Investigation of Ultrashort Electron Beam Interaction with the DNA Molecule

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These are topical problems of modern radiobiology and medicine, and they directly related to radiotherapy

What is radiotherapy?

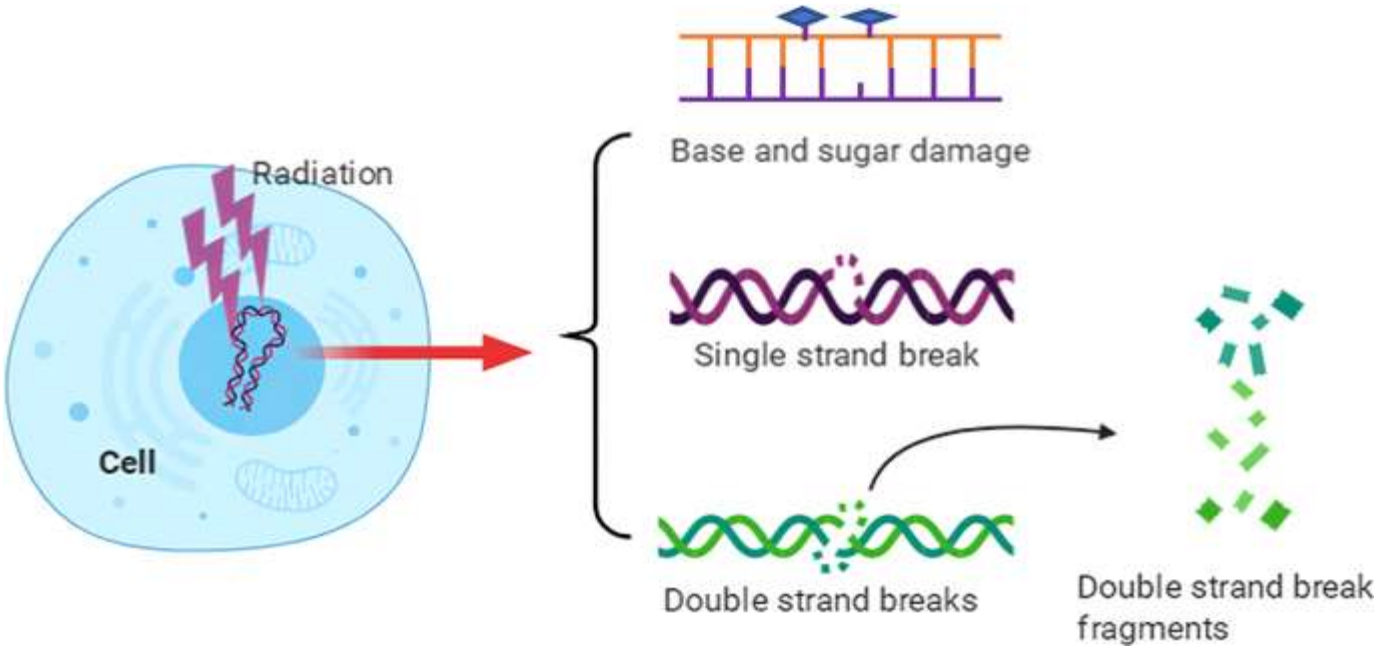
Radiation therapy, also called radiotherapy, is a type of cancer treatment. This treatment uses beams of intense energy (ionizing radiation) to kill cancer cells. Radiation therapy most often uses X-rays. In now days intensively using other types of radiation therapy exist, gamma rays, high-energy electrons or heavy particles.

With the development of accelerators and ability to control beams has led to an increase in the use of linac in medicine.

What Is the Biologic Basis for Radiation Therapy?

Radiation therapy works by damaging the DNA of cells and destroys their ability to reproduce.

Both normal and cancer cells can be affected by radiation, cancer cells have generally impaired ability to repair this damage, leading to cell death.

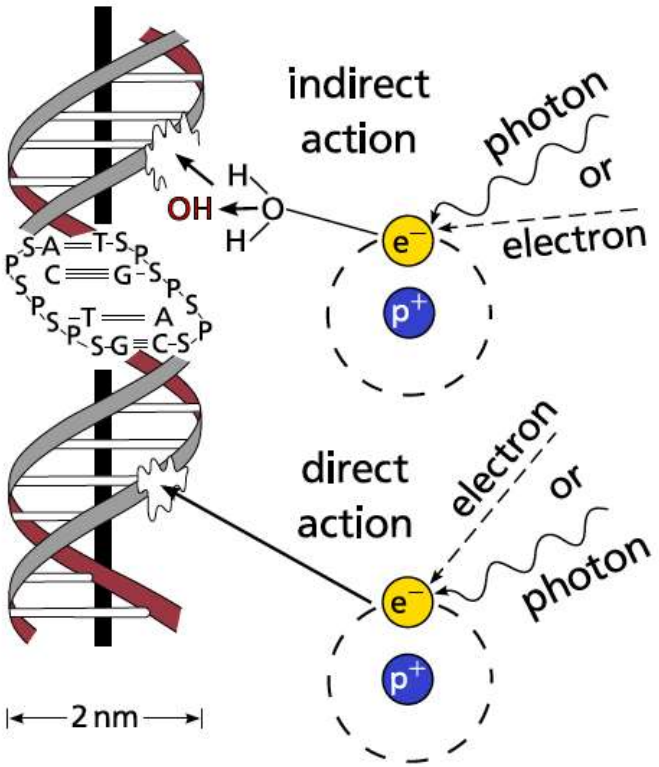


What Is the Physics Basis for Radiation Therapy?

Ionizing radiation can occur radiochemical damage of DNA either by direct action or indirect action.

Direct damage is caused by energy deposition in direct hits from electrons liberated in ionization processes.

Free radicals formed by ionization in the hydrolysis of water, can cause indirect damage to the DNA in chemical reactions.

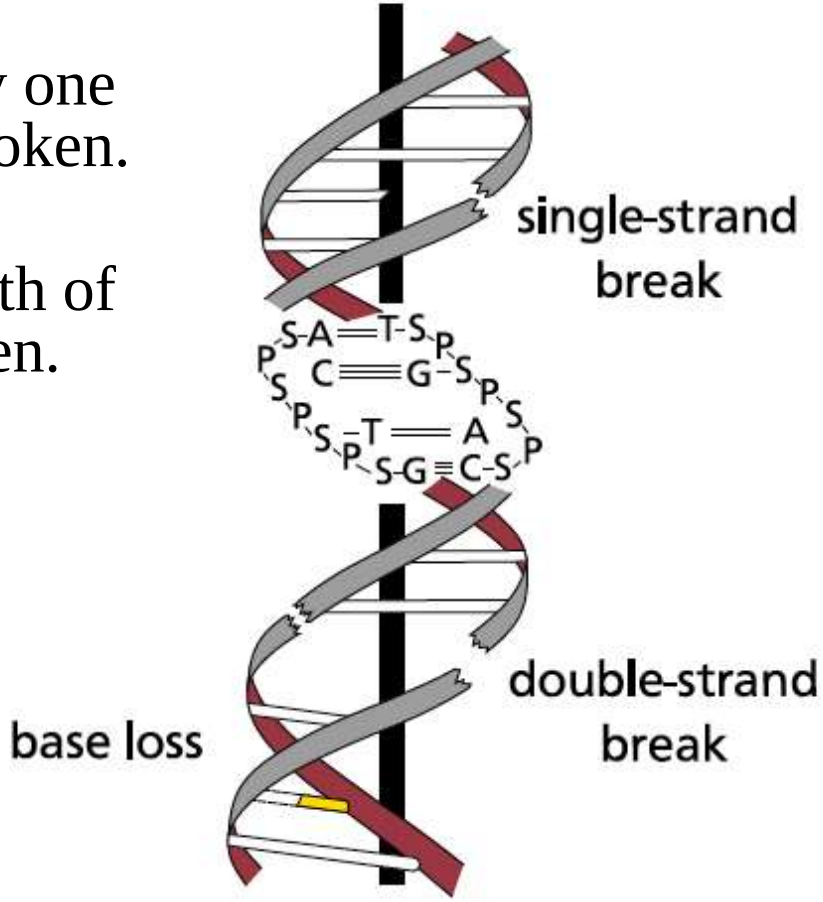


DNA damage

Two types of breaks in the sugar phosphate backbone can caused by ionizing radiation.

A single strand break occurs when only one of the sugar phosphate backbones is broken.

Double-strand breaks occurs when booth of the sugar phosphate backbones is broken.



Radiation therapy combination

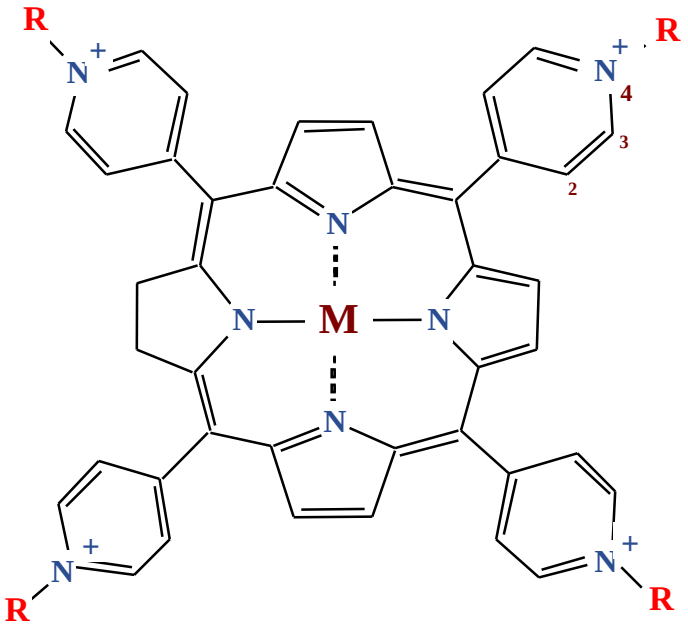
In recent years, radiation therapy has been used in combination with other methods (chemotherapy, photodynamic therapy, etc.), which significantly increases the effectiveness of radiation therapy. Have been shown some compounds, such as cisplatin, which is widely used in chemotherapy, make radiation therapy more effective. So drug–radiotherapy combinations has clear potential to increase the effectiveness of radiotherapy and reduce side effects.

Interaction of porphyrins with biopolymers

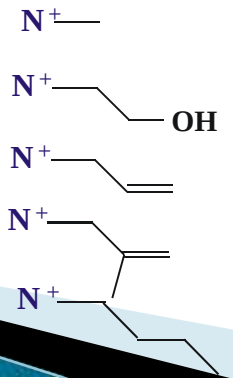
Previously, for last 20 years, in our laboratory we widely investigated the interaction of width class of biologically active compounds - cationic porphyrins with biopolymers, particularly with DNA via spectroscopic, calorimetric methods:

- Uv/vis spectrometry
- Circular dichroism
- Microcalorimetry

Porphyrins



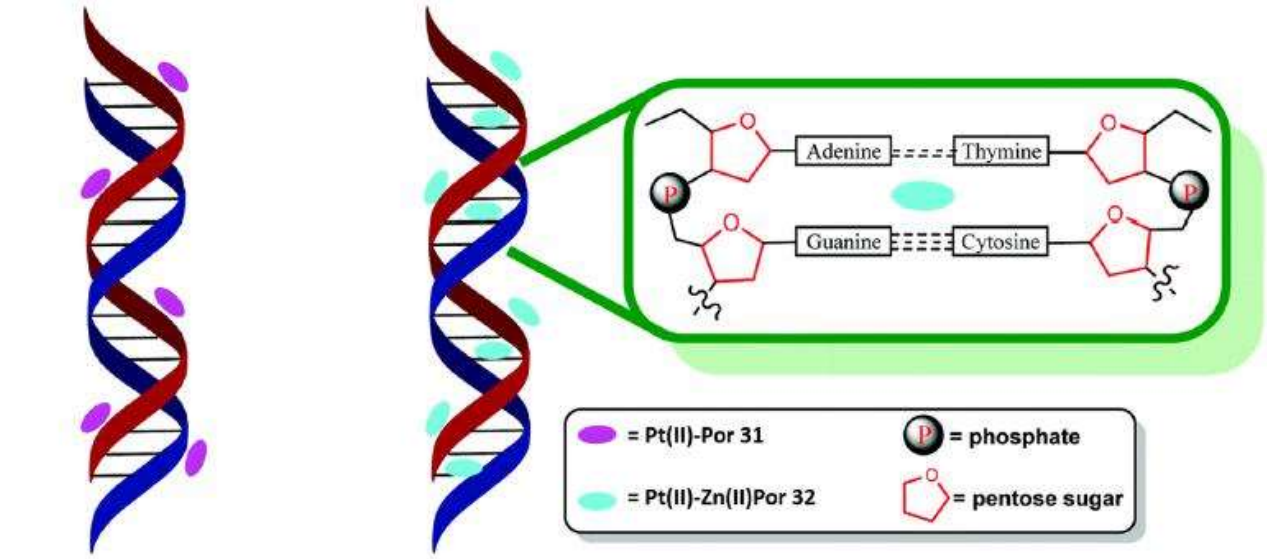
M = 2H, Zn, Cu, Co, Mn, Au, Ag



R=CH_3	TMPyP
R = CH_2-CH_2-OH	TOEtPyP
R = CH_2-CH=CH_2	TAlPyP
R = CH_2-C(-CH_3)=CH_2	TMetAlPyP
R = CH_2-CH_2-CH_2-CH_3	TButPyP

Schematic representation of the main types of porphyrin binding to DNA:

- intercalation
- external stacking interaction and external groove binding

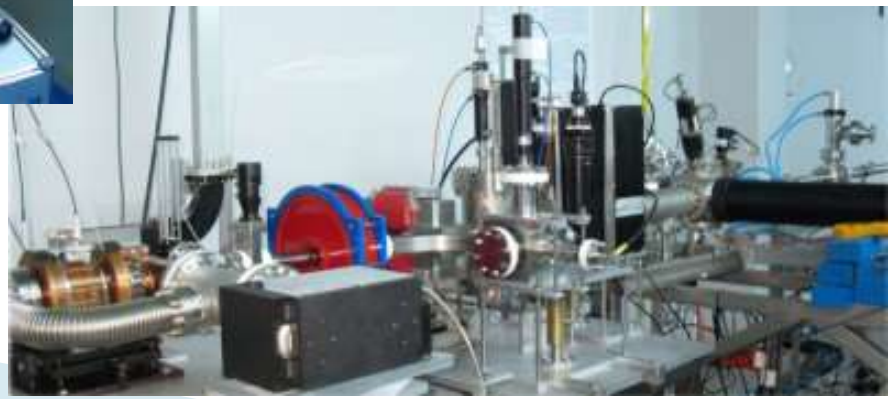


Main Idea

The goal of our investigations is to identify the structural changes that occur in the DNA molecule when irradiated with an electron beam, when the solution contains potentially antitumor compounds - porphyrins. These studiesmake it possible to determine the possible increase in the effect of radiation on DNA molecules. Also determine the optimal values of concentrations of compounds and radiation doses that can be used in radiation therapy.

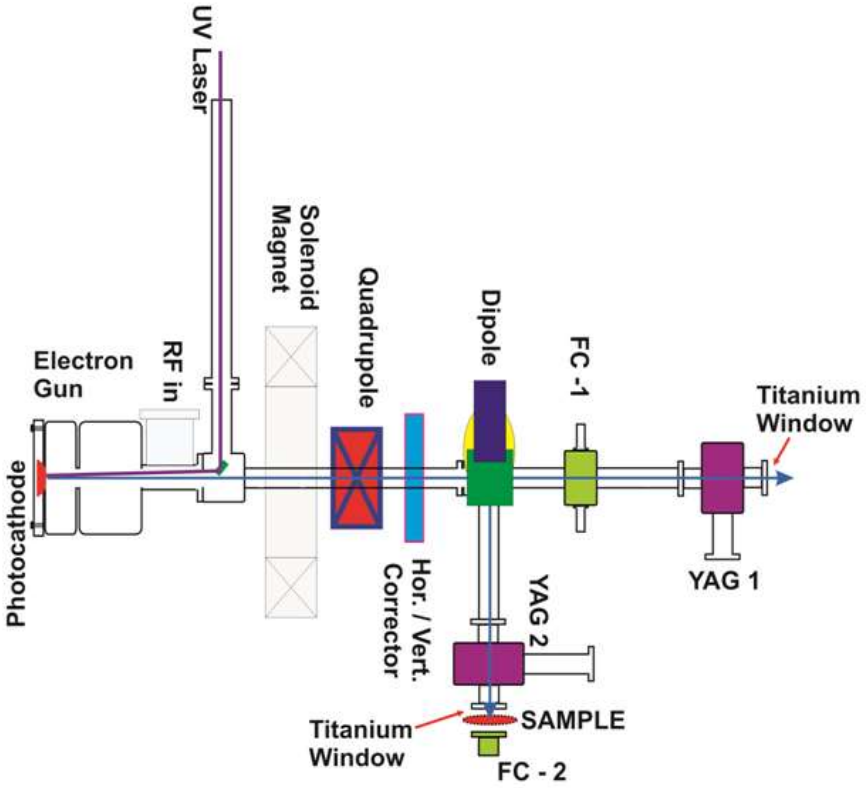
Electron beam source

AREAL-Advanced Research Electron Accelerator Laboratory is an electron linear accelerator facility based on photocathode RF gun. Currently the facility is able to provide ultra-short electron bunches with about 0.5 ps bunch length with a particle charge up to 800 pC. For irradiation researches sub-picosecond long electron bunches with energies up to 5 MeV guarantee a short interaction time with the sample material, meanwhile delivering sufficient radiation dose due to bunch energy and hundreds of pico-Coulombs charge. Two experimental stations of AREAL facility provide a possibility to extract machine electrons (out of machine vacuum) and perform irradiation experiments in-air.

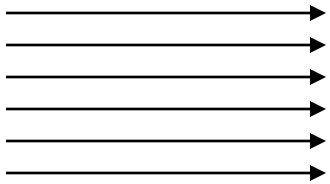


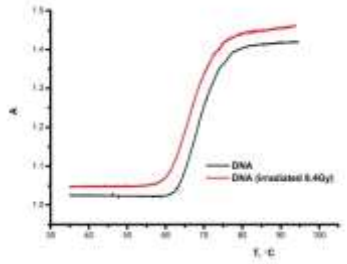
Sources of electron beam

3 MeV beam energy,
500 fs pulse duration and
5 Hz frequency.



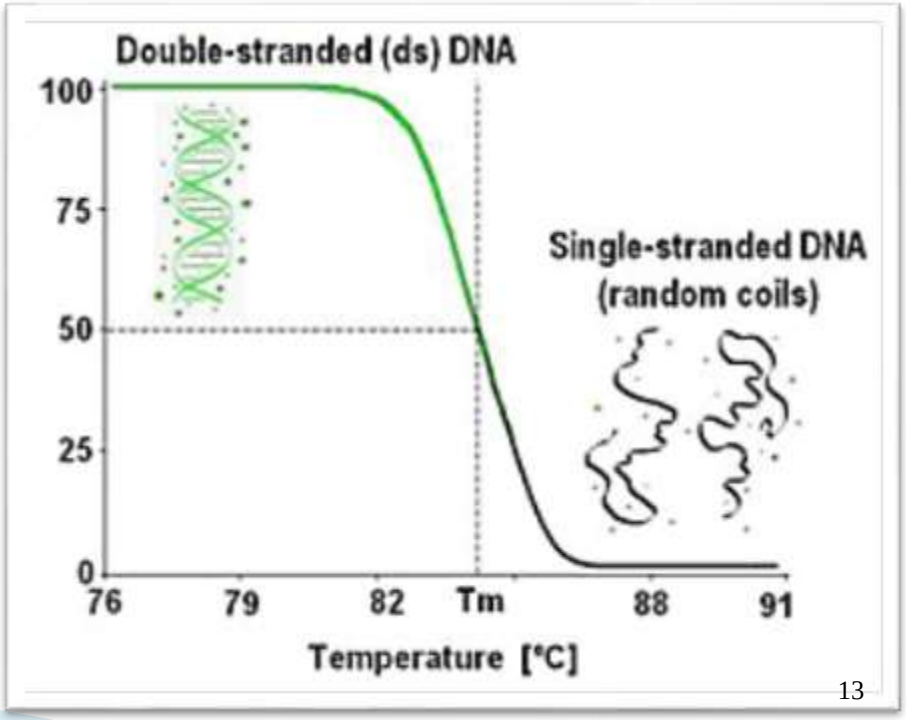
electron beam



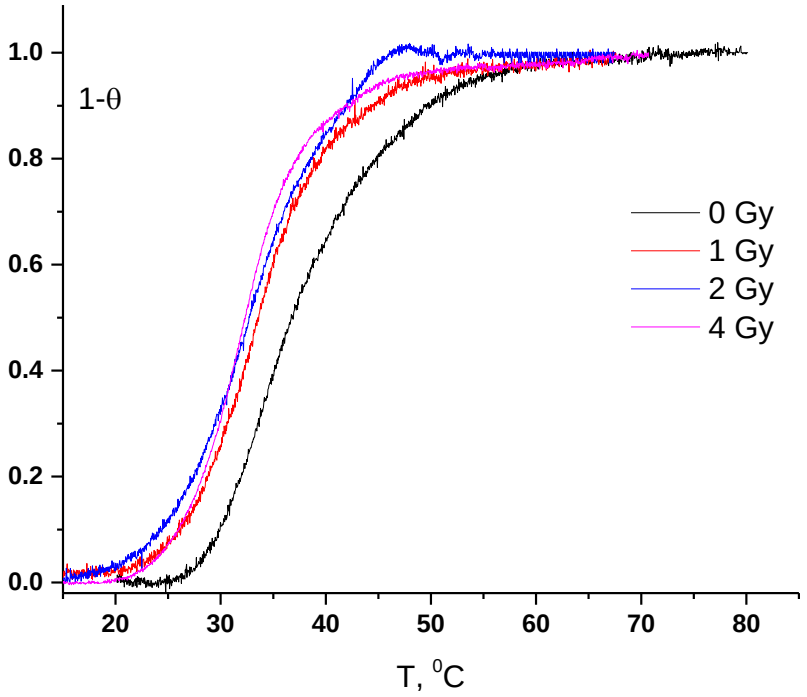


Methodology

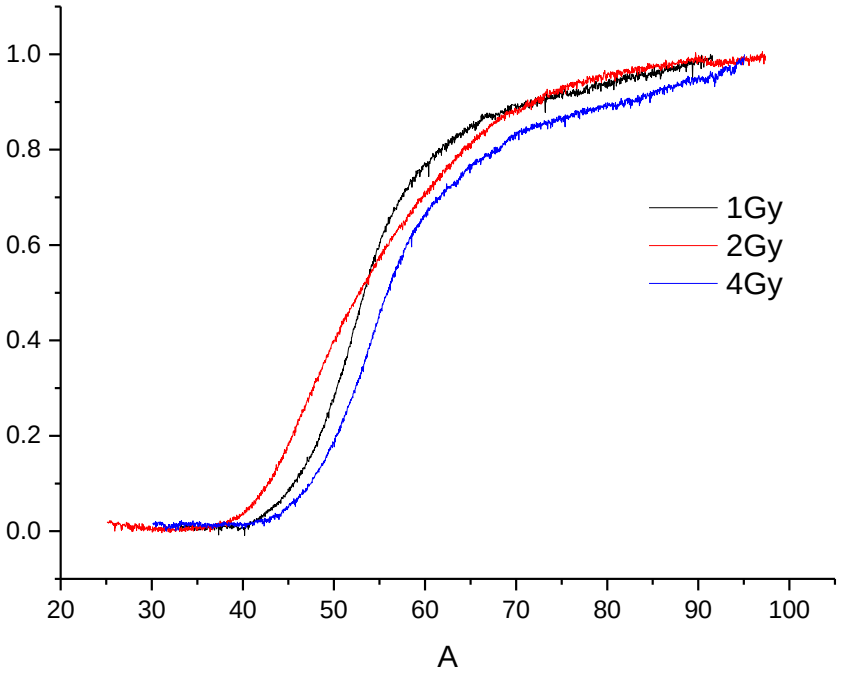
It is known, that the melting parameters (Tm and ΔT) of DNA is sensitive to the structure of double helix. Conclusion about the changes occurred in DNA can be made from melting parameters of the DNA ligand complexes. Therefore, it can be used as an indicator of strand breaks of DNA molecules after irradiation.



Results



DNA



DNA/porphyrins complexes at r=0.04

ԴՆԹ/TOETPyP4 $r=C_{porph}/C_{DNA}$	T_m (∘C)	ΔT (∘C)
№1. r=0 (DNA)	53.6	9.8
№2. r=0.01	54.3	10.7
№3. r=0.04	56.1	14.5

1 Gy

ԴՆԹ/TOETPyP4 $r=C_{porph}/C_{DNA}$	T_m (∘C)	ΔT (∘C)
№1. r=0 (մաքուր ԴՆԹ)	51.5	9.9
№2. r=0.01	54.3	19
№4. r=0.04	53.9	22

2 Gy

ԴՆԹ/TOETPyP4 $r=C_{porph}/C_{DNA}$	T_m (∘C)	ΔT (∘C)
№1. r=0 (մաքուր ԴՆԹ)	49.3	9.8
№2. r=0.01	54.4	21.3
№3. r=0.04	53.6	22.4

4 Gy

ԴՆԹ/TOETPyP4 $r=C_{porph}/C_{DNA}$	T_m (∘C)	ΔT (∘C)
№1. r=0 (մաքուր ԴՆԹ)	49.2	10
№2. r=0.01	54.5	16.5
№3. r=0.02	53.6	16.7
№4. r=0.04	56	20.2

Summary

- At a relative concentration of r = 0.01, there is no change in the melting temperature of the complexes at different radiation doses, while an increase in the melting interval is observed. We conclude, that at these concentrations, porphyrins exert a protective effect.
- At a relative concentration of r = 0.02 and a radiation dose of 4 Gy, the melting temperature of the complexes decreases and the melting interval increases. Which indicates the optimal values of the combination of these two parameters, which can be used in X-ray therapy.
- At a relative concentration of r=0.04, the appearance of a protective effect of porphyrins is observed as the radiation dose increases. That is, at a relative concentration of r=0.04 and an irradiation dose of 4 Gy, perphyrins demonstrate a protective role.

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Thank you for attention!!!