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Science B-47: Molecules of Life

First Exam

November 1st 2007

ID #:_____Exam Key_____
TF:_____

Instructions: Questions are either short answer or short essay. You have 1 hour and 20 minutes to take this exam. Consider your time and skip any question that you have difficulty with and go back to them at the end. Finally, the short answer questions are meant to be short. Two sentences or less is adequate. Good luck!

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Essay Questions: Please <u>choose four of the five essay</u> questions to answer. Each question is worth 12 points.

1) A certain 'morning after' pill developed in the 1950's later became a successful breast cancer drug. Describe 1) how this compound was meant to function as a contraceptive and 2) why such a drug is effective in breast cancer therapy.

Two steroids, estradiol (E2) and progesterone are involved in ovulation and fertilization. Therefore it was predicted that estrogen and progesterone receptor antagonists and agonists should be effective small molecule birth control agents. A progesterone agonist would signal a 'pregnancy' (norethindrone, norgestrel) while a progesterone antagonist could be an effective morning after pill (mifepristone.) As it turns out, ER antagonists have never worked as effective birth control drugs. However, Tamoxifen originally a morning after pill developed in the 1950's as an ER antagonist, effectively blocks the growth of ER+ cancer cells and was later approved for use as a breast cancer therapeutic.

Estradiol (E2) plays a role in growth regulation, differentiation and function of female reproductive organs, including breast, uterus and ovaries. During development, breast growth is regulated by estradiol signaling through the estrogen receptor (ER.) Breast cancer can be divided into two diseases based on whether the progenitor cells were ER+ or ER-. Cancer cells that are ER+ may also rely on estradiol signaling for (unregulated) cell growth. Therefore, blocking the receptor or inhibiting aromatase (blocking estrogen production) should affect growth of ER+ breast cancer cells.

Examples of ER antagonists (Tamoxifen, Raloxifene) and aromatase inhibitors (Exemestane, Arimidex, Femara.)

2) The two medical conditions given in the table below were discussed in class. Fill in each column in the table provided. For example, in the first column write whether an affected individual with either CAIS or CAH has XX or XY for their chromosomal sex.

	Chromosomal Sex (XX, XY)	Morphological Sex (Male or Female)	Hormonal Sex (Male or Female)	Gonadal Sex (Male or Female)	Biological cause of the disorder (10 words or less):
Complete Androgen Insensitivity Syndrome (CAIS)	XY	Female	Male	Male	Faulty androgen receptors
Congenital Adrenal Hyperplasia (CAH)	XX	Male or Female or Ambiguous	Male	Female	High levels of testosterone (because they can not hydroxylate progesterone)

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3) Gene duplication is a common phenomenon in evolution. How does gene duplication facilitate the development of new capabilities? Define gene duplication and include an example of hormones or receptors that evolved in this manner.

Gene duplication is the process of making an extra copy of a gene inside the genome. Gene duplication is different from DNA replication which is making two copies of the entire genome before a cell divides into two. Gene duplication results in more than one copy of the same gene in the genome. (Duplications can arise from unequal crossing-over, called recombination, or transposition. The mechanism of gene duplication is not required for answering this question in midterm.) The two copies of the duplicated gene can evolve independently. One approach is that one copy stays the same and the other copy can gain novel functions by mutations. The unchanged copy can help the survival of the mutant copy by maintaining the original function of the gene. Another approach is the two copies of the gene will evolve independently by creating different mutations in the DNA sequence, thus gaining different capacities. Recent genomic sequence data provide substantial evidence for the abundance of duplicated genes in all organisms surveyed. Some examples from Science B47 are:

1) Oxytocin and Vasopressin were the results of the duplication of the gene called vasotocin. They employed the second approach to gain different functions.

2) There is usually more than one gene in our genome encoding different receptors for the same hormone. For example, adrenaline has alpha- and beta-, two major types of receptors, which regulate different responses to adrenaline. For each major type of receptors, there are also many subtypes which are the results of duplication and mutation from a common alpha- or beta- ancestor.

4) It is projected that within 10 years full human genome sequencing will cost less than $1,000 and will take less than a day. Raise 3 issues associated with widely available personal genomes and discuss their positive and negative implications. Support each issue with a specific example.

a) People will have access to details about risk factors, some genetic risk factors are well understood and some are not. People may use the knowledge of their risk factors to modify their lifestyle, doctors may use them to modify treatment, but people may also misunderstand their risk factors and possibly act inappropriately. Example: Craig Venter might choose a heart healthy lifestyle to mitigate his slightly raised heart attack risk or he might decide not to bother since he has the "heart attack gene" and will die anyways.

b) Insurance companies might have access to these genomes. They could use them to deny people coverage or use them to calculate better more exact rates based on your risk just like car insurance companies do by profiling. This could be positive or negative depending on your risk factors and if you think this is fair or not. Example: If you had risk factors for a chronic disease like diabetes this might make your insurance more expensive.

c) Sequencing your personal genome could reveal information about a family member. This could be good if it revealed a risk factor and then preventative action was taken or bad if they did not want to know this information. Example: A daughter might not want to know if she has a breast cancer risk factor gene. However, if her mother is tested and has it then statistically speaking you can make predictions about the daughter's genes. Many answers possible – all should include a recognizable issue, discussion of positives and negatives and an example

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5) The “war between the soups and the sparks” was a disagreement about the mechanism of neuronal transmission. Briefly describe the two models that were being debated and then explain a critical experiment that helped demonstrate which model was ultimately correct. Make sure to mention who “won the war” and why.

This heated debate was centered upon whether transmission of a neural signal (from the presynaptic to the postsynaptic cell) occurred via electricity or via a small molecule (chemical) signal. Those in favor of electrical transmission came to be known as the "Sparks", while those favoring chemical transmission were termed the "Soups." The experiment which settled this debate involved stimulating the vagus nerve of a frog heart, which caused the heart rate to slow. The fluid directly surrounding the stimulated heart was then collected and applied to a second heart. It was observed that transfer of this fluid induced a decrease in heart rate of the second, recipient heart. These results showed that transmission between neurons occurs via a diffusible factor, or small molecule, proving the Soups right.

Short answer: Please answer the following question in two sentences or less. 4 points each

6) What would happen if you administered vasopressin to a male Montane vole (non-monogamous species of vole) directly before mating? Would he form an attachment to the female? Why or why not?
No, an attachment would not be formed because the male Montane vole is missing receptors for vasopressin in key areas of the brain.

7) Transporters are membrane proteins, which are responsible for transporting some necessary small molecules into the cell interior. Why do some small molecules require transporters?
Often small molecules are too polar to cross a lipid membrane. Transporters help the small molecule do this.

8) What are two main roles for cholesterol in the body? (10 words or less each)

a) precursors for steroid hormones

b) lipid bilayer (membrane) rigidity enhancer or blood pressure elevator

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9) Give two specific examples of shape complementarity discussed in class besides DNA and survival machines.

a) any ligand, antagonist, agonist and receptor complex

b) a substrate or inhibitor and its enzyme

10) Define agonist and antagonist:

Agonist: A ligand that mimics the abilites of an endogenous ligand to activate a receptor

Antagonist: A ligand that inhibits the ability of an endogenous ligand to activate a receptor

11) Give one advantage and one disadvantage of using a gene knockout as compared to a small molecule antagonist to study a biological process.

Advantage: Key advantages of gene knockout include that knockouts only target one gene and do not have any chance of antagonizing other receptors as small molecules do, knockouts are often 100% complete unlike small molecules that may not be as robust, and knockouts do not require constant administration as small molecules do.

Disadvantage: Key disadvantages include that knocking out a gene that has multiple functions may disrupt unintended and very important cellular functions, gene knockouts are often more difficult to achieve, we can not test gene knockouts on humans, gene knockouts are permanent and do not allow any temporal control like small molecule administration would.

12) Why did the pseudohermaphrodites described in the first lecture develop female-like genitalia before puberty?

Prenatally, a problem with 5alpha-reductase caused a deficiency of DHT which is the hormone that stimulates male physical development.

13) How could genetic information be used to personalize depression medication in the future? What improvements would this make on current depression treatment?

Current depression treatment is trial and error and only 60% accurate. We do not know what receptor problems are present in a person's brain and so we guess which medications a person needs. Genetic information that showed exactly what receptor was the problem would allow for a quicker, less side-effect inducing therapy as we could give the correct drug immediately.

14) Adrenaline often has to perform different functions in the same organ such as contracting one eye muscle and relaxing another. How can one molecule perform two such different functions?

One molecule can stimulate multiple different receptors each of which can perform a different action (for example, one can contract and the other relax an eye muscle). This is known as multiplexing.

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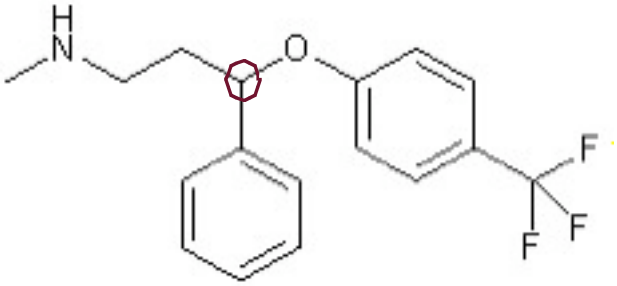
Use the following structure and information for questions 15 and 16:
Fluoxetine (Prozac) is a racemic mixture of the molecule shown below.



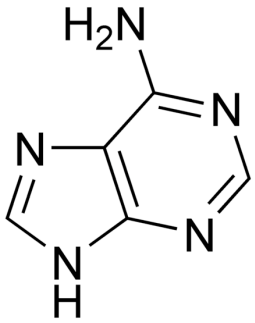
15) Please circle the stereocenter and describe why it is important.

The stereocenter is the only carbon attached to four different things. It is important because it is the point from which an enantiomer can be formed. It is the chiral center. Further, enantiomers can have different receptors and thus different biological activities.

16) Imagine that the patent for this drug is about to expire, what is the easiest way that a drug company might try to find a new drug to patent?

The above drug is a racemic mixture which means that it is a 50:50 mix of enantiomers. A drug company might was to isolate or synthesize a single enantiomer and try to get a new patent on that drug.

17) Adenine is shown below. What is the molecular formula of adenine and why is the molecular formula evolutionarily significant?



$C_5H_5N_5$ is made of 5 X HCN which is a prebiotic gas molecule. Thus, adenine could have arisen prebiotically by five HCN molecules coming together.

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18) Draw all seven isomers of the following molecular formula (no stereoisomers): $C_4H_{10}O$. Any of the drawing conventions used in class are acceptable (e.g. hydrogen atoms drawn out or implied). (Hint: this is the same molecule as from your homework!)