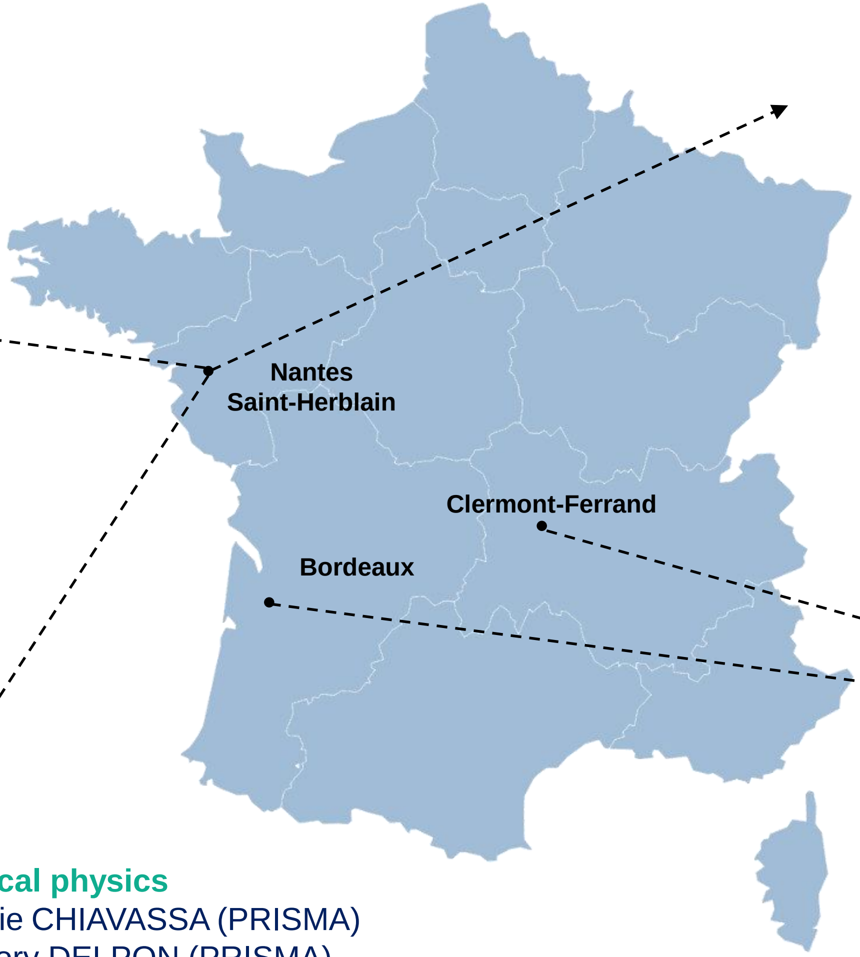
Bilan du projet FLASHMOD
Etude pluridisciplinaire des mécanismes de la radiothérapie Flash à Arronax

Sophie Chiavassa

Assemblée Générale GdR Mi2B – 9-11 octobre 2024

FLASHMOD – financement PCSI (36 + 6 mois – fin juin 2024)

Collaboration with:
- Université de Namur
- Université de Louvain
- Société IBA



PRISMA team (Physics of Radiation Interactions with Matter and Applications)
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Quentin MOUCHARD
Noël SERVAGENT
Ferid HADDAD
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Émeline CRAFF
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Grégory DELPON (PRISMA)
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Radiobiology
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Vincent POTIRON
Gaëlle SAADE
Stéphane SUPIOT

Simulation GATE/Geant4-DNA
Lydia MAIGNE
Giovanna FOIS
Hoang Tran

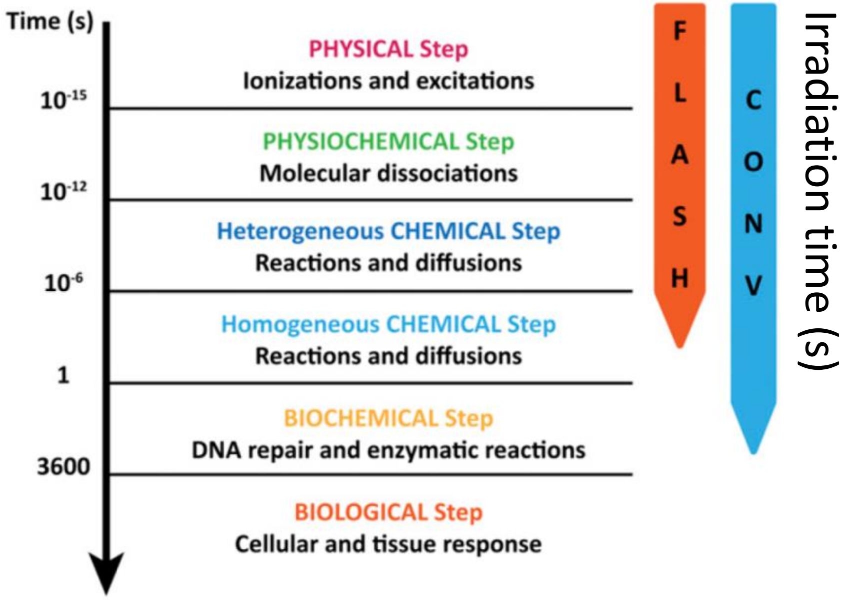
Contexte

Main goals of the FLASHMOD project

Avancer dans la compréhension des mécanismes du Flash

Relever les défis techniques liés au Flash

LET, O2, ROS, biological effect, …



Montay-Gruel,P., et al. (2019). DOI: 10.1073/pnas.1901777116

Multidisciplinary team around the ARRONAX cyclotron

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**

Favaudon et al. Science Translational Medecine 2014, Vozenin et al. Clinical Cancer Research 2018, Vozenin et al. Clinical Oncology 2019

Physique

ARRONAX preclinical irradiation line

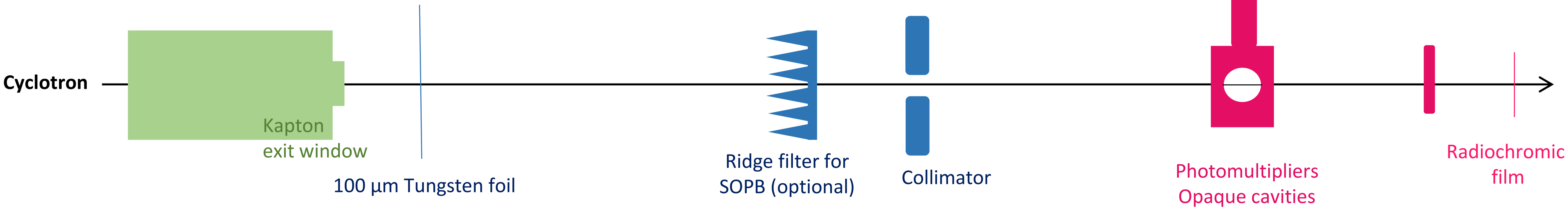
Sample or animal
positioning and targeting

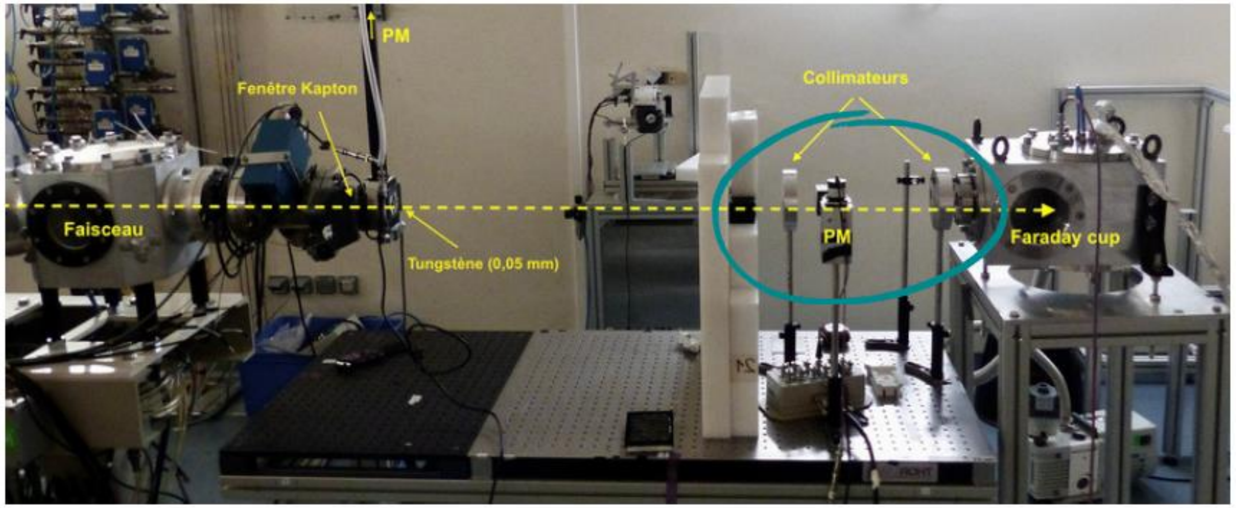
Beam shaping
Lateral and distal homogeneity, field size and geometry

Beam monitoring

Applications

Beam creation
Energy and temporal structure





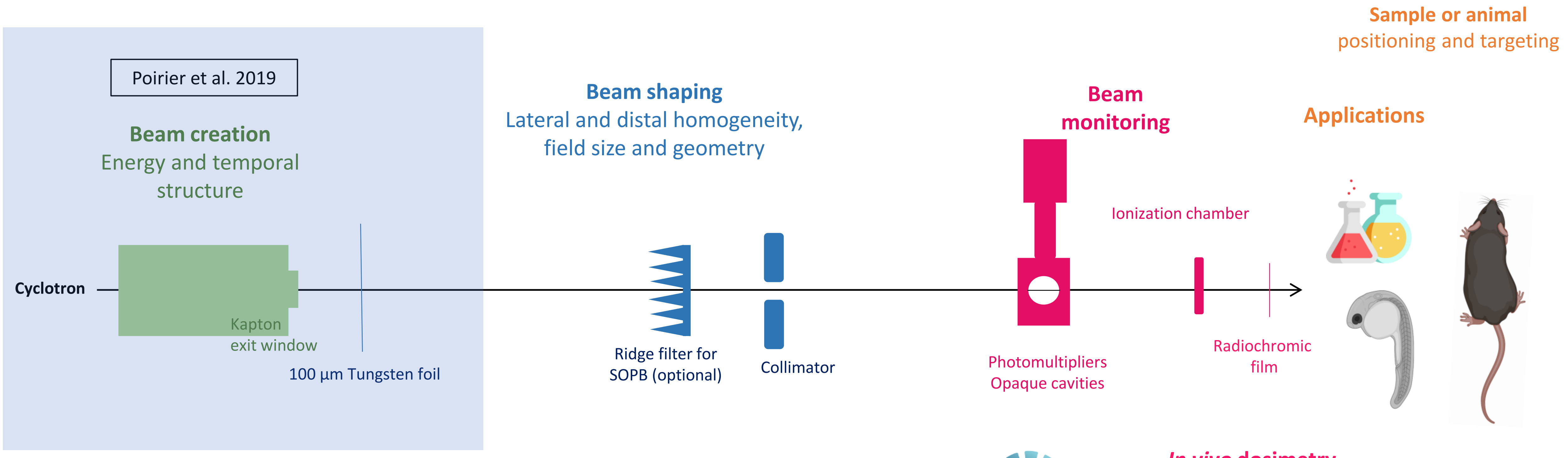
GATE

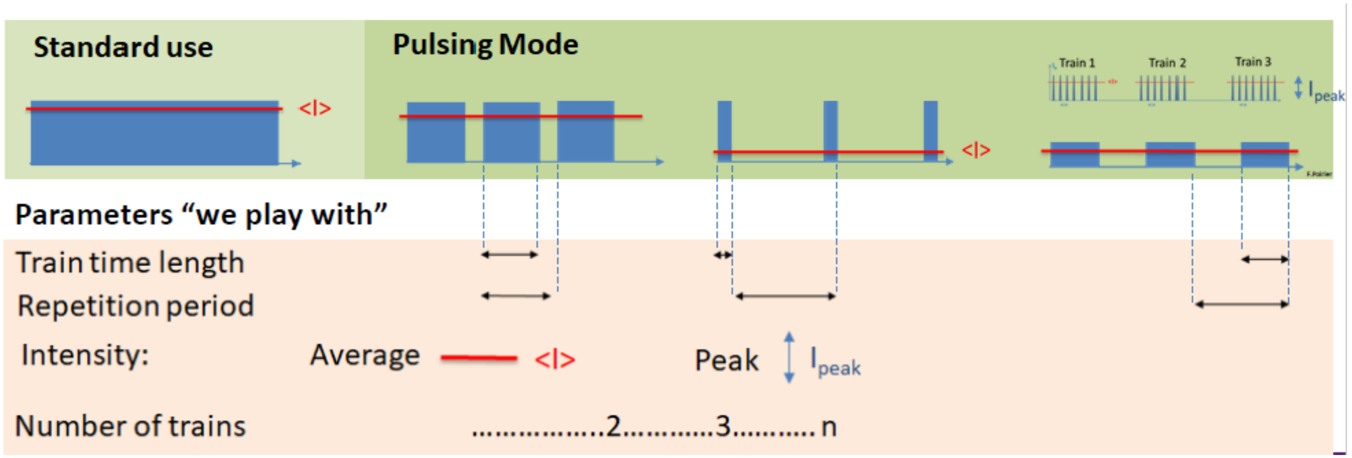
***In vivo* dosimetry**

Innovative dosimetry
through radiation emitted by the irradiated medium

Physique

ARRONAX preclinical irradiation line





Physique

ARRONAX preclinical irradiation line

Bongrand et al. Cancers 2021
Evin et al. Phys. Med 2024

Beam shaping
Lateral and distal homogeneity, field size and geometry

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Energy and temporal structure

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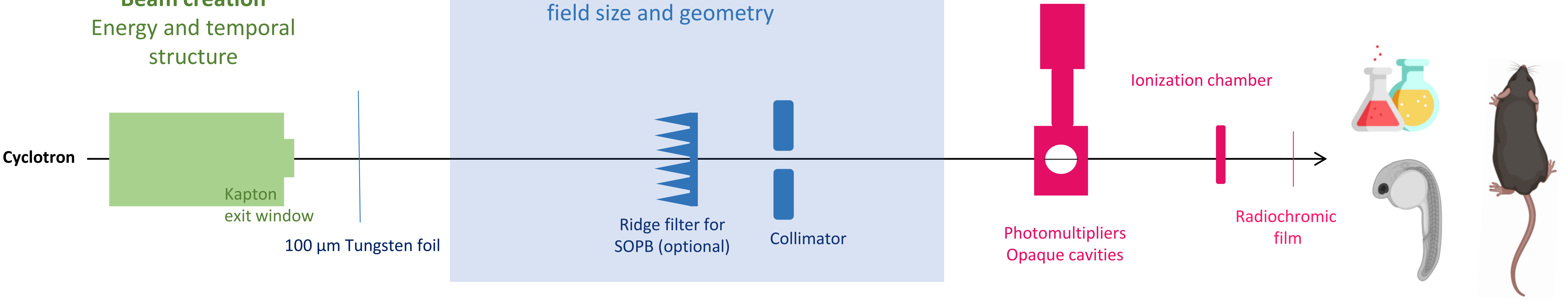
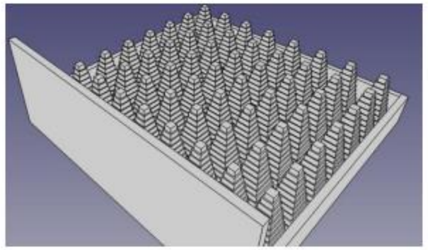
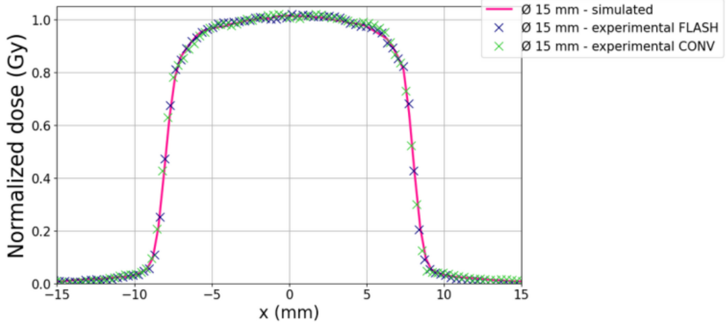
Applications

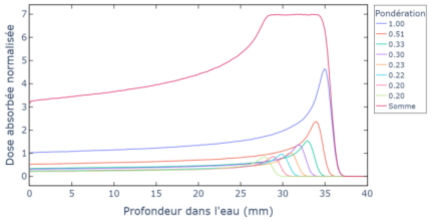


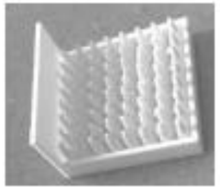
***In vivo* dosimetry**

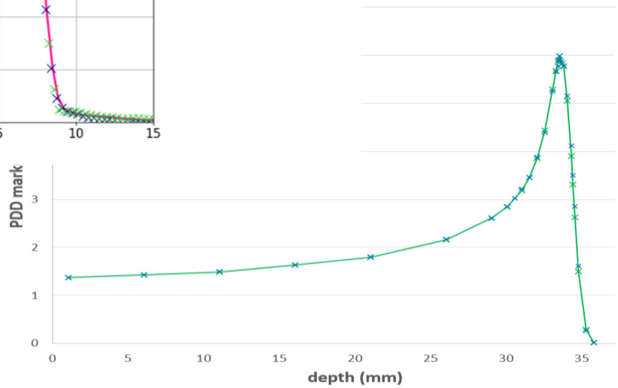
Innovative dosimetry
through radiation emitted by the irradiated medium











Physique

ARRONAX preclinical irradiation line

Mouchard et al. FRPT 2022
Villoing et al. Med. Phys. 2022

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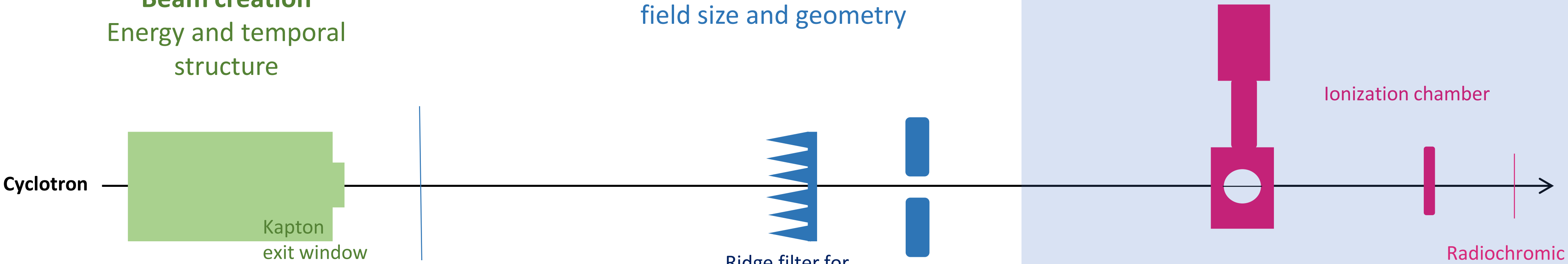
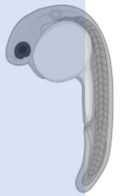
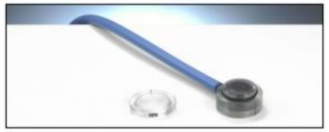


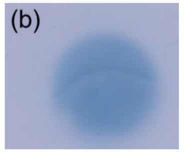


***In vivo* dosimetry**

Innovative dosimetry
through radiation emitted by the irradiated medium

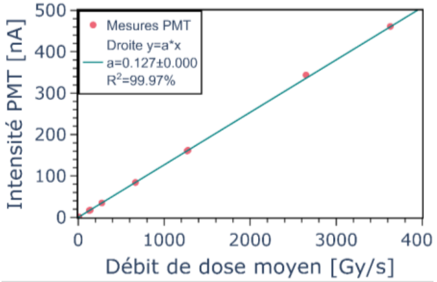
Débit de dose de référence (TRS398)
Markus Advanced

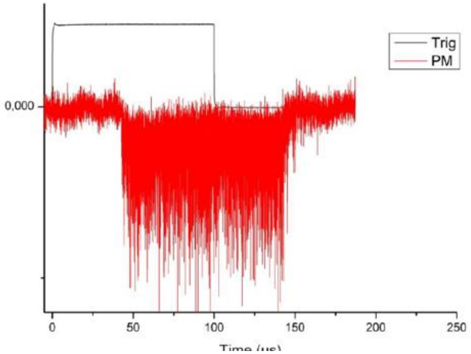




Etude de la sensibilité des films au débit de dose (OC-1, EBT, EBTXD)

PM: Fluorescence du diazote de l'air





Physique

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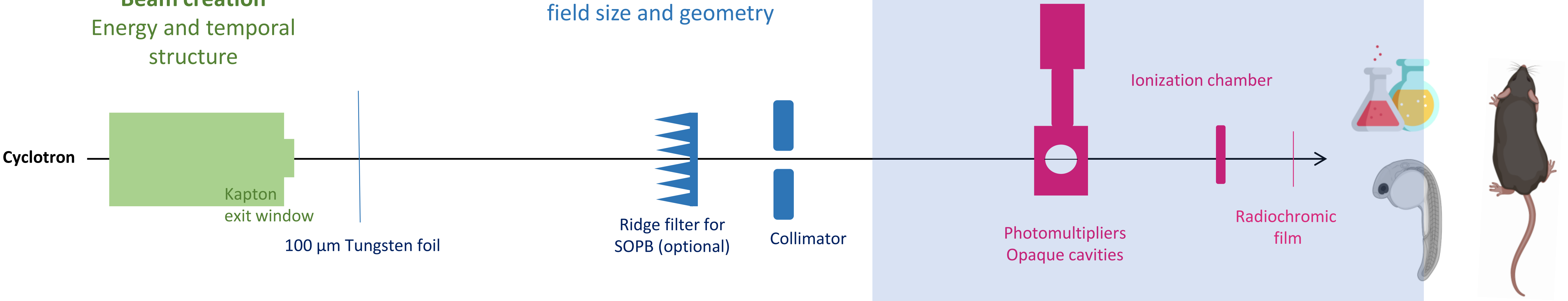
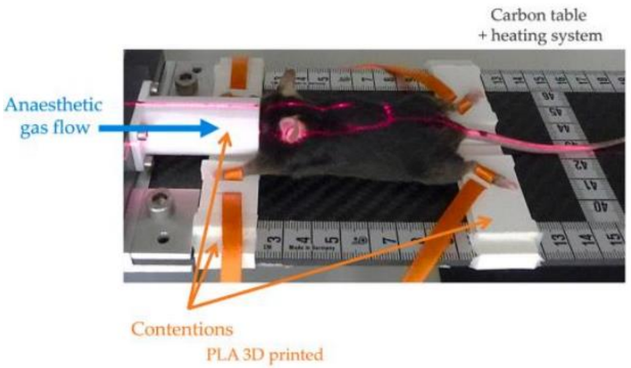


***In vivo* dosimetry**

Innovative dosimetry
through radiation emitted by the irradiated medium

Evin et al. Phys. Med. 2024

Optimisation du ciblage des souris



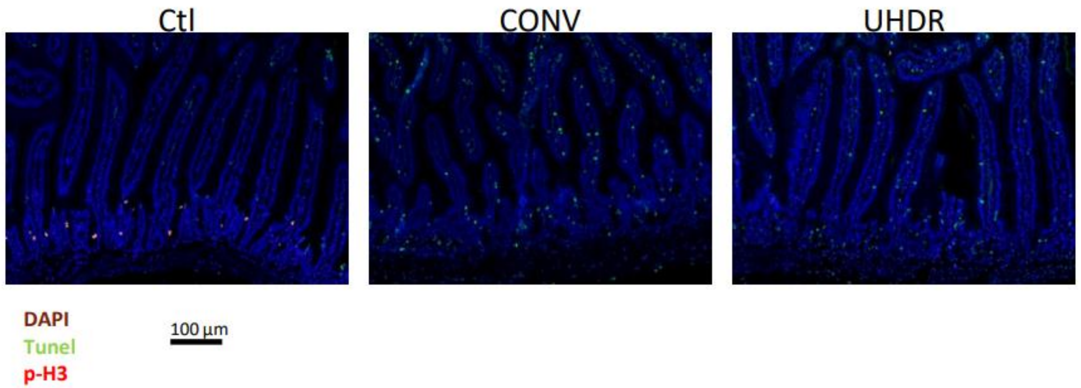
Impact de la respiration en Flash sur MOBY

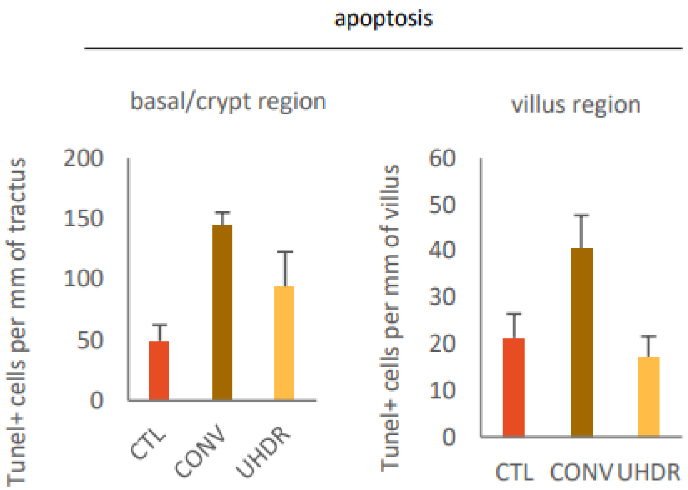
Biologie

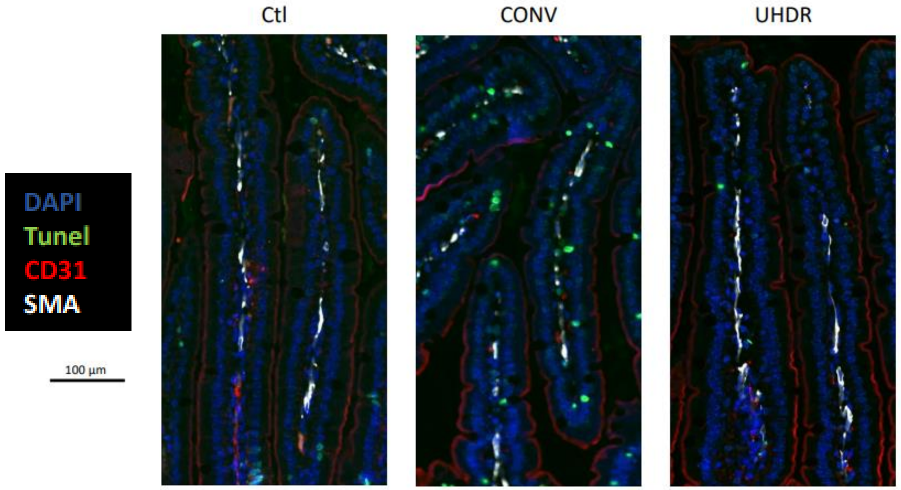
UHDR-PT protects from apoptosis in mouse jejunum

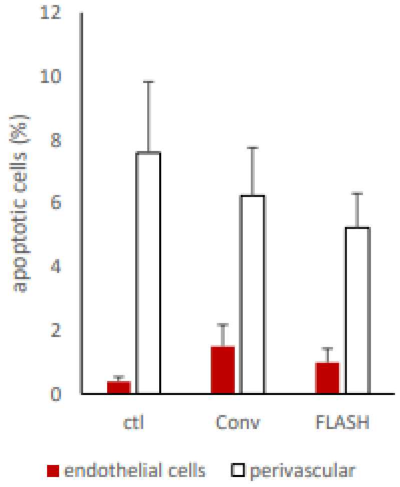
Manip préliminaire (2s/c): premières souris à ARRONAX (nov. 2023)

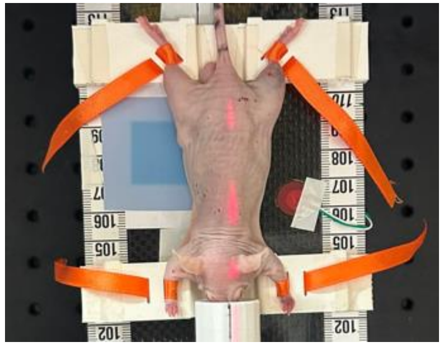
Intestin 15Gy
Protons 68MeV
(plateau)









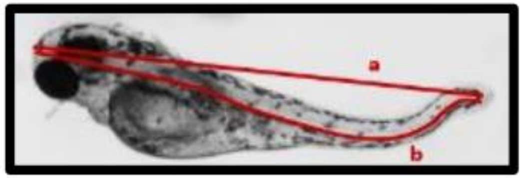


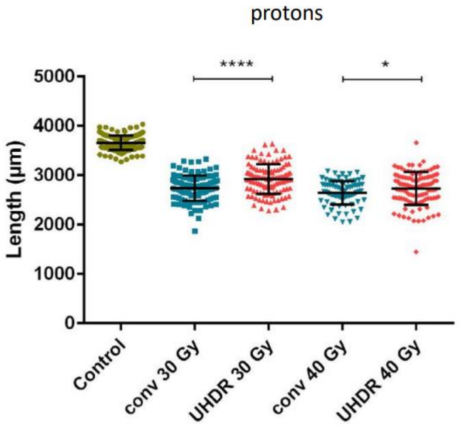
Nouvelle manip souris (10 s/c) (25 sept. 2024): impact du Flash sur le système vasculaire tumoral

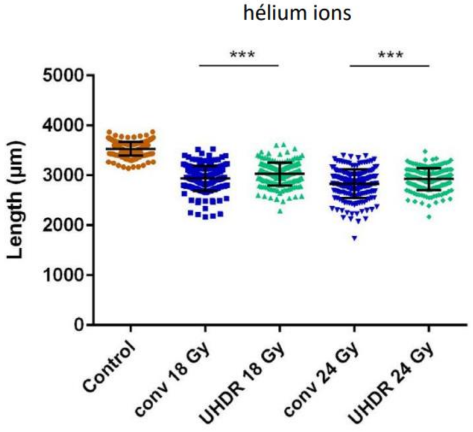
Diffenderfer et al. 2020, Ruan et al. 2021, Evans et al. 2022, Bel et al. 2024

UHDR-PT and He2+ protect zebrafish development

Slide from V. Potiron, Webinar FRPT2024



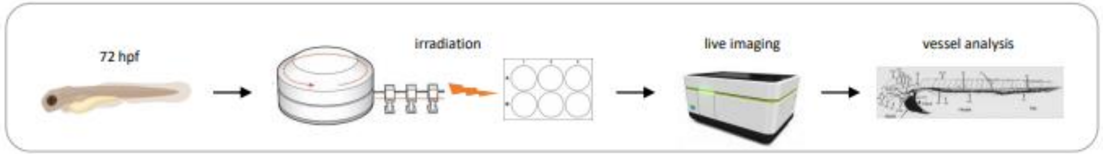


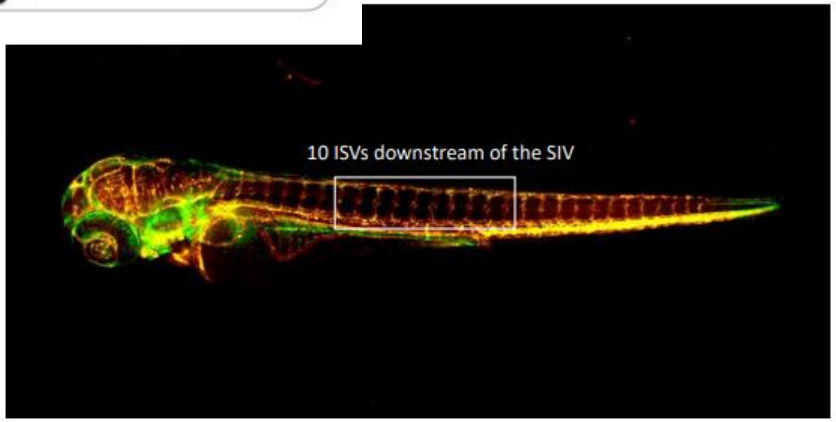


Saade et al. Adv Rad Onc 2022
Ganham et al. Radiother Oncol 2023

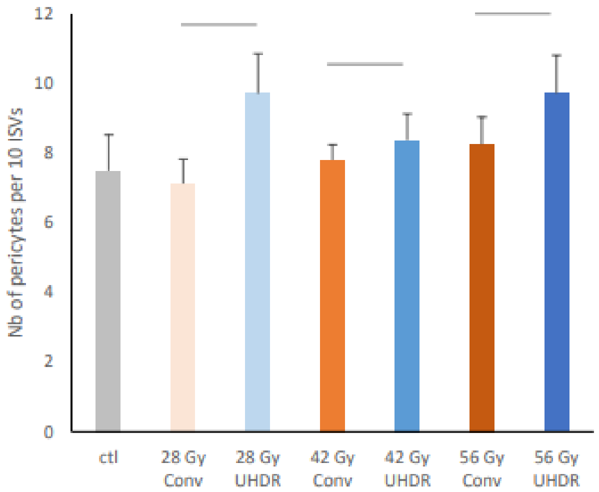
Vozenin et al. Clin Oncol 2019, Montay-Gruel et al. PNAS 2019, Pawelke et al. Radiother Oncol 2021, Karsch et al. Radiother Oncol, 2022, Horst et al. Radiother Oncol 2024

UHDR-PT effects 2-6h post IR





2-way anova
dose: ns
type: * UHDR vs Conv

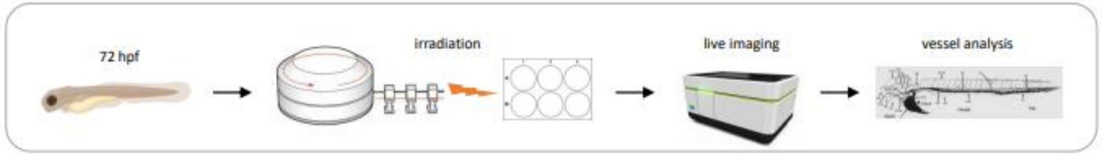


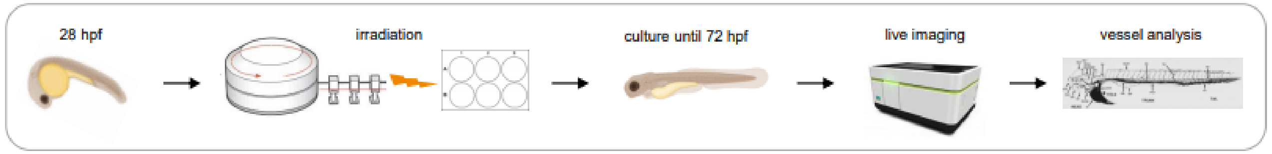
➢ UHDR protège les péricytes

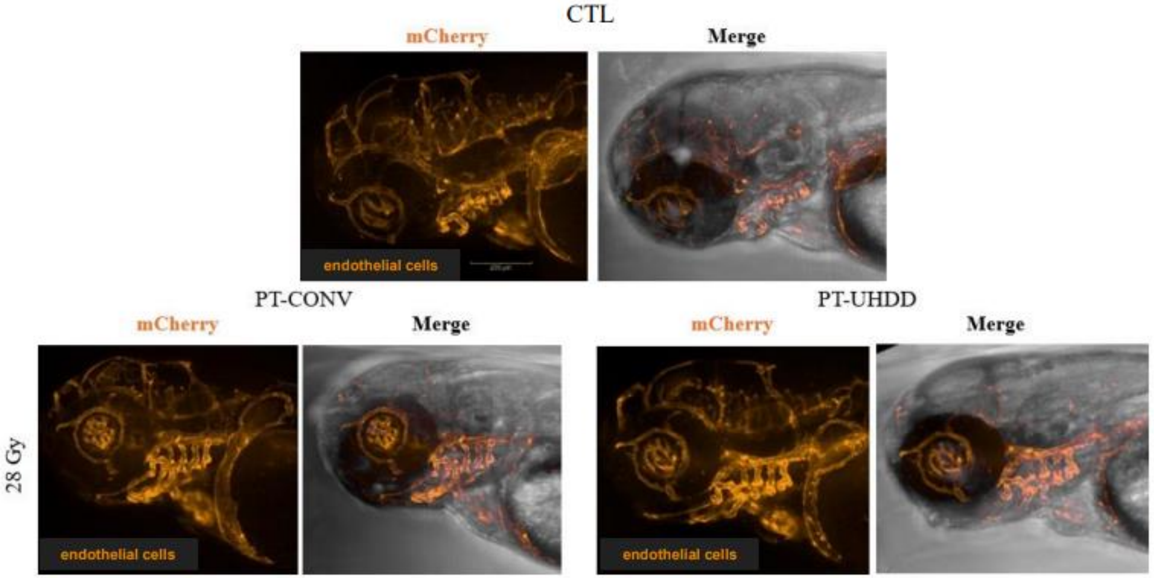
Biologie

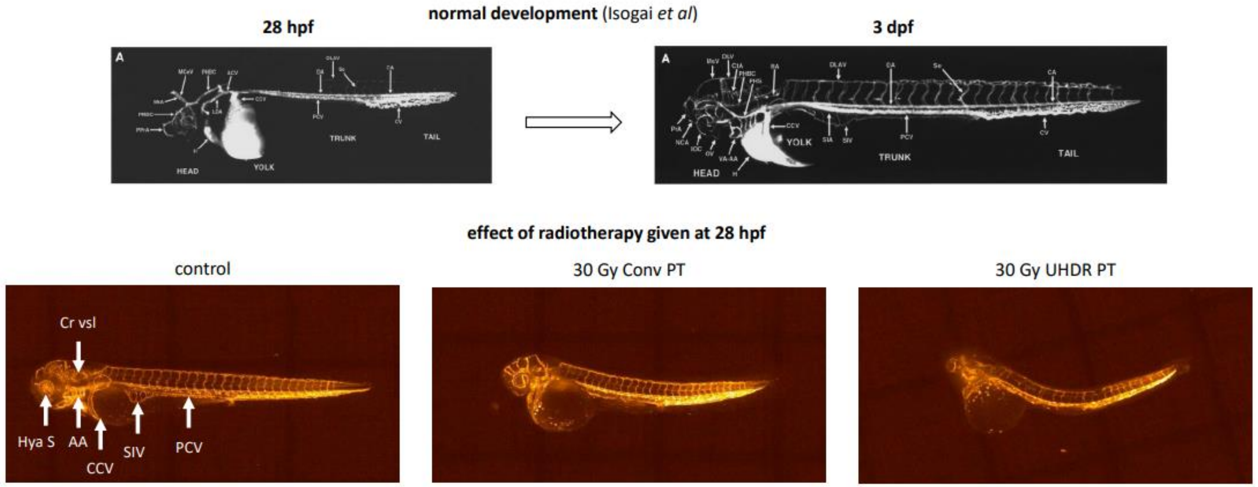
acute effect on blood vessels

Slide from V. Potiron, Webinar FRPT2024









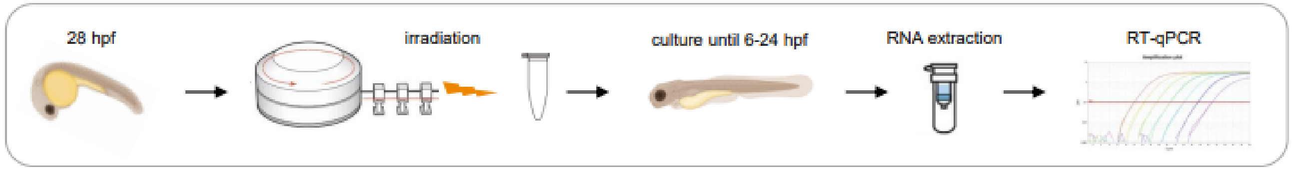
- Vaisseaux déjà formés = radiorésistants
- Pas d’effet du débit

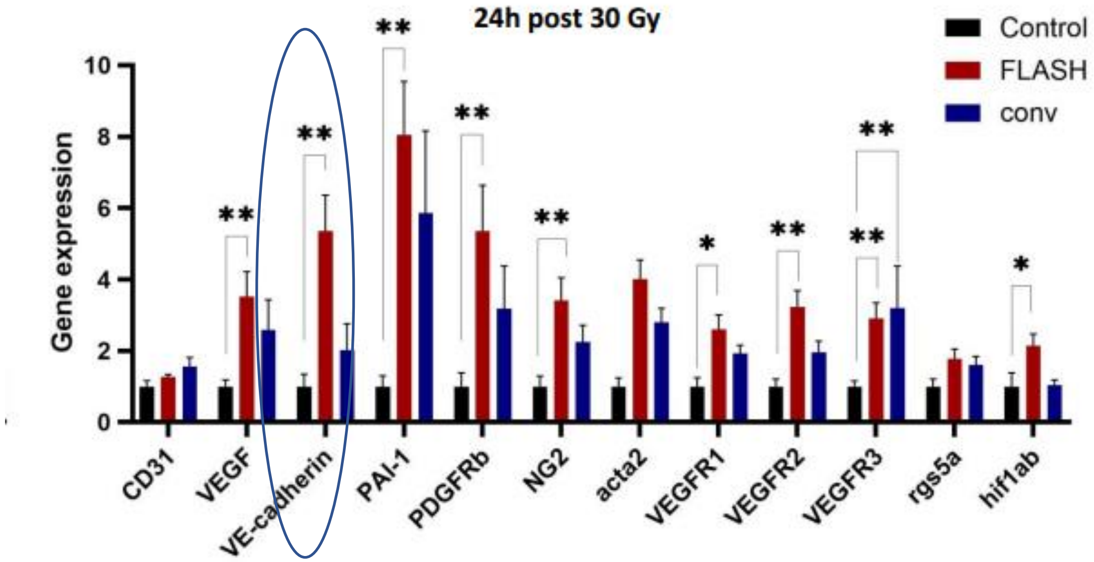
- Blocage de l’angiogenèse
- Pas d’effet du débit

Biologie

Slide from V. Potiron, Webinar FRPT2024

UHDR-PT induces vascular gene expression in 28 hpf zebrafish

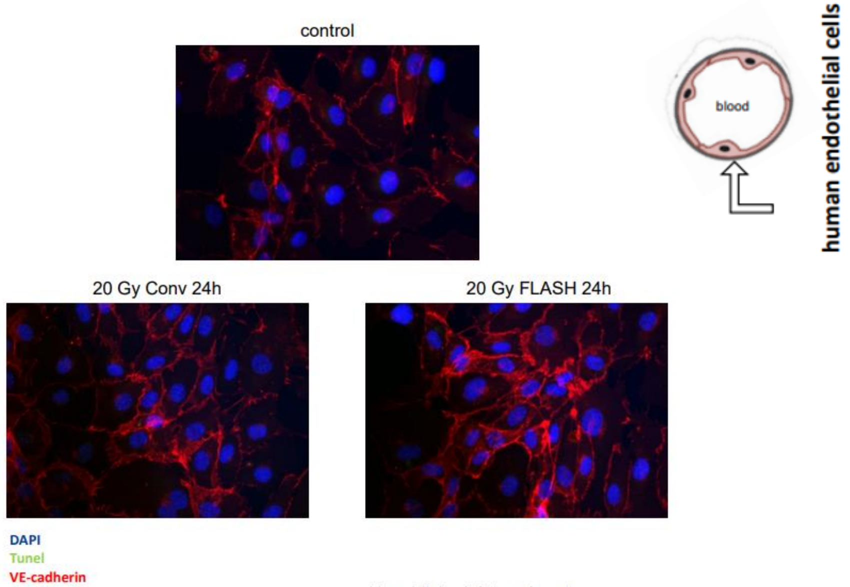




La VE- cadherin forme la jonction intercellulaire endothéliale

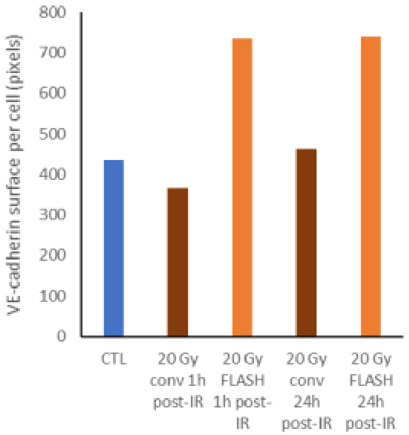
Unpublished data - do not copy

Effects of UHDR-PT on VE-cadherin *in vitro*



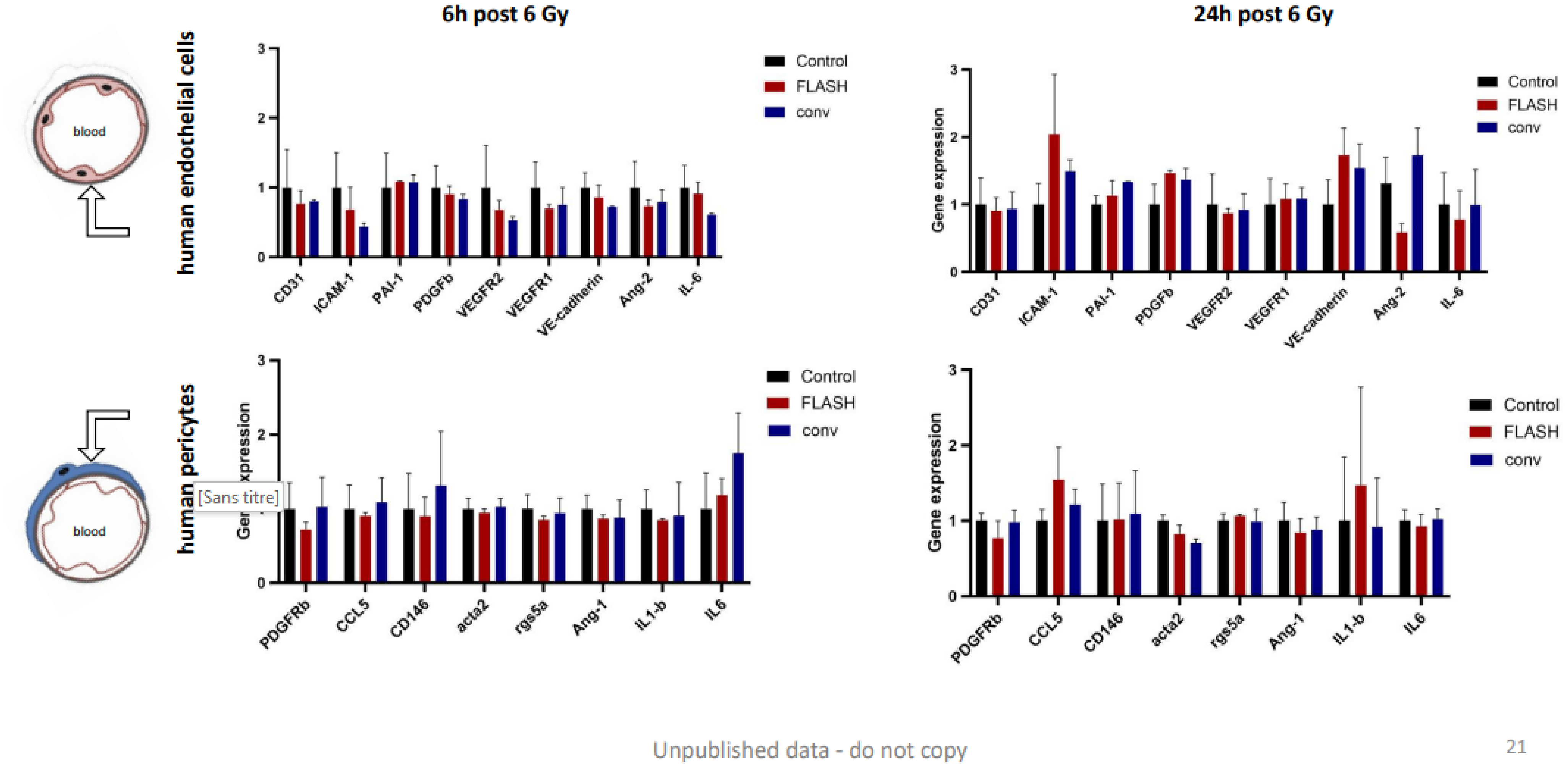
Unpublished data - do not copy

preliminary data (n=1)



Biologie

Effects of UHDR-PT on vascular genes are not recapitulated *in vitro*



➢ Cellules en normoxie. Rôle O2 ?

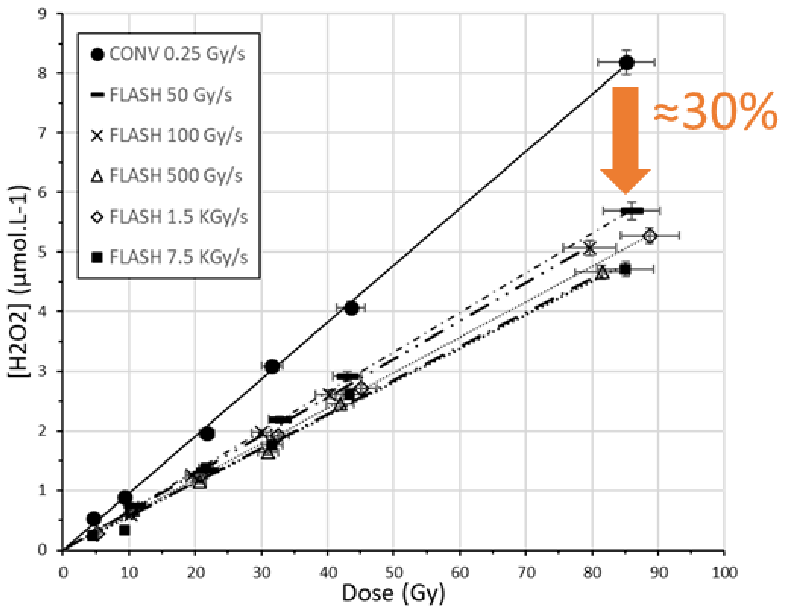
Jansen et al. Radiother Oncol 2022, Grilj et al. Radiother Oncol 2024

Slide From V. Potiron, Webinar FRPT2024

Chimie

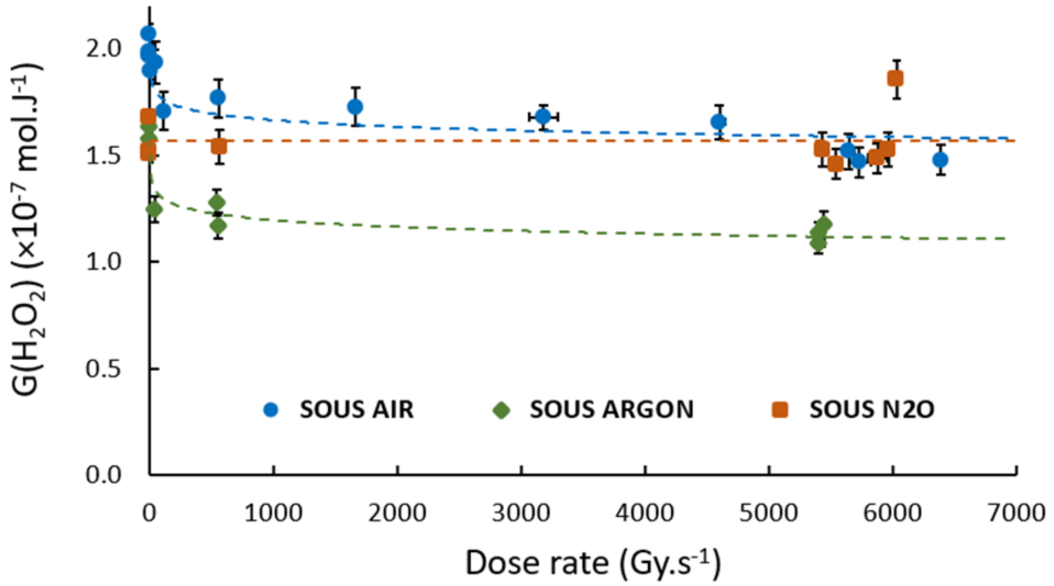
Effet UHDR dès l'étape chimique dans l'eau ?

➢ Hypothèse des recombinaisons radicalaires différentes liées au débit de dose



Blain G et al. Radiation Research, 2022

- Moins de H_2O_2 produit en UHDR Vs. CONV
- Confirmation de *Montay-Gruel et al. PNAS 2019* (électrons 500Gy/s)



N2O = piégeur de e^-_{aq} + absence d'O2

→Plus d'effet UHDR

$$e^-_{aq} + HO^{\bullet} \longrightarrow HO^-$$ k = 3.0×10^{10} L mol^{-1} s^{-1}

$$H_2O_2 + e^-_{aq} \longrightarrow HO^{\bullet} + HO^-$$ k = 1.1×10^{10} L mol^{-1} s^{-1}

Kusumoto et al. RSC advanced 2020, Labarbe et al. Radiotherapy and Oncology 2020, Kusumoto et al, Radiation Research 2024, Pastina et al. The Journal of Physical Chemistry 2001

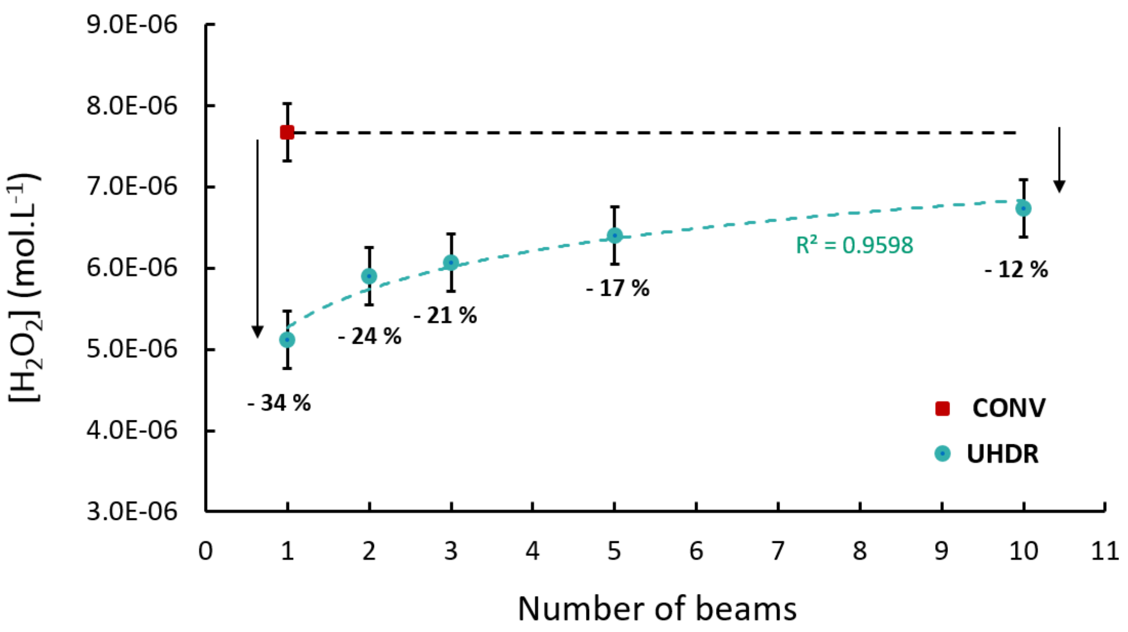
Chimie

Effet UHDR dès l'étape chimique dans l'eau ?

- Exploration de la structure temporelle des faisceaux

Etude multifaisceaux

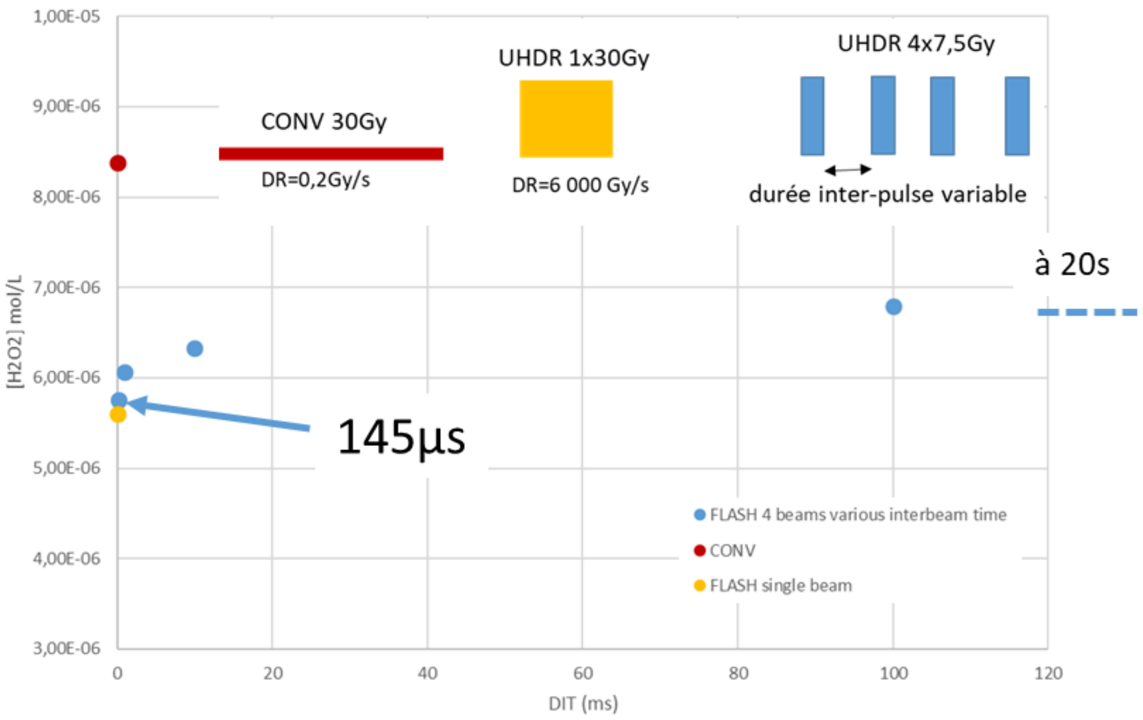
30Gy UHDR, 68MeV protons, <u>20s</u> entre les faisceaux: 1x30Gy, 2x15Gy, 3x10Gy … 10x3Gy



- impact du Flash ↘ nombre de faisceaux ↗
  dose par faisceau ↘

Evin M et al. ESTRO 2023

Variation de la durée inter-faisceaux



- Effet Flash retrouvé avec durée inter-faisceau faible

Sorensen et al. IJROBP 2024

Chimie

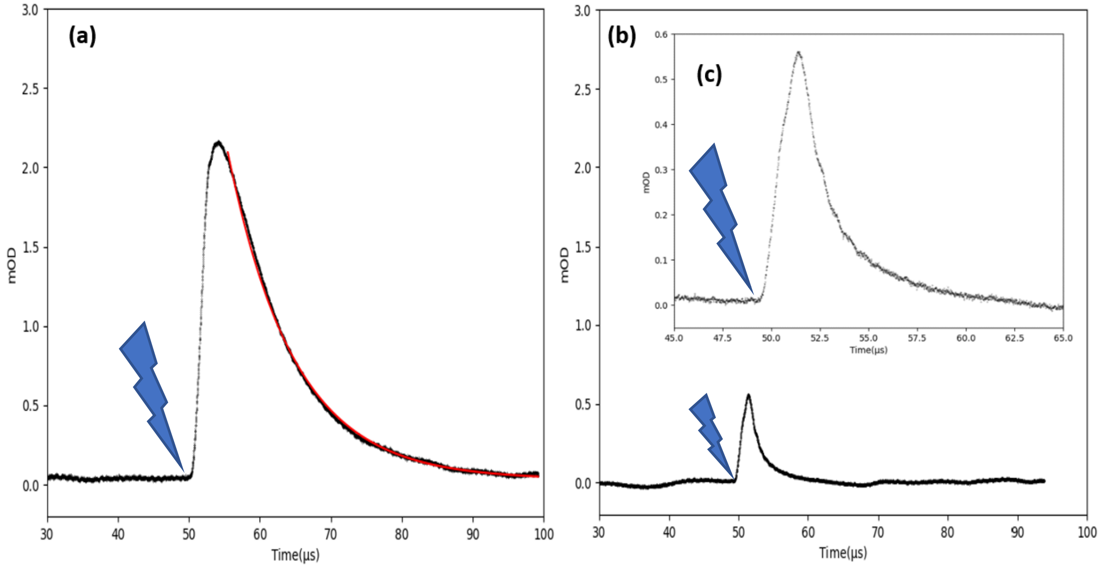
Effet UHDR dès l'étape chimique dans l'eau ?

- Lien $H_2O_2 \leftrightarrow e^-_{aq} \leftrightarrow O_2$

Mesure de l' e^-_{aq} en direct sous le faisceau de protons → Thèse de Sarra Terfas (Subatech, G. Blain)

Protons 67.4 MeV
Débit = 240 kGy/s
Durée du pulse = 2µs
Dose = 0,48Gy/pulse

mOD : optical density x10^{-3}



Sous argon :

e^-_{aq} +
H^+
$HO^{\bullet}$
H_2O_2
O_2 résiduel
H3O+

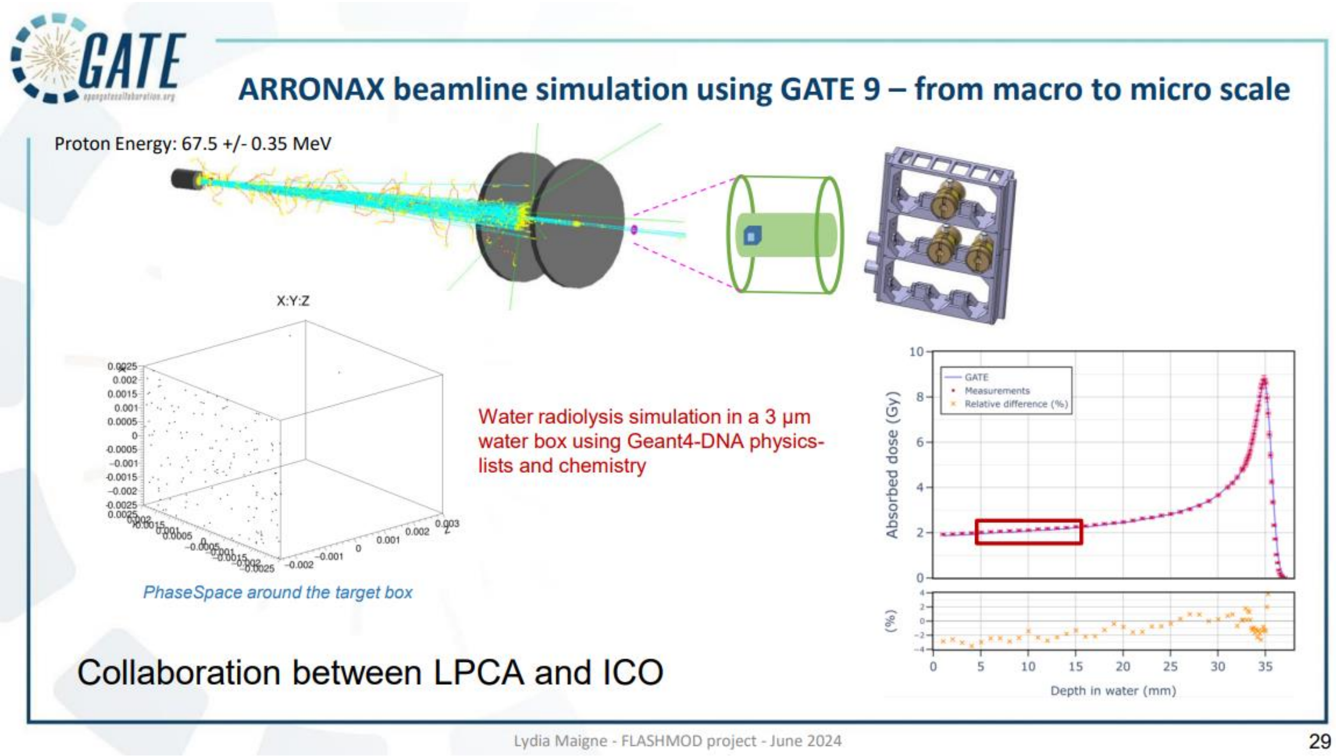
Sous air :

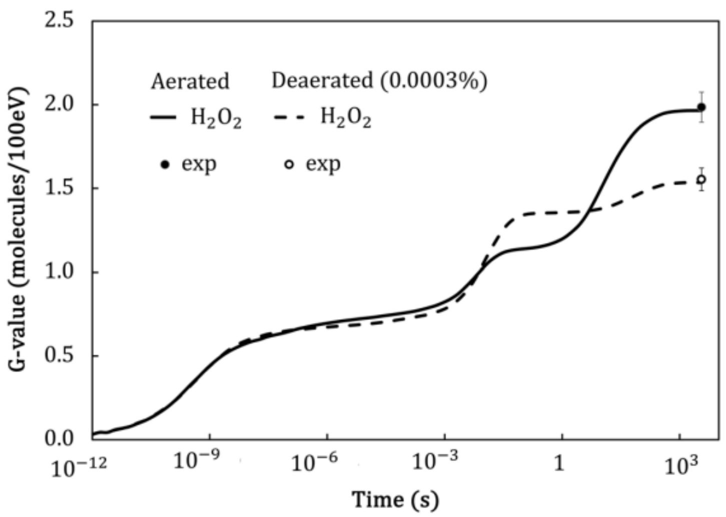
$$e^-_{aq} + O_2 \longrightarrow O_2^{\bullet -}$$

Et donc G et ½ vie ↘

Modélisation

Modélisation radiochimique du Flash avec GATE/Geant4-DNA





From Fois et al. Med. Phys. 2024

- Présentation de Daeun Kwon ce matin

Nouvelle approche pour la modélisation du débit dans Geant4-DNA

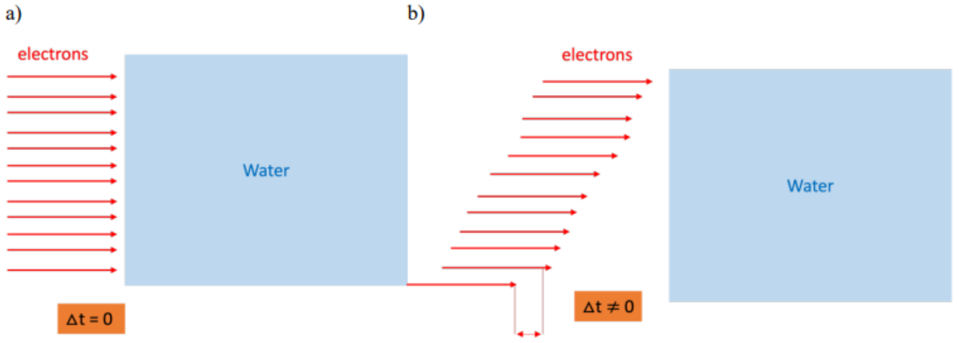


Figure 1: 1 MeV electron beam irradiation. Simulation volume: water cube (in blue). a): Infinite (= instantaneous) single-pulse irradiation: all incident electrons are shot simultaneously as a parallel beam onto the volume until the total absorbed dose is reached. b): « Time-structured » single-pulse irradiation. The sequence of irradiation can be changed by the user. Δt is the delay time between two successive electrons within a beam irradiation.

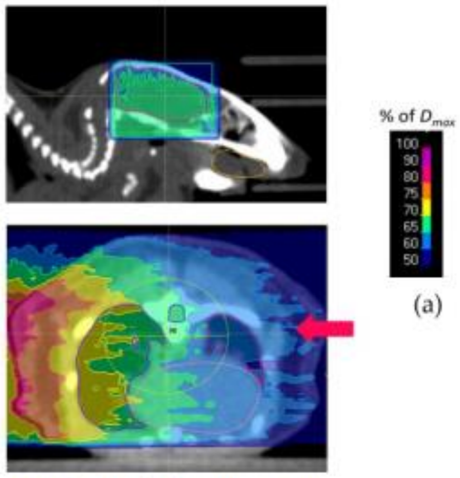
Tuan et al. Modeling water radiolysis with Geant4-DNA: Impact of the temporal structure of the irradiation pulse under oxygen conditions*arXiv 2024*

Conclusion et perspectives

- Physique

  Environnement permettant les études à tous les débits en protons et ions hélium
  Irradiations possibles dans le plateau, pic de Bragg, SOBP
  Maitrise de la dose délivrée, du débit, de la durée des pulses, …
  modélisation GATE de la ligne → dosimétrie dans les cibles complexes

GATE



Simulation of a lateral proton beam on a mouse.
From Evin et al. 2024

- Biologie

  Effet Flash obtenu sur différents modèles *in vivo* (ZF, souris)
  Effet vasculaire du Flash: péricytes (ZF), jonction intercellulaire endothéliale (ZF et *in vitro*)
  Pas d’effet Flash sur les vaisseaux déjà formés et l’angiogenèse
  Pas d’effet Flash sur l’activation des gènes vasculaire *in vitro*

- Chimie

  Baisse de H_2O_2 dans l’eau en Flash
  rôle de l’ e^-_{aq} démontré
  Impact de la dose par faisceau et de l’intervalle entre 2 faisceaux
  → Confirmation de la théorie de la recombinaison radicalaire

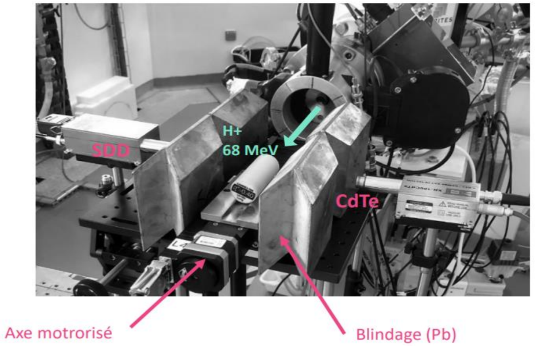
- Modélisation

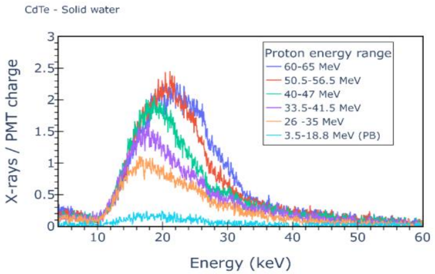
  Comparaison modèle/expérimental en débit conventionnel pour différentes conditions (O2, pH)

Conclusion et perspectives

- Développements dosimétriques

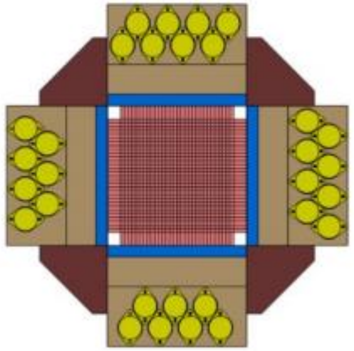
Dosimétrie in vivo par mesure du spectre d'émission Bremsstrahlung



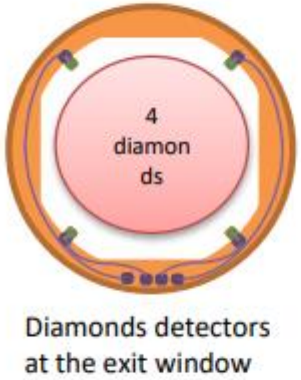


Evin et al. EXRS 2024

PMT-profiler



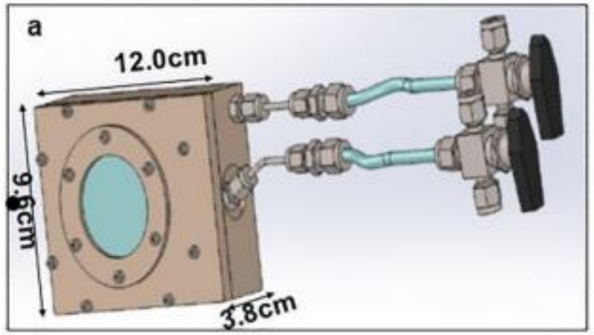
Diamonni
(Nicola André, Robin Molle)



PEPITES
(C. Thiebaux)

PEPITES

- Développement d'un dispositif hypoxique pour étude cellulaire



Chaudhary et al. Research Square 2021

- Etude du Flash à différents TEL (*Tinganelli et al. FRPT 2023*)
  - Collaboration avec le Ganil (Carbone) F. Chevalier
  - Utilisation du faisceau Hélium sur cellules en hypoxie
- Etude du remodelage vasculaire tumoral en Flash chez la souris
- Mesure d'autres espèces radiochimiques (O2°-, …)
- Mesure indirecte de l' e^-_{aq} (Collaboration avec Q. Raffy)
- Lien entre Chimie et Biologie
  - milieu différent de l'eau (Collaboration avec J. Seco)
  - H2O2 dans les cellules (Collaboration avec P. Vidi)
  - Etude multifaisceau sur cellules en hypoxie
- Poursuite de la collaboration G4-DNA (L. Maigne et H. Tran)

- A Monte Carlo Determination of Dose and Range Uncertainties for Preclinical Studies with a Proton Beam. Bongrand *et al*, Cancers 2021
- Ultrahigh-Dose-Rate Proton Irradiation Elicits Reduced Toxicity in Zebrafish Embryos. Saade *et al*, Adv Rad Onc 2022
- Proton Irradiations at Ultra-High Dose Rate vs. Conventional Dose Rate: Strong Impact on Hydrogen Peroxide Yield. Blain G *et al*, Radiat Res 2022
- Technical note: Proton beam dosimetry at ultra-high dose rates (FLASH): Evaluation of GAFchromic™ (EBT3, EBT-XD) and OrthoChromic (OC-1) film performances. Villoing D *et al*, Med Phys 2022
- Methodology for small animals targeted irradiations at conventional and ultra-high dose rates 65 MeV proton beam. Evin M *et al*, Phys Med 2024
- Monte Carlo simulations of microdosimetry and radiolytic species production at long time post proton irradiation using GATE and Geant4-DNA. Fois *et al*, Med Phys 2024
- First evidence of in vivo effect of FLASH radiotherapy with helium ions in zebrafish embryos. Ghannam et al, radiotherapy and Oncology 2023
- Validation of the proton FLASH effect in a zebrafish model: a mechanistic study. Bogaerts et al, under review

- Session recherche commune avec le GdR Mi2b
- Session dosimétristes
- Session « Ma thèse en 180 secondes »
- Session Poster-discussion
- Labélisation REEVE

cnrs
Depuis 80 ans, nos connaissances bâtissent de nouveaux mondes

Mi2b

RESEAU ECO-EVENEMENT

ÉVÉNEMENT ÉCO-ENGAGÉ EN PAYS DE LA LOIRE

sfpm

Contexte

FLASH Radiotherapy: Ultra-High Dose Rate (UHDR, > 40Gy/s)

❑ First « official » FLASH-RT paper in 2014

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

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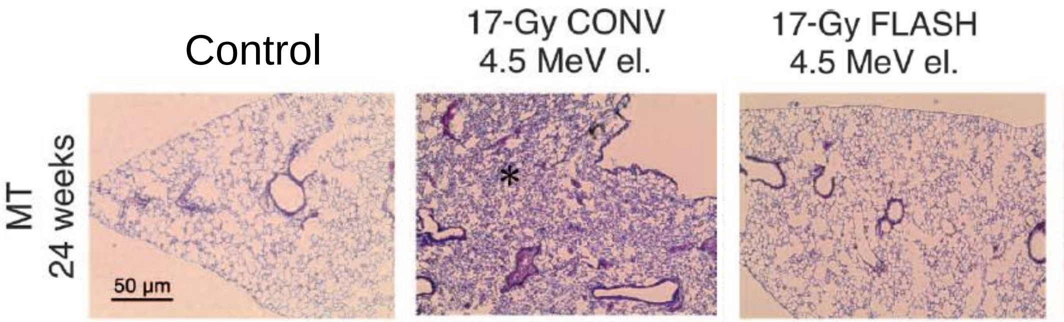
SCIENCE TRANSLATIONAL MEDICINE • 16 Jul 2014 • Vol 6, Issue 245 • p. 245ra93 • DOI: 10.1126/scitranslmed.3008973

❑ FLASH effect observed on mice

- ❑ Lung protection from radiation-induced fibrosis
- ❑ No loss of anti-tumor efficiency
- ❑ 4.5 MeV electrons



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FLASH EFFECT

Increase in therapeutic index