



Dosimetric environment of preclinical FLASH hadrontherapy studies at the ARRONAX cyclotron

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FLASHMOD project

→ Development of FLASH external radiotherapy

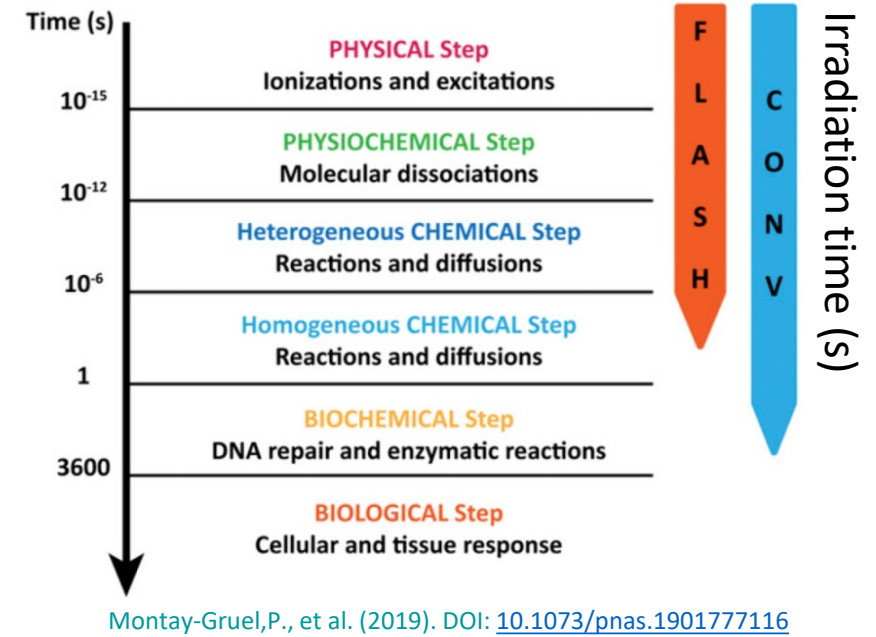
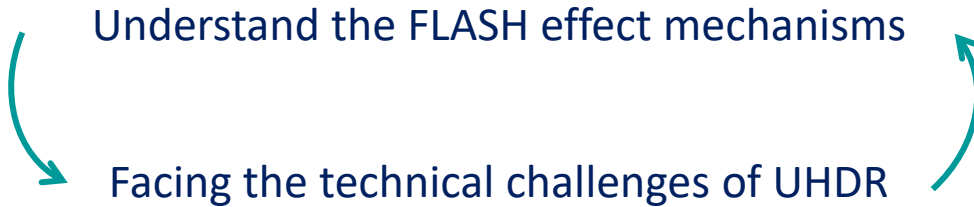
FLASH effect

Increase in **dose rate** from **0.1 Gy/s** (CONV) to at least **40 Gy/s** (UHDR):

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

→ Enlargement of the therapeutic window

Main goals



→ 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

Beam creation
Energy and temporal structure

Beam shaping
Lateral and distal homogeneity, field size and geometry

Beam monitoring

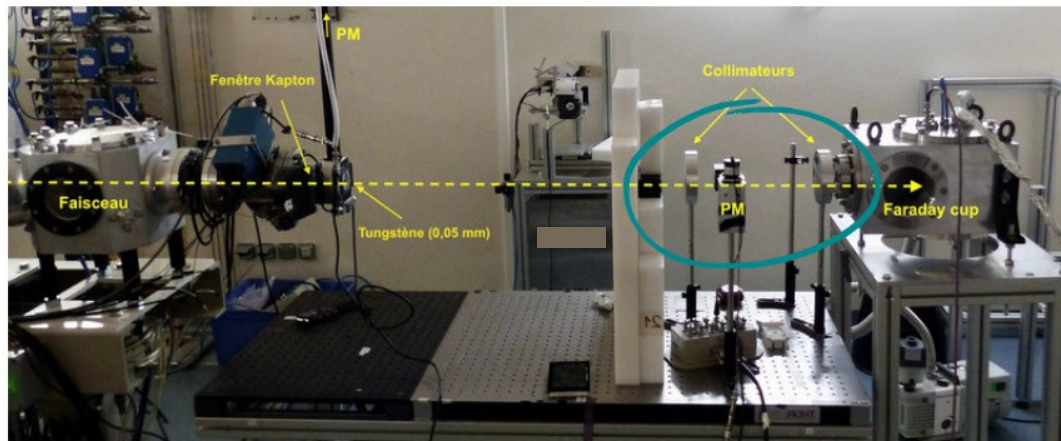
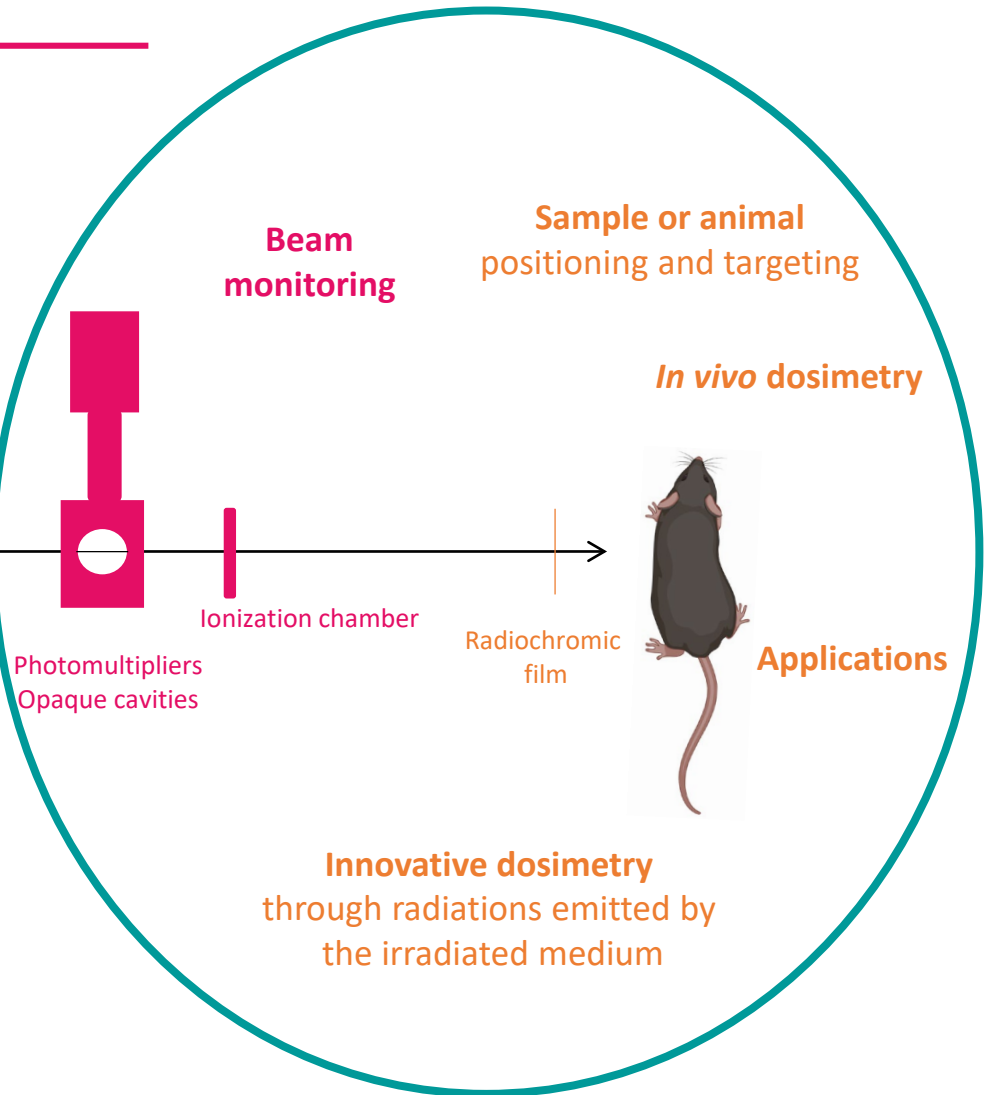
Sample or animal positioning and targeting

***In vivo* dosimetry**

Applications

Innovative dosimetry
through radiations emitted by the irradiated medium

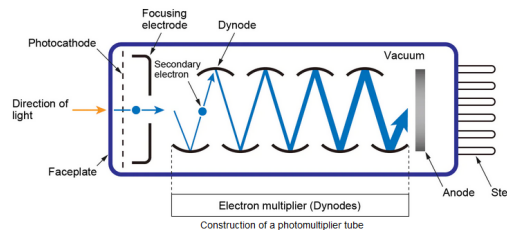
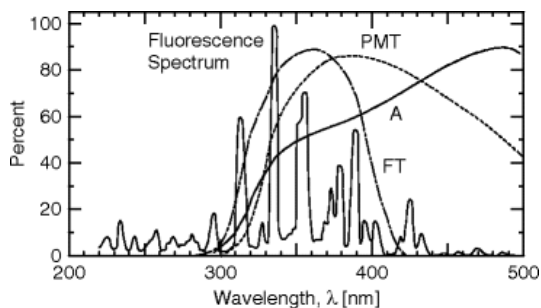
Cyclotron



UHDD and CONV beam monitoring

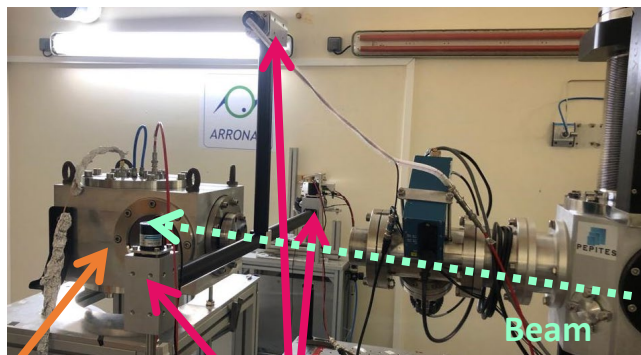
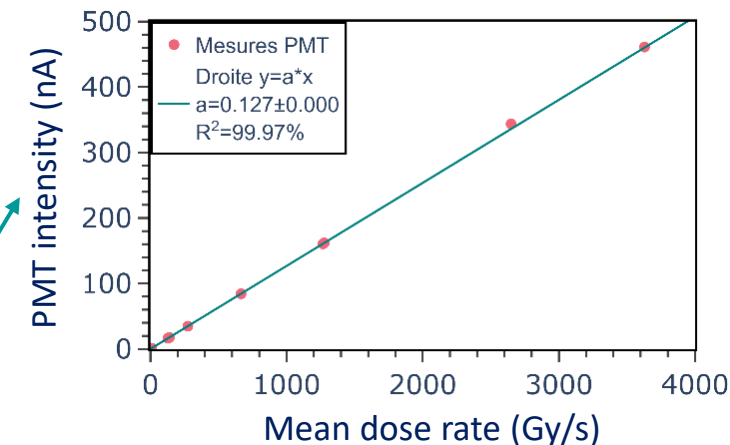
Quentin Mouchard

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



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

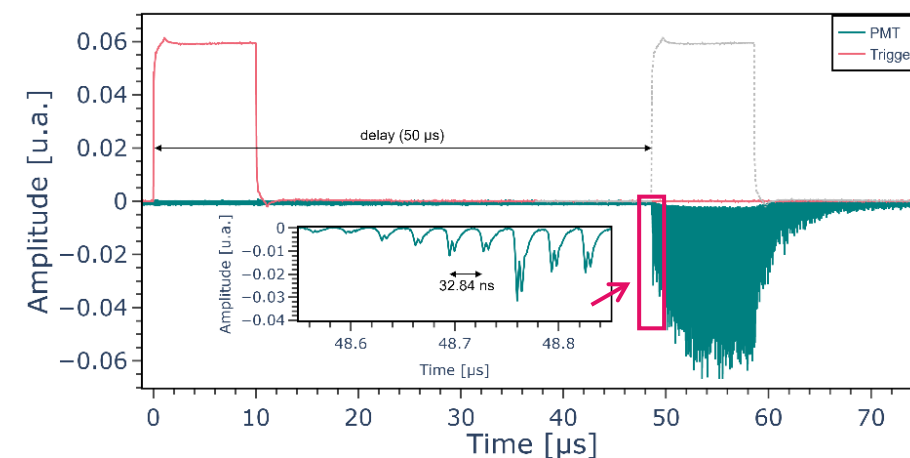
Linearity with dose rate



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

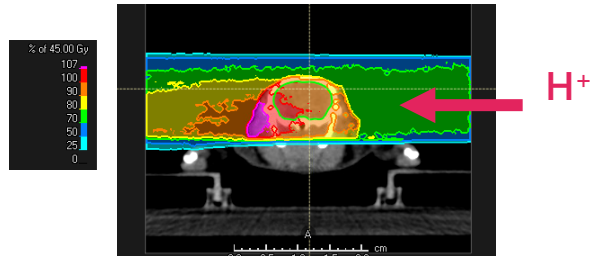
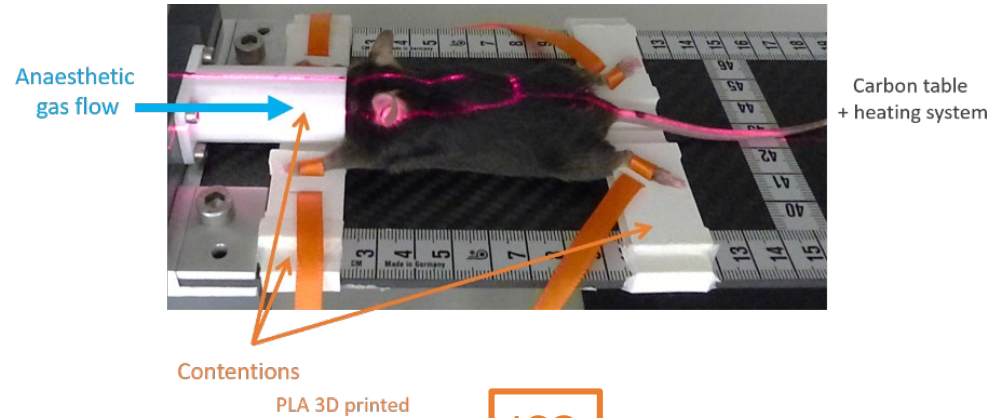
Temporal structures of beams



Preclinical irradiations at ARRONAX

Workflow and methodology for:

- Internal **organs targeting** without online imaging
- **Fixed collimators**



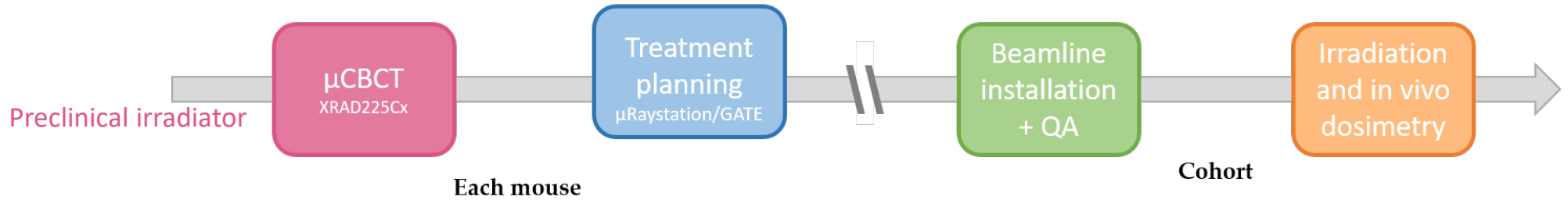
ARRONAX

3D printed bed

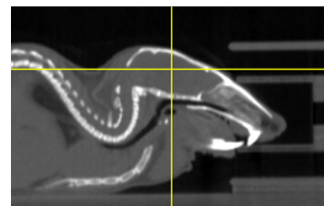
ICO

Week prior to irradiation

Day of irradiation



Reference isocenter



μRaystation

- Organ delineation: size and barycenter coordinates

GATE

- Monte Carlo dose simulation (Dose to Water)

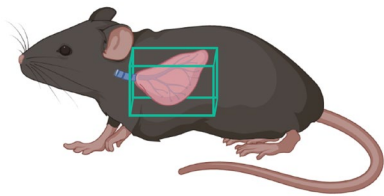
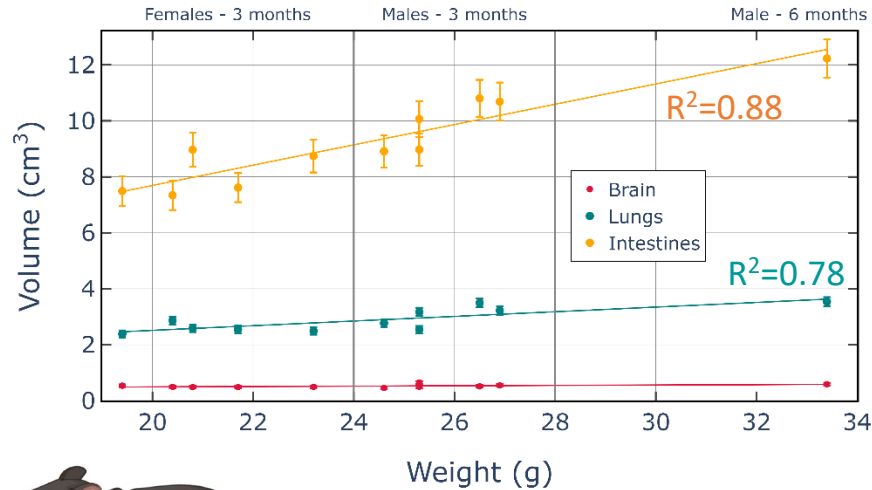
- Optimal collimator aperture for the cohort
- QA protocol including daily reference ionometric measurement and beamtransversal homogeneity with films

- Individual isocenter using lasers and graduations
- In vivo dosimetry using OC-1 radiochromic films (OrthoChrome)

Irradiation field sizes and margins

Study with 11 mice using the XRAD225Cx

$$\text{Optimal homogeneous field size (cohort)} = \text{Organ size (cohort)} + \text{Margins}_{\text{Targeting}} + \text{Margins}_{\text{Respiratory}}$$

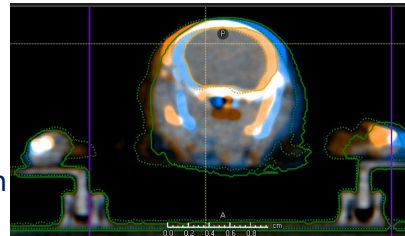


→ Selection of a cohort based on the weight enables the use of a unique field size

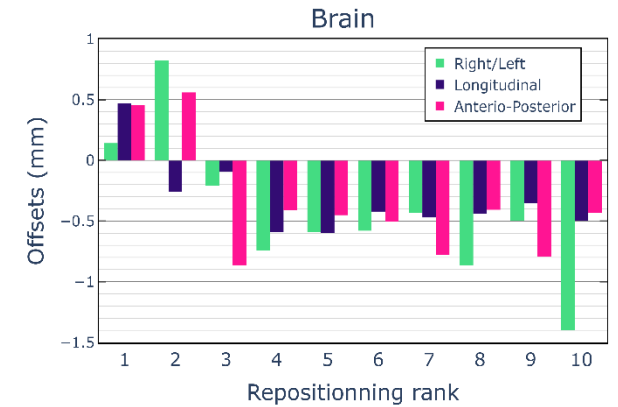
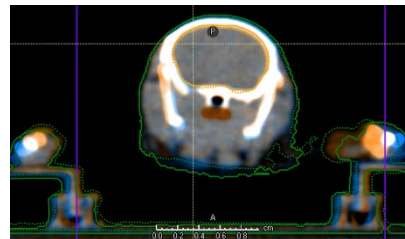
$$\text{Margins}_{\text{Targeting}} = 2 \times \text{Maximal offsets}$$

Reference image (orange)
Repositioning image (blue)

Before registration



After registration



Maximum offsets with respect to the reference image in mm (± 0.1 mm)

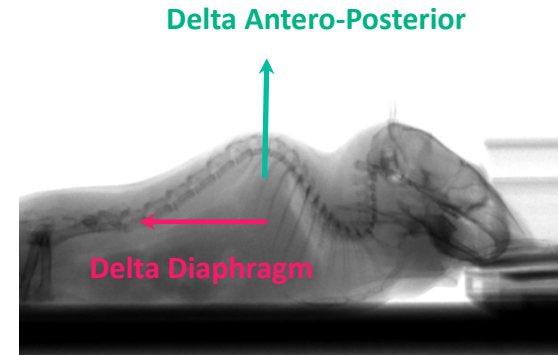
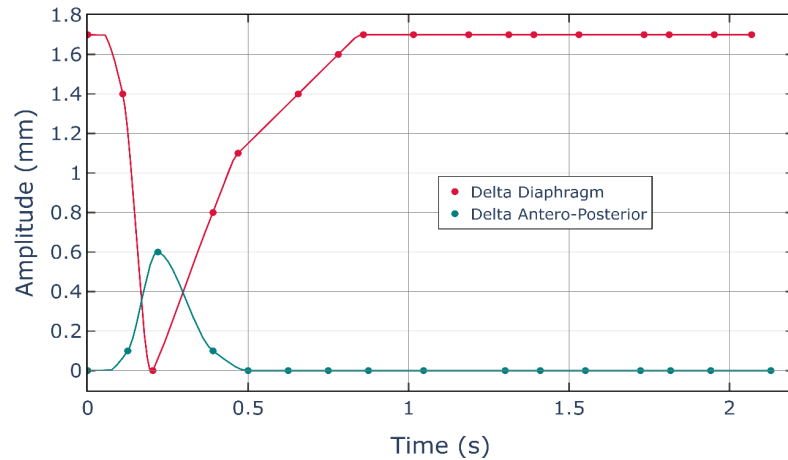
	Right-Left	Longitudinal	Antero-Posterior
Brain	1.4	0.6	0.9
Lungs	2.0	3.4	0.4
Intestines	2.3	3.0	0.7

Irradiation field sizes and margins

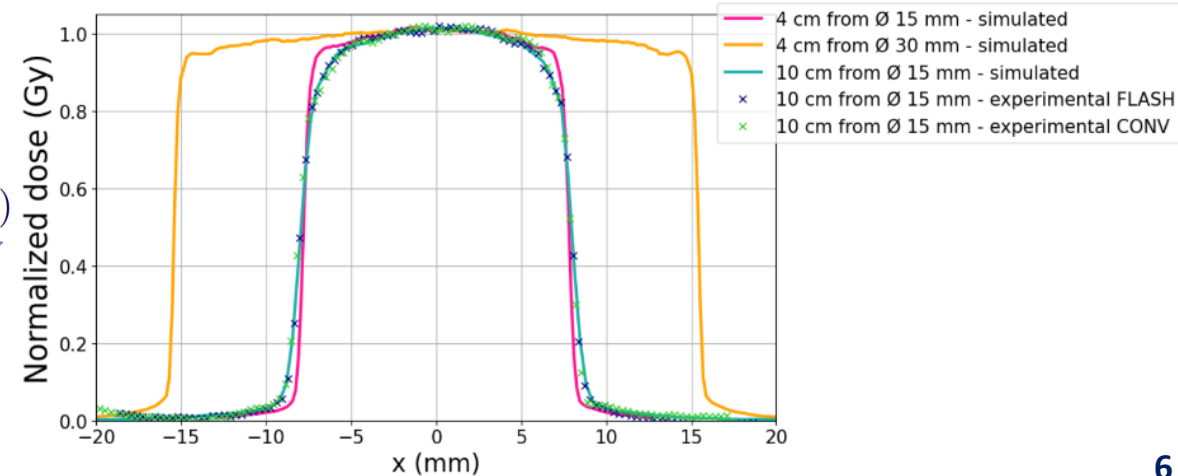
Optimal homogeneous field size (*cohort*) = Organ size (*cohort*) + Margins Targeting + Margins Respiratory

Fluoroscopy mode XRAD225Cx (8 images/s)

Maximal amplitudes over 10 cycles of an anaesthetized mouse



→ Collimator aperture (*cohort*) = Optimal homogeneous field size (*cohort*) + Geometric penumbra



Impact of the respiratory cycle under FLASH-RT

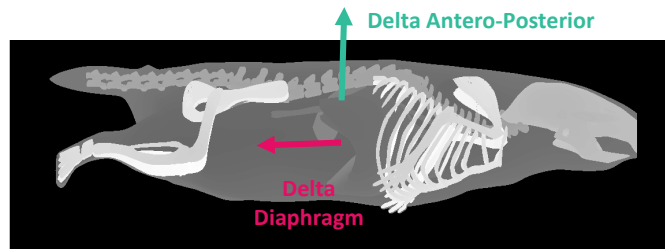
Vertical irradiation

FLASH-RT irradiation time ~ ms

Dosimetric impact ?

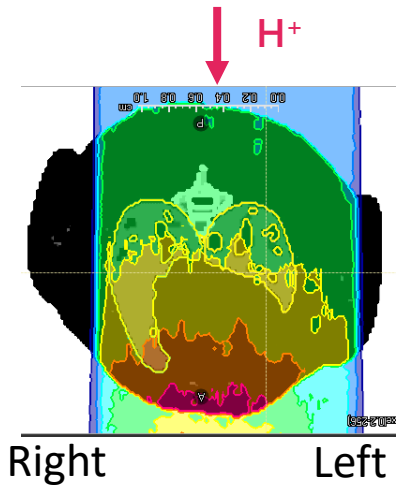


MOBY (Mouse Whole Body 4D Digital Fantom) V.2

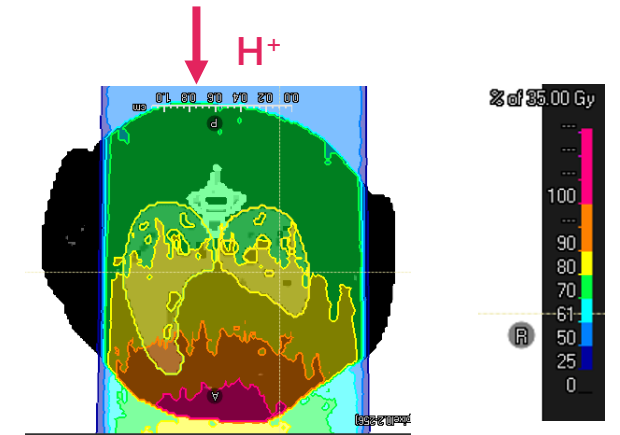


Full expiration and full inspiration
(density, composition ICRU and volume)

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

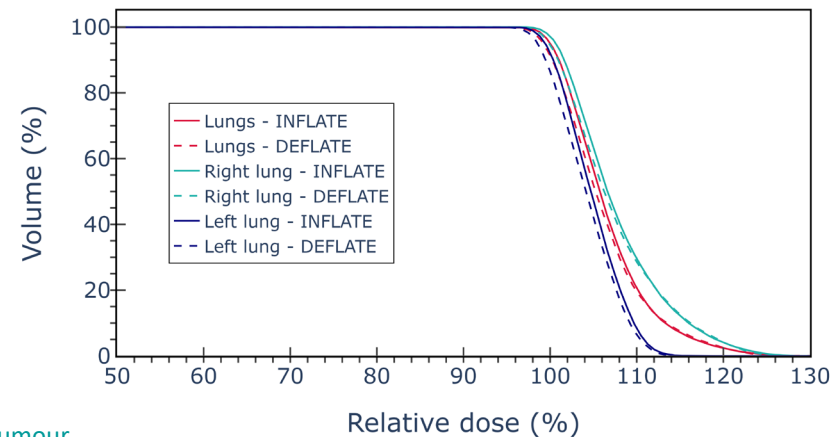


Full inspiration
($d=0,26 \text{ g/cm}^3$, volume $0,79 \text{ cm}^3$)



Antero-Posterior irradiation

Cumulative Dose-Volume Histogram



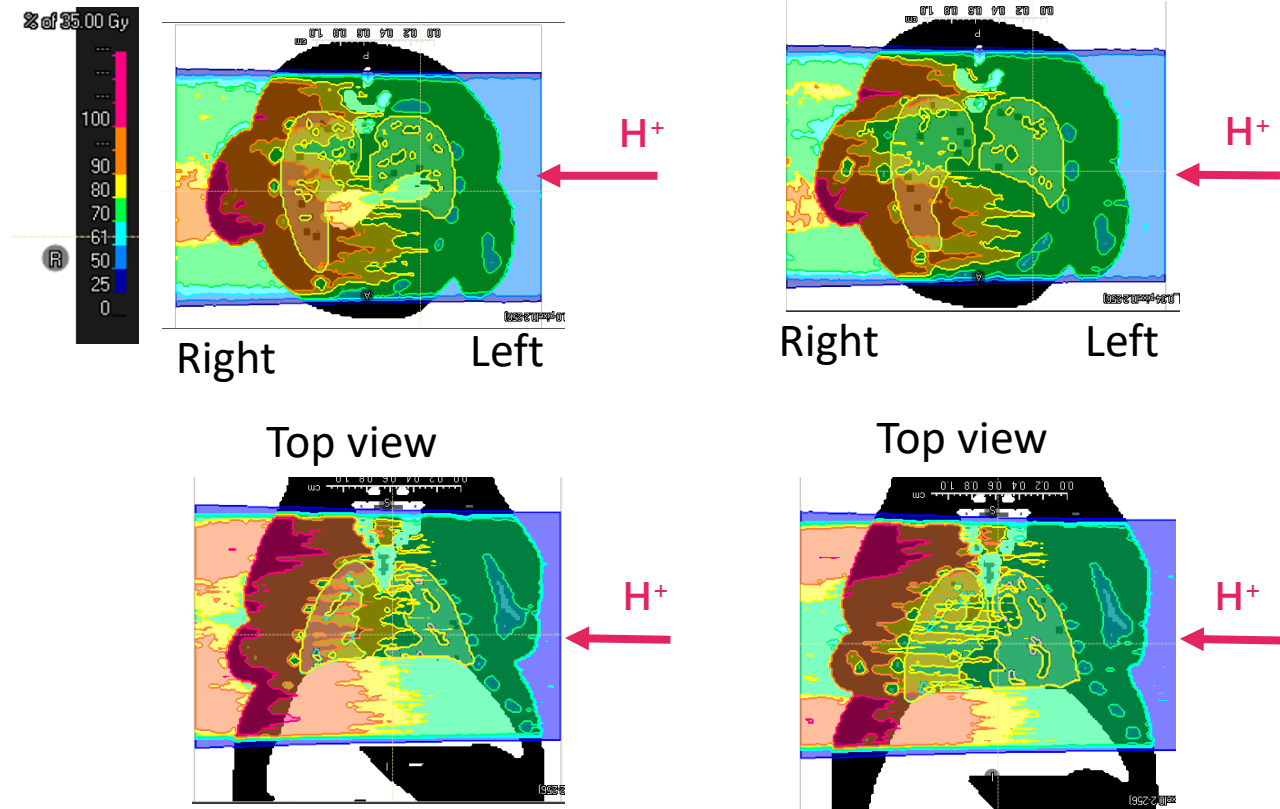
Differences in
homogeneity and
mean dose < 1 %

Impact of the respiratory cycle under FLASH-RT

Lateral irradiation

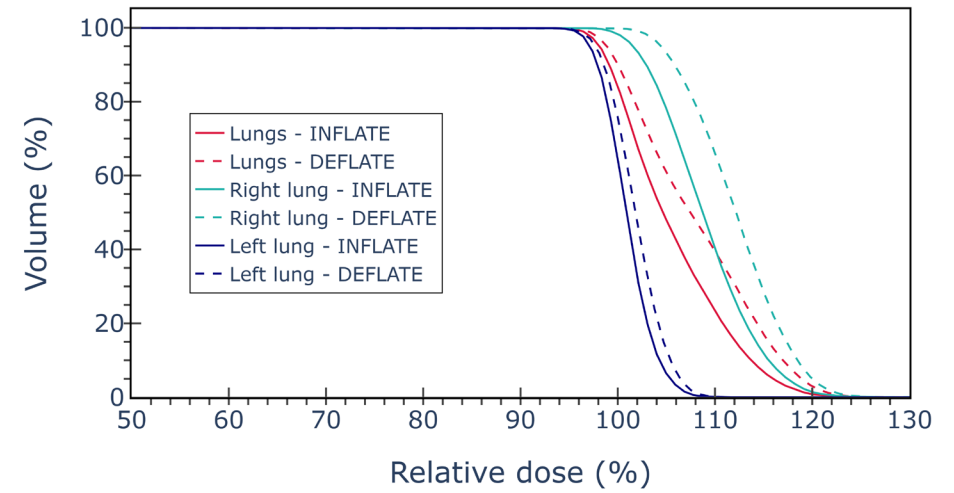
Full expiration (Deflate)
($d=0,45 \text{ g/cm}^3$, volume $0,56 \text{ cm}^3$)

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



Lateral (left side) irradiation

Cumulative Dose-Volume Histogram

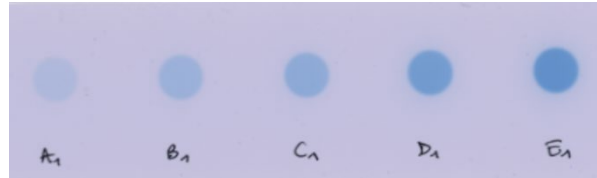
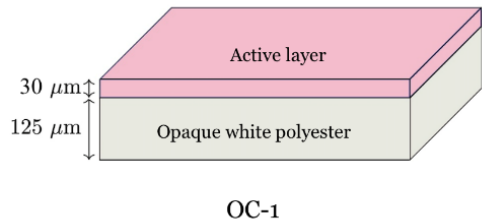


Differences in **homogeneity** and **mean dose**:

- **< 1 %** for entrance lung → the one to be considered for biological analyses
- **[1-3] %** for exit lung and both lungs

In vivo dosimetry with radiochromic films

OrthoChromic Films OC-1



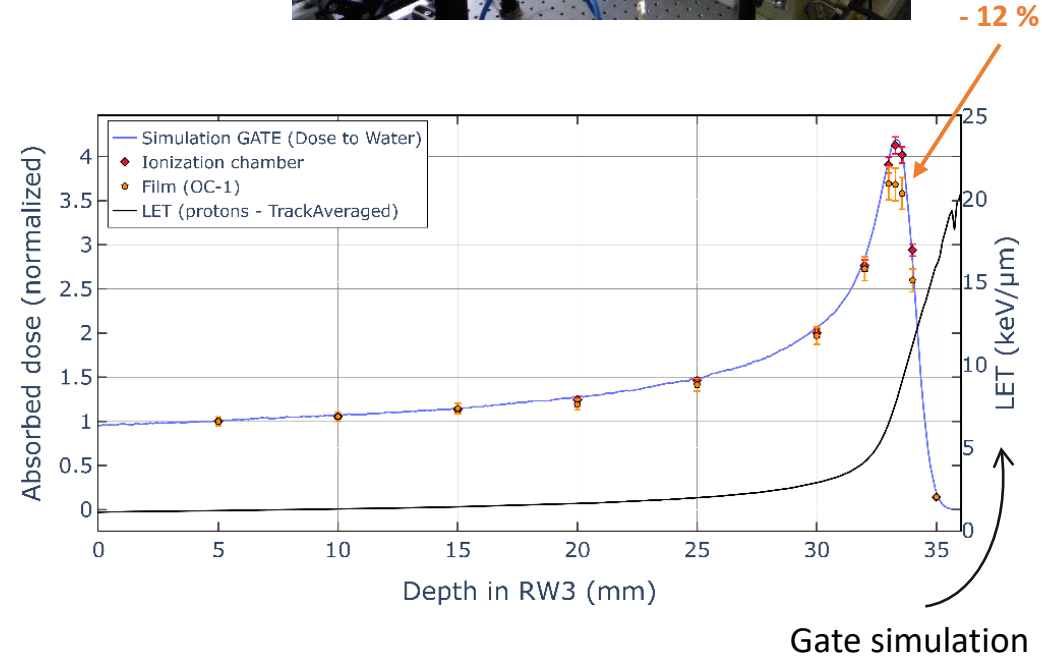
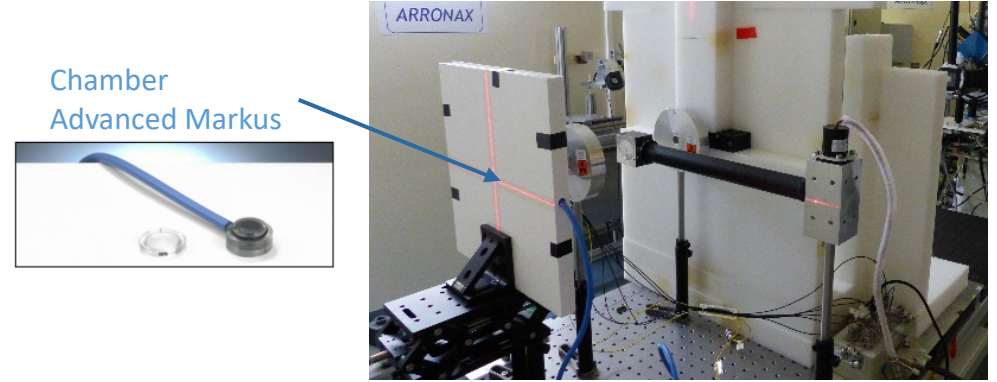
Absorbed dose (2, 5, 10, 20, 30 Gy)

✓ 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)

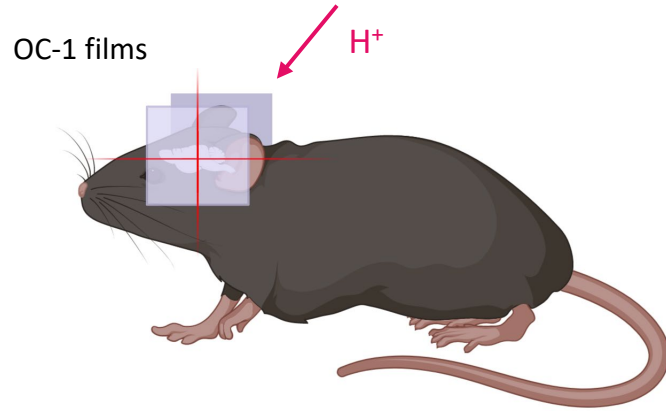
LET (Linear Energy Transfert) dependency



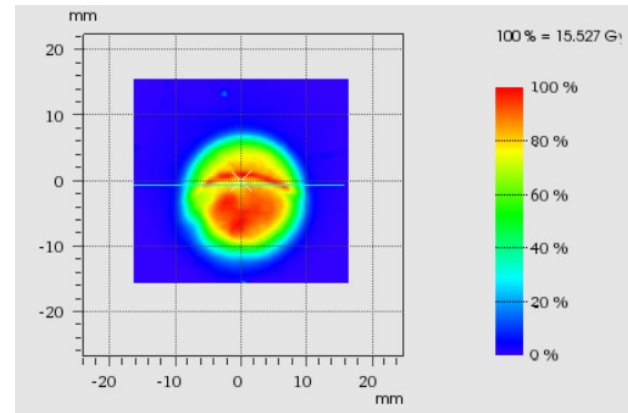
➔ Determination of the correction factor **f(LET)**

In vivo dosimetry with radiochromic films

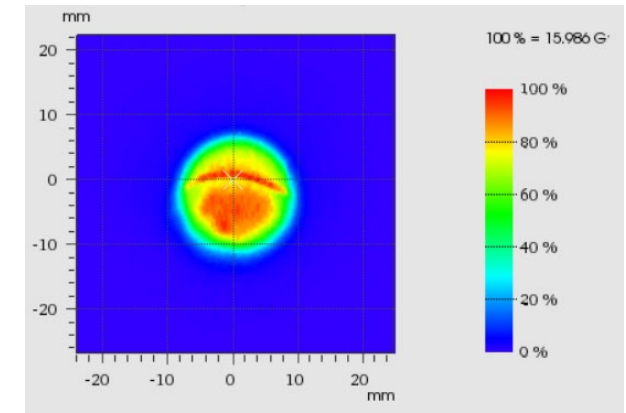
Mouse whole brain irradiation: GATE simulation from XRAD225Cx μ CBCT and targeting without image guidance at ARRONAX



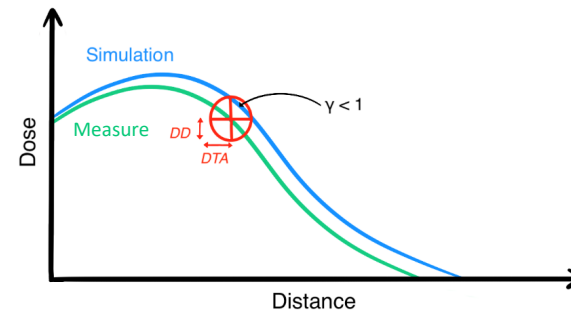
Experimental



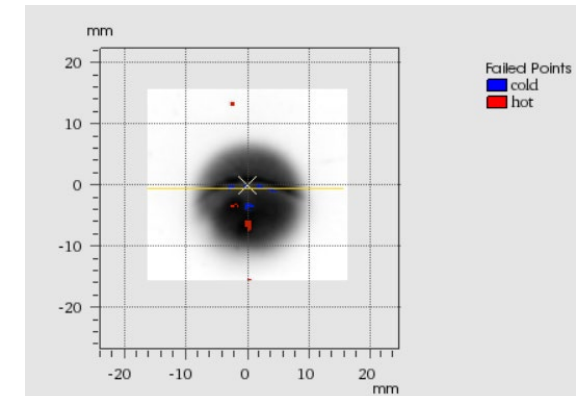
Simulated



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



1D illustration of the gamma index metric



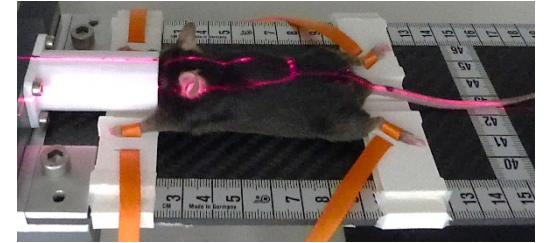
Conclusion and perspectives

PMT for beam control
through light emitted by air

In vivo dosimetry
with OC-1 films

Methodology for internal organs
targeting without image guidance

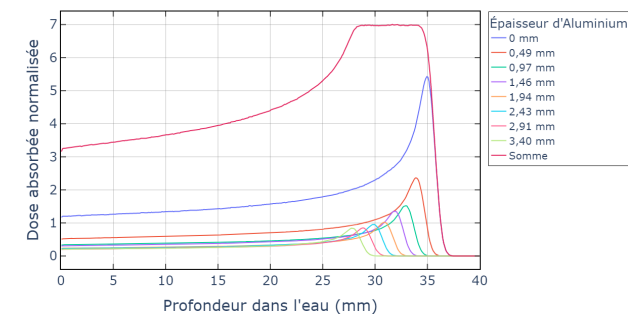
Dosimetric environment of preclinical
FLASH hadrontherapy at ARRONAX



✓ Ready for irradiation of small animals (tumors and healthy tissues)

Other main perspective:

→ Design of a ridge filter for Spread Out Bragg Peak irradiations (SOPB)
as for clinical irradiation



- Patriarca A, et al. « Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System », International Journal of Radiation Oncology*Biophysics, DOI: 10.1016/j.ijrobp.2018.06.403.

Thank you for your attention

FLASHMOD project



Collaboration with:

- Université de Namur
- Université de Louvain
- Société IBA



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

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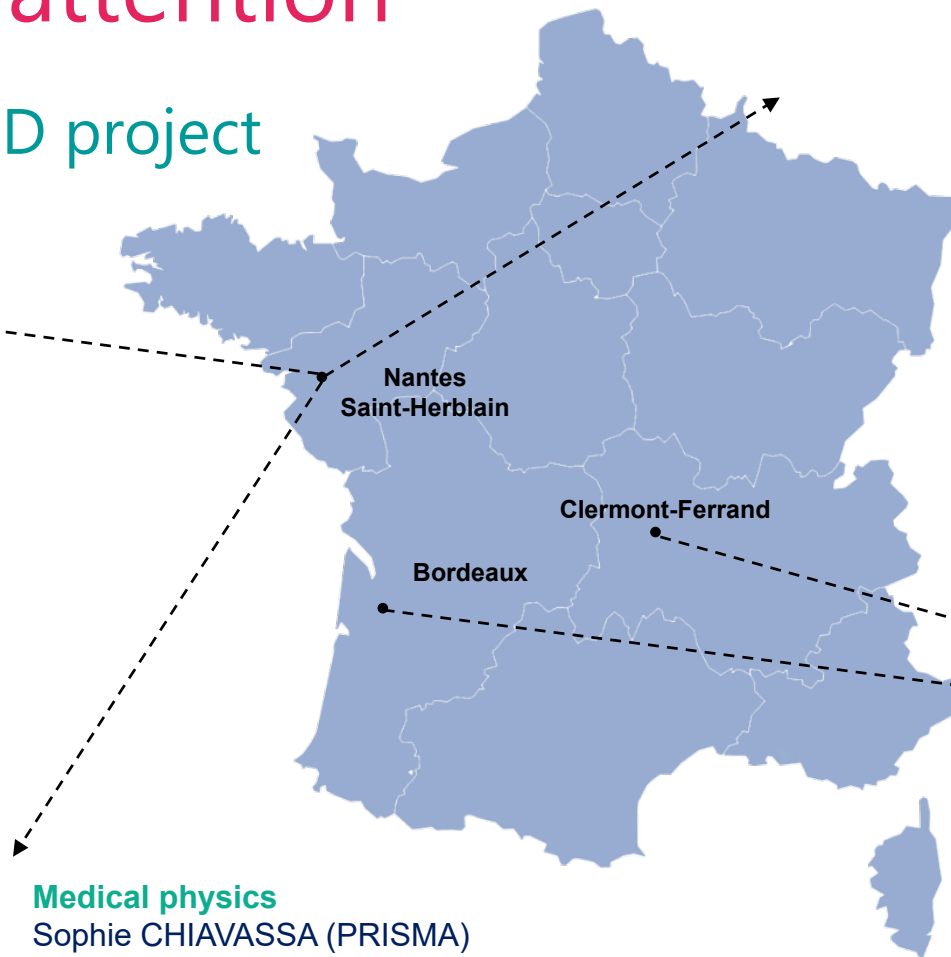


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