

Name: _____ Answer Key _____

2007 7.013 Problem Set 7

Due before 5 PM on FRIDAY, May 11, 2007.

Turn answers in to the box outside of 68-120.

PLEASE WRITE YOUR ANSWERS ON THIS PRINTOUT.

Question 1. (7.5 pts)

1a. (3 pts) Several changes occur during cancer progression. Number each of the following events to indicate their most likely order of occurrence, with **1** indicating the earliest stage and **6** indicating the most advanced stage.

- | | |
|----------|---|
| <u>6</u> | Cells in a state of metastasis |
| <u>5</u> | Cells intrude upon basement membrane |
| <u>2</u> | Hyperplasia |
| <u>3</u> | Cells form benign tumor, less than 1 mm in diameter |
| <u>1</u> | Cells in a state of homeostasis |
| <u>4</u> | Tumor cells induce angiogenesis |

1b. (0.5 pts) At which of the above stages (#1-6) does mutation of one or more genes play a significant role?

2-6. Each stage of cancer progression can involve mutations.

In multicellular organisms (e.g. humans), certain developmental circumstances or certain environmental insults may cause cells to undergo a process of controlled cell death (apoptosis). Apoptosis is a normal process in such organisms, helping to maintain an optimal number of cells in a given tissue.

1b. (0.5 pts) Which is more likely to be associated with the development and progression of cancer: an increase in the amount of apoptosis or a decrease in the amount of apoptosis among cells of the human body? Explain your answer in 15 words or fewer.

A decrease in the amount of apoptosis as this would result in over-growth.

1c. (0.5 pts) In some cancer cells, Cyclin Dependent Kinase 6 (CDK6) enhances phosphorylation the Retinoblastoma protein (Rb). Indole-3-carbinol (I3C), a compound found in vegetables such as Brussels sprouts (yuck), inhibits CDK6 activity. Knowing the cell cycle as you do (for a refresher, revisit Chapter 9 in your text book), would you expect I3C to **promote, suppress** or **have no net effect on** the progression of cancerous cells?

Suppress. CDK6 inhibits Rb, which inhibits the cell cycle, by phosphorylating it. So CDK6 promotes the cell cycle. I3C inhibits CDK6, so it inhibits the cell cycle, eat those Brussels sprouts!

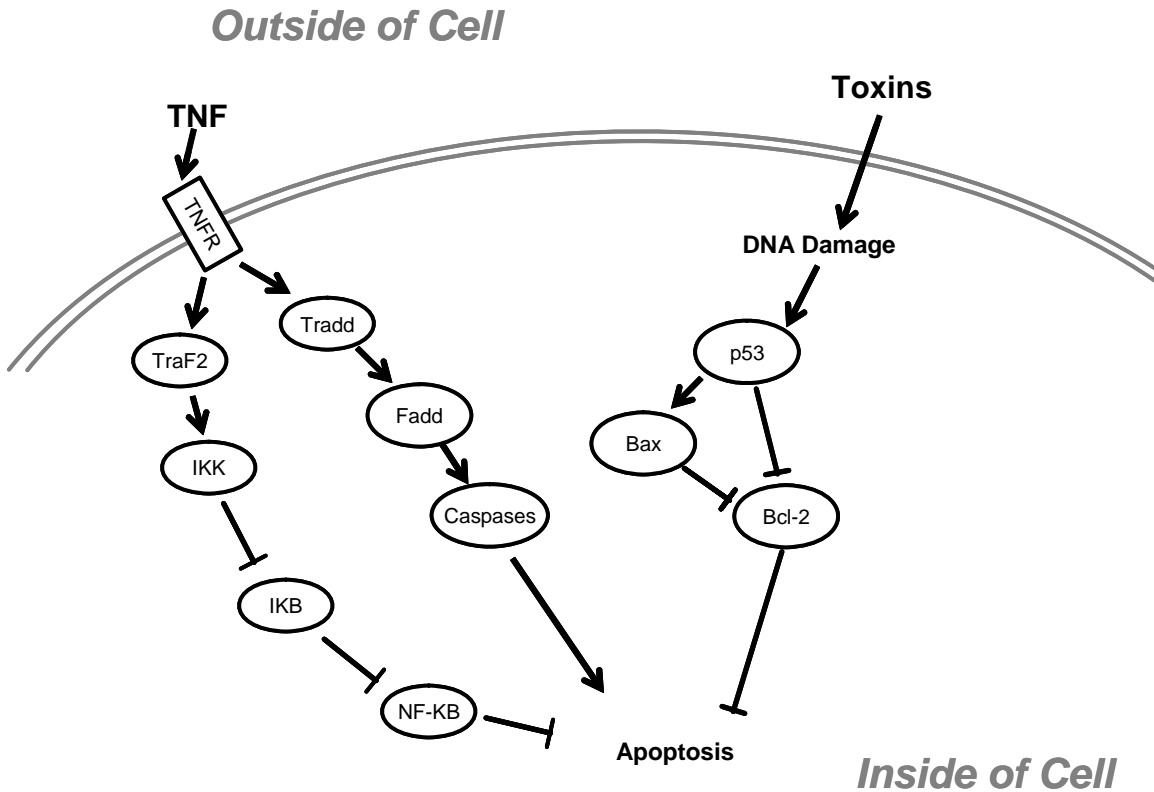


Figure 1. The above diagram depicts some of the factors that influence a cell's decision to undergo apoptosis. In this diagram lines that end with arrowheads (→) indicate activation of another factor or process, whereas lines ending with a perpendicular bar (—|) indicate inhibition of another factor or process.

1c. (0.5 pts) Isothiocyanates are compounds found in vegetables such as broccoli. Such compounds have been shown to induce the expression of proteins called caspases in cervical cancer cells. Based on the above diagram, would you expect ingestion of broccoli to **promote, suppress** or **have no effect on** the progression of cervical cancer cells?
Suppress. Isothiocyanates induce caspases, which promote apoptosis and so would inhibit the growth of cancer cells.

1d. (0.5 pts) Genistein is a compound found in soybeans that is known to increase the expression of a protein called Bax in certain breast cancer cells. Based on the above diagram, would you expect ingestion of soybeans to **promote, suppress** or **have no effect on** the progression of breast cancer cells.
Suppress. Genistein activates Bax, which activates apoptosis, thereby inhibiting uncontrolled growth.

1e. (0.5 pts) Many different food components, for example benzo(a)pyrenes in barbecued foods or aflatoxins in peanut butter, can cause DNA damage. In general, would you expect such DNA damage to **increase, decrease** or **have no effect on** the likelihood of apoptosis, based on the information in Figure 1?
Increase. DNA damage induces apoptosis.

Name: _____ Answer Key _____

1f. (0.5 pts) If ingesting aflatoxins caused a mutation in the gene encoding p53 (rendering this protein non-functional), would you expect further DNA damage to **increase, decrease or have no effect on** the likelihood of apoptosis, based on the information in Figure 1?

No effect. P53 is necessary to sense DNA damage and induce apoptosis, without p53, DNA damage will not induce apoptosis.

1g. (0.5 pts) Turmeric is a spice often used to make a delicious currie. Curcumin is a compound found in turmeric. Experimental evidence has shown that curcumin inhibits the activity of an enzyme called IKK in colon cancer cells. Based on the information in Figure 1, would you expect ingestion of turmeric to **promote/suppress/have no net effect on** the progression of colon cancer?

Suppress. If curcumin keeps IKK inactive, then IKB will be active so NF-KB will be inhibited. Therefore, NF-KB would not be inhibiting apoptosis anymore, and aberrant cell division is more likely to be held in check through apoptosis.

1h. (0.5 pts) Not all cancer cells express all of the proteins depicted in Figure 1. For example, some colon cancer cells do not express the TNF receptor (TNFR). Would you expect ingestion of turmeric to **promote/suppress/have no net effect on** the progression of this type of colon cancer?

No effect. Without the TNF receptor the pathway will never be activated, so IKK will never be activated, so adding an inhibitor of IKK will have no effect.

Name: Answer Key

Question 2. (8 pts)

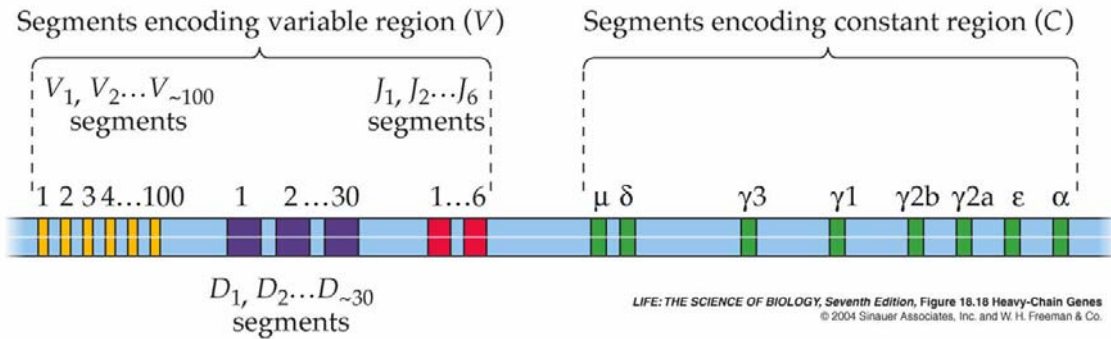


Figure 2. Composition of the heavy chain locus in mouse cells.

Alternative splicing during expression of the Down Syndrome Cell Adhesion Molecule (DSCAM) permits the formation of approximately 38,000 different protein products. In contrast, VDJ recombination permits the formation of approximately 144,000 different antibody heavy chain proteins. How does VDJ recombination differ from alternative splicing in terms of the following:

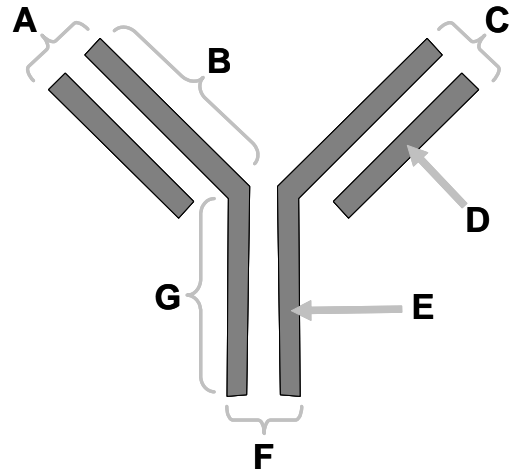
2a. (1 pt) What type of molecule recombines to give rise to diversity at the protein level?

For heavy chain diversity: DNA For DSCAM diversity: RNA

2b. (1 pt) How many different kinds of protein can be made by a single cell that is actively expressing either heavy chains or DSCAM?

Heavy chains: 1 DSCAMs: ~38000

2c. (2 pts) To the right is a schematic of an IgG molecule. Use the letters provided to indicate which of the following terms would be the most appropriate label for each portion of the molecule:



Label	Letter
Heavy chain	<u>E</u>
Light chain	<u>D</u>
Constant region	<u>G</u>
Region with V,D & J domains	<u>B</u>

2d. (0.5 pts) Assume that the IgG molecule depicted in the schematic has typical antigen specificity. Using the letters provided in the schematic, where would you expect an antigen to bind?

A, C

2e. (0.5 pts) How many antigen molecules can be bound by this IgG simultaneously?

2, an antigen can bind to A and another antigen can bind to C.

Name: _____ Answer Key _____

2f. (1 pt) When a T cell recognizes the MHCII/antigen complex, what additional proteins are required on the surface of the T cell to trigger an immune response?
TCR and CD4.

2g. (1 pt) Cancer cells are derived from an organism's native cells, and any cancer-associated antigens that they present on their cell surfaces will themselves be derived from self-proteins. If this is true, then what property of the cancer antigens might make it possible for a healthy immune system to recognize and eliminate cancer cells (15 words or fewer)?

Mutations in the coding sequences of genes that lead to different polypeptide sequences. These mutant peptide sequences may be displayed by MHC proteins and then T cells could bind to the mutant peptides and recognize them as non-self.

2h. (1 pt) HIV infection proceeds by a mechanism that requires a specific interaction between the virus and the CD4 protein on the surface of helper T cells. Imagine that you were able to develop an animal model to study HIV infection. When you expose normal animals to HIV, you find that the number of HIV particles (virions) circulating in their blood increases dramatically, and the animals typically die within 3 months from opportunistic infections. In transgenic animals, you eliminate the genes encoding CD4 protein, so HIV is unable to infect helper T cells. When you expose these animals to HIV, you find that no virus particles accumulate in their blood. You are elated! Then, much to your dismay, you find that most of the animals die anyway within 3 months from opportunistic infections. Explain this result in 15 words or fewer.

Helper T cells cannot function properly without CD4 so the animal is susceptible to infections.

Question 3. (4.5 pts)

3a. (1 pt) Like retroviruses, pararetroviruses are viruses with RNA genomes. Following entry into a host cell, reverse transcriptase creates a cDNA copy of the pararetroviral genome, which then replicates independently in the cell. Expression of genes on the double stranded cDNA leads to production of more pararetroviruses, which then go on to infect other cells. Which step in this process differs from the infection cycle of the more familiar retroviruses? Explain this difference in 15 words or fewer.

Retroviruses do not replicate independently within the host cell, they integrate into the host's genome.

3b. (1 pt) During viral invasion, replication, and propagation, viruses typically employ more host-derived proteins than virus-specific proteins. Why does this make it difficult to develop drugs to destroy virus-infected cells? Explain in 15 words or fewer.

Most of the potential targets are necessary for normal cell function. You can not design drugs against the proteins that the virus uses that are host-derived because it would also harm the host's cells. So it is difficult to develop drugs to destroy viruses because there are few virus-specific proteins that you can target.

Name: _____ Answer Key _____

Infections with filoviruses such as Ebola or Marburg are typically lethal, causing death within a few days. In contrast, infections with adenoviruses, which cause the common cold, are very well tolerated, causing discomfort for a week to 10 days but almost never causing death.

3c. (1 pt) Which of these viruses, the filoviruses or the adenoviruses, are more likely to cause wide-ranging epidemics? Explain in 15 words or fewer?

Adenoviruses. For filoviruses the host dies quickly, limiting its exposure to other potential hosts; adenoviruses are well-tolerated and so **the host will likely pass the infection on to many other people.**

3d. (0.5 pts) Which of these viruses, the filoviruses or the adenoviruses, are likely to cause greater morbidity in a given year?

Adenoviruses, as many more people will be afflicted with this infection each year.

Historically, influenza viruses have caused several disease outbreaks, ranging from the familiar “flu seasons” (which affect many people but cause relatively few deaths) to global pandemics, such as that in 1918, which caused 20-50 million deaths worldwide. Influenza viruses are particles with two predominant surface proteins called hemagglutinins (H antigens) and neuraminidases (N antigens). The pathogenicity of a given strain of influenza (its host range and its infectivity) is largely dependent on the type of H and N antigens it possesses. When an organism (e.g. a bird) is infected with two different influenza viruses, recombination between the two viruses can lead to a new strain with the H antigen from one strain and the N antigen from the other strain.

3e. (1 pt) For many viral diseases, an initial infection causes the host to develop immunity that prevents subsequent infections. Despite this ability, people who are infected with influenza during one flu season are just as likely to fall victim to another influenza infection in a later year. Why does influenza virus appear to be resistant to such acquired immunity? Explain in 15 words or fewer.

Since new influenza strains are made through recombination and mutation the immunity to a previous strain does not make one immune to a new and different strain.