This assignment is due on Friday Feb 26 at 8:30am. No assignments will be accepted after this deadline.

Please read carefully through this quiz before Monday Feb 22. I will answer questions about it in class. I can’t take questions during office hours since I want the entire class to have access to the same information (from me). You can email me questions but I will only address them during class.

Rules for working this quiz: This is an open-note, open-book, open-internet quiz. You may discuss these questions with your fellow classmates but, you MUST write up your answers independently. In other words, if any answers look suspiciously similar I will divide the total possible points between the similar answers. Also please do not consult other faculty members about the quiz. You can google any term or topic that you want, but this should not be necessary for any of the questions.

Please word-process the text of your answers and label each part of the assignment clearly. Diagrams should be neatly laid out and labelled, but it is fine if they are hand drawn. If I can’t easily read your answers, I will not grade them.
Problem 1. (10 pts.) GENE X ENVIRONMENT INTERACTIONS

Risk or likelihood of a particular phenotype. By definition the wild-type genotype with no environmental exposure has a risk of 1.0.

Part A: In 1-2 sentences summarize the main point(s) from Panel A.

Part B: In 1-2 sentences summarize the main point(s) from Panel B

Part C: State explicitly the main difference(s) between panels A and B. 

Part D: Review text and lecture material on phenyketonuria. Do either of these graphs accurately depict the gene X environment interaction in this disease state (consider postnatal phenotype only). Defend your answer in a maximum of three sentences. Assume variant genotype means homozygous for a loss-of-function mutation. If you make any other assumptions, state them explicitly. Your answer should include a very brief statement describing the general features of the disease state.

Part E: Read about the Xeroderma Pigmentosum in the text. Answer the question in part D for this disease state.
Part A Explain in detail why this ribavirin causes “genetic meltdown”.

1. What general class of mutagens does ribavirin belong to? No explanation here -- just the proper category: base analog
2. Using correct terminology describe the type of mutations that will occur at the RNA level. One sentence. Ribavirin will results in transitions
3. Include a diagram that shows how a mutation could occur in a segment of the genome with this sequence: 5’ GAACUCA 3’ (+ strand of the genome). NOTE: there is more than one possible mutagenic event. Just show one. Be sure to label the 5’ and 3’ ends of each strand and to indicate the + and – strands.

Net change a single base pair substitution: C→ U transition

4. In three sentences or less explain why this compound is by definition a mutagen and compare to the natural bases which also can interconvert between two different forms. The fidelity of base pairing is essential to all aspects of storage and retrieval of genetic information. This compound is by definition a mutagen because it increases the error rate during the replication of the viral genome. This purine analog will pair readily with either cytosine or uracil and cause a dramatic loss of fidelity during genome replication. In contrast, the purines found naturally in nucleic acids misbase pair at a considerably lower frequency. ARRGG I see I used four sentences….
Part B
1. What modification needs to occur to ribavirin before it can be used as a substrate for RNA polymerase? *One sentence or a labelled diagram.* No explanation needed. Ribavirin needs to be converted to the triphosphate form (3 P’s attached to the hydroxyl on the 5’ carbon) before it can serve as a substrate for RNA polymerase.

2. Why does ribavirin specifically cause mutations in RNA viruses but not in human DNA? *One sentence.* Ribavirin will not serve as a substrate for DNA polymerase since it does not have a 2’ hydroxyl.

3. Speculate as to why this compound doesn’t interfere with transcription in the host cells. *One sentence. Any reasonable idea will suffice.* Most likely – host RNA polymerases are more discriminating than viral RNA polymerases and will not accept ribavirin as a substrate.

Part C. The graph in problem 8 indicates that even in the absence of a mutagen, RNA viruses “operate” near the “outer limit” of mutation tolerance. How/why does a virus tolerate a normal error rate of $2 \times 10^{-4}$ mutations per nt? Compare this error rate to that of DNA replication in a prokaryotic or eukaryotic cell. What factors are important when considering what rate of mutation is “tolerable” for a virus or an organism? *4 sentences max.*

*Your answer should consider:*

- **GENOME SIZE:** A statement comparing the 10 kilobase pair genome size of a typical RNA virus (from figure legend) to the human (or other eukaryote) genome size: 3 billion bps per haploid genome.

- **MISTAKE RATE PER ROUND OF REPLICATION:** A viral mutation rate of $2 \times 10^{-4} = 1$ mistake per 5000 bp replicated means 2 mistakes per genome replication. A euk mistake rate of $1 \times 10^{-9} = one$ mistake per billion bp replicated = $\sim 3$ mistakes per round of replication of a single human genome. [Much lower if we’re thinking about prokaryotes which have about the same mistake rate and much smaller genomes.]

- **LIFESTYLE DIFFERENCE BETWEEN viruses and living organisms.** Viruses crank out many genome copies and live on the edge of the tradeoff between generating inviable genomes and generating genetic diversity that allows the virus to be a successful parasite in the face of genetic diversity of the host and other factors.
Problem 3. (10 pts.) Examine table in problem 18 on Assignment Set 5. Then answer these questions.

a. Examine the table. What is meant by a neutral sequence variation? *One sentence maximum.* A neutral sequence variation has no effect on the Darwinian fitness of the individual.

b. Examine the data on PM7: Is this sequence variation a polymorphism? *Briefly explain (one sentence). No credit if no explanation.* Yes. The frequency of the “rarer” allele far exceeds the 1% minimum frequency required to designate the variation as a polymorphism.

c. You want to set up a genetic screen to identify individuals at high risk for early onset breast cancer. What is the significance of the data in this table in the context of this goal? *(Two sentences maximum.)*

The sequence variations listed in table 1 are neutral polymorphisms that do not cause disease. In setting up genetic screens it is obviously crucial to distinguish between disease causing variations and neutral sequence variations.

d. Is the sequence variation PM2 likely to result in a neutral missense mutation or silent (same sense) mutation? *Briefly explain (one sentence). No credit if no explanation.* Survey the genetic code. This change is in the third base of codon and will result in a silent mutation. All amino acids with codons ending in a pyrimidine, are specified by the first two bases followed by either U or C.

e. Is sequence variation PM3 likely to result in a neutral missense mutation or a silent (same sense) mutation? *Briefly explain (one sentence). No credit if no explanation.* Survey the genetic code. This change is in the first base of codon and will likely result in a neutral missense mutation.
4. (5 pts.) Mutations that alter renal salt absorption alter blood pressure.

Autosomal dominant mutations in the mineralcorticoid receptor (MR gene) can cause either decreased or increased blood pressure. In some family groups, frameshift or nonsense mutations in the MR gene cause hypotension (decreased blood pressure). One family has been studied in which a missense mutation causes hypertension (increased blood pressure).

a. Which phenotype results from haploinsufficiency? No explanation required.

Hypotension (frameshift and nonsense mutations typically cause loss-of-function not gain-of-function)

b. Which phenotype results from a gain-of-function mutation? No explanation required.  hypertension

c. The gene therapy technique currently used in clinical trials involves the “addition” to somatic cells of a single wild-type copy of a gene. In other words, a single normal copy of the gene is inserted into the genome of the mutant somatic cell, but the mutated copy of the gene is not removed or replaced. Will this strategy work for individuals who are heterozygous for a gain-of-function dominant mutation? 1-2 sentence explanation

NO, in fact this type of gene therapy could exacerbate the problem since the gain-of-function phenotype (hypertension) is due to hyperactivity of the gene product not loss of gene function. [Addition of an extra copy of the gene may have no effect but it certainly wouldn’t alleviate any symptoms.]