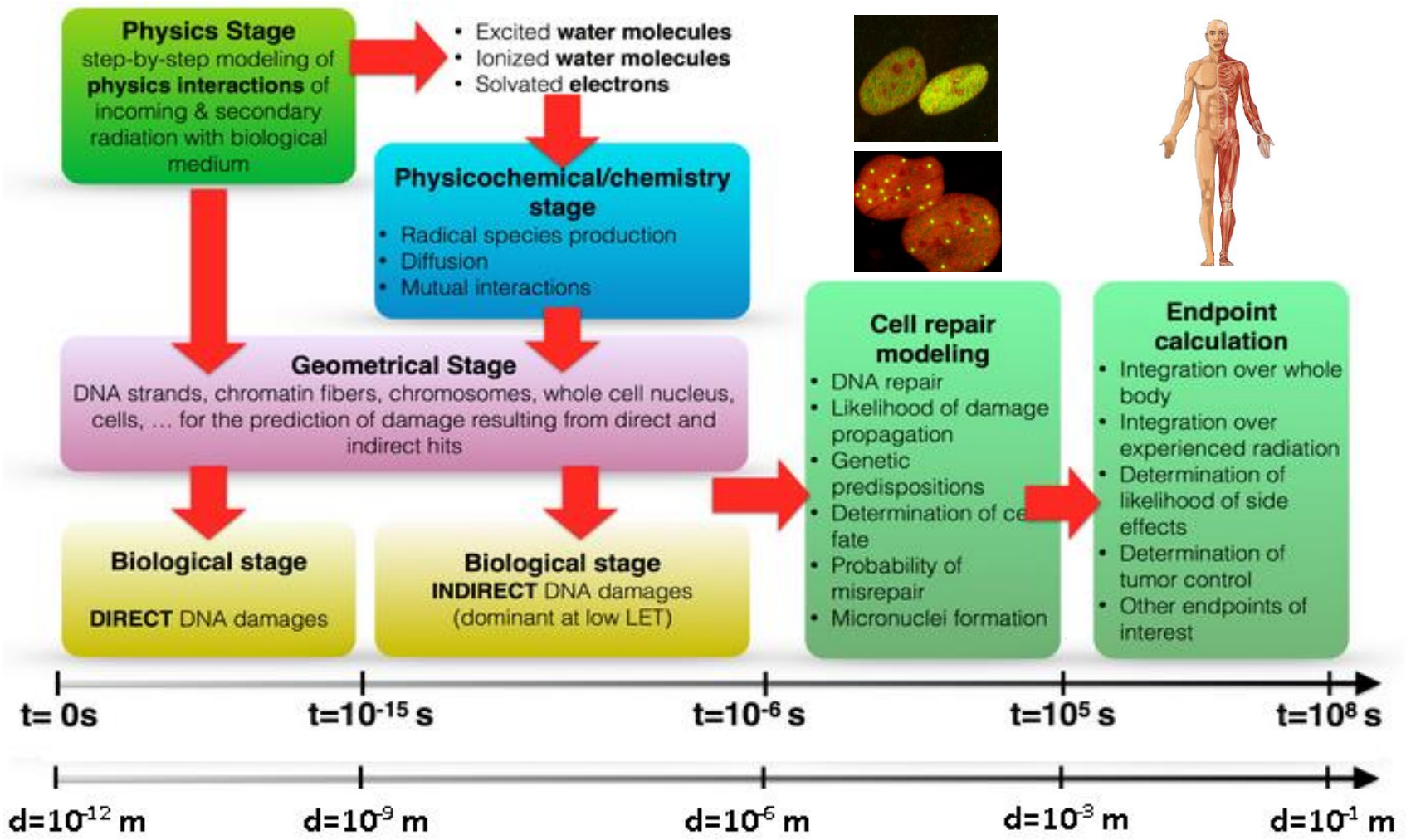
Développements instrumentaux: pour une optimisation spatiale et/ou temporelle de la dose différente en radiothérapie

L De Marzi
Institut Curie, Hospital, France
Institut Curie, Research Centre, France

Introduction

Irradiation : multiscale spatio-temporal optimisation



Introduction

Irradiation : multiscale spatio-temporal optimisation

	Spatial optimisation of the irradiation	Temporal optimisation of the irradiation
Examples (research project)	Minibeam radiation therapy	FLASH radiation therapy
Simulation (radiation modelling)	Dose distribution and optimization algorithms	Bio-physico-chemistry to be validated (eg RBE, geant4-DNA)
Measurements (radiation dosimetry)	Dosimeters with high spatial resolution (microdosimeters)	Dosimeters for ultra-high dose-rates (recombination effects)
Installations (radiation production)	Beamlines with improved spatial parameters	News treatment rooms for ultra-high dose-rates

Temporal optimisation of the irradiation

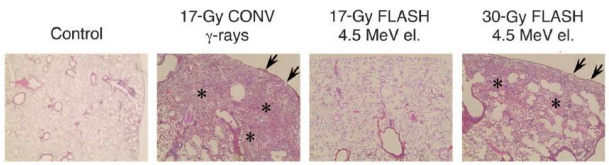
FLASH radiation therapy

www.ScienceTranslationalMedicine.org 16 July 2014 Vol 6 Issue 245 245ra93

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2]* Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[6,12§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

[1]Institut Curie, Centre de Recherche, 91405 Orsay, France. [2]INSERM U1021, 91405 Orsay, France. [3]Pathology Laboratory, Ecole Nationale Vétérinaire d'Alfort, Université Paris-Est, 94704 Maisons Alfort, France. [4]Université Paris-XI, 91405 Orsay, France. [5]INSERM U1030, Institut Gustave-Roussy, 94805 Villejuif, France. [6]Institut Curie, Centre de Recherche, 75248 Paris 05, France. [7]INSERM U900, 75248 Paris, France. [8]Mines ParisTech, 77305 Fontainebleau, France. [9]CNRS, UMR144, 75248 Paris, France. [10]Radio-Oncologie/Radiothérapie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland. [11]INSERM U967, Commissariat à l'Énergie Atomique (CEA), Division des Sciences du Vivant (DSV), Institut de Radiobiologie Cellulaire et Moléculaire (IRCM), 92265 Fontenay aux Roses, France.
*Corresponding author. E-mail: vincent.favaudon@curie.fr



A promise for radiation therapy?

FLASH irradiation : delivery time ≤ 0,5 s - mean dose rate ≥ 40 Gy/s

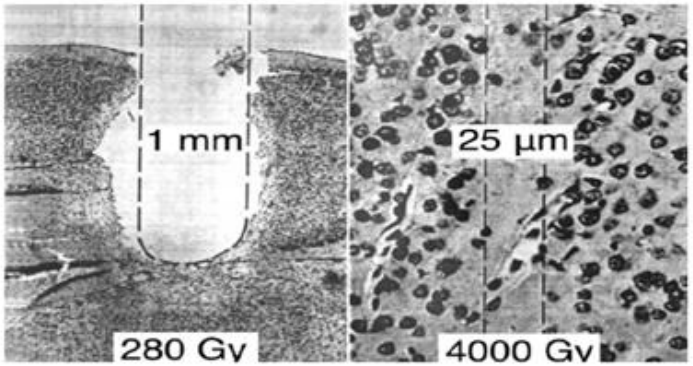
Tests on mice lung tumors with a 4.5 MeV electron linac have shown :

- ✓ Same anti-tumoral efficiency
- ✓ Enhancement of the differential responses between normal and tumor tissues vs CONV (dose rate ≤ 0.03 Gy/s) radiotherapy

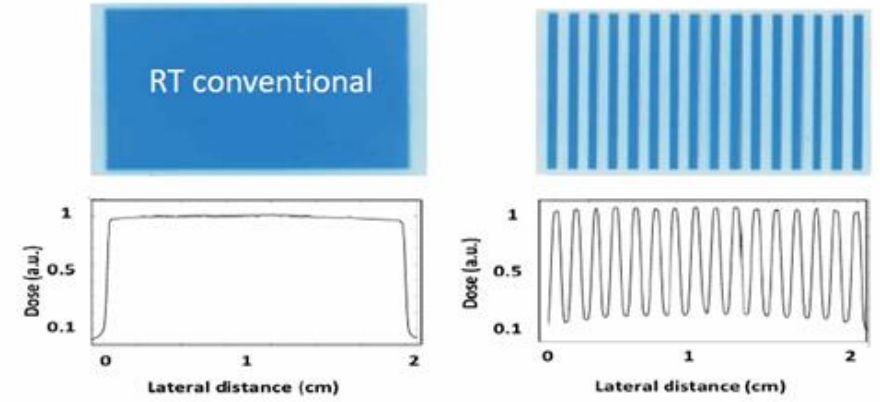
Spatial optimisation of the irradiation

Proton minibeam radiation therapy

Very small beam sizes (< 1 mm²) + Spatial Fractionation of Dose

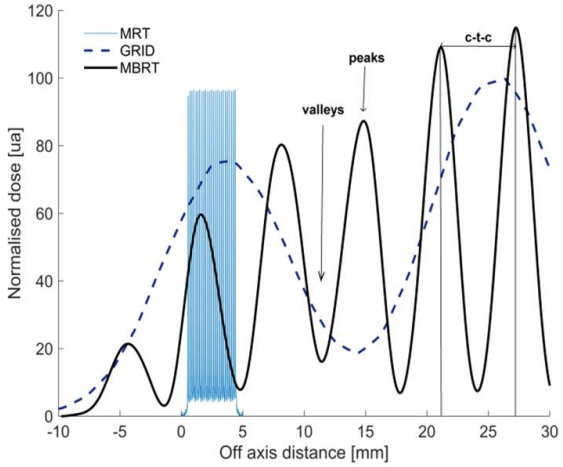


Zeman et al., Science (1959)



→ Dose-volume effect = the smaller the beam size, the higher the tolerance dose in healthy tissues.

Différentes techniques possibles



GRID with MV beams

- Large mini-beams (around 1×1 cm²)

Microbeam radiation therapy (MRT)

- 27 µm MRT beams spaced at 210 µm

Minibeam radiation therapy (pMBRT)

- Larger beams (500-700 µm)

Temporal optimisation of the irradiation

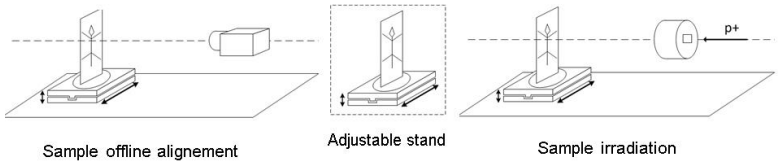
From an experimental setup for FLASH preclinical studies …

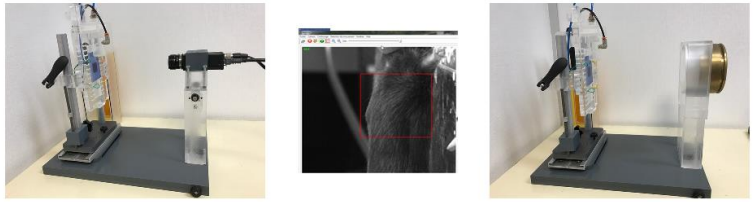
Biology Contribution

Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System

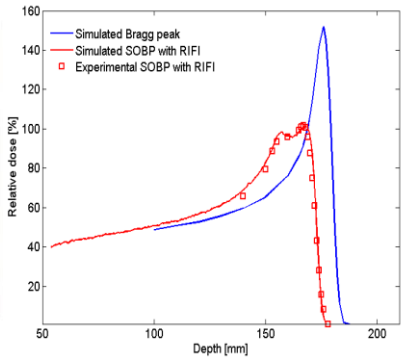
International Journal of Radiation Oncology biology • physics
www.redjournal.org

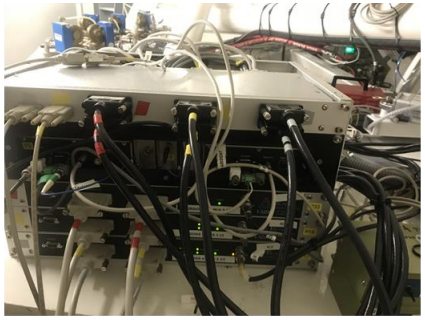
Annalisa Patriarca, PhD,* Charles Fouillade, PhD,*,† Michel Auger, MSc,* Frédéric Martin, MSc,* Frédéric Pouzoulet, PhD,‡ Catherine Nauraye, PhD,* Sophie Heinrich, PhD,‡ Vincent Favaudon, PhD,† Samuel Meyroneinc, MSc,* Rémi Dendale, MD,* Alejandro Mazal, PhD,* Philip Poortmans, MD, PhD,* Pierre Verrelle, MD, PhD,*,§ and Ludovic De Marzi, PhD*





Several experimental set-up developed at CPO: between 40 and 1000 Gy/s





Beamline modifications

1st FLASH setup: with a scattered beam

IC23 electrometers modifications + Gantry room – 230 MeV

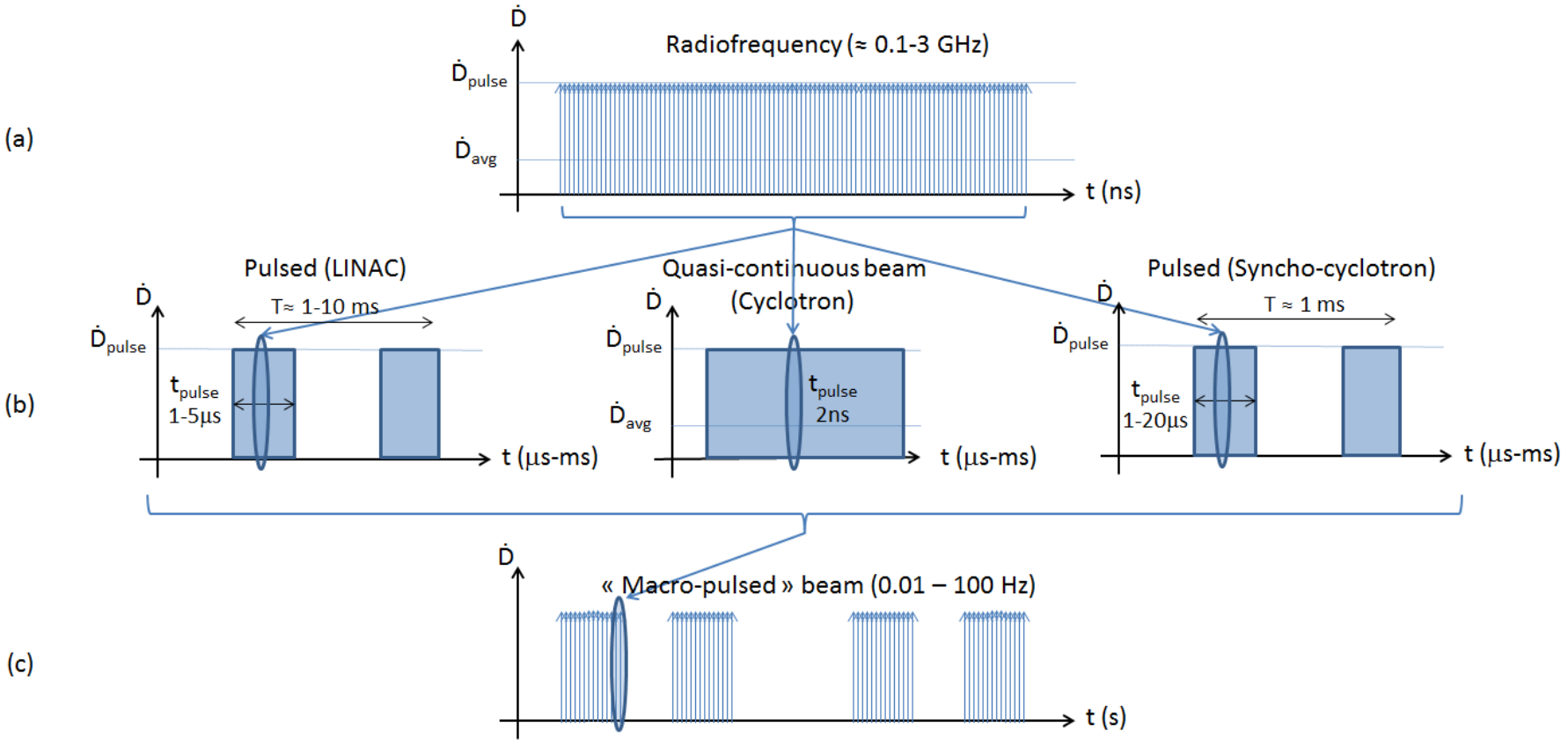
Effective collaboration with IBA initiated in 2018

2nd FLASH setup: with a scanned beam

Temporal optimisation of the irradiation

… to the design of a machine capable of delivering FLASH dose rates?

Temporal considerations …

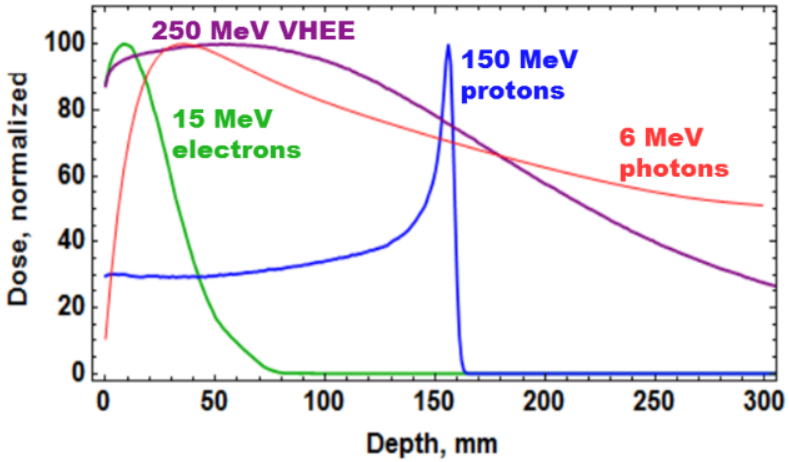


The mean dose-rate can be the same with completely different doses per pulse

Temporal optimisation of the irradiation

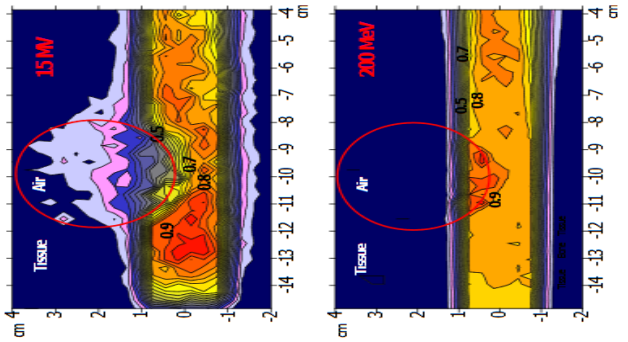
… to the design of a machine capable of delivering FLASH dose rates?

What about very high-energy electron beams (VHEE) ?

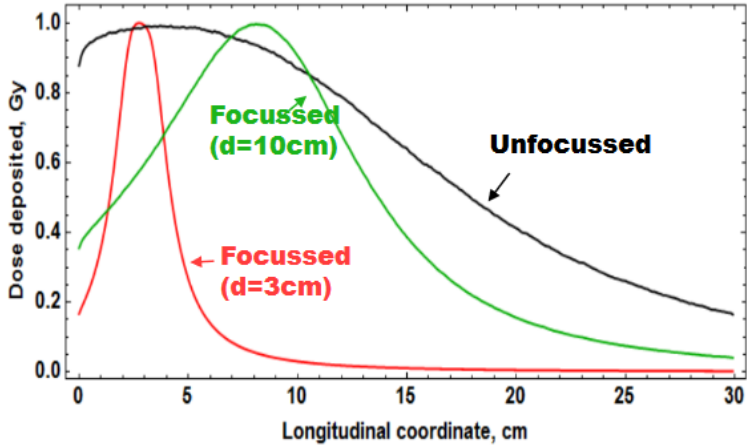


Comparison of relative depth dose distributions of photons, electrons and protons (since 2000s, Lagzda et al. 2019)

The combination of FLASH-VHEE with the benefits of grid therapy and/or pencil beam scanning has been recently proposed



Low energy electrons VHEE/protons



Temporal optimisation of the irradiation

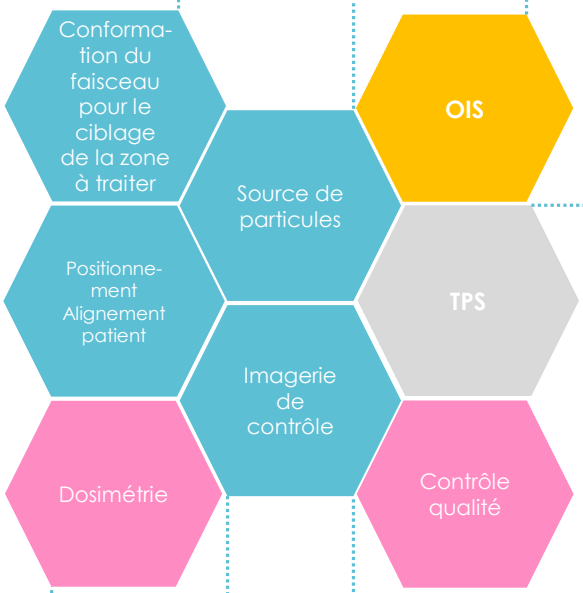
… to the design of a machine capable of delivering FLASH dose rates?

Collaboration Thales – Curie - CEA

Chaque membre du consortium apporte une brique essentielle au système

THALES

- Fournisseur de la solution d'accélérateur
- Développement du système d'irradiation
- Intégrateur système



institut Curie

- Physique médicale
- TPS
- Conformation faisceau
- Radioprotection ASN/ISRN
- Radiobiologie Flash
- Radiophysique Flash

cea

- Etudes de radioprotection
- Instrumentation pour la dosimétrie
- Support et expertises accélérateur

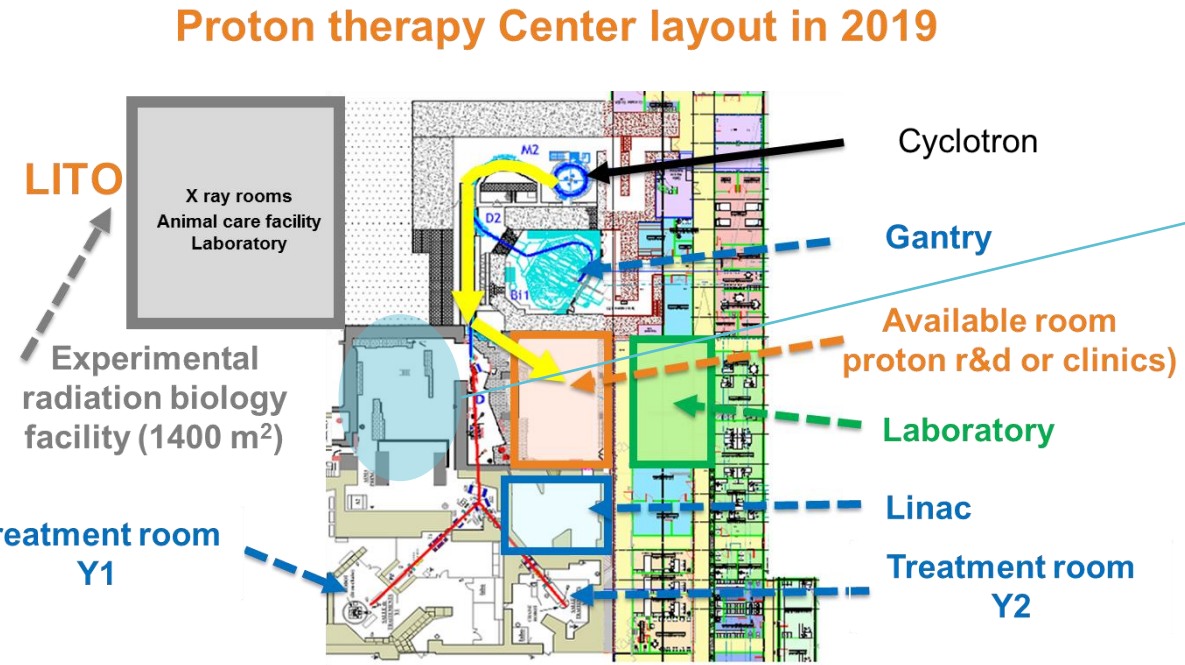
Fournisseurs

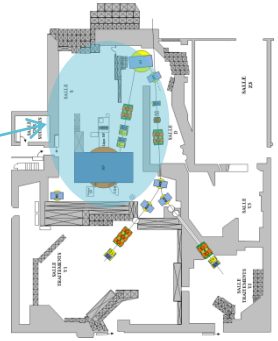
- Composants et système d'imagerie
- Solution de contrôle du positionnement
- Logiciel de C&C et TPS

Temporal optimisation of the irradiation

… to the design of a machine capable of delivering FLASH dose rates?

La plateforme, une opportunité pour le plateau d'Orsay:





Projet : Démontage du Synchrocyclotron (salle S)= nouvelle salle possible pour les VHEE

- Adapted planning for the experiments (evening and weekend)
- Specific transit area for radiobiological experiments (in vitro, in vivo)

Temporal optimisation of the irradiation

… to the design of a machine capable of delivering FLASH dose rates?

Prochaines étapes et rôle de l'institut Curie

Mise en place des démarches de demande de support et de financement

Chiffrage et dimensionnement du projet sur Orsay

- Projet sur 3 à 5 ans
- Budget du développement et de la première machine : 30 à 40 M€
- Ressources humaines
- Equipement à financer
- Aménagement d'1 salle au CPO

Campagne de présentations vers les acteurs clés

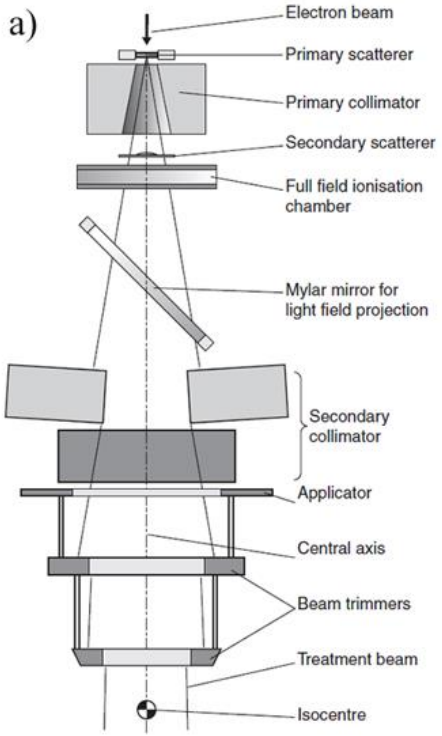
- CSF, DGE, ministère de la Recherche, région Ile de France: plusieurs réunions déjà en cours et à venir.

Temporal optimisation of the irradiation

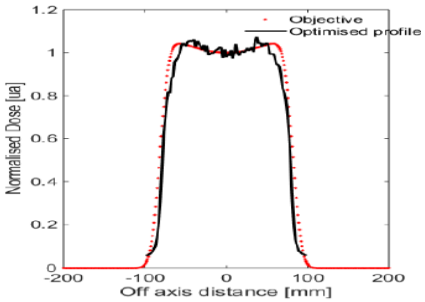
… to the design of a machine capable of delivering FLASH dose rates?

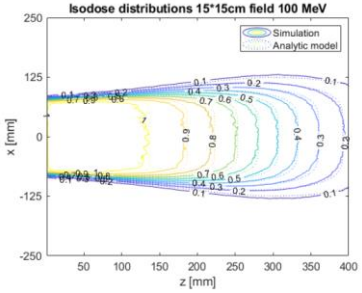
Thèse CIFRE en cours (Maria Grazia RONGA)

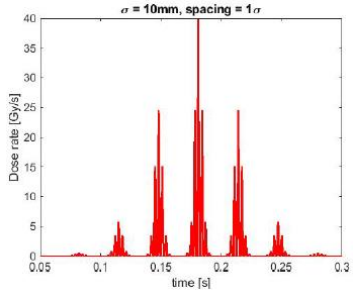
- **Objectives: design of the treatment head and comparison of scattered vs scanned beams for FLASH-VHEE application**



- **Methods: Monte Carlo simulations and analytical models :**
  - Specifications of the linac (Hz, mA, MeV, …).
  - Fast 3D dose calculation model.
  - Biological models and clinical applications (time resolved computations, RBE).



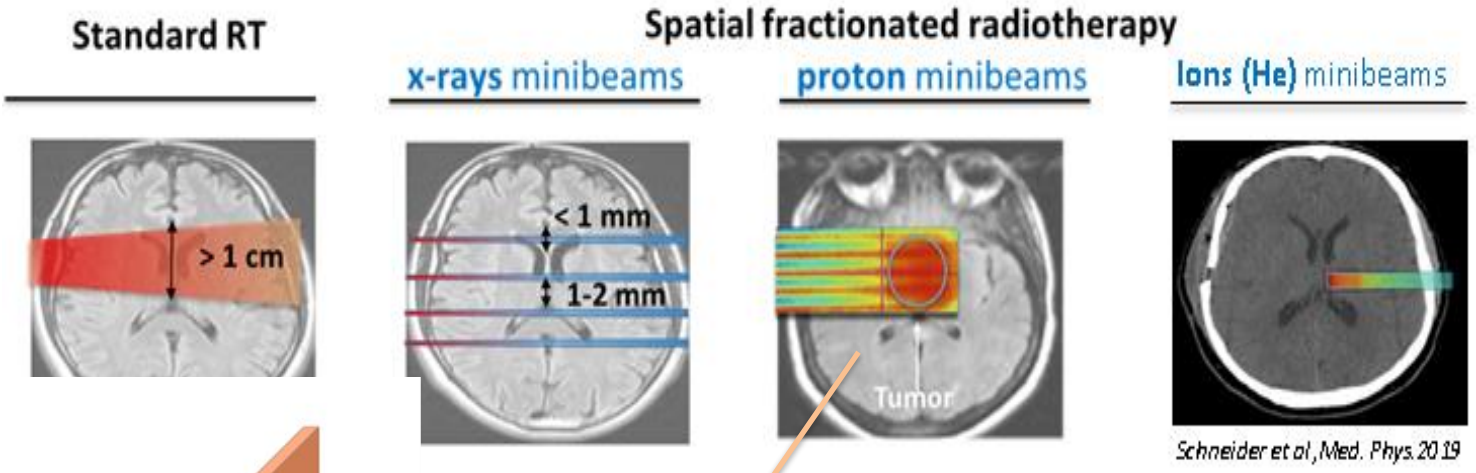




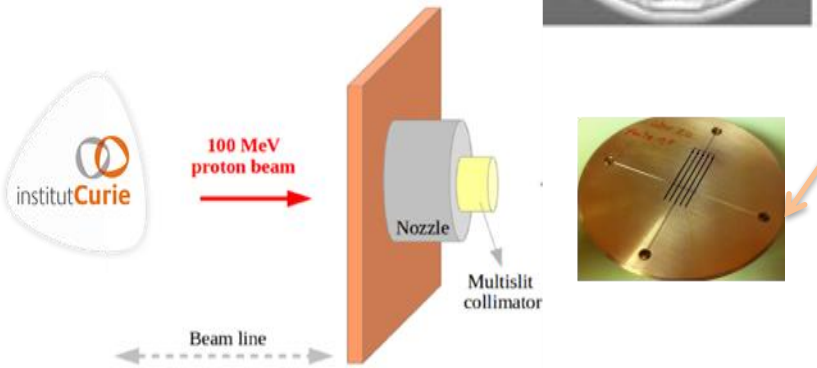
Spatial optimisation of the irradiation

Proton minibeam radiation therapy

Y Prezado's team ("New Approaches in Radiotherapy" UMR 3347/U1021) + Radiation oncology departement, Institut Curie:



Schneider et al, Med. Phys. 2019



Peucelle et al, Med. Phys.2015
De Marzi et al, Med Phys 2018

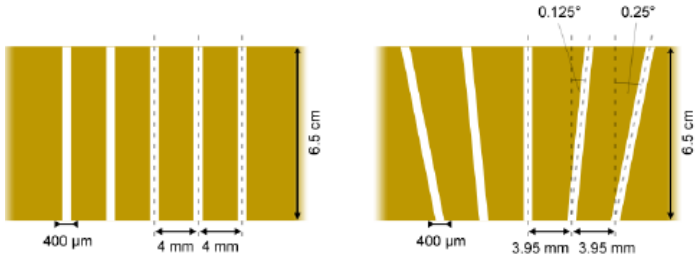
1st implementation in a clinical centre (CPO)!

- 100 MeV minibeams (400 μm)
- Scattered beamline, limited dose rate
- Multislit static collimators (2 to 4mm centre distance)

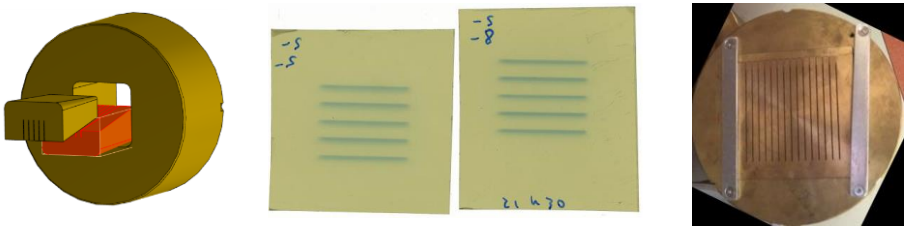
Spatial optimisation of the irradiation

From an experimental setup for pMBRT preclinical studies …

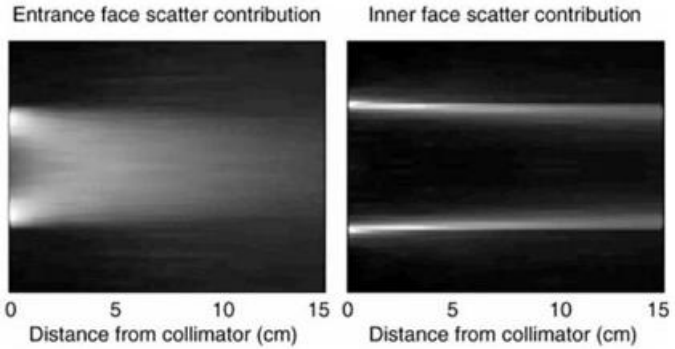
Pre-clinical and clinical trials preparation with clinical pencil beam scanning



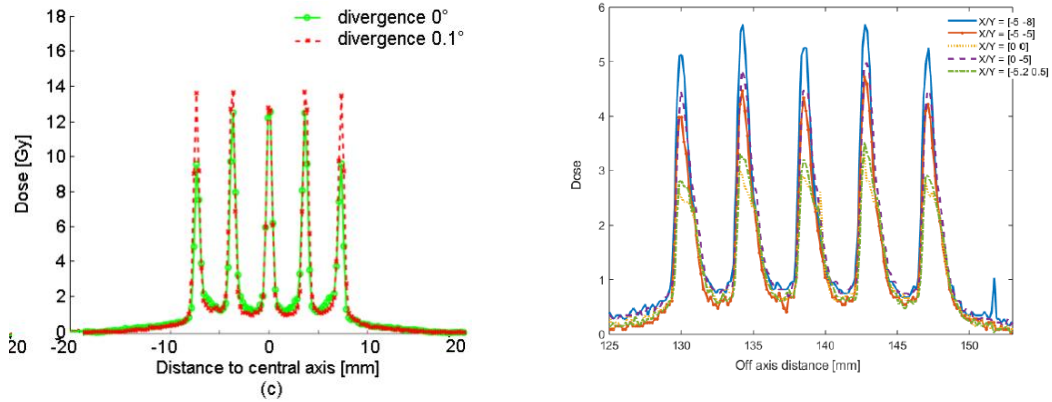
Theory



Manufacturing uncertainty: slits width, homogeneity issues



Secondary particles: contamination from the collimator



Dose distribution: PVDR, alignment issues…

Spatial optimisation of the irradiation

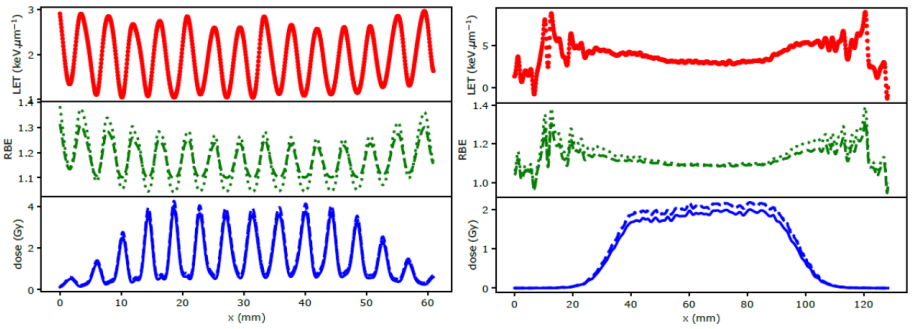
From an experimental setup for pMBRT preclinical studies …

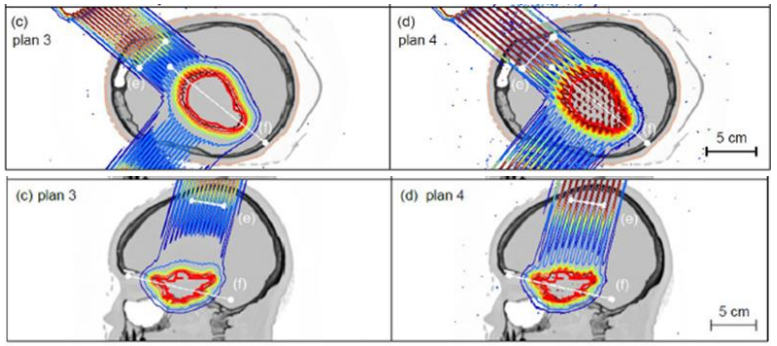
Possible translation of pMBRT towards clinical trials

SCIENTIFIC REPORTS
nature research

First proton minibeam radiation therapy treatment plan evaluation

P. Lansonneur[1], H. Mammar[1], C. Nauraye[1], A. Patriarca[1], E. Hierso[1], R. Dendale[1], Y. Prezado[2,3] & L. De Marzi[1,2,3]





The RBE distribution vary between 1.05 and 1.4 in healthy tissues, 1.07 and 1.1 in PTV

LET, RBE and dose profiles measured in healthy tissues (left) and in the PTV (right) (meningioma, field 1). The RBE is calculated using the models (dashed line) and (dotted line) with a dose per fraction set at 2 Gy and an α/β parameter equal to 3 Gy (brain healthy tissues) and 10 Gy (PTV).

Spatial optimisation of the irradiation

… to the design of a machine capable of delivering pMBRT small beams?

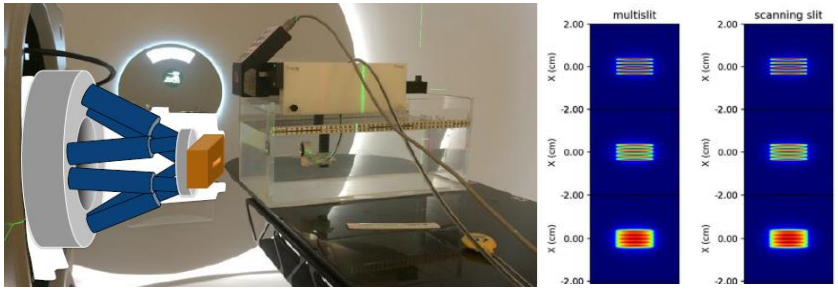
Possible translation of pMBRT towards clinical trials

scientific reports

OPEN

A scanning dynamic collimator for spot-scanning proton minibeam production

Marios Sotiropoulos & Yolanda Prezado



- Possible collaboration with IBA
- European Patent Application PCT/EP21306092
- Pro and cons of collimators:
  Flexibility, efficiency, secondary particles, robustness

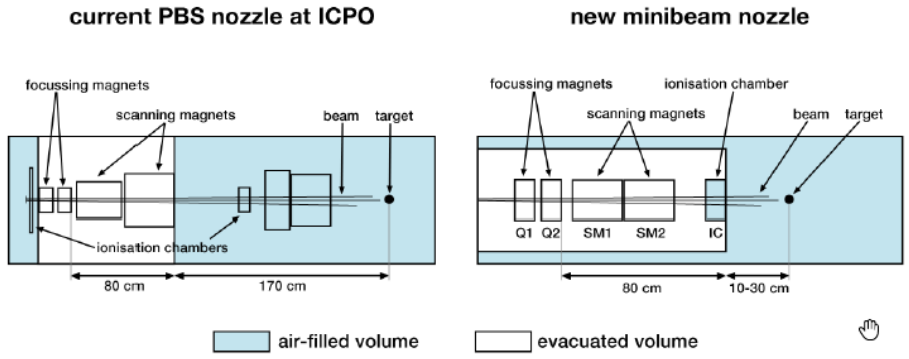
cancers

MDPI

Article

Conceptual Design of a Novel Nozzle Combined with a Clinical Proton Linac for Magnetically Focussed Minibeams

Tim Schneider [1,*], Annalisa Patriarca [2], Alberto Degiovanni [3], Manuel Gallas [3] and Yolanda Prezado [1]



- Possible collaboration with AVEO
- International Patent Application PCT/EP2020/082766
- Pro and cons of magnetic nozzle:
  Efficiency, secondary particles, optimization, complexity

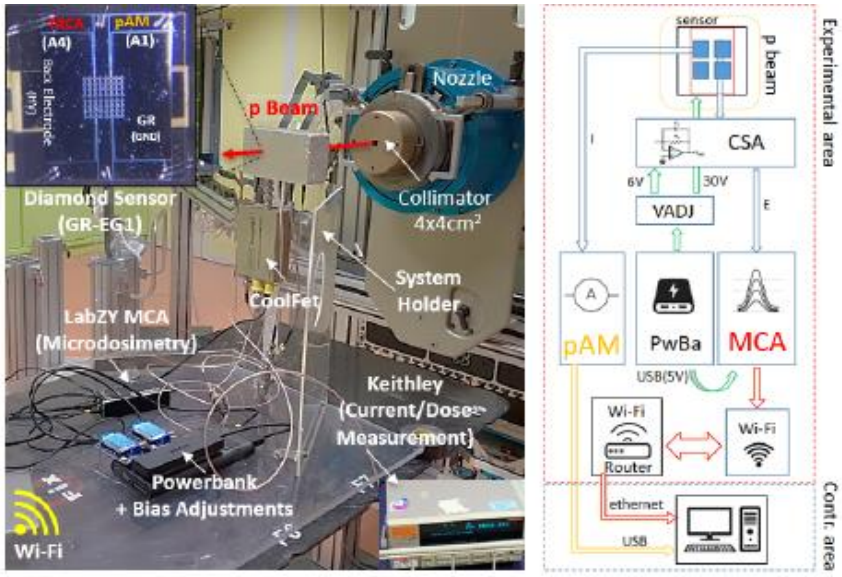
Radiobiological study of the irradiation

… to the design of a system capable of monitoring FLASH or pMBRT ?

sensors
Communication

Simultaneous Measurements of Dose and Microdosimetric Spectra in a Clinical Proton Beam Using a scCVD Diamond Membrane Microdosimeter

Oluwasayo Loto [1,*,†], Izabella Zahradnik [1], Amelia Maia Leite [2], Ludovic De Marzi [2,3], Dominique Tromson [1] and Michal Pomorski [1,*]



Experimental Setup for the GR Sensor, CPO measurements

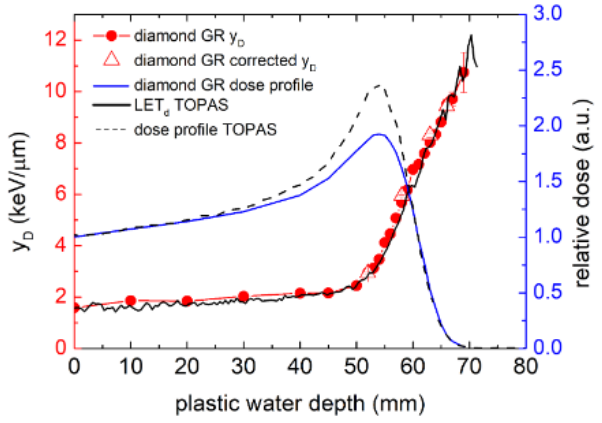
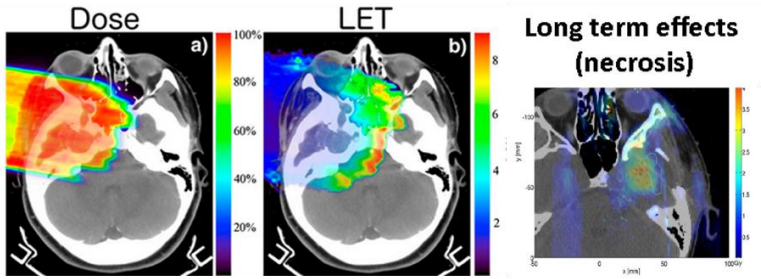


Figure 8. $\bar{y}_D$ along the dose profile measured with a diamond GR microdosimeter compared with dose profile and LET$_d$ from TOPAS simulations.

Models and data are still needed as well as a link between experimental/clinical data

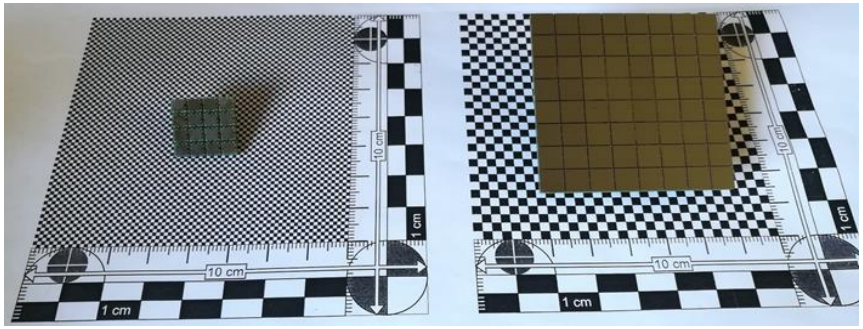


Radiobiological study of the irradiation

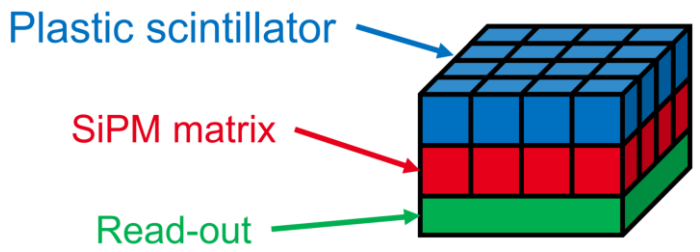
… to the design of a system capable of monitoring FLASH or pMBRT ?

Results: new solutions are tested at Institut Curie (vs calorimeter, SiPM, ionisation chamber, alanine ..)

Fast scintillator based device for on line FLASH beam dosimetry: ASTROLABE project (ongoing)



Example of SiPM matrices



Example of a pixelated dosimeter prototype

- **Dosimetric system for dose measurement of FLASH electron beams**
- **Monolithic and pixelated dosimetric system for on line FLASH electron beams**

Radiobiological study of the irradiation

… to the design of a machine capable of imaging for FLASH and pMBRT ?

No X-rays, accuracy/reproducibility, animals confined

Imaging and set-up for mouse/rat irradiation: offline animal immobilization and alignment system including a camera, an adjustable stand and the aperture for irradiation→ submillimetric positioning accuracy achieved.

Concluding remarks

Questions?

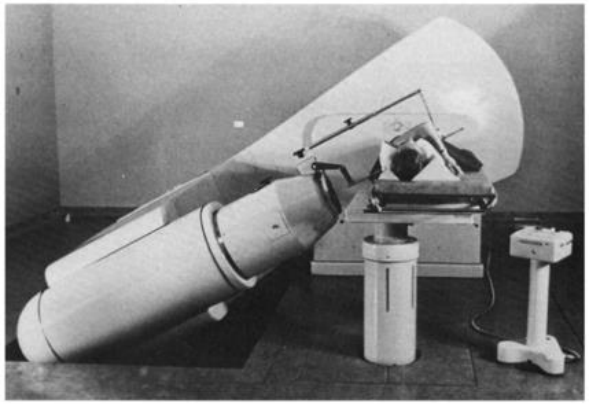


Fig. 1. First orientable linear accelerator—The Orthotron.