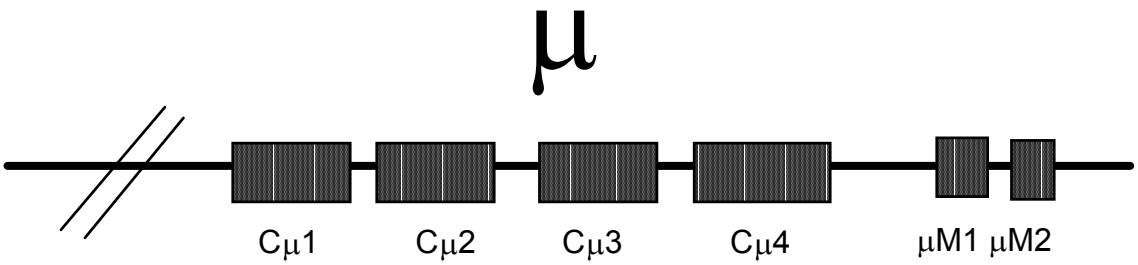
HST 175 Midterm examination
October 9th 2001

Please read the questions carefully. Answer all questions. Please be as brief as possible. Please remember to write your name on each answer sheet and use a separate answer sheet for question 5.

1. A knockout mouse was generated in which the last two exons of the mouse IgM heavy chain constant region depicted below were homozygously deleted.



a. B cell development was blocked in this mouse. Schematically describe the membrane bound receptor that fails to be generated at the checkpoint at which B cell development is blocked in this mouse. (5)
b. V(D)J rearrangement at the Ig heavy chain locus was examined in the arrested B lineage cells in this mouse. Would you expect typically to see 1) no completed VDJ rearrangements, 2) one complete VDJ rearrangement, or 3) 2 completed VDJ rearrangements in the developmentally arrested cells? Briefly explain your answer. (5)
c. A similar phenotype to that seen in the mouse above is noted in a relatively common inherited human immunodeficiency disorder. What is this disease known as, and mention the kind of protein that is encoded by the normal version of the gene that is defective. (3 + 2)

2. A proportion of Severe Combined Immunodeficient (SCID) patients have inherited two defective Rag-1 or two defective Rag-2 alleles.
a. Where do you think lymphocyte development will be blocked in a patient incapable of making any Rag-2? (5)
b. Briefly describe the phenomenon known as “receptor editing”. (5)
c. What is the 12/23 rule? (5)

3. CD40L is induced in activated T cells and is encoded by an X-linked gene.
a) A pneumococcal polysaccharide vaccine is known to produce specific antibodies in immunized healthy children. Do you think that immunization with pneumococcal polysaccharide will or will not result in specific antibodies being generated in a boy with a CD40L deficiency? Briefly explain your answer. (5)

b) Will immunization with tetanus toxoid (a denatured form of the tetanus toxin protein) result in similar or different antibodies being generated in a boy with a CD40L deficiency and a normal unaffected cousin? Provide a brief explanation for your answer. (5)

4.The Mycobacterium that causes tuberculosis is an intracellular pathogen that can multiply in macrophages. Much of the pathology in this disease results from a type of immune response known as "delayed type hypersensitivity". Describe this process in a stepwise manner, mentioning any relevant secreted proteins that you have heard of. (10)

5.There have been outbreaks of an OBL virus induced hemorrhagic fever in a number of refugee camps in northeastern Afghanistan. The majority of patients have a brief self-limiting illness. Although many people come in contact with acutely ill and convalescing patients, only a fraction develop a severe life-threatening form of the disease. Many of these severely ill patients have been flown out to the Dushanbe General Hospital where a team of ID specialists and nephrologists from Boston and Paris have set up a special unit where patients are rehydrated and dialyzed if necessary. Mortality in severely ill patients remains high. The Boston-Paris Immunogenetics consortium has typed 4200 unaffected, mildly affected, and severely ill Pashtuns with OBL fever.

Based on a large number of results, investigators decided to focus on one HLA Class I allele that is found at a high frequency in Pashtuns. The percentage of controls and patients who inherited this allele is listed in the table below.

	Unaffected Pashtuns (n=2208)	*Short duration fever (fever<10d); (n=1702)*	*Severe hem. fever (n=290)*
HLA B*5301	42%	66%	0.3%

a. What kind of T cell do you think is critical for protection against the severe form of OBL hemorrhagic fever? What is it "restricted" to? Draw a simple diagram of this molecule/restriction element. (3+2+5)
b. What is a co-receptor? What is the co-receptor on the type of T cell referred to above? (4+1)
c. Describe, with the aid of a diagram, the cellular pathway that is directly involved in presenting antigen to the T cell in "a". (15)

The OBL nucleoprotein contains a peptide SLIRFEKLwhich was shown to bind to the HLA molecule of interest. A specific target cell line expressing this HLA molecule was loaded with radioactive chromium, pulsed with each of the peptides listed below, and mixed with activated T cells from a selected convalescing patient who had a mild form of the disease (and also had inherited the above HLA allele). In a chromium release assay radioactive chromium spills out of target cells recognized by cognate activated T cells. Each of the peptides was also tested in a specific HLA binding assay. Here are the results:

Peptide		Specific HLA binding	Chromium release
WT:	SLIRFEKL	+++	+++
2:	SGIRFEKL	-	-
3:	SLARFEKL	+++	+++
4a:	SLIKFEKL	+++	+++++
4b:	SLIMFEKL	+++	-
6:	SLIRFKKL	+++	-
7:	SLIRFEEL	-	-

d. Residues 2, 3, 4, 6, and 7 of the SLIRFEKL octapeptide were "mutated" in the studies described above (S or serine is residue 1). Comment as specifically as possibly on the results seen with peptides 2, 3, 4a, 4b, 6, and 7. (10)

The OBL virus can damage parenchymal cells in the liver. Activated T cells enter the liver.

e. Describe the events that occur at the hepatic postcapillary venule endothelium that facilitate this T cell accumulation. Mention the types of molecules that facilitate this process in a stepwise manner. (15)