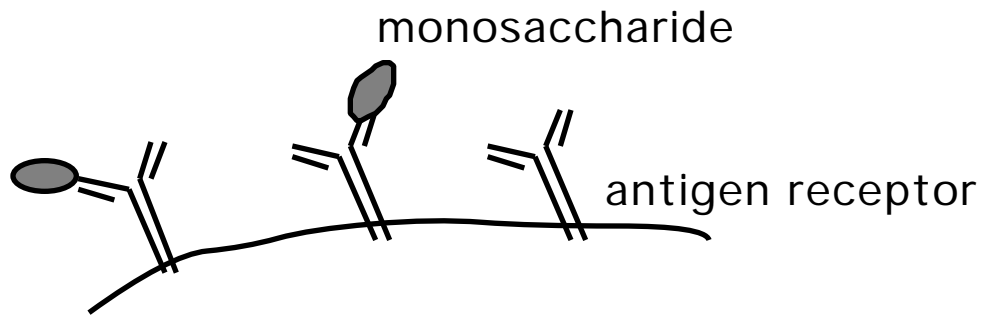
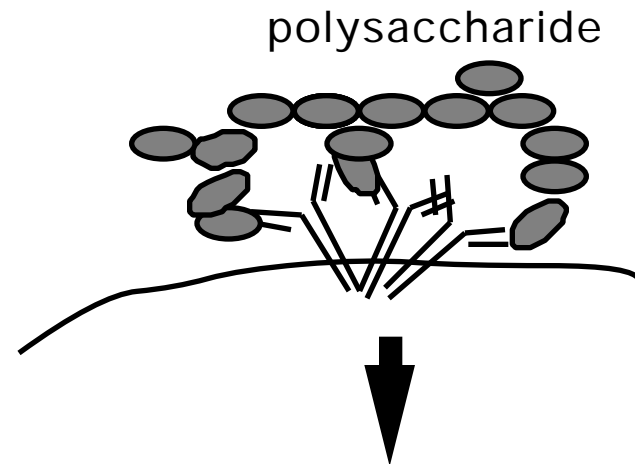


Hapten

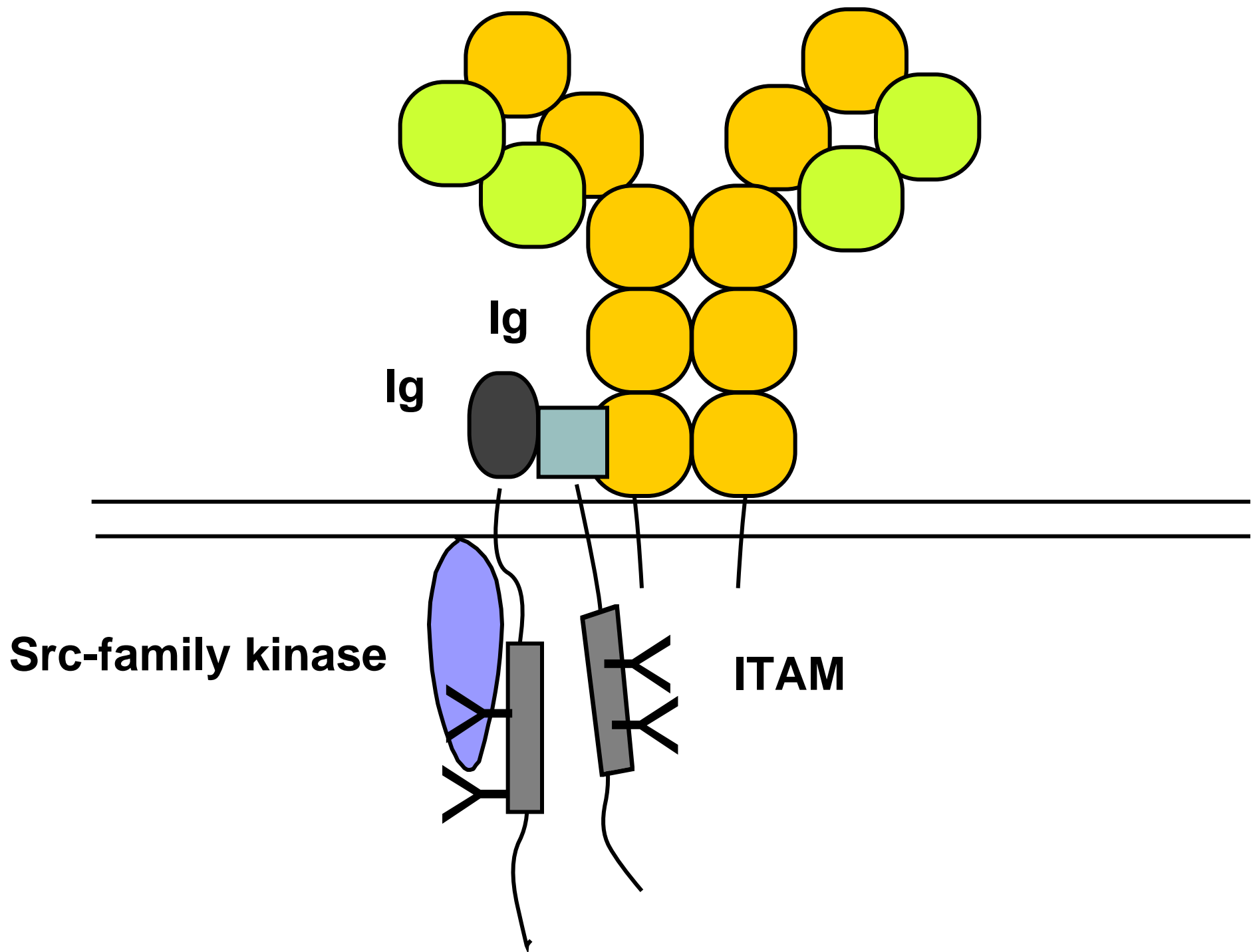


NO SIGNAL

Polyvalent antigen



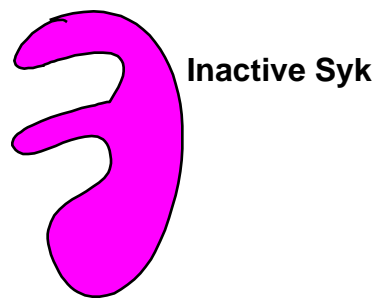
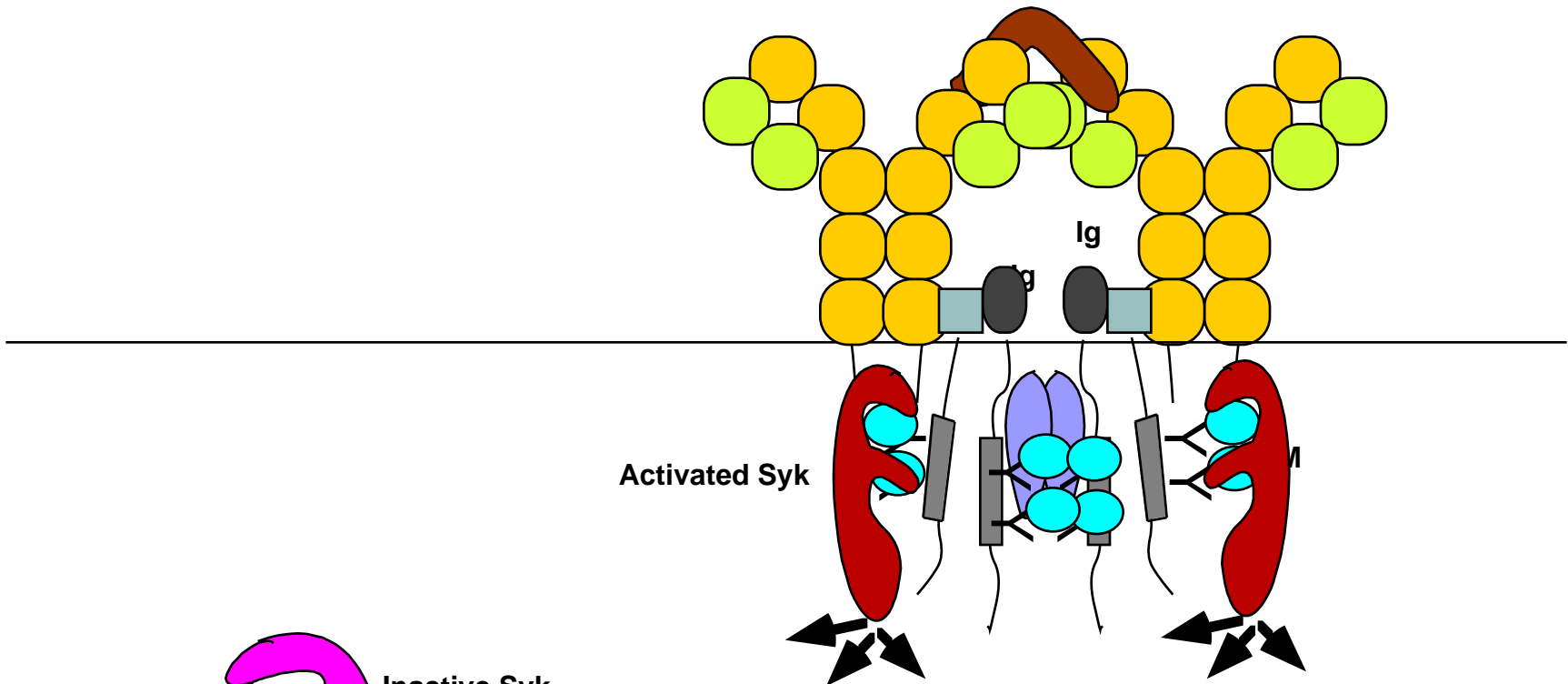
SIGNAL TRANSDUCTION



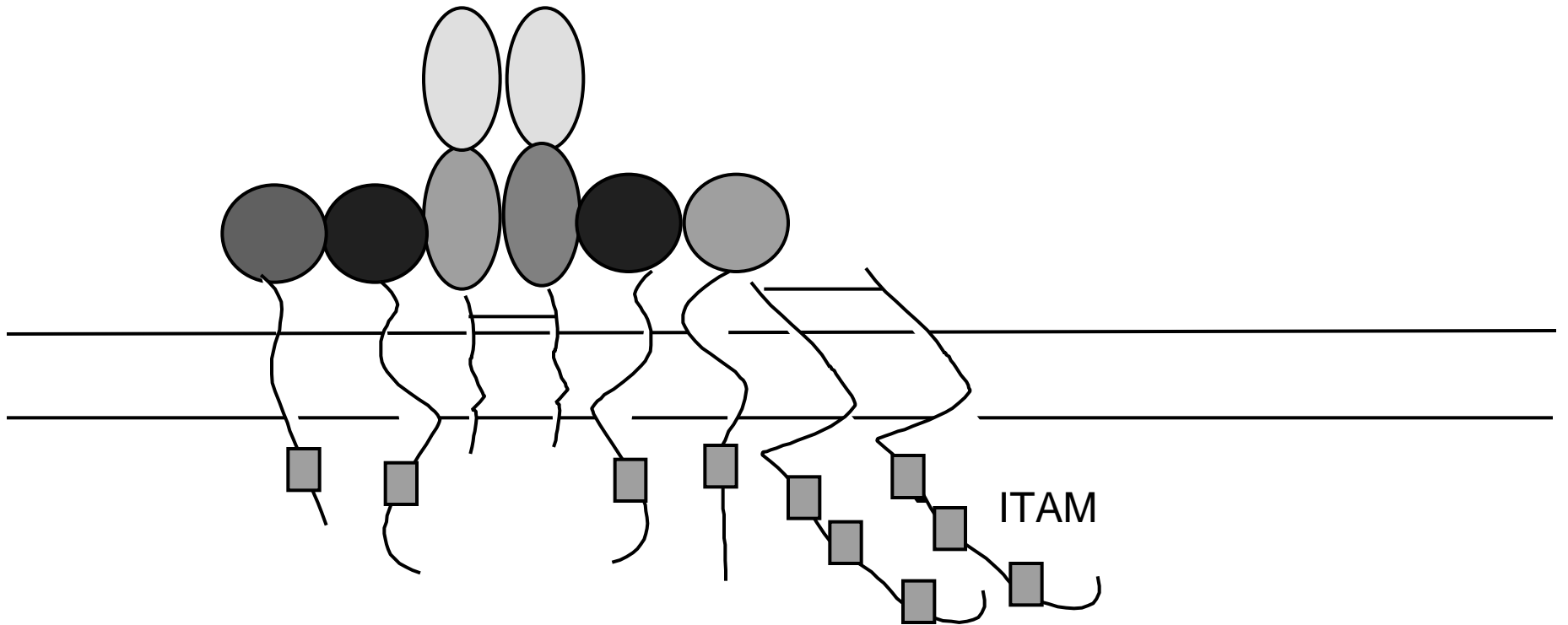
ITAM

YxxL/IxxxxxxYxxL/I

Immune-receptor Tyrosine based
Activation Motif



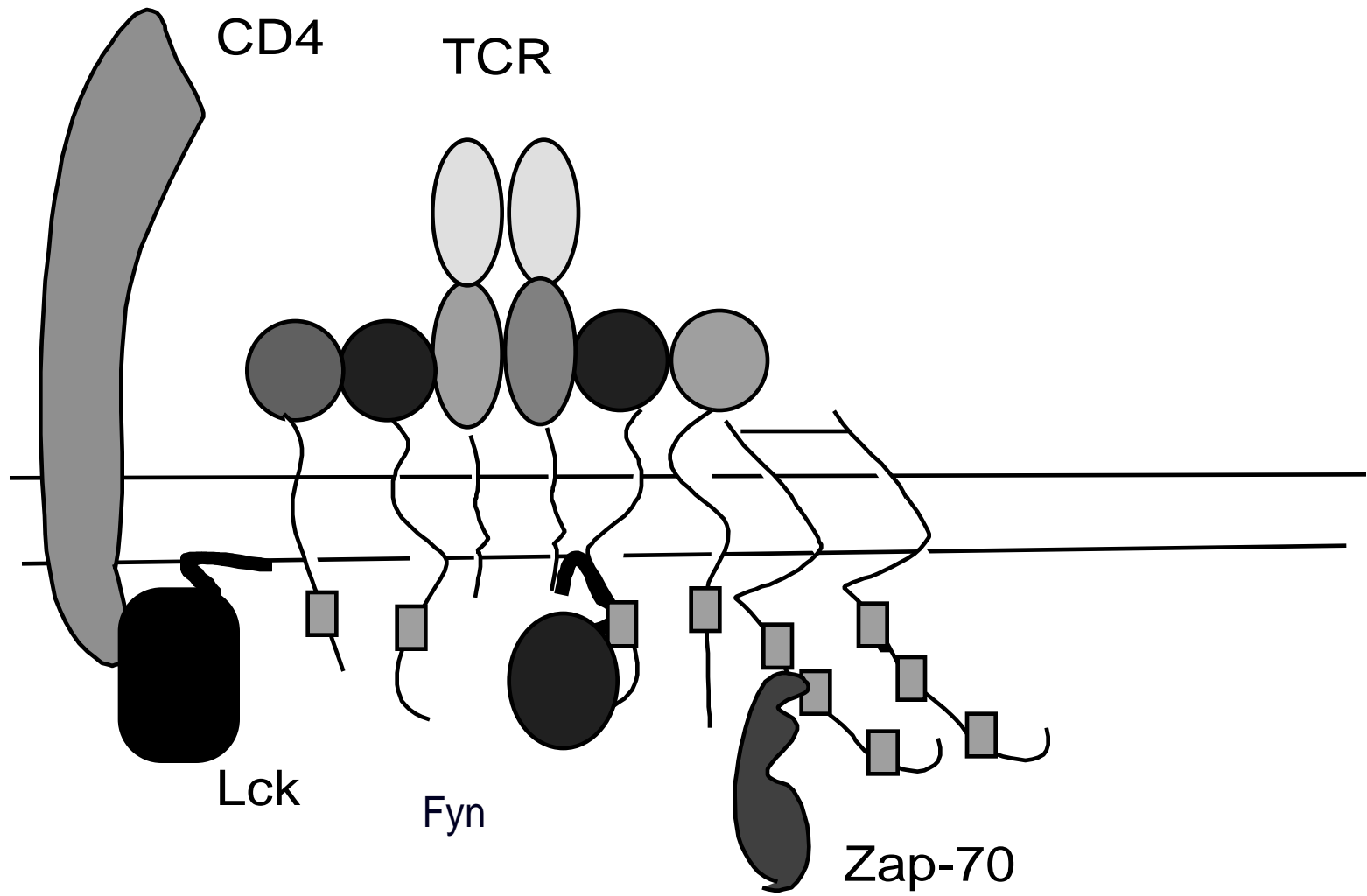
The T cell receptor



CO-RECEPTORS

CELL SURFACE PROTEINS THAT
BIND TO THE SAME ANTIGEN
AS THE ANTIGEN RECEPTOR

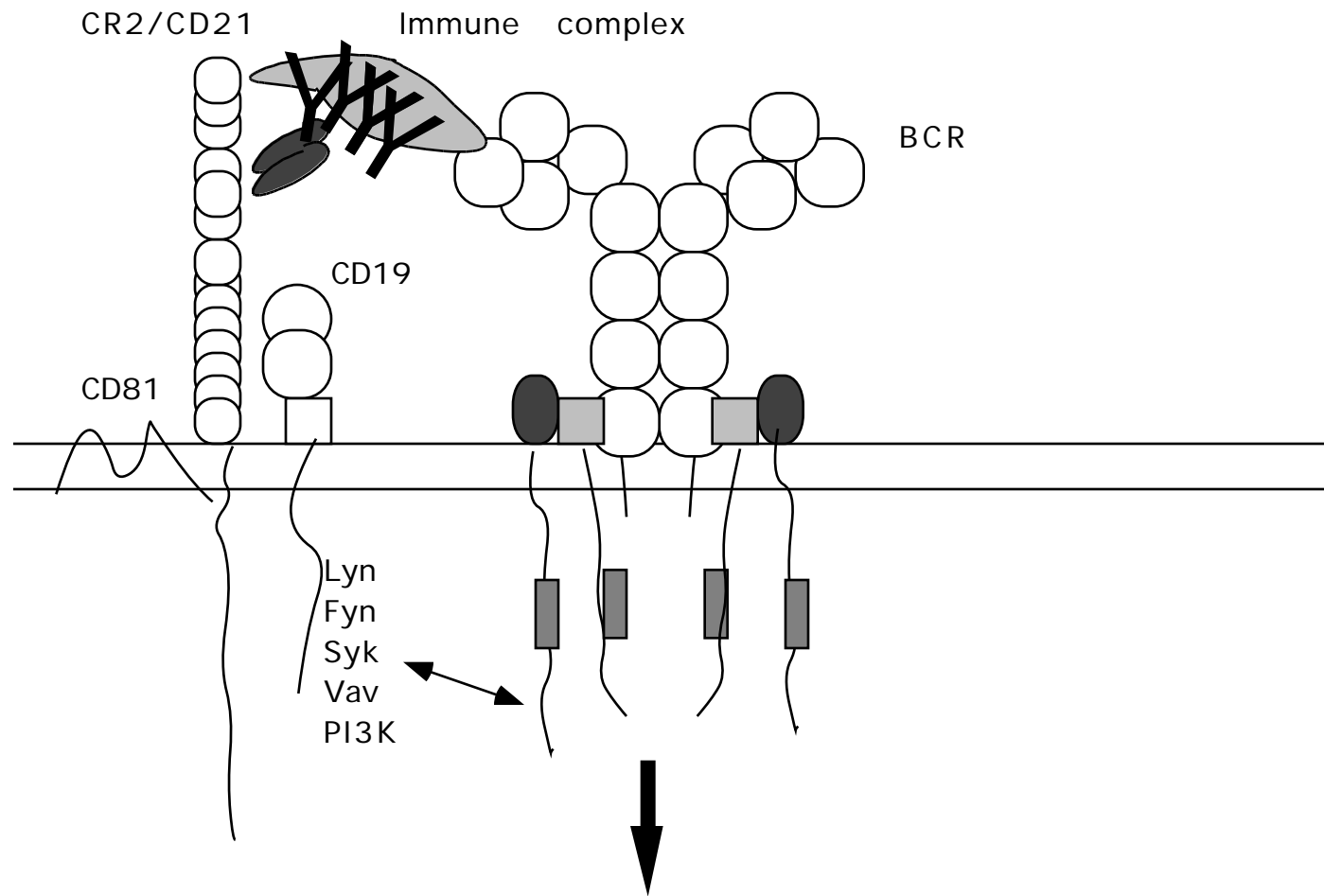
DISTINGUISHABLE FROM
COSTIMULATORS



CO-RECEPTORS

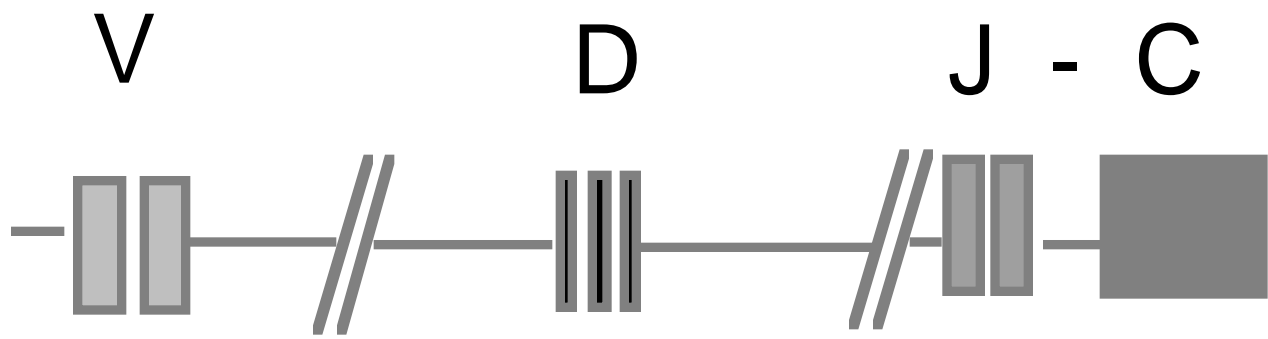
- CD4 ON HELPER T CELLS
- CD8 ON CYTOTOXIC T CELLS
- CD21/CR2 ON B CELLS

CD21/CR2 is a co-receptor and a positive regulator of BCR signaling

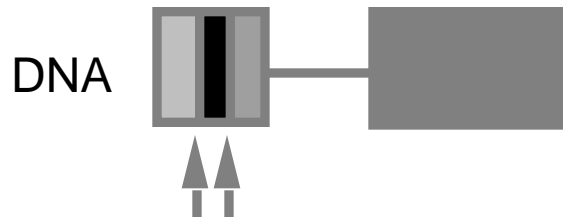


Generation of Diversity

- 1. V(D)J Recombination
 - Combinatorial Diversity
 - Junctional Diversity
 - N Regions
 - P nucleotides
- 2. Somatic Mutation



V D J



junctional diversity, bases added and removed



mRNA

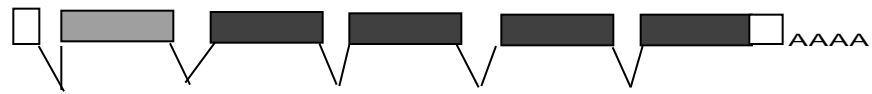
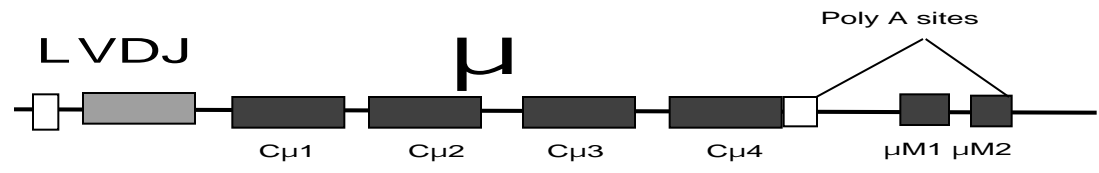
Rearrangement is temporally ordered

- B LINEAGE

- IgH D to J
- Then V to DJ
- Then Ig Kappa V to J

- T LINEAGE

- TCR D beta to J beta
- Then V beta to DJ
- Then TCR V alpha to J alpha



Choice of first polyadenylation site



Choice of second polyadenylation site



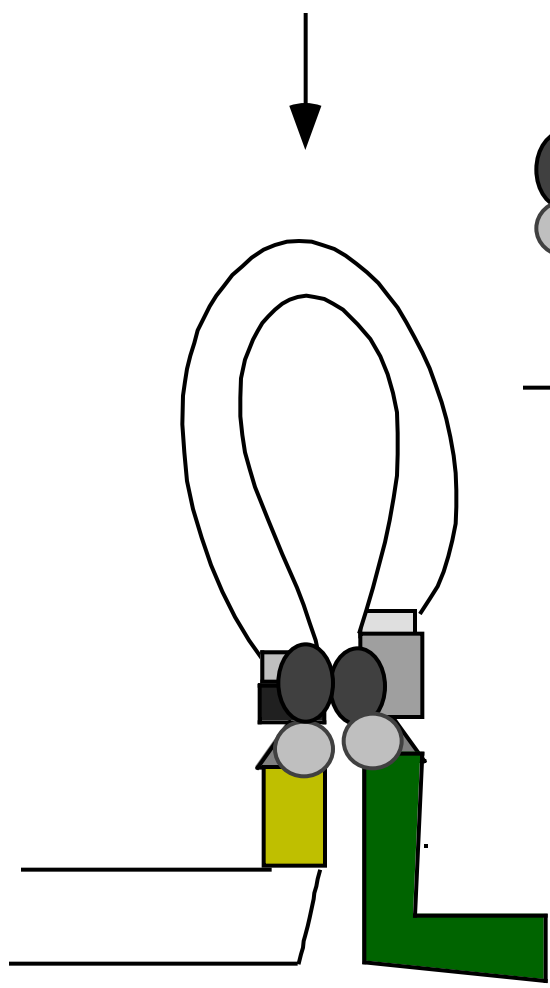
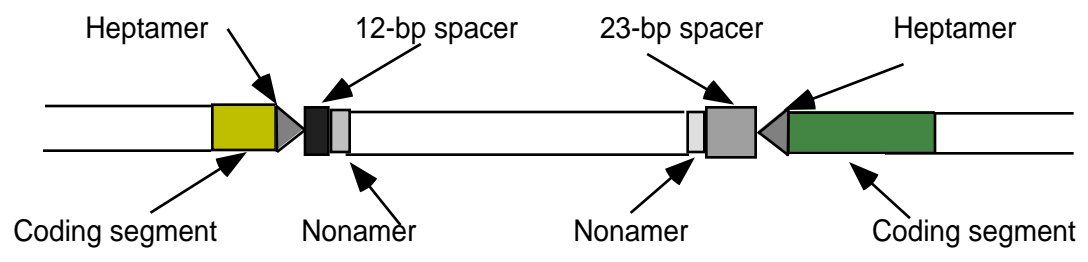
μs mRNA



μm mRNA

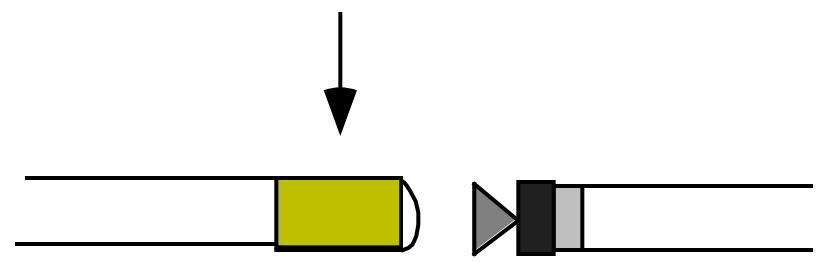
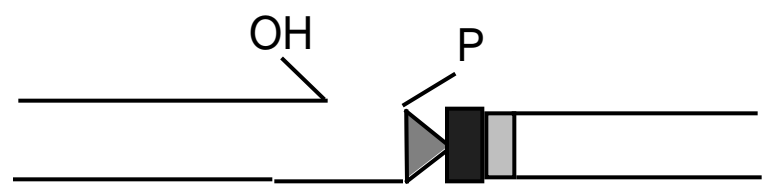
V(D)J Recombination

- Lymphoid specific
- Locus-specific, cell-type specific, stage specific
- Accessibility model



RAG-2
RAG-1

NICK PRECEDES CUT



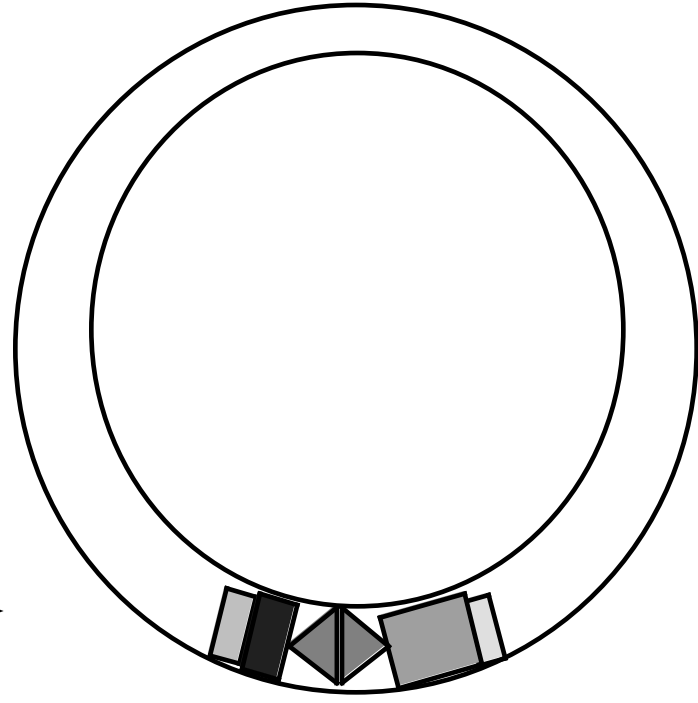
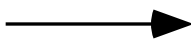
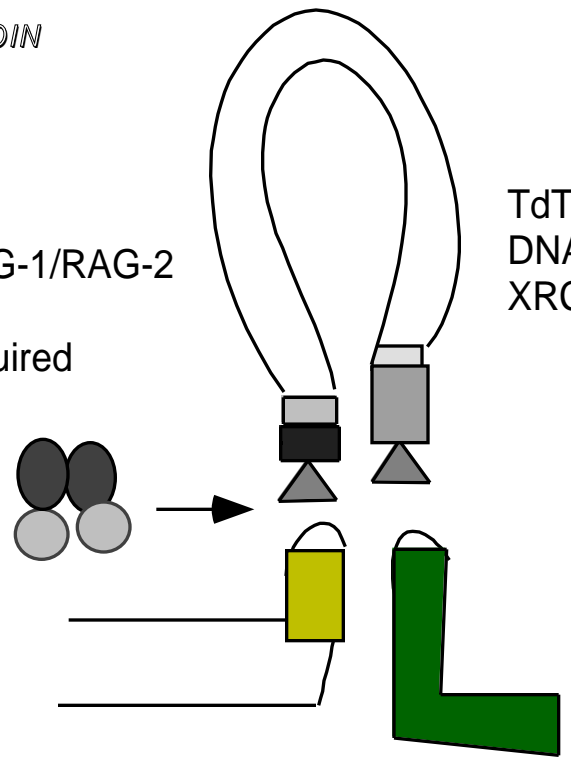
CLEAVE AND MAKE HAIRPINS

SIGNAL JOINT

TRIM
ADD N REGIONS
JOIN

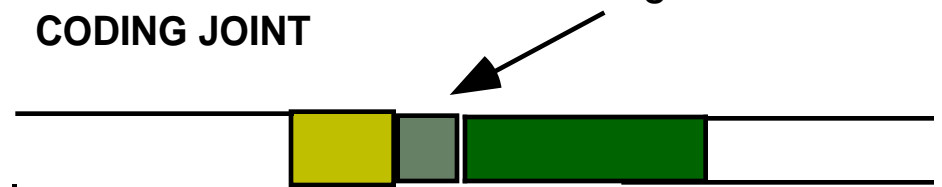
RAG-1/RAG-2
still
required

TdT
DNA-PK/Ku70/Ku80
XRCC4/DNA ligase



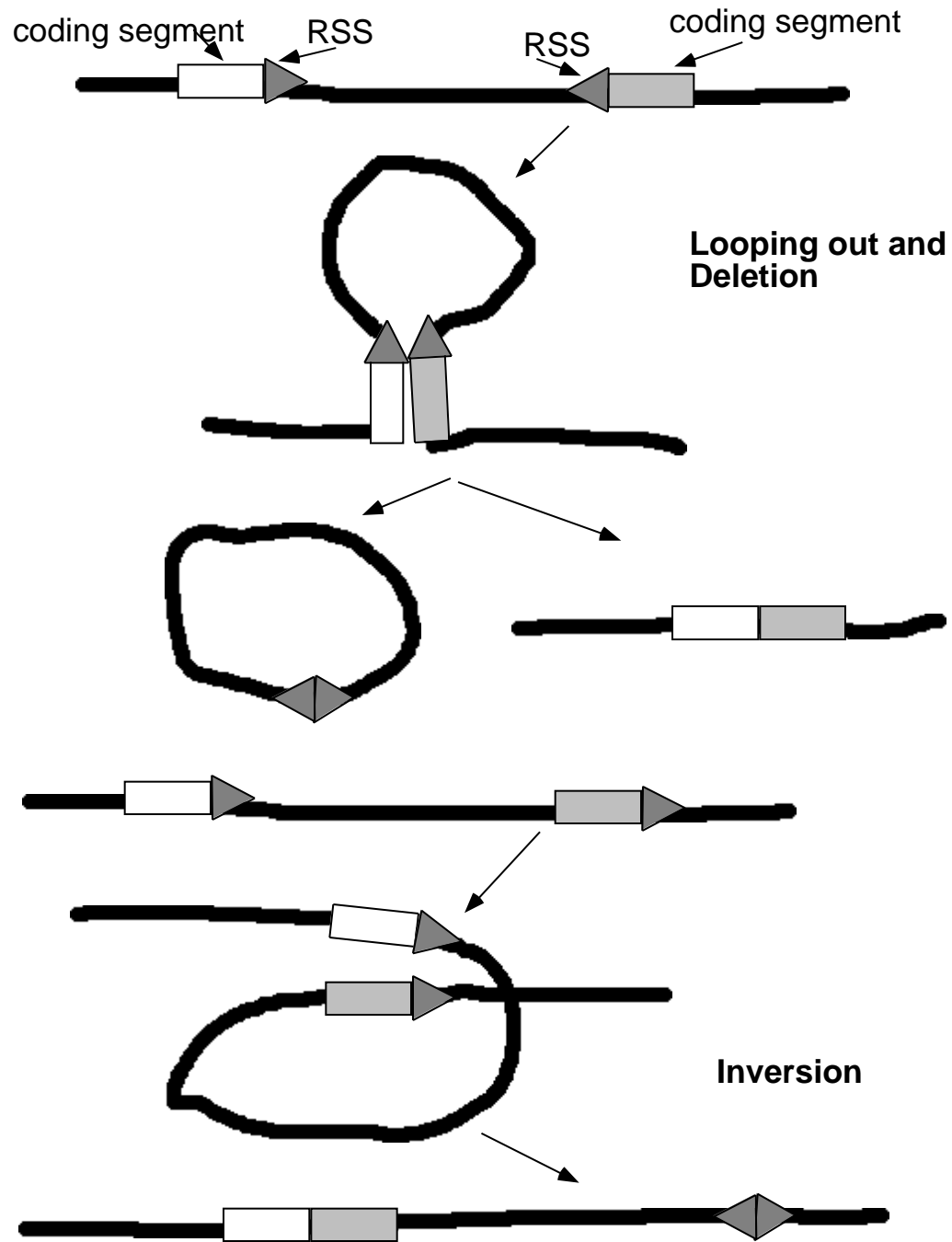
N-region

CODING JOINT

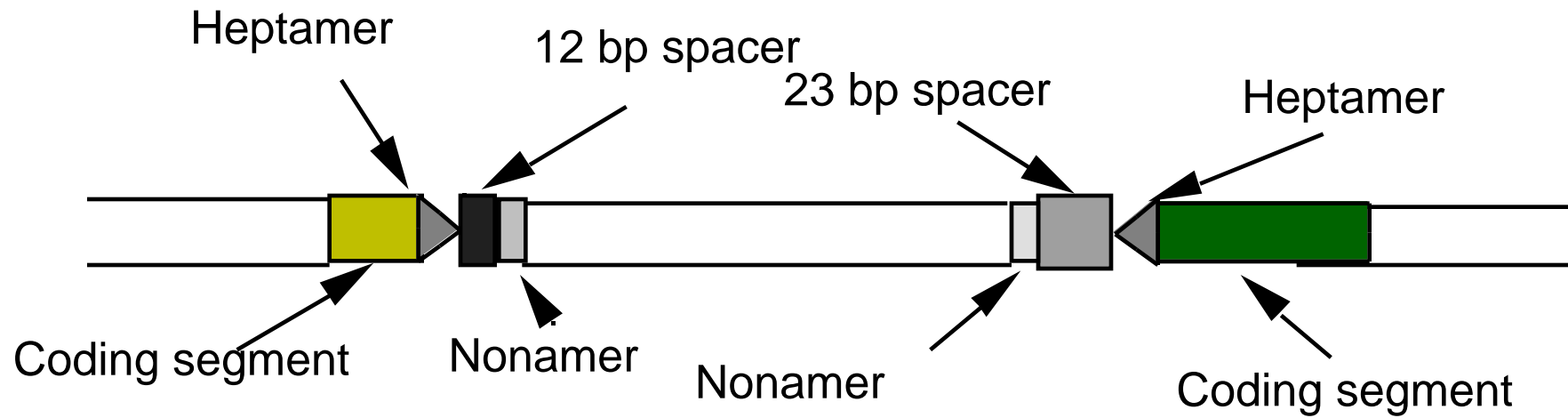


RAG time

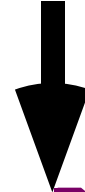
- RAG-1 dimers associate with RAG-2 dimers
- RAG-1 dimers bind to nonamers, cleave DNA
- RAG-2 has a beta-propeller like structure - probably brings in other proteins such as accessibility factors
- Rag genes evolved from a transposable element?



The 12/23 Rule



Cleave at heptamer junction

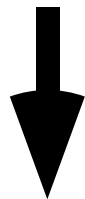


ATTCTTTGAGATAGCTCGA
TAAGAACTCTATCGAGCT



heptamer

ATTCTTTGAGATAGCTCGA
TAAGAACTCTATCGAGCT



Open up hairpin

ATTCTTTGAGATAGCTCGATCG
TAAGAACTCTATCGAGCTAGC

Add P nucleotides

HAIRPINS

Resolved by Artemis, an enzyme
which works in conjunction with
DNA-PKcs

Severe Combined Immunodeficiency

Rag-1 and Rag-2 deficiencies: SCID

No VDJ recombination

Artemis deficiency: SCID

Defective coding joints

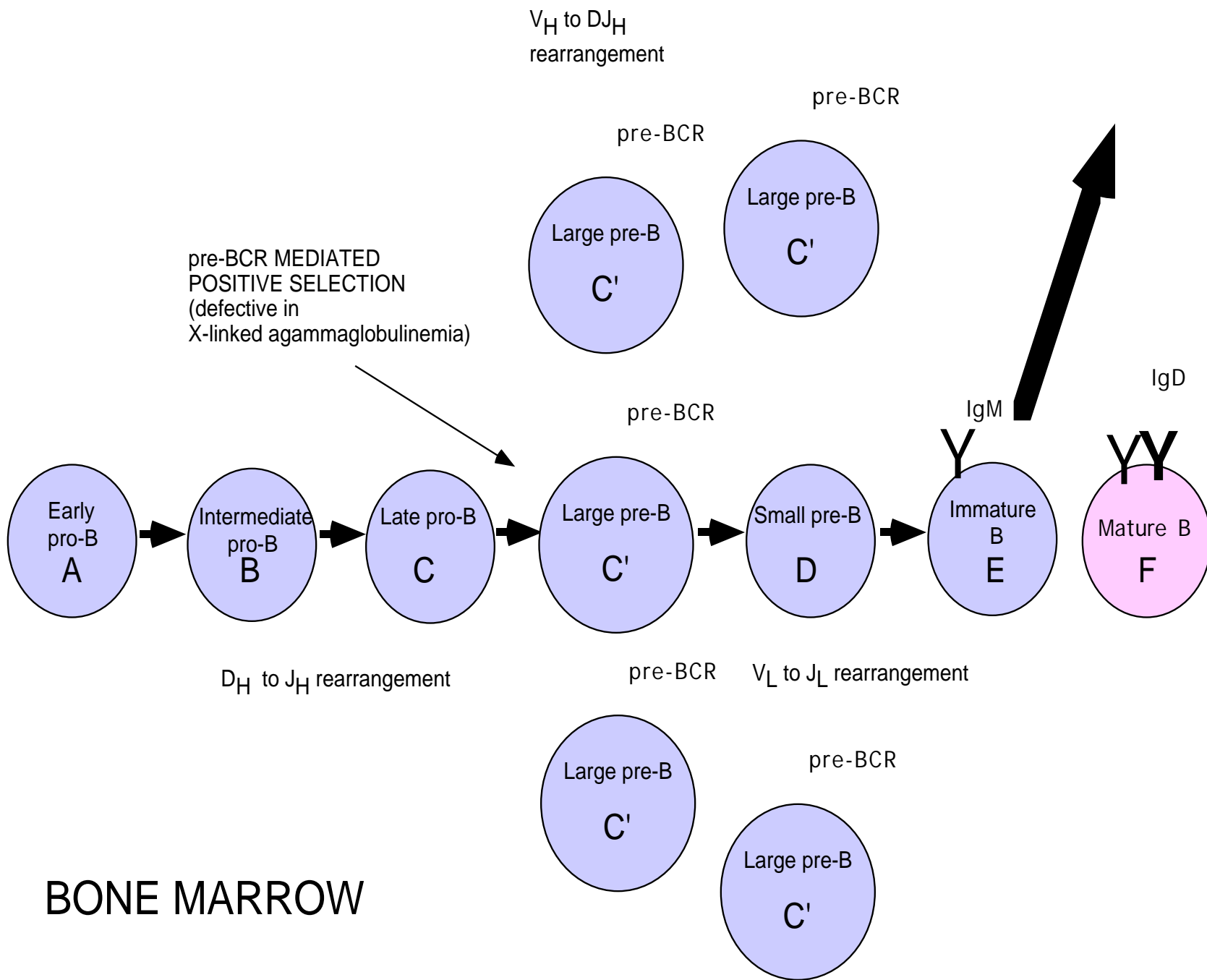
Many other causes of SCID

V(D)J recombination and human lymphomas

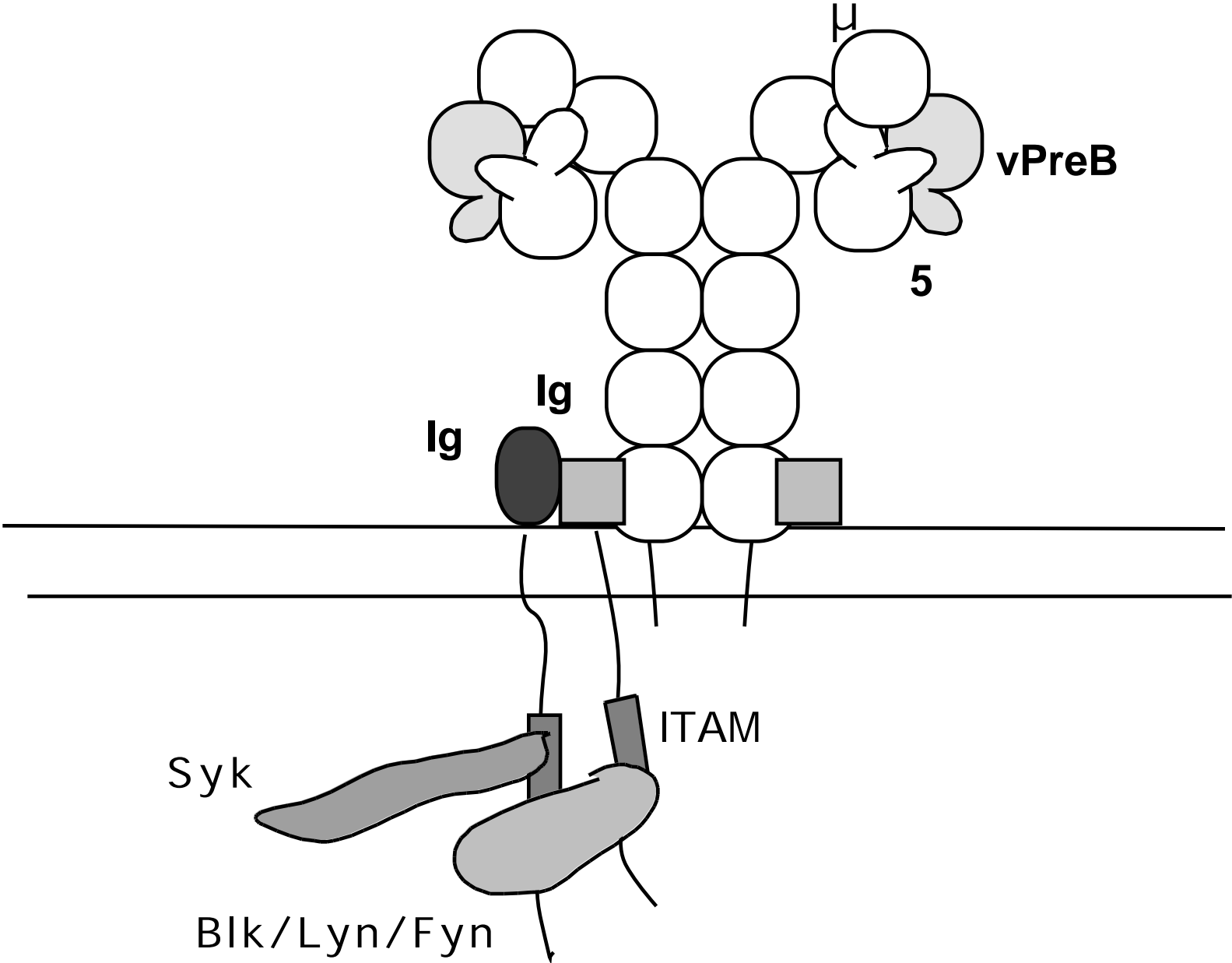
- Many human lymphomas involve chromosomal translocations
- In some lymphomas (e.g. follicular lymphomas, lymphomas associated with Ataxia Telangiectasia, etc) the machinery involved in V(D)J recombination drives the translocation process

Regulation of V(D)J recombination

1. Allelic exclusion - role of pre-antigen receptors
2. Receptor editing

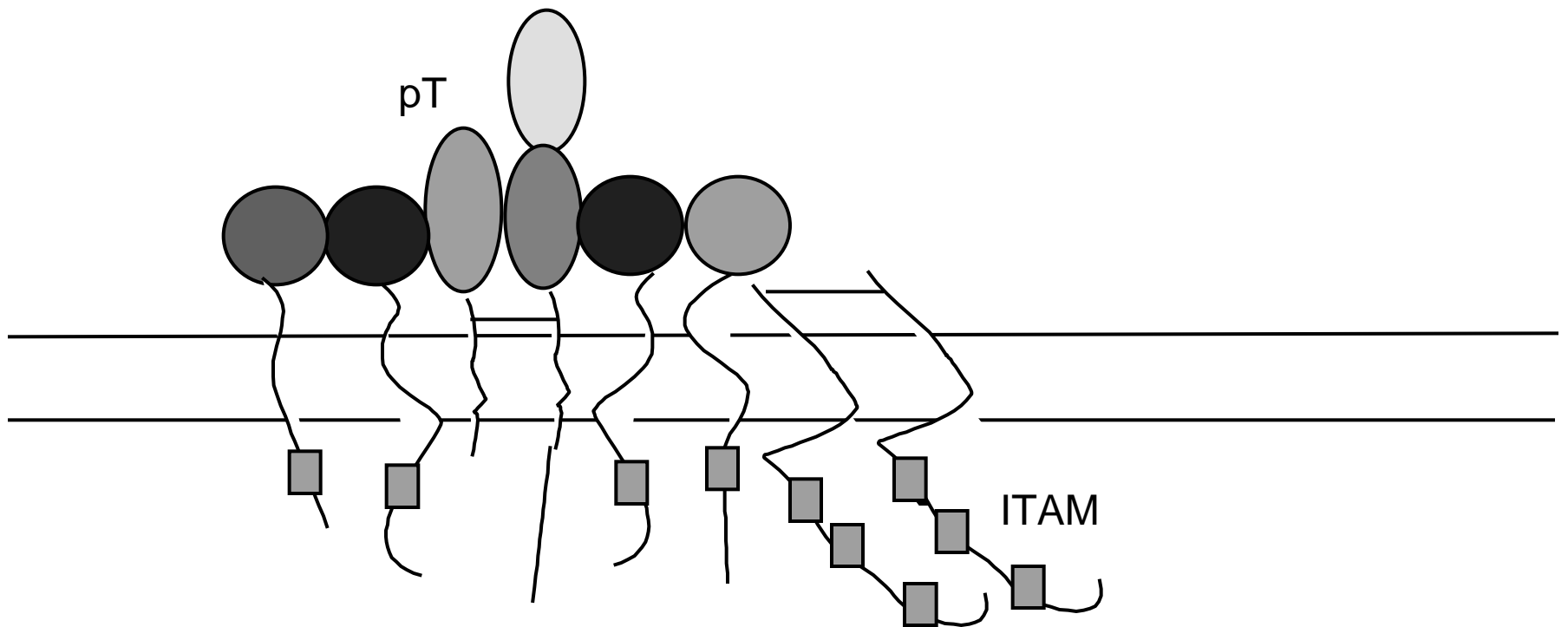


Pre-B receptor



Pre-TCR

No known ligand

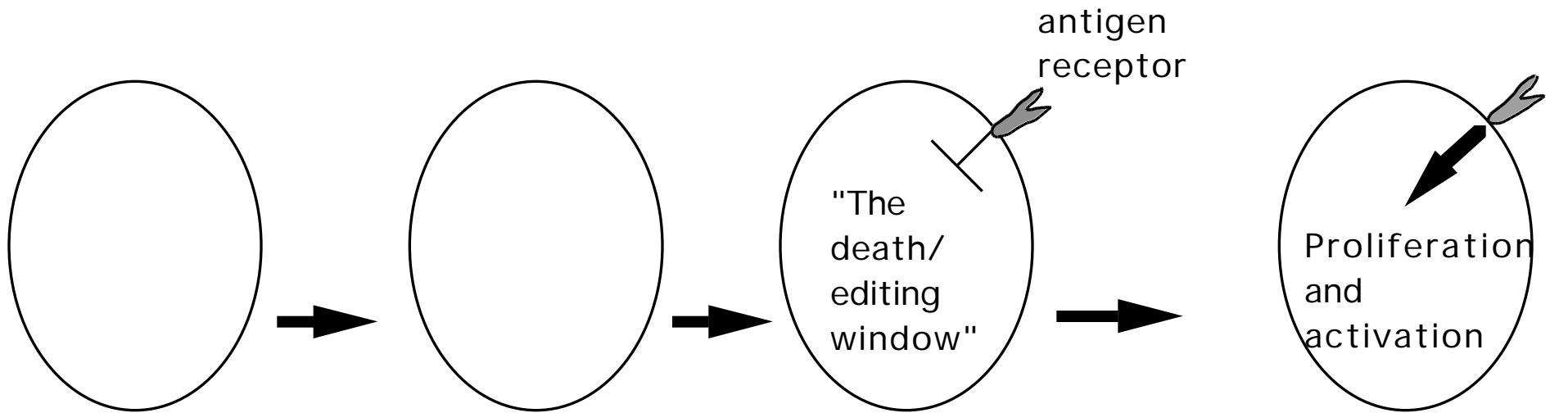


Pre-antigen receptors

- Select cells that have made in-frame rearrangements
- Signals for survival, proliferation and allelic exclusion (rearrangement at second allele is shut off)

Central lymphoid organs

Periphery



Rearrangement of Ig heavy chain or TCR chain genes

Selection by pre-antigen receptor of cells with in-frame Ig heavy chain or TCR chain rearrangements

Elimination or editing of self reactive cells

Final repertoire in responders

For more information and examples, see Immunobiology, by Janeway,C., Travers, P., Walport, M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular and Molecular Immunology by Abbas, A., Pober, J., and Lichtman, A., W B Saunders; 4th edition.