FRIDA: status WP2

FLASH Radiotherapy with hIgh Dose-rate particle beAms

Proton Acceleration

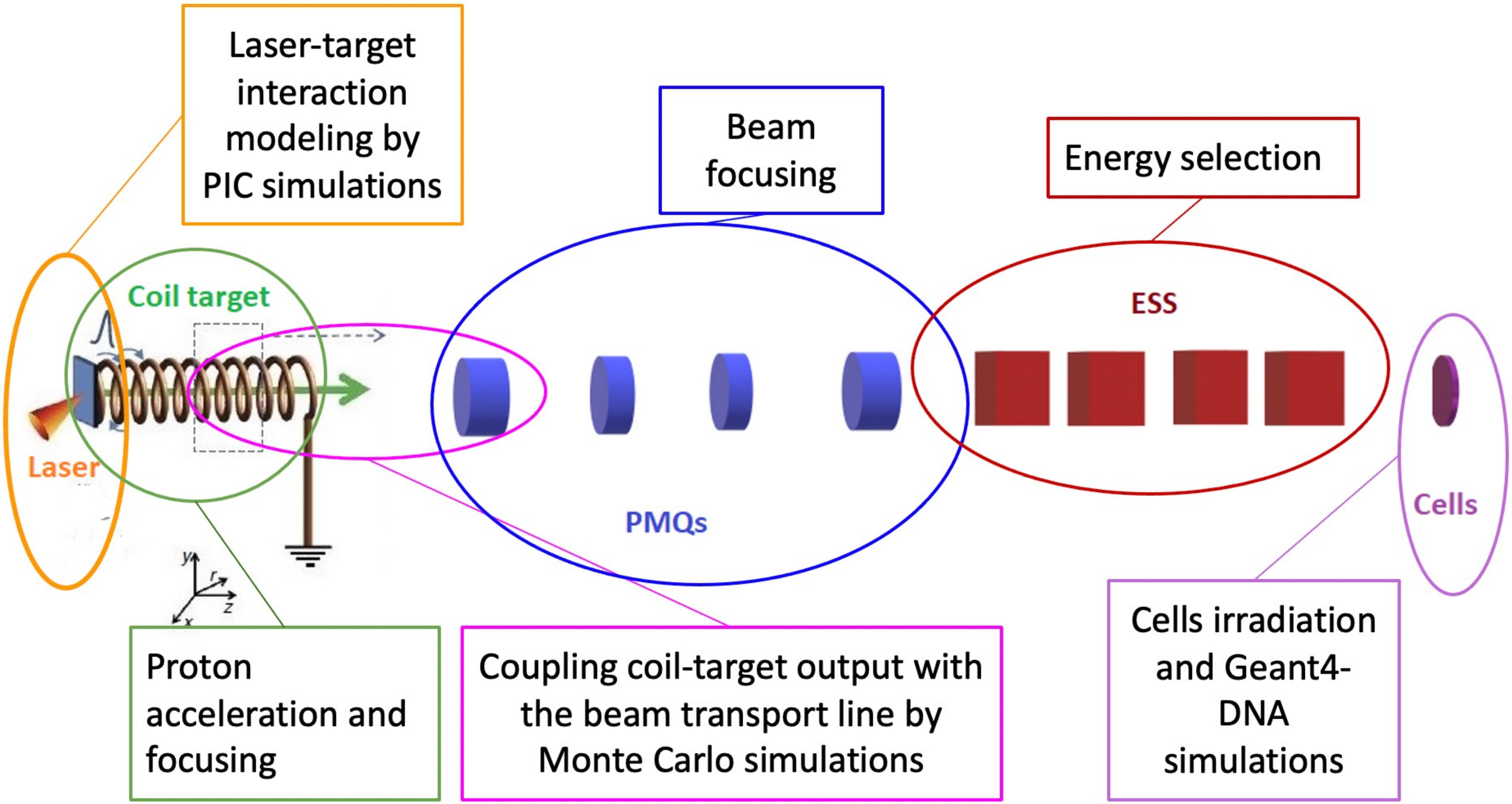
Status Milestones - 2022

M2.3.1.1 - Monte Carlo and analytical simulations (in collaboration with QUB and ELI) of the new laser-matter interaction and transport scheme using coil target coupled with the quadrupoles. Final design of the coil-target for the use with the QUB and ELI laser-generated beams.

Percentuale di completamento: 50%
Giustificazione: La simulazione Monte Carlo del sistema di trasporto basato sui quadrupoli a magneti permanenti è stata interamente realizzata. Per quel concerne la simulazione del coil target è in carico al gruppo di ricerca della Queen's University (QUB). A LNS si sta procedendo all'inserimento mediante opportuno spazio delle fasi di un fascio reale ottenuto sperimentalmente mediante l'utilizzo dei coil in condizioni di interazione laser-target analoghe a quelle preveste nel turno sperimentale già schedulato per il 2022 e che verrà svolto alla fine di quest'anno.

M2.3.1.2 - Acquisition of the new developed targets from RAL laboratory
Percentuale di completamento: 100%

Configurazione di lavoro



Current Status

Cosa è stato fatto:

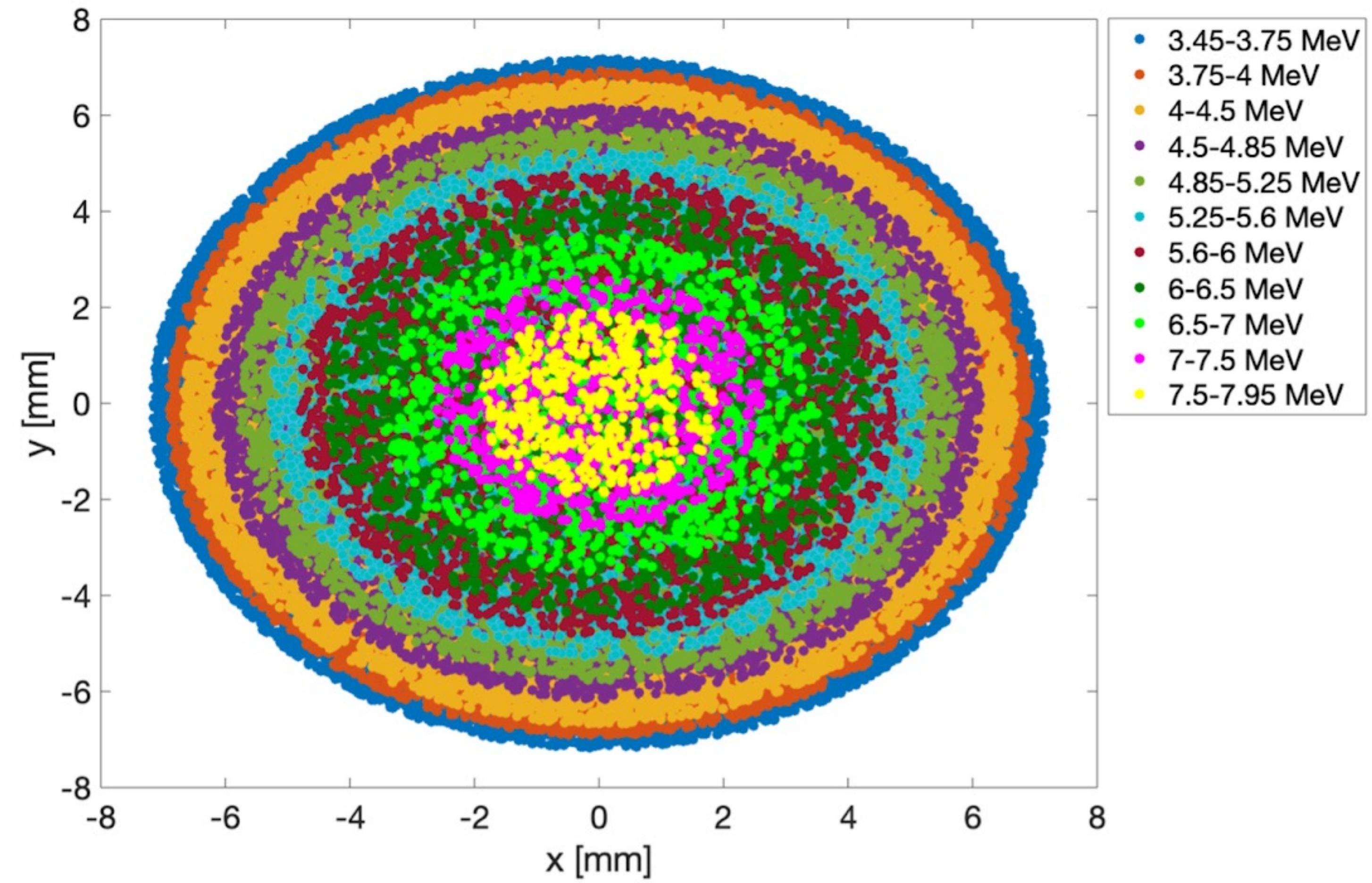
- [x] Simulazione della sorgente in assenza di coil target (Geant4)
- [x] Simulazione dei campi magnetici all'interno di quadrupoli e selettore (TraceWin)
- [x] Trasporto del fascio all'interno dei quadrupoli e del selettore in assenza di coil target (Geant4)

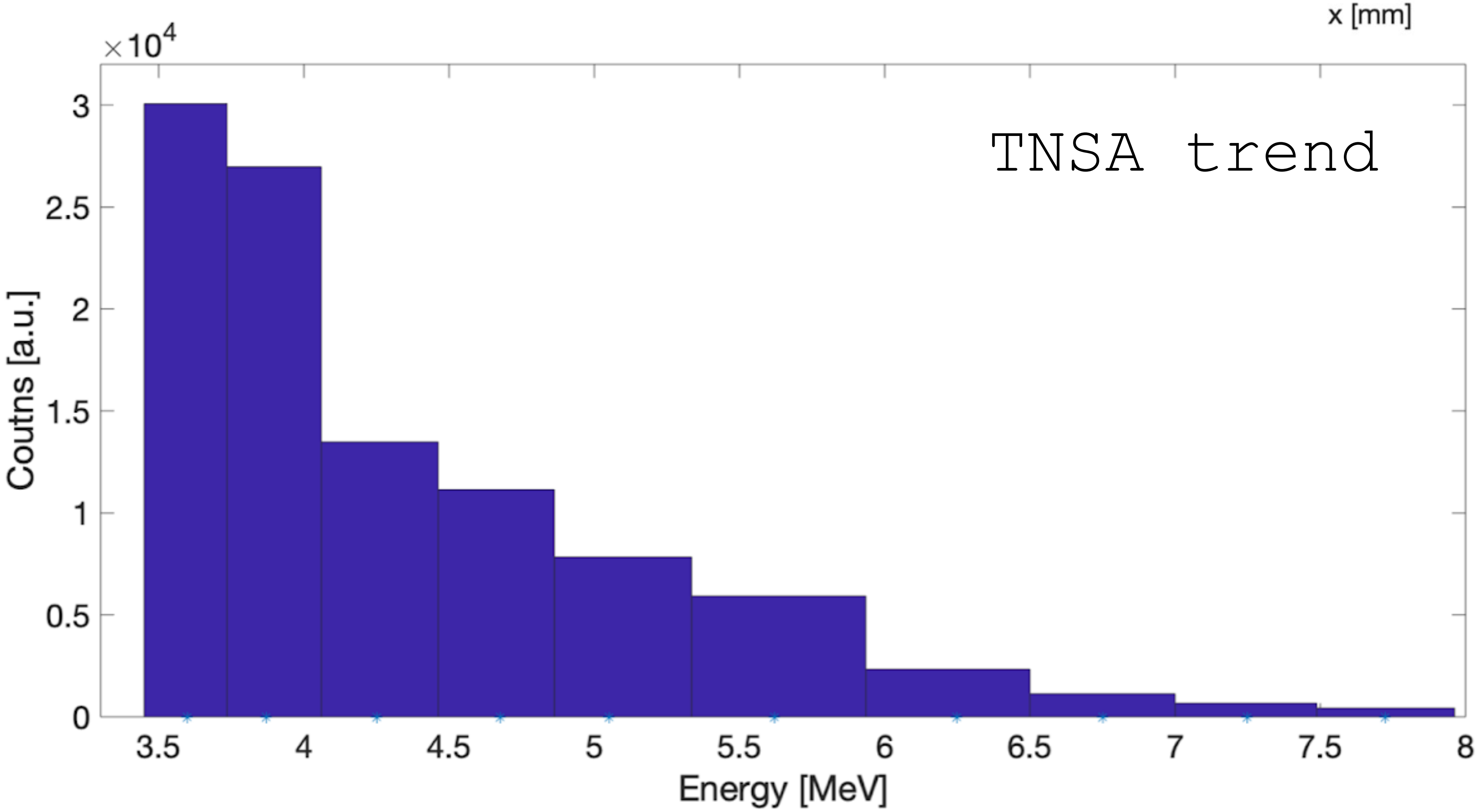
Cosa manca:

- [ ] Simulazione e trasporto del fascio in presenza del coil target (Geant4)
- [ ] Misura sperimentale a TARANIS (QUB)

Sorgente

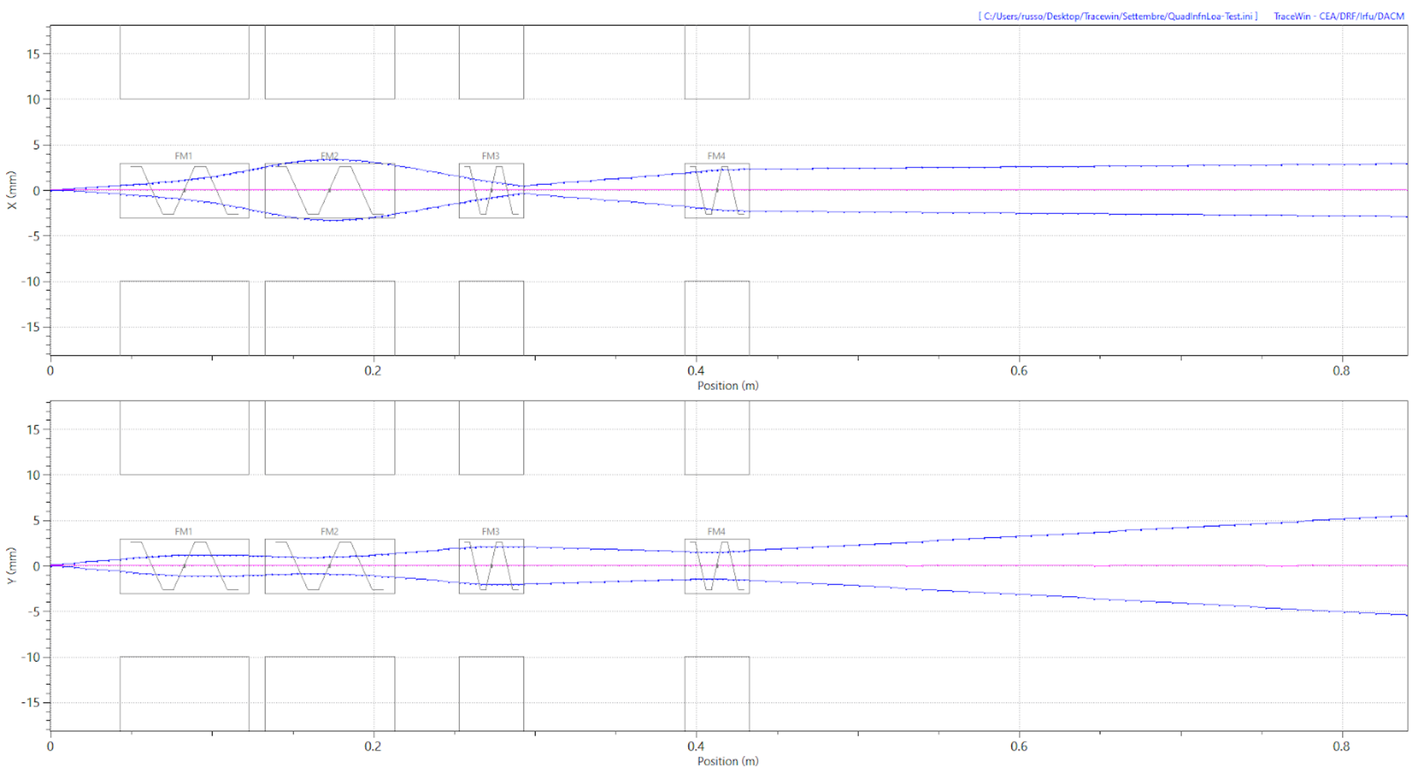
Proton beam @TARANIS facility
(cut off 8 MeV)

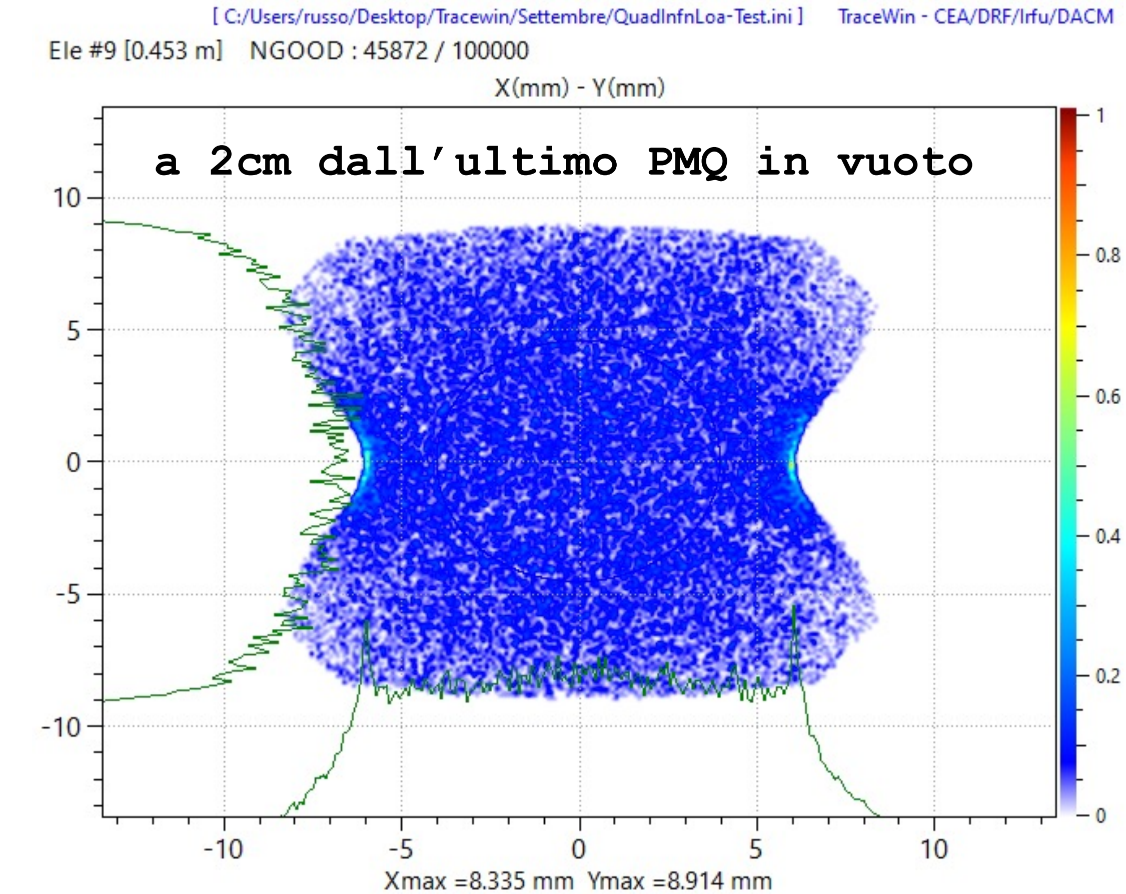


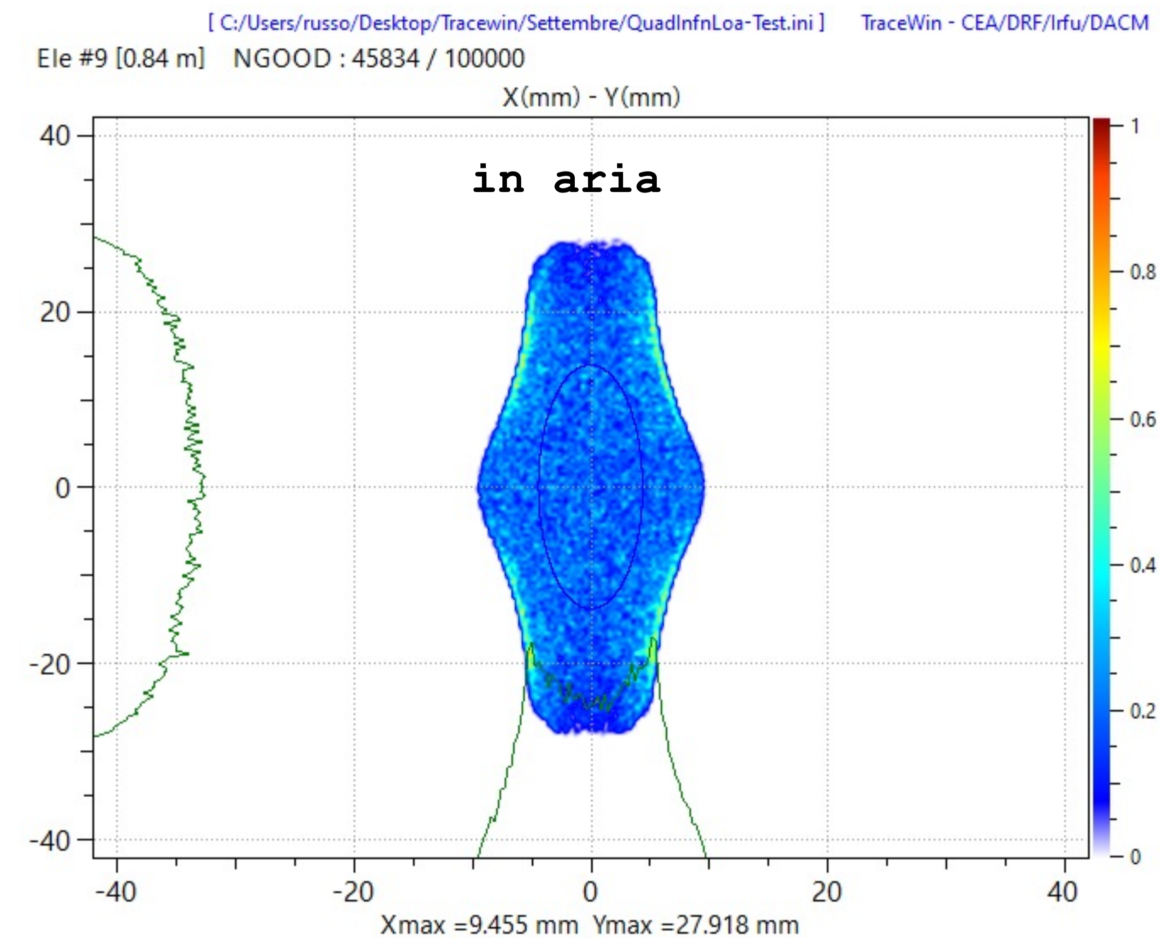


Configurazione PMQ

Studio configurazione trasporto a 5 MeV

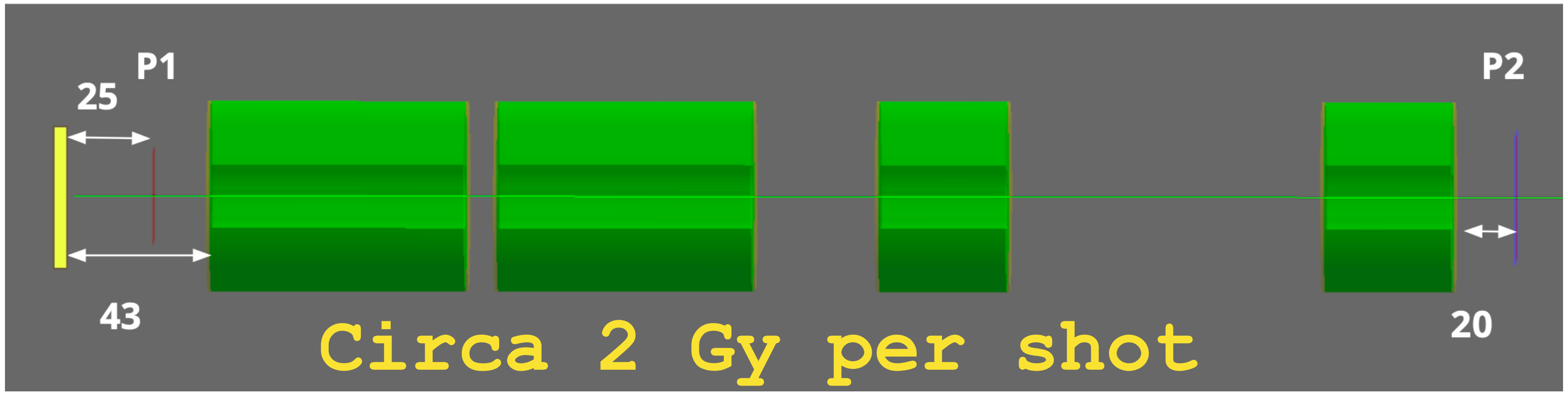






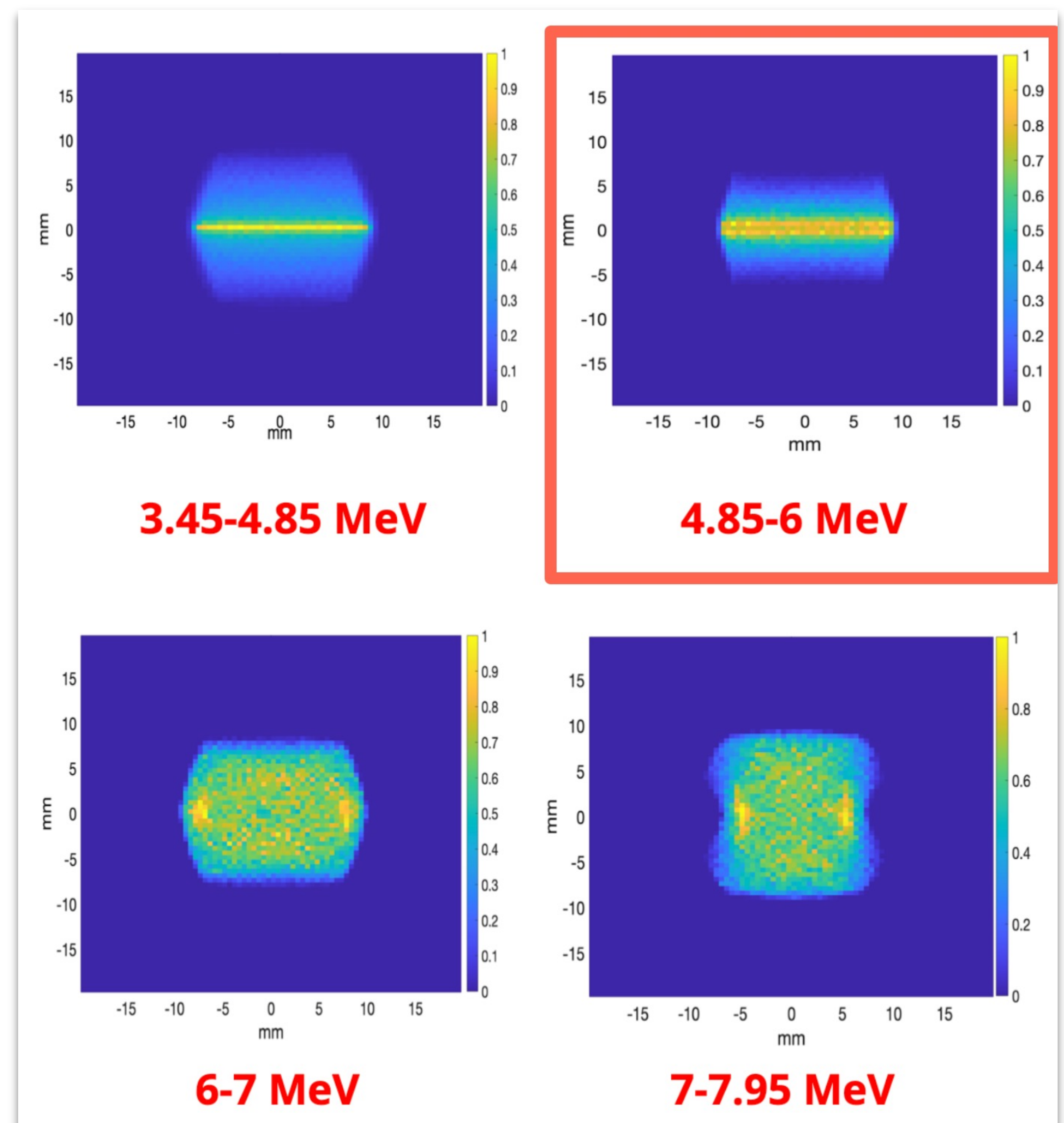
PMQ Geometry

Configurazione a 5 MeV implementata all'interno di G4



Supponendo uno stack di film radiocromici posizionato in vuoto a 2 cm dall'ultimo quadrupolo

(volume sensibile di acqua con spessore di 355um)



Open questions

	Beam transport solution	Selected energy [MeV]	Spot dimension and shape	Dose per shot [Gy]	Dose uncertainty (%)	Dose-rate [Gy/s]	Laser
Yogo et al. 2011	Four permanent dipoles	2.25	Circular; 5 mm in diameter	0.25	8	10^7 (single bunch) 0.2 (1 Hz)	J-KAREN (Japan) Ti:sapphire, 0.3 PW, 1 J
Hanton et al. 2019	Single permanent dipole	10	Rectangular; 10 x 1 mm^2	1 - 2	15	10^9 IDR	GEMINI (UK) Ti:sapphire, 0.5 PW, 12 J
Pommarel et al. 2017	Four magnet quadrupoles	5	Rectangular; 10 mm x 15 mm	1.15	20	2 x 10^8 IDR	SAPHIR (France) Ti:sapphire, 200TW, 3 J
Bayart et al. 2019	Four magnet quadrupoles	5	Rectangular; 10 mm x 15 mm	0.72	23	1.5 x 10^8 IDR	SAPHIR (France) Ti:sapphire, 200TW, 3 J
Brack et al. 2020	Two pulsed solenoids	25	Circular; 5 mm in diameter	0.7-2.3	8.5	0.012 MDR	DRACO (Germany) Ti:sapphire, PW, 13 J
Manti et al. 2017	Single permanent dipole	6 - 14	Rectangular; 10 x 1 mm^2	1.8 - 4.5	33 - 18	-	LULI PICO2000 (France), Nd:glass 150 TW, 100 J
Doria et al. 2012	Single permanent dipole	1 - 5	Circular; 2.5 mm in diameter	0.8 - 5	20	10^9 IDR	TARANIS (UK) Ti:sapphire - Nd:glass, multi-TW, 20 J
Bin et al. 2012	Miniature quadrupole doublet	5.2	Circular; 9 mm in diameter	4.6	4	7 x 10^9 IDR	ATLAS (Germany) Ti:sapphire, multi-TW, 0.4 J
Bin et al. 2022	Argon-filled active plasma lens (APL) + dipole magnet	7.4 - 34	Circular; 10 mm in diameter	0.74 - 1.24	20	(2.3 - 3.8) x 10^7 IDR (0.15 - 0.25) MDR	BELLA (California) Ti:sapphire, PW, 35 J

Open questions

How we can obtain a "flash" condition?

- On average we today are able to obtain on average, **1 Gy per shot over a beam spot size of 1 cm in diameter**;
- Increasing the repetition rate up to 100 Hz order we could reach an average dose-rate of 100 Gy per second while the instantaneous dose-rate is 10E8 Gy/sec
- This is not yet feasible with today available lasers even if the possibility to have few MeV protons at 100 Hz or kHz will become possible in the next few years

- **Increasing the dose per shot** ==> coil target

with the coil target of FRIDA we expect to reach a dose per shot of 10/15 Gy in 60 ns

FRIDA: status WP2

Optimizing laser-driven VHEE pencil beams – MC simulation of deep seated brain tumor FLASH-RT at ILIL – INO - CNR

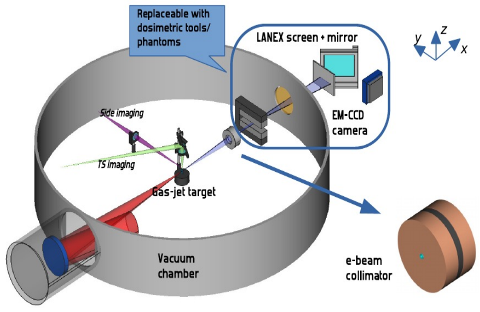
D. Del Sarto, L. Labate, L.A. Gizzi

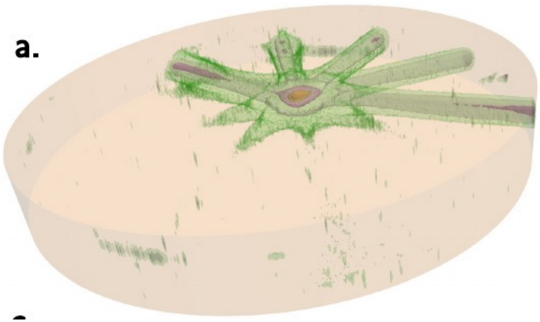
Intense Laser Irradiation Laboratory
Consiglio Nazionale delle Ricerche
Istituto Nazionale di Ottica
Sezione di Pisa, Italy

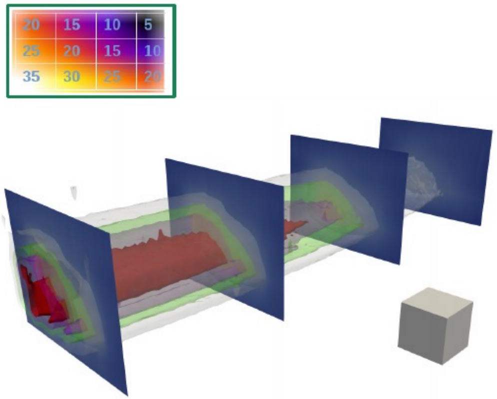
Istituto Nazionale di Fisica Nucleare
Sezione di Pisa, Italy

Past and ongoing experiment with VHEE beam

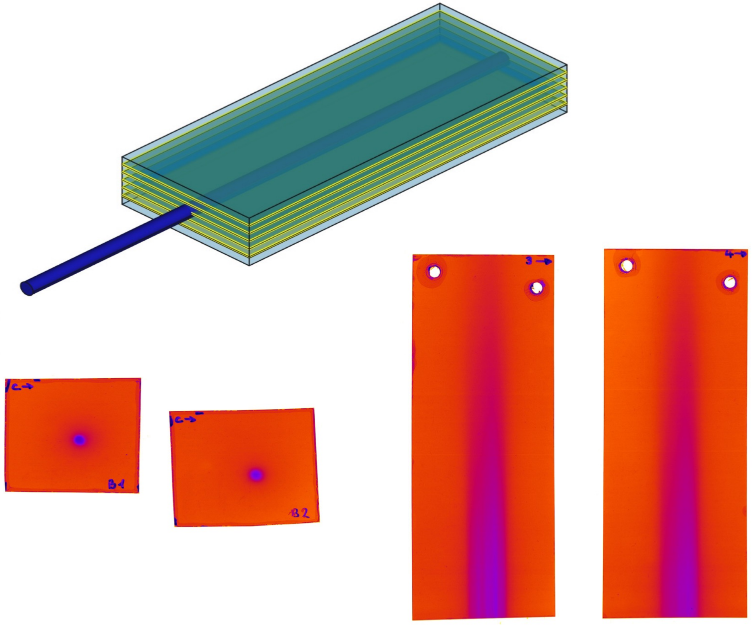
Experiment with laser-driven VHEE electrons: optimizing and tailoring dose deposition with pencil beams







L. Labate *et al.*, Sci. Rep. 2020



Currently available VHEE beam:

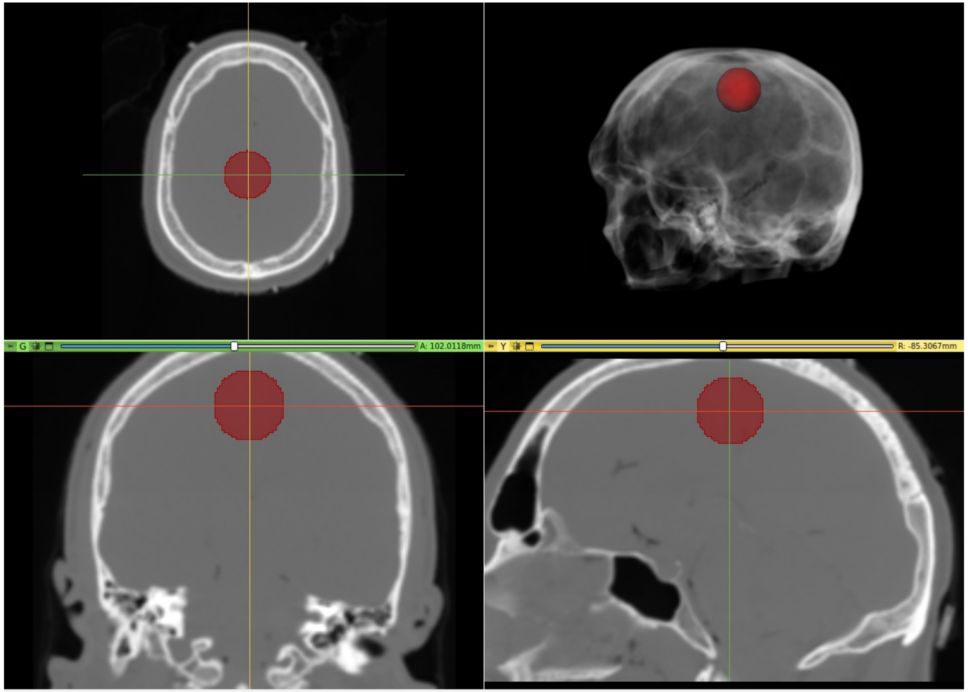
- sub-Gy VHEE pencil beams with 10s of cGy/s dose rates
- investigating fundamental radiobiology vs dose-rate

Exploring applicability of laser-driven-like **pencil beams**

MC simulations of deep tumor treatment with VHEE pencil beams

We investigated the challenge of a deep seated tumor irradiation with pencil beam scanning technique to better understand the needed techincal improvements.

- Developed an in house code to import DICOM files (standard in medical 3D imaging) in a GEANT4-based MC code.
- Density is assigned to each voxel using a calibration curve (HU units vs density).
- Fine tuning available (e.g. group materials in subgroups of densities)
- “Advanced” analysis possible (segmentation of relevant volumes, ...)
- Particle interactions fully customizable by the end user



First test aimed at a studying a possible treatment of a brain tumor (for instance a GBM, one of the most “compelling” case for a possible FLASH treatment, due to the difficult access for surgical treatments and the very irregular shape).
Tumor introduced *ad hoc* as a small sphere of approximately 10cc

VHEE Electron Source and Setup

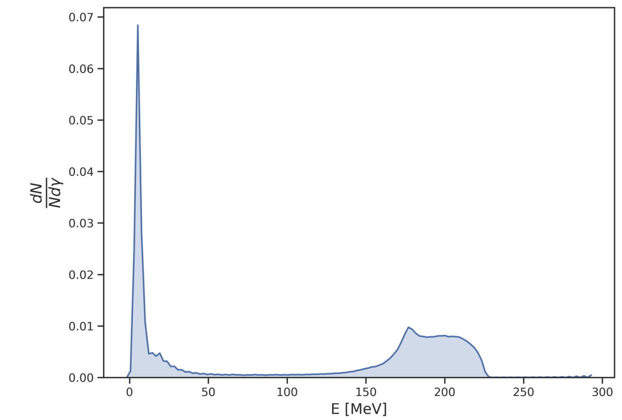
Input spectrum obtained using PIC simulations (FBPIC)
Charge/bungh ~60pC, average energy ~190MeV, energy spread ~20%, beam divergence ~14mrad, gaussian shaped.

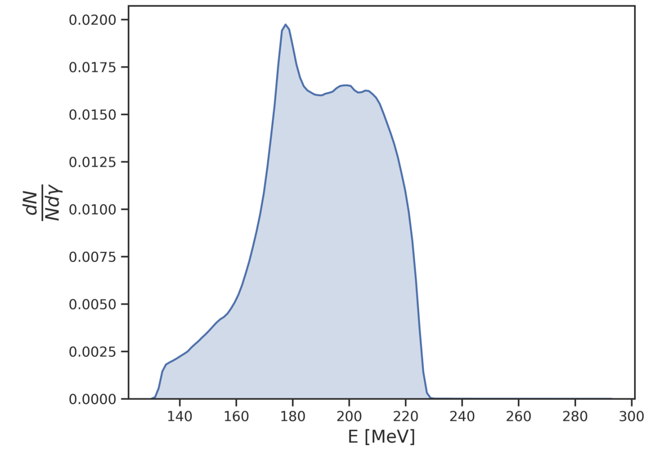
In the MC simulation, the “low energy” (E<50 MeV) component was not taken into account (expected to actually deliver a dose too high at shallow depths). Two different “cuts” at low energy were considered (50 and 100MeV)

Transverse beam profile quasi square, 2x2 mm^2 after an ad hoc “collimator” placed ~30cm from target, “patient” placed at ~1m from target → “pencil beam”

First stage of the simulations aimed to assess the dosimetric characteristics of the single gaussian beamleat passing trough the collimator and all the experimental devices.

The tumor was then irradiated with ~55 beams. Beam overlap was not optimized.





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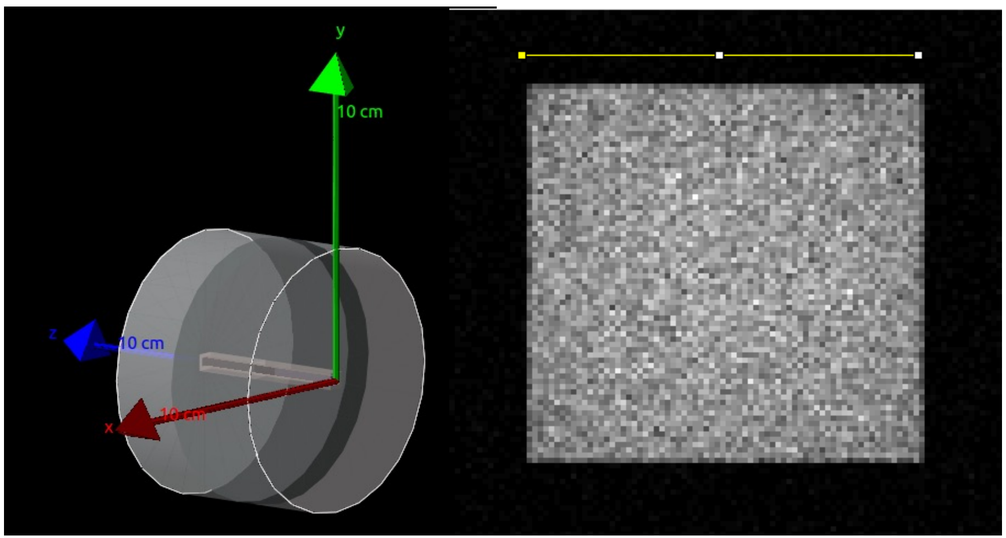
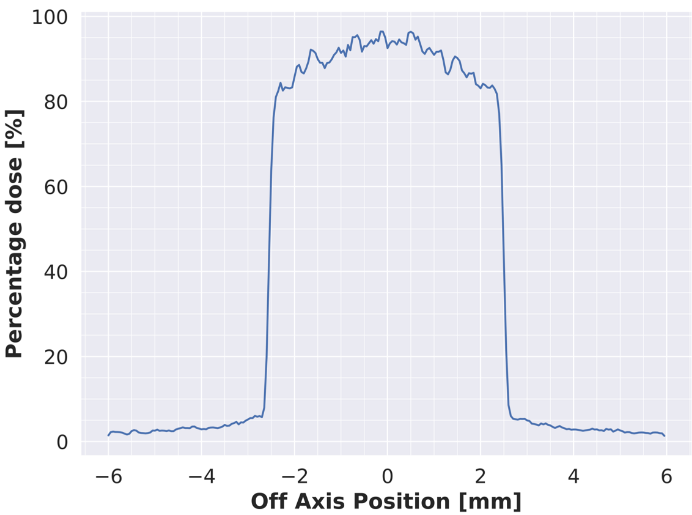
CONSIGLIO NAZIONALE DELLE RICERCHE

VHEE beamlet dosimetry 1/2

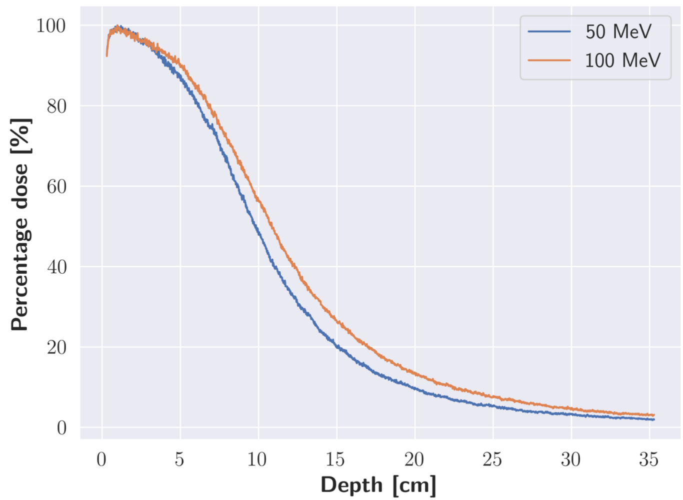
- Dose delivery with pencil scan irradiation → beam shaping needed to optimize the tumor volume coverage and normal tissue sparing.
- We decided to achieve the desired beamlet features by appropriately designing a collimator capable of reducing the angular divergence of the beam and producing a quasi square profile (0.5x0.5 cm at 70 cm from the source).
- Collimator mainly composed of lead and PMMA layered to reduce bremsstrahlung.
- Dose (and dose rate) inhomogeneity at <10% across the beam, although charge waste is not negligible ← probably cannot be avoided if FLASH effect has to be exploited over the entire field

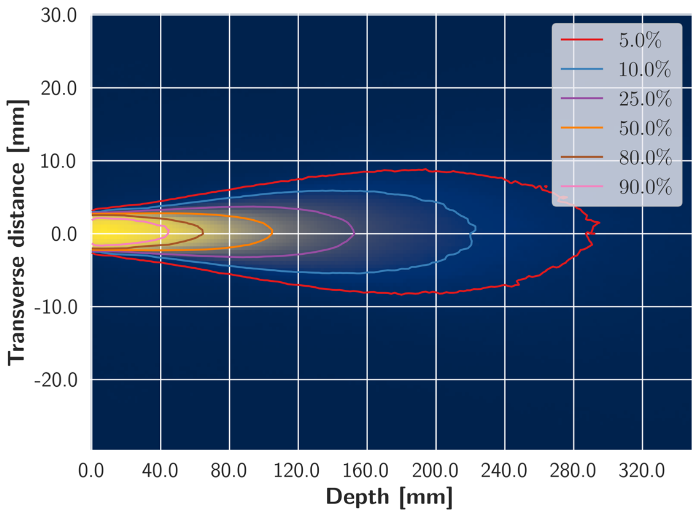




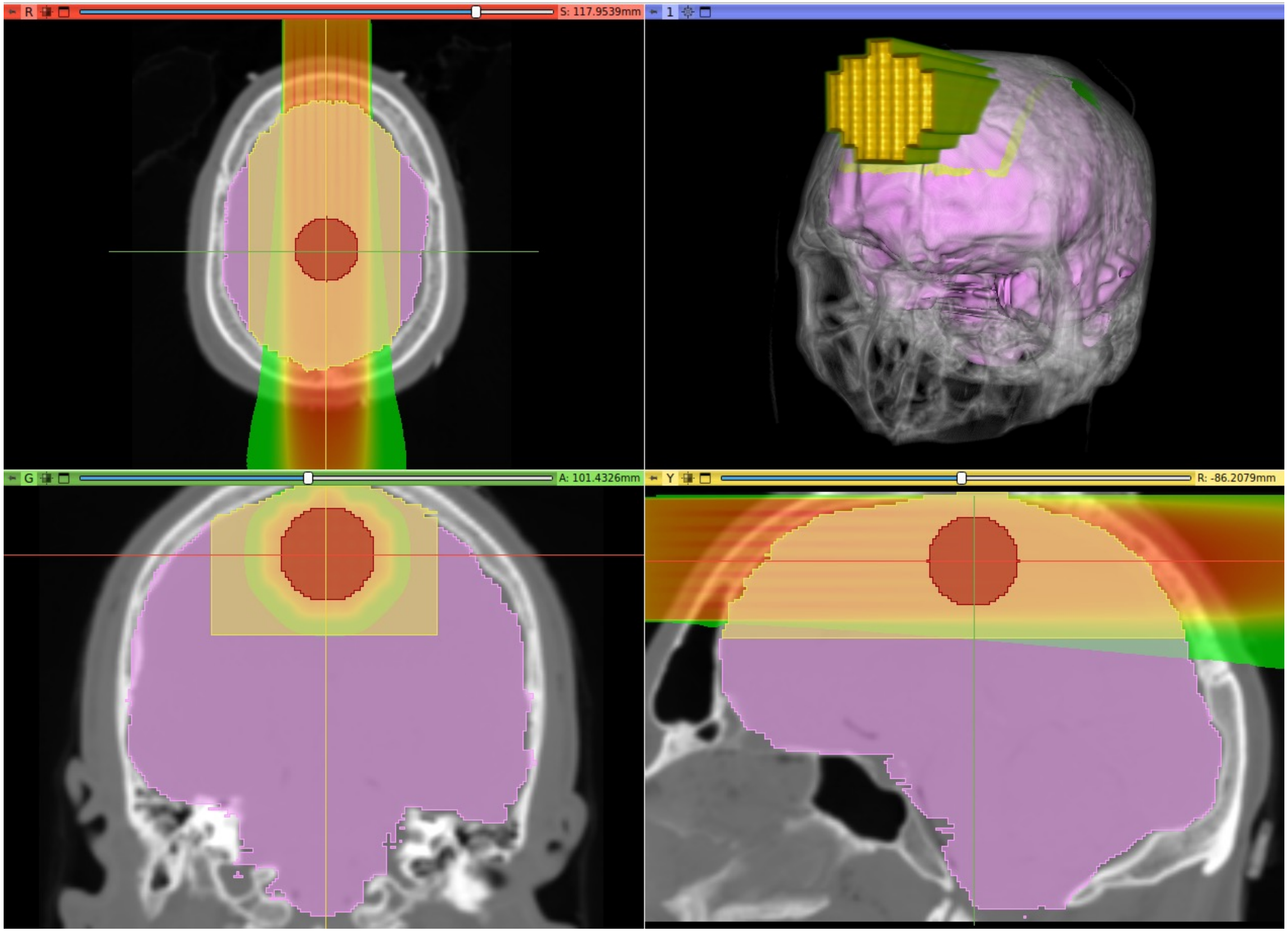
VHEE beamlet dosimetry 2/2

- We obtained PDD curves in a 30x30x30 cm water phantom. The curve shows that getting rid of energy components <100MeV is relevant. Large energy spectrum at >100MeV can be tolerated (already found in previous works by Bazalova-Carter et al.)
- Lateral spread of the beamlet acceptable when traveling in several cm of water, once the 100MeV threshold condition is fulfilled
- The PDD curve has a reduced buildup zone due to the smallness of the field (i.e. no lateral particle equilibrium), nonetheless we estimate a therapeutic range of 7cm for the single beamlet
- For each pencil beam irradiation the isodoses curves will always be at an increased depth in comparison to the single beamlet.



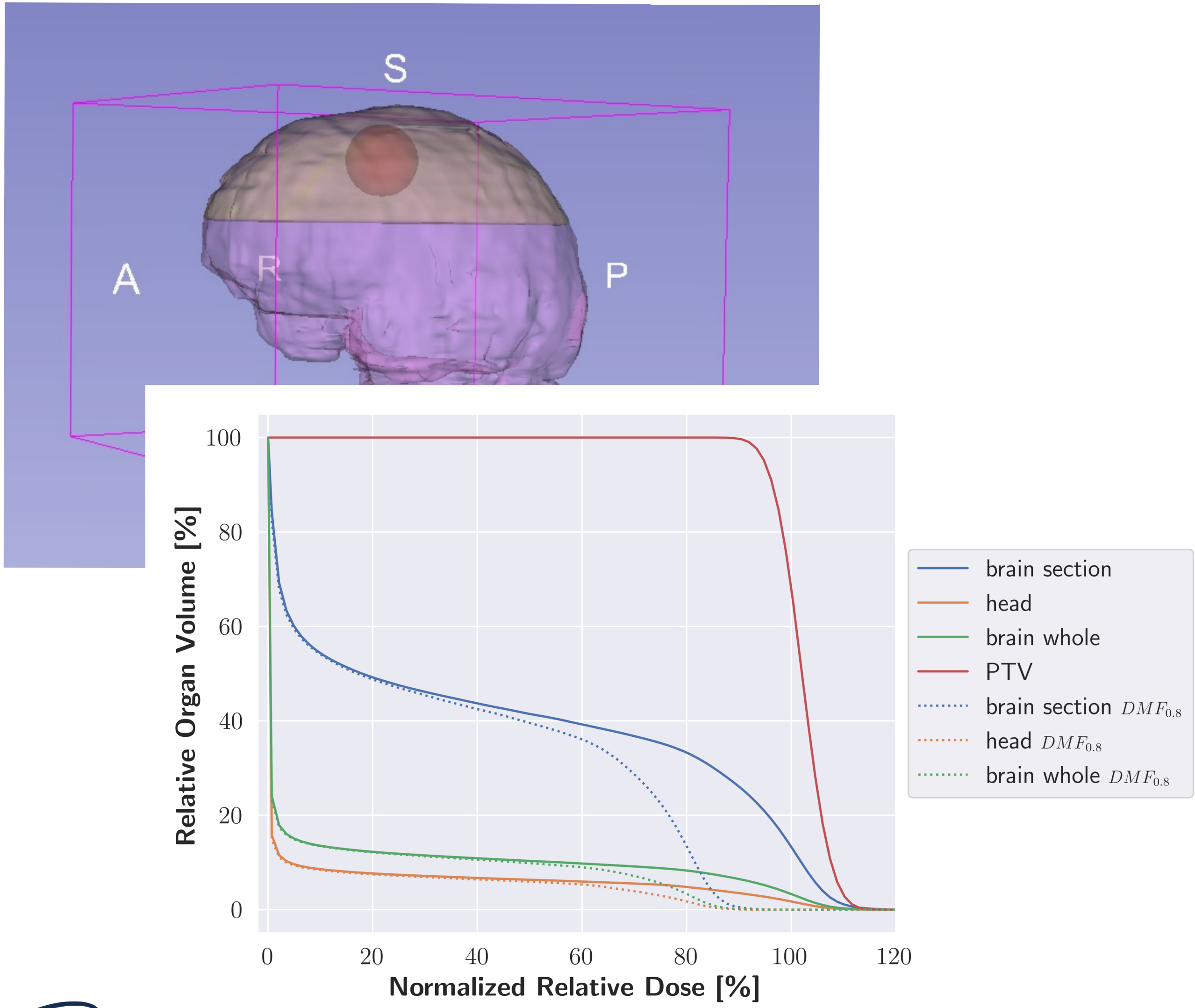


Pencil beam irradiation of a brain tumor



- Good target conformation thanks to precise pencil beam scanning.
- Extra margin added to tumor to guarantee target coverage requirements
- Dose peaks due to beam overlapping disappears at increasing depth
- FLASH effect could compensate for higher entrance dose

Dose Volume Histogram of irradiated organs with and w/o FLASH effect



- Encouraging result highlighted in the DVH plot
- Nice target coverage along the majority of its volume
- A bit of dose overshoot in the proximal area
- Highest dose value in the front part of the brain. Within ~5% to the maximum target dose
- Other organ not severely affected due to high beam conformation
- When the FLASH effect is taken into account a whole new picture presents to us…
- General comment of preliminary findings: dose pattern already comparable to existing protocols, once one considers room for improvements when using multiple fields (directions)

Summary and open challenges

- Pencil beams “naturally” arising when using (laser-driven) e-beams (but this likely for other FLASH-ready sources as well)
- With adequate energy cut (>100 MeV) the source at ILIL shows potential for VHEE irradiation of deep seated tumor.
- Unwanted superficial dose distribution could be compensated if the FLASH effect is taken into account.
- Beam overlap should be troughfully studied and the irradiation pattern should be optimized accordingly.
- A magnetic focusing line could help in reducing the need of a mechanical collimator thus reducing the bremsstrahlung production.
- Multi field modulated irradiation could be implemented following new evidence of FLASH effect about dose fractionation.

Towards FLASH capable source

Quantity	Actual	FLASH Capable
Repetition rate [Hz]	10	1000
Charge/shot [pC]	~100	1000

PNRR: Tuscan Health Ecosystem ("THE")

"THE - Tuscany Health Ecosystem" mira a stimolare e sostenere la crescita e il consolidamento dell'ecosistema delle scienze della vita della Toscana

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2. University of Pisa (UNIPI)
3. University of Siena (UNISI)
4. School of Advanced Studies – Pisa (SSSA)
5. Scuola Normale Superiore (SNS)
6. IMT School for Advanced Studies Lucca (IMT)
7. University for Foreigners of Siena (UNISTRASI)
8. Istituto Italiano di Tecnologia (IIT)
9. National Research Council (CNR)
10. National Institute for Nuclear Physics (INFN)
11. Toscana Life Sciences (TLS)
12. Museo Galileo - Istituto e Museo di Storia della Scienza(MGS)
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14. Medea S.r.l (MED)
15. Orthokey Italia S.r.l. (ORT)
16. Dedalus (DED)
17. Fondazione Pisana per la Scienza (FPS)
18. Digital Innovation Hub Toscana (DIH)
19. WEARABLE ROBOTICS SRL
20. IUVO S.r.l.
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22. WEART S.r.l.

- CENTRAL HUB AS COORDINATING UNIT
- SPOKE 1: **ADVANCED RADIOTHERAPIES AND DIAGNOSTICS IN ONCOLOGY**
- SPOKE 2: PREVENTIVE AND PREDICTIVE MEDICINE;
- SPOKE 3: ADVANCED TECHNOLOGIES, [] FOR HUMAN HEALTH AND WELL-BEING;
- SPOKE 4: NANOTECHNOLOGIES FOR DIAGNOSIS AND THERAPY;
- SPOKE 5: IMPLEMENTING INNOVATION FOR HEALTHCARE AND WELL-BEING;
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- SPOKE 8: BIOTECHNOLOGIES AND IMAGING IN NEUROSCIENCE;
- SPOKE 9: ROBOTICS AND AUTOMATION FOR HEALTH;
- SPOKE 10: POPULATION HEALTH.

Finanziamento totale 110 M€

Il personale CNR partecipante: 130 unità di personale strutturato

SPOKE 1: ADVANCED RADIOTHERAPIES AND DIAGNOSTICS IN ONCOLOGY

Un approccio multidisciplinare allo sviluppo della radioterapia FLASH, dallo sviluppo di acceleratori di nuova concezione alla traslazione clinica.

ASSET STRUMENTALI INNOVATIVI

- INTENSE LASER LAB @ CNR-INO
- CPFR center @ UNIPI/AOUP
- OFFICINA FARMACEUTICA CNR-IFC

COMPETENZE MULTIDISCIPLINARI

- FISICA DELLE RADIAZIONI IONIZZANTI
- BIOLOGIA CELLULARE
- BIOLOGIA MOLECOLARE
- RADIOBIOLOGIA
- PRECLINICA IN VITRO
- PRECLINICA IN VIVO
- MEDICINA TRASLAZIONALE
- CLINICA

OBIETTIVO

STUDIO DEI MECCANISMI DI BASE DELL'EFFETTO FLASH E TRASLAZIONE CLINICA DELLA RADIOTERAPIA FLASH

COORDINAMENTO LOCALE CNR, UNIPI, UNIFI, INFN GIÀ COINVOLTI IN COLLABORAZIONI (eg. FRIDA) SULLA R. FLASH

FORTI SINERGIE CON PROGETTI "INFRASTRUTTURE" CNR PER LO SVILUPPO DI SORGENTI LASER-DRIVEN

IN FASE CON ANALOGHE INIZIATIVE SULLA RADIOTERAPIA FLASH A LIVELLO INTERNAZIONALE

FINANZIAMENTO SPOKE 1: 7.5 M€