Name: ______________________________ Date: __________________

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

1. What is the typical size range of viruses?

2. Are eukaryote cells larger or smaller than prokaryotes?

3. What is a stem cell? (explain)

4. What is the S-phase? (explain)

5. A worker in a nuclear plant receives radiation with a dose rate of 50 μGy/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 percentage of coding DNA? (tick the correct answer)

a. 0.1 %
b. 1.5 %
c. 10. %
d. 90 %
e. 99 %

7. Using the table below, find **a.** how many of H_2O_2 molecules are produced, on average, when 10^4 electrons – each with 20 keV kinetic energy – stop in water. And **b.** how many e^-_{aq} ions are produced by a single 5 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 10 cm^3 sample of water is given a dose of 100 mGy from 1 keV electrons. Use the table in exercise 7 to find how many H_3O^+ ions are produced in the sample.

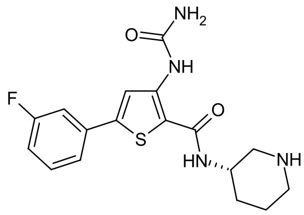
9. Radiation causes damage both directly and indirectly. Explain the difference between direct and indirect effects.

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

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

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

13. AZD7762 is a novel drug that is administered in combination with DNA-damaging agents, to enhance the efficacy of both conventional chemotherapy and radiotherapy and increase patient response rates in a variety of settings.



AZD7762

It works by abrogating the S and G2 checkpoints. How does this explain its radiosensitizing activity?

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

15. What is the mathematical expression of the TCP in the context of the multitarget 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. List the 5 R's of radiobiology, along with a short description of their meaning.

18. Explain the concept of Equivalent Uniform Dose.

Answers

1. From about 30 nm to about 250 nm.

2. Eukaryote cells are typically 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.

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 S phase is where the duplication of DNA takes place; it is also the phase with the longest duration.

5. The total dose is 0.18 Gy. Since the LD_{50} radiation dose for humans is about 5 Gy. this dose is considerably less than the LD_{50} radiation dose.

6. 1.5 %

7. $3.6 \cdot 10^6$ H_2O_2 molecules; 44.5 e^-_{aq} ions.

8. 10 cm^3 of water have a mass of 0.01 kg, and therefore 100 mGy correspond to a deposited energy of 0.001 J. Since 1 eV ≈ 1.6 10^{-19} J, the deposited energy in eV is ≈ 6.25 10^{15} eV. Using the table in exercise 7, this gives on average a production of 3.0 10^{14} H_3O^+ ions.

9. In direct action, the radiation interacts directly with a critical target in the cell, by breaking chemical bonds. Charged particles can do this without intermediate steps. Neutral particles (e.g., photons) must first be absorbed, and the damage is caused by the charged particles that are emitted after the primary interaction (e.g., the electrons and positrons in the electromagnetic cascade produced by a high-energy photon). In indirect action, the ROS produced by incoming radiation break the chemical bonds in the affected targets. It is estimated that indirect damage accounts for as much as 2/3 of the total radiation damage.

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

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. 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. When DNA is damaged a proliferating cell stops at checkpoints to repair DNA and the cell cycle restarts only when the repair is complete. By abrogating checkpoints in combination with DNA-damaging agents, it is thus possible to kill proliferating cells.

14. 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.

15. 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

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

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. 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.

18. 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.