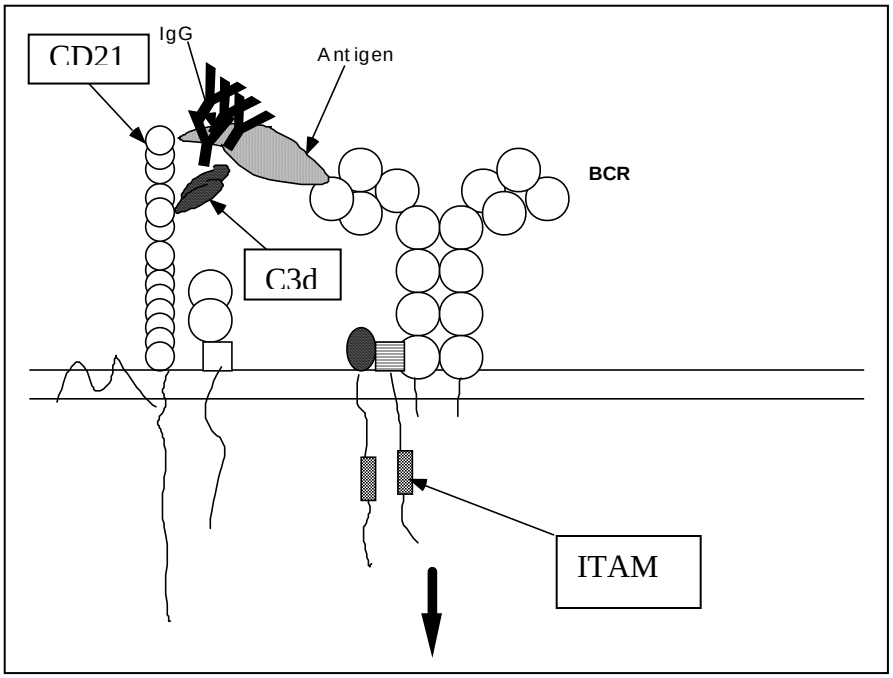
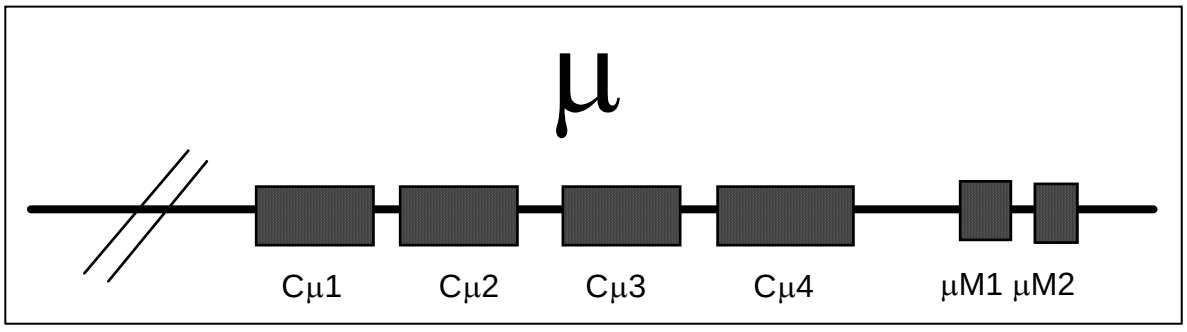
HST 175 Midterm Answer Key
10.25.2004



1. (8 points) **Humoral Immunity** (only 1a is related to the figure above)
   a. (2) Please fill in short labels for the three unlabeled arrows in the figure above.
   b. (3) List three functions of the pre-BCR
      i. Survival, proliferation
      ii. Allelic exclusion of the Ig heavy chain locus
      iii. Downregulation of the surrogate light chains once the preBCR is recognized
      iv. Induction of kappa light chain rearrangement
   c. (3) What is the secretory component? The secretory component is the remaining piece of the poly-Ig receptor that remains attached to the IgA dimer (which is composed of two IgA molecules attached by a J-chain) after it traverses the intestinal epithelium and emerges in the gut lumen. The poly-Ig receptor binds the IgA dimer on the basal side of the intestinal epithelial cells and allows it to traverse the cells to get to the lumen. The receptor is cleaved during the transport process, yielding the secretory component as the remnant that remains attached.

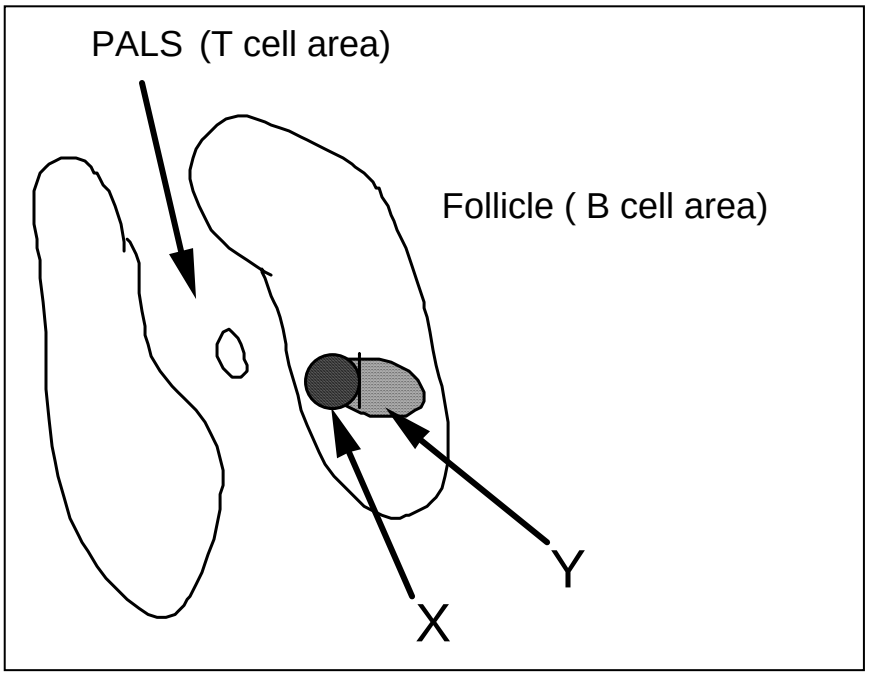


2. (22 points) **Antigen Receptors.** The constant exons of a normal IgM heavy chain gene are depicted in the figure above.

a. (10) A child has been identified with a homozygous lack of the μM1 exon. In one or two lines describe the predicted clinical presentation:
The child would lack mature B cells since he could not synthesize a BCR without the two transmembrane domains. Without B cells, there would be a clinical syndrome of immunodeficiency, especially seen by an increase in extracellular bacterial infections. There would be a block at the pro-B to pre-B cell checkpoint.

b. (5) A clone was obtained including the leader exon and the VDJ exon upstream of the exons shown above. This clone was transfected into a human IgG expressing B cell line. Assuming that DNA was introduced into the recipient line and the gene was efficiently transcribed, would IgM be secreted by this cell line? Why?
This cell is already capable of secreting antibody, so this line will be able to secrete the child's IgM antibody (the mutation in the child's locus effects membrane bound Ig, not the secreted form).

c. (10) Would the child's serum contain IgM antibodies? Explain why or why not.
No, without a BCR there cannot be mature B cells so no antibody can be secreted. (There can never be a signal for secretion!)



3. (22 points) **Adaptive Immune Response**

a. (2) The above is a schematic view of a portion of the spleen.
Please give the names for locations X and Y:

i. Location X: germinal center dark zone
ii. Location Y: germinal center light zone

b. (4) The generation of the above structure requires the presence of a membrane protein on activated T cells. What is this membrane protein? CD40L

c. (4) What subset of T cells drives the above process? CD4+ T cells (Th2)

d. (4) What type of antigens drive the above type of response? Proteins (T dependent)

e. (4) List three known genetic syndromes/mutations in humans that contribute to defects in processes linked to the structure depicted above.

i. CD40L -/-
ii. CD40 -/-
iii. AID -/-
iv. Defect in NEMO or IKK-gamma

(all 4 of the above result in a hyper-Igm syndrome)

(also accepted: CD4-/-, MHC II antigen processing defects including HLA-DM -/-, etc, homing defects including CCR7-/-, complement deficiencies including CD21 and CD19 -/-. Not accepted: btk deficiency, RAG -/-, SCID, DSB repair -/-).

f. (4) Please describe two processes that AID is involved in and its mechanism of action in one of those two processes

i. CSR
ii. SHM

Mechanism: AID serves as a cytidine deaminase of ssDNA. In SHM, AID is able to deaminate C→U which is then removed by UNG and, depending on the repair process that is initiated, the sequence is either repaired to wildtype or a transition or transversion is generated.

4. (25 points) **Antigen Presentation**

Please hypothesize the effect of each mutation below on antigen presentation and the mechanism for that effect (including whether it effects MHC Class I or Class II presentation or both):

1. Please hypothesize the effect of each mutation below on antigen presentation and the mechanism for that effect:

a. (5) TAP -/-:

Almost complete defect in MHC I presentation because appropriate peptides that are generated by the proteasome in the cytosol (usually from cytoplasmic antigens) cannot be transported from the cytosol to the ER for loading on MHC I molecules.

b. (5) Cathepsin B, L, D, S -/-:

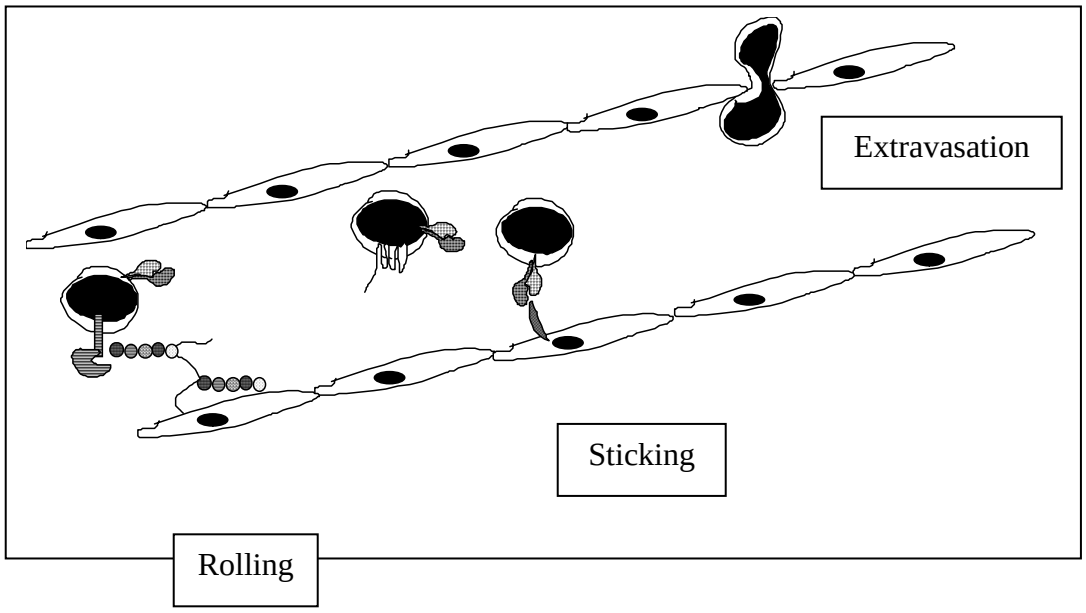
Almost complete defect in MHC II presentation because peptides cannot be readily generated from extracellular antigens in acidified endocytic vesicles for presentation on MHC II molecules and CLIP cannot be generated from Ii on MHC II molecules. There are other proteases that function in this capacity, but cathepsins were emphasized.

c. (5) Invariant chain Ii -/-:
Almost complete defect in MHC II presentation since the MHC II is not stabilized (or protected from inappropriate peptide binding) in the ER before it is transported to endocytic vesicles (which also involves Ii)

d. (5) HLA-DM -/-:
Almost complete defect in MHC II presentation because CLIP cannot be removed from MHC II in endocytic vesicles and other peptides cannot be added, so no appropriate peptides are presented on MHC I

e. (5) B2m (beta 2 microglobulin) -/-:
Almost complete defect in MHC I presentation because B2m (and the appropriate short peptide) stabilize the MHC I complex, allowing it to go to the surface of the cell and be recognized by the cognate CD8+ T cell TCR

5. **(20 points) Lymphocyte Homing**



a. Lymphocytes from mutant mouse strain X were isolated, labeled with a fluorescent dye, and injected back into a strain X mouse. When the HEV is examined by intra-vital microscopy the lymphocytes are seen to neither roll nor stick.

Cells are then again extracted from strain X of mutant mouse, again labeled with a fluorescent dye but are injected this time into a wild-type mouse and observed by intravital microscopy. In this scenario, the cells still do not roll or stick.

i. (5) Is it more likely that the lymphocytes or the endothelial cells are altered?
Lymphocyte
ii. (5) Name a molecule that may be the cause of this defect:

1. L-selectin

b. Lymphocytes from a second mutant mouse strain, strain Y, were isolated, labeled with a fluorescent dye, and injected back into a strain Y mouse. When the HEV is examined by intra-vital microscopy the lymphocytes are seen to roll but not stick.

Cells are then again extracted from strain Y, again labeled with a fluorescent dye but are injected this time into a wild-type mouse and observed by intravital microscopy. In this scenario, the cells now roll and stick.

i. (5) Is it more likely that the lymphocytes or the endothelial cells are altered?

Endothelial cells

ii. Name two molecules that may be the cause of this defect:

1. (2.5) ICAM
2. (2.5) CCL21