Application of laser-accelerated particles (protons and electrons) to radiation biology.

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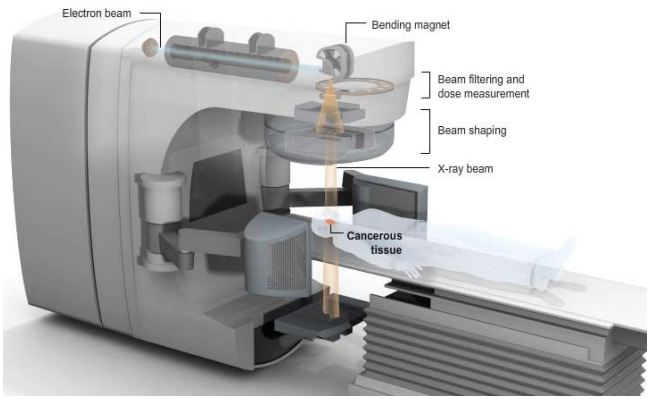
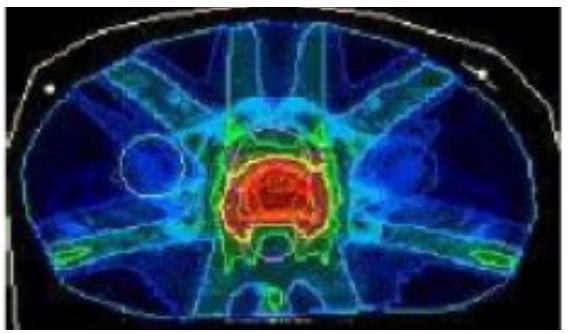
Outline

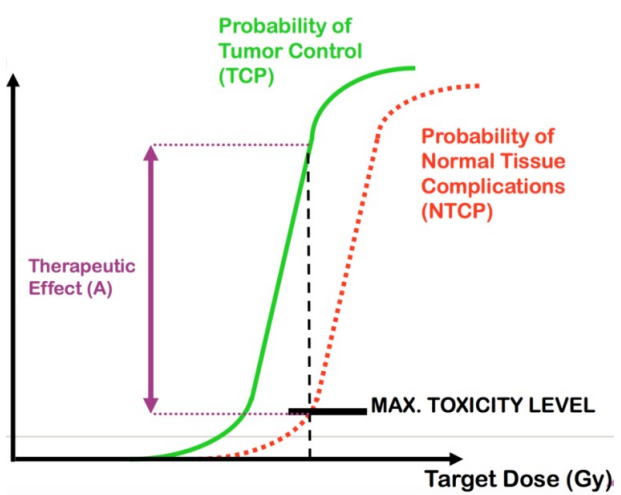
- Fundamentals of radiation therapy
- Interest of laser-driven particle sources
- Radiation biology on SAPHIR
- Laser-based pre-clinical lines

Radiation theraphy, therapeutic index



Treatment plan, 6 MV photons, 6 axis



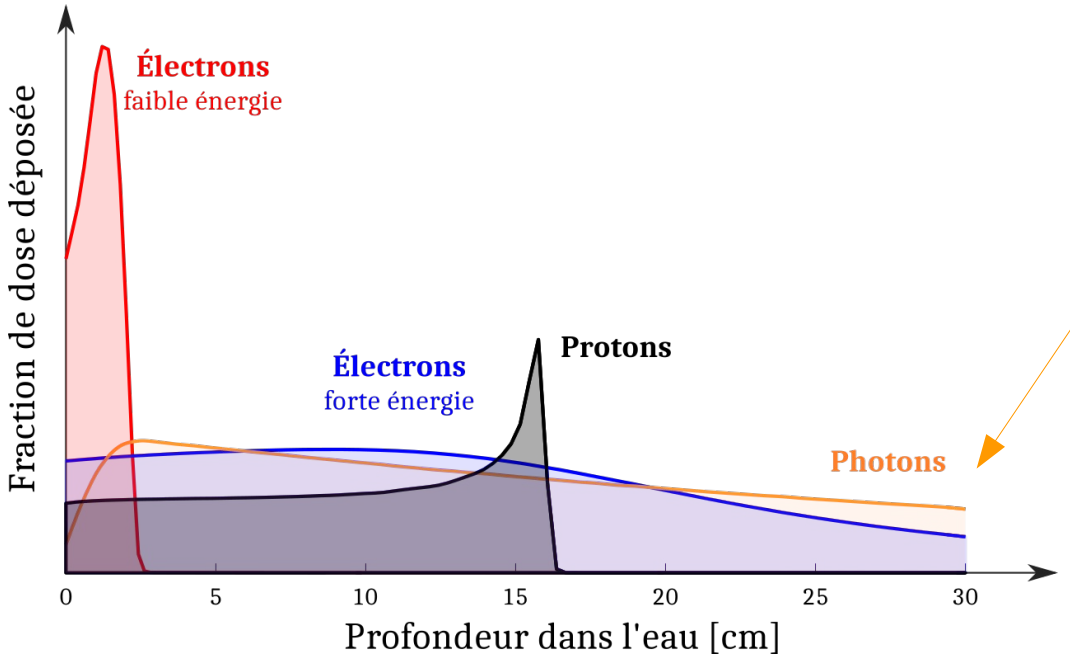


Radiotheraphy: **60% of treatments**

Therapeutic index:

- Conformality (geometry, physics)
- Radiation toxicity (radiation biology: energy, space, time)

Geometry and physics of dose deposition



Photons 6 MV:
90% therapy of choice

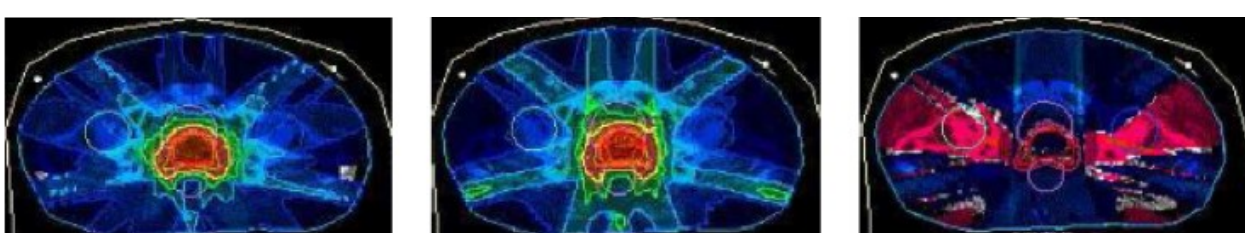
Treatment: 10s Gy
Dose rate: Gy/min

Deposited dose

E_1 → ϱ,V → E_2

$\mathbf{Gy = J/kg}$

V. Malka
Phys. Med.



Électrons VHEE | Photons 6 MV | Différence: -20%

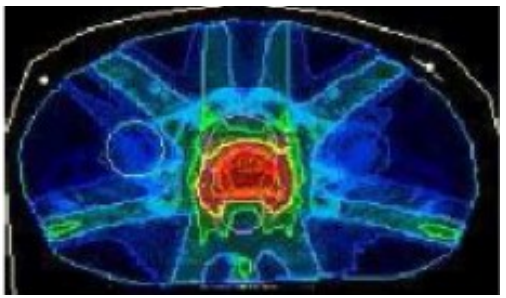
Conformality therapy: IMRT, VMAT

IMRT (Varian) : *Intensity Modulated Radiation Therapy*

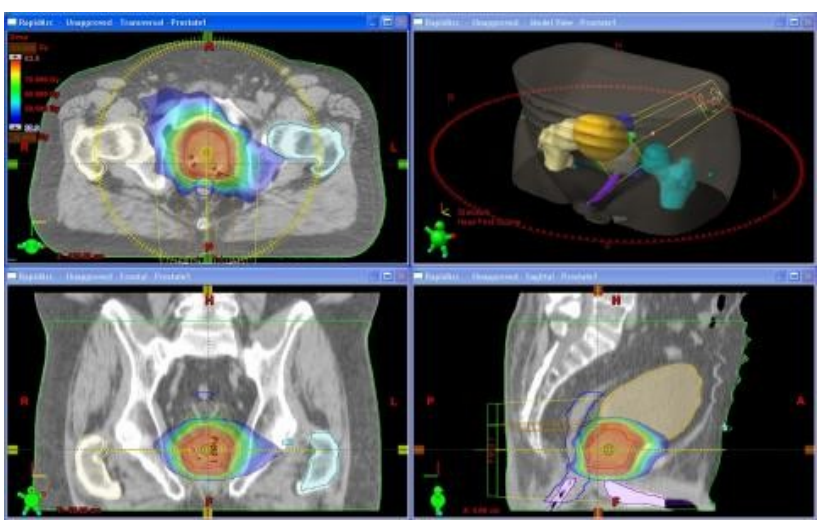
VMAT *(CyberKnife, Tomotherapy) : Volumetric Modulated Arc Therapy*

- Intensity modulated
- Shape modulated
- Angle : 2 π × π
- High treatment speed
- Included tomography

Blade collimator
(Varian)



7 angles, 6 MV
X-ray treatment plan



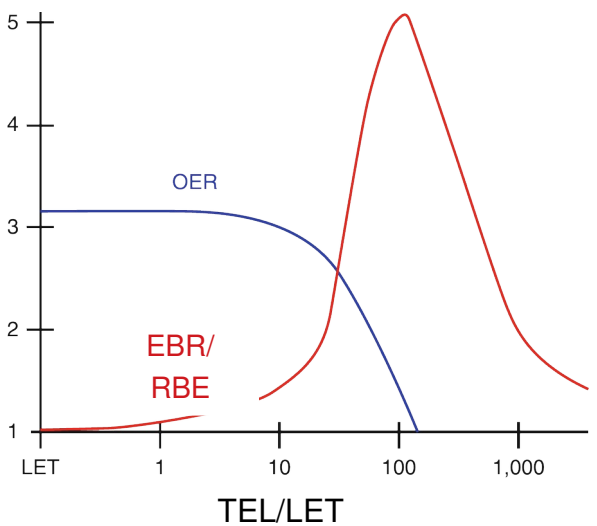
Continuous multi-beam treatment plan

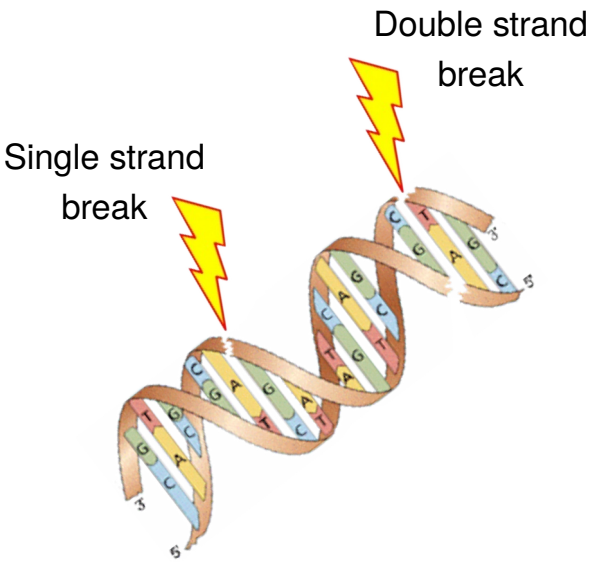
RBE, LET and biological effect

Therapeutic index

- Conformality (geometry, physics)
- Toxicity of IR (radiation biology, radiation chemistry, physiology, **time**)

Different radiation, varying LET, varying RBE



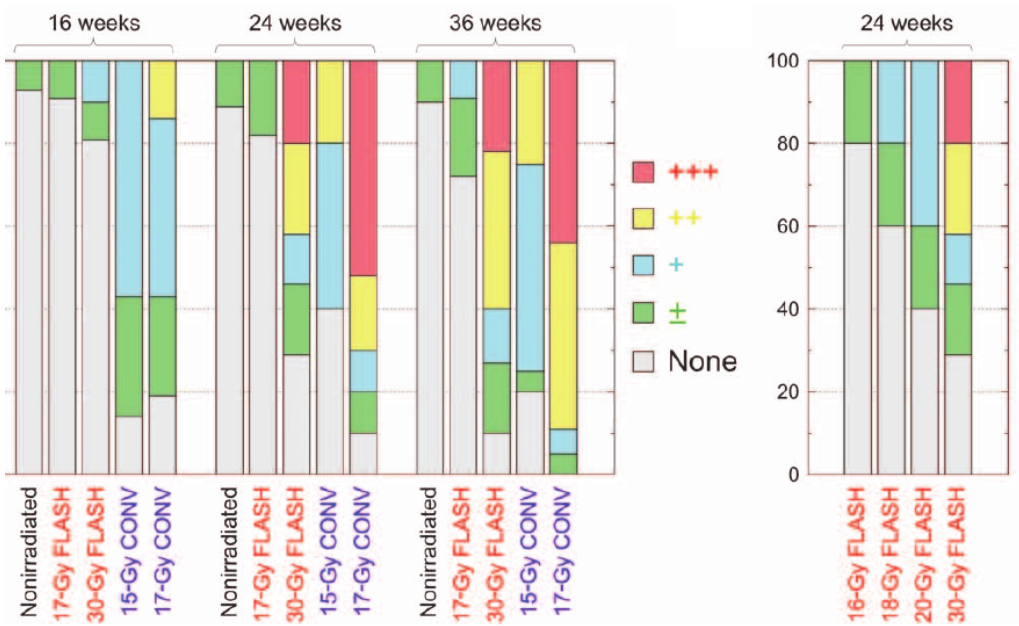


Radio-oncology: the therapeutic effect depends only on deposited dose

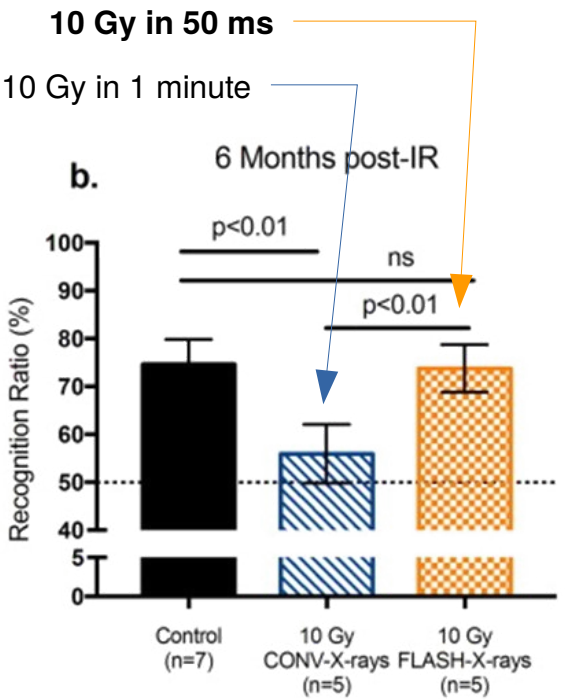
The FLASH effect

Reduced radiation toxicity on healthy tissue at **high dose rate and short irradiation** *(in vivo*, Orsay, Stanford, Lausanne*)*

Fibrosis in irradiated mice lung tissue



Cognitive capabilities in irradiated mice brains



Favaudon, et al "Ultrahigh Dose-Rate FLASH Irradiation Increases the Differential Response between Normal and Tumor Tissue in Mice." Science Translational Medicine 6 (245): 245ra93-245ra93. https://doi.org/10.1126/scitranslmed.3008973.

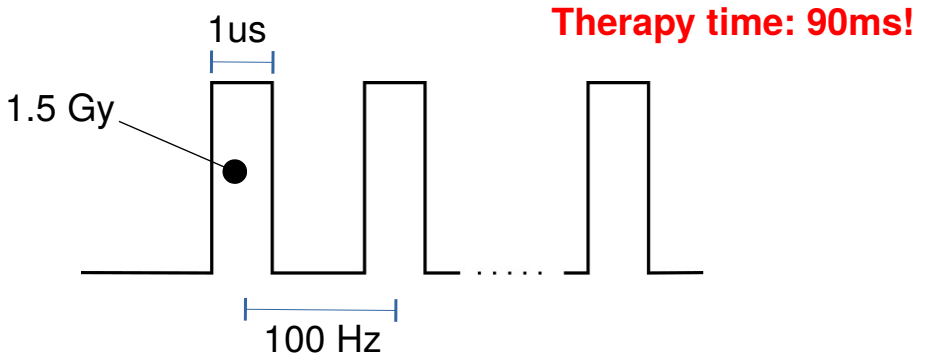
Montay-Gruel et al. "X-Rays Can Trigger the FLASH Effect: Ultra-High Dose-Rate Synchrotron Light Source Prevents Normal Brain Injury after Whole Brain Irradiation in Mice." Radiotherapy and Oncology, August. https://doi.org/10.1016/j.radonc.2018.08.016.

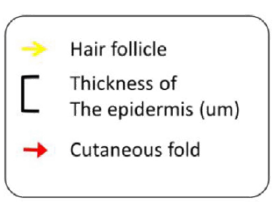
The FLASH effect: first human patient

Conventional protocol: 20 Gy in 6-10 fractions

FLASH protocol: **15 Gy** in a single fraction :

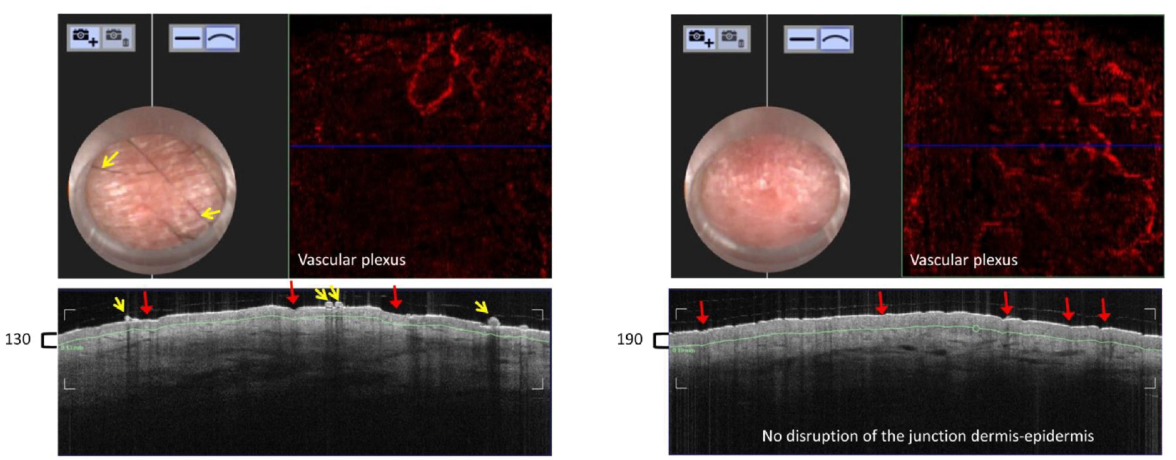
- complete tumor control on FLASH whereas no tumor control on conventional
- no secondary effects past 5 weeks





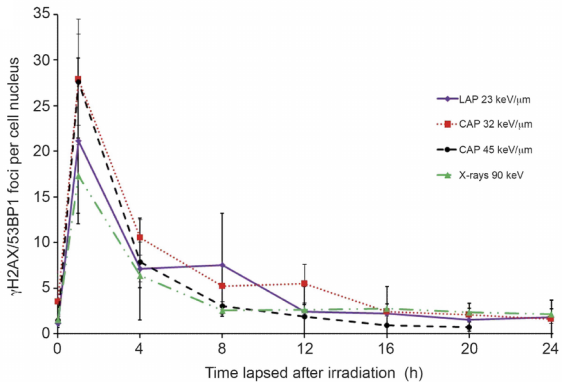
before irradiation

after irradiation

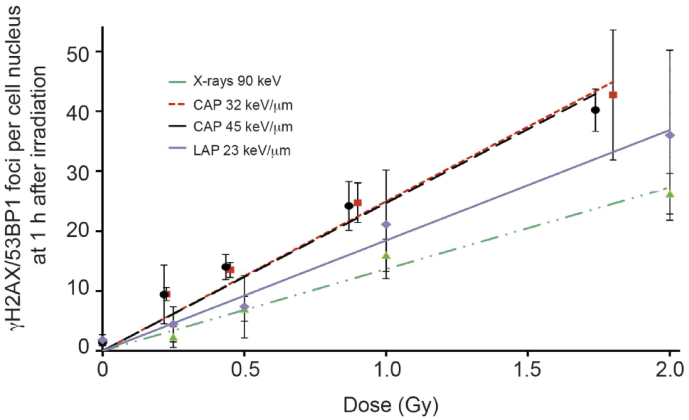


J. Bourhis et al. Treatment of a first patient with FLASH-radiotherapy. Rad.Oncol. *June 2019*

Reduced nitro-oxidative stress at similar DNA damage

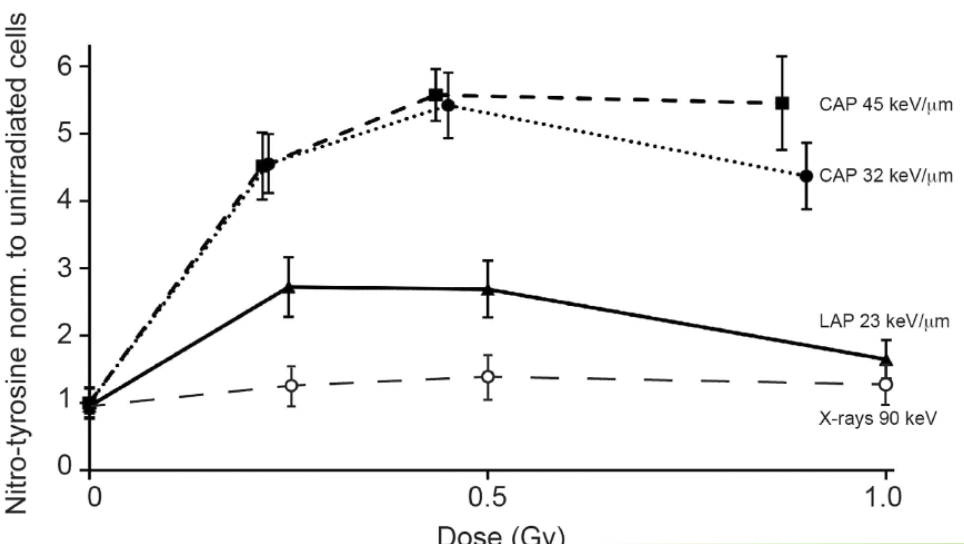


DNA damage foci formation in time (at 1Gy)



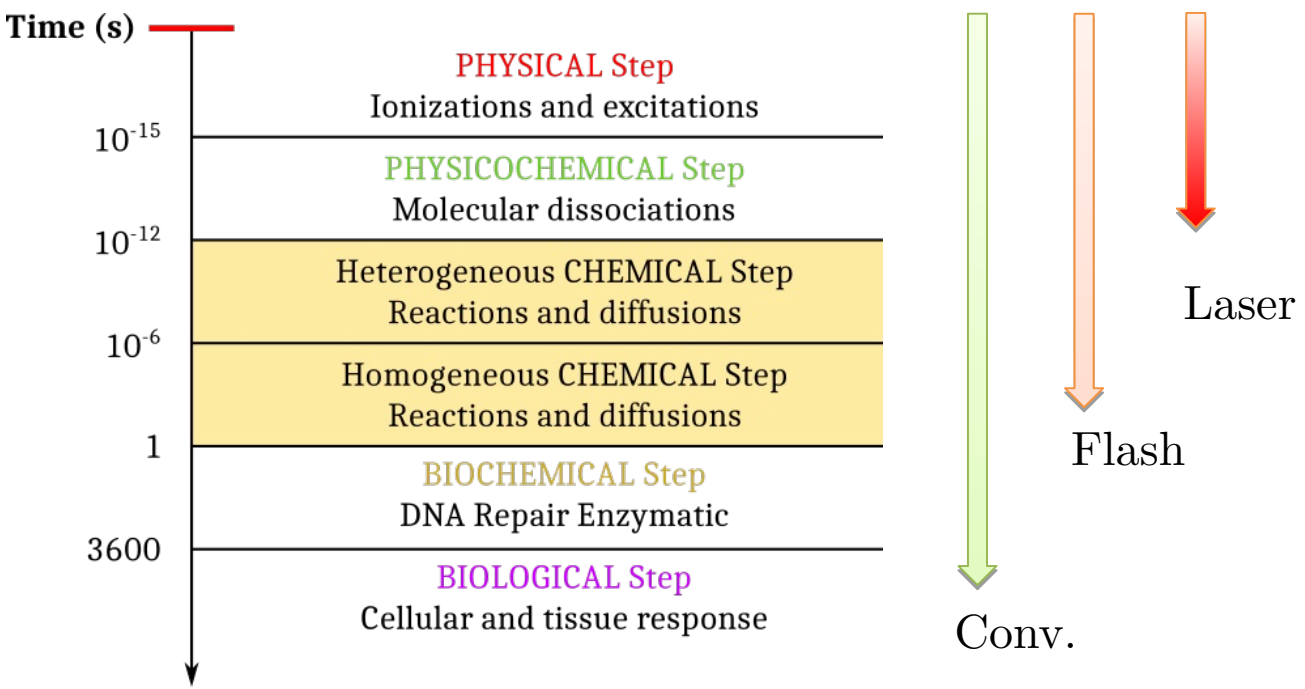
Dose response to DNA foci formation

Nitro-oxidative stress



Raschke, S. et al., Scientific Reports 6:32441, doi:10.1038/srep32441

Temporal scales



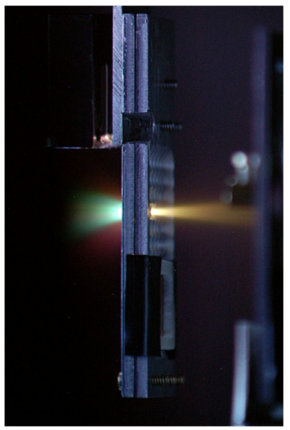
Radiation Biology on SAPHIR (2013-2015)

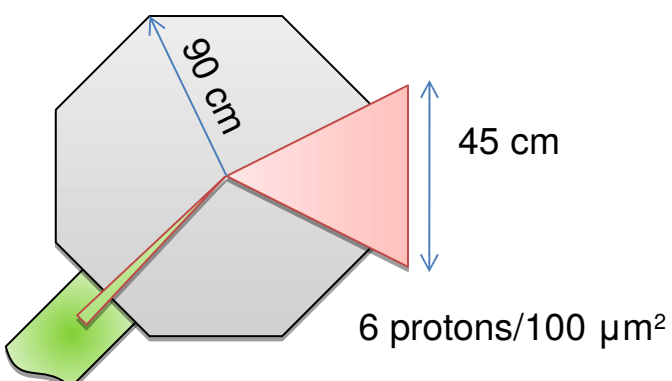
Laser:

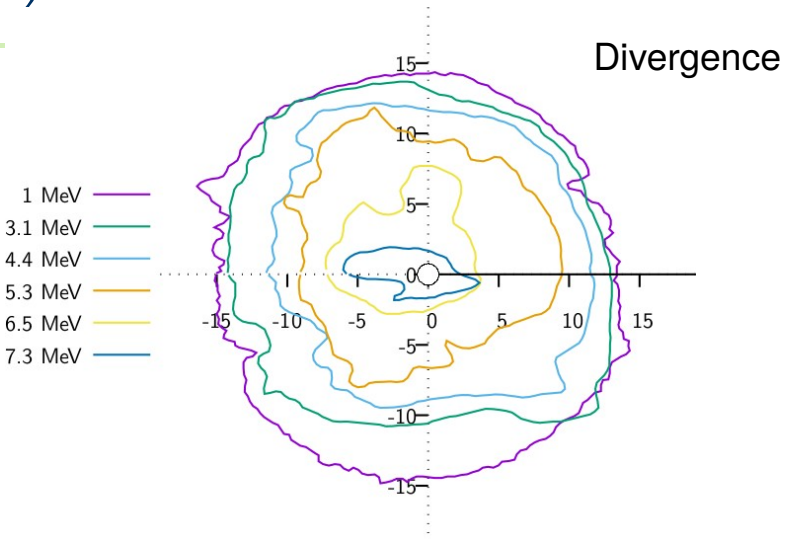
- 4 J, 26 fs (200TW)
- 5 Hz

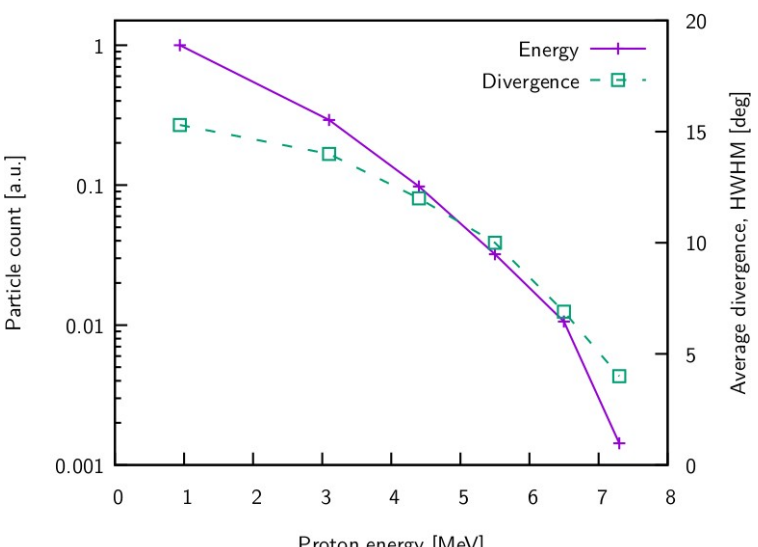
Protons:

- Titanium, **5um**
- **~1 nC/shot**
- 0.5 Hz max

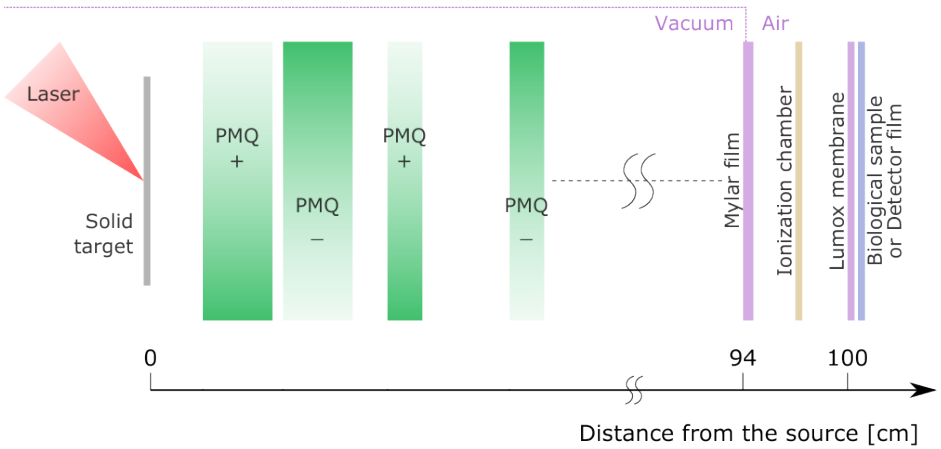


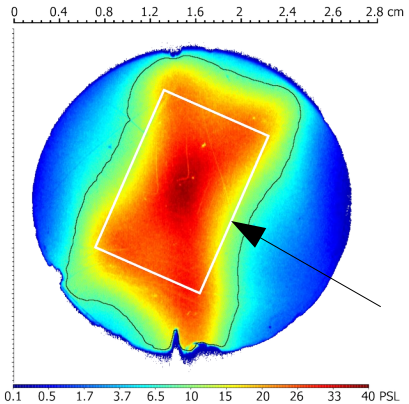






Transport, shaping, dosimetry





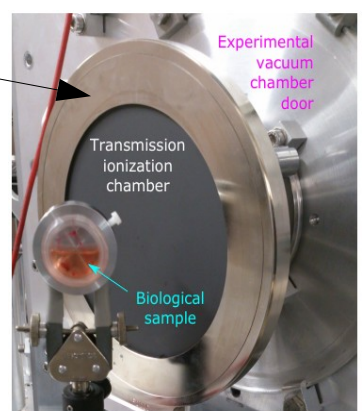
10^8 protons/2 cm^2
(~50/100 um^2)

Pommarel et al. PRAB 2017

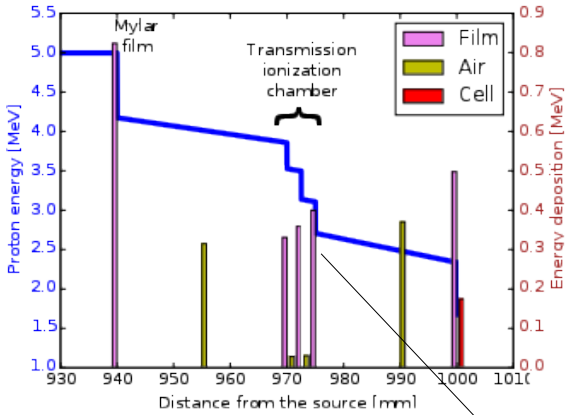
Schillaci et al. J.Inst 2016

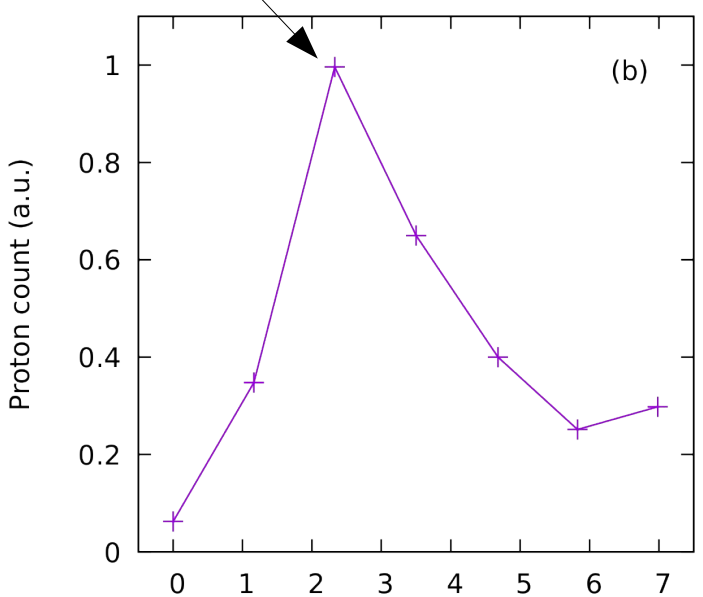
Transmission ionization chamber:

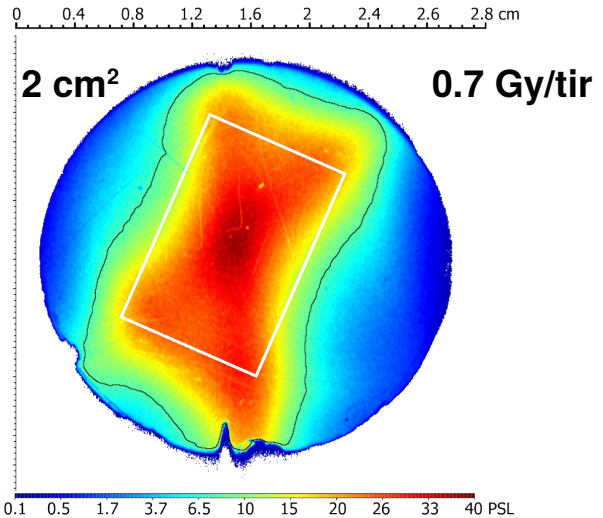
- 100um water equivalent
- 15cm diameter

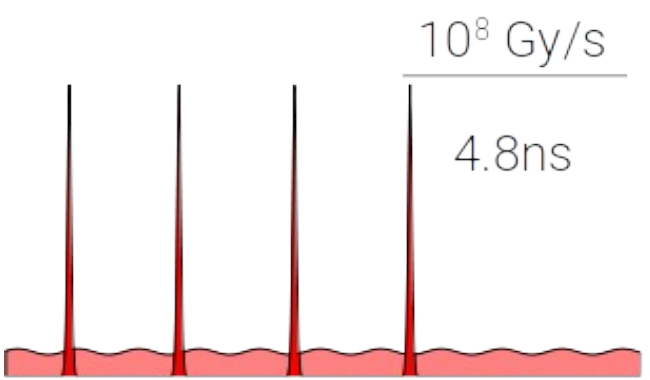


Irradiation conditions (5 MeV)



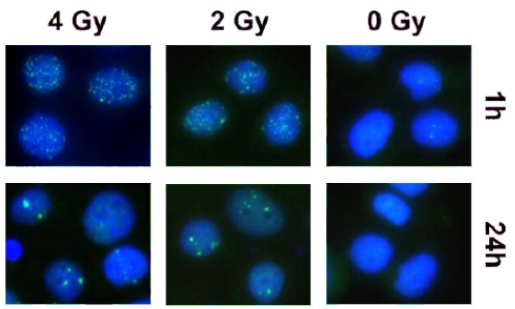




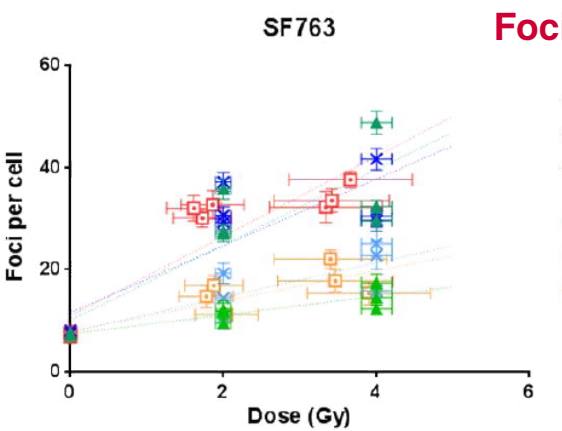


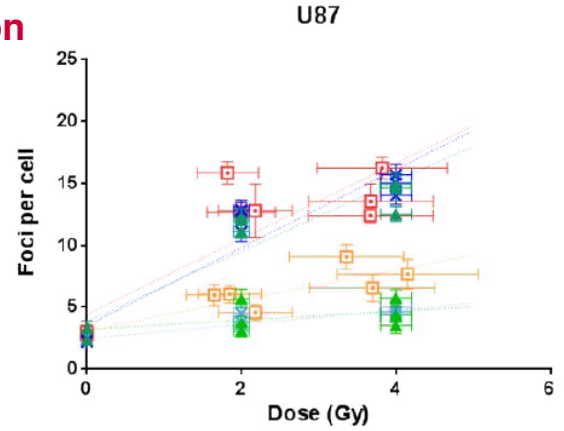
1.5 M

LPA: RBE and dosimetry validation

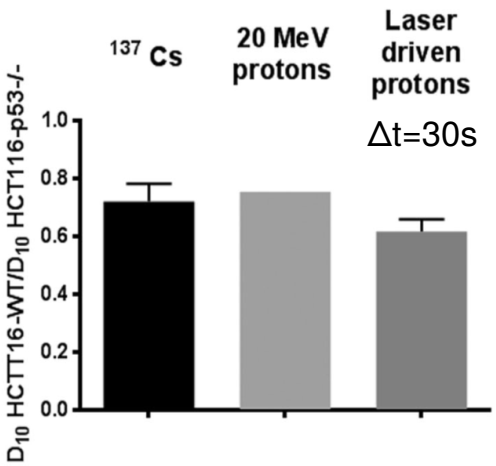


Foci generation



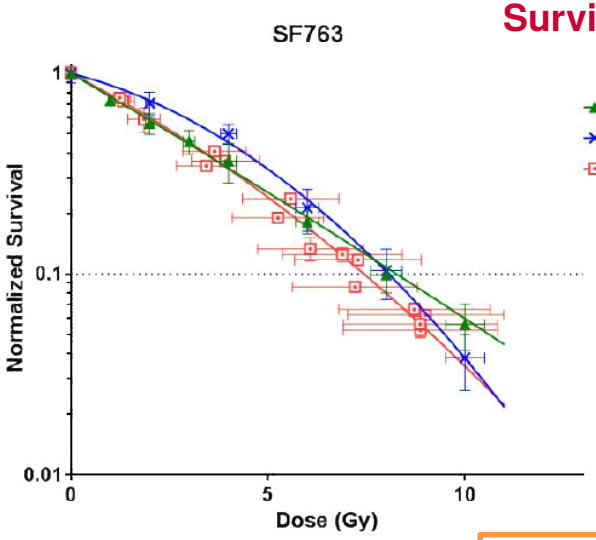


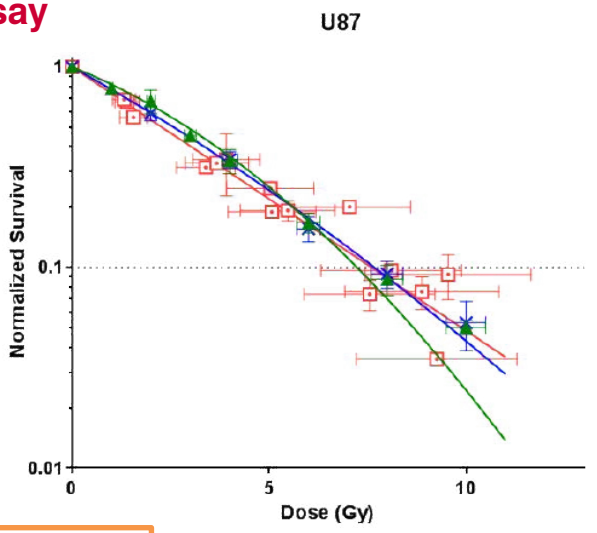
RBE @1.4Gy/min



Pommarel et al., PRAB 2017

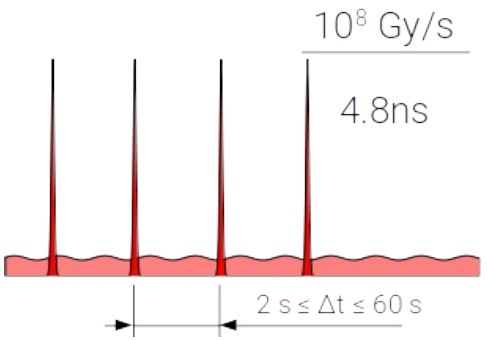
Survival assay

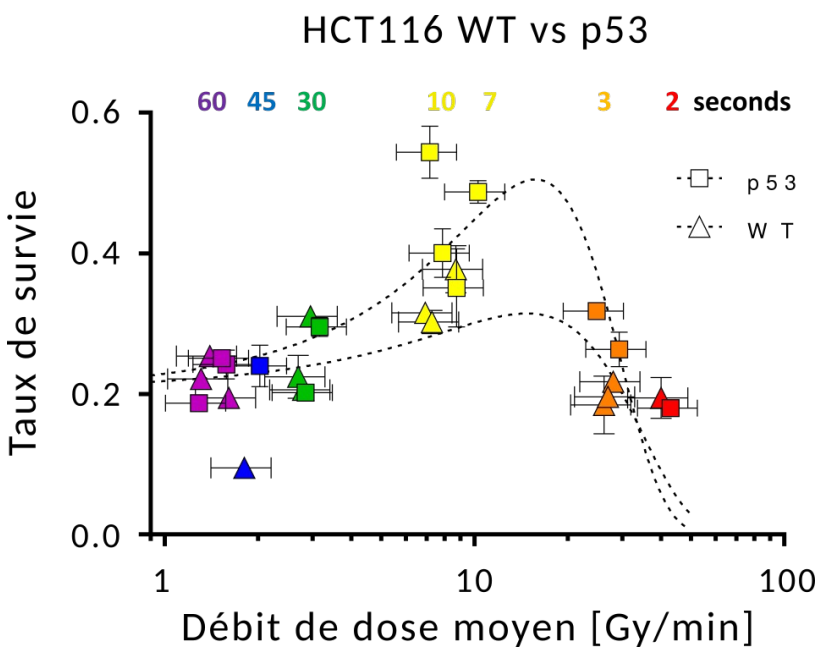


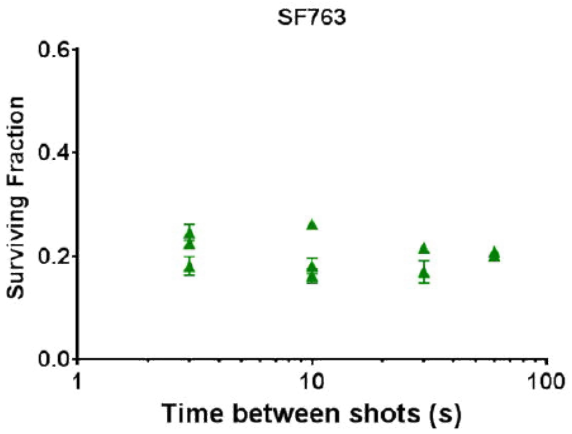


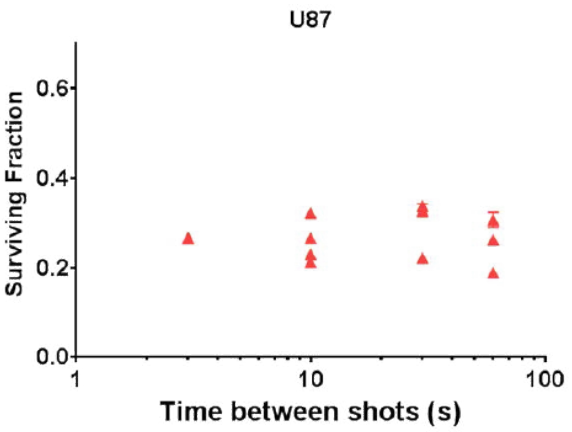
Bayart et al. Sci.Rep. 2019

LPA: *In-vitro* fast fractionation



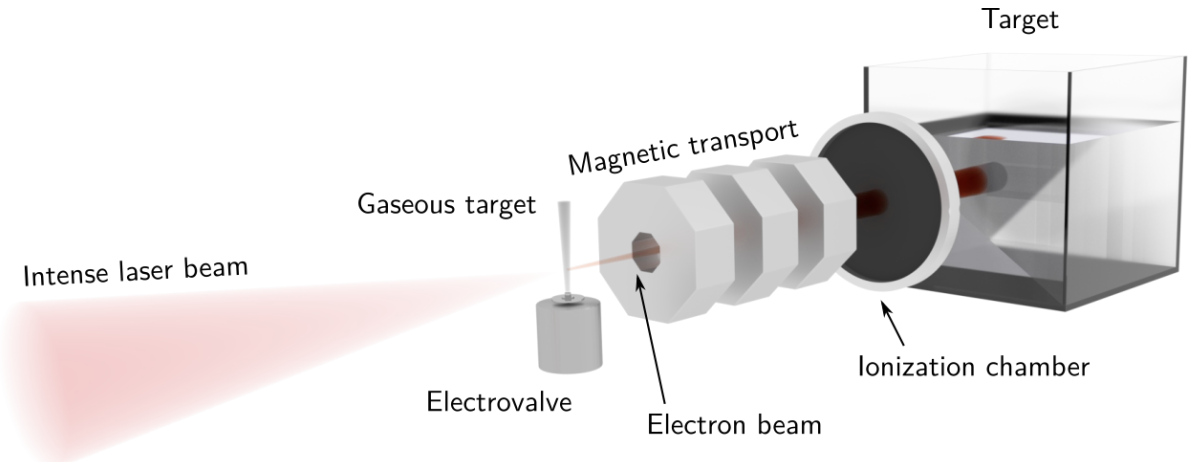


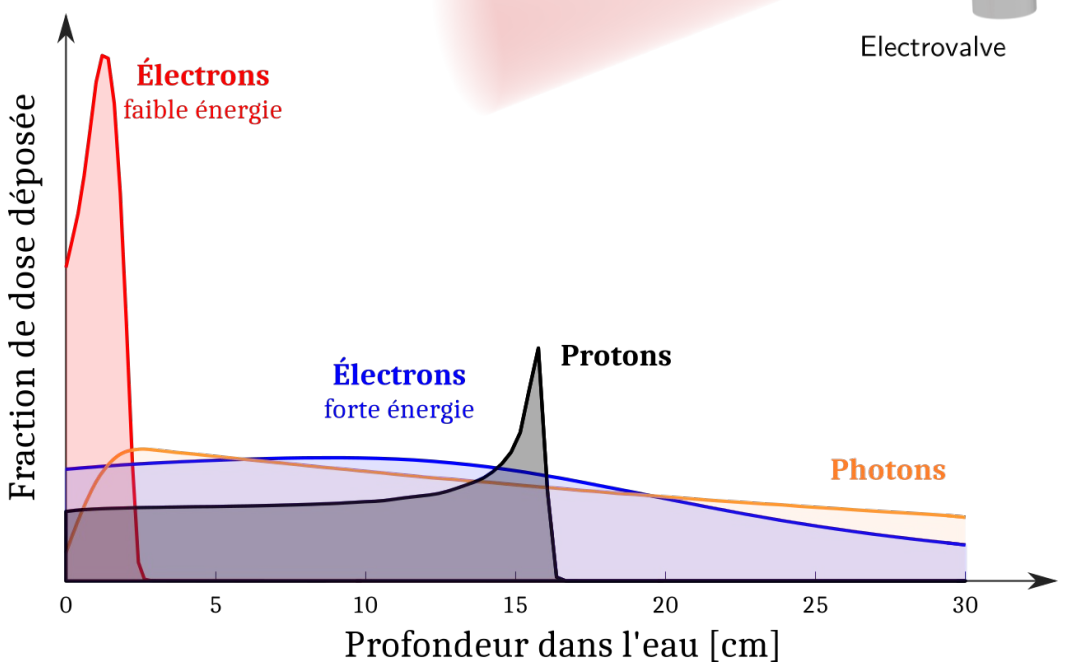




Bayart et al., *SciRep 2019*

Perspectives: electron pre-clinical line

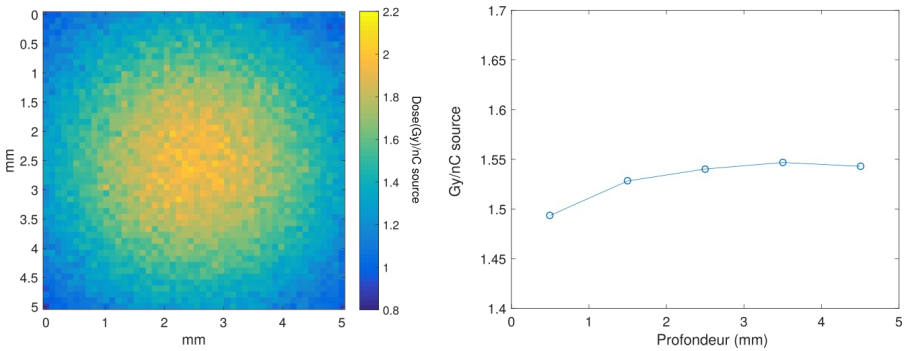




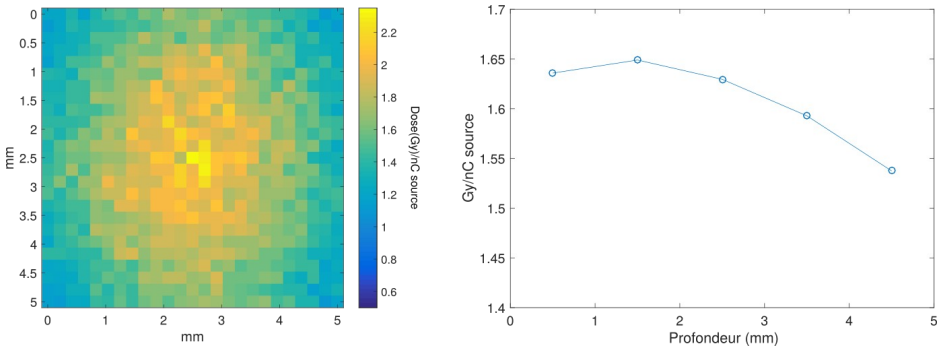
- Slowly varying LET
- High repetition rate
- Less demanding than TNSA
- In-vivo possible (E>150MeV)
- Charge may pose limitations

Irradiation conditions with LWFA

High energy (150 MeV)

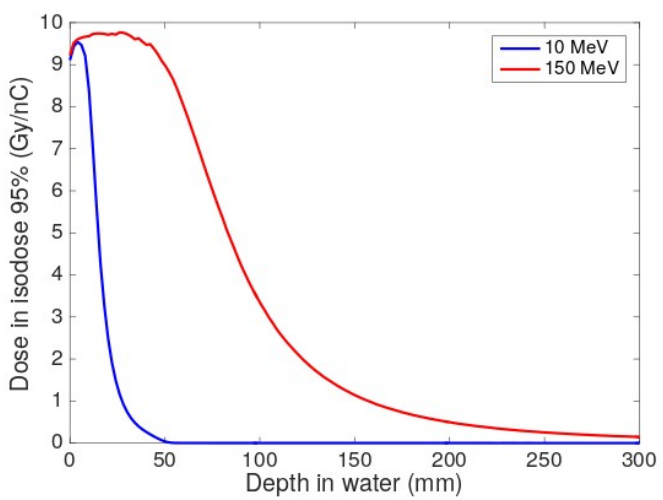


Low energy (10 MeV)

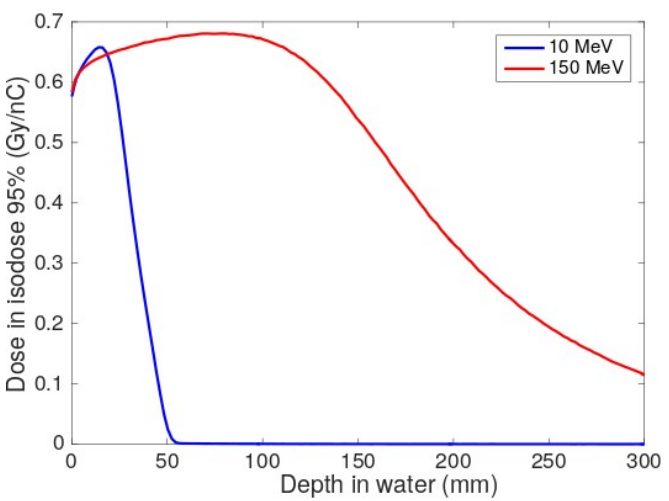


Guillaume, E. et al. doi:10.1103/PhysRevSTAB.18.061301

5 mm beam



20 mm beam



Conclusions

- Laser-driven particle sources to explore temporal aspects in radiation biology
- Pre-clinical line for applications:
  - shaping
  - dosimetry
  - quality assessment
- Laser-plasma related matters:
  - stability
  - charge
  - surface
- FLASH effect and fast-fractionation: a unique possibility!

Impact of proton therapy

La protonthérapie est le traitement de choix pour : mélanome de l'oeil, tumeurs du crane, de la base du crane, du rachis, tumeurs pédiatriques (1 % des radiothérapies en France).

Tableau 1: Activité de protonthérapie identifiée par les données du PMSI, année 2013

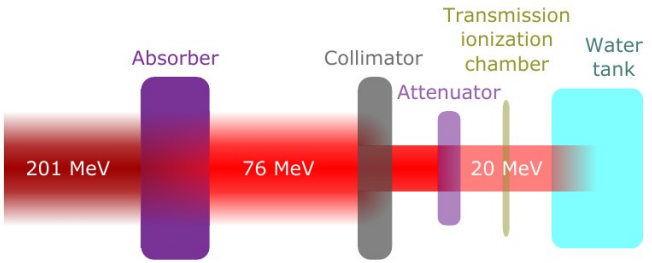
	Nice	Orsay
Nombre d'hospitalisations/séances	1731	7211
Nombre de personnes	222	466
Nombre de personnes avec tumeur maligne	220	423
Nombre de personnes avec :		
- Tumeur maligne de l'œil	219	318
- Tumeur maligne du système nerveux central	0	27
- Os, articulations, cartilage articulaire	0	34
- Glande endocrine sans précision	0	25
- Autre tumeur maligne	1	19
Age des personnes traitées		
- 0-15 ans	0	42
- 16-24 ans	2	17
- 25 ans et +	220	407

Rapport SFCE-7 : estimation à **410** le nombre d'enfants et jeunes adultes par an pouvant relever d'une indication de protonthérapie pour des tumeurs intracrâniennes et au maximum de **100** à **150** pour des localisations extra-crâniennes soit un total de 510 à 560 patients par an.

TIC Calibration protocol

known dose deposited in TIC (by calibrated beam)

attenuated proton beam 201MeV → 20MeV: low energy tail



(Geant4 sim)

electrometer calibration: nC/Gy

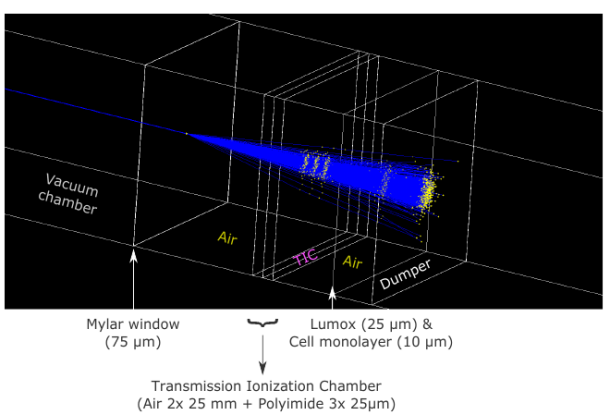
(Geant4 sim)

TIC gives proton count during irradiation

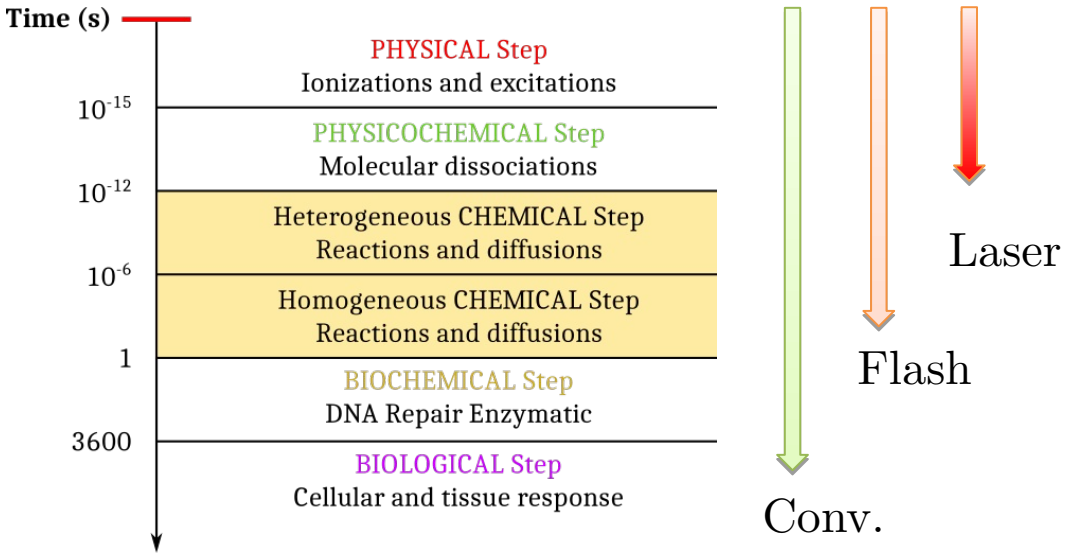
laser-accelerated protons broad spectrum

position dependent spectrum

2D binning (9x9)



Water radiolysis and temporal scale



Radiation chemistry and water radiolysis at t<200fs is active subject of research.

The importance of **radical production** in radiation toxicity is not completely clear.