Module 1: Study Guide Questions Answers

1. Cancers and cancer cells arise through changes that provide them growth advantages over normal cells. Most generally, these changes result in a breakdown in the proper regulation of cellular proliferation. These rapidly proliferating cells give rise to clonal colonies or tumors from a single cell. Cancer is a significant health issue because two in five (40%) of Americans (i.e. people you know) will develop cancer, and one in five (20%) will die from cancer.

2. Cancers have been, and generally still are classified histologically (stained microscope images) in two levels. The first system includes benign, malignant and metastatic. The second, parallel system is by apparent tissue/cell type of origin. Most generally, cancers are classified as epithelial (carcinomas, from tissues organized as a layer of cells) and non epithelial (sarcomas, etc.), with some, like melanomas fitting into neither of these categories.

3. The progression in cancer development can be observed in the series of changes in cervical cancer (and colon cancer) in cellular and tumor morphology. Second, the incidence of most cancers, in particular carcinomas, increases exponentially with age indicative of the multiple changes required.

4. Epidemiologic studies have indicated that environment and lifestyle (geographic location), not hereditary origin, correlates with the frequency of the types of cancers a population develops (see lecture 2 slides, Figure 20-20 p. 1224 MBoC; Scientific American Article). For example, Japanese that emigrate to the U.S. take on the cancer types most frequently developed in the populations of their new location (decrease stomach cancers, increase prostate, colon, breast cancers). The factors include food, occupation, air, habits (like smoking), and customs. They are generally classified as 1. chemical (cigarette smoke, coal tar), 2. physical (x-rays, UV light), and 3. lifestyle (women having children or not). Based on this data it has been estimated that 80-90% of cancers are "avoidable." It also indicates that cancers are the result of factors and agents external to our bodies and cells. Unfortunately, it has proven difficult to determine exactly what to avoid to protect ourselves from cancer. On the bright side, this data also indicates that our cells and bodies contain substantial protective mechanisms.

5. The age-adjusted death rates from many of the most prevalent cancers have remained level or increased. In addition, much of the improvements that have been seen are due to early detection and prevention. Prior to 1975 we possessed no real understanding of the molecular and cellular basis of cancer. Most of the anticancer treatments employed today are based on the pre-1975 understanding of cancer and target their rapid proliferation. Many new anticancer strategies are being developed based on the much more detailed understanding of the changes that occur in cancer cells that provide vulnerabilities that can be exploited to kill the cancer cell and leave the normal cells unharmed. Success through this

approach requires accurate, specific identification of the changes in a particular cancer through 'omics. Gleevic is a prime example of a small molecule drug developed to specifically inhibit the protein gene product that is responsible for cancer development. Gleevic has been shown to kill CML leukemia cells without harming normal blood cells. Unfortunately, CML leukemia cells develop resistance to Gleevic at a rate of around 5% per year. The new and improved approach will be to hit the cancer cells with two or three anticancer drugs targeting different cancer-causing proteins simultaneously, since it is highly unlikely that a cell will acquire multiple changes leading to drug resistance simultaneously.

6. Structure-activity relationship studies start with a compound (a drug) with a known inhibitory activity or pharmacological activity and a known "active area" or structure required for its activity. In these studies researchers modify the chemical structure by adding, taking away or modifying functional groups, then test the activity of the new compound. Paul Ehrlich originally developed this approach while he was searching for the "magic bullet" drug that would cure syphilis with minimal side effects for the patient.

7. Computer modeling or "in silico" studies are being used to design new drugs that fit within the computer modeled active site (based on x-ray crystallography data) of the oncoprotein enzyme being targeted. The second, more empirical approach is combinatorial chemistry where large libraries consisting of 1000s, sometime millions of molecules, with slight functional group differences are tested for their ability to inhibit the target oncoprotein enzymes with high throughput assays and screening.

8. Anticancer drugs should be low molecular weight and relatively easy to synthesize. This allows them to more easily enter tumors and cancer cells and reduces the manufacturing costs. The targets of these drugs should be "druggable". This means they are generally proteins with an enzymatic function that is crucial for cancer development (Ras GTPase active site is not a good target). Enzyme active sites usually are defined clefts that the drug can be designed to fit into and bind tightly. Tyrosine kinases like Abl (in Bcr-Abl) have turned out to be "druggable." Pro-proliferation signal receptor hormone binding sites have also proven to be "druggable."

9. The main steps to analyzing anti-cancer drugs are as follows:

a. target enzyme activity inhibition assays;

b. testing the effectiveness and specificity of inhibiting cancer cell growth (or even better killing them) in cell culture (can do this in "nude" mice with human tumors and a cancers, as well);

c. measuring the pharmacodynamics (how well the drug is kept at the right concentration) and the side effects of the drug in humans (sometimes there is testing first in model animals like mice, but only if they are a good model for the human cancer);

d. phase I studies in humans for testing the toxicity of the drug for patients versus the effectiveness in reducing the growth of the cancer;

e. phase II and III (sometime IV) studies comparing the new drug to currently used treatments in effectiveness to increase patient survival rate and time.

10. Iressa is a drug developed through the cutting edge approaches described in the answers to questions 6 through 9. Iressa is very effective in greatly reducing a proportion of non-small-cell lung cancers in patients. Unfortunately, as is seen with Gleevec and CML cells, after months to years of treatment with Iressa a percentage of the cancers become resistant to the drug. In addition, drugs like Iressa and Gleevec are only effective against those cancers that have "oncogene addictions" – dependent on a single oncoprotein for proliferation and survival.

11. Each of you will have your own answer to this question. Personally, I do not think most cancers will be "curable", but I do think they will be controllable. Just as HIV-1 infections are now controllable. We have just begun to develop drugs, antibodies, and other anticancer treatments based on our newly acquired knowledge of cancer cell molecular biology. The sequence and annotation of the human genome indicates there are nearly 300 gene products causally related to cancer. Many of these should be "druggable", so there is potential for development of many more anticancer drugs. Multi-drug therapies may greatly reduce the development of drug resistant cancers. The new "-omics" tools for detailed analysis of each individual cancer should allow very fine-tuned anticancer treatments. Over the past decades promising potential cures have fooled me, but also stunning success stories have pleasantly surprised me. Clearly, there is much more to learn about the causes of cancer and many more approaches to cancer treatment to try. I do not expect cancer researchers to be out of a job within my lifetime.

12. The four main classifications of cellular chemical components or macromolecules are proteins, lipids, saccharides and nucleic acids. These four main types of macromolecules are built from building blocks; amino acids, fatty acids, mono saccharides (sugars) and nucleotides, respectively. These compounds are the building blocks of proteins, lipids (fats, phospholipids, etc.), polysaccharides (and oligosaccharides) and nucleic acids (DNA, RNA), respectively.

13. Cells are made up primarily of C, N, O, and H (96.5% of dry weight), followed by Ca, P, K, and S (another 1.5%). This is highly skewed from the composition of the earth's crust (see the figure from Alberts et al. in the slides). Cells are 70% water, 29% organic compounds (99% of dry weight), and 1% inorganic compounds. Two key parameters or characteristics that determine the properties of these elements are valence and electronegativity. The properties determined are the number and types of bonds formed. All of these elements are small, have outer shells that are about half full or more, the valence electrons are in the first, second or third shell, and have similar enough electronegativity to form covalent bonds rather than ionic bonds. The electronegativity of C, H, O, N, P and S varies enough to form either polar or nonpolar covalent bonds. O and N are sufficiently electronegative that they form polar covalent bonds with C, H, P. C, H and S form non polar bonds with each other. P is generally only found as phosphate (PO_4) containing polar covalent bonds with O.

14. Water. Water's key properties are its dipolarity and the resulting propensity to form hydrogen bonds (H-bonds). Water can form up to four hydrogen bonds with other water molecules and other polar molecules. Water also has the ability to ionize, forming acid (hydronium, + charged) and base (hydroxyl, - charged) forms (amphoteric).

15. Water forms H-bonds with other polar molecules. The tendency to H-bond with up to four other water molecules gives water a high surface tension, specific heat, and boiling point so it is a liquid a room temperature. In addition, water is a good solvent for polar molecules.

16. Carbon is a small element with relatively low electronegativity. Carbon forms four covalent bonds that can be single, double, and triple bonds. Single bonds are tetrahedral and free rotation occurs about these bonds. Double and triple bonds are planer and rotation about these bonds is greatly restricted. Carbon forms polymers that are stable, but not too stable. These polymers are not too reactive with water, but reactive enough. Carbon can form branched polymers for forming functional groups. Carbon can form rings and molecules with resonance (alternating double and single bonds).

17. The relative electronegativity of the four predominant elements in cells is as follows: O > N > C > H. The more electronegative atoms (O, N), when covalently bonded to the less electronegative atoms (C, H), form polar bonds and groups due to the uneven sharing of electrons. Covalent bonds between the two more equally electronegative atoms (C, H) forms groups that are not polar (nonpolar) due to even sharing of electrons.

18. The diagram that does not represent a functional group that forms an organic acid and base is mod1_Q18_C.png

19. Once established in ancient cells, the themes and patterns of macromolecular construction and the extraction of energy have been highly conserved. While some adaptive pathways and intracellular communication networks have been added in the process of cellular evolution, apparently there was little need to develop new classes of compounds. Some things can be explained and predicted by the selection for best function, but some things are chosen by history (natural) and lack of a strong selection against their continued use.