PISA
18-20 Ottobre 2023

Optimisation and setup for quantitative in vitro/vivo experiments with low energy UHDP electrons in FLASH RT

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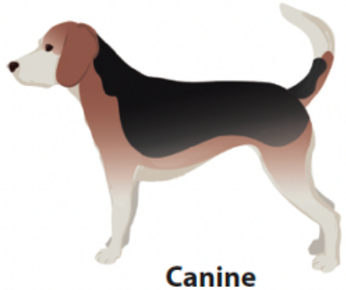
Presentation outline

- FLASH effect - *what we know*
- Clinical transition of FLASH - *what is needed*
- UHDP dosimetric challenges and possible solutions
- In vitro experiments
- In vivo experiments

The FLASH effect

Experimental evidences

Dose	> 5 - 10 Gy
Dose Rate	> 100 Gy/s
Dose-per-pulse	> 1 Gy
Instantaneous Dose Rate	> 10^6 Gy/s
Irradiation time	< 100 - 200 ms



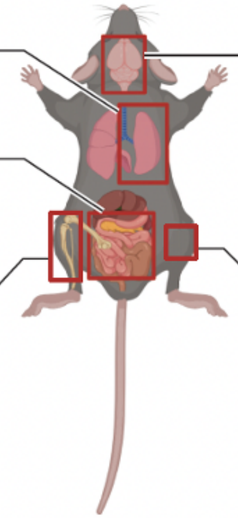
Canine
Konradsson et al. (2021)

Feline
Vozenin et al. (2019a)

Mouse lung
Favaudon et al. (2014)
Fouillade et al. (2020)

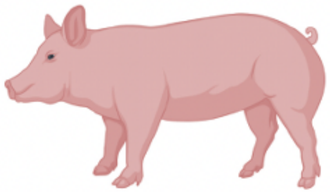
Mouse gut
Levy et al. (2020)
Velalopoulou et al. (2021)
M.M. Kim et al. (2021)

Human hematopoiesis
Chabi et al. (2021)



Mouse brain
Montay-Gruel et al. (2017)
Montay-Gruel et al. (2018)
Montay-Gruel et al. (2019)
Simmons et al. (2019)
Allen et al. (2020)
Montay-Gruel et al. (2020)
Alaghband et al. (2020)

Mouse skin
Field & Bewley (1974)
Inada et al. (1980)
Hendry et al. (1982)
Soto et al. (2020)
Cunningham et al. (2021)
Velalopoulou et al. (2021)
Sorensen et al. (2022)



Miniature pig skin
Vozenin et al. (2019a)

Zebrafish embryo
Montay-Gruel et al. (2019)
Vozenin et al. (2019b)
Kacem et al. (2022)
Karsch et al. (2022)

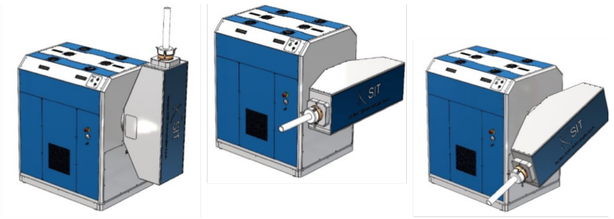
Most of the experiments have been conducted using low energy electron beams

Clinical Transition of FLASH RT

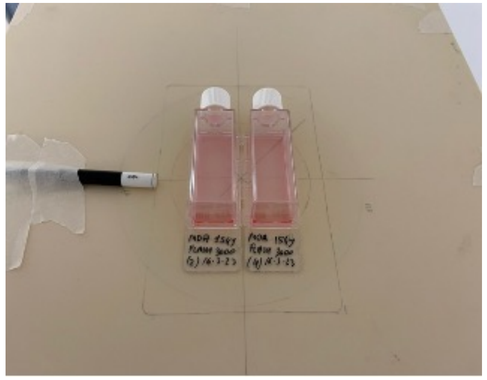
Study of different beam parameters ⟶ Comprehension of the radiobiological mechanisms

Dedicated research FLASH LINAC

ElectronFlash

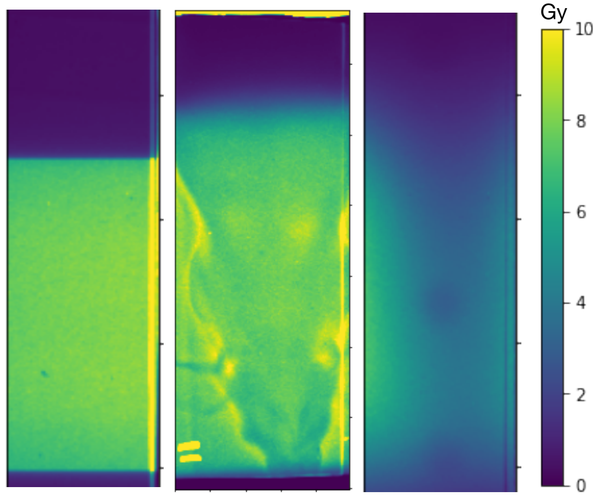


In vitro experiments



The most simple and controllable case for studying radiobiological effects

In vivo experiments



More complex situation (dosimetry + setup) respect to in vitro experiments

UHDP dosimetry

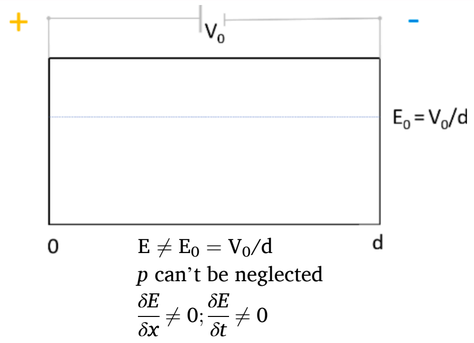
Challenges mainly due to saturation of active dosimeters

frontiers in Physics

ORIGINAL RESEARCH
published: 02 November 2020
doi: 10.3389/fphy.2020.570697

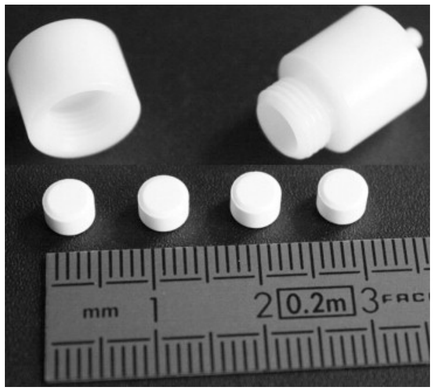
FLASH Radiotherapy With Electrons: Issues Related to the Production, Monitoring, and Dosimetric Characterization of the Beam

Fabio Di Martino[1], Patrizio Barca[1], Salvatore Barone[2], Eleonora Bortoli[1], Rita Borgheresi[1], Silvia De Stefano[2], Massimo Di Francesco[2], Luigi Faillace[3], Lucia Giuliano[3], Luigi Grasso[2], Stefania Linsalata[1], Daniela Marfisi[1], Mauro Migliorati[3], Matteo Pacitti[2], Luigi Palumbo[3] and Giuseppe Felici[2]**

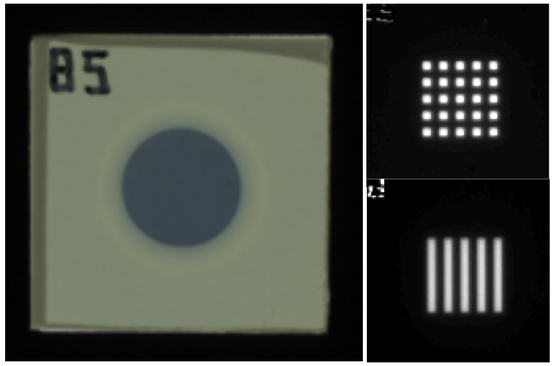


Dosimetric challenges...

Passive dosimeters ✓



Alanine



Gafchromic films

Active dosimeters ✗

Ionization chambers

SCIENTIFIC REPORTS
nature research

Check for updates

The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams

M. McManus[1,2✉], F. Romano[5,1], N. D. Lee[1], W. Farabolini[4,6], A. Gilardi[4], G. Royle[2], H. Palmans[3,1] & A. Subiel[1✉]

Scintillators

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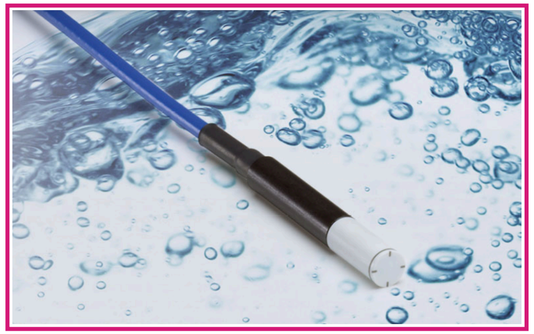
Available online at www.sciencedirect.com
ScienceDirect
Radiation Measurements 41 (2007) S124–S133

Radiation Measurements
www.elsevier.com/locate/radmeas

Plastic scintillation dosimetry and its application to radiotherapy

A.S. Beddar*
Department of Radiation Physics, Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Diodes



… and possible solutions

Calorimeter

(NPL and INFN Catania)

FlashDiamond

(University of Tor Vergata)

SIC

(INFN Catania)

applied sciences — MDPI

Article

First Characterization of Novel Silicon Carbide Detectors with Ultra-High Dose Rate Electron Beams for FLASH Radiotherapy

Francesco Romano [1,2], Giuliana Milluzzo [1,*], Fabio Di Martino [3,4], Maria Cristina D'Oca [1,5], Giuseppe Felici [6], Federica Galante [6], Alessia Gasparini [7,8], Giulia Mariani [6], Maurizio Marrale [1,5], Elisabetta Medina [9,10], Matteo Pacitti [6], Enrico Sangregorio [11,12], Verdi Vanreusel [8,13], Dirk Verellen [7,8], Anna Vignati [9,10] and Massimo Camarda [14,15]

Scintillators

(University of Pisa)

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Experimental characterization and Monte Carlo simulation of scintillator detectors in online electron FLASH radiotherapy dosimetry

Matteo Morrocchi,[a,b] Jake Harold Pensavalle,[a,b,*] Esther Ciarrocchi,[a,b] Fabio Di Martino,[b,c,d] Giuseppe Felici,[e] Federica Galante,[e] Alessia Gasparini,[f,g] Luigi Grasso,[e] Stefania Linsalata,[c] Maurizio Massa,[b] Andrea Moggi,[b] Matteo Pacitti,[d] Verdi Vanreusel,[f,g] Dirk Verellen[f,g] and Maria Giuseppina Bisogni[a,b,d]

ELSEVIER — Contents lists available at ScienceDirect — Physica Medica — journal homepage: www.elsevier.com/locate/ejmp

A new solution for UHDP and UHDR (Flash) measurements: Theory and conceptual design of ALLS chamber

Fabio Di Martino [a,b,d,*], Damiano Del Sarto [b], Maria Giuseppina Bisogni [b,c,d], Simone Capaccioli [b,c], Federica Galante [e], Alessia Gasparini [f,g], Stefania Linsalata [a], Giulia Mariani [e], Matteo Pacitti [e], Fabiola Paiar [b,d,h], Stefano Ursino [b,d,h], Verdi Vanreusel [f,g], Dirk Verellen [f,g], Giuseppe Felici [e]

ELSEVIER — Contents lists available at ScienceDirect — Physica Medica — journal homepage: www.elsevier.com/locate/ejmp

A new calculation method for the free electron fraction of an ionization chamber in the ultra-high-dose-per-pulse regimen

Fabio Di Martino [a,b,d,*], Damiano Del Sarto [b], Salvatore Barone [e], Maria Giuseppina Bisogni [b,c,d], Simone Capaccioli [b,c], Federica Galante [e], Alessia Gasparini [f,g], Giulia Mariani [e], Luigi Masturzo [c,d], Marco Montefiori [c,d], Matteo Pacitti [e], Fabiola Paiar [b,d,h], Jake Harold Pensavalle [c,d], Francesco Romano [i], Stefano Ursino [b,d,h], Verdi Vanreusel [f,g], Dirk Verellen [f,g], Giuseppe Felici [e]

Ionization Chambers

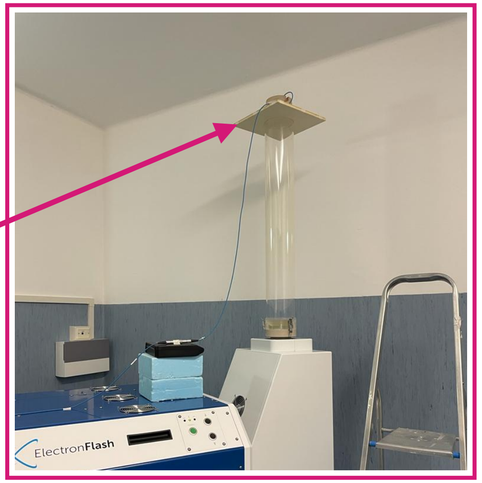
(University of Pisa)

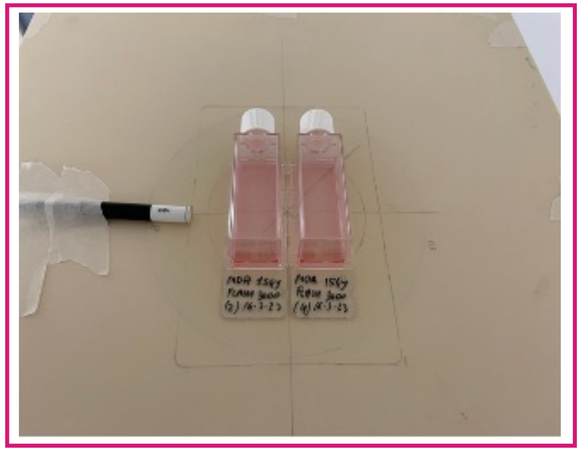
In vitro experiments

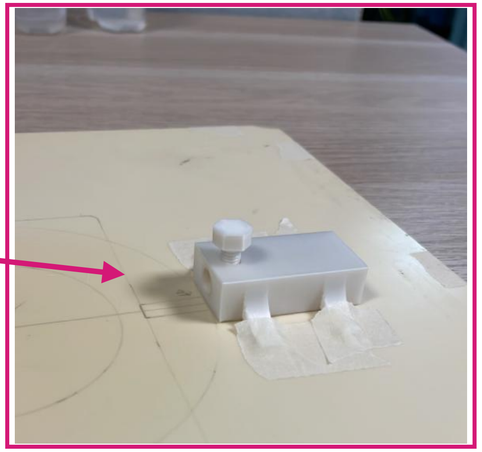
Aim: to explore and quantify the biological effects of different beam parameters one by one

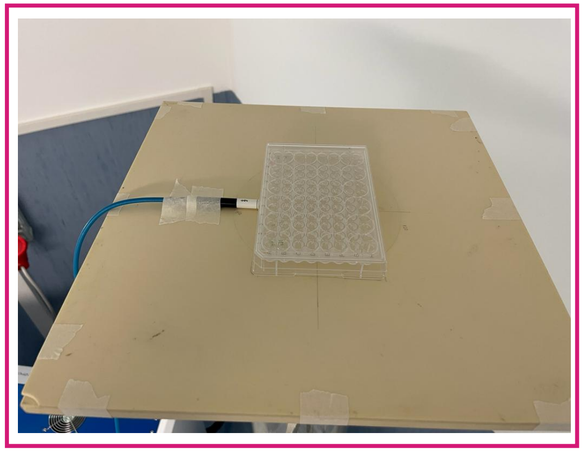
Dosimetric (standardized) setup

- Irradiations at the build-up region (13 mm solid water, EF in vertical position)
- Flat dose distribution + corrective factors from GAF and simulations
- Dosimetric check (before, simultaneous, after irradiation) using FD and MU
- First FLASH, later CONV (same dose requested)









In vitro experiments

	FLASH		CONV		
Nominal dose [Gy]	**Delivered Dose [Gy]**	**DR [Gy/s]**	**Delivered Dose [Gy]**	**DR [Gy/min]**	**Difference**
3	3.09	241	3.09	5	0.09%
6	6.15	241	6.14	5	0.11%
9	9.31	241	9.31	5	0.08%
12	12.32	241	12.30	5	0.16%

In vivo experiments

Additional variables respect to the in vitro counterpart ⟶ essential for preclinical translation

- Dose distribution no longer flat (target with different densities)
- Not interested in punctual dose
- Need of an accurate and reproducible positioning system (+ imaging system)
- Need of a Treatment Planning System (planning + dose quantification)

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

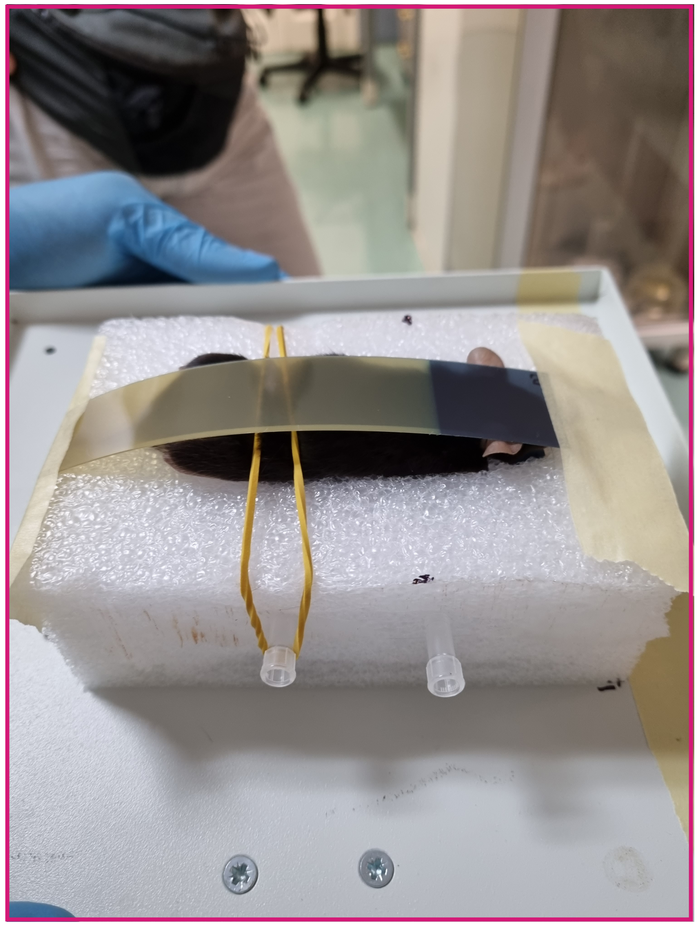
Dose- and Volume-Limiting Late Toxicity of FLASH Radiotherapy in Cats with Squamous Cell Carcinoma of the Nasal Planum and in Mini Pigs

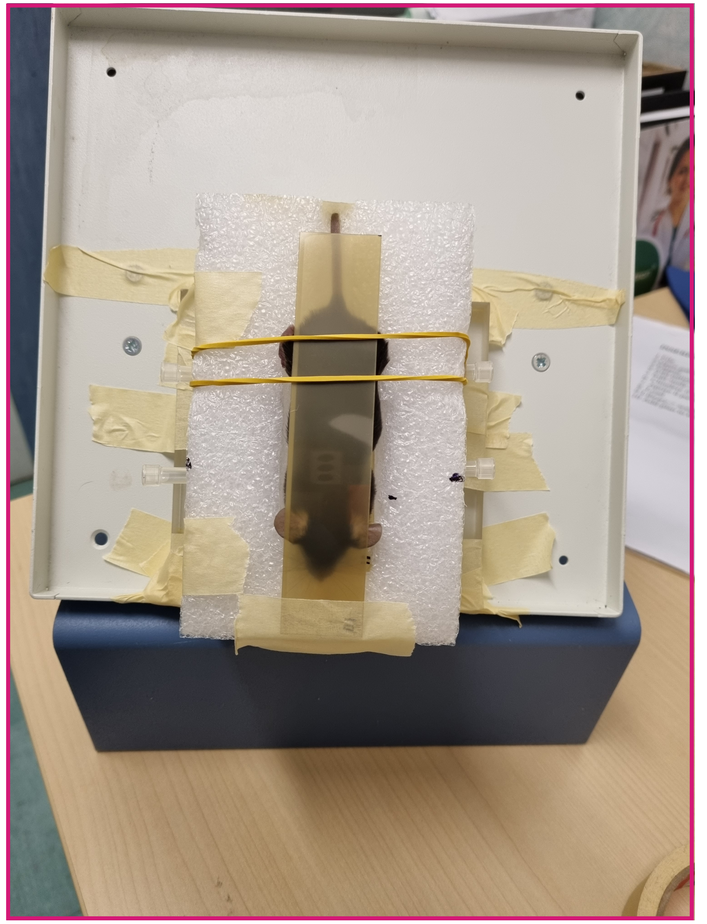
Carla Rohrer Bley[1], Friederike Wolf[1], Patrik Gonçalves Jorge[2,3,4], Veljko Grilj[2,3,4], Ioannis Petridis[2,3], Benoit Petit[2,3], Till T. Böhlen[4], Raphael Moeckli[4], Charles Limoli[5], Jean Bourhis[2], Valeria Meier[1], and Marie-Catherine Vozenin[2,3]

In conclusion, our study is the first to shed light on certain caveats in the path toward clinical translation of FLASH-radiotherapy and shows that implementation of single-high-dose and large field irradiations will present challenges for minimizing long-term toxicities even with FLASH dose rates. We believe that clinical trials with domestic animal patients (cats and dogs) are safe and quick way to investigate FLASH-radiotherapy benefit and avoid possible failure in human clinical trial. At the technological level, implementation of state-of-the art ballistics, imaging and treatment plan should be coupled with FLASH capabilities and systematic characterization of the beam parameters will be required to unravel the full potential of FLASH-radiotherapy, which remains a significant hurdle with existing technology.

In vivo experiments - first experiments @ CPFR

- Patient: mouse (3x7x2 cm^3)
- Handmade polystyrene housing
- GAF positioned above and under the mouse for dose quantification
- 100 mm diameter applicator + Tecapeek shaper for emifields
- Results: it was not possible to determine the delivered dose to the targeted organs and perform a proper positioning of the mouse





In vivo experiments - ongoing experiments @ CPFR

Aim: optimize spatial distribution of the beam

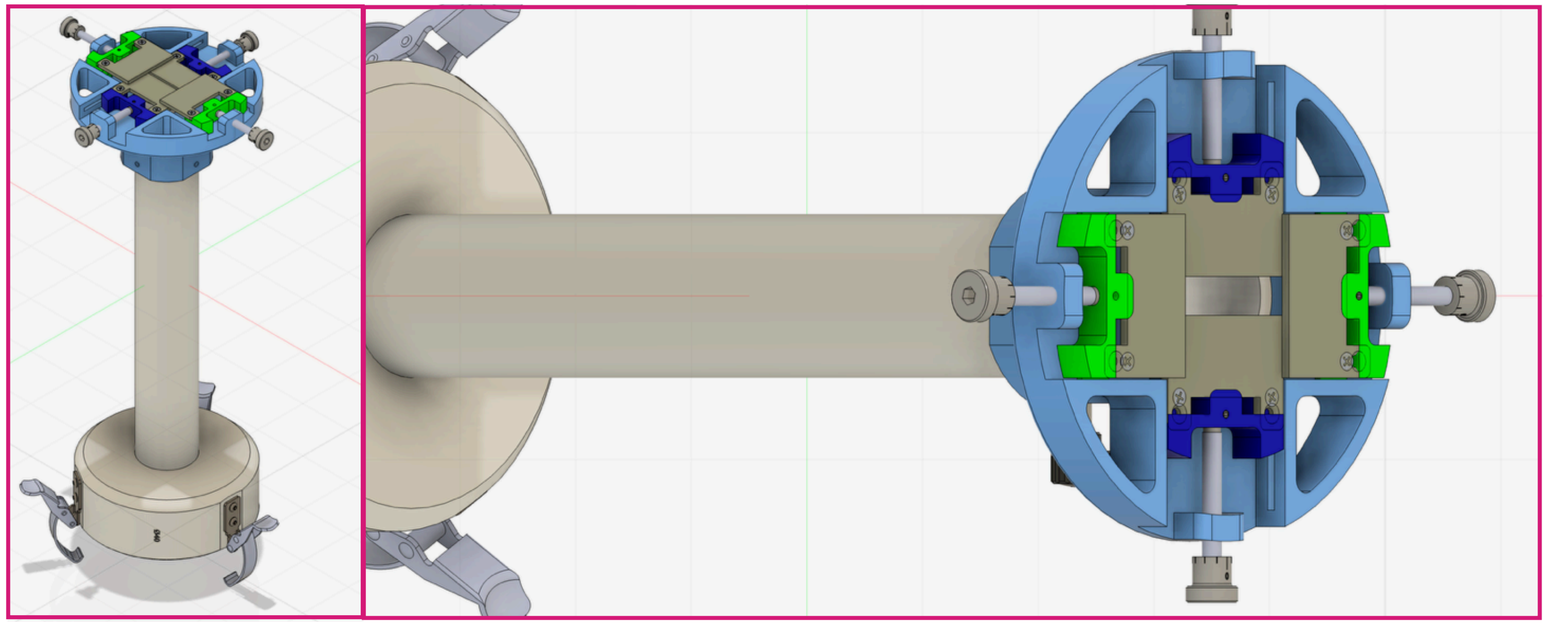
Applicator of 40 and 50 mm diameter (suits well for mouse irradiations)

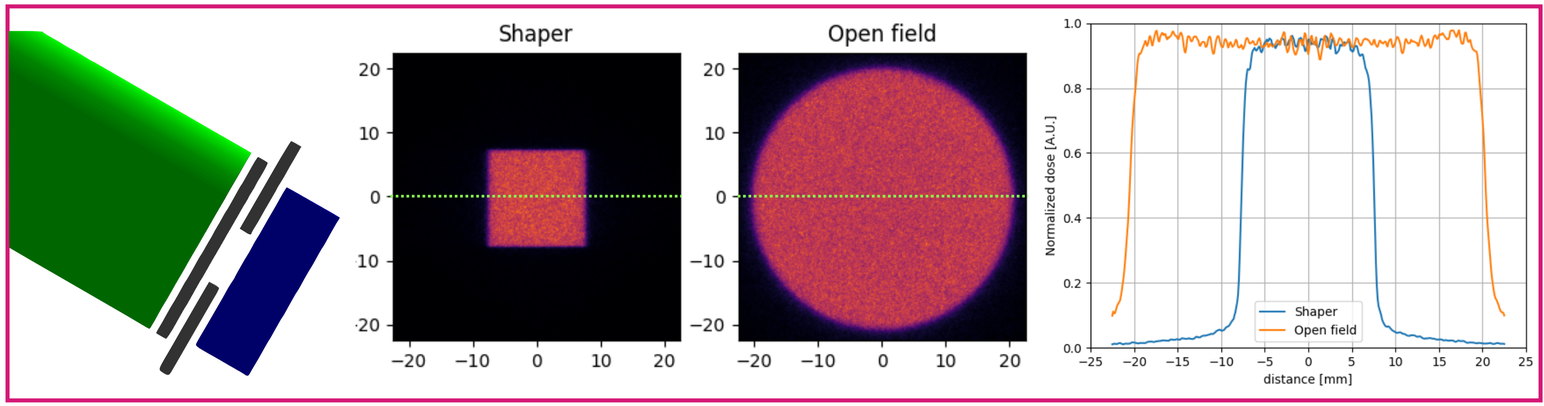
Solution: beam shaper
- 2+2 coupled leafs
- Made of W (3 mm thick)

Z = 74

W

ρ =19.3 g/cm^3

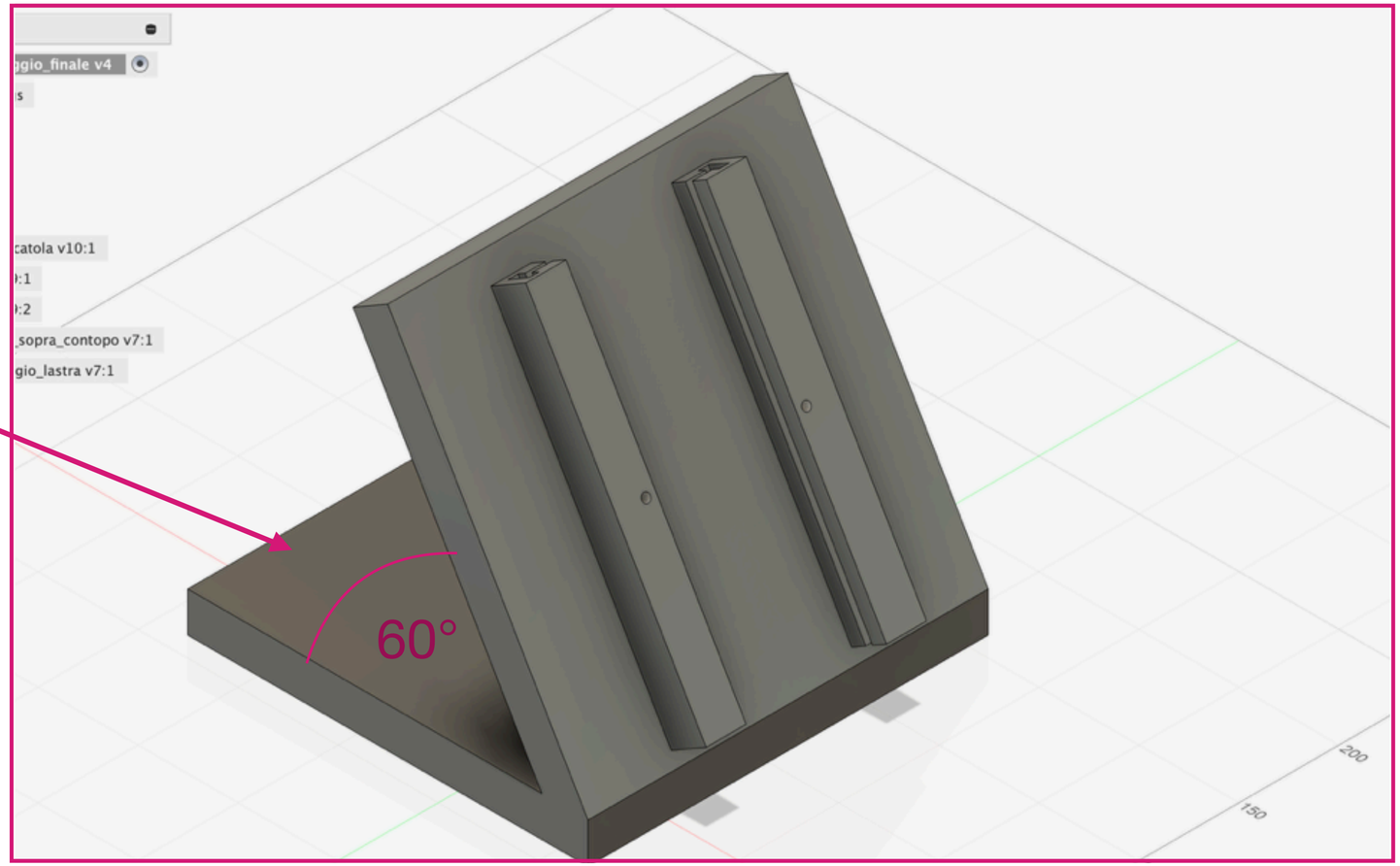




In vivo experiments - ongoing experiments @ CPFR

Positioning system

- First version: very simple and easy to fabricate (all 3D printed)
- Designed for EF irradiation position (oblique)
- Modular (6 pieces)
- 4 degrees of freedom
- Low Z materials (minimise backscatter)
- GAF placements for dose verification



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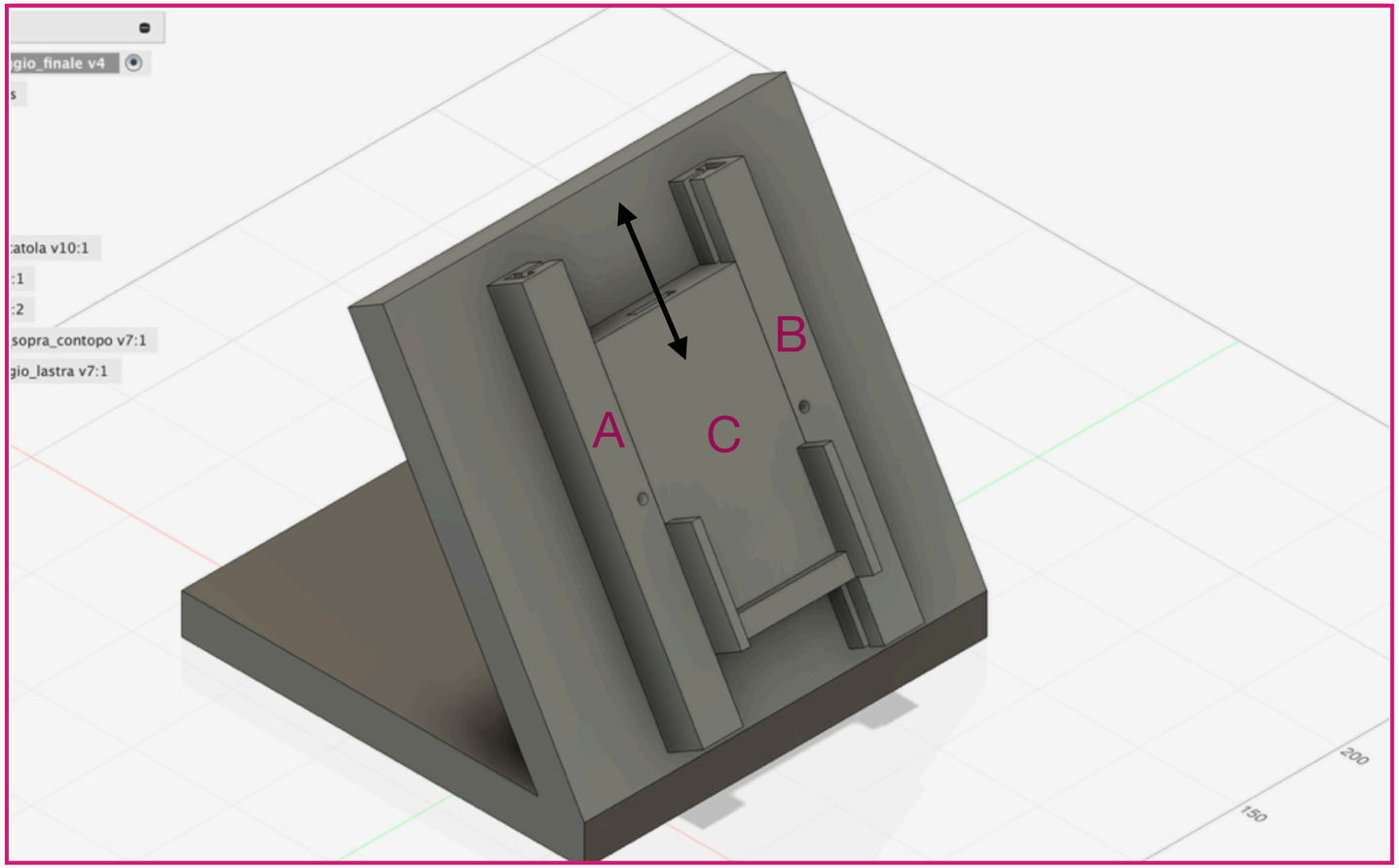

In vivo experiments - ongoing experiments @ CPFR

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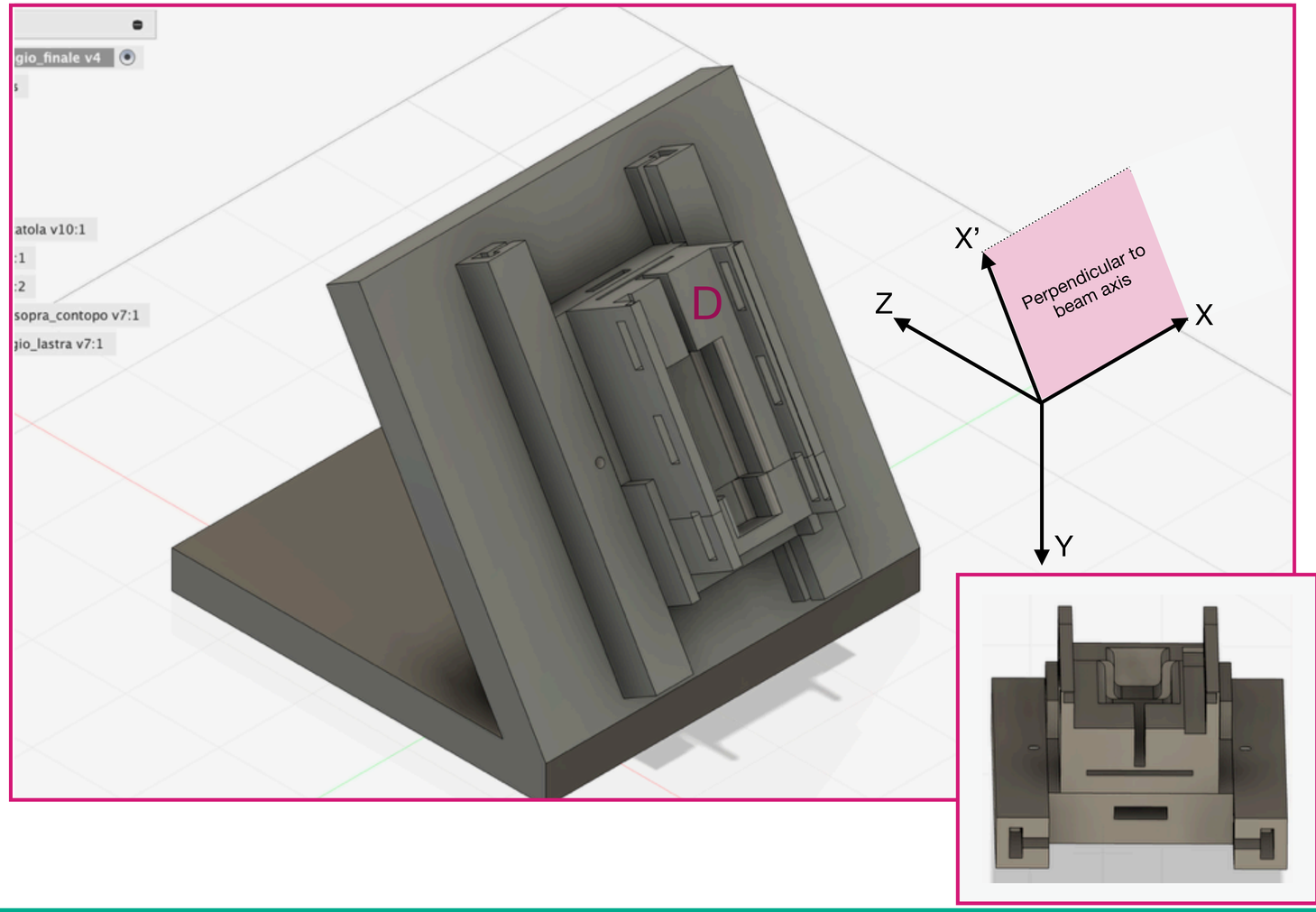
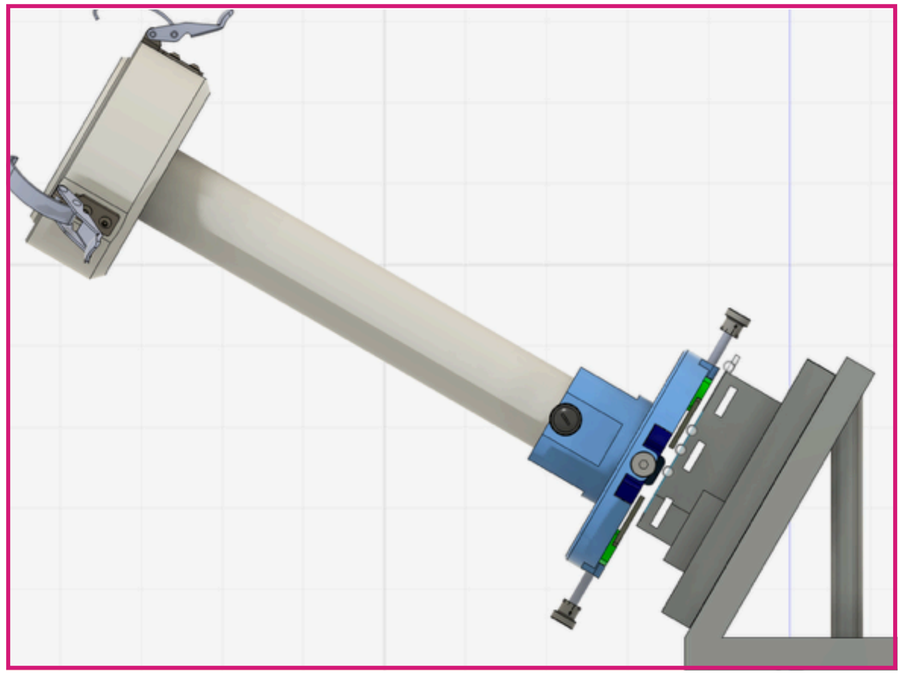
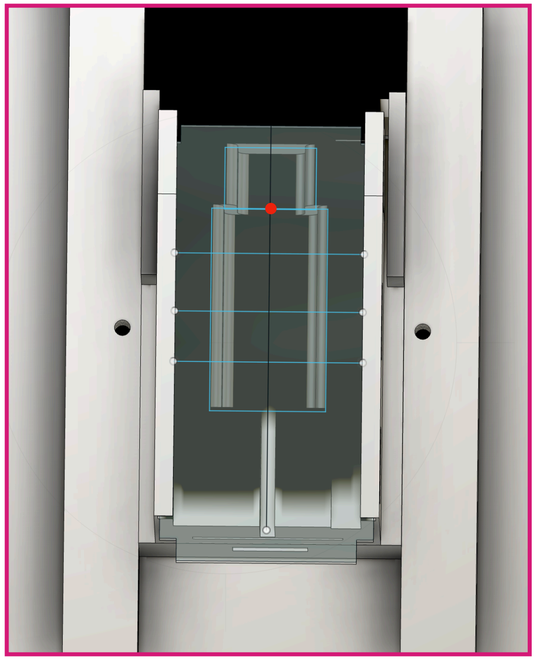
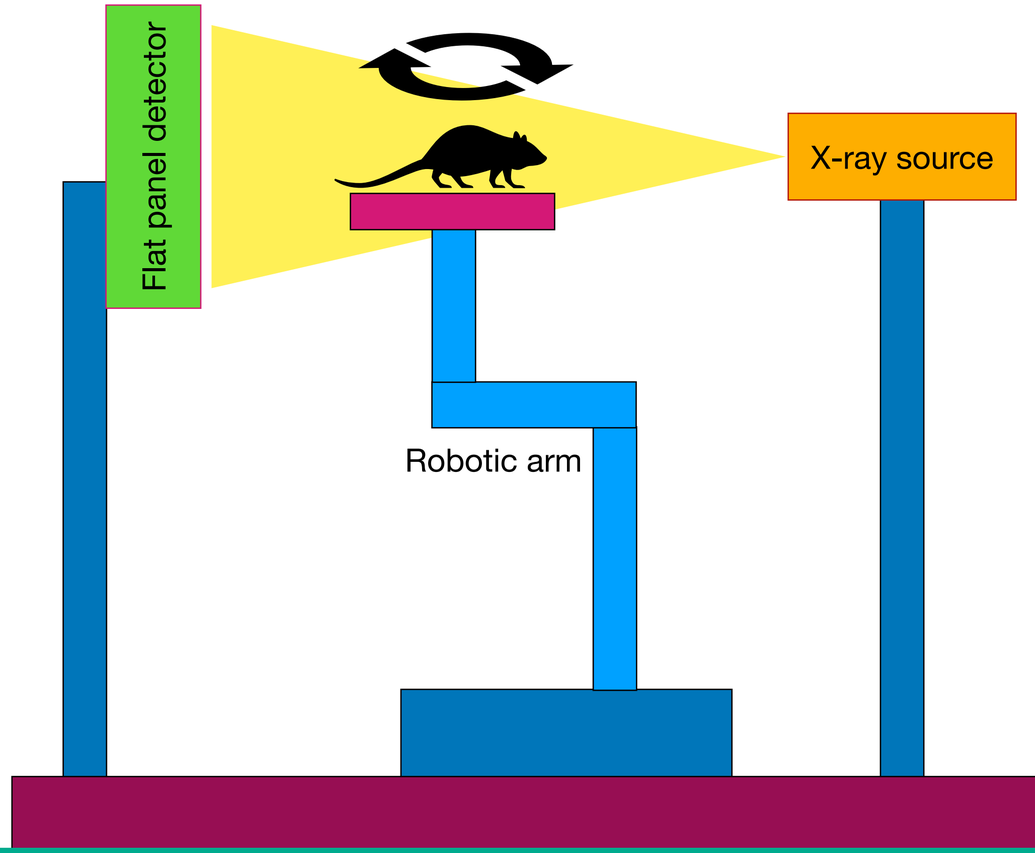


In vivo experiments - ongoing experiments @ CPFR

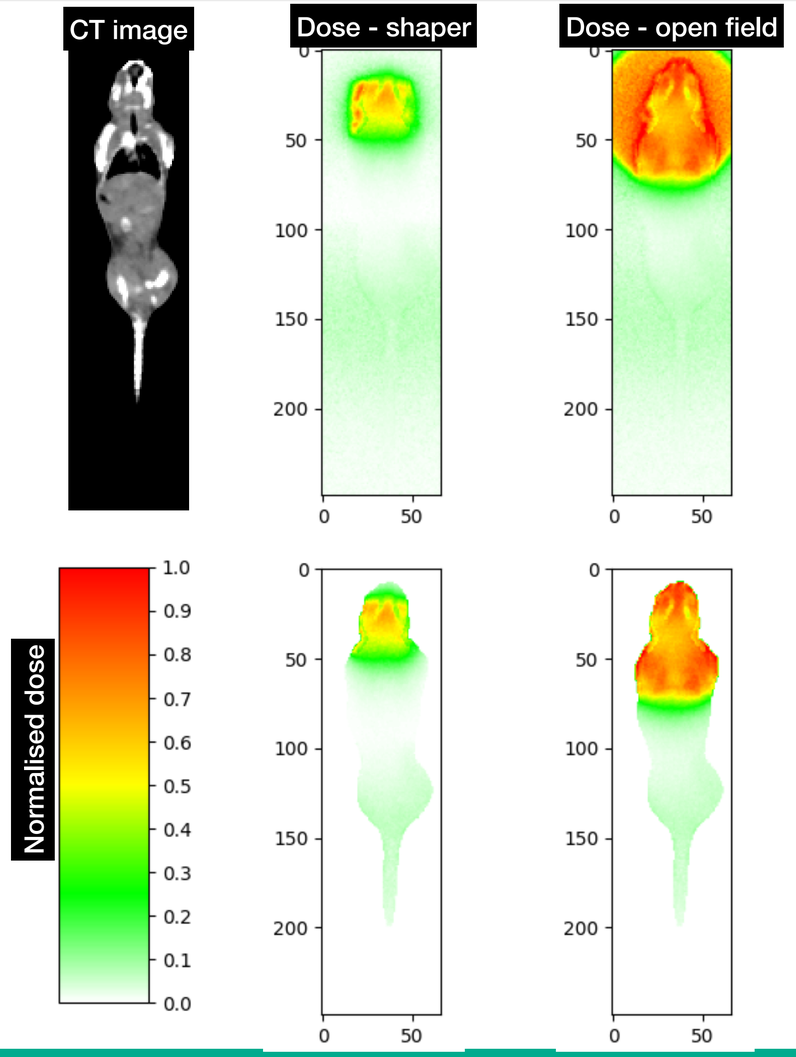
Movements used in simulation | Transparent slab for positioning + laser | MicroCT imaging

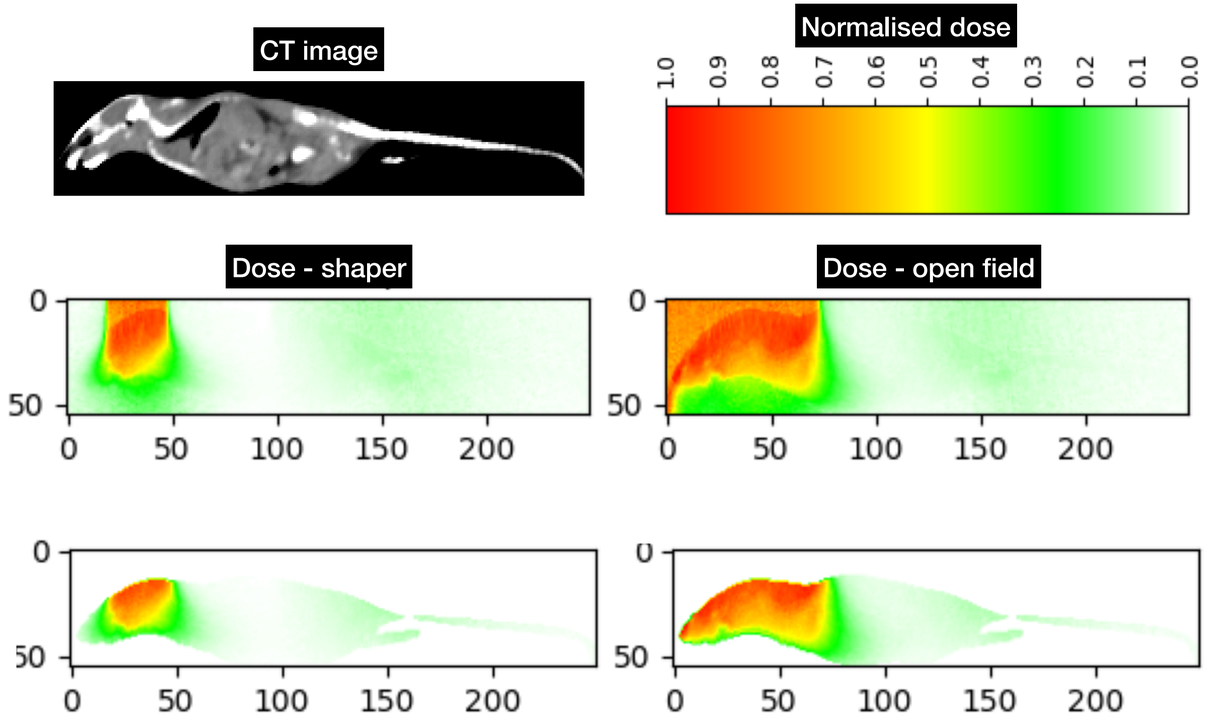




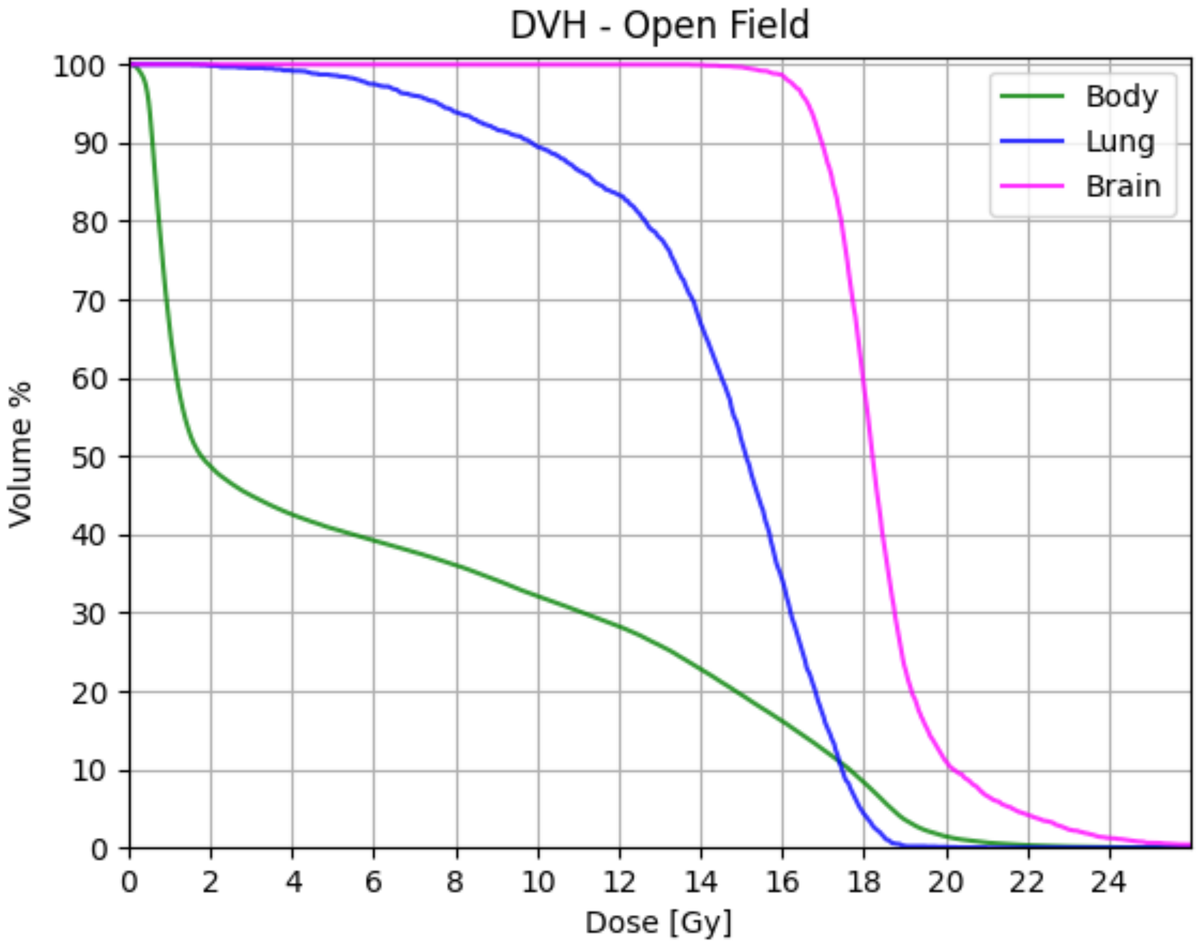


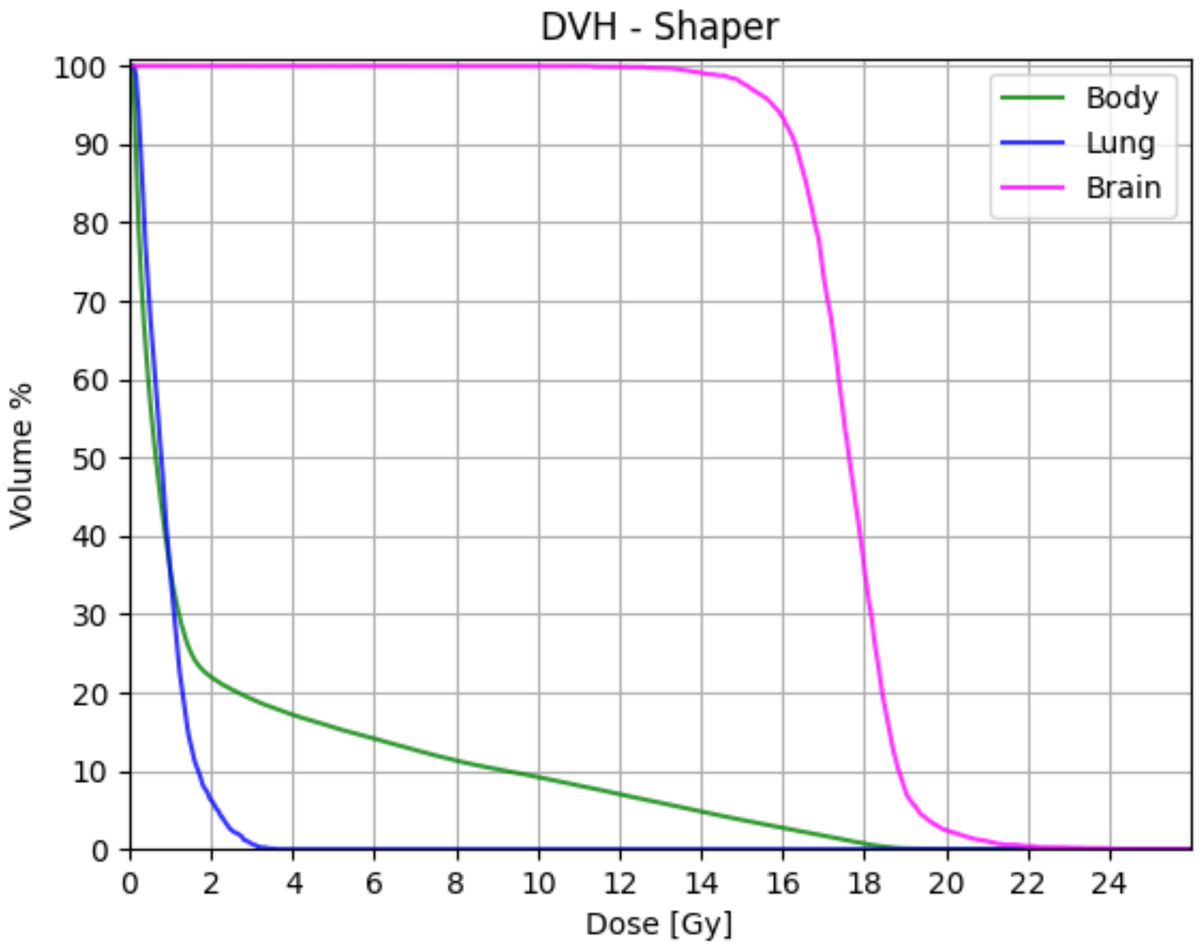
In vivo experiments - ongoing experiments @ CPFR





In vivo experiments - ongoing experiments @ CPFR





Conclusions

In vitro experiments

quantitative evaluation on the optimization of the beam parameters

In vivo experiments

quantitative radiobiological evaluations taking into account metabolic aspects

LIAC FLASH

First clinical application of FLASH RT

Very High Energy Electrons **VHEE**

Implementation of FLASH RT in the radiotherapy routine

PAST / PRESENT → **FUTURE** → **DREAM**