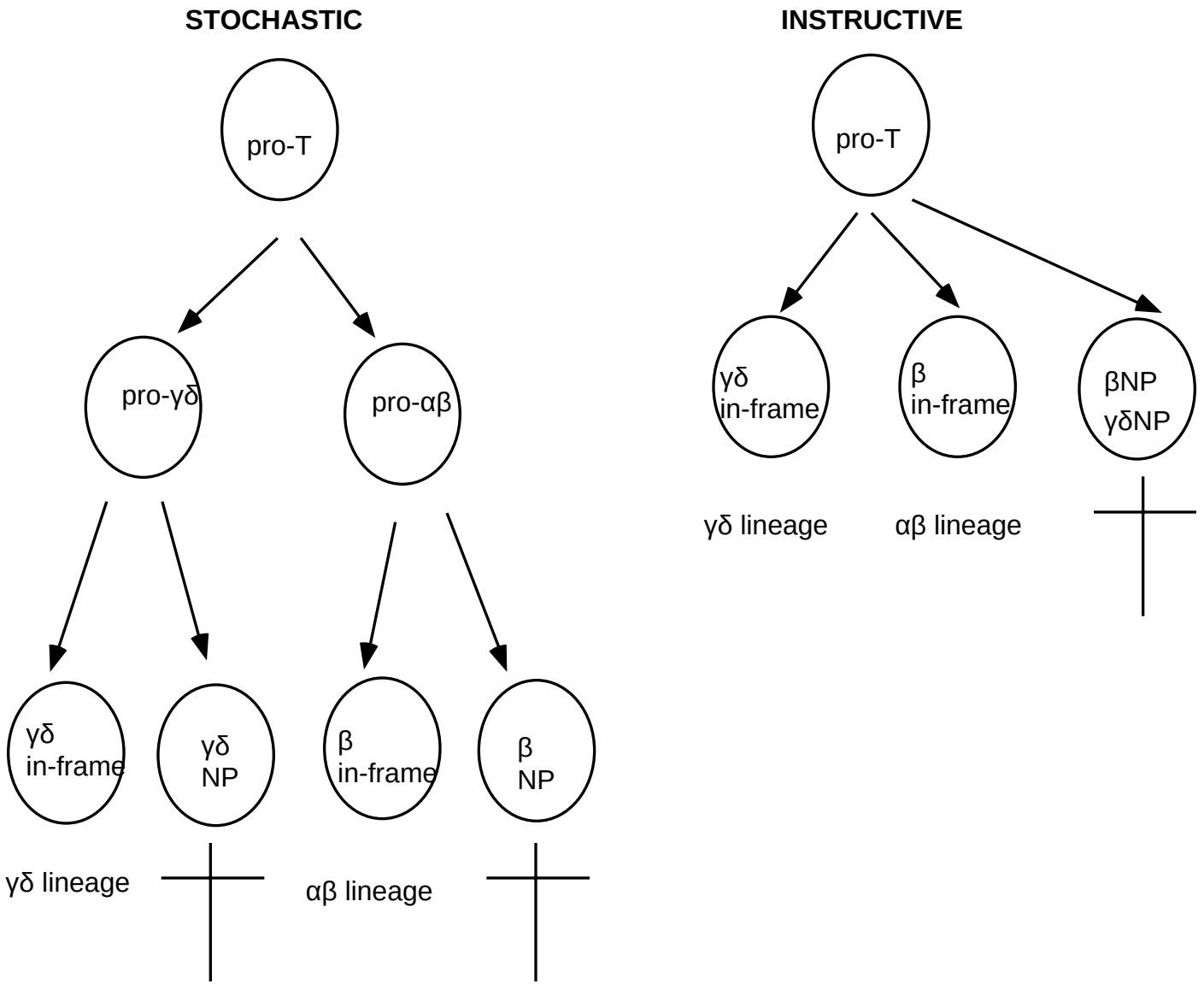
Duration of signaling

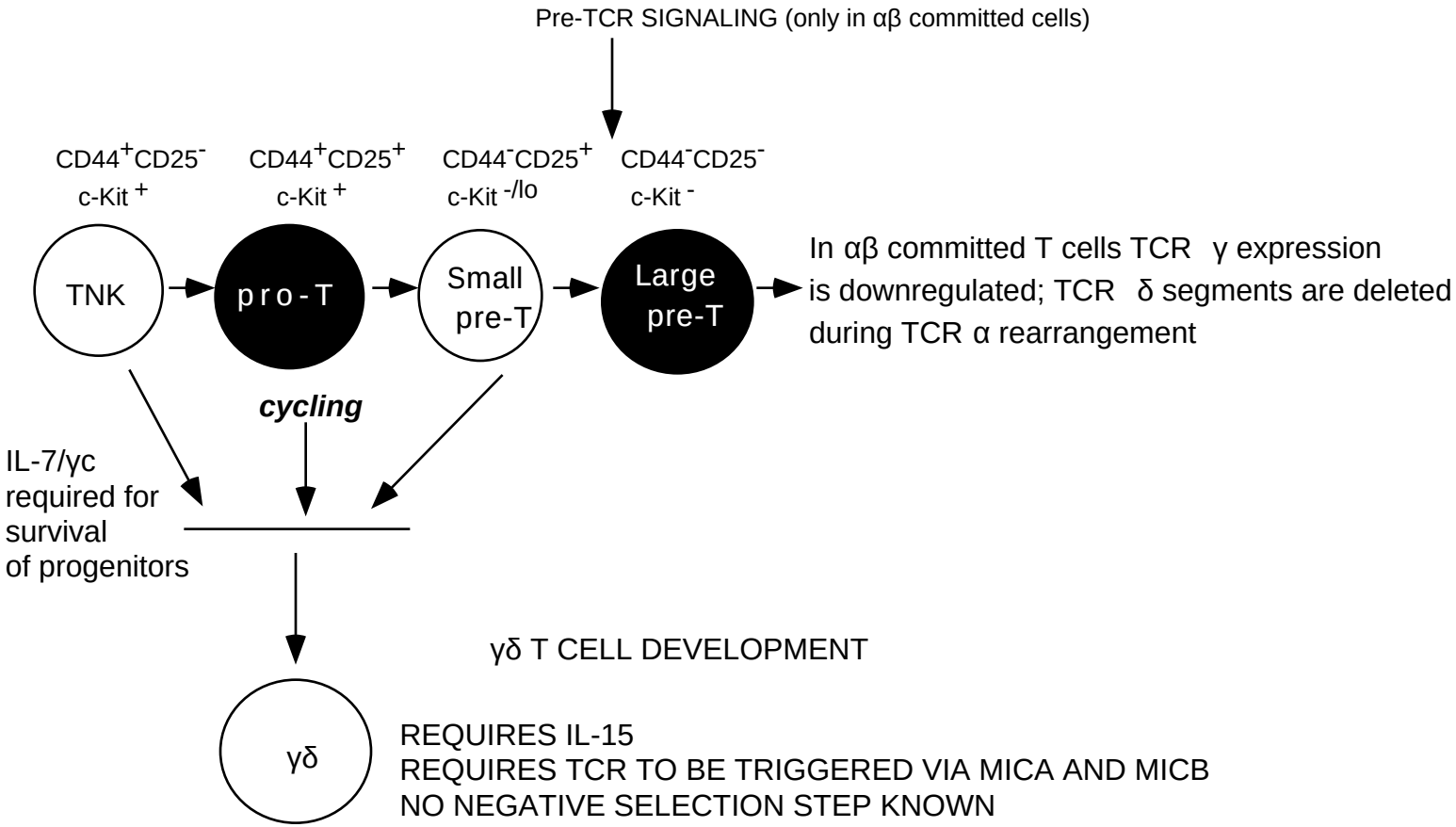
Notch attenuates signal strength?

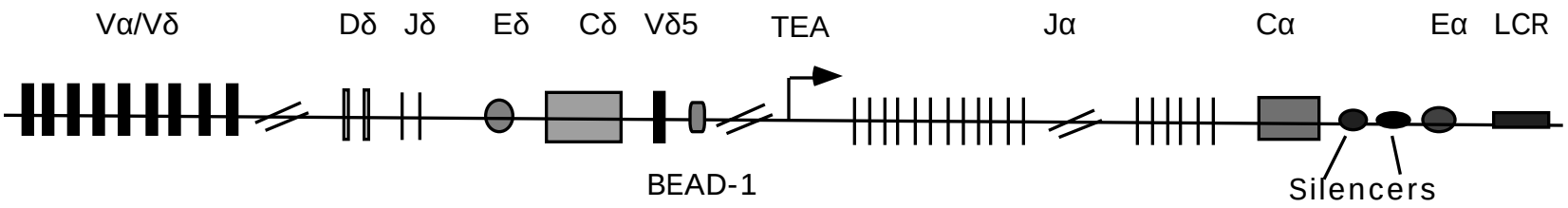

DP
CD5lo
CD69lo
TCR/CD3 signaling
DP
CD5hi
CD69hi
Bcl-2lo
TCRlo
4+8lo
Default
TCR and CD8 signals
Notch signaling
CD4 committed
DP cell
DP
CD5lo
CD69lo
Bcl-2hi
TCRhi
4+8lo
CD8 committed
DP cell
DP
CD5lo
CD69lo
Bcl-2hi
TCRhi
4lo8+
SP
CD4
TCR sees
MHC class II
SP
CD4
TCR sees
MHC class I
SP
CD8
TCR sees
MHC class I
SP
CD8
TCR sees
MHC class II
Selected CD4 cells
Selected CD8 cells

γδ T cells

1. Not educated in the thymus
2. Often develop extrathymically
3. Most IELs (intraepithelial lymphocytes) are γδ T cells
4. Either use CD8 or no coreceptor
5. Innate immunity?


STOCHASTIC
pro-T
pro-γδ
pro-αβ
γδ
in-frame
γδ
NP
β
in-frame
β
NP
γδ lineage
αβ lineage
INSTRUCTIVE
pro-T
γδ
in-frame
β
in-frame
βNP
γδNP
γδ lineage
αβ lineage


Pre-TCR SIGNALING (only in αβ committed cells)
CD44+CD25-
c-Kit +
CD44+CD25+
c-Kit +
CD44-CD25+
c-Kit -/lo
CD44-CD25-
c-Kit -
TNK
pro-T
Small pre-T
Large pre-T
In αβ committed T cells TCR γ expression is downregulated; TCR δ segments are deleted during TCR α rearrangement
cycling
IL-7/γc required for survival of progenitors
γδ T CELL DEVELOPMENT
γδ
REQUIRES IL-15
REQUIRES TCR TO BE TRIGGERED VIA MICA AND MICB
NO NEGATIVE SELECTION STEP KNOWN


Vα/Vδ
Dδ
Jδ
Eδ
Cδ
Vδ5
TEA
Jα
Cα
Eα
LCR
BEAD-1
Silencers