PROJECT 19 06 02 02

Development of research infrastructure and techniques at IFIN-HH Tandem accelerators with new experimental setups and analytical methods

PN Responsible: Gihan Velisa

DFNA Seminar, 7th of December 2021

CORE PROJECT: 19 06 02 02

Phase 6:

Designing and developing a new ion beam setup for radiobiology studies (I & II)

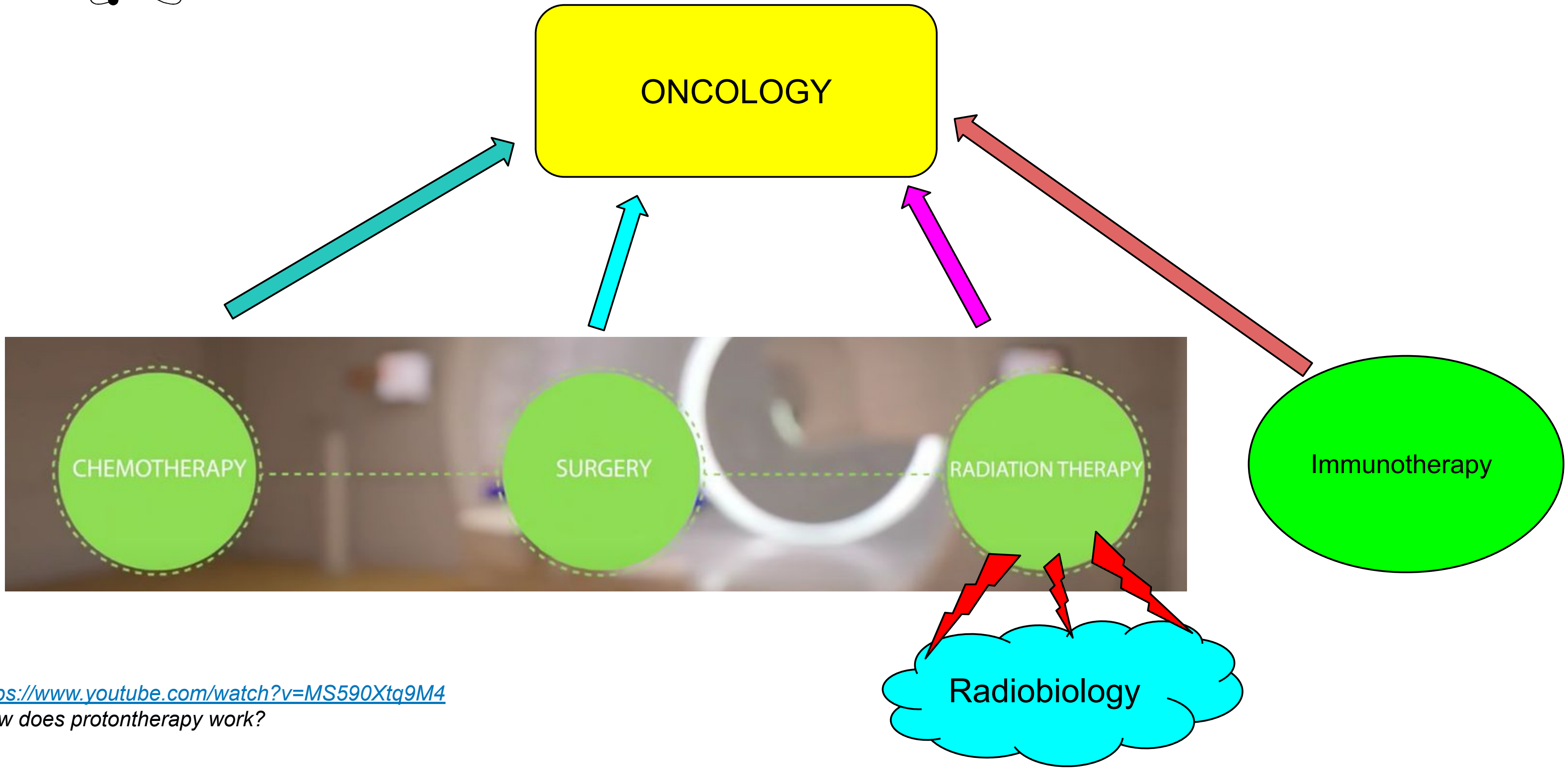
Mihai Straticiuc, Mihaela Bacalum, Călin Mircea Rusu, Radu Andrei, Ion Burducea, Ioan Cenusa, Constantin Cenusa, Irina Dinescu, Simona Dirleci, Alexandru Enciu, Decebal Iancu, Radu Vasilache, Mina Raileanu, Mihai Radu

DFNA Seminar, 7th of December 2021

Project objectives:

1. Innovative technological developments at the Tandem accelerators, in order to maintain the capacity for analysis and irradiation at the highest level.
2. Technological developments of the experimental area, in order to meet the new needs of the users of the research infrastructure.
3. Development of new techniques and technologies that will find their applicability in the industrial, environmental and/or security area.
4. Prototype developments for international projects where IFIN-HH act as a member.

MOTIVATION



ONCOLOGY

CHEMOTHERAPY

SURGERY

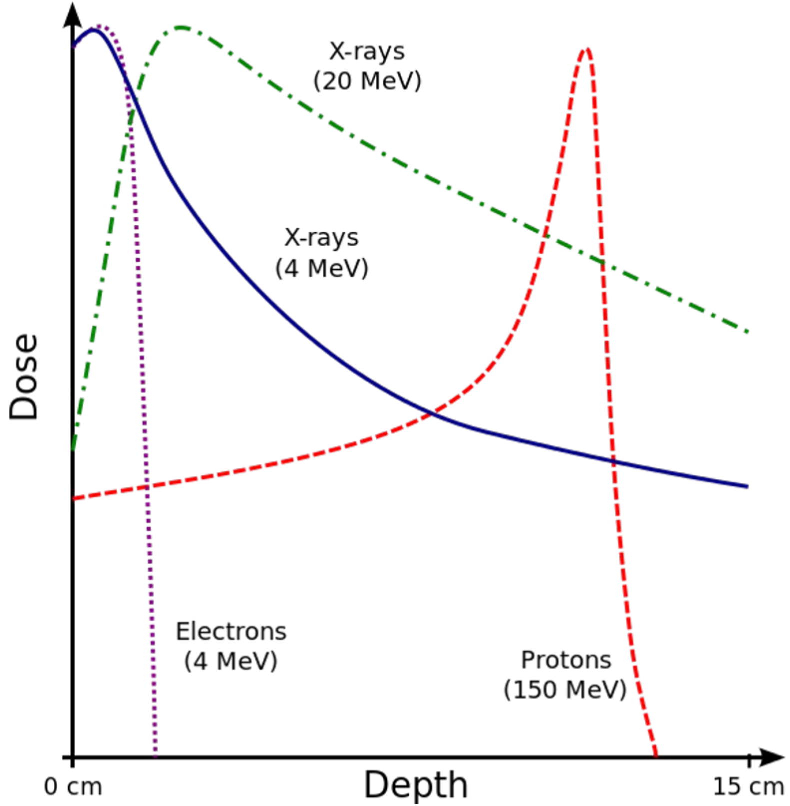
RADIATION THERAPY

Immunotherapy

Radiobiology

https://www.youtube.com/watch?v=MS590Xtq9M4
How does protontherapy work?

MOTIVATION: photons vs ions

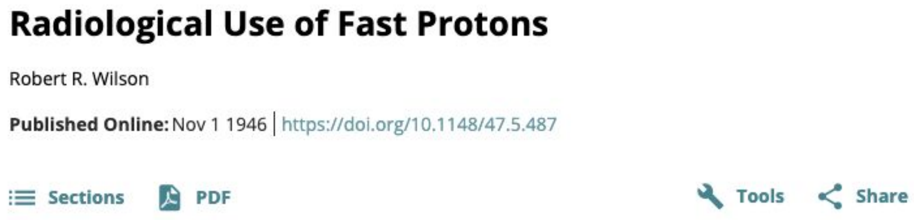


Beer-Lambert (photons):

$$I = I_0 * e^{-\mu x}$$

Bethe-Bloch (ions):

$$-\frac{dE}{dx} = \frac{4\pi n z^2}{m_e v^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e v^2}{I}\right)\right]$$



Radiological Use of Fast Protons

Robert R. Wilson

Published Online: Nov 1 1946 | https://doi.org/10.1148/47.5.487

3 MV HVE Tandetron™ accelerator installed at IFIN-HH

I. Burducea et al., NIM B, 359, 12-19, 2015

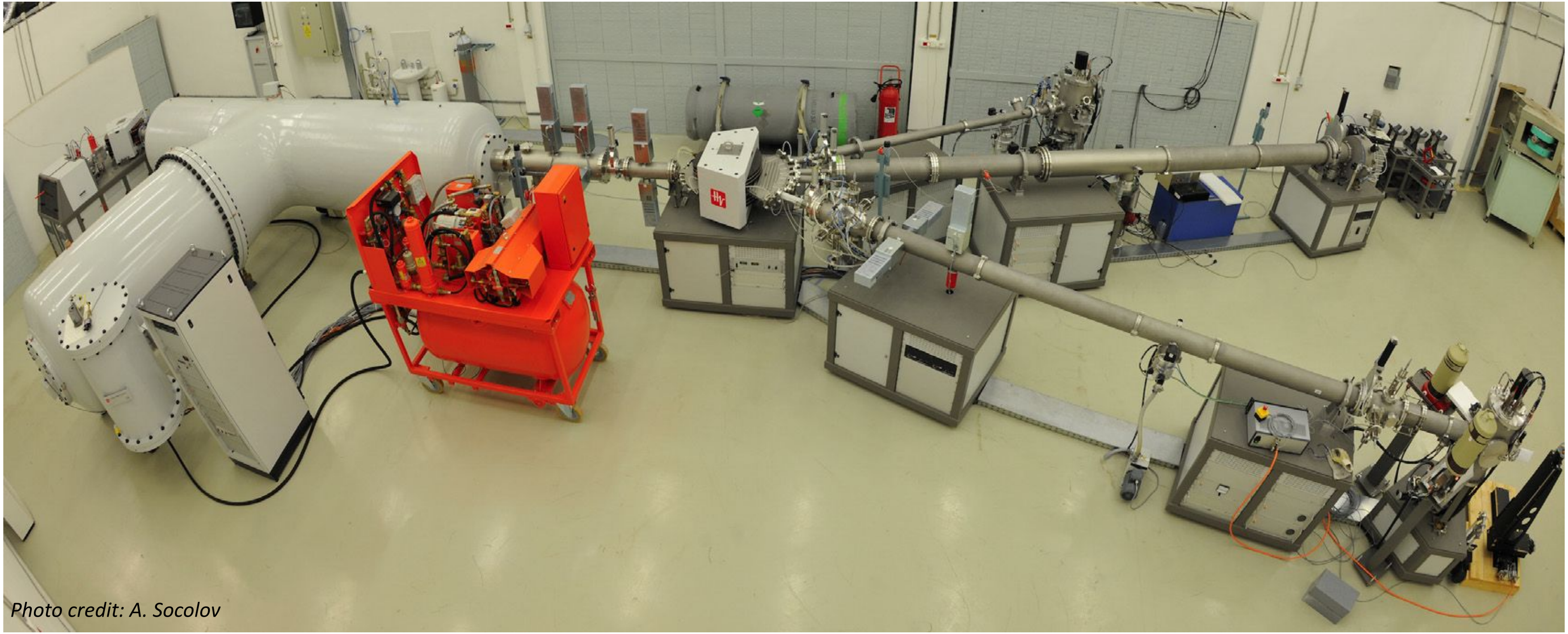
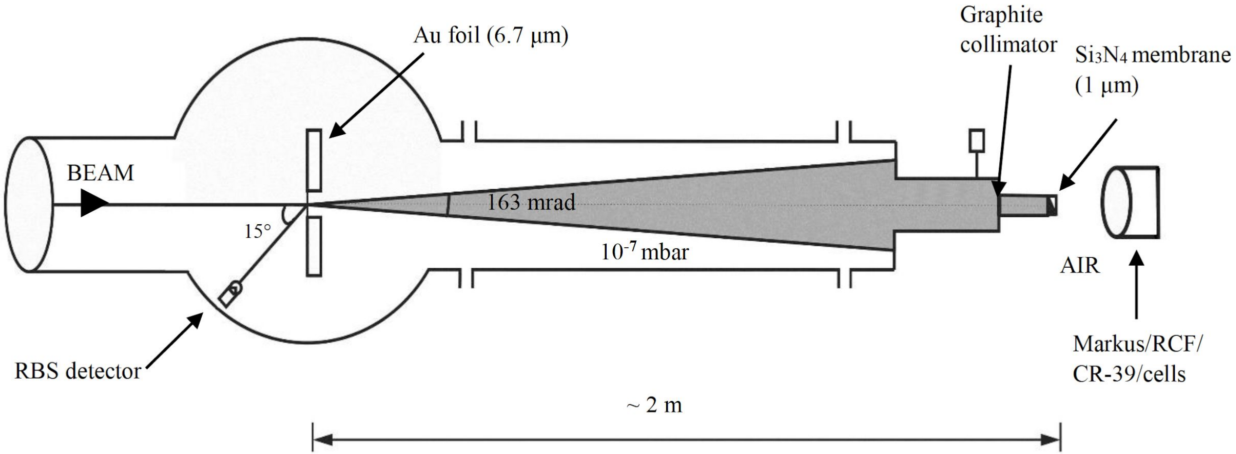
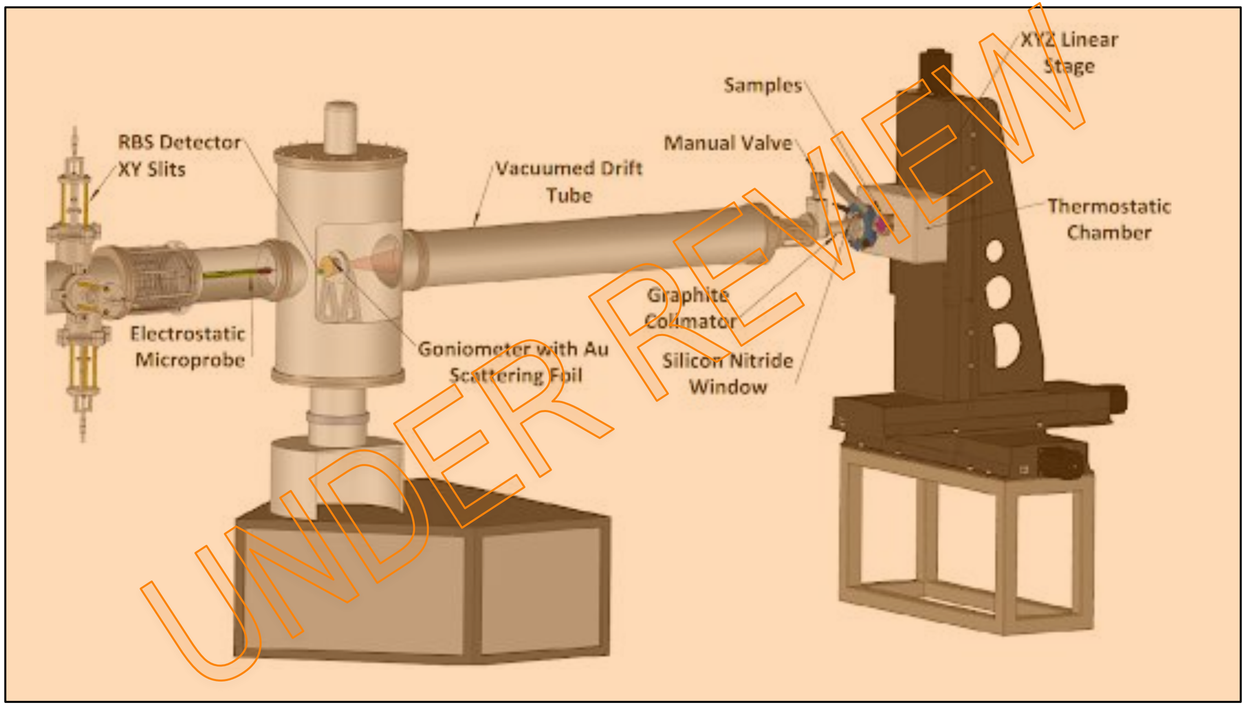


Photo credit: A. Socolov

2D Experimental Setup (v1)



3D Experimental Setup (v2)



UNDER REVIEW

Courtesy of A. Enciu

Experimental Setup (6th of December 2021)

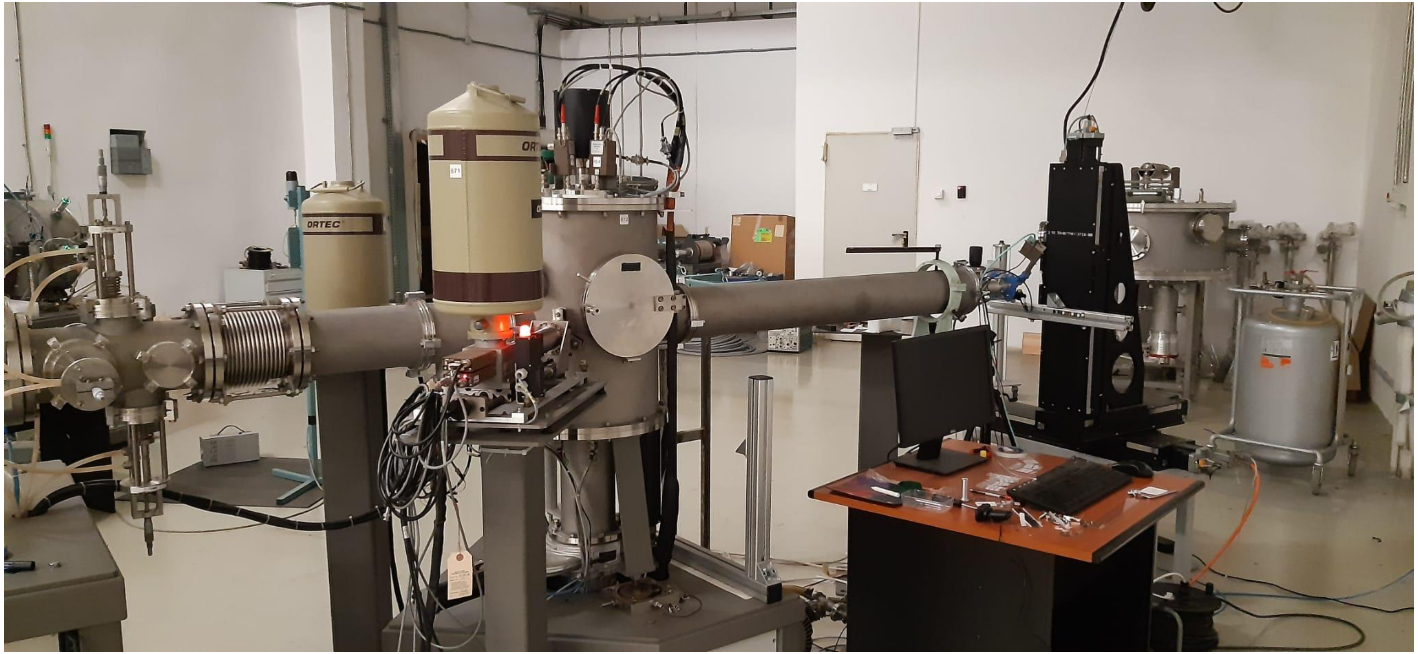
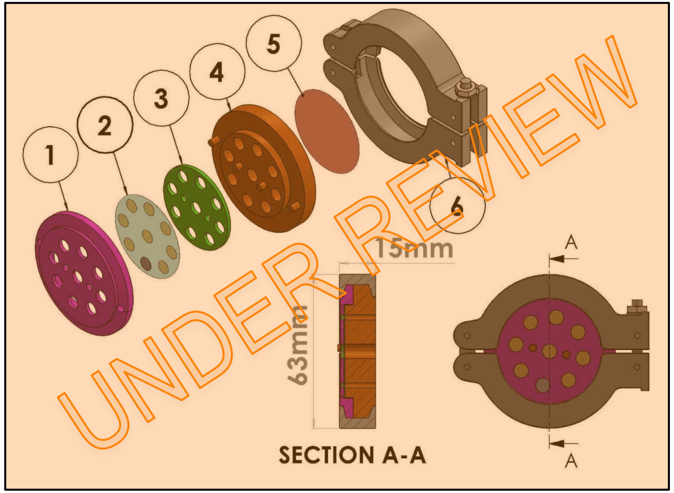


Photo credit: D. Iancu

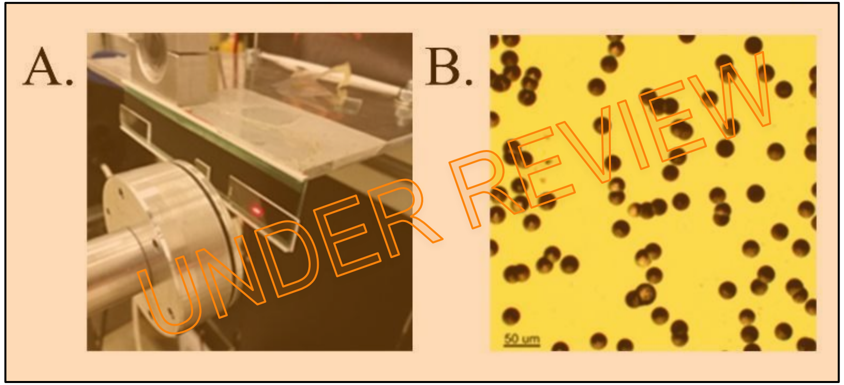
Cell culture "homemade" chamber & 1st dosimetry attempts with Tastrak® detectors



UNDER REVIEW

Scheme of a cell culture chamber (1. Aluminum front cover; 2. Mylar foil; 3. Silicone gasket; 4. Teflon chamber; 5. Breathable sealing tape sterile; 6. KF63 vacuum clamp)

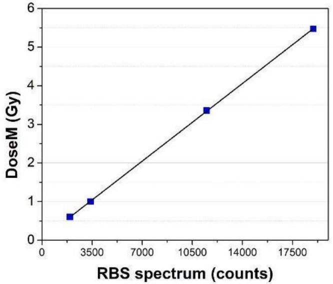
$$D\,[\mathrm{Gy}] = 1.6 * 10^{-9} * \phi\,(\mathrm{p/cm^2}) * \mathbf{dE/dx}\,(\mathrm{keV/\mu m})$$

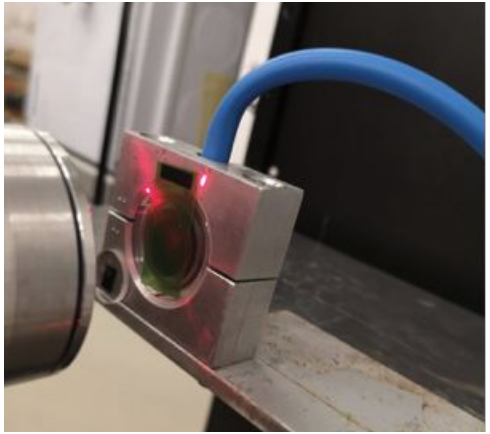


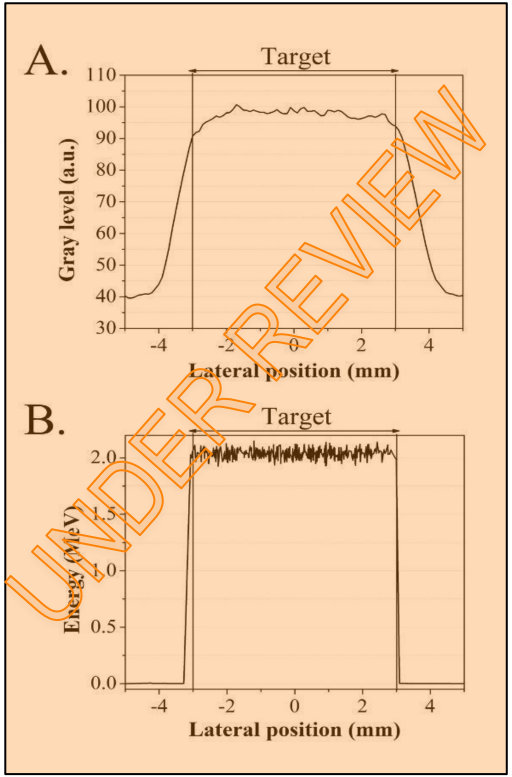
UNDER REVIEW

A. Tastrak® detectors irradiation (1. Si_3N_4 window holder; 2. Tastrak® detector) ; B. photo taken under microscope after etching procedure was applied.

Beam dosimetry (Markus ionization chamber, RCF & Si particle detector)



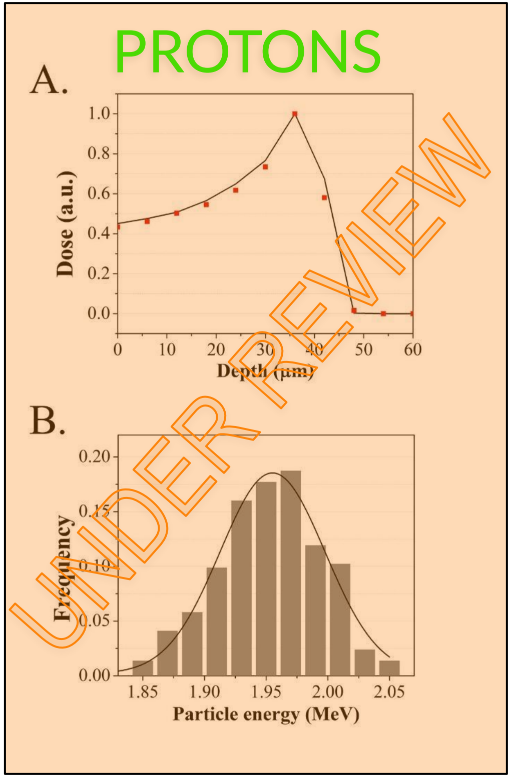




UNDER REVIEW

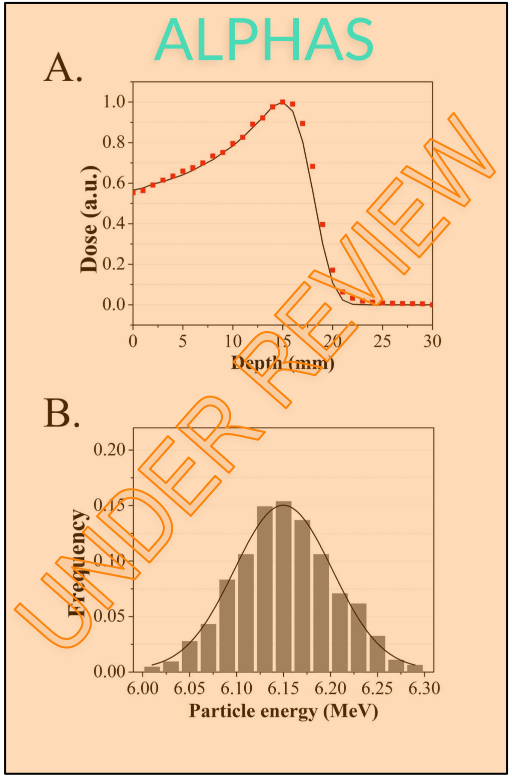
A. Lateral uniformity of the beam as recorded with radiochromic film expressed as gray level distribution along the spot diameter; B. Lateral energy distribution simulated with Geant4 expressed as the energy profile along the diameter at the air target interface in the same position as the film.

Depth dose profile measured with Markus vs Geant4 simulation



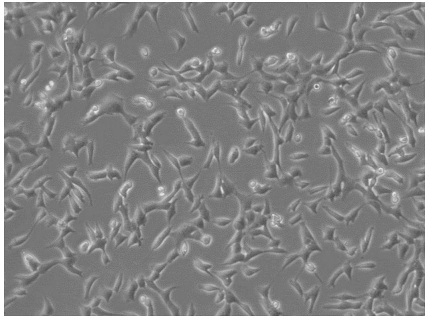
A. Experimental recording (red points) and Geant4 simulation (line plot) of protons/alphas Bragg peak in Mylar/air, x = 0 represents the air-mylar interface position during irradiation

B. energy distribution of the proton beam at the air-Mylar interface and Gauss fit (LEFT) and energy distribution of the alpha beam at the air-Mylar interface (RIGHT).

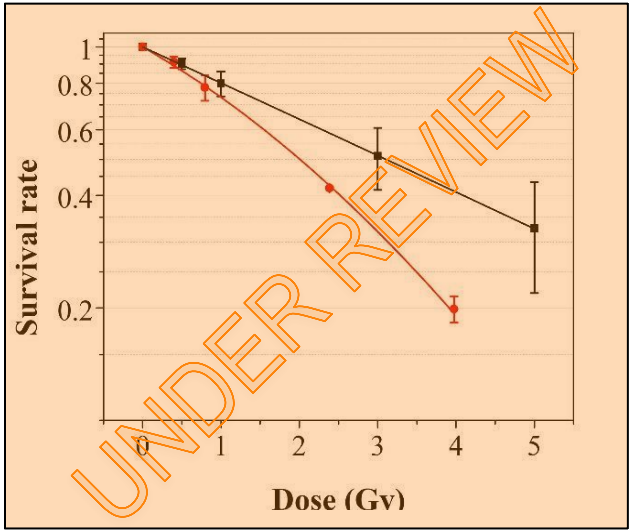


UNDER REVIEW
UNDER REVIEW

Experimental results



V79-4 cells 1d after seeding in EMEM with 10% FBS



Cell survival rate of V79 cells irradiated with doses between 0-5 Gy. The red line and dots represent the survival rate for protons. The black line and dots represent the survival rate for X-rays.

$$SF = exp\left(-\alpha D - \beta D^2\right)$$

SF- survival fraction

D - dose (Gy)

α, β - linear & quadratic fit coefficients

Radiation type	$\alpha \pm$ sd (Gy^{-1})	$\beta \pm$ sd (Gy^{-2})	D_{50}; ($^*D_{10}$) (Gy)	RBE 50; (RBE 10)
Protons	0.27 ± 0.02	0.035 ± 0.007	2; (5)	1.5; (2)
X rays	0.22 ± 0.005	0.0005 ± 0.002	3; (10)	1.00

*D_{10} was estimated by fitting function.

Conclusions

→ a new cell culture irradiation setup for basic radiobiological investigations and preliminary experimental results obtained for the first time at IFIN-HH 3 MV Tandetron^{TM} are reported.

→ the proton beam was extracted into the air through a Si_3N_4 membrane, and the dose was estimated by several methods.

→ preliminary cell survival results show a similarity to data reported in the literature using other proton beam facilities for V79 cells.

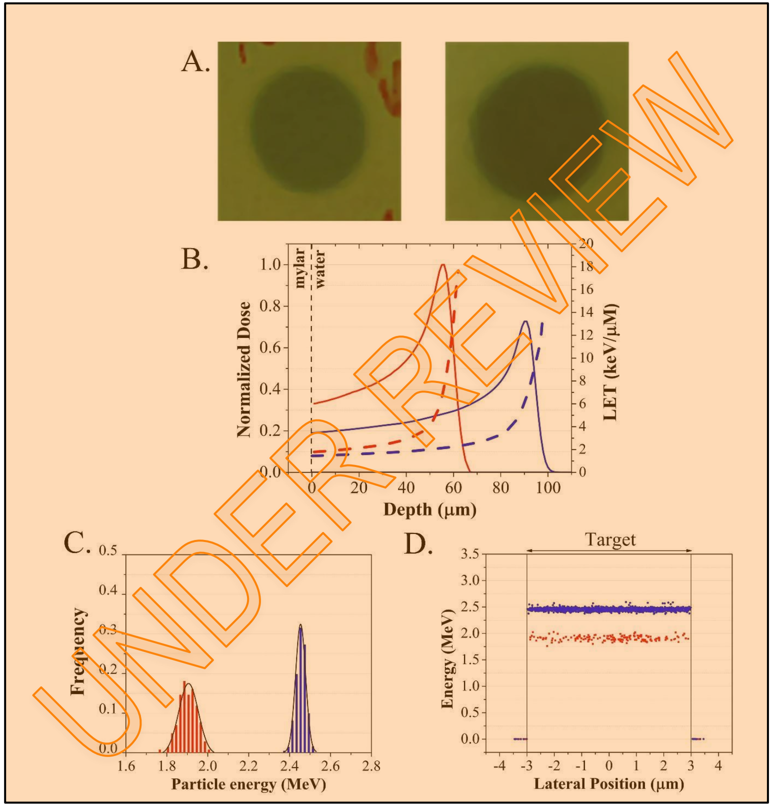
→ Geant4 simulations confirmed the experimental data of the Bragg peak for two ion species (protons and alpha) and provided promising predictions for switching to the FLASH regime and also the use of high ion beams with high LET ($^{7}Li^{3+}$, $^{11}B^{5+}$ and $^{12}C^{6+}$) which could be supplied by IFIN-HH's 9 MV Van de Graaff tandem accelerator.

Perspectives - high dose rate (FLASH regime)

Review > Front Oncol. 2020 Jan 17;9:1563. doi: 10.3389/fonc.2019.01563. eCollection 2019.

Ultra-High Dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool's Gold?

Joseph D Wilson [1], Ester M Hammond [1], Geoff S Higgins [1], Kristoffer Petersson [1 2]



UNDER REVIEW

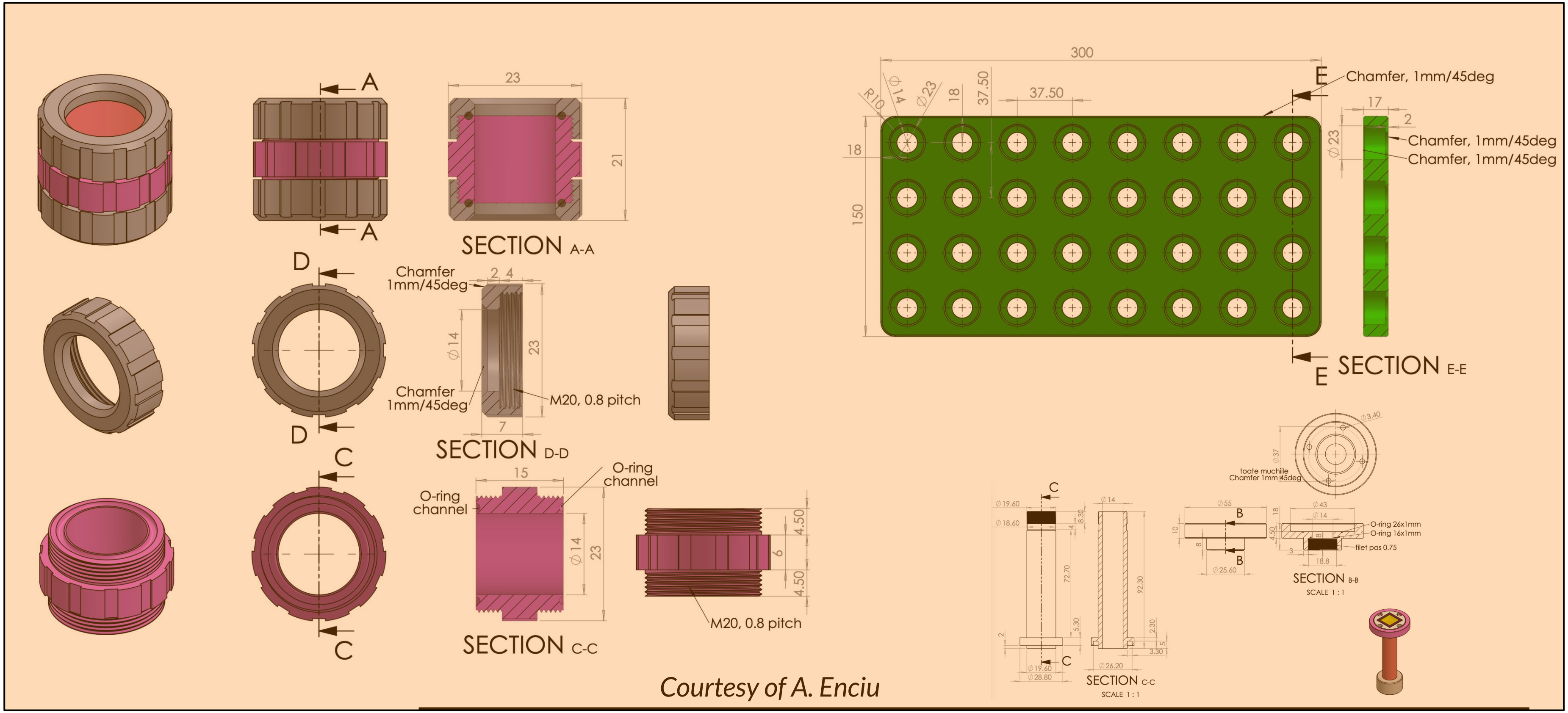
A. RCF irradiated at 100 Gy/s (left) RCF irradiated at 250 Gy/s (right);

B. Geant4 simulation of dose (line plot) and LET (dashed plot) in water after protons propagation through different thin foils; red: low flux protons through the 6.7 μm Au foil, blue: high flux protons through the 2 μm Al foil;

C. Lateral energy distributions of the low and high flux proton beams at the Mylar-water interface simulated by Geant4 expressed as the energy profile along the target diameter;

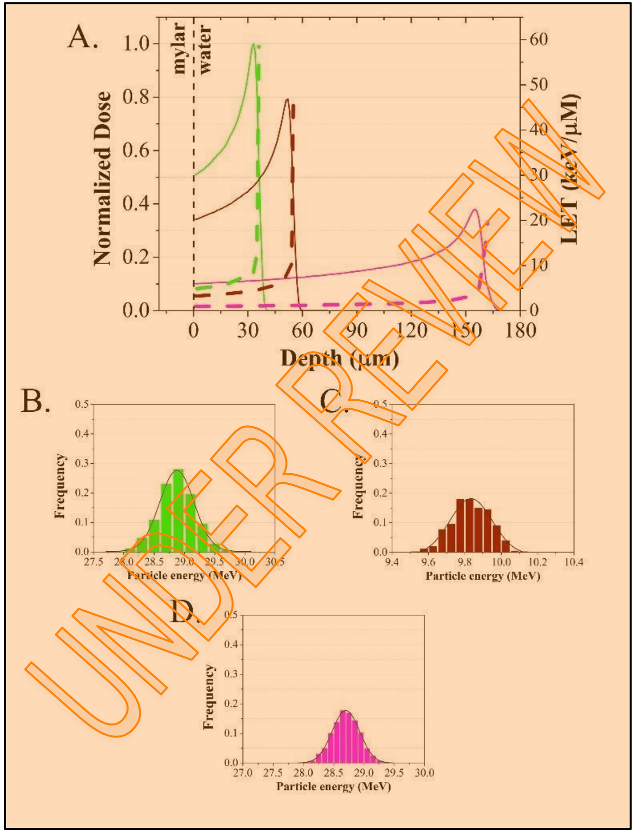
D. Energy distribution of the low and high flux proton beams at the mylar-water interface (low flux: mean energy = 1.9 MeV, FWHM = 104.02 keV; high flux: mean energy = 2.45 MeV , FWHM = 56.18 keV).

Perspectives - high dose rate (FLASH regime)



Courtesy of A. Enciu

Perspectives - heavy ions



UNDER REVIEW

A. Geant4 simulation of dose (line plot) and LET (dashed plot) in water after heavy ions propagation through the 2 µm Al thin foil; green: $^{12}C^{6+}$ of 56 MeV, brown: $^{7}Li^{3+}$ of 32 MeV, magenta: $^{11}B^{5+}$ of 48 MeV;
B. Energy distribution of the 56 MeV $^{12}C^{6+}$ beam at the mylar-water interface (mean energy = 28.87 MeV, FWHM = 679.63 keV);
C. Energy distribution of the 48 MeV $^{11}B^{5+}$ beam at the mylar-water interface (mean energy = 9.83 MeV, FWHM = 245.14 keV); D. Energy distribution of the 32 MeV $^{7}Li^{3+}$ beam at the mylar-water interface (mean energy = 28.7 MeV, FWHM = 523.62 keV);

Dissemination & References

1. G. Velişa, R. F. Andrei, I. Burducea, A. Enciu, D. Iancu, D. A. Mirea,A. Spiridon, M. Straticiuc, **Joint research activities at the 3 MV Tandetron™ from IFIN-HH**, *Eur. Phys. J. Plus* 136 (2021) 1171. https://doi.org/10.1140/epjp/s13360-021-02156-7.
2. Mihai Straticiuc, Mihaela Bacalum, Calin Mircea Rusu, Radu Andrei, Ion Burducea, Ioan Cenusa, Constantin Cenusa, Irina Dinescu, Simona Dirleci, Alexandru Enciu, Decebal Iancu, Radu Vasilache, Mina Raileanu, Mihai Radu, **New setup for basic radiobiology studies using a 3 MV Tandetron™: design and developments,** NIM B, under review

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Page: 1 of 1 (1 total submissions)

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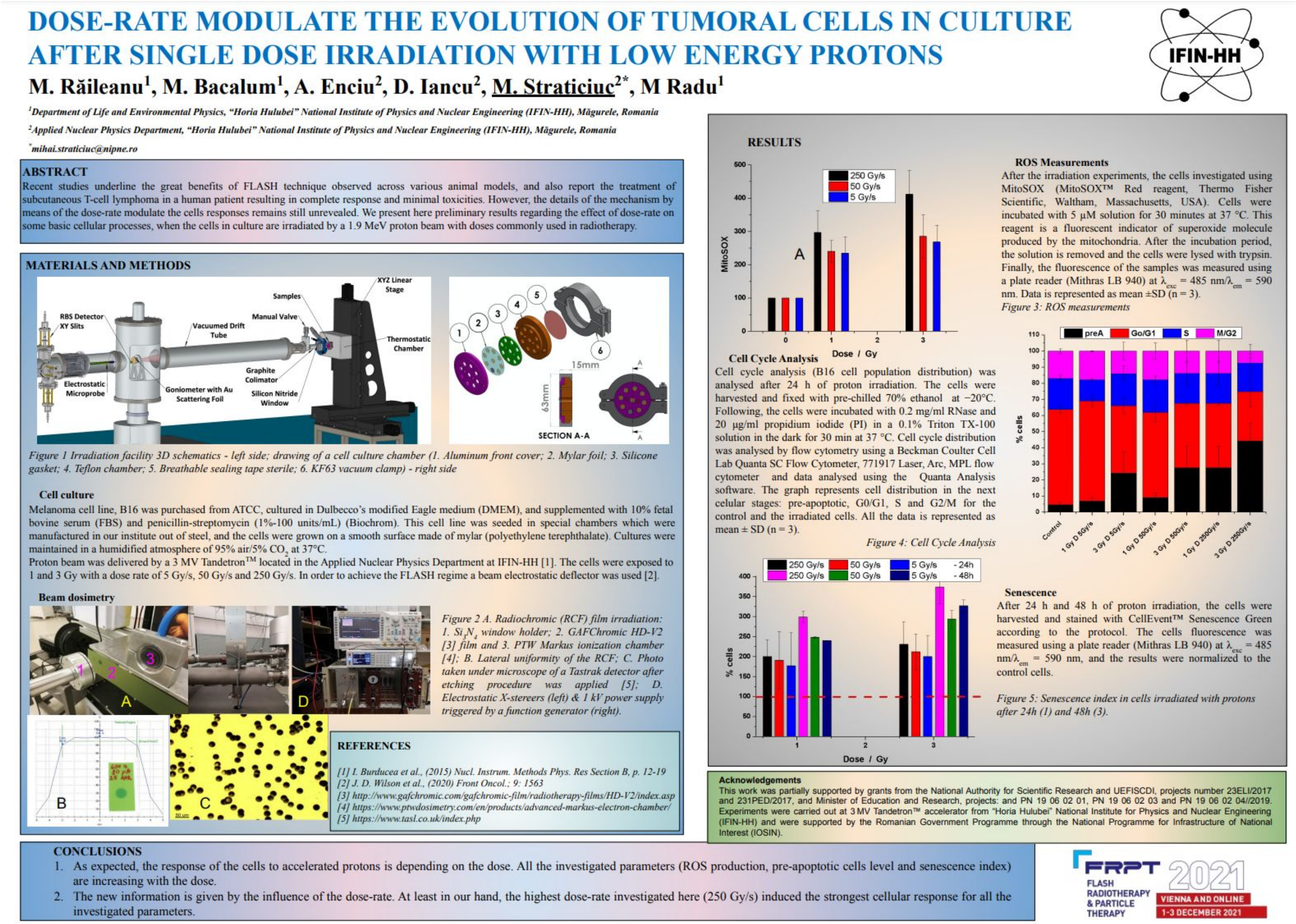
[1] B. Jones, S. J. McMahon, and K. M. Prise, "The Radiobiology of Proton Therapy: Challenges and Opportunities Around Relative Biological Effectiveness.," Clin. Oncol. (R. Coll. Radiol)., vol. 30, no. 5, pp. 285–292, May 2018, doi: 10.1016/j.clon.2018.01.010.
[2] H. Paganetti, Proton Beam Therapy. IOP Publishing, 2017.
[3] K. Ilicic, S. E. Combs, and T. E. Schmid, "New insights in the relative radiobiological effectiveness of proton irradiation," Radiat. Oncol., vol. 13, no. 1, p. 6, 2018, doi: 10.1186/s13014-018-0954-9.
[4] I. Burducea et al., "A new ion beam facility based on a 3MV TandetronTM at IFIN-HH, Romania," Nucl. Instruments Methods Phys. Res. Sect. B Beam Interact. with Mater. Atoms, vol. 359, pp. 12–19, 2015, doi: 10.1016/j.nimb.2015.07.011.
[5] N. Podaru, F. Hoef, A. Gottdang, and D. Mous, "Design and performance of the HVE electrostatic nuclear microprobe," Nucl. Instruments Methods Phys. Res. Sect. B Beam Interact. with Mater. Atoms, vol. 306, pp. 25–28, 2013, doi: 10.1016/j.nimb.2012.11.044.
[6] R. A. Vasilache, M. A. Popovici, M. Straticiuc, M. Radu, and A. Groza, "THE DEVELOPMENT OF A NOVEL ARRAY DETECTOR FOR OVERCOMING THE DOSIMETRY CHALLENGES OF MEASURING IN VERY SHORT PULSED CHARGED PARTICLE BEAMS: THE ELIDOSE PROJECT.," Radiat. Prot. Dosimetry, vol. 183, no. 1–2, pp. 285–289, May 2019, doi: 10.1093/rpd/ncy253.
[7] S. Agostinelli et al., "Geant4—a simulation toolkit," Nucl. Instruments Methods Phys. Res. Sect. A Accel. Spectrometers, Detect. Assoc. Equip., vol. 506, no. 3, pp. 250–303, 2003, doi: https://doi.org/10.1016/S0168-9002(03)01368-8.
[8] M. Durante, E. Bräuer-Krisch, and M. Hill, "Faster and safer? FLASH ultra-high dose rate in radiotherapy.," Br. J. Radiol., vol. 91, no. 1082, p. 20170628, Feb. 2018, doi: 10.1259/bjr.20170628.



DOSE-RATE MODULATE THE EVOLUTION OF TUMORAL CELLS IN CULTURE AFTER SINGLE DOSE IRRADIATION WITH LOW ENERGY PROTONS

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[1]Department of Life and Environmental Physics, "Horia Hulubei" National Institute of Physics and Nuclear Engineering (IFIN-HH), Măgurele, Romania

[2]Applied Nuclear Physics Department, "Horia Hulubei" National Institute of Physics and Nuclear Engineering (IFIN-HH), Măgurele, Romania

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ABSTRACT

Recent studies underline the great benefits of FLASH technique observed across various animal models, and also report the treatment of subcutaneous T-cell lymphoma in a human patient resulting in complete response and minimal toxicities. However, the details of the mechanism by means of the dose-rate modulate the cells responses remains still unrevealed. We present here preliminary results regarding the effect of dose-rate on some basic cellular processes, when the cells in culture are irradiated by a 1.9 MeV proton beam with doses commonly used in radiotherapy.

MATERIALS AND METHODS

Figure 1 Irradiation facility 3D schematics - left side; drawing of a cell culture chamber (1. Aluminum front cover; 2. Mylar foil; 3. Silicone gasket; 4. Teflon chamber; 5. Breathable sealing tape sterile; 6. KF63 vacuum clamp) - right side

Cell culture

Melanoma cell line, B16 was purchased from ATCC, cultured in Dulbecco's modified Eagle medium (DMEM), and supplemented with 10% fetal bovine serum (FBS) and penicillin-streptomycin (1%-100 units/mL) (Biochrom). This cell line was seeded in special chambers which were manufactured in our institute out of steel, and the cells were grown on a smooth surface made of mylar (polyethylene terephthalate). Cultures were maintained in a humidified atmosphere of 95% air/5% CO_2 at 37°C.

Proton beam was delivered by a 3 MV Tandetron™ located in the Applied Nuclear Physics Department at IFIN-HH [1]. The cells were exposed to 1 and 3 Gy with a dose rate of 5 Gy/s, 50 Gy/s and 250 Gy/s. In order to achieve the FLASH regime a beam electrostatic deflector was used [2].

Beam dosimetry

Figure 2 A. Radiochromic (RCF) film irradiation: 1. Si_3N_4 window holder; 2. GAFChromic HD-V2 [3] film and 3. PTW Markus ionization chamber [4]; B. Lateral uniformity of the RCF; C. Photo taken under microscope of a Tastrak detector after etching procedure was applied [5]; D. Electrostatic X-stereers (left) & 1 kV power supply triggered by a function generator (right).

REFERENCES

[1] I. Burducea et al., (2015) Nucl. Instrum. Methods Phys. Res Section B, p. 12-19
[2] J. D. Wilson et al., (2020) Front Oncol.; 9: 1563
[3] http://www.gafchromic.com/gafchromic-film/radiotherapy-films/HD-V2/index.asp
[4] https://www.ptwdosimetry.com/en/products/advanced-markus-electron-chamber/
[5] https://www.tasl.co.uk/index.php

RESULTS

ROS Measurements

After the irradiation experiments, the cells investigated using MitoSOX (MitoSOX™ Red reagent, Thermo Fisher Scientific, Waltham, Massachusetts, USA). Cells were incubated with 5 µM solution for 30 minutes at 37 °C. This reagent is a fluorescent indicator of superoxide molecule produced by the mitochondria. After the incubation period, the solution is removed and the cells were lysed with trypsin. Finally, the fluorescence of the samples was measured using a plate reader (Mithras LB 940) at λ_{exc} = 485 nm/λ_{em} = 590 nm. Data is represented as mean ±SD (n = 3).

Figure 3: ROS measurements

Cell Cycle Analysis

Cell cycle analysis (B16 cell population distribution) was analysed after 24 h of proton irradiation. The cells were harvested and fixed with pre-chilled 70% ethanol at −20°C. Following, the cells were incubated with 0.2 mg/ml RNase and 20 µg/ml propidium iodide (PI) in a 0.1% Triton TX-100 solution in the dark for 30 min at 37 °C. Cell cycle distribution was analysed by flow cytometry using a Beckman Coulter Cell Lab Quanta SC Flow Cytometer, 771917 Laser, Arc, MPL flow cytometer and data analysed using the Quanta Analysis software. The graph represents cell distribution in the next celular stages: pre-apoptotic, G0/G1, S and G2/M for the control and the irradiated cells. All the data is represented as mean ± SD (n = 3).

Figure 4: Cell Cycle Analysis

Senescence

After 24 h and 48 h of proton irradiation, the cells were harvested and stained with CellEvent™ Senescence Green according to the protocol. The cells fluorescence was measured using a plate reader (Mithras LB 940) at λ_{exc} = 485 nm/λ_{em} = 590 nm, and the results were normalized to the control cells.

Figure 5: Senescence index in cells irradiated with protons after 24h (1) and 48h (3).

Acknowledgements
This work was partially supported by grants from the National Authority for Scientific Research and UEFISCDI, projects number 23ELI/2017 and 231PED/2017, and Minister of Education and Research, projects: and PN 19 06 02 01, PN 19 06 02 03 and PN 19 06 02 04//2019. Experiments were carried out at 3 MV Tandetron™ accelerator from "Horia Hulubei" National Institute for Physics and Nuclear Engineering (IFIN-HH) and were supported by the Romanian Government Programme through the National Programme for Infrastructure of National Interest (IOSIN).

CONCLUSIONS

1. As expected, the response of the cells to accelerated protons is depending on the dose. All the investigated parameters (ROS production, pre-apoptotic cells level and senescence index) are increasing with the dose.
2. The new information is given by the influence of the dose-rate. At least in our hand, the highest dose-rate investigated here (250 Gy/s) induced the strongest cellular response for all the investigated parameters.

FRPT 2021
FLASH RADIOTHERAPY & PARTICLE THERAPY
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Vă mulțumesc pentru atenție, dar mai ales pentru reziliență!

"A good head and a good heart are always a formidable combination."
Nelson MANDELA

AOB

14th European Conference on Accelerators in Applied Research and Technology
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