Name: _____ Date: _____

In this exam sheet there are 18 questions.
Each answer yields up to 2 points according to its correctness and completeness.

1. Is a prokaryote cell larger or smaller than a virus?

2. Are eukaryote cells larger or smaller than prokaryotes?

3. What is the difference between stem cells and mature cells? (explain)

4. What is the cell cycle? (explain)

5. What is the LD_{50} radiation dose for humans? Do animals with larger LD_{50} doses exist? (explain)

6. What is the difference between sarcomas, carcinomas, and blastomas? (explain)

7. Using the table below, find **a.** how many of OH ions are produced, on average, when a 20 keV electron stops in water. And **b.** how many H_3O^+ ions are produced by a 5000 eV electron that stops in water?

Table 13.3 *G* Values (Number per 100 eV) for Various Species in Water at 0.28 μs for Electrons at Several Energies

	Electron Energy (eV)							
Species	**100**	**200**	**500**	**750**	**1000**	**5000**	**10,000**	**20,000**
OH	1.17	0.72	0.46	0.39	0.39	0.74	1.05	1.10
H_3O^+	4.97	5.01	4.88	4.97	4.86	5.03	5.19	5.13
e^-_{aq}	1.87	1.44	0.82	0.71	0.62	0.89	1.18	1.13
H	2.52	2.12	1.96	1.91	1.96	1.93	1.90	1.99
H_2	0.74	0.86	0.99	0.95	0.93	0.84	0.81	0.80
H_2O_2	1.84	2.04	2.04	2.00	1.97	1.86	1.81	1.80
Fe^{3+}	17.9	15.5	12.7	12.3	12.6	12.9	13.9	14.1

8. A 10 cm^3 sample of water is given a dose of 200 mGy from 10 keV electrons. Use the table in exercise 7 to find how many H_2O_2 molecules are produced in the sample.

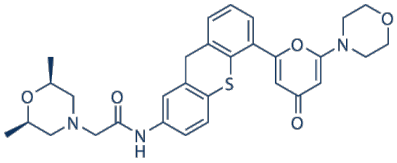
9. What is oxidative stress? How do cells counter oxidative stress? (explain)

10. What are single strand breaks and double strand breaks, and how can they cause disease and carcinogenesis? (explain)

11. What is the multitarget model? What is the expression of the survival probability in the multitarget model?

12. What is the Oxygen Effect? (explain)

13. KU-60019 is a novel, highly effective radiosensitizer, which is in a preclinical test phase.



It works by inactivating the ATM gene. How does this explain its radiosensitizing activity?

14. What is the mathematical expression of the TCP in the context of the multitarget model?

15. What is the mathematical expression of the NTCP in the Lyman model?

16. The U-251MG cell line (one of the cell lines of the brain tumor *glioblastoma multiforme*) has the following LQ parameters: $\alpha = 0.36$ Gy^{-1} and $\beta = 0.06$ Gy^{-2}. When we irradiate these cells in a fractionated treatment with a series of 2 Gy doses, what is the effective D_0?
(Hint: the effective D_0 is defined in the Poisson model description of the surviving fraction: $S(D) = e^{-D/D_0}$)

17. Explain the concept of Equivalent Uniform Dose.

18. List the 5 R's of radiobiology, along with a short description of their meaning.

Answers

1. Prokaryotes are generally larger than viruses. Some large viruses can match the size of small prokaryotes.

2. Eukaryote cells are larger than prokaryotes.

3. Stem cells are undifferentiated cells that can differentiate into specialized cells and can divide (through mitosis) to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells, and adult stem cells, which are found in various tissues.
Mature cells are fully differentiated and do not exhibit mitotic activity.

4. The cell cycle is the sequence of different steps required to duplicate a cell. Each step is called *phase*. The main phases are G1, S, G2, M. The duplication of DNA takes place during the S phase, and mitosis takes place in the M phase. Phases have different durations: the shortest phase is the M phase.

5. The LD_{50} radiation dose for humans is about 5 Gy. Animals with much higher LD_{50} doses exists, such as tardigrades and extremophile bacteria like *D. radiodurans*.

6. *Sarcomas*, are cancers that arises from transformed cells of mesenchymal origin, i.e., from cells that lack polarity and are surrounded by a large extracellular matrix. Malignant tumors made of cancellous bone, cartilage, fat, muscle, vascular, or hematopoietic tissues are, by definition, considered sarcomas.
Carcinomas, are malignant tumors originating from epithelial cells.
Blastomas, are tumors – more common in children – caused by malignancies in precursor cells (blast cells or simply blasts). Blasts are unipotent cells (cells that have lost most or all of the stem cell multipotency)

7. 220 OH ions; 251.5 H_3O^+ ions.

8. 10 cm^3 of water have a mass of 0.01 kg, and therefore 200 mGy correspond to a deposited energy of 0.002 J. Since 1 eV ≈ $1.6\ 10^{-19}$ J, the deposited energy in eV is ≈ $1.25\ 10^{16}$ eV. Using the table in exercise 7, this gives on average a production of $2.3\ 10^{14}$ molecules of H_2O_2.

9. Oxidative stress is caused by the Reactive Oxygen Species, and it can be both endogenous and exogenous. Radiation is a powerful exogenous source of ROS. Cells counter oxidative stress with an array of different enzymes, like catalase and superoxide dismutase.

10. The terminology *single strand break* and *double strand break* refers to damage caused to DNA, that can affect just one or both strands of the DNA molecule. Both kinds of damage can be repaired, however single strands break are more easily repaired by cells, with fewer errors, because the intact strand acts as a template for the repair process. In double strand breaks a template for repair is not always available.

11. In the multitarget model we assume that a cell dies only when multiple targets are all hit. So, if the probability of not hitting a given target is e^{-D/D_0}, then the probability of hitting the same target *at least once* is $1 - e^{-D/D_0}$, and therefore the probability of hitting all of the n targets at least once is $(1 - e^{-D/D_0})^n$, and finally the probability of NOT hitting all of them at least once is

$$S(D) = 1 - (1 - e^{-D/D_0})^n$$

12. The oxygen effect consists in an enhanced ROS production when the concentration of oxygen dissolved in the cytoplasm is high.

13. The ATM gene is an important component of the cellular DNA repair circuit. Therefore, by inactivating the ATM gene, KU-60019 stops the DNA repair process and facilitates cell killing by radiation.

14. The TCP is the probability of killing all the cells in a tumor. If the tumor has N cells then the average number of surviving cells is $NS(D)$, and the probability that no cell survives is $e^{-NS(D)}$. When we use the multitarget model, we find

$$TCP = e^{-NS(D)} = e^{-N(1-(1-e^{-D/D_0})^n)}$$

15. The Lyman model of the NTCP for a specific organ is the sigmoid response function

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2} dt\,; \qquad u = \frac{D - D_{50}}{m\, D_{50}}$$

where D_{50} is the whole-organ dose that corresponds to $NTCP$ = 50%, and where m is a dimensionless parameter that tunes the slope at the inflection point of the sigmoid curve.

16. The surviving fraction in the LQ model is described by the expression

$$S(D) = e^{-(\alpha D + \beta D^2)}$$

In the present case $\alpha D = 0.72$; $\beta D^2 = 0.24$, and therefore $\ln S(2\text{ Gy}) = -0.96 = -(2\text{ Gy})/D_0$. Thus, $D_0 \approx 2.083$ Gy.

17. For any dose distribution, the corresponding Equivalent Uniform Dose (EUD) is the dose in Gy, which, when distributed uniformly across the target volume, causes the survival of the same number of clonogens. Therefore, two different nonuniform target dose distributions are equivalent, i.e., they have the same EUD, if the corresponding expected number of surviving clonogens are equal.

18. The 5 R's of radiobiology are:

- *Repair*: repair of sublethal damage must be taken into account because it affects the tolerance of healthy tissue to radiotherapy (allowing cells to repair we can continue a treatment that should otherwise be interrupted), and because tumor cells often have a reduced ability to repair damage, e.g., when they have a mutated P53 gene
- *Redistribution of cells within the cell cycle*: Proliferating cells have different radiosensitivities, in particular cells in the S phase are *less* sensitive to radiation. After a session, more of the cells in the S phase survive, and waiting for a redistribution of cells in different phases helps in killing them.
- *Repopulation*: Repopulation takes place both in healthy and in diseased tissues. At least some tumors display accelerated repopulation after 4-5 weeks into treatment. This means that this repopulation must be countered in long treatments.
- *Reoxygenation*: Many tumor tissues are hypoxic, and this protects tumor cells from radiation because of the Oxygen Effect. Therefore, one useful strategy consists in helping oxygen diffuse through tissues. Reoxygenation can be achieved by killing cells closer to blood vessels, so that oxygen penetrates more deeply into the tumor tissue.
- *Radiosensitivity*: Radiosensitivity differs in different cell types, and this factor must be included in therapeutic strategies. Radiosensitivity can also be enhanced in tumor cells with proper sensitizing chemicals.