



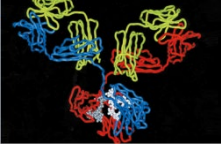
FOCIS BASIC, 2023

Shiv Pillai MD, PhD

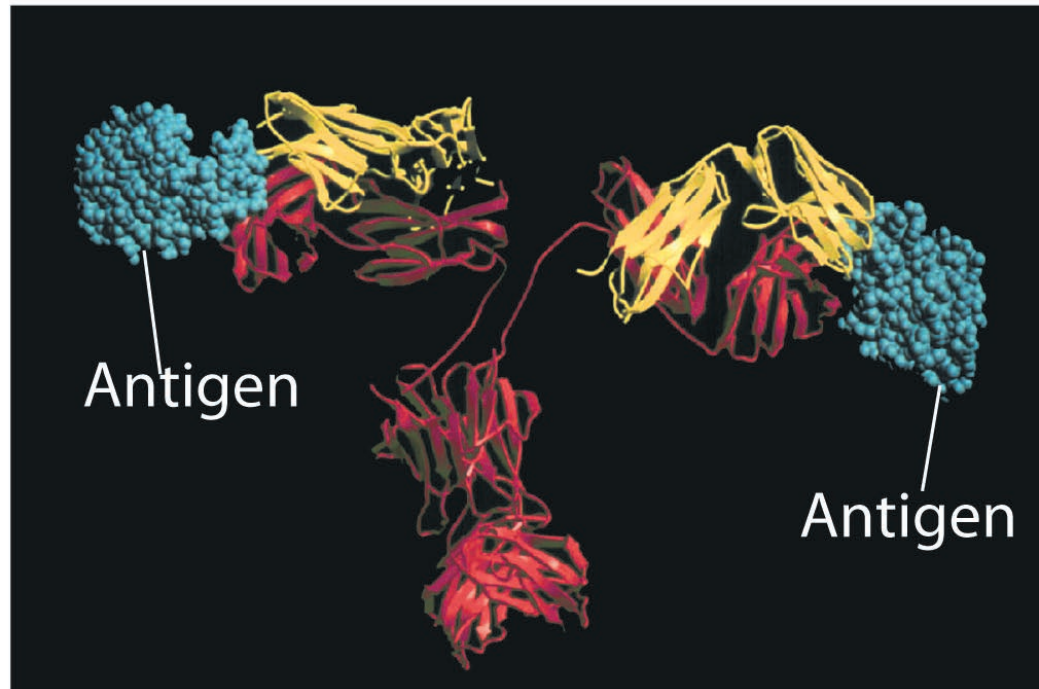
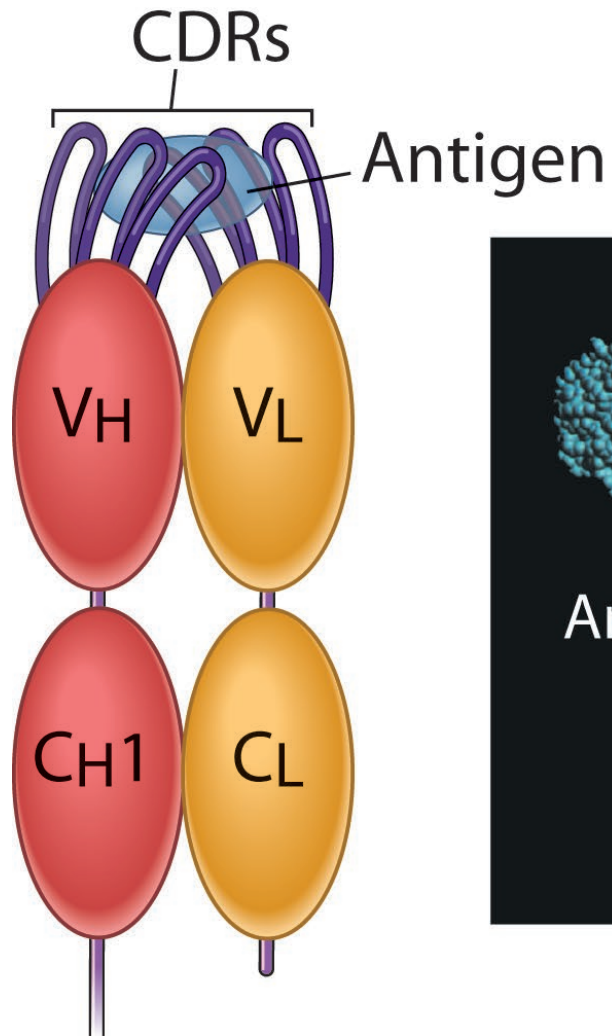
Ragon Institute of MGH, MIT and Harvard
Harvard Medical School

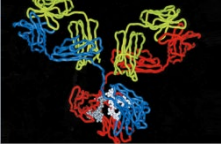
T-B Collaboration

1. T independent Activation
2. T Dependent Activation
3. The Extrafollicular focus
4. The Germinal Center Response
5. Somatic hypermutation and isotype switching
6. “The Lymphocyte Rap”

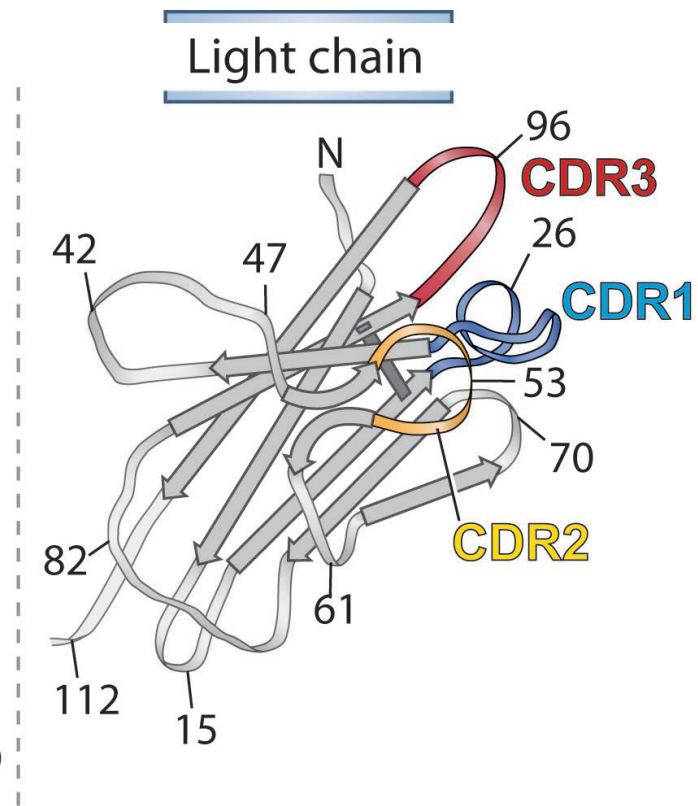
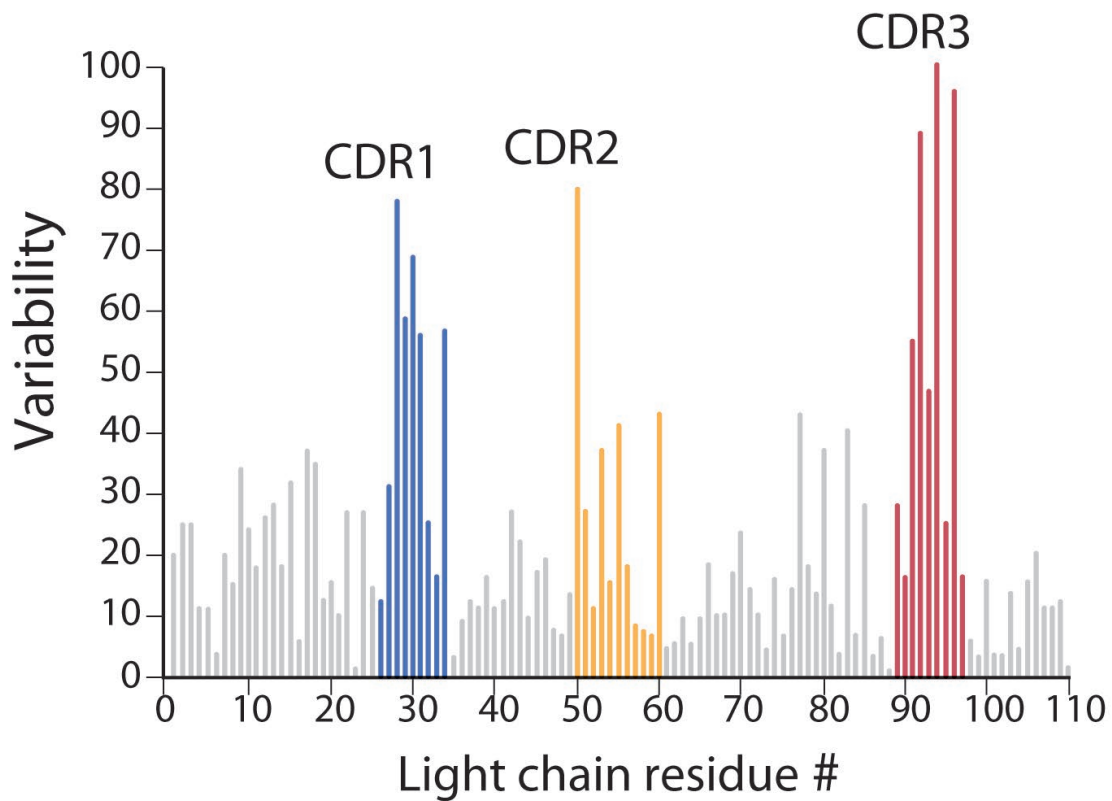


Binding of an Antigen by an Antibody



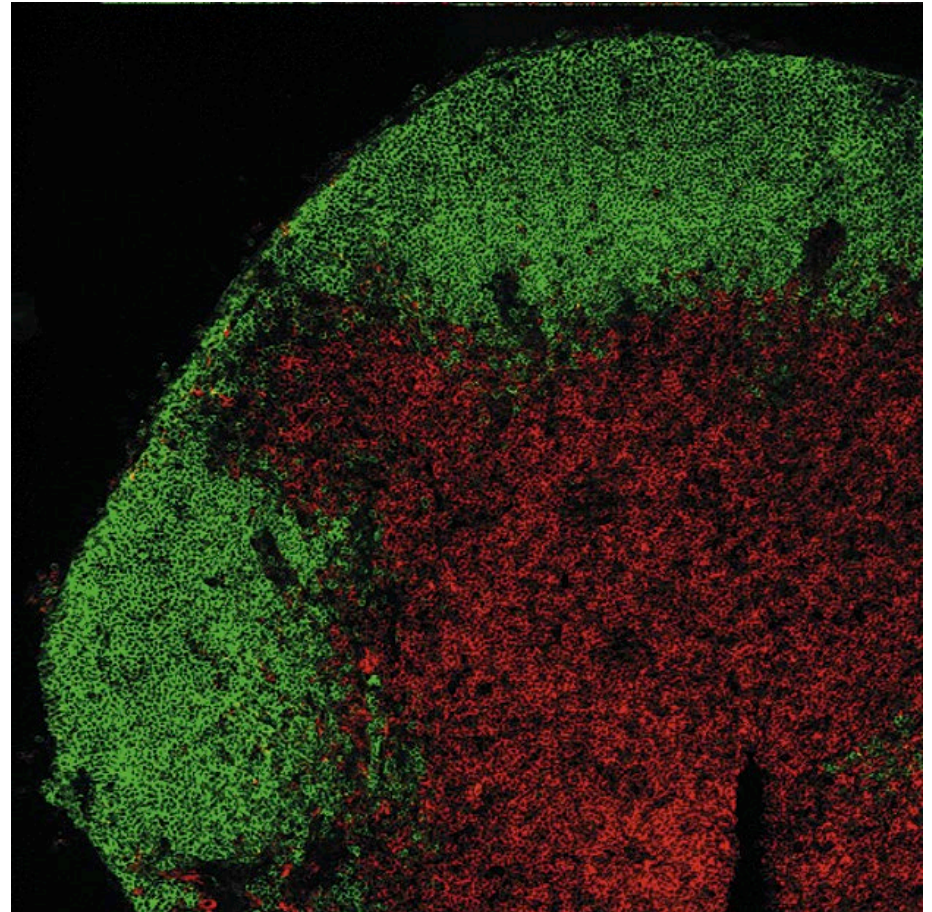
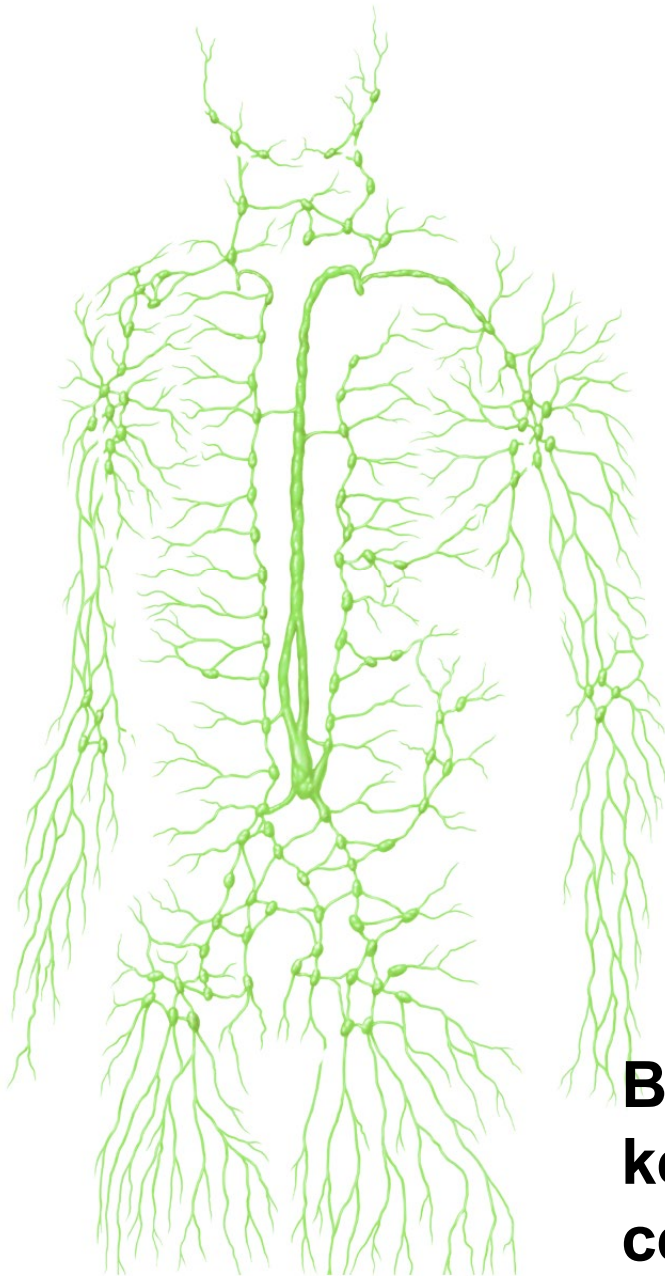


Ig Light Chain Hypervariable Regions



SLOs - T and B cell zones

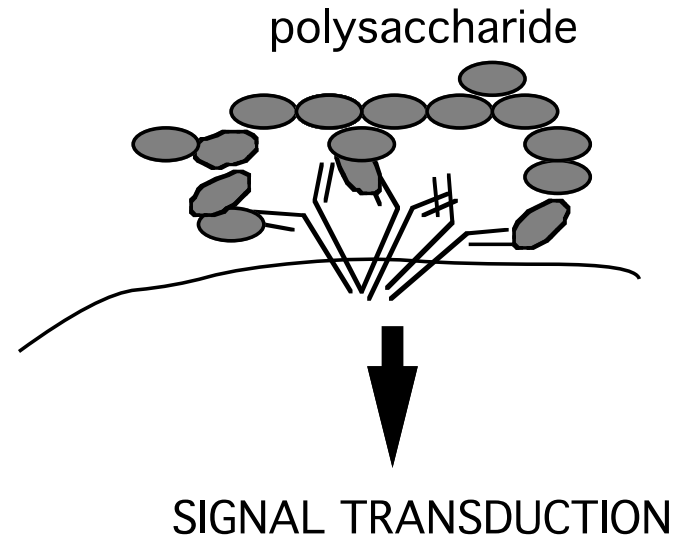
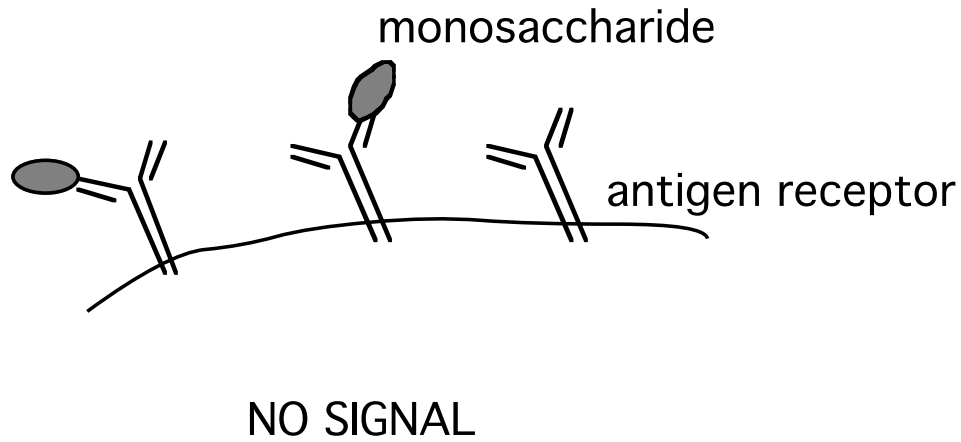
CXCL 13 brings naive B cells to follicle



BAFF
keeps B
cells alive

CCL19 and CCL21
draw naïve T cells
to T cell zones

Multivalent Structures can be T-independent antigens



Haptens, Antigens, Immunogens

- Haptens are small molecules or moieties. They are antigens but not immunogens
- All immunogens are antigens
- All antigens are not immunogens

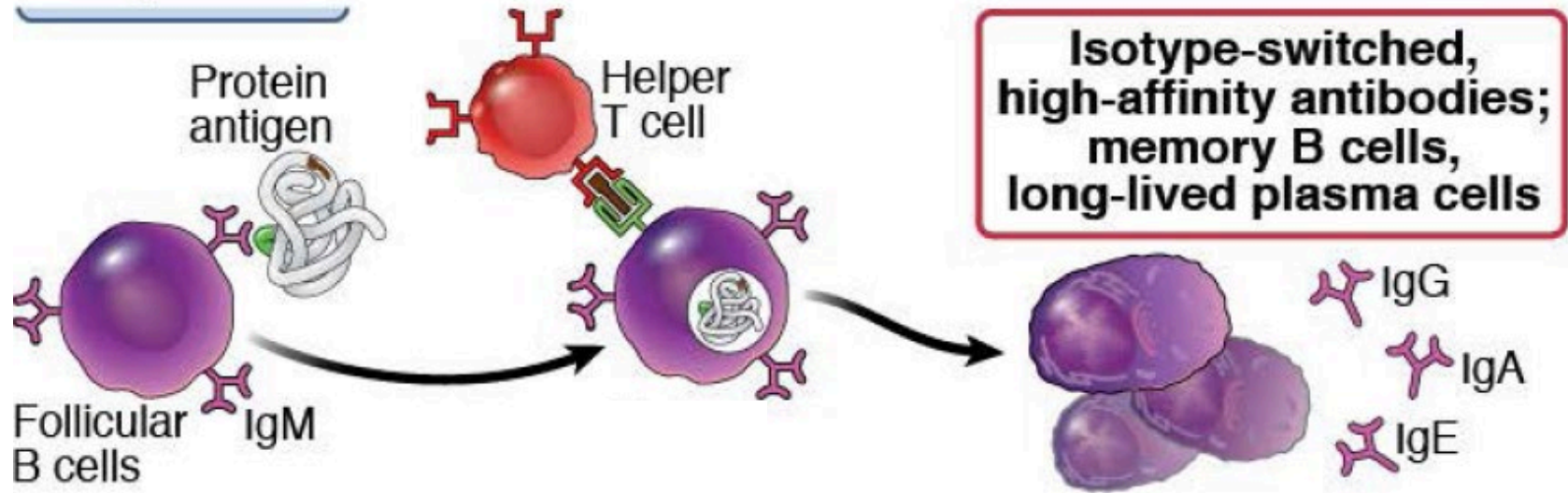
TYPES OF ANTIGENS

Haptens

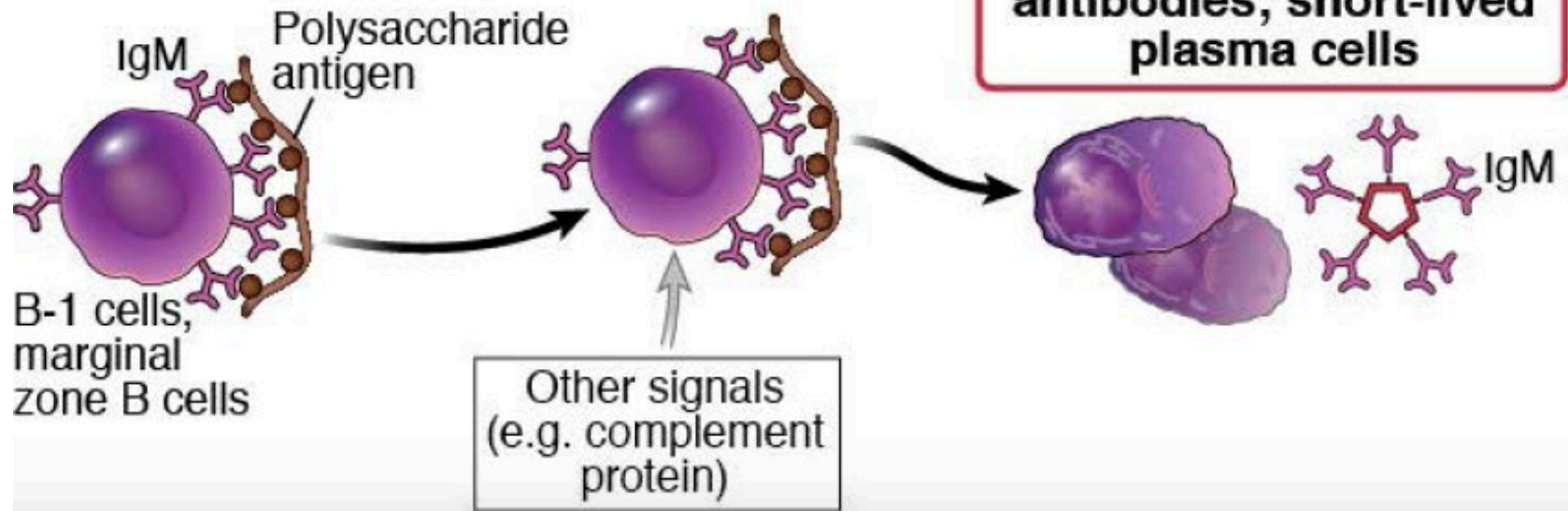
T-independent ANTIGENS

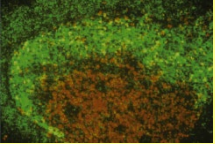
T-dependent ANTIGENS

T-dependent



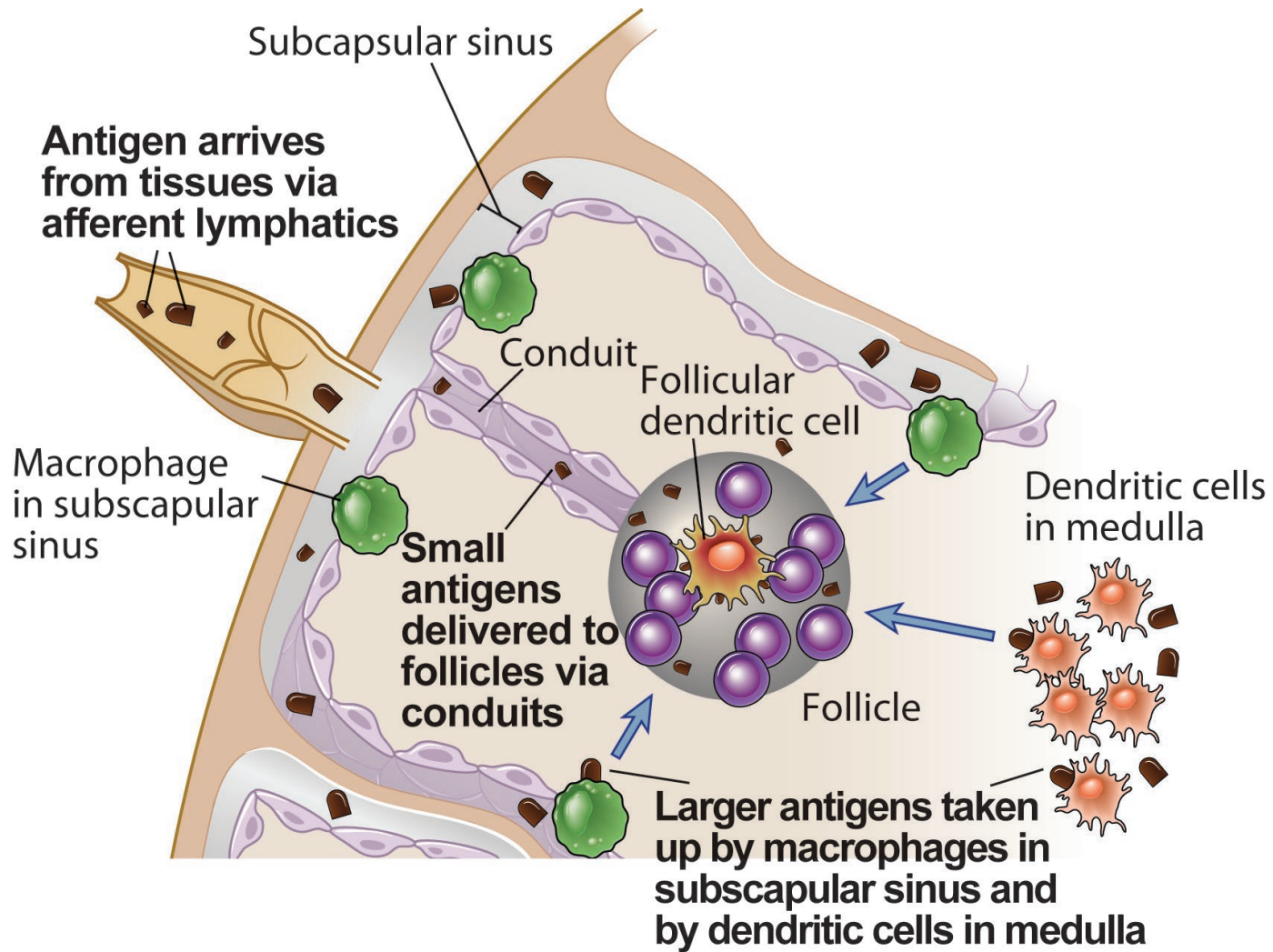
T-independent



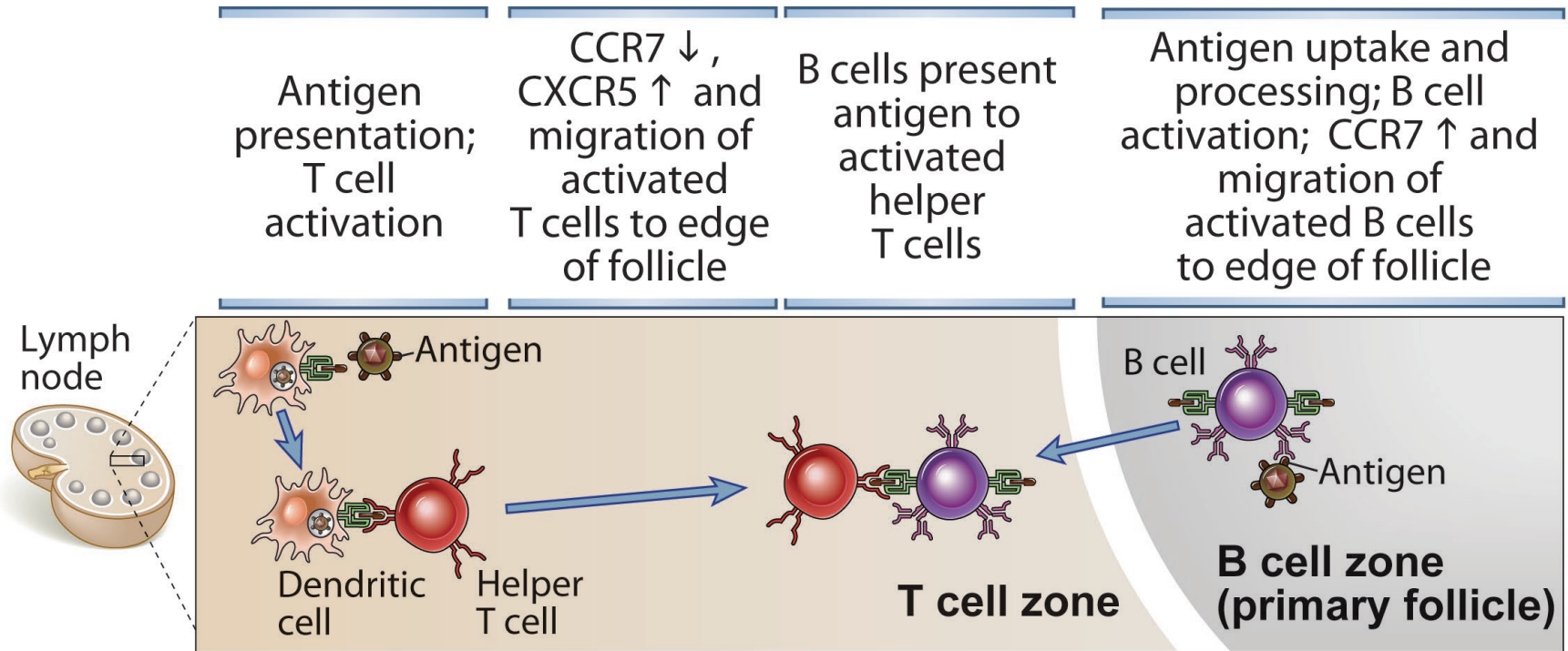


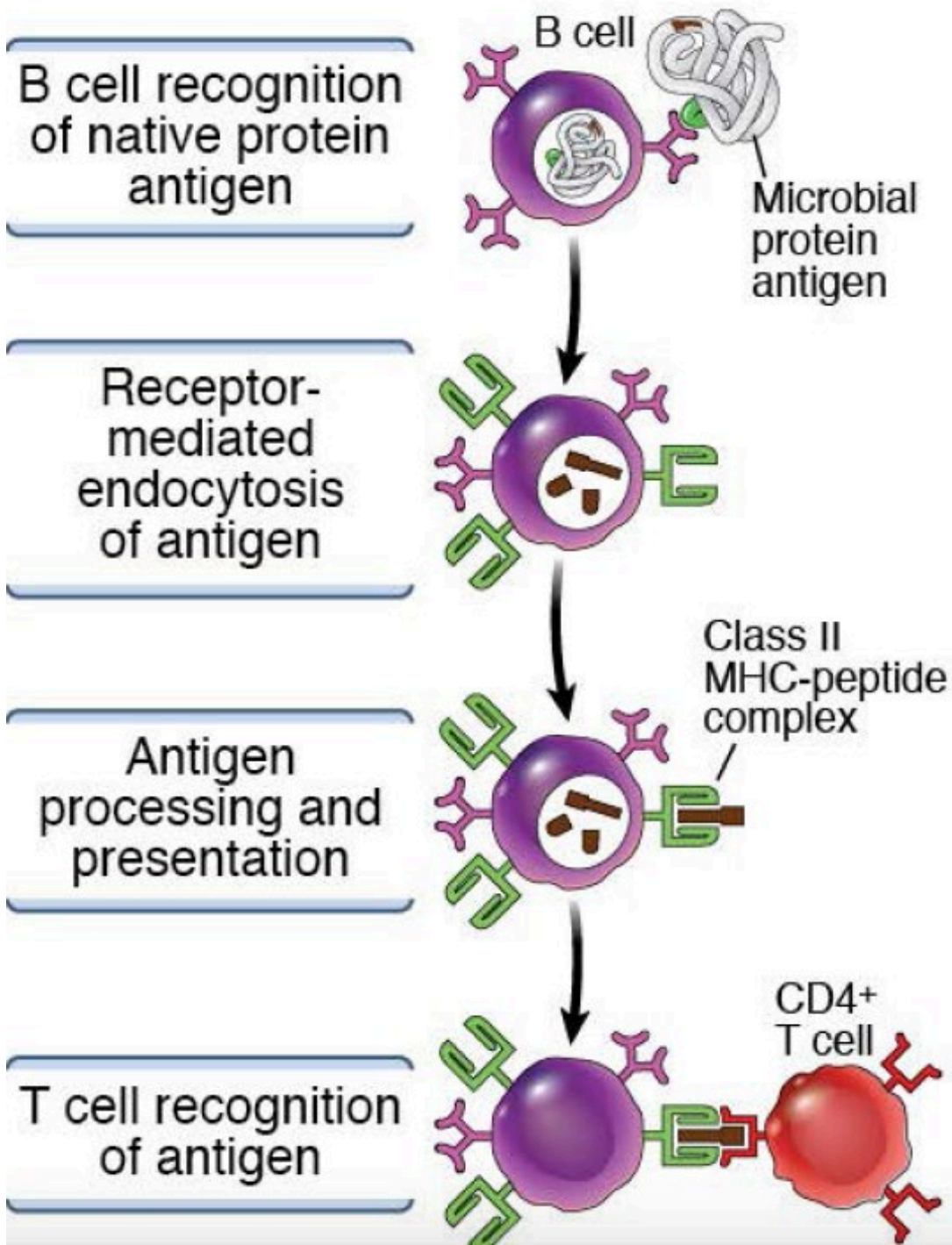
T-DEPENDENT ACTIVATION OF B CELLS

Antigen Delivery to Follicular B cells

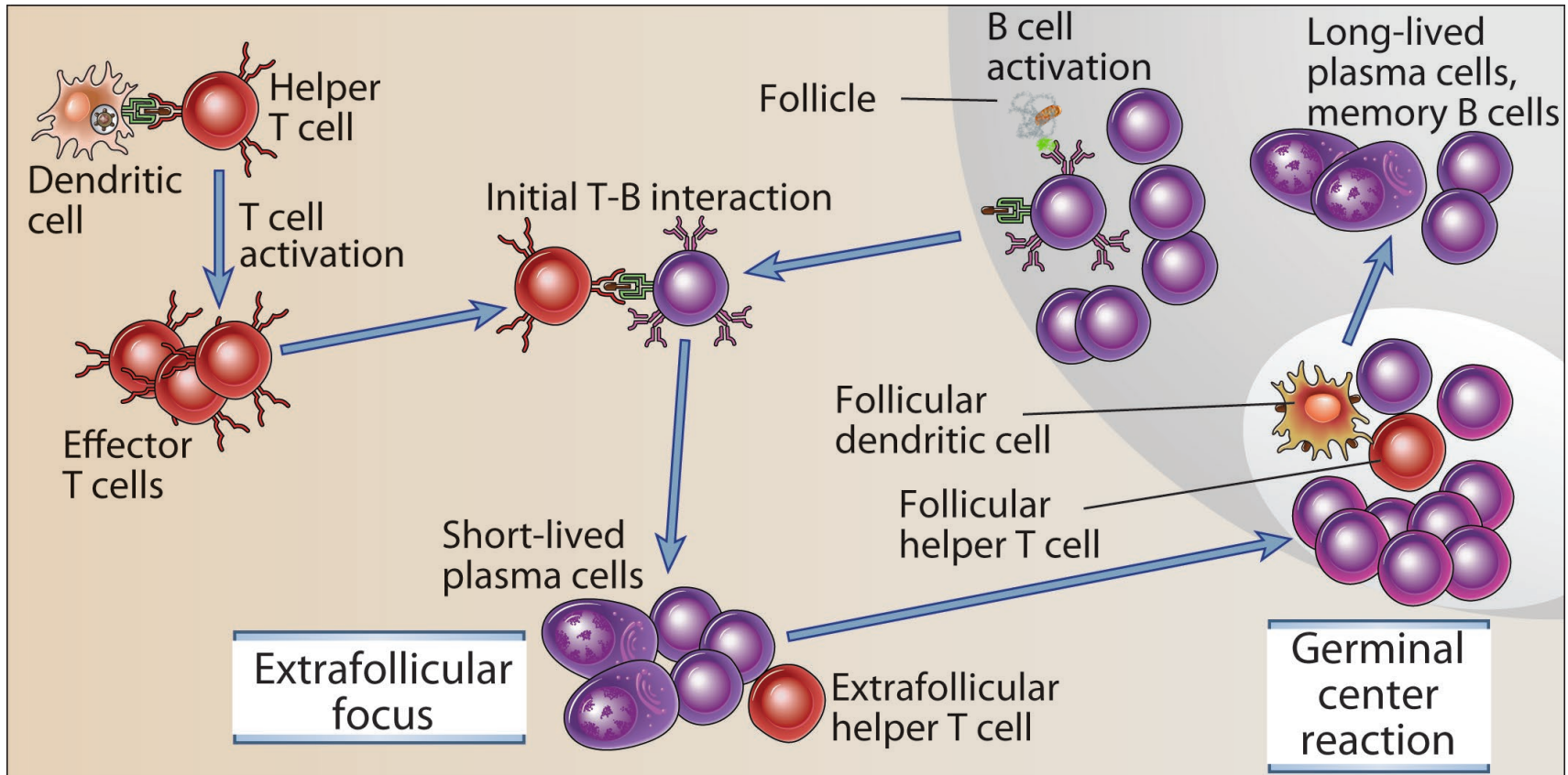


T-B cell Migration and Interactions

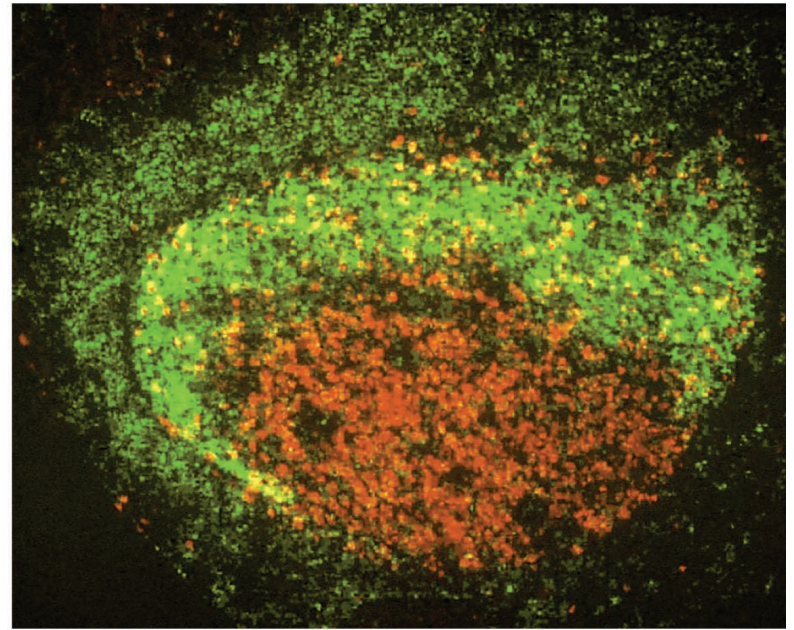
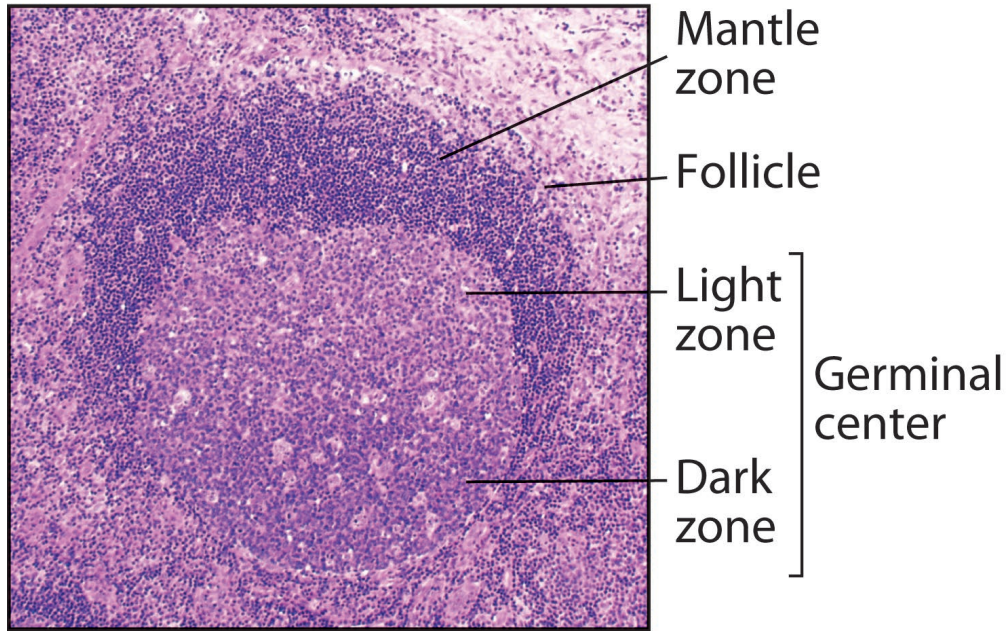




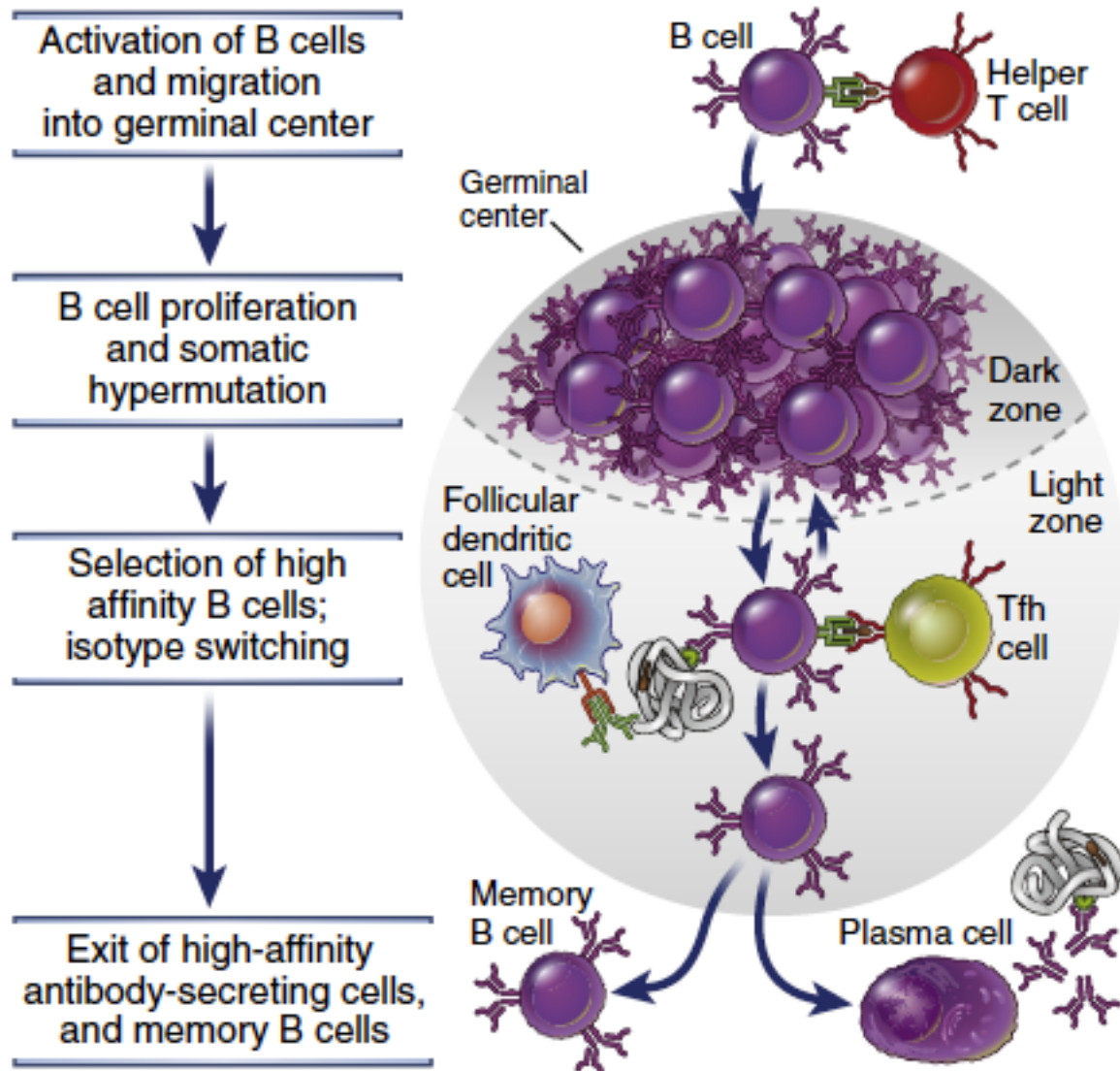
Events in T-Dependent Humoral Responses



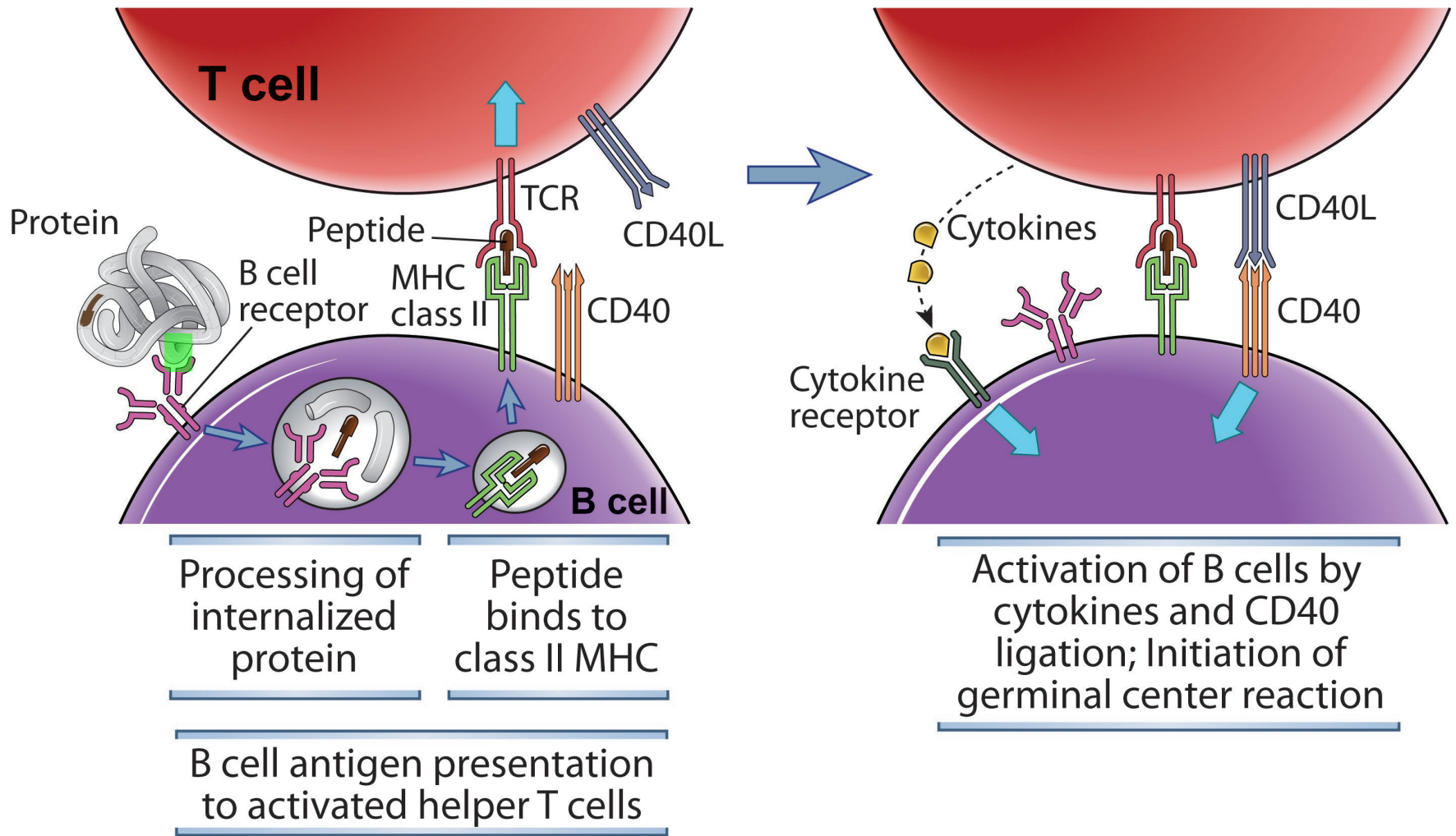
Germinal Centers in Lymphoid Organs

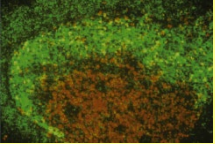


THE GERMINAL CENTER REACTION

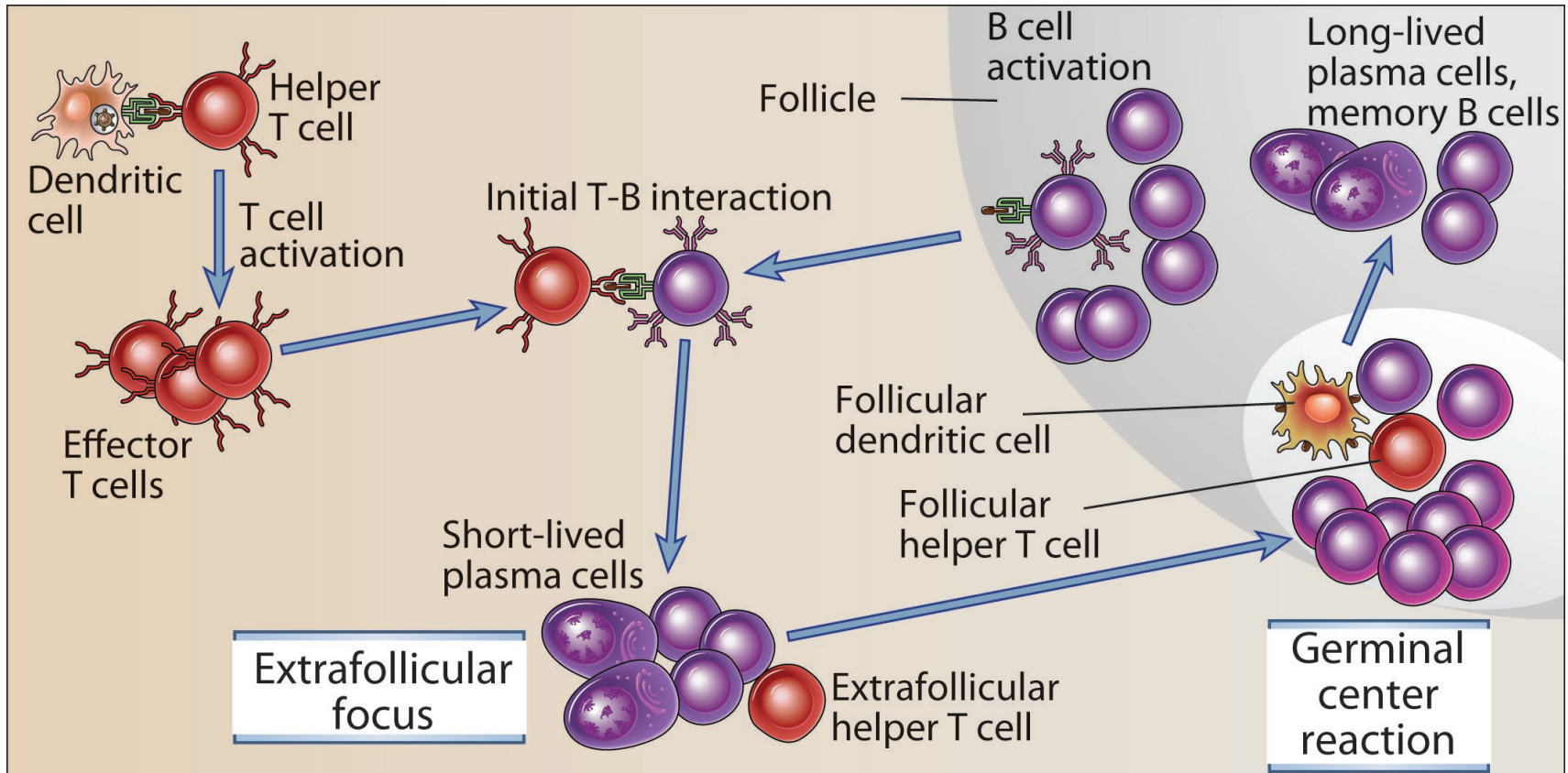


Helper T cell Activation of B Cells





Events in T-Dependent Humoral Responses

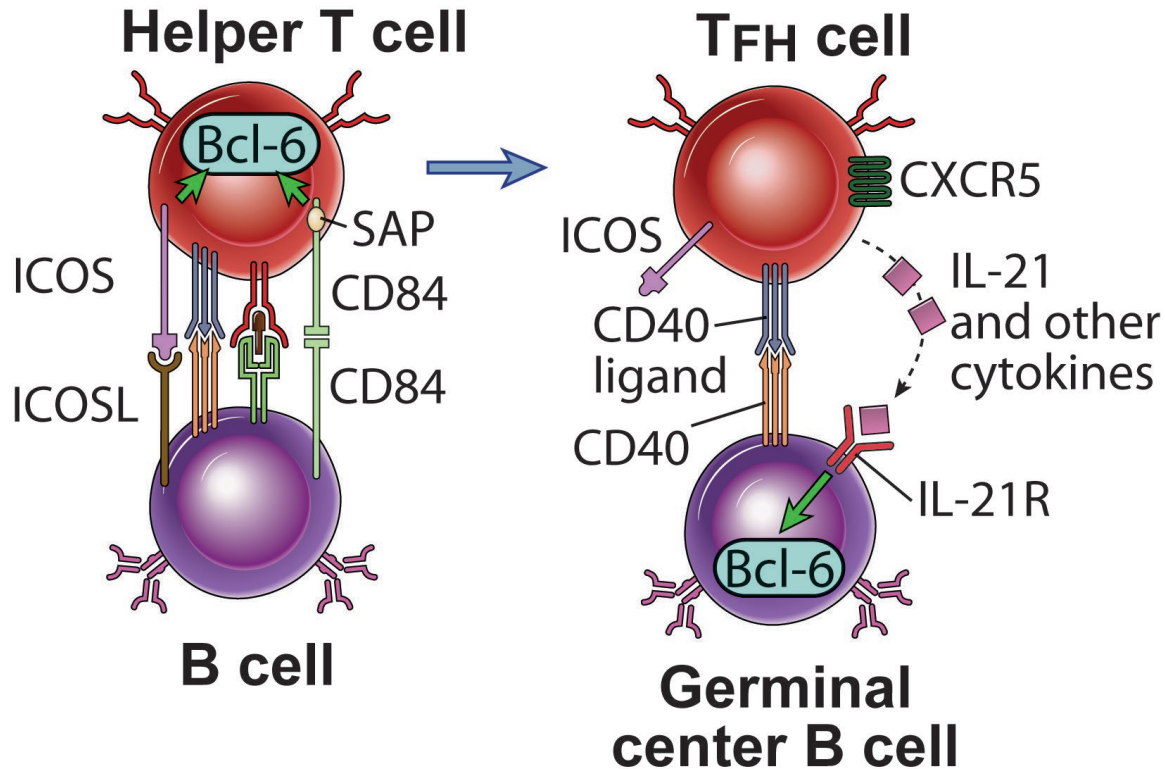


**MOST ISOTYPE
SWITCHING
HAPPENS HERE**

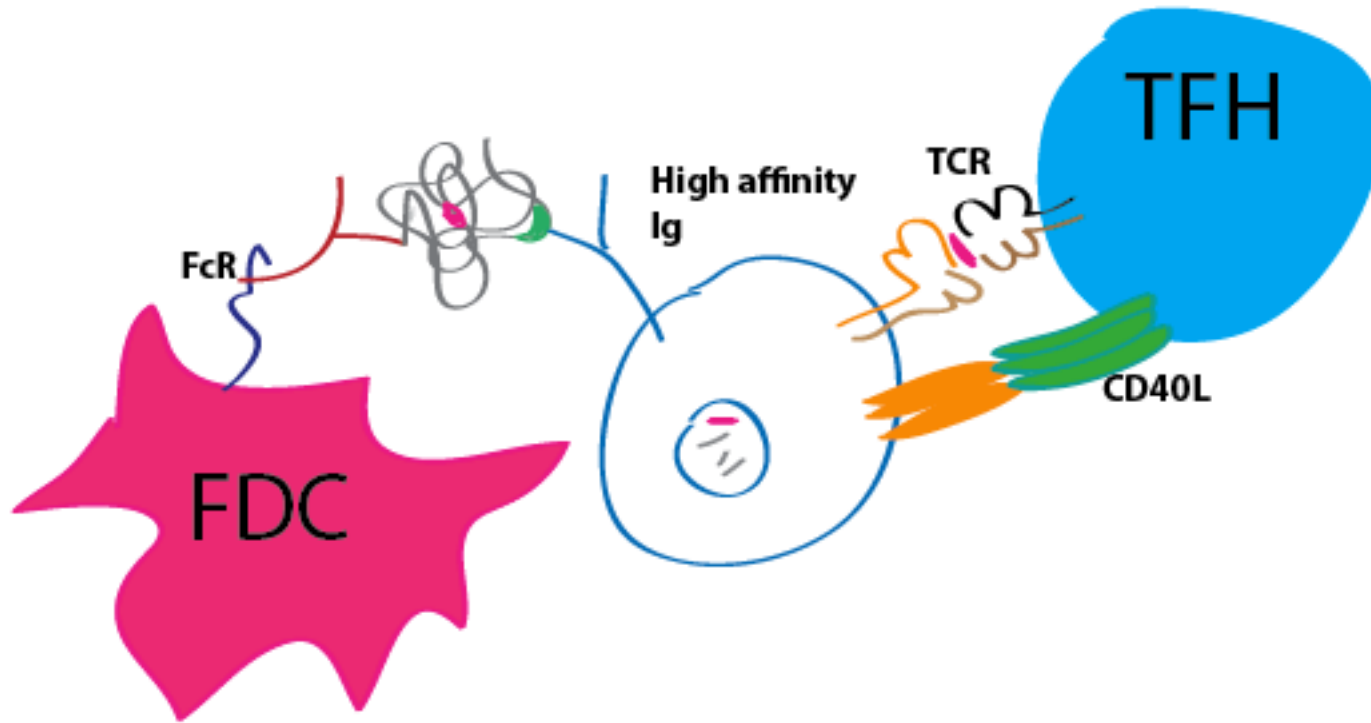
T Follicular Helper Cell Induction and Function

Induction of
 T_{FH} cells
by B cells

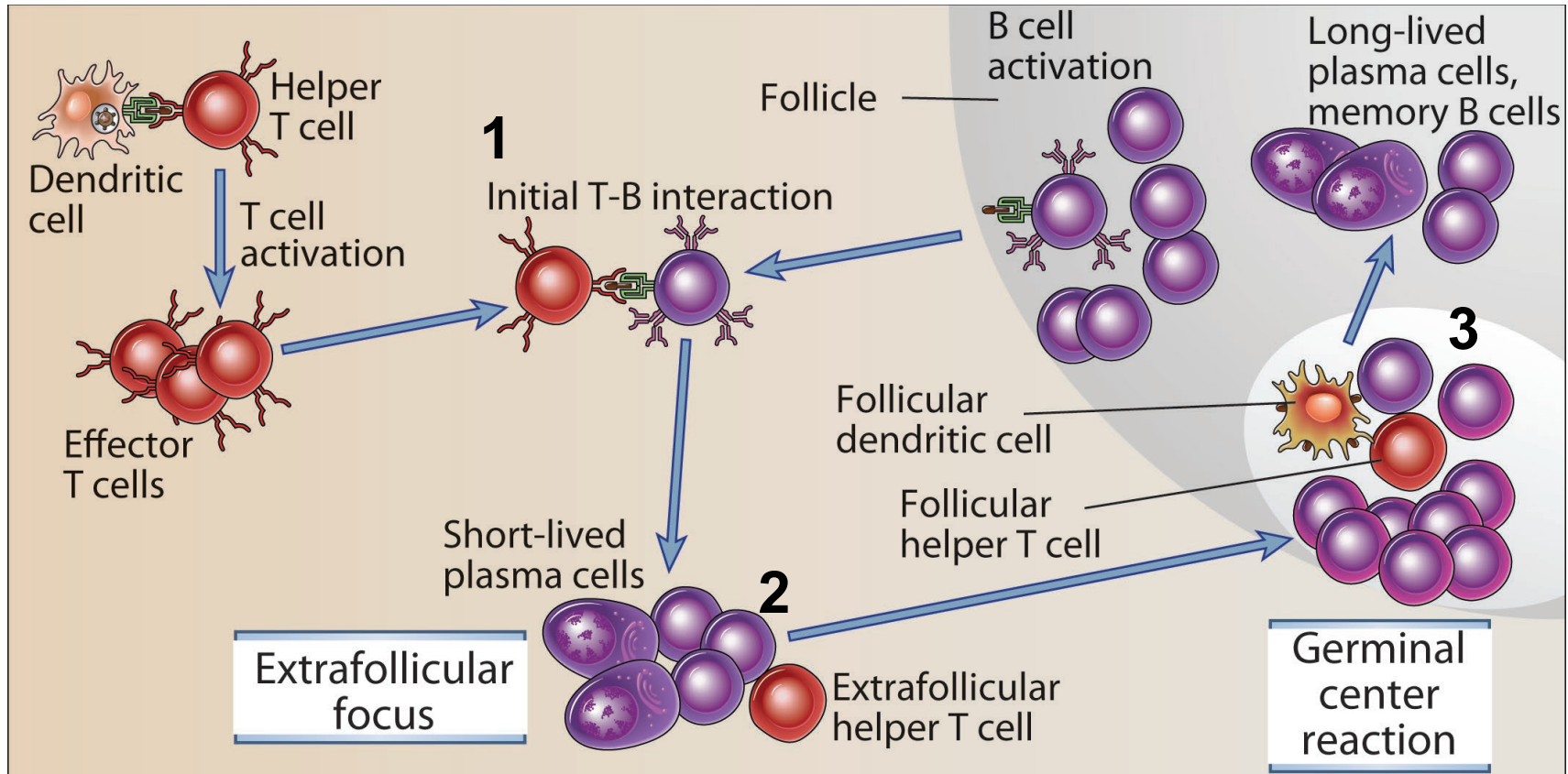
Induction of
germinal center
B cells by T_{FH} cells

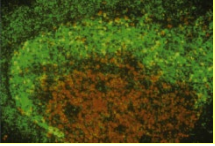


High Affinity B cells capture antigen from FDCs



Events in T-Dependent Humoral Responses

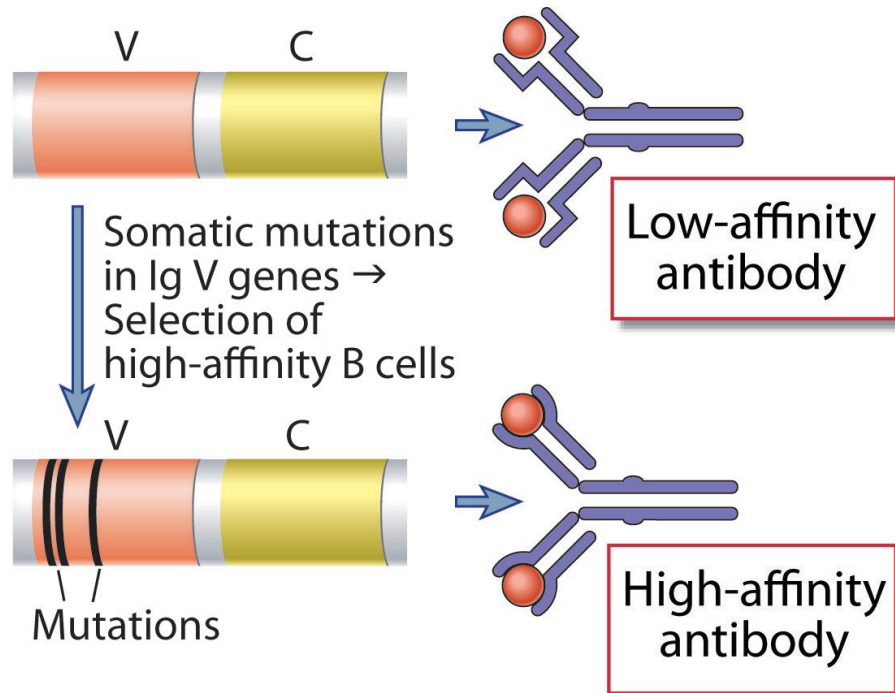




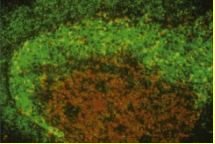
Sequential T-B interactions in immunity

1. **T → B - Forms extrafollicular B cell focus**
2. **B → T - Generates T follicular helper cells**
3. **T → B - Selection of high affinity B cells in light zone by T_{FH} cells**

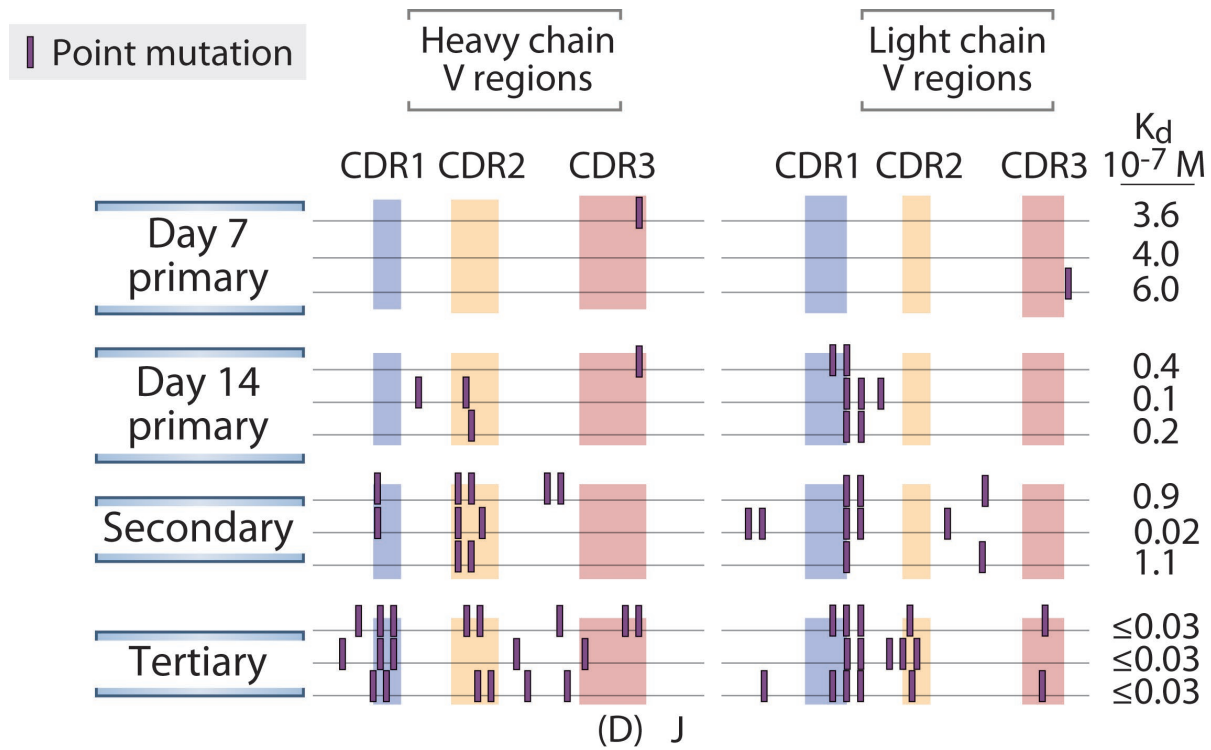
An Overview of Affinity Maturation



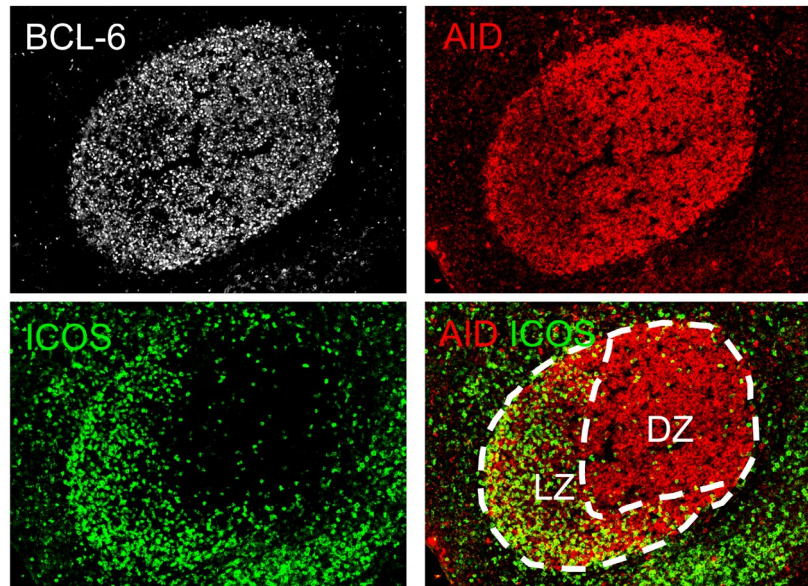
Somatic Hypermutation



Somatic Mutations in Ig V genes



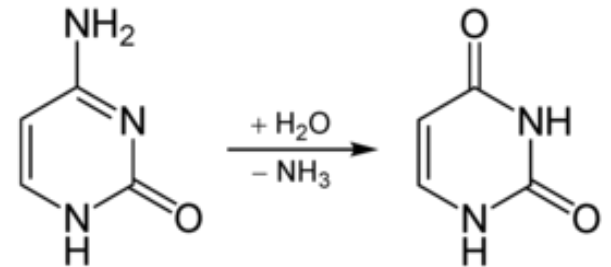
AID, ICOS AND BCL6 HELP DEFINE THE ANATOMY OF THE GERMINAL CENTER



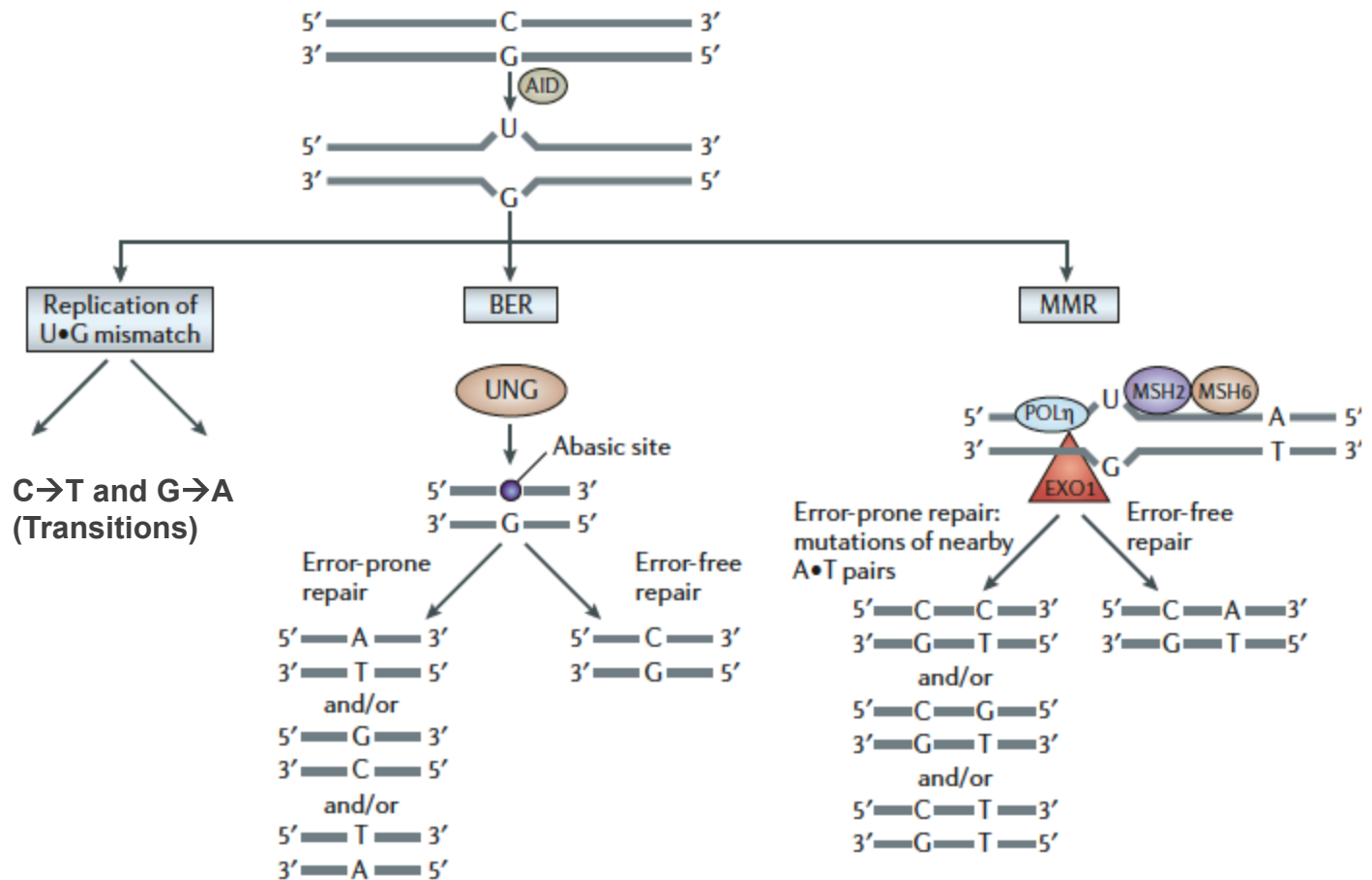
AICD (aka AID)

Activation Induced Cytidine Deaminase

CONVERTS C TO U IN SINGLE
STRANDED DNA



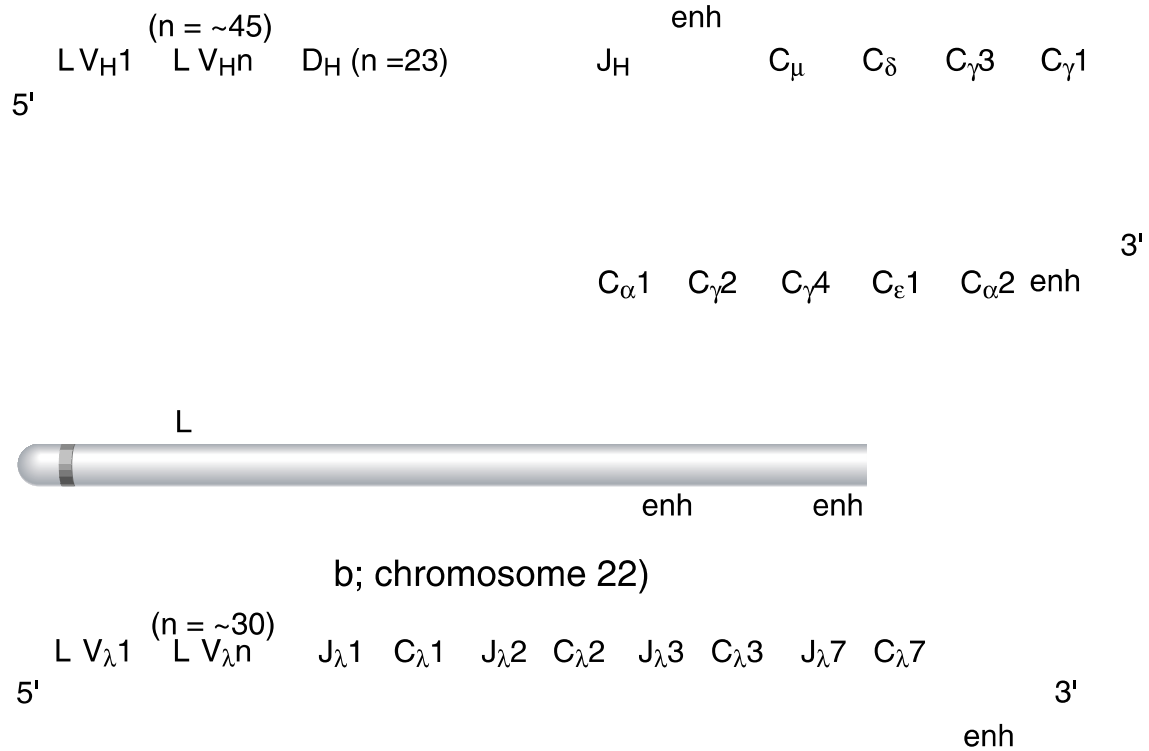
AID C→U MUTATION FOLLOWED BY ERROR-PRONE REPAIR CREATES SOMATIC HYPERMUTATION



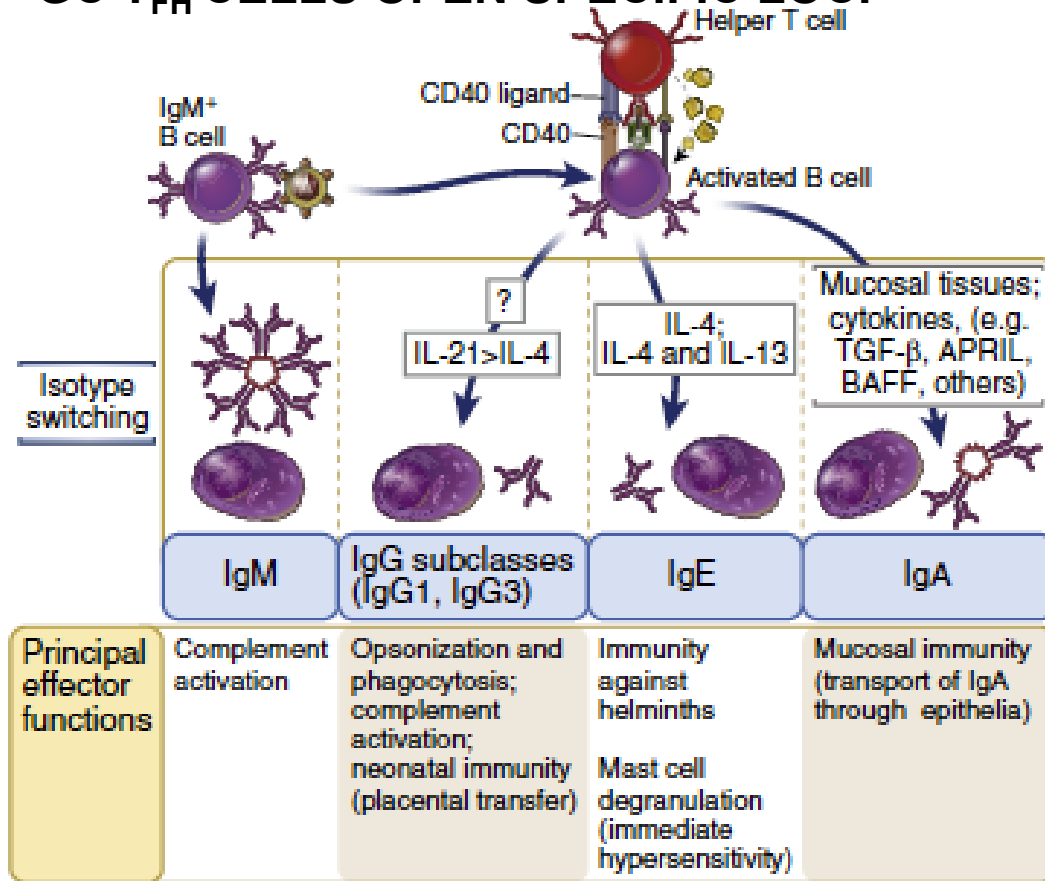
Based on Odegard and Schatz, NRI 2009

Isotype Switching

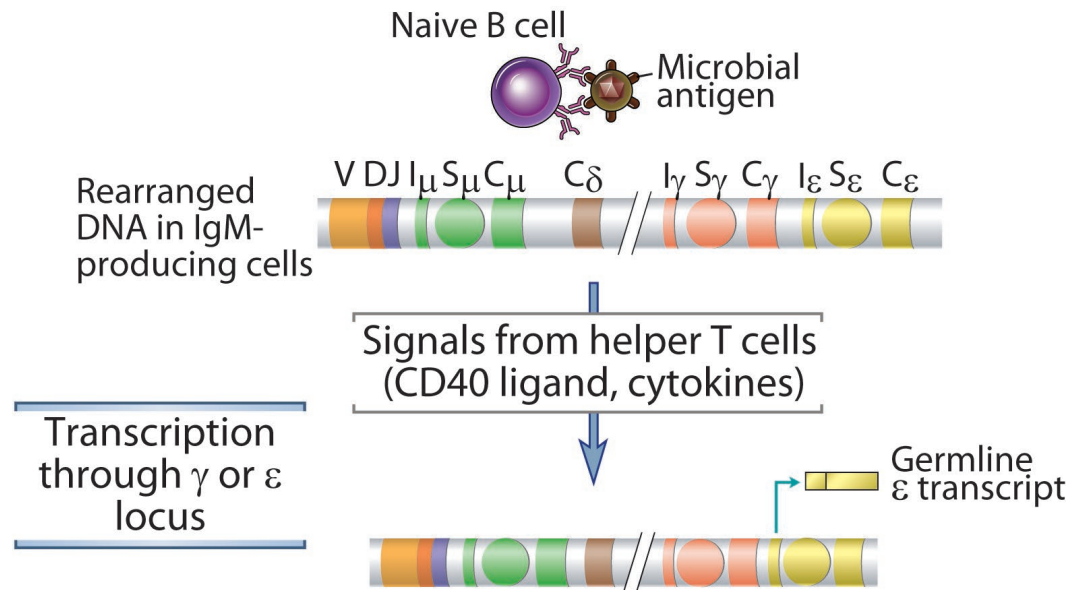
HUMAN IMMUNOGLOBULIN GENES

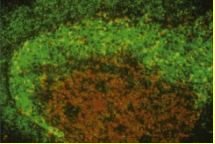


CD40 INDUCES AID AND CYTOKINES MADE BY PRE- GC T_{FH} CELLS OPEN SPECIFIC LOCI

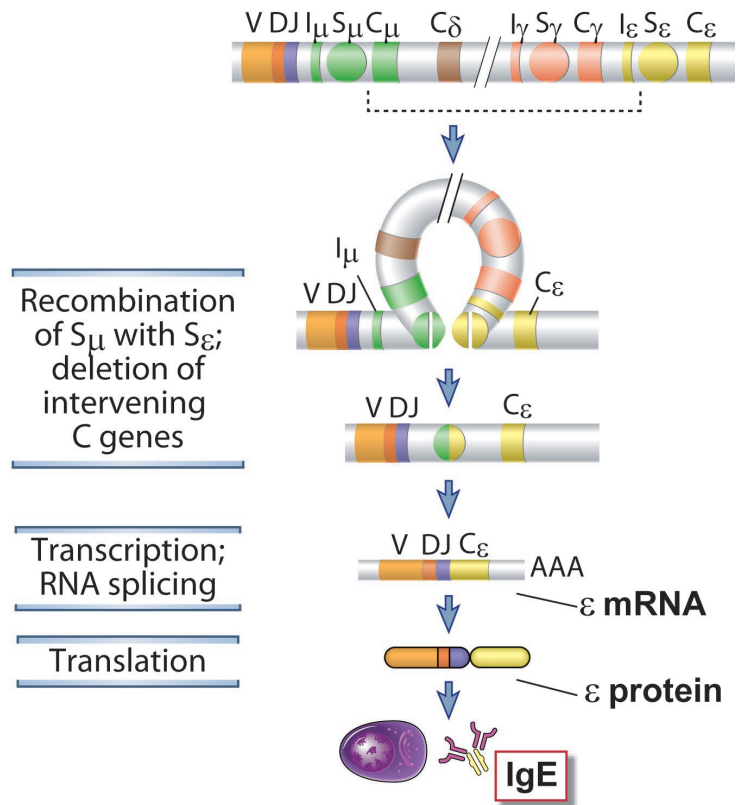


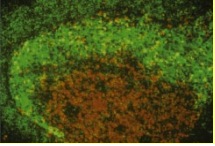
Heavy Chain Isotype Switching





Heavy Chain Isotype Switching





The Lymphocyte Rap