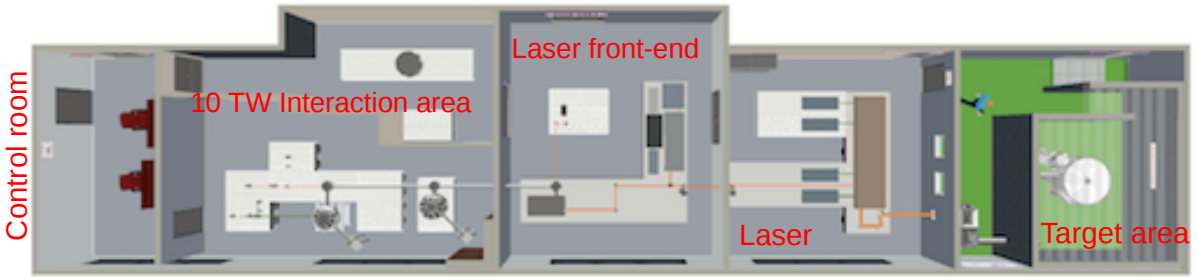
Nuova sigla CSN5

LPA2 (Laser driven Proton Acceleration Applications)

A INFN-CNR proposal
Collaboration with IEO, HSRF and LOA Ecole Polytechnique - Parigi

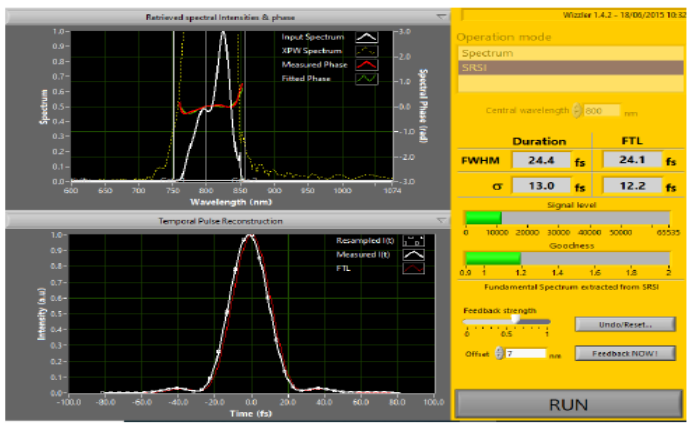
Background: The ILIL-PW laser system

The laser system at the CNR-INO-ILIL is now fully commissioned and routinely operating at a power level of >150TW*, with a "complete set" of diagnostics provided for each experiment

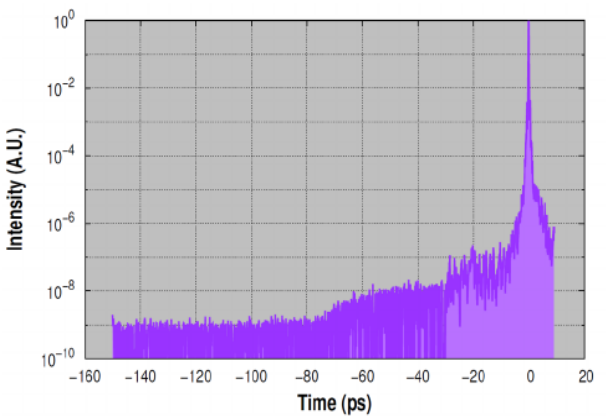


The ILIL laser pulse time structure

Time duration (spectral amplitude, spectral phase, ...) diagnostics



Temporal contrast (3rd order autocorrelation)



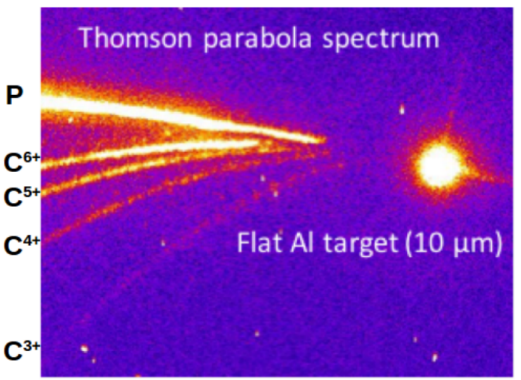
*final upgrade to ~200TW to be completed within 2020

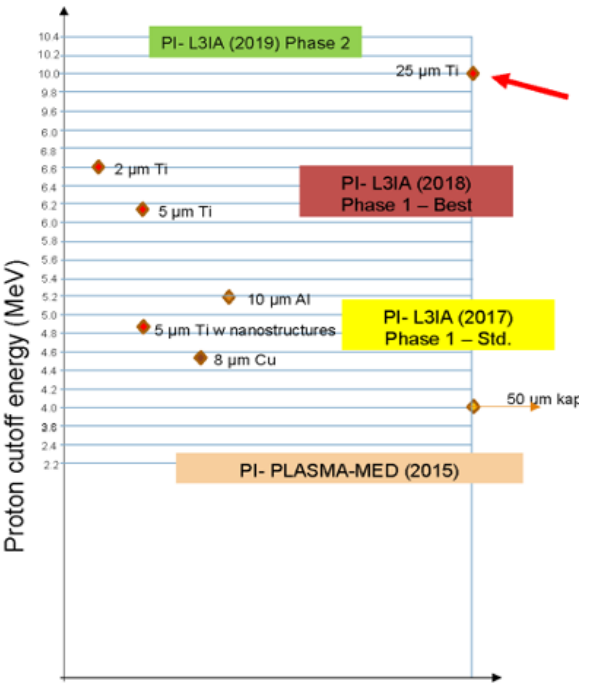
Background: The L3IA proton/ion beamline

Two (particle) "beamlines" have been setup, one for electron acceleration (up to ~600 MeV already established) and one for proton/light ions.

The L3IA beamline was jointly established by INFN and CNR (CSN5 2016-2019) as a "proton/ion" beamline for fundamental studies in TNSA and preliminary applications

"Complete set" of devices/diagnostics commissioned:
- TOF detectors
- Thomson Parabola spectrometer
- Preliminary dosimetry carried out

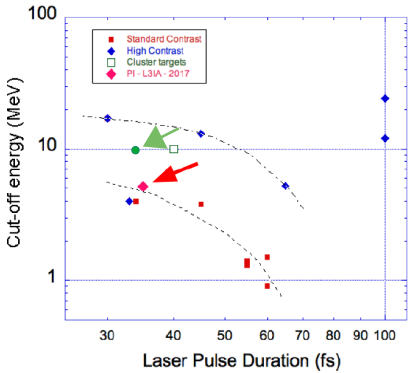


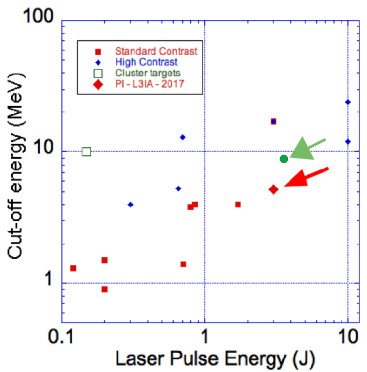


Background: the L3IA proton/ion beamline. Proton beam characterization

Max. proton cutoff energy : 10 MeV
Charge/bunch (laser shot) : 2.7 10^{10} p/shot
(results obtained in 2019)

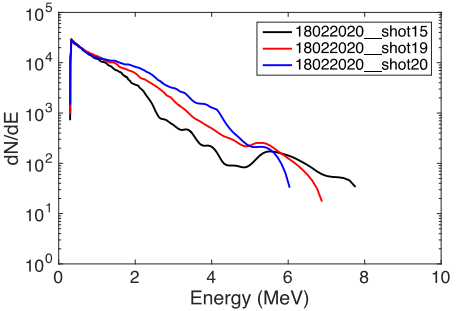
Results consistent with those obtained in comparable facilities worldwide



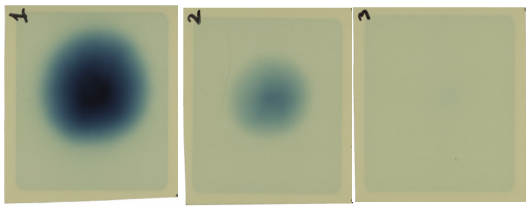


"Fundamental" research ongoing on targets, laser pulse time structure, aimed at increasing cut-off energy

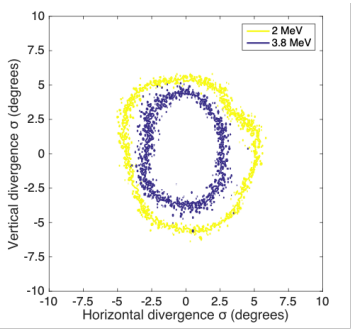
"Final" experiment in 2020 (February) aimed at studying main beam figures for transport and dosimetry, and assessing stability

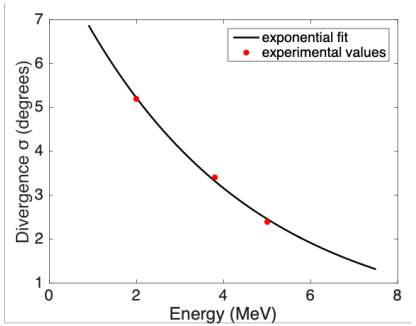


Retrieved p spectrum on 3 different shots



"Raw" GAF films (EBT3) after 21 shots irradiation





Retrieved divergence vs. energy

*Gizzi, L.A. et al., NIMA 909, 160 (2018)

The LPA2 proposal

Scenario:

- Consolidated beamline and expertise on TNSA proton acceleration and related diagnostics established within previous activity:

  Proton beams with cutoff energy up to >10MeV demonstrated

  Stable beams with energy 6-8 MeV can be safely considered

  Remarkable measured beam divergence (few deg), compatible with transport/applications

  Charge/shot (>1nC) may provide good dose values on "target" (~Gy, over ~cm wide regions)

- Growing interest for laser-driven particle acceleration for applications in medicine (radiotherapy), even in view of possible novel protocols (see FLASH radiotherapy)

- Peculiar time structure of laser-driven particle bunches (very short duration) → very high *instantaneous* dose rates on "targets" → need for further studies on biological response

The LPA2 proposal (2)

Activity focused on *exploiting* the established beamline to carry out *in vitro* **radiobiology** experiments, aimed at comparing radiation damage on cells (for different endpoints) to "known" response

- Transport and "focusing" to sample (vacuum-to-air)
- Dosimetry (development)
- Cell irradiation and damage studies

LPA2 project activity organized in four working packages:

1. **Laser and plasma source** (WP leader: Luca Labate)
2. **Beamline and experimental set-up** (WP leader: Dario Giove)
3. **Diagnostic and and absolute dosimetry** (WP leader: G.A.P. Cirrone)
4. **Radiobiology** (WP Leader: L.A. Gizzi)

WP1 activity

- The current performance level of the laser system is fully in line with similar >100TW class laser systems worldwide concerning, **intensity**, temporal **contrast**, **stability** etc ...
- Work on laser and laser-plasma interaction systems/diagnostics (including those required by LPA2) are expected to be carried out by the ILIL staff:
  - providing a **full set of laser parameters** on a week-by-week basis;
  - implementing a **full characterization of both the temporal and spatial** features of the laser systems;
  - commission **shot-by-shot diagnostics** of main laser figures, such as energy, wavefront, pointing, etc.
  - implement further control of laser **spot quality** (phase front correction);
  - improving (and speeding up) **laser-target alignment** operations;
  - optimizing **laser-plasma coupling**, using a set of plasma diagnostics including:
    - Laser backscattering and reflection imaging/spectroscopy
    - Optical Transition Radiation diagnostics
    - X/gamma-ray spectroscopy
    - Basic ion diagnostic (Thomson Parabola spectroscopy)

Preliminary transport simulations (WP2 activity)

Preliminary simulations carried out, starting from the beam parameters as measured during 2020 run

Two operating energy points considered (at 6 MeV and 8 MeV).

Two magnetic beamlines studied: a) 4 PMQs (100 T/m gradient, 20 mm bore) available from the INFN-LNS ELIMED project; b) LMU designed PMQs (340 T/m gradient, 10 mm bore).

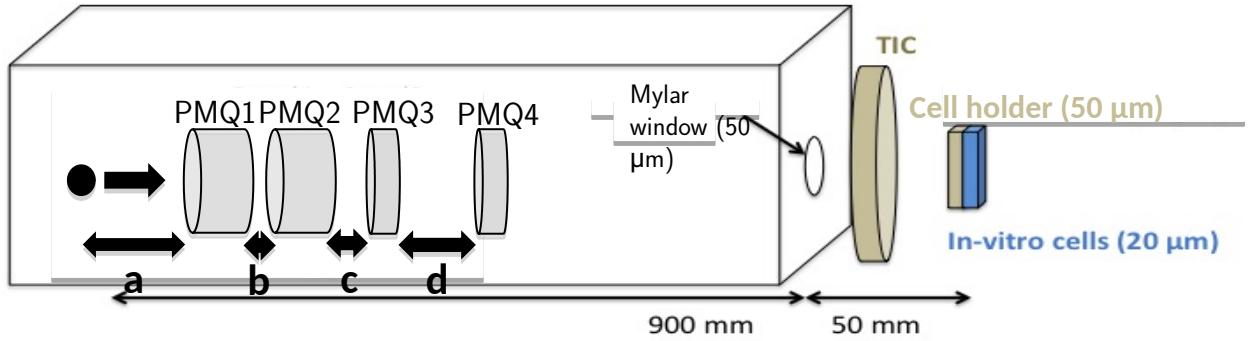
Preliminary estimates of the effects of the vacuum-air interface (50 micron kapton window) performed

Setup (aka dish/flask structure) for *in vitro* cell irradiation preliminary sketched/simulated (50 micron thick substrate, possibly to be reduced to 20 micron thick)*.

First (minimum) irradiation surface area: 10x10mm2

* Energy loss due to the total 100 micron Kapton is of 970 KeV and 750 KeV for 6 and 8 MeV proton beams

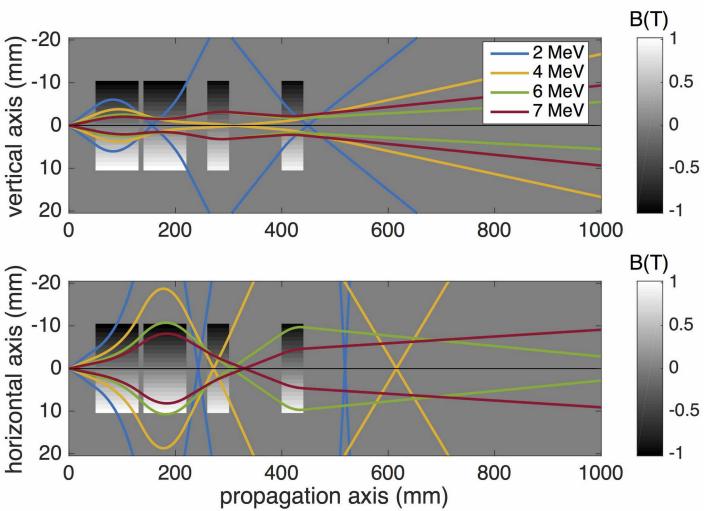
Beamline study: 6MeV protons, "LNS" PMQ



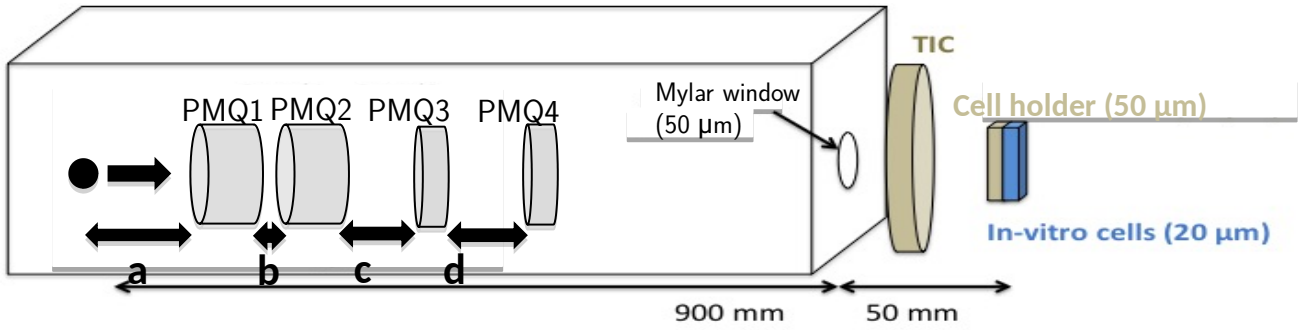
LOA configuration for 6 MeV focusing
DOI: 10.1103/PhysRevAccelBeams.20.032801

- A=50, b=10.3, c=40, d=100
- PMQ1,2: G≅100 T/m, length=80 mm, bore=20 mm
- PMQ3,4: G≅100 T/m, length=40 mm, bore=20 mm

Envelopes in ±σ angle



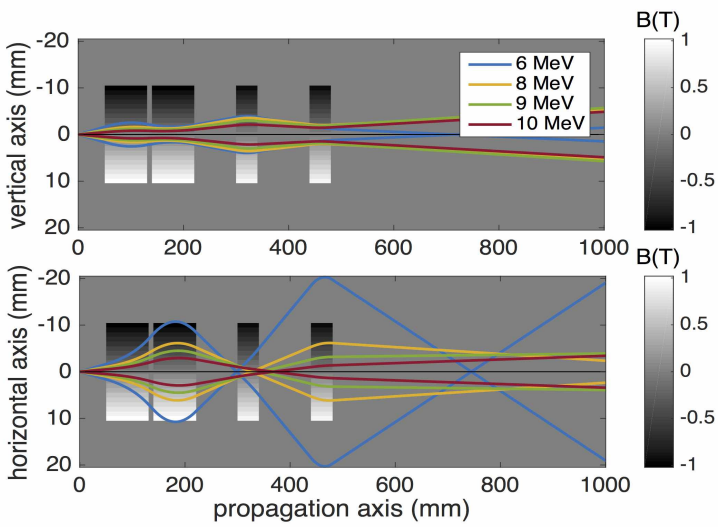
Beamline study: 8MeV protons, "LNS" PMQ



The reference configuration of LOA to focus 6 MeV is modified . C is increased in order to focus the spectral components around 8 MeV
DOI: 10.1103/PhysRevAccelBeams.20.032801

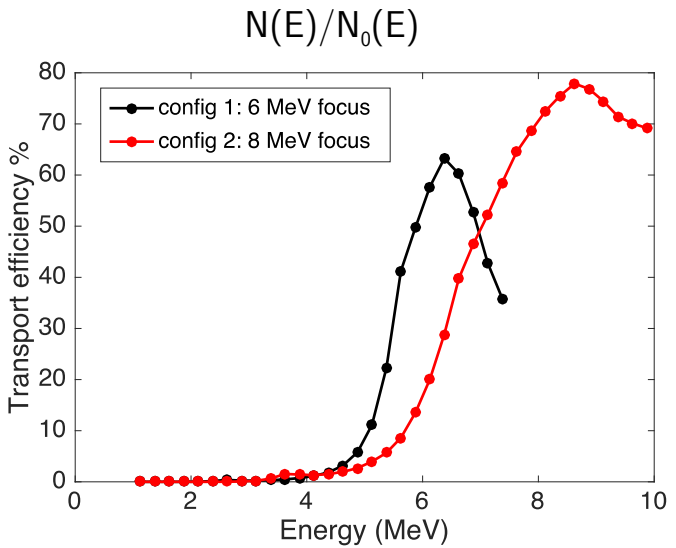
- A=50, b=10.3, c=80, d=100
- PMQ1,2: G≅100 T/m, length=80 mm, bore=20 mm
- PMQ3,4: G≅100 T/m, length=40 mm, bore=20 mm

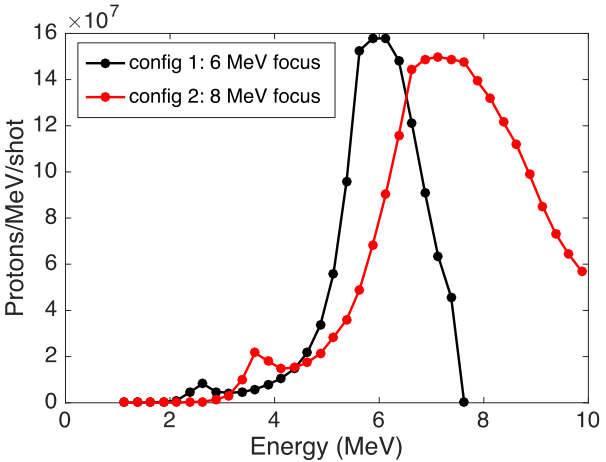
Envelopes in ±σ angle



Beamline study: "LNS" PMQ

Transport efficiency for each energy component over a 1x1 cm^2 surface placed before the exit window



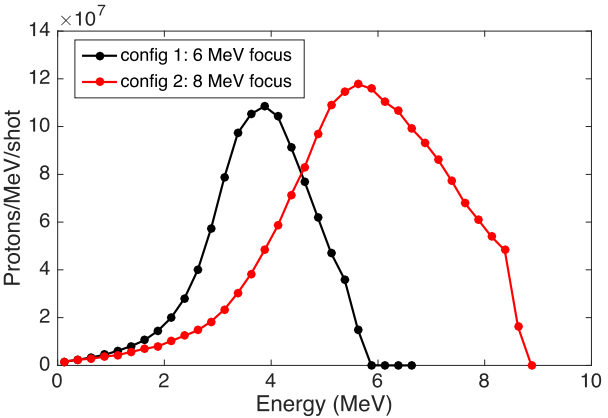


- Total charge 0.052 nC/shot
- Total transport efficiency= 3.05 %
- Total charge 0.09 nC/shot
- Total transport efficiency= 5.3 %

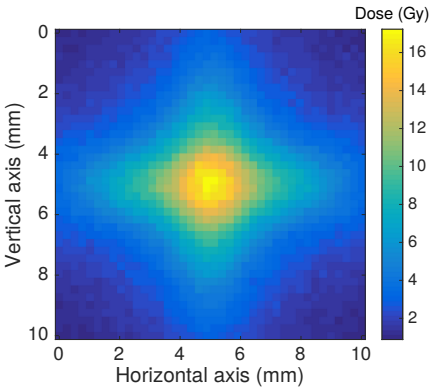
Beamline study: "LNS" PMQ

- Total charge 0.044 nC/shot (2.7x10^8 protons)
- Total charge 0.076 nC/shot (4.7x10^8 protons)

Spectra at cell sample position (1x1 cm^2 surface)

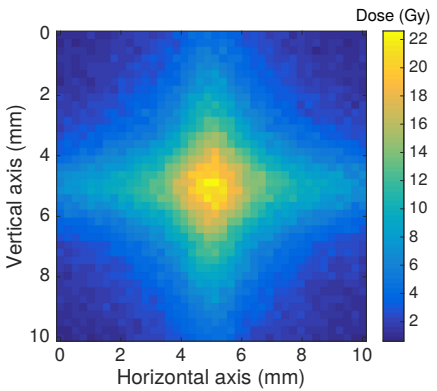


Config 1



Average dose=4.32 Gy/shot

Config 2



Average dose=5.6 Gy/shot

Absolute dosimetry (WP3)

1. At the energies expected both CR39 and calibrated EBT3 and HD radiochromic films can be used as a preliminary check of absolute dose
2. Proton beam energy spectra must be reconstructed at the irradiation point using radiochromic films in stack configuration
3. A Faraday Cup with a front-end properly designed to read < 200 nsec and intense (10^6 - 10^8 protons) beam pulses, will be positioned with the entrance window located at the irradiation point
4. The dose from Faraday Cup, cross-checked with the radiochromic reading, will be used to calibrate the multi-gaps ionisation chambers
5. Proton beam fluence will be monitored at each shot via a secondary electron monitoring detector installed in air or in vacuum just after the focusing quadrupole system. SEM front-end electronics will be developed at INFN-LNS, as well.
6. Multi-gaps chamber may be used to measure the dose in real-time; this will allow the correction for the recombination effects

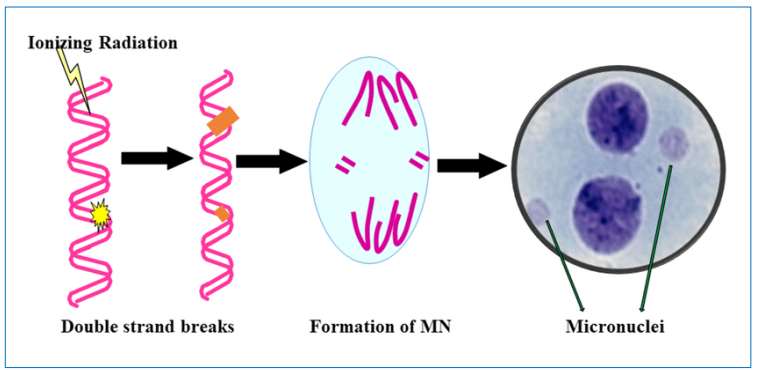
Radiobiology

The activity of the Radiobiology WG will take advantage of:

- **existing collaboration** between the National Institute of Optics (INO-CNR) and the Institute of Clinical Physiology (IFC-CNR) and the Cefalù Unit of the Institute of Molecular Bioimaging and Physiology (IBFM-CNR)
- **source characterization and specifications** by the Dosimetry WG.

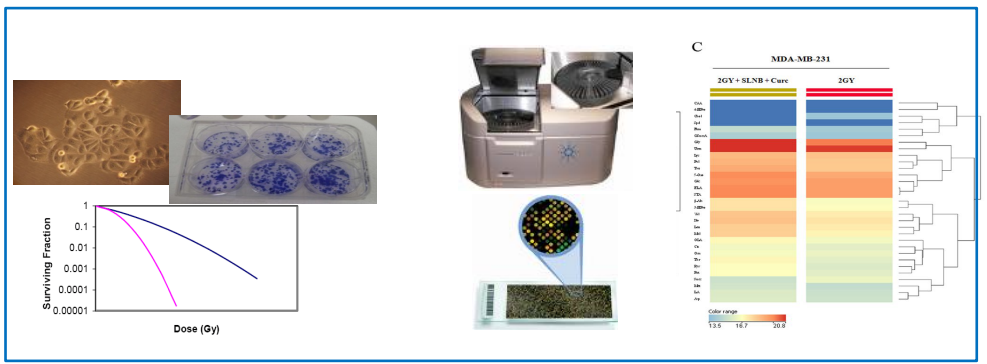
Aim of this working group is to:

- perform radiobiological **assays on cell samples** exposed to the laser proton source
- **compare the results** with those obtained following exposure to conventional sources
- focus on two main studies:



Micronuclei (MN) assay

Activity 1 - IFC-CNR



Cell survival study and gene expression profiling (GEP)

Activity 2 - IBFM-CNR

Radiobiology: activity 1.

AIM: study the dose-dependent response to chromosomal damage in human lymphocytes irradiated with laser accelerated proton beams and to estimate the relative biological effectiveness (RBE) of protons compared to 50 kV X-rays.

APPROACH: The micronucleus assay (MN) on peripheral blood lymphocytes, represents a well-validated[1] and sensitive method in radiation biology to identify and quantify chromosomal damage as MN formation.

- Will be performed after laser proton irradiation and the results will be compared to the conventional MN assay.

METHOD: Peripheral whole blood obtained from healthy donors will be irradiated in the dose range up to 4Gy with 6 MeV protons and compared with X-rays. All X-ray irradiation will be performed using the same holder that will be used for the laser-driven proton accelerator irradiation at the same temperature.

ANALYSIS: MN assay will be conducted to analyze irradiated cells according to standard protocols of IFC-CNR group [Andreassi MG et al 2016][1]. The RBE will be calculated as the ratio between the dose of 50 kV X-rays and 6 MeV protons which produces the equal biological effect.

EXPECTED OUTCOME: Determine the radiobiological response, reflected by the induction of MN in blood cells after irradiation in vitro with laser-generated protons.

[1]Andreassi MG, et al. *Radiobiological Effectiveness of Ultrashort Laser-Driven Electron Bunches: Micronucleus Frequency, Telomere Shortening and Cell Viability*, Radiat Res. 2016; 186:245-53.

Radiobiology: activity 2.

AIM: analyze cell and molecular response induced by laser proton beams on the metastatic breast cancer (BC) MDA-MB-231 cell line. This cell line, well-characterized by IBFM-CNR group, represents an in vitro model of a subgroup of BC particularly radioresistant and refractory to conventional therapies [Bravatà et al 2019][2] .

APPROACH 1: In a first step, cell viability will be studied after different proton doses delivered (1, 2, 3, 4, 5 Gy) on the MDA-MB-231 cells by clonogenic survival assay. Cell survival results will be compared with those previously obtained on the same cell line following irradiation with clinical X-rays [Minafra et al 2019][3] using the same dose delivered. RBE will be also calculated.

APPROACH 2: In a second step, considering that genes may function as biomarkers to predict the response to radiation treatment based on identification of molecular signatures by gene expression profiling (GEP), we are interested in performing comparative studies of molecular responses to laser driven versus conventional ionizing radiation.

METHOD: Molecular response will be evaluated by GEP using cDNA microarray technique on the MDA-MB-231 cells laser irradiated with 2 Gy proton dose. These results will be compared with that one previously obtained on the same cell line using the same dose delivered by clinical X-rays [Minafra et al 2019][3] and protons [Bravatà, et al 2019][4].

EXPECTED OUTCOME: Evaluate basic cell survival against response to conventional source. Identify gene signatures as biomarkers of radioresponse.

[2]Bravatà V, et al.Gene Expression Profiles Induced by High-dose Ionizing Radiation in MDA-MB-231 Triple-negative Breast Cancer Cell Line. Cancer Genomics Proteomics. 2019 Jul-Aug;16(4):257-266.[3]Minafra L,et al. *Radiosensitizing effect of curcumin-loaded lipid nanoparticles in breast cancer cells*. Sci Rep. 2019 Jul 31;9(1):11134. [4]Bravatà V et al. *Proton-irradiated breast cells: molecular points of view. J Radiat Res. 2019 Jul 1;60(4):451-465.*

Tentative time schedule

2020 (4 months)

- line set-up and proton source characterization (experimental activities)
- Radiobiological test plan definition
- Source optimization
- SEM dosimetry development

Milestones

- 31.12.2020: radiobiological Test Plan
- 31.12.2020: Laser energy of 4.5 J over 30 fs
- 31.12.2020: Laser pulse length stable over repetitive shots (less than 30 fs)
- 31.12.2020: Laser contrast on ns scale (10^{-8}) and ps scale
- 31.12.2020: New large parabola available (NO FUND REQUESTED)
- 31.12.2020: SEM dosimeter available

2022

- further radiobiological experiments
- IC design and test with conventional proton beam
- flash-like experiment
- (foreseen 2-3 experimental runs at Pisa each one of the order of 2 weeks each and 1-2 experimental runs on a proton beam available at an Italian Lab for detector calibration - LNL)

Milestones

- 30.7.2022: IC available and tested
- 30.12.2022: Radiobiological Experimental Results

2021

- line setup and proton source characterization
- cellular line(s) definition
- set-up of the front-end radio-biological lab
- Development of a specific transverse beam profile monitor
- Development of a dosimetric Faraday Cup and characterization on a suitable beam line
- Experimental test of the dosimetric system
- First sets of radiobiological experiments
- (foreseen 2-3 experimental runs at Pisa each one of the order of 2 weeks each and 1-2 experimental runs on a proton beam available at an Italian Lab for detector calibration - LNL)

Milestones

- 30.07.2021: Laser energy of 5.5 J over 30 fs
- 30.07.2021: Laser energy stability shot-shot
- 30.07.2021: Proton Beam Energy suitable for the LPA2 scenarios in terms of values and stability
- 30.10.2021: PMQ based lattice verified along with experimental beam diagnostics operative
- 30.7.2021: Dosimetric Faraday Cup available
- 30.12.2021: First radiobiological Experimental Results

People

Bologna Unit (2.8 FTE): RL Gastone Castellazzi
Castellazzi Gartone 60% Matteuzzi Tommaso 30% Sala Claudia 50% Sumini Marco 80% Zironi Isabella 60%
Napoli Unit (2.1 FTE): RL Renato Fedele
De Nicola Sergio 50% Fedele Renato 50% Fiore Gaetano 20% Iovine Pasqualina 50% Masullo Maria Rosaria 10% Savino Federica 30%
Pisa Unit (1 FTE): RL Luca Umberto Labate
Leonida Antonio **Gizzi** 50%
Luca Umberto **Labate** 50%
The Pisa Group also includes additional CNR staff
- for Lab operations, Laser and plasma diagnostics, ion source optimization:

Lorenzo **Fulgentini** (Laser), Federica **Baffigi** (Laser & Diagn.), Fernando **Brandi** (Target and Plasma), Petra **Koester** (Plasma & Diagn), Gabriele **Cristoforetti** (Plasma and Diagn), Daniele **Palla** (Diagn. and Control) – CNR-INO

- for radiobiology studies from Istituto di Fisiologia Clinica – CNR-IFC

Maria Grazia **Andreassi**, Andrea **Borghini**, Cecilia **Vecoli**, Daniele **Panetta**
Milan Unit (3.3. FTE): RL e RN Dario Augusto Giove
Bazzocchi Anna 10% Calandrino Riccardo 40% Castriconi Roberta 20%
Cialdi Simone 10%
Fazzi Alberto 30%
Giove Dario Augusto 70% Giulini Castiglioni Agosteo Stefano 10% Groppi Flavia Maria 20% Maero Giancarlo 20% Manenti Simone 20% Mangili Paola Adele 40% Passoni Matteo 40%
Pola Andrea 10% Romè Massimiliano 10%
LNS Unit (1,4 FTE): RL: GAP Cirrone
Luigi Minafra 50% Cirrone: 30% Mele: 30% Petringa: 10%
Tudisco 20%

Non ci sono richieste di servizi per la Sezione