Nuclear Physics applications in Medicine: State of the Art

Francesco Tommasino

Dep. Physics, University of Trento
INFN TIFPA

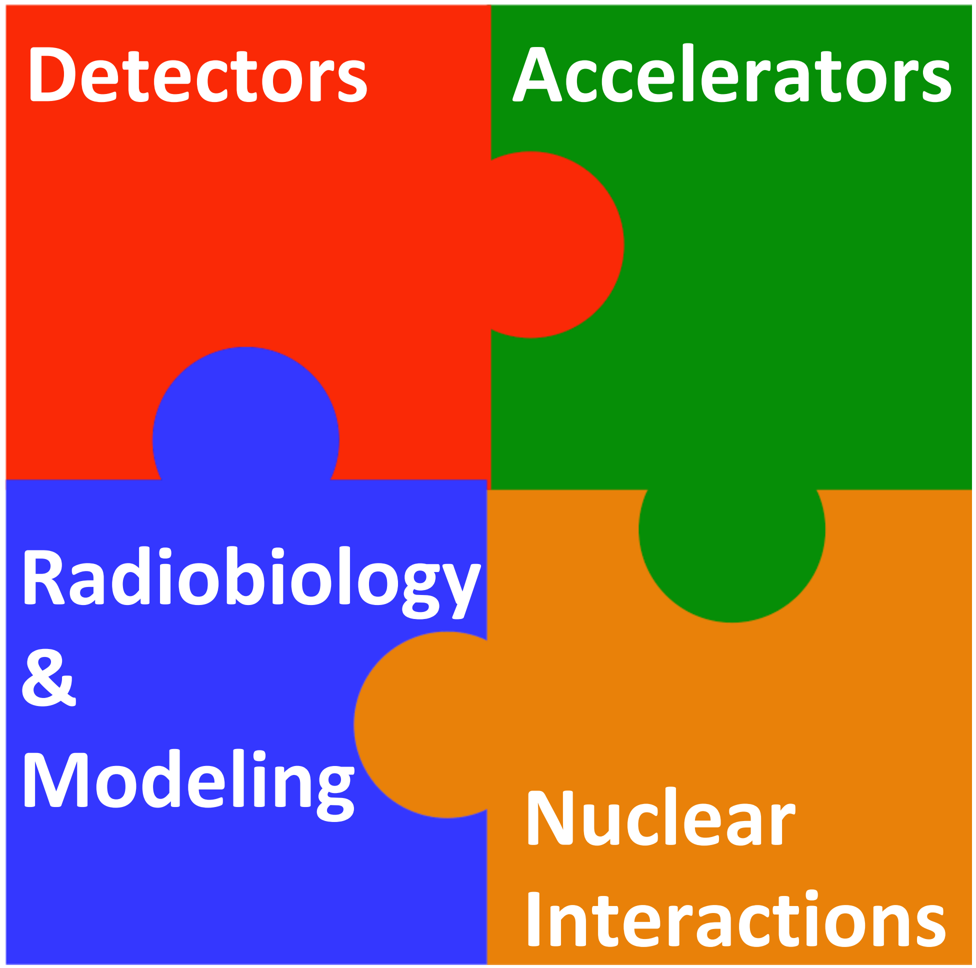
Outline

- Nuclear Physics applications in Medicine: a quick overview

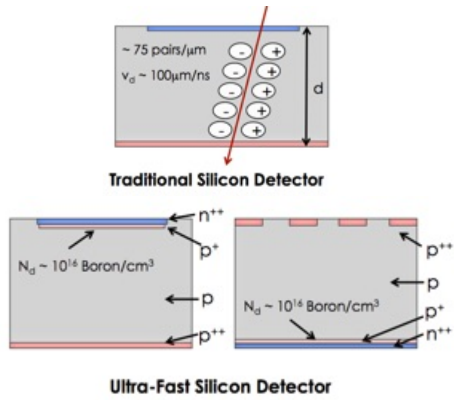
- Charged particle therapy: protons, carbon and more

- What’s next: FLASH radiotherapy

Medical Applications @INFN

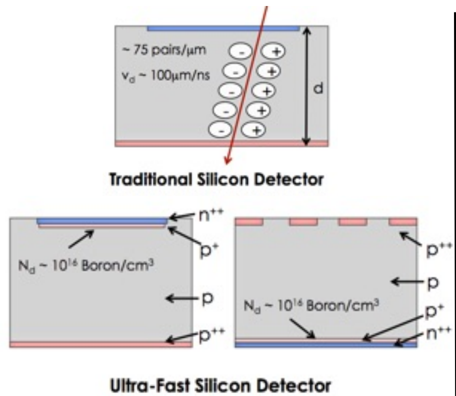


Detectors



- Ultra-fast silicon detectors for monitoring
- Flexible organics Ionizing Radiation dEtectors (FIRE)
- Detectors for range monitoring and particle imaging
- Micro-diamonds for ultra-high dose rates
- Microdosimetry detectors

Detectors



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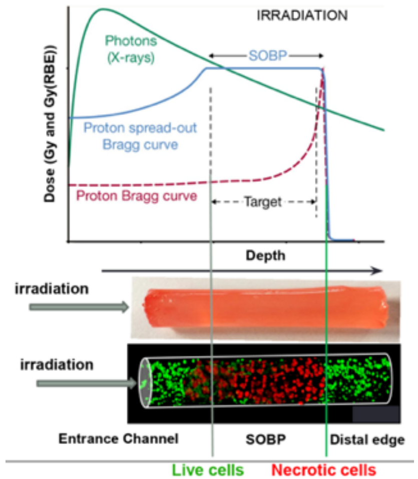
- ELI-Beamlines MEDical and multidisciplinary applications
- Selective Production of Exotic Species (SPES)
- Linear accelerators for VHEE

Accelerators

Radiobiology & Modeling



- Modeling and Verification for Ion beam Treatment planning (MoVe IT)
- MICROdosimetry-based assessment of Biological Effectiveness in Ion Therapy (MICROBE-IT)
- Pre-clinical Experimental and THeoretical studies to Improve treatment and protection by Charged particleS (ETHICS)

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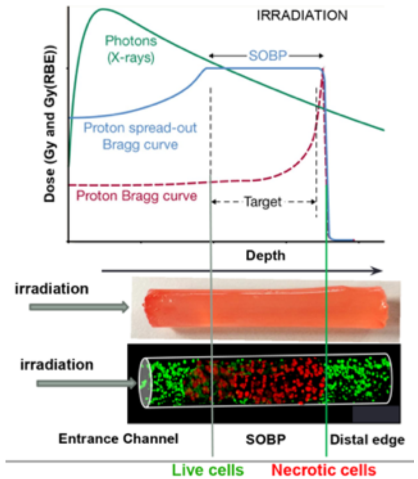

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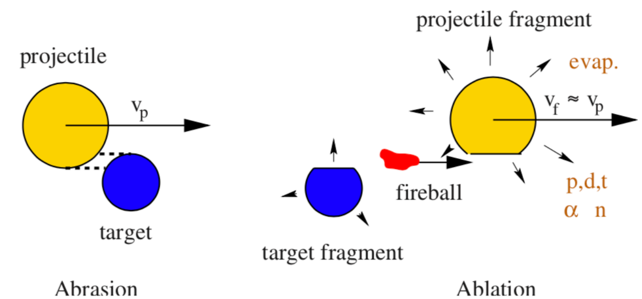
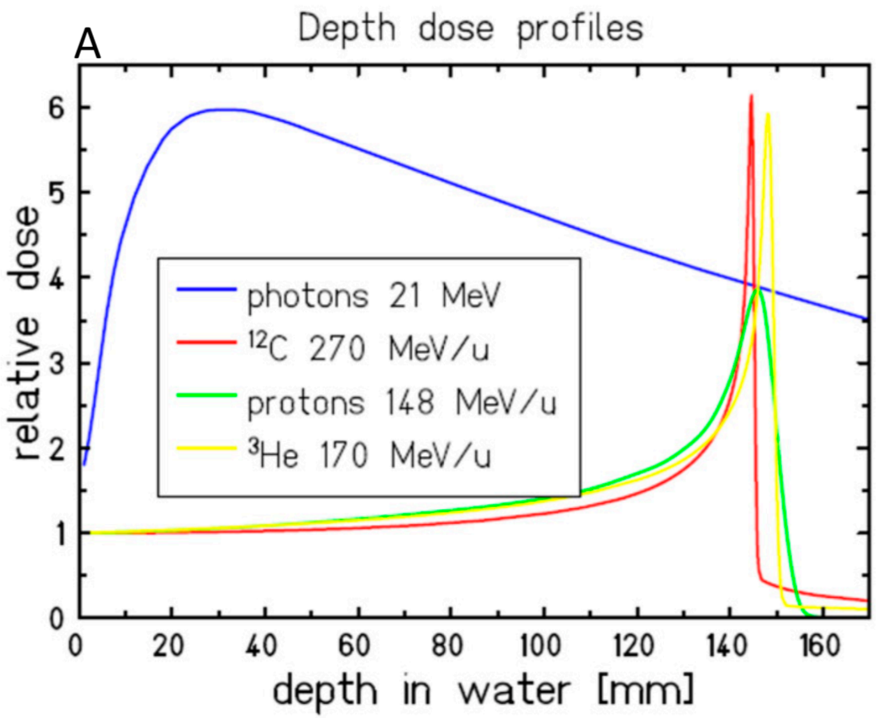
- FragmentatiOn Of Target (FOOT)
- Boron-Neutron Capture Therapy (ENTER-BNCT)
- Nuclear process-driven Enhancement of Proton Therapy UNravEled (NEPTUNE)



Nuclear Interactions

Charged particle therapy

Rationale: exploiting the Bragg peak



Fokas 2009 Bioch Biophys Acta

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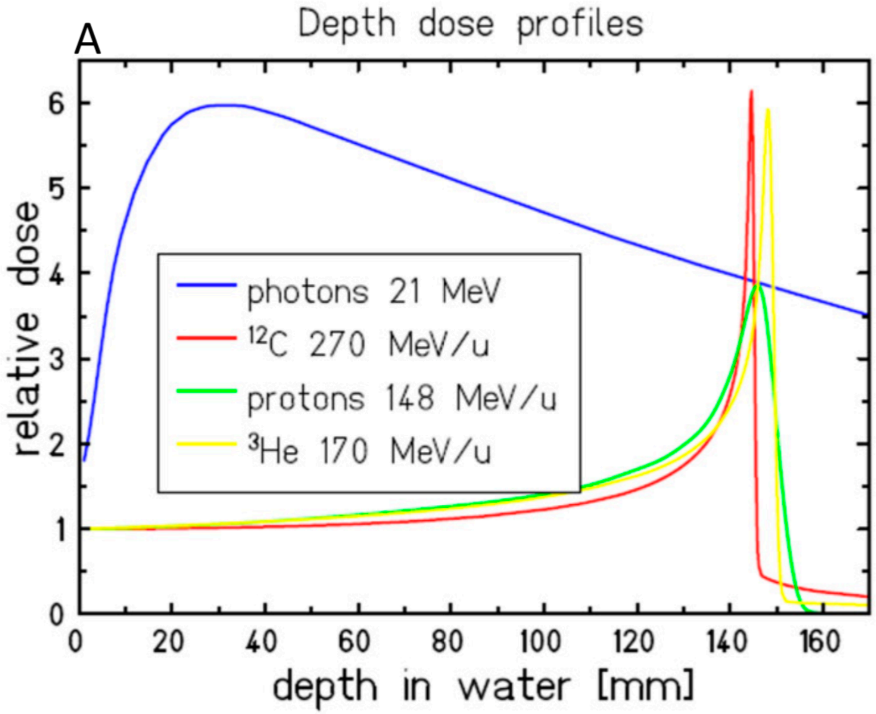

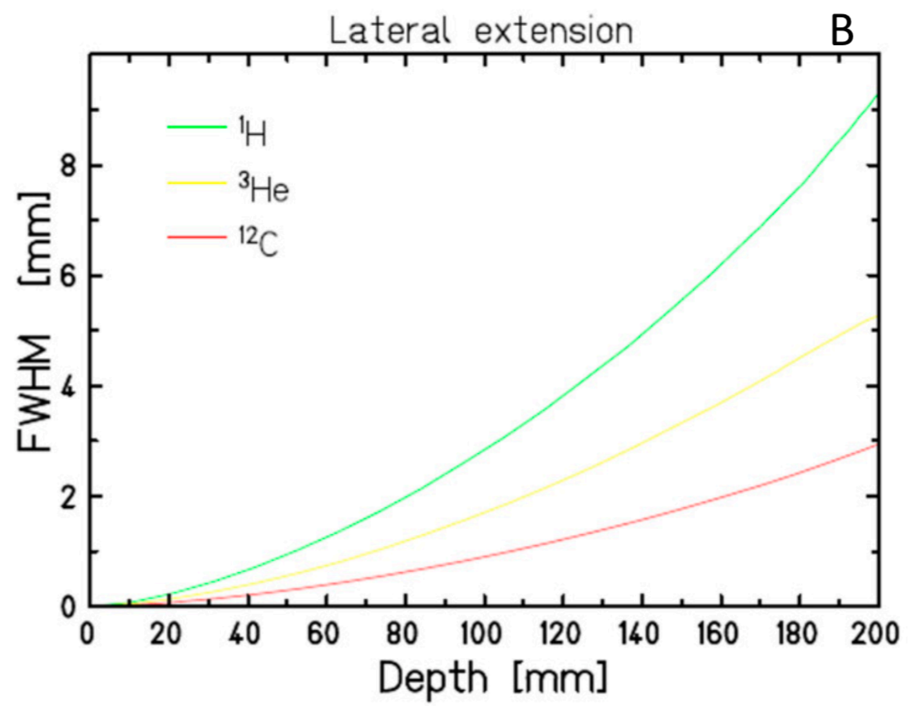

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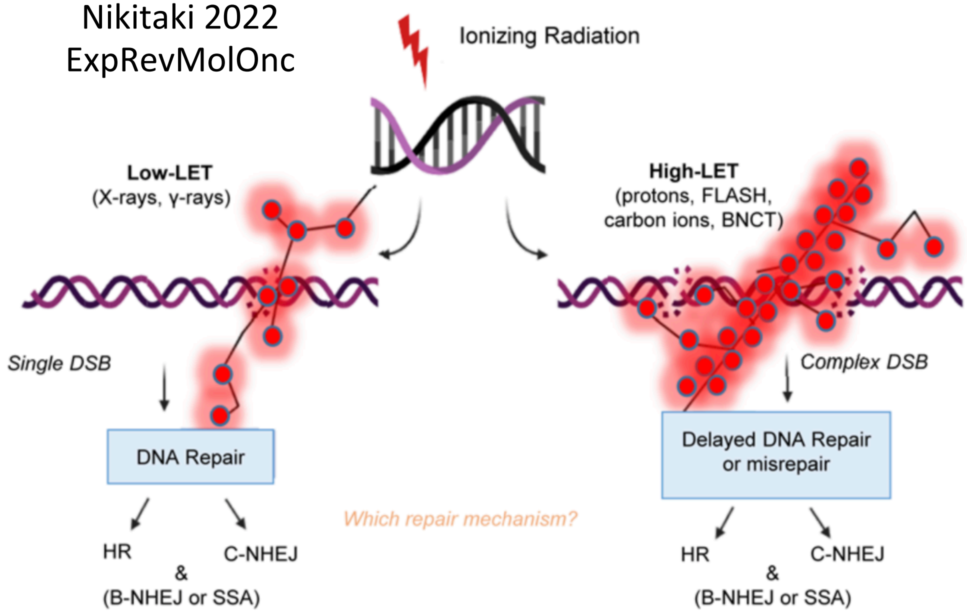
Rationale: exploiting the Bragg peak

Nikitaki 2022
ExpRevMolOnc



$$RBE = \left.\frac{Dose_{Photons}}{Dose_{Ions}}\right|_{Isoeffect}$$

Rationale: exploiting the Bragg peak

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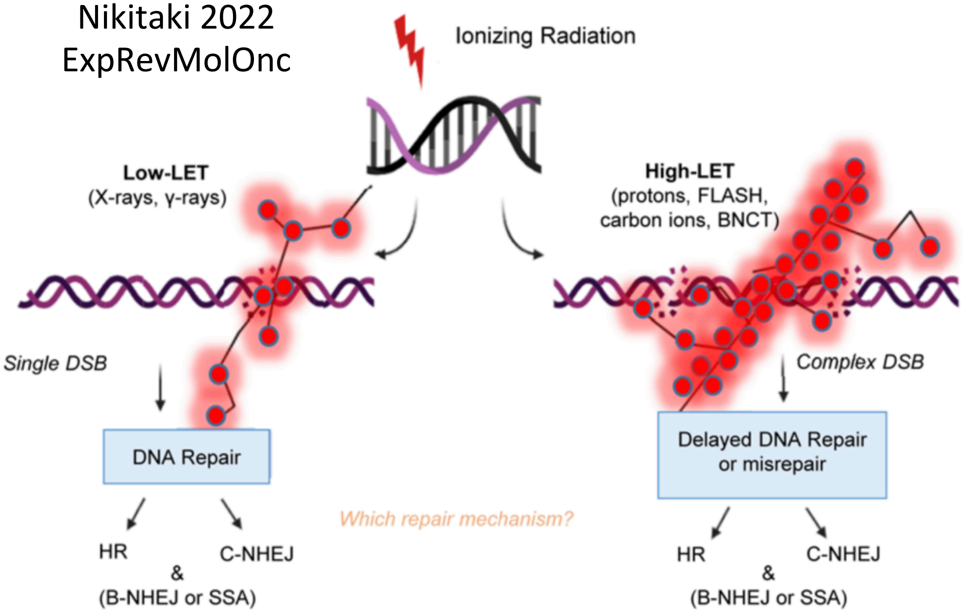

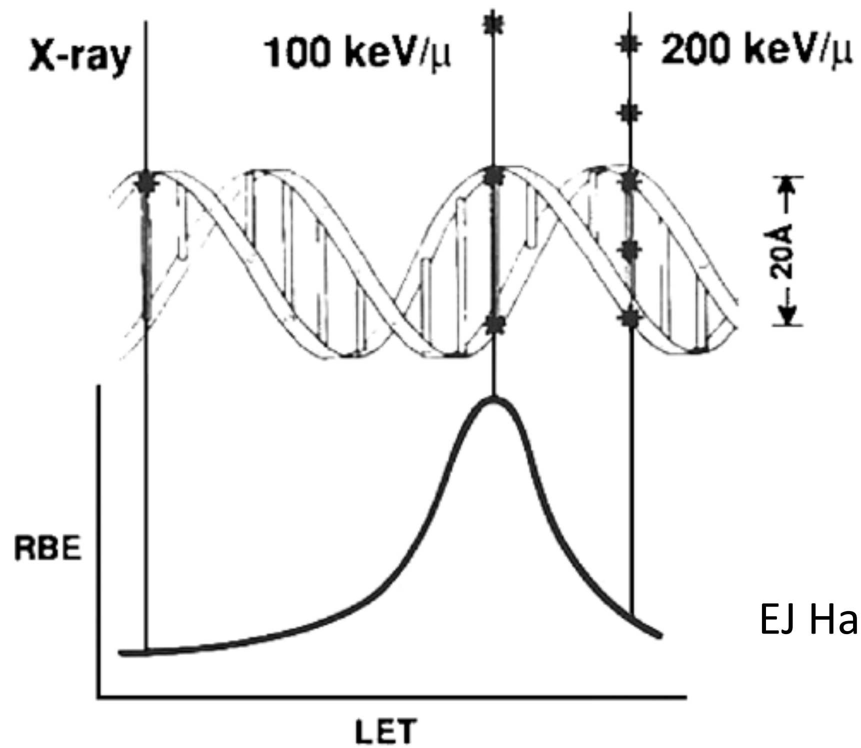

EJ Hall

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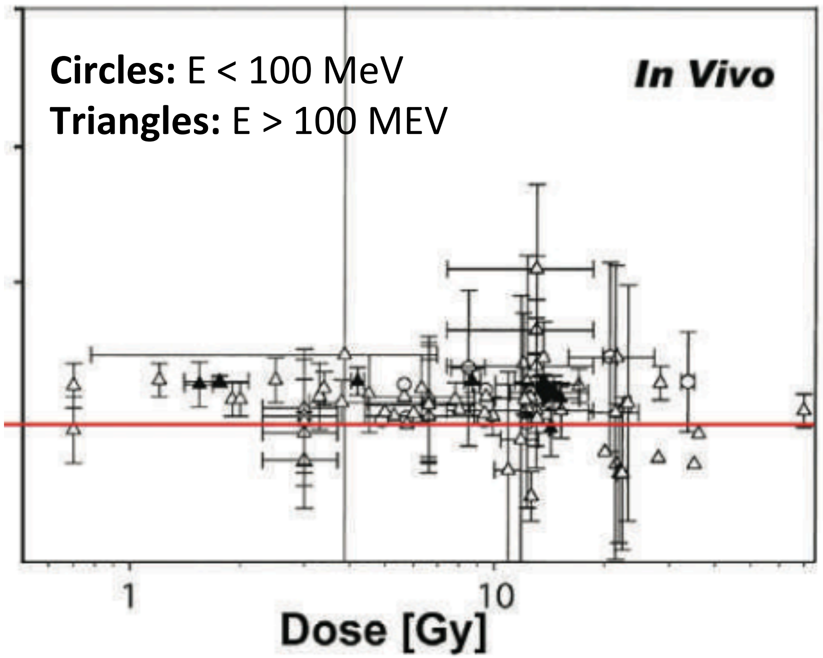
Target fragmentation in proton therapy

Paganetti 2002 PMB



RBE=1.1 in clinical practice

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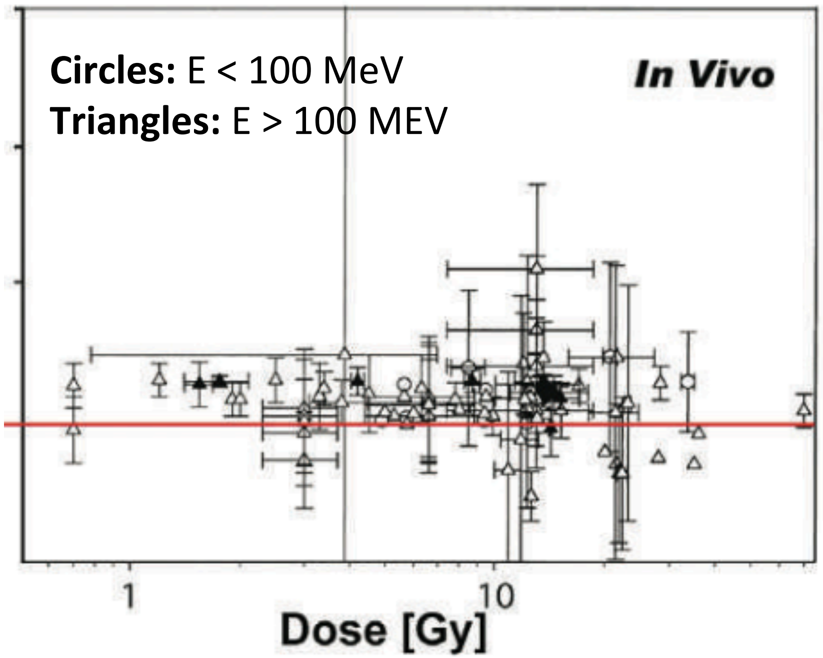

RBE=1.1 in clinical practice

What about target fragments?

↓

Contributions from He, C, Be, O

↓

Low residual energies, high LET -> high RBE

Target fragmentation in proton therapy

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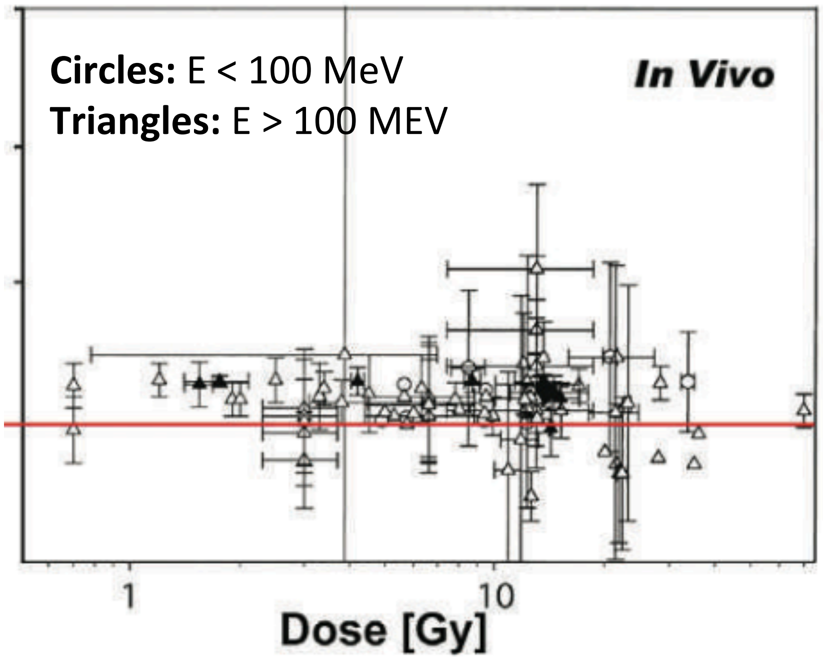

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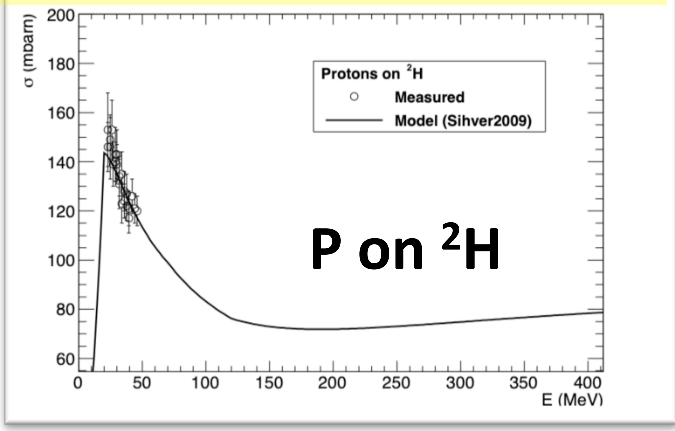

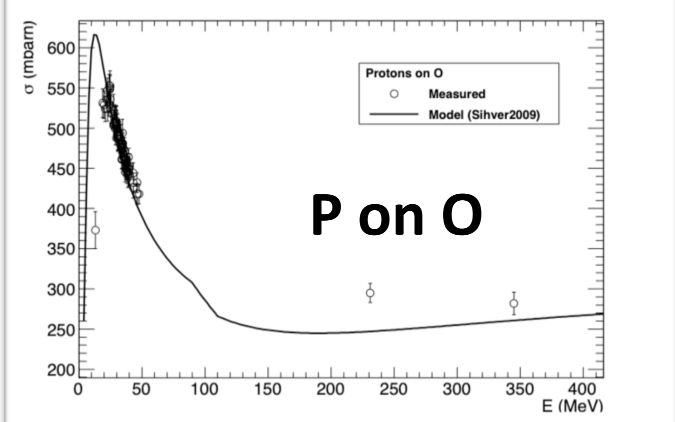

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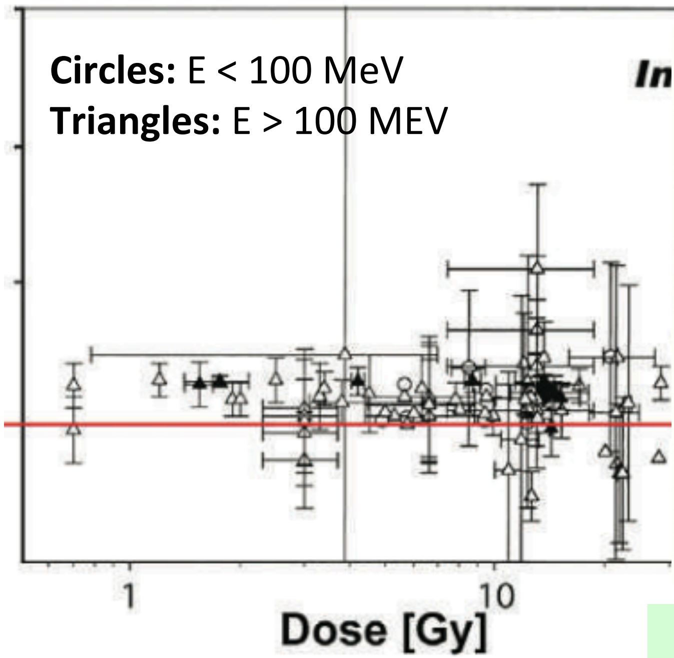
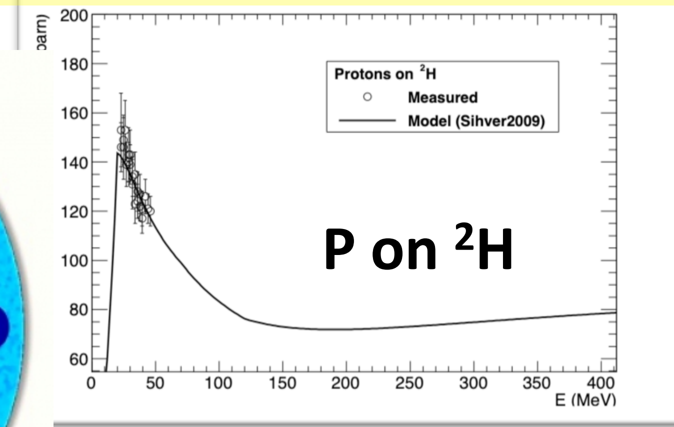
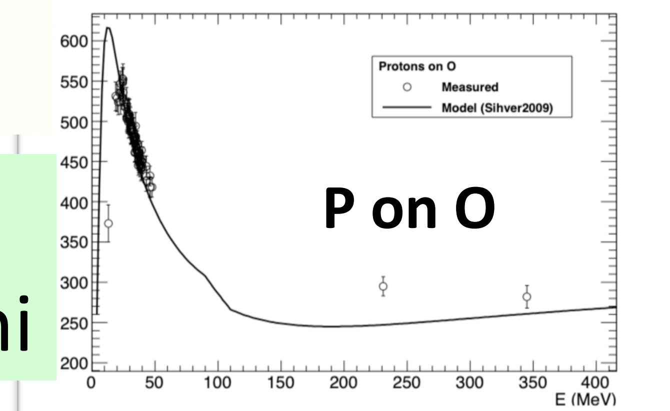


F O O T

Next talk by M. Morrocchi





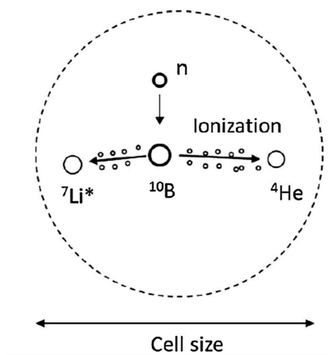
RBE=1.1 in clinical prac

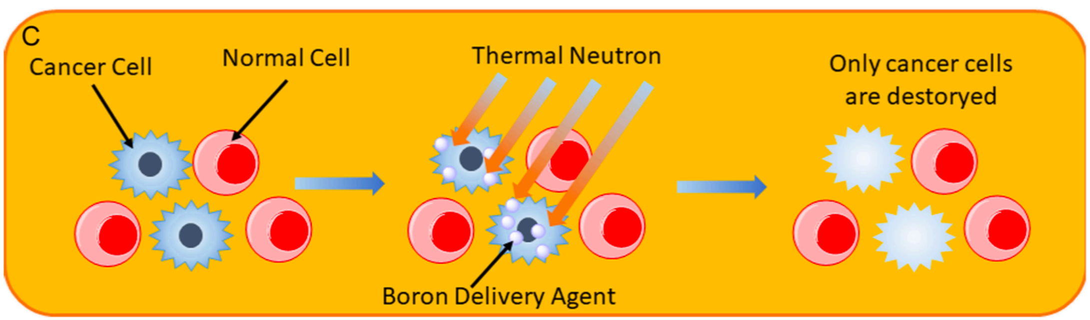
Boron-Neutron Capture Therapy (BNCT)

Rationale

$$\sigma \propto \frac{1}{\sqrt{E_n}}$$

$$n + {}^{10}\mathrm{B} \rightarrow {}^{7}\mathrm{Li}^{*} + {}^{4}\mathrm{He} + 2.31\ \mathrm{MeV} \quad (93.7\%)$$
$$\phantom{n + {}^{10}\mathrm{B} \rightarrow} {}^{7}\mathrm{Li} + {}^{4}\mathrm{He} + 2.79\ \mathrm{MeV} \quad (6.3\%),$$





Seki 2017 Rad Phys Tech
Wang 2022 FONC

→ ENTER-BNCT INFN Pv & Others

Advantages

- Exploiting high LET features
- Low dependence on oxygenation
- Selective targeting of cancer cells

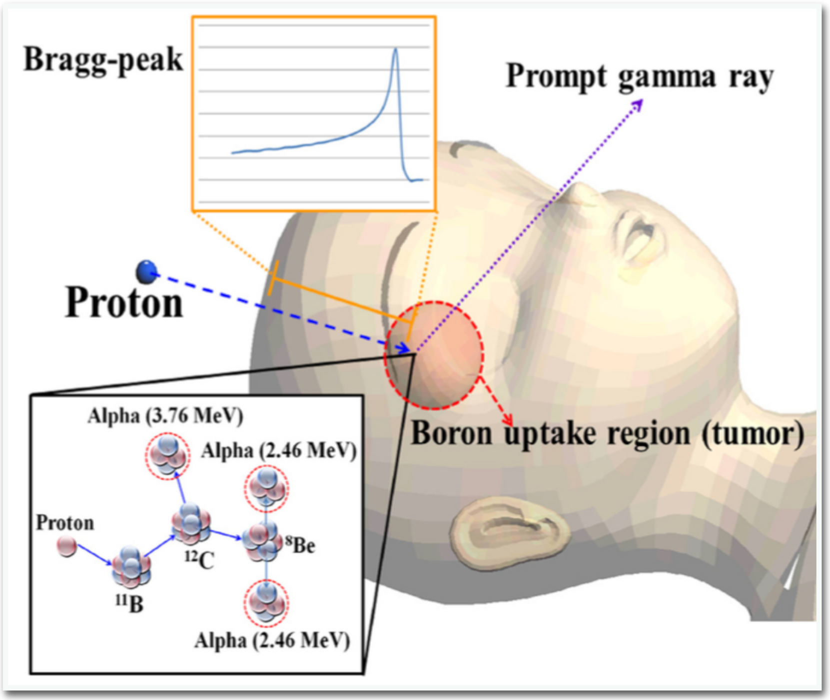
(Current) Limitations

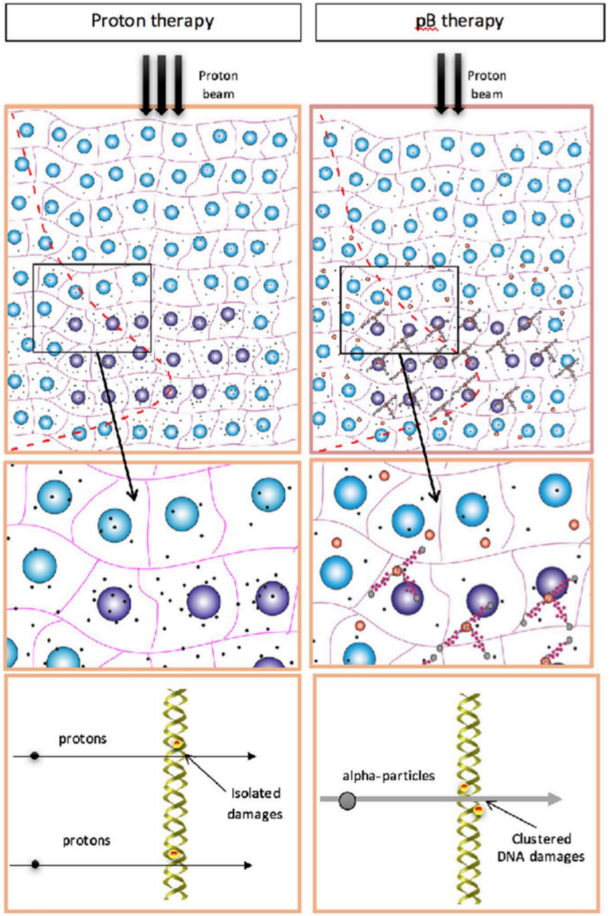
- Finding an efficient and selective boron carrier
- Low number of facilities
- Limited information from past clinical trials

Proton-Boron Capture Therapy

NEPTUNE
Nuclear process driven Enhancement of Proton Therapy UNravEled

$p + {}^{10}B \rightarrow 3\alpha$

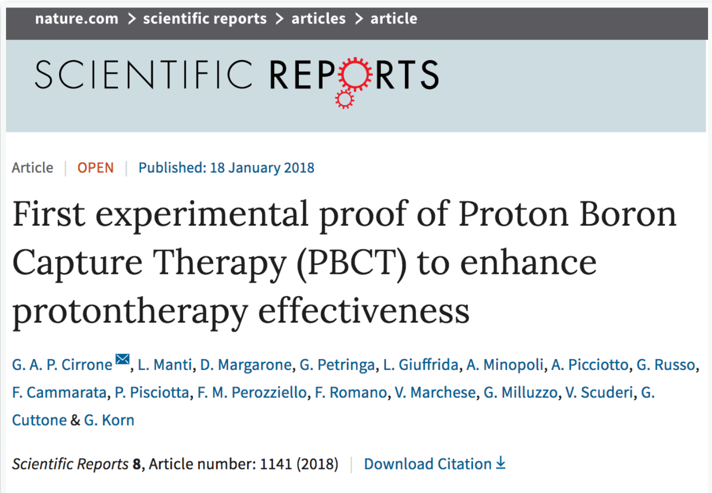




Trento Institute for Fundamental Physics and Applications

NEPTUNE — Nuclear process driven Enhancement of Proton Therapy UNravEled

UNIVERSITÀ DI TRENTO


nature.com > scientific reports > articles > article

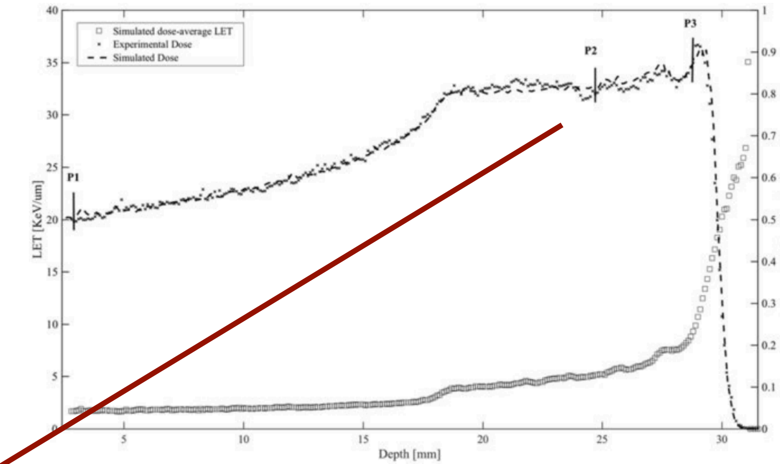
SCIENTIFIC REPORTS

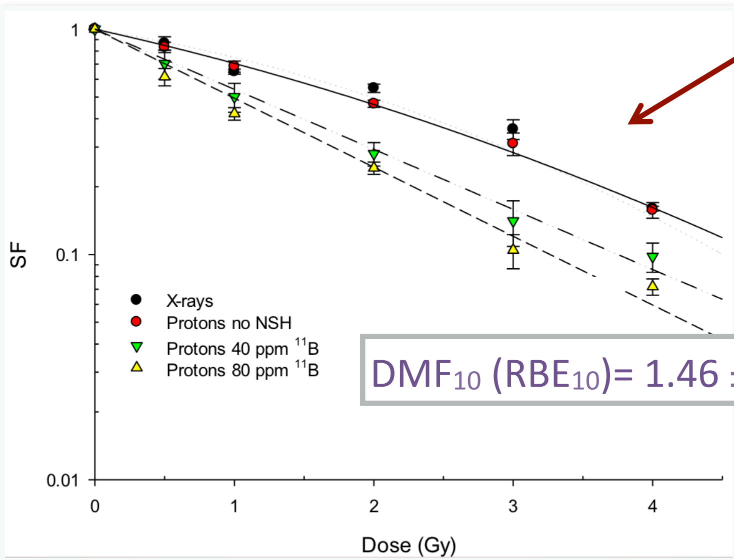
Article | OPEN | Published: 18 January 2018

First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness

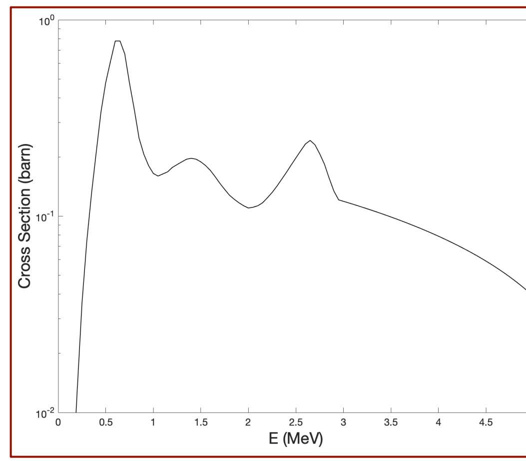
G. A. P. Cirrone, L. Manti, D. Margarone, G. Petringa, L. Giuffrida, A. Minopoli, A. Picciotto, G. Russo, F. Cammarata, P. Pisciotta, F. M. Perozziello, F. Romano, V. Marchese, G. Milluzzo, V. Scuderi, G. Cuttone & G. Korn

Scientific Reports **8**, Article number: 1141 (2018) | Download Citation





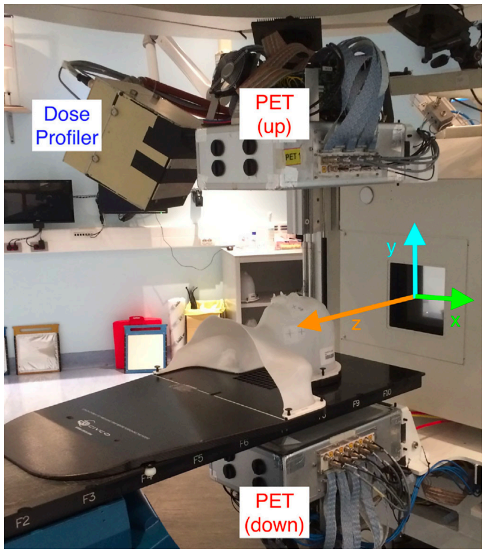
DMF$_{10}$ (RBE$_{10}$)= 1.46 ± 0.12



Workshp Proton-Boron fusion
5-8th Sep 2022 - Catania

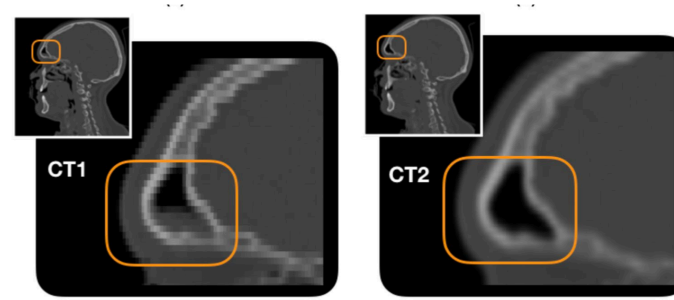
Cirrone 2018 Sci Rep

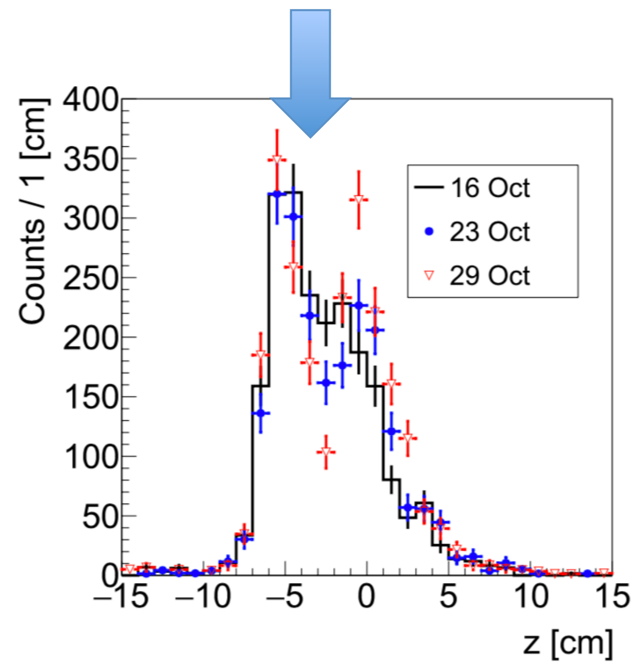
INSIDE: INnovative Solution for In-beam Dosimetry in hadronthErapy

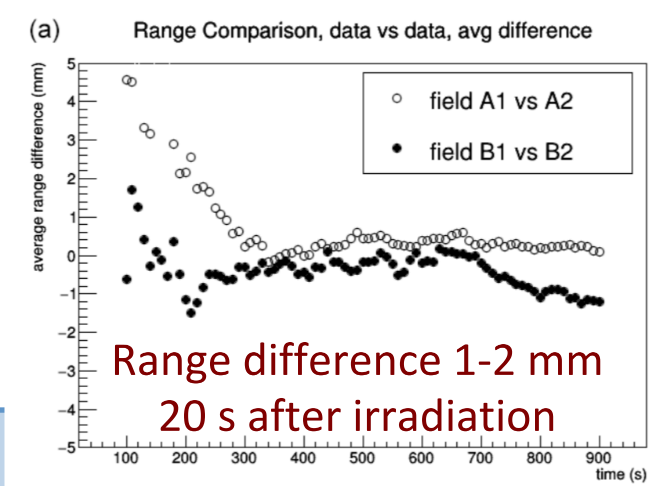


In-beam PET: online range monitoring for proton and carbon ions

Dose Profiler: monitoring for adaptive planning in carbon ion therapy





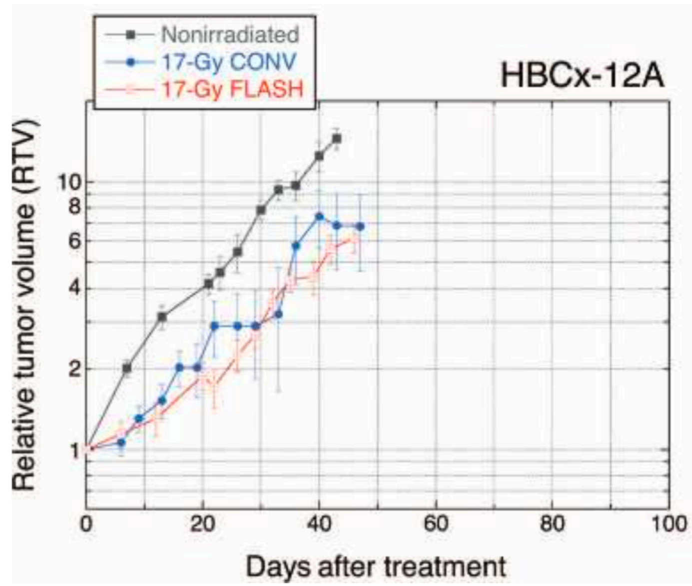


Pennazio 2018 PMB
Fischetti 2020 Sci Rep

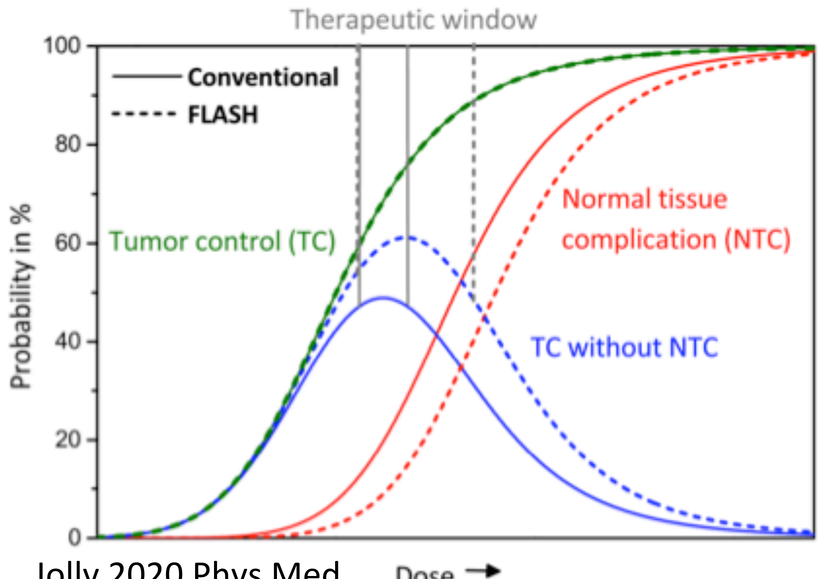
What’s next

Back to the future: ultra-high dose rate radiotherapy

- Late '50s: observation of "protective" effect of very high dose rates
- 2014: renewed interest after paper by Favaudon et al on so-called **FLASH effect**
- Since 2019: exponential increase of publications on the topic

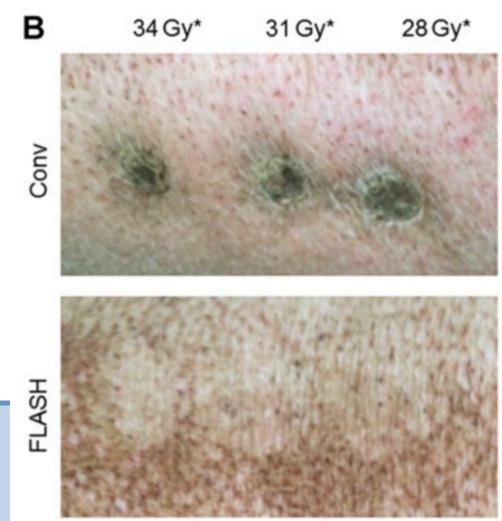


CONV 10^{-2} Gy/s **->** **FLASH** 10^{2} Gy/s

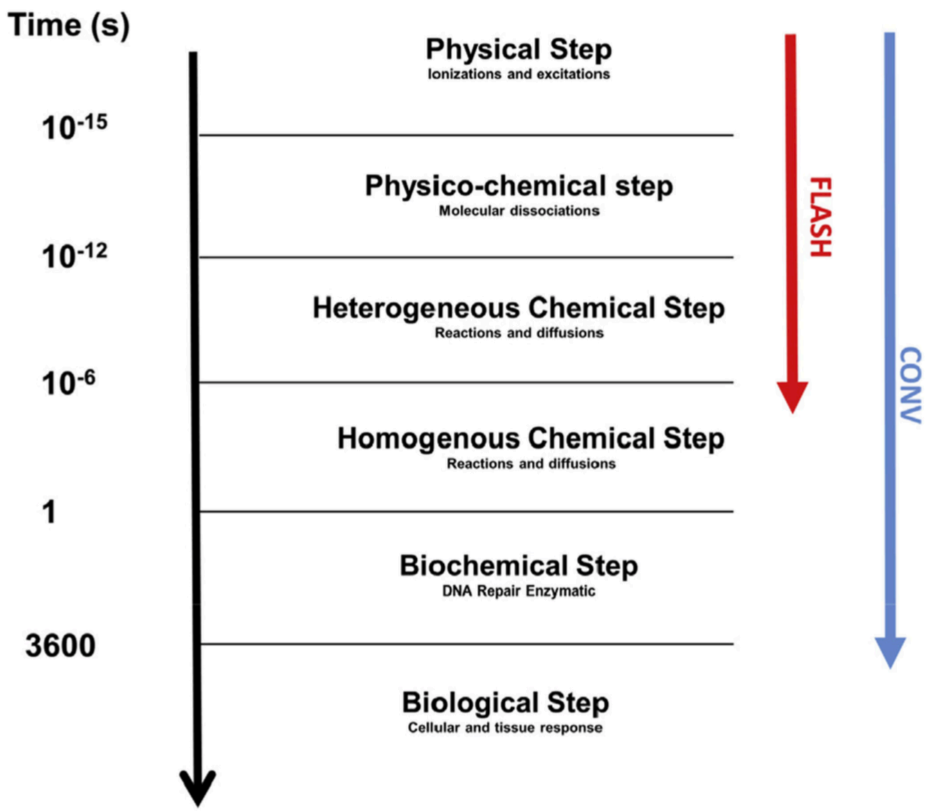


Jolly 2020 Phys Med

Favaudon 2014 Sci Transl Med



Back to the future: ultra-high dose rate radiotherapy



Why the FLASH effect?
Some hypotheses :

- Transient hypoxia
- Radical recombination
- Inter-track effects
- Immune system

Vozenin 2019 Clin Oncol

How to deliver UHDR?

$$\dot{D} = \frac{i_p}{A}\frac{S}{\rho}\left[\frac{Gy}{s}\right]$$

i_p current at ISO ≈2 nA
A ≈ 25 cm2
S/ρ ≈ 5 MeV cm^2/g
Dose rate ≈0.4 Gy/s

Need to increase by about factor 100

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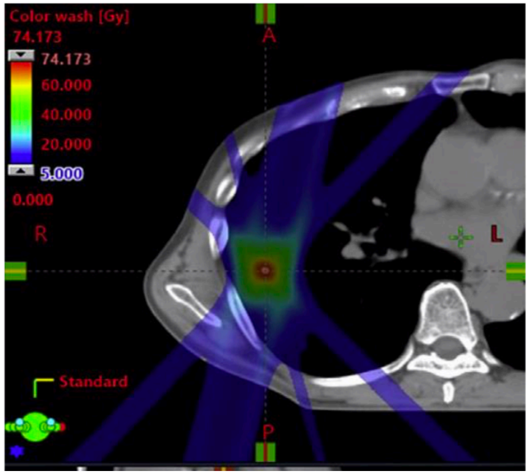
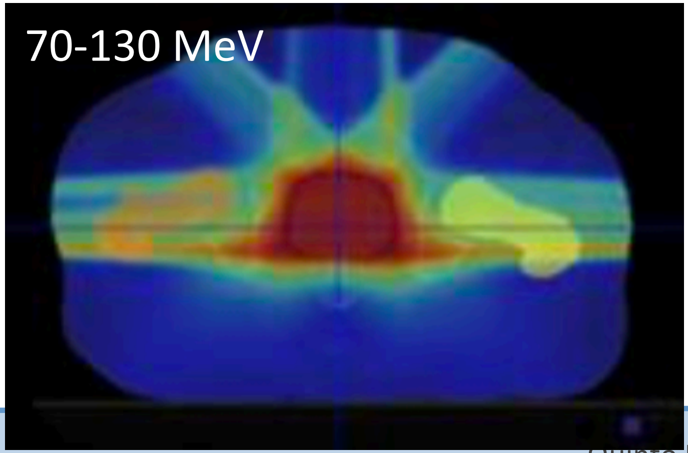
Protons Shot-through



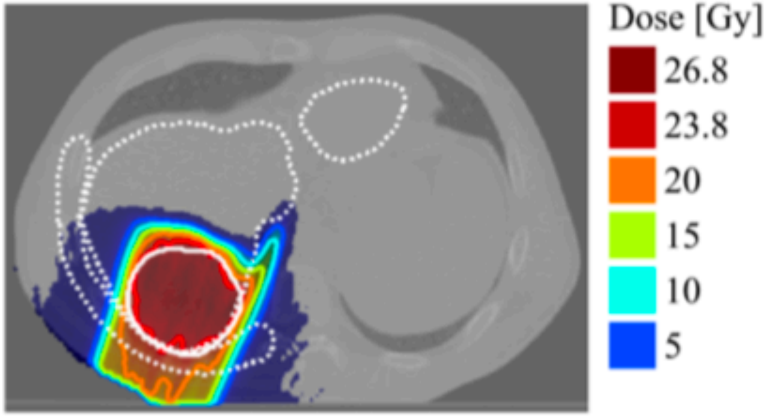
Van Marlen 2020 IJROBP

Very High Energy Electrons



Sarti 2021 FONC

Protons 3D Range Modulator

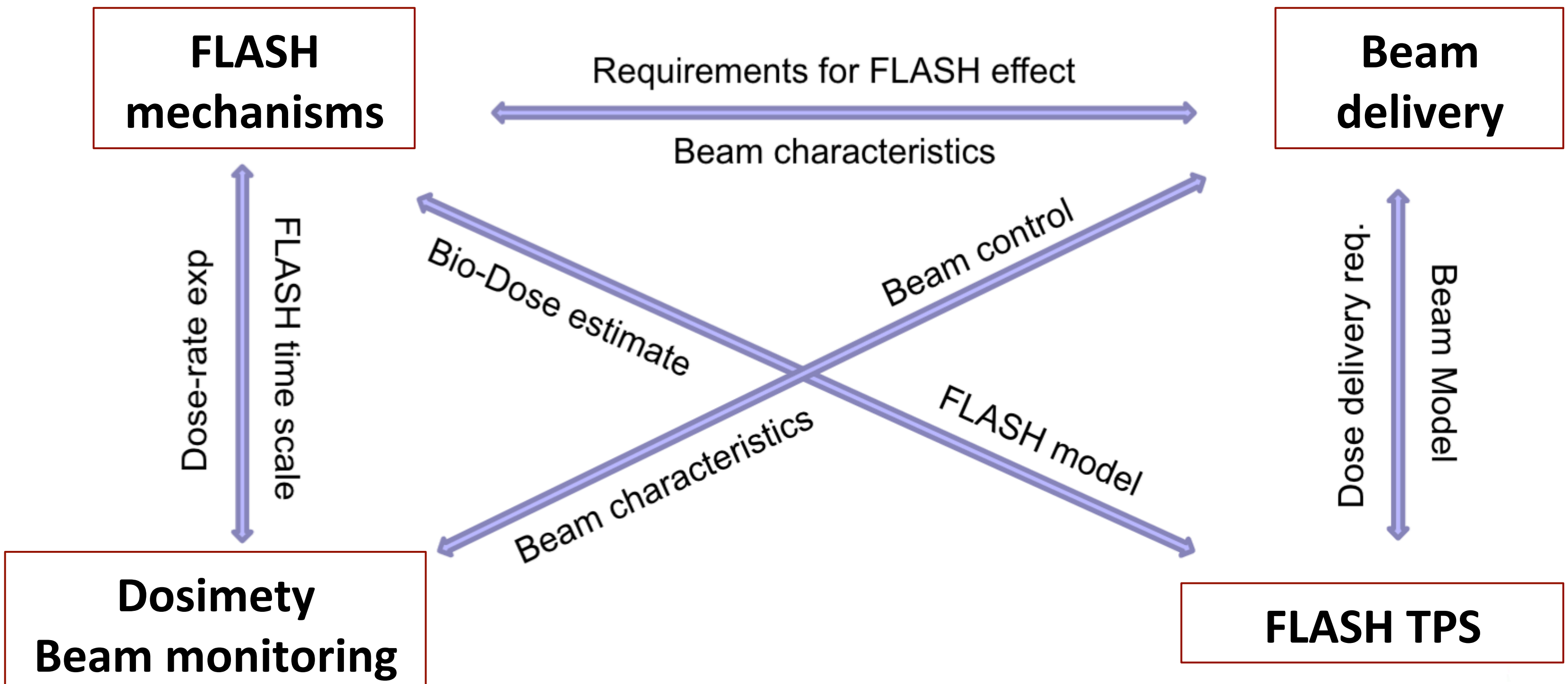


Schwarz 2021 Med Phys

INFN for FLASH: FRIDA

FLASH Radiotherapy with hIgh Dose-rate particle beAms

Call CSN 5
Started in 2022, PI A. Sarti

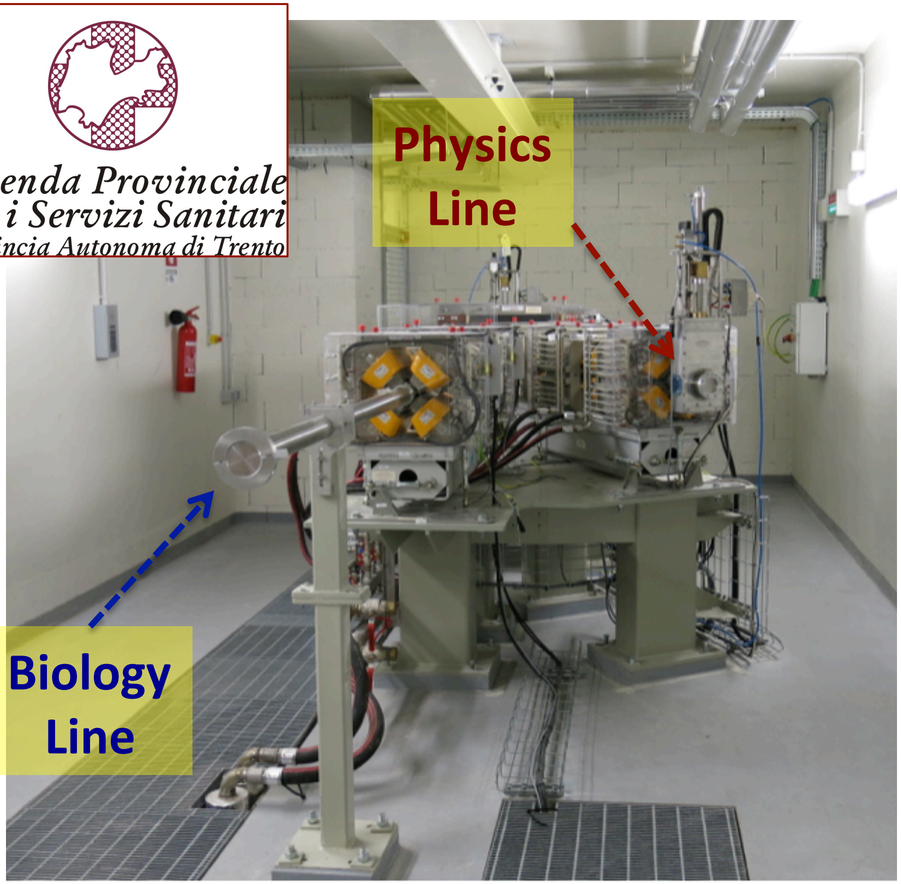


TIFPA
Trento Institute for Fundamental Physics and Applications

UNIVERSITÀ DI TRENTO

Experimental Room, Proton Therapy Center - Trento

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento



<u>Beam availability</u>
Monday-Friday 19:00-22:30
Saturday 8:00-14:00

E range: 70-230 MeV

Beam Current: up to 320 nA

Transport efficiency: 0.1-10%

Pencil beam and large-field irradiation

84 proposals evaluated since 2018 (≈50% INFN)

Beam time requests:
https://www.tifpa.infn.it/sc-init/med-tech/p-beam-research/

Conclusions

- Nuclear physics in medicine: much work done, new avenues opening.

- INFN contributions cover a large spectrum of activities (from accelerators to radiobiology).

- Demanding challenges in front of us: FLASH RT (and more).

- INFN could play a pivotal role in a field getting more and more interdisciplinary and technological.

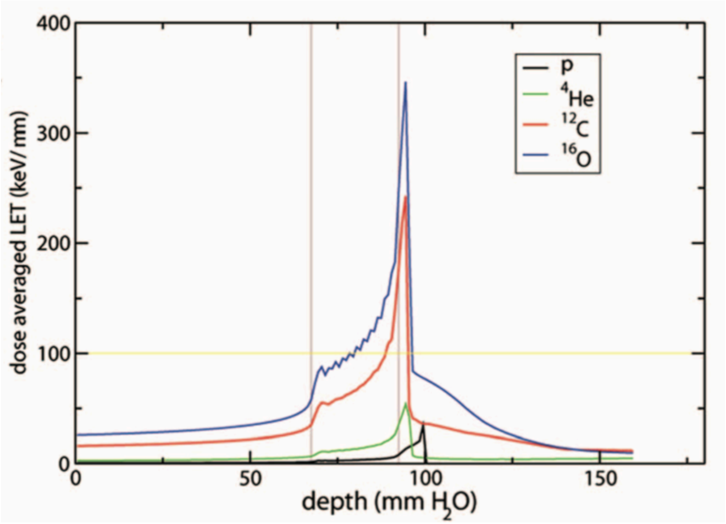
Thank you for your attention

BiMeR
Bio—Medical Radiation physics lab

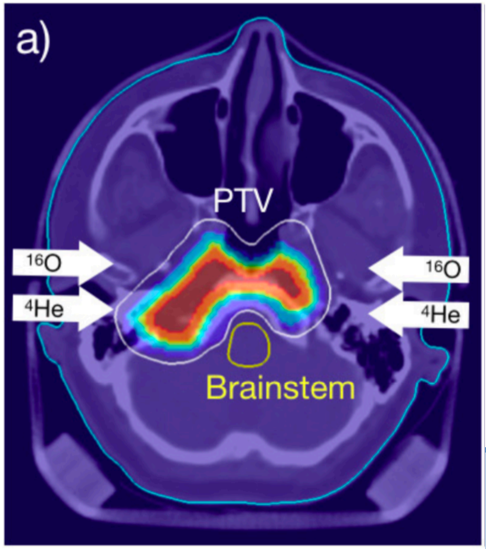
Spare slides

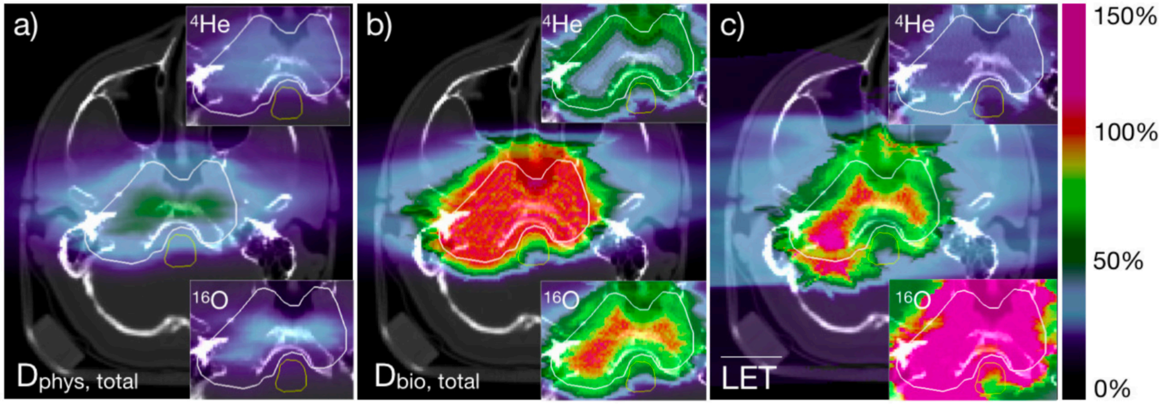
Towards multi-ion therapy

- Different ion species associated with peculiar physical and radiobiological features
- No magic bullet but possibility to exploit that in combined treatments



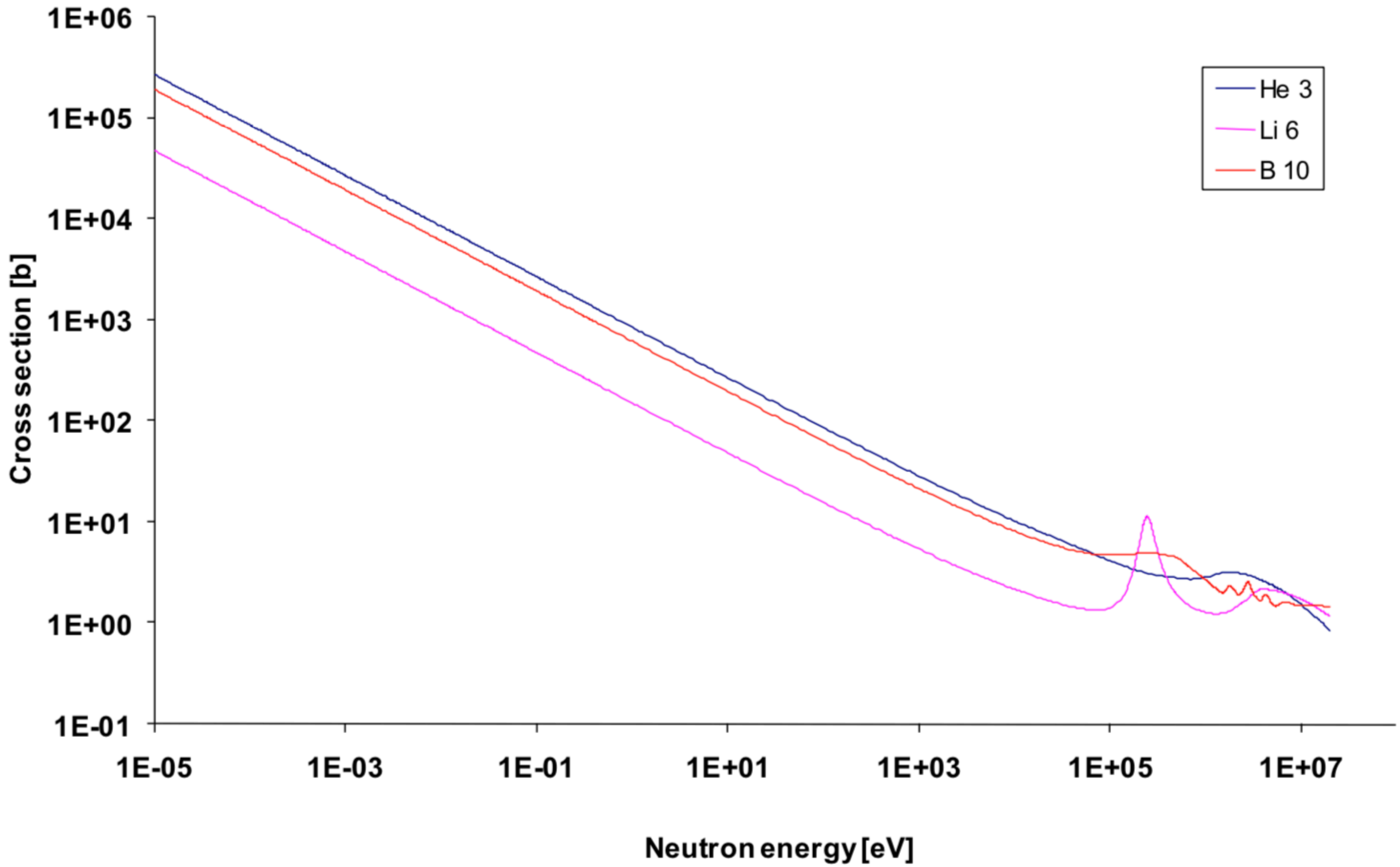
Tommasino 2015 IJPT





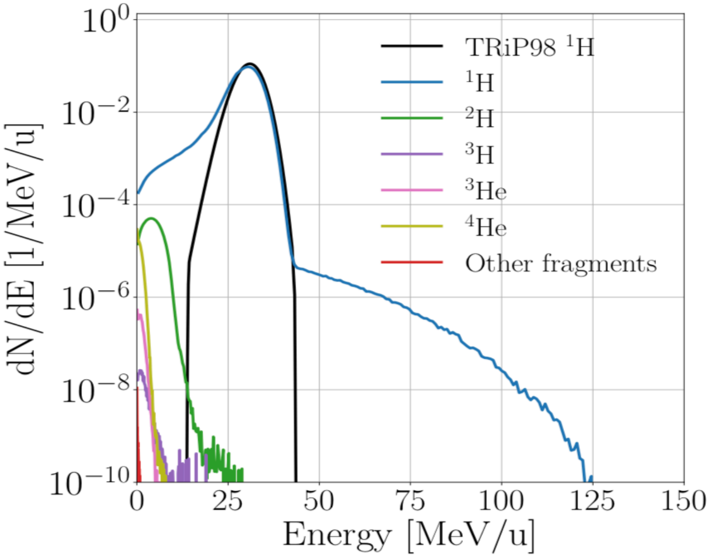
Sokol 2019 PMB

BNCT: Neutron Capture Cross Section



Target fragments: which biological impact?

MoVe IT



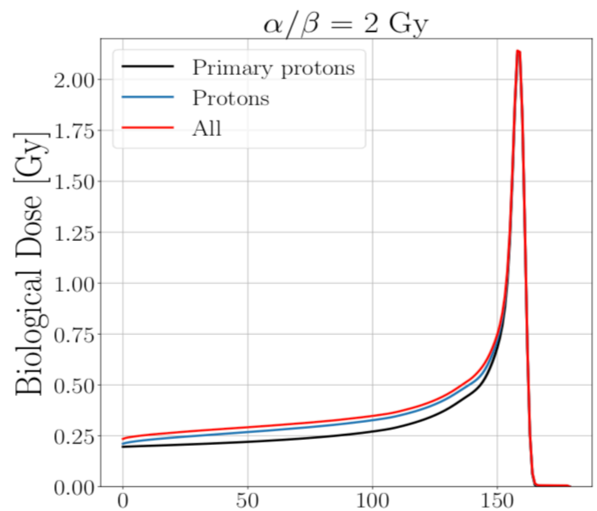
$$\bar{\alpha} = \left(\sum_l w_l \frac{dE}{dx}(l)\right)^{-1} \sum_l w_l \frac{dE}{dx}(l)\alpha_l$$

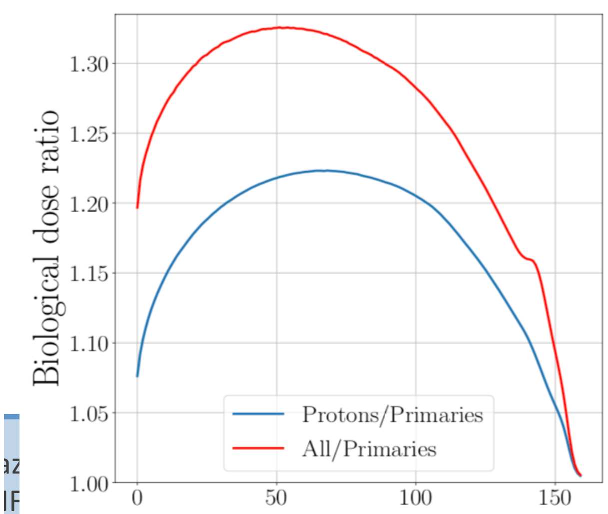
$$\sqrt{\bar{\beta}} = \left(\sum_l w_l \frac{dE}{dx}(l)\right)^{-1} \sum_l w_l \frac{dE}{dx}(l)\sqrt{\beta_l}$$

$$w_l = \frac{\mathrm{d}N}{\mathrm{d}E}(B_i, z_h, T, E) N_{spot}(B_i, x_i, y_i)\zeta_{ik}$$

$$Survival = e^{-(\alpha D + \beta D^2)}$$

Bellinzona
2021 Cancers





FOOT

The "standard" paradigm

<u>1 Gy γ-rays in one nucleus:</u>

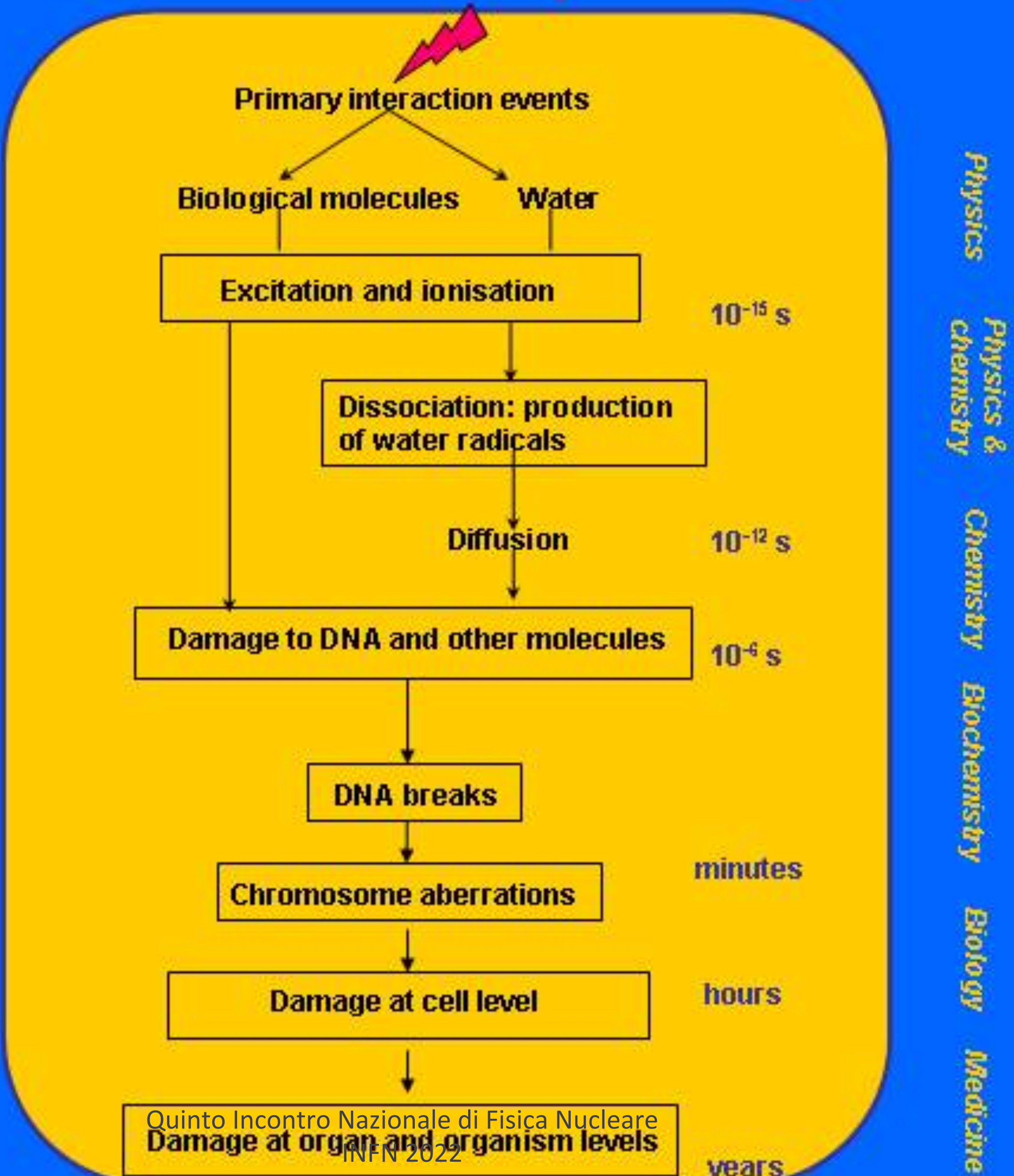
≈ 100,000 ionizations
(≈ 2,000 in the DNA)

≈ 40 DNA DSBs,
≈-1 "complex lesion"

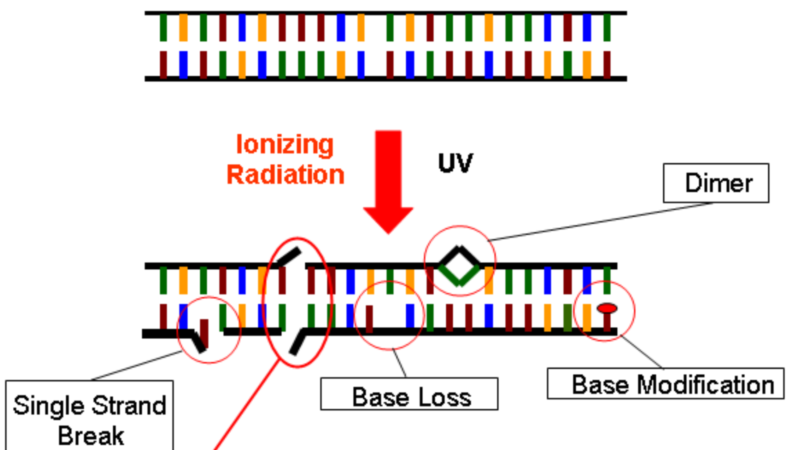
≈ 0.5-1 chromosome aberrations

≈ 0.5-1 lethal lesions
≈ 10^{-5} HPRT mutations
≈ 10^{-5} neoplastic transformations

<< 10^{-5} cancers



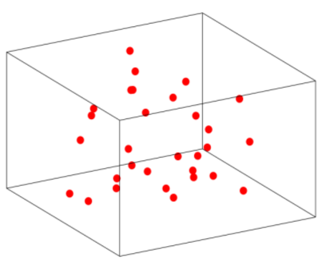
LET and DNA damage



- the DNA **Double Strand Break (DSB)** is considered the type of lesion most directly related to cell killing
- different radiation qualities produce the same spectrum of DNA lesions
- **BUT** the distribution of lesions inside the target can be very different

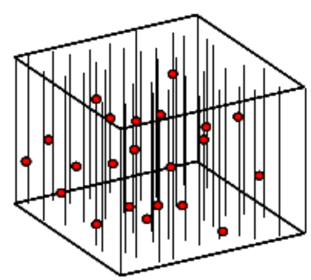
Photons
x-rays

Random
DSB distribution



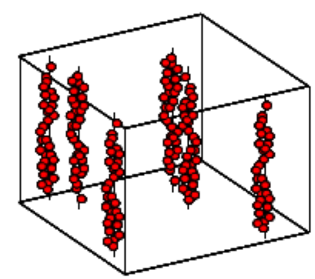
^{12}C Low LET
200 MeV/u, ≈ 16 keV/μm

Random
DSB distribution
(photon-like)

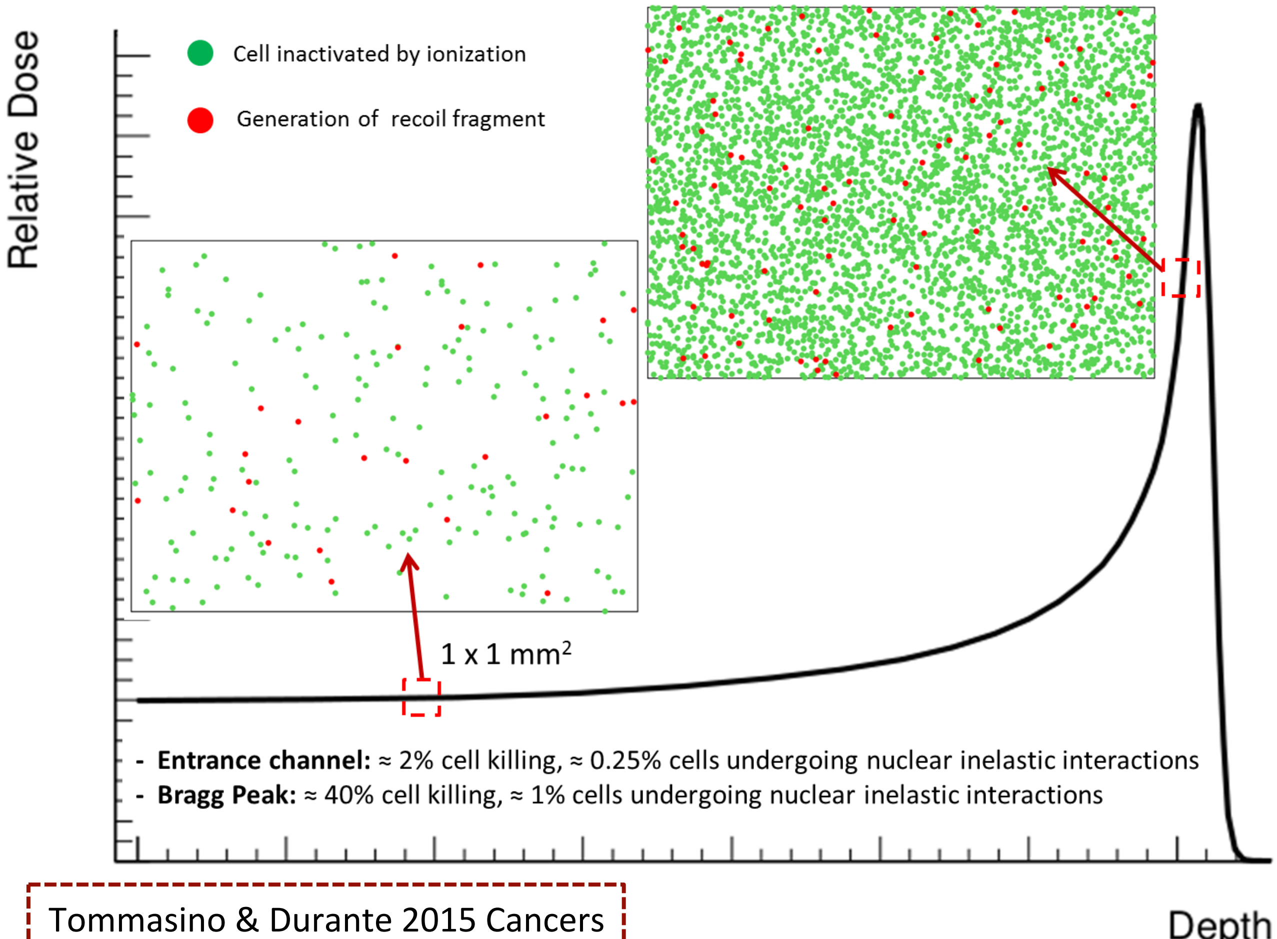


^{12}C High LET
1 MeV/u, ≈ 690 keV/μm

Non-random
DSB distribution
(RBE>>1)



Target fragmentation in proton therapy



Tommasino & Durante 2015 Cancers

About 10% of biological effect in the entrance channel due to secondary fragments

↓

Largest contributions of recoil fragments expected from **He, C, Be, O, N**

↓

Heavy fragments have low residual energies and release low doses -> high RBE

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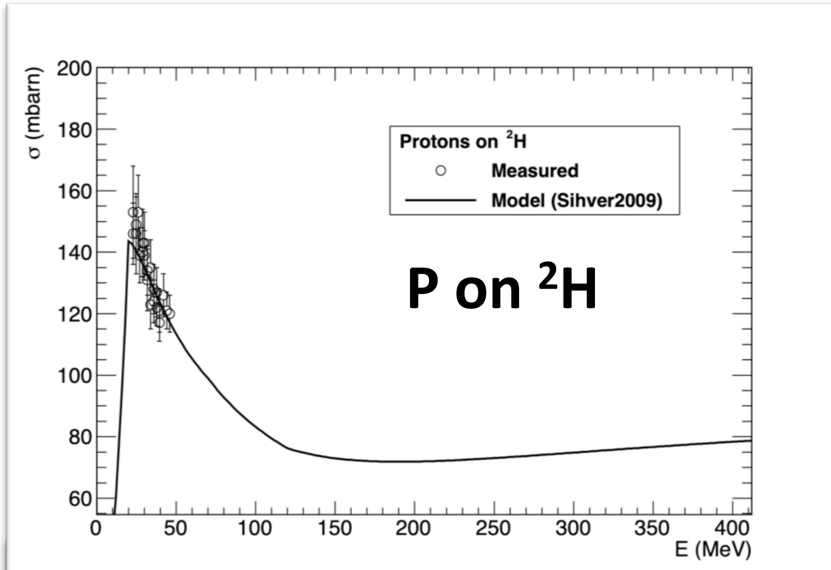
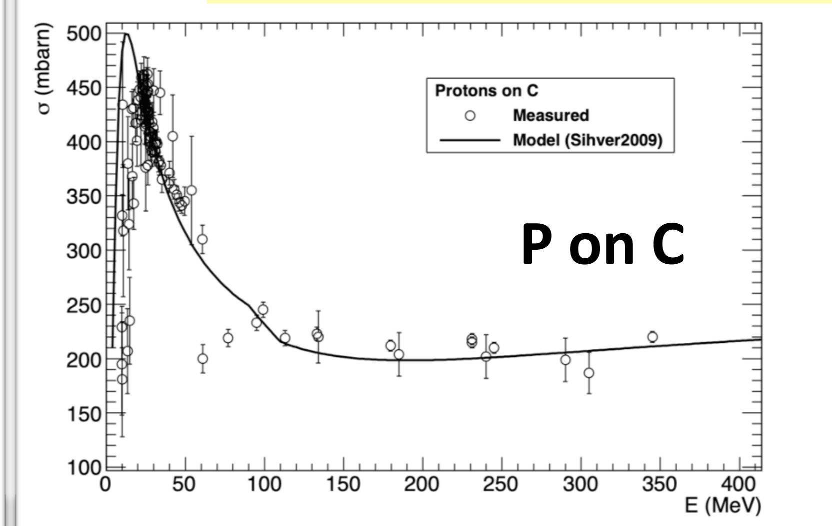
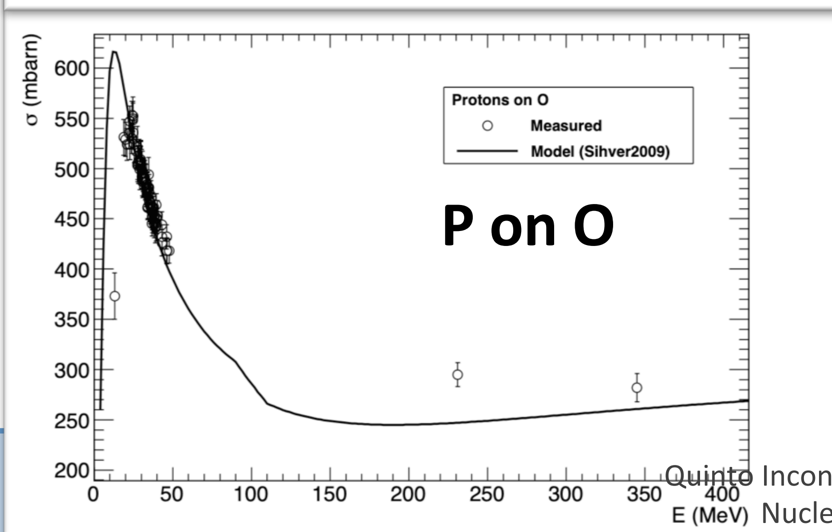
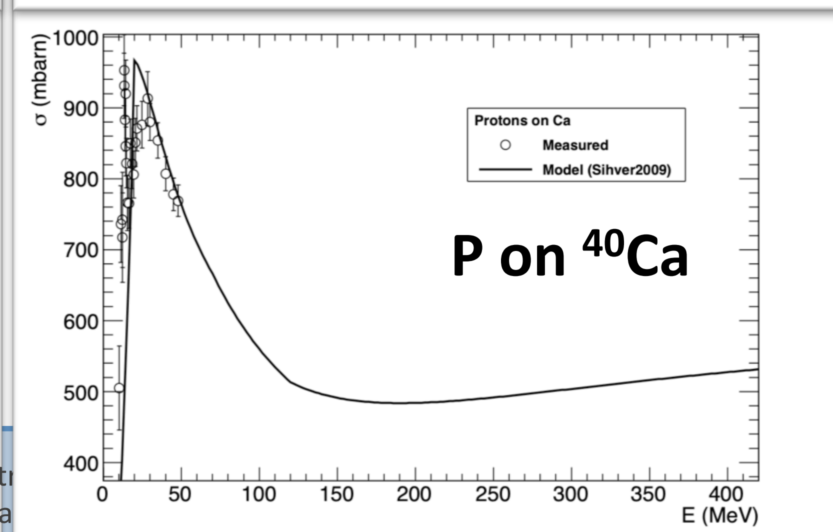
Cross sections: what's on the market

Experimental data taken from Carlson 1996 Atomic Data and Nuclear Data Tables

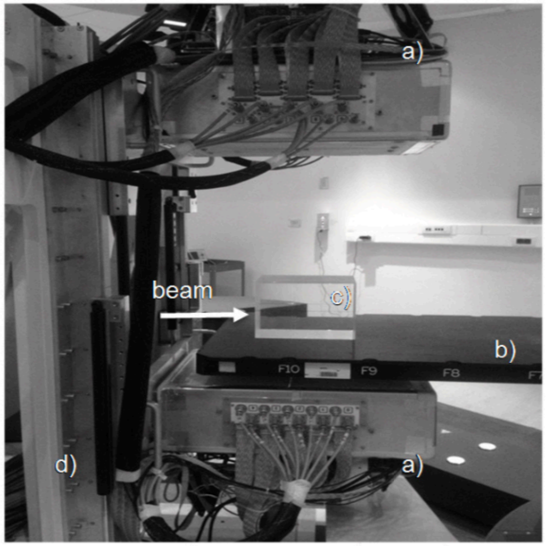




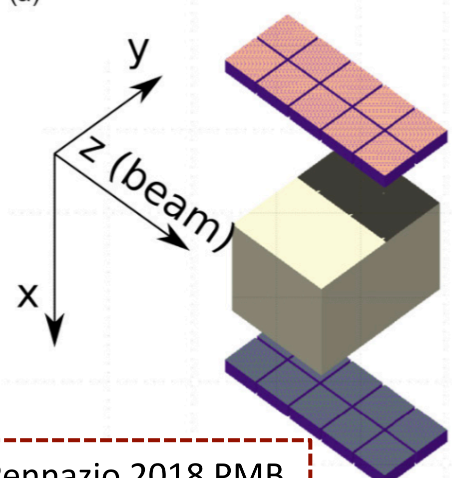




Range monitoring for charged particle therapy



(a)

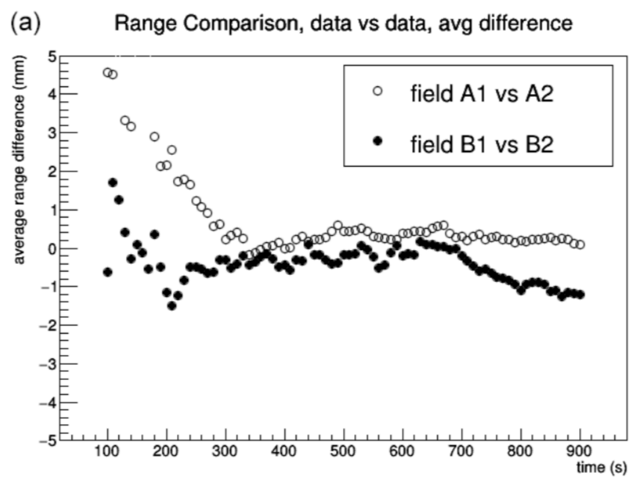


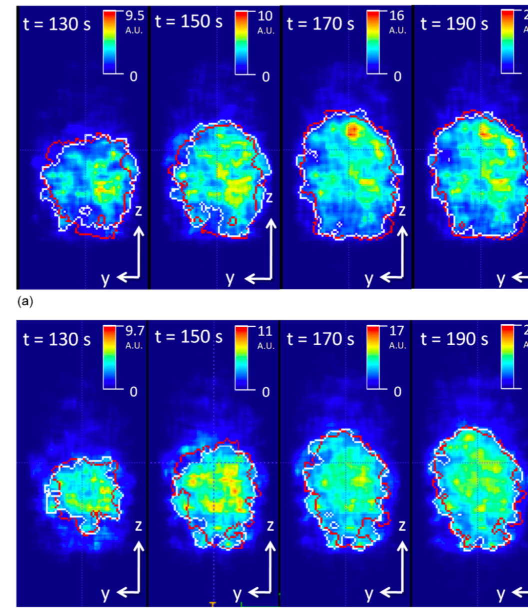
Pennazio 2018 PMB

INSIDE – In-beam PET

Two planar heads
10x25 cm^2 active area

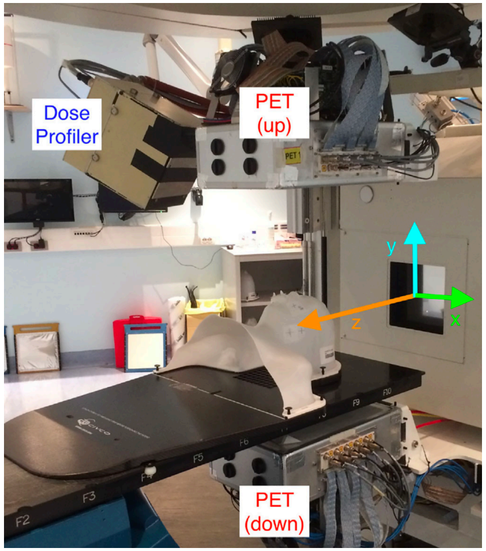
Range monitoring for
protons and carbon ions

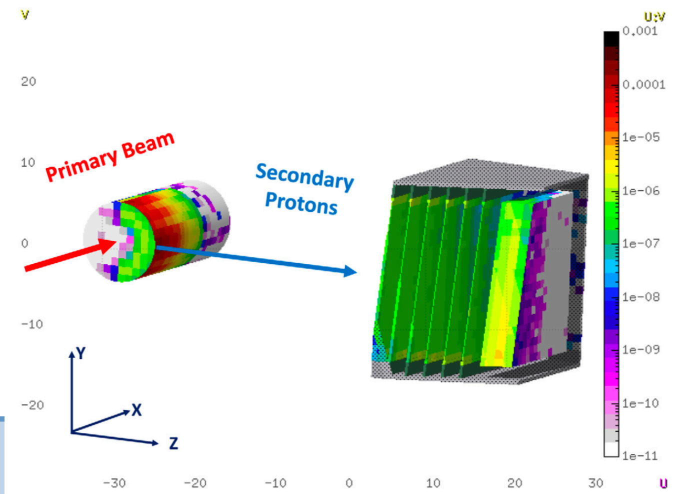




Range difference
1-2 mm 20 s after
irradiation

Range monitoring for charged particle therapy



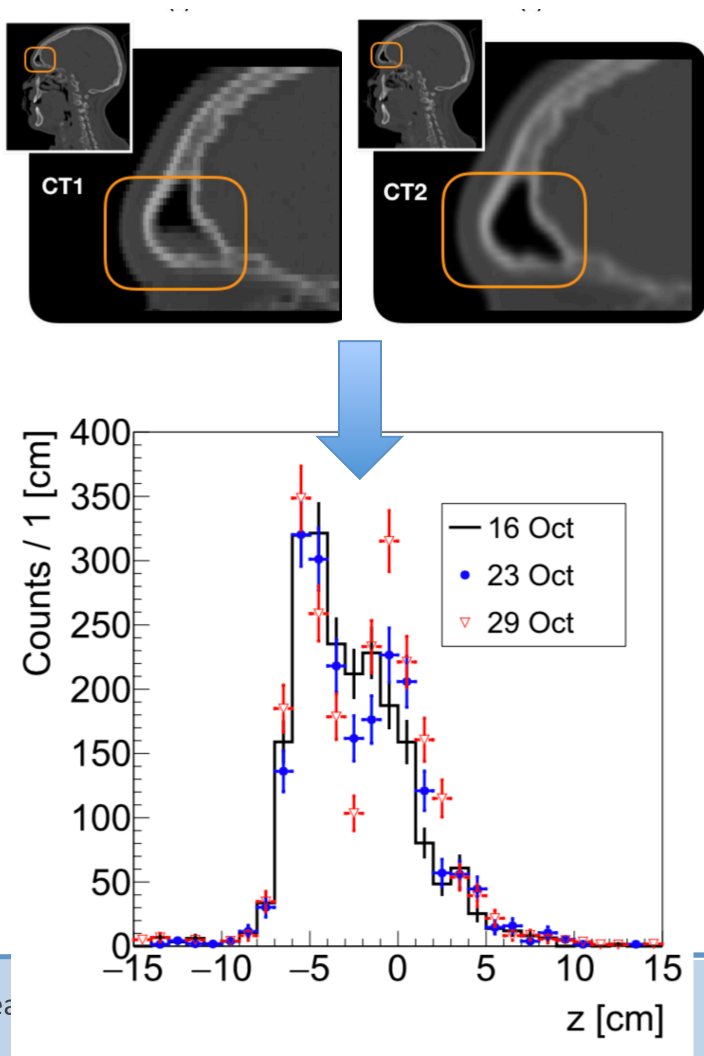


INSIDE – Dose Profiler

System installed at CNAO

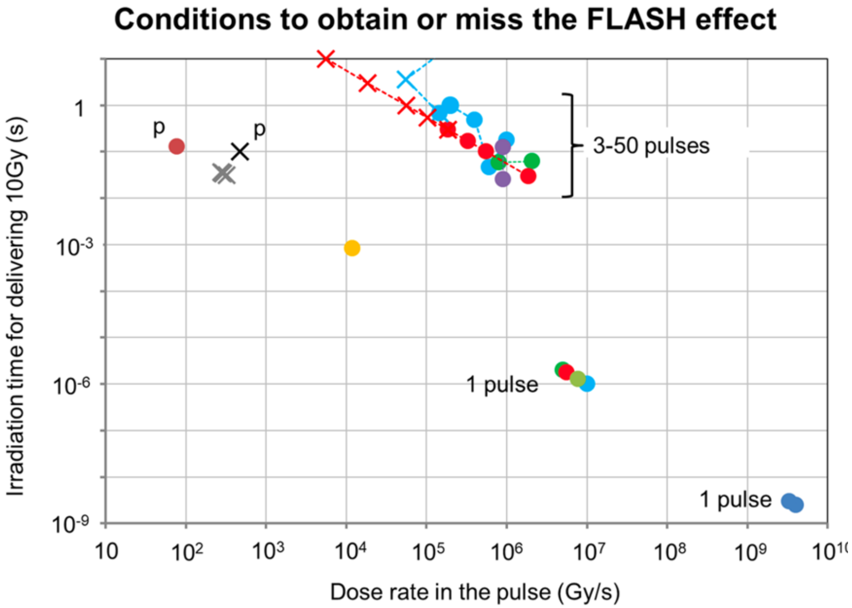
Monitoring for carbon ions by detection of secondary charged particles

Fischetti 2020 Sci Rep



Back to the future: ultra-high dose rate radiotherapy

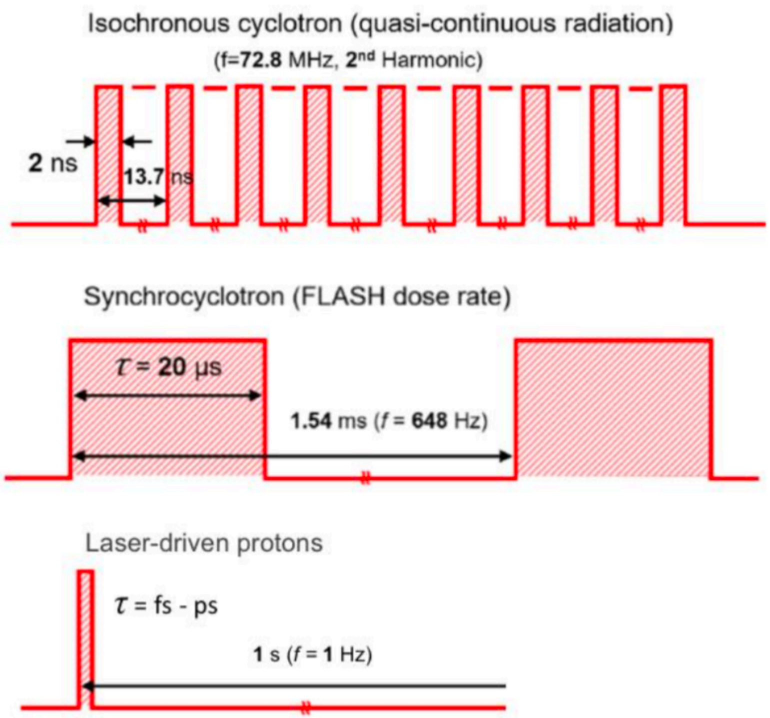
- UHDR: from 0.01 Gy/s to >40 Gy/s
- Is the dose rate enough? Not really...



Circles -> FLASH effect
Crosses -> No FLASH effect

Montay-Gruel 2021 Clin Cancer Res

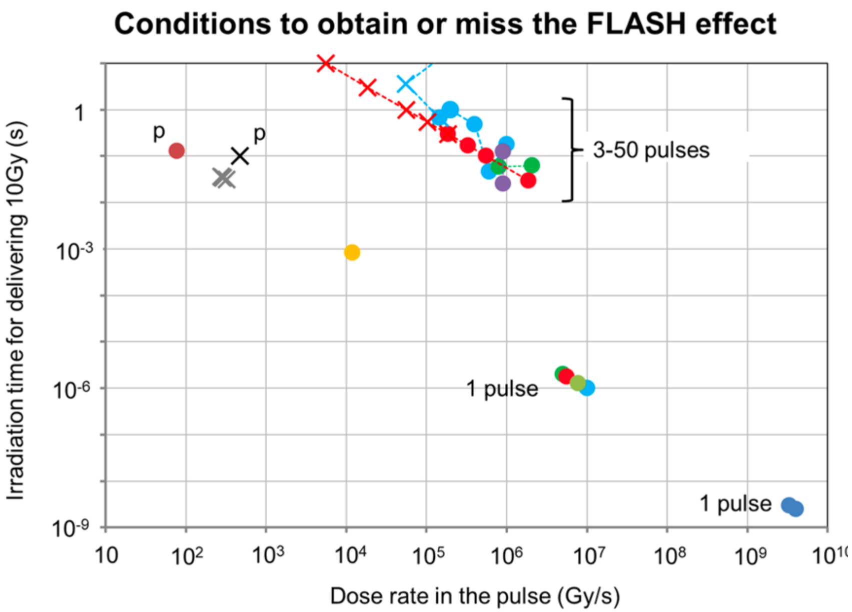
PROTONS



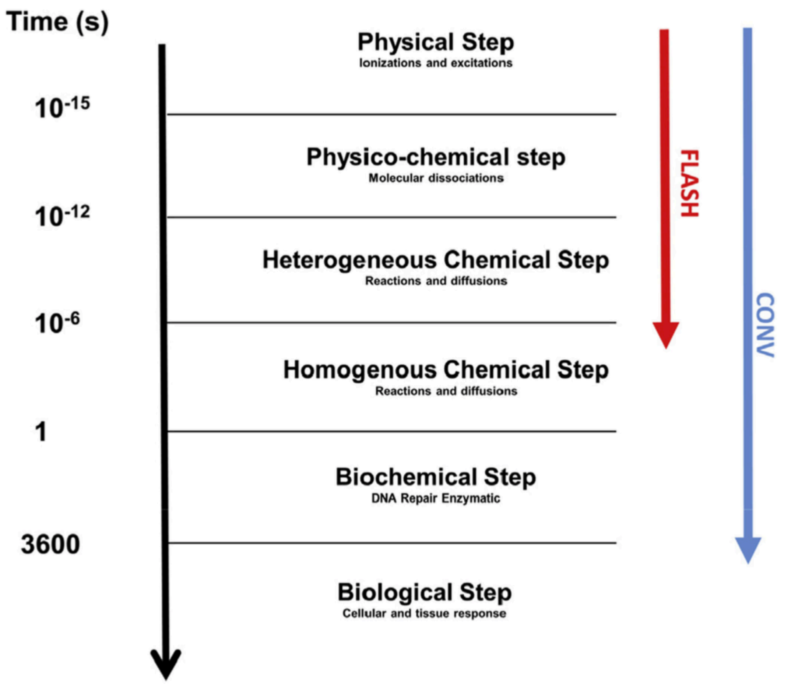
Romano 2022 Med Phys

Back to the future: ultra-high dose rate radiotherapy (FLASH)

- UHDR: from 0.01 Gy/s to >40 Gy/s
- Is the dose rate enough? Not really...



Circles -> FLASH effect
Crosses -> No FLASH effect



Why the FLASH effect?
Some hypotheses :

- Transient hypoxia
- Radical recombination
- Inter-track effects
- Immune system

Montay-Gruel 2021 Clin Cancer Res
Vozenin 2019 Clin Oncol

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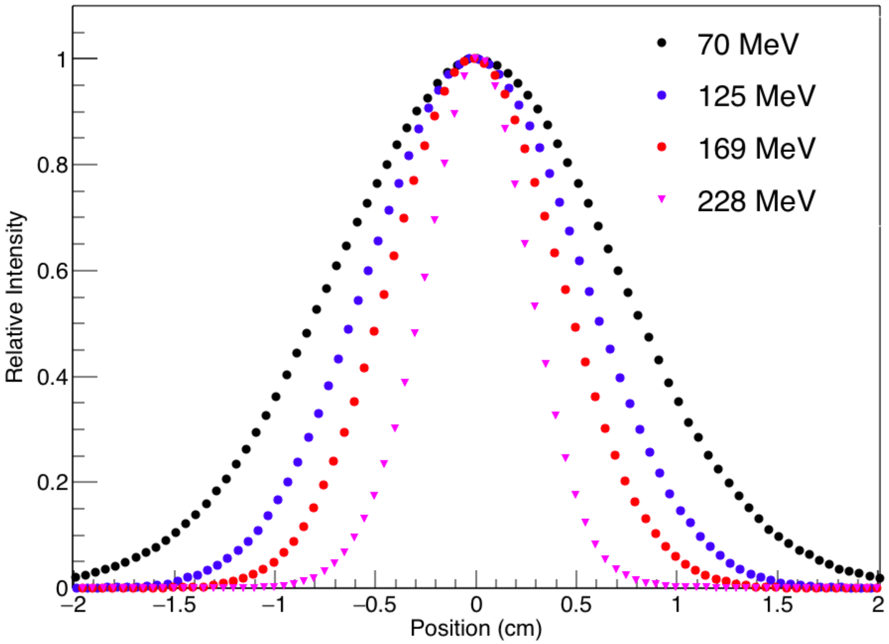
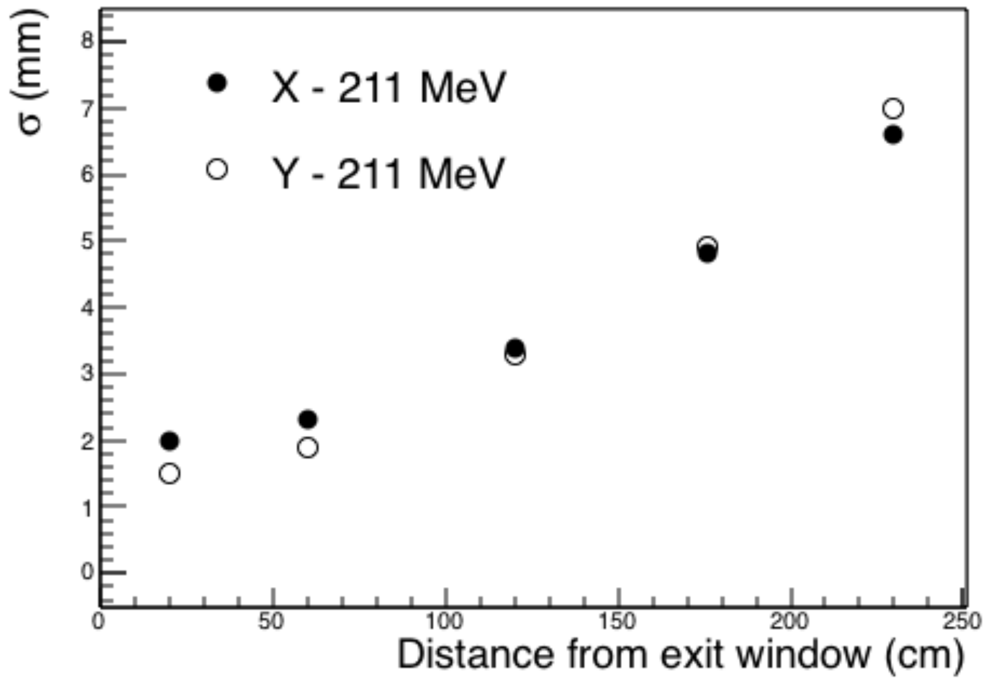
Experimental Room, Proton Therapy Center - Trento





- Scintillating panel coupled to CCD cameras
- Gaussian profile at Isocenter
- Sigma from 2.7 to 6.9 mm from lowest to highest E

Tommasino et al. 2017 NIM A