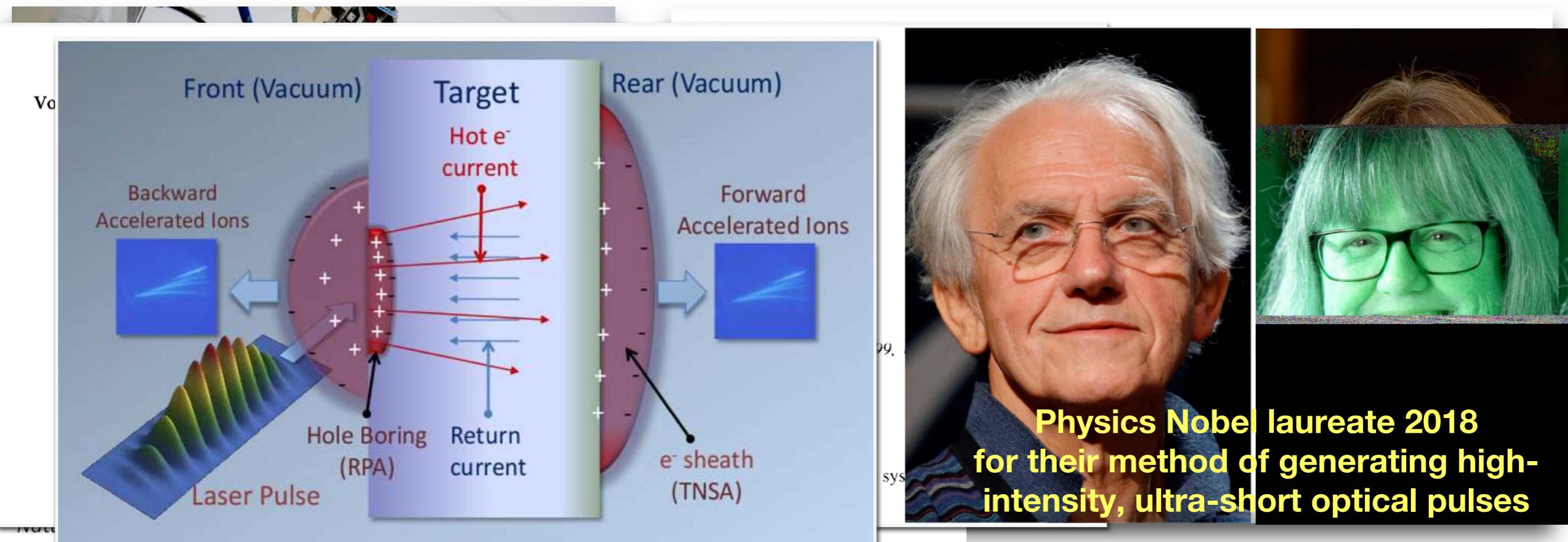




Hadrontherapy from the conventional approach to the laser-driven applications

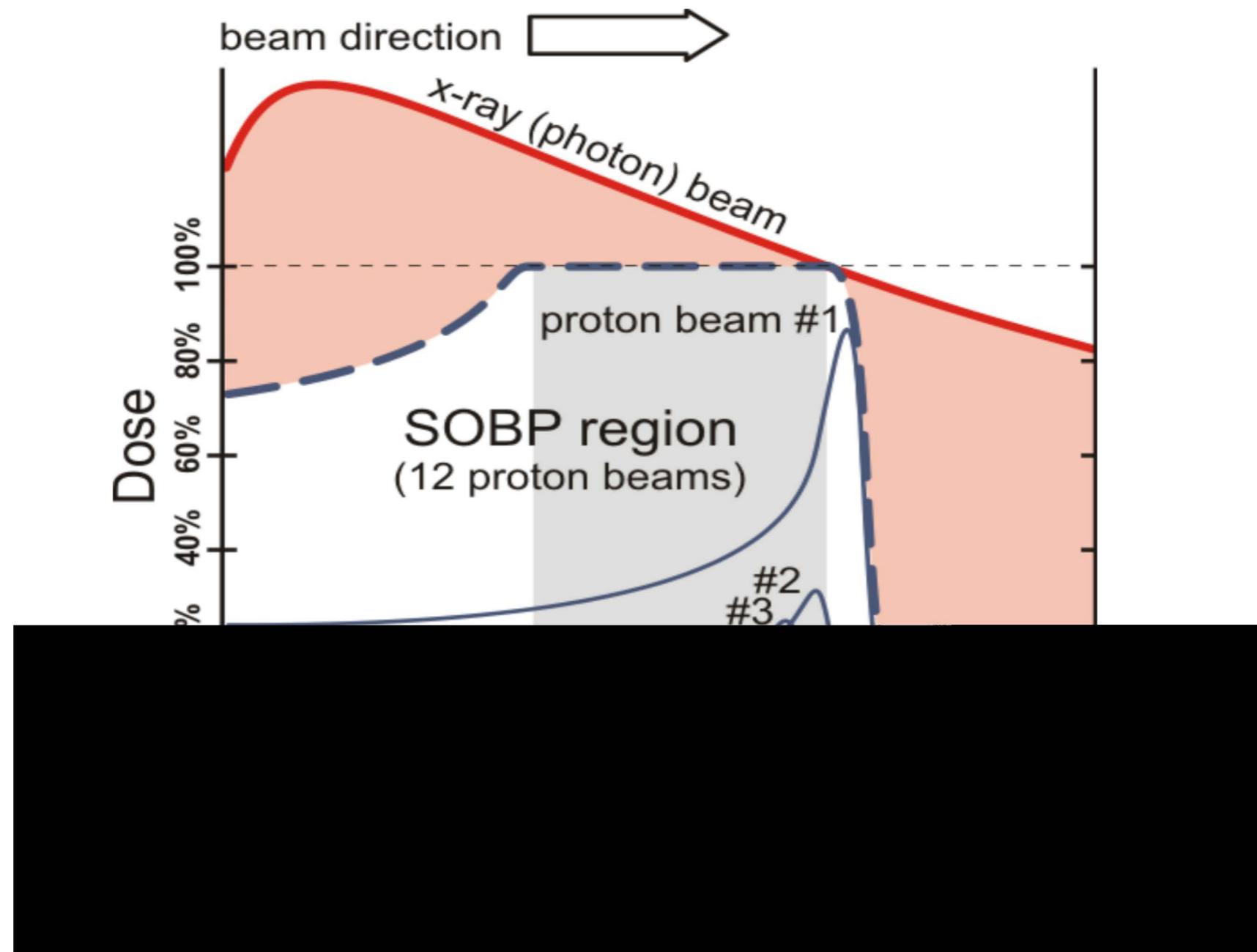
Hadrontherapy from the conventional approach to the frontier of biological enhancement and laser-driven applications



Conventional hadrontherapy

The rationale

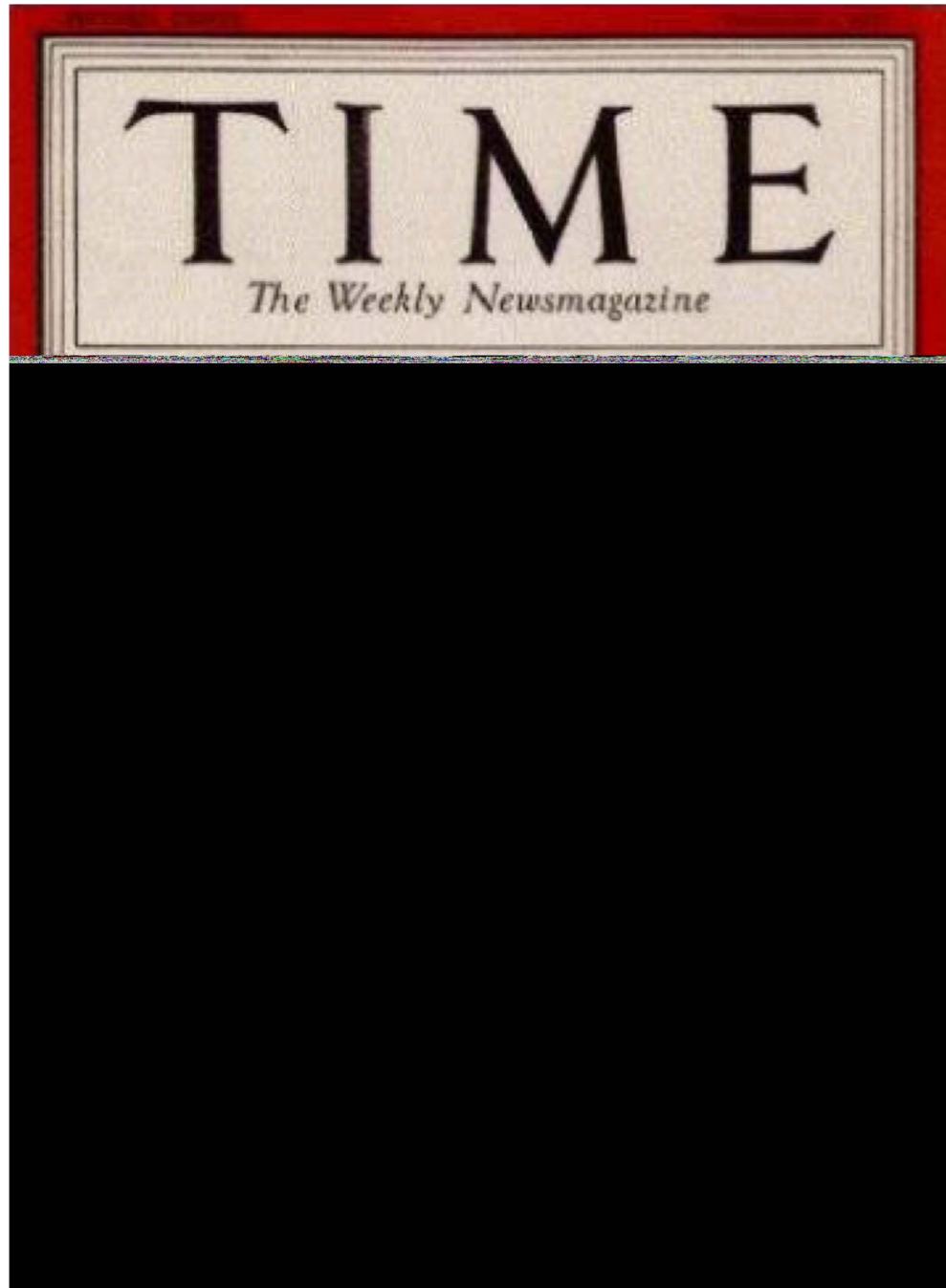
4



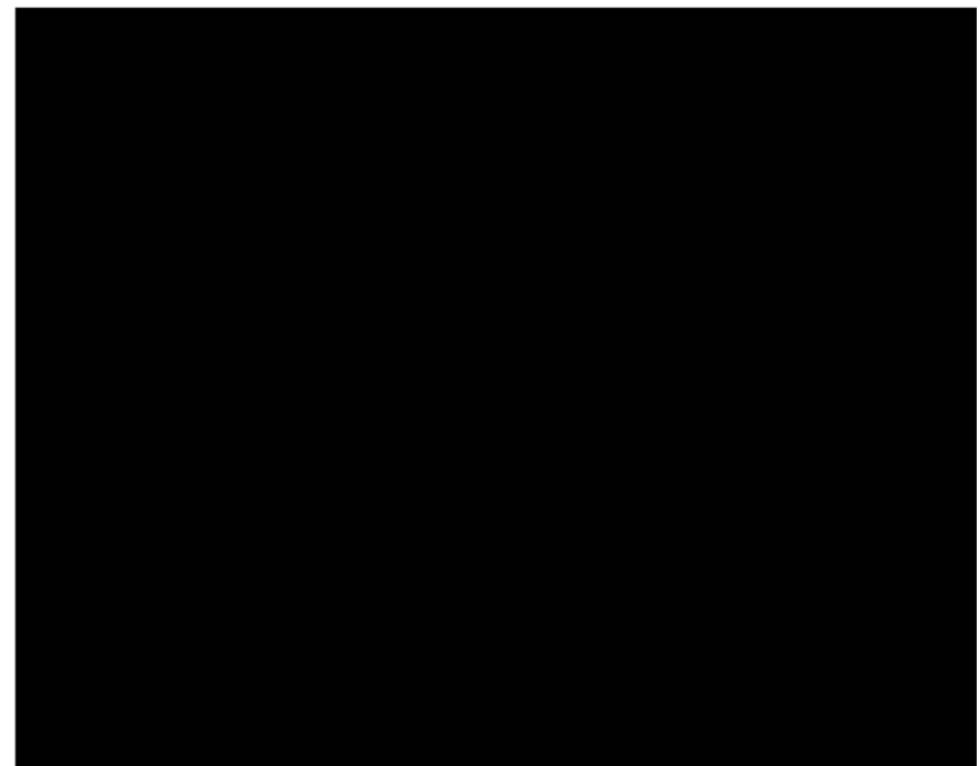
Levin WP, Kooy H, Loeffler, DeLaney TF. Proton beam therapy. Br J Cancer. 2005;93(8):849-854

Hadrontherapy history

5



Ernest Orlando Lawrence Nobel
Prize 1939
“Palm-size Cyclotron”



Hadrontherapy history

6



September 1938: the **first 24 patients** were treated at the **Lawrence Berkeley National Laboratory** with neutrons produced by the 37-inch cyclotron through the reaction of 8 MeV deuterons on a beryllium target

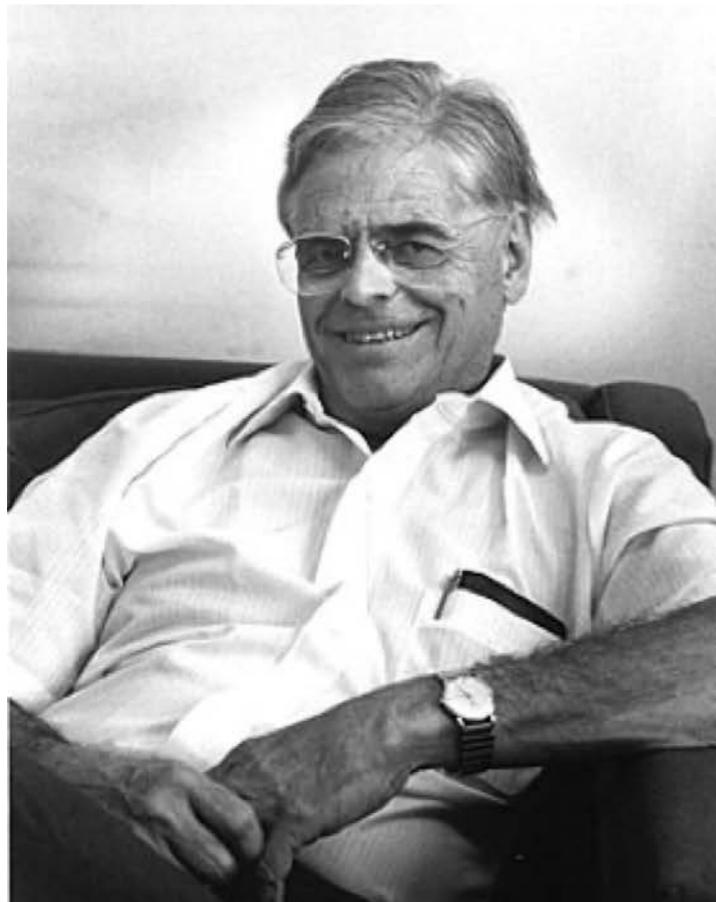
Neutron irradiations continued with the 60-inch cyclotron till 1943 when the cyclotron was expropriated for the atomic bomb programme.

In 1948 the **effects on 226 patients treated with neutrons** where evaluated and was concluded:

"Neutron therapy as administered by us has resulted in such bad late sequels in

Hadrontherapy history

7



In **1946 Robert Rathbun Wilson** proposed a possible potential application of proton and ion beams

Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate intensely a strictly localized region within the body, with but little

First patients were treated with **protons** in 1954 and, later, with **Helium** and **Neon**

Hadrontherapy history

8



- 1946 Iontherapy for deep seated tumors
- 1954 Lawrence Berkeley Laboratory, USA starts protontherapy
- 1957 Uppsala starts proton treatments
- 1975 Lawrence Berkeley Laboratory, USA starts using heavy charged particle
- 1990 **Opening of the Proton Therapy Center in Loma Linda (USA)**
- 1993 **Start of Carbon Ion Therapy in Chiba (Japan)**
- 1996 Protonentherapy starts in Villingen/Schweiz
- 1997 Carbon ion Radiotherapy starts at the University Hospital of Heidelberg, Germany at GSI in Darmstadt
- 2009 **Heidelberg Ion Therapy Center (HIT)**
- CNAO, Hyogo, Gunma, MedAustron,...**

Fundamental
Research

Clinical
Research

Clinical
Application

Hadrontherapy history



Facilities being built **at existing research accelerators**
Fixed energy machines with moderate flexibility (if at all)
 Dose delivery **not tumor-conform**

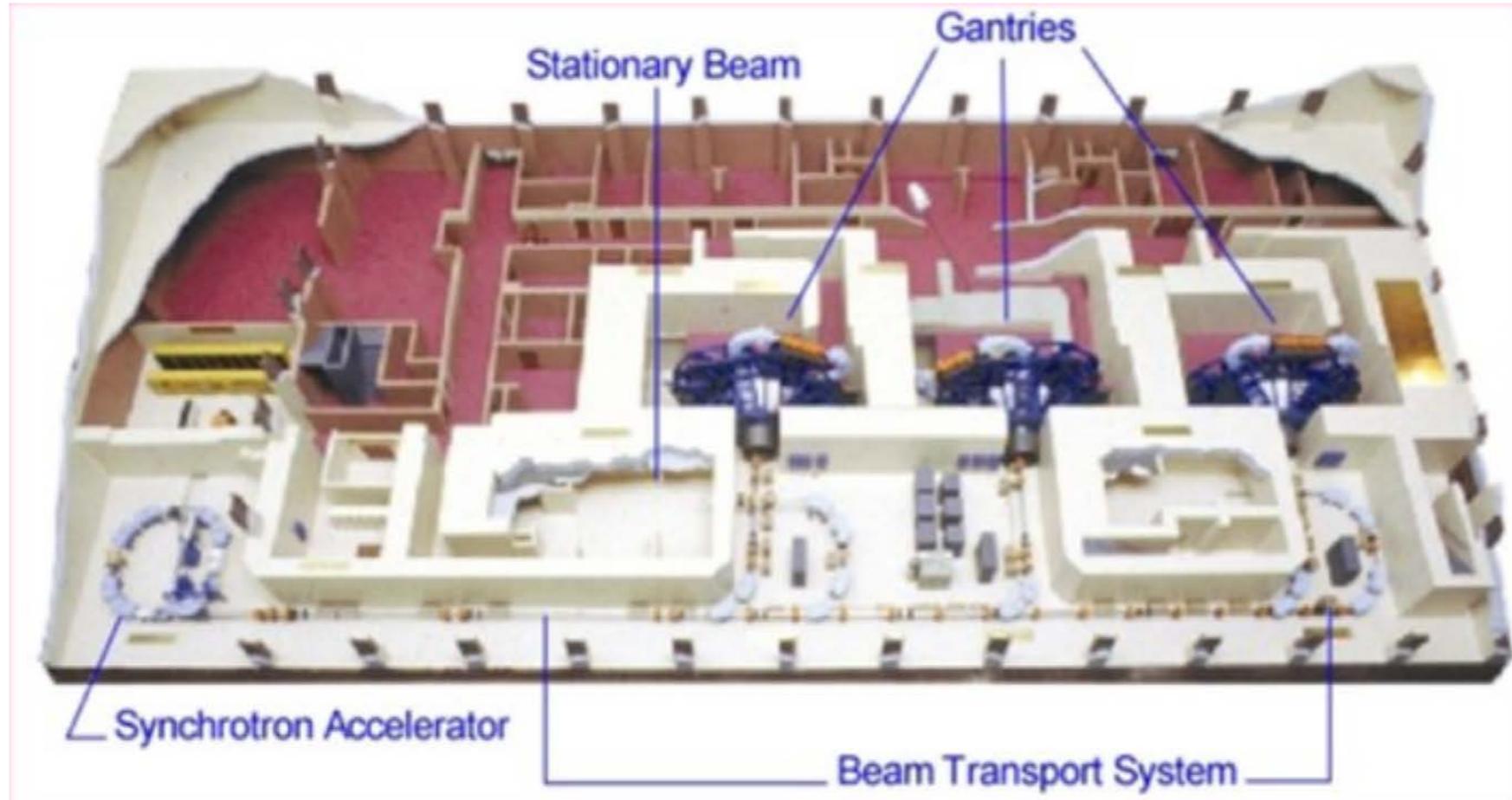


Hospital-based facilities

Variable energy, current, angle, position

On-line verification of deposited dose

Loma Linda protontherapy center, CA

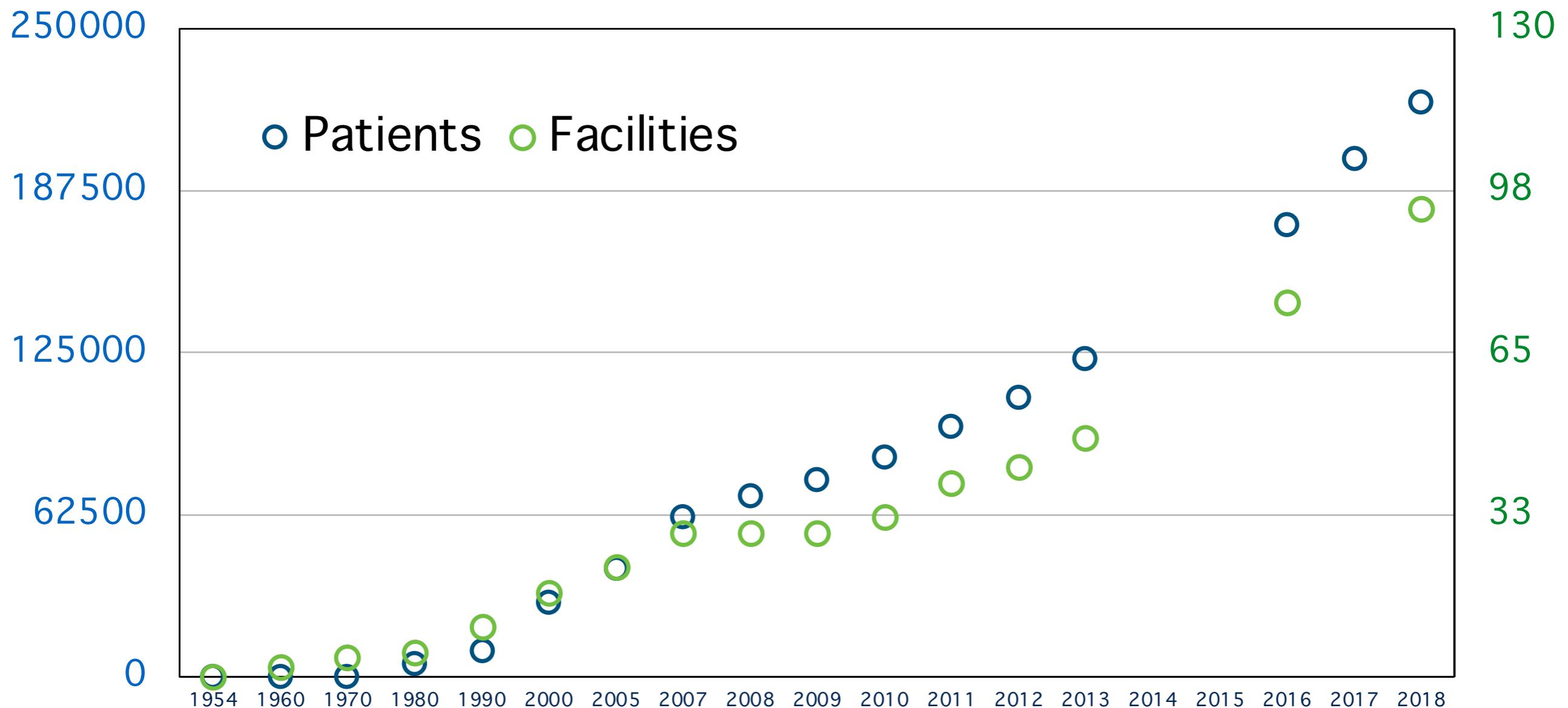


1990: first **hospital-based** facility

FNAL design	
diameter	6.5 m
Energy	Fews
Gantries	3
Beam delivery	Passive

Hadrontherapy faces a fast growing demand

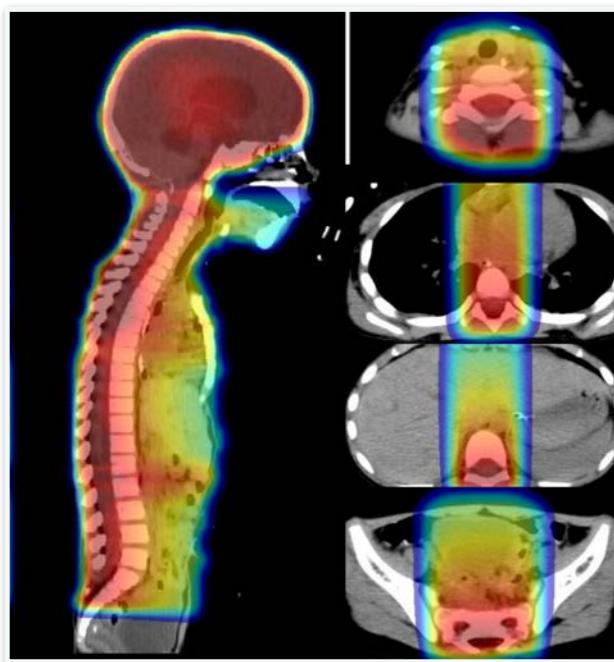
Under realisation + planned: 67



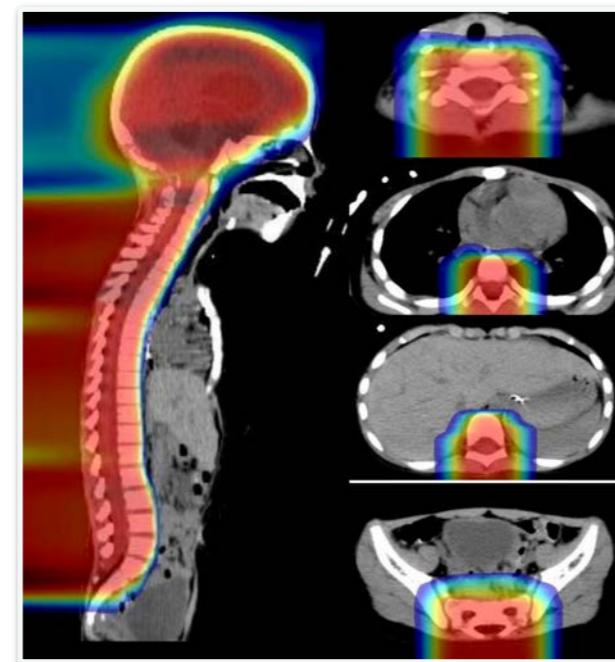
Particle Therapy Cooperative Group (PTCOG). <http://www.ptcog.ch>

Clinical advantages of proton beams

12



x-Ray therapy



Protontherapy

Mirabell RA et al.

Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of paediatric tumor,

Int. Jour. Rad. Onc. Phys. 2002, 54 (3) 824

Pediatric Medulloblastoma: The yearly risk of getting a secondary tumor was estimated to be 8 times greater with X-rays than with proton therapy²

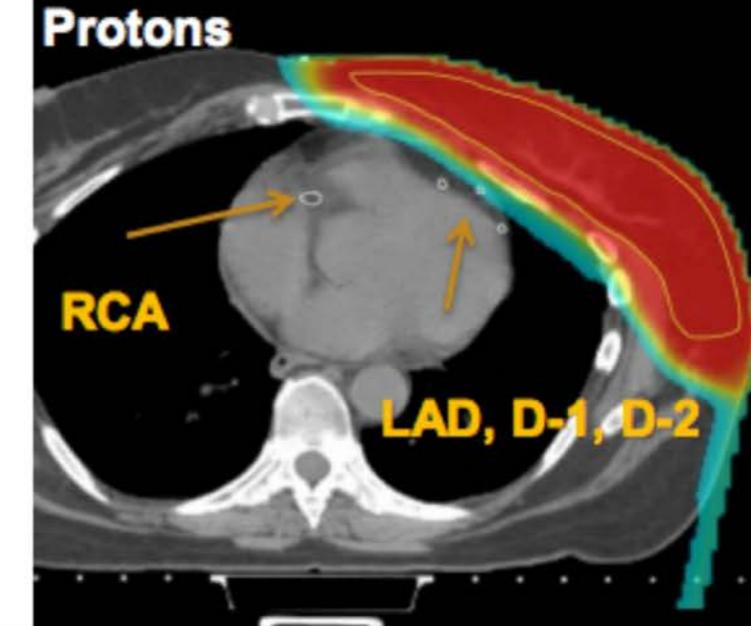
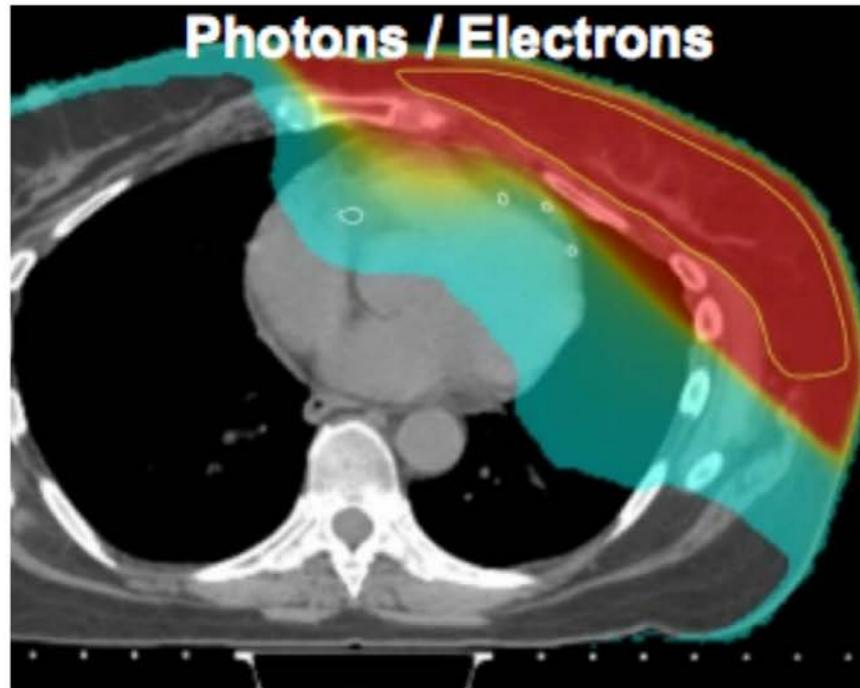
Tumor Site	Proton Therapy	X-rays/IMRT
Stomach and esophagus	0%	11%
Colon	0%	7%
Breast	0%	0%
Lung	1%	7%
Thyroid	0%	6%
Bone and connective tissue	1%	2%
Leukemia	3%	5%
All Secondary Cancers	5%	43%

This chart compares the rates of secondary tumors for a pediatric patient treated for medulloblastoma.

Data shown are from a study that compared treatment plans.

IMRT= intensity modulated radiation therapy (a type of X-ray therapy)

Breast cancer case



	Left-sided breast cancer	Right-sided breast cancer
Coronary artery disease	25%	10%
Chest pain	26%	12%
Myocardial infarction	15%	5%

Harris ERR et al.

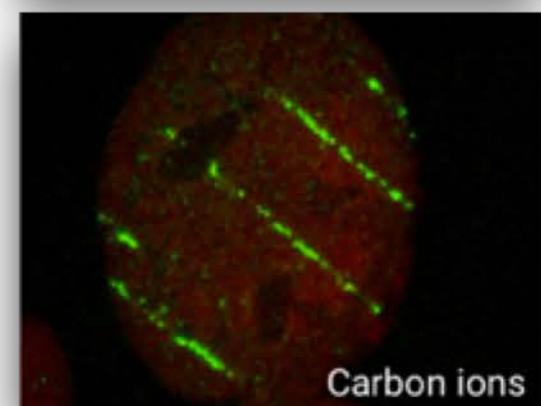
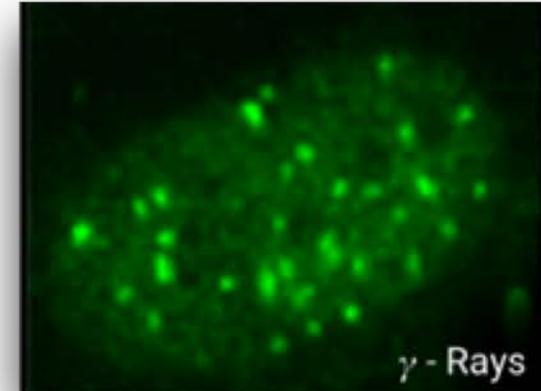
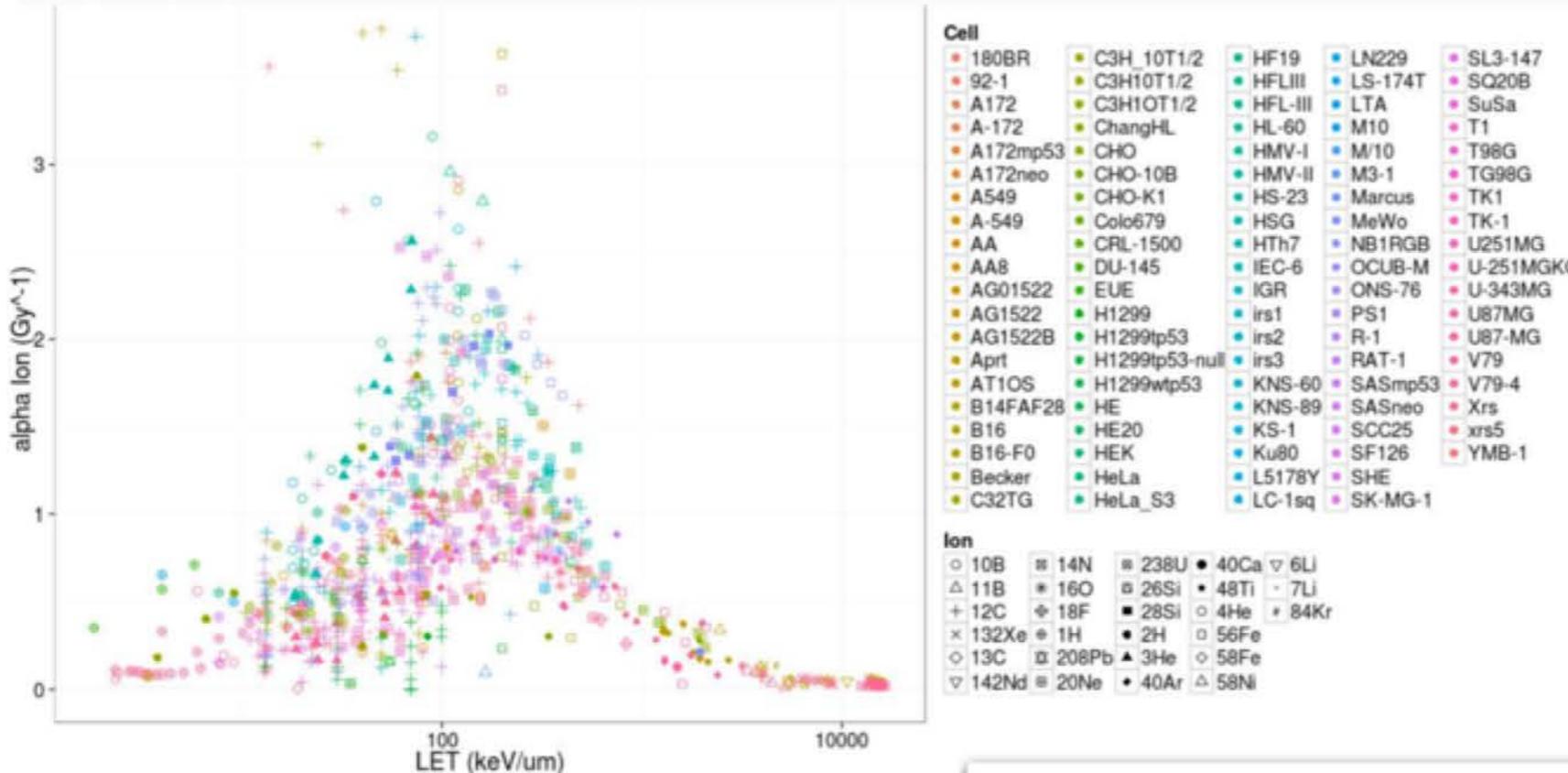
Potential impact
Coronary artery stenosis
Secondary malignancy
Lung function

Late cardiac mortality and morbidity in early stage breast cancer patients after breast conservation treatment,
J. Clin. Oncol. 2006 24 (25) 4104

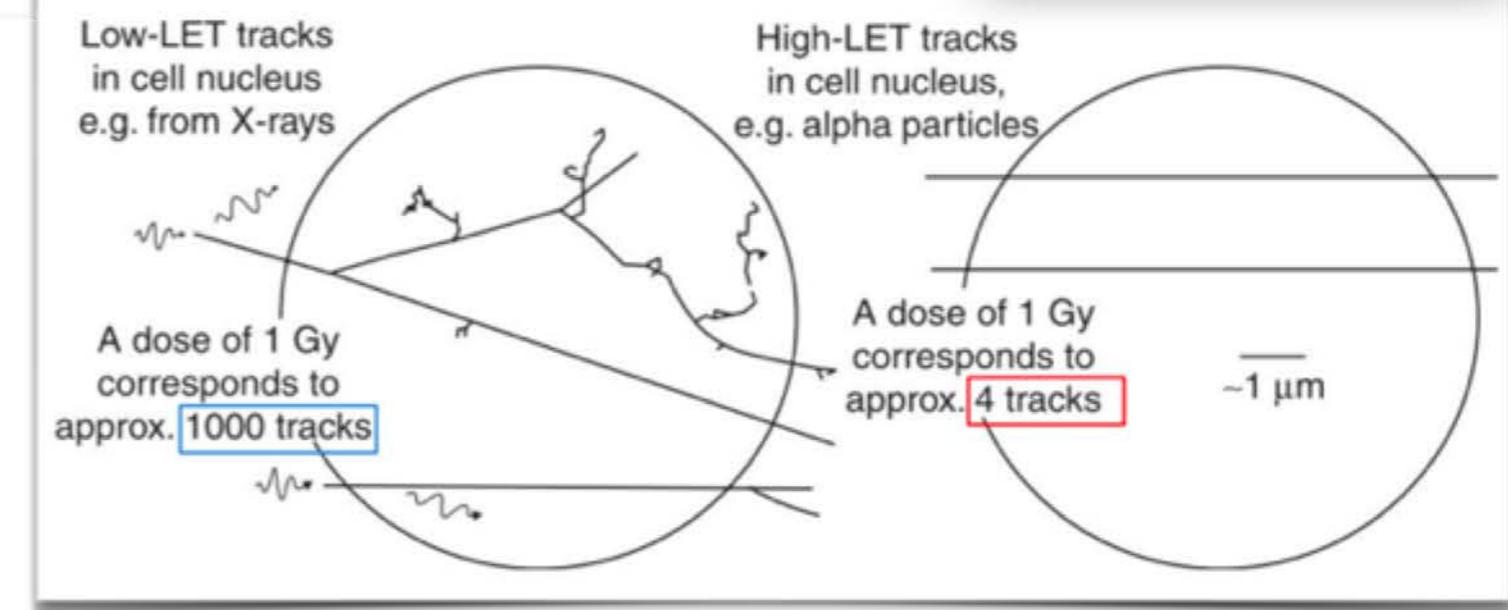
Biological properties

14

Friedrich, T., Scholz, U., Elsässer, T., Durante, M., & Scholz, M. (2012). *Journal of Radiation Research*.

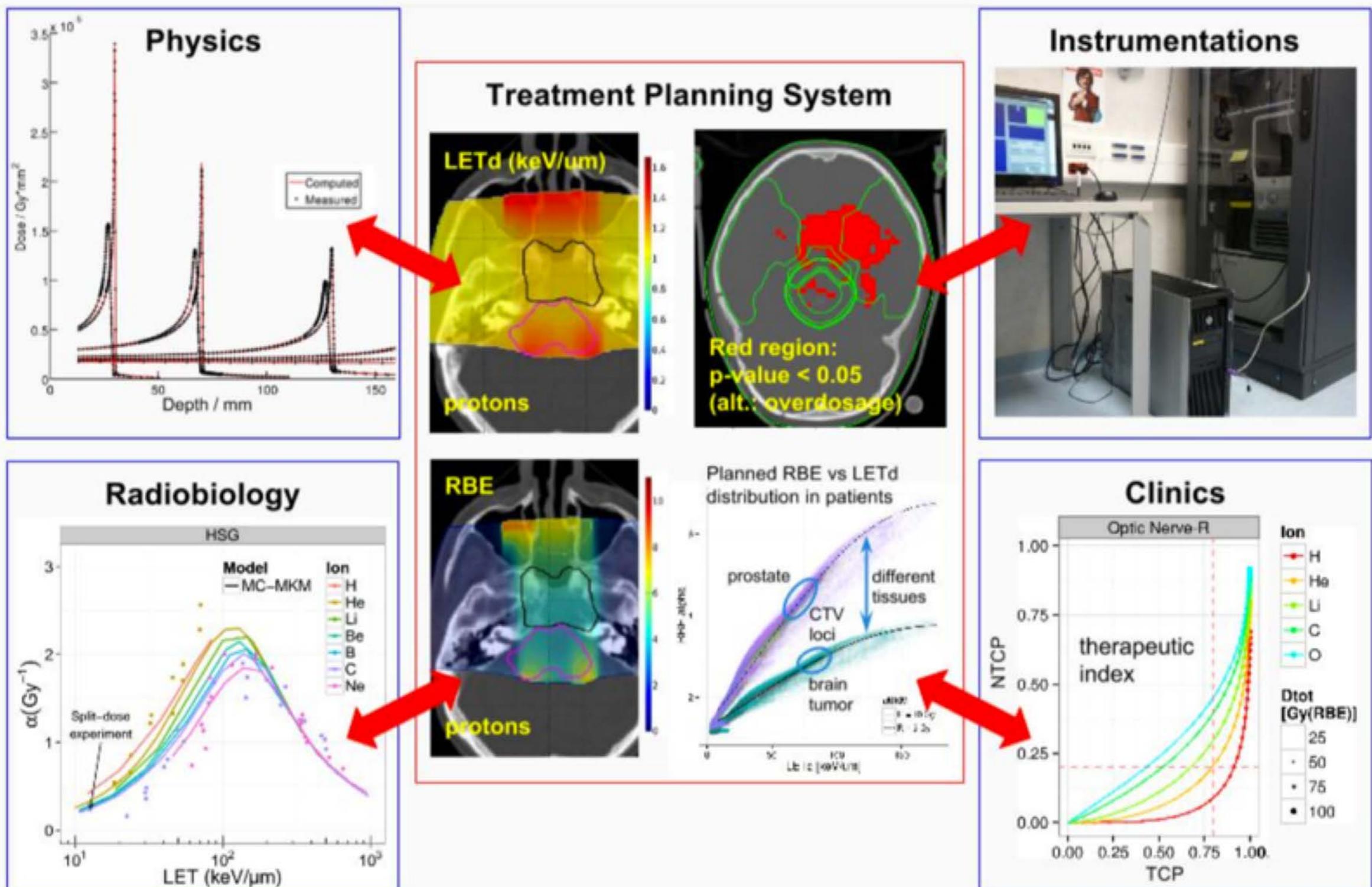


The biological damage is strictly related to the radiation quality

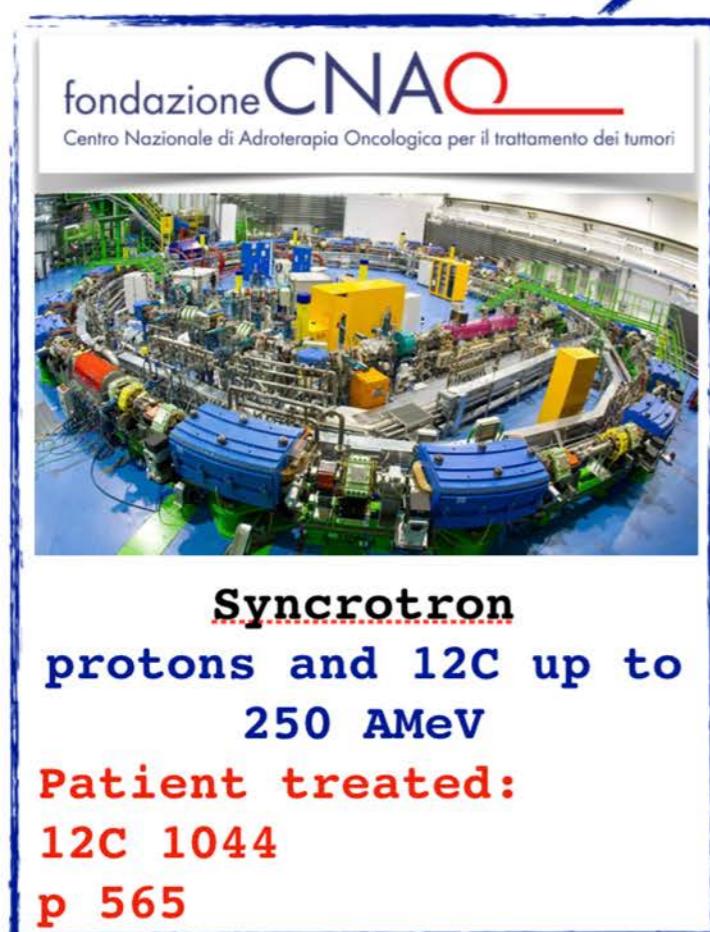


Biological and physical aspects

15

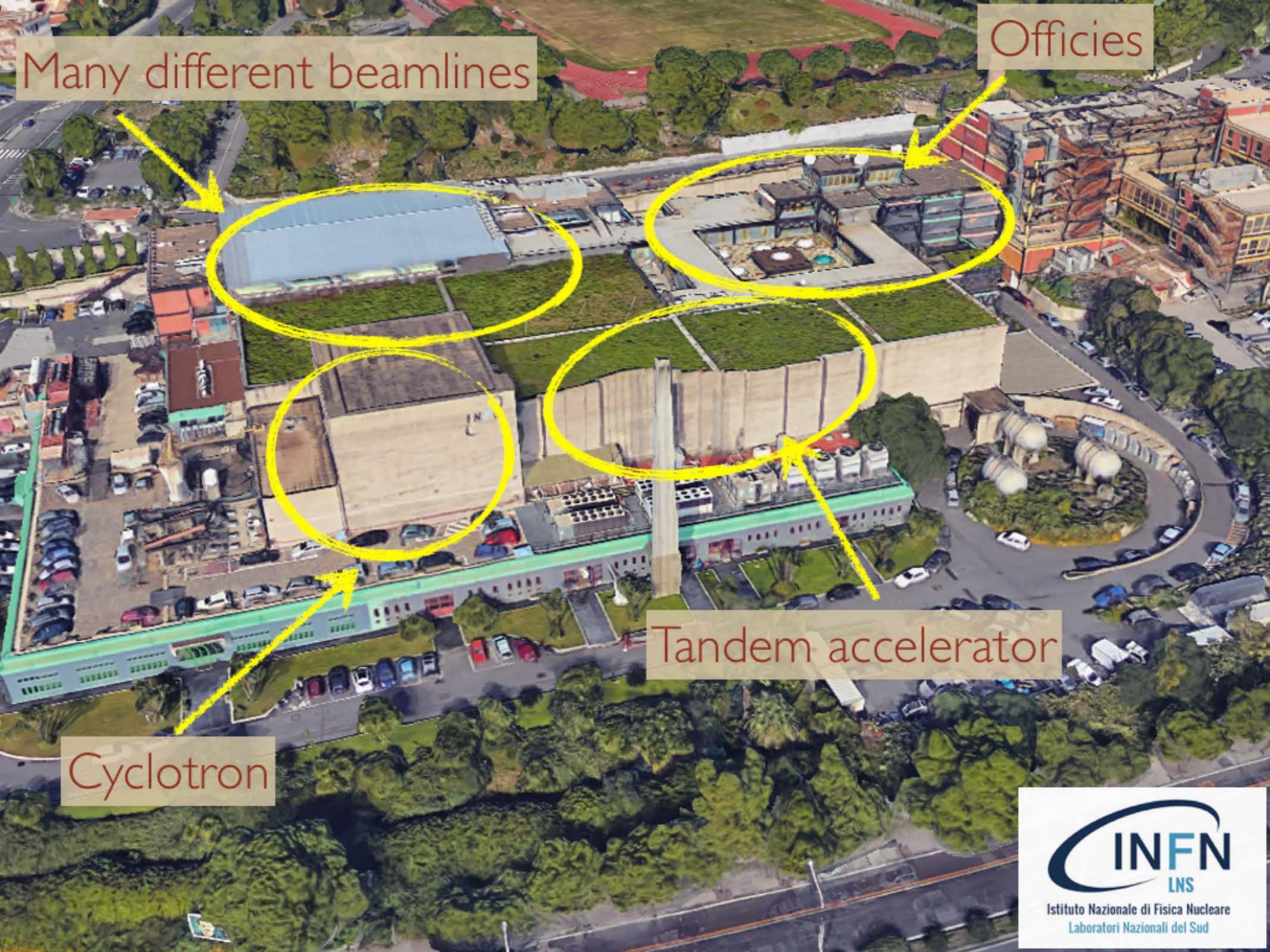


Hadrontherapy in Italy



Offices

Many different beamlines



Cyclotron

Tandem accelerator



Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali del Sud

CATANA eye protontherapy facility



CATANA
Centro di
AdroTerapia
ed Applicazioni
Nucleari Avanzate

First Italian proton therapy facility

First Patient treated on **March 2002**
(about 400 treated)

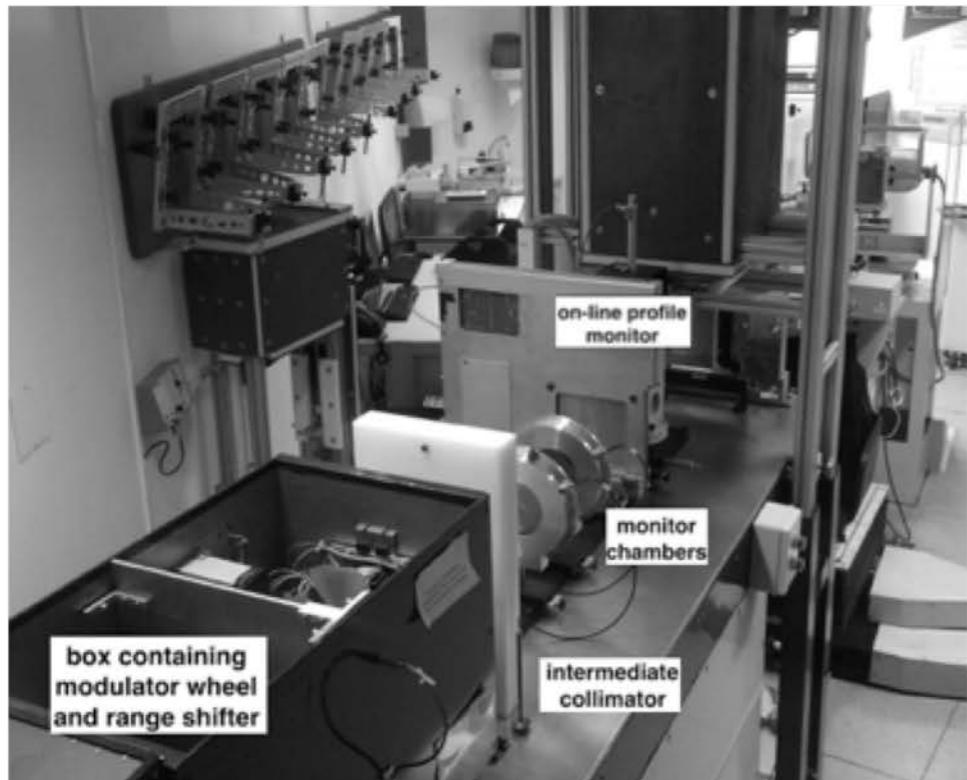
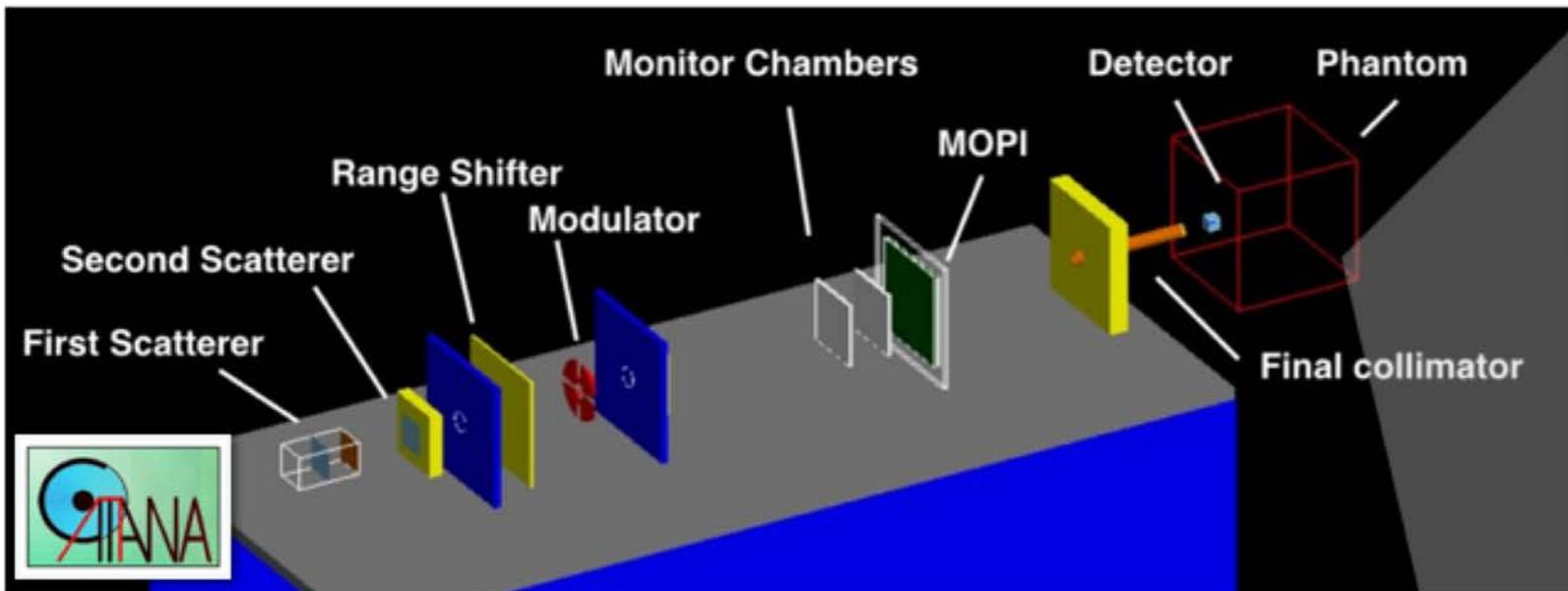
Passive proton beam line

62 MeV of energy

30 mm of penetration



CATANA eye protontherapy facility

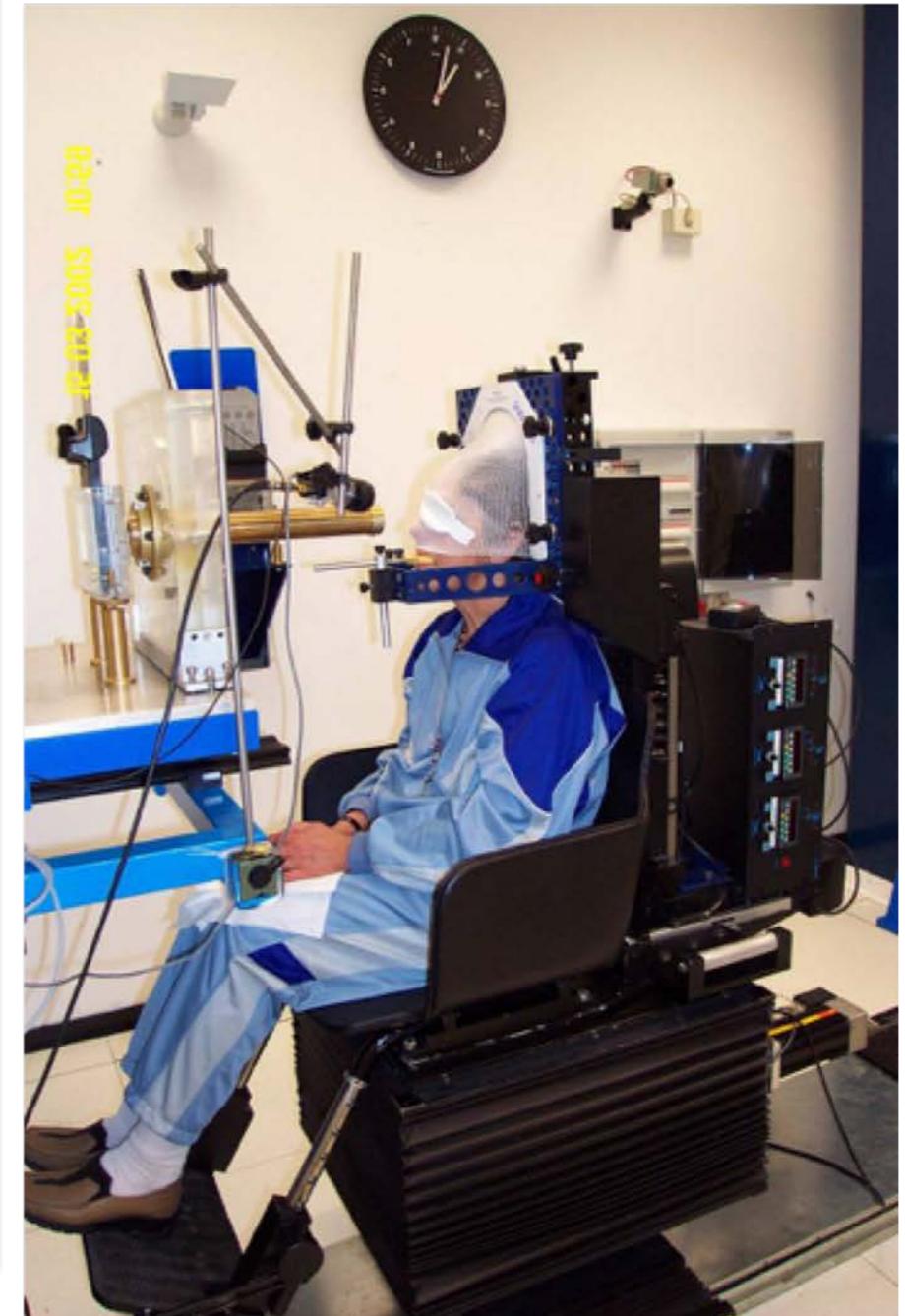


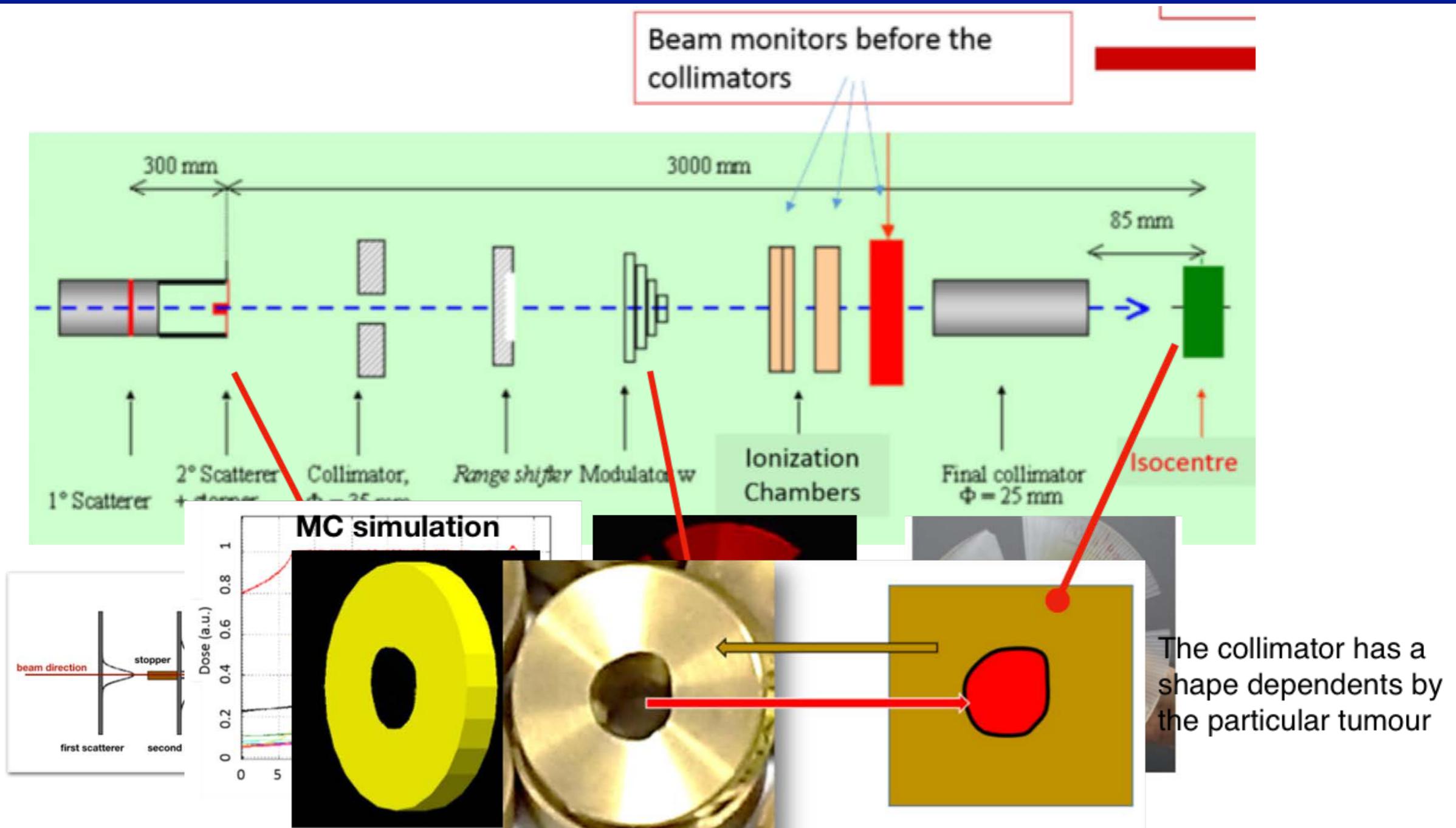
Dose: 15 CGE per fraction

Treatment time: 40-50 sec

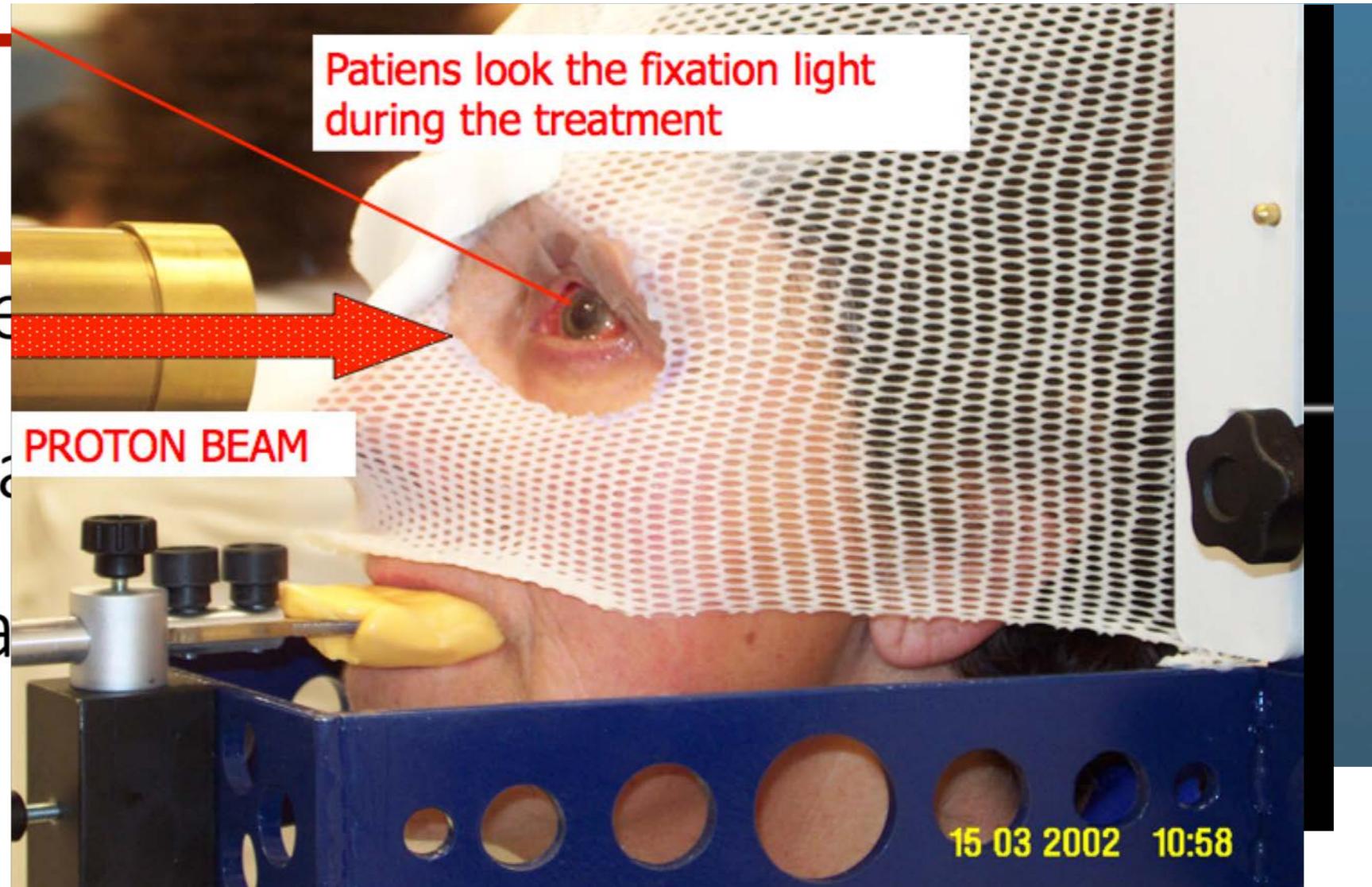
Total dose: 60 CGE

Fractions: 4





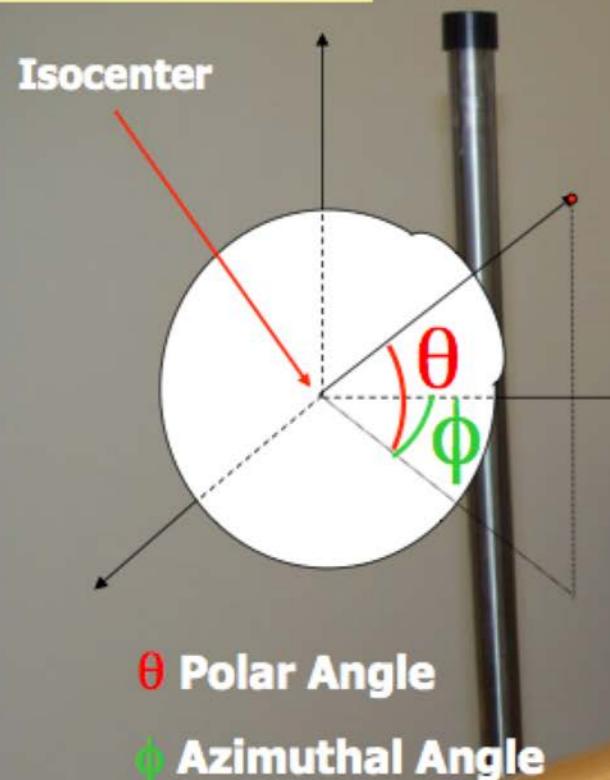
Eye protontherapy treatment





Posizionamento paziente

Fixation Point



Uveal Melanoma	89.89 %
Conjunctival Melanoma	4.04 %
Conjunctival rhabdomyosarcoma	1.01 %
Eyelid Carcinoma and metastases	2.02 %
Conjunctival MALT-NHL	1.01 %
Conjunctival Papilloma	2.02 %

Patients statistics

Patients	
Sex	Male: 176 Female: 118
Age	Range between: 12-88 Median: 59
Diagnosis	Uveal melanoma: 252 pts Conjunctival melanoma: 5 pts Orbital rhabdomyosarcoma: 3 pts Orbital non-Hodgkin lymphoma: 4 pts Conjunctival papilloma: 1 pt Eyelid/periorbital carcinoma: 18 pts Other orbital tumors: 11 pt

Dead patients	4
	Metastasis
	Other
Eye retention rate	92,68 %
TOTAL SURVIVAL	95 %
LOCAL CONTROL	97 %

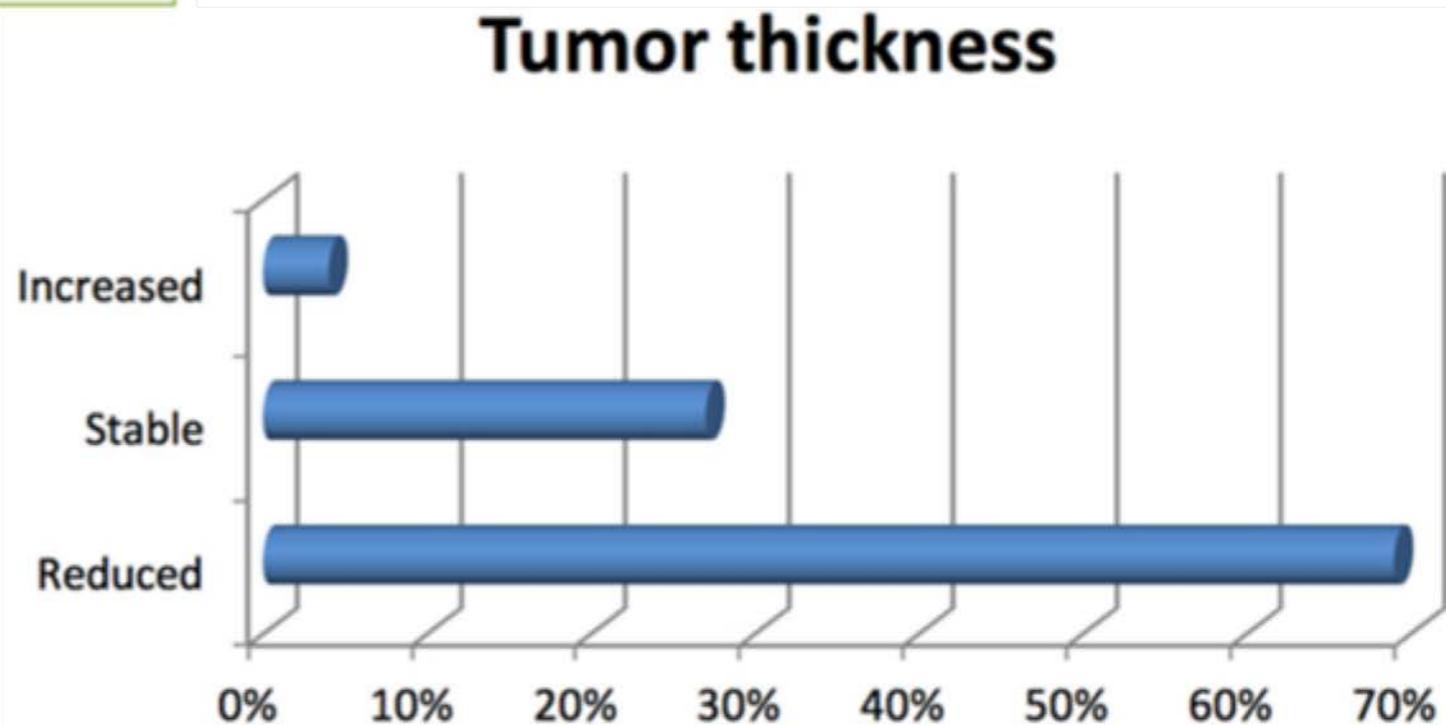
Front. Oncol., 19 September 2017 | <https://doi.org/10.3389/fonc.2017.00223>



Clinical and Research Activities at the CATANA Facility of INFN-LNS: From the Conventional Hadrontherapy to the Laser-Driven Approach

Giuseppe A. P. Cirrone^{1*}, Giacomo Cuttone¹, Luigi Raffaele^{1,2}, Vincenzo Salamone^{1,2}, Teresio Avitabile², Giuseppe Privitera², Corrado Spatola², Antonio G. Amico¹, Giuseppina Larosa¹, Renata Lanza¹, Daniele Margarone¹, Giuliana Milluzzo¹, Valeria Patti^{1,4}, Giada Petringa¹, Francesco Romano^{1,5}, Andrea Russo¹, Antonio Russo¹, Maria G. Sabini^{1,4}, Francesco Schillaci¹, Valentina Scuderi^{1,5} and Lucia M. Valastro^{1,4}

First Patient treated on March 2002 (**about 400 treated**)



Approaches to enhance protontherapy efficacy

*Can we exceed the great biological capacity of carbon ions
with proton or ‘easier’ ions like helium?*

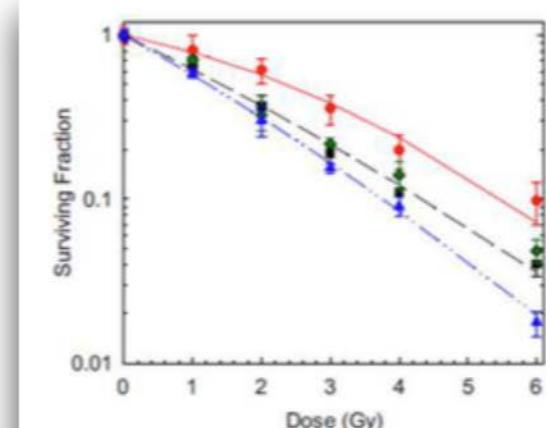
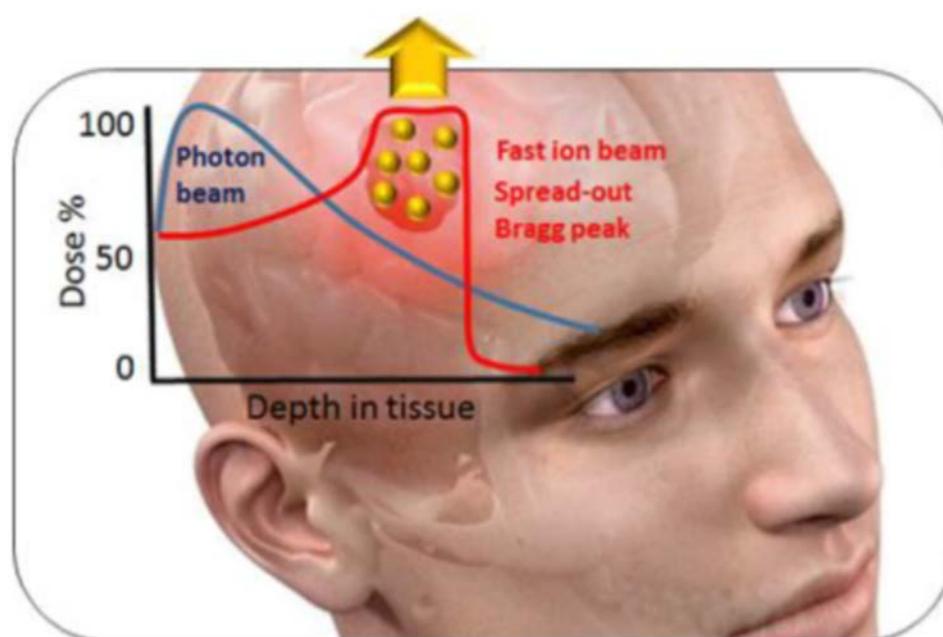
Use of nanoparticles

27

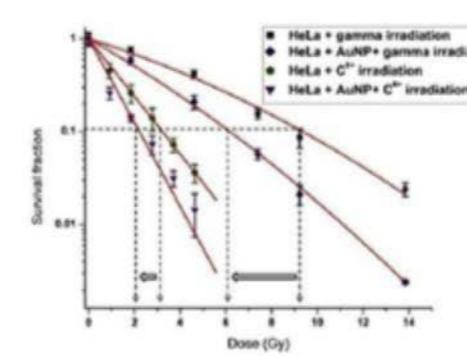

OPEN

Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles

 SUBJECT AREAS:
 CANCER
 GENERAL PHYSICS
 MODELLING
 NANOTECHNOLOGY

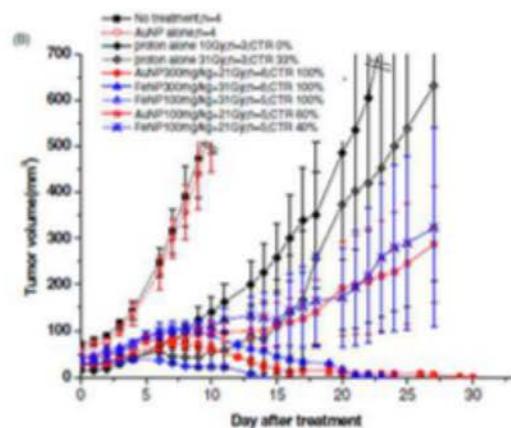
 Stephen J. McMahon^{1,3}, Wendy B. Hyland^{2,1}, Mark F. Muir¹, Jonathan A. Coulter², Suneil Jain^{3,5}, Karl T. Butterworth³, Giuseppe Schettino³, Glenn R. Dickson³, Alan R. Hounsell^{3,4}, Joe M. O'Sullivan^{3,5}, Kevin M. Prise³, David G. Hirsh² & Fred J. Currell¹


p+NP, pc, 15% enhancement
 Polf et al., Appl.Phys.Lett. 98(2011)



C 5 MeV/u +NP, HeLa, 40% enhancement
 Kaur 2012

Preclinical data evidence, no explanation



p+NP, mouse tumour,
 Kim et al. PMB 57(2012)

Use of 'fast' beams

28

BJR

Received: 26 August 2017 | Revised: 11 November 2017 | Accepted: 22 November 2017

Cite this article as:
Durante M, Bräuer-Krisch E, Hill M. Faster and safer? FLASH ultra-high dose rate in radiotherapy

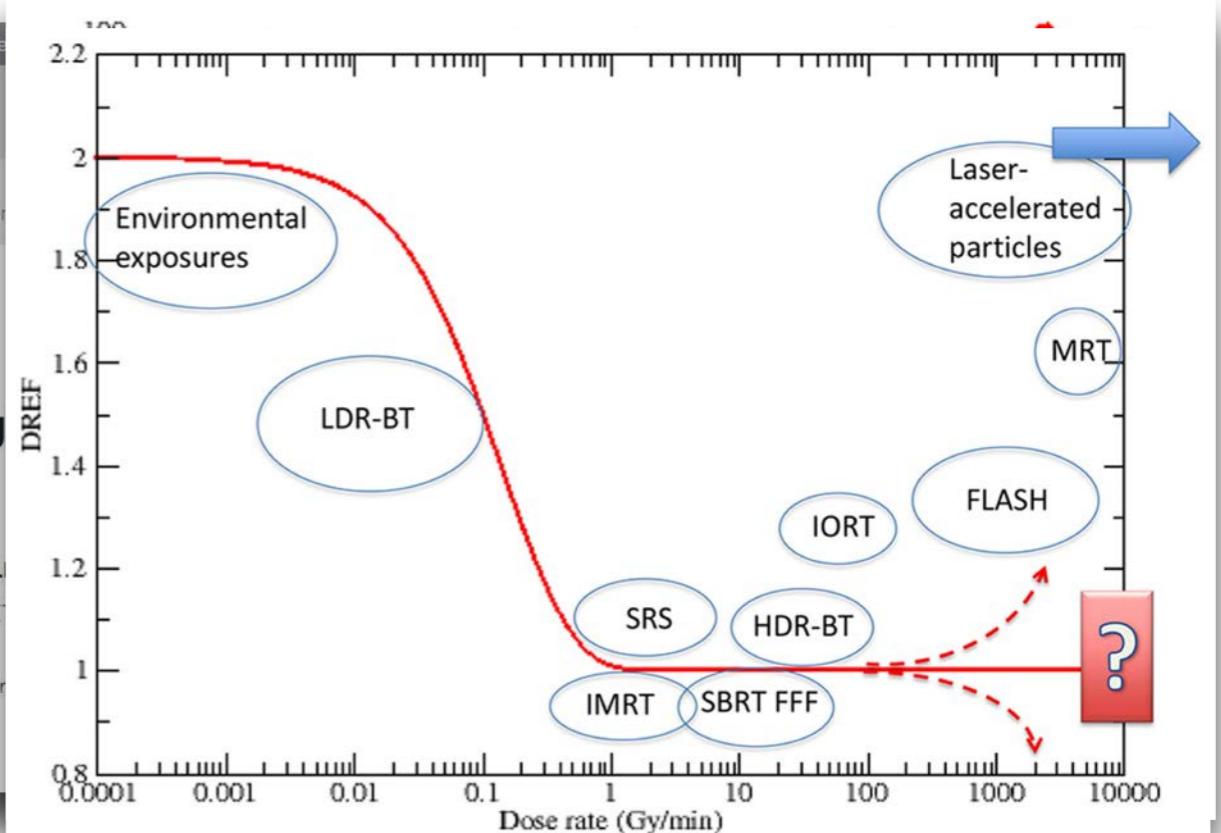
COMMENTARY

Faster and safer? FLASH ultra-high dose rate in radiotherapy

1MARCO DURANTE, PhD, ²ELKE BRÄUER-KRISCH, PhD and ³MARK HILL

¹National laboratories, Trento Institute for Fundamental Physics and Applications (TIFPA), University of Trento, Trento, Italy
²National laboratories, ESRF-The European Synchrotron, Grenoble, France
³Department of Oncology, CRUK/MRC Oxford Institute for Radiation Oncology, Gr

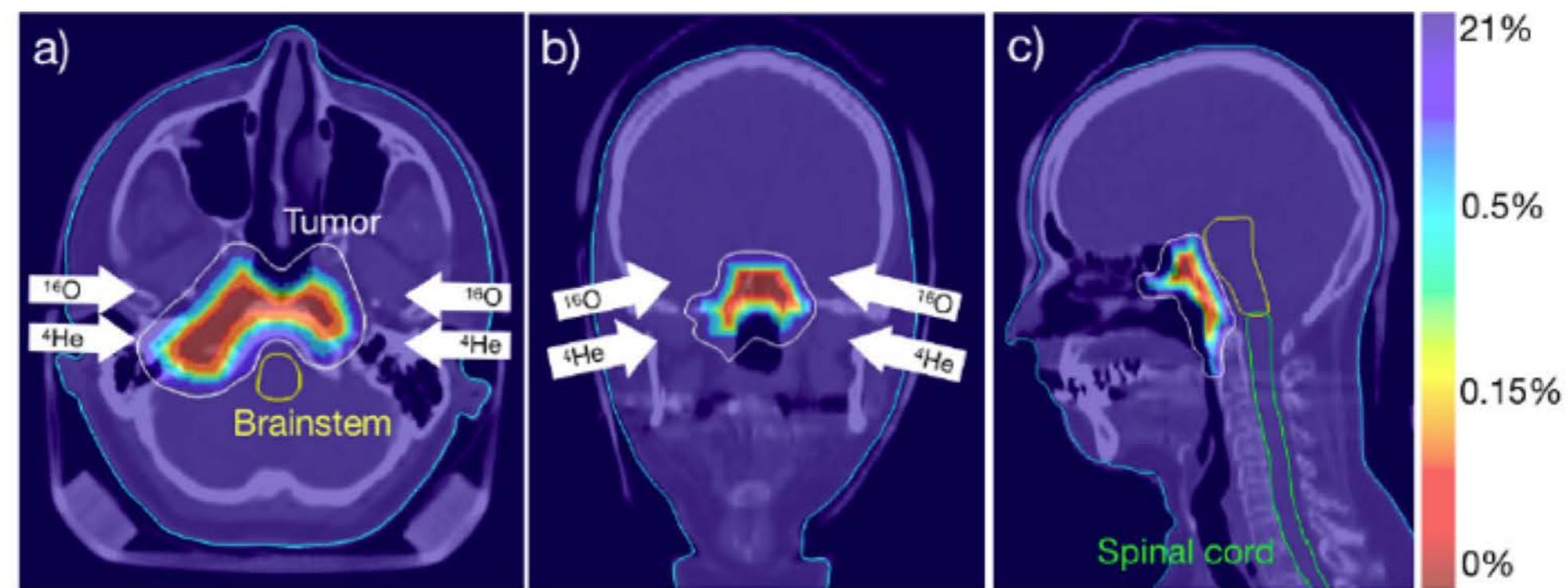
Address correspondence to: Professor Marco Durante
 E-mail: Marco.Durante@tifpa.infn.it



Use of multiple ions

29

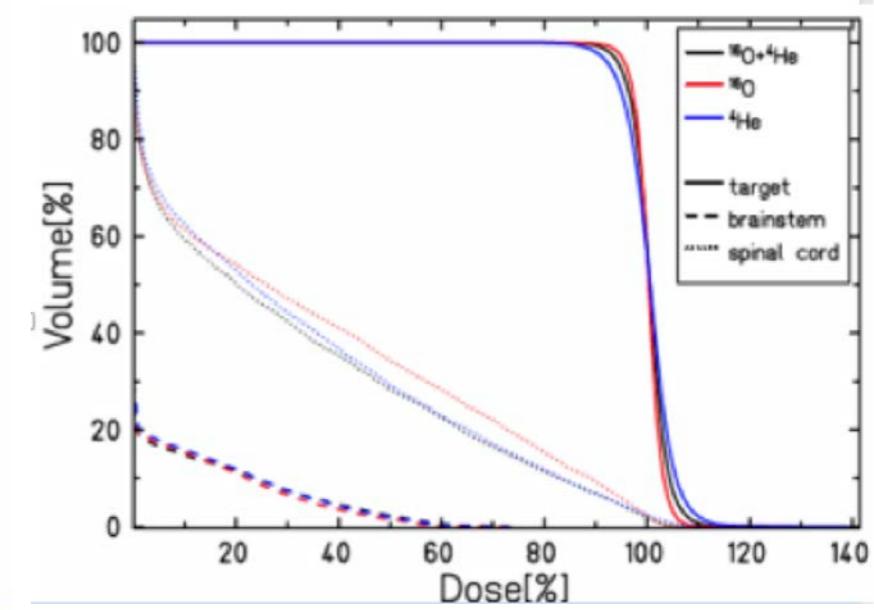
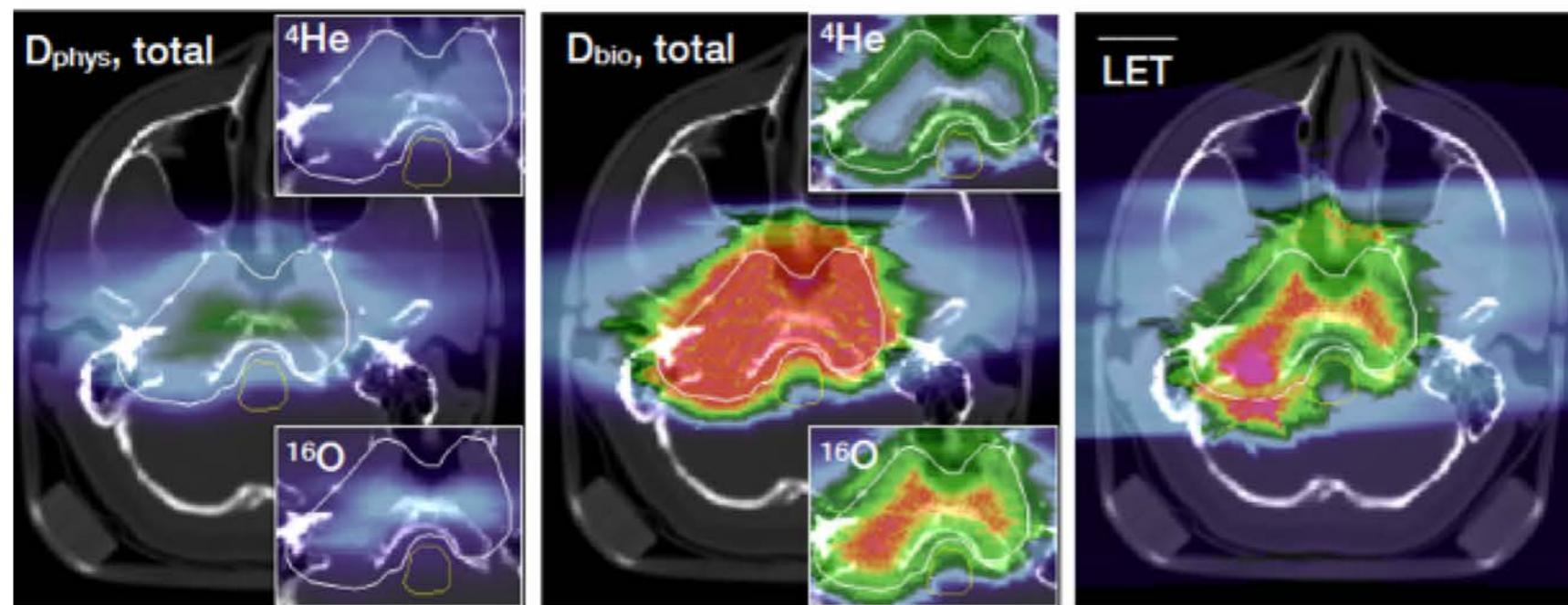
The beam spots are correctly selected by the optimization in order to concentrate high LET particles in the hypoxic regions



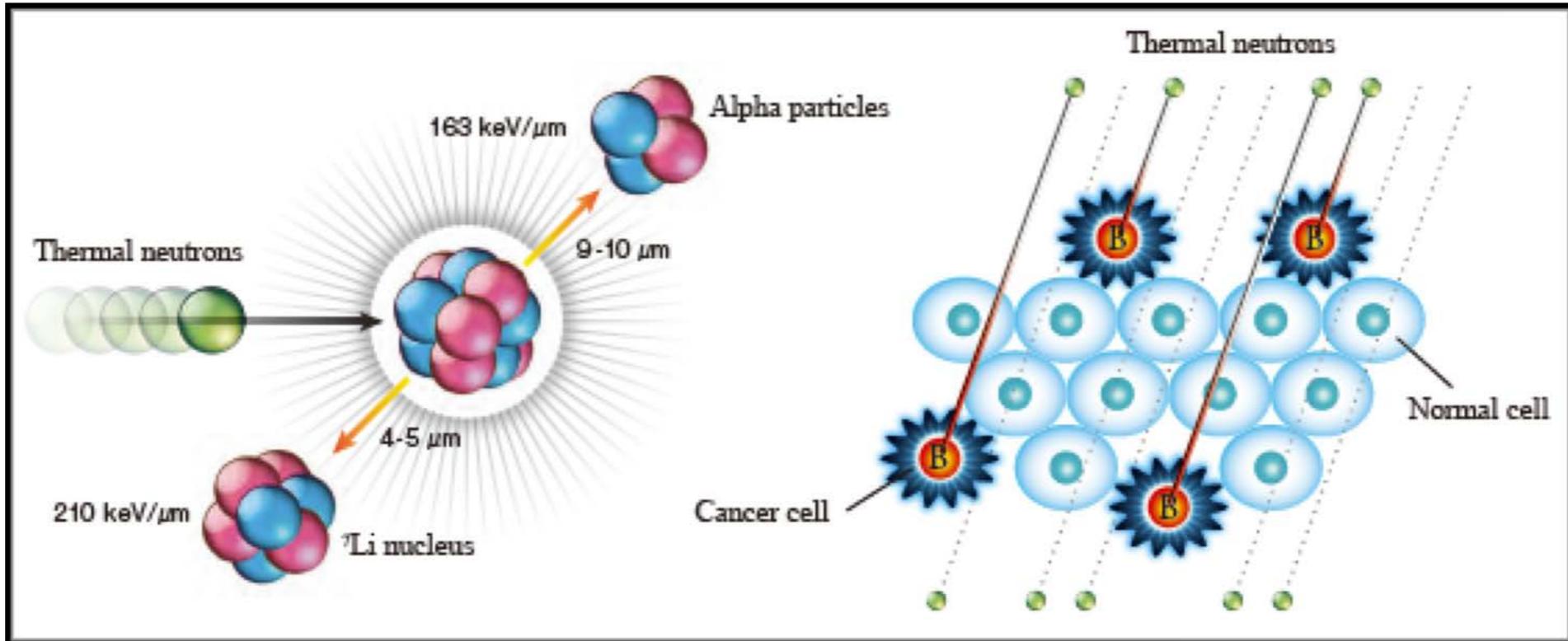
Sokol et al. to be subm PMB (2018)

*100% dose = 2 Gy

100% LET = 65 keV/um



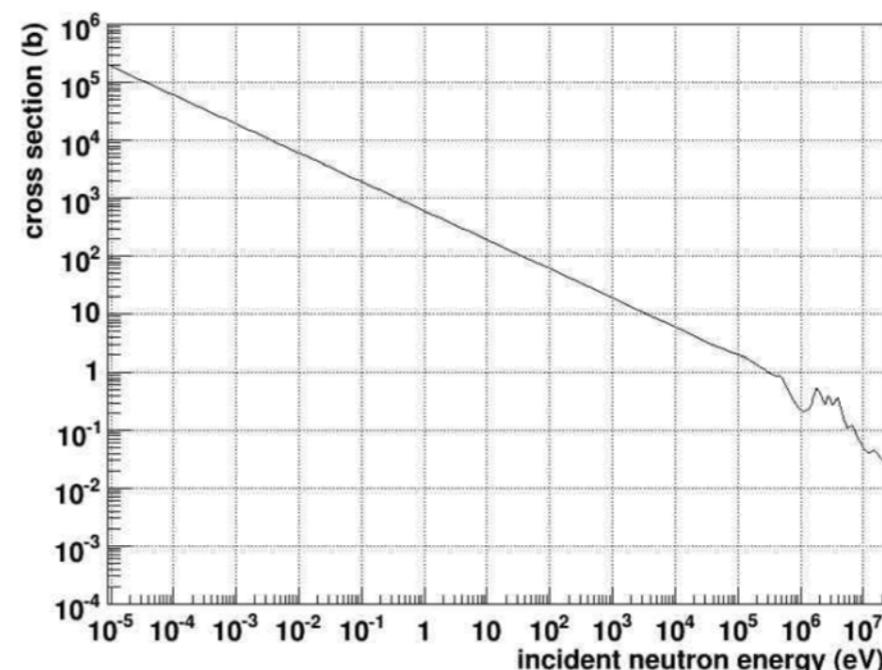
Use of nuclear reactions: Boron Neutron Capture Therapy (BNCT)



Boron Neutron Capture Therapy (BNCT) is a binary radiotherapy exploiting the synergistic effects of the stable, less frequent (19.9% natural abundance) isotope of boron ^{10}B and a low energy neutron field

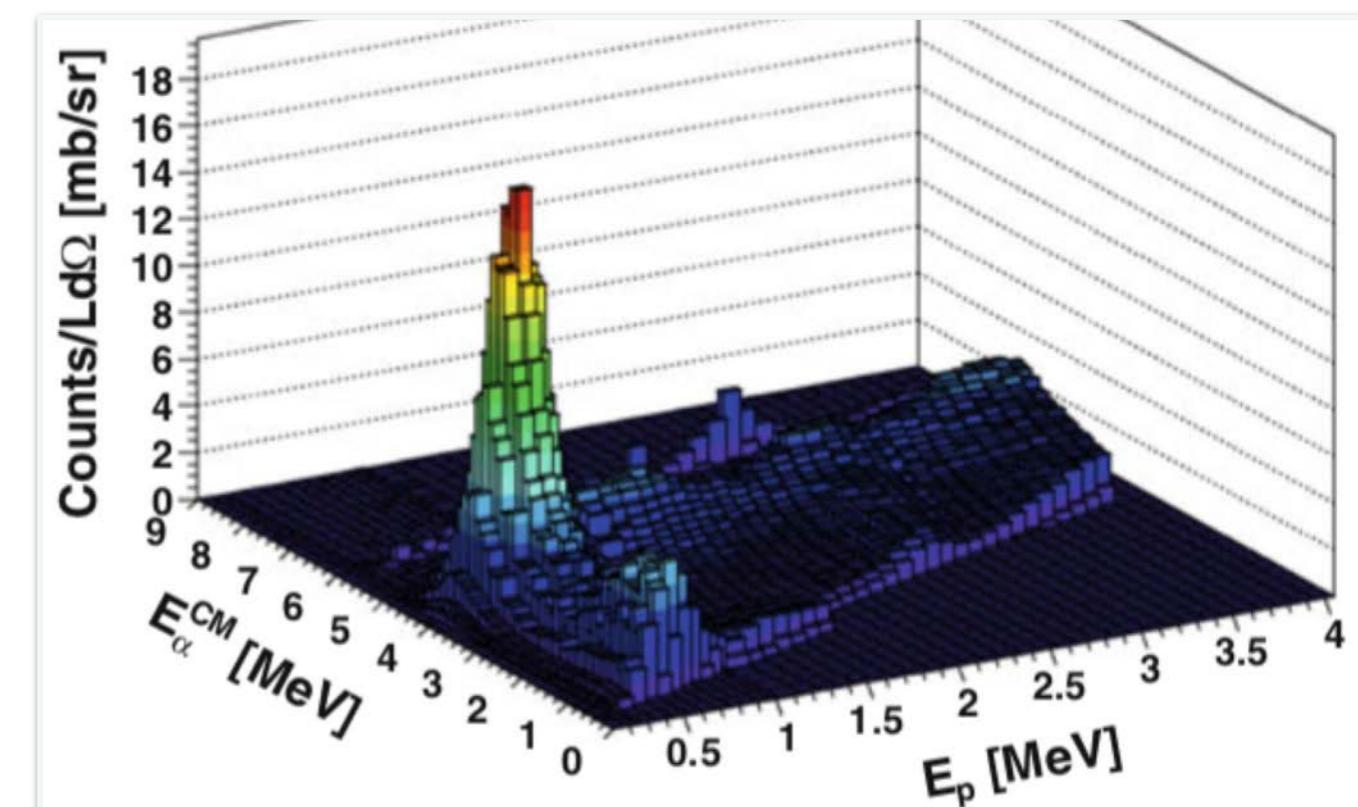
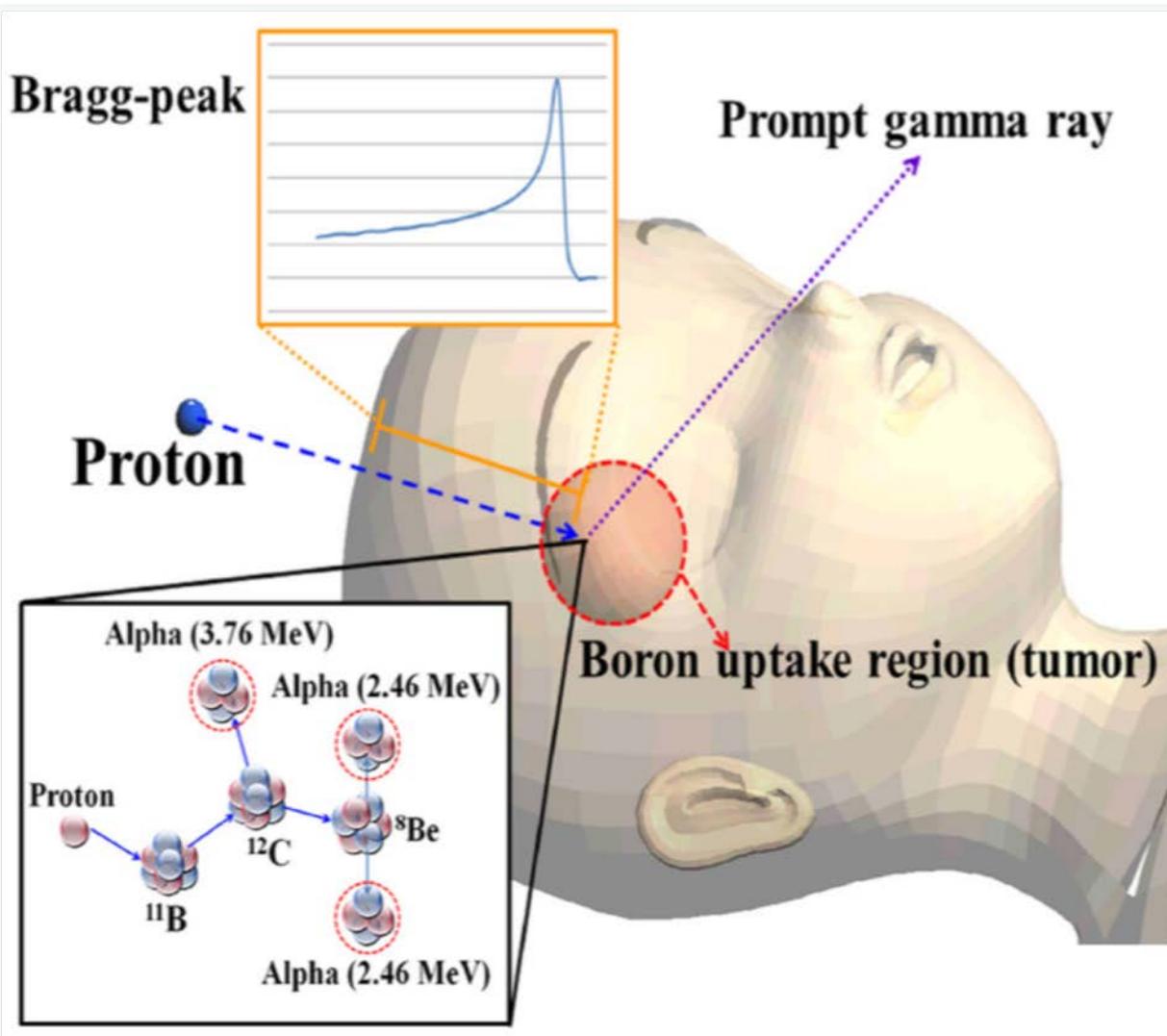
$\sigma = 3837 \text{ b}$ for 0.025 eV neutrons

Q-value=2.79 MeV



Use of nuclear reactions: The proton-Boron capture therapy (PBCT)

31

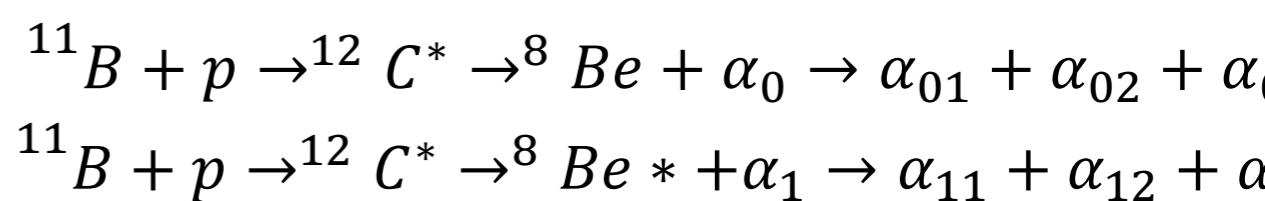


M.H.Sikora, H.R.Weller, A new evaluation of the $^{11}\text{B}(p,a)\text{aa}$ reaction rates, J. Fusion Energy (2016) 35:538

Reaction channels

The idea:

D.-K. Yoon et al,
Application of proton boron fusion reaction to radiation therapy: A Monte Carlo simulation study
Applied Physics Letters 105, (2014);



Future perspectives with laser-accelerated charged particles

Review Article | Published: 21 May 2013

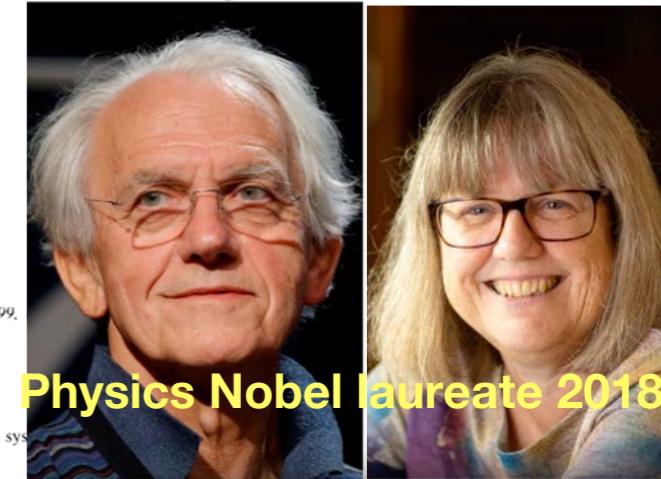
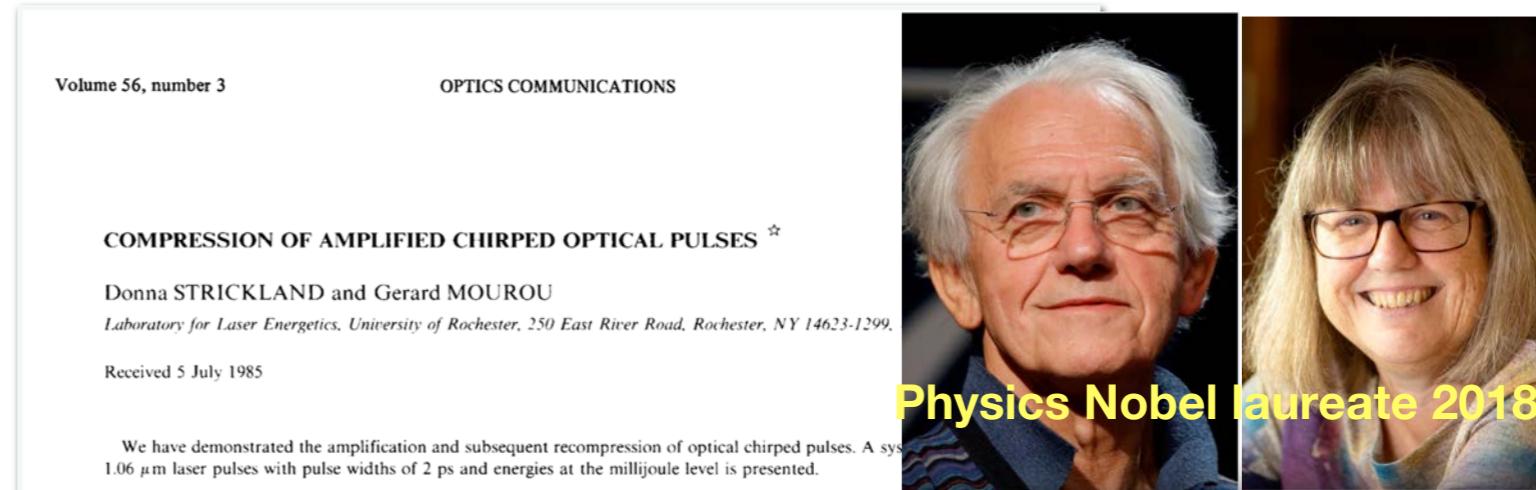
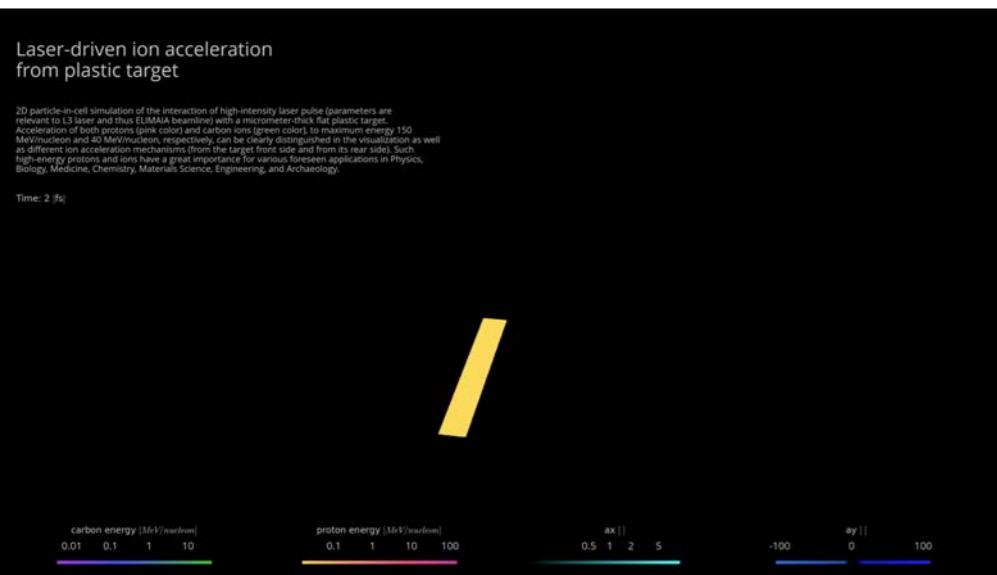
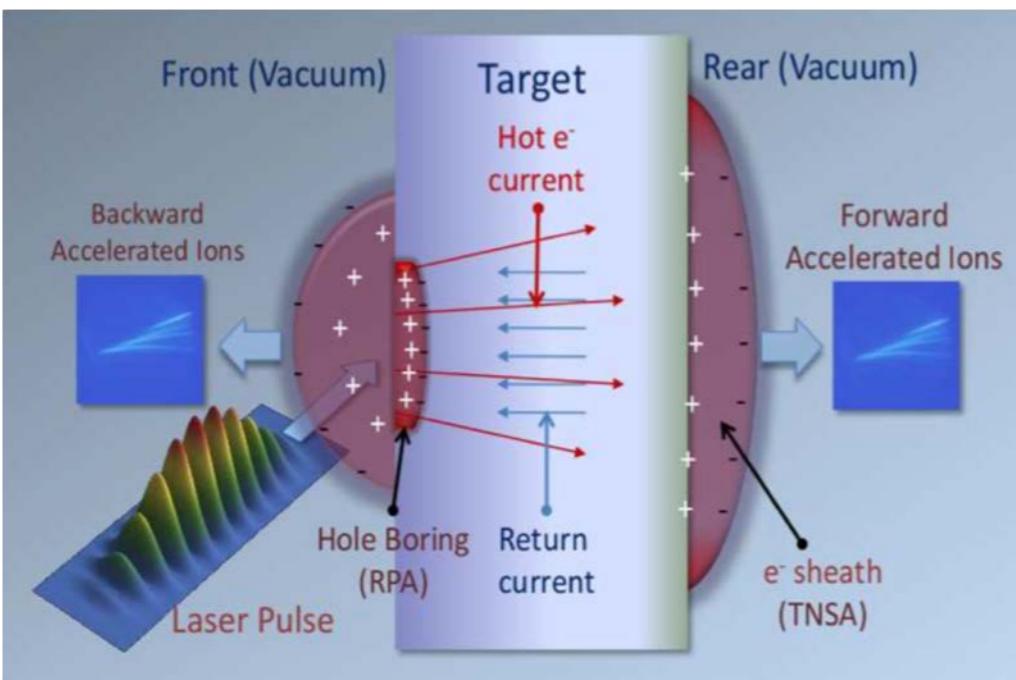
Charged particle therapy—optimizing challenges and future direction

Jay S. Loeffler & Marco Durante 

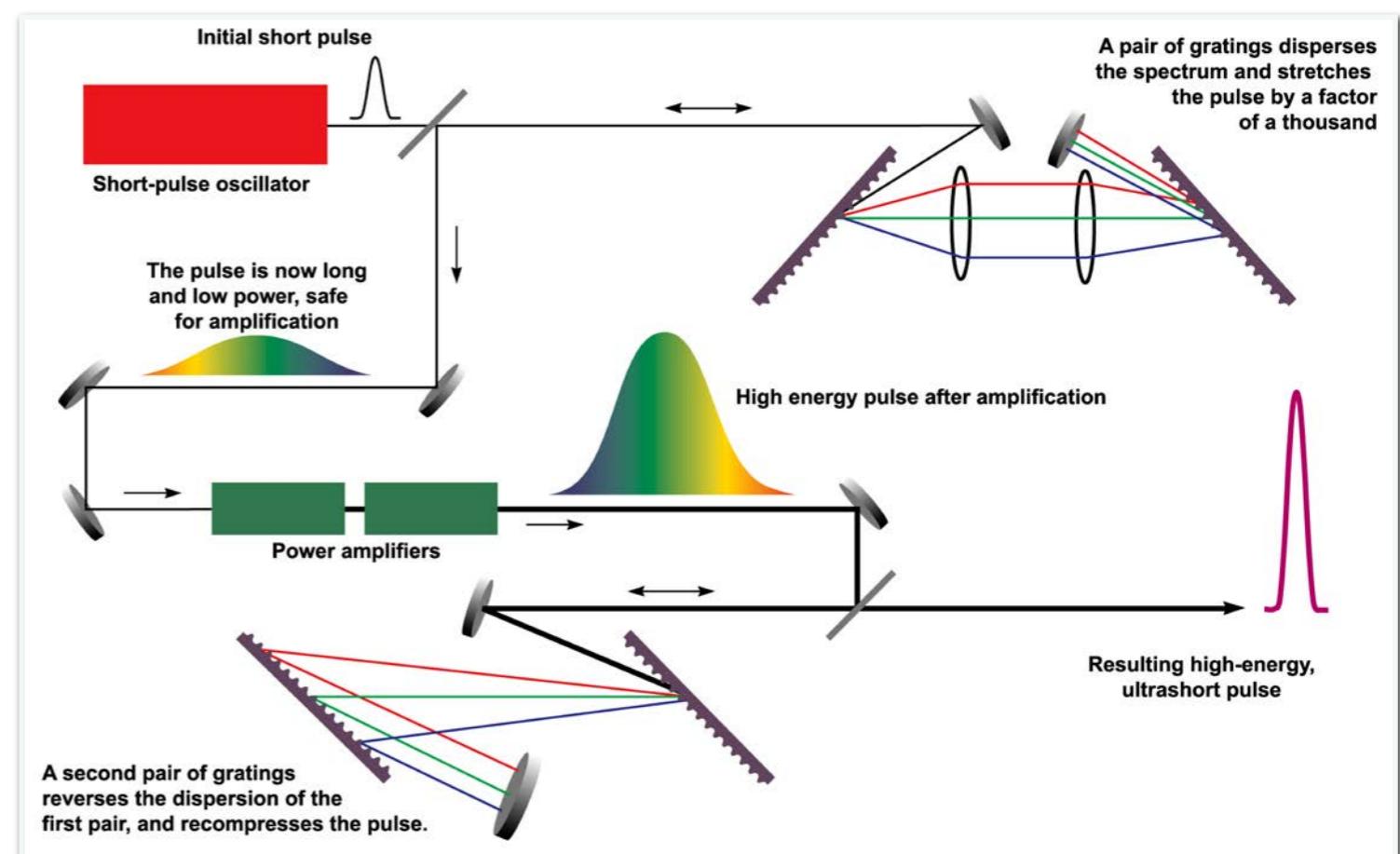
Nature Reviews Clinical Oncology 10, 411–424 (2013) | Download Citation

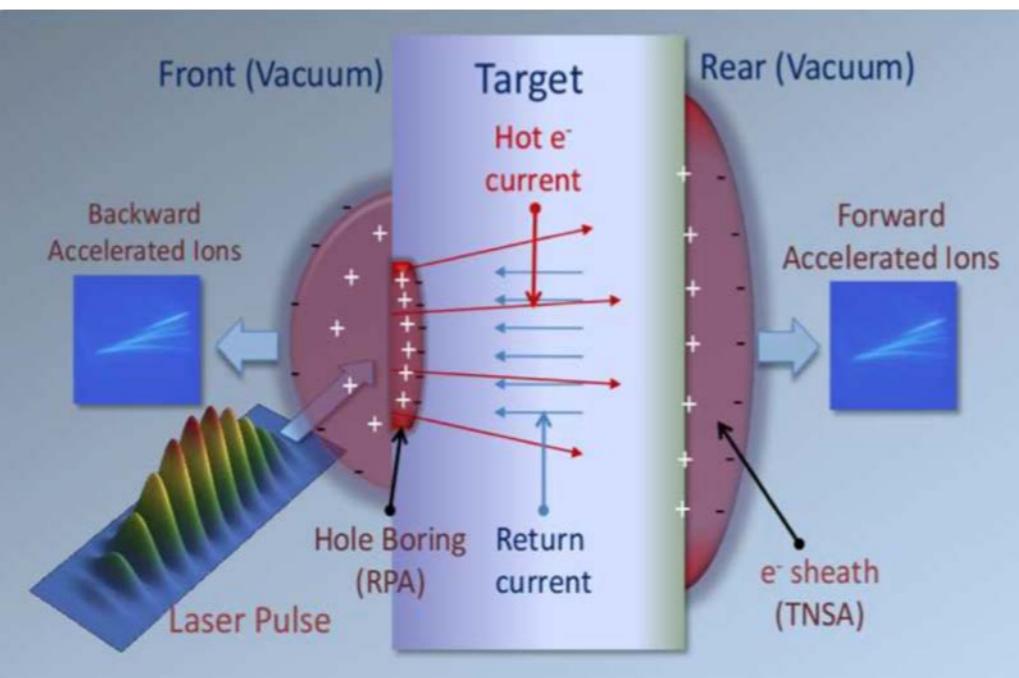


Research and development in the field of accelerators should be towards a reduction of costs, while maintaining or improving the performances of the current machines. Possible new accelerators for CPT¹²² include synchrocyclotrons, rapid cycling synchrotrons, fixed-field alternating gradient rings, cyclotron–linac combinations, dielectric wall accelerators, and laser-driven plasma accelerators.¹²³ These options are at very different stages of design maturity, but all offer promising design features to offset the shortcomings of current synchrotrons, including fast scanning capabilities, reduced size, complexity and power consumption, increased dose rate capability, and ultimately a lower cost and a shorter treatment time.¹⁴



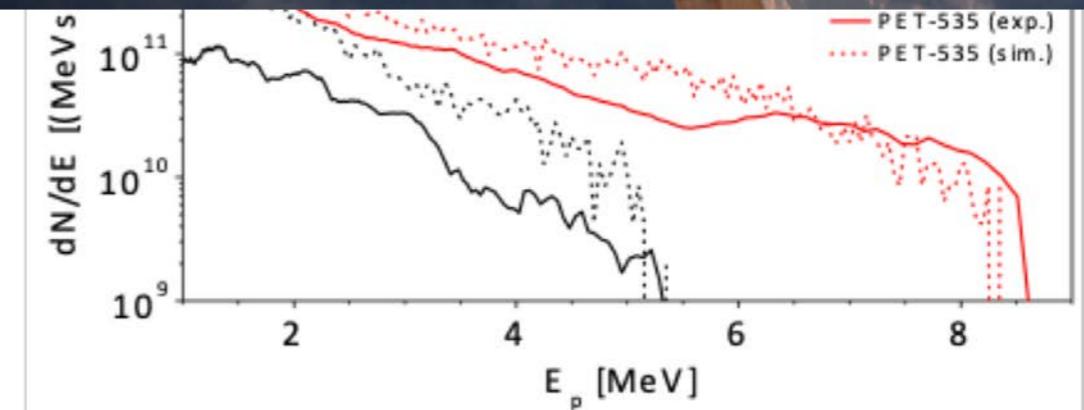
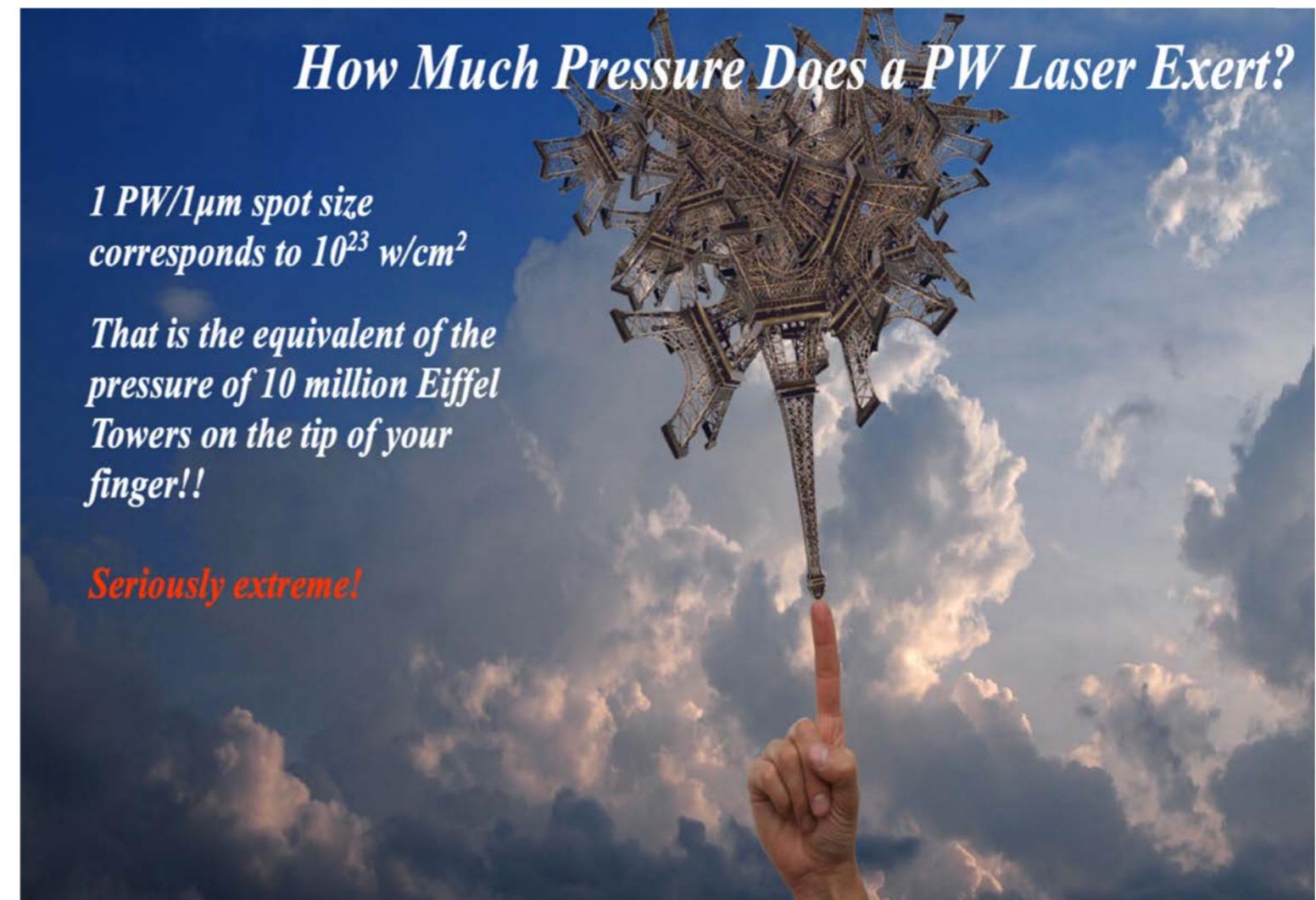
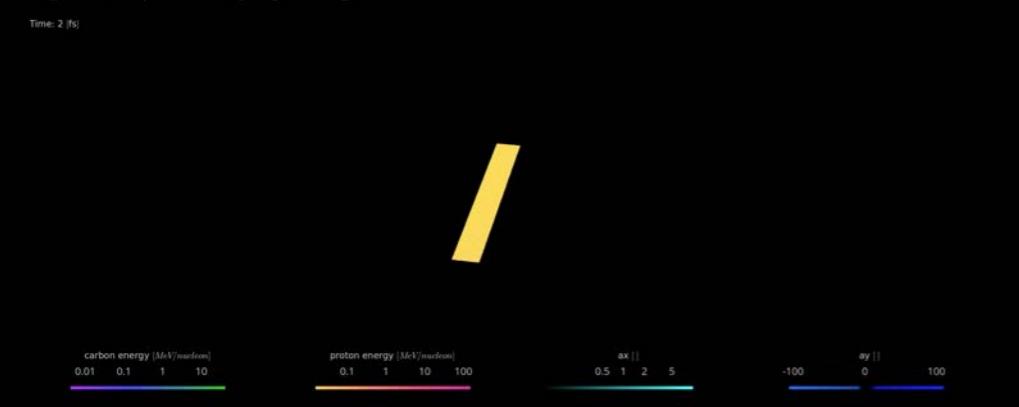
Chirped Pulse Amplification (CPA)





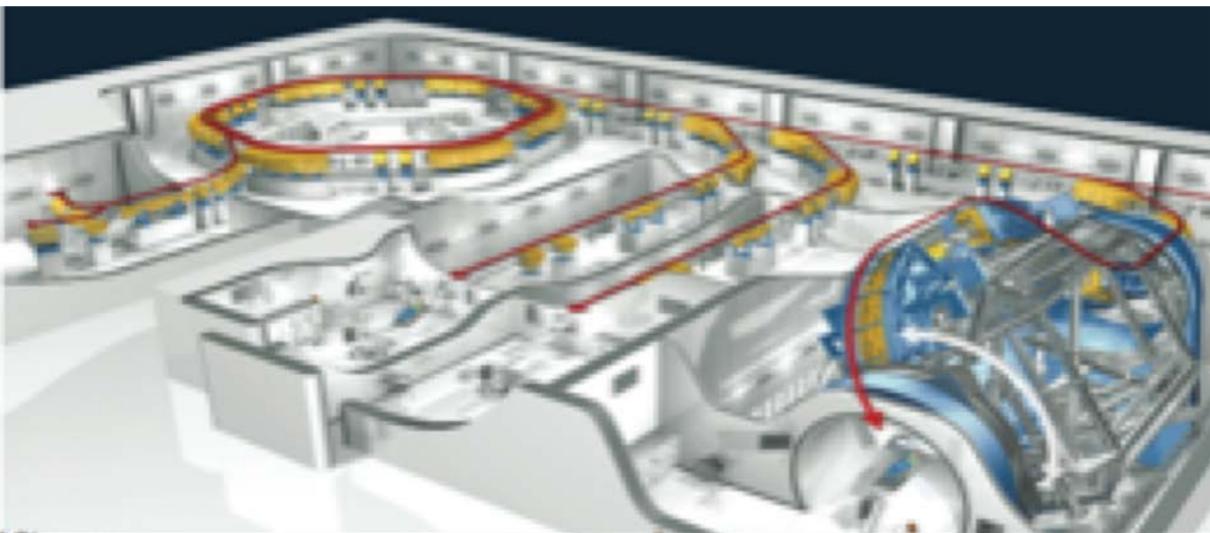
Laser-driven ion acceleration
from plastic target

2D particle-in-cell simulation of the interaction of high-intensity laser pulse (parameters are not relevant for this presentation). Acceleration of both protons (pink color) and carbon ions (green color), to maximum energy 150 MeV/nucleon and 40 MeV/nucleon, respectively, can be clearly distinguished in the visualization as well as different ion acceleration mechanisms from the target front side and from its rear side! Such high-energy protons may have a great impact on many applications in Physics, Medicine, Biology, Chemistry, Materials Science, Engineering, and Archaeology.



Using laser-generated ions form medical applications?

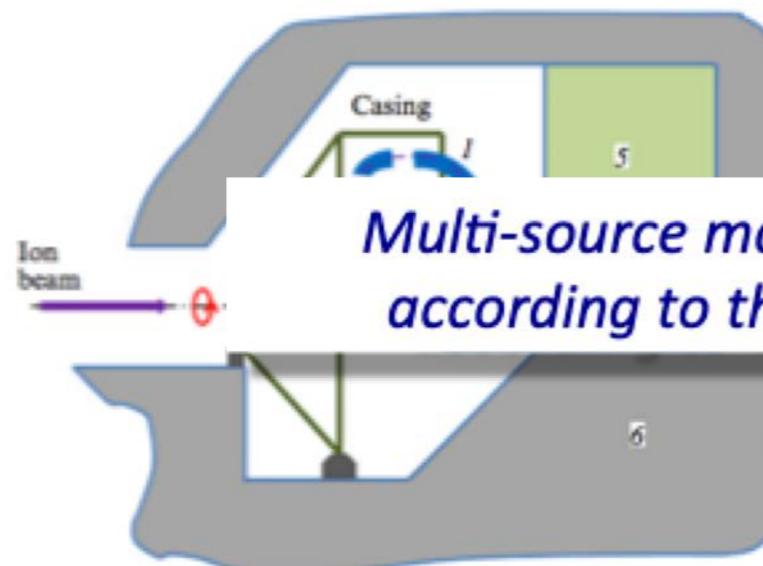
37



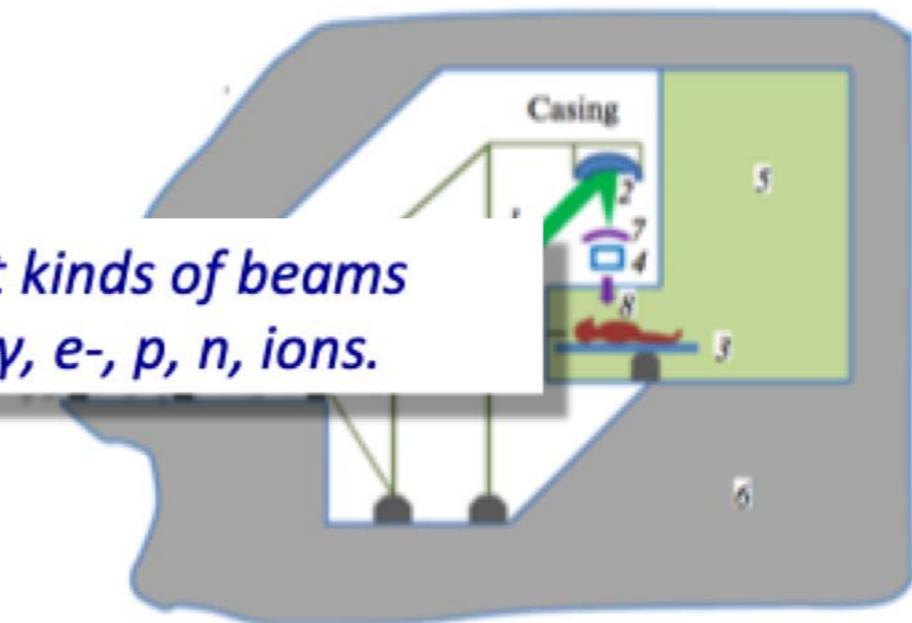
Quite large accelerators
Sophisticated beam transport (gantry)
High costs
Limited number of hadrontherapy centres
Alternative solutions

"If 200 MeV proton accelerators would be as cheap and small as the 10 MeV electron linacs used in conventional radiotherapy, at least 90% of the patients would be treated with proton beams"

U. Amaldi et al., NIM A 2010.



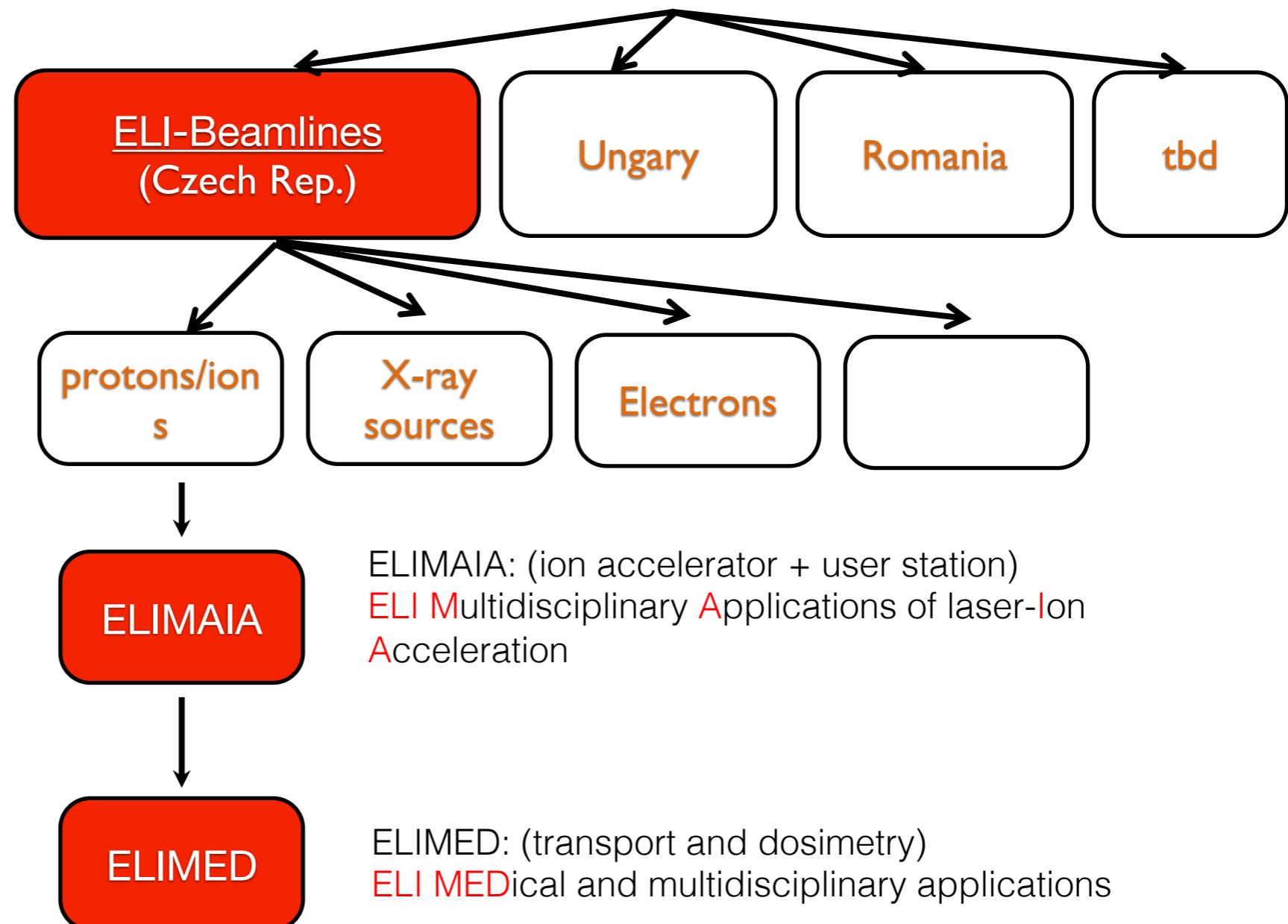
*Multi-source machine to deliver different kinds of beams
according to the specific requirements: γ , e-, p, n, ions.*



Bulanov et al. REVIEWS OF TOPICAL PROBLEMS (2014)

ELI (Extreme Light Infrastructure)

new type of European large scale laser infrastructure
specifically designed to produce the highest peak power (10 PW) and focused intensity;



Laser Building

Support Room
Cryogenic systems, power supply cooling, auxiliary systems

First Floor

Laser 1
100 mJ 1kHz beamlines

Laser 2
PW / 20 J / 10 Hz beamline

Laser 3
PW / 30 J / 10 Hz beamline

Laser 4
10 PW / 1.5 kJ beamline

Ground Floor

Experimental Hall 1
Material & biomolecular applications

Experimental Hall 2
X-ray sources

Experimental Hall 3
Plasma Physics

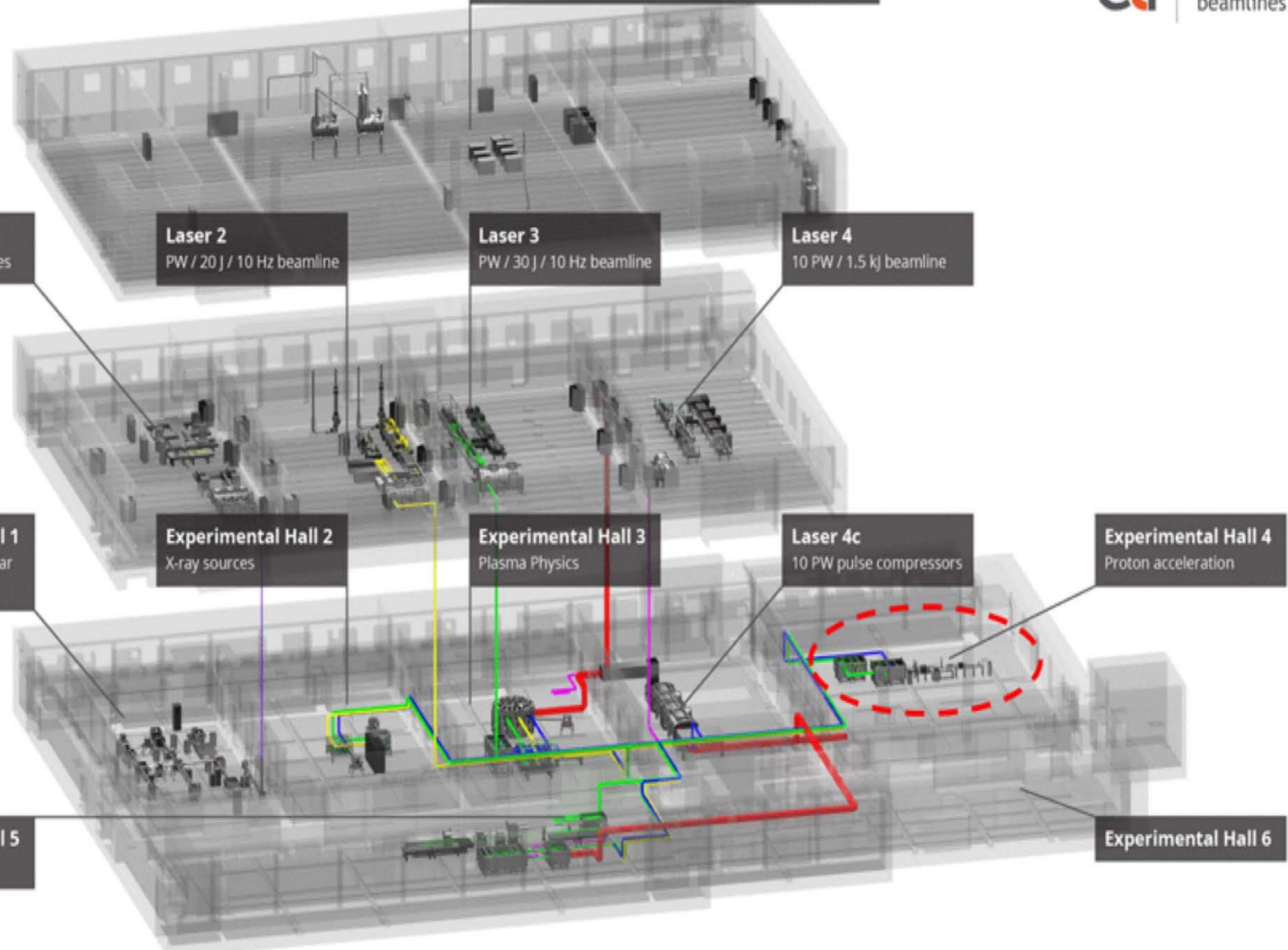
Laser 4c
10 PW pulse compressors

Experimental Hall 4
Proton acceleration

Basement

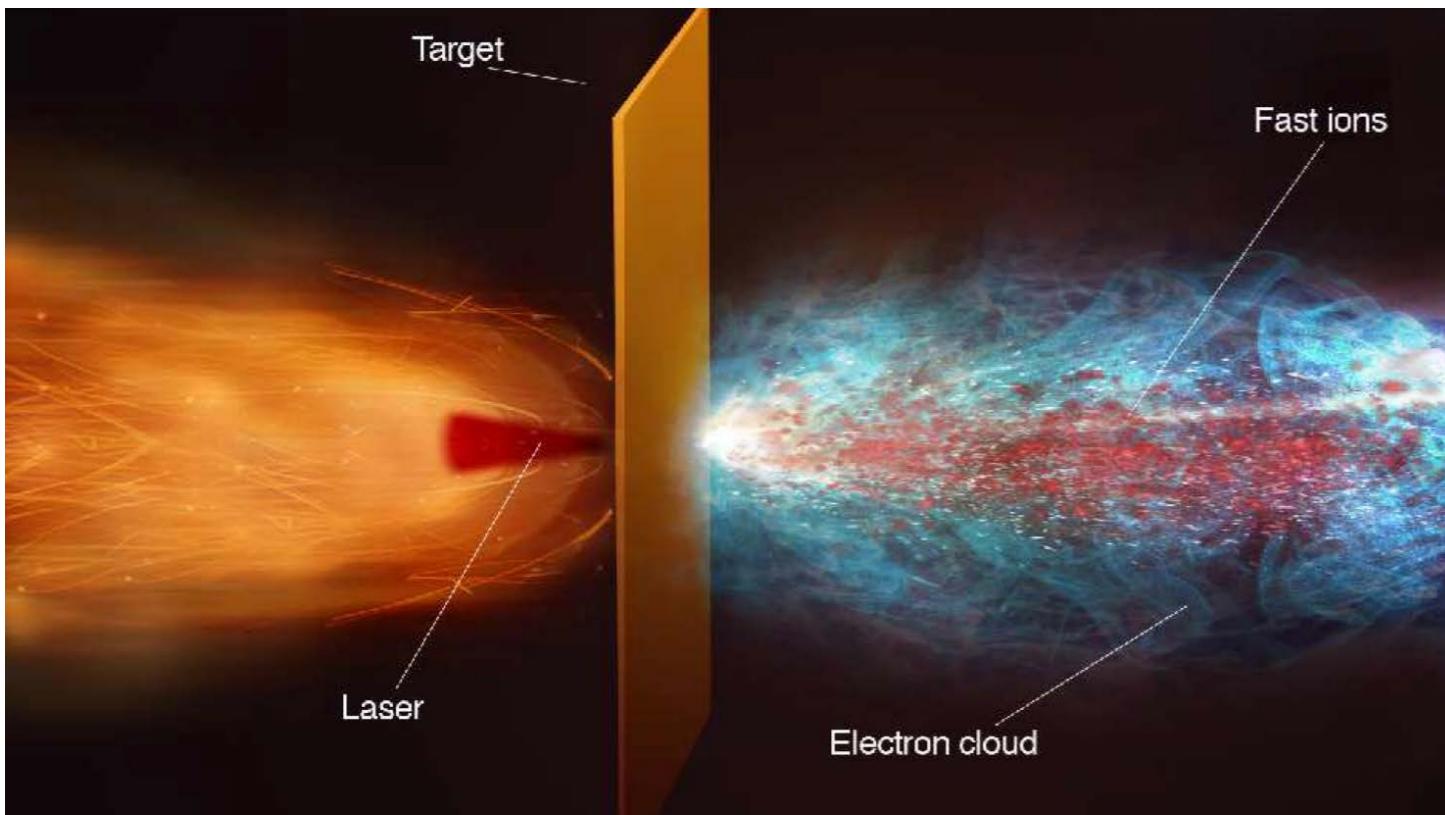
Experimental Hall 5
Electron acceleration

Experimental Hall 6

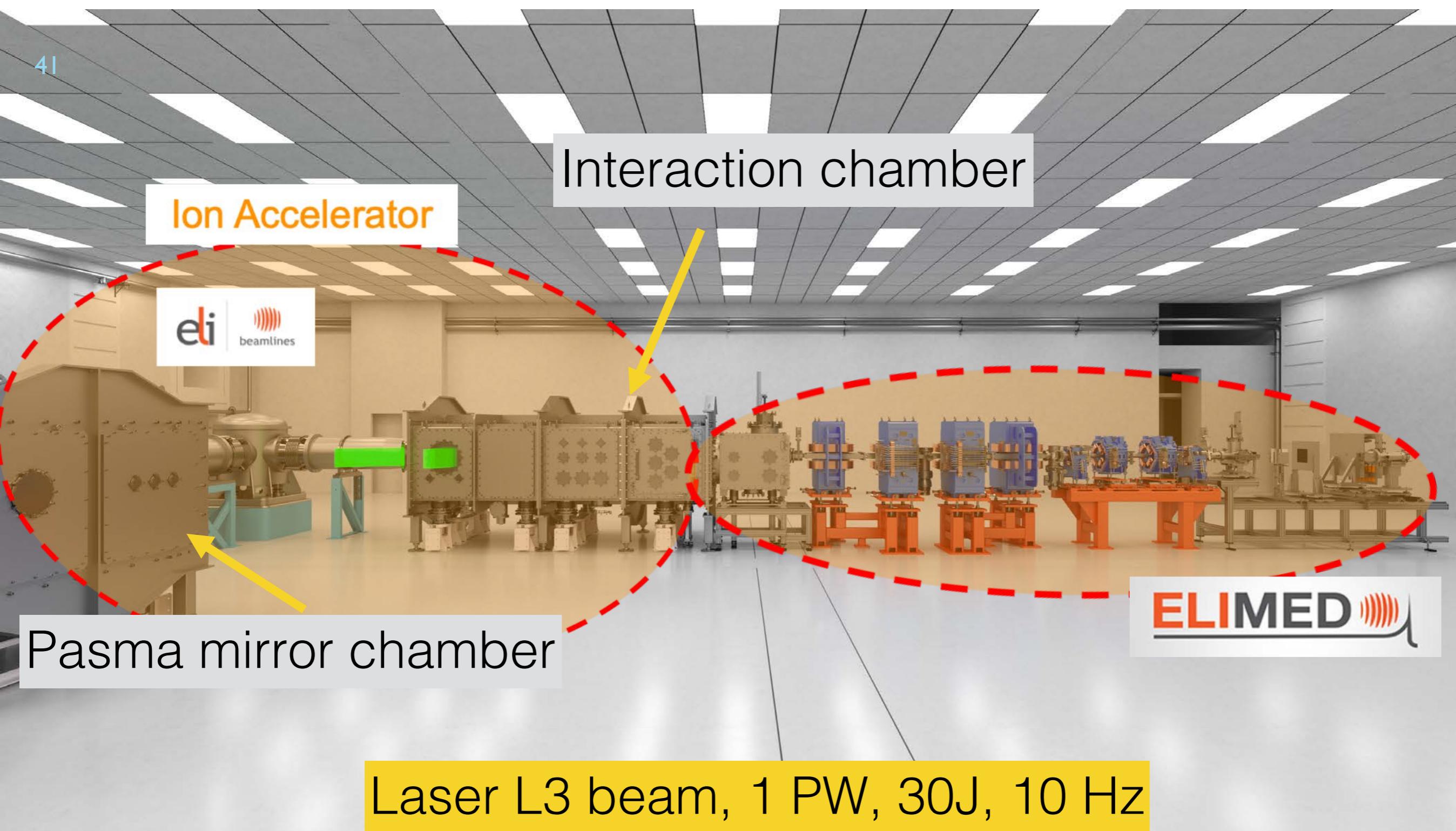


Why ELIMED?

40



A bucketful of particles



INFN-LNS staff install ELIMED (July 2018)

42



Luciano Allegra

Antonio Amico

Nino Amato

Simona Argentati

Renato Avolio

Luciano Calabretta

Giacomo Candiano

Carmelo Caruso

Fausta Caruso

Sarah Cesare

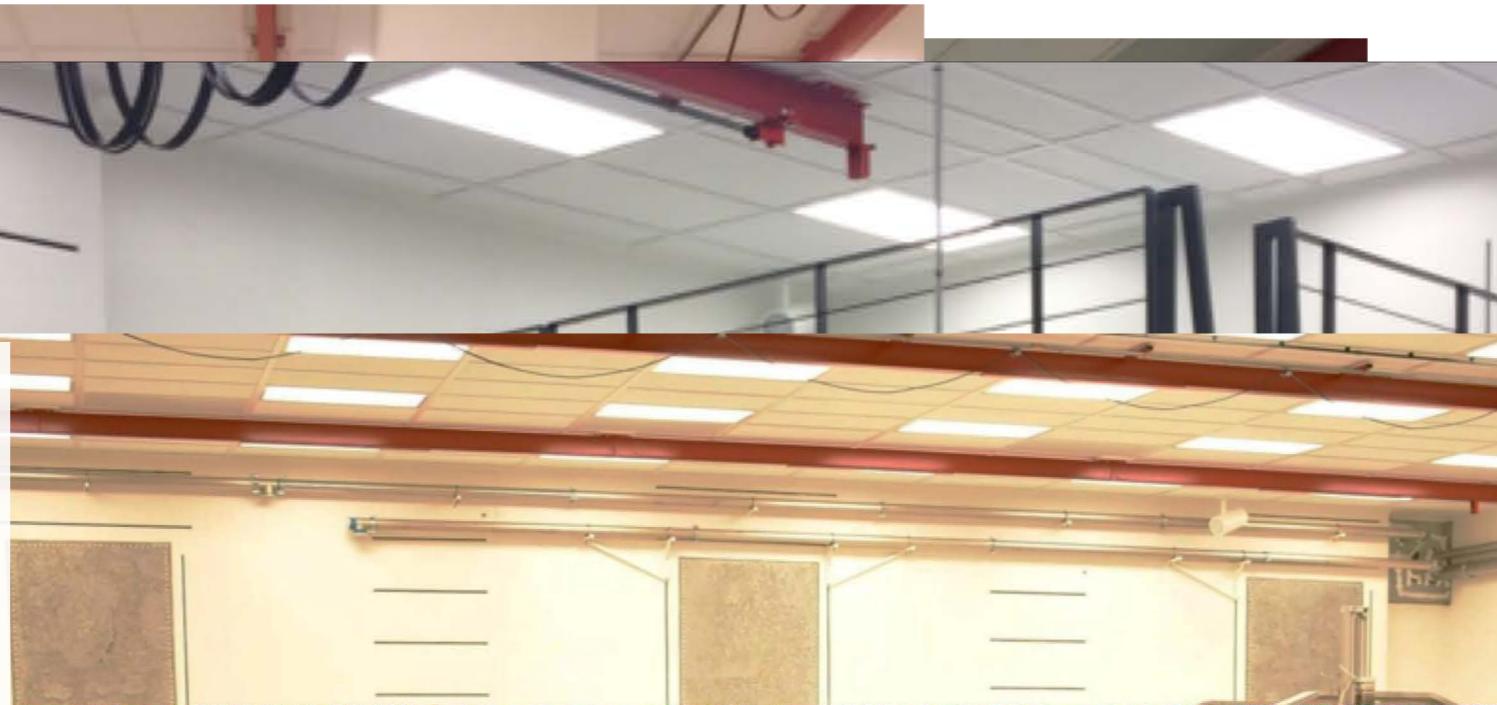
Giacomo Cuttone

Dora Di Nunzio

Enzo Lo Vecchio

Santo Gammino

Giusi Larosa



Mario Maggiore
July 2018
Rosanna Manna

Letizia Marchese

Nino Maugeri

Giuliana Milluzzo

Nello Salamone

Roberto Pellegrini

Giada Petringa

Pietro Pisciotta

Salvo Pulvirenti

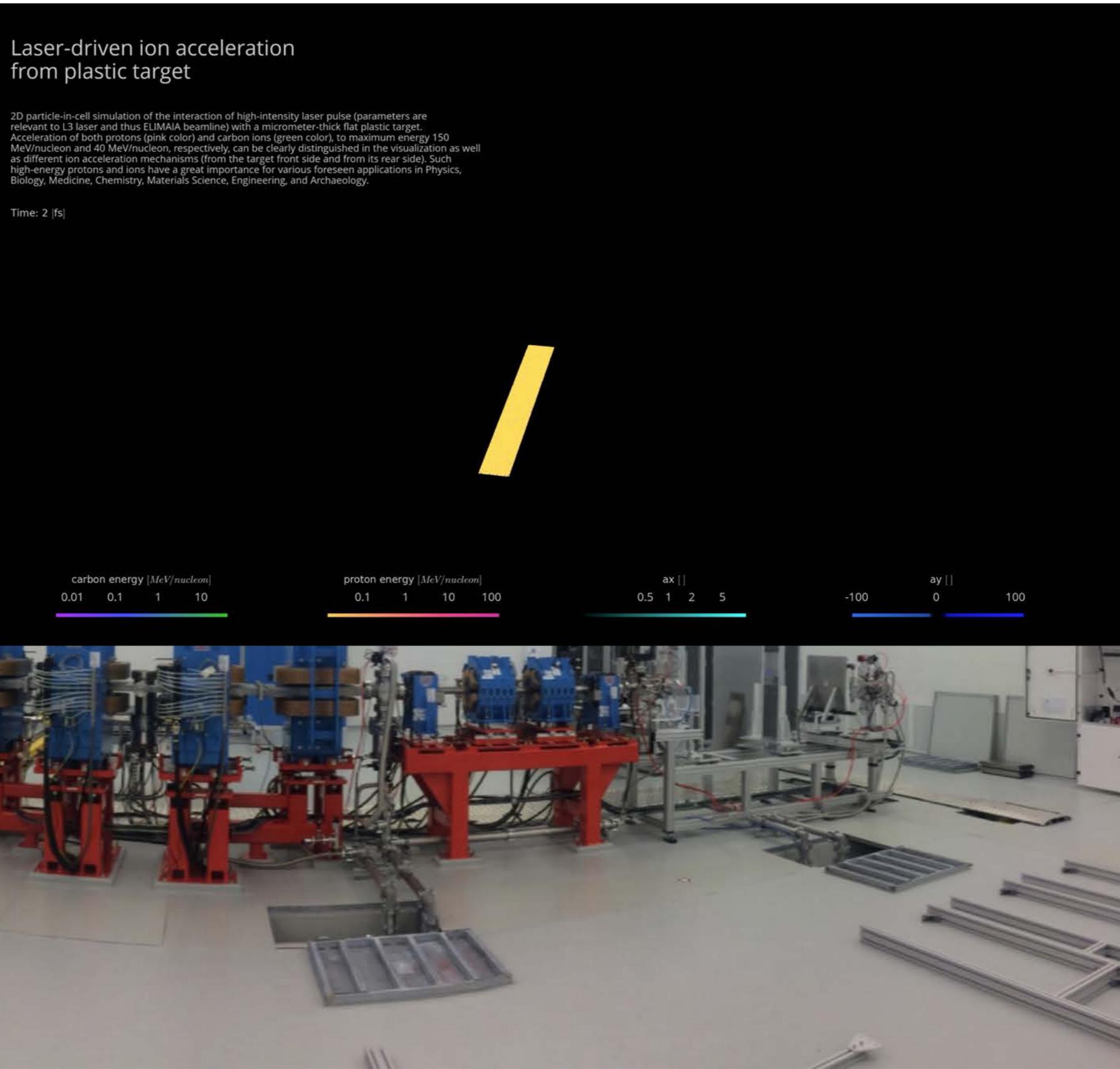
Daniele Rizzo

Francesco Romano

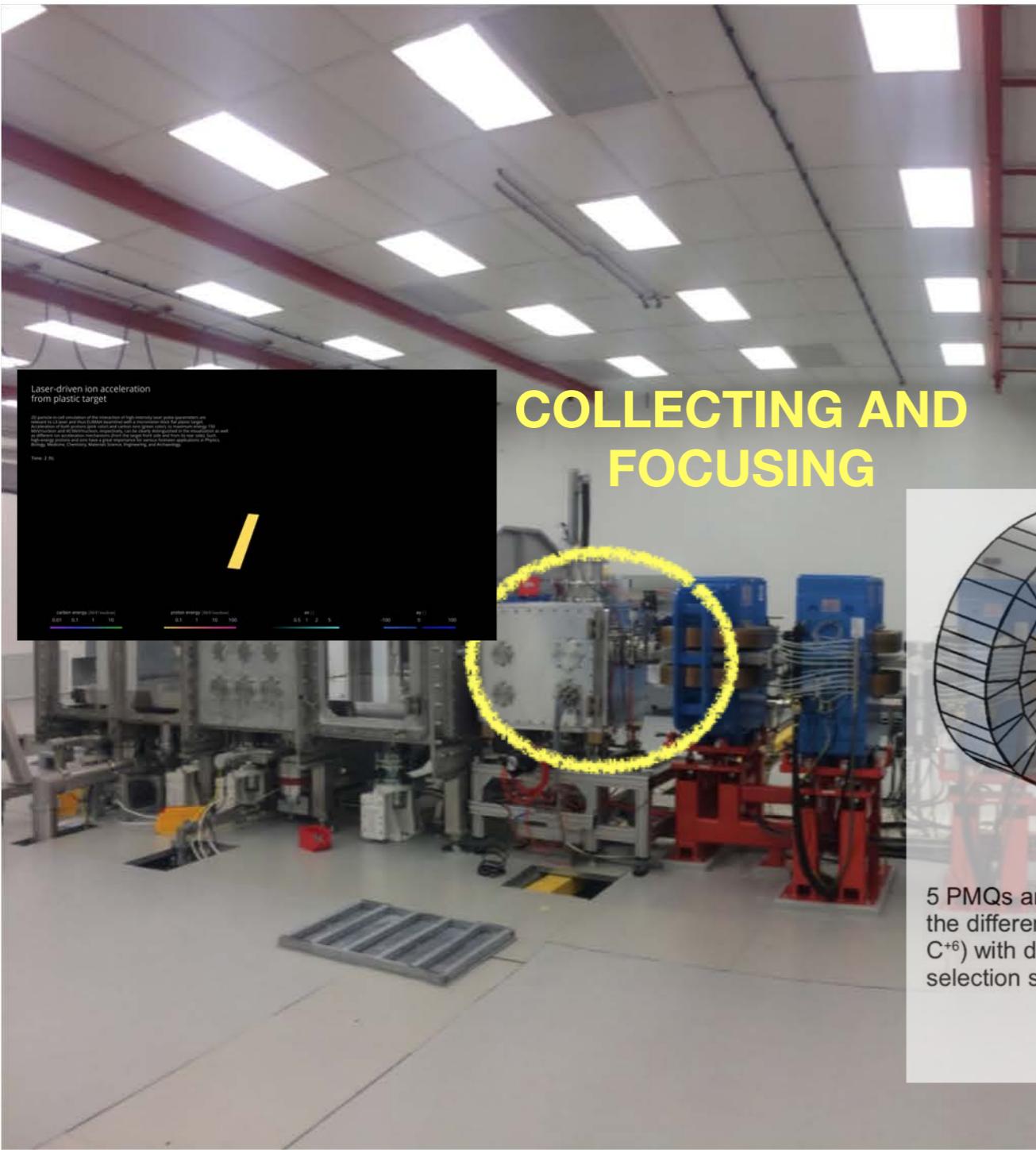
Francesco Schillaci

Valentina Scuderi

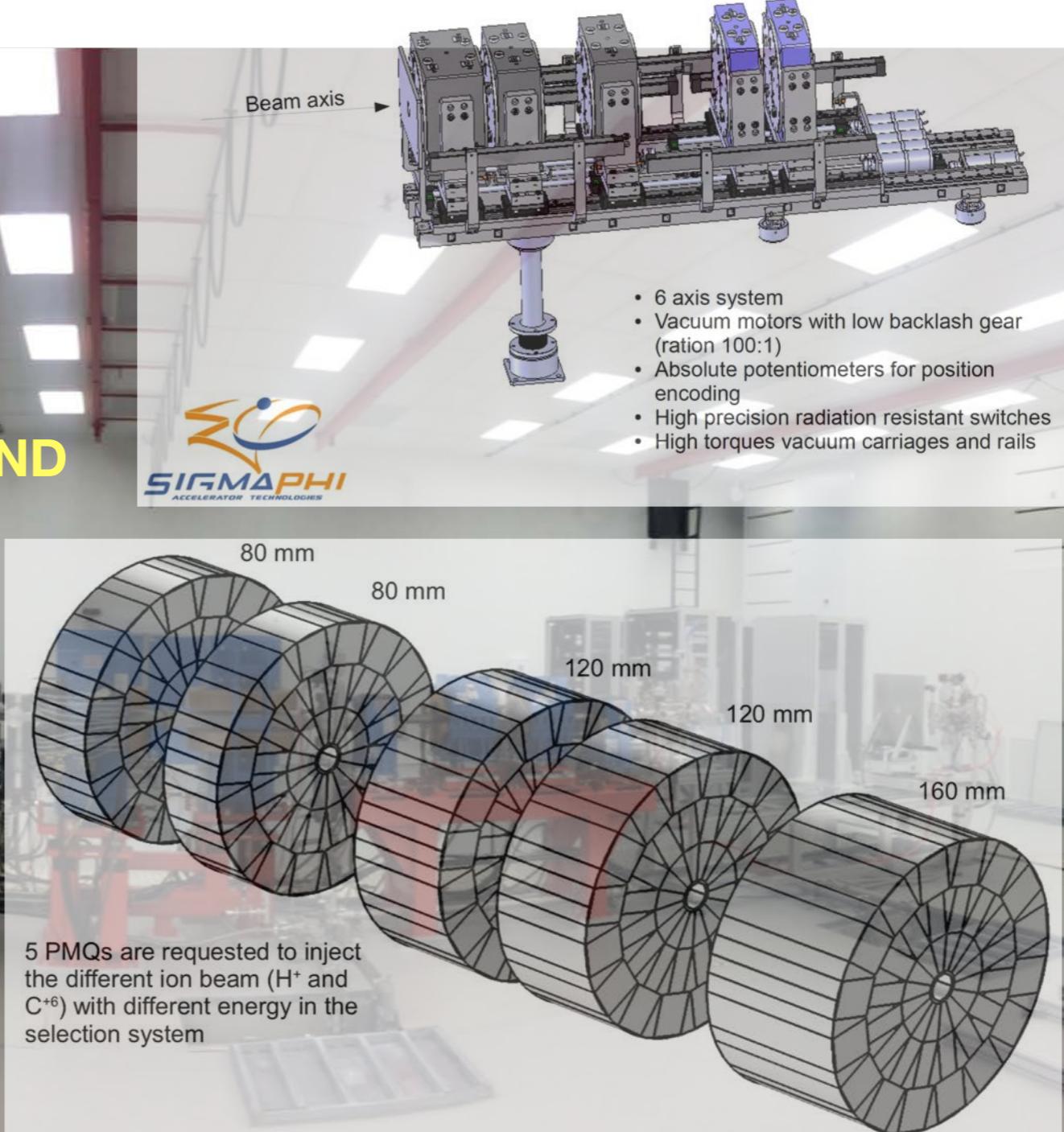
Salvatore Vinciguerra



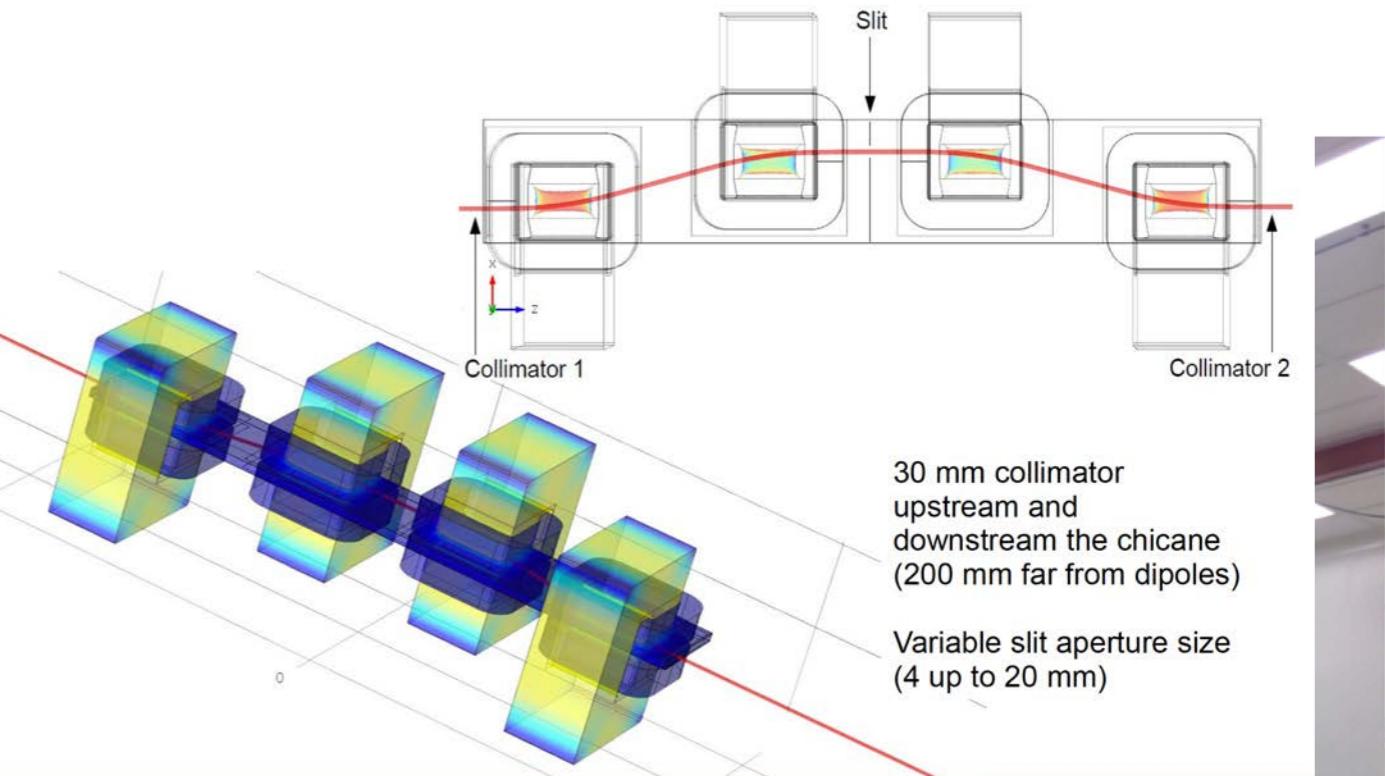
D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for Multidisciplinary Applications", *Quantum Beam Sci.* 2 (2018) 8



COLLECTING AND FOCUSING



D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for Multidisciplinary Applications", Quantum Beam Sci. 2 (2018) 8



Not just a magnetic chicane: energy change shot-by-shot

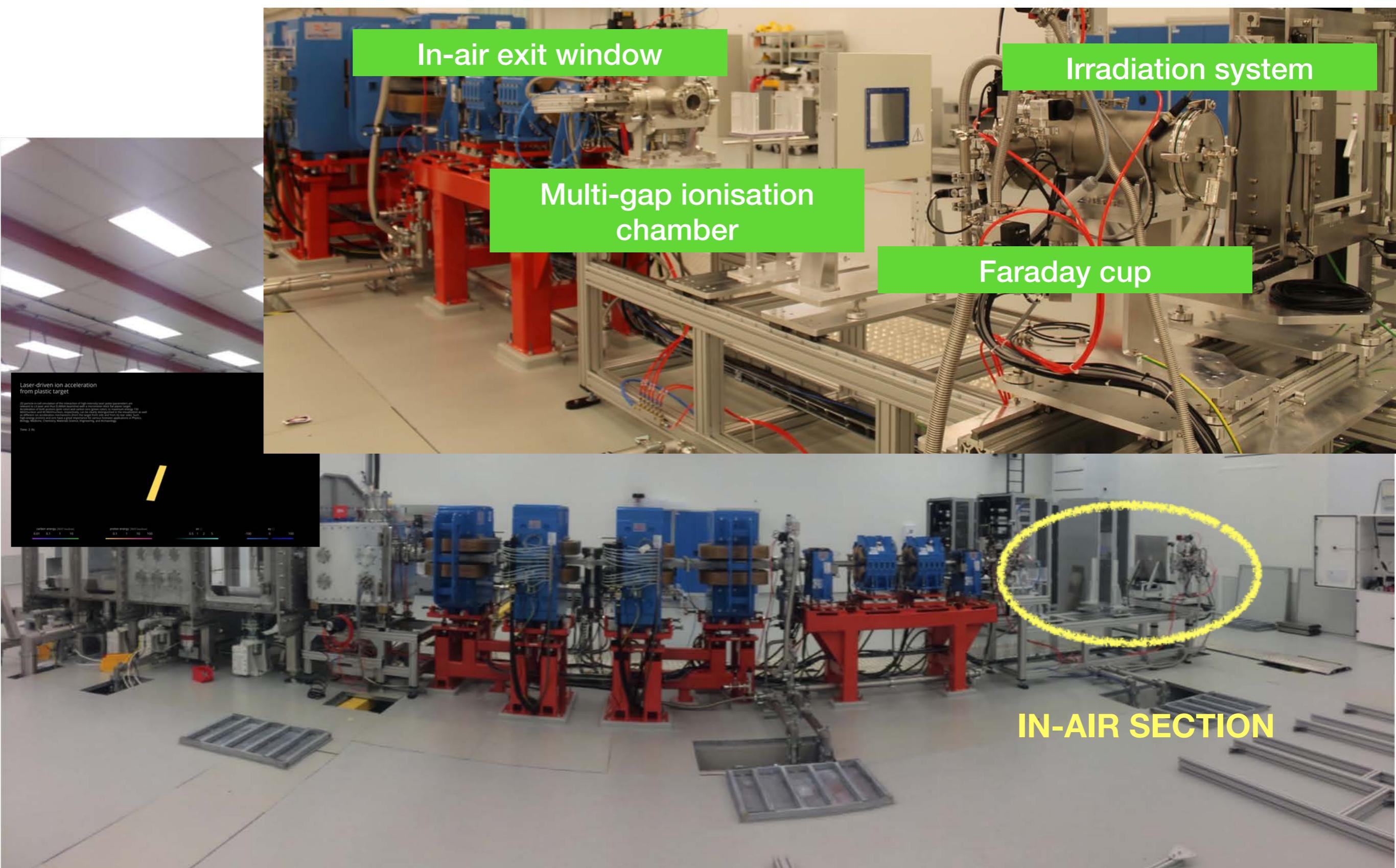
ENERGY SELECTION

D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for Multidisciplinary Applications", *Quantum Beam Sci.* 2 (2018) 8

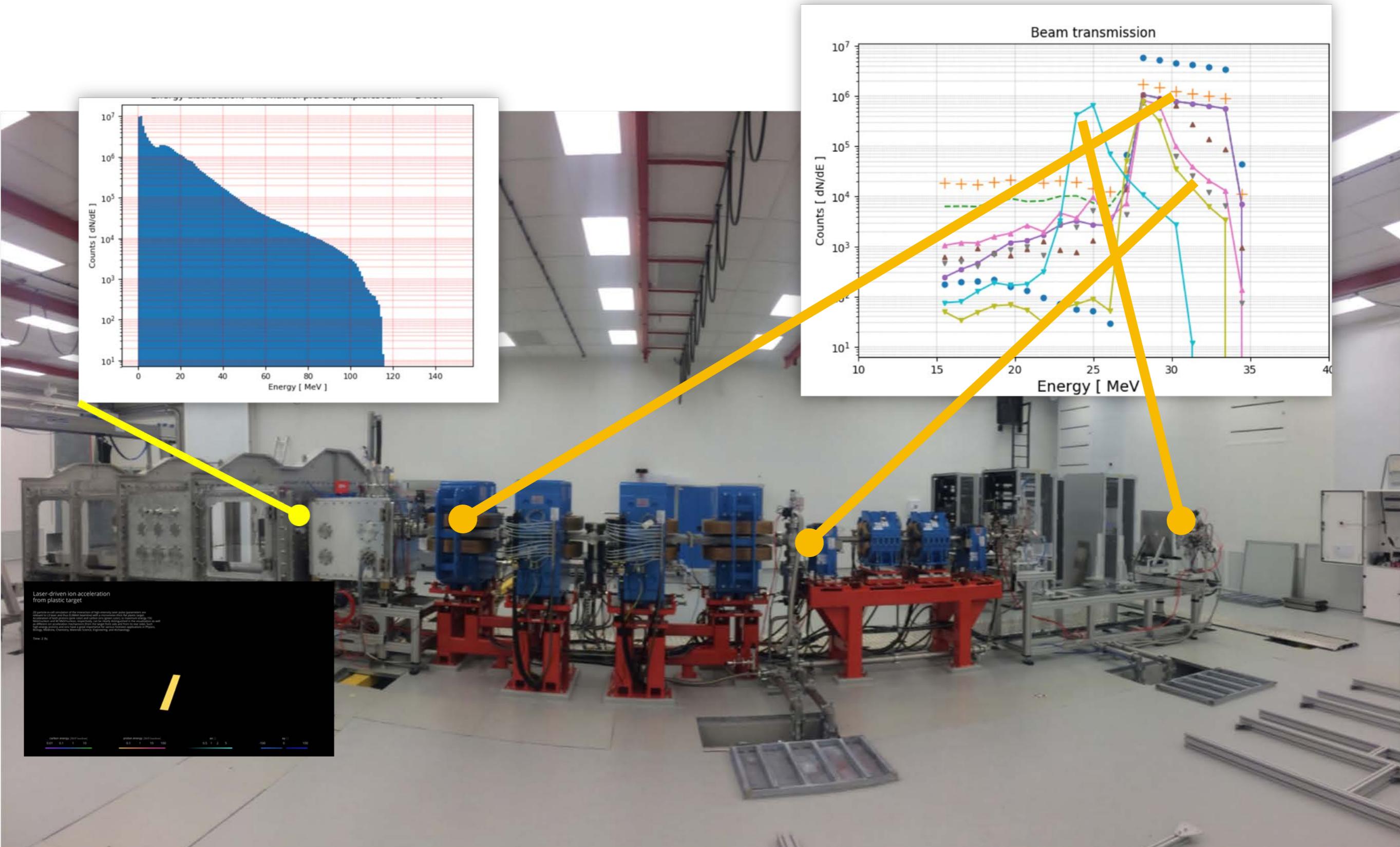


CONVENTIONAL
SECTION

D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for Multidisciplinary Applications", *Quantum Beam Sci.* 2 (2018) 8



D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for Multidisciplinary Applications", *Quantum Beam Sci.* 2 (2018) 8

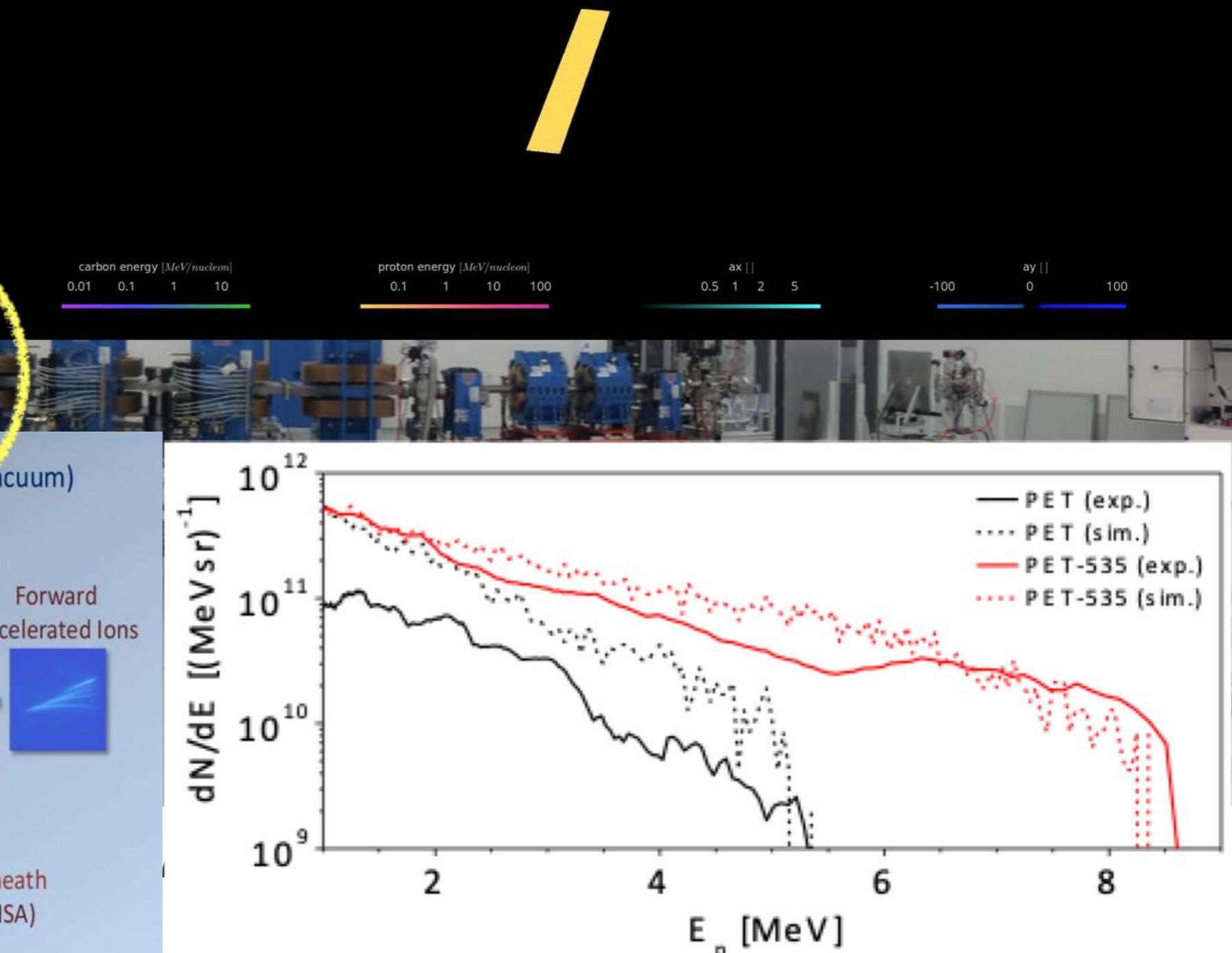
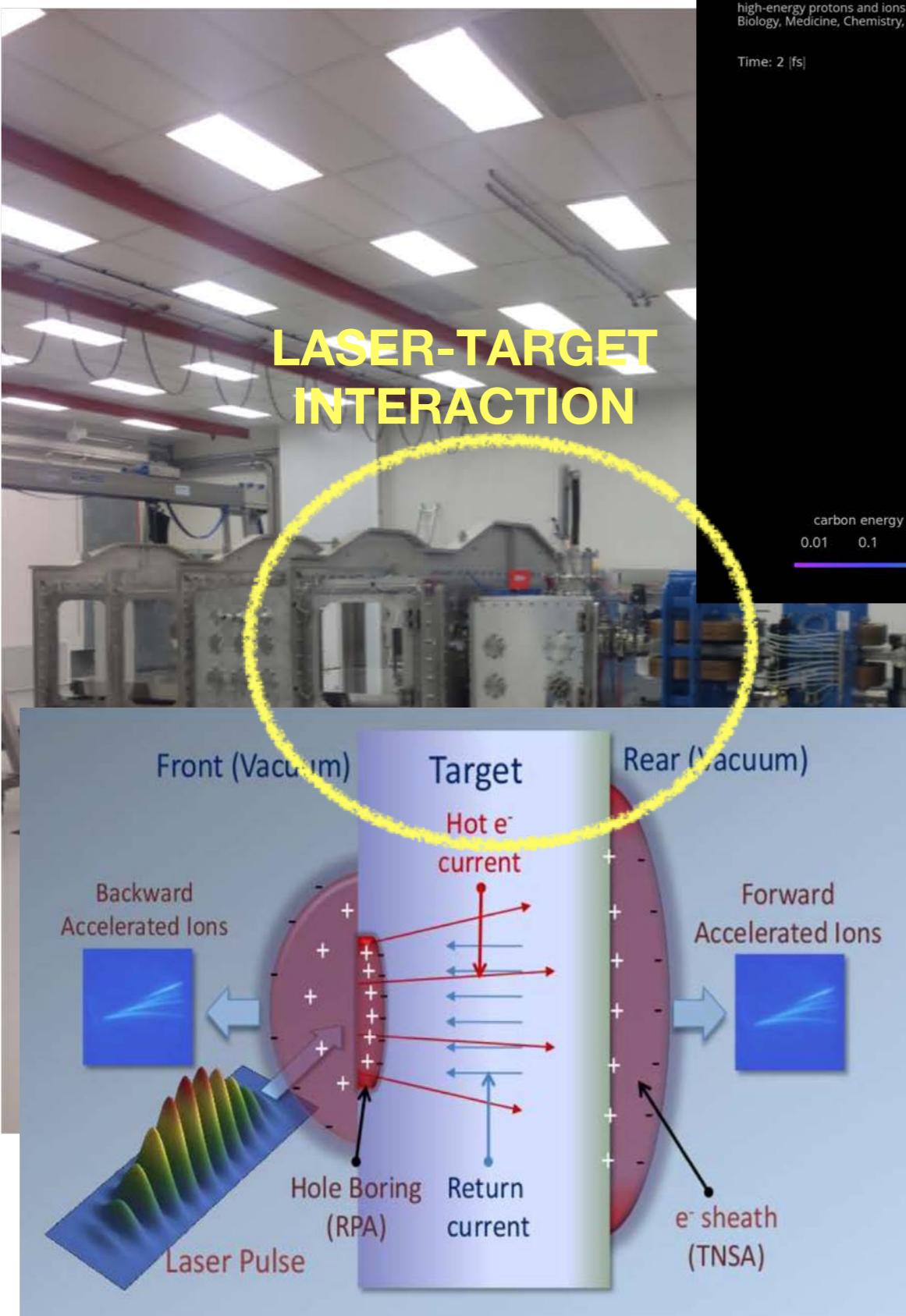


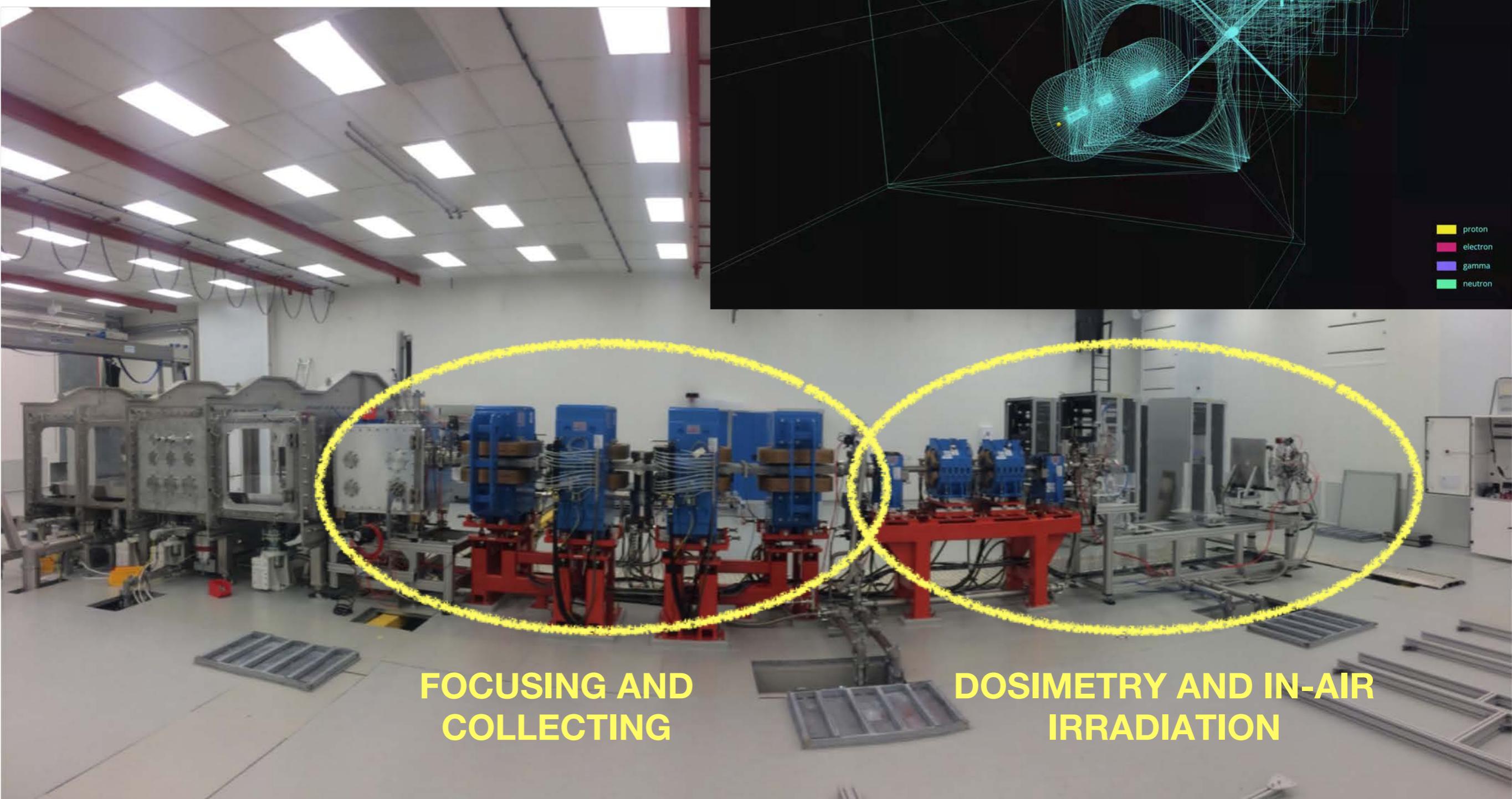
D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for Multidisciplinary Applications", *Quantum Beam Sci.* 2 (2018) 8

Laser-driven ion acceleration from plastic target

2D particle-in-cell simulation of the interaction of high-intensity laser pulse (parameters are relevant to L3 laser and thus ELIMAIA beamline) with a micrometer-thick flat plastic target. Acceleration of both protons (pink color) and carbon ions (green color), to maximum energy 150 MeV/nucleon and 40 MeV/nucleon, respectively, can be clearly distinguished in the visualization as well as different ion acceleration mechanisms (from the target front side and from its rear side). Such high-energy protons and ions have a great importance for various foreseen applications in Physics, Biology, Medicine, Chemistry, Materials Science, Engineering, and Archaeology.

Time: 2 [fs]





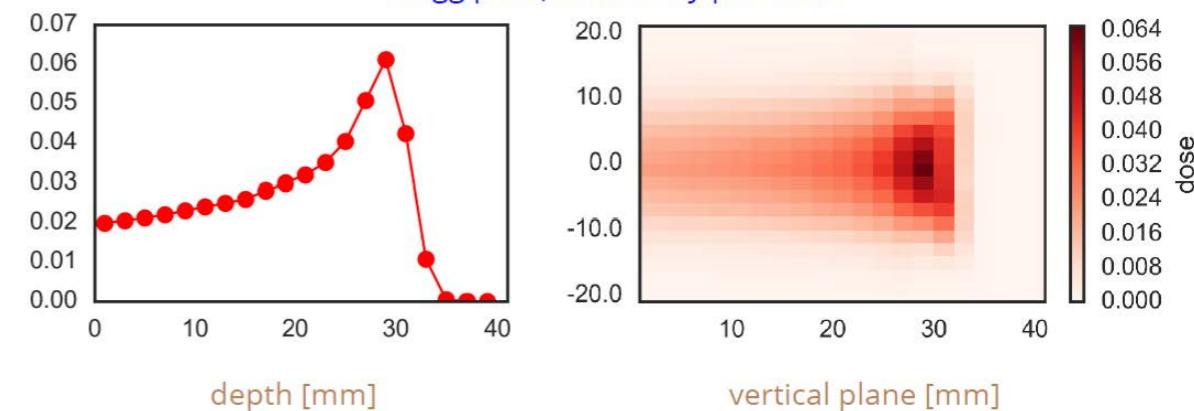
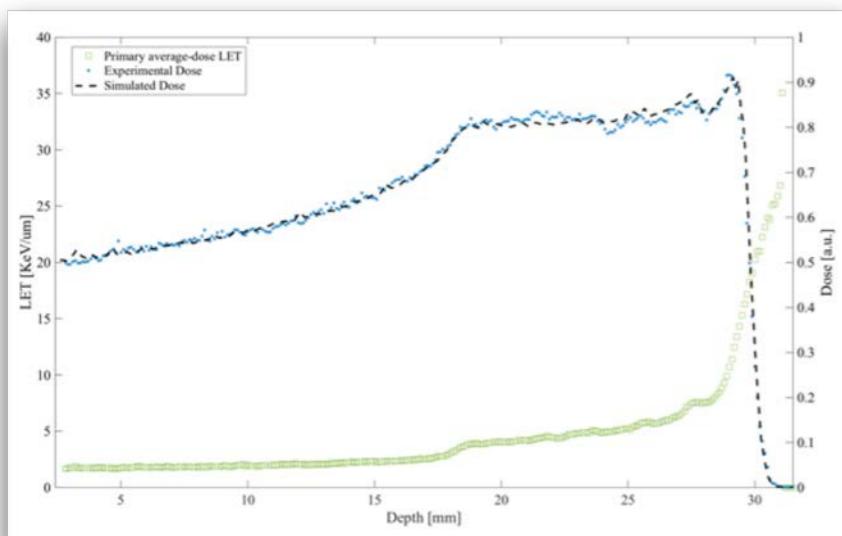
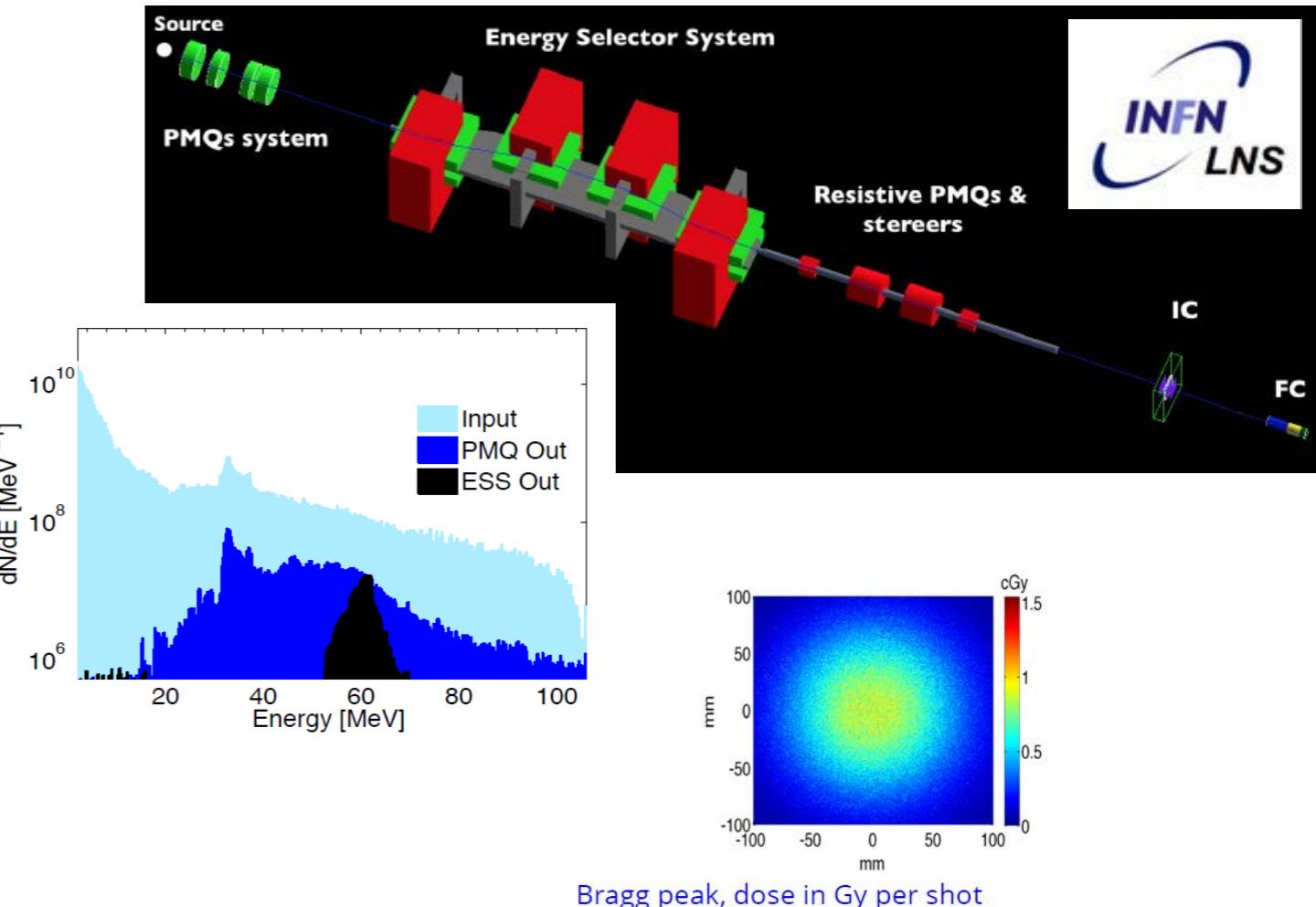
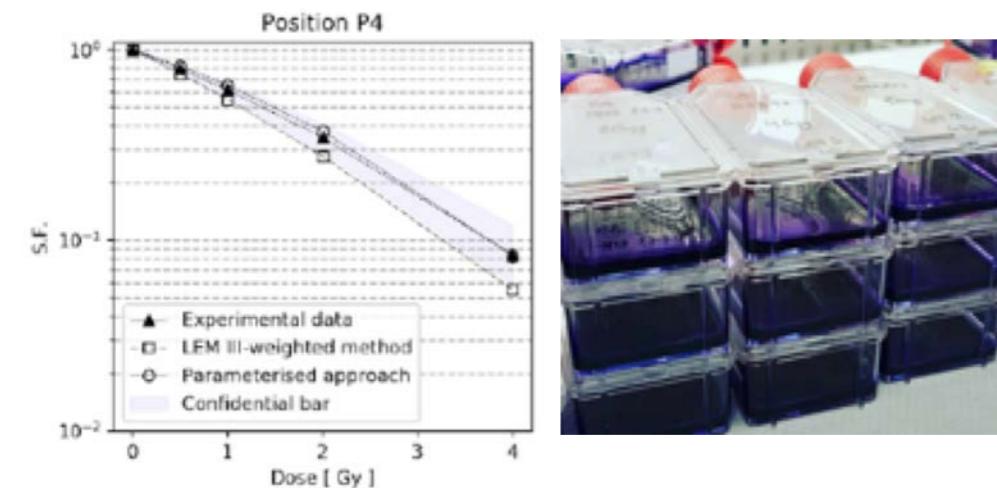
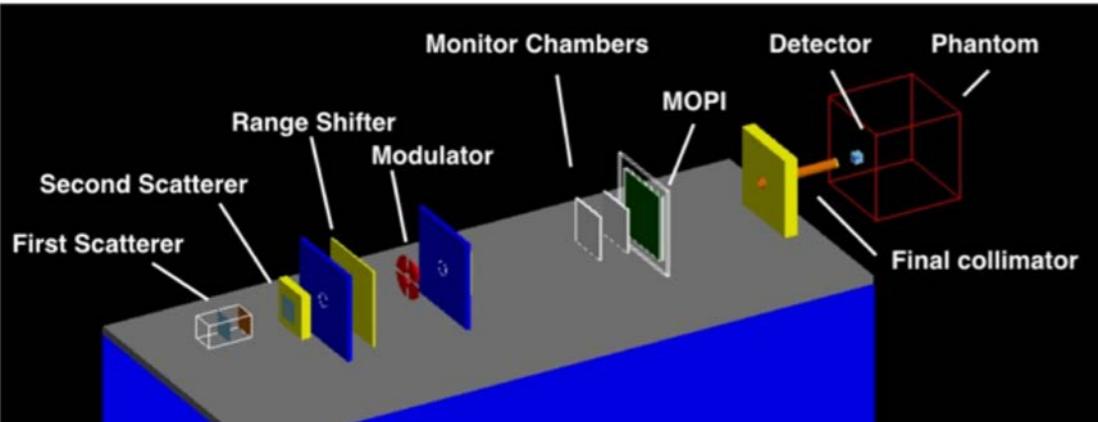
D. Margarone, G.A.P. Cirrone et al., "ELIMAIA: A Laser-Driven Ion Accelerator for M

Monte Carlo simulations



Many others in specialised field

Monte Carlo simulations





Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali del Sud



Vinča Institute of
Nuclear Sciences



ASSOCIAZIONE ITALIANI E SERBI SCIENZIATI E STUDIOSI
АСОЦИЈАЦИЈА ИТАЛИЈАНСКИХ И СРПСКИХ НАУЧНИКА И ИСРАЖИВАЧА

ENSAR2 MediNet

TOPICS

- Basic lectures on the GEANT4
- Monte Carlo toolkit
- Practical sessions
- C++ programming basic elements

ORGANIZING COMMITTEE

- Davide Chiappara, INFN-LNS (I)
Pablo Cirrone, INFN-LNS (I)
Giacomo Cuttone, INFN-LNS (I)
Otilija Keta, VINS-UB (SRB)
Luciano Pandola, INFN-LNS (I)
Giada Petringa, INFN-LNS (I)
Ivan Petrović, VINS-UB (SRB)
Aleksandra Ristić-Fira, VINS-UB (SRB)



https://agenda.infn.it/e/VIII_InternationalGeant4School

<https://www.facebook.com/SoftwareandGeant4School/>

PARTICIPANTS

A maximum number of 50 participants will be admitted

SCHOOL FEE

The school fee is fixed at 150 euro

.... can be of interest for the community

55



First dosimetry and radiobiology irradiation with laser-driven fast beams

Within June 2020, 30 MeV, 20 ns protons

We are discussing the participation of ELI with ELIMED in the next ENSAR program

A radioisotopes production study is ongoing for new more advantageous schemes and modalities

Thanks for listening



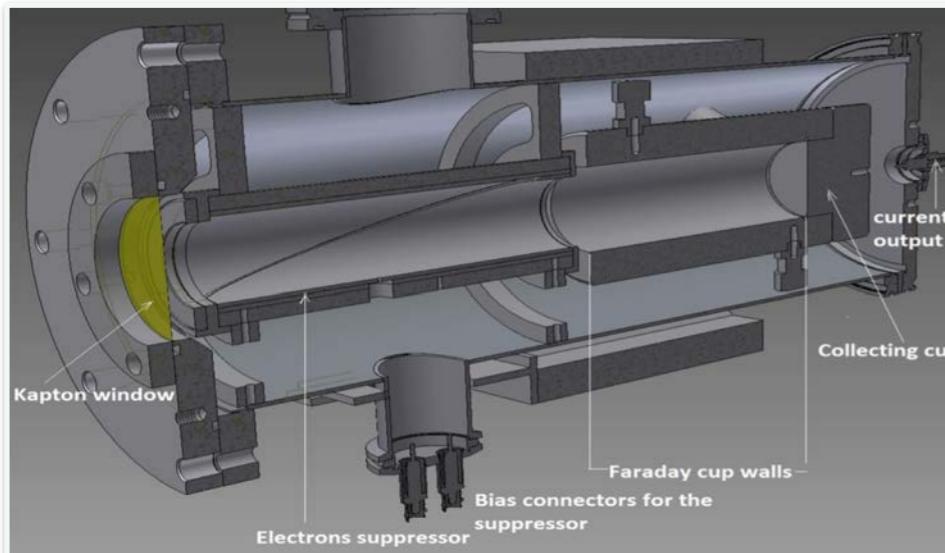
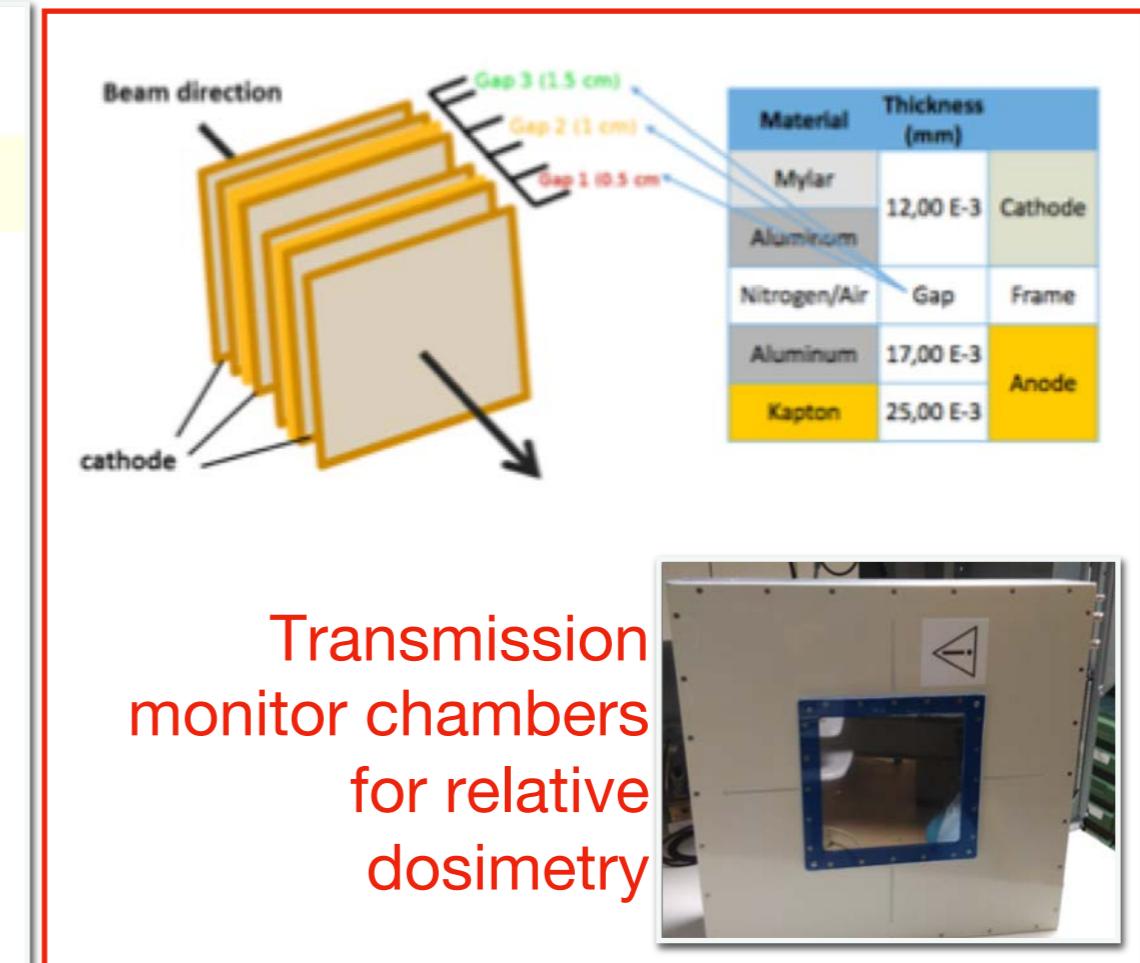
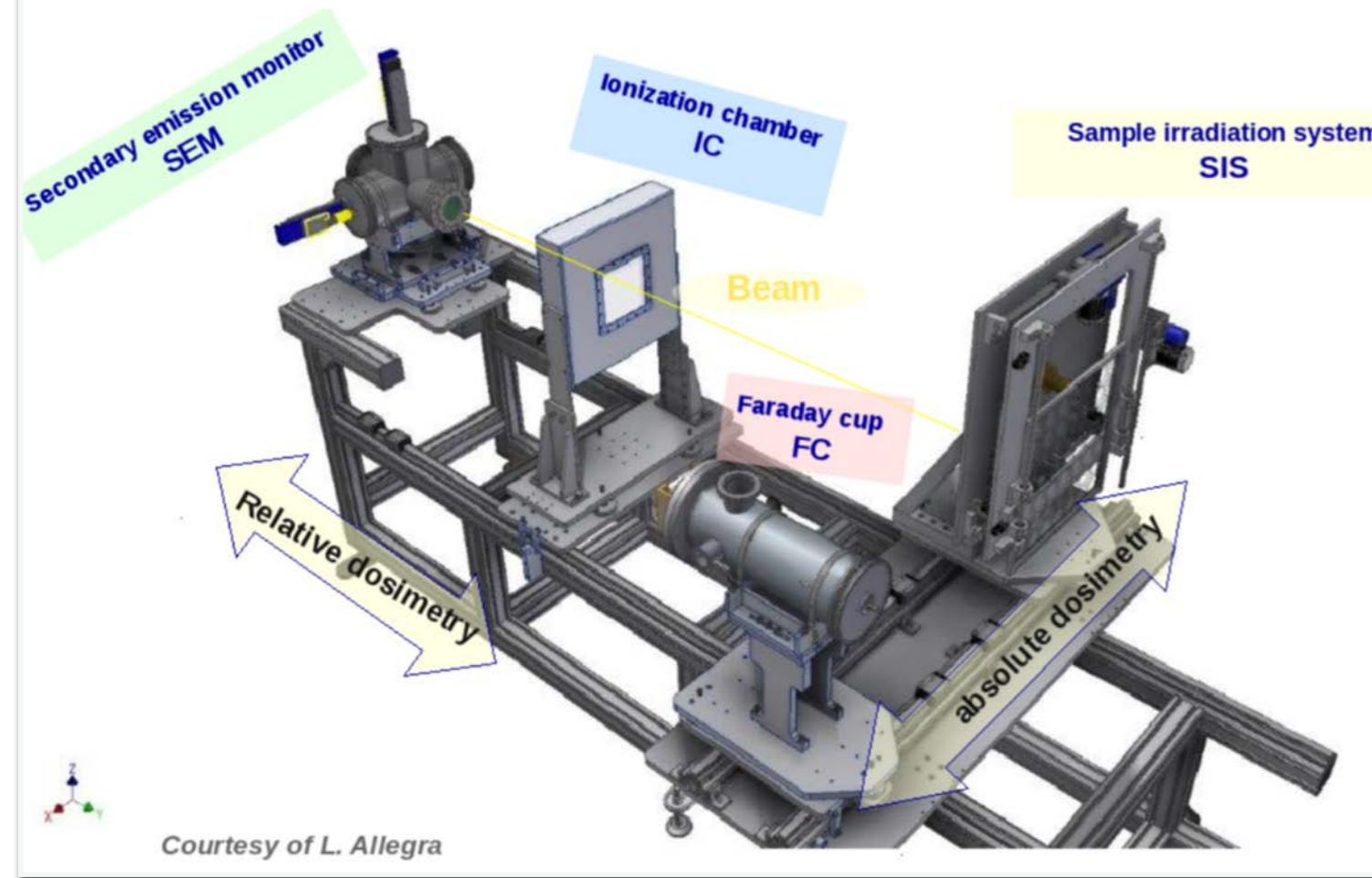
Left to right:

Roberto Catalano, Giovanni Manno, Emilio Zappalà, Antonio Russo, Gustavo Messina, Pablo Cirrone, Milena Ficarra, Gaetano Savoca, Cristina Guarnera, Giusi Larosa, Antonino Amato, Giada Petringa, Giacomo Cuttone, Rhuani Khanna, Giuseppe Fustaino, Beatrice Cagni, Cinzia Gigliuto, Nello Salomone, Chidera Opara, Daniele Rizzo, Giuseppe Pastore, Salvo Tudisco, Nelly Puglia, Marco Calvaruso, Luigi Minafra, Giorgio Russo, Piero Lojacono

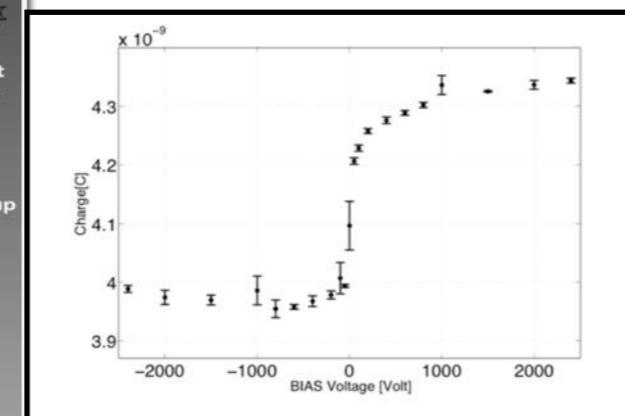
The INFN-LNS Medical Physics Group - Catania, March 20, 2019

Dosimetric System

57



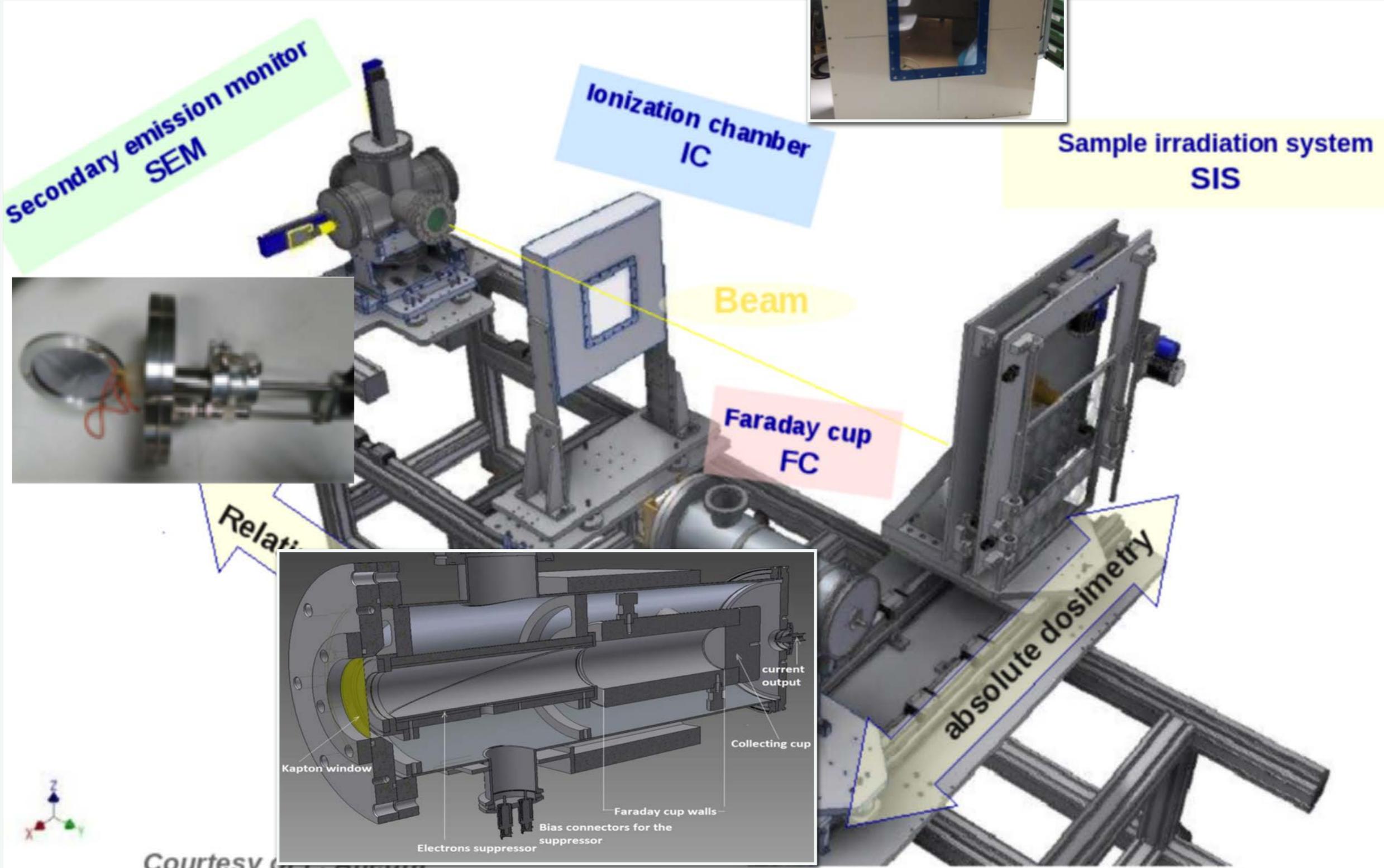
Faraday Cup for absolute dosimetry



Secondary Emission Monitor

Dosimetric System

58



Laser-beam hadrontherapy: potential advantages

Reduced cost/shielding

59

Laser transport rather than ion transport (*vast reduction in radiation shielding*)

- Possibility to reduce size of gantry

Flexibility/modularity

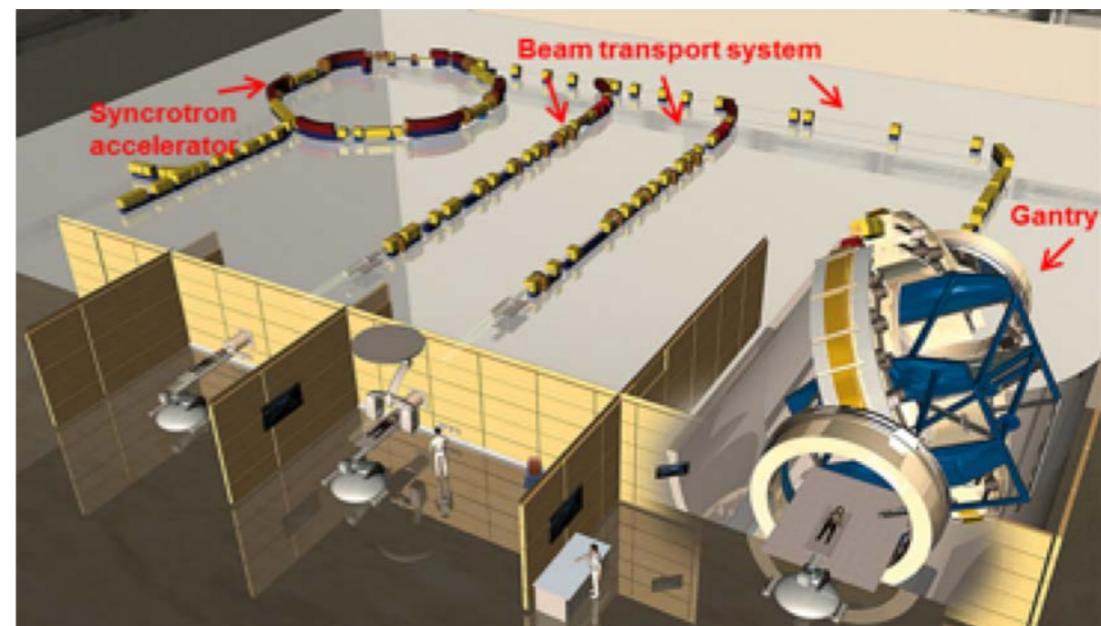
- Possibility of controlling output energy and spectrum
- Possibility of varying accelerated species
- Spectral shaping for direct “painting” of tumor region (no degrader needed)

Novel therapeutic/diagnostic options

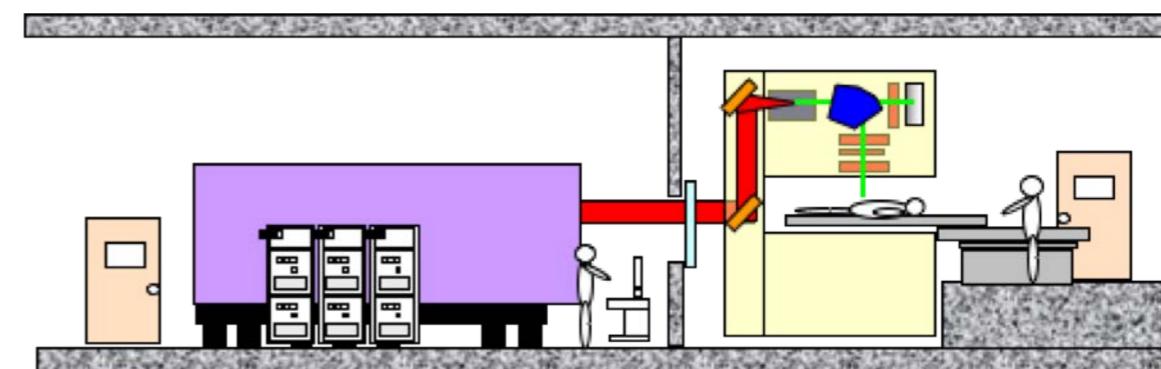
- Mixed fields: ions, X-rays, electrons, neutrons
- In-situ diagnosis (PET, X-rays)

Radiobiological advantages

Conventional hadrontherapy



Laser-based hadrontherapy

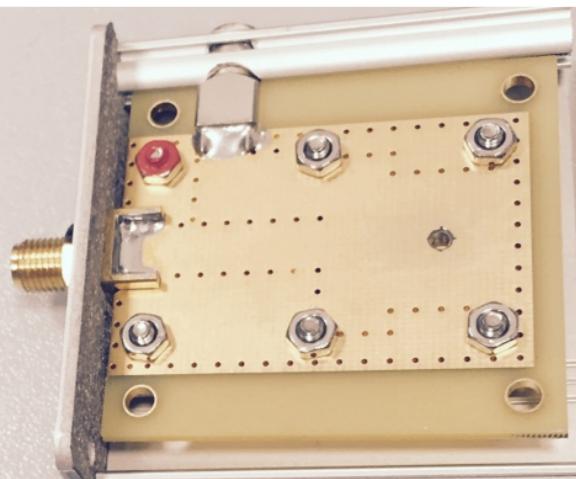


Monitoring System: TOF detectors

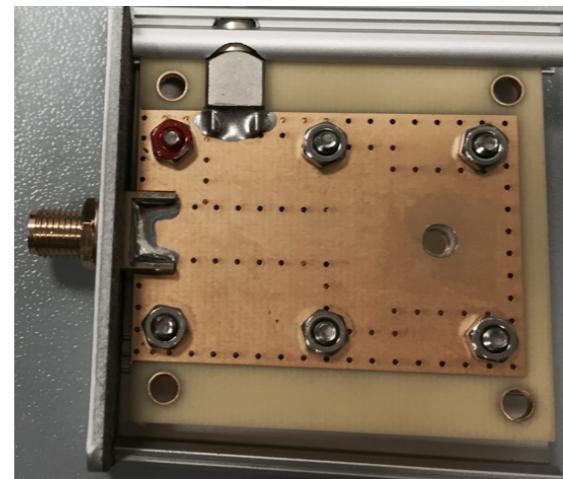
60

Main goal: *ONLINE* proton energy spectrum and fluence measurement along the beam line

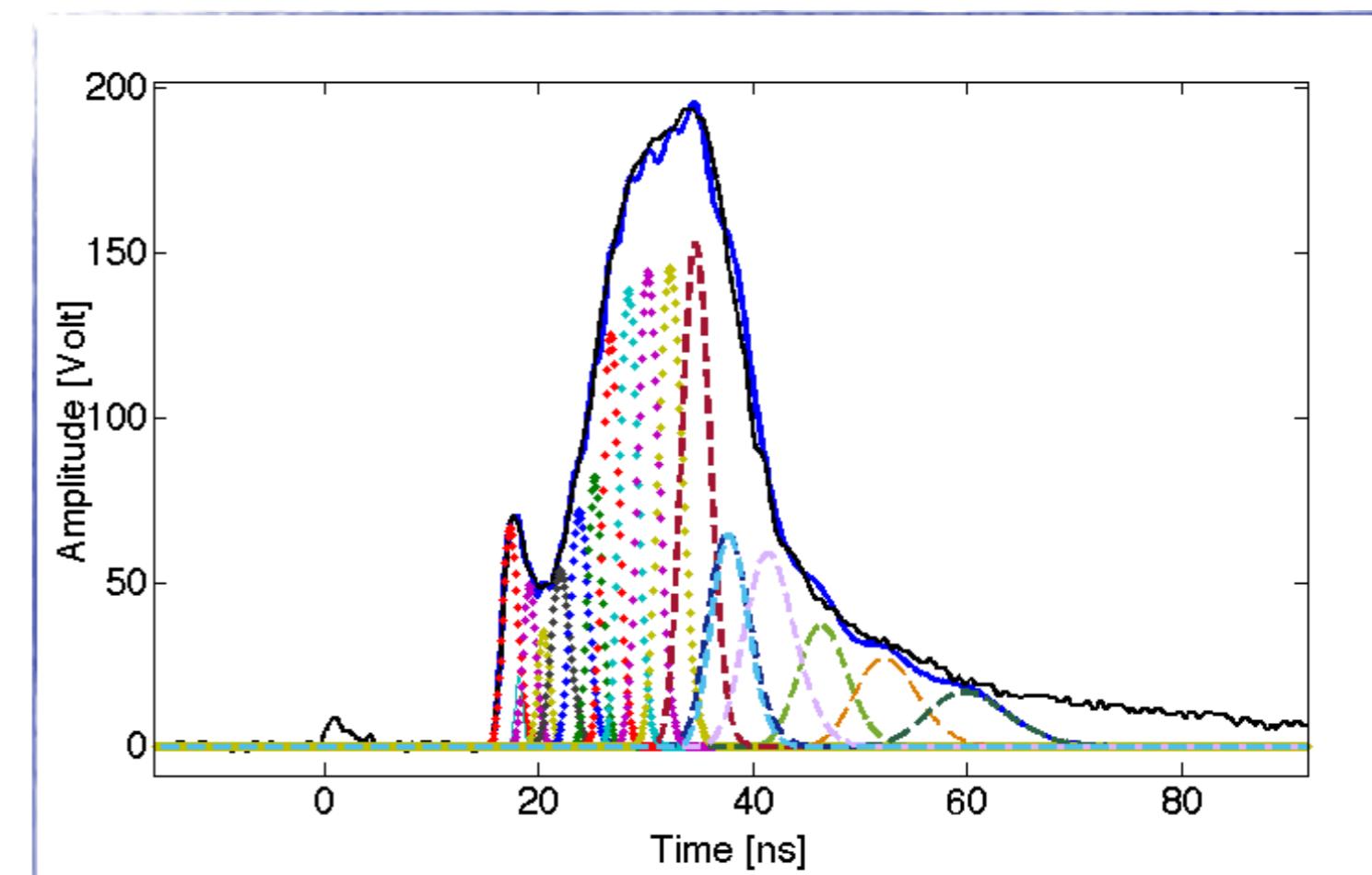
pCVD



SCVD



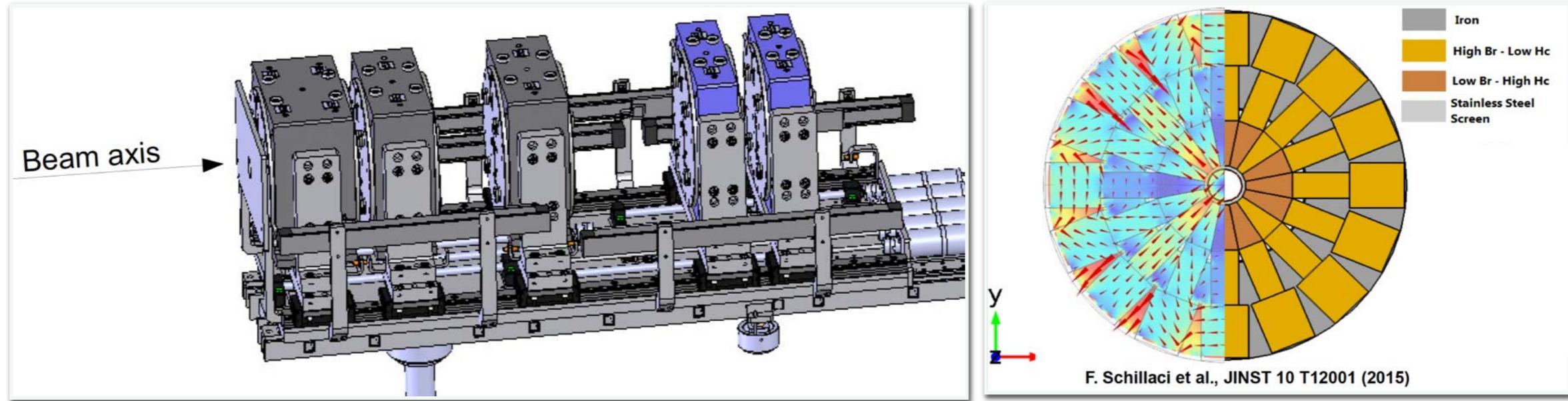
- ▶ *high radiation diamond detector*
- ▶ *linear response for very high intensity (up to 10^9 ppp)*
- ▶ *good time resolution*
- ▶ *excellent signal-to-noise ratio (low noise)*



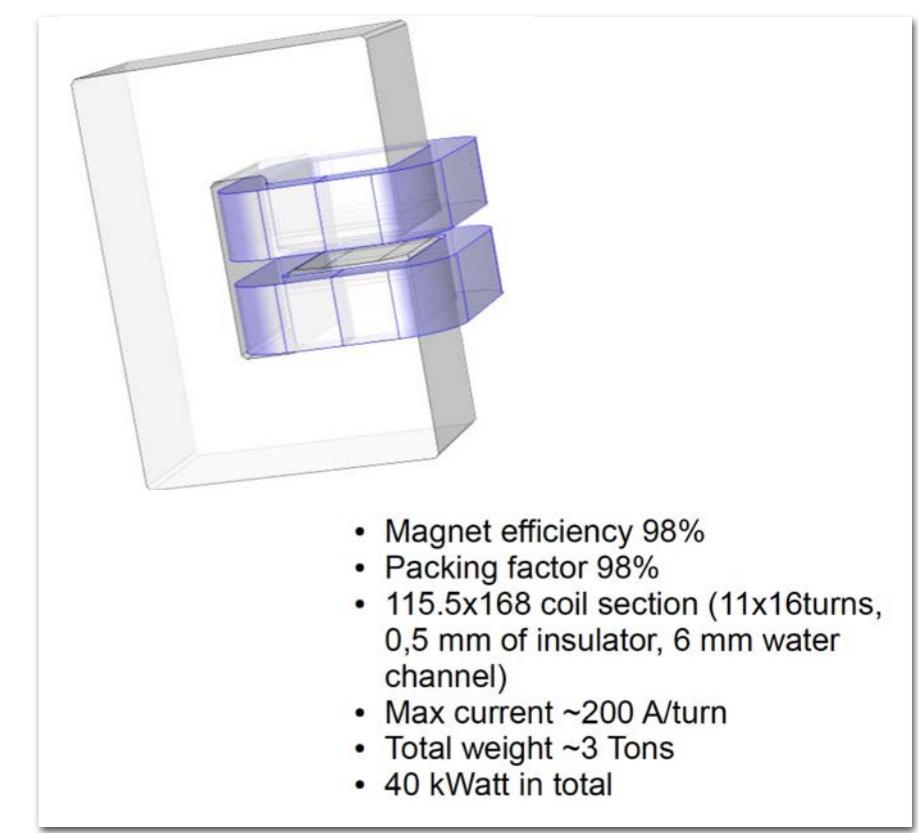
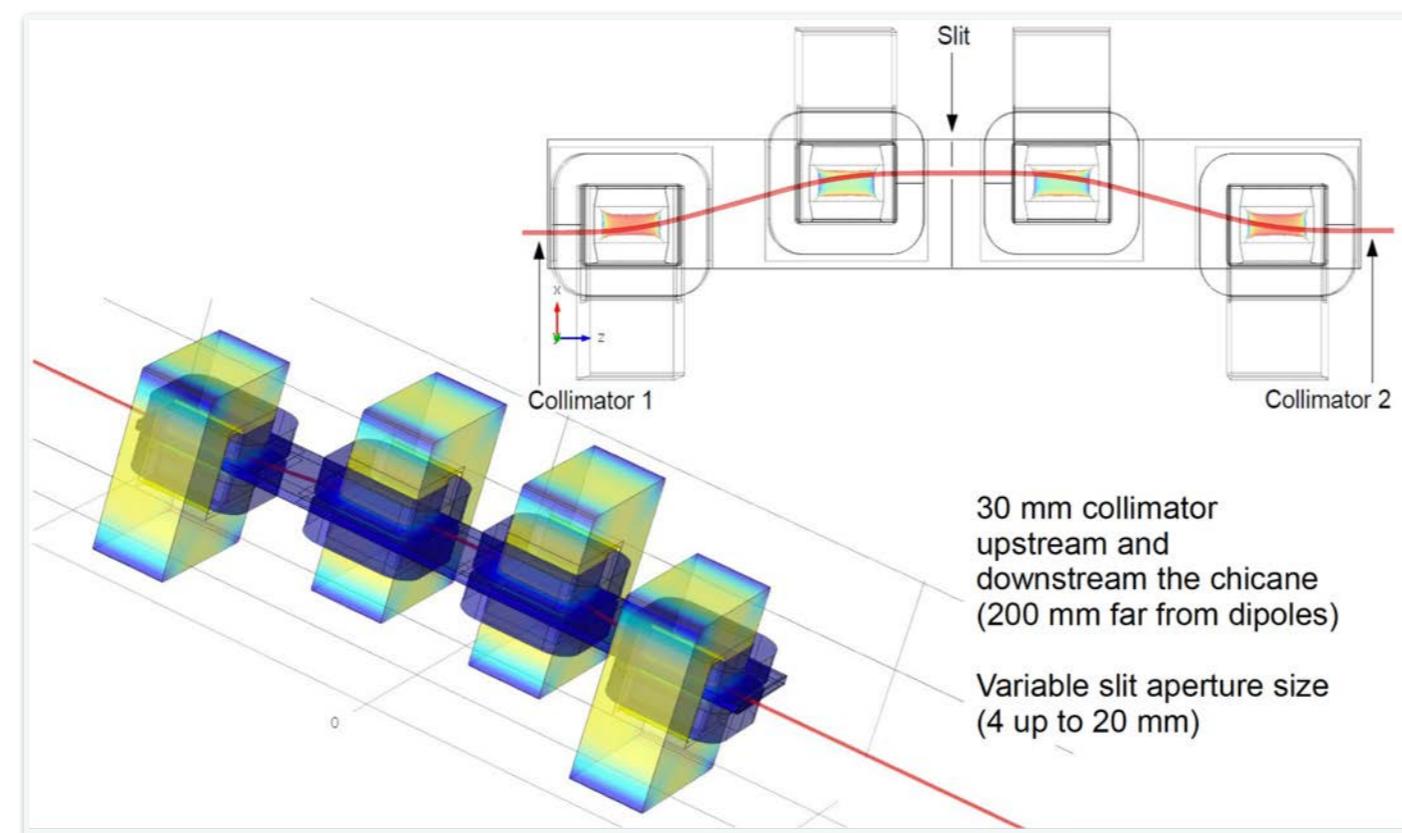
Focusing and Collecting

61

Permanent magnets: Quadropoles



Energy Selector System



Focusing and Collecting

62

Angular divergence = 5° (FWHM)

Transmission efficiency $\sim 12\%$ ($9.2 \times 10^7 H^+$ /bunch)

