



Dosimetric environment and first results of the studies on the physicochemical and biological mechanisms of FLASH hadrontherapy at the ARRONAX cyclotron



Manon Evin, Charbel Koumeir, Quentin Mouchard, Guillaume Blain, Emeline Craff, Gregory Delpon, Vincent Fiegel, Giovanna Rosa Fois, Youssef Ghannam, Ferid Haddad, Lydia Maigne, Vincent Potiron, Gaëlle Saade, Noël Servagent, Stéphane Supiot, Sarra Terfas, Johan Vandenborre, Vincent Métivier, Sophie Chiavassa



FLASHMOD project

→ Development of FLASH external radiotherapy

FLASH effect

Increase in **dose rate** from **0.1 Gy/s** (CONV)

to at least **40 Gy/s** (UHDR):

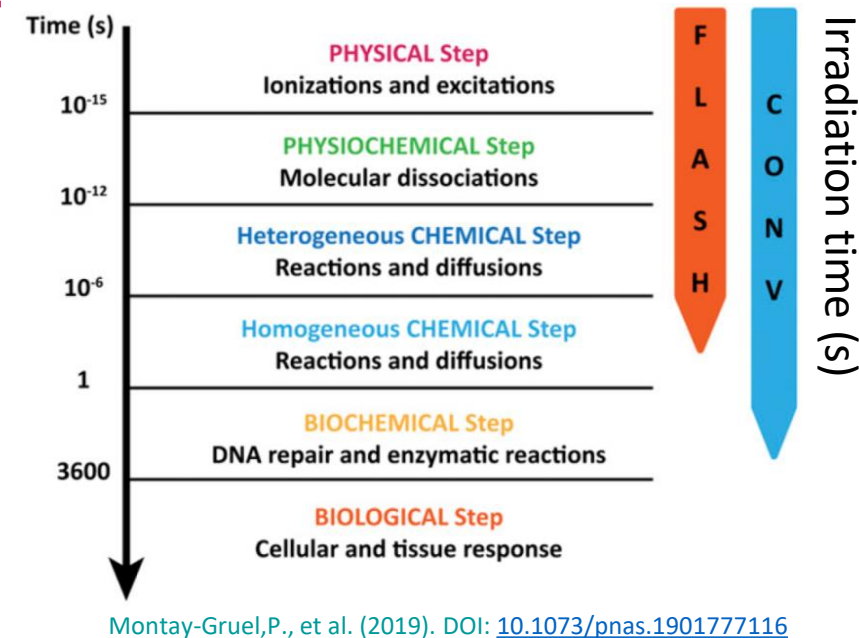
- Reduced toxicity to healthy tissues
- Same anti-tumoral efficiency

→ Enlargement of the therapeutic window

Main goals

Understand the FLASH effect mechanisms

Facing the technical challenges of UHDR



→ Multidisciplinary team around the ARRONAX cyclotron

Accélérateur pour la Recherche en Radiochimie et Oncologie à Nantes-Atlantique



Extracted particles	Maximal energy (MeV)	Range in water (cm)	LET at plateau entrance (keV/μm)
H ⁺	70	4,08	1
He ²⁺	70	0,34	11

Dose rates

- CONV : ~ **0.1 Gy/s**

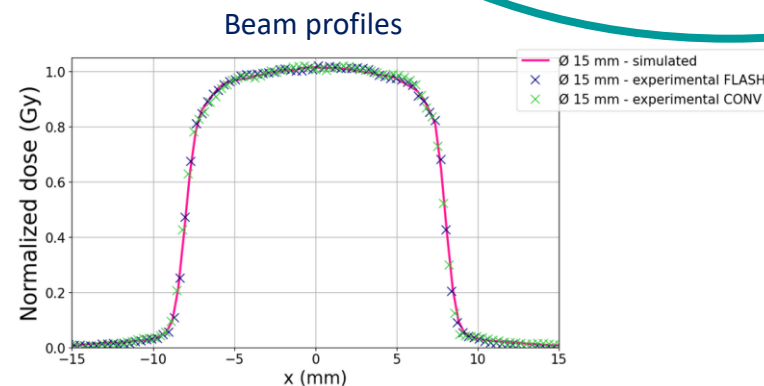
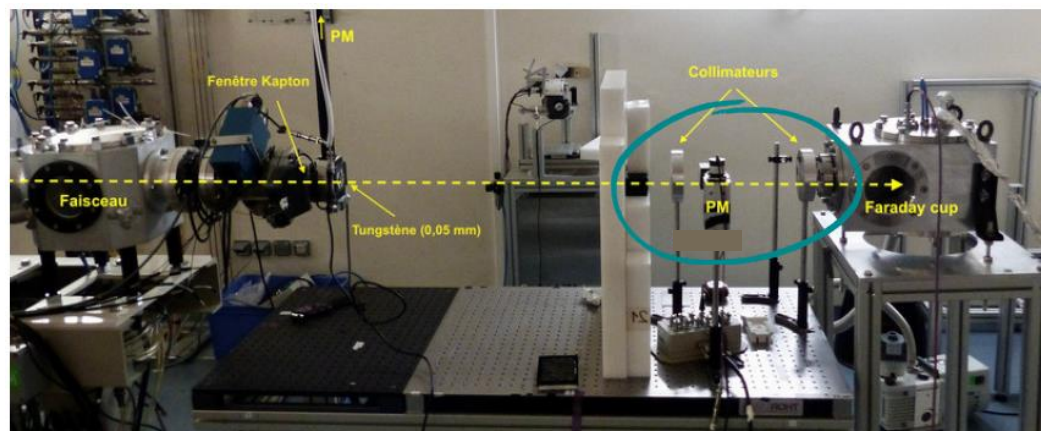
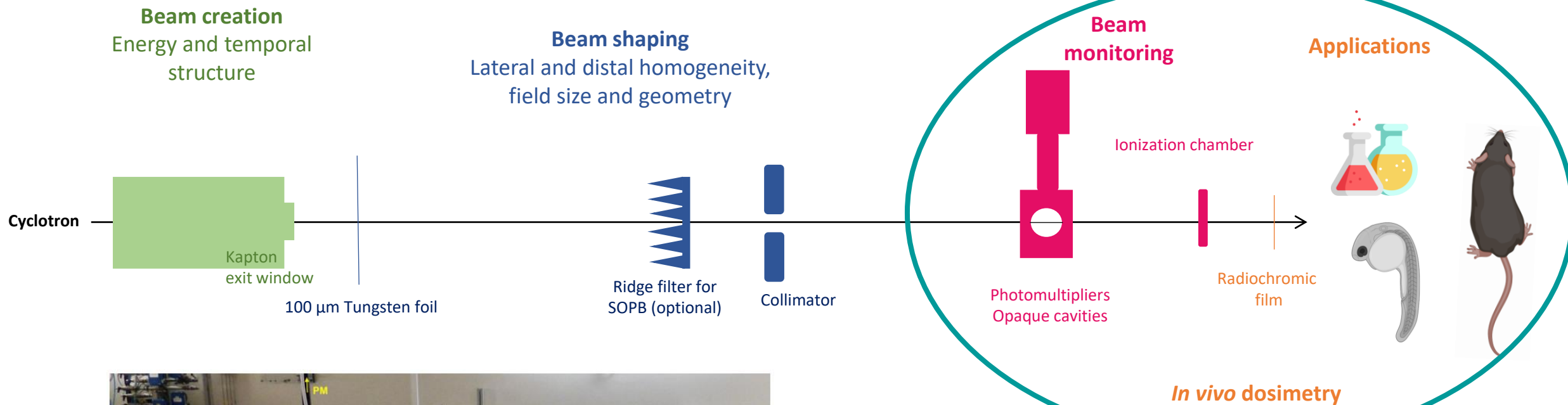


- UHDR:
Up to several hundred of **kGy/s**

ARRONAX preclinical irradiation platform

Sample or animal
positioning and targeting

Poster « Preclinical on small animals at the ARRONAX research cyclotron: repositioning, margins and field sizes.»

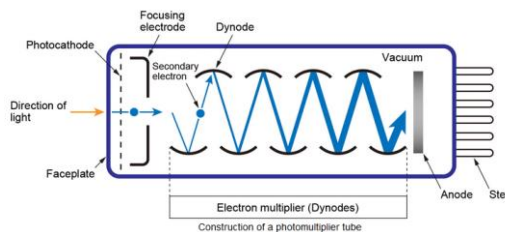
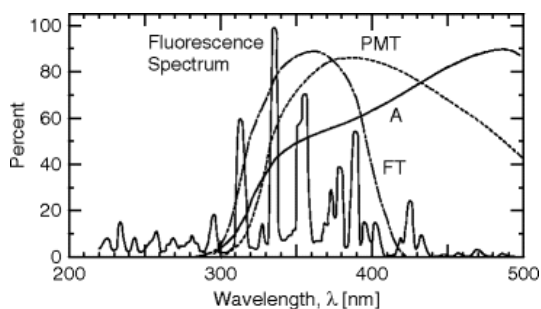


Innovative dosimetry
through radiation emitted by the irradiated medium

UHDR and CONV beam monitoring

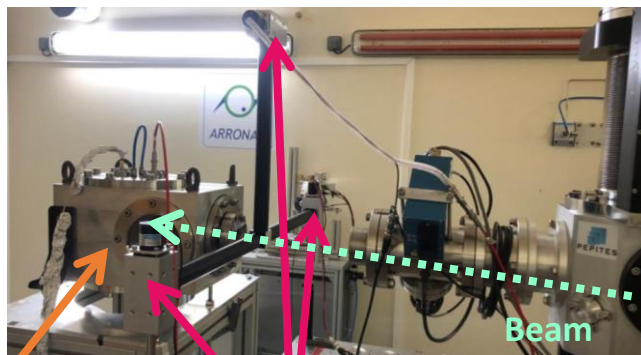
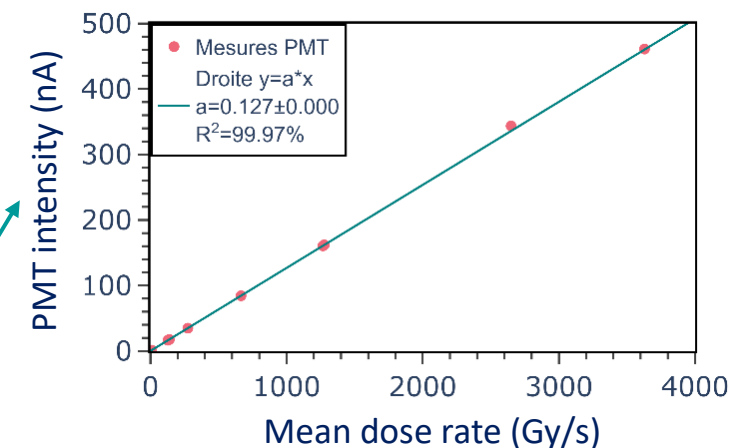
Quentin Mouchard

Fluorescence of the air dinitrogen: peak at 337 nm (UV) → Photomultiplier tube (PMT)



Matsuada website, « Photomultiplier Tube (PMT) ». [31/05/2023].

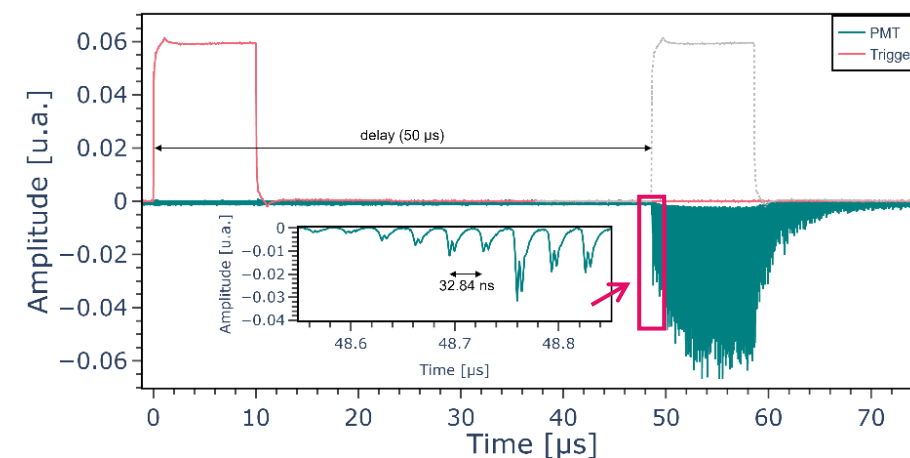
Linearity with dose rate



Charaterization of the method

- ✓ Selection of the best PMT candidates
- ✓ Feasibility of UHDR and CONV monitoring
- ✓ Feasibility of temporal monitoring
- ✓ Feasibility of a geometric profile

Temporal structures of beams

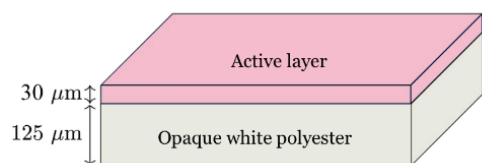


Vacuum faraday cage with guard ring

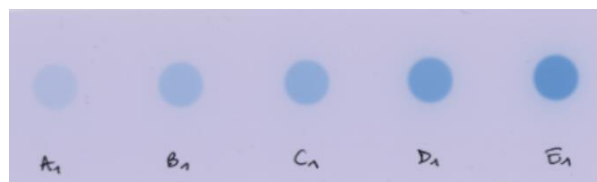
PMT

In vivo dosimetry with radiochromic films

OrthoChromic Films OC-1



OC-1



Absorbed dose (2, 5, 10, 20, 30 Gy)

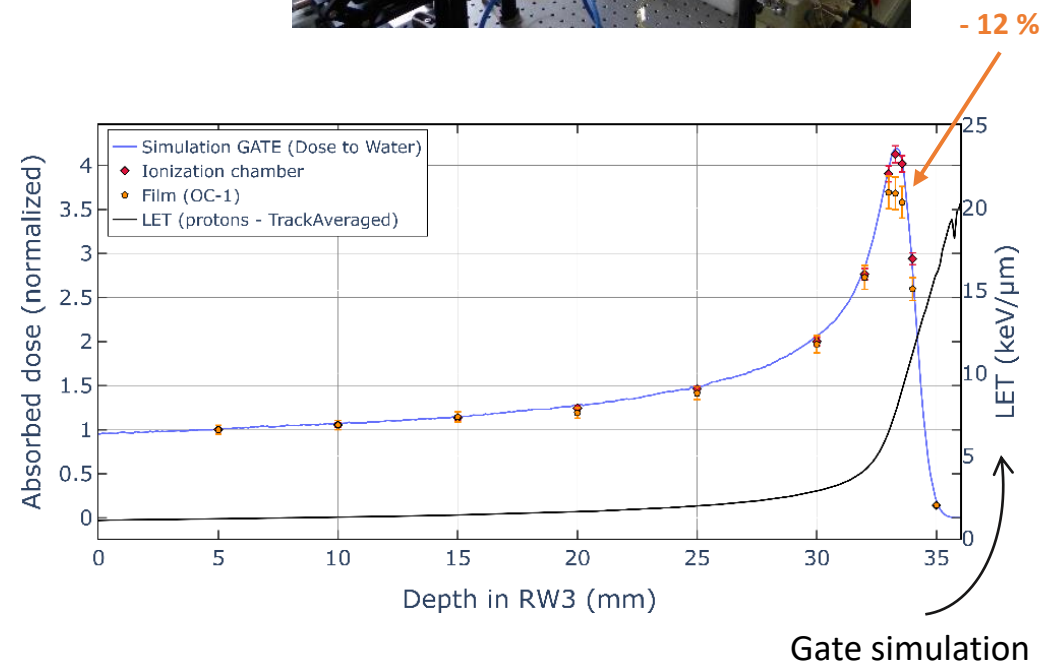
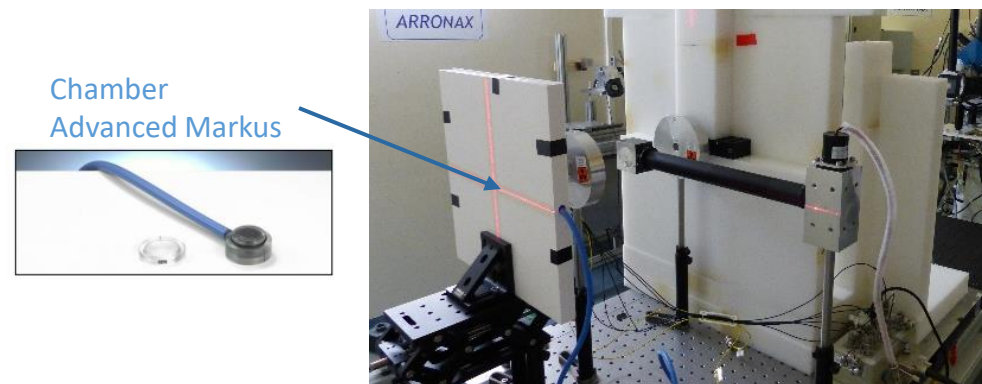
✓ Independent of dose rate

➔ Calibration for proton in CONV with TRS-398 formalism (PTW Advanced Markus)

• Villoing, et al. « Proton Beam Dosimetry at Ultra-High Dose Rates (FLASH): Evaluation of GAFchromic™ (EBT3, EBT-XD) and OrthoChromic (OC-1) Film Performances ». *Medical Physics*, 2022. <https://doi.org/10.1002/mp.15526>.

• Villoing., et al., « Response characterization of a new radiochromic film to ultra high dose rates for light ions beams. » (*ESTRO 2022*). [hal-03680039](https://hal.archives-ouvertes.fr/hal-03680039)

LET (Linear Energy Transfert) dependency



Gate simulation

➔ Determination of the correction factor $f(\text{LET})$

Radiobiology: zebrafish embryos

- ✓ Biologically complex
- ✓ Rapid growth
- ✓ High statistical power

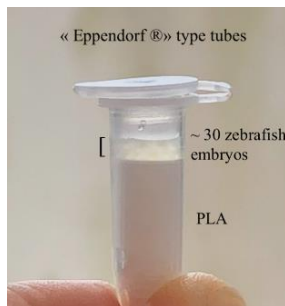
→ Study of the irradiation parameters triggering the FLASH effect

→ Dose rate effect on healthy tissues

Protocol



Collection of viable embryos



Assembling the samples → Hypoxia Bragg plateau

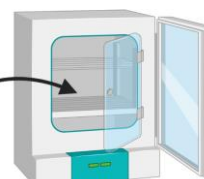
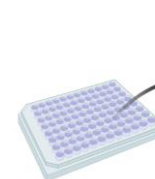
28 hpf



OC-1 Films

Irradiation

Culture (28°C)



4 days

Anesthesia (cold) and fixation



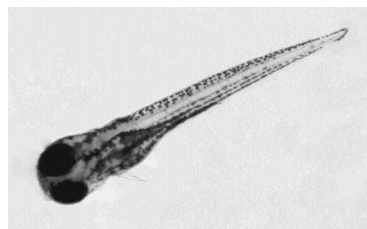
Acquisition of images and analysis

Results

- Length
- Curvature
- Pericardial oedema

~ 100 embryos/irradiation condition

Control (unirradiated)



7500 Gy/s



0,25 Gy/s



Photograph : Gaëlle Saadé

✓ Protective effect of FLASH with H^+ et He^{2+}

Mechanisms ?

Biological

Radiochemical

- Saadé et al., « Ultrahigh-Dose-Rate Proton Irradiation Elicits Reduced Toxicity in Zebrafish Embryos, *Advances in Radiation Oncology*, 2022. DOI: 10.1016/j.adro.2022.101124
- Ghannam Y. et al., « First evidence of in vivo effect of FLASH radiotherapy with helium ions in zebrafish embryos », 2023. <https://doi.org/10.1016/j.radonc.2023.109820>.

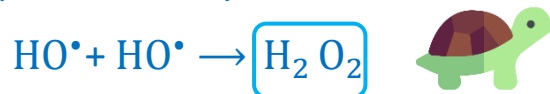
Radiochemistry: experimental

ROS → indirect effects of radiations

Reactive oxygen species produced by the radiolysis of water

$[H_2O_2]$ ↘ when the dose rate increases ↗
Mechanism ?

- Main production by



Recombination process of HO^\bullet ?



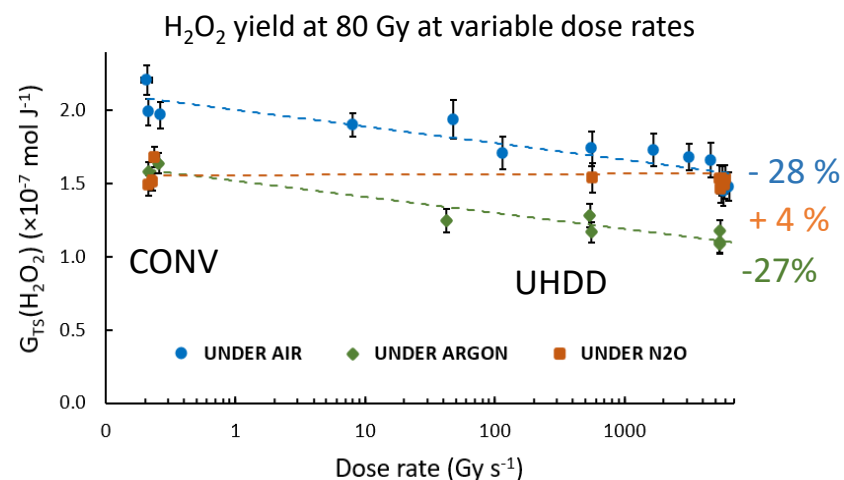
- Under N_2O : no e_{aq}^- , no O_2 in solution

- Under Argon: no O_2 in solution

Protocol

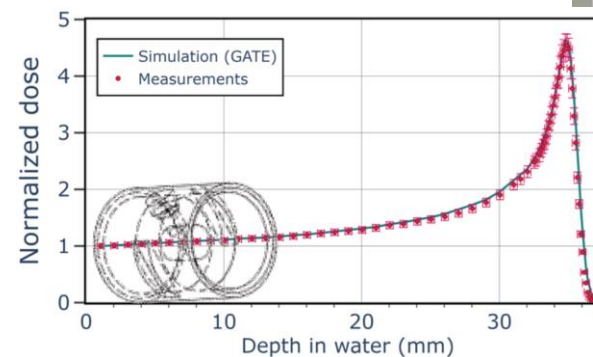
- PEEK cells
- Ultrapure water
- Atmospheres :
 - Air
 - N_2O
 - Argon

Results



- Key role of e_{aq}^- at the radiolysis step
- O_2 depletion has a minor impact

Irradiation



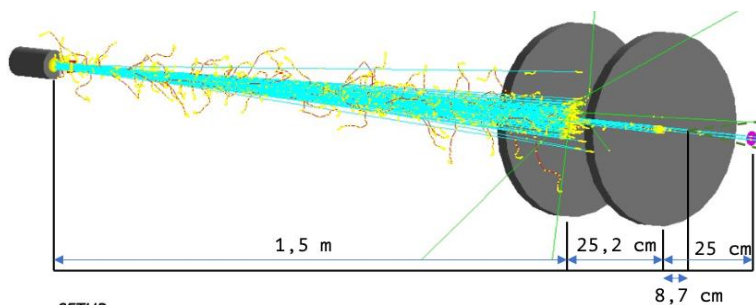
Protons in plateau



OC-1 films

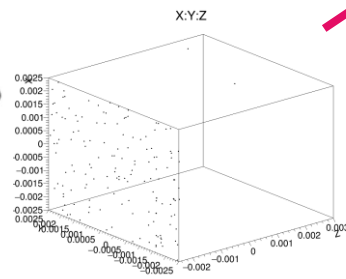
→ Spectro-photometry
 UV-Visible

Radiochemistry: simulation Geant4-DNA



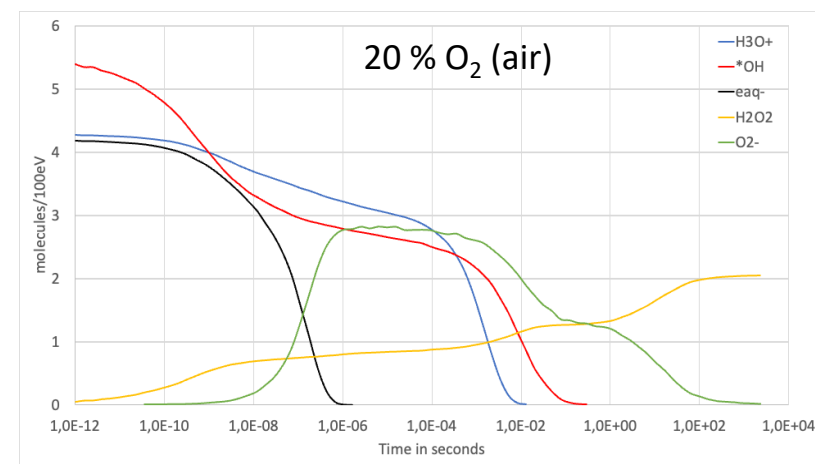
GATE macroscopic description of the beam and the setup

Geant4-DNA microscopic scale



Comparison of simulated and experimental yields

Temporal monitoring of ROS concentrations according to experimental conditions

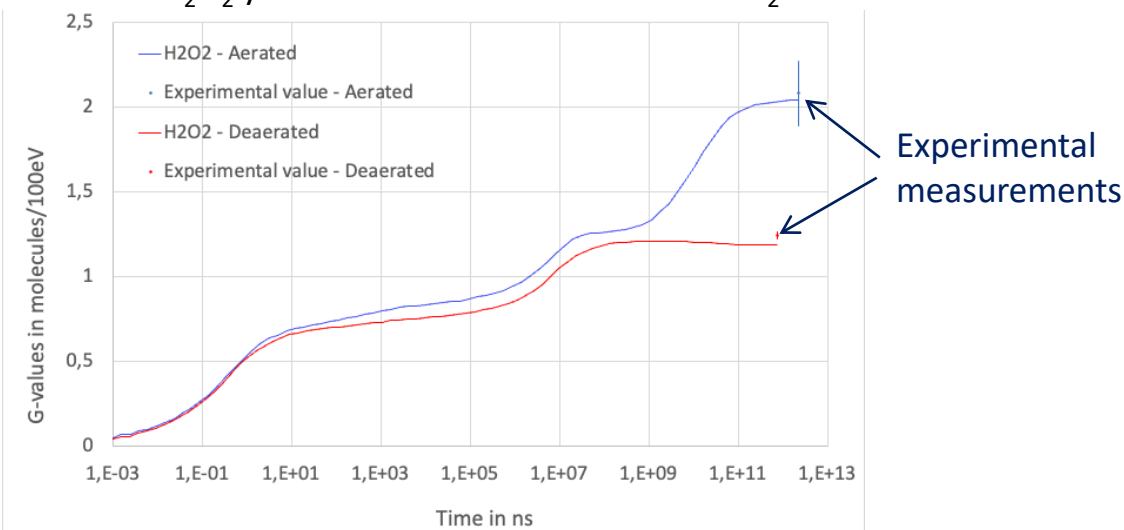


Validation at conventional flow rates (0.2 Gy/s)

- ✓ Understanding the role of oxygen and radiolytic species
- ✓ Reproduction of reference conditions (Fricke dosimetry)

→ Work in progress to model UHDR

H₂O₂ yield with and without dissolved O₂



Future application: mouse irradiations

Study both healthy tissues and tumors responses to UHDR

Study of preclinical set-up and instrumentation

Poster

Methodology for:

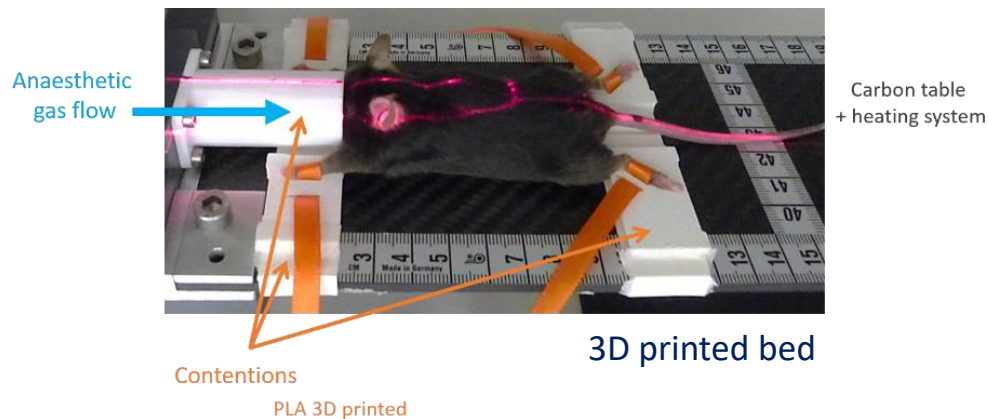
- **Optimal field size with fixed collimators**

Optimal homogeneous field size (*cohort*) = Organ size (*cohort*) + Margins_{Targeting} + Margins_{Respiratory}

- **Internal organs targeting without online imaging**

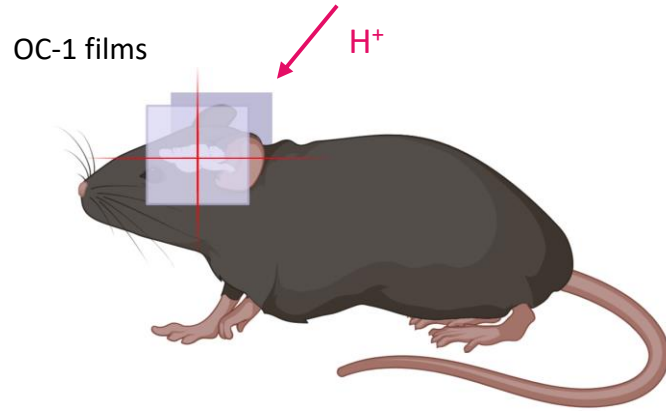
- *In vivo* dosimetry with radiochromic OC-1 films

- Impact of the respiratory cycle on the dose distribution on FLASH-RT

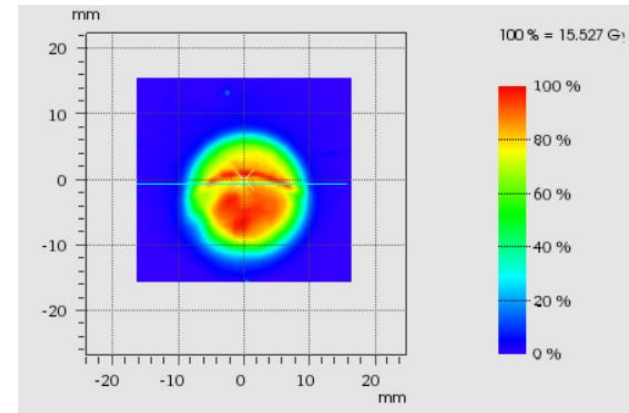


In vivo dosimetry with radiochromic films

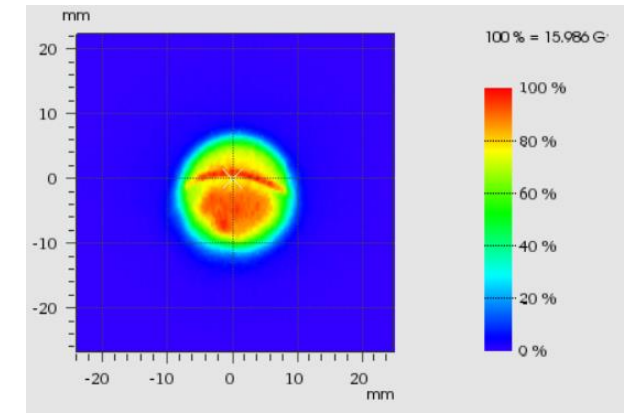
Mouse whole brain irradiation: simulation from XRAD225Cx μ CBCT image and targeting without image guidance at ARRONAX



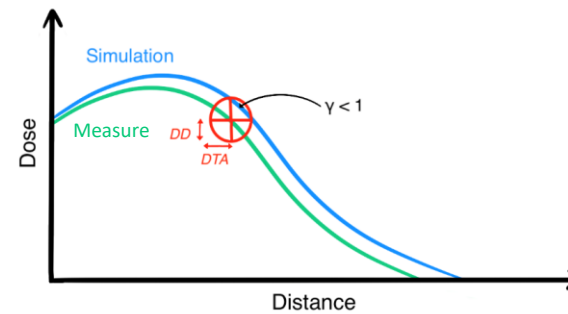
Experimental



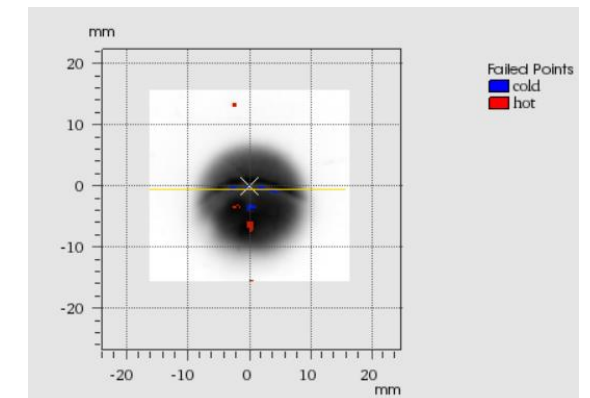
Simulated



Local gamma index 2D (DD 1% - DTA 1 mm):
pass rate 98,2 %



1D illustration of the gamma index metric



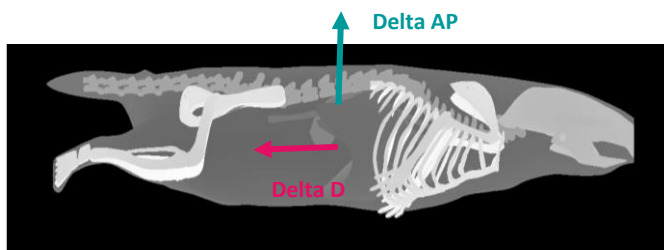
Impact of the respiratory cycle in FLASH-RT

FLASH-RT irradiation time ~ ms

Dosimetric impact ?



MOBY (Mouse Whole Body 4D Digital Fantom) V.2

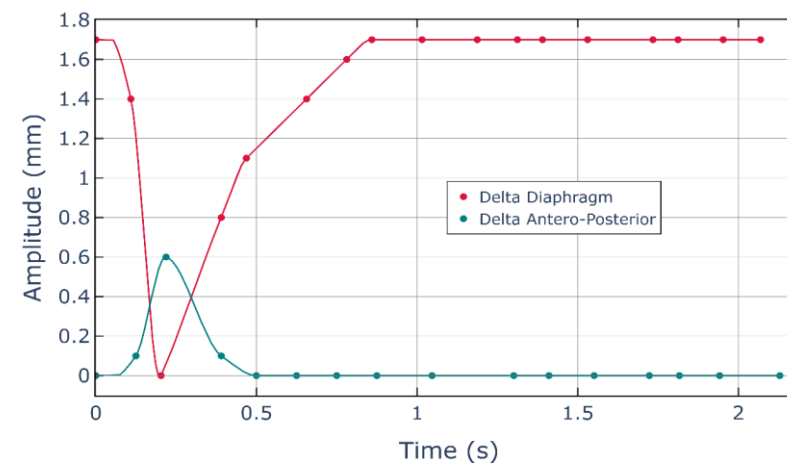


Full expiration and inspiration
(density, composition and volume)

Fluoroscopic mode XRAD225Cx (8 images/s)



Maximal amplitudes over 10 cycles of an anaesthetized mouse

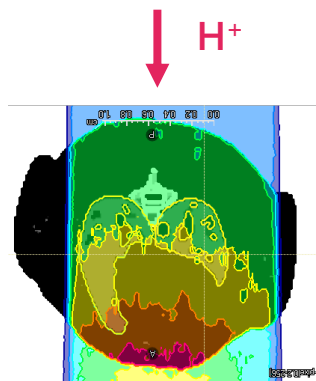


- Heyden, Brent van der, et al.. « The Influence of Respiratory Motion on Dose Delivery in a Mouse Lung Tumour Irradiation Using the 4D MOBY Phantom ». *The British Journal of Radiology* 90, n° 1069 (janvier 2017): 20160419. <https://doi.org/10.1259/bjr.20160419>.

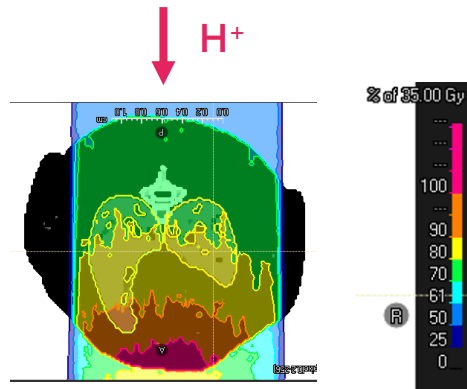
Impact of the respiratory cycle in FLASH-RT

Vertical irradiation

Full expiration (Deflate)
($d=0,45 \text{ g/cm}^3$, volume $0,56 \text{ cm}^3$)

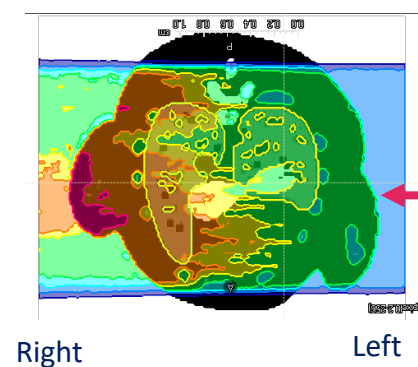


Full inspiration (Inflate)
($d=0,26 \text{ g/cm}^3$, volume $0,79 \text{ cm}^3$)

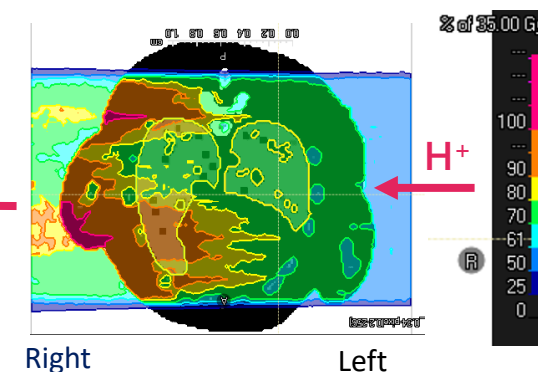


Lateral irradiation

Full expiration (Deflate)
($d=0,45 \text{ g/cm}^3$, volume $0,56 \text{ cm}^3$)

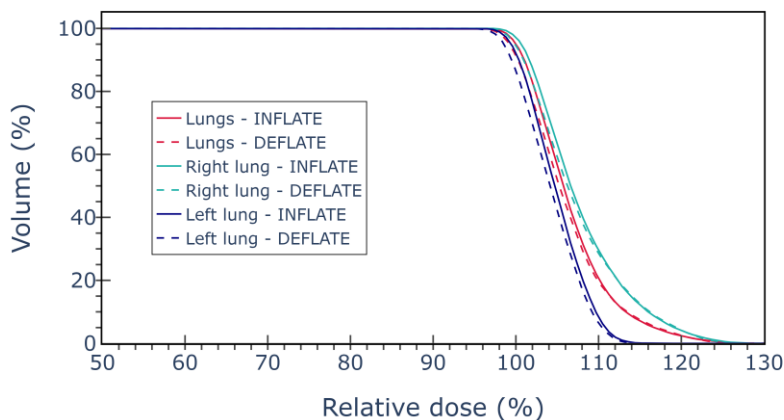


Full inspiration (Inflate)
($d=0,26 \text{ g/cm}^3$, volume $0,79 \text{ cm}^3$)



Antero-Posterior irradiation

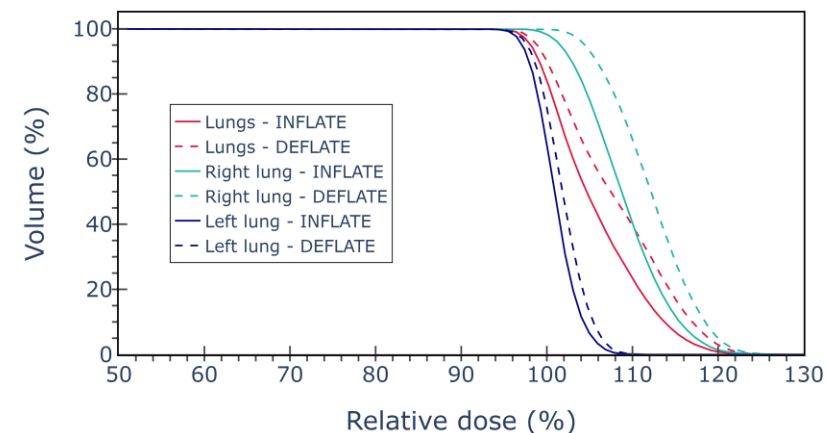
Cumulative Dose-Volume Histogram



Differences in
homogeneity and
mean dose < 1 %

Lateral (left side) irradiation

Cumulative Dose-Volume Histogram



Differences in **homogeneity**
and **mean dose**:

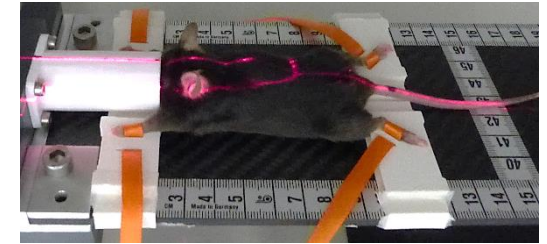
- < 1 % for entrance lung
- [1-3] % for exit lung

Conclusion and perspectives

CONV and UHDR monitoring
with PMT

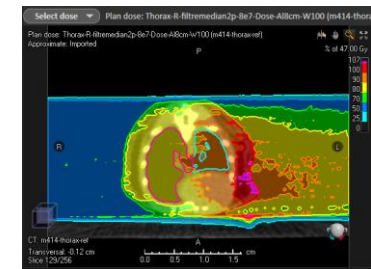
In vivo dosimetry
with OC-1 films

Poster: repositioning, margins and field sizes
for mouse targeted irradiations



- ✓ *Demonstration of the effect of the dose rate on zebrafish embryos and in vitro*
- ✓ *Advances in physico-chemical mechanisms and development of a simulation code*

- Zebrafish embryos: analysis of gene activation
- Radiochemistry: radiolysis in biological media
- Irradiation of small animals (tumors and healthy tissue)
- Design of a ridge filter for irradiation in the Spread Out Bragg Peak (SOPB)



Thank you for your attention

FLASHMOD project



PRISMA team (Physics of Radiation Interactions with Matter and Applications)

Manon EVIN
Arnaud GUERTIN
Vincent METIVIER
Quentin MOUCHARD
Noël SERVAGENT
Ferid HADDAD
Charbel KOUMEIR
Freddy POIRIER



Radiochemistry team

Guillaume BLAIN
Émeline CRAFF
Sarrah TERFAS
Johan VANDENBORRE

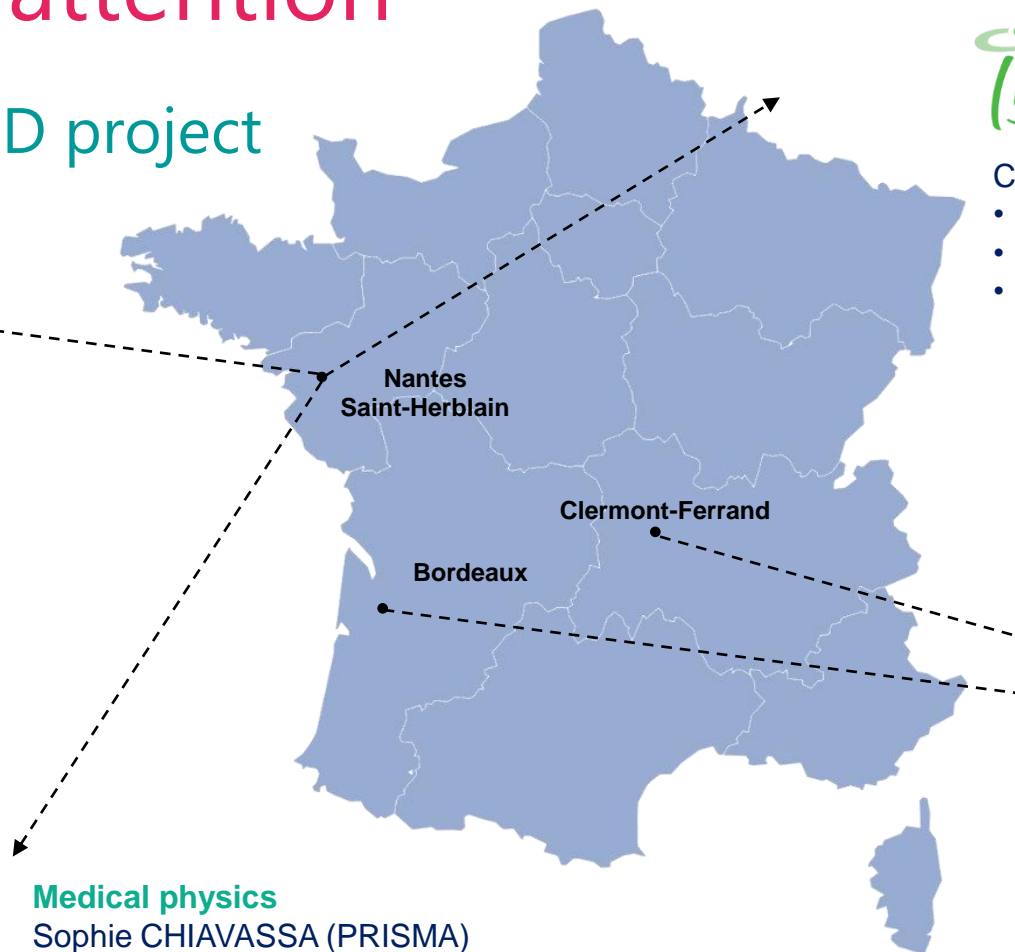


Medical physics

Sophie CHIAVASSA (PRISMA)
Grégory DELPON (PRISMA)

Radiobiology

Mathieu CHOCRY
Vincent POTIRON
Gaëlle SAADE
Stéphane SUPIOT



Collaboration with:

- Université de Namur
- Université de Louvain
- Société IBA



Simulation GATE/Geant4-DNA

Lydia MAIGNE
Giovanna FOIS



Hoang Tran