Project

Proton radiotherapy for the treatment of patients with central nervous system tumors: an experimental and modeling approach

Topics: Health Physics, Medical Physics, Radiobiology

Partners

IFJ PAN coordinator: Justyna Miszczyk, PhD., Assoc. Prof

IJCLab coordinator: Mathilde Badoual, PhD, Prof

Teams

IFJ PAN

First name / Family name	Function (Researcher, Engineer etc)	Role in the pre-project	% of participation
Justyna Miszczyk	Researcher	Radiobiology experiments	30%
Anna Zając-Grabiec/Beata Biesaga/IP PAN	Researchers	Radiobiology experiments/ 3D cells visualization	10%
Monika Krzyżowska	Technical person	Laboratory procedures and cell culturing	10%
Joanna Depciuch-Czarny	Researcher	2D visualization of cells	10%

IJCLab

First name / Family name	Function (Researcher, Engineer etc)	Role in the pre-project	% of participation
Mathilde Badoual	Researcher	Mathematical modeling	30%
Stéphane Plaszczynski	Researcher	Data analysis, numerical simulations	10%

Context

- Glioblastoma are the most aggressive type of brain tumors, with a very poor prognosis.
- Surgery is the main approach to treatment for malignant gliomas. However, some tumor cells are always left behind, in the margins of the resection area, because of the highly invasive nature of tumor cells.
- Postoperative radiotherapy (usually X-ray therapy, or XRT) is the standard treatment for malignant gliomas, in combination with chemotherapy.
- Proton Beam Therapy is interesting for gliomas because of the Bragg Peak that allow to spare normal tissues.

There is a lack of scientific data comparing proton radiotherapy and photon radiotherapy in the treatment of patients with CNS tumors at different grades (mainly gliomas), for individual cells in two dimensions as well as for cells organized in three dimensions (spheroids).

⟹We propose to characterize, quantify and model the response of CNS cancer cells of various degrees of malignancy in 2D and 3D cultures that will be subjected to irradiation with protons.

Objectives

The objectives of the project are:

- To quantitatively characterize the growth/morphology/proliferation/ distribution/invasiveness/ senescence called biomarkers of 2D and 3D cell populations (spheroids) before and after different doses and modalities of irradiation (PBT), then try to correlate the response to irradiation to the biomarkers and the physical characteristics;

- To build a mathematical model that could describe the evolution of two and three-dimensional tumor cell populations under the applied type of irradiation;

- To study whether our model can be predictive of the response of irradiation in the 3D situation, based only on the biomarkers and the 2D response.

In the longer term, this project could participate in the effort of more personalized medicine: the objective would be to predict which modality of radiotherapy (PBT, XRT) and which protocol (how many doses, at which frequency) would be useful in clinical practice.

Work plan: Biological part

Radiobiological part (Poland):

-Selected CNS cell lines that represent cancer's model and are located near critical organs that should be treated with the most precise techniques (see table below).

-The cells will be irradiated in the range of: 0.0-8.0 Gy (doses 2 Gy, 4 Gy, 8 Gy; average dose rate 0.075 Gy/s) with proton radiation. PBT will be carried out at 4 positions of the broadened Bragg peak.

-3D pediatric glioma model will be jointly developed by IFJ PAN and a commercial partner in project "Science for Society", NdS-II/SP/0295/2023/01.

-Changes in the cell growth (CellTiter-Blue® test)/morphology/proliferation (Ki-67 expression) /distribution/invasiveness (epithelial-mesenchymal transition) /senescence(X-Gal) after irradiation will be observed using holotomography, high-resolution (200 nm), in-situ, real-time imaging in IFJ PAN, which allows to show changes occurring even for 12 hours by every 5 minutes. The high throughput automated confocal microscope (Opera Phenix Plus system), purchased for CEPHARES (Center for Development of New Pharmacotherapies of Central Nervous System Disorders) established in The Maj Institute of Pharmacology(IP PAN) in Krakow will be used for 3D measurements.

Cell lines	Grade	Cells provider
SF188 Human Glioblastoma cell line	GIV	MiliporeCor. (SigmaAldrich)/Cat. # SCC282
HOG	GI/GII	MiliporeCor. (SigmaAldrich)/Cat. # SCC282
Primary Dermal Fibroblast (HDFa), PCS-201-012™	Normal skin cells	ATCC®

Theoretical part

Theoretical part (France):
The different steps are:
•Data analysis from images in 2D: we will either count cells (if possible) or measure the confluence (the total area occupied by the cells) as a function of time under different modalities of irradiation. We develop our codes or we use existing Python functions.
•Data analysis from images in 3D: the radius of spheroids in 3D will be measured as a function of time, in the same conditions as in 2D.
•Development of a model and fitting of the biological data
•Studying if it is possible to predict the efficacy of PRT.

The model that will be used will be a phenomenological one, describing the effect of radiation on a cell population. Since we want it to be predictive, it should not be a very detailed model with a lot of parameters. We expect to keep the number of parameters under 6. We will start with a compartmental model, with damaged cells that undergo a DNA-reparation process. At the end of this process, cells can either be repaired and resume proliferation or be unable to repair and either die or become senescent.

Budget request for 2024

IFJ PAN

Type of expenses	Amount
Personnel	3600 EUR
Equipment	-
Consumables	3000 EUR
Travel & subsistence	1000 EUR
Total	7600 EUR

IFJ PAN: 3000 EUR will needed for consumambles like cell culture media, laboratory plastics, and cellular and molecular tests (CellTiter-Blue® test, Ki-67 expression, X-Gal). We ask for 3600 EUR for team training and salaries. We are also asking for 1000 euros for traveling to France for presentations, consultations, and paperwork.

IJCLab

Type of expenses	Amount
Personnel	3600 EUR (6-month internship)
Equipment	-
Consumables	-
Travel & subsistence	1000 EUR
Total	4600 EUR

IJCLab: we are asking for an internship of 6 months for a master's student, in 2025. We also ask for 2000 for a good laptop. We are also asking for 1000 euros for missions.