Laboratoire d'Optique appliquée
CNRS 7639 – ENSTA – Ecole Polytechnique

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EFFECT OF ULTRA-SHORT LASER-ACCELERATED PARTICLE PULSES PACE ON CELLS SURVIVAL

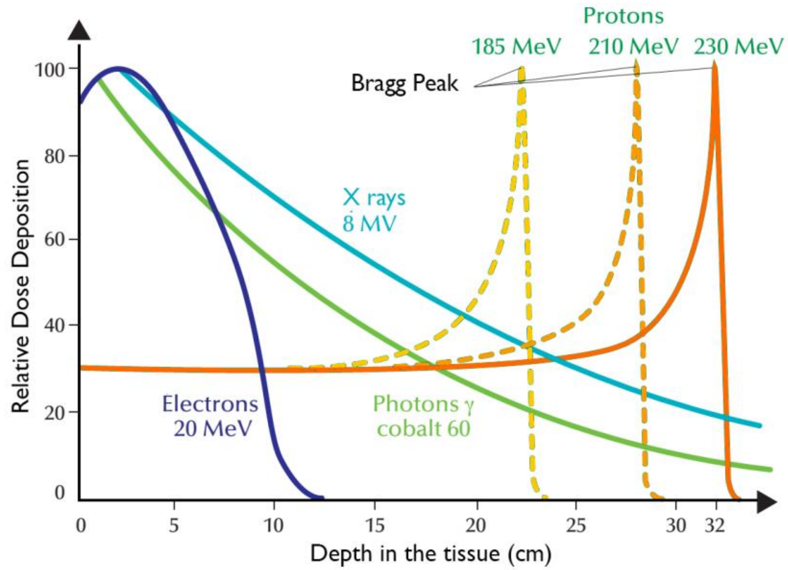
INSERM U1030
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

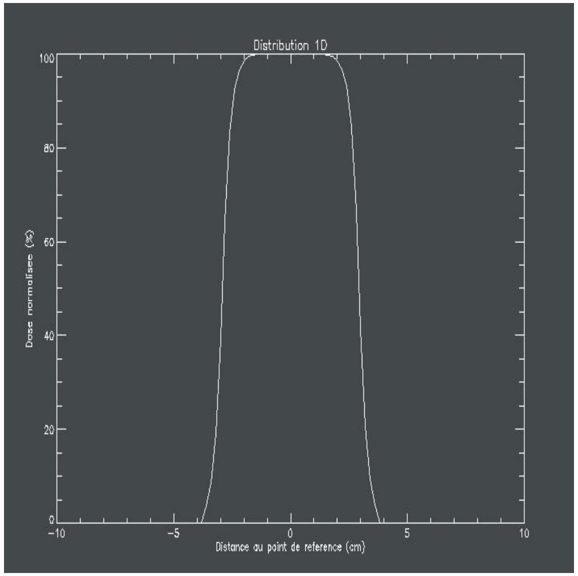
2018/10/09

PRAE International Workshop

Hadrons

- **Favorable ballistic** of hadrons (**protons** and heavy ions)

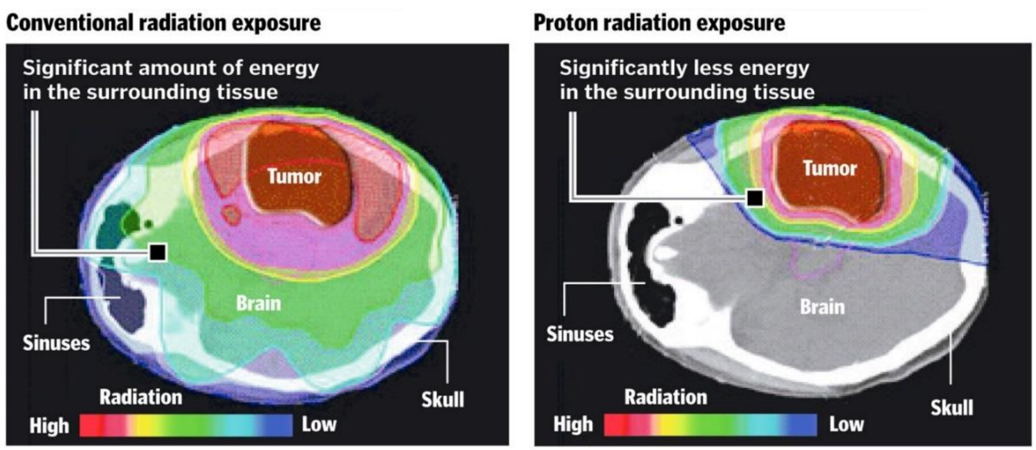




- Sharp lateral penumbra and distal dose fall-off
- high conformation of the dose distribution to the target volume

Protontherapy

- Dose **"Focused"** into the tumor.



SOURCES: University Hospitals Seidman Cancer Center; ProCure

ANGELA TOWNSEND, JAMES OWENS | THE PLAIN DEALER

↗ of the dose into the tumor

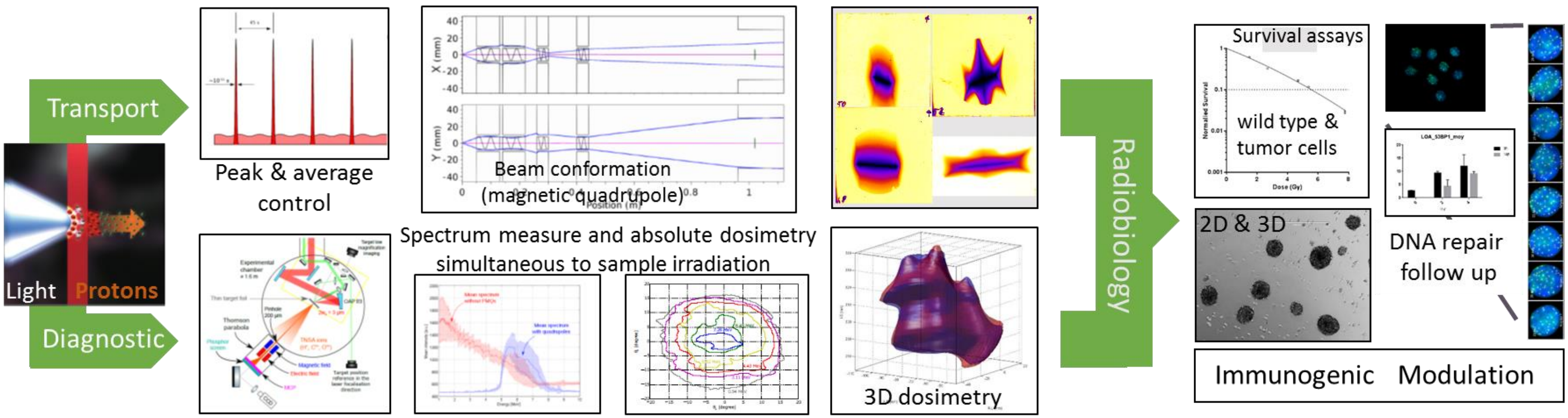
↘ of the **dose** received by neighboring healthy **tissues**

↘ of **side effects**

- **Organ-at-risk: brain, base-of-skull, eye** and **head-and-neck** tumors
- **Pediatrics**

SAPHIR project

SAPHIR : Source Accélérée de Protons par Laser de Haute Intensité pour la Radiothérapie



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Amplitude TECHNOLOGIES
Nothing but ultrafast

oséo

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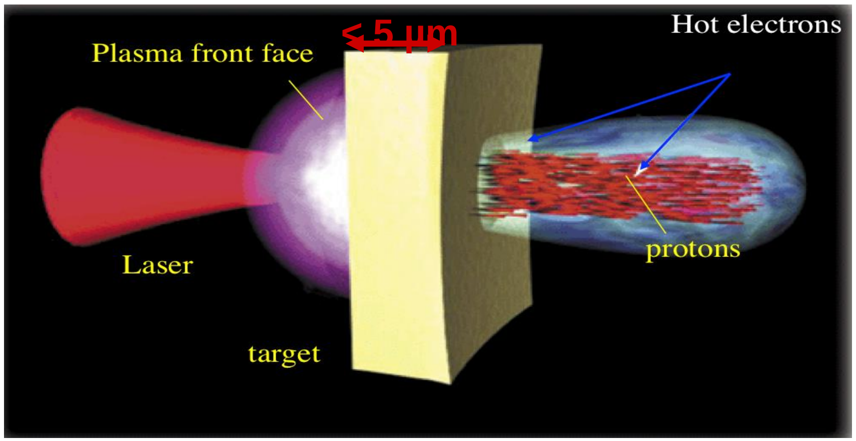
Ultra-Intenses lasers & protontherapy



Up to the solid target,

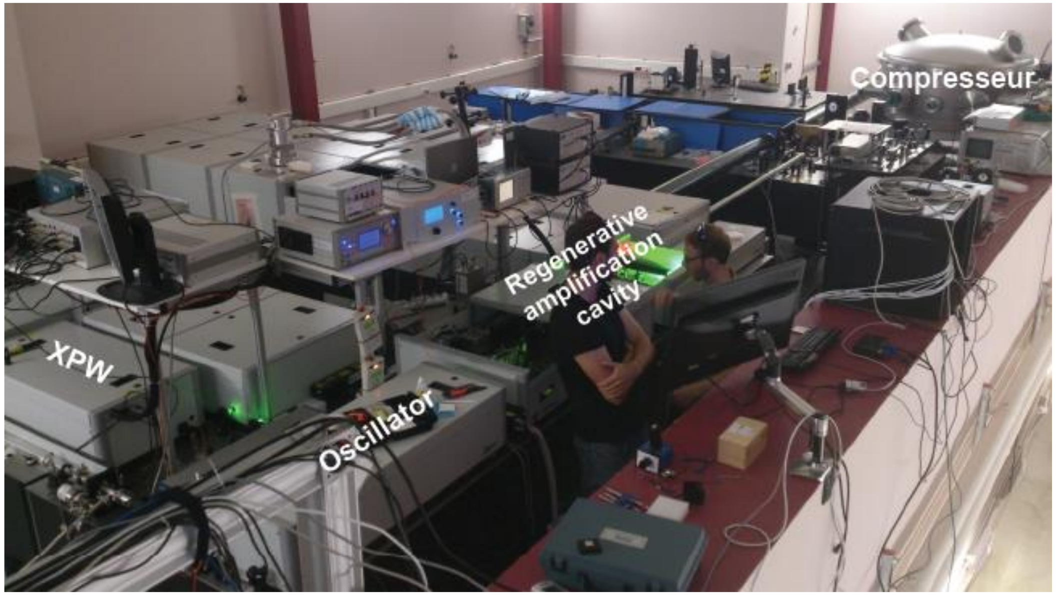
➡ **light transport**

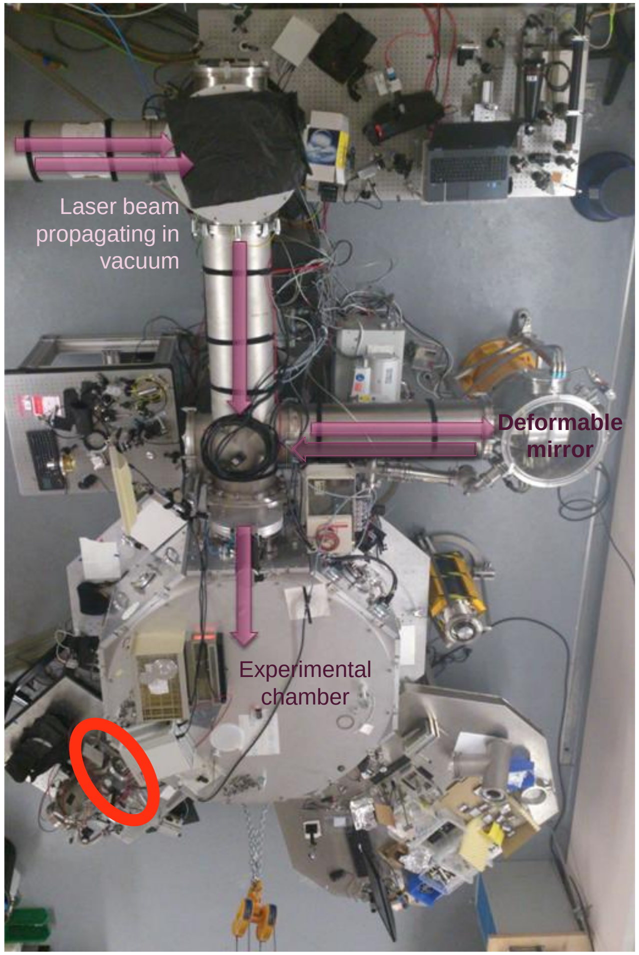
- **Reduced radioprotection equipments**

- **More compact** and **less expansive** than conventional beams
- **Laser-plasma accelerators** deliver protons **in short pulses (ns)** and **ultimate dose rate (up to 10^{12} Gy/s compared to continuous Gy/min).**

- Relative biological efficiency **(RBE) evaluation of such pulsed protons is required** before any clinical application

SAPHIR facility





Laser Installation

Experimental chamber

Laser Parameters

Gain medium : **Ti:Sapphire crystal**

Output energy : **6 J** (uncompressed)

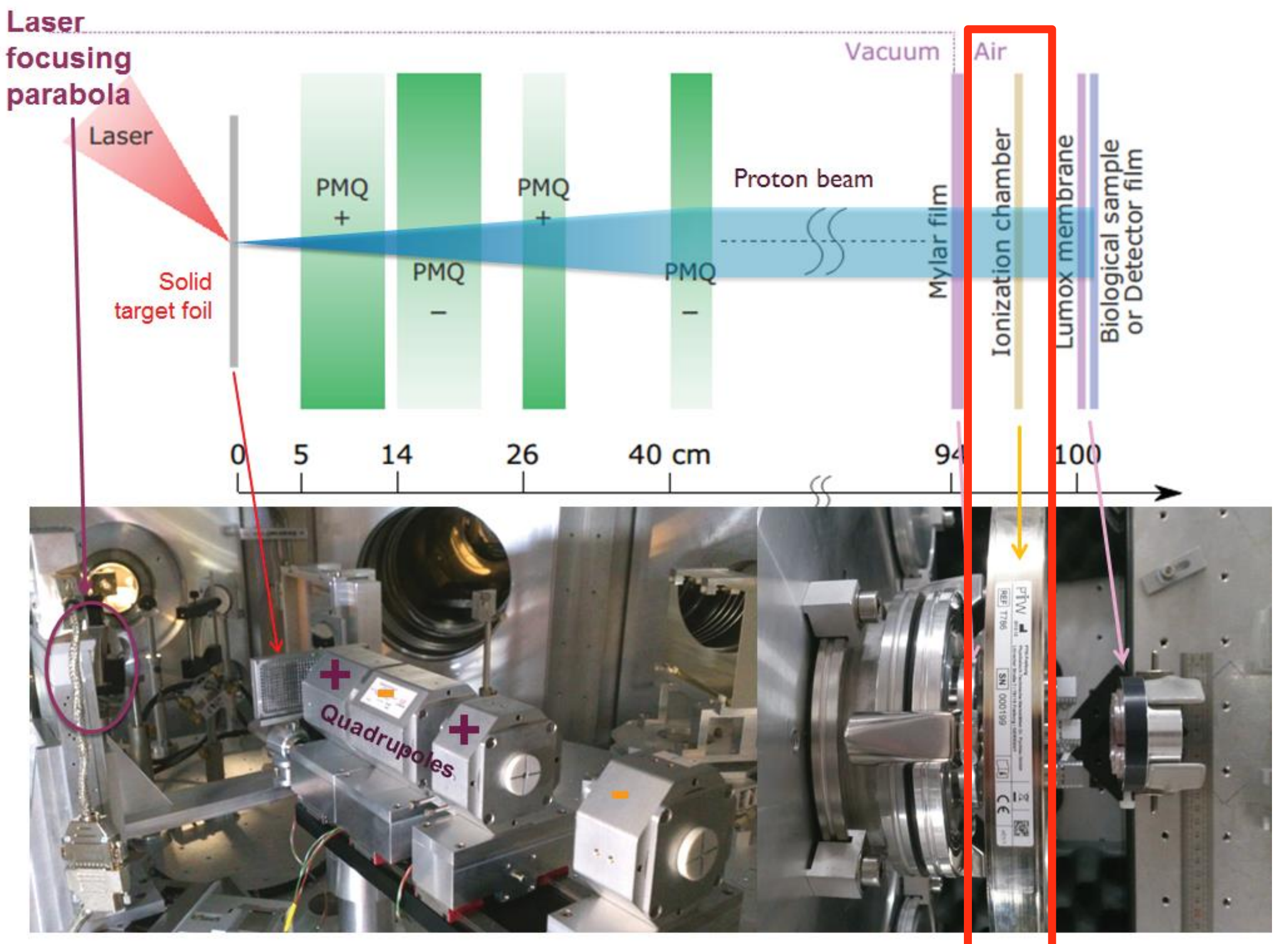
Pulse duration : **25 fs**

Focal spot diameter : **10 µm**

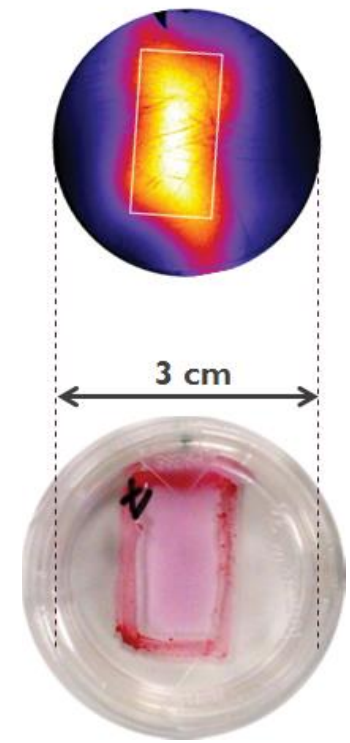
Intensity on target : **$2x10^{20}$ W.cm-2**

Contrast with XPW : **10^{-10}**

After Beam Shaping



Dose inhomogeneity on the irradiated area σ=22%



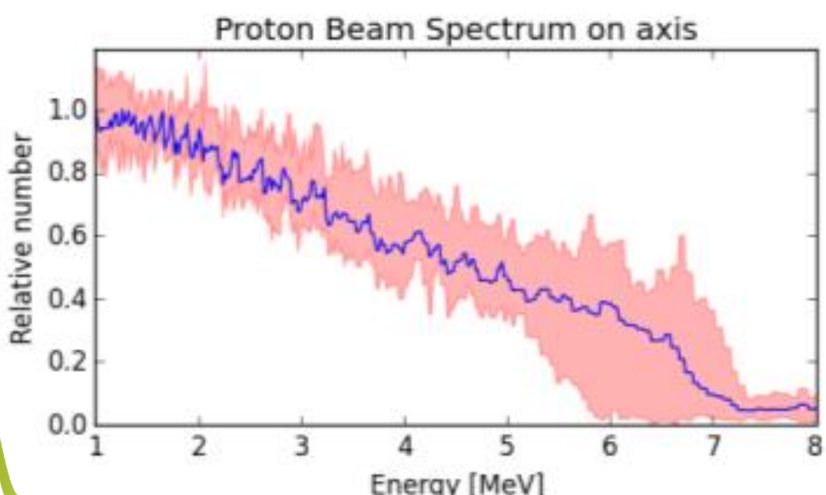
Bottom thickness = 25 µm

- Online Dosimetry with a transmission ionization chamber (calibrated by ICPO)

Pommarel *et al.* (2017)

Pulsed-Protons’ RBEs evaluation

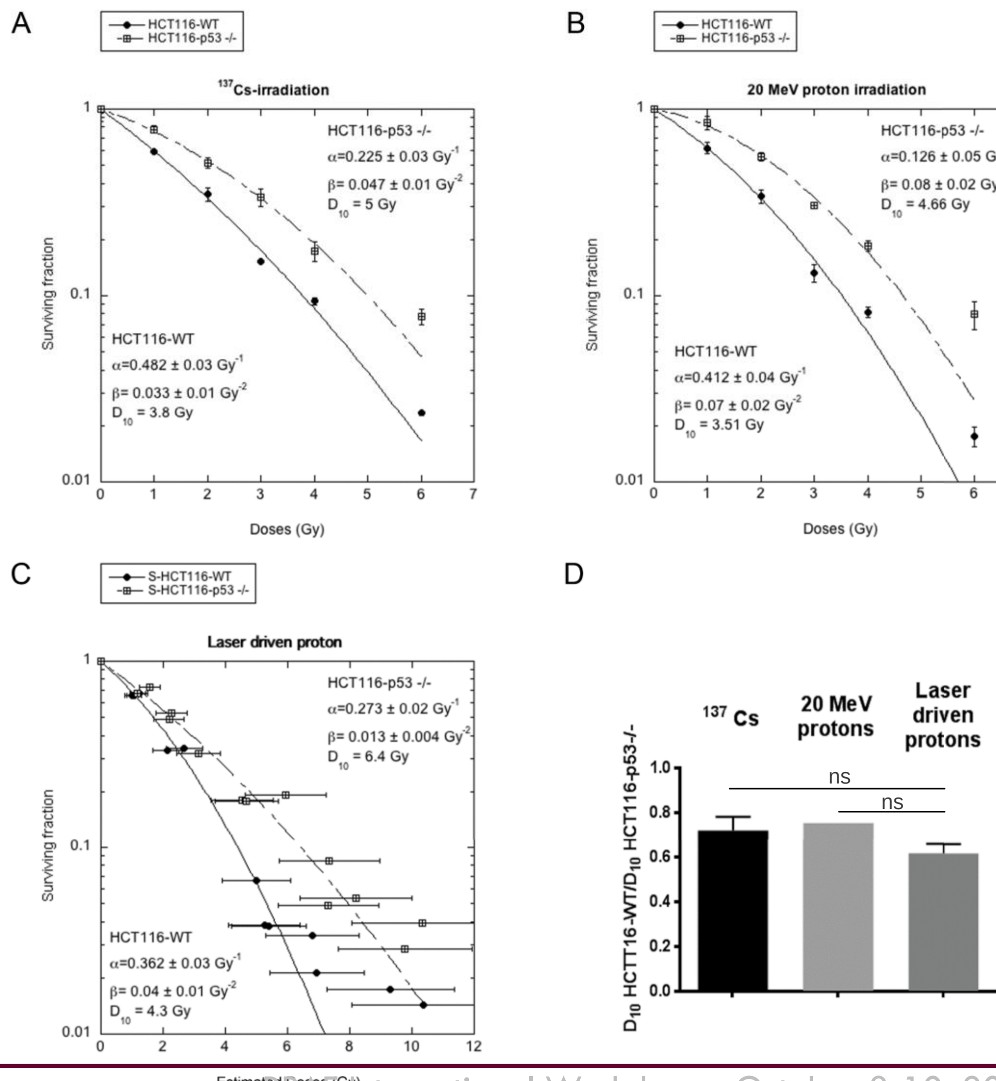
- **Laser Irradiations :**
  - **5 MeV**
  - **0.7 ± 0.25 Gy/bunch** (9,7nC)
  - pulse ≈ **6 ns**
  - **2 x 10^8 Gy/s**
  - **40s between shots**



- **Conventionnal Beams :**
  - ^{137} Césium
  - Photons X, 20-200kV, 1,23Gy/Min
  - Medical Protons, 20MeV, 1-3Gy/min (ICPO)

- **Cell lines :**
  - HCT116 = colorectal cancer, radiosensitive (WT & $p53^{-/-}$)
  - SF763 & U87 = glioblastomas radioresistant

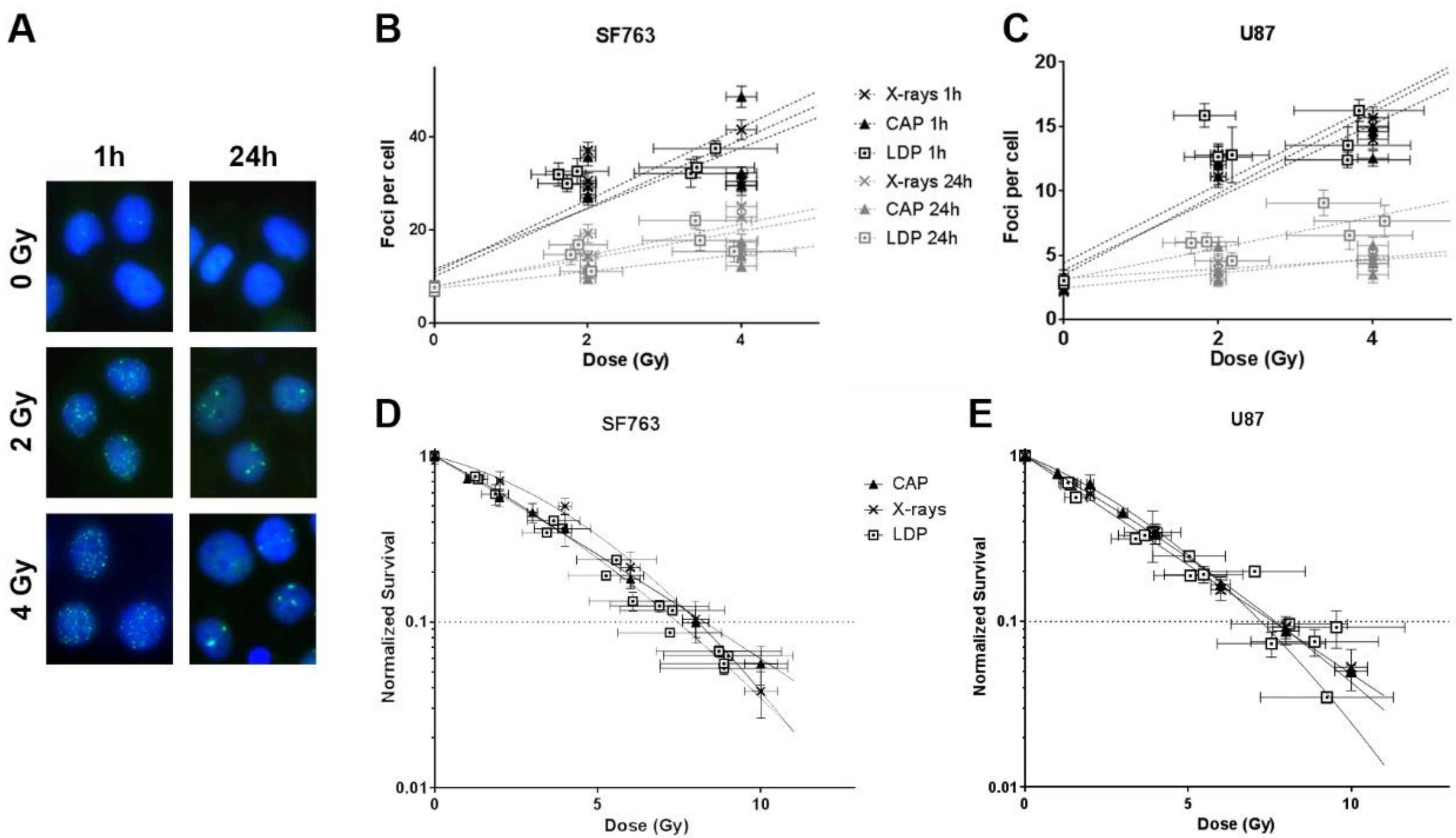
Survival assays – Radiosensitive cells



- No difference on survival ratios between the different beams
- Similar efficacy on radiosensitive tumoral model

Pommarel *et al.* (2017)

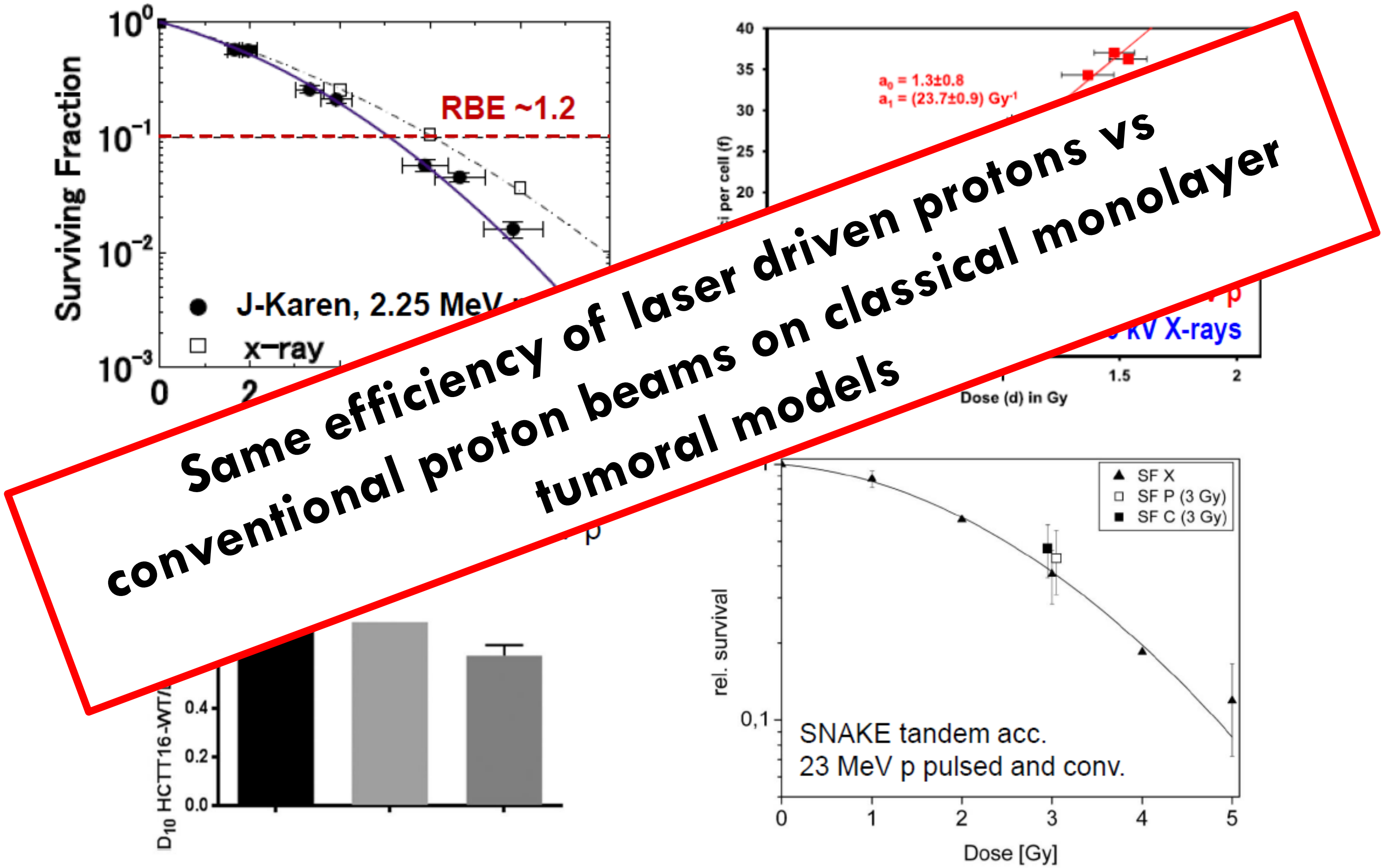
Glioblastoma models



- Laser driven protons (LDP) are as efficient as conventional accelerated protons (CAP) and X-rays in inducing DNA double strand breaks and cell killing on glioblastoma cell lines.

Bayart *et al., in prep*

Ultra-Intenses lasers & protontherapy



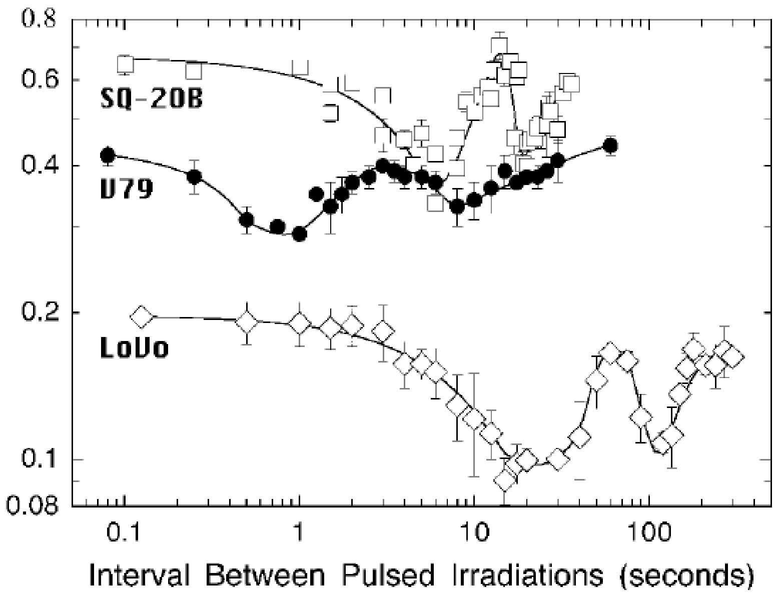
Same efficiency of laser driven protons vs conventional proton beams on classical monolayer tumoral models

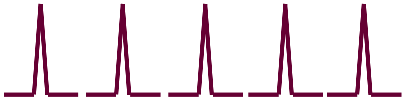
Yogo et al. APL 2011; Auer et al. Radiat Oncol 2011; Bin et al. APL 2012; Pommarel et al. PhysRevAcceBeams 2017

From E.Beyreuther, 2017/05/09

Playing with the cadence of bunches

W effect (Ponette *et al*, 2000)

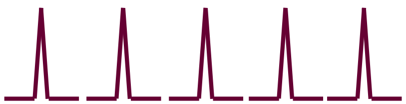


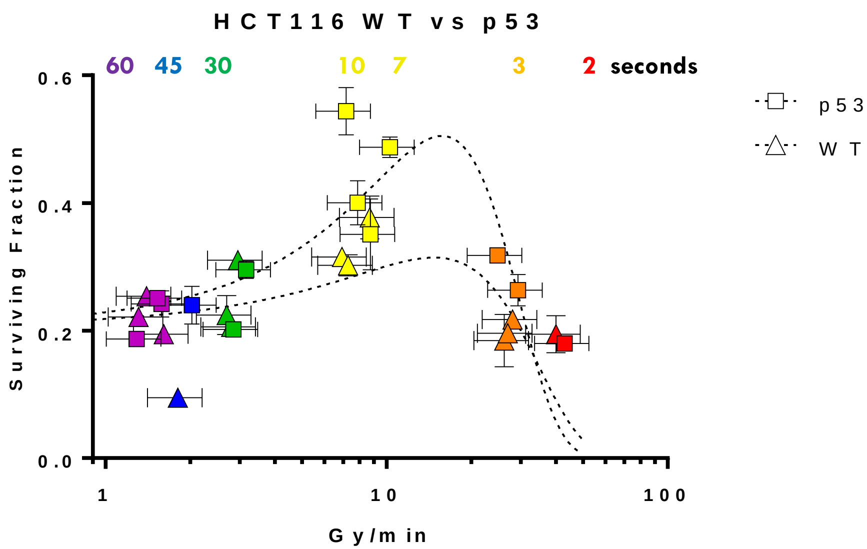


- Application of several laser pulses
- 5 shots
- Interval ranging from 2s to 60s

- Cell survival oscillation

Playing with the cadence of bunches

 , **5 shots, 2s to 60s**

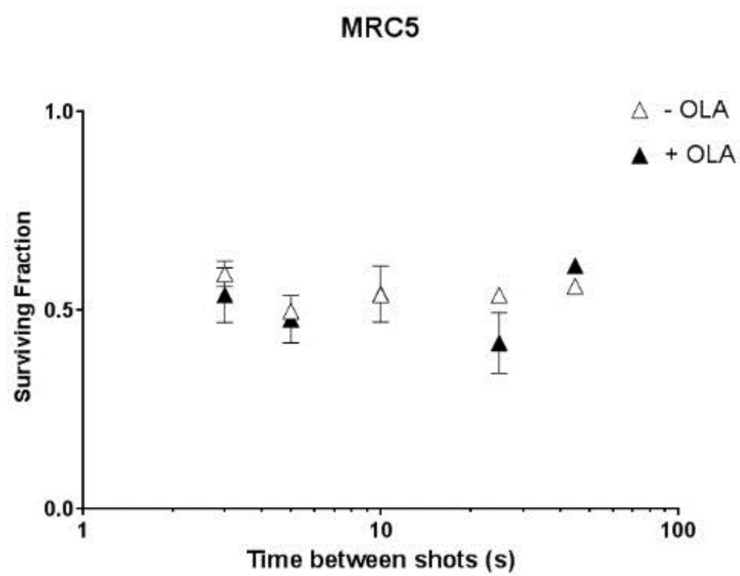


- In HCT116 cells, **variation of proton bunches cadency affects cell survival**
- Best survival of p53$^{-/-}$ cells compared to WT (result validation)
- **W-like effect ?**
- **Cell survival of HCT116 p53$^{-/-}$ converged to the HCT116 WT one at the shortest delays** (2 and 3 seconds)
- The **increase of proton bunches cadency could lead,** depending on cell type, **to increase cell mortality.**

Bayart *et al., in prep*

Laser cadence effect & healthy cells

- Tests on healthy fibroblasts MRC5



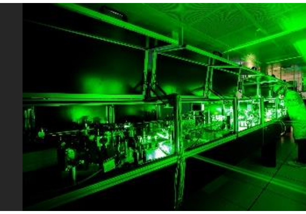
➢ Normal fibroblasts cell survival is **not affected by variation of the repetition rate of Laser protons bunches.**

Bayart *et al., in prep*

Conclusions

- Data consolidation on the **non-inferiority of laser accelerated protons vs conventional beams :** DNA damage generation and cell survival
- The temporal dose deposition modality (repetition rate) of laser bunches can affect cancer cell survival
- Demonstration of a **great therapeutic potential of the pulsed regimen of dose deposition :** HCT116 p53-/- reach HCT116 WT one
- Preliminary results suggest that no cell survival oscillation happen in healthy fibroblastic cells: **great potential for differential response**

Perspectives

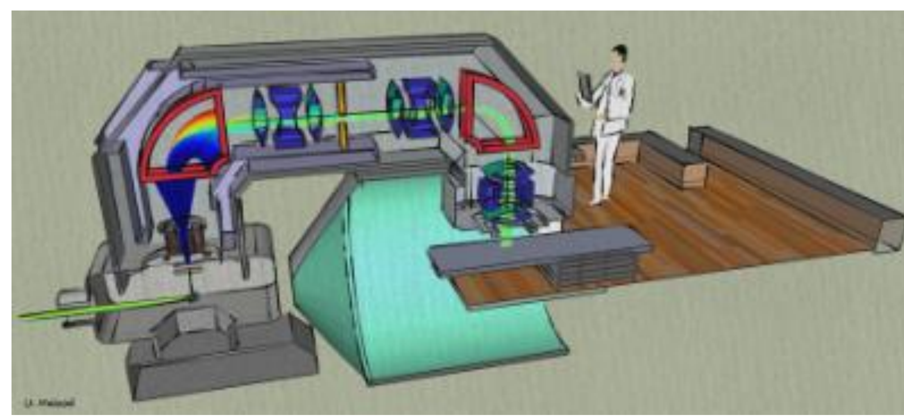


- ❑ **DNA repair signature** analysis :
- ➢ **NHEJ** vs **HR** ? (cf Big *et al.*, 2014; Fontana *et al.*, 2015)
- ➢ **DNA Damage Cluster** ? (Carter et al., 2018)

- ➢ Investigate the **differential response** between **normal** and **tumor** tissue.
- ➢ Laser-accelerated protons **associated immunogenic response**
- ➢ **Normal tissue sparing (Laser FLASH) ?**

Technological challenges

- **Laser upgrade is under going** (estimated delivery: January 2019)
  SAPHIR facility => **PHENIX facility**
- Increased repetition rate : laser-target interaction optimization
- Increased dose per bunch => preclinical studies
- Electrons & photons acceleration :
- At the same time ? Multiparticles radiotherapy ?
- In parallele? Real time imaging ?
- Gantry developpement
- Accurate **dosimetry**

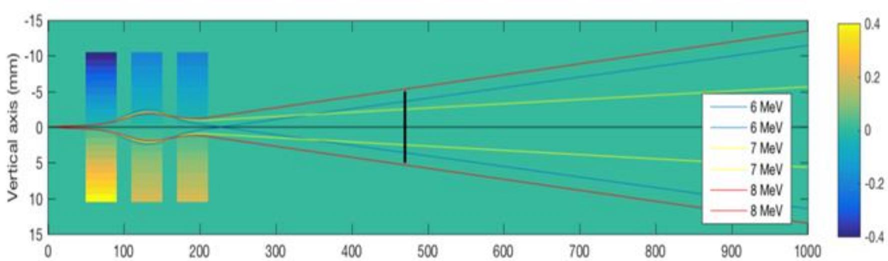


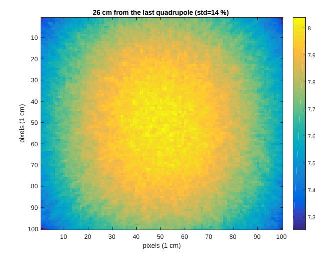
U. Masood and M. Baumann, Dresden, Germany, 2014

Perspectives

- Development for **pulsed electrons delivery**

- From 6 to 200 MeV: relevant for preclical & clinical use

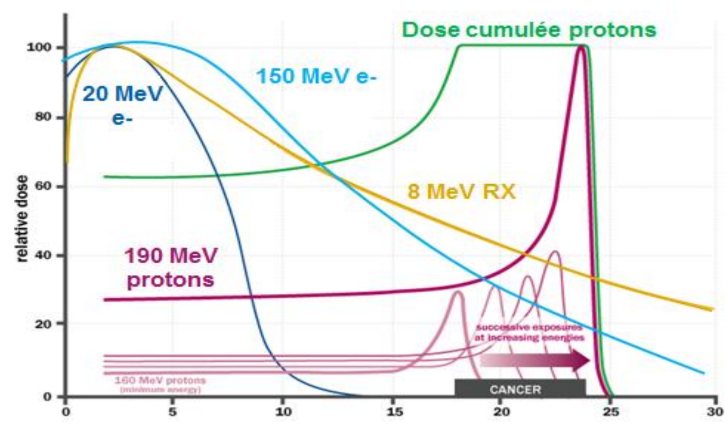




STD=14%

- Investigation of FLASH effect with pulsed electrons (better differential response between normal and tumoral tissue)

- Investigation of pulsed Very High Energy Electron (VHEE)



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Thank you for your attention !