Name: ________________________________ Date: ___________________

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

1. Are eukaryote cells larger or smaller than prokaryotes?

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

3. What is a stem cell? (explain)

4. What is the cell cycle? (explain)

5. A worker in a nuclear plant receives radiation with a dose rate of 2 mGy/s for a total time of one hour. What is the total dose? Is this total dose smaller or larger than the LD_{50} dose for humans?

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

7. Using the table below, find **a.** how many of H_2O_2 molecules are produced, on average, when 10^5 electrons – each with 5 keV kinetic energy – stop in water. And **b.** how many H^3O^+ ions are produced by a single 10 keV 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 100 cm^3 sample of water is given a dose of 100 mGy with 10 keV electrons. Use the table in exercise 7 to find how many e_{aq}^- ions are produced in the sample.

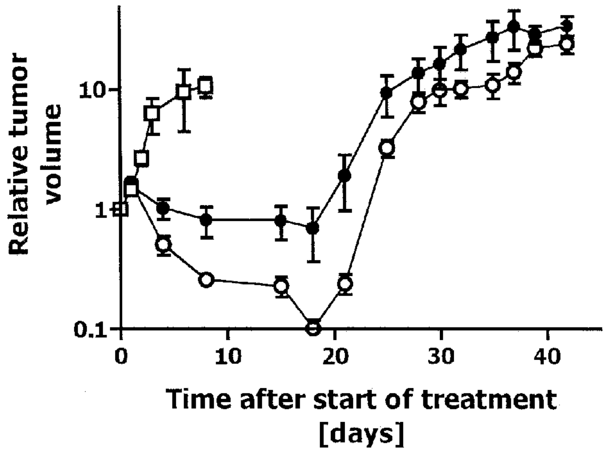
9. What is oxidative stress? How do cells counter oxidative stress? (explain)

10. Explain how the degree of hypoxia of the tumor microenvironment can affect radiotherapy.

11. What is the difference between the Poisson model and the multitarget model? What is the expression of the survival probability in the multitarget model?

12. What is the Relative Biological Effectiveness? (explain)

13. The following image – taken from Smirnia et al., Acta Oncologica 40:7, 870-874 (2009) – compares tumor growth (Rat RH1 tumor) after radiotherapy carried out in two different conditions:



Black dots show the tumor volume after irradiation carried out while the animals were breathing normal air; the white dots show tumor volume with animals breathing carbogen (95% O_2, 5% CO_2); finally, the white squares show the growth of tumor volume in unirradiated, control animals. Explain the difference between tumor growth with normal air and carbogen breathing.

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 3 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. Eukaryote cells are larger than prokaryotes.

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

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 total dose is 7.2 Gy. Since the LD_{50} radiation dose for humans is about 5 Gy, this dose is definitely higher than the LD_{50} radiation dose.

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. $9.3 \cdot 10^6$ H_2O_2 molecules; 519 H^3O^+ ions.

8. 100 cm^3 of water have a mass of 0.1 kg, and therefore 100 mGy correspond to a deposited energy of 0.01 J. Since 1 eV ≈ $1.6\ 10^{-19}$ J, the deposited energy in eV is ≈ $6.25\ 10^{16}$ eV. This means that about $6.25\ 10^{12}$ electrons have been absorbed in the sample, and using the table in exercise 7, this gives on average a production of about $7.375\ 10^{14}$ e_{aq}^- ions.

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. Radiation kills cells more effectively when oxygen is copious: this is the Oxygen Effect. A hypoxic tumor microenvironment means that radiation is less effective in killing tumor cells.

11. In the Poisson model, a cell dies if a single sensitive target is hit; in this model, the probability of NOT being hit is $S(D) = e^{-D/D_0}$. In the multitarget model we assume that a cell dies only when multiple targets are all hit. So, if the Poisson 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. If a dose D of a given type of radiation produces a specific biological endpoint, then RBE is defined as the ratio

$$\mathrm{RBE} = \frac{D_X}{D}$$

where D_X is the X-ray dose needed under the same conditions to produce the same endpoint.

13. The fraction of O2 in carbogen (95%) is much higher than in normal air (21%), therefore it is expected that the average tissue oxygenation level is higher with carbogen, and that there is an enhanced oxygen effect.

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 $\alpha D = 1.08$; $\beta D^2 = 0.54$, and therefore $\ln S(3 \text{ Gy}) = -1.62 = -\frac{3 \text{ Gy}}{D_0}$.
Thus, $D_0 \approx 1.85$
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.